FIFTH EDITION

PATHOPHYSIOLOGY

A Practical Approach

Lachel Story

The Pedagogy

Pathophysiology: A Practical Approach, Fifth Edition focuses on driving comprehension through a variety of strategies that meet the learning needs of students while generating enthusiasm about the topic. This interactive approach addresses different learning styles, making this the ideal text to ensure mastery of key concepts. The pedagogical aids that appear in most chapters include the following:

FIFTH EDITION

PATHOPHYSIOLOGY

A Practical Approach

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Preface

While teaching pathophysiology for more than 14 years and nursing for more than 25 years, I noticed a lack of pathophysiology books that students could relate to and encountered high student frustration with learning the sometimes-convoluted material. Pathophysiology—while being the foundation of much of nursing education, from medical–surgical care to pharmacology—is often an insurmountable barrier for students. They face a copious amount of complicated information that they must weed through and synthesize. While some students become bogged down in an information marsh, others seek more information than is provided in a skeleton book that has been cut to the bone. Nursing faculty join the students on this frustrating Goldilocks journey by trying to make the available resources fit. Unfortunately, nursing students and faculty often have pathophysiology books available that provide either far too much information or far too little.

This text provides the right fit. It is a practical guide to pathophysiology that presents information in an understandable student-friendly way. Here, extraneous information is omitted, leaving only necessary information. The information in this text is also presented in a more accessible manner by considering readability, providing colorful graphics, and giving the content context and meaning.

This unique text will provide a springboard for faculty and students to come together as co-learners to ex-plore this fascinating content. When such co-learning is stimulated, pathophysiology is no longer just mindlessly deposited into the students in a stifling manner; rather,

learning for the students and the faculty becomes an empowerment pedagogy. This approach has been supported by experts at the Institute of Medicine (2011), the Robert Wood Johnson Foundation (Committee on the Robert Wood Johnson Foundation Initiative on the Future of Nursing at the Institute of Medicine, 2010), and nursing leaders (Benner, Sutphen, Leonard, & Day, 2010), among others, who have sought to change how nurses are educated to meet the changing landscape of health care and needs of new generations.

This *Fifth Edition* organizes content in a conceptual manner to provide students with an understandable and practical resource for learning pathophysiology. New and updated material has been added to every chapter. Emerging research has been incorporated to provide state-of-the-science insights into selected topics. Life span considerations have been expanded throughout. New and updated case studies add to students' understanding and ability to apply their learning on a practical level. Instructor resources include active learning activities that support the "flipped" classroom approach. Faculty will appreciate having a resource that speaks to and engages students. Health professionals will also be able to refer to the text to refresh their memory on concepts in a pragmatic way.

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Pathophysiology

LEARNING OBJECTIVES

- Define pathophysiology and identify its importance for clinical practice.
- Identify key health and disease concepts.

KEY TERMS

acute
chronic
compensatory mechanism
complication
congenital
convalescence
degenerative
developmental
diagnosis
disease
epidemic
epidemiology
etiology
exacerbation
genetic

health
hereditary
homeostasis
iatrogenic
idiopathic
inflammatory
insidious
manifestation
metabolic
morbidity
mortality
negative feedback system
neoplastic
pandemic
pathogenesis
pathophysiology
positive feedback systems
predisposing factor
prevention
prognosis
remission
signs
symptoms
syndrome
treatment

Pathophysiology Concepts

What is meant by **pathophysiology**? And why is it so important to understand, especially for nurses? Essentially, pathophysiology is the study of what happens when normal anatomy and physiology go wrong. Veering off this normal path can cause **diseases** or abnormal states. Pathophysiology is the foundation upon which all of nursing is built. It is the “why” that unlocks all the mysteries of the human body and its response to medical and nursing therapies. Understanding pathophysiology provides insight into why patients look the way they

do when they have a certain disease, why the medicines we give them work, why the side effects of **treatments** occur, and why **complications** sometimes transpire. Pathophysiology provides the rationale for evidence-based medicine.

Why are so many students mystified by pathophysiology? Unfortunately, students often get lost in the minute details and the complicated nuances of pathophysiology. Pathophysiology, when brought back to the basics and framed in a practical context, can bring meaning and understanding to the world of **health** and disease in which people live.

Health and Disease

To understand disease, the definition of health must first be clarified. Health may be considered the absence of disease—but this concept can also be expanded to include wellness of mind, body, and spirit. The normal state may vary due to **genetic**, age, and gender differences, and it exists relative to the individual's baseline. Negative events in any one of these three areas can cause issues in the others—these areas coexist. Humans are complicated and do not live in a vacuum. Instead, just as the mind, body, and spirit are interrelated, humans are interrelated with their environment, including their physical ecology, as well as social factors. These external factors play a significant role in an individual's health, whether negatively or positively.

On the flip side of health is disease. Disease is a state in which a bodily function is no longer occurring normally. The severity of diseases ranges from merely creating temporary stress to causing life-changing complications. Health and disease may be considered as the two extremes of a continuum. At one end are severe, life-threatening disease states that cause significant physical and emotional issues; at the other end is optimal health that supports mind, body, and spirit well-being.

Diseases can be classified in several ways. First, a disease may be **hereditary**, meaning it is transmitted before birth. Disease may also be present at birth, or **congenital**. Genetic diseases are caused by abnormalities in the individual's genetic makeup, such as differences in chromosomal numbers or mutations (see the Cellular Function chapter). **Developmental** diseases occur as a result of an issue that arises during embryonic or fetal development. Other diseases may develop over the life span. **Inflammatory** diseases trigger the inflammatory response (see the Immunity chapter). **Degenerative** diseases include conditions that cause parts of the body to deteriorate (e.g., arthritis). Conditions that affect metabolism, such as diabetes mellitus, are referred to as **metabolic diseases**. **Neoplastic** diseases are caused by abnormal or uncontrolled cellular growth, which can lead to benign and malignant tumors (see the Cellular Function chapter).

Exploring concepts of **homeostasis** is a good place to start in understanding the origins of disease.

Homeostasis

Many words can be used to describe homeostasis, such as equilibrium, balance, consistency, and stability. Some examples of this relative consistency can be seen in vital signs such as blood pressure, pulse, and temperature. Every part of the human body—from the smallest cells to the largest organs—needs balance to maintain its usual functions. In some cases, such as with pH, even minimal changes can cause significant and life-threatening problems. The human body is constantly engaging in multiple strategies to maintain this balance and addressing external stressors, such as injury or organism invasion, that might tip the balance in one direction or another.

Homeostasis is a self-regulating, give-and-take system that responds to minor changes in the body through compensation mechanisms. Compensation mechanisms attempt to counteract those changes and return the body to its normal state (**FIGURE I-1**). Several brain structures are instrumental in maintaining this balance,

including the medulla oblongata, hypothalamus, reticular formation, and pituitary gland. The medulla oblongata is located in the brainstem and controls vital functions such as blood pressure, temperature, and pulse. The reticular formation is a network of nerve cells in the brain stem and the spinal cord that also controls vital functions; it relays information to the hypothalamus. The hypothalamus, in turn, controls homeostasis by communicating information to the pituitary gland. The pituitary gland, also known as the master gland, regulates other glands that contribute to growth, maturation, and reproduction.

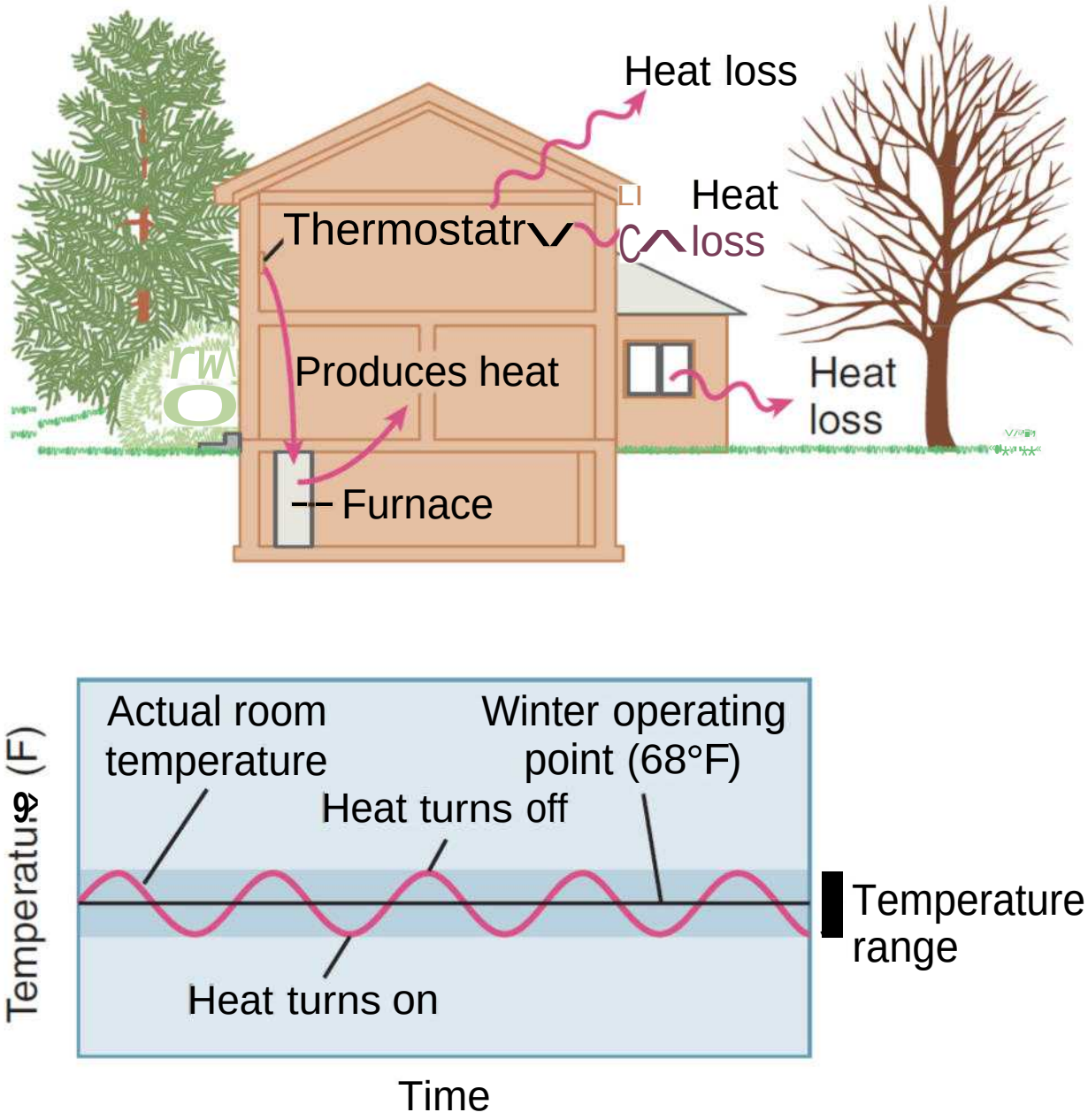


FIGURE I-1 Homeostasis is like a house. (A) Heat is maintained in a house by a furnace, which compensates for heat loss. (B) A hypothetical temperature graph.

Description

Two types of feedback systems exist to maintain homeostasis: negative and positive. A **negative feedback system**—the most common type—works to maintain a deficit in the system. Such negative feedback mechanisms work to resist any change from normal. Examples include temperature and glucose regulation.

Positive feedback systems, though few in number, move the body away from homeostasis. With this type of feedback, an amplified response occurs in the same direction as the original stressor. Examples of positive feedback systems include childbirth, sneezing, and blood clots.

Disease Development

Etiology is the study of disease causation. Etiologic factors may include infectious agents, chemicals, and environmental influences, to name a few. Etiologic factors may also be unknown, or **idiopathic**. Additionally, diseases can be caused by an unintended, or **iatrogenic**, effect of a medical treatment.

Predisposing factors are tendencies that put an individual at risk for developing certain diseases. Examples of predisposing factors are similar to etiologic factors and may include dietary imbalances and carcinogen exposure.

Identifying the etiology and predisposing factors for a disease can be instrumental in preventing the disease by distinguishing at-risk populations who can be targeted with **prevention** measures. Today, the healthcare system is focusing more on disease prevention because investing resources before a disease develops can decrease the long-term financial burden associated with its treatment.

How a disease develops is referred to as **pathogenesis**. Some diseases are self-limiting, whereas others are **chronic** and never resolve. Some diseases cause reversible changes, while others cause irreparable damage. To limit the damage from diseases, the body activates **compensatory mechanisms**—that is, physiological strategies the body employs during homeostatic imbalance to maintain normalcy. When those mechanisms can no longer maintain relative consistency, disease occurs.

Sometimes, the onset of the disease may be sudden or **acute**. Acute onset of a disease may include pronounced indicators, such as pain or vomiting. By comparison, a gradual, or **insidious**, onset may be associated with only vague signals. Hypertension, for example, can occur in this subtle manner.

Disease duration is another important concept to consider. A disease may be short term, or acute, occurring and resolving quickly. Gastroenteritis and tonsillitis are examples of acute diseases. When an acute disease does not resolve after a short period, it may move into a chronic state. A chronic disease often has fewer notable signs and occurs over a longer period. Chronic diseases may not ever resolve but may sometimes be manageable. Diabetes mellitus and depression are examples of chronic diseases. Additionally, people with chronic diseases can experience an acute event of that disease, complicating care. An example of this phenomenon can be seen when a patient with asthma (a chronic disease) has an acute asthma attack.

Recognition of a disease when it is encountered is important in **diagnosis**, or identification, of disease. **Manifestations** are the clinical effects or evidence of a disease. They may include both **signs**—what can be seen or measured—and **symptoms**—what the patient describes but is not visible to the healthcare practitioner. Manifestations may include issues identified during a physical assessment (e.g., heart murmur), diagnostic results (e.g., laboratory levels), patient complaints (e.g., pain), and family reports (e.g., unusual behavior). A **syndrome** comprises a group of signs and symptoms that occur together. Some chronic diseases may include episodes of **remission** and **exacerbation**. Remission occurs when the manifestations subside, and exacerbation occurs when the manifestations increase again. Systemic lupus erythematosus and heart failure are examples of diseases that demonstrate remissions and exacerbations. Manifestations may vary depending on the point at which they occur in the pathogenesis. For instance, an early sign of shock may be tachycardia, whereas bradycardia occurs late in the disease process. Manifestations are often a critical component of disease diagnosis. Additionally, a detailed patient history may be used to facilitate accurate diagnosis.

Treatment refers to strategies used to manage or cure a disease. Treatment may focus on eliminating the cause of the disease, or it may be used to alleviate the disease's clinical manifestations. For example, an antibiotic may be prescribed to target the specific

organism causing a patient's pneumonia, or an antiemetic may be administered to relieve vomiting associated with acute pancreatitis. Treatment regimens often require the services of an interdisciplinary team (e.g., nurses, nurse practitioners, dietitians, respiratory therapists, physical therapists, occupational therapists, physiotherapists, physicians, and pharmacists). Such a team is often necessary when a swift, aggressive approach is required or when long-term management is needed.

Some of the same treatment strategies are used for disease prevention. Prevention includes strategies to avoid the development of disease in individuals or groups. Such strategies may include screening, vaccinations, lifestyle changes, or prophylactic interventions (e.g., medication to reduce high cholesterol levels to prevent strokes, mastectomy in a person at high risk of developing breast cancer).

Recovering from a disease and limiting any residual effects are important aspects of disease management. **Convalescence** is the stage of recovery following a disease, which may last for days or months. **Prognosis** refers to an individual's likelihood of making a full recovery or regaining normal functioning. The death rate from a particular disease is referred to as **mortality**. Complications are new problems that arise because of a disease. For example, renal failure can be a complication of uncontrolled hypertension or diabetes mellitus.

Understanding the factors that affect the health and diseases experienced by populations is the cornerstone to understanding prevention and containment. **Epidemiology** is the branch of science that analyzes patterns of diseases in a group of people. Such tracking of disease patterns includes the occurrence, incidence, prevalence, transmission, and distribution of a disease. **Morbidity** refers to disease rates within a group. **Epidemics** occur when increasing numbers of people have a certain disease within a specific group. When the epidemic expands to a larger population, it becomes a **pandemic**.

Summary

Pathophysiology is the basis for understanding the intricate world of the human body, its response to disease, and the rationale for treatment. Understanding pathophysiology can assist the nurse in better anticipating situations, correcting issues, and providing appropriate care. The concepts of health and disease, although complex, need not cause stress to nursing students or patients. Instead, these concepts can open a world of wonder of which to be in awe.

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CHAPTER 1

Cellular Function

LEARNING OBJECTIVES

- Describe basic cellular structures and functions.
- Discuss how cells exchange materials.
- Identify how cells obtain and produce energy.
- Explain how cells replicate and specialize.
- Describe the different types of tissues.
- Describe common cellular adaptations and possible reasons for the occurrence of each.
- List common causes of cell damage.
- Discuss cancerous cellular damage.
- Describe common genetic and congenital alterations.

KEY TERMS

active transport
adaptation
alleles
anaphase
anaplasia
apoptosis
atrophy
autosomal dominant
autosomal recessive
autosome
benign
cancer

carcinogenesis
caseous necrosis
cell membrane
chromosome
coagulative necrosis
congenital
crenation
curative
cytoplasm
deoxyribonucleic acid (DNA)
differentiation
diffusion
dominant
dry gangrene
dysplasia
electrolyte
endocytosis
enzyme
exocytosis
facilitated diffusion
fat necrosis
free radicals
gangrene
gas gangrene
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infarction
karyotype
lipid bilayer
liquefaction necrosis

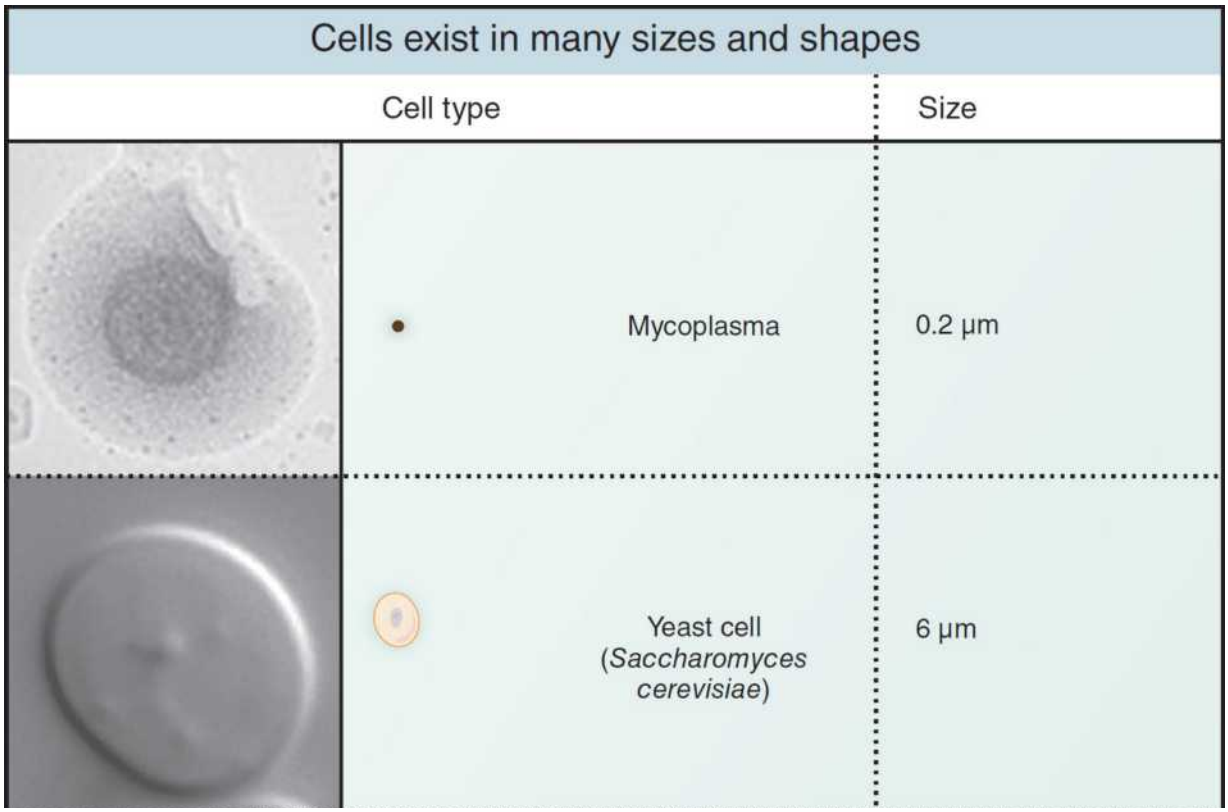
lysis
malignant
meiosis
metaphase
metaplasia
metastasize
mitosis
multifactorial disorders
necrosis
neoplasm
nucleotide
nucleus
organelle
osmosis
osmotic pressure
palliative
phagocytosis
phenotype
pinocytosis
plasma membrane
prognosis
programmed cell death
progression
proliferation
promotion
prophase
prophylactic
protoplasm
recessive
remission
selectively permeable
sex-linked
telophase
teratogens
TNM staging
tumor
wet gangrene

Understanding pathophysiology begins with exploring the basic building blocks of living organisms. Cells give organisms their immense diversity. Organisms can be made up of a single cell, such as a bacteria or virus, or billions of cells, such as humans. In humans, these building blocks work together to form tissues, organs, and organ systems. These basic units of life are also the basic units of disease. As understanding increases about specific diseases, many diseases can be explained at the cellular level. Diseases are likely to occur due to some loss of homeostatic control, and the impact is evident from the cellular level up to the system level. Understanding the various cellular dysfunctions associated with diseases has led to improved prevention and treatment of those diseases. Therefore, understanding basic cellular function and dysfunction is essential to understanding pathophysiology.

Basic Cell Function

Cells are complex mini-organisms resulting from millions of years of evolution. These mini-organisms come together to form specialized tissues with specific functions, and these tissues then form organs with precise purposes. Organs, in turn, form systems that are responsible for maintaining and performing complex actions and meeting the body's needs. This organized interaction is essential to life and optimal health.

Cells can arise only from another preexisting cell. **Genes** interact with the cells to ensure they are specialized for a particular purpose —a process called **differentiation**. Although they vary greatly in size and shape (**FIGURE 1-1**), cells have the remarkable ability to exchange materials with their immediate surroundings, obtain energy from organic nutrients, synthesize complex molecules, and replicate themselves.



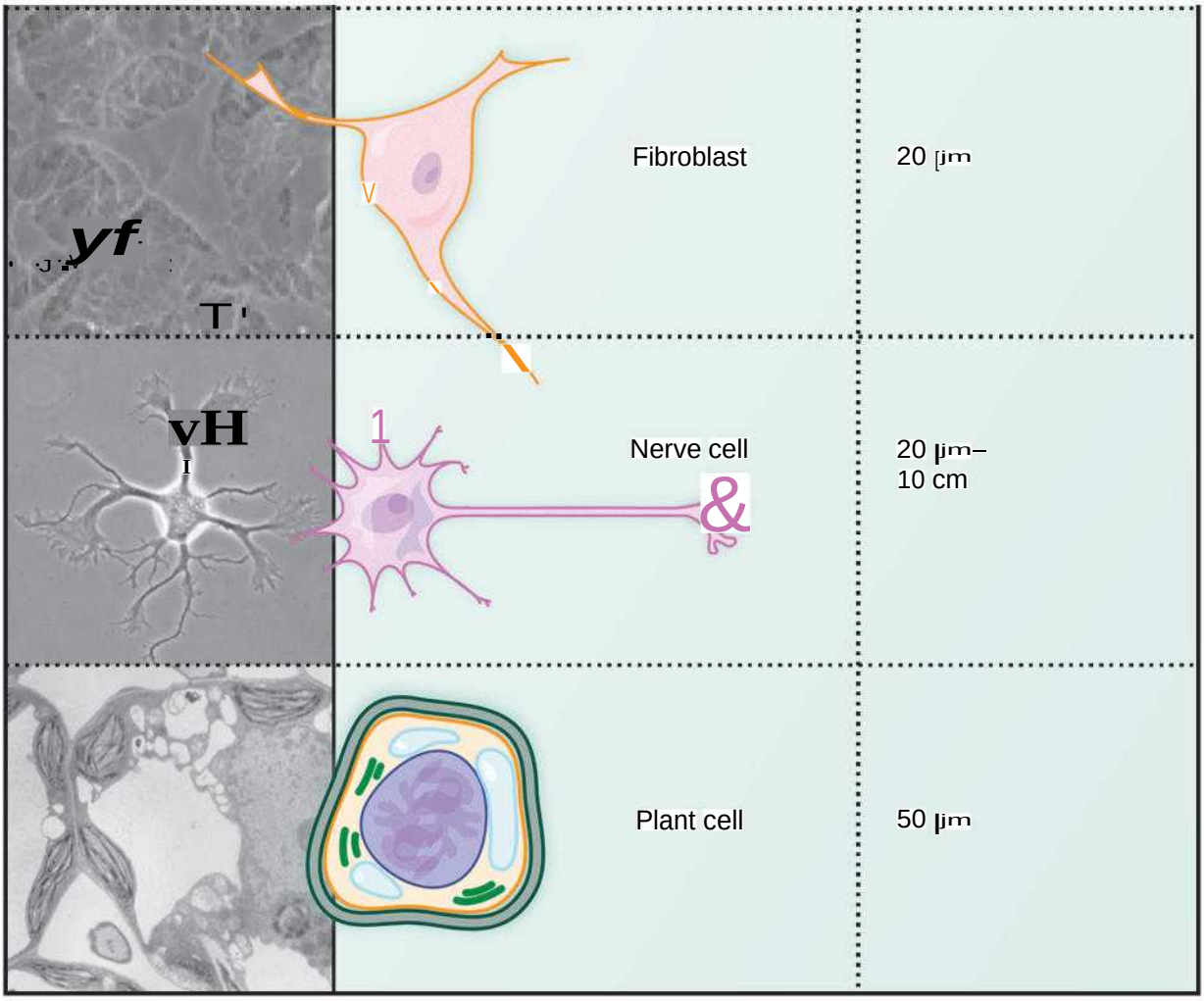


FIGURE 1-1 Cells vary greatly in size and shape. Some cells are spherical, while others are long extensions.

Courtesy of Tim Pietzcker, Universitat Ulm University.

Courtesy of Fred Winston, Harvard Medical School.

Courtesy of Junzo Desaki, Ehime University School of Medicine.

Courtesy of Gerald J. Obermair and Bernhard E. Flucher, Innsbruck Medical University.

Courtesy of Ming H. Chen, University of Alberta.

Description

The basic components of cells include the **cytoplasm**, **organelles**, and **cell membrane**. The cytoplasm, or **protoplasm**, is a colorless, viscous liquid containing water, nutrients, ions, dissolved gases, and waste products; this liquid is where the cellular work takes place. The

cytoplasm supports all of the internal cellular structures called organelles (**FIGURE 1-2**). Organelles ("little organs") perform the work that maintains the cell's life (**TABLE 1-1**). The cytoplasm also surrounds the **nucleus**. The nucleus, which acts as the control center of the cell, contains all the genetic information (deoxyribonucleic acid [DNA]) and is surrounded by a double membrane (**FIGURE 1-3**). The nucleus regulates cell growth, metabolism, and reproduction. The cell membrane, also called the **plasma membrane**, is the semipermeable boundary containing the cell and its components (Figure 1-3). A **lipid bilayer**, or fatty double covering, makes up the membrane. The interior surface of the bilayer is uncharged and primarily made up of lipids, whereas the exterior surface is charged and is less fatty than the interior surface (i.e., lipid bilayer). This fatty cover protects the cell from the aqueous environment in which it exists, while allowing it to be permeable to some molecules but not others.

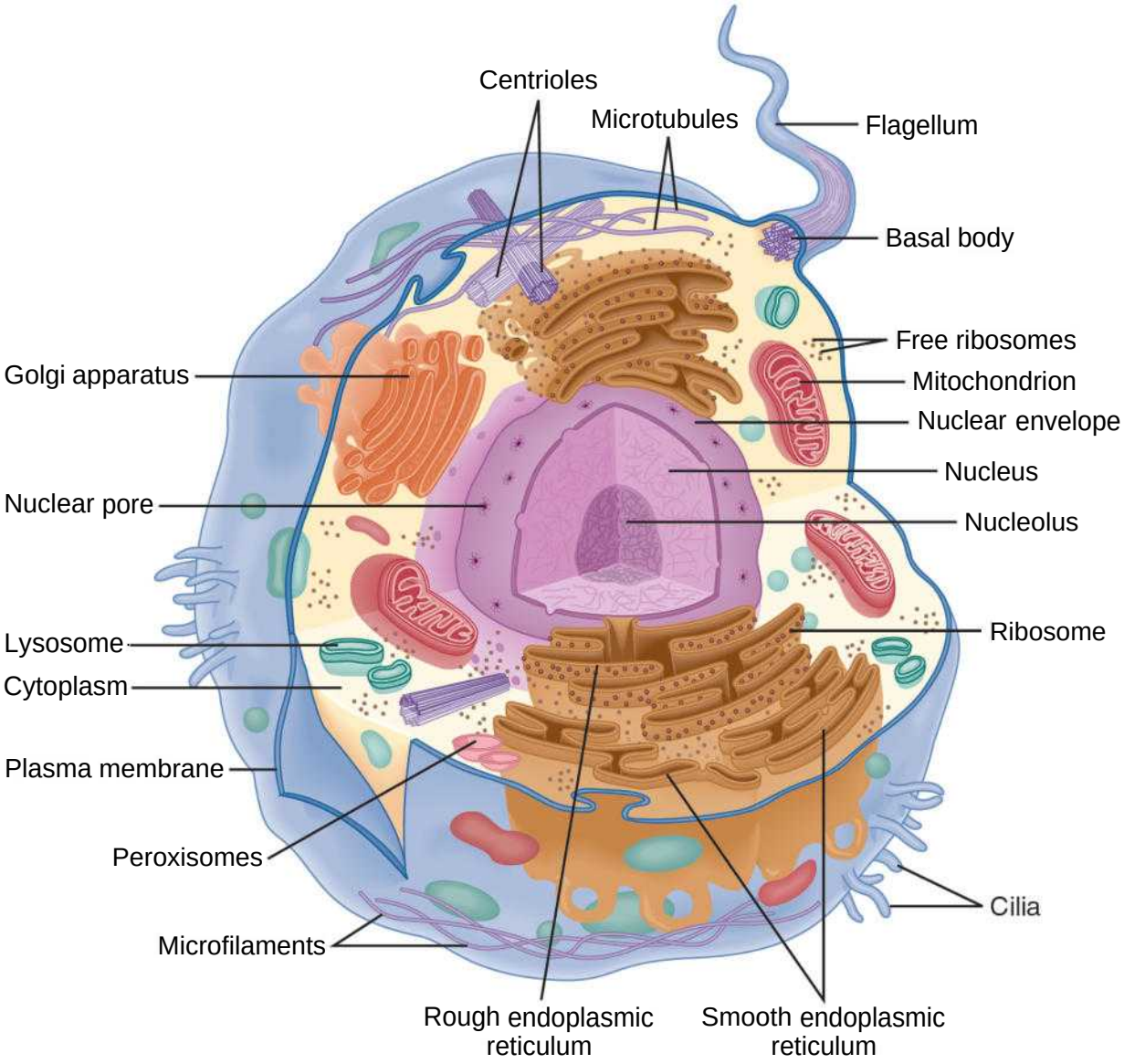


FIGURE 1-2 The basic human cell.

Description

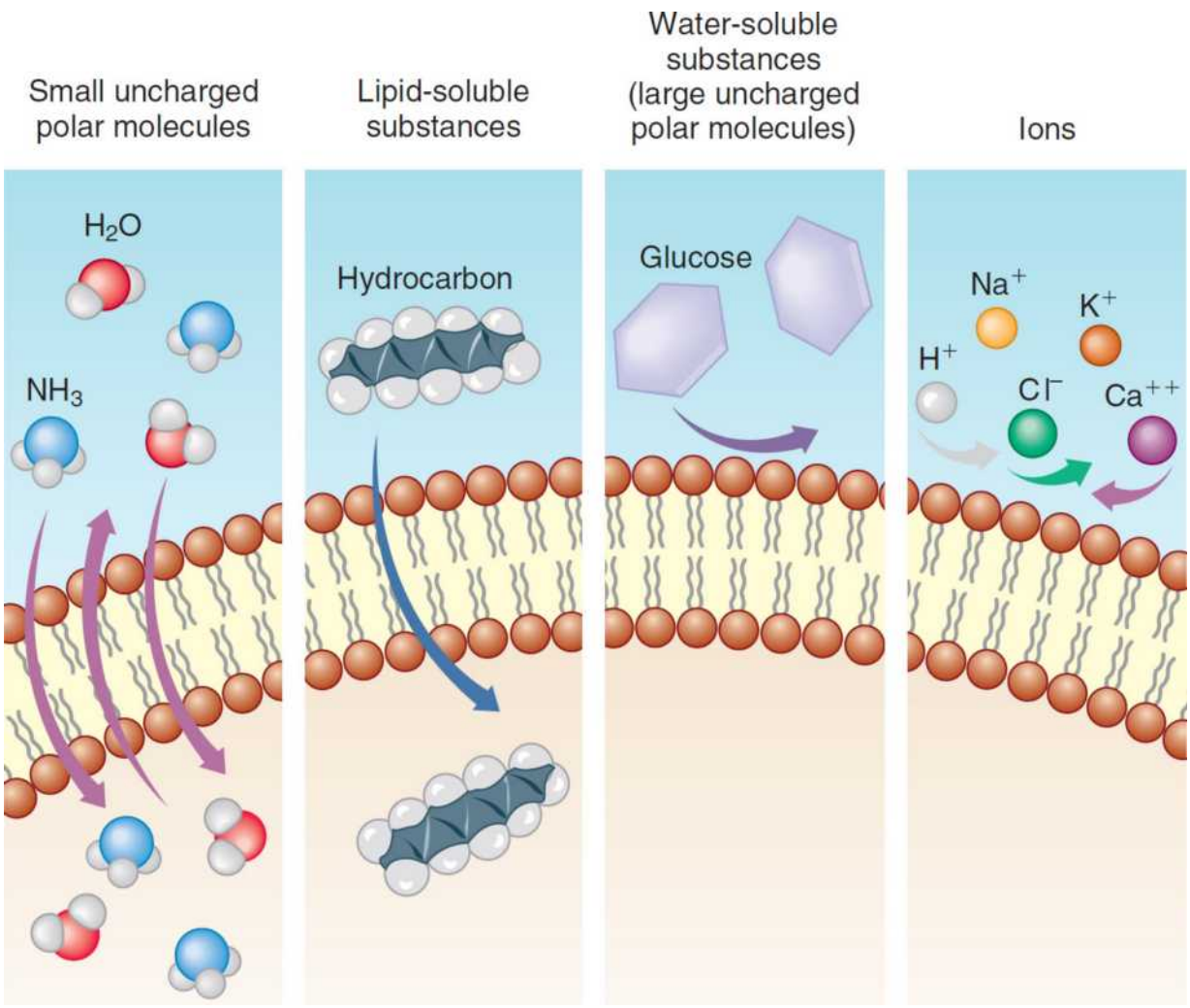


FIGURE 1-3 A selectively permeable membrane maintains homeostasis by allowing some molecules to pass through while preventing others from entering or exiting.

Description

TABLE 1-1 Overview of Cell Organelles

Organelle	Structure	Function

Organelle	Structure	Function
Nucleus	Largest organelle. Round or oval body surrounded by a nuclear envelope (a lipid bilayer membrane that allows for communication with the rest of the cell).	Contains the genetic information necessary for control of the cell's structure, function, and replication. In the nucleus, histones (proteins) bind deoxyribonucleic acid (DNA) to form chromosomes, and DNA contains sections of genes that hold hereditary information.
Nucleolus	Round or oval body in the nucleus.	Produces ribosomal ribonucleic acid (RNA) subunits (rRNA) and sends them out into the cell, where they form ribosomes.
Endoplasmic reticulum (ER)	Network of membranous tubules in the cytoplasm of the cell that is a continuation or extension of the nucleus. Smooth endoplasmic reticulum (SER) contains no ribosomes. Rough endoplasmic reticulum (RER) is studded with ribosomes.	SER produces lipids and hormones, stores and metabolizes calcium ions, and performs a variety of other functions depending on the cell type (e.g., metabolizing wastes in the liver). RER is the site of the synthesis and transport of lysosomal enzymes and proteins for intracellular (e.g., Golgi apparatus) and extracellular use.
Ribosomes	Small particles found in the cytoplasm (free) or attached to the ER that are made of rRNA and protein.	Aid in protein production on the RER and form polysomes (clusters of ribosomes held together by messenger RNA).
Golgi complex	Series of flattened sacs usually located near the nucleus.	Sorts, chemically modifies, and packages proteins produced in the RER.
Secretory vesicles	Membrane-bound vesicles containing proteins produced by the RER and repackaged by the Golgi complex. Contain protein hormones or enzymes.	Store protein hormones or enzymes in the cytoplasm, awaiting a signal to release them from the cell.

Organelle	Structure	Function
Food vacuole	Membrane-bound vesicle containing material engulfed by the cell.	An intercellular stomach that stores ingested material and combines it with lysosomes to be broken down.
Lysosome	Round, membrane-bound structure containing digestive enzymes.	Combines with food vacuoles and digests materials (e.g., bacterial and viruses) engulfed by cells. Also digests excessive or worn-out organelles.
Peroxisomes	Small structures containing enzymes.	Contain enzymes crucial for metabolic activity. Break down various potentially toxic intracellular molecules (e.g., fatty acids). Also play a role in alcohol digestion.
Mitochondria	Round, oval, or elongated structures with a double membrane. The inner membrane is shaped into folds.	Primarily responsible for cellular respiration and energy production. Act much like the digestive system by consuming nutrients, breaking them down, and creating energy-rich molecules for the cell. Complete the breakdown of glucose, producing nicotinamide adenine dinucleotide (NAD) and adenosine triphosphate (ATP) for cellular energy (a process called “cellular respiration”).
Cytoskeleton	Network of microtubules and microfilaments in the cell.	Gives the cell internal support, helps transport molecules and some organelles inside the cell, and binds to enzymes of metabolic pathways.
Cilia	Small projections of the cell membrane containing microtubules. Found on a limited number of cells.	Propel materials along the surface of certain cells.
Flagella	Large projections of the cell membrane containing microtubules. In humans, found only on sperm cells.	Provide motive force for sperm cells.

Organelle	Structure	Function
Centrioles	Small cylindrical bodies composed of microtubules arranged in nine sets of triplets. Found in animal cells, but not in plant cells.	Help organize the spindle apparatus necessary for cell division.

Exchanging Material

Cellular permeability is the ability of the cell to allow passage of some substances through the membrane, while not permitting others to enter or exit. To accomplish this function, cells have gates that may be opened or closed by proteins, chemical signals, or electrical charges. Being **selectively permeable** allows the cell to maintain a state of internal balance, or homeostasis. Some substances have free passage in and out of the cells, including **enzymes**, **glucose**, and **electrolytes**. Enzymes are proteins that facilitate chemical reactions in cells, while glucose is a sugar molecule that provides energy. Electrolytes are chemicals that are charged conductors when they are dissolved in water. Passage across the cell membrane may occur through several mechanisms, including **diffusion**, **osmosis**, **facilitated diffusion**, **active transport**, **endocytosis**, and **exocytosis**. Exchanging material is critical in maintaining bodily functions, so disruption of any of these mechanisms can result in disease development.

Diffusion, or simple diffusion, is the movement of solutes—that is, particles dissolved in a solvent (i.e., liquid)—from an area of higher concentration to an area of lower concentration (**FIGURE 1-4**). The degree of diffusion depends on the permeability of the membrane and the concentration gradient, which is the difference in the concentrations of substances on either side of the membrane. Simple diffusion will continue to occur until the concentrations of particles are equal on both sides of the membrane. Smaller particles (e.g., water) and lipid-soluble particles (e.g., steroids) diffuse more easily than larger ones, and less viscous solutions diffuse more rapidly than

thicker solutions. Additionally, the thinner and more permeable the membrane, the faster particles will diffuse across it. Many substances, such as oxygen, enter the cell through diffusion.

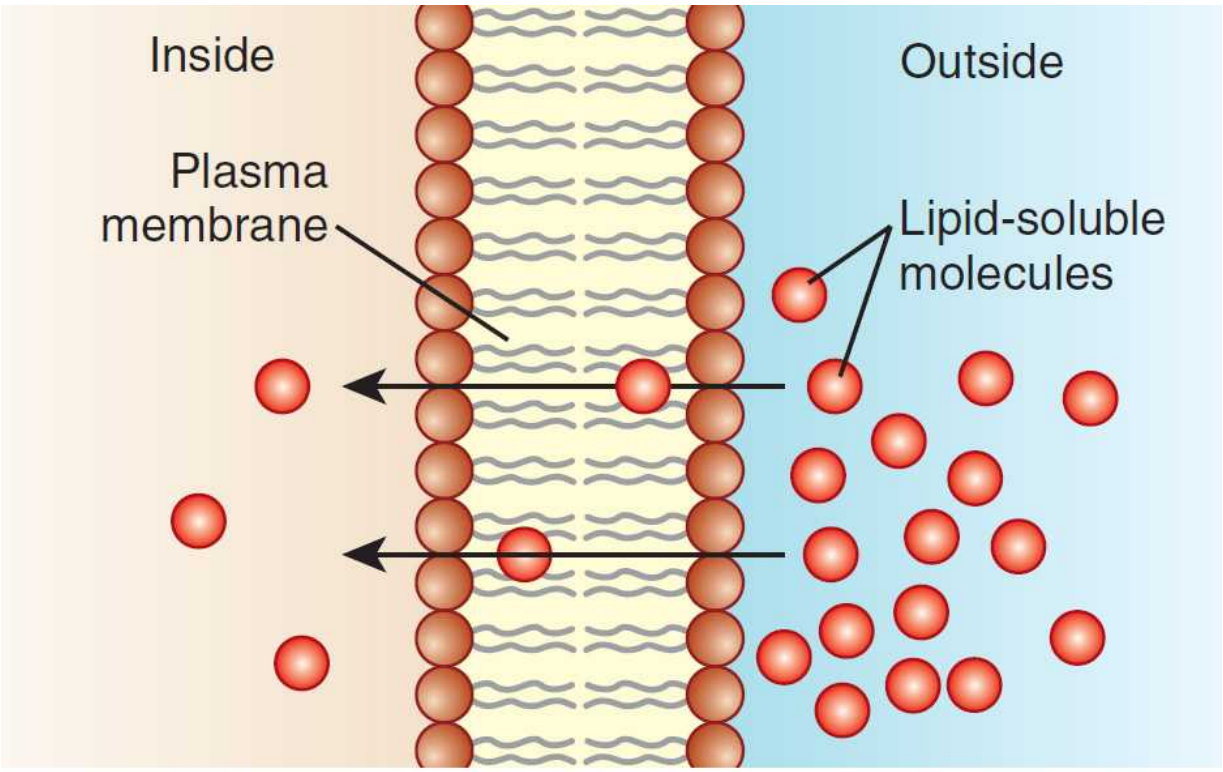


FIGURE 1-4 Lipid-soluble substances pass through the membrane directly by simple diffusion.

Description

Learning Points

Simple Diffusion

To illustrate simple diffusion, consider an elevator filled beyond capacity with people. When the door opens, the people near the door naturally fall out—moving from an area of high concentration to an area with less concentration without exerting any effort or energy. In the body, gases are exchanged in the lungs by diffusion. Unoxygenated blood enters the pulmonary capillaries (low concentration of oxygen, high concentration of carbon dioxide), where the blood picks up oxygen from the inhaled air of the alveoli (high

concentration of oxygen, low concentration of carbon dioxide), while dropping off carbon dioxide to the alveoli to be exhaled.

Learning Points

Osmosis

To understand osmosis, envision a plastic bag filled with sugar water with holes punched in it that allows only water to pass through it. If this bag is submerged in distilled water (which contains no impurities), the bag will begin to swell because the water is attracted to the sugar. The water shifts to the areas with higher concentrations of sugar in an attempt to dilute the sugar concentrations (FIGURE 1-5). In our bodies, the process of osmosis allows the cells to remain hydrated.

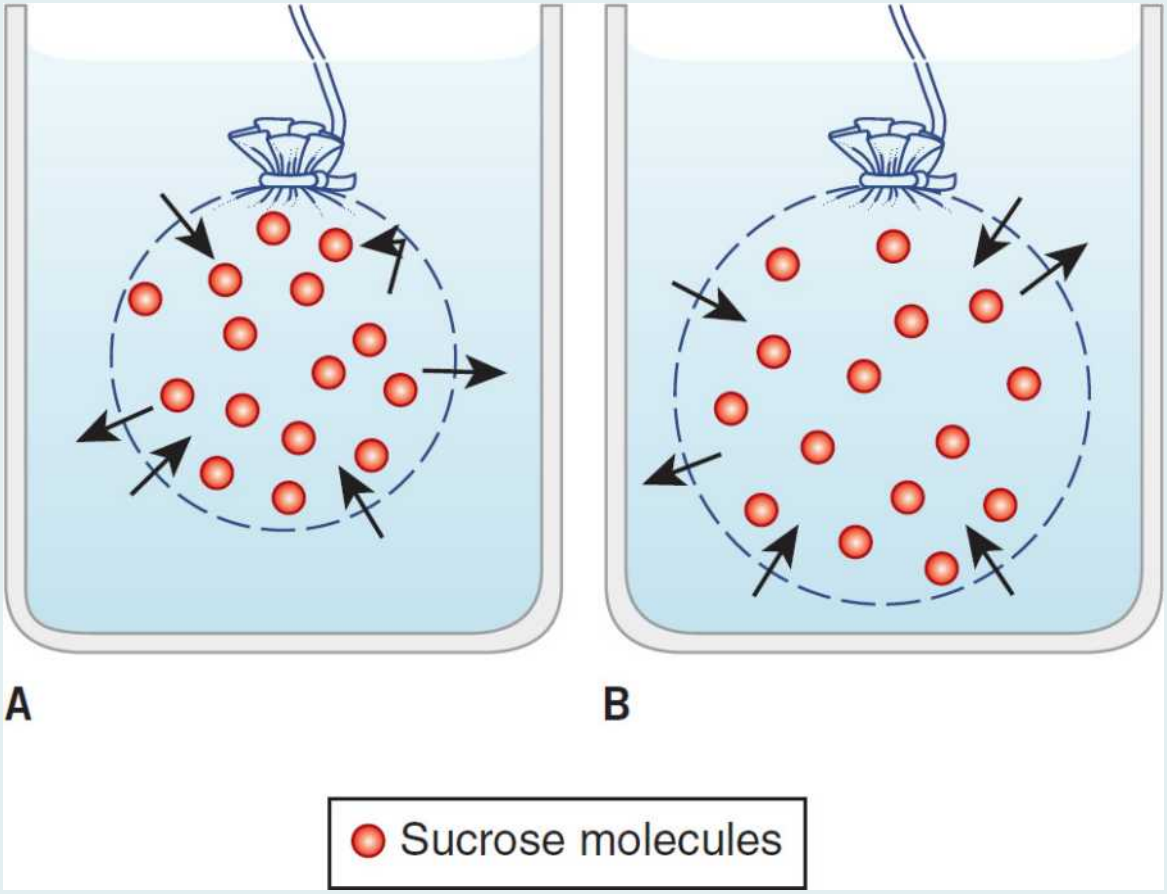


FIGURE 1-5 **(A)** When a bag of sugar water is immersed in a solution of pure water, **(B)** water will diffuse into the bag toward the lower concentrations of water, causing the bag to swell.

Description

Facilitated diffusion is the movement of substances from an area of higher concentration to an area of lower concentration with the assistance of a carrier molecule (**FIGURE 1-6**). Energy is not required for this process, and the number of molecules that can be transported in this way is directly equivalent to the concentration of the carrier molecule. Insulin transports glucose into the cells using this method.

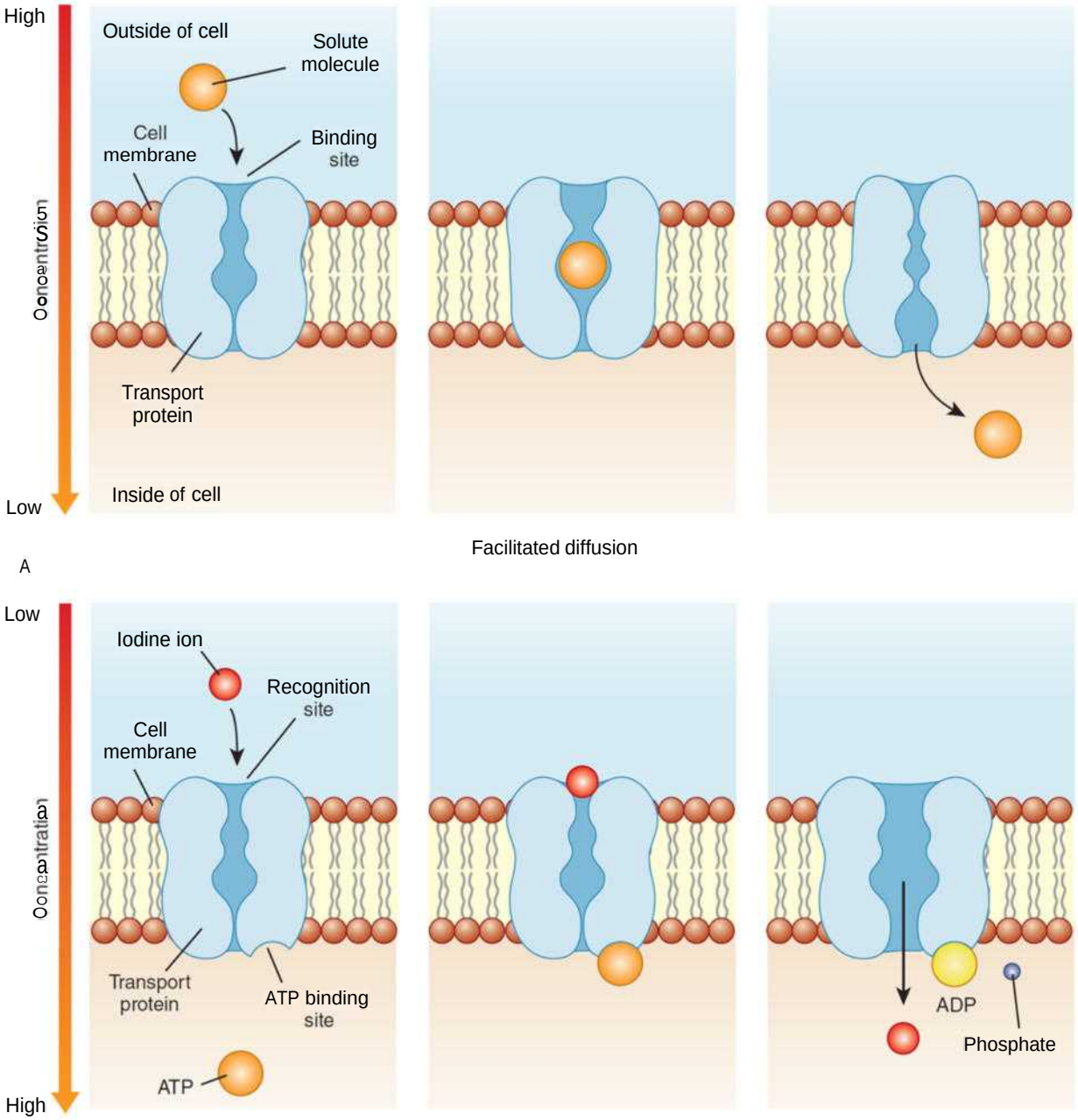


FIGURE 1-6 Facilitated diffusion and active transport. **(A)** Water-soluble molecules can also diffuse through membranes with the assistance of proteins in facilitated diffusion. **(B)** Other proteins use energy from ATP to move against concentration gradients in a process called active transport.

Description

Water is critical to cellular survival. Osmosis is the passive movement of water or another solvent across the cellular membrane from an area of low solute concentration to an area of high solute concentration. The membrane is permeable to the solvent (liquid) but not to the solute (dissolved particles). The movement of the solvent usually continues until concentrations of the solute equalize on both sides of the membrane. **Osmotic pressure** refers to the tendency of water to move by osmosis—in other words, the solute's ability to attract water. This ability depends on the concentration of the solute. If too much water enters the cell membrane, the cell will swell and burst (**lysis**). If too much water moves out of the cell, the cell will shrink (**crenation**). Osmosis helps regulate fluid balance in the body; an example can be found in the functioning of the kidneys. In addition to osmotic pressure, hydrostatic and colloid osmotic pressures cause the movement of water (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter).

Active transport is the movement of a substance from an area of lower concentration to an area of higher concentration against a concentration gradient (Figure 1-6). This movement requires a carrier molecule and energy (usually adenosine triphosphate [ATP]) because of the effort necessary to go against the gradient. The sodium–potassium (Na^+-K^+) pump is an example of active transport.

Endocytosis is the process of bringing a substance into the cell (**FIGURE 1-7**). The cell membrane surrounds the entering particles, engulfing them. **Phagocytosis**, or cell eating, occurs when this process involves solid particles. **Pinocytosis**, or cell drinking, takes place when this process involves a liquid. Components of the immune system use endocytosis, and particularly phagocytosis, to consume and destroy bacteria and other foreign material. Exocytosis is the release of materials from the cell, usually with the assistance of a vesicle (a membrane-bound sac) (Figure 1-7). Often glands secrete hormones using exocytosis.

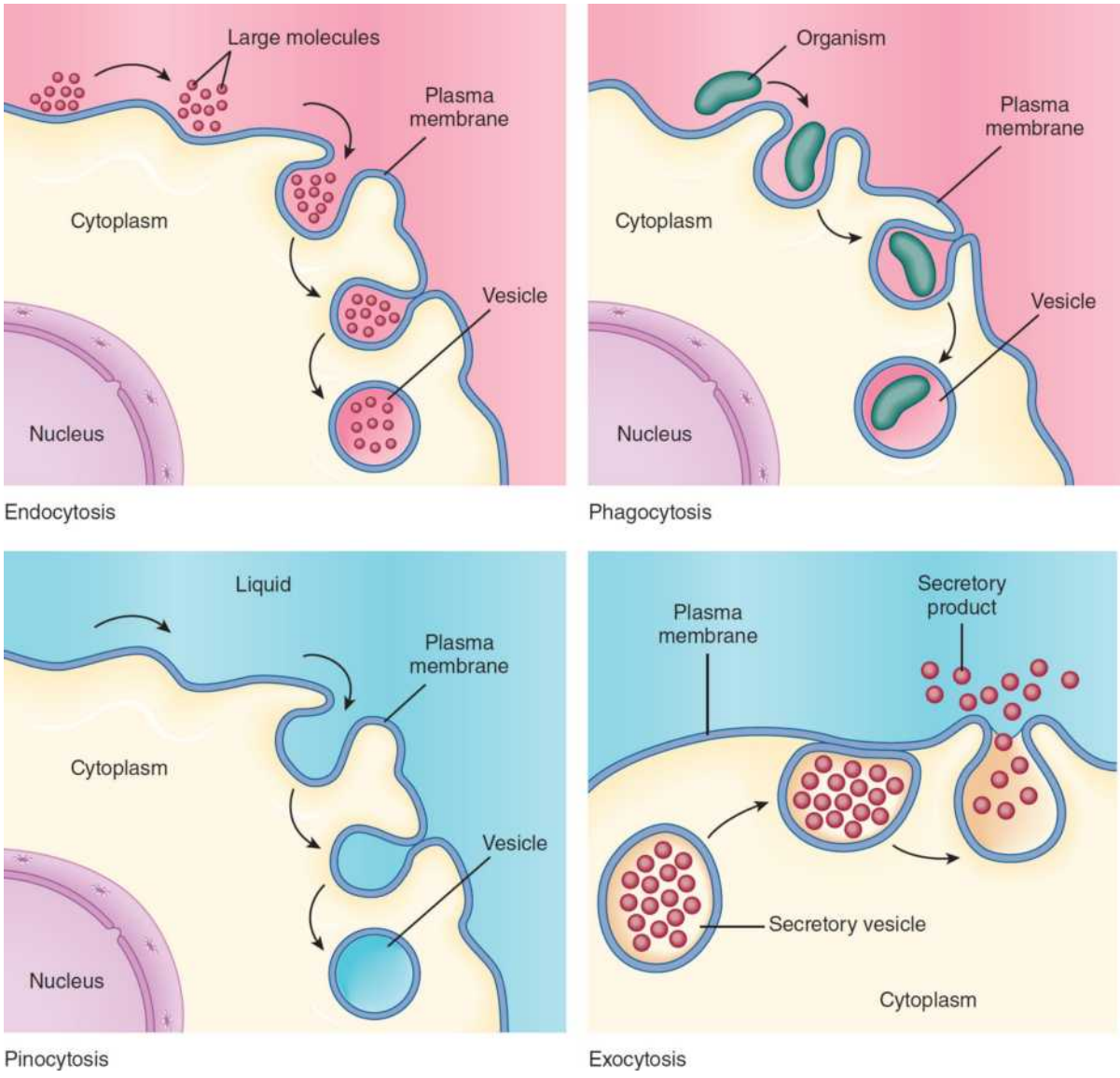


FIGURE 1-7 **(A)** Cells can engulf large particles, cell fragments, liquids, and even entire cells. **(B)** Cells can also get rid of large particles.

Description

Learning Points

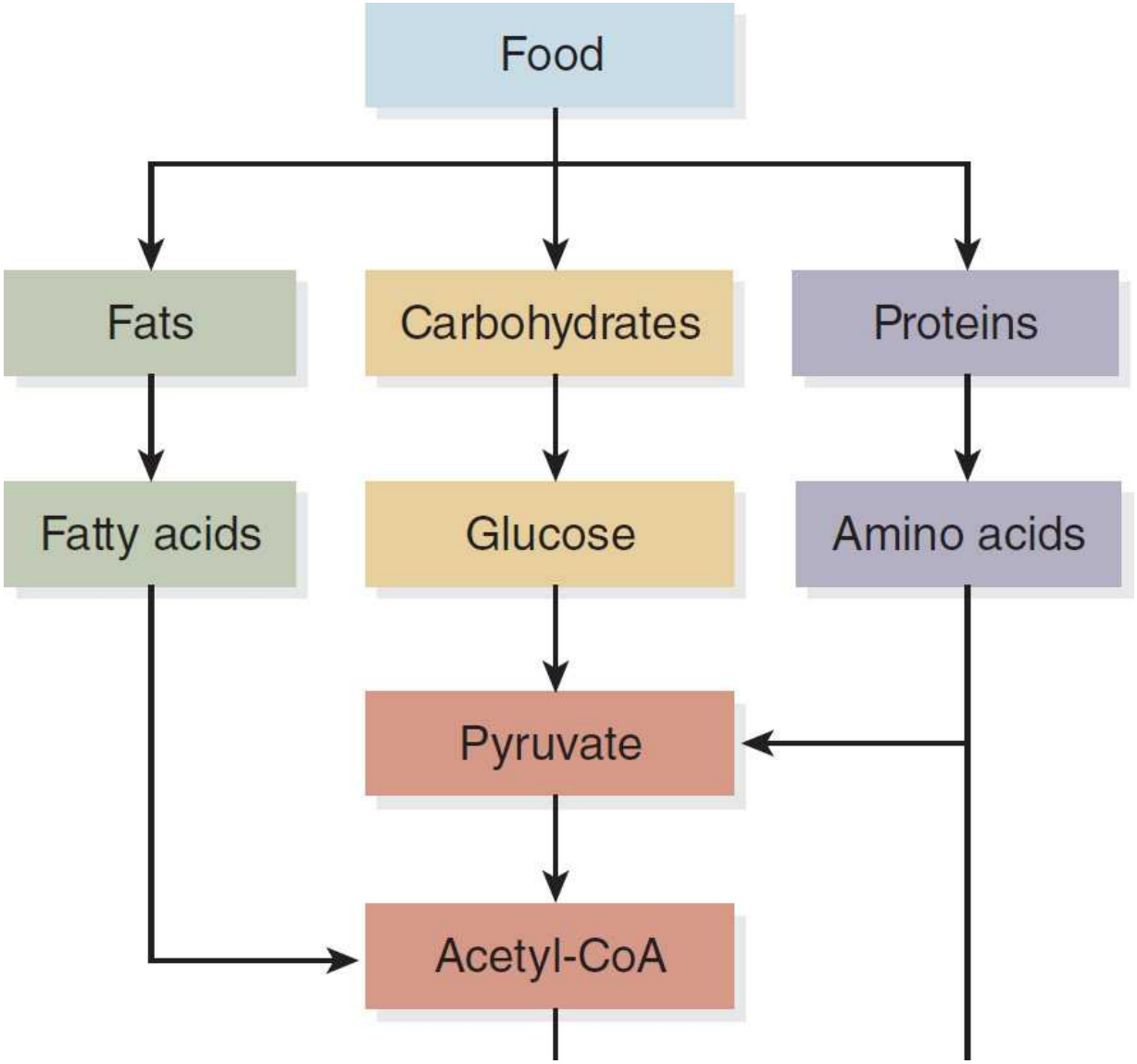
Active Transport

To understand active transport, consider the overfilled elevator again. If the door opens and someone from outside the elevator attempts to get in, it will require a great deal of effort (energy) to enter the already full elevator. The sodium–potassium pump is an example of active transport in the body. Energy is required both to

move sodium out of a cell, where the concentrations are high, and to move potassium into a cell, where the concentrations are high.

Energy Production

Cellular energy can be a mystery to many of us. To understand this energy, first we must understand that it comes in many forms (**FIGURE 1-8**). Cells can obtain energy from two main sources: the breakdown of glucose (a type of carbohydrate) and the breakdown of triglycerides (a type of fat). When these sources are not readily available, cells can turn to protein for energy.



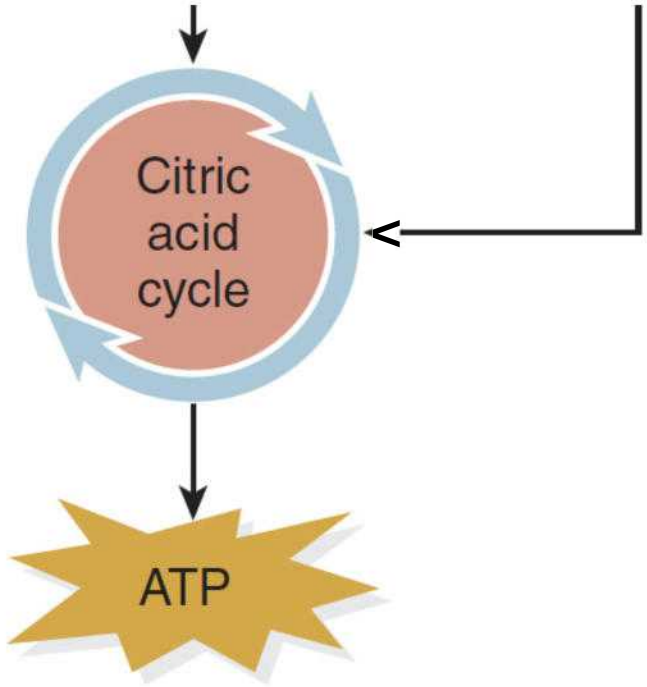


FIGURE 1-8 Energy production.

Description

The energy production process begins when food enters the gastrointestinal tract, where it is broken down into sugars, amino acids, and fatty acids. These substances are then either converted to larger molecules (e.g., glucose to glycogen, amino acids to proteins, and fatty acids to triglycerides and fats), stored until needed, or metabolized to make ATP. When used to make ATP, all three sources of energy must first be converted to acetyl coenzyme A (acetyl CoA). Through glycolysis, glucose is converted to pyruvate in the cytoplasm; the pyruvate is then converted to acetyl CoA. Amino acid catabolism also produces acetyl CoA, and fatty acids are oxidized to be converted to acetyl CoA as well. The acetyl CoA from all these sources enters the Krebs cycle (i.e., the citric acid cycle), a high-electron-producing process that occurs inside the mitochondria. During the Krebs cycle, these molecules go through a complex series of reactions that consume oxygen, produce carbon dioxide and water as waste products, and convert adenosine diphosphate (ADP) to ATP.

This process works best when oxygen is readily available (i.e., aerobic respiration), but energy can be produced less efficiently when oxygen is not readily available (e.g., tissue hypoxia and exercise) through anaerobic respiration. Glycolysis does not need oxygen, but the pyruvate produced in the anaerobic process will be converted to lactic acid instead of acetyl CoA without it. Lactic acid excess can cause muscle pain and fatigue, metabolic acidosis, kidney failure, respiratory failure, and death.

Replication and Differentiation

A cell's basic requirement for life is ensuring that it can reproduce. Many cells divide numerous times throughout the life span, whereas others die and are replaced with new cells. **Proliferation** is the regulated process by which cells divide and reproduce. Genes (e.g., proto-oncogenes) and growth factor proteins (e.g., cytokines and erythropoietin) regulate this process, by either stimulating it or suppressing it. Environmental factors (e.g., temperature, chemical exposure, nutrition, and infections) at any stage of life can influence proliferation either positively or negatively.

The most common form of cell division, in which the cell divides into two separate cells, is **mitosis** (**FIGURE 1-9**). In mitosis, the division of one cell results in two genetically identical and equal daughter cells (i.e., diploid cells). This process involves four steps: **prophase**, **metaphase**, **anaphase**, and **telophase**. In prophase, the **chromosomes** condense, and the nuclear membrane disintegrates. In metaphase, the spindle fibers attach to centromeres, and the chromosomes align. The chromosomes separate and move to opposite poles in anaphase. Finally, the chromosomes arrive at each pole, and new membranes are formed in telophase.

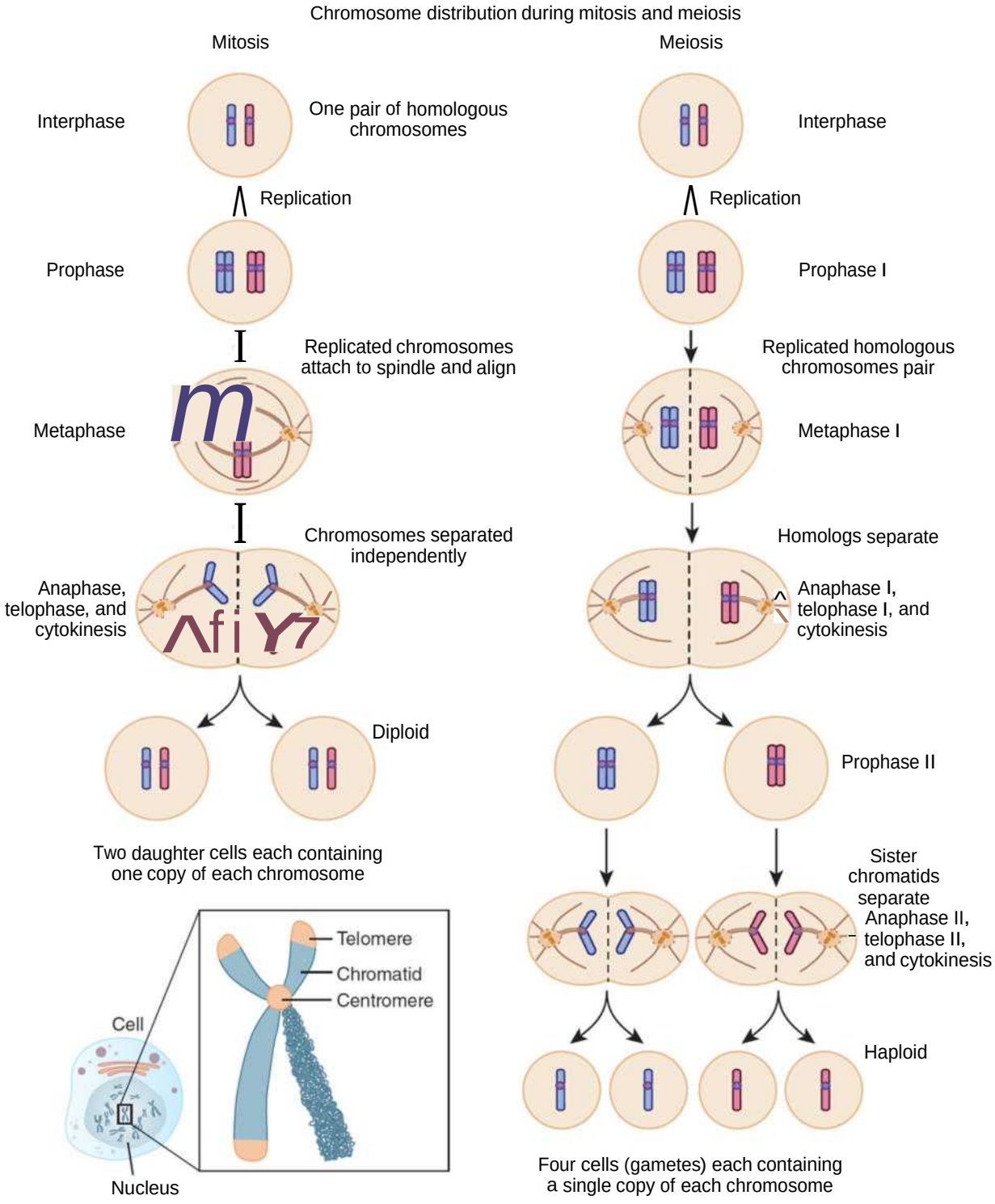


FIGURE 1-9 Mitosis and meiosis.

Description

The average cell will divide 50 to 70 times before it dies. As the cell divides, the telomere on the end of the chromosome gets smaller—a mechanism of cell aging, according to the Hayflick limit theory. The telomere shortens with each division until it is no longer present, causing the cell to be broken down by **programmed cell death**.

Interphase refers to the period of the cycle between each mitosis phase. A typical cell spends most of its life in interphase. During this period, the cell is growing and preparing for mitosis—that is, organelles double in number, DNA replicates, protein is synthesized, and the environment is assessed and primed.

Meiosis is a form of cell division that occurs only in mature sperm and ova. Meiosis also has four phases (prophase, metaphase, anaphase, and telophase) and is separated by an interphase. In males, testicles continuously produce sperm, and then the sperm travels to the epididymis to mature (i.e., spermatogenesis) and be stored until released during ejaculation. In females, a set number of ova are present at birth and mature in the ovaries (oogenesis). One or more eggs are released once a month during ovulation, approximately 2 weeks before menstruation starts. In the ovaries, the ova remain in the prophase for up to 45 years.

As the woman and her ova age, the risk of abnormal meiosis resulting in chromosomal defects increases. Normally, human cells contain 46 chromosomes, but sperm and ova contain 23 chromosomes each (i.e., haploid cells). One of the chromosomes determines sex. When a sperm and ovum join, the resulting organism (i.e., zygote) has 46 chromosomes (23 pairs). The zygote gets one sex chromosome from the ovum and one from the sperm. If the resulting pair is XX (homologous), the resulting fetus will be female. If the resulting pair is XY (heterologous), the resulting fetus will be male.

Differentiation is the process by which cells become specialized in terms of their type, function, structure, and cell cycle (**FIGURE 1-10**). Through this process, the primitive stem cells of the embryo (i.e., pluripotent) develop into more than 200 highly specialized cells found in the human body (e.g., cardiac cells and nerve cells). In the first 24 hours after fertilization, the zygote rapidly grows, producing cells as it

does so (i.e., cleavage). Over the next few weeks, cells start developing into two groups. The outer layer forms tissue that supports the embryo (e.g., placenta), and the inner core forms the different tissues and organs. The inner core divides into three germ layers—ectoderm, mesoderm, and endoderm. The ectoderm (outer layer) differentiates into the epidermis, hair, nails, brain, spinal cord, and peripheral nervous system. The mesoderm (middle layer) differentiates into the muscle, bone, connective tissue, kidneys, gonads, and circulatory system. The endoderm (inner layer) differentiates into the gastrointestinal tract, colon, liver, bladder, and lungs.

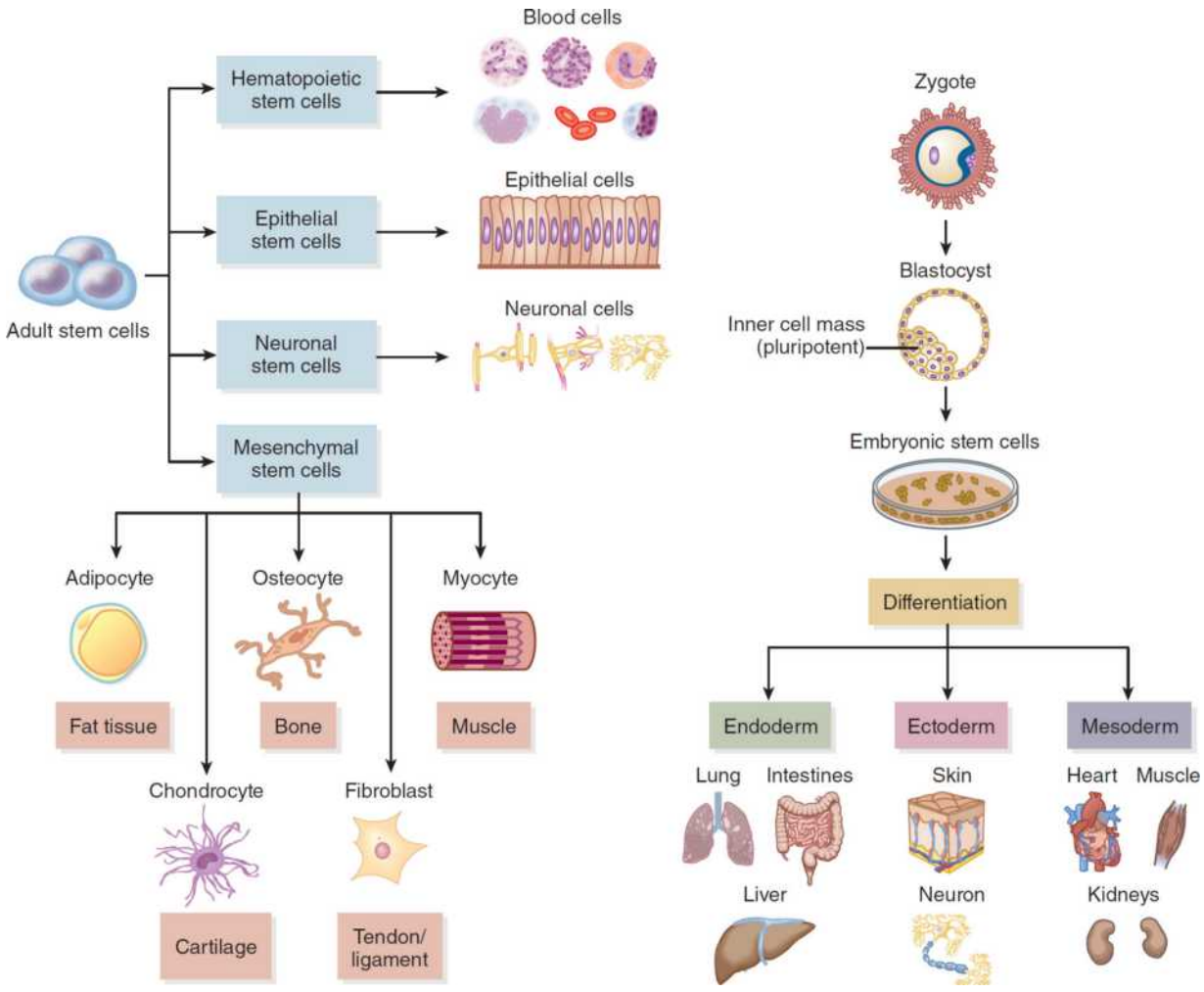


FIGURE 1-10 Differentiation.

Description

Gene expression and growth factor proteins (e.g., fibroblast growth factor and vascular endothelial growth factors) stimulate differentiation. This process does not begin until approximately 15 to 60 days after the sperm fertilizes the ovum. During this time, the embryo is highly susceptible to damage from environmental influences. However, environmental factors (e.g., temperature, chemical exposure, nutrition, and infections) at any stage of life can influence differentiation both positively and negatively.

The stem cells found in the embryo are also present in adulthood. These somatic cells maintain and repair tissue, but they are multipotent in adulthood—that is, they can only make cells of the same type. For example, blood stem cells can make any type of blood cell (e.g., erythrocyte, leukocyte, or platelets). All stem cells can proliferate into more undifferentiated stem cells and differentiate into more specialized cells. Embryonic stem cells have been used to test new drugs (e.g., antitumor drugs) and show promise as a treatment for macular degeneration, spinal cord injury, stroke, burns, heart disease, diabetes mellitus type 1, osteoarthritis, and rheumatoid arthritis. Adult stem cells found in cord and placental blood as well as bone marrow have been used to treat leukemias (National Institutes of Health [NIH], 2016).

Emerging Research: Stem Cells

Stem cells have been a source of great interest for some time. They have shown promise in treating and curing many diseases, referred to as stem cell therapy or regenerative medicine. Stem cells can help us understand how diseases occur, replace cells affected by disease, and test new drugs for safety and effectiveness. The National Institutes of Health increased guidelines for human stem cell research in 2009 that included how they can be used and acquired. Stem cells can either be embryonic or adult (NIH, 2009). Embryonic stem cells for research are donated eggs that were fertilized at in vitro fertilization clinics but were never implanted in women's uteruses, and adult stem cells are donated from bone marrow or fat. Recently, researchers learned that adult stem cells may be used to create more types of cells than originally thought (e.g., bone or heart muscle cells). Scientists have successfully transformed connective tissue cells using genetic reprogramming to become functional heart cells. Animals with heart failure that were injected with new heart cells experienced improved heart function and survival time. Stem cells can also be obtained from amniotic fluid and umbilical cord blood (NIH, n.d.).

Stem cells have been used for some time to treat **cancers** such as leukemia, lymphoma, neuroblastoma, and multiple myeloma. Early-stage clinical trials are exploring the use of adult stem cells to treat neurological and heart diseases. Along with treating and curing diseases, researchers are also exploring how to control the growth and differentiation of embryonic stem cells, as well as how to prevent potential complications from the therapy (e.g., immune reaction).

Therapeutic cloning is a technique to create versatile stem cells independent of fertilized eggs. The nucleus is removed from an unfertilized egg and replaced with a donor nucleus. The egg is then allowed to divide, creating a line of stem cells identical to the donor cell (i.e., a clone). However, this technique has not been successfully

performed in humans despite success in several other species (Goldenberg et al., 2021).

Tissue

Many cells in the body are organized into tissues and work together to perform specific functions. Two or more tissues can combine to form organs that perform a specific function, and groups of organs working together form systems. Humans have four basic types of tissues: epithelial, connective, muscular, and nervous (**FIGURE 1-11**).

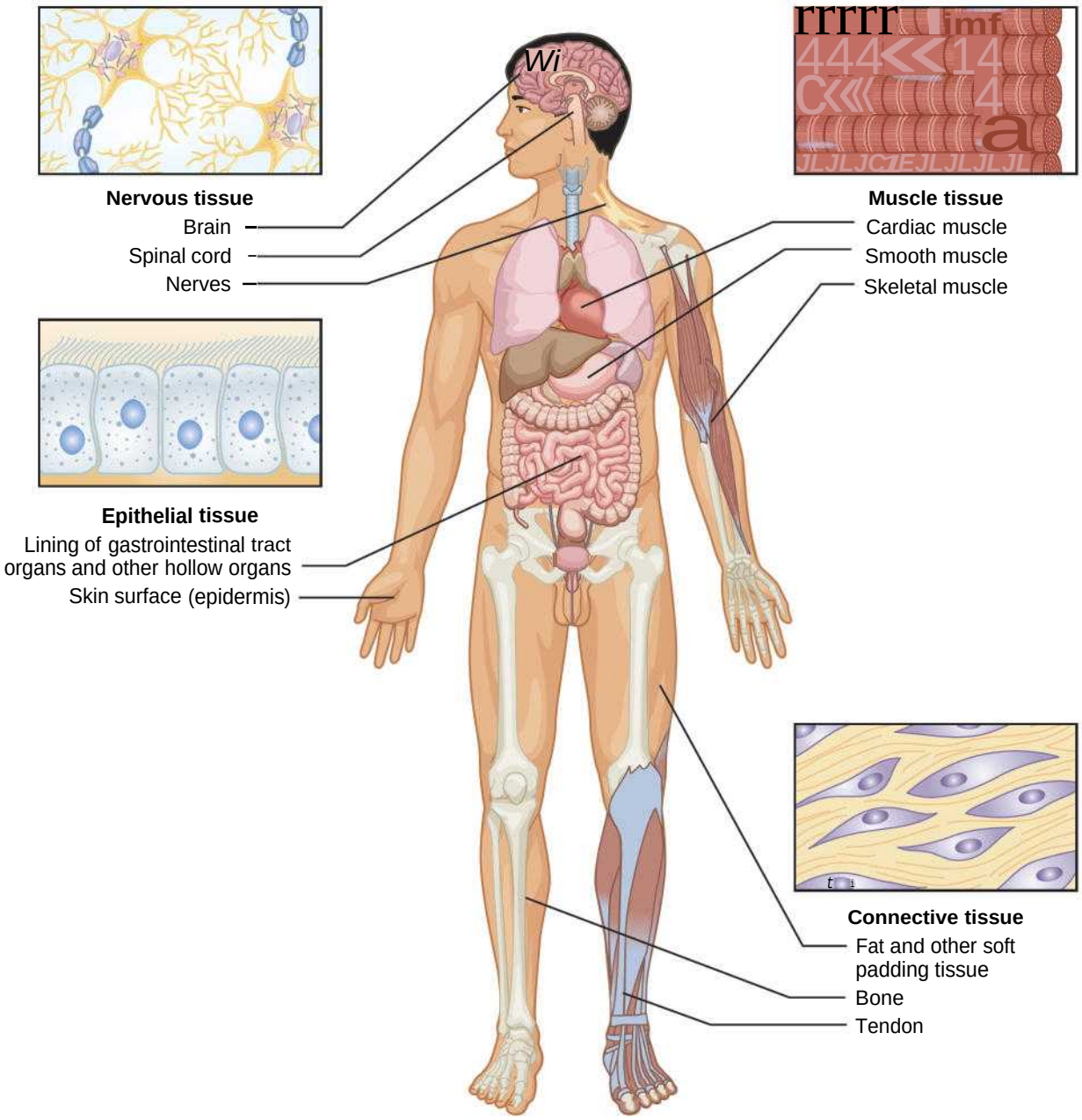


FIGURE 1-11 Types of tissue.

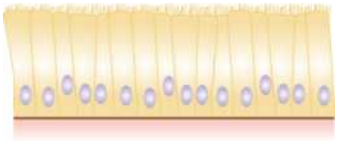
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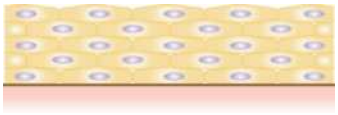
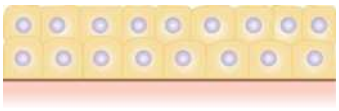
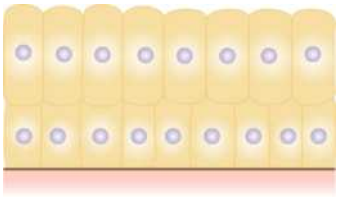
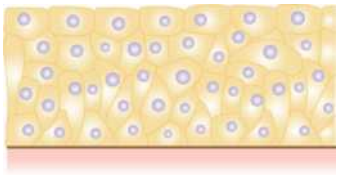
Epithelial Tissue

Epithelial tissue is made up of tightly packed sheets of cells, allowing them to act as a barrier (**TABLE 1-2**). These sheets of cells can be present as a single layer (i.e., simple epithelium) or as multiple layers (i.e., stratified epithelium). Epithelial tissue is made up of three types

of cells—squamous, cuboidal, and columnar. This type of tissue lines exterior (e.g., skin) and interior (e.g., body cavities, gastrointestinal tract, and hollow organs) surfaces. In addition to serving as a barrier, epithelial tissue is involved in absorption (e.g., lungs and small intestines), secretion (e.g., mucus), excretion, and movement of substances.

TABLE 1-2 Epithelial Tissue Cells

Cells	Locations	Function
Simple squamous epithelium	Alveoli in the lungs and the lining of the heart, blood vessels, and lymphatic vessels	Permits materials to exchange through diffusion and filtration and secretes lubricating substances
Simple cuboidal epithelium 	Ducts and secretory portions of small glands as well as the kidney tubules	Secretes and absorbs
Simple columnar epithelium 	Ciliated tissues including the bronchi, uterine tubes, and uterus; smooth (nonciliated) tissues are found in the digestive tract bladder	Absorbs; secretes mucus and enzymes
Pseudostratified columnar epithelium 	Ciliated tissue lines the trachea and a majority of the upper respiratory tract	Secretes mucus; ciliated tissue shifts mucus

Cells	Locations	Function
Stratified squamous epithelium 	Lines the esophagus, mouth, and vagina	Prevents abrasion
Stratified cuboidal epithelium 	Sweat, salivary, and mammary glands	Protects by creating an impermeable surface
Stratified columnar epithelium 	The male urethra and the ducts of some glands	Secretes and protects
Transitional epithelium 	Lines the bladder, urethra, and ureters	Allows for expansion of the urinary organs

Learning Points

Emerging Research: Precision Medicine

In 2016, the National Institutes of Health (NIH) was charged with making precision medicine a priority (Holst, 2015). Precision medicine is an approach to disease treatment and prevention strategies that accounts for the similarities and differences among individuals. The traditional approach to care is a standardized treatment for all. In contrast, the individual's genes, microbiome, environment, and lifestyle are considered when determining treatment strategies with precision medicine.

As a part of this initiative, NIH started the *All of Us* research program. This program collects information on participants' medical history, lifestyle, and physical measurements

(e.g., blood pressure, height, weight), as well as blood and urine samples to be used to develop preventive care and treatments (NIH, 2022). Targeted molecular drugs or therapy, also called “precision drugs,” have already been developed for several diseases, such as cystic fibrosis. In cancer, several types of targeted drug therapies are available, such as monoclonal antibodies (immunotherapy) and hormones. In comparison to traditional chemotherapy, these drugs are designed to attack only the cancer cells, while having less effect on normal cells.

Connective Tissue

Connective tissue consists of cells suspended in an extracellular matrix (**FIGURE 1-12**). This matrix is typically made up of protein (e.g., collagen and fibrin) in a solid, liquid, or semi-solid substance. Connective tissue supports and connects other tissues. Connective tissue may be either loose (most common) or dense. Loose connective tissue supports organs and blood vessels as well as connects epithelial tissue to muscle. Dense connective tissue is fibrous and found in the tendons and ligaments that connect muscles to bone and bones to each other. Other forms of connective tissue include adipose tissue, bone, cartilage, and blood.

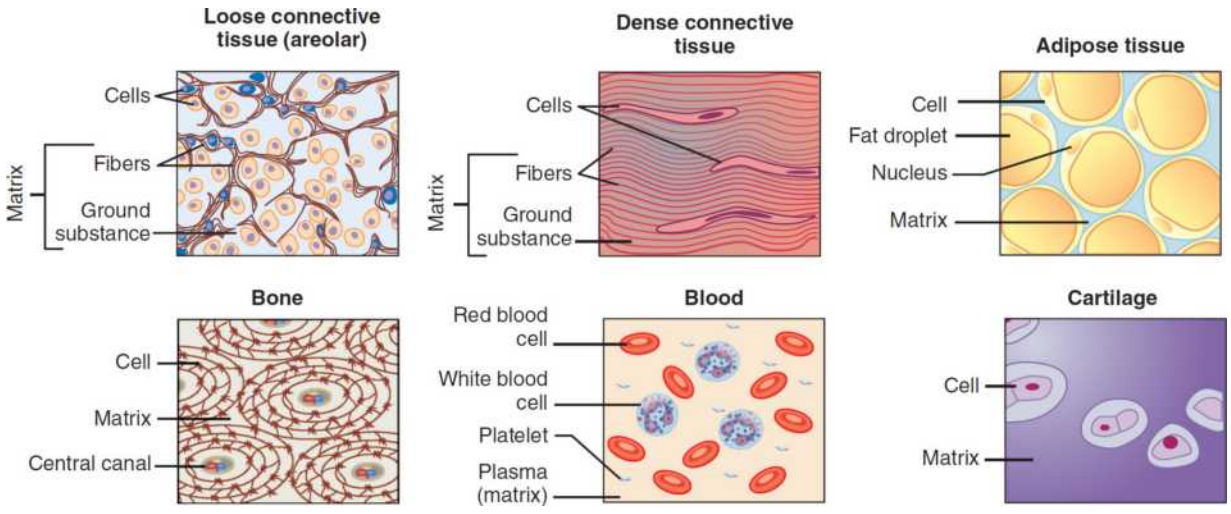


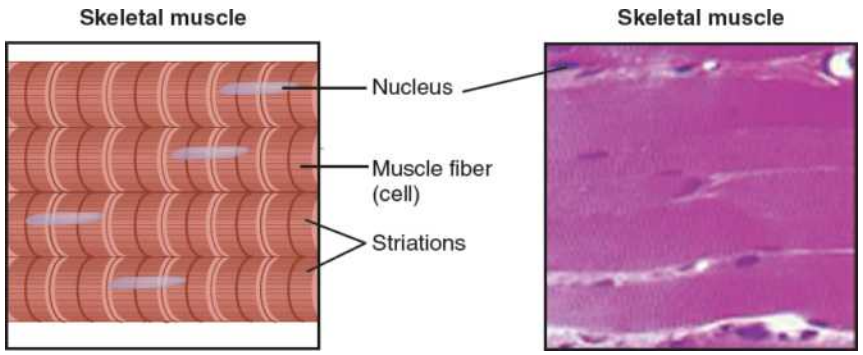
FIGURE 1-12 Types of connective tissues.

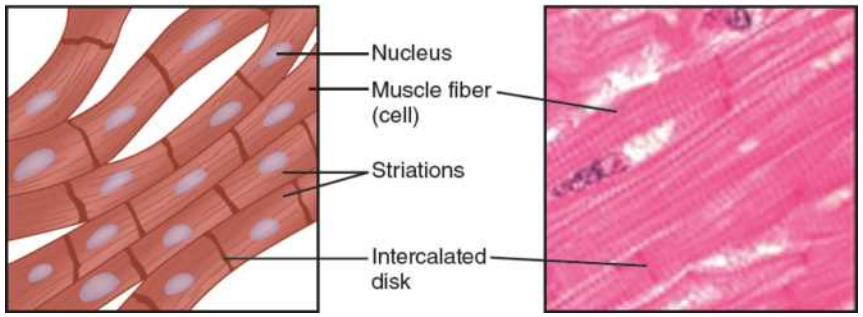
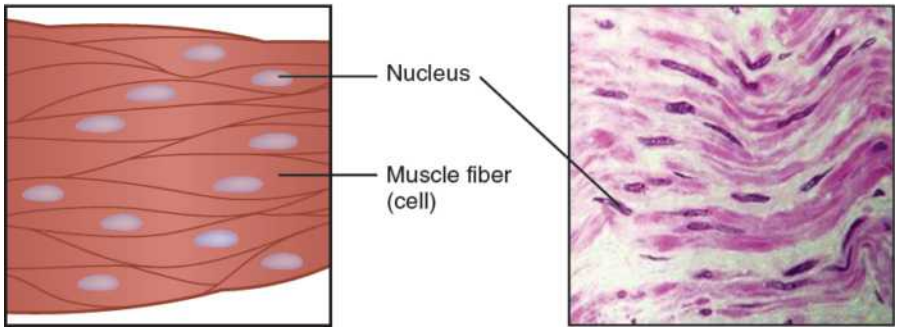
Description

Muscle Tissue

Muscle tissue is made up of cell fibers (i.e., myocytes) that contain contractile proteins (i.e., actin and myosin) (TABLE 1-3). Muscle fibers contract when myosin pulls the actin filaments, causing them to slide over themselves. The myosin attaches to the actin when calcium is released from smooth endoplasmic reticulum (ER) inside the muscle fibers. Impulses from nerve cells (i.e., motor neurons) and neurotransmitters (i.e., acetylcholine) trigger this release of calcium from the muscle fiber. Once the calcium causes the head of the myosin to attach to the actin filament, ATP in the muscle provides the energy needed to pull the actin filament inward. To meet the muscle fibers' high energy needs, ATP is recycled repeatedly in rapid succession. During vigorous activity, ATP stores become depleted, oxygen levels drop sharply, glucose production ceases, and lactic acid accumulates.

TABLE 1-3 Muscle Tissue

Characteristics	
• Long and cylindrical • Multinucleated • Striated • Voluntary	
• Shorter and branched • Uninucleated • Striated • Involuntary • Intercalated disks	

	Cardiac muscle  Cardiac muscle	
• Spindle-shaped • Uninucleated • Nonstriated • Involuntary	Smooth muscle  Smooth muscle	

Images in column 3 are courtesy of the Centers for Disease Control and Prevention.

Muscle tissue allows the body to maintain an upright stance and to move, and it helps substances, such as blood and food, move through the body. Muscles may be under voluntary or involuntary control. Three main types of muscles are distinguished: skeletal, cardiac, and smooth. Skeletal muscle tissue is striated or striped. This tissue attaches bone to tendons and allows for voluntary movement. Cardiac muscle is found in the walls of the heart and is also striated, but it is not under voluntary control. Cardiac muscle fibers are connected by intercalated disks that allow them to contract in coordination. Smooth muscle tissue is found in the walls of blood vessels, the gastrointestinal tract, the uterus, the urinary bladder, and other internal structures. This tissue is not striated, and it is under involuntary control.

Nervous Tissue

Nervous tissue senses, processes, and responds to internal and external stimuli. It consists of two basic types of cells: neurons and

neuroglia (**FIGURE 1-13**). Neurons, the basic functional units of nervous tissue, generate and transmit nerve impulses. These cells can occur in several sizes and shapes, but they all share similar characteristics. Neurons do not have the ability to divide, and they require a constant supply of oxygen and glucose. Neurons contain projections called axons that transmit impulses away from the cell body, as well as dendrites that make connections with nearby cells and transmit impulses toward the cell body. Neuroglia cells scaffold neural tissue (e.g., astrocytes and ependymal cells), isolate and protect neurons, speed up nerve transmission (e.g., Schwann cells), regulate interstitial fluid, defend neurons against pathogens, and assist with neural repair.

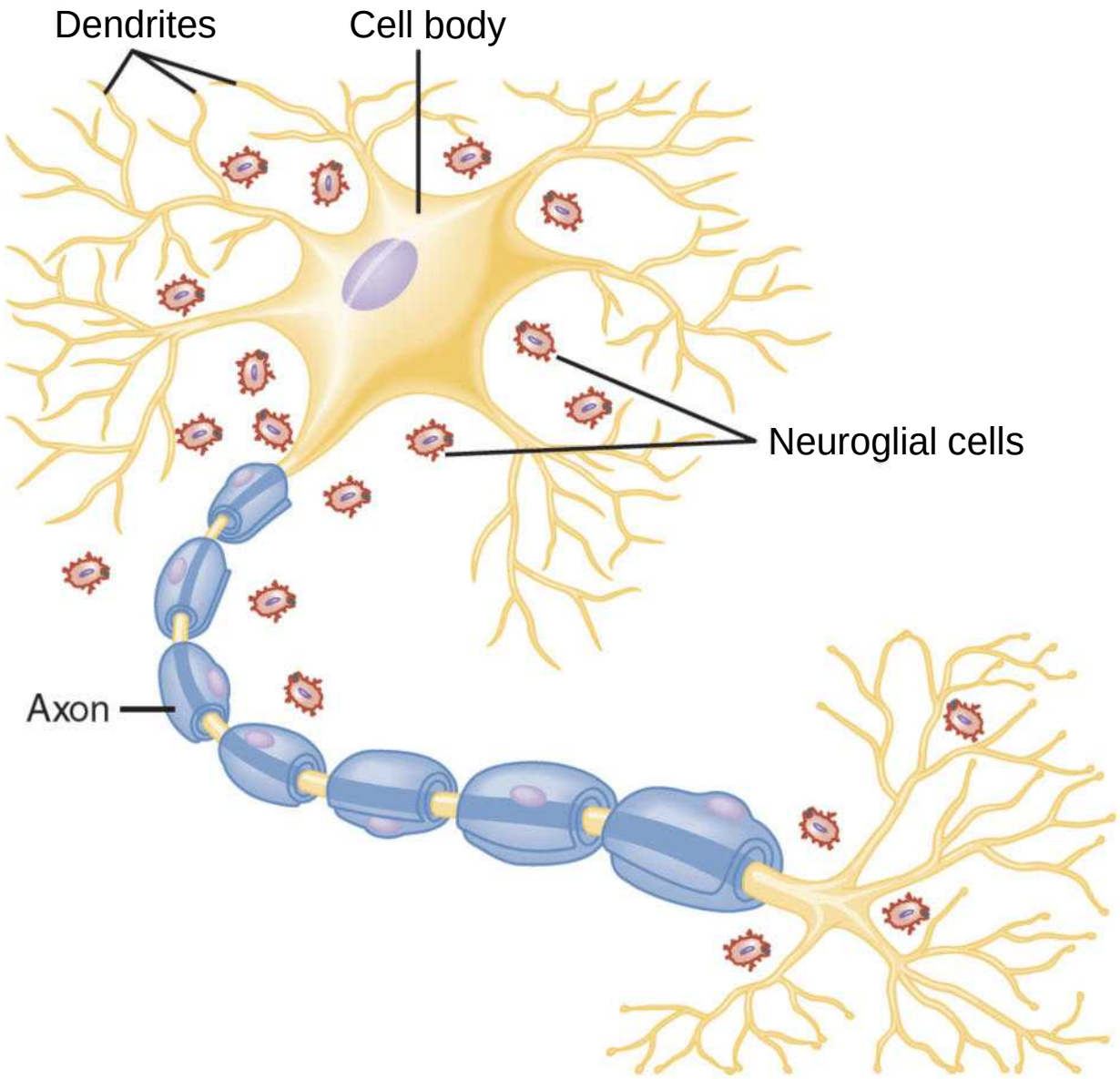


FIGURE 1-13 Nervous tissue cells.

Description

Cellular Adaptation and Damage

Cellular Adaptation

Cells are constantly exposed to a variety of environmental factors that can cause damage. Cells attempt to prevent their own death from environmental changes through **adaptation**. That is, they may modify their size, numbers, or types in an attempt to manage these changes and maintain homeostasis. Adaptation may involve one or a combination of these modifications. These modifications may be considered normal or abnormal depending on whether they were mediated through standard pathways. They may also be permanent or reversible. Once the stimulus is removed, however, adaptation ceases. Specific types of adaptive changes include **atrophy**, **hypertrophy**, **hyperplasia**, **metaplasia**, and **dysplasia** (**FIGURE 1-14**).

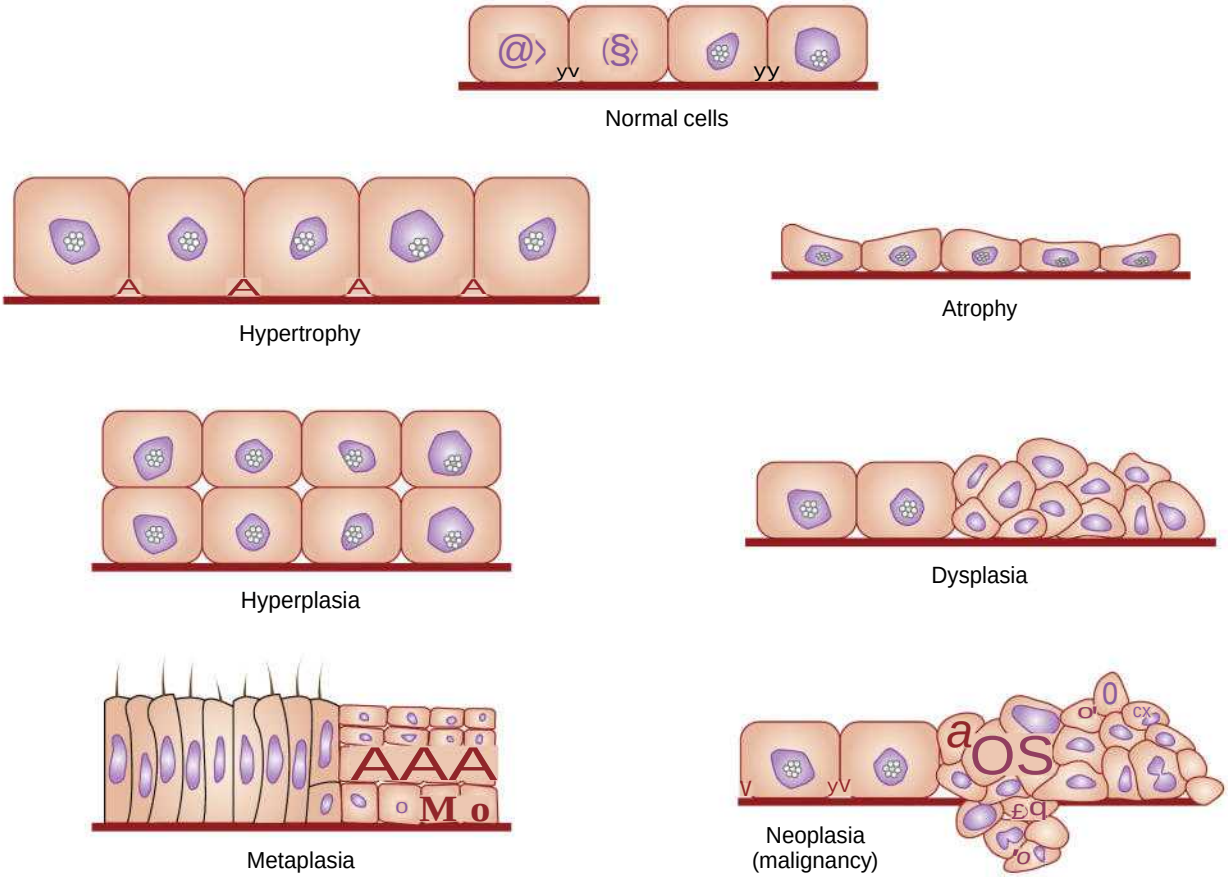


FIGURE 1-14 Cellular adaptation: abnormal cellular growth patterns.

Description

Atrophy occurs because of decreased work demands on the cell. Under all circumstances, the body attempts to work as efficiently as possible to conserve energy and resources. Thus, the cells decrease in size and number when cellular work demands decrease. These atrophied cells utilize less oxygen, and their organelles decrease in size and number. Causes of atrophy may include disuse, denervation, endocrine hypofunction, inadequate nutrition, and **ischemia**. An example of disuse atrophy can be seen when a muscle shrinks in an extremity with a fracture that has been in an immobilizing cast for an extended period. Denervation atrophy is closely associated with disuse; it can be seen when a muscle shrinks in a paralyzed extremity. Atrophy because of a loss of endocrine function occurs when the reproductive organs of postmenopausal women shrink. When these organs are not supplied with adequate nutrition and

blood flow, cells shrink due to a lack of substances necessary for their survival—much like when water and fertilizer are withheld from a plant.

The opposite of atrophy is hypertrophy. Hypertrophy occurs when cells increase in size in an attempt to meet increased work demands. This size increase may result from either normal or abnormal changes. Such changes are commonly seen in cardiac and skeletal muscle. For example, consider what happens when a bodybuilder diligently performs biceps curls with weights—the biceps get larger. This type of hypertrophy is a normal change. An abnormal hypertrophic change can be seen with hypertension (high blood pressure). Just as the biceps muscle grows larger from increased work, so the cardiac muscle will thicken and enlarge when hypertension places an increased workload on it. The biceps muscle increases in strength and function when its workload is increased; in contrast, the heart loses the flexibility to fill with blood and pump the blood when the cardiac muscle increases in size. This abnormal hypertrophic change can lead to complications such as cardiomyopathy and heart failure (see the *Cardiovascular Function* chapter).

Hyperplasia refers to an increase in the number of cells in an organ or tissue. This increase occurs only in cells that have the ability to perform mitotic division, such as epithelial cells. Hyperplasia differs from hypertrophy, but these processes often occur together because they have similar triggers. The hyperplasia process is usually a result of normal stimuli. Examples of such normal hyperplasia include that seen in menstruation, liver regeneration, wound healing, and skin warts. Hyperplasia can also be abnormal, especially when caused by excessive hormone or growth factors. Examples of pathologic hyperplasia include endometrial hyperplasia, which can result from an oversecretion of estrogen and a subsequent progesterone imbalance. Pathologic hyperplasia is not necessarily cancerous, but it can create a supportive environment for cancerous proliferation.

The process in which one adult cell is replaced by another cell type is called metaplasia. This change is usually initiated by chronic irritation and inflammation, such that a more virulent cell line emerges.

The cell types do not cross over the overarching cell type. For instance, epithelial cells may be converted into another type of epithelial cell, but they will not be replaced with nerve cells. Examples of metaplastic changes are the ciliary changes that can occur in the respiratory tract because of chronic smoking or vitamin A deficiency. Metaplasia does not necessarily lead to cancerous changes; however, cancerous changes will likely occur if the stimulus is not removed.

The final cellular adaptation is dysplasia. In dysplasia, cells mutate into cells of a different size, shape, and appearance (i.e., atypical cells). Although dysplasia is abnormal, it is potentially reversible by removing the trigger. Dysplastic changes are often implicated as precancerous cells. The reproductive and respiratory tracts are common sites for this type of adaptation because of their increased exposure to carcinogens (e.g., human papillomavirus and cigarette smoke).

Cellular Injury and Death

Cellular injury can occur in many ways and is usually reversible up to a point. Whether the injury is reversible or irreversible usually depends on the severity of the injury and intrinsic factors (e.g., blood supply and nutritional status). Cell injury can occur because of (1) physical agents (e.g., mechanical forces and extreme temperature), (2) chemical injury (e.g., pollution, lead, and drugs), (3) radiation, (4) biological agents (e.g., viruses, bacteria, and parasites), (5) low oxygen levels (e.g., hypoxia or ischemia), and (6) nutritional imbalances. Such an injury often causes ATP depletion, cell membrane dysfunction, metabolic waste accumulation, or abnormal immune responses (e.g., phagocytizing and storing abnormal substances). The cell's resistance to and tolerance of the injury can influence its ability to survive. For example, nervous and cardiac cells can survive only a few minutes without oxygen, while connective tissue may be able to survive for a few days.

Death is a normal part of human existence, and matters are no different at the cellular level. When cellular injury becomes

irreversible, it usually results in cell death. The process of eliminating unwanted cells, called “programmed cell death,” usually occurs through the **apoptosis** mechanism. Programmed cell death occurs at a specific point in development; apoptosis specifically occurs because of morphologic (structure or form) changes. This mechanism of cell death is not limited to developmental causes but may also result from environmental triggers. Apoptosis is important in tissue development, immune defense, and cancer prevention. If unregulated, this mechanism can result in inappropriate destruction of cells. Such inappropriate activation of apoptosis can occur in degenerative neurologic diseases, such as Alzheimer's disease (see the *Neural Function* chapter).

Not all cell death is apoptotic, however. Cell death can also occur because of ischemia or **necrosis** (**FIGURE 1-15**). Ischemia refers to inadequate blood flow to tissue or an organ. This lack of blood flow essentially strangles the tissue or organ by limiting the supply of necessary nutrients and oxygen. Ischemia can leave cells damaged to the extent that they cannot survive, a condition called **infarction**. Necrosis is another type of cell death, which can occur due to injury, disease, or ischemia. The difference between apoptosis and necrosis lies mostly in the cell’s morphologic changes. In apoptosis, the cells condense or shrink; in necrosis, the cells swell and burst.

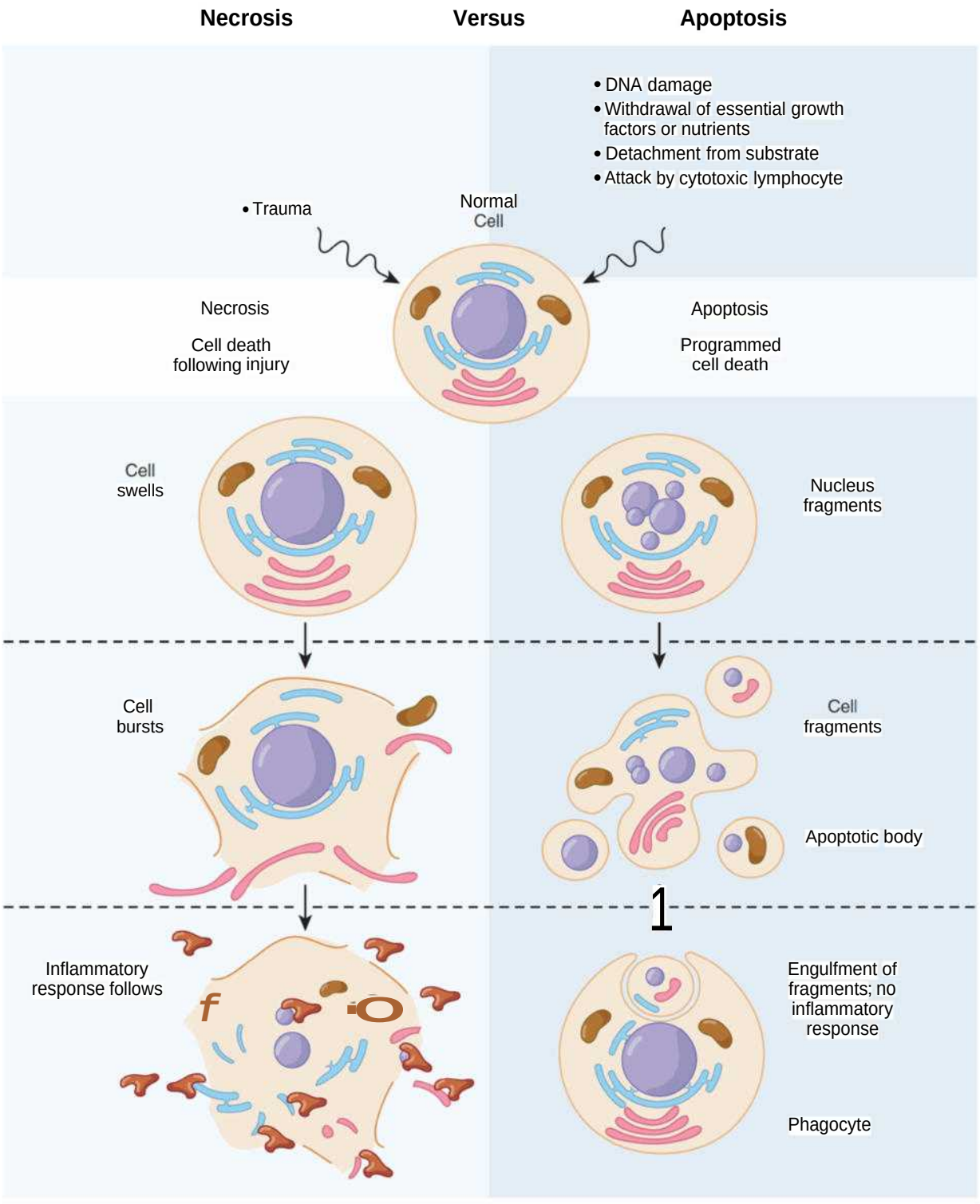


FIGURE 1-15 Cellular damage can result in necrosis, which has a different appearance from that of apoptosis, as organelles swell and the plasma membrane ruptures.

Description

Necrosis can take one of several pathways. **Liquefaction necrosis** (**FIGURE 1-16**) occurs when caustic enzymes dissolve and liquefy necrotic cells. The most common site of this type of necrosis is the brain, which contains a plentiful supply of these enzymes. **Caseous necrosis** (**FIGURE 1-17**) occurs when the necrotic cells disintegrate, but the cellular debris remains in the area for months or years. This type of necrosis, which has a cottage cheese-like appearance, is most commonly noted with pulmonary tuberculosis. **Fat necrosis** (**FIGURE 1-18**) occurs when lipase enzymes break down intracellular triglycerides into free fatty acids, which then combine with magnesium, sodium, and calcium to form soaps. These soaps give fat necrosis an opaque, chalky appearance. Fat necrosis is commonly associated with breast injury (e.g., surgery, radiation, or trauma) or acute pancreatitis. **Coagulative necrosis** (**FIGURE 1-19**) usually results from an interruption in blood flow. In such a case, the pH drops (acidosis), denaturing the cell's enzymes. This type of necrosis most often occurs in the kidneys, heart, and adrenal glands.

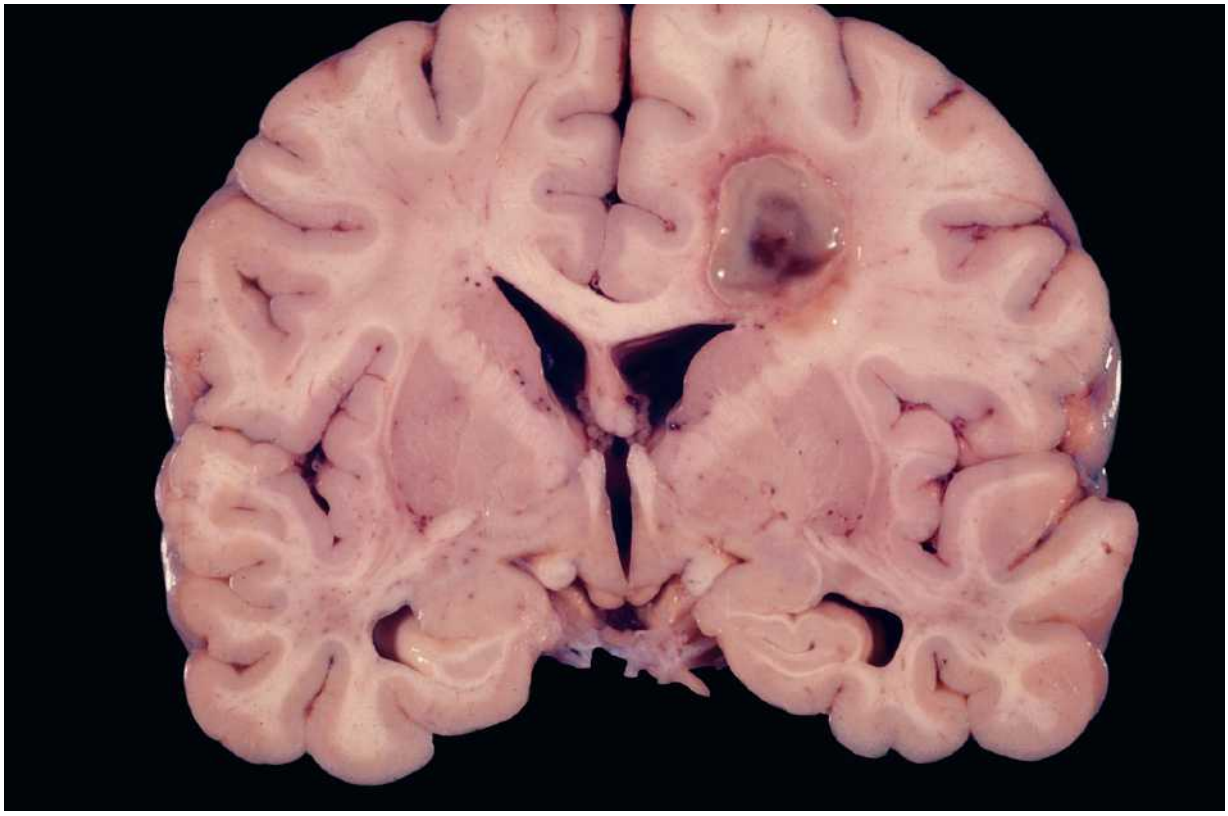


FIGURE 1-16 Liquefaction necrosis.

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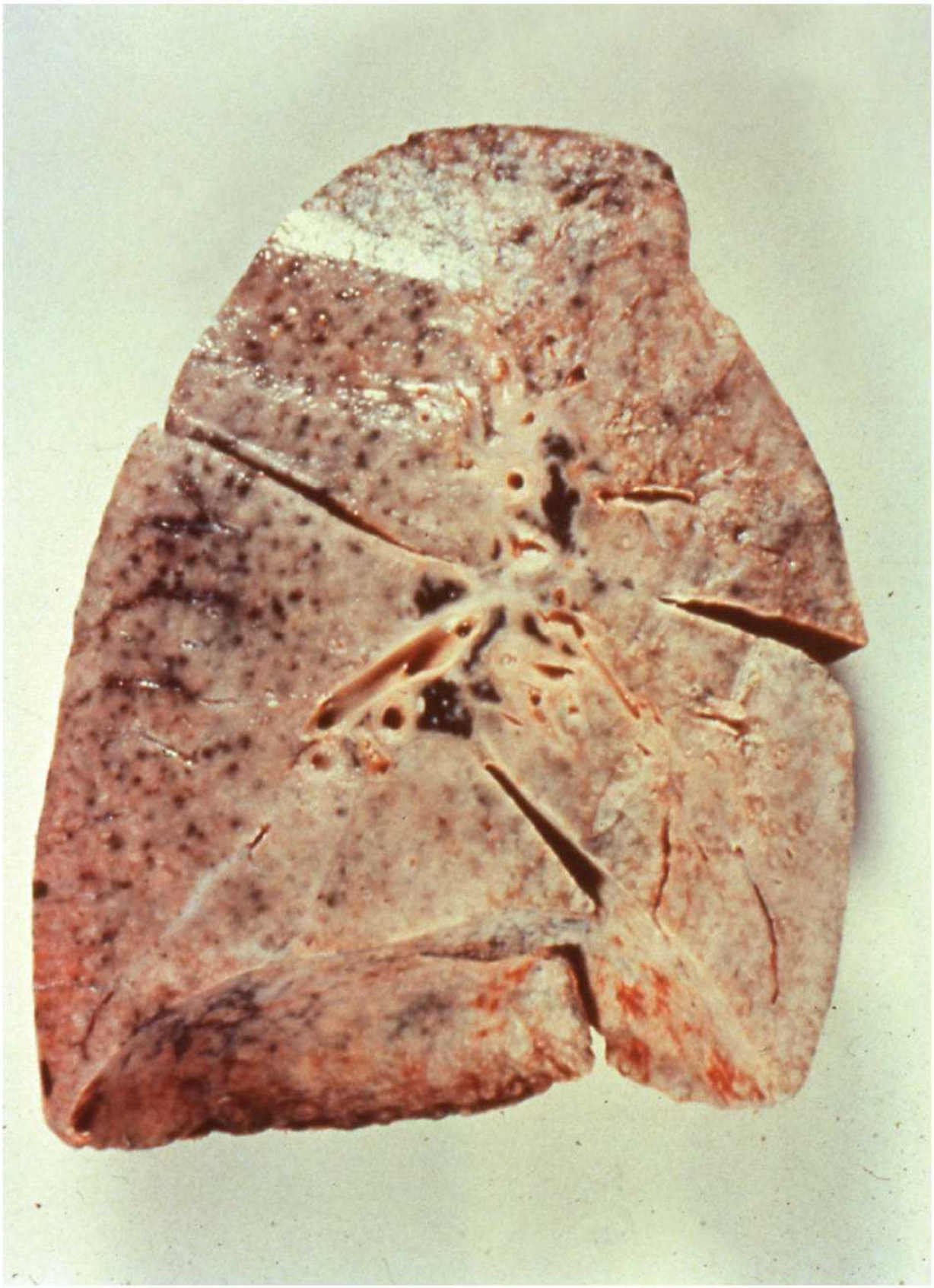


FIGURE 1-17 Caseous necrosis.

Courtesy of CDC.

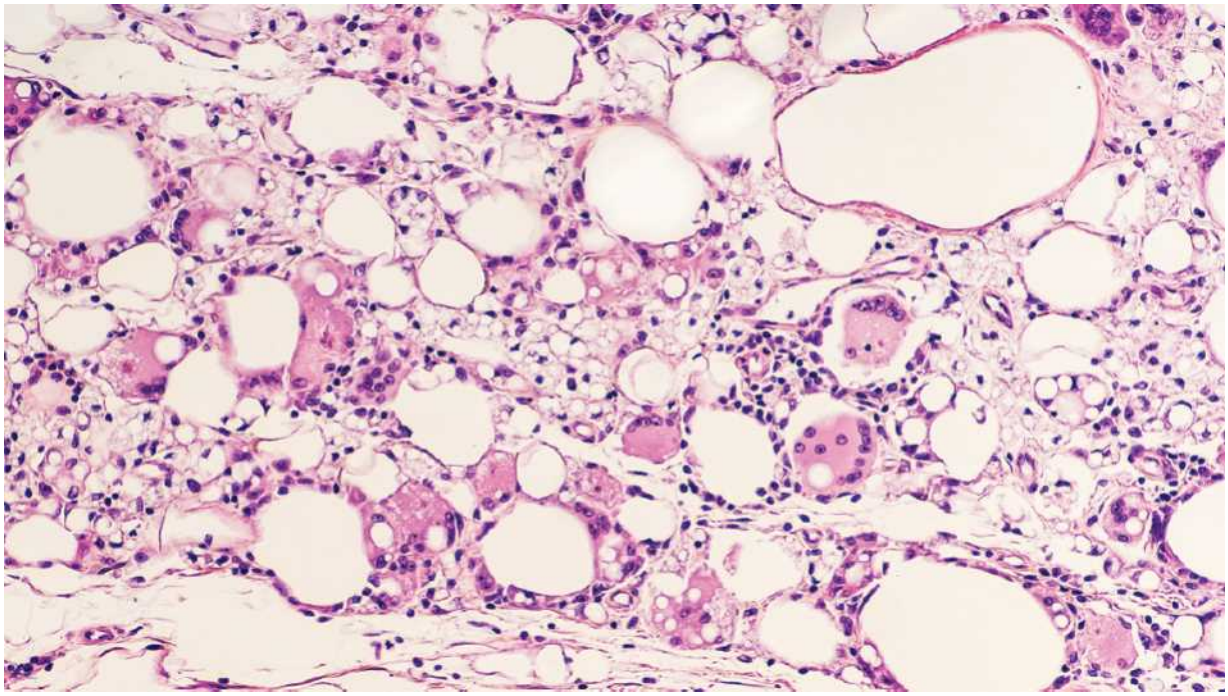


FIGURE 1-18 Fat necrosis.

© David A Litman/Shutterstock

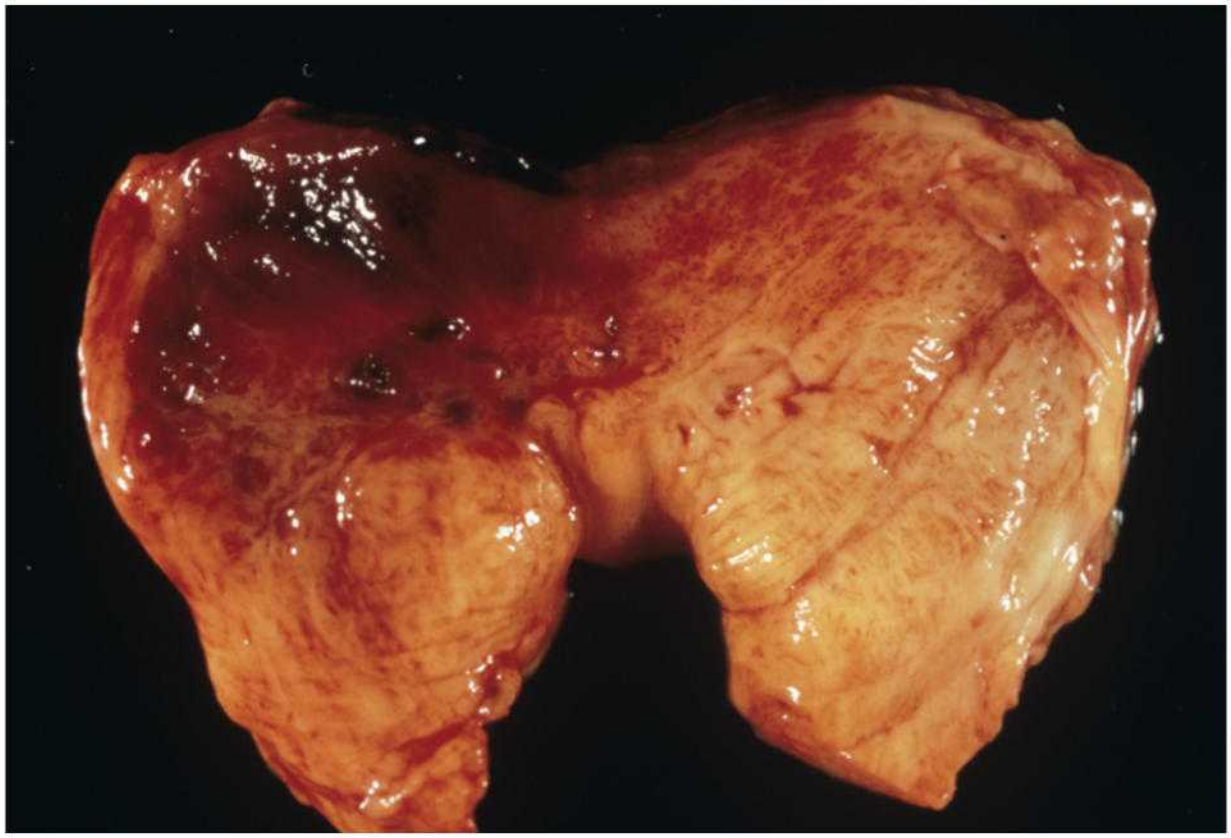


FIGURE 1-19 Coagulative necrosis.

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Gangrene is a form of coagulative necrosis that represents a combination of impaired blood flow and a bacterial invasion. Gangrene usually occurs in the legs because of arteriosclerosis (hardening of the arteries) or in the gastrointestinal tract. It most commonly takes one of three forms: dry, wet, or gas. **Dry gangrene** (**FIGURE 1-20**) occurs when bacterial presence is minimal, and the skin has a dry, dark brown, or black appearance. **Wet gangrene** (**FIGURE 1-21**) occurs with liquefaction necrosis. In this condition, extensive damage from bacteria and white blood cells produces a liquid wound. Wet gangrene can occur in the extremities as well as in internal organs. **Gas gangrene** (**FIGURE 1-22**) develops because of the presence of *Clostridium*, an anaerobic bacterium. This type of gangrene is the most serious and has the greatest potential to be fatal. The bacterium releases toxins that destroy surrounding cells, so

the infection spreads rapidly. The gas released from this process bubbles from the tissue, often underneath the skin. Other less common, but often serious types of gangrene, include necrotizing fasciitis (caused by group A *Streptococcus*), Fournier gangrene (affects the penis and genitalia), and Meleney synergistic gangrene (seen in patients after surgery; *Staphylococcus aureus* and *Streptococcus* organisms are present).



FIGURE 1-20 Dry gangrene.

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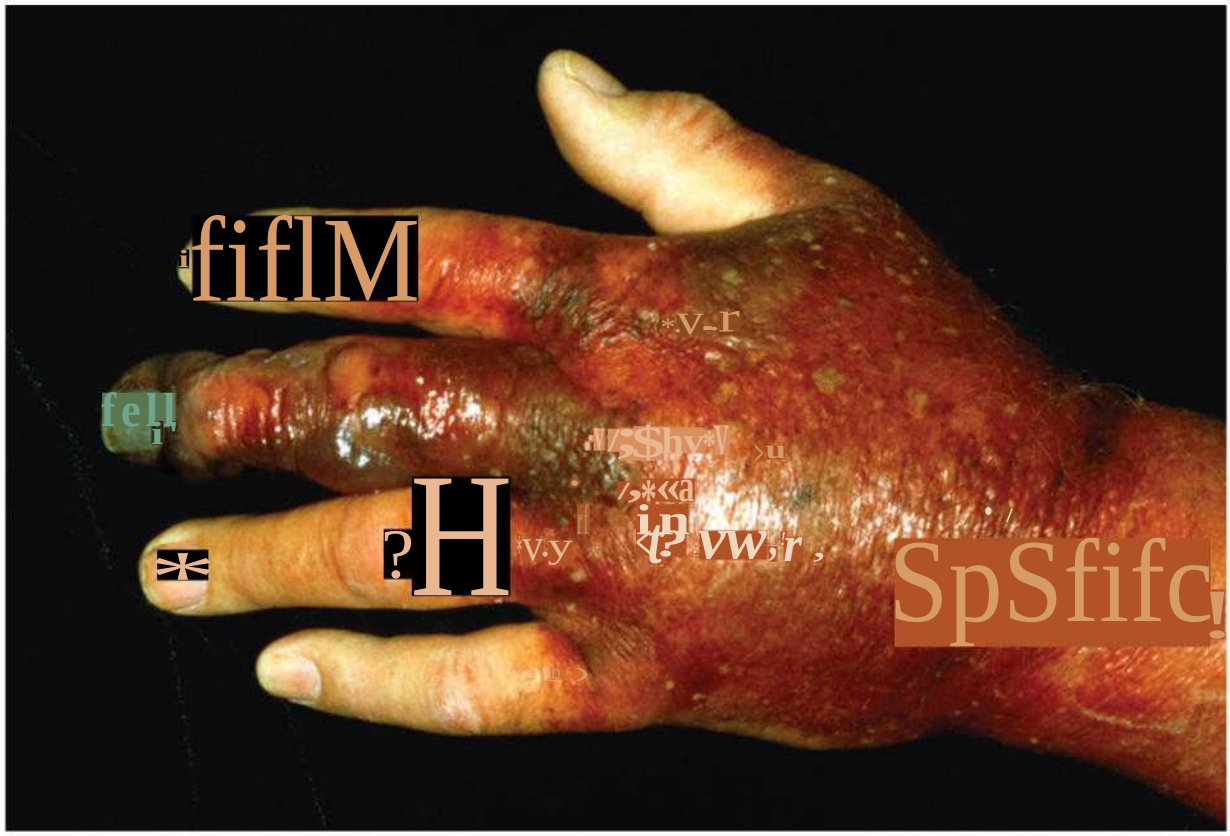


FIGURE 1-21 Wet gangrene.

© SPL/Science Source



FIGURE 1-22 Gas gangrene.

Courtesy of CDC/ Dr. Robert Fass, Ohio State Dept. of Medicine.

Another important mechanism of cellular injury is **free radicals** (e.g., reactive oxygen species). Free radicals are injurious, unstable agents that can cause cell death. A single unbalanced atom initiates this pathway, which can rapidly produce a wide range of damage. Such an atom has an unpaired electron, making it unstable. In an attempt to stabilize itself, the atom borrows an electron from a nearby atom, usually rendering it unstable. This newly unstable atom will then borrow an electron from its neighbor, creating a domino effect that continues until the atom giving the electron is stable without it. The extent of damage that this process causes depends on how long this chain of events continues. The immune system is equipped with agents to protect or limit the damage (see the *Immunity* chapter) that might occur because of this process, and certain dietary components can aid in this fight (e.g., antioxidants, such as vitamins C and E and beta-carotene). Free radicals have

been linked to cancer, aging, and a variety of other conditions (e.g., heart disease, diabetes mellitus, and hypertension).

Neoplasm

When the process of cellular proliferation or differentiation goes wrong, **neoplasms** can develop. A neoplasm, or **tumor**, is a group of cells whose growth is no longer responding to (i.e., constrained by) normal regulatory processes, usually because of a mutation. The disease state associated with this uncontrolled growth is termed "cancer." Cancer's key features include rapid, uncontrolled proliferation and a loss of differentiation (i.e., **anaplasia**). To varying degrees, cancer cells differ from normal cells in size, shape, number, differentiation, purpose, and function. The less the cell resembles the original cell, the more anaplastic the cell is. Anaplastic cells may begin functioning as completely different cells, often producing hormones or hormone-like substances. This uncontrolled proliferation and changes in differentiation are a result of genetic, epigenetic (gene expression), and environmental factors. Such changes result from a series of events or factors, not just one.

A healthy body is equipped with the necessary defenses to shield it against cancer (see the *Immunity* chapter). When those defenses fail, however, cancer prevails. **Carcinogenesis**, the process by which cancer develops, occurs in three phases: **initiation**, **promotion**, and **progression** (**FIGURE 1-23**).

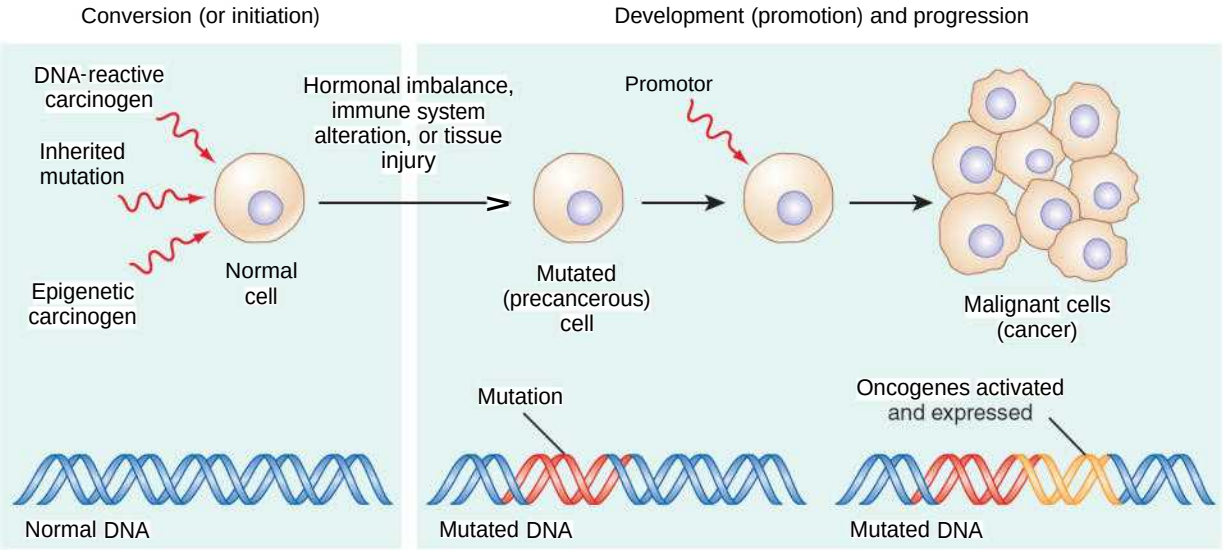


FIGURE 1-23 Carcinogenesis: the stages leading to cancer.

Description

Initiation involves the exposure of the cell to a substance or event (e.g., chemicals, viruses, radiation, hormones, or other environmental agents) that causes DNA damage or mutation, especially affecting proto-oncogenes and tumor suppressor genes. Usually, the body has enzymes that detect these events and repair the damage. If the event is overlooked, the mutation can become permanent and be passed on to future cellular generations, making it vulnerable if additional insults occur. Additionally, risk for DNA replication and repair errors and carcinogen exposure increases over time, resulting in higher rates of cancer with aging.

Promotion involves the mutated cells' exposure to factors (e.g., hormones, nitrates, or nicotine) that promote growth through epigenetic mechanisms (e.g., DNA methylation, histone modification, and microribonucleic acids). This phase may occur just after initiation or years later, and it can be reversible if the promoting factors are removed. Many new cancer therapies aim to reverse this phase.

In progression, the tumor invades, **metastasizes** (spreads), and becomes resistant to drug therapy. The microenvironment (e.g., available blood flow, nearby tissue or cells, or hormones present) surrounding the cancer cells influences its ability to proliferate, survive, invade, and metastasize. Additionally, this environment

influences the cancer cell's response to treatment. Moreover, the immune system is impaired during stress states, which can affect its ability to find and respond to carcinogenesis. This final phase is permanent or irreversible.

More than 100 diseases are classified as a cancer, and most organs and tissues are vulnerable to this condition. Cancer **prognosis** depends on the type of cancer and the individual's health. Some cancers are aggressive (e.g., pancreatic cancer), whereas others are easy to treat (e.g., testicular cancers). In recent years, the survival rates for some cancers have significantly improved because of advancements in screening and treatment (e.g., breast cancer). Even though cancer deaths decreased by 33% between 1991 and 2020, cancer remains the second leading cause of death in the United States (Centers for Disease Control and Prevention, 2020; National Cancer Institute, 2020).

Benign and Malignant Tumors

The two major types of neoplasms are **benign** and **malignant** (**TABLE 1-4**; **FIGURE 1-24**). Benign tumors usually consist of differentiated (less anaplastic) cells that are reproducing more rapidly than normal cells. Because of their differentiation, benign tumors are more like normal cells and cause fewer problems. Benign cells are usually encapsulated and unable to metastasize. The tumor, however, can compress surrounding tissue as it grows. Benign tumors usually cause problems due to that compression. Regardless of its size, if the tumor arises in a sensitive area, such as the brain or spinal cord, it can cause devastating problems.

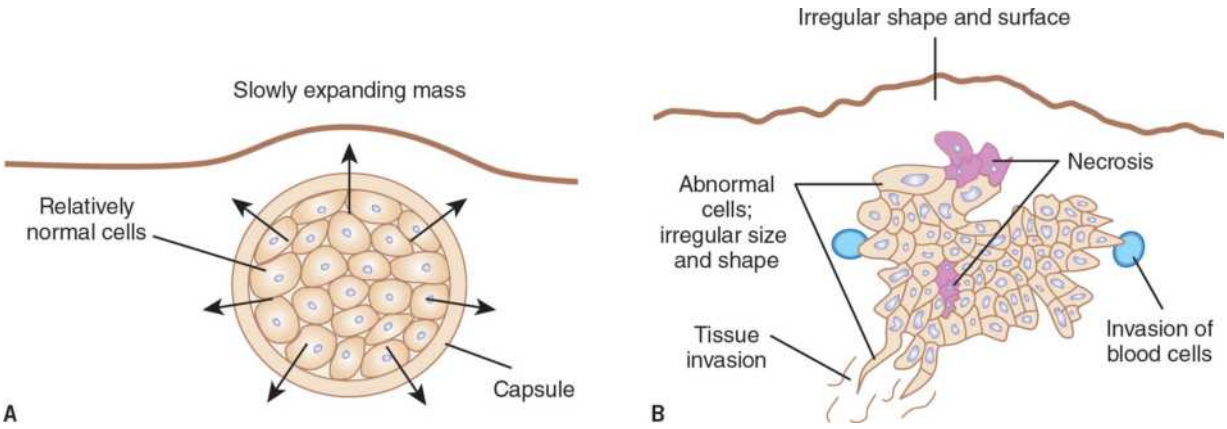


FIGURE 1-24 Characteristics of **(A)** benign and **(B)** malignant tumors.

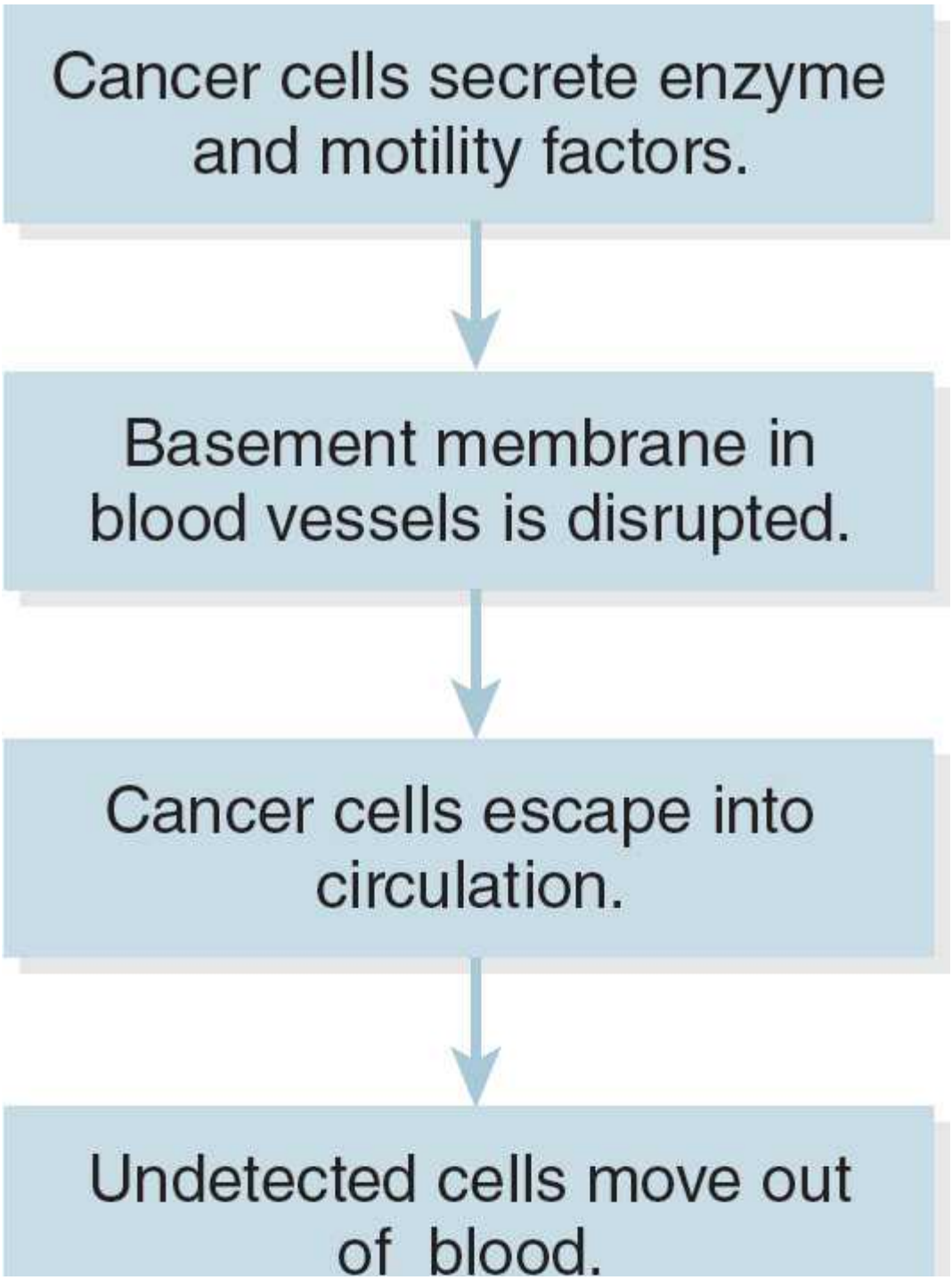
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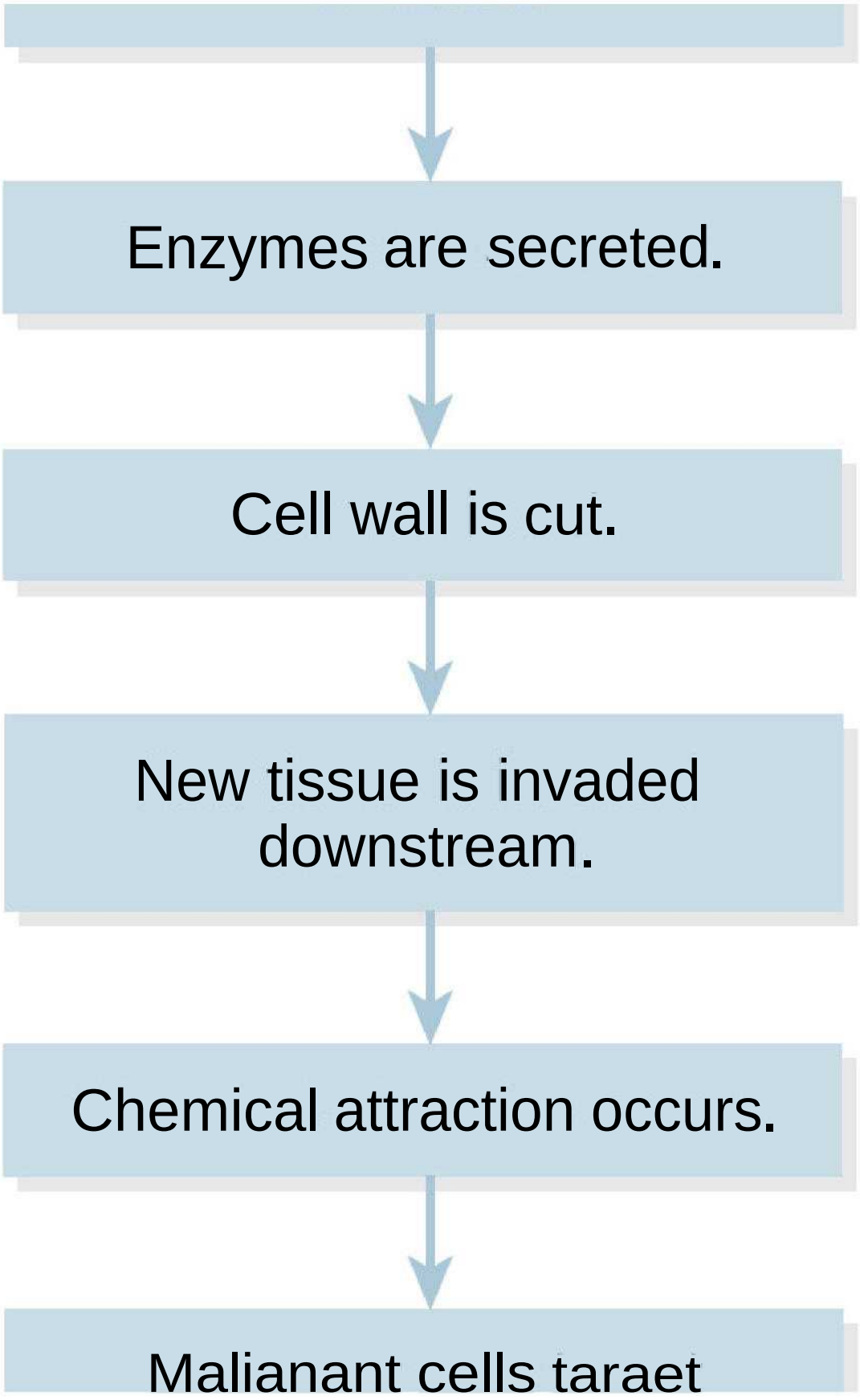
TABLE 1-4 Characteristics of Benign and Malignant Tumors

	Benign Tumors	Malignant Tumors
Cells	Similar to normal cells Differentiated Mitosis is fairly normal	Varied in size and shape Many undifferentiated Mitosis is increased and atypical
Growth	Relatively slow Expanding mass Frequently encapsulated	Rapid growth Cells are not adhesive, infiltrate tissue No capsule
Spread	Remains localized	Invades nearby tissue or metastasizes to distant sites through blood and lymph vessels
Systemic effects	Rare	Common

Malignant tumors usually consist of undifferentiated (more anaplastic), nonfunctioning cells that are reproducing rapidly. Such tumors often penetrate surrounding tissue and spread to secondary

sites. The tumor's ability to metastasize (**FIGURE 1-25**; **FIGURE 1-26**) depends on its ability to access and survive in the circulatory or lymphatic system. Most commonly, the tumor metastasizes to tissue or organs near the primary site, but some tumor cells may travel to distant sites (**TABLE 1-5**).




Enzymes are secreted.
Cell wall is cut.
New tissue is invaded downstream.
Chemical attraction occurs.
Malianant cells taraet

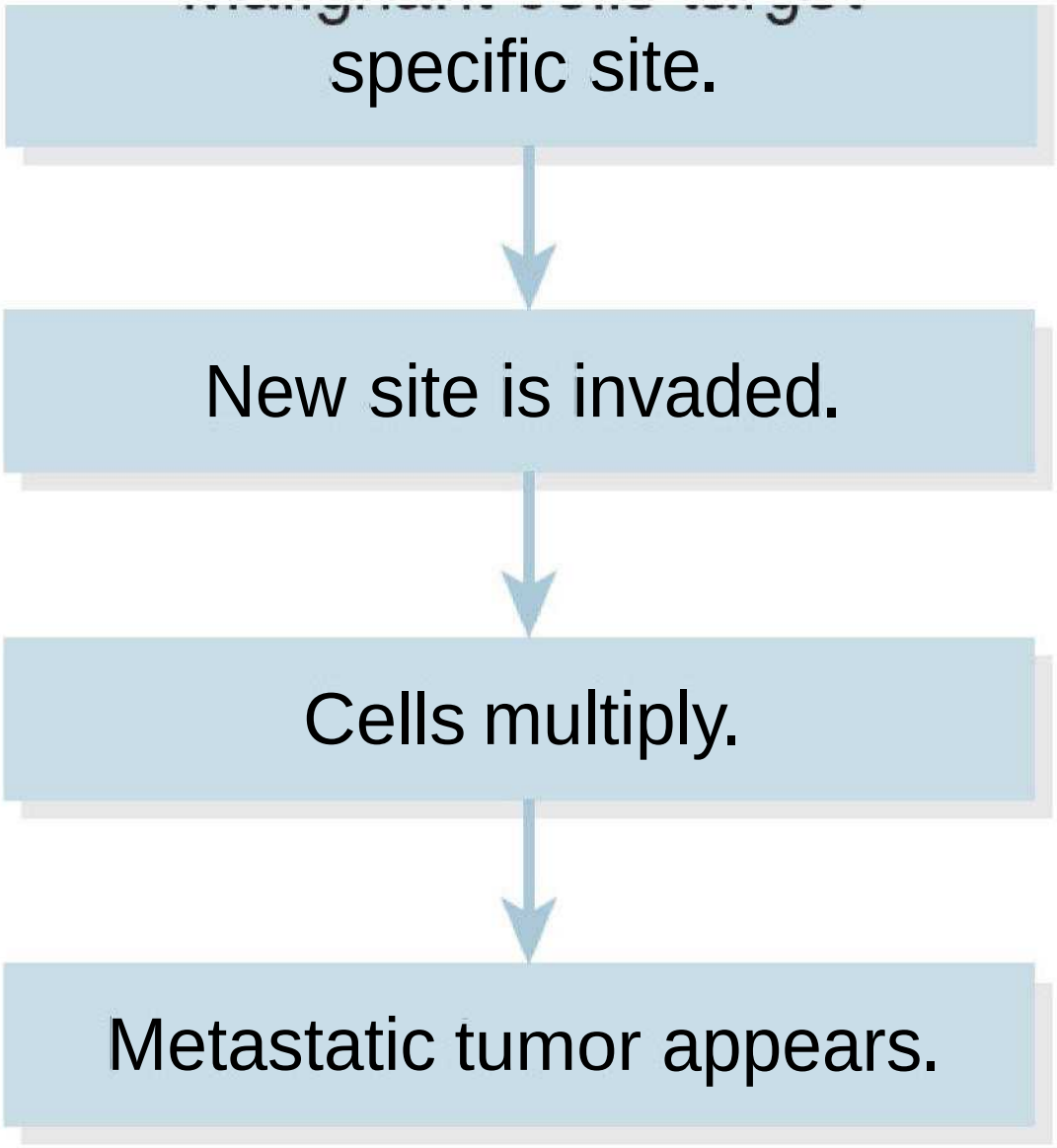


FIGURE 1-25 How cancer metastasizes.

Description

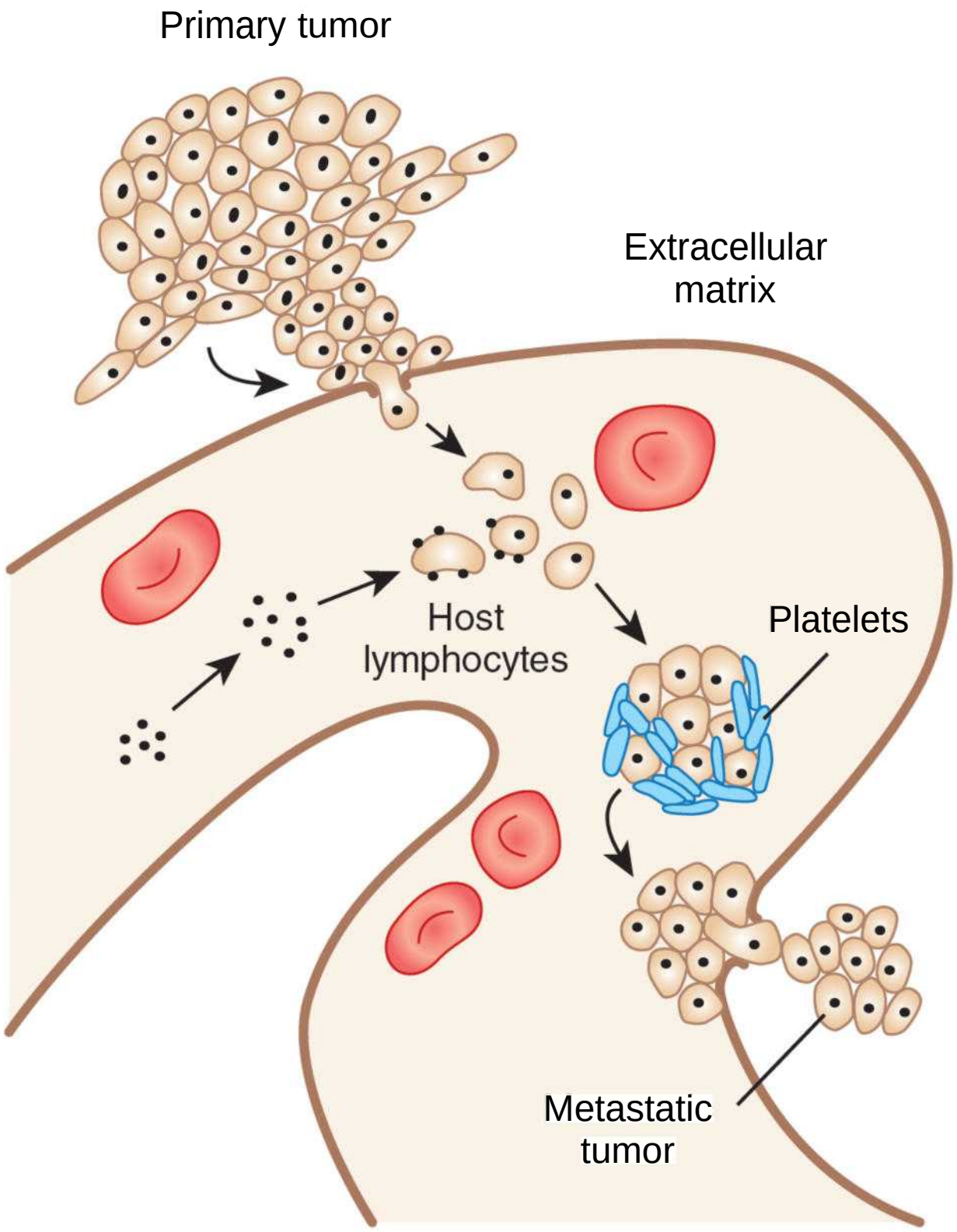


FIGURE 1-26 Pathogenesis of metastasis.

Description

TABLE 1-5 Common Sites of Metastasis

Cancer Type	Main Sites of Metastasis*
Bladder	Bone, liver, lung
Breast	Bone, brain, liver, lung
Colorectal	Liver, lung, peritoneum
Kidney	Adrenal gland, bone, brain, liver, lung
Lung	Adrenal gland, bone, brain, liver, other lung
Melanoma	Bone, brain, liver, lung, skin, muscle
Ovary	Liver, lung, peritoneum
Pancreas	Liver, lung, peritoneum
Prostate	Adrenal gland, bone, liver, lung
Stomach	Liver, lung, peritoneum
Thyroid	Bone, liver, lung
Uterus	Bone, liver, lung, peritoneum, vagina

* In alphabetical order.

Reproduced from National Cancer Institute. (2020). Metastatic cancer: When cancer spreads. Retrieved from http://www.cancer.gov/about-cancer/what-is-cancer/metastatic-fact-sheet

Regardless of the type of tumor, several factors are essential for the tumor's progression and survival. The tumor must have an adequate blood supply, and sometimes it will divert the blood supply from surrounding tissue to meet those needs. The tumor will grow only as large as what the blood supply will support. Location is critical because it determines the cytology of the tumor as well as the tumor's ability to survive and metastasize. Host factors, including age, gender, health status, and immune function, will also affect the tumor.

Alterations in some of these host factors can create a prime environment for the tumor to grow and prosper.

Clinical Manifestations

In most cases, a patient's prognosis improves the earlier the cancer is detected and treated. Healthcare providers, patients, and family members detect many cases of cancer first through the recognition of manifestations. Heeding these warning signs is vital to initiating treatment early. Unfortunately, people often ignore or do not recognize the warning signs for a variety of reasons (e.g., denial and symptom ambiguity).

As the cancer progresses, the patient may present with manifestations of advancing disease, including anemia, cachexia, fatigue, infection, leukopenia, thrombocytopenia, and pain. Anemia—that is, decreased red blood cells—can be a result of bloodborne cancers (e.g., leukemias), chronic bleeding, malnutrition, chemotherapy, or radiation. Cachexia, a generalized wasting syndrome in which the person appears emaciated, often occurs due to malnutrition. Fatigue, or feeling of weakness, results from the parasitic nature of a tumor, anemia, malnutrition, stress, anxiety, and chemotherapy. Factors that can increase the risk for infection include bone marrow depression, chemotherapy, and stress. Leukopenia (low leukocyte levels) and thrombocytopenia (low platelet levels) are common side effects of chemotherapy and radiation due to bone marrow depression. Pain is often associated with cancer due to tissue pressure, obstructions, tissue invasion, visceral stretching, tissue destruction, and inflammation. Other manifestations depend on the type and location of the cancer (see the specific cancer discussions in their relevant chapters).

Myth Busters

Myth 1: Cancer is a death sentence.

While cancer remains the second leading cause of death in the United States, cancer deaths have dropped 33% since 1990 due to improvements in screening, treatments, lifestyle choices, and education (National Cancer Institute, 2020). Additionally, new cases of cancer decreased 8% from 1999 and 2020, and patients with cancer are living longer. The overall 5-year cancer survival rate improved from 40% in 1975 to 71% in 2014.

Myth 2: Standing in front of a microwave oven while it is cooking food can increase your risk for cancer.

This myth may hold a grain of truth. An increased cancer risk has been linked to increased levels of ionizing radiation (e.g., X-rays) because such radiation detaches electrons from atoms. Microwaves use nonionizing microwave radiation to heat food. Early microwave ovens emitted higher levels of this radiation, which may have increased users' cancer risk to a slight extent. Research has never been able to determine whether cancer risk increases with exposure to nonionizing radiation. Currently, Food and Drug Administration guidelines limit the amount of the nonionizing radiation microwave ovens can emit, further decreasing the cancer risk associated with these devices.

Myth 3: Using cell phones can increase your risk of cancer.

Cell phones use the same nonionizing microwave radiation as microwave ovens do to emit a signal. Even though these devices may be in close proximity to your head while in use, evidence does not support the assertion that they increase your risk of brain cancer. Using a cell phone for an extended period at one time will heat your ear for the same reason that the microwave heats your food, but no clear evidence suggests that this extended use increases cancer risk.

Myth 4: Artificial sweeteners cause cancer.

Numerous studies have been focused on the safety of artificial sweeteners, and no evidence suggests that they cause cancer.

Myth 5: A biopsy or surgery makes cancer spread.

Some believe that exposing cancer to the air during surgery or biopsy can cause the cancer to spread. This fear may originate from the fact that some patients learn that their cancer has gotten worse following these procedures. The likelihood of this causing cancer to spread is very low, and precautions are taken to prevent further damage.

Myth 6: A family member with cancer guarantees I will get it, or I am completely safe because no one in my family has it.

A family history of cancer does increase your risk, but **genetics** is not the only factor. Approximately 90% of cancers have no relation to heredity or genetic mutations. These mutations are typically caused by lifestyle choices (e.g., smoking, diet) or environmental factors (e.g., radiation or pollution exposure). The longer you live, the more the impact of these factors increases, leading to a higher risk of developing cancer.

Diagnosis

Diagnosis of cancer is complex and specific to the type of cancer suspected. This section provides a basic overview of cancer diagnostic procedures; more specifics are presented in other chapters as specific cancers are discussed. A set of diagnostic procedures usually follows a thorough history and physical examination. These procedures may vary depending on the type of cancer suspected. The intention of the diagnostic tests is to identify cancer cells, establish the cytology, and determine the primary site and any secondary sites; however, all these goals are not always accomplished. The healthcare provider will gather as much information as possible to paint the clearest and most complete picture possible of the patient so as to develop an appropriate treatment plan.

Some screening tests are used for early detection of cancer cells as well as for staging the cancer (TABLE 1-6). These screening tests include X-rays, radioactive isotope scanning, computed tomography scans, endoscopies, ultrasonography, magnetic resonance imaging, positron emission tomography scanning, biopsies, and blood tests. Some of the blood tests may include tumor markers—substances secreted by the cancer cells—for specific cancers (TABLE 1-7). These tumor markers not only aid in cancer detection but also assist in tracking disease progression and treatment response.

TABLE 1-6 Cancer Screening Guidelines

Screening Area	Recommendations
Breast	

Screening Area	Recommendations
Mammogram	Every year at age 40 and older or every 2 years at ages 50–74; can discontinue after age 75 unless expected to live longer than 10 years
Clinical breast examination	Every year at age 40 and older; every 3 years at ages 20–39
Breast self-examination	Suggested monthly for age 20 and older
BRCA1 and *BRCA2* genetic testing	Only recommended for women with a family history
Ovary	
BRCA1 and *BRCA2* genetic testing	Only recommended for women with a family history
Cervix	
Papanicolaou (Pap) test	Every 3 years between the ages of 21 and 65 Not necessary after age 65 unless serious cervical precancer or cancer present in the past 20 years
Human papillomavirus (HPV)	Every 5 years between the ages of 30 and 65
Endometrium	
Endometrial biopsy or pelvic ultrasound	Yearly beginning at age 35 for those women at risk for colon cancer
Prostate	
Prostate-specific antigen (PSA)	Frequency depends on risk factors; may begin as early as age 40
Digital rectal examination	Frequency depends on risk factors; may begin as early as age 40
Colon and Rectum	

Screening Area	Recommendations
Fecal occult blood test	Yearly at age 50 and older
Fecal immunochemical test	Yearly at age 50 and older
Stool DNA test	Every 3 years at age 50 and older
Flexible sigmoidoscopy	Every 5 years at age 50 and older
Barium enema	Every 5 years at age 50 and older
Colonoscopy	Every 10 years at age 50 and older
Virtual colonography	Every 5 years at age 50 and older

Data from American Cancer Society. (2018). American Cancer Society guidelines for the early detection of cancer. Retrieved from http://www.cancer.org/National Cancer Institute. www.cancer.gov; United States Preventive Services Task Force recommendations. https://www.uspreventiveservicestaskforce.org/BrowseRec/Index

TABLE 1-7 Common Tumor Cell Markers

Marker	Malignant Condition	Nonmalignant Condition
Alpha-fetoprotein	Liver cancer Ovarian germ cell cancer Testicular germ cell cancer	Ataxia telangiectasia Cirrhosis Hepatitis Pregnancy
Anaplastic lymphoma kinase (ALK)	Lung cancer Large-cell lymphoma	Unknown
BCR-ABL	Chronic myeloid leukemia Acute lymphocytic leukemia	Unknown

Marker	Malignant Condition	Nonmalignant Condition
$Beta_2$ microglobulin (B2M)	Multiple myeloma Chronic lymphocytic leukemia Some lymphomas	Kidney disease
Carcinoembryonic antigen	Bladder cancer Breast cancer Cervical cancer Colorectal cancer Kidney cancer Liver cancer Lung cancer Lymphoma Melanoma Ovarian cancer Pancreatic cancer Stomach cancer Thyroid cancer	Inflammatory bowel disease Liver disease Pancreatitis Chronic obstructive pulmonary disease Rheumatoid arthritis Tobacco use
CA 15-3	Breast cancer Lung cancer Ovarian cancer Prostate cancer	Benign breast disease Endometriosis Hepatitis Lactation Benign ovarian disease Pelvic inflammatory disease Pregnancy
CA 19-9	Bile duct cancer Colorectal cancer Pancreatic cancer Stomach cancer	Thyroid disease Rheumatoid arthritis Cholecystitis Inflammatory bowel disease Cirrhosis Pancreatitis

Marker	Malignant Condition	Nonmalignant Condition
CA 27-29	Breast cancer Colon cancer Kidney cancer Liver cancer Lung cancer Ovarian cancer Pancreatic cancer Stomach cancer Uterine cancer	Benign breast disease Endometriosis Kidney disease Liver disease Ovarian cysts Pregnancy (first trimester)
CA 125	Colorectal cancer Gastric cancer Ovarian cancer Pancreatic cancer	Endometriosis Liver disease Menstruation Pancreatitis Pelvic inflammatory disease Peritonitis Pregnancy
Human chorionic gonadotropin	Choriocarcinoma Embryonic cell carcinoma Liver cancer Lung cancer Pancreatic cancer Stomach cancer Testicular cancer	Marijuana use Pregnancy
Lactate dehydrogenase	Almost all cancers Ewing sarcoma Leukemia Non-Hodgkin's lymphoma Testicular cancer	Anemia Heart failure Hypothyroidism Liver disease Lung disease
Neuron-specific enolase	Kidney cancer Melanoma Neuroblastoma Pancreatic cancer Small-cell lung cancer Testicular cancer Thyroid cancer Wilms tumor	Unknown

Marker	Malignant Condition	Nonmalignant Condition
Prostatic acid phosphatase	Prostate cancer	Benign prostate conditions
Prostate-specific antigen	Prostate cancer Multiple myeloma Lung cancer	Benign prostatic hyperplasia Prostatitis

Malignant cancer cells are classified based on the degree of differentiation (**grading**) and extent of disease (staging). The grading system determines the degree of differentiation on a scale of 1 to 4, in order of clinical severity. For instance, grade 1 cancers are well differentiated, meaning they are less likely to cause serious problems because they are more like the original tissue. By comparison, grade 4 cancers are undifferentiated, meaning they are highly likely to cause serious problems because they do not share any characteristics of the original tissue. The **TNM staging** system evaluates the tumor size, nodal involvement, and metastatic progress (**FIGURE 1-27**).

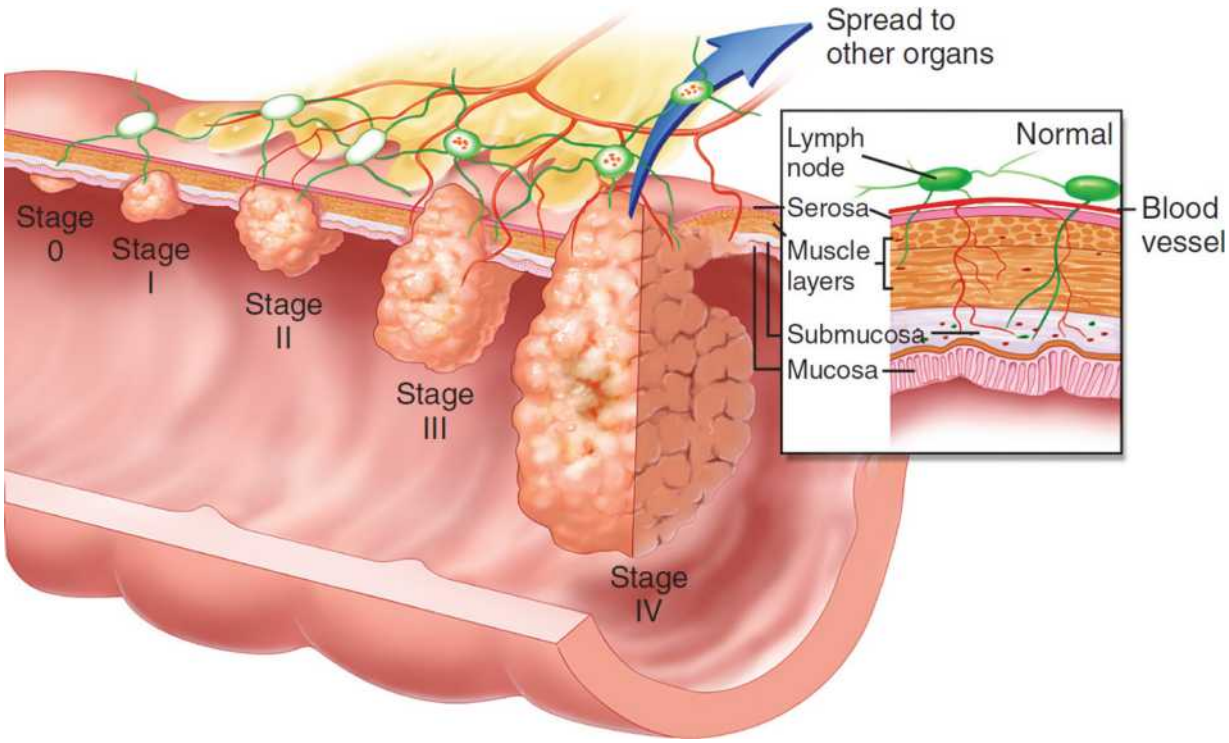


FIGURE 1-27 TNM staging system. The example shown is staging of colorectal cancer.

© 2005 Terese Winslow, U.S. Govt. has certain rights.

Description

Treatment

Cancer treatment usually consists of a combination of chemotherapy, radiation, surgery, targeted therapy, hormone therapy, immunotherapy, hyperthermia, stem cell transplants, photodynamic therapy, and laser treatment. Additionally, other strategies may include watchful waiting and alternative therapies (e.g., herbs, diet, and acupuncture). The goal of treatment may be **curative** (eradicate the disease), **palliative** (treat symptoms to increase comfort), or **prophylactic** (prevent the disease).

When surgery is undertaken, attempts are made to remove the tumor and its surrounding tissue. Chemotherapy involves the administration of a wide range of medications that destroy replicating tumor cells. With radiation therapy, ionizing radiation is used to cause cancer cellular mutation and interrupt the tumor's blood supply. Radiation may be administered by external sources or via internally implanted sources.

Targeted therapy is a newer type of treatment that uses drugs to identify and attack cancer cells while sparing normal cells; this drug therapy differs from traditional chemotherapy. Hormone therapy involves administering specific hormones that inhibit the growth of certain cancers. Immunotherapy focuses on the use of specific immune agents (e.g., interferons and interleukins) to alter the host's biological response to the cancer.

Hyperthermia precisely delivers heat to a small area of cells or part of the body to destroy tumor cells. This technique can also increase the effectiveness of radiation, immunotherapy, and chemotherapy. Stem cell transplants may include peripheral blood, bone marrow, or umbilical cord blood. These transplants are used to restore stem cells in bone marrow destroyed by disease or treatment. In photodynamic therapy, specific drugs are combined with light to kill cancer cells; these drugs work only when they are activated by certain types of

light. Lasers may be used to shrink or destroy a tumor through the application of heat, perform precise cuts in surgery, or activate a chemical.

Prognosis

A cure for cancer is usually defined as a 5-year survival without recurrence after diagnosis and treatment. Prognosis refers to the patient's likelihood of surviving the cancer. Prognosis is heavily dependent on the cancer's ability to metastasize. The more the cancer spreads to other sites by way of the circulatory or lymph system, the worse the patient's prognosis is. Early diagnosis and treatment usually improve the prognosis by treating the cancer before metastasis has occurred.

Remission refers to a period when the cancer has responded to treatment and is under control. Remission may occur with some cancers, and generally, the patient does not exhibit any manifestations of cancer during that time.

Many cancers are preventable, so health-promoting education (e.g., smoking cessation, proper nutrition, and weight management) is vital to decrease the incidence and prevalence of all cancers. Although the likelihood of these cancers can be diminished with these strategies, cancer can develop in people with no risk factors. This unpredictable development contributes to the mystery and challenges surrounding cancer.

Genetic and Congenital Alterations

Genetic and **congenital** defects are important to understand because of the encompassing nature of the disorders associated with these alterations. Such diseases affect all levels of health care and people in all age groups, by involving almost any tissue type and organs.

Genetics is the study of heredity—the passing of physical, biochemical, and physiologic traits from biological parents to their children. Disorders and genetic mutations can result in serious disability or death and can be transmitted through genetic material to offspring. Genetic disorders may or may not be present at birth. Congenital defects, often referred to as birth defects, usually develop during the prenatal phase of life and are apparent at birth or shortly thereafter. There are three types of genetic diseases: single-gene defects, **multifactorial disorders**, and chromosomal abnormalities (**TABLE 1-8**).

TABLE 1-8 Genetic Disorders and Inheritance

Single-Gene Disorders	Multifactorial Disorders	Chromosomal Disorders
Autosomal Dominant	Anencephaly	Cri du chat syndrome
Adult polycystic kidney disease	Cleft lip and palate	Down syndrome
Familial hypercholesterolemia	Clubfoot	Monosomy X (Turner syndrome)
Huntington's disease	Congenital heart disease	Polysomy X (Klinefelter syndrome)
Marfan syndrome	Myelomeningocele	Trisomy 18 (Edwards syndrome)
	Schizophrenia	

Single-Gene Disorders	Multifactorial Disorders	Chromosomal Disorders
Autosomal Recessive Albinism Color blindness Cystic fibrosis Phenylketonuria Sickle cell anemia Tay-Sachs disease ***X-Linked Recessive*** Duchenne muscular dystrophy Hemophilia A		

Genetics

The cell's instructions and information are carried within its genes. A gene is a segment of **deoxyribonucleic acid (DNA)** that serves as a template for protein synthesis. DNA is a long double-stranded chain of **nucleotides** called "chromosomes." Each nucleotide consists of a five-carbon sugar (deoxyribose), a phosphate group, and one of four nitrogen bases (cytosine, thymine, guanine, or adenine). An estimated 3 billion nucleotides make up the human genome, and each gene can contain hundreds to thousands of these nucleotides. Recall that there are 46 total chromosomes; the 22 sets of paired chromosomes are called **autosomes**, and the remaining two chromosomes are the sex chromosomes (a pair of X chromosomes for females and an X and a Y for males). The representation of a person's unique set of chromosomes is referred to as the **karyotype**, and the physical expression of those genes is called the **phenotype** (e.g., blue eyes). Not all genes in the code are expressed.

Patterns of Inheritance

During reproduction, each parent contributes one set of chromosomes to the fertilized egg. Some characteristics, or traits,

are determined by a single gene (monogenic) that may have many variants (**alleles**). Other traits are determined by multiple genes (polygenic), which are coded on a segment of the chromosome (i.e., locus). An allele is a variant form of a given gene. A person who has identical alleles of each chromosome is **homozygous** for that gene; if the alleles are different, then the person is said to be **heterozygous** for that gene. For unknown reasons, one allele on a chromosome may be more influential than the other in determining a specific trait. The more powerful, or dominant, allele is more likely to be expressed in the offspring than the less influential, or **recessive**, allele. Offspring will express the dominant allele in both homozygous and heterozygous allele pairs. In contrast, offspring will express the recessive allele only in homozygous pairs.

The sex chromosomes (X and Y) can pass on genes when they are linked, or attached, to one of the sex chromosomes. For example, a male will transmit one copy of each X-linked gene to his daughter but none to his son, whereas a female will transmit a copy of her X-linked gene to each offspring, whether male or female. An example of an X-linked disorder is Klinefelter syndrome.

The manifestation of some traits depends on a combination of two or more genes and environmental factors, a condition known as multifactorial inheritance. Examples of traits showing this type of inheritance include height, diabetes mellitus, and obesity.

Learning Points

Punnett Square

A Punnett square is a graph that predicts possible genotypes for a single gene locus of offspring from a specific set of parents. The graph requires that the parent genetic information is known for a particular gene and represents the possibilities of one fertilization event. Dominant genes are represented with capital letters, and recessive genes are represented with lowercase letters (e.g., Aa).

As an example, let's consider eye color. We can determine the offspring's chances of having blue or brown eyes based on the parent's genetic information (**FIGURE 1-28**). As shown in the figure, based on the genetic information of these parents, each offspring would have a 75% chance of having brown eyes and a 25% chance of having blue eyes.

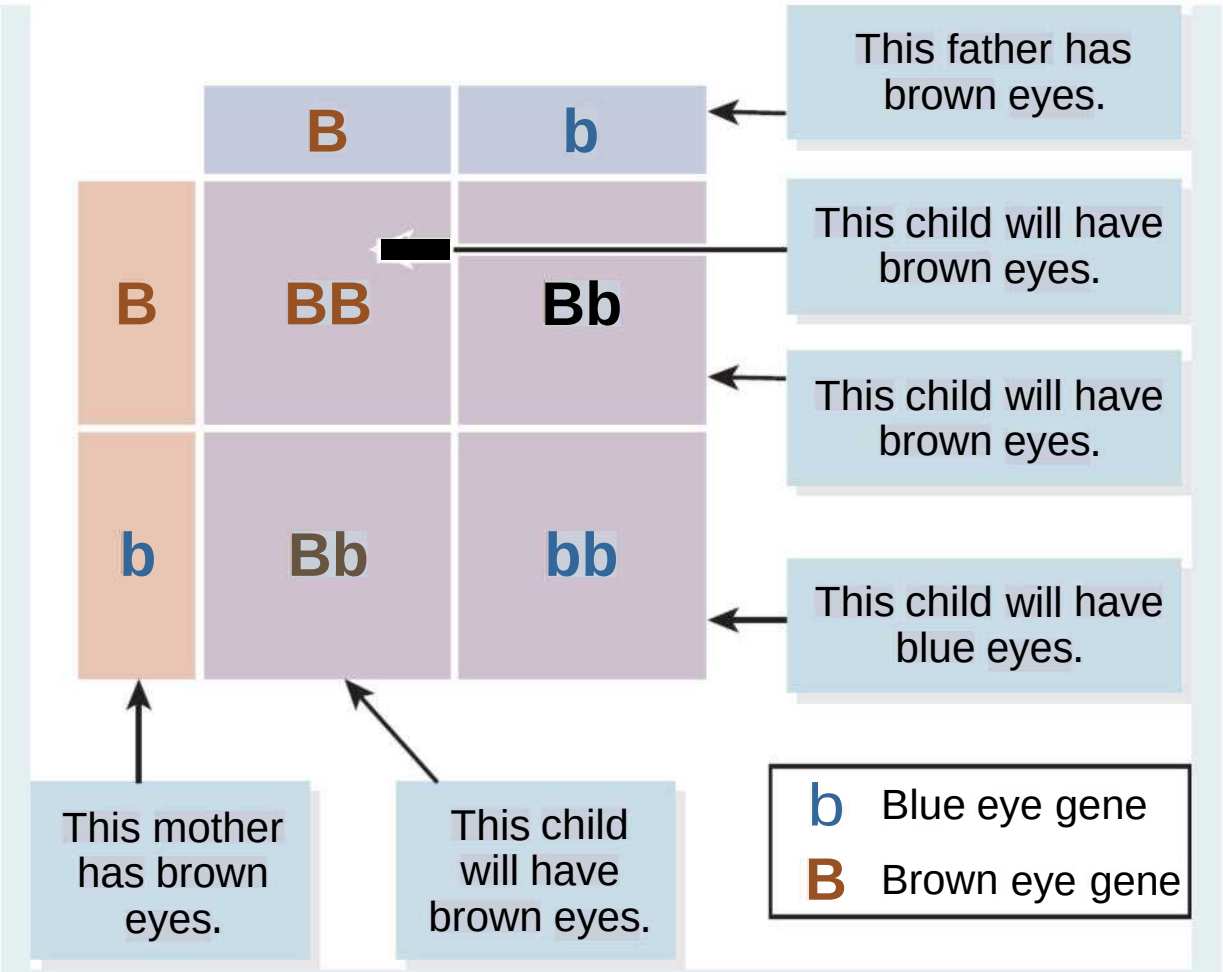


FIGURE 1-28 Punnett square.

Description

application to practice

History

Mrs. Coleman is a 38-year-old African American female who has been admitted to the general surgical floor with a lump in her right breast. She generally has enjoyed good health up to this admission. Mrs. Coleman neither smokes nor drinks alcohol, and she walks for about 20–30 minutes 2–3 times a week in her local park. Her BMI is 26. Approximately 2 months ago, Mrs. Coleman noticed a small lump in her right breast. She gave this finding little attention, assuming that the lump was like the many others she tended to experience around her menses. The lump failed to resolve after her menses, and Mrs. Coleman became concerned when it seemed to grow bigger.

Mrs. Coleman is the mother of two children, 8 and 6 years old. Mrs. Coleman took birth control pills for 5 years after the birth of her second child. Last year she chose to discontinue birth control pill use and turned to an alternative method of birth control.

Mrs. Coleman is the oldest of three children. Her father is alive and well, but her mother died of breast cancer 5 years ago. A family history revealed a strong history of both heart disease and cancer on both sides of Mrs. Coleman's family.

Current Status

On exam, a 2- to 3-cm mass was palpated in the upper quadrant of Mrs. Coleman's right breast. This mass felt firm, was fixed to the chest wall, and was tender to the touch. The remaining breast skin was normal in appearance with no discoloration or retraction of the skin. One node, approximately the size of a pea, was palpated under the right axilla. Palpation of the left breast revealed two 1- to 2-cm soft, movable masses. Mrs. Coleman said that she noticed these lumps in her left breast 2 weeks ago but stated the lumps in her left breast became palpable and bothersome about 12 days from the start of menses. A reproductive history disclosed the onset of menses occurred at the age of 10. There is no history of dysmenorrhea associated with her periods, although Mrs. Coleman states her breasts become tender and lumpy 1 to 2 weeks before her menses. She has had no pregnancies that were delivered by cesarean section. Her one and only Papanicolaou (Pap) smear was done 2 years ago and produced a normal result. The remaining exam findings were unremarkable. Mammography confirmed the presence of a 3-cm mass in the upper quadrant of the right breast and three 1.5-cm masses in the left breast. The results of a bone scan and other diagnostic procedures were negative.

1. Mrs. Coleman is considered to be at increased risk for developing breast cancer. Select all of the following factors that are most positively related to this high-risk profile.
   a. History of breast cancer in family members
   b. History of fibrocystic breast masses
   c. Early onset of menarche
   d. Trauma related to the birth of her children
   e. Ethnicity
   f. Age
   g. BMI of 26
   h. Being premenopausal
2. Which of the following best explains the existence of an enlarged right axillary lymph node in Mrs. Coleman?
   a. The lymph node is the result of an inflammatory reaction that normally occurs with the onset of her current menses.
   b. The existence of the node is the result of an increased strain on the lymphatic system as a result of cellular degeneration.
   c. The lymph node exists to provide nutrients to the rapidly growing cancer cells.
   d. The lymph node is the result of cancer cells spreading to different tissues within the body.

A modified radical mastectomy was performed 3 days later. A histological exam was used to classify the tumor using the TNM staging system. An estrogen receptor assay performed on the removed tissue confirmed that Mrs. Coleman's tumor was estrogen dependent. She returned to her hospital room with a drain in place. Her surgical dressing was dry and intact. She was able to turn, cough, and breathe deeply on her own. Her temperature remained within normal limits after surgery. Progesterone therapy was initiated daily. Ambulation was started on the second postoperative day.

1. Mrs. Coleman's tumor was staged at stage III using the TNM staging system. A pathological exam of the surgically removed tissue sample placed Mrs. Coleman's tumor in category type II. Characterizing and classifying tumors is important for which of the following reasons?
   a. Treatment is based on the knowledge of tumor size, extent, and tissue type.
   b. Tumor staging is useful for studying a number of researchable factors, from survival to treatment response.
   c. A consistent classification system provides a way to categorize individuals with breast tumors for statistical analysis.
   d. All of the above.
2. Which activities by Mrs. Coleman increase her likelihood of a good prognosis?
3. What was the rationale for hormone therapy with Mrs. Coleman?

Autosomal Dominant Disorders

Autosomal dominant disorders are single-gene mutations that are passed from an affected parent to an offspring regardless of sex. These disorders occur with both homozygous (e.g., AA) and heterozygous (e.g., Aa) allele pairs. In most cases, offspring with the homozygous pair will have a more severe expression of the disorder as compared to offspring with the heterozygous pair because the homozygous pair provides a "double dose" of the gene. Autosomal dominant disorders typically involve abnormalities with structural proteins. Examples of autosomal dominant disorders include Marfan syndrome and neurofibromatosis.

Marfan Syndrome

Marfan syndrome is a degenerative generalized disorder of the connective tissue with an incidence of 1 in 5,000 persons (**FIGURE 1-29**). While 3 out of 4 individuals will inherit the condition, some will be the first in their families to develop Marfan syndrome as a

spontaneous mutation. The condition results from a single-gene mutation (*FBN1*) on chromosome 15. This gene provides instructions for making a protein called fibrillin-1. Fibrillin-1 binds to other fibrillin-1 proteins and other molecules to form threadlike filaments called “microfibrils.” Microfibrils provide strength and flexibility to connective tissue as well as store and release growth factors to control growth and tissue repair. The *FBN1* mutation causes excess growth factors to be released, and elasticity in many tissues is decreased; together, these two processes lead to overgrowth and instability of tissues. These defects produce a variety of ocular, skeletal, and cardiovascular disorders.



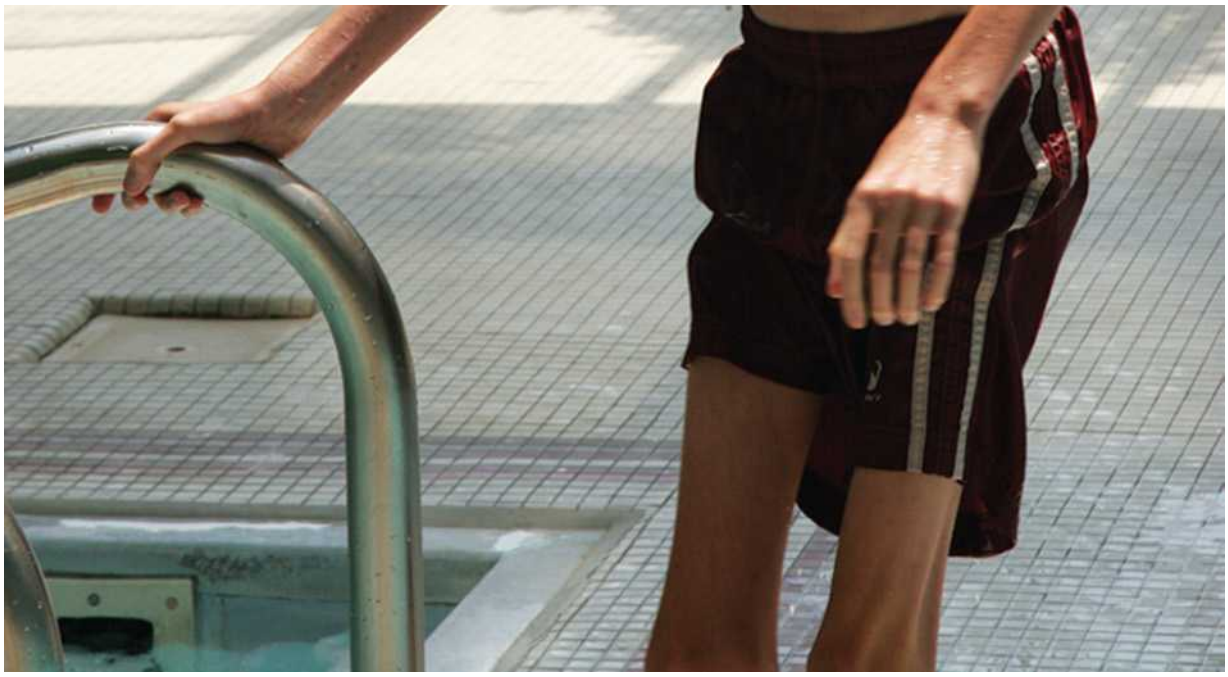


FIGURE 1-29 Marfan syndrome.

Courtesy of Rick Guidotti/Positive Exposure/National Marfan Foundation.

Clinical Manifestations

Clinical manifestations of Marfan syndrome vary widely in their severity, timing of onset, and rate of progression. These manifestations include the following:

- Aortic defects (e.g., coarctation, aneurysm, dissection)—most life threatening
- Myopia (nearsightedness) and lens displacement (ocular hallmark)
- Increased height
- Long extremities
- Arachnodactyly (long, spiderlike fingers)
- Sternum defects (e.g., funnel chest or pigeon breast)
- Chest asymmetry
- Spine deformities (e.g., scoliosis or kyphosis)
- Flat feet
- Hypotonia and increased joint flexibility

- Highly arched palate, crowded teeth, small lower jaw
- Thin, narrow face
- Valvular defects (e.g., redundancy of leaflets, stretching of the chordae tendineae, mitral valve regurgitation, and aortic regurgitation)

Multiple complications can occur with Marfan syndrome, including the following:

- Aortic rupture and internal bleeding
- Weak joints and ligaments that are prone to injury
- Cataracts
- Glaucoma
- Retinal detachment
- Severe mitral regurgitation
- Spontaneous pneumothorax
- Inguinal hernia

Diagnosis and Treatment

A thorough history and physical examination are vital in diagnosing Marfan syndrome. A physical examination would reveal the presence of the hallmark lens displacement and other symptoms of the disease. Diagnostic procedures include a skin biopsy, which would be positive for fibrillin; X-rays, which would confirm the skeletal abnormalities; an echocardiogram, which would reveal the cardiac abnormalities; and a DNA analysis for the gene. The Ghent nosology criteria are used to aid in diagnosis. These criteria consider manifestations and family history. With the Ghent nosology, numerous manifestations are possible, and each manifestation is assigned points (e.g., dural ectasia +2). The criteria and easy-to-use calculators can be found at http://www.marfan.org/dx/home.

Typical treatment focuses on relieving symptoms and may include the following measures:

- Surgical repair of aneurysms and valvular defects

- Surgical correction of ocular deformities
- Steroid and sex hormone therapy to aid in the closure of long bones, thereby limiting height
- Beta-adrenergic blocking agents (which decrease blood pressure and heart rate) to limit complications from cardiac deformities
- Bracing and physical therapy for mild scoliosis and surgical correction for severe cases

Other strategies include avoiding contact sports, supportive care for the patient and family, and frequent checkups.

Neurofibromatosis

Neurofibromatosis is a condition involving neurogenic (nervous system) tumors that arise from Schwann cells and other similar cells. Schwann cells keep peripheral nerve fibers alive. Although most cases of neurofibromatosis are inherited, 30% to 50% occur spontaneously. There are three main types.

Type 1 neurofibromatosis (**FIGURE 1-30**) results from mutations in the *NF1* gene on chromosome 17. This gene provides instructions for making a protein called “neurofibromin” that acts to suppress tumor development. The defect caused by the mutations results in cutaneous lesions that may include raised lumps, café au lait spots (brown pigmented birthmarks), and freckling. Type 1 neurofibromatosis occurs in 1 in 2,500 to 3,000 people.



FIGURE 1-30 Neurofibromatosis type 1.

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Type 2 neurofibromatosis results from mutations in the *NF2* gene on chromosome 22. This gene provides the instructions for making a protein called “merlin,” which acts to suppress tumor development. The defect caused by the mutations results in bilateral acoustic (eighth cranial nerve) tumors that cause hearing loss. Type 2 neurofibromatosis occurs in 1 in 35,000 people.

Schwannomatosis is a rare form of neurofibromatosis that affects fewer than 1 in 40,000 people. In this condition, benign tumors called schwannomas develop usually on the spinal and peripheral nerves. Schwannomatosis is caused by mutations on at least two genes—*SMARCB1* or *LZTR1* tumor suppressor gene located on chromosome 22. Manifestations usually occur between ages 30 and 60. The most common manifestation is chronic pain, which can occur anywhere on the body. Other manifestations include numbness, tingling, weakness, bowel and bladder dysfunction, vision changes, and headaches.

People with neurofibromatosis can be affected in many ways. For example, this genetic disorder is associated with an increased incidence of learning disabilities and seizure disorders. Vision (e.g., optic gliomas and cataracts), skeletal (e.g., scoliosis), and cardiac (e.g., hypertension) issues may also be present, particularly with type 1. Some individuals with type 1 neurofibromatosis may develop cancerous tumors, and neurofibromatosis increases the risk of developing other cancers (e.g., brain and leukemia). The appearance of the lesions may vary between individuals, but the lesions can be disfiguring in some cases.

Diagnosis and Treatment

Genetic testing can be used for diagnosis as well as screening at-risk family members. Although there is no cure for neurofibromatosis, surgeries may be necessary to remove the lesions for palliative or safety reasons. Other symptom management will be needed (e.g., pain management and hearing aids). Targeted tumor therapy using monoclonal antibodies is currently being explored as a treatment option.

Autosomal Recessive Disorders

Autosomal recessive disorders are single-gene mutations passed from an affected parent to an offspring regardless of sex, but they occur only in homozygous (e.g., aa) allele pairs. Those persons with heterozygous pairs (e.g., Aa) are carriers only and exhibit no symptoms. The age of onset for these disorders is usually early in life, and they occur most commonly as deficiencies in enzymes and inborn errors in metabolism. Examples of autosomal recessive disorders include phenylketonuria (PKU) and Tay-Sachs disease.

Phenylketonuria

PKU is a deficiency of phenylalanine hydroxylase (PAH), the enzyme necessary for the conversion of phenylalanine to tyrosine, due to a mutation in the *PAH* gene on chromosome 12. Phenylalanine is a building block of proteins that is obtained in the diet (all proteins and

aspartame), and it plays a role in melanin production. A deficiency of PAH leads to toxic levels of phenylalanine in the blood, causing central nervous system damage. Rarely, the phenylalanine can accumulate when tetrahydrobiopterin (BH4) is not synthesized. BH4 is an essential cofactor for multiple enzymes, including PAH. The occurrence of PKU varies worldwide, but it is found in 1 in 10,000 to 15,000 newborns.

Clinical Manifestations

If untreated, PKU leads to severe intellectual disability. Symptoms develop slowly and can go undetected. Because untreated cases almost always lead to intellectual disability, all newborns in the United States are screened for PKU shortly after birth by testing for high serum phenylalanine levels. If untreated, children can develop the following clinical manifestations:

- Failure to meet milestones
- Microcephaly
- Progressive neurologic decline
- Seizures
- Hyperactivity
- Electrocardiograph (EKG) abnormalities
- Learning disability
- Mousy-smelling urine, skin, hair, and sweat
- Lighter skin and hair than unaffected family members
- Eczema
- Behavioral problems (e.g., hyperactivity disorders)
- Psychiatric disorders

Diagnosis and Treatment

In addition to measuring phenylalanine levels 24 to 48 hours after birth, prenatal screening through chorionic villus sampling and amniocentesis can be done for at-risk women. Initiating treatment early within the first days of life prevents severe manifestations.

However, mild cognitive deficits and mental health issues may result even with appropriate dietary measures. Treatment for PKU involves the consumption of a diet low in phenylalanine. Newborns may be breastfed, but the quantity of breastmilk taken in must be monitored. Special infant formulas are available for supplementation. Dietary restrictions include avoiding proteins and aspartame as well as minimizing starches. Oral medications are available to lower phenylalanine (e.g., sapropterin [Kuvan]). Additionally, gene and enzyme therapy has demonstrated promise in treating PKU. Frequent monitoring of phenylalanine levels is critical to ensure measures are controlling levels.

Tay-Sachs Disease

Tay-Sachs disease is a progressive disorder that results from a mutation in the *HEXA* gene on chromosome 15. This gene provides the instructions for making part of a lysosomal enzyme called hexosaminidase A. Hexosaminidase A is necessary to metabolize certain lipids called "gangliosides." These lipids accumulate in the lysosomes of nerve cells and gradually destroy and demyelinate nerve cells. This destruction of nerve cells leads to progressive mental and motor deterioration, often causing death by 5 years of age.

Tay-Sachs disease is rare in the general population and almost exclusively affects individuals of Jewish descent, of whom about 1 in every 27 is a carrier. The mutation is also more common in certain French-Canadian communities in Quebec, the Old Order Amish community in Pennsylvania, and the Cajun population in Louisiana.

Clinical Manifestations

Tay-Sachs disease is divided into three forms based on symptom onset: infantile (most common), juvenile, and adult (extremely rare). Clinical manifestations of Tay-Sachs usually appear between 3 and 10 months and include the following:

- Exaggerated Moro reflex (startle reflex) at birth
- Apathy to loud sounds by age 3–6 months

- Inability to sit up, lift head, or grasp objects
- Difficulty turning over
- Cherry-red macular spot
- Progressive vision loss
- Deafness and blindness
- Seizure activity
- Paralysis
- Spasticity
- Pneumonia

Diagnosis and Treatment

This genetic disorder is diagnosed by a thorough history and physical examination as well as deficient serum and amniotic hexosaminidase A levels. Because of the devastating nature of Tay-Sachs disease, genetic counseling is important for persons of Jewish ancestry and individuals with a positive family history. No cure for the disease exists; most treatments are supportive. Those supportive approaches include parenteral nutrition (tube feedings), pulmonary hygiene (e.g., suctioning and postural drainage), skincare, laxatives, and psychological counseling.

Sex-Linked Disorders

Genes located on the sex chromosomes cause a variety of genetic disorders. Most **sex-linked** disorders are X-linked. Females are frequently carriers of the trait because they have two X chromosomes, whereas men with the defective X gene will be affected because they have only one X chromosome. X-linked disorders may be either recessive or dominant. Fragile X syndrome is an example of an X-linked disorder.

Fragile X Syndrome

Fragile X syndrome (**FIGURE 1-31**) is an X-linked dominant disorder associated with a single trinucleotide gene sequence (*FMR1*) on the

X chromosome. Normally, this sequence is repeated about 5 to 40 times, but in people with fragile X syndrome, it is repeated more than 200 times, turning off the *FMR1* gene. The *FMR1* gene provides the instructions for making a protein called “familial mental retardation protein” (FMRP), which regulates the production of other proteins and plays a role in synapse development. Synapses are critical in relaying nerve impulses. The more repeats of this gene sequence, the more severe the condition.



FIGURE 1-31 Fragile X syndrome.

© Courtesy of Nikki Deal

Fragile X syndrome is more common and usually more severe in males (it occurs in 1 in 4,000 males and 1 in 8,000 females). This

condition is unique in terms of its inheritance pattern as an X-linked dominant disorder. Males generally are not carriers of X-linked dominant disorders, but they can be carriers of the fragile X mutation and not be affected by the disease. Males can become carriers because they carry a permutation in *FMR1*.

The *FMR1* gene goes through stages as it is transmitted in families. It can begin as a normal gene, then permutates, and then fully mutates. Other X-linked disorders do not have a permutation stage. The affected alleles can have 45 to 54 sequence repeats, termed “gray area alleles.” These alleles are unstable and may result in a permutation. A permutation is defined as 55 to 200 sequence repeats, and a full mutation and disease occur when more than 200 trinucleotide sequence repeats are present.

Clinical Manifestations

Males with permutations will always pass this carrier gene to their daughters, but not the full mutation. While they do not have fragile X syndrome, these males may develop tremors and ataxia with aging. Females with permutations are at risk of transmitting the abnormal genes—the more sequence repeats, the higher the risk and the more likely the permutation will be a full mutation. While they do not have fragile X syndrome, these females have health issues such as menstrual irregularities, infertility, and premature ovarian failure.

Clinical manifestations of fragile X syndrome include the following:

- Intellectual, behavioral, and learning disabilities
- Prominent jaw and forehead
- Long, narrow face with long or large ears
- Connective tissue abnormalities
- Large testes
- Hyperactivity and inattentiveness
- Seizures
- Speech and language delays
- Tendency to avoid eye contact

* Autism spectrum disorders

Diagnosis and Treatment

The average age at diagnosis is 36 months for males and 42 months for females. Diagnosis of fragile X syndrome involves the identification of clinical manifestations and a positive genetic test. No cure for this condition exists, so treatment focuses on controlling individual symptoms. Genetic counseling is appropriate for persons with a positive family history. Behavioral and psychological support may be indicated for both parents and the affected child. Other supportive interventions include physical, speech, and occupational therapy.

Multifactorial Disorders

Most multifactorial disorders result from an interaction between genes and environmental factors. These disorders do not follow a clear-cut pattern of inheritance, but researchers are discovering that most diseases have a multifactorial component. Multifactorial disorders may be present at birth, as with cleft lip or palate, or they may be expressed later in life, as with hypertension. Environmental factors that play roles in these disorders may include any of a number of birth defect–causing agents, such as infections, chemicals, or radiation.

Cleft Lip and Cleft Palate

Cleft lip and palate are birth defects that occur when soft tissues of the lip or mouth do not form properly. Cleft lip and palate may occur either together or separately. These conditions usually develop in the second month of pregnancy, when the fetus's facial structures are forming. Every year in the United States, approximately 2,650 babies are born with cleft palate, and approximately 4,440 babies are born with a cleft lip with or without a cleft palate. Maternal smoking, preexisting diabetes, and seizure medication use (especially in the first trimester) are significant risk factors. Additionally, these defects

are more prevalent in Native Americans and Asian Americans, with African Americans having the lowest prevalence.

Clinical Manifestations

The deformities with cleft lip and palate may be unilateral or bilateral. The severity of the deformity ranges from a mild notch to involvement of the lip, palate, and tongue (**FIGURE 1-32**). Feeding and nutritional issues may occur because of these structural problems, which affect the ability to nurse and eat.



FIGURE 1-32 Cleft lip and palate.

Courtesy of Leonard V. Crowley, MD, Century College.

Diagnosis and Treatment

Clinical manifestations are obvious at birth but can also be detected prior to birth with a prenatal ultrasound. A series of surgeries are performed to close the gap in the lip and palate. Speech therapy and feeding devices can minimize speech delays and nutritional deficits.

Parental support is important to ensure the child's proper care and minimize caregiver stress.

Chromosomal Disorders

Chromosomal disorders are a major category of genetic disorders that result most often from an alteration in chromosomal duplication or number. Oftentimes these disorders occur in utero because of some environmental influences (e.g., maternal age, drugs, and infections). The most vulnerable time for the fetus is at 15 to 60 days' gestation. This period immediately follows fertilization and implantation when much of the cellular differentiation is occurring. More than 60 disorders fall in this category, many of which prompt parents to seek first-trimester abortions. The more common examples of these disorders include trisomy 21, monosomy X, and polysomy X.

Trisomy 21

Trisomy 21, or Down syndrome, is a spontaneous chromosomal mutation that usually results in three copies of chromosome 21, resulting in 47 chromosomes instead of 46 (**FIGURE 1-33**). These extra copies are thought to disrupt the course of normal development. Rarely, individuals with this condition will have 46 chromosomes, but they have an extra chromosome 21 translocated to another chromosome. The most common location for the translocation is on chromosome 14. The risk of this mutation increases with greater parental age and environmental teratogen exposure. Trisomy 21 occurs in about 1 in 800 births.



FIGURE 1-33 Down syndrome.

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Clinical Manifestations

Clinical manifestations can vary widely and are apparent at birth and often in utero. These manifestations typically include the following characteristics:

- Hypotonia
- Distinctive facial features (e.g., low nasal bridge, epicanthic folds, protruding tongue, low-set ears, and small, open mouth)
- Congenital heart defects
- Single crease on the palm (simian crease)
- White spots on the iris
- Varying intellectual disability that typically worsens with age
- Developmental delay

- Behavioral issues (e.g., inattention, obsessive/compulsive behavior, stubbornness, and tantrums)
- Strabismus and cataracts
- Poorly developed genitalia and delayed puberty

Early death can occur due to cardiac and pulmonary complications (e.g., hypertension and pneumonia). Persons with trisomy 21 have increased susceptibility to leukemia and infections. These individuals are also at increased risk for developing gastrointestinal (e.g., intestinal obstruction, gastroesophageal reflux disease, and celiac disease) and thyroid (e.g., hypothyroidism) issues. Approximately half of all persons with trisomy 21 will develop Alzheimer's disease, usually starting around age 50.

Diagnosis and Treatment

Clinical manifestations in fetuses with trisomy 21 can be detected using four-dimensional ultrasounds. Other prenatal testing includes amniocentesis and serum hormone levels. No cure for trisomy 21 exists. Treatment strategies focus on symptom and complication management.

Monosomy X

Monosomy X, or Turner syndrome, is the result of a deletion of part or all of an X chromosome (**FIGURE 1-34**). This abnormality usually occurs spontaneously during the formation of reproductive cells (eggs and sperm) in the parents. It is not completely understood which genes on the X chromosome are associated with the features of Turner syndrome. This condition occurs in about 1 of every 2,500 live births but is much more common among pregnancies that do not survive to term.

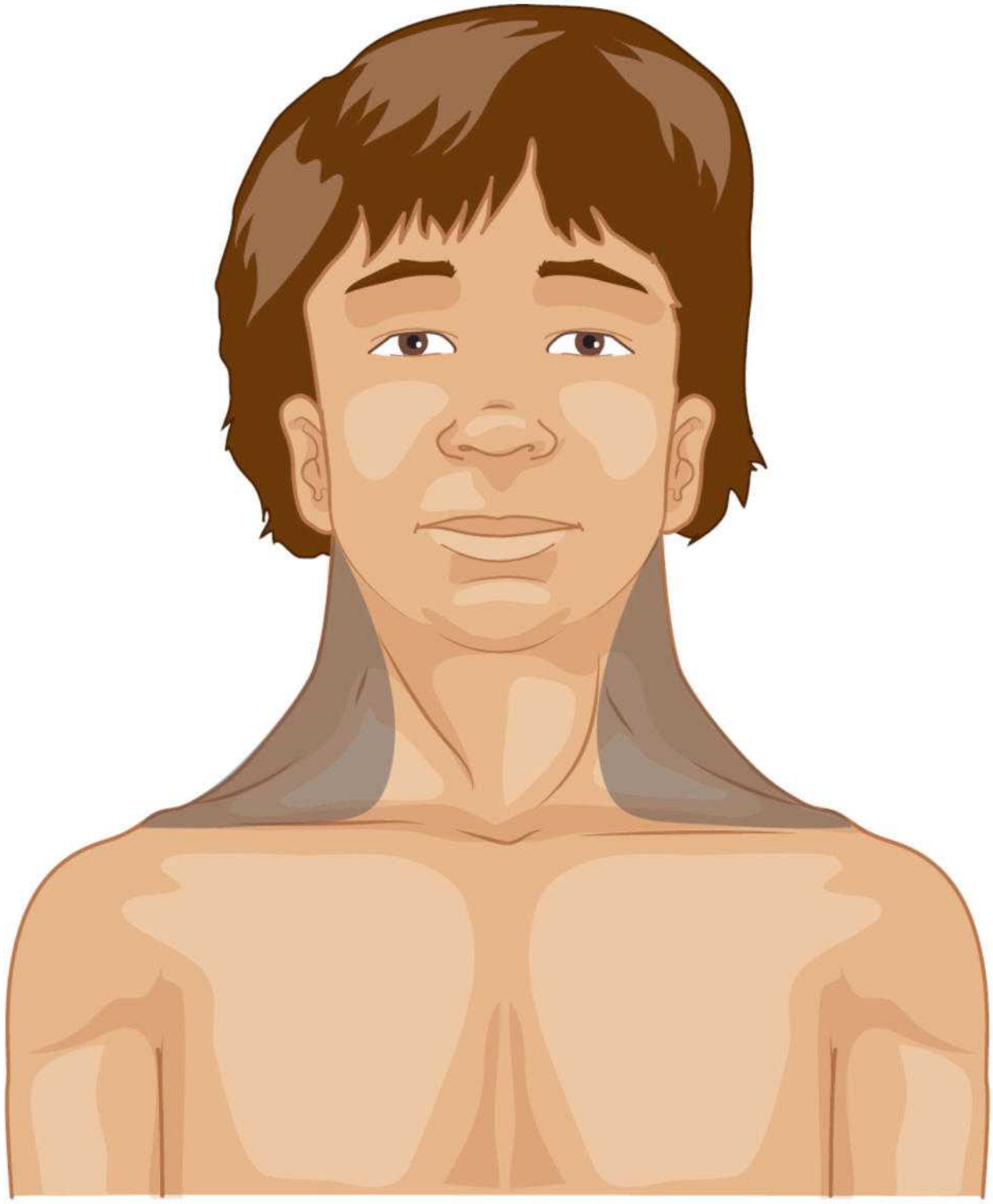


FIGURE 1-34 Turner syndrome.

Clinical Manifestations

Turner syndrome affects only females. Affected females develop gonadal streaks instead of ovaries; therefore, they will not menstruate. Other clinical manifestations may vary but often include the following:

- Short stature
- Lymphedema (swelling) of the hands and feet
- Broad chest with widely spaced nipples
- Low-set ears
- Small lower jaw
- Drooping eyelids
- Increased weight
- Small fingernails
- Webbing of the neck
- Coarctation of the aorta
- Horseshoe kidney
- Ear infections
- Reduced bone mass

Complications of monosomy X include vision (e.g., cataracts), skeletal (e.g., osteoporosis, pathological fractures, and scoliosis), hearing, metabolic (e.g., diabetes mellitus and thyroid), cardiac (e.g., hypertension and valvular defects), and renal (e.g., kidney failure) issues.

Diagnosis and Treatment

Diagnosis is usually accomplished through a history, physical examination, serum hormone levels, and genetic testing (either before or after birth). To treat Turner syndrome, healthcare providers administer female sex hormones to promote the development of secondary sex characteristics and skeletal growth. Growth hormones may also be administered to improve skeletal growth. Identification of this condition is often delayed until late childhood or early adolescence if the clinical presentation is more subtle, but

chromosomal analysis can confirm the diagnosis. Early treatment allows for early hormone replacement to minimize problems and detect complications.

Polysomy X

Polysomy X, or Klinefelter syndrome, is a relatively common abnormality that results from an extra X chromosome, which creates an XXY sex chromosome. Because of the presence of a Y chromosome, persons with this syndrome are male. Klinefelter syndrome affects 1 in 500 to 1,000 newborn males. The syndrome usually becomes apparent at puberty when testicles fail to mature, rendering affected boys infertile. The extra copies of the X chromosome interfere with male sexual development.

Clinical Manifestations

Clinical manifestations (**FIGURE 1-35**) of Klinefelter syndrome include the following:

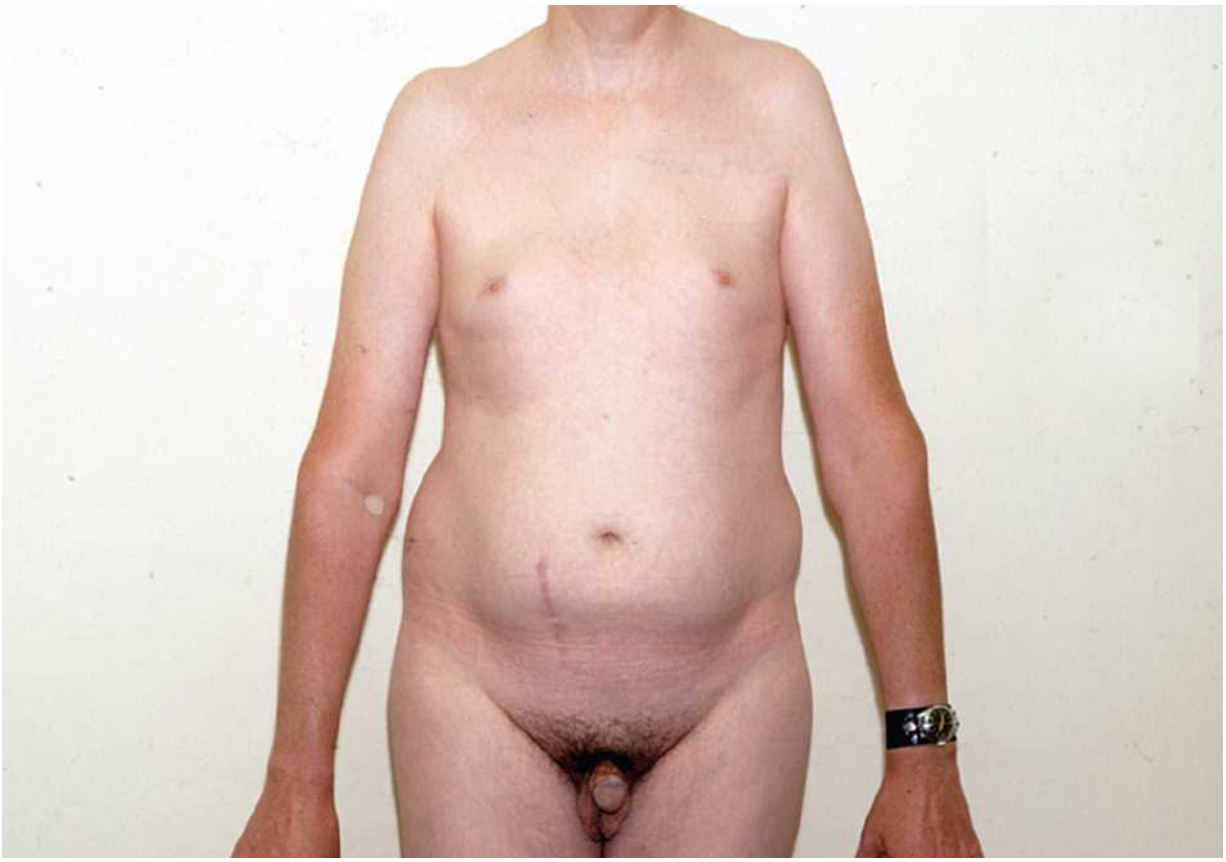




FIGURE 1-35 Klinefelter syndrome.

Courtesy of www.dermnet.com

- Small penis, prostate gland, and testicles
- Sparse facial and body hair
- Sexual dysfunction (e.g., impotence, decreased libido)
- Gynecomastia (female-like breasts)
- Long legs with a short, obese trunk
- Tall stature
- Behavioral problems
- Learning disabilities
- Delayed speech and language development
- Increased incidence of pulmonary disease and varicose veins

Other problems that can develop include osteoporosis and breast cancer.

Diagnosis and Treatment

Diagnostic procedures consist of a history, physical examination, hormone levels, and chromosomal testing. Treatment includes male hormone replacement to promote secondary sex characteristics. A mastectomy may be performed in cases of gynecomastia and breast cancer. Psychological counseling and support may be beneficial to the patient and the parents.

application to practice

A 12-year-old male Caucasian presents with shortness of breath on exertion. His parents report that they noticed he was having trouble keeping up with his peers at baseball practice. Upon exam, a systolic murmur was noted, and lung sounds were clear. He is in the 95th percentile for height but in the 10th percentile for weight. Parents deny any recent respiratory infections. Routine blood tests were within normal limits.

1. What is some potential diagnosis for this patient?
   a. Marfan syndrome
   b. Turner syndrome
   c. Klinefelter syndrome
   d. Fragile X
   e. Lung cancer
2. Which of the following additional tests should be ordered? (Select all that apply)
   a. Genetic testing
   b. Chest X-ray
   c. Biopsy
   d. Echocardiogram
   e. Eye exam
3. Based on the likely diagnosis, treatment would include which of the following?
   a. Chemotherapy, radiation, and surgical excision
   b. Monitoring and symptom management
   c. Hormone replacement

SUMMARY

Cells are the basic units of life, and they face many challenges in their struggle to survive. These challenges include hypoxia, nutritional changes, infection, inflammation, and chemicals. Cells adapt to the challenges in an attempt to prevent or limit damage as well as death. This adaptation may be reversible or permanent.

Neoplasms arise from abnormal cellular proliferation or differentiation. They can be either benign or malignant. Benign neoplasms are more differentiated; therefore, they are more like the parent cells. Benign tumors are less likely to cause problems in the host or metastasize except in terms of location. Malignant tumors are less differentiated; therefore, they are more like the parent cells. Malignant tumors are more likely to cause problems in the host and metastasize.

Genetic and congenital disorders can develop from factors that disrupt normal fetal development or interact with defective genes. These factors, or **teratogens**, can include radiation, infections, or chemicals. Genetic and congenital disorders may be present at birth or may not appear until later in life. Exploring these basic cellular and genetic concepts and issues lays the foundation for understanding where disease begins.

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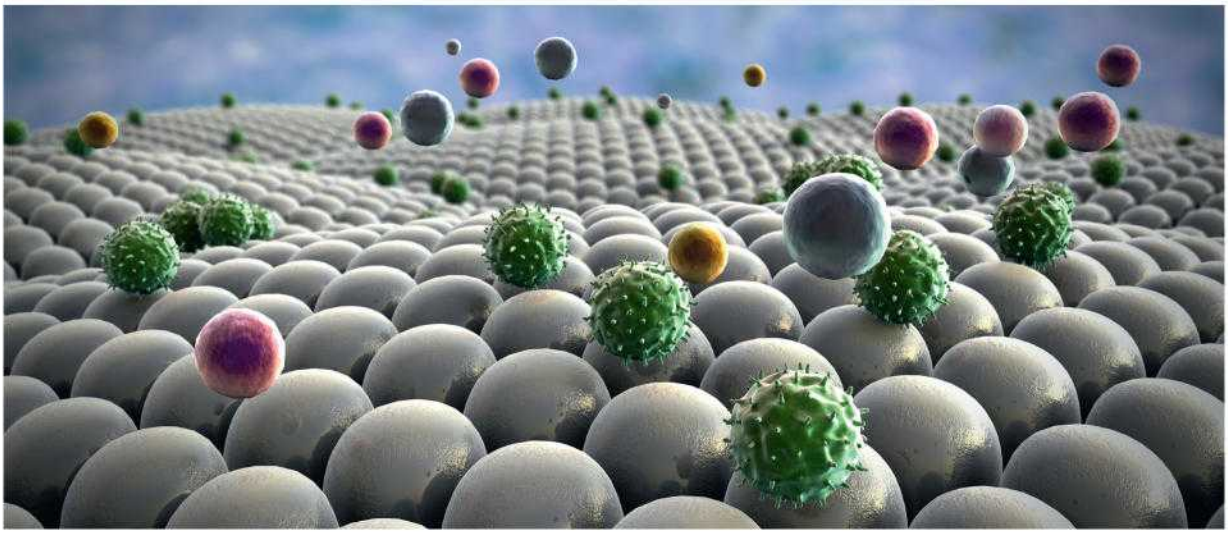
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CHAPTER 2

Immunity

LEARNING OBJECTIVES

- Describe the effects of stress on the body.
- Explain the role of the body's normal defenses in preventing disease.
- Compare and contrast the immune response and the inflammatory response.
- Differentiate between innate and adaptive immunity.
- Compare and contrast the types of hypersensitivity reactions.
- Explain immunodeficiency and explore an example.
- Explain autoimmune responses and explore an example.
- Identify factors that enhance and impair the body's defenses.

KEY TERMS

acquired immunity
active acquired immunity
acute tissue rejection
adaptive or acquired defenses
alarm
allogeneic
antibody-producing cell
antigen
autoimmune
autologous
B cell
chronic tissue rejection
cytotoxic cell
effector cell

exhaustion
general adaptation syndrome
graft-versus-host rejection
host-versus-graft rejection
hyperacute tissue rejection
hypersensitivity
immunodeficiency
inflammatory response
innate immunity
interferon
killer T cell
local adaptation syndrome
memory cell
opportunistic infections
passive acquired immunity
primary immunodeficiency
pyrogen
regulator cell
resistance
secondary or acquired immunodeficiency
suppressor T cell
syngeneic
systemic lupus erythematosus (SLE)
T cell
T-helper (Th) cell
type I hypersensitivity
type II hypersensitivity
type III hypersensitivity
type IV hypersensitivity
xenogenic

A variety of entities that have the potential to cause harm constantly bombard the human body. These entities include things such as stressors, organisms, and environmental toxins. The body's ability to resist damage and deal with these events will determine their effects. Humans can arm themselves with an arsenal

of health behaviors (e.g., proper nutrition, exercise, adequate sleep, hand washing, skincare, vaccinations) that can help defend against these adversaries, yet humans often increase their vulnerability to harm through other behaviors (e.g., smoking, drug misuse, alcohol abuse, exposure to crowds or sick individuals). All patients we encounter as healthcare providers are affected by this constant state of warfare. Many of these patients have either fallen victim to such an attack or are attempting to defend against it. Healthcare providers can identify those persons at risk or under attack and help them take up arms to defeat these persistent adversaries.

Stress

Stress is a universal experience of human existence that can negatively affect the body's fragile homeostasis state (see the *Introduction to Pathophysiology* section at the beginning of the text). Stress can contribute directly to the development or exacerbation of disease, as well as to the propensity to engage in negative behaviors, such as smoking and drug abuse, as individuals attempt to cope with this state. Stress can arise from many events, including those that may be otherwise perceived as positive (e.g., weddings and vacations). Understanding the nature of stress and the effects that it can have on the body is vital for healthcare providers in their interactions with patients.

The Stress Response

Hans Selye first described the bodily changes associated with stress in the 1930s. He noted that the body responds to any stimuli, or stressor, with a series of nonspecific events (**FIGURE 2-1**). Selye described this protective stress response as the **general adaptation syndrome**, referring to a cluster of systemic manifestations that represent an attempt to cope with a stressor. Several factors can affect adaptation, including natural reserves, time, genetics, age, gender, health status, nutrition, sleep–wake cycles, hardiness, and psychosocial factors.

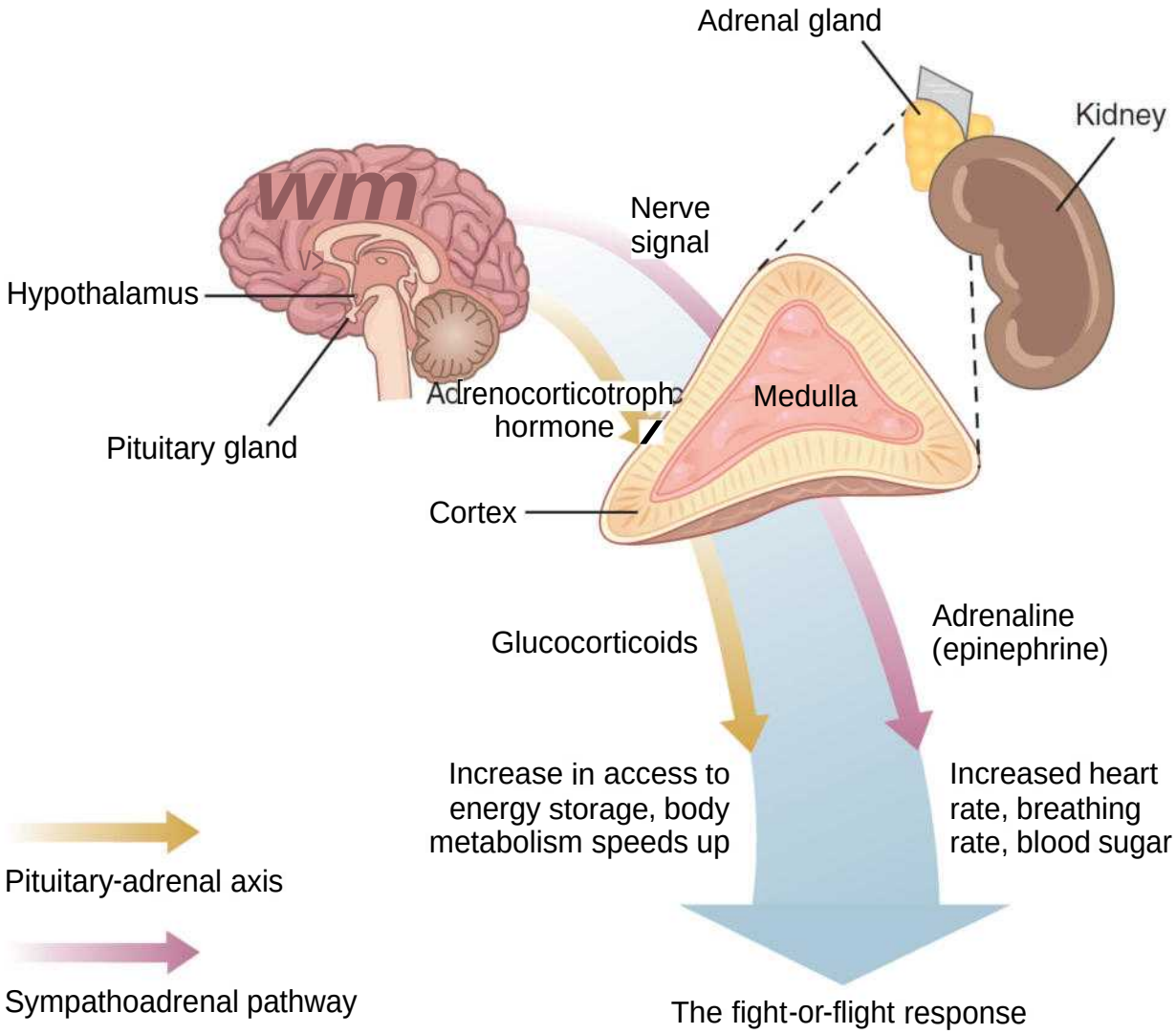


FIGURE 2-1 Physiological response to stress.

Description

The general adaptation syndrome includes three stages—**alarm**, **resistance**, and **exhaustion** (**FIGURE 2-2**). The alarm stage is characterized by the generalized stimulation of the sympathetic nervous system, resulting in the release of catecholamines and cortisol, also known as “the fight-or-flight response.” In the resistance stage, the body chooses the most effective and advantageous defense. Cortisol levels and the sympathetic nervous system return to normal, causing the fight-or-flight symptoms to disappear. The body either adapts or alters its workings in an attempt to limit problems or become desensitized to the stressor. Stress management techniques

(e.g., meditation and relaxation) can assist in this desensitization process. However, the exhaustion phase is initiated if the stressor is prolonged or overwhelms the body. During this phase, the body becomes depleted and damage may appear as homeostasis can no longer be maintained through compensatory mechanisms. As the body's defenses are utilized, disease or death results. Diseases and ailments that have been attributed to stress include anxiety, depression, headaches, insomnia, infections, and cardiovascular disease (**FIGURE 2-3**).

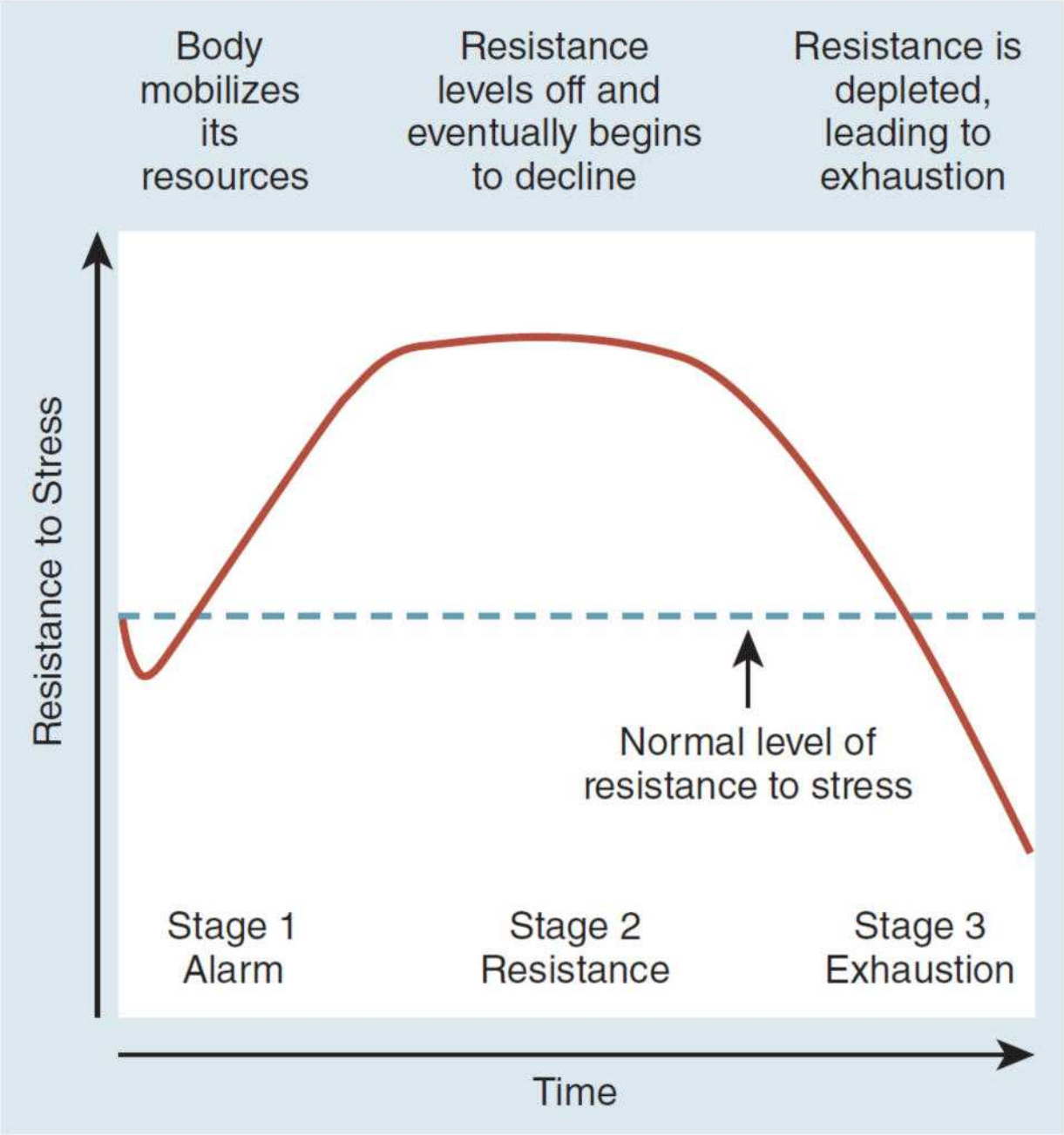


FIGURE 2-2 General adaptation syndrome.

Description

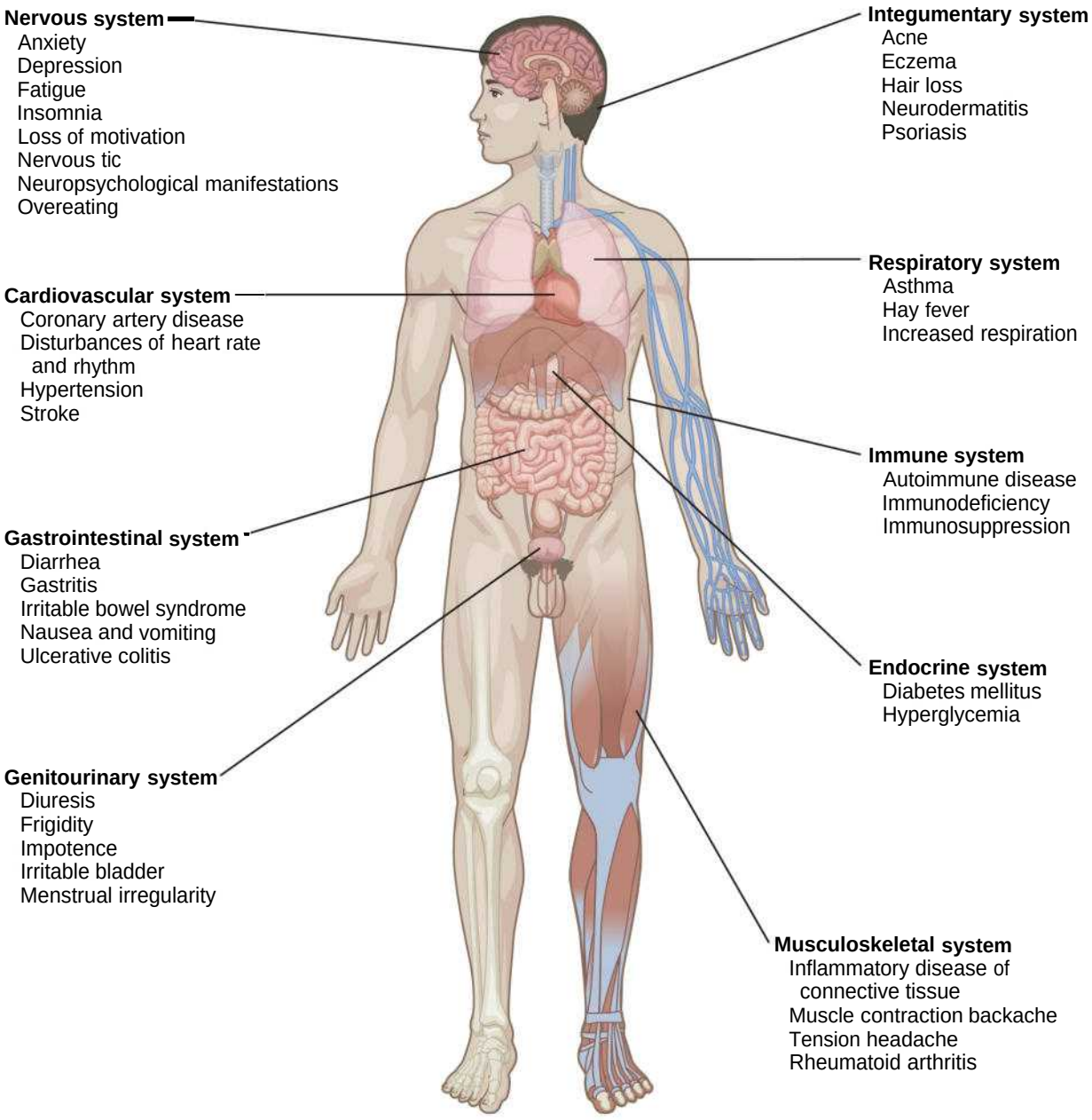


FIGURE 2-3 Effects of stress.

Description

Emerging Research: Work Stress and Sleep Disturbances

Is stress at work causing you to have trouble sleeping? If so, this issue may be more serious than you think. Impaired sleep is the most common problem associated with work stress. Taken together, work stress and impaired sleep are linked to a threefold higher risk

of cardiovascular death in employees with hypertension (Li et al., 2019). One-third of the working population has hypertension. In a study of nearly 2,000 hypertensive workers aged 25 to 65 without cardiovascular disease or diabetes, people with both work stress (defined as high demand and low control) and poor sleep (defined as difficulty falling asleep and/or maintaining sleep) had a three times greater likelihood of death from cardiovascular disease than those workers with no work stress and good sleep. People with work stress alone had 1.6-fold higher risk, and those people with poor sleep alone had a 1.8 higher risk. The impact of work stress on nurses and other health professionals and frontline workers reached a critical point during the COVID-19 pandemic. In nurses across the world, the prevalence of stress was 43%, sleep disturbances was 43%, depression was 35%, and anxiety was 37% (Maqbali, Sinani, & Al-Lenjawi, 2021). Additionally, hypertension was the most prevalent comorbidity reported by healthcare workers who worked the COVID-19 frontlines (Chutiyami et al., 2022).

Stress, whether acute or chronic, directly increases cardiovascular risk because it triggers the release of adrenaline and cortisol. These stress hormones increase blood glucose, cholesterol levels, coagulation, and vasoconstriction, all of which can cause cardiovascular disease and death. Impaired sleep also triggers the stress response, further worsening the cardiovascular risk.

Healthcare professionals should inquire about stress and sleep as a part of their regular assessment of patients, so that targeted strategies (e.g., antihypertensive agents, cholesterol-lowering agents, and lifestyle changes) can be employed early to prevent cardiovascular-related death (e.g., from myocardial infarction and stroke). Additionally, healthy lifestyle choices (e.g., smoking cessation, weight loss, moderate alcohol consumption, stress reduction, proper nutrition, and adequate sleep) can be emphasized for those individuals who are hypertensive, experience work stress, and/or are having sleep difficulties. Employers can support overall health by creating a culture of health through workplace initiatives (e.g., providing access to gyms, incentive programs for healthy behaviors or goals, reimbursing preventive health services, on-site clinics, stress-reduction programs, banning tobacco use at work, offering healthy food and snack options on-site) (Centers for Disease Prevention and Control [CDC], 2017).

The **local adaptation syndrome** is the localized version of the general adaptation syndrome. In this syndrome, the body attempts to limit the damage associated with the stressor by confining the stressor to one location. An example of this response can be seen in the local inflammatory reaction that results from tissue trauma. The **inflammatory response** is discussed in an upcoming section.

Although the stress response is predictable to some extent, individual variability exists due to numerous conditioning factors—for example, genetics, age, gender, life experiences, dietary status, and social support. The positive presence of these factors can limit or eliminate the likelihood of damage, disease, or death. Likewise, the

implementation of one or more coping strategies can minimize and eliminate negative stress effects. These strategies include lifestyle modifications, such as physical activity, adequate sleep, and optimal dietary status. Other strategies include relaxation, distraction, and biofeedback.

Unfortunately, individuals may occasionally use maladaptive coping strategies instead of these kinds of positive strategies. Such maladaptive strategies cause more problems than benefits; they include activities such as smoking, substance abuse, and overeating. Healthcare professionals can assist patients in replacing those negative strategies with more positive ones.

Immunity

The body is under constant assault by life-threatening microbes. Although the vast majority of microbes are harmless, some are not. The immune system is responsible for protecting the body against, and eliminating, an array of microorganisms (e.g., bacteria, viruses, fungi, protozoans, parasites, prions), environmental toxins (e.g., chemicals, pollution, metals, pesticides, drugs), and other foreign particles (e.g., splinters, ingested or inhaled foreign bodies). Additionally, the immune system removes damaged or dead cells as well as destroys cancer cells. It provides this protection through two major actions—defending and attacking. Thus, a properly functioning immune system is essential for survival.

The immune system functions through multiple layers and processes, including innate defenses (e.g., skin, mucous membranes, phagocytes, and the inflammatory response), adaptive defenses (e.g., cellular and humeral immunity), and the lymphatic system. Fundamental to a properly functioning immune system is the ability to recognize and respond to a foreign agent, or **antigen**. Some immune cells circulate constantly, always on alert for an invasion, whereas others remain passively in tissue and organs, waiting to be activated (TABLE 2-1). Additionally, some of the body's structures serve as barriers to antigens, preventing their invasion.

TABLE 2-1 Major Components of the Immune System

Antigen	A foreign agent that triggers the production of antibodies by the immune system.
Antibody	A protein used by the immune system to identify and neutralize foreign agents, such as viruses and bacteria. Unlike immunoglobulins, a protein floats in the blood and does not have a transmembrane.
Autoantibody	An antibody made by the immune system that attacks an individual's

	own proteins.
Immunoglobulin	A protein used by the immune system to identify and neutralize foreign agents, such as viruses and bacteria. Unlike antibodies, an immunoglobulin attaches to the B cell's membrane and has a transmembrane.
Thymus	A gland located in the anterior superior mediastinum; the source of T lymphocytes and thymosins.
Lymphatic tissue	Connective tissue containing many lymphocytes. It transports immune cells, antigen-presenting cells, fatty acids, and fats; it also filters body fluids.
Bone marrow	Soft, fatty tissue found inside of bones; it contains stem cells and leukocytes.

Cells

Neutrophils	Infection-fighting agents, which are usually the first to arrive on the scene of an infection. These cells are attracted by various chemicals released by infected tissue; they escape from the capillary wall, migrate to the site of infection, and phagocytize microorganisms.
Basophils	White blood cells that bind immunoglobulin E (IgE) and release histamine in anaphylaxis.
Eosinophils	White blood cells involved in allergic reactions.
Monocytes	White blood cells that replenish macrophages and dendritic cells in normal states and respond to inflammation by migrating to infected tissue to become macrophages and dendritic cells; their conversion elicits an immune response.
Macrophages	White blood cells within tissues, produced by differentiation of monocytes; they phagocytize and stimulate lymphocytes and other immune cells to respond to pathogens.
Mast cells	Connective tissue cells that contain histamine, heparin, hyaluronic acid, slow-reacting substances of anaphylaxis, and serotonin.
B cells (B lymphocytes)	Cells that mature in the bone marrow, where they differentiate into memory cells or immunoglobulin-secreting (antibody) cells. B cells eliminate bacteria, neutralize bacterial toxins, prevent viral reinfection, and produce the immediate inflammatory response.

Memory B cells	B cells that stimulate a quick response with subsequent exposures to an antigen; they recognize (recall) the antigen as foreign, leading to rapid antibody production.
Plasma cells	White blood cells that develop from B cells and produce large volumes of specific antibodies.
T cells (T lymphocytes)	Produced in the bone marrow and mature in the thymus—hence “T” cell. They include two major types that work to destroy antigens: regulator cells and effector cells.
Killer T cells	T cells that destroy virus-infected cells by releasing lymphokines that degrade cell walls; they are also called cytotoxic cells and effector cells.
Helper T cells	Regulator cells that activate, or call up, B cells to produce antibodies.
Natural killer lymphocytes	Cells that destroy cancer cells, foreign cells, and virus-infected cells.

Chemical Mediators

Complement	A group of inactive proteins in the circulation that, when activated, stimulate the release of other chemical mediators, promoting inflammation, chemotaxis, and phagocytosis.
Histaminev	Released by mast cells and basophils, especially during allergic reactions, triggering the inflammatory response. Histamine increases the permeability of the capillaries to white blood cells and other proteins, allowing them to engage foreign invaders in the infected tissues.
Kinins (e.g., bradykinin)	Induce vasodilation and contraction of smooth muscle.
Prostaglandins	A group of lipid compounds that have a variety of effects, including constriction or dilation of vascular smooth muscle cells, control of cell growth, and sensitization of spinal neurons to pain.
Leukotrienes	Fatty molecules of the immune system that contribute to contraction of bronchiolar smooth muscle.
Cytokines (messengers)	Small cell-signaling protein molecules that are extensively involved in intracellular communication; they include interleukins, interferons, and lymphokines.
Tumor necrosis factor (TNF)	A group of cytokines that can cause cell death (apoptosis).

Chemotactic factors	Attract phagocytes to the area of inflammation.

Innate Versus Adaptive Immunity

The immune system takes multiple approaches to protect the body from antigens, including the use of innate and adaptive defenses. **Innate immunity** provides immediate protection and is nonspecific, meaning it provides protection against all invaders. Adaptive or **acquired immunity** can take 7 to 10 days to provide protection and is specific to the antigen.

Innate Immunity

Barriers

The first innate or nonspecific approach relies on physical and chemical barriers that indiscriminately protect against all invaders. The most prominent barriers used in this approach are the skin and mucous membranes. The skin is a thick, impermeable layer of epidermal cells overlying a rich vascular layer known as the “dermis.” As newly produced skin cells push the dead ones outward, the dead cells produce a waterproof layer because of the keratin inside them.

Although the skin does protect the human body from microbe invasions, some passageways (respiratory, digestive, and genitourinary tracts) allow direct access to the body’s interior. These passageways are lined with a protective mucous membrane that is not as thick as skin but does provide a moderate layer of protection. The mucous membranes are made up of epithelial cells that are produced in the inner layer and rapidly push their way to the outer layer; the continuous shedding of this top layer prevents microorganisms from remaining on these surfaces. Additionally, fluids and secretions mechanically wash these surfaces of microorganisms and other foreign substances.

The physical barriers also include chemical barriers to prevent invasion. The skin, for example, produces a slightly acidic substance (hyaluronic acid) and proteins (cathelicidins and defensins) that inhibit bacterial growth. Hydrochloric acid in the stomach destroys many

ingested bacteria. Tears and saliva contain lysozyme, an enzyme that dissolves bacterial cell walls.

Emerging Research: Human Microbiome Project

The Human Microbiome Project (HMP) was launched in 2007 by the National Institutes of Health to generate research resources and expertise needed to study the microbial communities that live in and on our bodies and play a role in our health and disease (National Institutes of Health [NIH], 2020). The HMP serves as a "road map" for discovering the roles that these microorganisms play in health, nutrition, immunity, and disease. A primary goal of the HMP is to characterize these innate microorganisms in terms of their DNA sequence (i.e., metagenomics) and metabolic capacities. Until the HMP, these microorganisms were largely unstudied.

Once the initial phase of characterization was complete, the second phase created integrated data sets of multiple biological properties from both the microbiome and the host over time in people with specific microbiome-associated diseases. The intention was that these data sets be used to develop community resources to evaluate these properties and gain new understanding of health and disease. To date, some of the HNP's major accomplishments include the following:

- Sequencing of 3,000 reference bacterial genomes from the human body
- Comprehensive profile of the microbiome from more than 300 healthy humans
- World's largest metagenome sequence data set from one human cohort
- World's only complete data set on the bacterial, fungal, viral, and protist (a heterogeneous group of microorganisms that are either a single cell or groups of similar cells joined together) community composition from one human cohort
- Integrated data sets of metagenomic, transcript, protein, and metabolite profiles from both microbiome and host in multiple human cohorts
- Software and online resources to aid in the study of the microbiome
- IHMP studies and data sets related to preterm birth, inflammatory bowel disease, and prediabetes
- More than 830 scientific papers by the end of 2022 (NIH, 2020)

A variety of microorganisms reside within and on the human body, which are collectively referred to as the "human microbiome" or "normal flora." These innate microorganisms outnumber the human cells 10 to 1. The microbiome aids the other barriers of the immune system by combating the growth of disease-producing microorganisms in two ways: by secreting chemicals and proteins as

well as by blocking pathogen attachment. The microorganisms of the microbiome do not generally cause disease unless overgrowth occurs or the individual's immune system is compromised.

The body's physical and chemical barriers are not completely impenetrable. Indeed, tiny breaks in the skin or in the lining of the respiratory, digestive, or genitourinary tracts may permit an antigen invasion. Additional bloodborne innate defenses are in place to respond to those antigens, including the inflammatory response, **pyrogens**, **interferons**, and complement proteins.

Inflammatory Response

Damage or trauma to body tissue, regardless of the cause, triggers a series of reactions referred to as the "inflammatory response." The inflammatory response is nondiscriminatory, meaning that the same sequence of events occurs regardless of the cause and that no memory is involved. The acute phase of the inflammatory response starts immediately after the injury and continues until the threat is eliminated (usually in hours to days). The chronic phase is initiated if the acute phase fails to resolve the issue; it lasts until healing and repair are complete (usually in weeks to months).

Both phases cause local and systemic effects because of the vascular response and the release of inflammatory mediators. The acute local inflammatory reaction is characterized by erythema (redness), edema (swelling), heat, and pain at the site of injury (**FIGURE 2-4**). This response is triggered by a set of mediators. Mast cells are a type of white cell (granulocyte) that is found in connective tissue throughout the body. Following the activation of cell surface receptors on mast cells, preformed mediators are released through degranulation (cellular release of molecules from secretory vesicles), including histamine, which stimulates vasodilation. Mast cells also promote the synthesis of new mediators, including prostaglandins, which stimulate pain receptors and vasodilatation as well as increase permeability, and leukotrienes, which stimulate vasodilation and increase permeability.

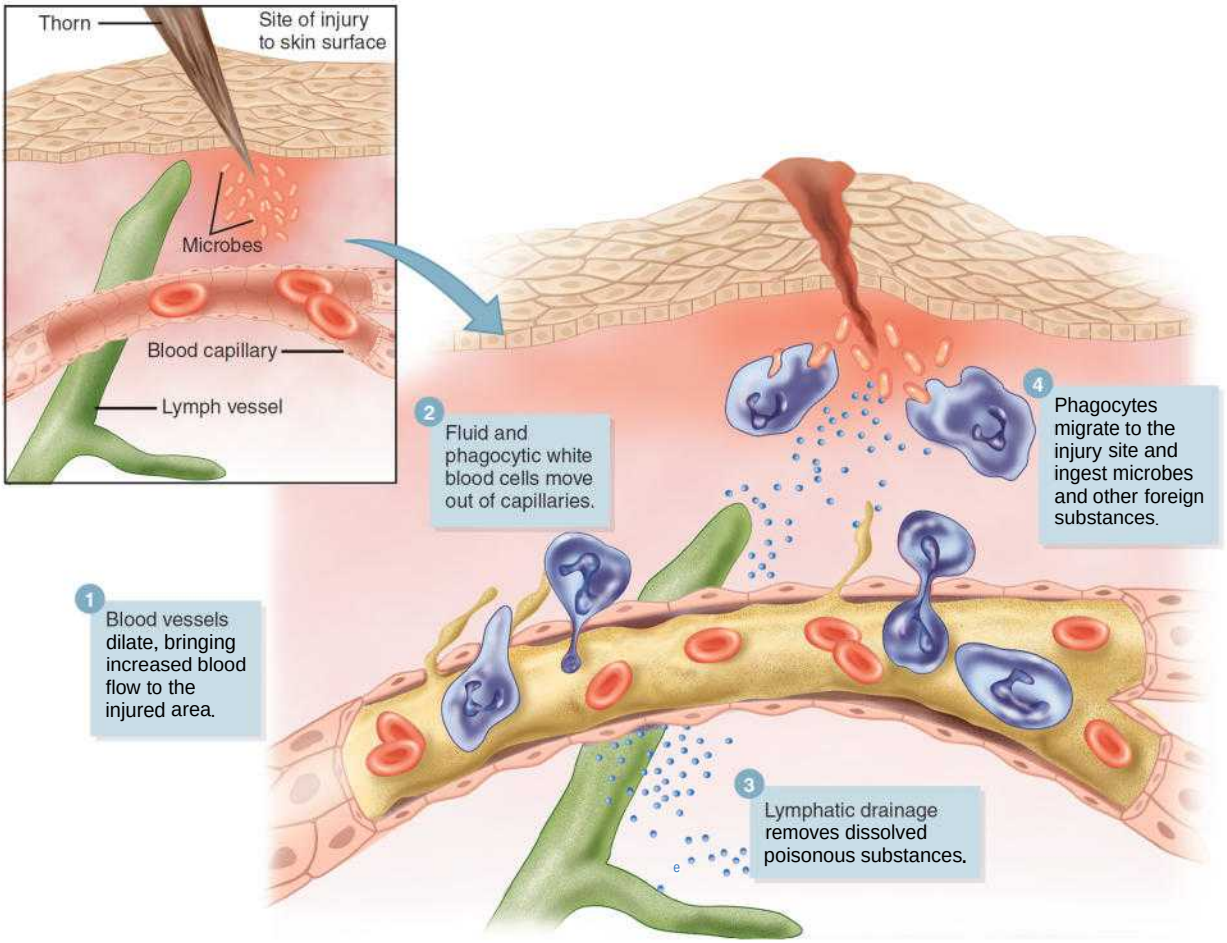


FIGURE 2-4 Inflammatory response.

Description

Immediately after an injury, arterioles in the affected area briefly go into spasm and constrict to limit bleeding and the extent of injury. This vasoconstriction is immediately followed by vasodilation, which increases blood flow to the injured area in an attempt to dilute toxins and provide the area with essential immune cells (e.g., neutrophils and monocytes), nutrients, and oxygen. The vasodilation increases capillary permeability, leading to edema. As permeability increases, leukocytes line the vessel wall in preparation for migration into the surrounding tissue. While the leukocytes are lining the vessel walls (i.e., margination), endothelial cells in the vessel walls react to biochemical mediators that cause these vessels to retract. This retraction gives the leukocytes enough room to migrate into the

interstitial space (i.e., transmigration) and begin the cleanup process of phagocytosis—that is, the engulfing and digestion of foreign substances and cellular debris. In conjunction with phagocytosis, fibrinogen is transformed into fibrin, which is used to wall off the injured area so that foreign substances are contained and cannot spread through the body. A meshwork of new cells forms to provide support for the healing process. Blood clotting begins if blood vessels have been damaged.

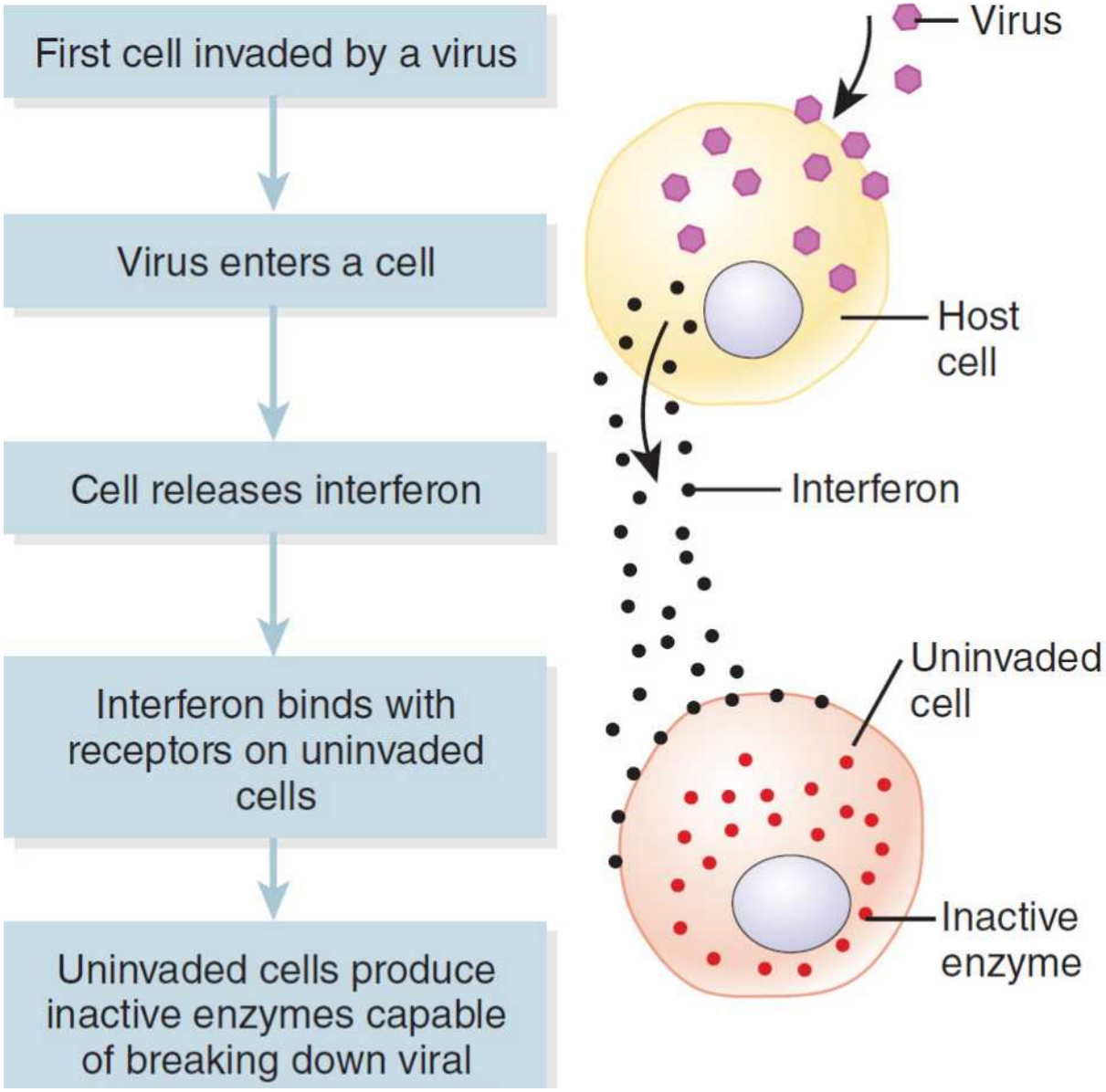
The chronic inflammation occurs when acute mechanisms fail or in the presence of resistant organisms—for example, *Mycobacterium tuberculosis*, which causes tuberculosis, and *Treponema pallidum*, which causes syphilis. Chronic inflammation results in more infiltration of macrophages and lymphocytes to the site. Neutrophils' and macrophages' activities continue. A granuloma—a mass of tissue that consists of macrophages and lymphocytes—develops in an attempt to separate and contain the infection. Granulation tissue development is a step in tissue repair that differs from granuloma formation. Granulation tissue comprises a mixture of new vasculature and fibroblasts, which produces connective fibers and collagen.

Pyrogens

Pyrogens are molecules that cause a systemic inflammatory response. These molecules are released by macrophages that have been exposed by bacteria (e.g., interleukins and prostaglandin E_2) or by bacteria themselves. Pyrogens travel to the hypothalamus, the portion of the brain primarily responsible for controlling body temperature. There, they turn the heat up on the bacteria, producing fever and creating an unpleasant environment for bacterial growth. Mild fevers cause the spleen and liver to remove iron from the blood; many bacteria require iron to reproduce, so this effect reduces their proliferation. Fever also increases metabolism, which facilitates healing and accelerates phagocytosis. However, severe fever (more than 105°F) can be life threatening because it begins to denature vital proteins, especially enzymes needed for biochemical reactions.

Interferons

Interferons are small proteins released from virus-infected cells (**FIGURE 2-5**). These molecules diffuse away from the site of invasion through the interstitial tissue and bind to receptors on the plasma membranes of uninfected cells. The binding of interferons to uninfected cells triggers the synthesis of enzymes that inhibit viral replication. Consequently, viruses cannot replicate and spread when they enter the previously uninfected cells. Interferons do not protect cells already infected by a virus but rather stop the spread of the virus to new cells. In essence, interferon production is the dying cells' attempt to protect other cells.



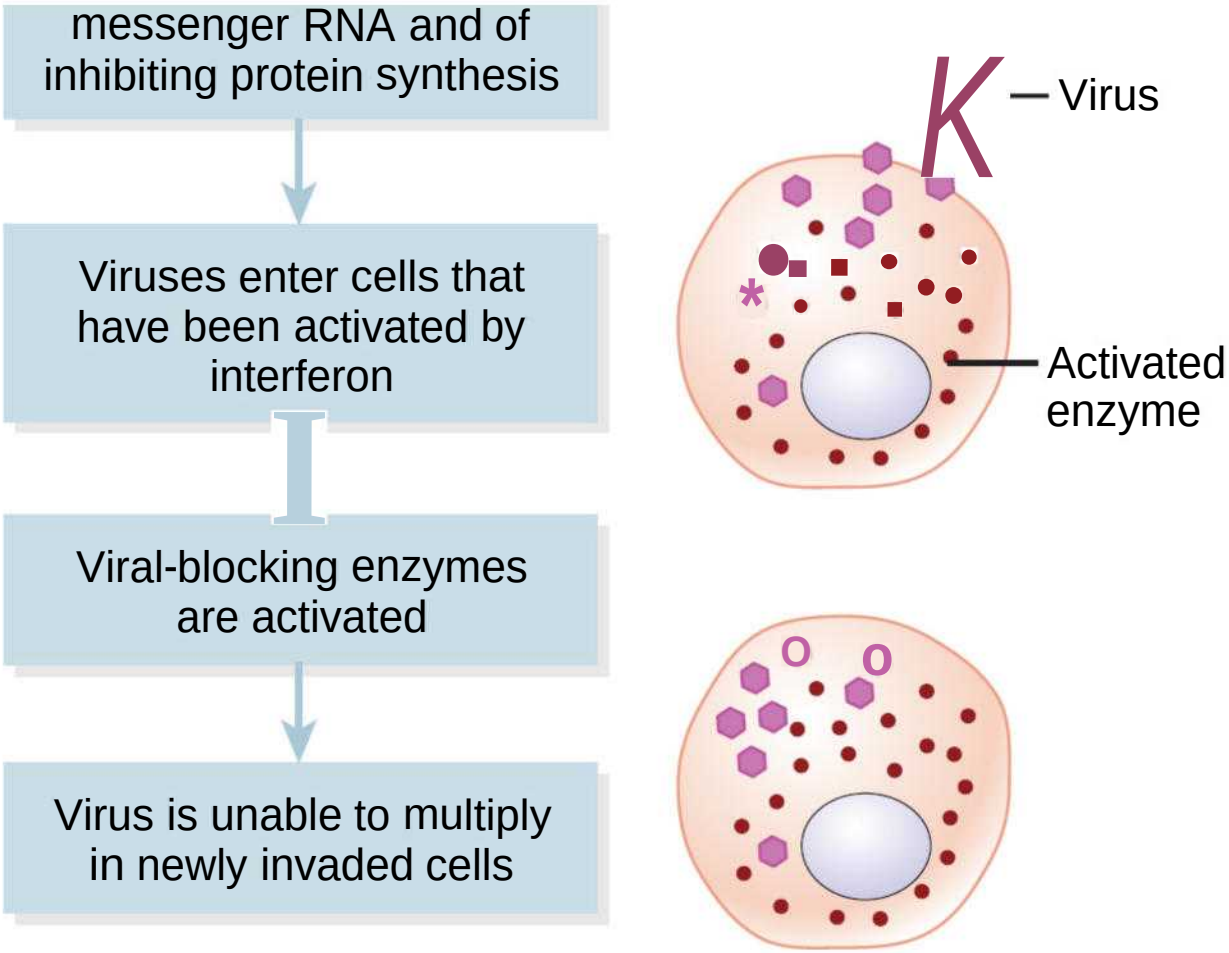


FIGURE 2-5 How interferon works.

Description

Complement Proteins

The complement system is a process that involves blood plasma proteins (approximately 20) and enhances the action of antibodies. Complement proteins circulate in the blood in an inactive state. When a foreign substance invades the body, these proteins become activated. Only a few activities in this complex process are described here (**FIGURE 2-6**).

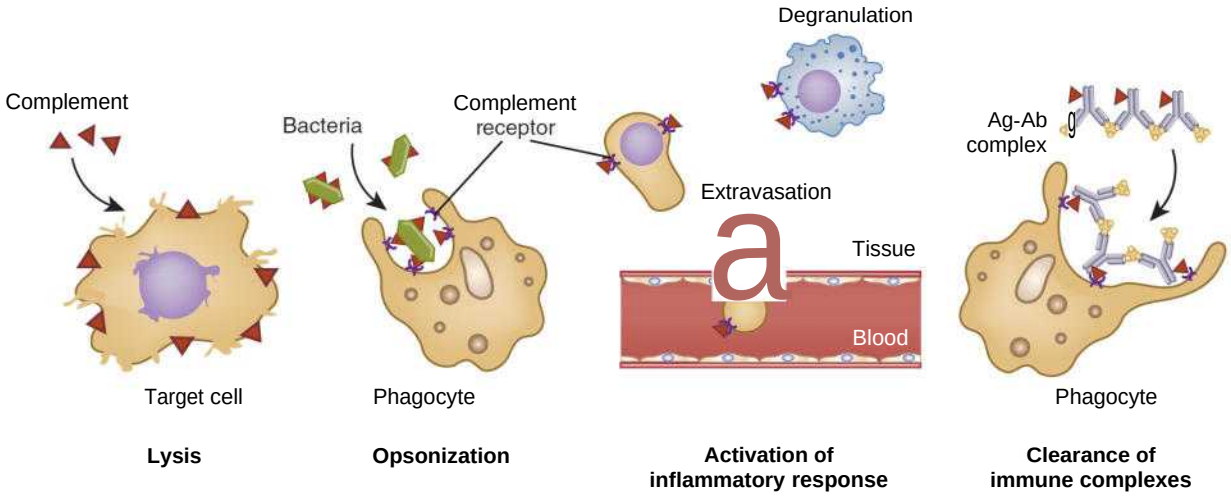


FIGURE 2-6 The complement system.

Description

Five complement system proteins join together to form a large molecule, or membrane-attack complex. The membrane-attack complex becomes embedded in the plasma membrane of bacteria, creating an opening into which water flows. The influx of water causes the bacterial cell to swell, burst, and die. Other complement proteins stimulate vasodilation in an infected area as part of the inflammatory response. Some complement proteins increase the permeability of vessels, allowing white blood cells and plasma to pass quickly through them to the infected area. Other complement proteins serve as chemical attractants, drawing macrophages, monocytes, and neutrophils to the infected area, where they phagocytize foreign cells (a process called “opsonization”). Still, other complement proteins bind to microbes, forming a rough coat on the invader that promotes phagocytosis.

Adaptive Defenses

Adaptive or acquired defenses are the body’s own individual immune system. These defenses recognize and attack antigens that make it through the innate defenses. They include two major approaches—cellular and humoral immunity. Key players in these approaches are **T cells** and **B cells** (**FIGURE 2-7**). T cells and B

cells mingle with antigens as they circulate throughout the body's fluids and peripheral lymphoid tissue (e.g., tonsils, lymph nodes, spleen, and intestinal lymphoid tissue). This interaction serves either to destroy the antigen (T-cell function or cellular immunity) or to produce antibodies against the antigen (B-cell function or humoral immunity).

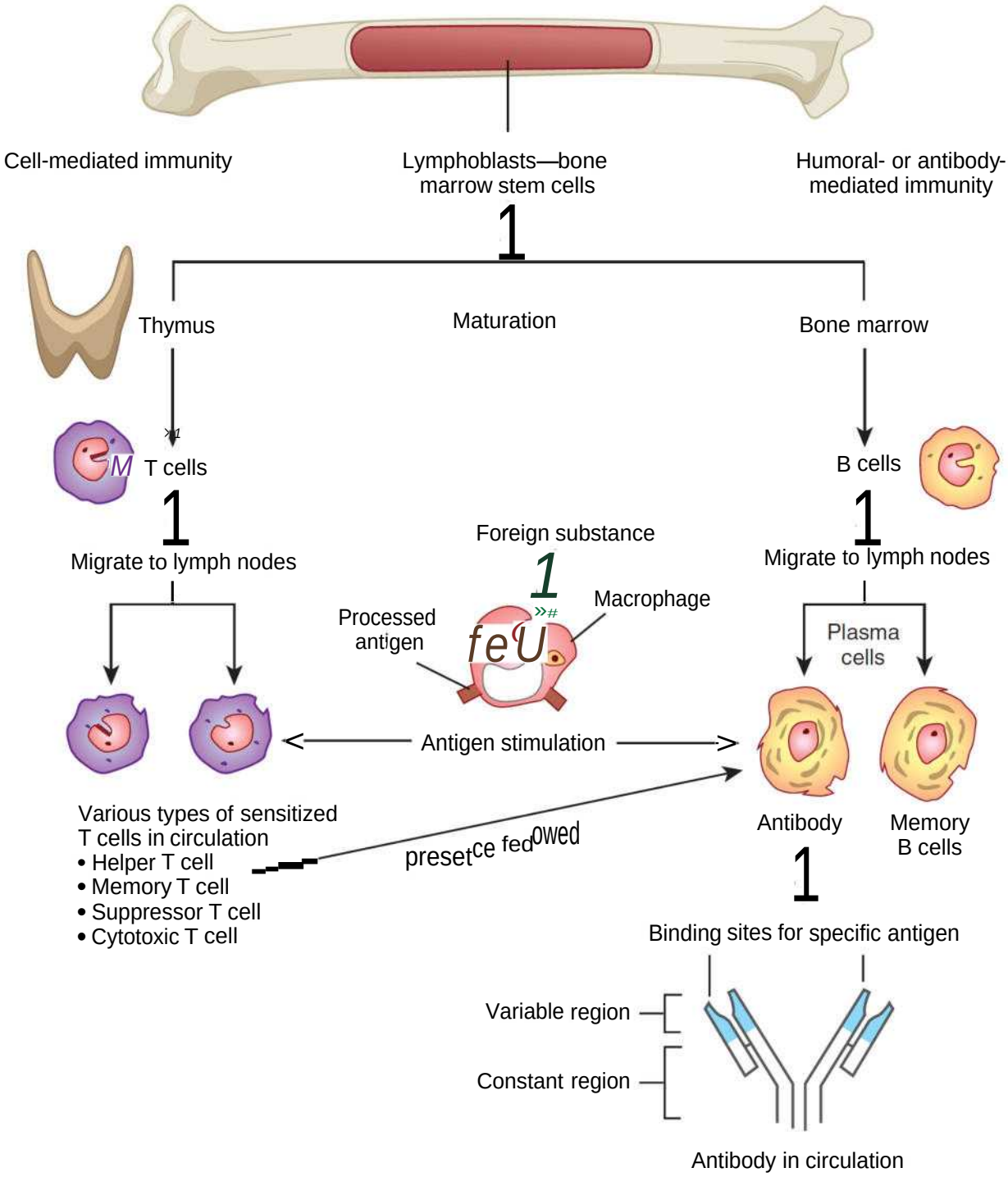


FIGURE 2-7 Development of cellular and humoral immunity.

Data from Gould, B. (2015). *Pathophysiology for the health professions* (5th ed.). Philadelphia, PA: Elsevier. Copyright Elsevier 2015.

Description

Cellular Immunity

Cellular immunity is a defense approach that is mediated by T cells, which recognize the presence of the antigen, bind to the antigen, and trigger a response by other immune cells. T cells get their name from the place where they mature, the thymus. T cells are produced in the bone marrow but then enter the bloodstream and travel to the thymus for maturation.

Two major types of T cells work to destroy antigens: (1) **regulator cells**, including helper T cells and **suppressor T cells**, and (2) **effector cells**, or killer cells. **T-helper (Th) cells** contain a protein called CD4+, which is why they are often referred to as CD4+ cells. Four types of Th cells have been identified:

- Th1 cells participate in inflammation by producing cytokines as well as stimulating macrophages.
- Th2 cells activate, or call up, B cells to produce antibodies.
- Tfh (T follicular helper) cells assist the B cells as they develop into antibody-secreting plasma cells in the lymph nodes.
- Th17 cells are involved in inflammation and protect surfaces (e.g., skin and intestinal lining) against bacteria.

Suppressor T cells turn antibody production off. **Killer T cells**, also called **cytotoxic cells**, destroy cells infected with viruses by releasing lymphokines that degrade cell walls. Cytotoxic T cells have a CD8+ protein on their surface, so they are often referred to as CD8+ cells. T cells work to protect the body against intracellular viruses, fungi, parasites, bacteria, and cancer cells, and they are responsible for **hypersensitivity** and transplant rejection.

T cells can detect intracellular pathogens because infected cells display peptide fragments derived from the pathogen's proteins. These foreign peptides are carried to the cell surface by specialized host-cell glycoproteins, referred to as the major histocompatibility complex (MHC) molecules. T cells recognize these small peptide fragments bound to the MHC molecule as an antigen. This recognition

is similar to the process by which immunoglobulins (Ig) recognize antigens, but there is no memory or antibody development involved.

Humoral Immunity

B cells mature in the bone marrow, where they differentiate into either **memory cells** or Ig-secreting (antibody) cells (**TABLE 2-2**). These cells eliminate extracellular bacteria, neutralize bacterial toxins, prevent viral reinfection, and produce immediate inflammatory response. Each B cell has receptor sites for a specific antigen; when it encounters this antigen, the B cell becomes activated and multiplies into either **antibody-producing cells** or memory cells. The antibody-producing cells produce millions of antibody molecules during their 24-hour life span. B cells can begin this antigen production within 72 hours after the initial antigen exposure. Subsequent exposures to the antigen then trigger a quicker response because memory cells recognize the antigen as foreign, and antibody production occurs rapidly. This reaction is referred to as “acquired immunity.”

TABLE 2-2 Immunoglobulins and Their Functions

IgG	Main defense against bacteria; can cross the placenta to protect the fetus against infections (passive immunity).
IgM	Fights blood infections and triggers additional production of IgG; present in lymphocyte cells; first antibody made by a developing fetus.
IgA	Found in membranes of the respiratory and gastrointestinal tracts, tears, saliva, mucus, and colostrum; important in local immunity.
IgE	Protects the body through its presence in mucous membranes and skin; triggers allergic reactions and responds to parasites.
IgD	Present in blood serum (in small amounts) and on B-cell surfaces; receptor for antigens; helps anchor cell membranes.

Data from Gould, B. (2014). *Pathophysiology for the health professions* (5th ed.). Philadelphia, PA: Elsevier.

Active acquired immunity refers to immunity gained by actively engaging with the antigen—that is, through invasion or vaccination. In active immunity, the person makes his or her own antibodies, and protection is usually long term. Examples of active immunity include both the case in which a person has a condition, such as varicella infection (chickenpox), and does not get it again and the case in which a person receives the varicella vaccine and never has the condition.

Emerging Research: COVID-19 Vaccines

Vaccines often prevent and decrease the severity of the condition. In 2020, an illness emerged caused by a novel virus, the severe acute respiratory syndrome cornonavirus-2 (SARS-CoV-2) or the COVID-19 virus. The virus quickly spread and caused widespread death and complications, especially in vulnerable populations. The healthcare system quickly became overwhelmed as it attempted to manage and respond. Global shutdowns and other measures to prevent the spread would do little to slow down the spread and minimize the impact until a vaccine and treatments were developed. Once developed, the virus quickly mutated in response to the efforts. To move quickly, researchers leaned on existing technology that included two mRNA, one adenovirus vector, and one subunit vaccine.

- The mRNA COVID-19 vaccine produced by Pfizer-BioNTech has been approved for use in people 16 years of age and older by the U.S. Food and Drug Administration (FDA). The vaccine has also received Emergency Use Authorization (EUA) for children 6 months to 15 years of age.
- The mRNA COVID-19 vaccine produced by Moderna is approved for use in people 18 years of age and older, and it has also received EUA for children 6 months to 17 years of age.
- The adenovirus vector COVID-19 vaccine produced by Janssen/Johnson & Johnson has EUA for people 18 years of age and older for whom other COVID-19 vaccines are not accessible or clinically appropriate, or who elect to it other than not receive any vaccine.
- The subunit COVID-19 vaccine produced by Novavax has EUA for people 12 years of age and older.

The mRNA vaccines do not contain viral antigens but rather deliver a small, synthetic piece of mRNA that encodes for the target antigen or spike protein. After entering the cells of the immune system, the vaccine mRNA degrades after instructing the cells to produce viral antigen. The antigen is then released and triggers the desired immune response to prevent severe infection. The adenovirus vector vaccine contains a piece of DNA that is used to make the distinctive spike protein of the COVID-19 virus, which then triggers the

desired immune response. The adjuvanted vaccine contains a recombinant form of the COVID-19 spike protein, which then triggers the desired immune response.

Vaccine hesitancy has been problematic with the COVID-19 vaccines due to questions regarding effectiveness and adverse effects. Often individuals experience break through infections or viral mutations that may not be covered by previous doses. In addition to the initial vaccine dosing, boosters are available that enhance the effectiveness and provides coverage for emerging variants. The CDC (2022b) is currently monitoring COVID-19 vaccine effectiveness.

In most cases, the mRNA vaccines are preferred due to lower risk of adverse events. The adenovirus vector vaccine has been associated with the rare and serious adverse event, vaccine-induced thrombosis with thrombocytopenia syndrome. The onset of the adverse event is usually 1-2 weeks after vaccination. Cases have occurred in males and females 18 years of age and older, and females 30-49 have the highest risk. Some cases have been fatal. A warning has also been issued by the FDA for mRNA vaccines and the adjuvanted vaccine that myocarditis and pericarditis have been reported, particularly within 7 days of the second does. The risk is highest is highest in young males. Vaccine recipients should seek medical attention immediately if they experience angina, dyspnea, tachycardia, or irregular heart rate (CDC, n.d.).

Passive acquired immunity refers to immunity gained by receiving antibodies made outside the body by another person, animal, or recombinant DNA. In passive immunity, the person is not actively producing antibodies, and protection is short lived. Examples of passive immunity include mother-to-fetus transfer of antibodies through the placenta and breastfeeding transference of antibodies.

Immunity Across the Life Span

To function optimally, the human immune system needs the opportunity to mature. At birth, the innate and adaptive immunity is not fully developed even in a normal full-term infant. Maternal IgG crosses the blood–placenta barrier and will remain present in the infant for approximately 3 to 6 months; the other maternal antibodies, however, do not cross the placenta. This temporary passive immunity gives the infant's immune system an opportunity to mature, but the maternal effects are short lived, and the transferred antibodies have low affinity (i.e., they bind weakly to antigen). Breastfeeding transfers additional antibodies, specifically IgA, for as long as the infant continues to breastfeed. Vaccinations can provide additional

protection. Newborns produce T cells, but their function is limited (e.g., produce small amounts of cytokines).

Newborns can respond to protein antigens but respond less vigorously to glycoproteins and polysaccharides, which is why most infections in infants are caused by low-virulence organisms (e.g., *Staphylococcus* and *Pseudomonas*). The immune system begins to respond to glycoproteins about 6 to 9 months after birth, but the response to polysaccharides does not improve until 12 to 24 months after birth. This understanding is used to develop vaccination guidelines for infants and children.

In infants, opsonic activity and the ability to activate the complement system are limited. Phagocytosis is impaired because the neutrophils have limited ability to interact with adhesion molecules in the endothelium and because the monocytes are slower owing to reduced ATP production.

During adolescence, the body experiences physical, physiological, and immunological alterations as a result of various hormone changes. Testosterone begins acting on males around age 12, and estrogen begins acting on females around age 10. In addition to producing the respective sex characteristics, these hormone changes affect immune system development and regulation (Bhatia, Sekhon, & Kaur, 2014). Hormone receptors are found on immune cells, particularly B cells and macrophages. The interaction of the sex hormones and the immune cells through these receptors affects cytokines that determine the proliferation, differentiation, and maturation of various immunocytes. As a result of these effects, the risk for inflammatory and **autoimmune** diseases increases. The hormone differences in both sexes result in immune dimorphism, which can lead to variations in males' and females' responses to infections and vaccinations. This immune dimorphism explains the differences in disease risk; for example, autoimmune conditions are more common in females.

Like many other aspects of the human body, the immune system works less efficiently as we age, a trend referred to as "immune senescence." The effects of aging on the immune system occur at multiple levels and primarily include a reduction of B-cell and T-cell

production in the bone marrow and thymus, increased rates of apoptosis for both types of cells, and diminished function of mature lymphocytes in lymphoid tissue (Montecino-Rodriquez, Berent-Maoz, & Dorshkind, 2013). These age-related changes are multifactorial, including changes in hematopoietic stem cells and progenitor cells (similar to stem cells, they can differentiate into a specific target cell such as a leukocytes). Antibodies become less able to attach to antigens, increasing the risk of death associated with infections, especially from pneumonia, influenza, infective endocarditis, and tetanus. The altered antibody function also decreases the effectiveness of vaccines, so boosters should be administered in older people. Additionally, complement protein and cytokine production decreases, affecting both the response to bacterial infections and the ability to robustly activate the inflammatory response.

Compounding the physiological changes directly related to aging, people often experience more comorbidity issues (e.g., heart disease, diabetes) as they age. These comorbid conditions can directly impair the immune system, as occurs with diabetes (see the *Endocrine Function* chapter) or indirectly as they deplete the body's reserves. As a result of these age-related changes, the immune system responds more slowly, increasing the risk for infection and slowing the healing process. The risk for autoimmune disorders increases because more circulating autoantibodies and immune complexes (i.e., antigen–antibody complexes) are present in the bloodstream, causing the body to misinterpret signals and lose the ability to distinguish self from nonself. Additionally, the immune system's ability to detect and correct cell defects declines, increasing risk for cancerous changes.

Altered Immune Response

A malfunction at any point in any of the numerous and highly complex immune responses can create a pathological state. Malfunctions may include exaggeration (hypersensitivity), misdirection (autoimmune), or diminution (**immunodeficiency**).

Hypersensitivity

Hypersensitivity is an inflated or inappropriate response to an antigen, which results in inflammation and destruction of healthy tissue. Hypersensitivity reactions may be immediate, occurring within minutes to hours of reexposure to the antigen, or delayed, occurring several hours after reexposure. Hypersensitivity is categorized based on pathogenesis and includes four types of reactions: type I (IgE mediated), type II (tissue specific), type III (immune-complex mediated), and type IV (cell mediated) (**TABLE 2-3**).

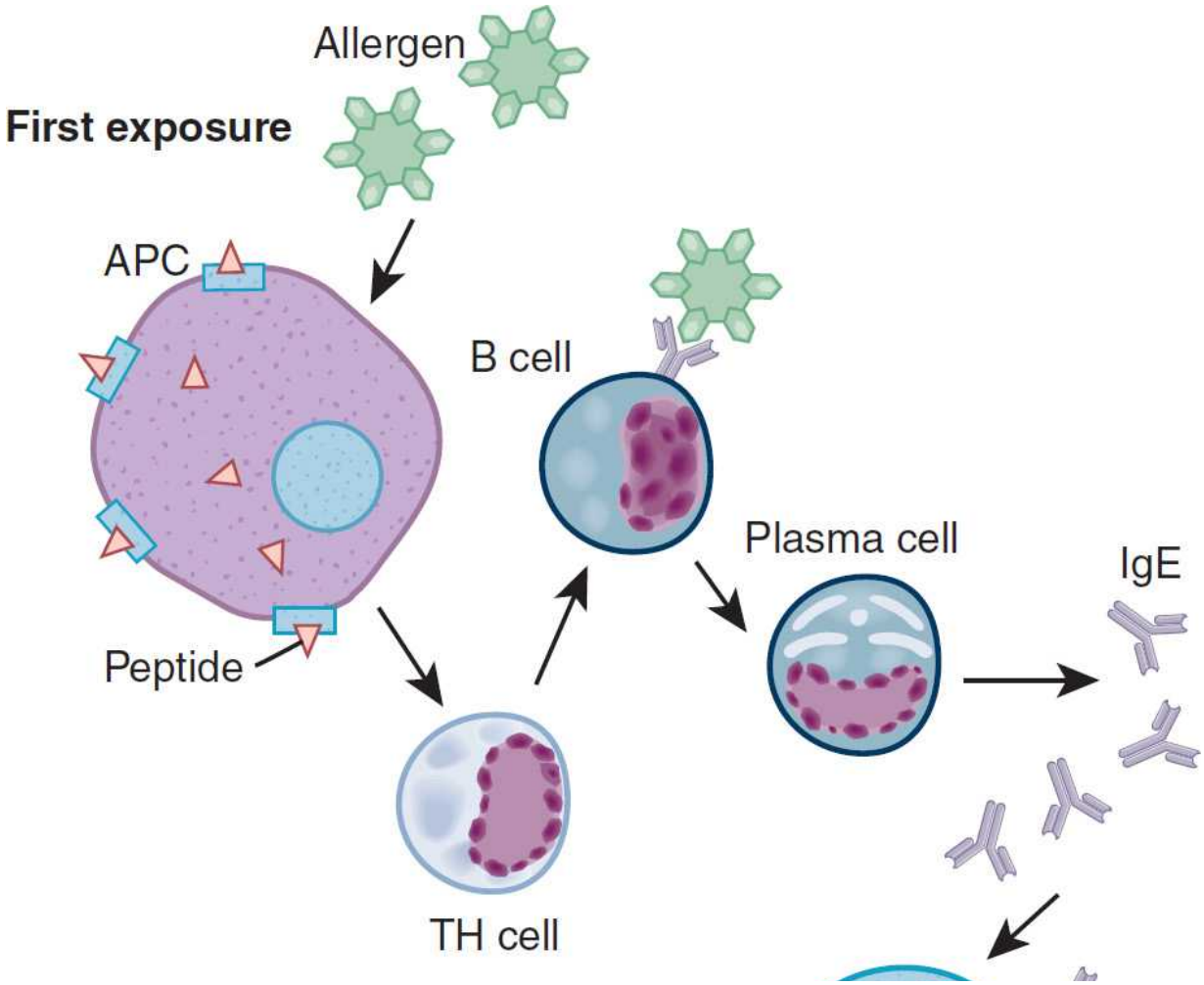
TABLE 2-3 Overview of Hypersensitivity Reactions

Hypersensitivity Type	Origin of Hypersensitivity	Antibody Involved	Cells Involved	Mediators Involved	Evidence of Hypersensitivity	Examples
Type I: IgE mediated	B lymphocytes	IgE	Mast cells Basophils	Histamine Serotonin Leukotrienes Prostaglandins	Immediate (30 minutes or less) or delayed (hours)	Allergic rhinitis Systemic anaphylaxis Asthma
Type II: Cytotoxic	B lymphocytes	IgG, IgM	RBCs WBCs	Complement	5–8 hours	Transfusion reactions Hemolytic disease of newborns
Type III: Immune complex	B lymphocytes	IgG	Host tissue cells	Complement	2–8 hours	Serum sickness Arthus phenomenon SLE Rheumatic fever Rheumatoid arthritis
Type IV: Cellular	T lymphocytes	None	Host tissue cells	Cytokines	1–3 days	Contact dermatitis Infection Allergy Crohn's disease

Description

With **type I hypersensitivity**, allergens activate T cells (usually helper cells), which bind to mast cells (**FIGURE 2-8**). These T cells stimulate B cells to produce IgE antibodies specific to the antigen, which is usually environmental (i.e., an allergen). The difference between a normal immune response and a type I hypersensitivity response is that the antibody produced is IgE instead of IgA, IgG, or IgM. The IgE coats the mast cell and basophils, making them sensitive to the allergen. Upon the next exposure to the same antigen,

the antigen binds with the surface IgE. This antigen binding to IgE causes mast cell degranulation and mediator (e.g., histamines, cytokines, and prostaglandins) release. The mast cell degranulation and mediator release activate the inflammatory process, attracting neutrophils and eosinophils and triggering the complement system. The effects of type I reactions include immediate inflammation and pruritus. Repeated exposure to relatively large doses of the allergens is usually necessary to cause a type I response. The response can be local (e.g., allergic rhinitis, food allergies, gastroenteritis, and asthma) or systemic (e.g., anaphylaxis) and range from minor (e.g., allergic rhinitis) to life threatening (e.g., asthma and anaphylaxis). Treatment of type I reactions may include epinephrine, antihistamines, corticosteroids, and desensitizing injections, all of which will suppress the inflammatory activity.



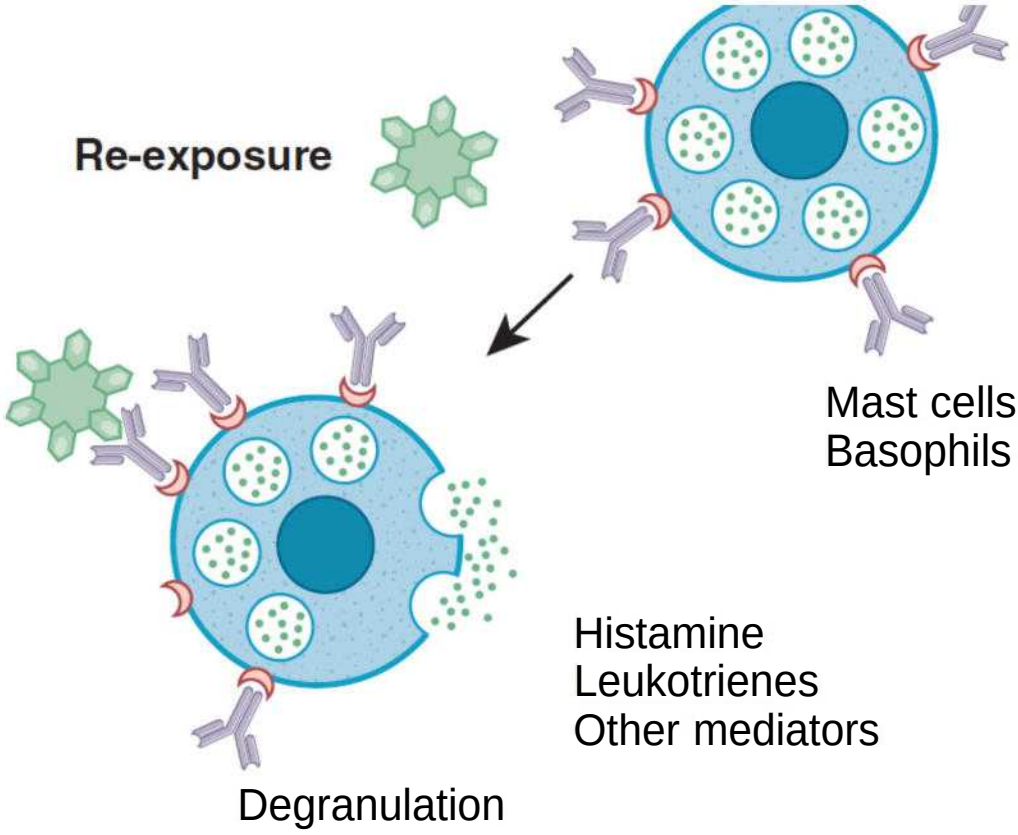


FIGURE 2-8 Type I hypersensitivity.

Description

Type II hypersensitivity generally involves the destruction of a target cell by an antibody-directed cell-surface antigen (**FIGURE 2-9**). IgG or IgM binds with an antigen on the cell's surface and destroys the cell. The antigen may be intrinsic (self; e.g., erythrocytes) or extrinsic (absorbed through exposure; e.g., microorganism). The destruction of the cell occurs by one of three mechanisms—complement-mediated cell lysis, antibody-dependent cell-mediated cytotoxicity (ADCC), or opsonization. The effects of type II reactions include cell lysis and phagocytosis. Examples of type II reactions include blood transfusion reactions (**FIGURE 2-10**) and erythroblastosis fetalis (**FIGURE 2-11**). Treatment focuses on prevention and includes ensuring blood compatibility prior to transfusions and administering medication to suppress immune activity (e.g., corticosteroids and cyclosporine) and prevent maternal antibody development (e.g., Rho[D] immune globulin [RhoGAM]).

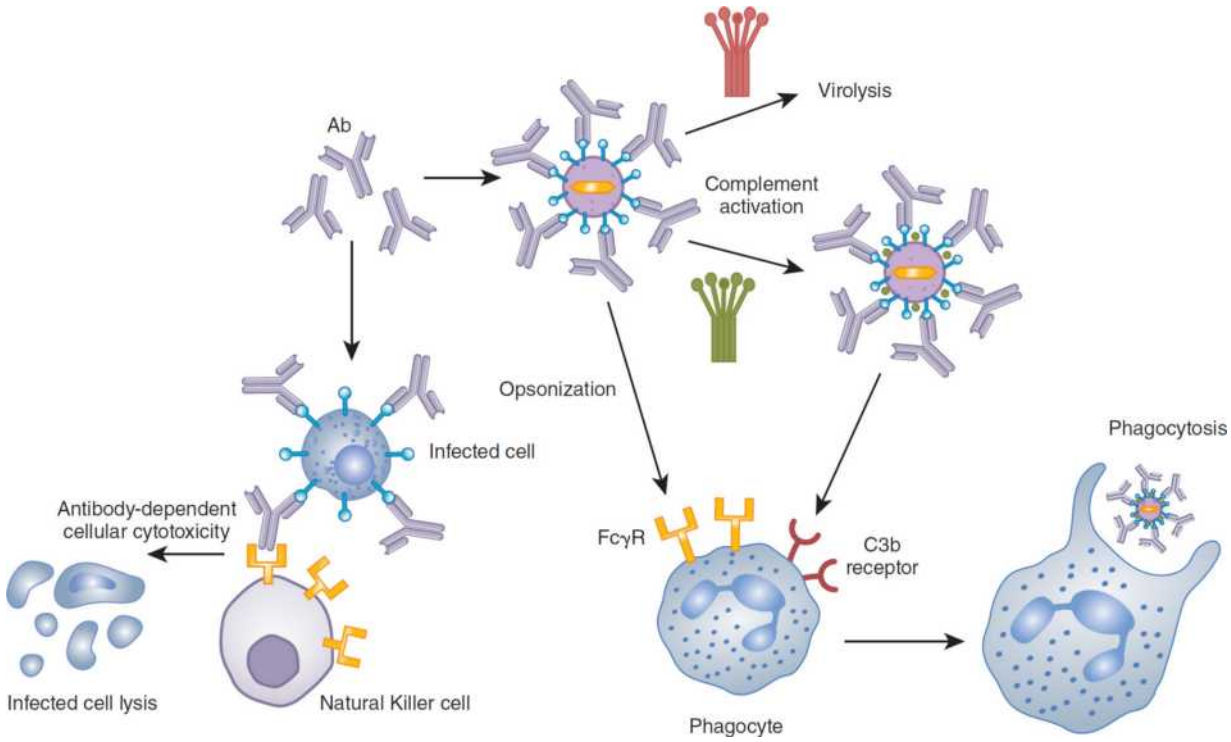


FIGURE 2-9 Type II hypersensitivity.

Description

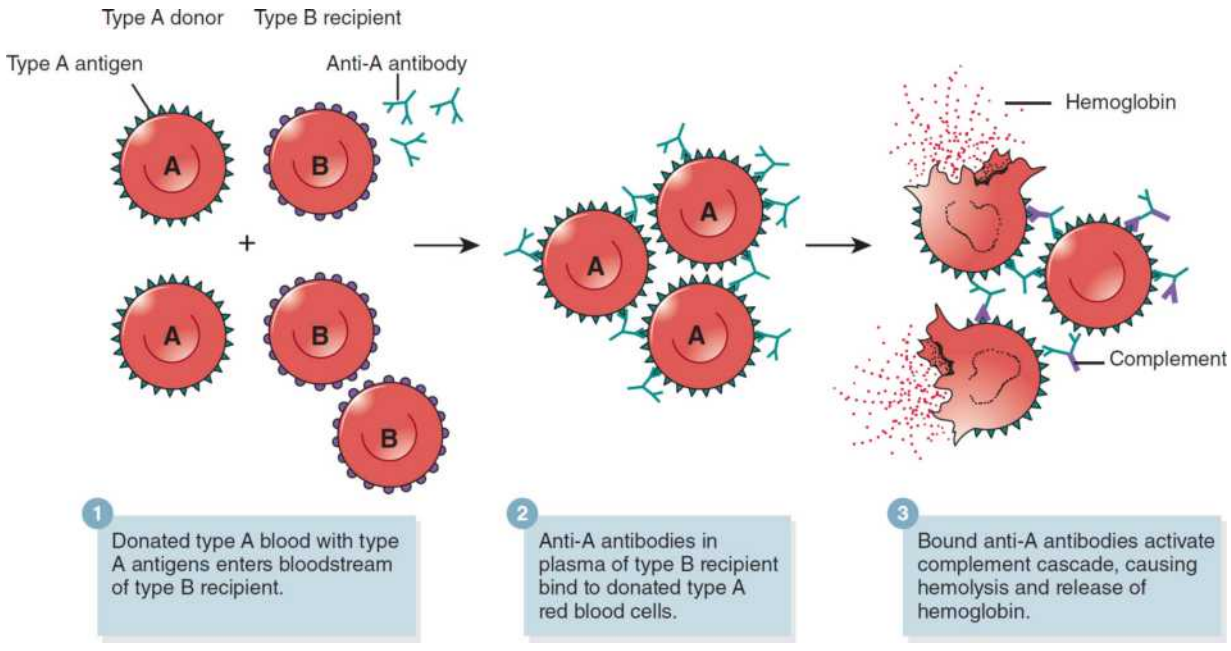


FIGURE 2-10 Blood transfusion reactions.

Description

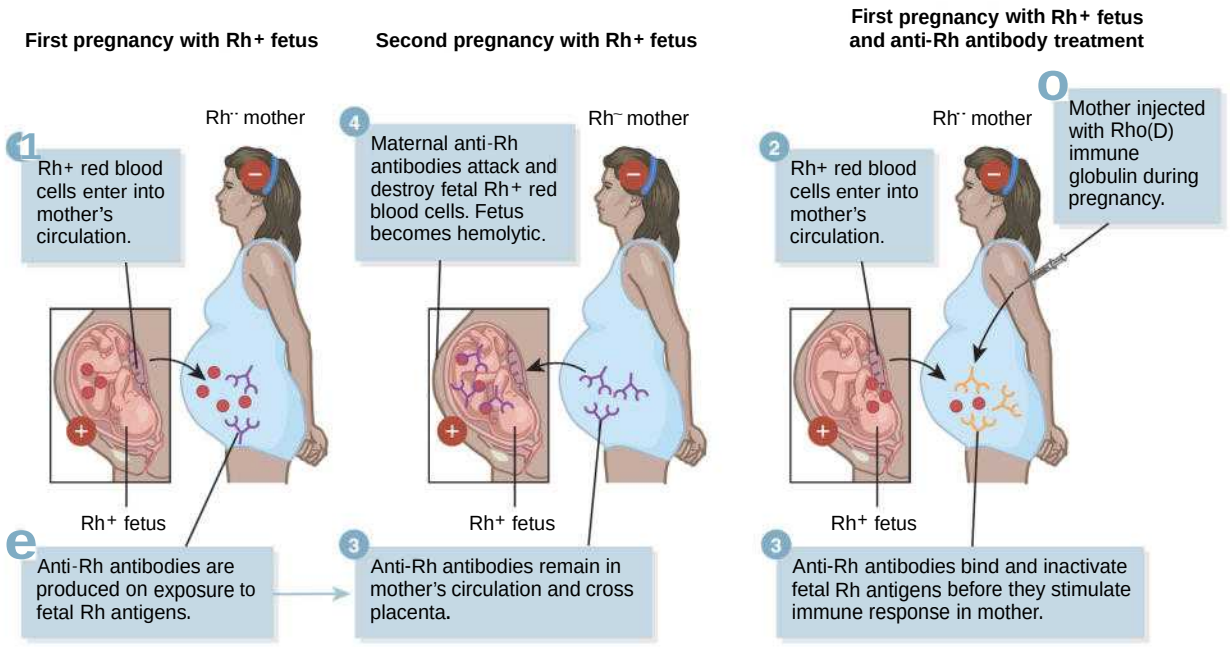


FIGURE 2-11 Erythroblastosis fetalis.

Description

In **type III hypersensitivity**, circulating antigen–antibody complexes that have not been adequately cleared by the innate bloodborne immune cells accumulate and become deposited in tissues (**FIGURE 2-12**). The reaction may be general (e.g., serum sickness) or involve individual organs (e.g., kidneys, joints, skin, and blood vessels). Antibody excess, primarily IgG, combined with relatively low concentrations of antigen, results in the formation of small immune complexes that are deposited on the surface of epithelial cells lining the inner lumen of small blood vessels or on the surface of tissues. The accumulation of the complexes leads to three effects: (1) IgG binding to antibody receptors on localized mast cells, resulting in degranulation; (2) complement system activation; and (3) increased vascular permeability with chemotaxis of neutrophils and macrophages. This cascade of events causes more complexes to accumulate at varying maturity or quality. Over time, these variations cause the remissions and exacerbations often associated with type III hypersensitivity. Examples of type III reactions include autoimmune disorders (e.g., **systemic lupus erythematosus [SLE]**,

glomerulonephritis, and rheumatoid arthritis). Treatment for type III reactions is disease specific.

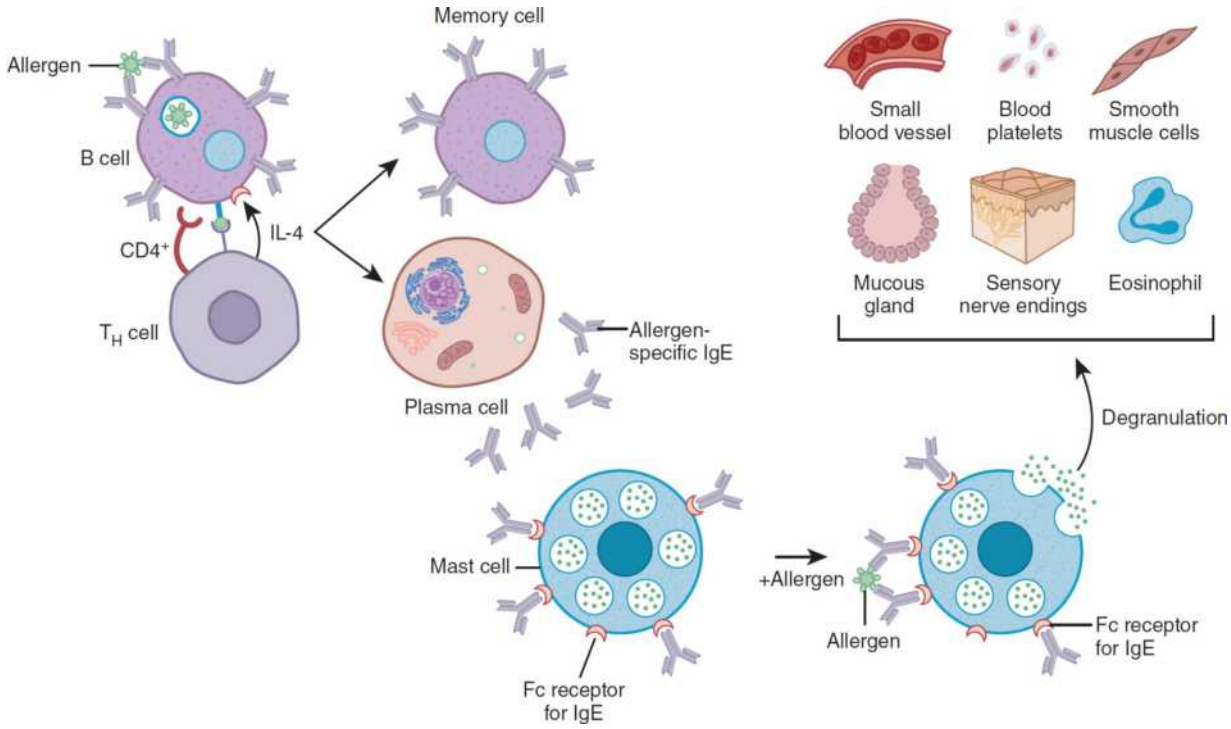


FIGURE 2-12 Type III hypersensitivity.

Abbreviations: $CD4^+$: Cluster of differentiation 4; Fc: Fragment crystallizable; IL-4: Interleukin-4; Th: T helper cells.

Description

Type IV hypersensitivity, also known as cell-mediated or delayed-type hypersensitivity, is not mediated by antibodies like the other hypersensitivities (**FIGURE 2-13**). Instead, it is controlled by T cells and involves the action of effector cells. Type IV reactions occur in two phases—sensitizing and effector. The initial sensitization phase is triggered by primary contact with the antigen. The antigen is processed and presented by antigen-presenting cells (APCs) to the Th (CD4+) cells, stimulating memory Th cells. The effector phase begins with the subsequent exposure. Upon subsequent exposure to the antigen, the sensitized memory Th cells release cytokines that activate macrophages and other inflammatory cells. These macrophages exhibit increased phagocytosis and release lytic

enzymes that damage surrounding tissue. In the case of infections, pathogens are generally killed with little damage to surrounding tissue. However, prolonged type IV reactions can be destructive, causing chronic inflammation. A granuloma develops from the continuous macrophage activity, gradually forming multinucleated giant cells. These giant cells displace normal cells, forming palpable nodules and releasing high concentrations of lytic enzymes that destroy surrounding tissue, leading to necrosis. Examples of type IV reactions include tuberculin skin testing, transplant reactions, and contact dermatitis. Treatment for type IV reactions is disease specific.

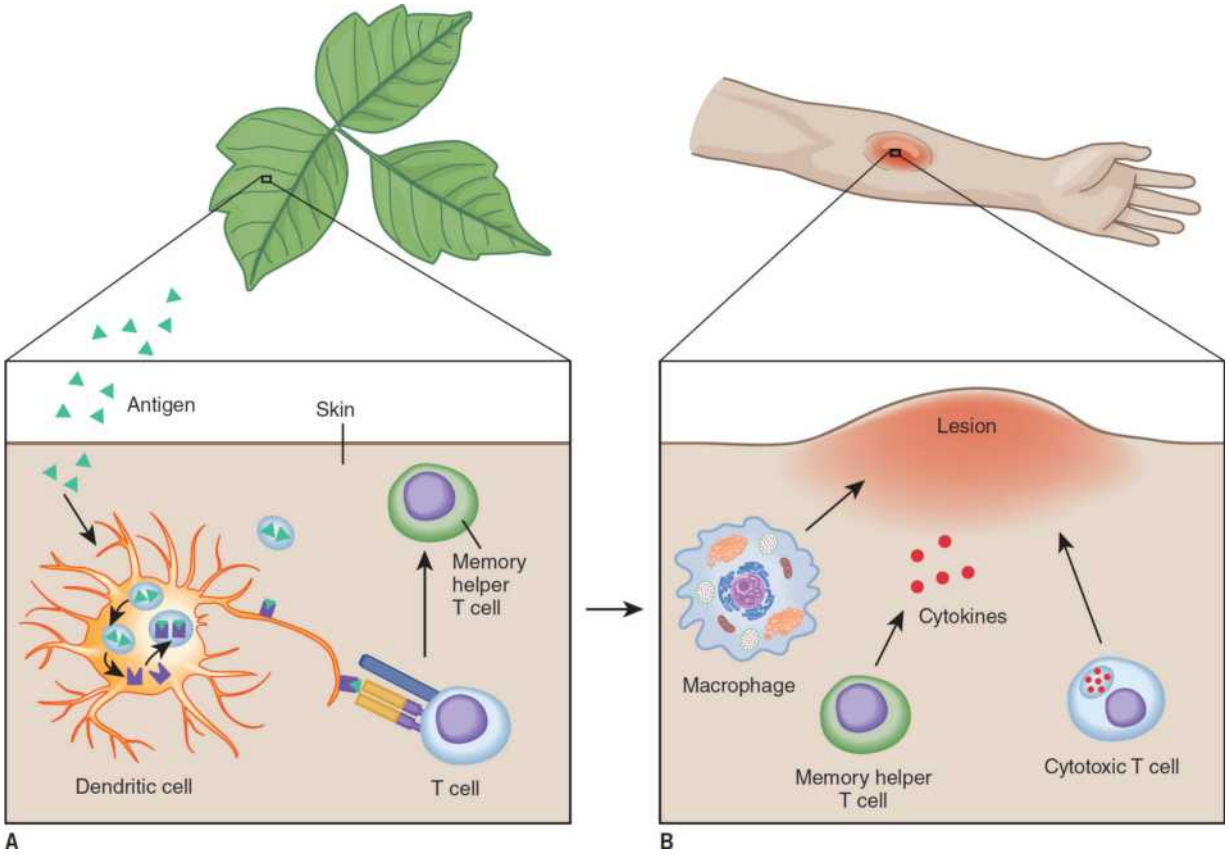


FIGURE 2-13 Type IV hypersensitivity. Exposure to hapten antigens in poison ivy can cause contact dermatitis, a type IV hypersensitivity. **(A)** The first exposure to poison ivy does not result in a reaction. However, sensitization stimulates helper T cells, leading to the production of memory helper T cells that can become reactivated on future exposures. **(B)** On secondary exposure, the memory helper T cells become reactivated, producing inflammatory cytokines

that stimulate macrophages and cytotoxic T cells to induce an inflammatory lesion at the exposed site. This lesion, which will persist until the allergen is removed, can inflict significant tissue damage if it remains present for a long enough period.

Description

Emerging Research: Cytokine Storm Associated with COVID-19

The COVID-19 disease caused by SAR-CoV-2 continues to pose a significant global health threat. This virus affects the respiratory tract, usually resulting in pneumonia in most patients and acute respiratory distress syndrome (ARDS) in 15% of cases. ARDS is one of the leading causes of death in patients with COVID-19, and it is primarily caused by acute overproduction and uncontrolled release of pro-inflammatory cytokines (locally and systemically), referred to as cytokine storm. Interleukins (e.g., IL-1, IL-6, IL-17) and tumor necrosis factor-alpha (TNF-α) impairs the respiratory epithelium and are primarily responsible for the lung damage associated with ARDS.

The underlying mechanisms for the extreme release of these inflammatory factors are still unclear; however, several hypotheses exist. The first hypothesis suggests that the viral replication leads to pyroptosis, a highly inflammatory form of apoptosis. In COVID-19 patients, pyroptosis causes pro-inflammatory cytokines to be released and affects macrophages and lymphocyte functions, resulting in peripheral lymphopenia. This viral replication is thought to be triggered by interferon (INF)-1. The second hypothesis involves adaptive immunity and the production of neutralizing antibodies against the surface antigen of the virus. Evidence suggests that immunoglobulin (Ig) Gs may be binding to the S protein and triggering the inflammatory cascades. This binding results in pro-inflammatory macrophages and monocytes to accumulate in the lungs because of the release of IL-8 and monocyte chemoattractant protein (MCP)-1.

The cytokine storm can affect nearly all cells and tissues in the body, resulting in multi-organ dysfunction and a wide range of clinical manifestations. In addition to ARDS, this surge of pro-inflammatory cytokines has been associated with myocardial injury due to interaction with the angiotensin-converting enzyme-2 (ACE2) receptors. The virus is thought to attack several organs expressing ACE2 receptors early, including the heart, brain, vessels, liver, kidney, and lungs. Brain damage is also thought to occur by a hypercoagulable state that leads to occlusion of cerebral vessels. Additionally, cytokines may have neurotoxic effects on the brain and can disrupt the blood–brain barrier. No specific treatment for critically ill patients with COVID-19 is available, but inhibiting these interleukins and TNF-α has shown promise in managing and improving survival rates of these patients (Montazersaheb et al., 2022).

Transplant Reactions

The immune system's protective nature presents challenges for patients who require tissue and organ transplants and blood transfusions. Transplant success is closely tied to ensuring the best possible tissue match. Four types of tissue transplants are possible—**allogeneic**, **syngeneic**, **autologous**, and **xenogenic**.

- Allogeneic transplants are those in which the tissue used comes from the same species and is of similar tissue type but is not identical. Most transplants use allogeneic tissue.
- Syngeneic transplants use tissue from the identical twin of the host.
- With autologous transplants, the host and the donor are the same person. An example of this type of transplant is someone storing up his or her own blood prior to a scheduled surgery.
- Xenogenic transplants use tissue from another species. An example of this type of transplant is the use of pig heart valves to replace diseased valves in a human.

Donors may be live or a cadaver, but no matter which source is used, a close tissue match is fundamental to preventing rejection.

Rejection reactions are classified based on their timing (**TABLE 2-4**). **Hyperacute tissue rejections** occur immediately to 3 days after the transplant. Such reactions occur due to a complement response in which the recipient has antibodies against the donor tissue. This complement response triggers a systemic inflammatory reaction. The response is so quick that often the tissue has not had a chance to establish vascularization; as a result, the tissue becomes permanently necrotic.

TABLE 2-4	Transplant Rejection

Type	Onset	Mechanism and Vessel History	Type of Hypersensitivity	Other
Host-Versus-Graft Rejection				
Hyperacute	Up to 3 days	Preformed antibodies directed against the donor tissue. Caused by accidental ABO blood type incompatibility. Presents while still in surgery with thrombosis and occlusion of graft vessels.	II	Very rare
Acute	4 days to 3 months	T-cell–mediated immune response directed against the foreign MHC. Inflammation and leukocyte infiltration of graft vessels results.	IV	Most common type
Chronic	4 months to years	T-cell–mediated process resulting from the foreign MHC "looking like" a self MHC carrying an antigen. Results in intimal thickening and fibrosis of graft vessels as well as graft atrophy.	III & IV	
Graft-Versus-Host Rejection				
	Varies	Donor T cells in the graft proliferate and attack the recipient's tissue.	IV	Associated with bone marrow transplants. Presents with diarrhea, rash, and jaundice.

Description

Reproduced from Transplant Rejection: Hyperacute, Acute, Chronic & Graft Versus Host by Stomp On Step1. Retrieved from https://www.stomponstep1.com/transplant-rejection-hyperacute-acute-chronic-graft-versus-host/

Acute tissue rejections are the most common and treatable type of rejection. These reactions usually occur between 4 days and 3 months following the transplant. Acute reactions are cell mediated and result in transplant cell destruction (lysis) or necrosis. The individual exhibits manifestations of the inflammatory process, including fever, redness, swelling, and tenderness at the graft site. Additionally, the individual may experience impaired functioning of the transplanted organ.

Chronic tissue rejection occurs from about 4 months to years after the transplant. This reaction is most likely due to an antibody-mediated immune response. Antibodies and complement molecules are deposited in the transplanted tissue vessel walls, resulting in decreased blood flow and ischemia.

Most rejection reactions are classified as **host-versus-graft rejection**; in other words, the host is fighting the graft. In another type of reaction, known as **graft-versus-host rejection**, the graft fights the host. This potentially life-threatening type of reaction occurs *only* with bone marrow transplants. The immunocompetent graft cells

recognize the host cells as foreign and organize a cell-mediated attack. The host is usually immunocompromised and unable to fight the graft cells' actions.

Identifying the rejection reaction quickly is crucial to reversing it. Assessment for manifestations of a healthy and unhealthy transplant organ is paramount. For example, decreased urine output may indicate a failing transplant when the transplanted organ is a kidney. Diagnostic procedures include laboratory tests to identify immune and inflammatory activity (e.g., white blood cell count and erythrocyte sedimentation rate) and specific tests to determine functioning of the transplanted organ (e.g., renal panel and urinalysis).

Treatment of transplant rejection usually begins with prevention—that is, by ensuring a tissue match and initiating immunosuppressive therapy (e.g., corticosteroids and cyclosporine). The transplant patient will likely require immunosuppressive therapy for life. Once a rejection is suspected, immunosuppression therapy is intensified to reverse it.

Autoimmunity

More than 80 diseases are classified as autoimmune disorders, including SLE, inflammatory bowel disease (which includes Crohn's disease and ulcerative colitis), type 1 diabetes mellitus, and rheumatoid arthritis. In autoimmune reactions, the body's normal defenses become self-destructive—that is, they perceive the self as foreign. What causes this misdirected response is unclear. Some proposed etiologies include viral, genetic, medicinal, hormonal, and environmental factors, but growing consensus suggests that autoimmune disease likely results from interactions between genetic and environmental factors (**FIGURE 2-14**). While the individual autoimmune conditions are relatively rare, collectively they are among the most prevalent diseases in the United States, and this prevalence is increasing for unknown reasons. Autoimmune disorders affect women more often than men, and the risk increases with age. They can affect any tissue or organ in the body, and some are systemic. These disorders are characterized by frequent, progressive periods of exacerbations (worsening of symptoms) and remissions (easing of symptoms). Physical and emotional stressors frequently trigger exacerbations.

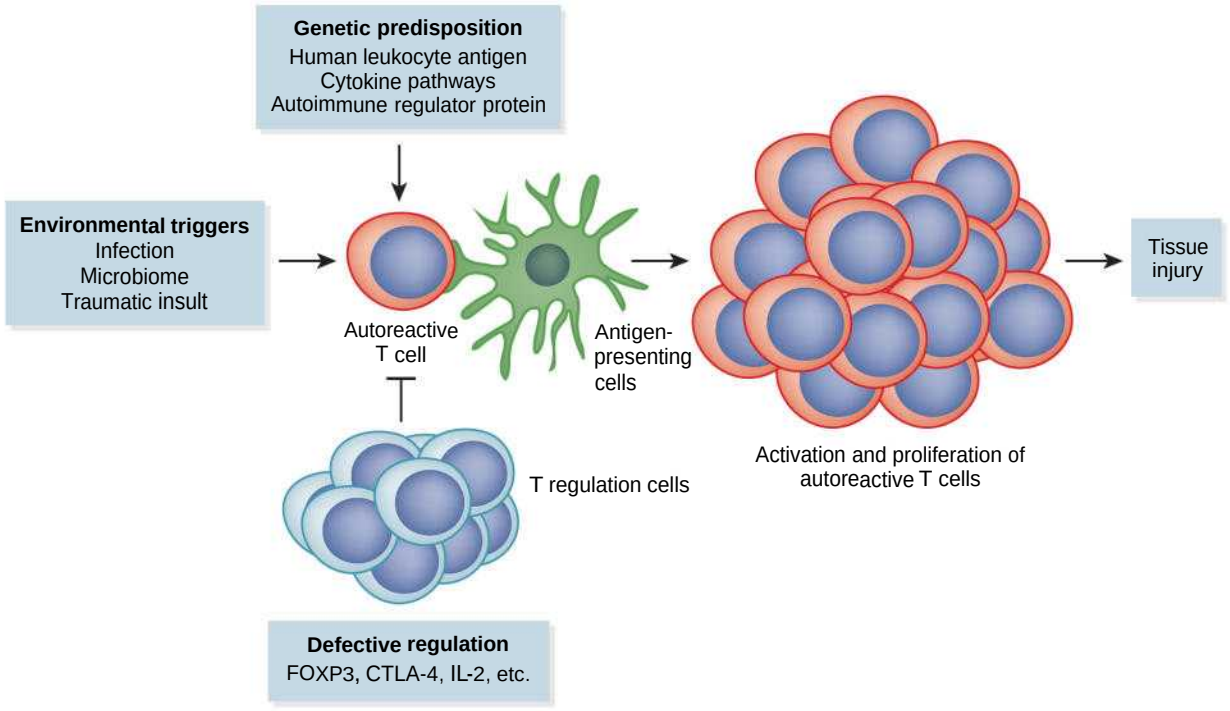


FIGURE 2-14 Genetic susceptibility, environmental stimuli, and defective regulation are responsible for initiating autoimmunity.

Description

Because of the somewhat mysterious nature of autoimmune disorders, diagnostic procedures often begin by eliminating all other causes. Sometimes laboratory tests are used that are specific to the suspected autoimmune disorder (e.g., rheumatoid factor for rheumatoid arthritis). Treatment for autoimmune disorders is disease specific but often includes coping and stress management strategies to prevent exacerbations.

Systemic Lupus Erythematosus

SLE is a chronic, inflammatory, autoimmune disorder that can affect any connective tissue. B cells are thought to be activated for unknown reasons to produce autoantibodies and autoantigens, which then combine to form immune complexes. These immune complexes fight against the body's own tissues (e.g., nucleic acids, red blood cells, platelets, and lymphocytes). Hyperactive helper T cells and subdued

suppressor T cells are thought to create a prime environment for B cells to overproduce.

This unpredictable disorder most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. SLE occurs 9 times more often in women than in men, especially between the ages of 15 and 50, and is more common in Asians and African Americans. X chromosome defects and the effects of estrogen on the immune system are thought to account for the gender differences. Incidence has increased dramatically due to improved diagnostic testing.

application to practice

Now that we have explored the different types of hypersensitivities, let's put that knowledge into practice. During the shift change, you receive reports on the following patients. Which patient would you see first following the report?

- An 11-year-old male with a history of a peanut allergy having an anaphylactic reaction
- A 28-year-old male diagnosed with contact dermatitis secondary to poison ivy exposure
- A 67-year-old female diagnosed with severe hay fever
- A 30-year-old female with a positive tuberculin skin test

When considering these types of situations, start by considering who is at risk of dying or losing a vital function (e.g., limb or organ failure) first. If none of the conditions are life threatening, then consider which ones are acute. Acute issues generally take priority over chronic conditions. Maslow's hierarchy of needs and patient safety are other important considerations.

Now let's get back to our group of patients. The anaphylactic reaction could be life threatening. It triggers a massive system inflammatory reaction, which causes fluid to leave the vascular system and move into the tissues. This systemic inflammatory reaction can cause tissue swelling that blocks the airway and significantly impairs respiratory efforts. The contact dermatitis, while quite uncomfortable, is not life threatening. The hay fever may be severe, but sneezing and watery eyes are not life threatening. The positive skin test may indicate an active tuberculosis infection, which may eventually be life threatening, but it is a chronic condition that does not require immediate life-saving measures. In this group of patients, the nurse should see the 11-year-old first because he requires immediate assessment and measures to prevent death.

Emerging Research: The Link Between Genes and Environment

The National Institute of Environmental Health Services (NIEHS) brought together an interdisciplinary group to focus on unraveling the connection between genetic predisposition and environmental factors and their role in the development of disease. Their comprehensive efforts include a website for participants to connect with active studies (http://joinastudy.niehs.nih.gov). Currently, there are 13 active studies focused on topics such as environmental influences on DNA, immune responses, myositis, vaccine confidence, women's reproductive health, calcinosis, and asthma. This group's findings have included the following discoveries:

- Exposure to solvents found in thousands of everyday products contributes to the development of systemic sclerosis.
- Smoking contributes to the development of rheumatoid arthritis.
- Exposure to fine crystalline silica particles (a component of quartz, granite, and other minerals) contributes to the development of several autoimmune diseases, particularly extensive exposure, such as occurs with occupational exposures.
- Eating gluten (found in wheat and some other grains) contributes to the development of celiac disease.
- Taking certain supplements containing L-tryptophan, an essential amino acid used as a dietary supplement, contributes to the development of eosinophilia-myalgia syndrome, an incurable and sometimes fatal condition involving severe muscle pain.

Manifestations can vary depending on age, gender, and ethnicity. These variations are based on complex interactions between genetics, hormones, and an array of other biological differences that are not completely understood. They can influence the organs that are involved or the severity of the disease. Despite these variations, a common set of manifestations is typically seen with SLE (**TABLE 2-5**). For example, men typically have lower incidence but worse outcomes; they also frequently have renal disease and hypertension. Women tend to have higher incidence but better outcomes, though they frequently develop Raynaud's phenomenon. In contrast, African Americans and Hispanic Americans have worse renal outcomes. Finally, children tend to have more severe manifestations, most often presenting with fever, malaise, weight loss, small-joint arthritis, and renal disease. Older adults usually have a milder presentation with a

higher rate of sicca (e.g., dry eyes and mouth), serositis, and respiratory and musculoskeletal manifestations.

TABLE 2-5 Common Manifestations of Systemic Lupus Erythematosus

Area Affected	Signs and Symptoms
Joints	Polyarthritis, with swollen, painful joints, without damage; arthralgia
Muscle	Myalgia
Skin	Butterfly rash with erythema on cheeks and over nose, or rash on body; photosensitivity—exacerbation with sun exposure; ulcerations in oral mucosa; hair loss
Kidneys	Glomerulonephritis with antigen–antibody deposits in glomerulus, causing inflammation with marked proteinuria and progressive renal damage, nephrotic syndrome
Lungs	Pleurisy—inflammation of the pleural membranes, causing chest pain
Heart	Carditis—inflammation of any layer of the heart, commonly pericarditis
Blood vessels	Raynaud's phenomenon—periodic vasospasms in fingers and toes, accompanied by pain
Central nervous system	Psychoses, depression, mood changes, seizures
Bone marrow	Anemia, leukopenia, thrombocytopenia, thrombosis
Other	Lymphadenopathy, splenomegaly

Because individuals with SLE can have a wide variety of symptoms and different combinations of organ involvement, no single test can definitively establish the diagnosis of this disorder. Until recently, an

11-item set of criteria was used to determine whether the individual had a minimum number of characteristic signs and symptoms. The new criteria use a point system that gives varying weight to each of 22 criteria (**TABLE 2-6**). A positive diagnosis requires a minimum score of 10 of these criteria, and all individuals diagnosed with SLE also must have an antinuclear antibody (ANA) titer of at least 1:80 on Hep-2 cells or an equivalent positive test. Thus, the individual is diagnosed with SLE if a individual has not met the minimum score but has a positive ANA. Likewise, the individual who has a high score of 20 to 30 points but a normal ANA is also diagnosed with SLE. In addition to the implications for diagnosis, the new criteria have implications for research.

TABLE 2-6 New American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) Criteria for Classification of SLE

All patients classified as having systemic lupus erythematosus (SLE) must have a serum titer of antinuclear antibody of at least 1:80 on human epithelial-2–positive cells or an equivalent positive test. In addition, a patient must tally at least 10 points from these criteria. A criterion is not counted if it has a more likely explanation than SLE. Occurrence of the criterion only once is sufficient to tally the relevant points, and the time when a patient is positive for one criterion need not overlap with the time when the patient is positive for other criteria. SLE classification requires points from at least one clinical domain, and if a patient is positive for more than one criterion in a domain, only the criterion with the highest point value counts:

Clinical Domains	Points	Immunologic Domains	Points
Constitutional Domain	2	***Antiphospholipid Antibody Domain***	
Fever		Anticardiolipin IgC > 40 GPL or anti-β2GPI IgC > 40 units or lupus anticoagulant	2
Cutaneous Domain		***Complement Protein Domain***	
Nonscarring alopecia	2	Low C3 or low C4	3
Oral ulcers	2	Low C4 and low C4	4
Subacute cutaneous or discoid lupus	4	***Highly Specific Antibody Domain***	
Acute cutaneous lupus	6	Anti-dsDNA antibody	6
Arthritis Domain		Anti-Smith antibody	7
Synovitis in at least two joints or tenderness in at least two joints, and at least 30 minutes of morning stiffness	6		
Neurologic Domain			
Delirium	2		
Psychosis	3		
Seizure	5		
Serositis Domain			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Hematologic Domain			
Leukopenia	3		
Thrombocytopenia	4		
Autoimmune hemolysis	4		
Renal Domain			
Proteinuria > 0.5 g/24 hr	4		
Class II or V lupus nephritis	8		
Class III or IV lupus nephritis	10		

Description

Data from Aringer, M., Costenbader, K., Daikh, D., Brinks, R., Mosca, M., Ramsey-Goldman, R...Johnson, S. (2019). 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatology*, *71*(9), 1400-1412.

In addition to the new diagnostic criteria, other tests can be helpful in evaluating individuals with SLE to determine the severity of organ involvement. These tests include routine testing of the blood to detect inflammation (e.g., erythrocyte sedimentation rate and C-reactive protein), blood-chemistry testing, complete blood count and differential, direct analysis of internal body fluids, and tissue biopsies.

Abnormalities in body fluids and tissue samples (kidney, skin, and nerve biopsies) can further support the diagnosis of SLE (e.g., urinalysis, serum creatinine, liver function tests, and echocardiography). The appropriate testing procedures are selected on an individual basis.

Treatment of SLE is directed at symptom management. General strategies include stress reduction, exercise, and sleep. Medical treatment includes nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce pain and inflammation in joints, muscles, and other tissues. Corticosteroids may also be used to treat SLE. Corticosteroids are more potent than NSAIDs in reducing inflammation and restoring function when the disease is active, particularly when internal organs are affected, but they have multiple side effects (e.g., weight gain, risk for infection, hyperglycemia, and high blood pressure) that must be considered. Biologic disease-modifying antirheumatic drugs (DMARDs) reduce pain and tissue damage as a result of inflammation. DMARDs are more potent than NSAIDs and corticosteroids, but they carry significantly more risks (e.g., risk for infection and organ damage). As the disease progresses, use of these agents may be necessary to prevent severe complications of SLE. Antimalarial drugs can treat fatigue, joint pain, rashes, and pleural inflammation by suppressing the immune system. Immunosuppressants may be used for patients with kidney and nervous system involvement. Additionally, plasmapheresis can remove antibodies and other immune substances from the blood to suppress immunity.

Immunodeficiency

A diminished or absent immune response increases susceptibility to infections. Immunodeficiencies may be either primary (reflecting a defect with the immune system) or secondary (reflecting an underlying disease or factor that is suppressing the immune system). **Primary immunodeficiencies** usually result from genetic and congenital abnormalities (e.g., hypogammaglobulinemia, asplenia, and severe congenital neutropenia). **Secondary or acquired**

immunodeficiencies are caused by infections (usually viral), iatrogenic reactions to therapeutic drugs (e.g., corticosteroids and chemotherapy) or splenectomy, malnutrition, liver disease, or stress. The underlying problem in such a case may be either acute or chronic.

Immunodeficiency states predispose individuals to **opportunistic infections**. Opportunistic infections are caused by pathogens that do not usually cause disease in healthy individuals (e.g., toxoplasmosis, Kaposi sarcoma, candidiasis infections). These infections often arise from a disruption of the normal flora. Opportunistic infections can be difficult to treat successfully and can become life threatening. These infections need to be identified and treated early to improve the individual's prognosis.

application to practice

Twenty-eight-year-old Steve Crosby is admitted to the hospital from his healthcare provider's clinic office. This patient was diagnosed as HIV positive 4 years ago. He presented to the clinic with fatigue, a productive cough, and a 10-pound weight loss over the past month. A tuberculosis (TB) skin test was administered in the clinic. Admission orders include "Isolation precautions for possible TB."

1. Which of the following statements by this patient indicates that he understands why he is at risk for TB?
   a. "I realize my helper T cells are diminished from HIV. Those are the cells needed to fight TB."
   b. "I may get TB because my viral load count is diminished."
   c. "I am at risk for developing TB because I was born with a low number of helper T cells."
   d. "I realize I am at risk for acquiring TB because I used intravenous drugs in the past."

One of the unlicensed assistive personnel (UAP) caring for Mr. Crosby says, "Now that Mr. Crosby's condition has worsened and he is symptomatic, shouldn't added precautions be posted on his door to protect staff members?"

1. Which information should the nurse give the UAP?
   a. Reverse isolation precautions should be implemented to protect the staff.
   b. Respiratory precautions are all that are needed, and those are already posted on the door.
   c. Following standard precautions will minimize the exposure to blood and body fluids.

d. Staff members caring for Mr. Crosby should begin prophylactic medications.

2. What should the nurse say to the UAP?
   a. “Wearing all that equipment is a waste of supplies, and we have already had budget cuts.”
   b. “Can you tell me what you are getting ready to do?”
   c. “Don’t you know all that equipment is not necessary?”
   d. “Wearing all that equipment may frighten Mr. Crosby.”

It is important that Mr. Crosby understand how to prevent the spreading of HIV before he is discharged home. When discussing infection control practices with the nurse, Mr. Crosby says, “I have heard that condoms don’t always prevent HIV.”

1. How should the nurse respond?
   a. “Where do you usually get your health information?”
   b. “I will have an AIDS educator come discuss condom use with you.”
   c. “I know you would feel terrible if you gave someone HIV because you didn’t use a condom.”
   d. “If used properly and regularly, latex condoms are highly effective in preventing HIV transmission.”

Diagnosis is often based on clinical suspicion, and referral to an immunologist is warranted if immunodeficiency is suspected. Diagnosis of the immunodeficiency state includes the identification of recurrent or persistent infections. Diagnostic procedures involve measurements of immunoglobulin levels, white blood cells (e.g., complete blood count with differential), and B-cell and T-cell counts (e.g., flow cytometry). Treatment for immunodeficiency states is individualized for the specific deficiency and may include gamma-globulin, bone marrow transplants, or thymus transplants. Reverse isolation precautions (e.g., hand washing, limiting visitors, and avoiding fresh flowers) can limit the person’s exposure to pathogens, thereby decreasing his or her risk for infection. Additionally, vaccinations should be used with caution because some may be potent enough to cause infection or because the immune system may not be capable of developing the antibodies.

AIDS

Acquired immunodeficiency syndrome (AIDS) is a deadly, sexually transmitted disease caused by HIV, a retrovirus. HIV attacks and weakens the immune system. There are two primary strains of the virus: HIV-1 is the most prevalent strain in the United States, and HIV-2 is the most prevalent strain in Africa.

According to the CDC (2022a), approximately 38.4 million people worldwide and 1.2 million people in the United States are living with HIV. HIV is the ninth leading cause of death in individuals 25 to 34 years of age in the United States, down from the number one cause of mortality in this age group in 1995. In 2020, African Americans made up only 14% of the U.S. population but accounted for 42% of all new cases of HIV infections. In 2020, men having sex with men (MSM) accounted for 68% of all new cases of HIV infections. Cases involving female-to-female transmission (women having sex with women) are rare. In terms of regional presence of AIDS in the United States, the South accounted for most new AIDS diagnoses (54%), persons living with an AIDS diagnosis (44%), and AIDS deaths (47%) (CDC, 2022a).

Emerging Research: New Strain of Human Immunodeficiency Virus

For the first time in nearly two decades, researchers discovered a new strain of the human immunodeficiency virus (HIV). This new strain is a subtype of HIV-1, referred to as subtype L of Group M. HIV has the ability to change and mutate over time, and this discovery provides an explanation to how the virus evolves. Identifying this new strain is also important to ensure screening tests are effective. While HIV-1 is the most prevalent strain in the United States, not many people are infected with this new subtype. To be classified as a new HIV strain, the virus must be detected in three independent cases. This new subtype was first identified in the Democratic Republic of Congo in 1983 and 1990, and a third case was identified in the Congo in 2001 as a part of an HIV viral diversity study. The strain was extremely unusual, so researchers tested the entire genome of the most recent case to compare it with the genomes of the older cases using

technology that was not available at the time. This strain's impact on the body, whether similar or different to previous impacts, is unknown. It is believed that current HIV antiretroviral therapies can be used to manage this new strain. This discovery serves as a reminder that continued surveillance and research are needed to ensure the most effective screening and treatments are used to battle the HIV pandemic (Yamaguchi et al., 2020).

HIV is transmitted through direct contact with infected blood, body fluids (e.g., breastmilk, vaginal secretions, semen, cerebrospinal fluid, and saliva), or blood products (rare). Even though saliva and tears can contain HIV, only very low concentrations of the virus are present in these fluids. HIV is not transmitted through saliva and kissing unless open sores are present. The risk of acquiring HIV from an accidental needle stick is minimal (1 in 300 or 0.3%), but the risk of transmission from sharing needles is significantly greater (1 in 150). There have been 58 confirmed cases of occupational HIV transmission to healthcare workers reported to the CDC since 1999; however, underreporting is possible because such reporting is voluntary.

There is a 13% to 40% chance of an infected mother transmitting this infection to her child, but early administration of antiretroviral therapy can decrease the transmission risk by approximately 1%. The antiretroviral drug most commonly used to prevent maternal transmission is Retrovir (zidovudine), which has a high safety index. HIV testing can be done during labor so that antiretroviral therapy can be given during labor or within hours of delivery to reduce the transmission. Cesarean delivery can further decrease the risk of HIV transmission to the fetus, but vaginal delivery is possible under certain circumstances (e.g., when the mother is on treatment and has a low viral load). However, breastfeeding should be avoided because it serves as another mode of maternal–child transmission.

As a retrovirus, HIV requires a host to survive (**FIGURES 2-15** and **2-16**). Once it gains access to the body, the virus invades the CD4+ cells. Once inside the CD4+ cells, it uses an enzyme, reverse transcriptase, to convert the viral RNA to DNA. The viral DNA then becomes integrated into the CD4+ cell's own DNA. As the infected CD4+ cell reproduces, it inadvertently produces viral copies.

Meanwhile, the virus replicates inside the CD4+ cell to the point that the cell membrane is compromised, releasing millions of viral copies into the bloodstream. Each viral copy then attaches to a new CD4+ cell to start the process over again.

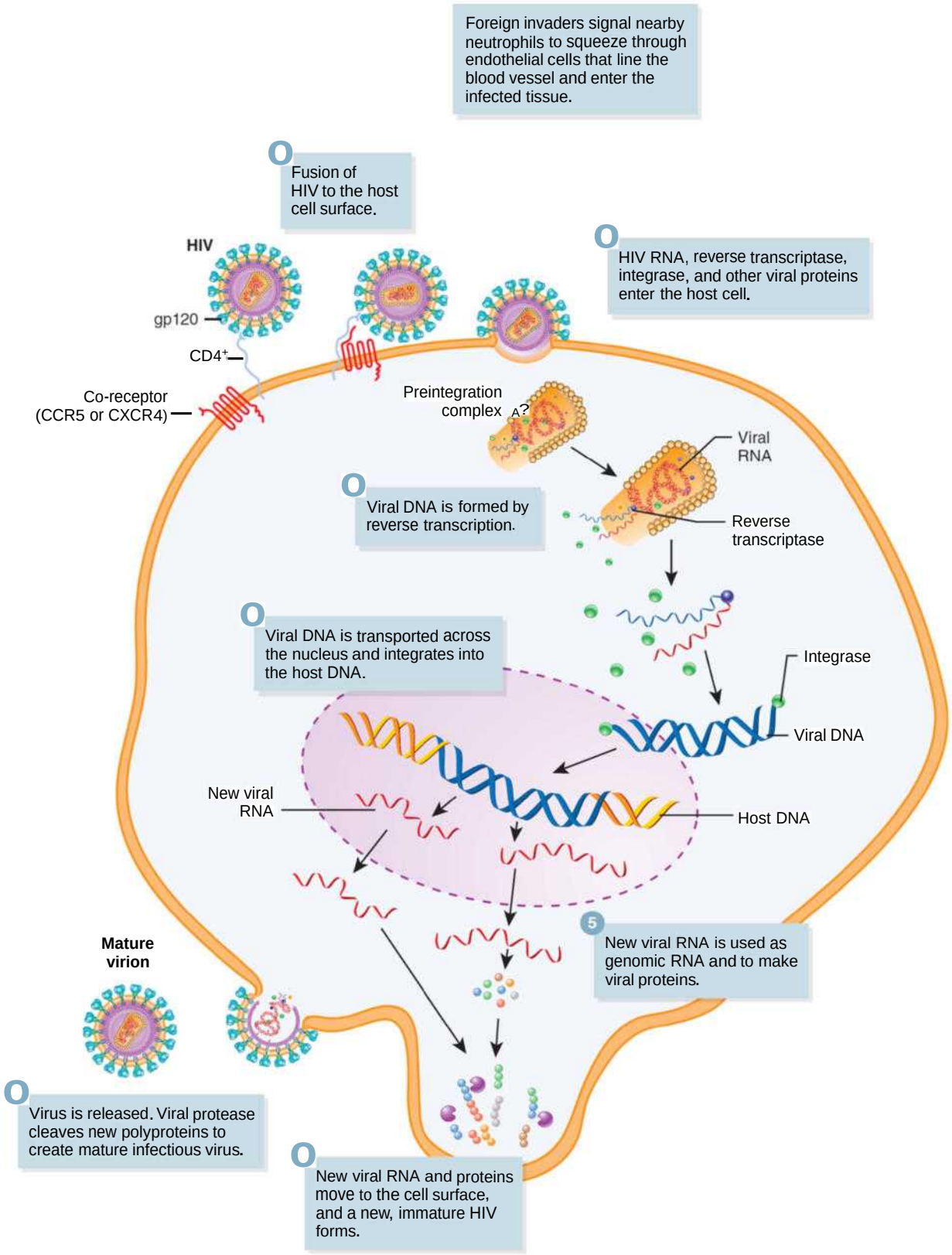


FIGURE 2-15 Human immunodeficiency virus (HIV).

Description

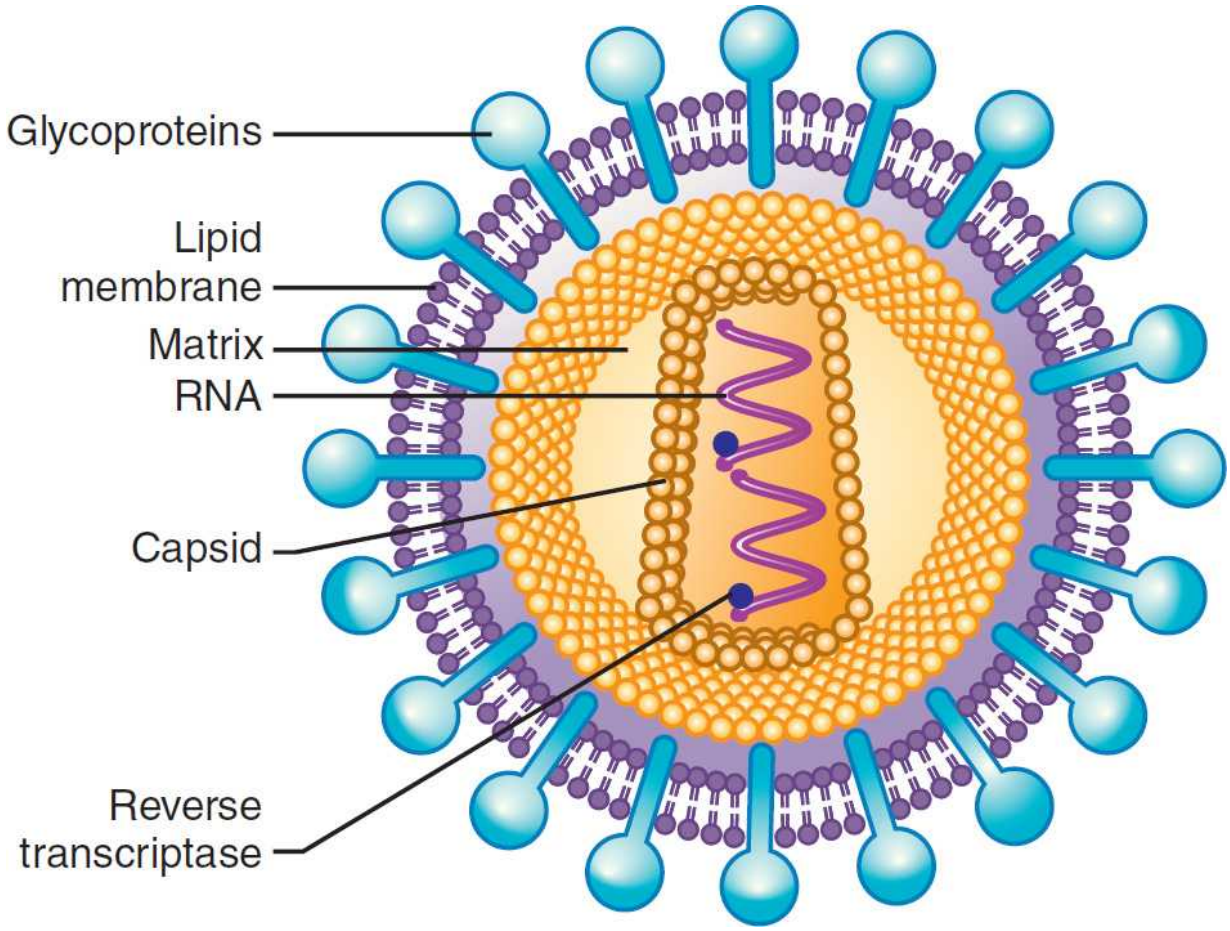


FIGURE 2-16 Structure of human immunodeficiency virus (HIV).

Description

The HIV infectious process takes three forms—immunodeficiency, autoimmunity, and neurologic dysfunction. The immunodeficiency aspect includes opportunistic infections. The autoimmunity aspect includes lymphoid interstitial pneumonitis, arthritis, and hypergammaglobulinemia. Finally, the neurologic dysfunction aspect includes the AIDS dementia complex, HIV encephalopathy, and peripheral neuropathies.

Once infected with HIV, an individual may not experience any symptoms other than a brief episode of flulike symptoms (e.g., fever, malaise, headache, and lymphopathy), referred to as acute retroviral

syndrome. After this brief early infection episode, the individual may remain asymptomatic for months to years while the virus is methodically infecting and destroying CD4+ cells. As more and more CD4+ cells are destroyed, the individual begins to have symptoms (e.g., lymphopathy, diarrhea, weight loss, fever, cough, shortness of breath). The individual becomes more symptomatic as more CD4+ cells are destroyed. Over the next 10 years, serious clinical manifestations begin appearing as the individual moves into the late phase of infections. Life expectancy once diagnosed with AIDS is usually about 3 years unless a serious opportunistic infection develops; then the life expectancy can decrease to 1 year. Disease progression can be improved with antiretroviral medications and adopting healthy lifestyle choices (e.g., exercise, healthy nutrition, safe sex, stress reduction) early.

HIV infection in children may appear differently than the progression just described for adults. Children who are HIV positive may experience the following manifestations:

- Difficulty gaining weight
- Difficulty growing normally
- Problems walking
- Delayed mental development
- Severe forms of common childhood illnesses, such as otitis media, pneumonia, and tonsillitis

Diagnosis can be established through a set of laboratory tests as early as 2 weeks after exposure to the virus. Three types of HIV tests are available—nucleic acid tests (NAT), antigen/antibody tests, and antibody tests. The NAT detects actual viruses in the blood, or viral load. While accurate at an early stage of infection, this test is expensive and not routinely used for screening unless the individual recently had a high-risk exposure or had a possible exposure and also has early symptoms of HIV infection. It is best to get the antigen/antibody test at the same time as the NAT to understand any negative results. An antigen/antibody test detects both HIV antigens

and antibodies. With HIV infection, an antigen called p24 is produced even before antibodies develop. Antigen/antibody tests are recommended as part of laboratory testing and are now common in the United States; a rapid antigen/antibody test is also available. Most rapid tests and home tests are antibody tests, which detect HIV antibodies in blood or oral fluids. Antibody tests performed on blood from a vein can detect HIV earlier than tests performed with blood from a fingerstick or with saliva.

Once HIV/AIDS is confirmed, the NAT is used to predict the probable disease progression, or viral load. The plasma viral load, or number of viral particles per milliliter of blood, is an indication of clinical progression. The higher the viral load, the further the disease has progressed. The NAT is the most appropriate test for infants because the mother's circulating antibodies will make the infants test positive. The aim of antiretroviral therapy is to reduce the viral load to a point that the body's immune system can keep the virus in check. Viral load can also be an indicator of treatment success, along with other indicators such as CD4+ count and presence of opportunistic infections.

HIV infection progression is classified using two systems: CD4+ count and symptom presentation (TABLE 2-7). These classification systems are used to track progression and treatment effectiveness.

TABLE 2-7 HIV/AIDS Classification System

CD4+ Classification System	
Category 1	CD4+ cell count ≥ 500 cells/mm^3
Category 2	CD4+ cell count 200–499 cells/mm^3
Category 3	CD4+ cell count < 200 cells/mm^3

Clinical Presentation Classification System

Category A	Asymptomatic HIV infection Persistent, generalized lymph node enlargement Acute HIV infection with accompanying illness or history of acute HIV infection
Category B	Bacillary angiomatosis (skin infection) Oropharyngeal or vaginal candidiasis (yeast) infection Fever or diarrhea lasting longer than a month Idiopathic thrombocytopenic purpura (autoimmune bleeding disorder) Pelvic inflammatory disease (infection of the female reproduction organs) Peripheral neuropathy (peripheral nerve damage)
Category C	Bacterial pneumonia, recurrent (≥ 2 episodes in 12 months) Candidiasis of the respiratory tract and esophagus Invasive cervical cancer Fungal infections Parasitic and protozoan infections (> 1-month duration) Cytomegalovirus disease Encephalopathy Herpes simplex: chronic ulcers (> 1-month duration) Histoplasmosis Kaposi sarcoma Lymphoma *Mycobacterium avium* complex *Mycobacterium tuberculosis* *Pneumocystis jiroveci* (formerly *carinii*) pneumonia Progressive multifocal leukoencephalopathy *Salmonella* septicemia Toxoplasmosis of the brain Wasting syndrome due to HIV (involuntary weight loss > 10% of baseline body weight) associated with either chronic diarrhea (≥ 2 loose stools per day ≥ 1 month) or chronic weakness and documented fever ≥ 1 month)

Although there is no cure for AIDS, antiretroviral therapy is used to control the reproduction of the virus and slow the progression of the disease. Most people can get the virus under control within six months. Treatment has become more streamlined and may include oral or injectable medications. Generally, oral medications are recommended for individuals who are just starting treatment. There are many FDA single-pill and combination medications available. The injectable medications are recommended for individuals who have had an undetectable viral load for at least three months. Highly active

antiretroviral therapy (HAART)—the recommended treatment approach—includes three or more antiretroviral medications from different classes. The approved classes include nucleoside/nucleotide reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, integrase strand transfer inhibitors, fusion inhibitors, CCR5 (C-C chemokine receptor type 5) receptor antagonists, and postattachment inhibitors. Pharmacokinetic enhancers may also be used to increase the effectiveness of the medication regimen. HAART has been very effective in suppressing HIV replication, but resistance can occur if the individual does not strictly adhere to the prescribed regimen. Genetic tests that can determine whether the individual's particular HIV strain is resistant to a particular drug are now available, and this information can be used to ensure that the best possible combination of drugs is prescribed. Other treatment strategies may include medications to treat specific opportunistic infections as they arise, manage the numerous drug side effects (e.g., high cholesterol and blood glucose levels), and prevent reexposure. Continued exposure to HIV can increase the viral load and introduce another strain—both factors that can accelerate the disease's progression.

Preventing HIV transmission is a worldwide public health priority. Medications can also be taken to prevent the development of HIV, known as "preexposure prophylaxis" (PrEP) and "postexposure prophylaxis" (PEP). PrEP consists of giving daily low doses of antiretroviral medications to individuals who are at high risk for HIV. This regimen prevents the HIV from attaching and spreading. It is effective if taken consistently. Daily PrEP can reduce HIV transmission from sex by 90% and from intravenous drug use by 70%. Risk is lowered further when PrEP is used in combination with other prevention. PEP consists of giving antiretroviral medications to someone who has potentially been exposed to HIV to prevent that person from becoming infected. PEP is used only in emergency situations and must be started within 72 hours after possible exposure.

Additional prevention includes the following strategies:

- Avoiding contact with bodily fluids
- Avoiding activities that increase the risk of exposure to those bodily secretions (e.g., drug use and multiple sexual partners)
- Education (e.g., safer sex practices, medication regimen)
- Using condoms with every sexual experience
- Male circumcision (reduces the risk of female-to-male transmission of HIV and other sexually transmitted infections)

Myth Busters

Despite efforts to educate the public, many misconceptions persist regarding HIV/AIDS.

Myth 1: I can get HIV by being around people who are HIV positive.

Evidence has consistently demonstrated that HIV cannot be spread through touch, tears, or saliva. In addition, HIV is not stable outside the body. The virus cannot be transmitted through toilet seats, water fountains, eating utensils, exercise equipment, hugging, or kissing.

Myth 2: I can get HIV from mosquitoes.

Although HIV spreads through blood, several studies have shown that mosquitoes cannot transmit HIV, even in areas with high numbers of mosquitoes and HIV cases. Mosquitoes do not inject the blood they consume into the next person they bite, and the virus lives only a short time in the insect.

Myth 3: If I'm receiving treatment, I can't spread the HIV virus.

Effective treatment can decrease the viral load in the blood, even to the point that the virus cannot be detected by a blood test. However, the virus can hide in other areas of the body, waiting for an opportunity to increase its replication again. The risk of transmission is lower when the viral load is lower, but transmission is still possible.

Myth 4: My partner and I are both HIV positive, so there's no reason to practice safer sex.

Continued exposure to HIV can increase the viral load and introduce another strain—both factors that can accelerate the disease's progression. Practicing safer sex (e.g., wearing condoms and using other barriers) can limit exposure to HIV and other sexually transmitted infections.

Myth 5: You can’t get HIV from oral sex.

It is true that the risk of transmission through oral sex is lower than with other types of sex, but HIV can be transmitted by having oral sex with either a man or woman who is HIV positive.

Developing a Strong Immune System

The key to preventing infectious diseases is building a strong immune system. Many people assume that the best way to stay healthy is to avoid exposure. However, it requires early exposure to antigens to operate optimally because the immune system is a memory system. Exposure to microbes is limited today because of small family units, good sanitation, and widespread antibiotic use. Research suggests that avoiding oversanitizing our environment can increase exposure to microbes earlier and help develop a stronger immune system. Lifestyle strategies that can support immune function include smoking cessation, proper nutrition, regular exercise, maintaining a healthy weight, moderate alcohol consumption, and stress management. Vaccinations can provide additional support whether healthy or immunocompromised.

application to practice

Let's put the things you have learned about the body's defenses into practice. Which of the following individuals would be at the highest risk for impaired immune function?

- A 23-year-old female who weighs 5% more than her ideal body weight
- A 78-year-old male with poorly controlled diabetes mellitus
- An 89-year-old male with controlled hypertension
- A 45-year-old female who was recently widowed

When considering this type of question, you start by counting things that might impair the immune system. The patient with the most risk factors is at the greatest risk. Eliminate any information that does not increase risk. For instance, being male or female does not impair immune function, so eliminate that factor from your consideration.

Let's look at each of the example patients. The 23-year-old is not in an older age range and is fairly close to her ideal body weight; she has no risk factors. The 78-year-old is assigned one risk factor for his increased age and another for his chronic disease. Go ahead and give him another risk factor because his diabetes is uncontrolled—now he has three risk factors. The 89-year-old has one risk factor for his increased age and another for having a chronic disease, but his hypertension is controlled. He has two risk factors. Finally, the 45-year-old has only one risk factor, the stress of being recently widowed. After

examining all of these patients, the 78-year-old male is at the most risk for impaired immune function owing to his three risk factors.

At-risk individuals and states that specifically put individuals at risk for an impaired immune system include the following:

- Very young or very old age
- Poor nutrition
- Impaired skin integrity
- Circulatory issues
- Alterations in normal flora due to antibiotic therapy
- Chronic diseases, especially diabetes mellitus
- Corticosteroid therapy
- Chemotherapy
- Smoking
- Alcohol consumption
- Immunodeficiency states

The following strategies can be employed to build a healthy immune system:

- Increasing fluid intake
- Eating a well-balanced diet
- Increasing antioxidants and protein intake
- Getting adequate sleep
- Avoiding caffeine and refined sugar
- Spending time outdoors
- Reducing stress

SUMMARY

Humans are in a constant state of warfare with often unseen enemies. The body takes a multilevel approach to prevent attacks and eliminate invaders. Problems can occur at any of these levels that can lead to overreactions, underreactions, and inappropriate reactions. These altered reactions can produce disease states that negatively affect the body. Multiple conditions can impair the body's ability to battle, but when armed with the appropriate weapons, the body becomes a fighting machine that can withstand many fierce invaders.

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CHAPTER 3

Hematopoietic Function

LEARNING OBJECTIVES

- Discuss normal hematopoietic function.
- Explain hematopoiesis and hemostasis.
- Describe and compare diseases of the white blood cells.
- Describe and compare diseases of the red blood cells.
- Describe and compare diseases of the platelets.

KEY TERMS

anemia
disseminated intravascular coagulation (DIC)
erythrocyte
hematocrit
hematopoiesis
hemoglobin
hemoglobin S
hemolysis
hemophilia A
immune thrombocytopenic purpura (ITP)
infectious mononucleosis
leukemia
leukocyte
leukocytopenia
leukocytosis
multiple myeloma
neutropenia

neutrophil
pancytopenia
plasma
plasmin
pus
thrombocyte
thrombocytopenia
thrombocytosis
thromboplastin
thrombotic thrombocytopenic purpura (TTP)
von Willebrand disease

Blood is the life fluid of the human body, and it is essential for health and homeostasis. The approximately 5 liters of blood continuously circulating in the human body provides nutrients and oxygen to tissues while aiding in the excretion of waste products. Blood consists of **plasma**, blood cells, and platelets. Disease occurs when there are too few, too many, or dysfunctional blood components. These conditions can result from congenital or genetic causes, but they can also be acquired from medical treatment (iatrogenic). Healthcare providers, especially nurses, play a pivotal role in identifying those persons at risk and assisting in the management of these diseases.

Normal Hematopoietic Function

Blood is both a viscous fluid and a tissue. Blood is considered a connective tissue because it contains a collection of specialized cells suspended in a liquid matrix (plasma) that serve particular functions. Blood accomplishes its functions through its various components: the plasma (liquid protein), **leukocytes** (white blood cells), **erythrocytes** (red blood cells), and **thrombocytes** (platelets) (**FIGURE 3-1**; **TABLE 3-1**).

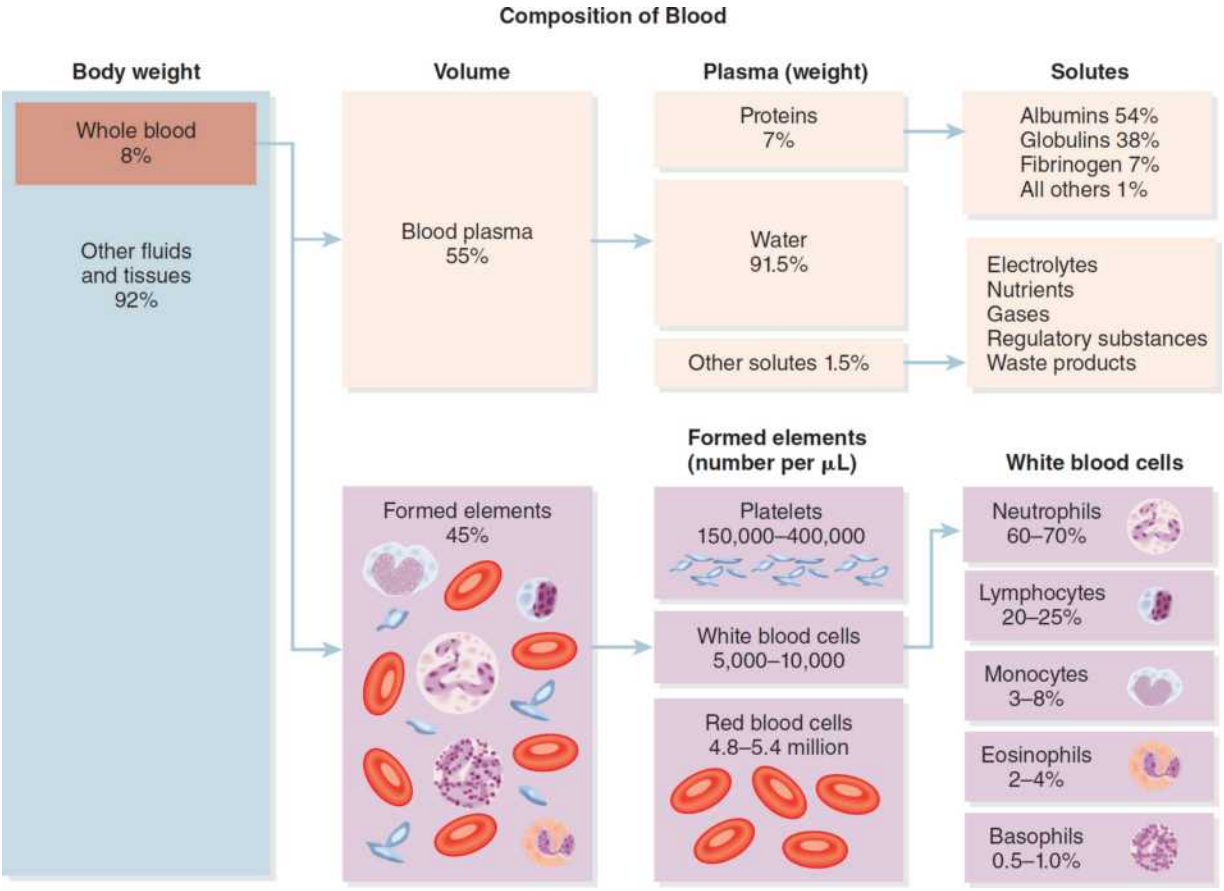


FIGURE 3-1 Composition of blood.

Description

TABLE 3-1	Summary of Blood Cells

Name	Light Micrograph	Description	Concentration (Number of Cells/mm3)	Life Span	Function
Red Blood Cells (RBCs)		Biconcave disk; no nucleus	4–6 million	120 days	Transport oxygen and carbon dioxide
White Blood Cells (WBCs)					
Neutrophil		Approximately twice the size of RBCs; multilobed nucleus; clear-staining cytoplasm	3,000–7,000	6 hours to a few days	Phagocytizes bacteria
Eosinophil		Approximately the same size as a neutrophil; large pink-staining granules; bilobed nucleus	lOO^t00	**8–12** days	Phagocytizes antigen–antibody complex; attacks parasites
Basophil		Slightly smaller than a neutrophil; contains large purple cytoplasmic granules; bilobed nucleus	20–50	A few hours to a few days	Releases histamine during inflammation
Monocyte		Larger than a neutrophil; cytoplasm is grayish blue; no cytoplasmic granules; U- or kidney-shaped nucleus	100–700	Lasts many months	Phagocytizes bacteria, dead cells, and cellular debris
Lymphocyte		Slightly smaller than a neutrophil; large relatively round nucleus that fills the cell	**1**,500–3,000	Can persist for many years	Involved in immune protection, either attacking cells directly or producing antibodies
Platelets		Fragments of megakaryocytes; appear as small dark-staining granules	250,000	5–10 days	Play several key roles in blood clotting

Plasma is the yellowish liquid portion of the blood that makes up the largest component of the blood. Mostly made up of water, plasma is a transport medium that carries the blood cells as well as antibodies, nutrients, electrolytes, hormones, lipids, and waste products. Plasma consists of dissolved proteins (e.g., albumin, globulins, and fibrinogen). These proteins—particularly albumin—maintain the colloid oncotic (osmotic) pressure, which keeps

electrolyte and fluid balance in the blood vessels. Protein consumption and production as well as hydration status can affect plasma's functions.

Leukocytes are key players in the inflammatory response and infectious process (see the *Immunity* chapter). All leukocytes have a nucleus, which distinguishes them from other blood cells. These white blood cells (WBCs) can be classified by their structure (e.g., granulocytes or agranulocytes) or by their cell lineage (e.g., myeloid or lymphoid cells). The five main types of WBCs are **neutrophils**, eosinophils, basophils, lymphocytes, and monocytes. These types can have subtypes, such as with lymphocytes: there are B cells, T cells, and natural killer cells. In infants (during the first year of life), monocytes and eosinophils are the most abundant. In adults, neutrophils are the most plentiful, followed by lymphocytes. Leukocyte numbers in general decrease with age, decreasing the immune response.

Erythrocytes are disk-shaped cells that carry oxygen to tissues and transport carbon dioxide out of the tissues for its subsequent removal from the body. These red blood cells (RBCs) contain proteins and **hemoglobin**, which binds to oxygen, giving blood its red color. The brighter the shade of red, the more the blood is saturated with oxygen. **Hematocrit** refers to how much of the blood volume consists of erythrocytes.

Thrombocytes, along with clotting factors, control coagulation. Carried passively in the blood, thrombocytes are coated with a sticky material that causes them to adhere to irregular surfaces. Clotting (i.e., coagulation) is a quick chain reaction stimulated by the release of **thromboplastin** from damaged cells lining the blood vessels in the area of an injury (**FIGURES 3-2** and **3-3**). In conjunction with the initiation of the clotting cascade (**FIGURE 3-4**), platelets containing contractile proteins pull the edges of the wound together. Blood clots do not persist indefinitely; if they did so, they would clog up the entire circulatory system. **Plasmin** is an enzyme that dissolves clots once healing has occurred.

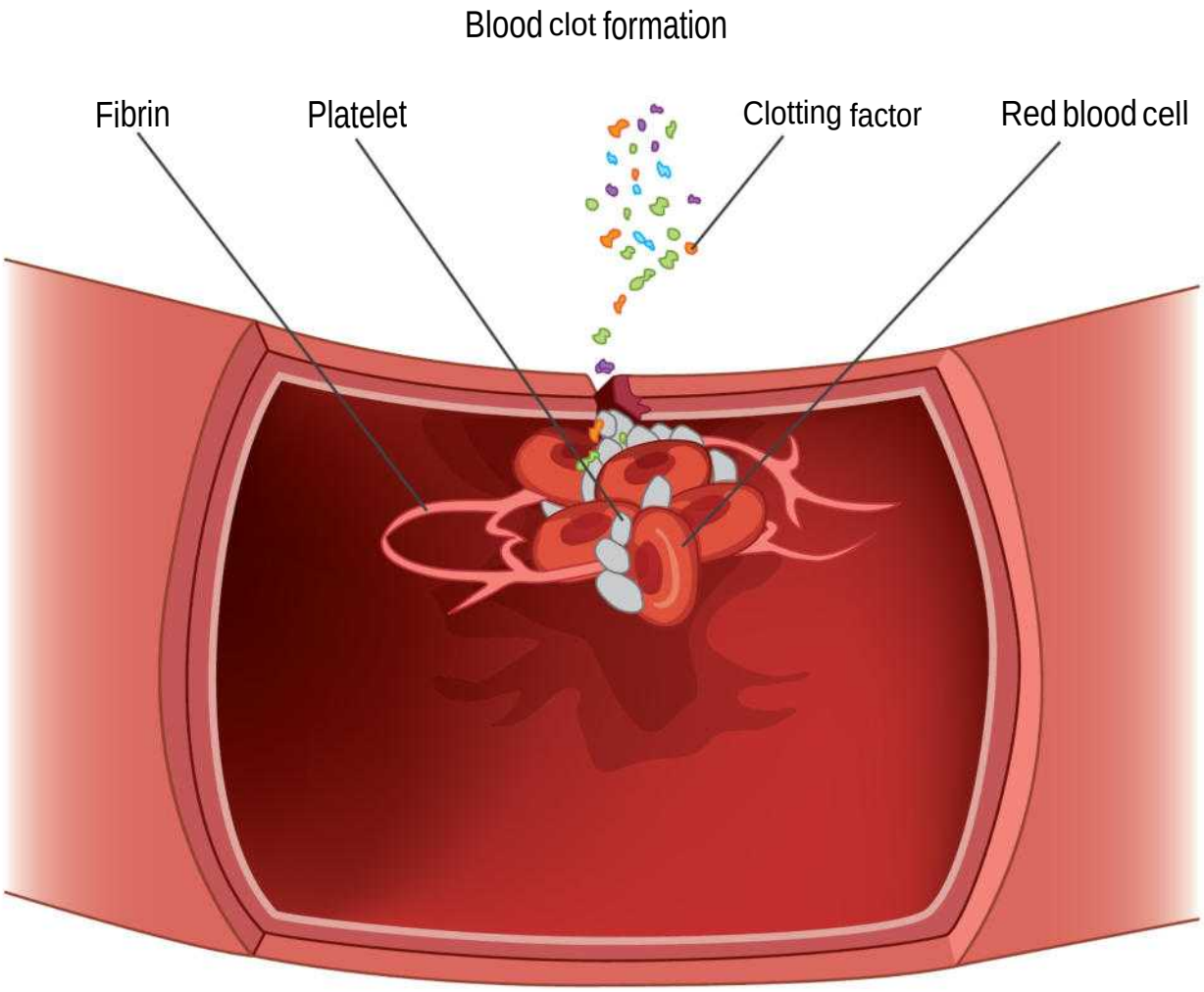


FIGURE 3-2 Blood clotting.

Description

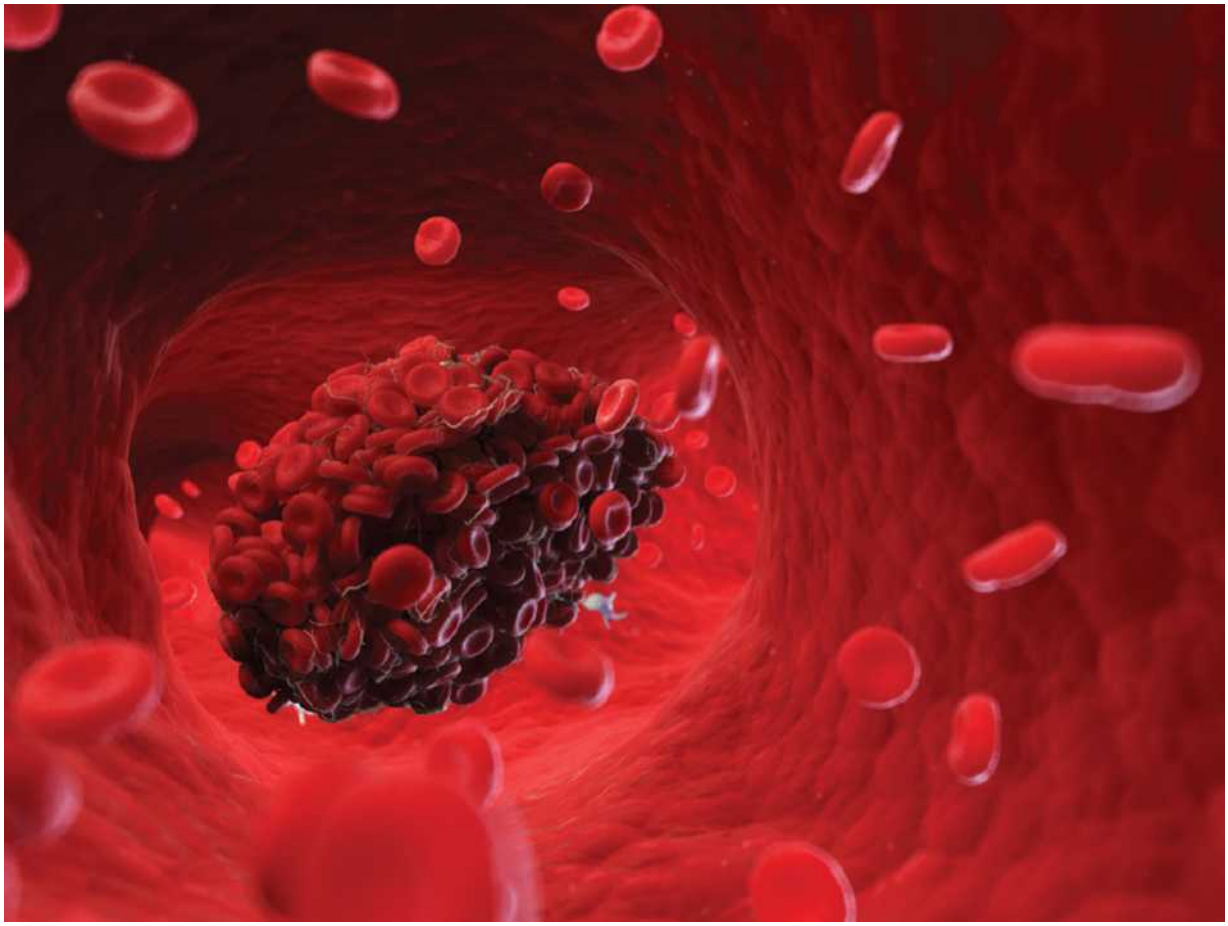
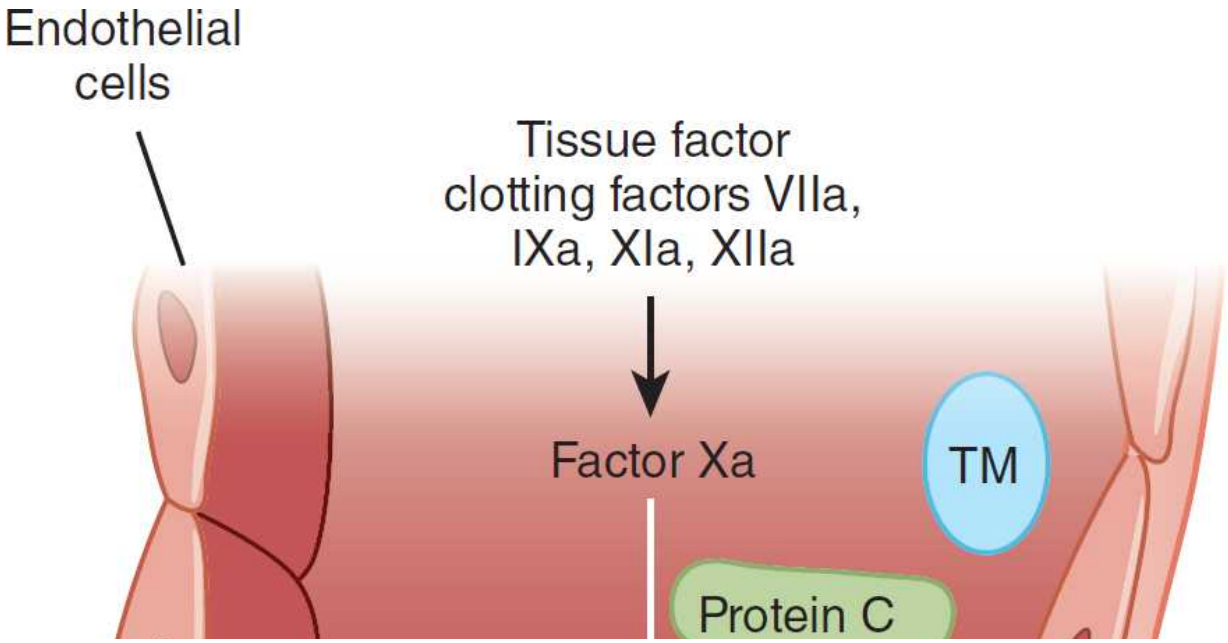


FIGURE 3-3 Blood clot.

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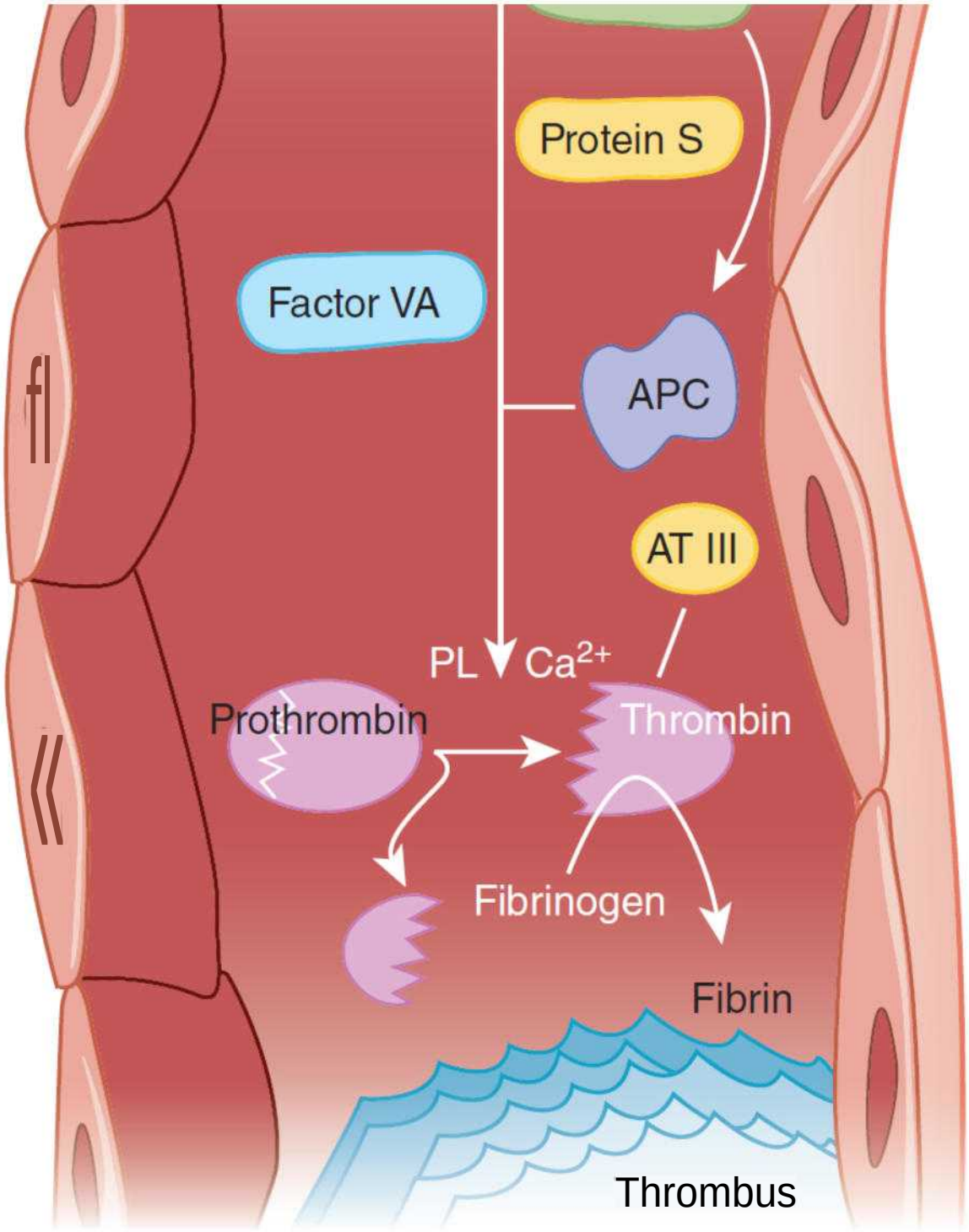


FIGURE 3-4 Clotting cascades.

Based on Dean, L. (2000). Mutations and blood clots: How point mutations in clotting factor genes conspire to increase the risk of thrombosis. In L. Dean, J. McEntryre (Eds.), *Coffee break: Tutorials for NCBI tools*. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK2318

Description

Hematopoiesis

Hematopoiesis is the process of blood formation that begins during the first weeks of embryonic development. In utero, the embryo produces only erythrocytes so that the developing organs can have oxygen. The yolk sac, the precursor to the placenta, controls hematopoiesis at this stage. As the embryo develops, this control shifts to the liver, spleen, and bone marrow; hematopoiesis begins to include other blood cells at this point. In adults, hematopoiesis of erythrocytes and platelets occurs primarily in the bone marrow, but it may also occur in the spleen and liver in infants and children. The lymph system (particularly the spleen, lymph nodes, and thymus) produces lymphocytes. The liver, spleen, lymph nodes, and other organs produce monocytes. With increasing age, both the number and the function of all blood cells decrease.

The rate of hematopoiesis depends on the body's needs. The body continuously produces new blood cells to replace old ones. For example, hypoxia and blood loss stimulate erythrocyte production, whereas infection and inflammation stimulate leukocyte production. Approximately 1% of the body's blood cells must be replaced daily. This process requires an adequate supply of hematopoietic stem cells. These stem cells (primitive cells) differentiate to form the precursors for the different types of blood cells, but they are not fully developed (**FIGURE 3-5**). Eventually, these immature cells divide and mature into the various blood cells. Maturation occurs in various locations, including the thymus (T cells), bone marrow (B cells), peripheral blood (erythrocytes, neutrophils, monocytes), and tissue (plasma).

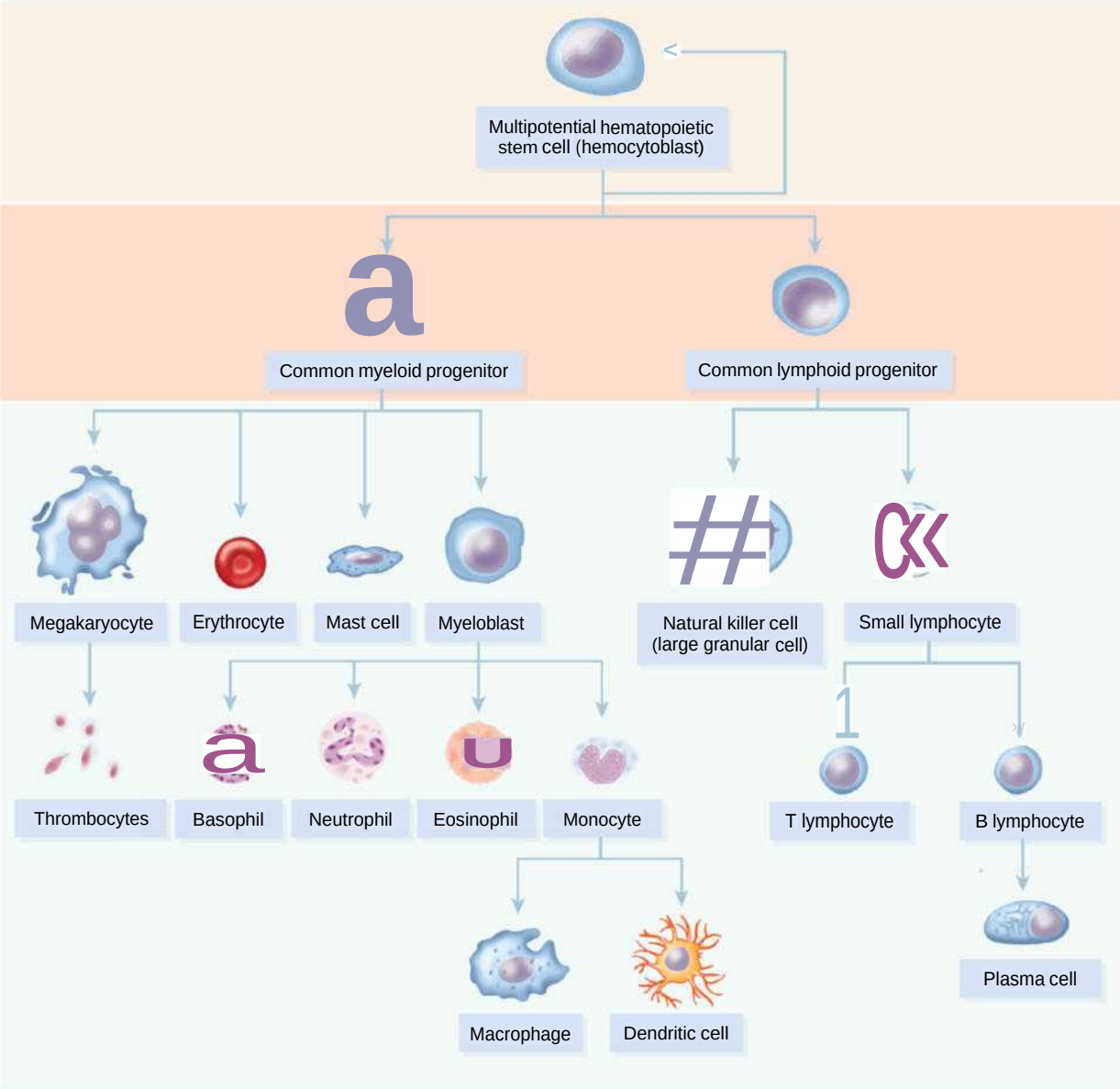


FIGURE 3-5 Hematopoiesis.

Description

Erythropoiesis refers to the hematopoiesis of RBCs. In response to reduced oxygen supply (hypoxia or ischemia), the kidneys (the liver in the fetus) produce a growth factor called "erythropoietin." Erythropoietin stimulates the development and differentiation of the myeloid and lymphoid stem cells and precursor cells. Vitamin B_{12} and folic acid (or folate) are also required for erythropoiesis. Usually obtained through dietary sources, these vitamins are required for

cellular DNA synthesis. Vitamin B_{12} absorption requires a protein called “intrinsic factor,” which is secreted by gastric parietal cells in the stomach. This protein binds with vitamin B_{12} so that it can be absorbed in the small intestine. Because both of these vitamins are water soluble, only small amounts of them can be stored in the body. Excess amounts are excreted in the urine.

In addition to these vitamins, iron is needed for the heme portion of hemoglobin (**FIGURE 3-6**). Hemoglobin is a protein in erythrocytes that carries oxygen, but iron must be present in this protein in the form of heme for oxygen to be transported and released. Iron is mostly obtained from dietary sources (**FIGURE 3-7**). Once absorbed in the duodenum, this mineral is unstable and must bind with apoferritin, a protein, to become ferritin. Ferritin can then be used, transported, or stored. Although some iron remains in the mitochondria to develop enzymes or heme, most of the iron is transported to the bone marrow to make hemoglobin. Approximately 75% of all iron present in the body is found in hemoglobin. Some iron is transported to the liver, where it binds to transferrin receptors and is stored as ferritin. Iron is also present in the spleen, where old erythrocytes are broken down by macrophages, releasing the iron to be recycled. Hepcidin is a protein produced by the liver that tightly regulates dietary iron absorption and transportation.

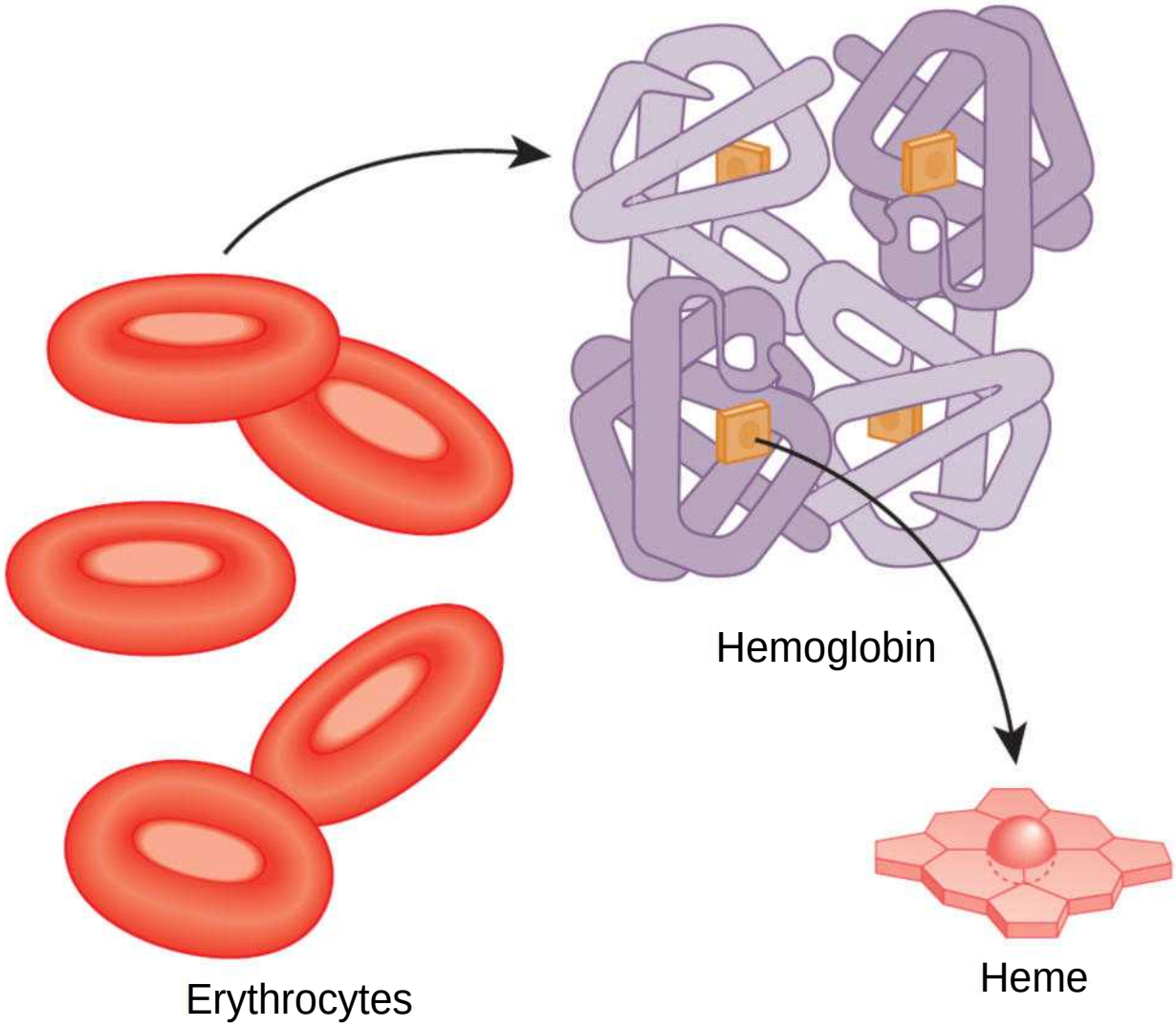


FIGURE 3-6 Hemoglobin.

Description

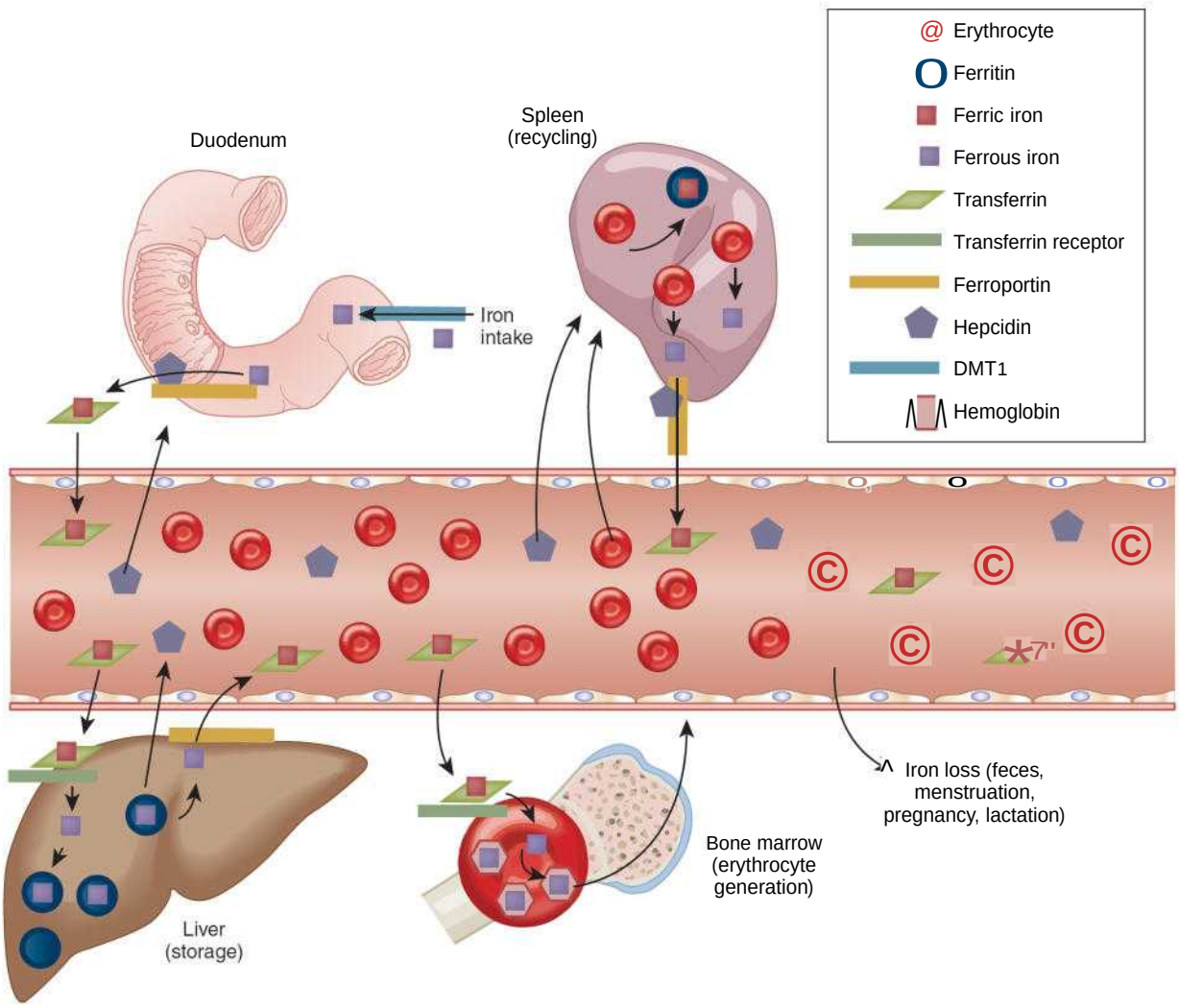


FIGURE 3-7 Oxygen and iron transported through the blood.

Description

During erythrocyte maturation, the cell gets smaller and expels its nucleus once most of the hemoglobin is synthesized, but it can still produce some hemoglobin. At this stage, the cell, now referred to as a "reticulocyte," is released from the bone marrow. The process from precursor to reticulocyte takes about 5 days. Once in circulation, the reticulocytes complete their differentiation into mature erythrocytes.

Hemostasis

Hemostasis is the process that stops bleeding resulting from an injury. The first stage of wound healing involves three steps: vasospasm (or vasoconstriction), platelet plug formation, and coagulation. Vasospasm is a brief reflex in which the blood vessel narrows to decrease blood flow to the injury and increase blood pressure. Next, platelet plug formation involves the activation, aggregation, and adherence of platelets into a plug that serves as a barrier against blood flowing out of the vessel. Coagulation, or clotting, changes blood from a liquid to a gel through a complex cascade of events. During coagulation, a fibrin mesh is cleaved (split) from fibrinogen. Fibrin acts like a kind of glue during clot formation, holding the platelet plug together. Once the blood flow is stopped, tissue repair can begin.

Normally, the endothelial cells of intact blood vessels prevent clotting by releasing fibrinolytic heparin molecules and thrombomodulin, which prevents platelet aggregation and stops the coagulation cascade. In the presence of an injury, vessels stop secreting these substances and produce von Willebrand factor instead, causing platelet adherence (stickiness). Platelets also release von Willebrand factor, serotonin (a vasoconstrictor), and adenosine diphosphate to further promote platelet aggregation. Thromboxane causes platelets to swell, grow filaments (or fibers), and start clumping together. At least 12 substances, called “clotting factors,” take part in the coagulation cascade, and each has a specific function. Platelets release fibrinogen and calcium, which are also necessary for the coagulation cascade. Fibrinogen becomes fibrin through the coagulation cascade catalyzed by the enzyme thrombin. Calcium is necessary for some of the coagulation factors (II, VII, IX, and X) to be activated. Vitamin K manufactured by the liver produces inactive precursors for these same factors. The coagulation process is initiated within 20 seconds of injury, but it may take several minutes for the platelet plug to be completely formed, depending on the size of the injury.

Coagulation inhibitors are important in containing the clot. Proteins C and S, along with antithrombin III, inactivate coagulation factors. Once the injury is stabilized, the fibrin clot is dissolved by the

fibrinolytic system. Thrombin, in addition to activating the coagulation process, activates the fibrinolytic system by stimulating tissue plasminogen activator (t-PA) and urokinase.

Lymphatic System

The lymphatic system plays a critical role in the hematologic, immune, and cardiovascular systems. The thymus, bone marrow, and spleen are the primary lymphoid tissues involved in the hematologic system. The thymus is the site of T cells' maturation. The bone marrow is the site of hematopoiesis. From the bone marrow, the blood cells are released into the circulation. The spleen filters the blood of damaged or aged erythrocytes.

Diseases of the White Blood Cells

Leukocytes are a diverse group of cells that trigger the inflammatory process and combat infections. Normal WBC concentrations range from 5,000 to 10,000 cells/mL of blood. The term **leukocytosis** describes states characterized by increased WBC levels and can indicate an active infectious process. In contrast, **leukocytopenia** refers to decreased WBC levels and can indicate an immune deficiency state (e.g., bone marrow suppression). The blood, by way of the circulatory system, transports leukocytes to the site of an infection. When the leukocytes arrive at the scene, they leak through the capillary wall to the site of trauma or invasion (**FIGURE 3-8**). Most leukocyte disorders originate from deficiencies of one or more of the varying leukocytes.

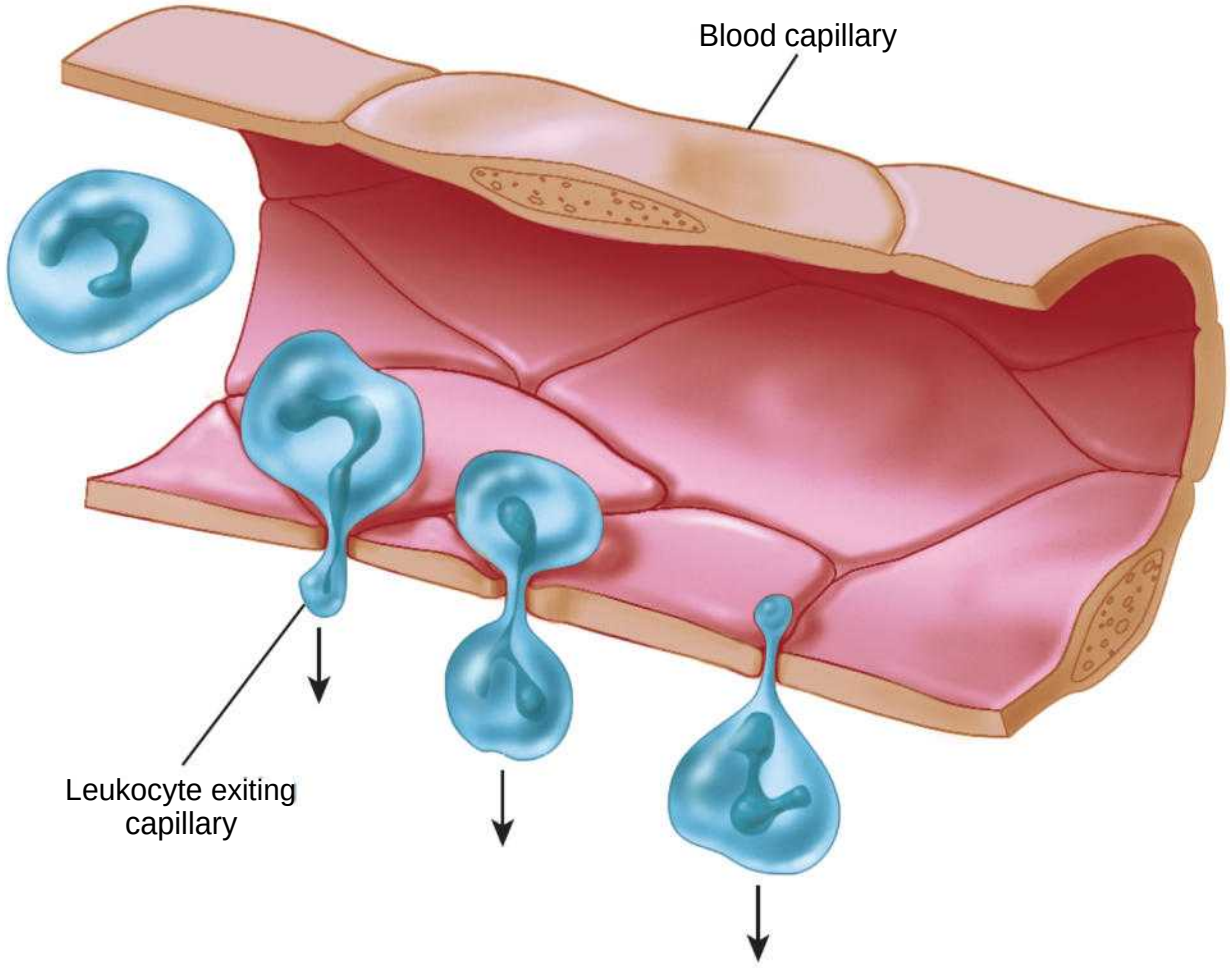


FIGURE 3-8 Leukocyte movement.

Neutropenia

Usually the first responders to arrive on the scene of an infection, neutrophils are attracted by various chemicals released by infected tissue (**FIGURE 3-9**). During times of infection, the number of circulating neutrophils increases, a condition called “neutrophilia.” These cells escape from the capillary wall and migrate to the site of infection. Once they reach the site, neutrophils phagocytize microorganisms, preventing the infection from spreading. As the neutrophils are fully utilized, the infected cells die and become part of the yellowish wound drainage, or **pus**.

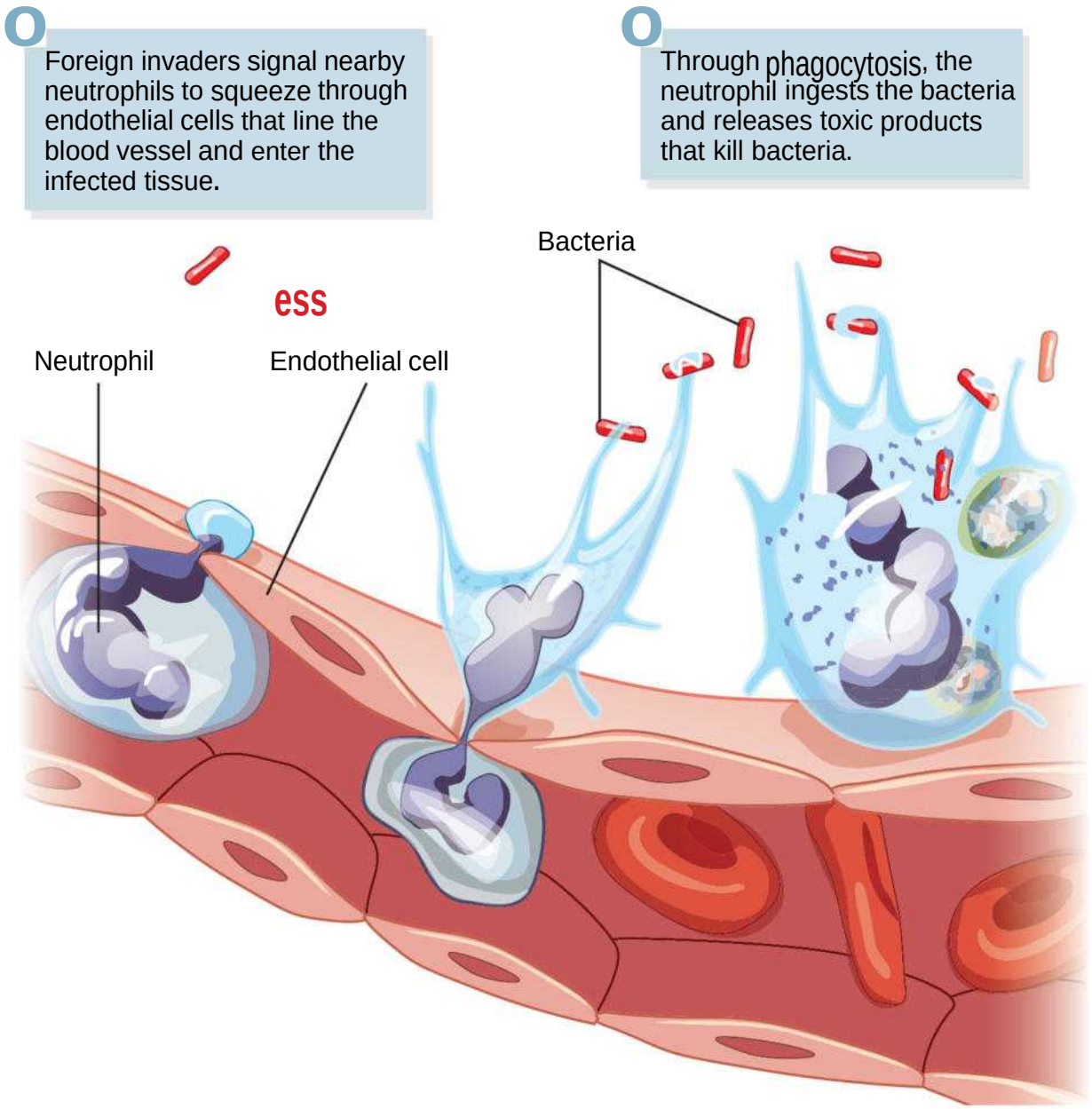


FIGURE 3-9 The role of neutrophils.

Description

Neutropenia refers to a decrease in circulating neutrophils to fewer than 1,500 cells/mL (the normal range is 2,000–7,500 cells/mL). When fewer of these first responders are available, the body is poorly equipped to fight infections. The degree to which the body can fight infections, especially bacterial infections, reflects the severity of the neutropenia. In other words, the lower the neutrophil

count, the lower the body's ability to fight infections, and these infections can be life threatening.

Neutropenia may be a result of decreased overall neutrophil production, production of immature or abnormal neutrophils, or increased utilization or destruction of neutrophils. The neutropenia may develop acutely, over hours to a few days, or neutropenia may be chronic, lasting months to years. Neutropenia may be primary, due to an intrinsic defect in marrow myeloid cells, or secondary, due to factors extrinsic to marrow myeloid cells. Causes of neutropenia may include the following conditions:

- Increased neutrophil usage (e.g., infection and inflammation)
- Iatrogenic bone marrow suppression as a result of drug therapies (e.g., immunosuppressants, chemotherapies, and radiation)
- Congenital conditions (e.g., periodic or cyclic neutropenia)
- Bone marrow cancers (e.g., leukemias and lymphomas)
- Spleen destruction (e.g., Felty syndrome)
- Vitamin deficiency (e.g., vitamin B_{12} and folate deficiency)

Clinical manifestations of neutropenia vary depending on the causes and generally reflect a state of immunodeficiency. They may initially include signs and symptoms of bacterial and fungal infections (e.g., malaise, chills, and fever). The respiratory tract is the most common site of infection. Mouth ulcerations are also often associated with neutropenia, as are ulcerations of the skin, vagina, and gastrointestinal tract.

Diagnostic procedures center primarily on serum neutrophil levels. Neutrophil counts can vary more over short periods as compared to other cell counts. These variations can depend on factors such as activity level, anxiety, infections, and drugs. Therefore, multiple measurements may be needed to determine the severity of neutropenia. Additionally, a bone marrow biopsy may be performed to determine the cause of the neutropenia. Antibiotic therapy is used to treat infections as they develop. Identification and treatment of the cause of the neutropenia are crucial for positive outcomes.

Suspected etiologic agents (e.g., drugs) should be discontinued. Hematopoietic growth factors, such as granulocyte colony-stimulating factors, may be used to stimulate maturation and differentiation of neutrophils. Infection control measures should be implemented until neutrophils return to normal levels (e.g., hand washing, avoiding crowds, etc.).

Infectious Mononucleosis

Infectious mononucleosis, also known as "mono" and the "kissing disease," is an infection most often caused by the Epstein-Barr virus (EBV), also known as human herpes virus 4 (**FIGURE 3-10**). EBV is one of the most common human viruses. Infectious mononucleosis is most frequently seen in adolescents and young adults (1 in 4 of those infected with EBV will develop infectious mononucleosis). Most people have been exposed to the virus as children (50% of children being infected before the age of 5), and because of this exposure, they have developed immunity to the virus (over 90% of adults being seropositive). Consequently, most people who are exposed to EBV do not develop infectious mononucleosis (Centers for Disease Control and Prevention [CDC], 2020).

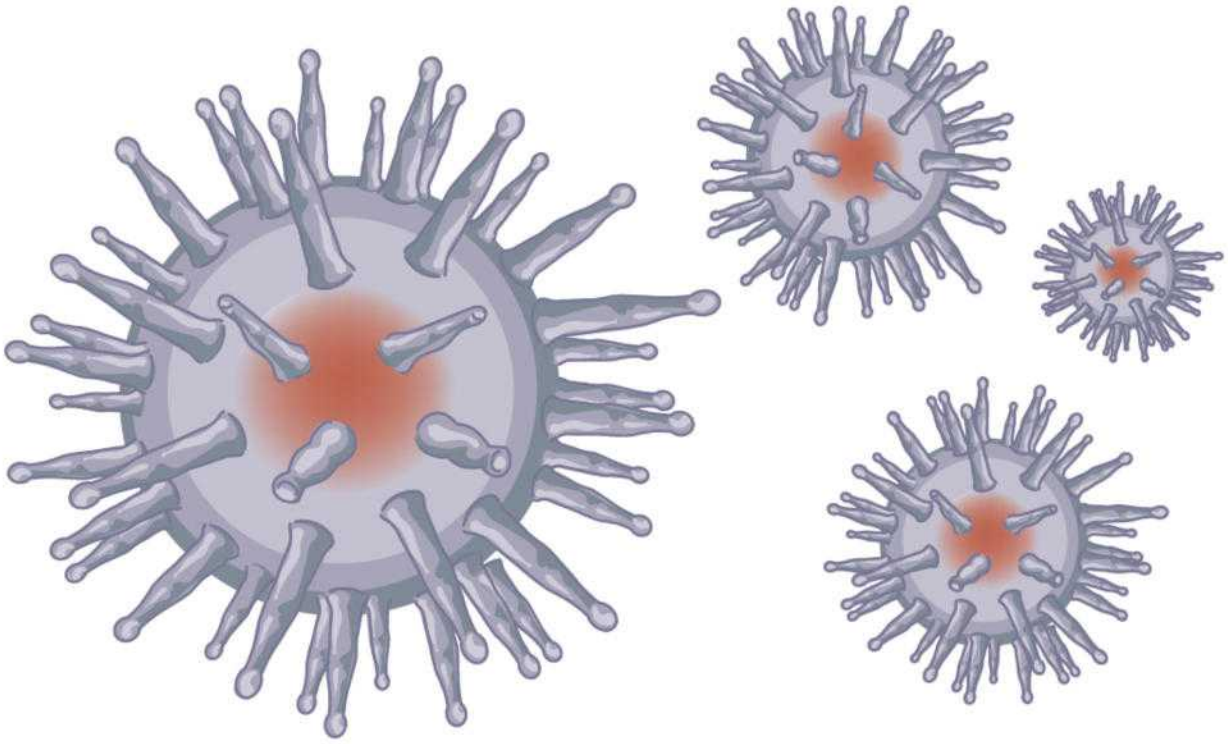


FIGURE 3-10 The Epstein-Barr wirus (EBV).

EBV infects B cells by either killing the cells or being incorporated into their genome. The B cells infected with EBV produce heterophile antibodies that can be identified to diagnose the disease. Once the disease is eliminated, a few B cells remain altered, giving the individual an asymptomatic infection for life and the potential to spread EBV to others if the virus becomes reactivated.

Infectious mononucleosis is usually spread by person-to-person contact. Although saliva is the primary method, transmission can also occur through coughing or sneezing. Coughing and sneezing cause small droplets of infected saliva and/or mucus to become suspended in the air, where they can be inhaled by other people. EBV can survive several hours outside the body, so transmission can occur through sharing toothbrushes, utensils, and glasses as well. The incubation period for infectious mononucleosis is between 4 and 6 weeks. During an infection, a person can transmit the virus to others for at least a few weeks.

Anywhere from 20% to 80% of people who have recovered from infectious mononucleosis will continue to secrete EBV in their saliva

for years due to periodic reactivations of the viral infection, depending on the method used to detect the virus. Because healthy people without symptoms also secrete the virus during reactivation episodes throughout their lifetime, isolation of people infected with EBV is not necessary. These healthy people who secrete EBV particles are believed to be the primary reservoir for transmission of EBV among humans. In addition to causing infectious mononucleosis, EBV can cause several hematological system (e.g., neutropenia, hemophagocytic lymphohistiocytosis, and acquired hypogammaglobulinemia), nervous system (e.g., meningitis, encephalitis, and Guillain-Barré syndrome), and other miscellaneous (e.g., pneumonia, pancreatitis, myocarditis) conditions. Additionally, EBV infection can cause several cancers, including Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma, and non-Hodgkin's lymphoma.

The onset of the clinical manifestations of infectious mononucleosis is usually insidious. The initial flu-like manifestations of malaise, anorexia, and chills can last 1 to 3 days. Following this period, the manifestations intensify and include severe sore throat, fever, and lymphopathy. The acute phase usually lasts 2 to 3 weeks. Some patients may not fully recover for 2 to 3 months, but most people recover without incident. Possible complications of infectious mononucleosis include hepatitis, ruptured spleen, and meningitis.

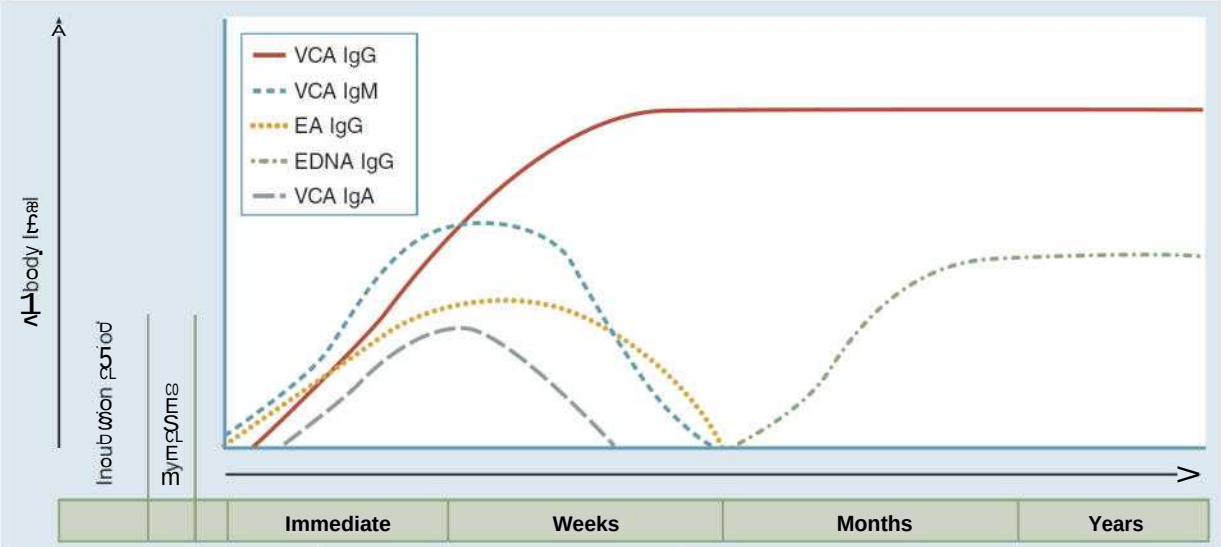
Diagnosis of infectious mononucleosis is typically made based on symptoms, and laboratory tests are not usually necessary. However, laboratory tests can determine whether someone has had a recent or past EBV infection. These tests include:

- Viral capsid antigen (VCA)
  - Anti-VCA IgM appears early and disappears within 4 to 6 weeks.
  - Anti-VCA IgG appears in the acute phase, peaks at 2 to 4 weeks after onset, and declines slightly; it persists for life.
  - Anti-VCA IgA appears early and disappears within 4 to 6 weeks.
- Early antigen (EA)

- Anti-EA IgG appears in the acute phase and usually decreases to undetectable levels after 3 to 6 months.

- EBV nuclear antigen (EBNA)
  - EBNA IgG is not seen in the acute phase but appears slowly 2 to 4 months after onset and persists for life.
- Monospot test
  - This test is not recommended for general use because the heterophile antibodies detected by this test can be caused by other conditions. Moreover, it can produce both false-positive and false-negative results.

People are considered to be susceptible to EBV infection if they do not have antibodies to VCA (**FIGURE 3-11**). They are considered to have a primary EBV infection if they have anti-VCA IgM but do not have antibodies to EBNA. The presence of antibodies to both VCA and EBNA suggests past infection with EBV. Additionally, increased lymphocytes, increased monocytes, atypical T lymphocytes (enlarged), decreased neutrophils, decreased platelets, and abnormal liver enzymes in the blood will be present during the acute phase of EBV infection. Other laboratory tests can be performed to exclude other disorders that present similarly to infectious mononucleosis (e.g., streptococcal pharyngitis). Leukocyte counts may also be increased when a person has infectious mononucleosis.



Interpretation	Non-specific tests		Antibodies against					
	Heterophylic antibodies	Atypical lymphocytes	VCA			EA		EDNA
			IgM	IgG	IgA	EA(D)	EA(R)	IgG
No infection	–	–	–	–	–	–	–	–
Infectious mononucleosis	+++	+++	++	+++	+	+	(±)	–
Past infection	–	–	–	++	–	–	(±)	++
Reactivation	–	–	(+)	+++	++	++	+	(+)

FIGURE 3-11 EBV diagnostic test profile.

Description

Treatment of infectious mononucleosis is primarily symptomatic and supportive. Strategies may include bed rest, hydration, analgesics, corticosteroids, and antipyretics. Vigorous contact sports should be avoided in the acute illness and recovery phases to prevent rupture of the spleen.

Lymphomas

Lymphomas are cancers that develop from lymphatic cells in the lymphatic system. They are the most common blood cancers. Lymphomas were once thought to be distinctive from **leukemia**, but

better understanding of cell markers and instrumentation to evaluate those markers now indicate this distinction is less clear. Lymphoma was once thought to be relatively restricted to the lymphatic system and leukemias to the bone marrow, but this is not always true. In the United States, they are the seventh most common cancers in adults and the fifth most common cancers in children (American Cancer Society, 2022). Lymphomas are more common in Caucasians compared to other ethnic groups, and risk is slightly higher in males. Several subtypes of lymphomas exist, with the two main types being Hodgkin's lymphoma and non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma is far more common than Hodgkin's lymphoma. Risk factors for both types of lymphomas include infection with the human immunodeficiency virus (HIV) or EBV. Additional risk factors for non-Hodgkin's lymphoma include (1) the presence of an inherited immune or autoimmune condition, (2) infection with *Helicobacter pylori* or human T-cell leukemia/lymphoma virus type 1 (HTLV-1), (3) exposure to pesticides, and (4) genetic factors (i.e., certain single nucleotide polymorphisms, family history of lymphoma).

Hodgkin's Lymphoma

Hodgkin's lymphoma can start in any lymph node of the lymphatic system, but most often arises in the lymph nodes of the upper body (e.g., neck, chest, and upper arms). Additionally, the spleen, liver, and bone marrow can be involved. The affected lymph nodes swell and compress the surrounding tissues. In a systematic way, the cancer cells spread from one lymph node to the next through the lymphatic vessels. In rare cases, the disease spreads into the blood vessels and other structures, in a process that continues until late in the disease. The cancer cells of Hodgkin's lymphoma are unique; they are called Reed-Sternberg cells (or Hodgkin cells) (**FIGURE 3-12**). An abnormal type of B lymphocyte, they are much larger than normal lymphocytes. The T lymphocytes also appear to have defects, and the total lymphocyte number decreases. While the Reed-Sternberg cells are low in number, they attract other cells and bring them into the neoplasm.

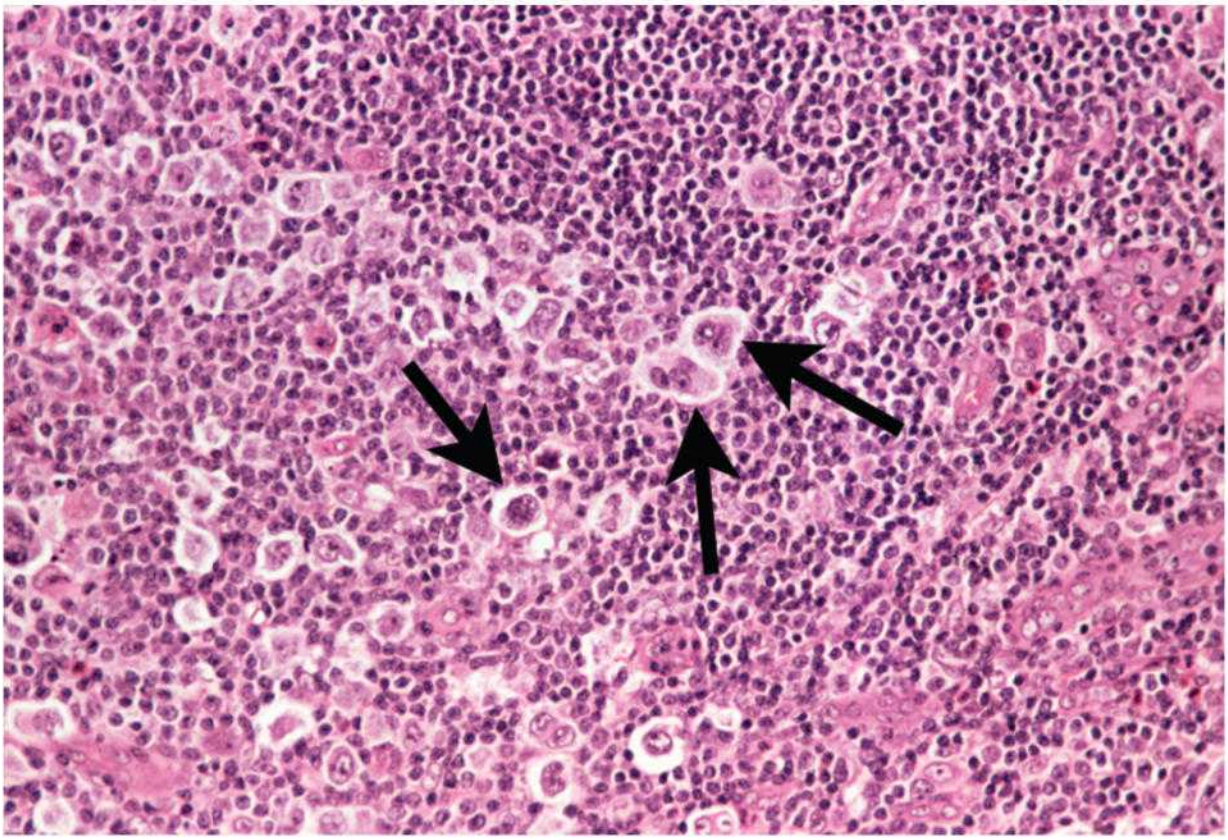


FIGURE 3-12 Reed-Sternberg cells associated with Hodgkin's lymphoma.

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The two main types of Hodgkin's lymphomas are classical Hodgkin's disease and nodular lymphocyte predominance Hodgkin's lymphoma. Classical Hodgkin's lymphoma has four subtypes and accounts for 95% of all cases, and EBV infection is likely the underlying etiology. Nodular lymphocyte predominance Hodgkin's lymphoma is rare, tends to be more localized, grows more slowly than the classical version, and is not caused by the EBV. These types and subtypes also differ in the way the cancer cells appear under a microscope. Identification of which type the patient is experiencing is important because these variants grow and spread in different ways, and they are often treated differently.

Although the incidence of this disease is on the decline, the CDC (2020) reports that Hodgkin's lymphoma occurs primarily in adults 20 to 30 years of age. A second peak occurrence is seen at 70 years of

age. Due to improvements in the treatment of Hodgkin's lymphoma, mortality has decreased by nearly 50% over the past 25 years. Over the same period, incidence has decreased at a much slower rate. Prognosis is further improved when the disease is localized and is treated early, with many cases considered cured. Although the prognosis is excellent for patients with Hodgkin's lymphoma, those who are treated with radiation may be at increased risk of stroke and transient ischemic attack (DeBruin et al., 2009).

Hodgkin's lymphoma has the following clinical manifestations:

- Swollen, painless lymph nodes (most often in the neck and/or supraclavicular area)
- Retrosternal chest pain, cough, and difficulty breathing secondary to a mediastinal mass commonly present
- Weight loss
- Persistent fever
- Night sweats
- Generalized pruritus
- Malaise
- Recurrent infections
- Splenomegaly

Although the mechanism is unclear, pain may rarely occur in the affected area immediately after consuming alcoholic beverages, providing an early indication of the diagnosis. Diagnostic procedures primarily center on a biopsy of the affected lymph node. Biopsy samples reveal the presence of Reed-Sternberg cells. Other diagnostic procedures consist of a physical examination, complete blood count (CBC), and chest X-rays.

A staging system is used to grade the severity and progression of the disease (**FIGURE 3-13**):

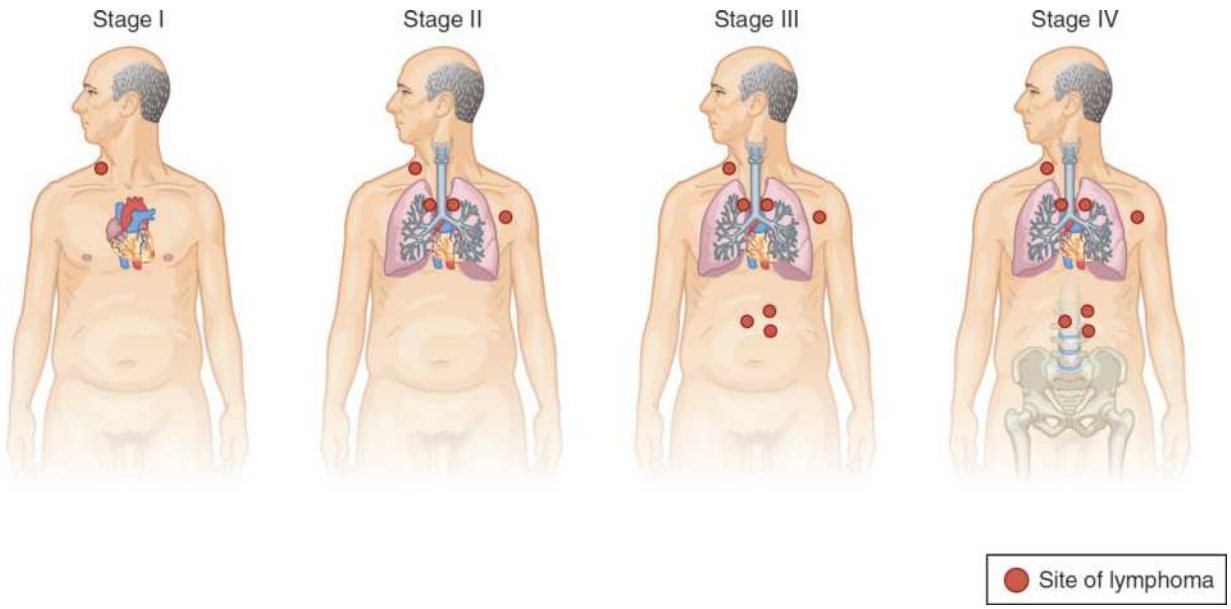


FIGURE 3-13 Stages of Hodgkin's lymphoma.

Description

- *Stage I:* The lymphoma cells are found in one lymph node group (such as in the neck or the underarm), or if the lymphoma cells are not in the lymph nodes, they are in only one part of a tissue or an organ (such as the lung).
- *Stage II:* The lymphoma cells are in at least two lymph node groups on the same side of (either above or below) the diaphragm, or the lymphoma cells are in one part of a tissue or an organ and the lymph nodes near that organ (on the same side of the diaphragm). Lymphoma cells may be in other lymph node groups on the same side of the diaphragm.
- *Stage III:* The lymphoma cells are in lymph nodes above and below the diaphragm. These cells may be found in one part of a tissue or an organ (such as the liver, lung, or bone) near these lymph node groups, and they may also be found in the spleen.
- *Stage IV:* Lymphoma cells are found in several parts of one or more organs or tissues, or the lymphoma cells are in an organ (such as the liver, lung, or bone) and in distant lymph nodes.
- *Recurrent:* The disease returns after treatment.

Staging is determined through a computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography scan, and bone marrow biopsy. Other staging procedures may include biopsies of other lymph nodes, the liver, or other tissue. After diagnosis, the usual cancer treatment is implemented—that is, a combination of chemotherapy, antibody-drug conjugate (e.g., brentuximab vedotin), immunotherapy (e.g., immune checkpoint inhibitors), radiation, autologous stem cell transplantation, and surgery. With early treatment, the 5-year survival rate is 88%, and a cure is possible in 75% of cases.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma accounts for 90% of all lymphomas, and it can start at any age and in any lymph node. However, risk increases with age. Many different types of this disease are possible. These types can be divided into aggressive (fast-growing; e.g., diffuse, large B-cell lymphoma, and Burkitt lymphoma) and indolent (slow-growing; e.g., follicular lymphoma) types, and they can arise from either B cells (80% of cases) or T cells (e.g., cutaneous T-cell lymphoma).

The exact cause of non-Hodgkin's lymphoma is unknown, but evidence suggests a viral cause. The following viruses have been associated with most types of non-Hodgkin's lymphomas: EBV, hepatitis B virus, hepatitis C virus, and human herpesvirus 8. These oncogenic viruses integrate their genome into their target cells (i.e., B cells or T cells).

Non-Hodgkin's lymphoma is similar to Hodgkin's lymphoma in its clinical manifestations, staging, and treatment; the differences lie in the spread and diagnosis of the disease. Non-Hodgkin's lymphoma involves multiple nodes scattered throughout the body and metastasizes in an unorganized manner. Metastasis is often present at diagnosis, but no Reed-Sternberg cells are present. Moreover, non-Hodgkin's lymphoma is more difficult to treat than Hodgkin's lymphoma. The prognosis for patients with this disease is improving (5-year survival rate is 73%).

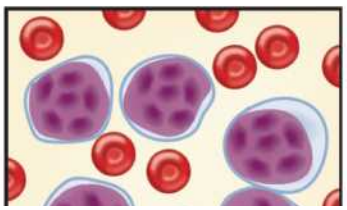
Leukemias

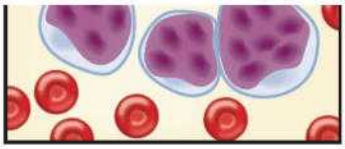
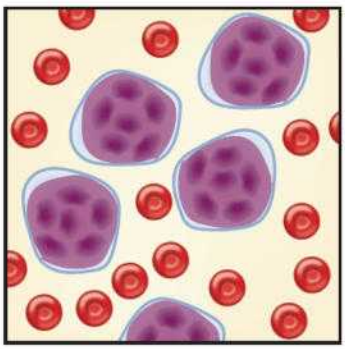
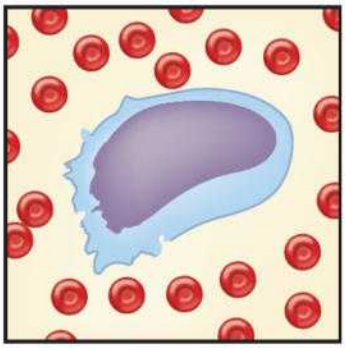
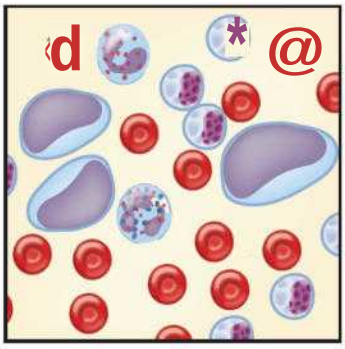
Leukemia is a cancer of the leukocytes. With this disease, the bone marrow stem cells make abnormal leukocytes, known as leukemia cells. These leukemia cells are released into the vascular system, affecting different organs. Unlike normal blood cells, leukemia cells do not die when they should, so they sometimes begin crowding normal leukocytes, erythrocytes, and thrombocytes. This crowding makes it difficult for normal blood cells to function properly. The exact cause of leukemia is unknown.

According to the American Cancer Society (2022), leukemia is the ninth most common cancer. Although it affects 10 times as many adults as children, this disease is the most common cancer among children. Incidence rates have remained relatively consistent over the past 20 years, but the mortality rates have decreased. Men are more likely to develop leukemia than women, and this type of cancer affects Caucasians more frequently than other ethnic groups. Other risk factors include exposure to chemical, viral, and radiation mutagens; smoking; use of chemotherapies; certain disease conditions (e.g., Down syndrome); and immunodeficiency disorders.

Leukemias are categorized as either acute (usually less differentiated) or chronic (cells are usually more differentiated) and based on their cell line (myeloid or lymphoid). Acute leukemias usually have a more rapid onset and progression. Chronic leukemias are more insidious in onset and less aggressive. The four most common types of leukemias are as follows (**TABLE 3-2**):

TABLE 3-2 Common Types of Leukemias

Types	Cell Involved	Cytology	Symptoms	Statistics	Prevalence
Acute lymphoblastic leukemia (ALL) 	Immature B or T cell and macrophages	Chromosomal aberration	Bone marrow dysfunction	Common in children	33%

 Acute myeloid leukemia (AML)	Immature myeloid WBCs	Oncogene mutations, single myeloblast mutation, cytogenetic abnormalities	Anemia, spontaneous bleeding	Both adults and children	80%
 Chronic lymphoid leukemia (CLL)	Lymphoid B or T cell	Chromosomal abnormalities	Swelling of lymph nodes, enlarged spleen	Commonly affects individuals older than age 55	30%
 Chronic myeloid leukemia (CML)	Myeloid stem cells	Chromosomal translocation, granulocytes	Anemia, low platelet count, enlarged spleen	Rare in children	90%
					

* *Acute lymphoblastic leukemia (ALL):* Most common leukemia (75% of all cases), affecting primarily children; responds well to therapy and carries a good prognosis.

- *Acute myeloid leukemia (AML):* Affects primarily adults; responds fairly well to treatment and carries a prognosis somewhat worse than that of ALL.
- *Chronic lymphoid leukemia (CLL):* Primarily affects adults; responds poorly to therapy, yet most patients live many years after diagnosis.
- *Chronic myeloid leukemia (CML):* Affects primarily adults; responds poorly to chemotherapy, but the prognosis is improved with allogeneic bone marrow transplant.

Leukemia has the following clinical manifestations:

- Leukopenia (frequent infections)
- Anemia (pallor, fatigue, dyspnea, and decreased activity tolerance)
- Thrombocytopenia (petechiae, bleeding gums, hematuria, and prolonged bleeding time)
- Lymphadenopathy
- Joint swelling
- Bone pain
- Weight loss
- Anorexia
- Hepatomegaly
- Splenomegaly
- Central nervous system dysfunction

Diagnostic procedures include a history, physical examination, peripheral blood smears, CBC (all or most levels will be low), and bone marrow biopsy. May see a high number of abnormal immature WBCs, referred to as “blasts.” Chemotherapy is the mainstay of treatment for leukemia, and several courses may be necessary to eradicate the cancer. Chemotherapy is more effective for the acute types of leukemias than for the chronic types. Bone marrow transplants may be attempted if chemotherapy is unsuccessful. Other

treatments may include targeted therapy, radiation, biological therapy, surgery, and donor lymphocyte infusion.

Multiple Myeloma

Multiple myeloma is a cancer of the plasma cells that most often affects older adults. This disease is characterized by excessive numbers of abnormal plasma cells in the bone marrow crowding the blood-forming cells and causing Bence-Jones proteins to be excreted in the urine. Chromosomal abnormalities associated with multiple myeloma include deletion of chromosome 17 and trisomy 47. These abnormalities result in activation of proto-oncogenes and inactivation of tumor suppressor genes, which lead to abnormal B-cell development (most often IgG or IgA) in the bone marrow. The abnormal B cells leave the bone marrow, become activated by an antigen, and differentiate into abnormal plasma cells with stimulation from T helper cells. These abnormal plasma cells then travel back to the bone marrow, proliferate, and destroy the bone marrow by increasing osteoclast activity. Multiple bone lesions (i.e., lytic or punched-out lesions) develop and bone destruction results in hypercalcemia, pathologic fractures, and decreased hematopoiesis. The most frequent bones involved are the vertebrae, ribs, pelvis, femur, clavicle, and scapula. Hypercalcemia leads to renal impairment and neuromuscular issues. Tumor cells can spread through the lymph nodes and infiltrate organs (e.g., kidneys, liver, spleen, and heart).

Multiple myeloma is relatively uncommon; however, its incidence has slowly increased (American Cancer Society, 2022). This disease is more common in men than in women. The incidence and mortality rates are relatively consistent across ethnic groups.

The onset of multiple myeloma is usually insidious, and malignancy is often well advanced at diagnosis. Clinical manifestations of multiple myeloma include the following:

- Persistent bone pain, especially in the back or thorax
- Anemia (pallor, fatigue, dyspnea, and decreased activity tolerance)

- Thrombocytopenia (petechiae, bleeding gums, hematuria, and prolonged bleeding time)
- Leukopenia (frequent infections)
- Decreased bone density (pathologic fractures)
- Hypercalcemia (neuromuscular dysfunction)
- Renal impairment

The diagnosis of multiple myeloma is often made incidentally during routine blood or imaging tests for other conditions. For example, the presence of **anemia** and a high serum protein may suggest further testing is needed. Diagnostic procedures include serum and urine protein, calcium, renal function tests, CBC, blood smear, erythrocyte sedimentation rate (ESR) blood chemistry, bone marrow biopsy, X-rays, CT, and MRI.

Multiple myeloma is not considered curable, but chemotherapy improves the remission rate. Additional treatments may include corticosteroids, monoclonal antibodies, angiogenesis inhibitors, targeted therapies, stem cell transplants, biological therapy, radiation therapy, and supportive care. Analgesics are used to treat bone pain, and blood dyscrasias, hypercalcemia, and renal impairment are treated as needed. The median survival time is 5 years.

Diseases of the Red Blood Cells

Erythrocytes are the most prevalent blood cells in the human body—millions can be found in a single drop of blood (the normal range is 4.2–5.9 million cells/mcL). These cells function primarily to transport oxygen to the tissue and the waste products for excretion. Most diseases of the RBCs are related to the quantity or quality of the erythrocytes.

Anemia

Anemia is a common acquired or inherited disorder of the erythrocytes that impairs the blood's oxygen-carrying capacity. This condition can result from (1) a decrease in the number of circulating erythrocytes (e.g., blood loss or decreased production), (2) a reduction in hemoglobin content, or (3) the presence of abnormal hemoglobin. Some anemias are treated easily, whereas others can cause lifelong problems. Regardless of the cause, the clinical manifestations of anemia reflect the decreased oxygen-carrying capacity; in turn, the severity of manifestations and the extent of compensatory mechanisms reflect the degree of the anemia. Manifestations include:

- Weakness
- Fatigue
- Pallor
- Syncope
- Dyspnea
- Tachycardia

Compensatory mechanisms for anemia include increased erythropoiesis to increase production, vasodilation and tachycardia to increase blood flow, and an increased respiratory rate to increase

oxygen saturation. In adults, anemia is diagnosed when hematocrit is less than 41% in males and less than 37% in females; that is, hemoglobin concentration falls to less than 13.5 g/dL in males and less than 12 g/dL in females. Treatment depends on the specific type of anemia experienced.

Iron-Deficiency Anemia

According to the World Health Organization (2023), iron-deficiency anemia is the most widespread anemia in the world. This type of anemia is most commonly seen in women of childbearing age, children younger than 2 years of age, and the elderly. Iron-deficiency anemia occurs when the supply of iron necessary to produce hemoglobin is inadequate to meet the demands of hemoglobin production. It may be caused by decreased iron consumption, decreased iron absorption, or increased bleeding (such as occurs during menstruation and as a result of some cancers).

Iron is ingested from both animal and plant sources. Failure to obtain an adequate iron intake is common, especially in developing countries. The average American ingests more than 10 mg of iron each day, which is within the recommended daily allowance, but only about 10% of the ingested iron is actually absorbed. Because iron absorption occurs in the upper gastrointestinal tract, conditions affecting this area (e.g., celiac disease, atrophic gastritis, bariatric surgery) can result in iron-deficiency anemia. When an iron deficiency exists, erythrocytes will become pale (hypochromic) and small (microcytic) (**FIGURE 3-14**).

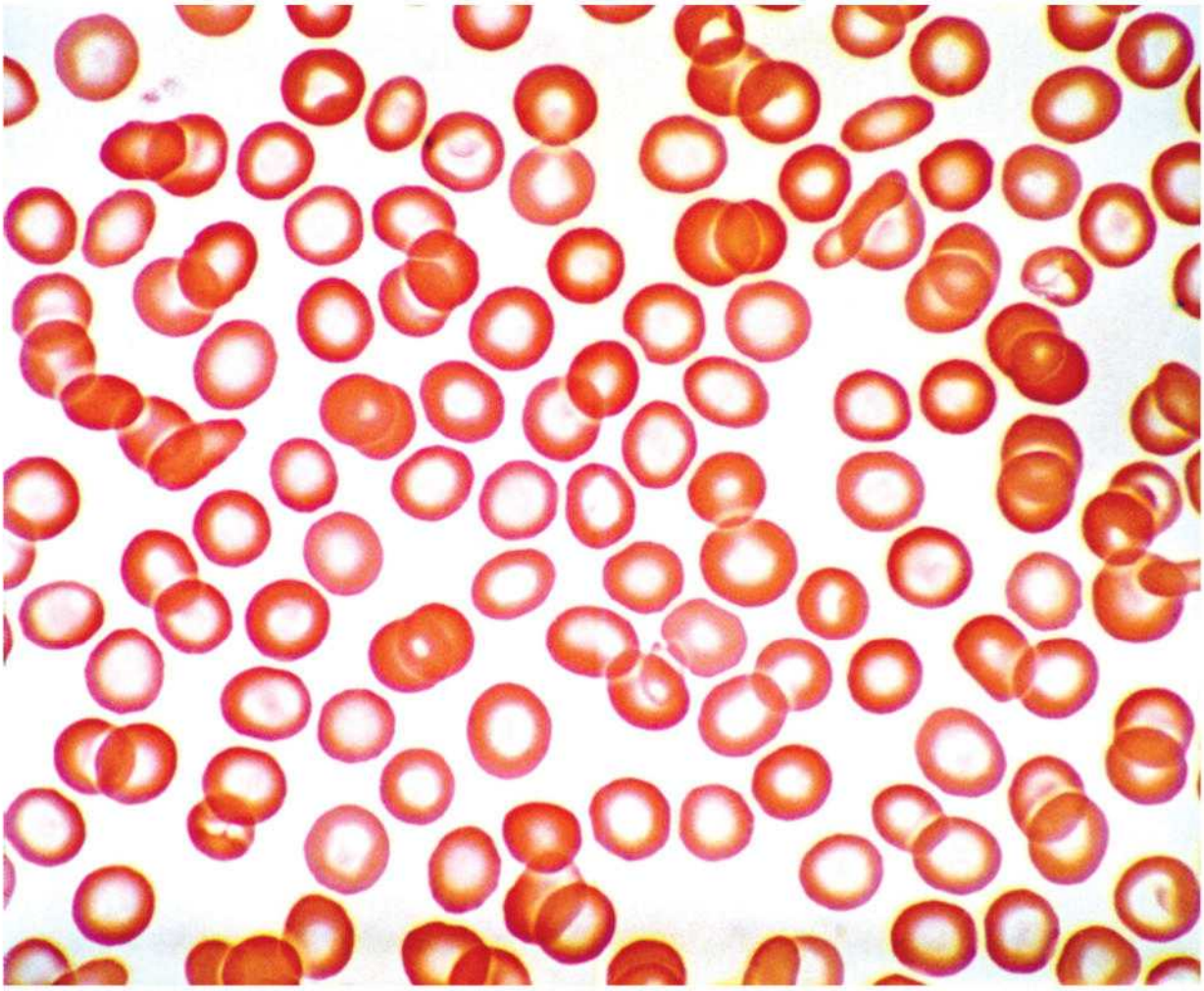


FIGURE 3-14 Iron-deficiency anemia.

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application to practice

Mrs. Hudson is 52-year-old female who presents to the clinic complaining of fatigue, worsening exercise intolerance the last 3 weeks, and shortness of breath that has developed over the past 24 hours. Mrs. Hudson has no past medical history and works as a social worker. Until recently, she has exercised (usually a spin class) 3 to 4 times weekly. She denies a history of tobacco use and consumes 2-4 glasses of wine weekly. Her respirations are 28 and somewhat labored. Her heart rate is 116 bpm, blood pressure is 146/88, temperature is 99.0, and pulse oximetry is 82%. Additionally, an erythematous rash is noted on her back and chest, and scattered ecchymosis is noted on her extremities. Her laboratory results reveal the following:

CBC	Result	Normal Range
WBC	175 × 10^9/L	4–10 × 10^9/L
RBC	3.2 × 10^6/mL	3.8–5 × 10^6/mL
Hgb	7.3 g/dL	14–18 g/dL
Hct	28%	35–46%
MCV	84 mcL/red cell	80–96.1 mcL/red cell
MCH	29 pg/red cell	27.5–33.2 pg/red cell
MCHC	34 g/L	33.4–35.5 g/L
Platelets	24,000/mL	150–400,000/mL
LDH	210 U/L	0–304 U/L

Abbreviations: g: gram; dL: deciliter; Hct: hematocrit; Hgb: hemoglobin; L: liter; LDH: lactate dehydrogenase; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; mcL: microliter; MCV: mean corpuscular volume; mL: milliliter; pg: pictogram; RBC: red blood cells; RDW: red blood cell distribution width; U: units; WBC: white blood cells.

Other findings include: WBC differential, peripheral blood smears, and bone marrow aspiration all indicate a high number of blasts present.

1. Which type of hematologic disorder would you suspect based on Mrs. Hudson's history, physical examination, and laboratory values?
   a. Thrombotic thrombocytopenic purpura
   b. Infectious mononucleosis
   c. Acute myeloid leukemia
   d. Thalassemia
2. Which of the following explains the high number of blasts with Mrs. Hudson's likely diagnosis?
   a. WBC proliferation is uncontrolled, creating a high number of abnormal and immature cells
   b. WBC proliferation is uncontrolled, crowding out other blood cells
   c. Blasts are a result of long-term anemia
   d. Blasts are a compensatory mechanism
3. Which of the following explains the anemia and thrombocytopenia?

a. WBC proliferation is uncontrolled, creating a high number of abnormal and immature cells
b. WBC proliferation is uncontrolled, crowding out other blood cells
c. Anemia and thrombocytopenia are a result of long-term leukocytosis
d. Anemia and thrombocytopenia are a compensatory mechanism

4. Which of the following factors is the most likely explanation for Mrs. Hudson's sudden onset of shortness of breath, tachypnea, and pulse oximetry of 82%?
a. Decompensation from a lack of exercise
b. Low oxygen carrying capacity as a result of low RBCs, Hct, and Hgb
c. Leukostasis occluding pulmonary circulation as a result of leukocytopenia
d. Increased oxygen demand as a result of tachypnea, elevated blood pressure, and fever

In addition to the previously mentioned anemia signs and symptoms, the following clinical manifestations may be associated with iron-deficiency anemia:

- Cyanosis (blue coloration) to the sclera of the eyes
- Brittle nails with koilonychia (spoon-shaped)
- Decreased appetite (especially in children)
- Headache
- Irritability
- Stomatitis
- Unusual food cravings (pica)
- Delayed healing
- Neurologic impairment (e.g., confusion and memory loss in the elderly) or neurologic damage (e.g., developmental delays in children)

Diagnostic procedures for iron-deficiency anemia include a CBC, serum ferritin, iron-binding capacity, serum iron, and transferrin saturation. The results from the CBC of the mean corpuscular volume (MCV), which reflects cell size, are used in part to differentiate the various types of anemia (**FIGURE 3-15**). Additional tests may be performed to determine the cause (e.g., fecal occult blood test).

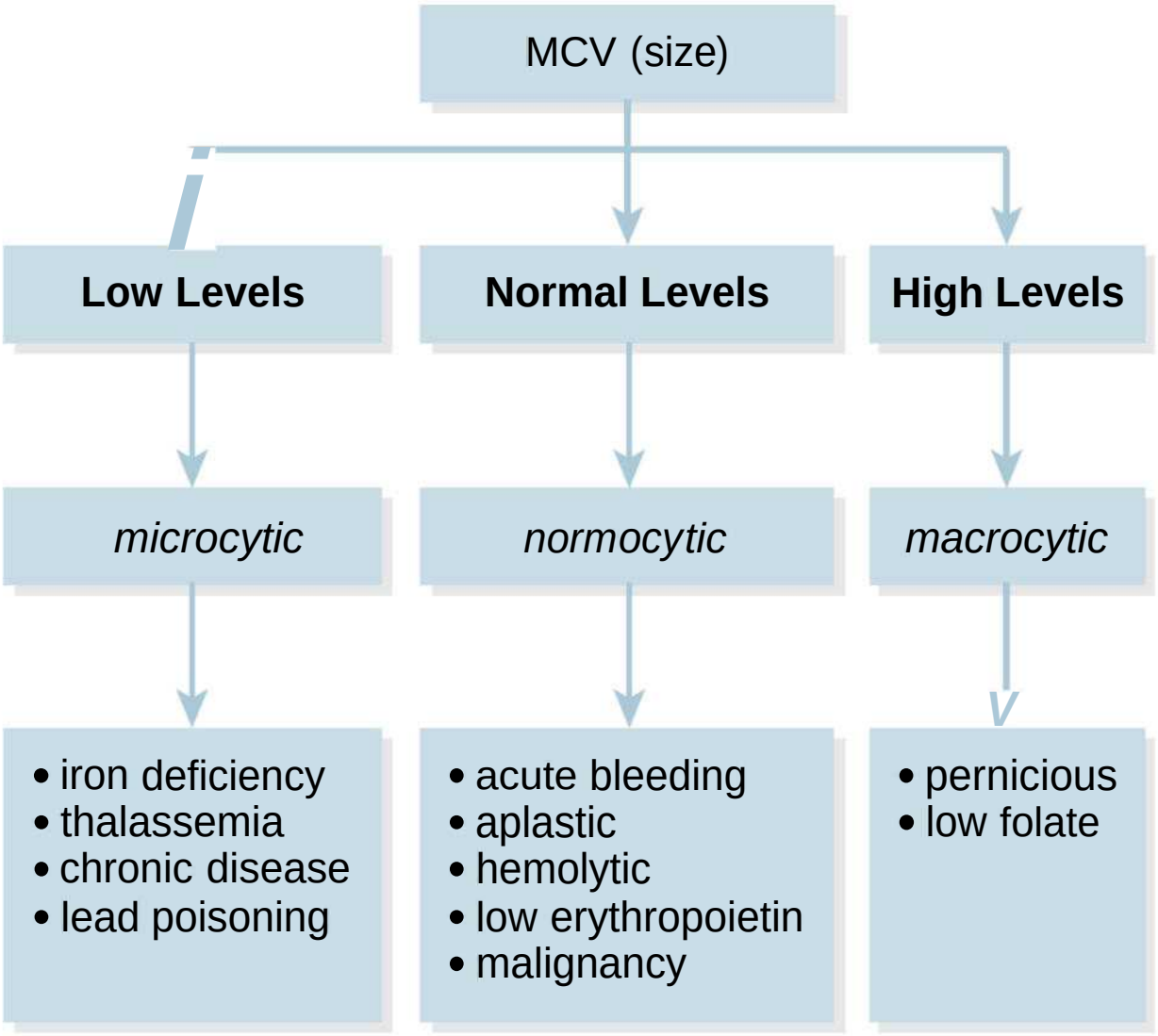


FIGURE 3-15 Mean corpuscular volume (MCV) changes with anemia.

Description

Treatment includes the identification and resolution of the underlying cause of the iron-deficiency anemia. Other strategies to increase iron levels include increasing consumption of iron-rich foods (e.g., liver, red meat, fish, beans, raisins, and green leafy vegetables) or administering iron supplements. Additionally, foods or supplements high in vitamin C should be increased because vitamin C promotes the absorption of iron.

Pernicious Anemia

Pernicious anemia, also known as vitamin B_{12} deficiency and megaloblastic anemia, is characterized by large (macrocytic) immature erythrocytes (**FIGURE 3-16**). This type of anemia most often results from cyanocobalamin (vitamin B_{12}) deficiency, which usually occurs gradually and is due to a lack of intrinsic factor. Intrinsic factor is a glycoprotein produced by the stomach that is necessary for vitamin B_{12} to be absorbed in the stomach. The lack of intrinsic factor arises because of the actions of autoantibodies, with the subsequent immune reaction leading to atrophy of the gastric mucosa and glands. These autoantibodies can be a result of any number of autoimmune diseases (e.g., chronic atrophic gastritis, Hashimoto thyroiditis, Graves' disease, and type 1 diabetes mellitus). Additionally, gastric surgeries (e.g., bariatric surgery or those for gastric cancer) can result in decreased secretion of intrinsic factor.

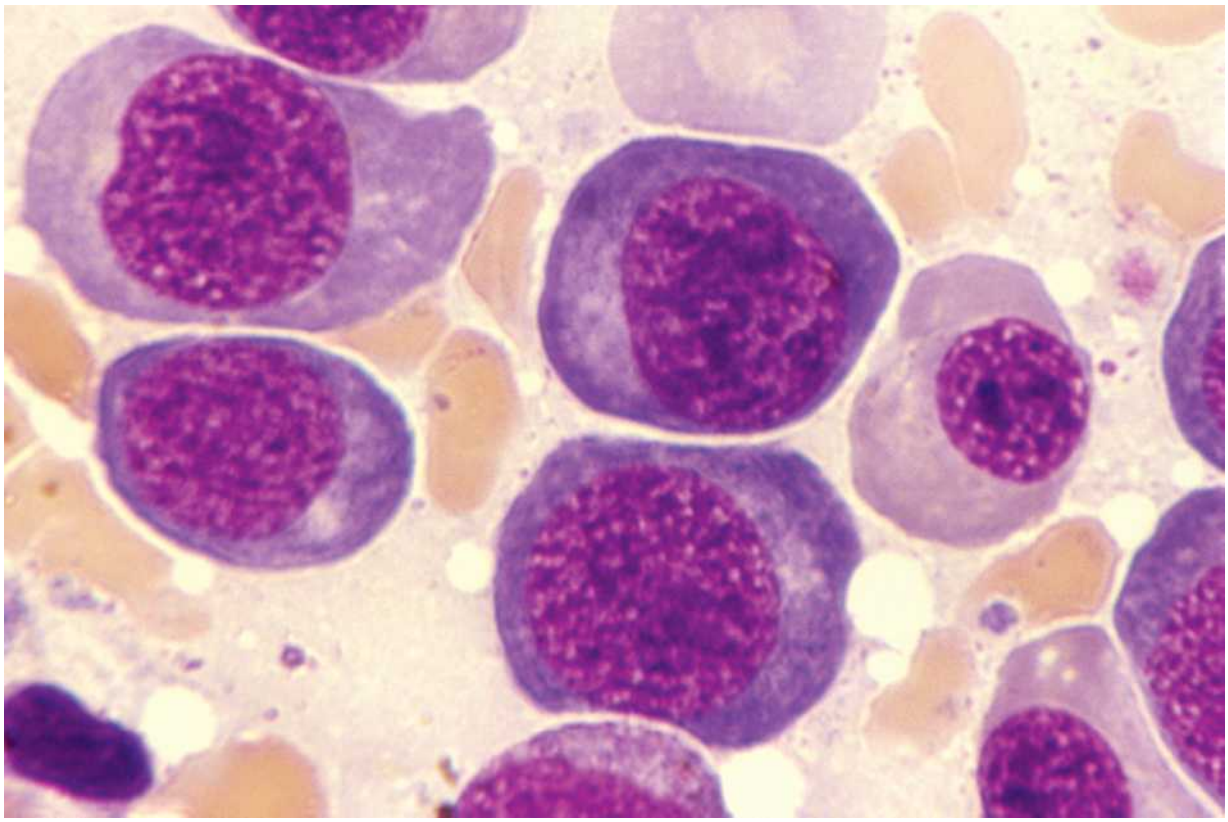


FIGURE 3-16 Pernicious anemia.

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Vitamin B_{12} is necessary for DNA synthesis, and a deficiency of this nutrient leads to decreased cell division and cell maturation. Too little vitamin B_{12} gradually causes neurologic problems because of a breakdown in myelin. The neurologic effects may be seen before anemia is diagnosed and can become irreversible. In addition to the usual signs and symptoms of anemia, pernicious anemia is associated with the following clinical manifestations:

- Bleeding gums
- Diarrhea
- Impaired sense of smell
- Loss of deep tendon reflexes
- Anorexia
- Personality or memory changes
- Positive Babinski sign (a pathological reflex in which the first toe extends and flexes toward the top of the foot and the other toes fan out when the sole of the foot is firmly stroked)
- Stomatitis
- Paresthesia of the hands and feet
- Unsteady gait, especially in the dark

Diagnostic tests for pernicious anemia include serum vitamin B_{12} levels, antibody testing (specifically for intrinsic factor, or anti-IF), CBC (high MCV), reticulocyte count, peripheral blood smear, gastric analysis, and bone marrow biopsy. Other testing may be necessary to identify the underlying cause.

Treatment of pernicious anemia includes parenteral vitamin B_{12} (injections) if no intrinsic factor is being produced; oral vitamin B_{12} can be administered for those individuals who are producing intrinsic factor. Additionally, vitamin B_{12} is available in sublingual and nasal forms.

Aplastic Anemia

Aplastic anemia is a rare but serious type of anemia that is a result of the bone marrow failing to make enough blood cells, usually as a result of decreased production of hematopoietic stem cells. This lack of erythrocytes, leukocytes, and platelets is referred to as **pancytopenia**. The cells in aplastic anemia are normal in every other sense. A lack of these blood cells can lead to a series of complications, such as infections, bleeding, hypoxia, fatty replacement of marrow, and death.

Aplastic anemia may be temporary or permanent. Causes of aplastic anemia include the following:

- Idiopathic conditions
- Autoimmune conditions (e.g., systemic lupus erythematosus and rheumatoid arthritis)
- Medications and treatments (e.g., chemotherapy and radiation)
- Viruses
- Toxins (e.g., pesticides, arsenic, and benzene)
- Genetic abnormalities (e.g., myelodysplastic syndrome)
- Infectious diseases (e.g., EBV, cytomegalovirus, parvovirus, and HIV)
- Pregnancy (the anemia often resolves after delivery)
- Cancer

Clinical manifestations include signs and symptoms of general anemia (e.g., weakness, pallor, and dyspnea), leukocytopenia (e.g., recurrent infections), and **thrombocytopenia** (e.g., bleeding). As blood cell levels decline, clinical manifestations worsen.

Diagnostic tests for aplastic anemia include a CBC and bone marrow biopsy. Prompt treatment of the underlying causes and any complications as they arise is crucial for positive outcomes. Treatment of underlying causes may include discontinuation of medications or treatments. Treatment of complications may include the following measures:

- Oxygen therapy

- Infection control measures (e.g., hand washing, avoiding groups, and avoiding fresh flowers)
- Infection treatment (e.g., antibiotics)
- Bleeding precautions (e.g., use of electric razors, use of soft-bristle toothbrushes, and injury prevention)
- Hematopoietic stimulants (e.g., erythropoietin and colony-stimulating factors)
- Immunosuppressant therapy (e.g., cyclosporine and methylprednisolone)
- Anti-infectives (e.g., antibiotics and antiviral medications)
- Blood transfusions
- Bone marrow transplant

application to practice

Mrs. Williams is a 45-year-old Caucasian woman who sought medical attention for fatigue that developed during the previous month. She reported no chest pain but did feel mildly short of breath with exertion, such as after walking up a flight of stairs. She denied any rectal bleeding, but she had heavy menstrual periods for about a year. Her past medical history included being treated for anemia following her third pregnancy 10 years earlier. She was not taking any prescribed medications. Her family history revealed that her parents were born in Italy and died in a car accident when she was in grade school. She did not know their medical history.

A physical examination revealed that Mrs. Williams's general appearance was pale but with no acute distress. Her vital signs were blood pressure 125/90 mm Hg, heart rate 118 beats/min regular, and respirations 26 breaths/min. No significant changes in the blood pressure and heart rate were noted between the supine and upright positions. Other findings included pale conjunctiva and moist mucous membranes without lesions. No adenopathy or hepatosplenomegaly was noted. Breath sounds were clear to auscultation, and the heart had a regular rate and rhythm with a murmur. The abdomen was soft, nontender, and nondistended. A rectal examination revealed no masses, and heme-negative brown stool was present. Additionally, Mrs. Williams reported that she was taking aspirin 81 mg daily, she is a vegetarian who eats a lot of cereal, and she did not have an urge to eat ice.

CBC	Result	Normal Range
WBC	8.2×10^3/mL	$4.8–10.8 \times 10^3$/mL

CBC	Result	Normal Range
Hgb	8.0 g/dL	12–15.6 g/dL
Hct	24%	35–46%
RBC	4.0×10^6/mL	$3.8–5 \times 10^6$/mL
MCV	60 mcL/red cell	80–96.1 mcL/red cell
MCH	20 pg/red cell	27.5–33.2 pg/red cell
MCHC	33 g/L	33.4–35.5 g/L
RDW	16.5	11.5–14.5
Platelets	500,000/mL	150–400,000/mL
Reticulocyte count	3%	0.5–1.7%
Absolute reticulocyte count	40,000/mL	25,000–75,000/mL
LDH	210 U/L	0–304 U/L

Abbreviations: g: gram; dL: deciliter; Hct: hematocrit; Hgb: hemoglobin; L: liter; LDH: lactate dehydrogenase; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; mcL: microliter; MCV: mean corpuscular volume; mL: milliliter; pg: pictogram; RBC: red blood cells; RDW: red blood cell distribution width; U: units; WBC: white blood cells.

Mrs. Williams' laboratory tests revealed the following results:

1. Which type of hematologic disorder would you suspect based on Mrs. Williams' history, physical examination, and laboratory values?
   a. Infectious mononucleosis
   b. Iron-deficiency anemia
   c. Pernicious anemia
   d. Thalassemia
2. Which of Mrs. Williams' clinical signs is reflective of the body's effort to compensate for her red blood cells' decreased oxygen-carrying capacity?
   a. Heart rate 118 beats/min and respiration rate 26 breaths/min
   b. Hematocrit 24% and hemoglobin 8 g/dL
   c. Blood pressure 125/90 mm Hg

d. Persistent fatigue

Mrs. Williams was placed on iron supplements. Her hemoglobin (Hgb) was expected to be normal after approximately 8 weeks of iron therapy, which was anticipated to raise the Hgb about 1 g/dL per week. However, her Hgb was 9.5 g/dL after 8 weeks.

Following those results, Mrs. Williams was asked whether she had been taking the iron supplements as ordered and whether she had been tolerating the medication. Additionally, she was asked whether she was having dark, tarry stools, which would indicate gastrointestinal bleeding. Mrs. Williams reported that she had taken the iron supplement for only 2 weeks because it made her nauseated and constipated. Mrs. Williams was instructed to take the iron supplement with a light carbohydrate, such as crackers or toast, to minimize the nausea and to take measures to prevent constipation (e.g., increasing fiber and water intake). After implementing these measures and taking the iron supplement as ordered for 8 weeks, Mrs. Williams' Hgb returned to normal.

1. In addition to iron supplements, which kinds of foods would be recommended for Mrs. Williams to consume?
   a. Milk, cheese, soybeans, broccoli, and almonds
   b. Green leafy vegetables and avocados
   c. Orange juice, raisins, bananas, cantaloupe, and fish
   d. Liver, red meat, eggs, dark green leafy vegetables, nuts, and legumes

Hemolytic Anemia

Hemolytic anemia results from excessive destruction, or **hemolysis**, of erythrocytes. Hemolytic anemia can result from idiopathic causes, autoimmune causes, genetics, infections (e.g., malaria), blood transfusion reactions, and blood incompatibility in the neonate. Several types of hemolytic anemias exist, including sickle cell anemia, thalassemia, and erythroblastosis fetalis. Specifics in regard to pathogenesis, clinical manifestations, diagnosis, and treatment vary based on the type.

Sickle Cell Anemia

Sickle cell anemia is a genetic type of hemolytic anemia in which the erythrocytes have a crescent or sickle shape (**FIGURE 3-17**). It is caused by an abnormal type of hemoglobin called **hemoglobin S**. Hemoglobin S distorts the shape of erythrocytes, especially when the body's supply of oxygen is low. These fragile sickle-shaped cells deliver less oxygen to the body's tissues. They also can clog small blood vessels and break into pieces that disrupt blood flow.

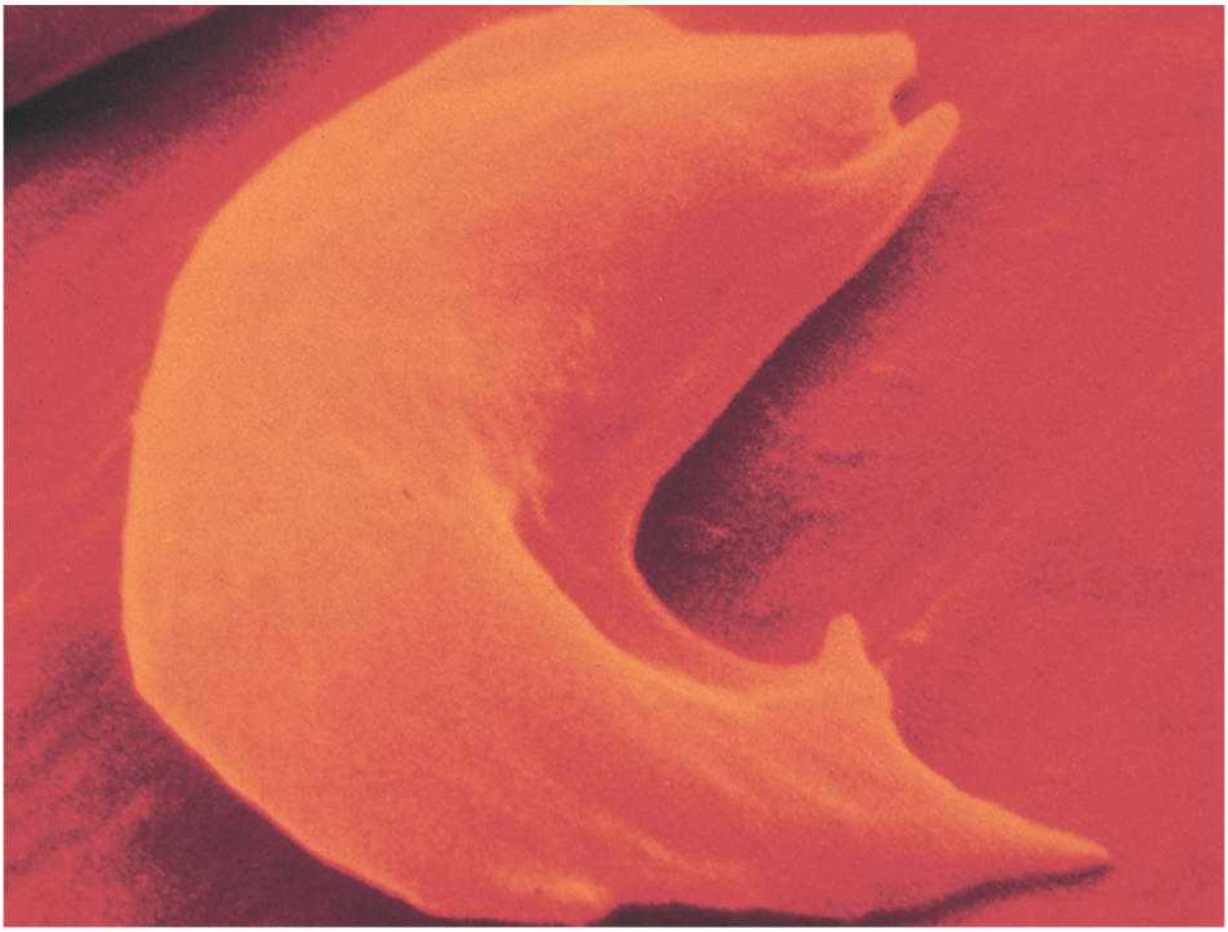


FIGURE 3-17 Sickle cell anemia.

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Sickle cell anemia is an inherited disorder that is neither recessive nor dominant (see the *Cellular Function* chapter). The allele for the sickle cell gene is codominant—meaning that if a person inherits the sickle cell gene from one parent and the normal erythrocyte gene from the other parent, both genes will be expressed. Someone who inherits the hemoglobin S gene from one parent and a normal hemoglobin gene (A) from the other parent—that is, a heterozygous pair of alleles—will have sickle cell trait. Persons with sickle cell trait do not have the symptoms of true sickle cell anemia because fewer than half of their erythrocytes are sickled. In contrast, individuals who inherit the hemoglobin S gene from both parents, creating a homozygous allele pair, have sickle cell disease. Sickle cell disease is

more severe than sickle cell trait because almost all of the individual's erythrocytes are abnormal. Sickle cell trait is much more common in people of African (1 out of every 13 births) and Mediterranean descent. Sickle cell disease occurs in about 1 in 13 African American births but is also seen in people from South and Central America, the Caribbean, and the Middle East.

Clinical manifestations usually do not appear in newborns because fetal hemoglobin protects the red blood cells from sickling. The fetal hemoglobin is replaced by adult hemoglobin, however, when a child reaches 4 to 5 months of age. Swelling in the hands and feet, often in conjunction with a fever, is usually the first symptom. The swelling occurs when the sickled cells occlude the blood vessels and block blood flow in and out of the hands and feet. Most patients will experience painful episodes, or crises, that can last for hours to days. Pain is caused by obstruction of small blood vessels as the sickled cells clog up the vessels, leading to ischemia and necrosis. The complications of these blood vessel occlusions depend on their location (TABLE 3-3). The number and severity of crises vary among patients, but episodes can be triggered by dehydration, stress, high altitudes, fever, and extreme temperatures. Because of improved disease understanding and management, most patients with sickle cell anemia now live into their 50s.

TABLE 3-3 Complications of Blood Vessel Occlusions in Sickle Cell Anemia

Area of Occlusion	Result
Bone	Susceptibility to osteomyelitis due to *Staphylococcus* infection
Papillae of renal medulla	Gross hematuria Renal tubular concentrating defects
Eye	Retinopathy Blindness

Area of Occlusion	Result
Sinus	Stroke
Spleen	Hyposplenism Susceptibility to infection
Liver	Jaundice Hepatomegaly
Miscellaneous	Cardiomegaly Slow-healing leg ulcers

Emerging Research: Sickle Cell Disease

The mutation associated with sickle cell disease was discovered in 1949. With hemoglobin S, glutamic acid (hydrophilic) is replaced with valine (hydrophobic). This discovery, though important, does not fully explain the series of events that trigger the crises associated with sickle cell disease.

A possible pathophysiological explanation involves the potential for abnormal polymerization of the critical actin protein in the spectrin–actin complex of the erythrocyte cytoskeleton meshwork. The cytoskeleton gives the erythrocyte its shape, which in turn impacts its function. Valine utilizes glucose differently from the way glutamic acid does, which may cause glucose levels within the erythrocytes to increase and, ultimately, lead to ATP G-actin concentration. This increase in ATP G-actin concentration leads to abnormal growth of stiff filament and/or loss of the equilibrium in the F-actin filaments. These effects may destabilize the hemoglobin S erythrocyte cytoskeleton, affecting the cell's shape and function. If correct, this proposed mechanism may lead to new treatment options for sickle cell disease as well as explain why patients with sickle cell anemia and diabetes mellitus often have underestimated hemoglobin A1c levels (Purnell, 2019).

In addition to this possible pathophysiological explanation of sickle cell disease, new treatments are emerging. In 2019, the first human sickle cell trials using a powerful gene-editing technique referred to as CRISPR (clustered regularly interspaced short palindromic repeats) began. CRISPR allows for precision edits to DNA. In patients with sickle cell disease, the treatment aims to reprogram the individual's DNA to produce fetal hemoglobin, which makes it harder for the cells to sickle and stick together. This process involves removing hematopoietic stem cells from the bone marrow, modifying them using CRISPR to produce fetal hemoglobin, and replacing them after a round of chemotherapy. CRISPR is also being explored as a treatment for thalassemia and other genetic disorders (Nedelman & Nigam, 2019; Stein, 2019).

Additionally, members of the Sickle Cell Branch of the National Heart, Lung, and Blood Institute have developed a drug to treat the inherited pyruvate kinase (PKR) deficiency seen in many sickle cell patients. They noted that sickle cell patients with a variation of the

gene *PKLR* had PKR deficiency which resulted in fragile red blood cells and anemia. If activating PKR can improve red blood cell health, it will decrease the severity of the sickle cell disease. The drug is still early in the research process, but it has the potential to break new ground (https://www.nhlbi.nih.gov/news/2022/researchers-study-new-way-treat-sickle-cell-disease).

The clinical manifestations of sickle cell anemia reflect the hypoxia and tissue ischemia that occurs in the disease and the complications that can result from them:

- Abdominal pain
- Bone pain
- Dyspnea
- Delayed growth and development
- Fatigue
- Fever
- Jaundice (yellowish skin)
- Pallor
- Tachycardia
- Skin ulcers on the lower legs
- Angina
- Excessive thirst
- Frequent urination
- Painful and prolonged erection (priapism)
- Vision impairment
- Frequent infections
- Acute chest syndrome (a potentially life-threatening condition that causes chest pain, coughing, difficulty breathing, and fever)
- Splenic sequestration (a potentially life-threatening condition that causes sudden weakness, pale lips, tachypnea, extreme thirst, left quadrant abdominal pain, and tachycardia)
- Leg ulcers

- Stroke

Carriers of the defective gene can be identified by hemoglobin electrophoresis, a simple blood test. Additionally, the sickle cell test can determine whether the hemoglobin is normal or sickled. A CBC and bilirubin test are useful in determining diagnosis and progression.

There is no single best treatment for all people with sickle cell disease. Stem cell transplants are an option for a cure. Medications (e.g., Hydrea [hydroxyurea]) are available to reduce the frequency of crises. Avoidance of sickling triggers is also helpful. Other strategies include the following measures:

- Oxygen therapy
- Hydration
- Pain management (e.g., opioids, relaxation techniques, distraction)
- Infection control measures
- Vaccinations
- Blood transfusions
- Bone marrow transplants
- Genetic counseling for those persons with sickle cell trait

Thalassemia

Thalassemia is another genetic type of anemia that results in abnormal hemoglobin (**FIGURE 3-18**). The abnormal hemoglobin results from an absence of one of the two proteins that collectively make up hemoglobin (alpha and beta globin; **FIGURE 3-19**). The two major types of thalassemias are named after defects in these proteins. Defects affecting alpha proteins occur on chromosome 16, and defects affecting beta proteins occur on 11.

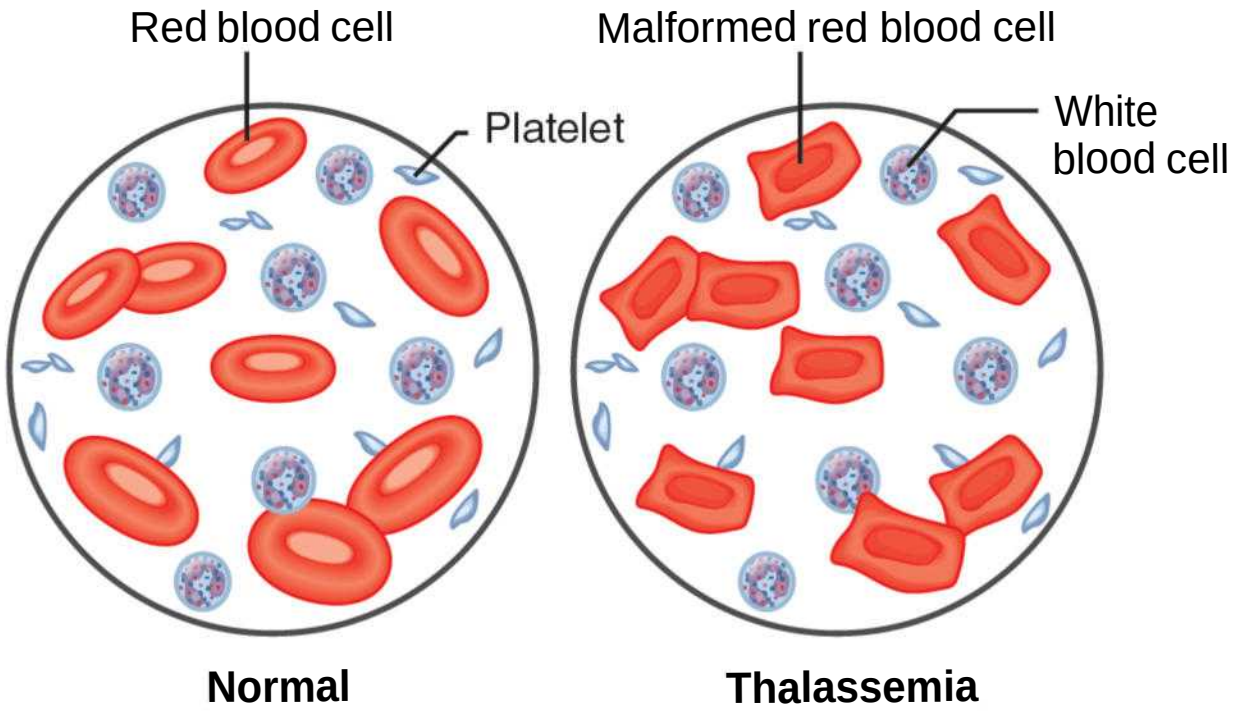


FIGURE 3-18 Thalassemia.

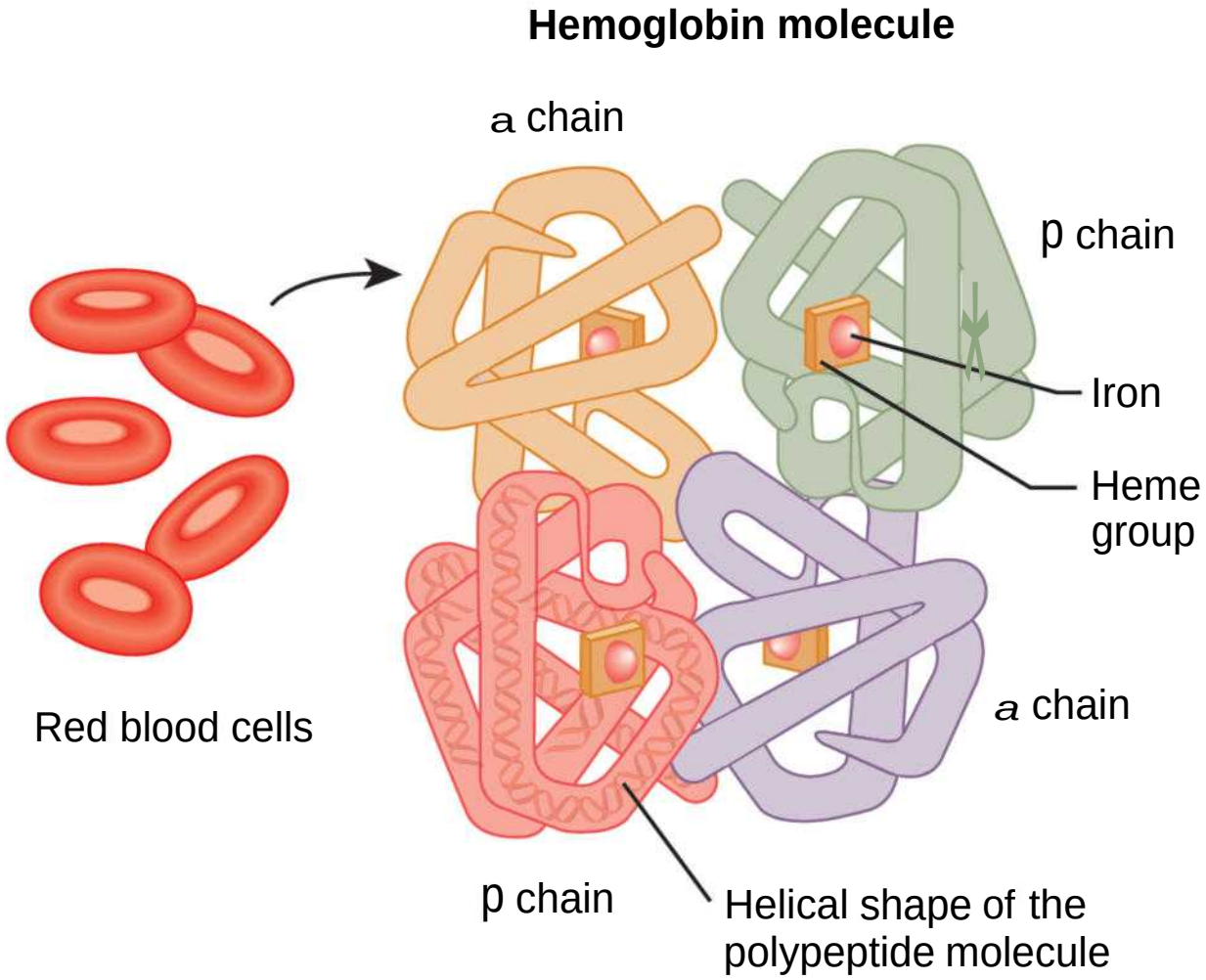


FIGURE 3-19 Hemoglobin structure.

Description

Four genes (two from each parent) are needed to make enough alpha protein. An individual becomes a carrier if one gene is missing and usually leads a normal healthy life. If two genes are missing, the individual has the trait and may have mild anemia. If three genes are missing, the individual will likely have hemoglobin H disease, which causes moderate to severe anemia. In rare cases, all four genes are missing; the most severe form of alpha thalassemia is called “alpha thalassemia major” or “hydrops fetalis.”

Two genes (one from each parent) are needed to make enough beta protein. Beta thalassemia occurs if one or both genes are altered. The severity of beta thalassemia depends on how much one

or both genes are affected. If one gene is altered, the individual is a carrier. This condition is referred to as beta thalassemia trait or minor, and it causes mild anemia. If both genes are affected, moderate or severe anemia results. The moderate form is referred to as beta thalassemia intermedia, and the severe form of beta thalassemia is called “thalassemia major” or “Cooley anemia.”

Most cases of thalassemia are inherited in an autosomal recessive pattern, but some cases are inherited in an autosomal dominant pattern. This condition affects both males and females. Thalassemia occurs most frequently in persons of Mediterranean descent, but also in individuals of Asian, Indian, and African descent.

Treatments for thalassemia have improved the prognosis, although severe cases can still lead to death in childhood. Notably, infants with alpha thalassemia major usually die before or shortly after birth. Individuals with moderate cases and those treated effectively are living longer and have a better quality of life. However, complications from thalassemia and their treatments frequently occur.

Thalassemia results in three major issues affecting the circulatory system: hypercoagulability, ineffective erythropoiesis, and hemolysis (**FIGURE 3-20**). Manifestations and complications reflect these issues but may also result from or be worsened by some of the treatments. They can vary greatly, from no symptoms to severe problems, depending on the severity of the disease. Mild cases are often mistaken for iron-deficiency anemia. In addition to the general anemia symptoms (e.g., pallor, fatigue), clinical manifestations of thalassemia may include:

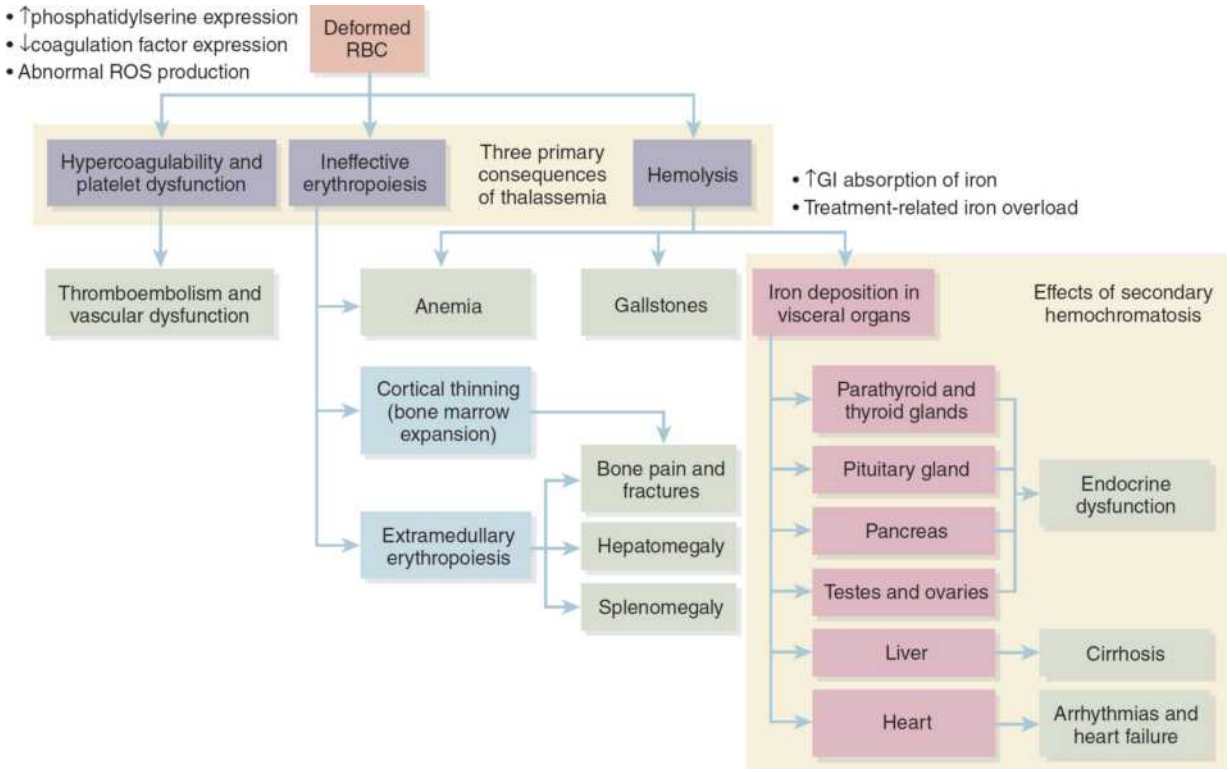


FIGURE 3-20 Effects of thalassemia.

Description

- Abortion
- Delayed growth and development
- Poor appetite
- Jaundice (as a result of bilirubin being released from erythrocytes as they hemolyze)
- Dyspnea
- Dark urine (as a result of erythrocytes being broken down)
- Cardiomegaly and heart failure
- Hepatomegaly
- Splenomegaly
- Bone deformities (e.g., wider, brittle bones), osteoporosis, and fractures
- Infections (often the main cause of death)

Laboratory tests aid in diagnosing thalassemia as well as monitoring progress. Upon examination, erythrocytes will appear microcytic, hypochromic, and variable in size. Iron levels may be increased, helping to rule out iron-deficiency anemia. A CBC is also useful in diagnosis, with affected individuals having a low MCV and mean corpuscular hemoglobin concentration (MCHC). A hemoglobin test can identify the presence of thalassemia as well as the type.

Genetic testing and counseling are important for families with a history of this disorder. For individuals who have thalassemia or are carriers, prenatal testing can identify whether the fetus is affected and how severe the disease may be. Treatment may not be necessary in mild cases. If treatment is warranted, it includes blood transfusion, iron chelation therapy, folic acid supplements, blood and bone marrow stem cell transplants (which have cured some patients), and splenectomy. Additionally, preventing infections (e.g., vaccinations, frequent hand washing, avoiding crowds) as well as early and aggressive treatment for any infections that arise are critical.

Polycythemia Vera

Polycythemia vera (PV) is a disorder in which the bone marrow produces too many erythrocytes and sometimes too many leukocytes and platelets. This rare condition is considered a neoplastic disease (i.e., myeloproliferative neoplasm) because of the uncontrolled proliferation of cells. As blood cell numbers increase, so does the blood volume and viscosity.

Emerging Research: Polycythemia Vera

Researchers are currently exploring new treatments for polycythemia vera. Low doses of selective serotonin reuptake inhibitors (SSRIs), normally used to treat depression, have been shown to reduce the pruritis associated with PV in clinical trials. Additionally, imatinib mesylate, an antineoplastic agent typically used to treat leukemia, has reduced the need for phlebotomy as well as helped reduce the splenomegaly associated with PV.

Researchers are also exploring treatments to block or limit the effects of the abnormal *JAK2* gene associated with primary PV.

Primary PV is a result of a mutation in the Janus kinase 2 (*JAK2*) gene, which is responsible for making a protein that controls hematopoietic stem cell growth. What causes this mutation is unknown. Primary PV is not inherited, but the gene tends to mutate in some families.

Secondary PV is not due to a mutation in the *JAK2* gene but rather a result of long-term low oxygen levels. A lack of oxygen over an extended period of time stimulates more erythropoietin to be produced, increasing erythrocytes. Risk factors include severe heart or lung disease, cigarette smoking, extended periods at high altitudes, and exposure to high levels of carbon monoxide (e.g., working underground in a car garage or mine, living with a poorly ventilated fireplace or furnace, etc.). Rarely, tumors can make and secrete erythropoietin.

Individuals can also experience relative PV. In relative PV, there is not actually an increased production of blood cells; instead, there is the appearance of increased blood cells because of a reduction in plasma (e.g., dehydration).

In PV, blood vessels become distended and blood flow is sluggish, causing the following complications:

- Tissue ischemia and necrosis
- Thrombosis
- Hypertension
- Heart failure
- Hemorrhage
- Splenomegaly
- Hepatomegaly
- Acute myeloblastic leukemia

PV occurs slightly more frequently in men and adults older than 60 years of age. It develops slowly and may not cause any symptoms for years. When they do occur, manifestations are a result of the thickened blood and decreased oxygen reaching the tissues. Clinical manifestations of PV include the following:

- Cyanotic or plethoric (reddish) skin
- Pruritus (especially after a warm bath) or a burning sensation
- Excessive perspiration
- High blood pressure
- Tachycardia
- Dizziness
- Weakness
- Dyspnea
- Headaches
- Visual abnormalities (e.g., double vision, blurred vision, or blind spots)
- Unexplained weight loss
- Painful swelling in a single joint (gouty arthritis as a result of increased uric acid production)

Because the disease may not cause symptoms for years, PV is often discovered during routine blood tests for other reasons. Diagnostic procedures for this condition include CBCs, blood smears, erythropoietin levels, bone marrow biopsy, and uric acid levels.

There is no cure for PV, so treatment strategies seek to relieve symptoms, prevent complications, and improve prognosis. These strategies include chemotherapy (specifically hydroxyurea), biological agents (specifically interferon alpha), radiation, and phlebotomy (removal of blood). Management of clotting and bleeding disorders and other complications (e.g., hypertension, gout) is employed as needed. Aspirin can relieve bone pain, pruritus, and burning sensations, as well as help reduce coagulation. Identifying risk factors is important in preventing PV.

Diseases of the Platelets

Platelets are vital components of the coagulation process. Normal platelet concentrations in the blood range from 150,000 to 350,000 cells/mL. **Thrombocytosis** refers to increased platelet levels, a condition that increases the risk of thrombus formation. In contrast, thrombocytopenia—decreased platelet levels—increases the risk of bleeding and infection.

Capillaries are relatively delicate structures that can leak from even minor injuries. Fortunately, the platelets, along with the coagulation process, quickly halt any such leaking. Diseases of the platelets include issues related to the quantity and quality of platelets.

Hemophilia

Hemophilia is an inherited bleeding disorder that results in decreased coagulation. It is caused by a mutation in one of the genes that provides instructions for making clotting factors; these genes are located on the X chromosome. Hemophilia is inherited in an X-linked recessive pattern, so males have the disease if they inherit an affected X chromosome. Females can also have hemophilia, although such cases are rare. Both X chromosomes would have to be affected, or one chromosome would have to be affected and the other one missing or inactive. A female with one affected X chromosome is a carrier of hemophilia. Sometimes, a female who is a carrier of hemophilia can have mild symptoms.

There are two main types of hemophilia, designated as A and B. **Hemophilia A**, or classic hemophilia, involves a deficiency or abnormality of clotting factor VIII. Hemophilia B, also known as "Christmas hemophilia," involves a deficiency or abnormality of clotting factor IX. Hemophilia A is four times more common than hemophilia B, and about half of hemophilia A cases are severe.

Hemophilia occurs in about 1 of every 5,000 male births. Because it is X-linked, this condition affects people of all races and ethnicities.

The severity of the disorder varies depending on the amount of clotting factor present in the blood. Severe forms of hemophilia become apparent early on. Bleeding is the main symptom of the disease and sometimes, though not always, occurs if an infant is circumcised. Additional bleeding problems may be seen when the infant starts crawling and walking. Mild cases may go unnoticed until later in life when they are detected during surgery or trauma. Internal bleeding may happen anywhere, and bleeding into joints, or hemarthrosis, is common. Other manifestations include petechiae, bruising, gastrointestinal bleeding, and hematuria. In rare cases, a person can develop hemophilia later in life. Most of these cases involve a middle-aged or elderly person or young women who have recently given birth or are in the late stage of pregnancy. This form usually resolves with treatment.

Diagnosis of hemophilia includes the examination of bleeding studies. Bleeding time and prothrombin time are usually normal, but partial thromboplastin time, activated partial thromboplastin time, and coagulation time are prolonged. Serum levels of factor VIII or IX are low. Genetic testing and counseling are warranted when there is a family history of hemophilia.

Treatment strategies include replacing clotting factors through transfusions and Advate (antihemophilic factor, a recombinant DNA product). To prevent a bleeding crisis, patients can be taught to give factor VIII concentrates at home at the first signs of bleeding. People with severe forms of the disease may need regular preventive treatment. Mild hemophilia may be treated with desmopressin acetate (DDAVP), which helps the body release factor VIII that is stored within the lining of blood vessels. Additionally, bleeding precautions should be employed (e.g., electric razors, soft-bristle toothbrushes, injury prevention).

In about 15% to 20% of cases, individuals develop antibodies (inhibitors) that prevent coagulation. Treatment of bleeding episodes in these patients can be difficult. In addition to aggressive treatment for bleeding, immune tolerance induction therapy may be necessary to stop the inhibitors.

Von Willebrand Disease

Von Willebrand disease (VWD) is the most common hereditary bleeding disorder. It results from a mutation on chromosome 12 that causes a deficit of von Willebrand factor, which ordinarily causes platelets to come together (aggregate) and stick (adhere) to the vessel wall in times of injury. VWD is the most common coagulation disorder (1 in every 100 people in the United States; CDC, 2022). It affects men and women equally, but women are more likely to notice the symptoms because of abnormal or heavy bleeding during menstruation or after childbirth. Although rare, VWD can result in bleeding severe enough to damage joints or internal organs or even be life threatening.

Several forms of VWD are distinguished:

- *Type 1* is the most common (85%) and mildest form. It follows an autosomal dominant inheritance pattern (see the *Cellular Function* chapter). The level of von Willebrand factor in the blood is reduced, and low levels of factor VII may also be seen. Because this form is often very mild, most cases go undiagnosed. Type 1 does not usually cause spontaneous bleeding, but significant bleeding can occur with trauma or surgery.
- *Type 2* occurs in 10% to 15% of cases. It can be either autosomal dominant or recessive. In type 2, levels of von Willebrand factor are normal, but the building blocks (multimers) that make up the von Willebrand factor are smaller than usual or break down easily. This type has four subtypes (2A, 2B, 2M, and 2N), each with its own treatment.
- *Type 3* occurs in about 3% of VWD cases and follows an autosomal recessive inheritance pattern. Severe bleeding problems are seen with this type due to the lack of measurable von Willebrand factor or factor VIII.
- *Acquired type* occurs in persons with Wilms tumor, congenital heart disease, systemic lupus erythematosus, and hypothyroidism. This type cannot be passed on to offspring.

- *Spontaneous type* happens without a family history. While rare, a spontaneous mutation may occur on chromosome 12. This mutation can be passed on to offspring.

Clinical manifestations of VWD include abnormal bleeding (e.g., frequent or hard-to-stop epistaxis, easy bruising, heavy menstruation, prolonged bleeding after injury or trauma). Diagnosis requires bleeding studies (e.g., bleeding time, prothrombin time, activated partial thromboplastin time, and fibrinogen test) and factor VIII levels. A CBC may reveal low erythrocytes and hemoglobin if bleeding is present. Factor VIII clotting activity (measures the amount of factor VIII), von Willebrand factor antigen (measures the amount of von Willebrand factor), ristocetin cofactor (measures how well the von Willebrand factor works), von Willebrand factor multimers (measures the structure of the von Willebrand factor), and platelet aggregation tests (measure how well the platelets are working) can help in diagnosing VWD or distinguishing it from another coagulation disorder.

Treatment, if needed, depends on the type and severity of the disease. Common treatments include the following options:

- Intravenous or intranasal administration of DDVAP to increase the release of von Willebrand factor and factor VII
- Intravenous administration of recombinant von Willebrand factor (e.g., Vonvendi)
- Intravenous administration of medications rich in von Willebrand factor or factor VIII (e.g., Humate P, Wilate, Alphanate, or Koate DVI)
- Parenteral or oral administration of antifibrinolytic medications (e.g., Amicar or Lysteda) to slow or prevent the breakdown of clots
- Oral contraceptives to increase the levels of von Willebrand factor and factor VIII and reduce menstrual blood loss
- Methods to control bleeding (e.g., pressure dressings) and injury prevention

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a rare (about 20,000 cases in the United States per year), life-threatening condition that can occur when tissue factor is exposed to blood, which triggers the coagulation cascade. Additionally, the fibrinolytic pathway is activated. Stimulation of endothelial cells by cytokines and disturbed microvascular blood flow causes tissue plasminogen activator (t-PA) to be released by the endothelial cells. Both t-PA and plasminogen attach to fibrin polymers, and plasmin (generated by t-PA division) cleaves fibrin into d-dimers and other fibrin degradation products. Normally, during injury, clotting factors (see Figure 3-4) become activated and travel to the injury site to help stop bleeding. In persons with DIC, these factors are abnormally active. Consequently, small blood clots form within the blood vessels, and some of these clots can occlude the blood supply to tissue and organs. Over time, the clotting factors become used up. When this happens, the person is at risk for serious bleeding from even a minor injury.

Learning Points

> n DIC, hypercoagulation uses up all the available clotting factors. Once available clotting factors are utilized, the patient begins excessively bleeding. In other words, the individual clots, clots, clots, and then bleeds, bleeds, bleeds!

It is unclear why certain disorders lead to DIC, but typical triggers follow three major pathways—endothelial cell injury, massive tissue destruction, or severe inflammation. Some conditions that can trigger DIC include the following:

- Blood transfusion reaction (causes profound intravascular hemolysis)
- Cancer (e.g., leukemia, aplastic anemia, adenocarcinomas of the pancreas and prostate, and metastatic carcinoma; tumor cells can release tissue factor)

- Infection in the blood caused by bacteria (particularly gram-negative organisms because endotoxins cause exposure to tissue factor activity in phagocytic, endothelial, and tissue cells) or fungi
- Obstetric complications (e.g., retained placenta after delivery, abruptio placentae, saline-induced therapeutic abortion, retained dead fetus or products of conception, amniotic fluid embolism, and eclampsia)
- Recent surgery or anesthesia
- Sepsis (an overwhelming infection)
- Severe liver disease
- Severe tissue injury (e.g., shock, burns, head injury, gunshot wound, and frostbite; ischemic tissue injury causes the release of tissue factor)
- Cardiac arrest
- Poisonous snakebite (enzymes in some venoms activate one or several coagulation factors, generate thrombin, or directly convert fibrinogen to fibrin)
- Aortic aneurysm or cavernous hemangioma (can cause vessel wall damage and areas of hemostasis)

DIC can develop and progress either slowly or rapidly. Slowly evolving DIC primarily causes venous thromboembolic manifestations (e.g., deep venous thrombosis and pulmonary embolism), occasionally causes cardiac valve vegetation, and infrequently causes abnormal bleeding. Rapidly evolving DIC is a more severe condition that causes thrombocytopenia, depletion of coagulation factors and fibrinogen, and bleeding. Bleeding into organs and microvascular thromboses may cause multiple organ dysfunction and failure.

Clinical manifestations of DIC include signs and symptoms of tissue and organ ischemia (e.g., angina, confusion, decreased level of consciousness, dyspnea, oliguria, and cyanosis) and abnormal bleeding with or without injury (e.g., petechiae, bruising, ecchymoses, epistaxis, hematuria, and gastrointestinal bleeding). Additionally, indicators of shock (e.g., tachycardia, hypotension) will appear.

Diagnostic procedures for DIC consist of CBCs (especially platelet counts) and bleeding studies (e.g., fibrinogen levels, prothrombin time, partial thromboplastin time, and fibrinogen degradation products, including the d-dimer test). Management of DIC is complicated but starts with the identification and treatment of the underlying cause. The treatment of the DIC disorder itself is a delicate balance between preventing clots and treating bleeding (**FIGURE 3-21**).

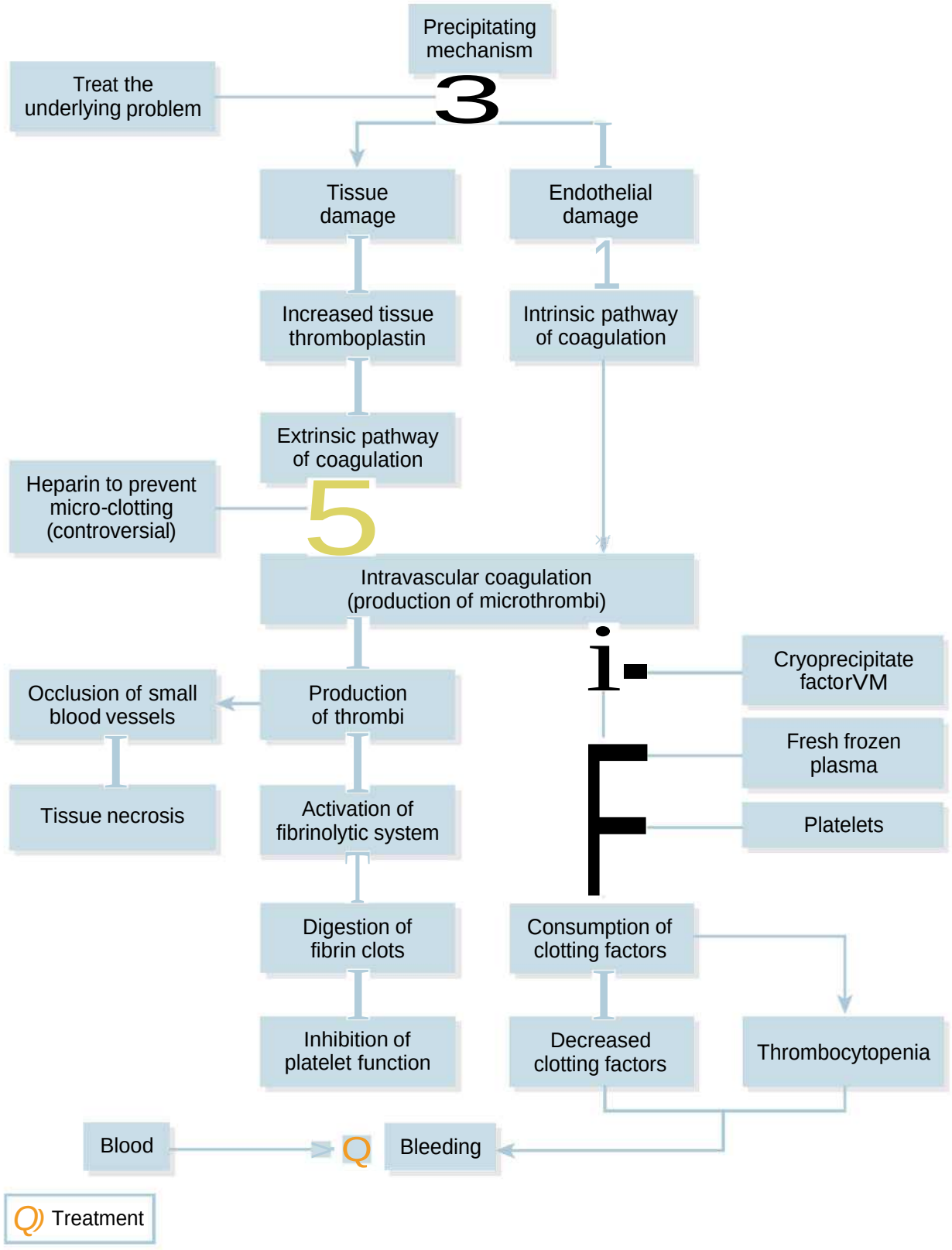


FIGURE 3-21 Understanding DIC and its treatment.

Description

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP), also known as "immune thrombocytopenia" and "idiopathic thrombocytopenic purpura," is a hypocoagulopathy state resulting from the immune system destroying its own platelets (autoantibodies). Circulating IgG reacts with the platelets, which are then destroyed in the spleen and liver.

Emerging Research: Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) causes both excessive clotting and excessive bleeding, making it difficult to treat. Treating the bleeding worsens clotting, and treating the clotting worsens the bleeding. Researchers at North Carolina State University have developed a new tool to treat DIC (Mihalko et al., 2021). The technique uses nanogel spheres that are engineered to bind to fibrin, the main protein found in blood clots. These tiny nanospheres travel through the bloodstream, searching for blood clots and binding to the fibrin in them. The nanospheres contain tissue-type plasminogen activator (tPA), a thrombolytic drug. The tPA contained in these nanospheres breaks the clots up, releasing the other clot components (e.g., platelets), which can be used for future clots. While the technology has not entered clinical trials, it has been shown to decrease clots by 77% to 93% in animal studies. Treating clots in this manner does not significantly increase overall bleeding risks.

ITP can be either acute or chronic. Acute ITP, which is more common in children, typically has a sudden onset and is self-limiting. Chronic ITP is more common in adults aged 20 to 50 and in women. Prognosis is usually good for both acute and chronic ITP.

Causes of ITP include the following:

- Idiopathic causes
- Autoimmune diseases
- Immunizations with a live vaccine
- Immunodeficiency disorders (e.g., AIDS)
- Viral infections

Clinical manifestations take the form of abnormal bleeding, such as petechiae, mucosal bleeding, epistaxis, and purpura. Gastrointestinal bleeding and hematuria are less common.

Diagnostic procedures are aimed at identifying the type of ITP as well as the cause. Diagnostic procedures include CBCs, bone marrow biopsy, bleeding studies (e.g., fibrinogen levels, prothrombin time, partial thromboplastin time), liver function tests, and humoral studies, including antiplatelet antibodies. Thrombocyte counts will often be less than 20,000/mL.

Treatment aims to increase the platelet count to prevent bleeding and to manage severe bleeding. Treatment strategies should be individualized based on the severity of the condition. Treatment strategies for ITP may include:

- Glucocorticoid steroids (to prevent further platelet immune destruction)
- Immunoglobulin infusions (to prevent further platelet destruction)
- Plasmapheresis
- Plateletpheresis
- Splenectomy
- Blood transfusions (particularly platelets)
- Immunosuppressant therapy (e.g., Rituximab, Fostamatinib)
- Thrombopoietin receptor agonist drugs (e.g., Romiplostim and Eltrombopag)

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a coagulation disorder resulting from nonimmunologic platelet destruction. Loose strands of platelets and fibrin are deposited in small vessels and damage passing platelets and erythrocytes, causing thrombocytopenia and anemia. Platelets are also collected within multiple small thrombi, further contributing to the thrombocytopenia. Thus, TTP is characterized by thrombi, thrombocytopenia, and bleeding.

TTP can be inherited, acquired, or idiopathic. Inherited TTP is caused by a mutation in the *ADAMTS13* gene, which provides the instructions for making an enzyme necessary for cleaving von Willebrand factor. This enzyme deficiency leads to increased clotting, which in turn decreases available platelets. The familial form of TTP follows an autosomal recessive inheritance pattern.

Most cases involve acquired TTP, which is characterized by the development of autoantibodies against the *ADAMTS13* gene. In many acquired cases, the cause of the autoantibody is unknown, but known causes and risk factors include the following:

- Female sex
- African American ethnicity
- Bone marrow transplants
- Cancer (most often as a result of chemotherapy)
- Medications (e.g., desmopressin, platelet aggregation inhibitors, immunosuppressants, and hormone replacement)
- Pregnancy
- HIV

With inherited TTP, manifestations may start in infancy and early childhood. In contrast, acquired cases typically occur in adults. Initial manifestations can range from mild and gradual to acute and severe. Manifestations reflect anemia (e.g., pallor, fatigue, weakness, and tachycardia), thrombocytopenia (e.g., purpura and other indications of bleeding), and organ ischemia. Neurologic manifestations include memory changes, headache, confusion, speech changes, and changes in consciousness. Renal manifestations may include oliguria and abnormal renal panel. Cardiac manifestations can include angina, arrhythmias, heart failure, and myocardial infarction. Gastrointestinal symptoms include abdominal pain, nausea, vomiting, and diarrhea. Jaundice may also be present as a result of bilirubin being released from the erythrocyte hemolysis. The pancreas, adrenal gland, and spleen can also be affected.

Diagnostic procedures are used not only to identify TTP but also to rule out other coagulation conditions (TABLE 3-4). Diagnostic procedures for TTP include a history, physical examination, CBCs, blood smears (which reveal fragmented erythrocytes called "schistocytes"), direct antiglobulin (Coombs) test, bleeding studies (e.g., fibrinogen levels, prothrombin time, partial thromboplastin time), *ADAMTS13* activity levels, lactate dehydrogenase levels (high levels indicate tissue injury), haptoglobin levels (low levels indicate erythrocytes are being destroyed more quickly than they are being produced), bilirubin levels, and *ADAMTS13* genetic testing (if inherited TTP is suspected).

TABLE 3-4 Distinguishing ITP Versus TTP Versus DIC

Parameter	ITP	TTP	DIC
Pathogenesis	Antiplatelet antibodies	Endothelial defect	Thrombin excess
Clinical condition	Not ill	Ill-appearing	Ill-appearing
Red blood cells	Normal	Schistocytes	Schistocytes
Prothrombin time (PT; international normalized ratio [INR])	Normal	Normal (slight increase)	Increased
Partial thromboplastin time (PTT)	Normal	Normal (slight increase)	Increased
Fibrinogen	Normal	Normal	Decreased
Fibrinogen degradation	Normal	Normal (slight increase)	Increased
D-Dimer	Normal	Normal (slight increase)	Increased
Management	Supportive Steroids Intravenous immunoglobulin (IVG) Splenectomy	Supportive Plasma exchange Steroids	Supportive

Description

application to practice

Now that we have learned about the various blood dyscrasias, let's put that knowledge into practice. During shift change, you receive reports on the following patients. Who would you see first following the report?

- A 32-year-old with pernicious anemia who needs to receive a vitamin B_{12} injection
- A 40-year-old with iron-deficiency anemia who needs an iron injection
- A 67-year-old with AML who has petechiae on the legs
- An 81-year-old with thrombocytopenia and an increased abdominal girth

Remember to go through the usual thought process—who would die first, acute versus chronic conditions, Maslow's hierarchy of needs, and patient safety. Starting with the patient with pernicious anemia, vitamin B_{12} is the mainstay of treatment, but the therapy is not a matter of life or death. The same is true for the patient with iron-deficiency anemia. Additionally, both of these conditions are chronic. The patient with AML and petechiae warrants consideration because that condition is acute and there is some mild bleeding—but hold off on making the decision until you look at all the patients. Finally, consider the thrombocytopenia patient experiencing increased abdominal girth. What would cause the increased abdominal girth? You must consider that this patient may be bleeding into the peritoneal cavity. This active bleeding would be worse than the mild bleeding in the patient with AML.

You should see the 81-year-old patient to assess for other manifestations of internal hemorrhage (e.g., hypotension and tachycardia) so that measures can be implemented immediately (e.g., notifying the healthcare provider and administering blood products).

Without treatment, TTP progresses and is often fatal. Plasmapheresis is the centerpiece of TTP treatment. Additionally, a splenectomy, glucocorticoid steroids, immunosuppressant agents (e.g., rituximab), and anti–von Willebrand factor immunoglobulin (e.g., Caplacizumab) may be necessary. Most patients experience only a single episode of TTP, but relapses occur in about 40% of individuals who have a severe deficiency of *ADAMTS13* activity caused by an autoantibody inhibitor. In such cases, more aggressive therapy may be necessary.

SUMMARY

Blood serves many purposes in the body. If this life fluid does not function properly, the body cannot maintain health and homeostasis; therefore, problems with any type of blood cells can lead to widespread and life-threatening problems. Hematologic problems can result from a variety of origins but usually lead to abnormal cell numbers or functions. Timely identification and treatment of these disorders are vital for positive healthcare outcomes.

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CHAPTER 4

Cardiovascular Function

LEARNING OBJECTIVES

- Discuss normal cardiovascular anatomy and physiology.
- Describe and compare cardiovascular alterations resulting in decreased cardiac output.
- Describe and compare cardiovascular alterations resulting in ineffective tissue perfusion.
- Explore cardiovascular alterations resulting in both decreased cardiac output and ineffective tissue perfusion.

KEY TERMS

afterload
aldosterone
anaphylactic shock
aneurysm
angina
antidiuretic hormone
aorta
aortic valve
arrhythmia
arteriole
artery
atherosclerosis
atresia
atrioventricular (AV) node
automaticity

baroreceptor
bundle branch
bundle of His
capillary
cardiac output
cardiac tamponade
cardiogenic shock
cardiomyopathy
chemoreceptor
chronotropic
compensatory mechanism
conductivity
constrictive pericarditis
coronary artery disease (CAD)
depolarization
diastole
diastolic dysfunction
dilated cardiomyopathy
dissecting aneurysm
distributive shock
dromotropic
dyslipidemia
dysrhythmia
eclampsia
edema
ejection fraction
embolus
endocardium
essential hypertension
excitability
exsanguination
fusiform aneurysm
heart failure
high-density lipoprotein (HDL)
hypertension
hypertrophic cardiomyopathy
hypovolemic shock
infarction

infective endocarditis
inferior vena cava
inotropic
left atrium
left-sided heart failure
left ventricle
lipid
low-density lipoprotein (LDL)
lung
lymph
lymphatic system
lymphedema
malignant hypertension
mitral valve
mixed dysfunction
myocardial infarction (MI)
myocarditis
myocardium
neurogenic shock
pacemaker
pericardial effusion
pericarditis
pericardium
peripheral vascular disease (PVD)
peripheral vascular resistance (PVR)
pregnancy-induced hypertension (PIH)
preload
primary hypertension
progressive stage
pulmonary artery
pulmonary circulation
pulmonary vein
pulmonic valve
pulse pressure
Purkinje network of fibers
Raynaud's disease
regurgitation
renin–angiotensin–aldosterone system

repolarization
restrictive cardiomyopathy
right atrium
right-sided heart failure
right ventricle
saccular aneurysm
secondary hypertension
septic shock
shock
sinoatrial (SA) node
stable angina pectoris
stenosis
stroke volume
superior vena cava
systemic circulation
systole
systolic dysfunction
thromboangiitis obliterans
thrombus
tricuspid valve
tunica adventitia
tunica intima
tunica media
unstable angina
varicose vein
vein
venule

The cardiovascular system is composed of the heart, blood vessels, **lymphatic system**, and blood (see the *Hematopoietic Function* chapter). This chapter focuses on normal and abnormal states of the heart and blood vessels. The components of the cardiovascular system work together to maintain life. Additionally, these components play a crucial role in the functioning of other systems. This pivotal role begins early in life, when the fetus is about 4 weeks old, and lasts until the end of life. Disorders of the

cardiovascular system are common and complex, as they often affect other systems. Such disorders are likely to be encountered in any practice setting, whether alone or in association with other disorders.

Anatomy and Physiology

The cardiovascular system is similar to the plumbing in a house. Both have a pump (the heart), a network of pipes (the blood vessels), and fluid (blood). The cardiovascular system delivers vital oxygen and nutrients to cells, removes waste products, and transports hormones. Circulation is divided into two branches—pulmonary and systemic (**FIGURE 4-1**). In the **pulmonary circulation**, the waste product—carbon dioxide—is exchanged for oxygen in the **lungs** through diffusion (**FIGURE 4-2**). In the **systemic circulation**, blood carries oxygen and nutrients to all cells and waste products to the kidneys, liver, and skin for excretion. To accomplish these transportation functions, the cardiovascular system requires a properly functioning heart to propel the blood by rhythmic contractions. The blood circulates through three types of vessels—**arteries**, **capillaries**, and **veins**. The lymphatic system assists in maintaining homeostasis by returning excess fluid from the body's tissues back to the circulatory system as well as by playing a vital role in the immune system (see the *Immunity* chapter). The following sections review the basic anatomy and physiology of the cardiovascular system.

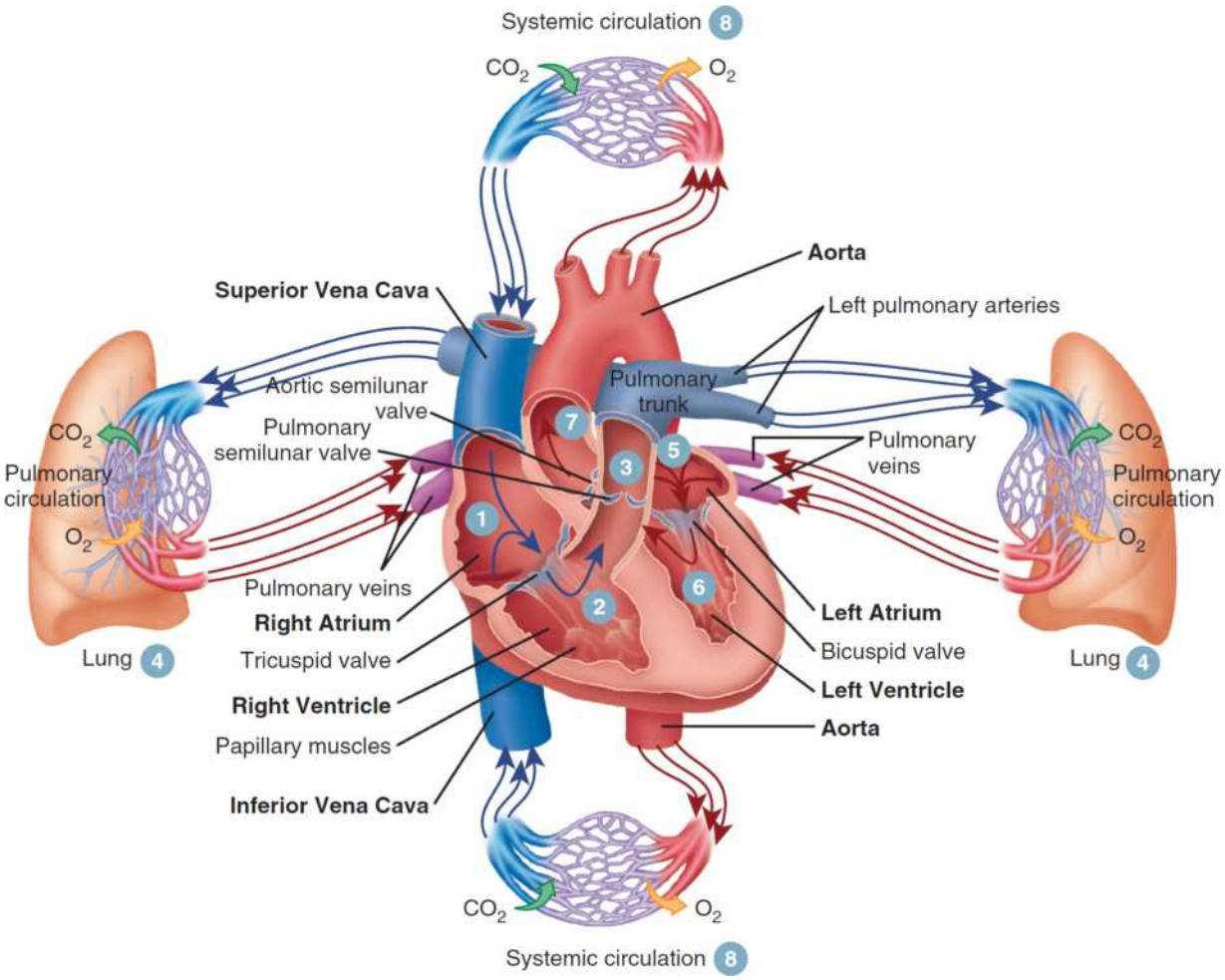
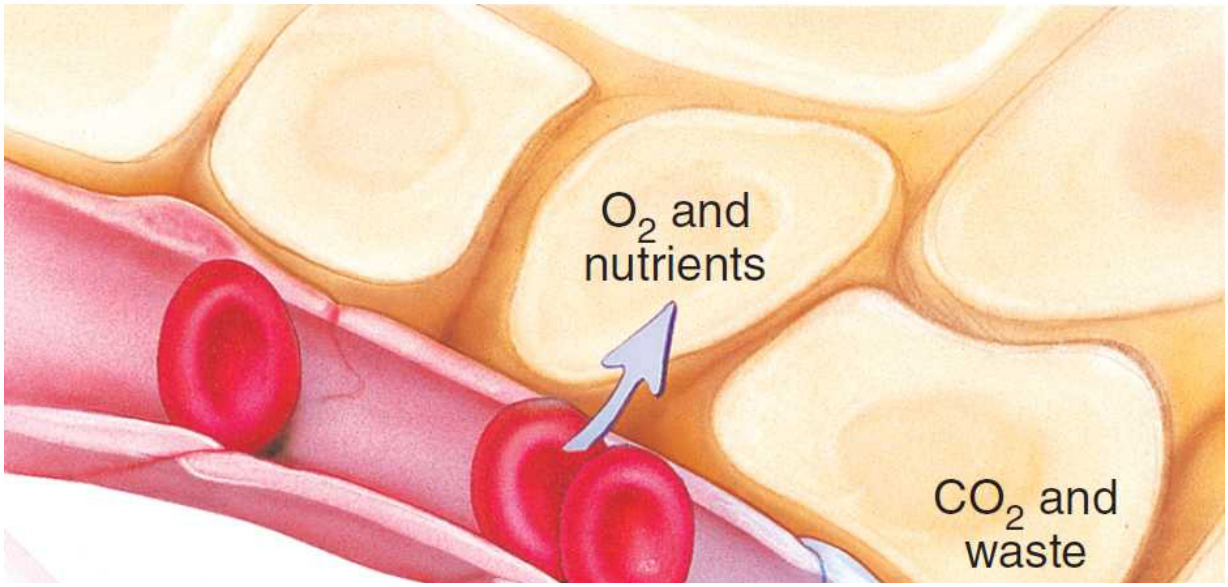
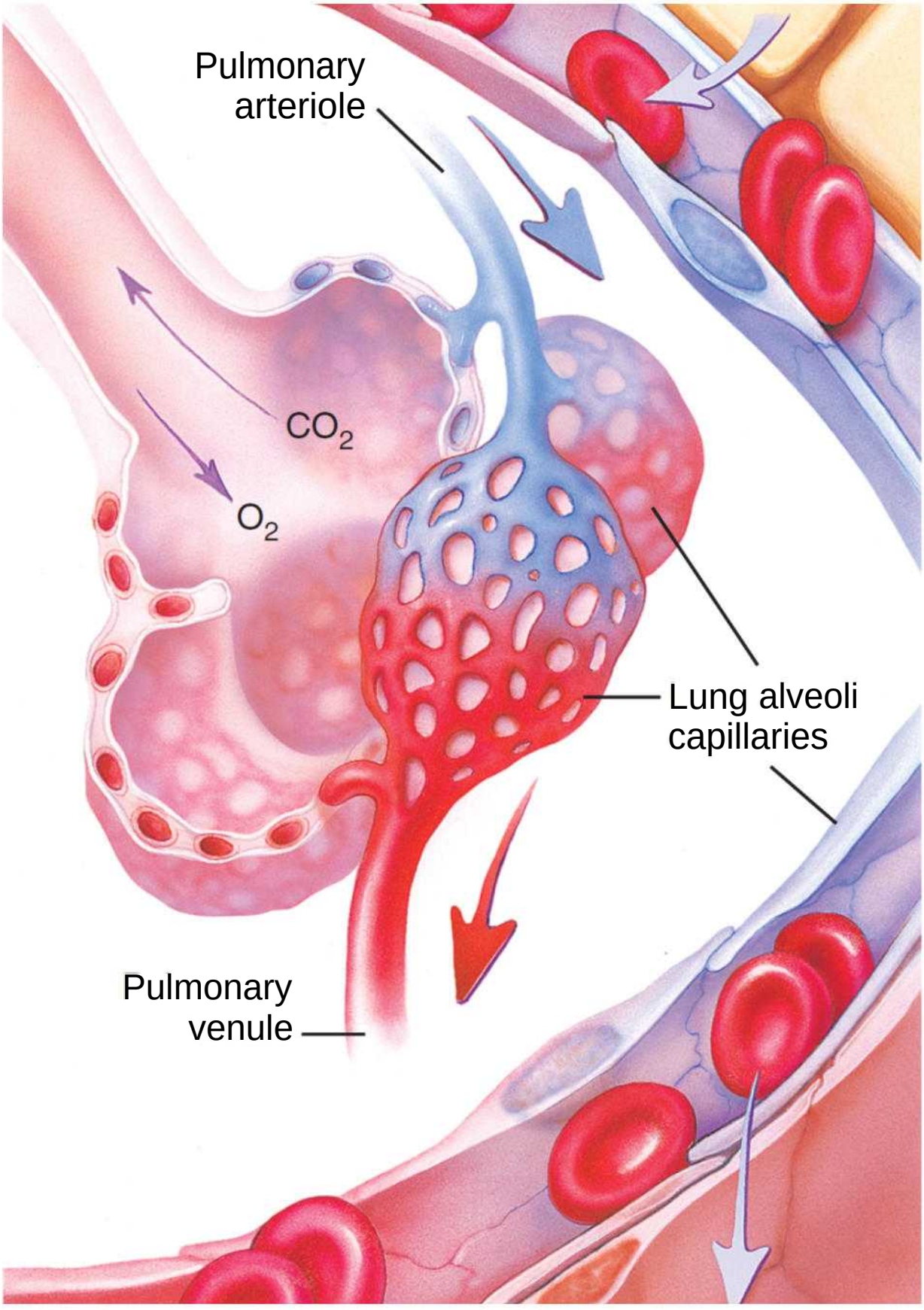


FIGURE 4-1 The cardiovascular system.

Description




Pulmonary arteriole
CO_2
O_2
Lung alveoli capillaries
Pulmonary venule

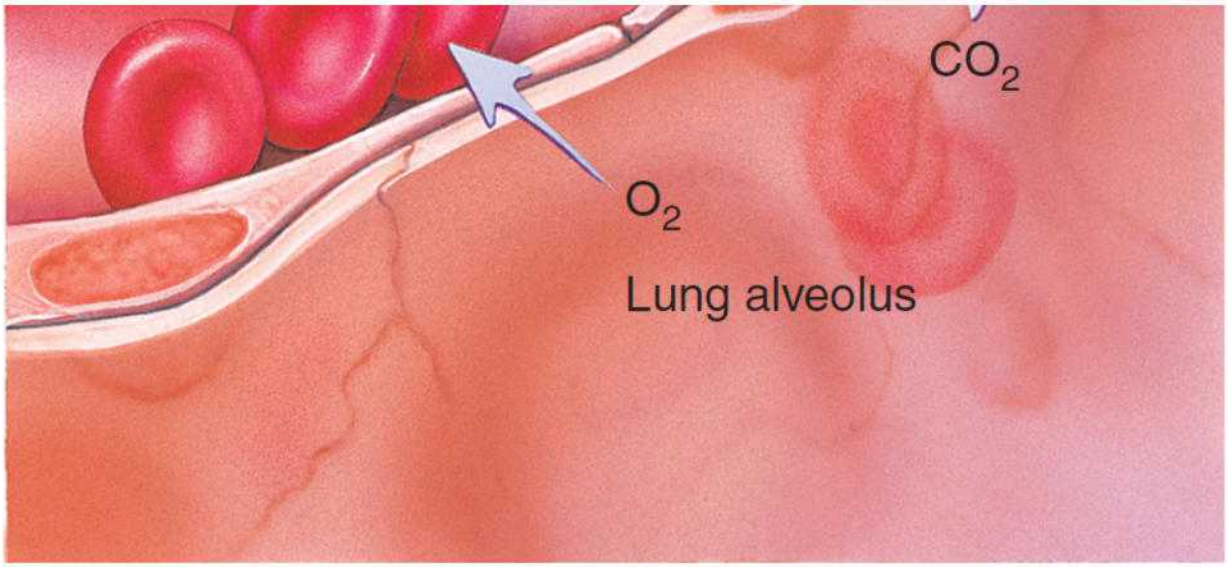


FIGURE 4-2 Pulmonary gas exchange.

Description

Heart

Roughly the size of a closed fist, the heart is a muscular organ that pumps blood throughout the body (**FIGURE 4-3**). It is the workhorse of the cardiovascular system, pumping blood through the body's 50,000 miles of blood vessels and beating approximately 100,000 times per day. If you received a dollar for every heartbeat, you would be a millionaire in just 10 days. The heart can quickly adjust its rate to meet the ever-changing needs of the body.

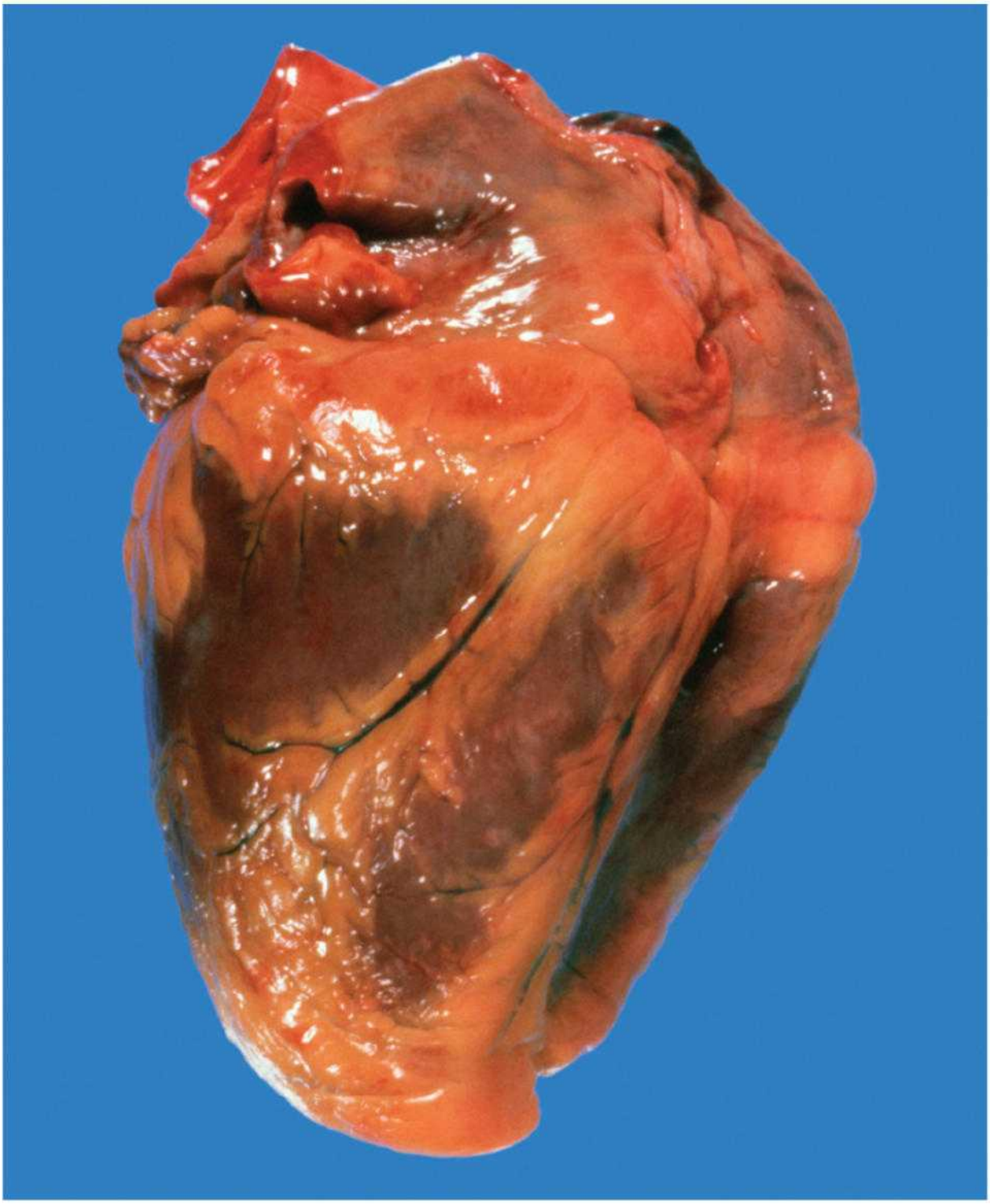


FIGURE 4-3 A normal heart.

© SIU/Visuals Unlimited, Inc.

The heart sits in the thoracic cavity between the lungs and behind the sternum. The pericardial sac, or **pericardium**, encloses the heart to provide protection and support. This sac is composed of three layers—the fibrous outer membrane, the parietal middle membrane, and the visceral inner membrane (also known as the "epicardium" because it makes up the other layer of the heart wall). The space between the inner visceral and middle parietal membranes contains approximately 50 mL of fluid. The pericardium protects the heart against trauma caused by contact with surrounding structures, invasions of foreign organisms, and friction from constant movement. It provides support in terms of anchoring the heart and prevents overdistention.

The **myocardium**, the middle layer of the heart, is the muscle portion of this organ. The walls of the ventricles, especially the **left ventricle**, are thicker than the walls of the atria because of the distance in the body to which those chambers must pump blood. The atria are receiving chambers that pump blood to their respective ventricles. The ventricles pump blood outside the heart to the lungs and the systemic circulation. The **endocardium** is the inner epithelial layer of the heart that makes up the cardiac valves; these valves function to ensure a one-way flow of blood through the heart (**FIGURE 4-4**).

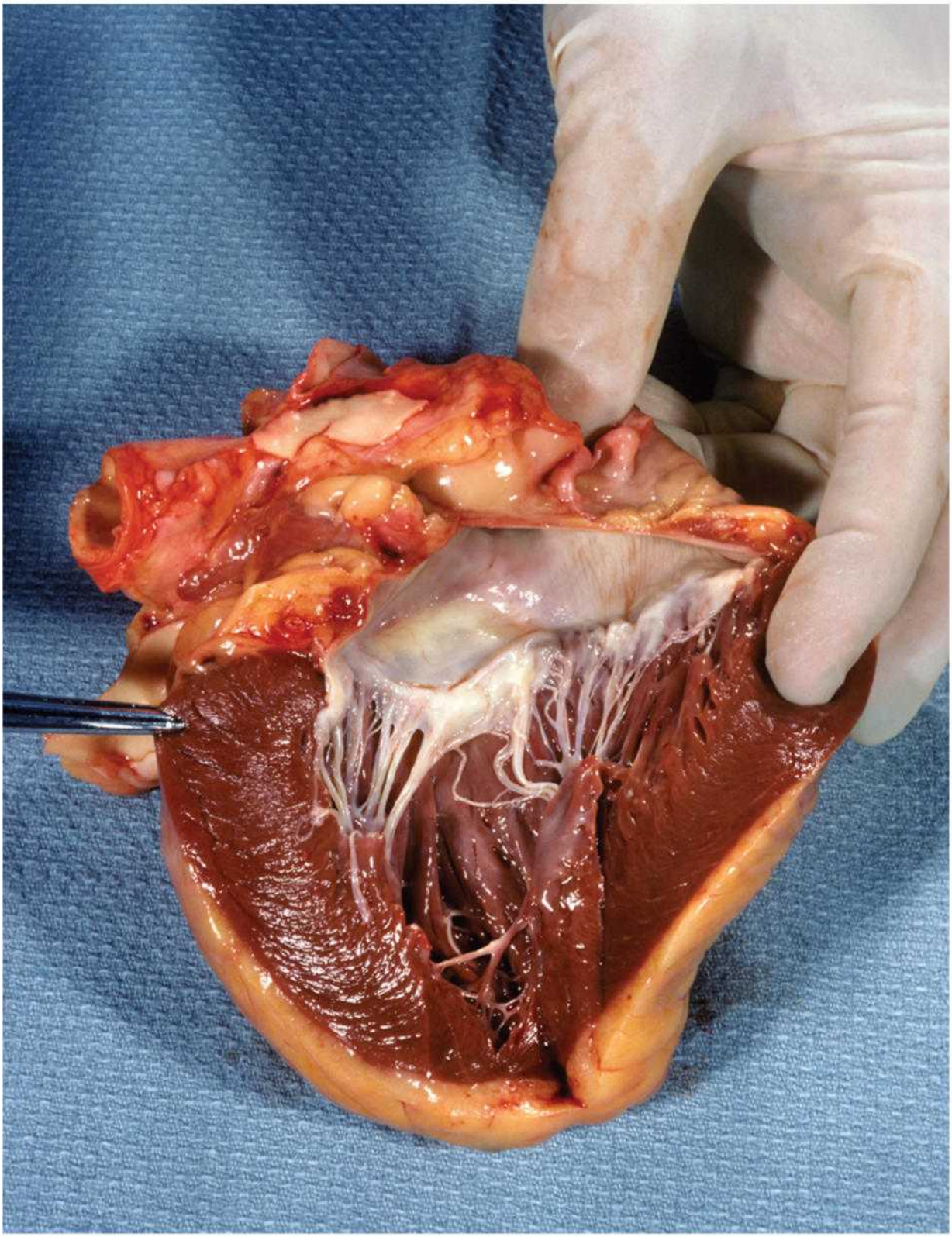


FIGURE 4-4 Heart valves.

© Phil Degginger/Alamy Stock Photo

Description

Cardiac Cycle

Understanding the blood flow through the heart is essential to understanding structural alterations and appreciating how they result in decreased **cardiac output** and/or ineffective tissue perfusion (**FIGURE 4-5**). As illustrated in blue in Figure 4-5, blood low in oxygen and rich in carbon dioxide enters the right side of the heart from the systemic circulation through the **superior vena cava** and the **inferior vena cava**. These veins empty blood directly into the **right atrium** during atrial **diastole** (i.e., relaxation). The right atrium pumps the blood through the **tricuspid valve** to the **right ventricle** during atrial **systole** and ventricular diastole. The right ventricle pumps the blood through the **pulmonic valve** to the **pulmonary arteries** during ventricular systole. The pulmonary arteries then carry the blood to the lungs for oxygenation.

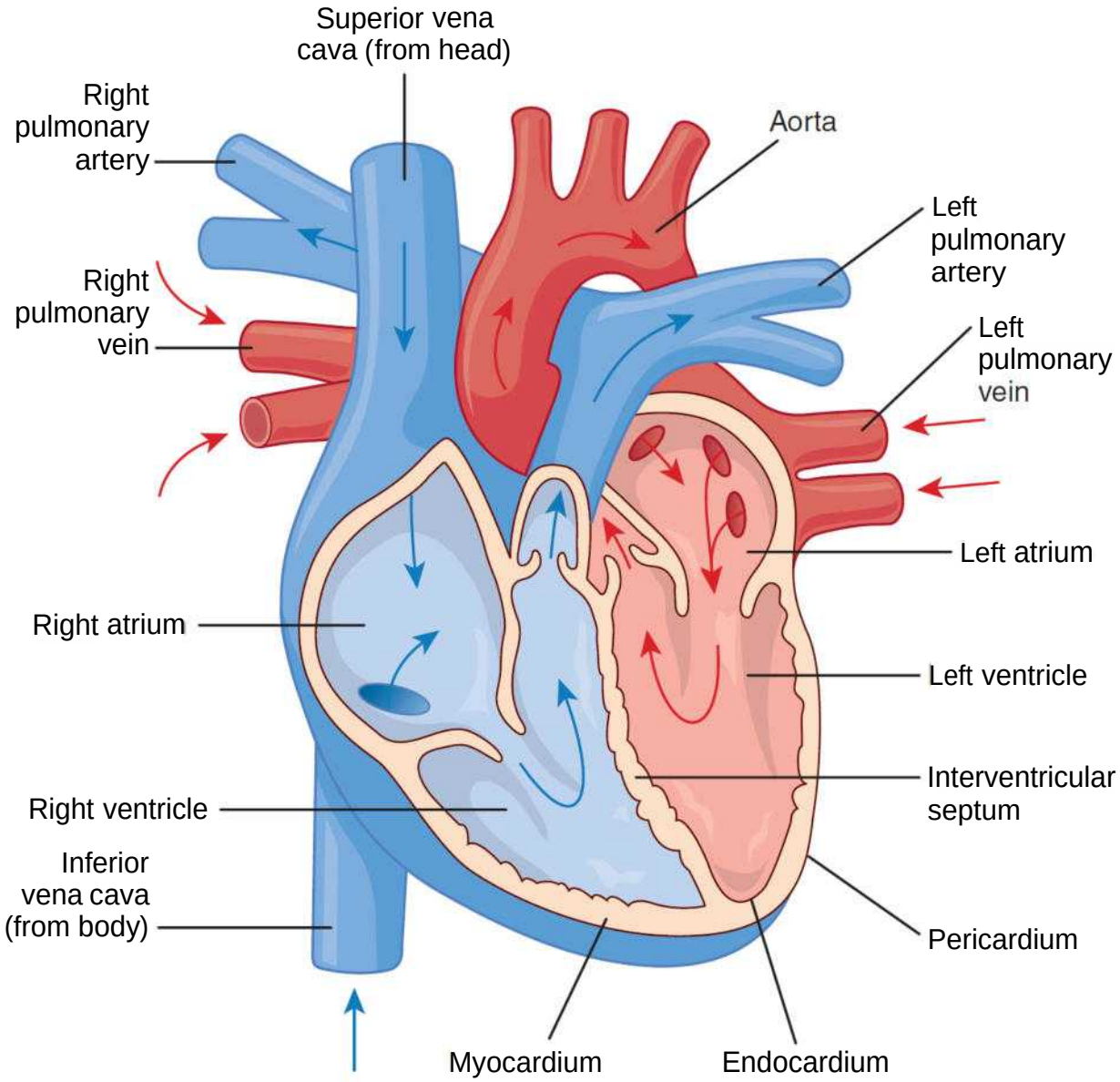


FIGURE 4-5 Blood flow through the heart.

Description

The newly oxygenated blood returns from the lungs to the heart through the **pulmonary veins**. From these veins, blood enters the **left atrium** during atrial diastole. The left atrium pumps blood through the **mitral valve** (i.e., bicuspid valve) to the left ventricle during atrial systole and ventricular diastole. The left ventricle then pumps blood through the **aortic valve** to the **aorta** during ventricular systole. From this point, the blood is transported throughout the body, beginning

with the coronary arteries (if the heart's needs are not met first, no other needs will be met) and the carotid arteries (the brain controls the vital bodily functions). Both atria fill (diastole) and contract (systole) simultaneously; likewise, both ventricles fill (diastole) and contract (systole) simultaneously (**FIGURE 4-6**). Pressure changes in each chamber open and close the valves. That is, the valves open when the pressure is high in the chamber (i.e., when it is filled with blood) and close when the pressure is low in the chamber (i.e., when it is empty). This coordinated contraction is regulated by the internal timing device, or **pacemaker**, of the conduction system.

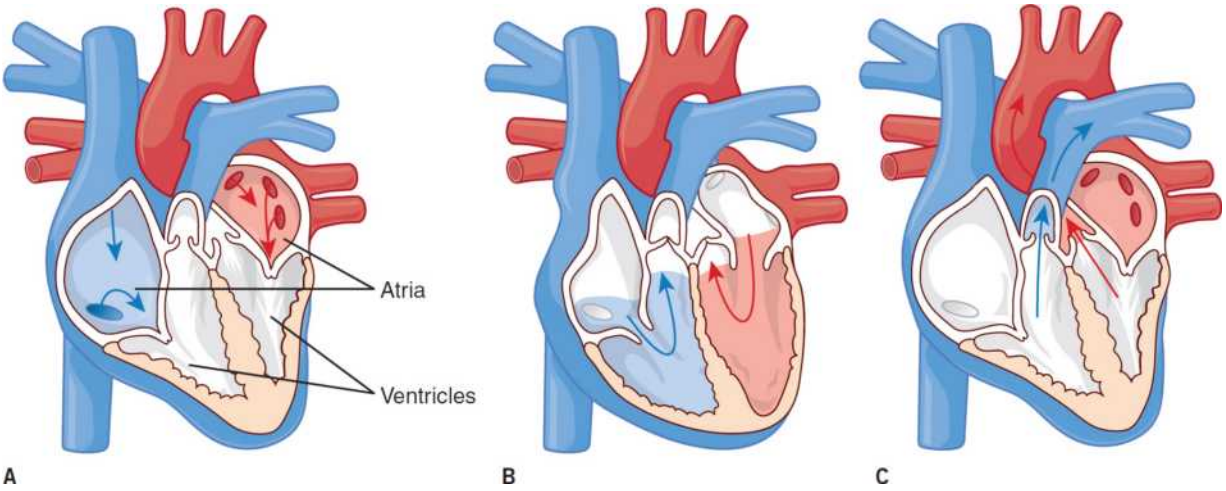


FIGURE 4-6 Blood flow through the heart. **(A)** Blood enters both atria simultaneously from the systemic and pulmonary circuits. **(B)** When full, the atria pump their blood into the ventricles. **(C)** When the ventricles are full, they contract simultaneously, delivering the blood to the pulmonary and systemic circuits.

Conduction System

Left to their own devices, cardiac muscle cells would contract individually, which would create a disorderly and ineffective contraction. The muscle cells are able to contract in an organized manner, however, due to the internal electrical stimulus (action potential) initiated by a pacemaker. The cardiac action potential refers to the brief change in voltage (membrane potential) across the cell membranes of cardiac cells (**FIGURE 4-7**). The action potential

passes along the cell membrane through gap junctions, causing the cell to shorten or contract (i.e., systole). Between impulses, the cells return to their usual length and rest (i.e., diastole). Basically, the heart's pacemaker acts like a generator creating an impulse for every heartbeat. **Conductivity** is the ability of cells to conduct electrical impulses. The ability of the cells to respond to electrical impulses is referred to as **excitability**. Cardiac cells are able to generate an impulse to contract even with no external nerve stimulus, a process called **automaticity**.

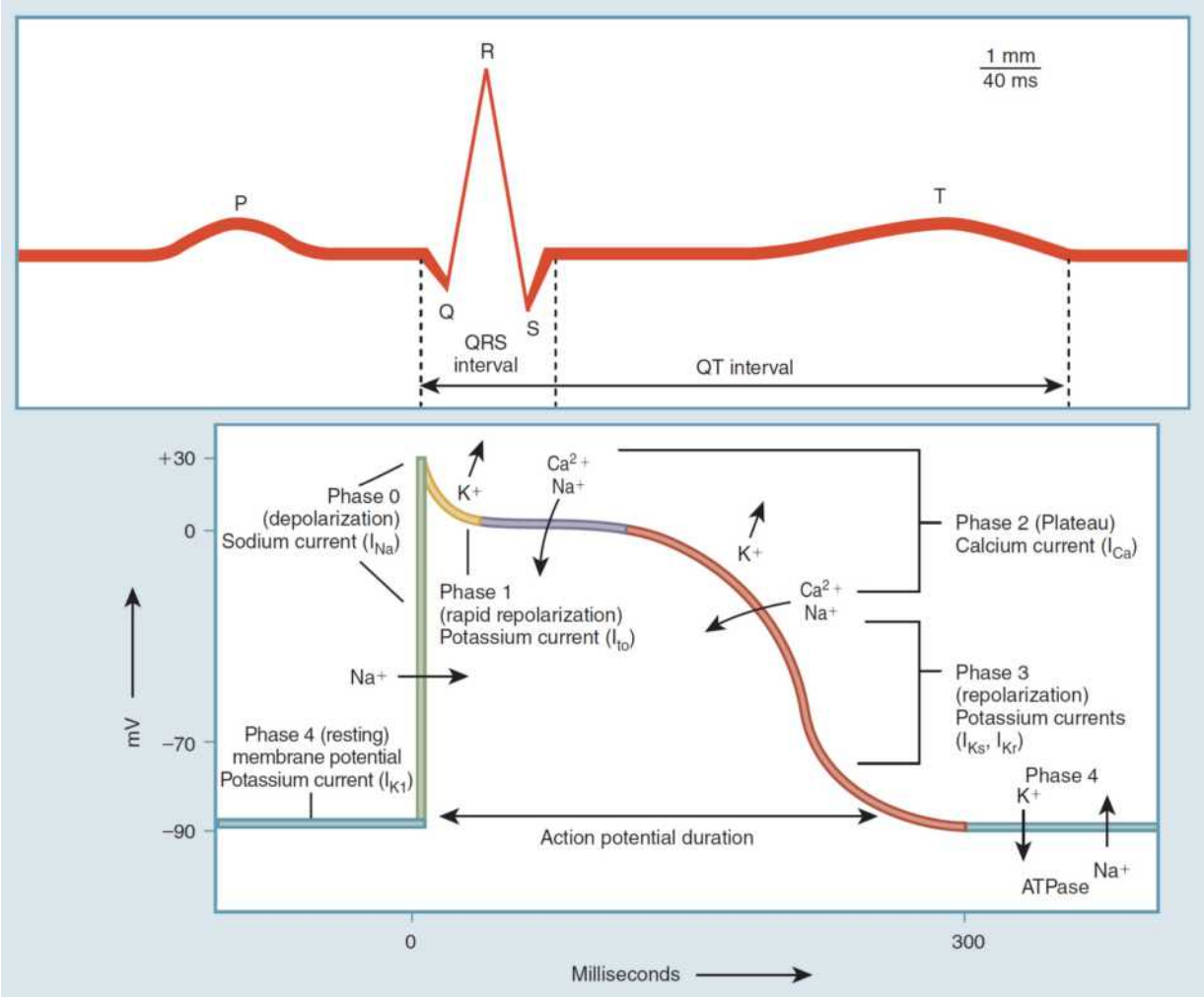


FIGURE 4-7 Characteristic features of a normal electrocardiogram.

Description

All cardiac muscle cells can initiate impulses, but normally the conduction pathway originates in the **sinoatrial (SA)** node located high in the right atrium (**FIGURE 4-8**). Impulses originating in the SA node travel through the right and left atria, resulting in atrial contraction. The SA node automatically generates impulses ranging from 60 to 100 beats per minute (sinus rhythm). The impulse then travels to the **atrioventricular (AV) node**, which is located in the right atrium adjacent to the septum. Although the AV node does not usually initiate impulses unless the SA node begins failing, the intrinsic rate of impulses in the AV node is 40 to 60 beats per minute. The impulses are delayed, or move slowly, through the AV node to allow for complete ventricular filling.

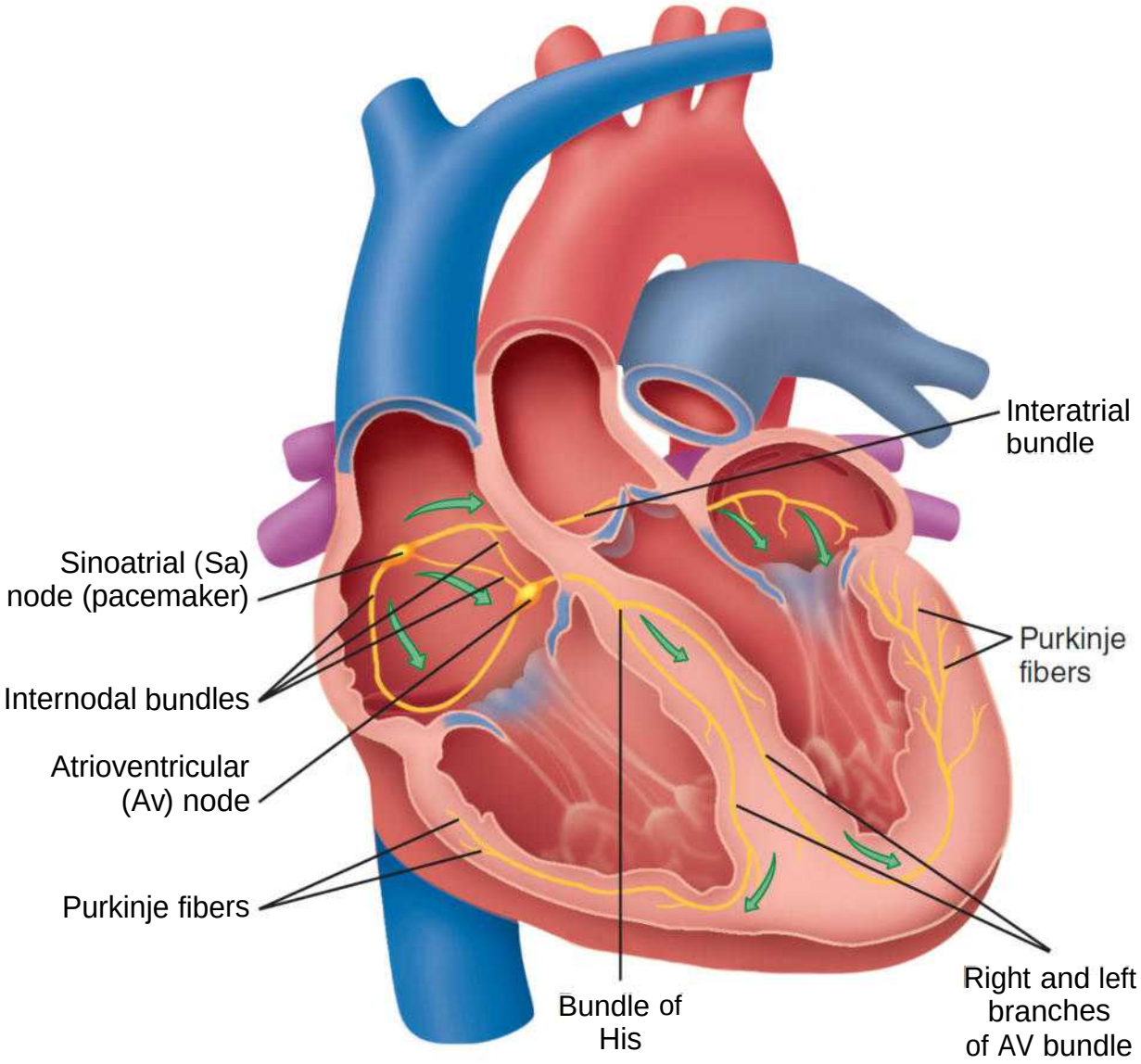


FIGURE 4-8 Electrical conduction through the heart.

Description

Next, the impulses move in rapid succession through the **bundle of His**, right and left **bundle branches**, and **Purkinje network of fibers**, which stimulates ventricular contraction. If the impulses fail to fire from the SA or AV node, the ventricles will attempt to pace themselves. The ventricles can generate impulses at 20 to 40 beats per minute, but that rate may not result in adequate cardiac output because the ventricles may beat before they have a chance to fill with

blood. These optional pacemakers in the heart function as a mechanism to sustain life when the primary pacemakers fail.

The cardiac impulse conduction produces an electric current that can be read by electrodes attached to the skin at various points of the body, producing an electrocardiogram (EKG) (see Figure 4-7). Organized **depolarization** (an increase in electrical charge through the exchange of ions across the cell membrane) of the cardiac cells generates cardiac muscle contraction. On the EKG reading, atrial contraction is represented by depolarization in the P wave, and ventricular contraction is represented by depolarization in the large QRS complex. The more intense the contraction, the higher the wave or complex. Because the force required for the atria to pump blood into the ventricles is minimal compared to the force required for the ventricles to pump blood throughout the entire body, the P wave is smaller than the QRS complex. The T wave represents **repolarization**, or recovery, of the ventricles. In repolarization, the ions line up on both sides of the cell membrane in preparation for depolarization. Repolarization of the atria does not appear on an EKG because the other more prominent waveforms hide it. Abnormal variations in the EKG, known as **arrhythmias** or **dysrhythmias**, may indicate acute problems, such as **infarction** or electrolyte imbalances.

Cardiac muscle cells require sodium (Na^+), potassium (K^+), and calcium (Ca^+) ions to initiate and conduct electrical signals as well as to perform the resulting muscular contraction. To initiate the depolarization that creates contraction, the sodium–potassium pump shifts these ions to generate a charge. Ca^+ balance is required for muscle contractility, especially in a muscle that contracts many times each minute. Additionally, the neurologic system controls cardiac function, and it requires Na^+ balance to function properly.

The brain (specifically the medulla) monitors and controls cardiac function through the autonomic nervous system, endocrine system, and cardiac tissue. These functions include the rate of contraction (**chronotropic** effect), rate of electrical conduction (**dromotropic** effect), and strength of contraction (**inotropic** effect). Receptors in the brain, heart, blood vessels, and kidneys continuously monitor

body functions to maintain homeostasis. **Chemoreceptors** detect chemical changes in the blood, and **baroreceptors**, located in the carotid arteries, detect pressure in the heart and arteries.

If homeostasis is interrupted, receptors begin to fire, and neurotransmitters or hormones that activate either the sympathetic nervous system (SNS) or the parasympathetic nervous system (PNS) are released. Stimulating the SNS will release norepinephrine, a catecholamine, from nerve endings on the myocardium, as well as epinephrine, another catecholamine. These catecholamines travel in the bloodstream and bind to adrenergic receptors on the heart; beta and alpha receptors are the most abundant. Beta-1 receptors are located on the conduction system and myocardium. Beta-2 receptors are found on the myocardium and smooth muscles. Beta-1 and beta-2 stimulation increases heart rate and contractility. Additionally, beta-2 stimulation causes the blood vessels to vasodilate. Beta-3 stimulation antagonizes (opposes) the effects of beta-1 and beta-2 stimulation, reducing contractility. Alpha receptors cause vasoconstriction (alpha-1) or centrally control blood pressure (alpha-2). The PNS causes the release of acetylcholine through vagal nerve stimulation, which decreases heart rate and contractility.

Blood Pressure

Blood pressure refers to the force that blood exerts on the walls of blood vessels. This pressure is described as a fraction, in which the systole (work) measurement is the top number, and the diastole (rest) measurement is the bottom number. A normal blood pressure reading should be in the range of 120/80 mm Hg to maintain health and limit chronic disease risk (Whelton et al., 2018). The systolic pressure is the force that the blood exerts on the arteries when it is ejected from the left ventricle. The diastolic pressure is the force that blood exerts in the arteries when the ventricles are relaxed. Blood pressure is commonly measured using a sphygmomanometer and the brachial artery. **Pulse pressure** is the difference between the systolic and diastolic pressures and represents the force that the heart generates each time it contracts.

Blood pressure changes in response to the individual's activity and stress level, and it also varies at different points of the body. Cardiac output and peripheral (systemic) vascular resistance significantly affect blood pressure (BP = CO × PVR, where BP is blood pressure, CO is cardiac output, and PVR is peripheral vascular resistance). Other variables that influence blood pressure include blood volume and viscosity, venous return, heart rate, cardiac contractility, and arterial elasticity. Typically, increases in these variables will increase blood pressure—with the exception of arterial elasticity, for which decreases increase blood pressure.

Cardiac output refers to the amount of blood that the heart pumps in 1 minute. This amount is determined by **stroke volume** and heart rate (CO = SV × HR, where CO is cardiac output, SV is stroke volume, and HR is heart rate). Stroke volume is the amount of blood ejected from the heart with each contraction. **Ejection fraction** is a measure of how much blood the left ventricle pumps out with each contraction, so an ejection fraction of 60% means that 60% of the total amount of blood in the left ventricle is being pushed out with every contraction. An ejection fraction in the range of 50% to 70% is considered normal; thus, this measure can help diagnose and track conditions that impact cardiac output.

Peripheral vascular resistance (PVR) is the force opposing the blood in the peripheral circulation; it increases as the diameter of the blood vessels decreases. Stimulation of the SNS can initiate systemic vasoconstriction to raise blood pressure. This vasoconstriction is helpful in mitigating hypotension, such as occurs with **shock**. PVR affects **afterload**, the pressure that the left ventricle must exert to get the blood out of the heart and into the aorta. The higher the afterload, the harder it is for the heart to eject the blood, thus lowering stroke volume. In addition to afterload, stroke volume is affected by **preload**, the amount of blood returning to the heart that the heart must then manage. Both afterload and preload can affect blood pressure; that is, as afterload and preload increase, blood pressure increases.

Hormones also influence blood pressure. **Antidiuretic hormone** increases water reabsorption in the kidney, which in turn increases

blood volume and blood pressure. Additionally, antidiuretic hormone is a vasoconstrictor, which increases PVR. **Aldosterone** increases blood volume by increasing the reabsorption of Na^+ in the kidneys; Na^+ attracts water. Increasing renal water reabsorption increases blood volume.

The **renin–angiotensin–aldosterone system** in the kidneys is another vital control and **compensatory mechanism** that becomes activated when renal blood flow is decreased, as is often the case in hypotensive states (**FIGURE 4-9**). When renal blood flow decreases, renin is released from the kidneys, activating angiotensin I, which is then converted to angiotensin II (a vasoconstrictor), and stimulating aldosterone secretion. In hypotensive states, this mechanism raises blood pressure and maintains the blood supply to vital organs. In chronic disease states such as **hypertension**, this mechanism is inappropriately activated because of vasoconstriction to the kidneys, further contributing to the hypertension.

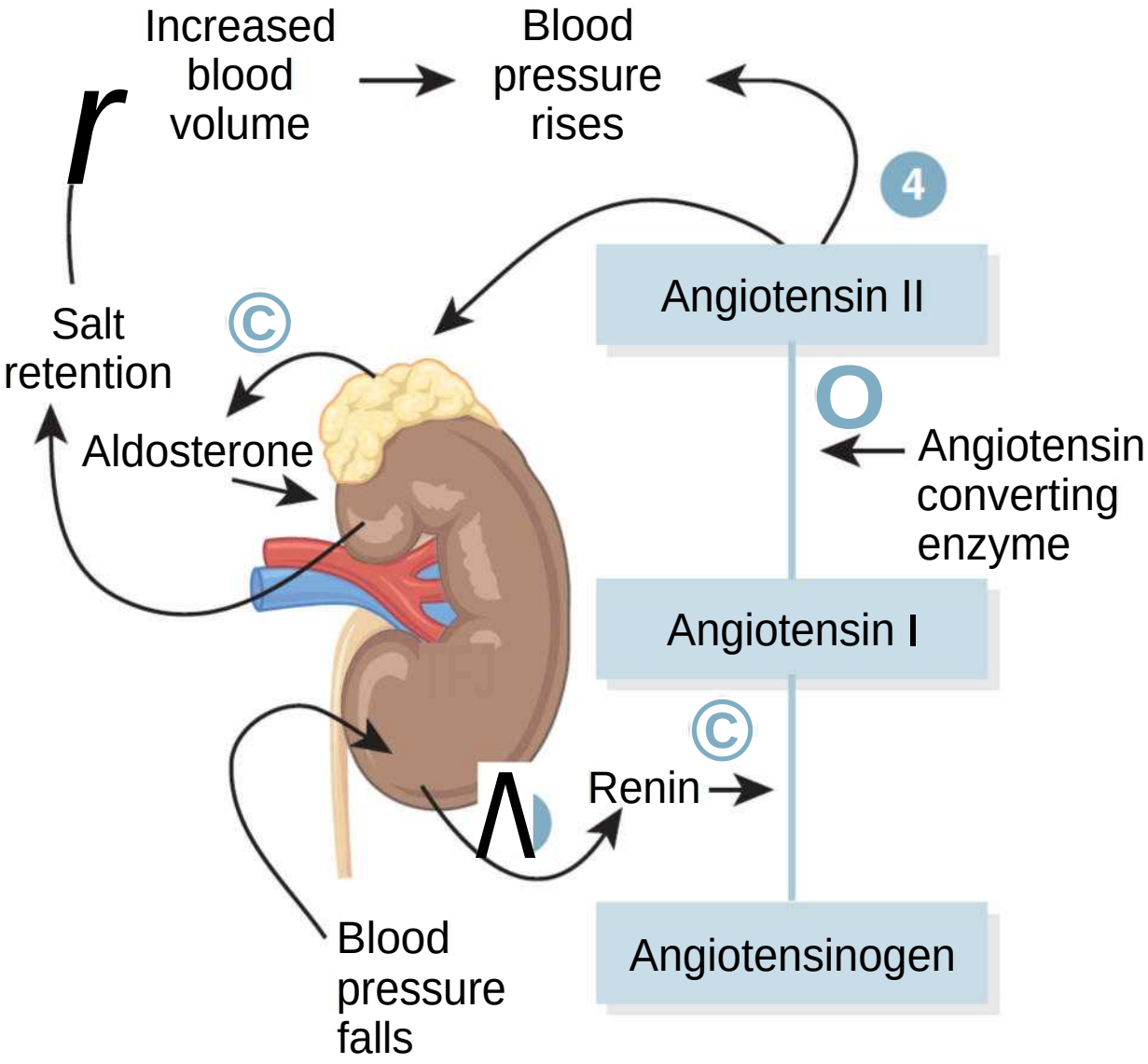


FIGURE 4-9 Role of kidneys in blood pressure.

Description

Blood Vessels

Blood vessels are the intricate highway system along which the blood travels within the body. Arteries carry blood away from the heart, while veins carry blood back to the heart. Left ventricular contractions project blood through the arteries, while valves in the veins assist in moving the blood back to the heart against gravity. Once arteries leave the heart, they begin branching into smaller vessels called **arterioles** (**FIGURE 4-10**). These vessels continue branching into

even smaller thin-walled vessels called capillaries. Their thin walls allow oxygen and nutrients to shift out of the capillaries into the cells. Additionally, carbon dioxide and waste products move from the cells into the capillaries. This exchange occurs through diffusion (see the *Cellular Function* chapter). Once blood is utilized at the cellular level, it moves through the capillaries and transitions into larger vessels known as venules. The venules continue to merge into larger vessels until they become veins, much as small streams unite to form a river.

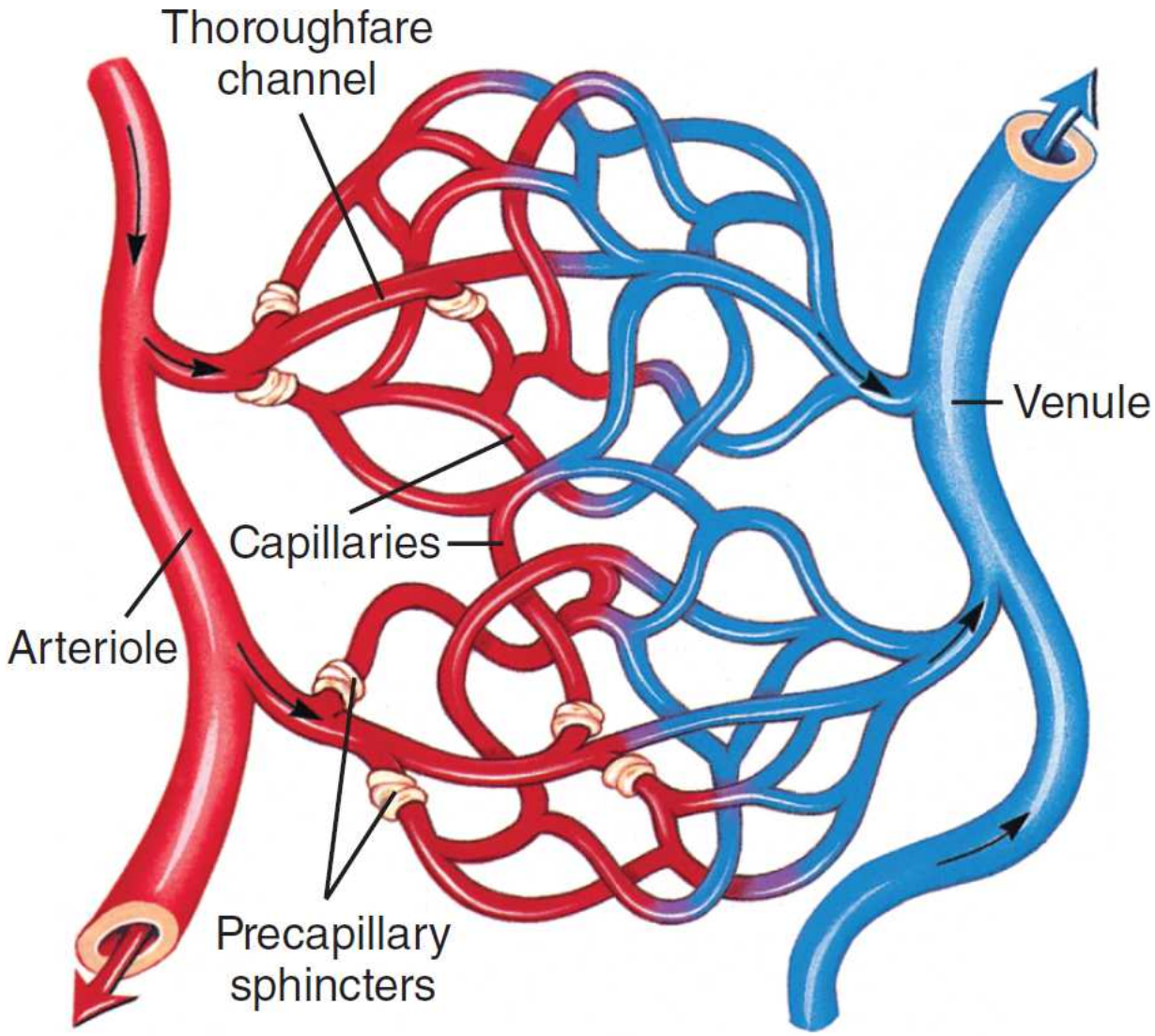


FIGURE 4-10 The circulatory system.

Description

Generally, arteries carry blood rich in oxygen and nutrients, while veins carry blood saturated with carbon dioxide and metabolic waste. One exception to this pattern occurs in the pulmonary arteries and veins. The pulmonary arteries carry oxygen-depleted blood away from the right side of the heart to the lungs for gas exchange (see Figure 4-2). Following gas exchange in the lungs, the oxygen-saturated blood returns to the left side of the heart through the pulmonary veins.

The coronary circulation comprises the blood vessels that supply blood to the heart (**FIGURE 4-11**). Because the heart must first receive adequate blood flow before it can maintain sufficient blood flow to the rest of the body, two main coronary arteries branch off the aorta just outside the heart—the left and right coronary arteries (LCA and RCA). These arteries branch several times, while creating multiple connections within and between each other (i.e., anastomoses). The coronary arteries can develop anastomoses (connections or openings) when blood flow is not sufficient for various reasons, such as with occlusions (e.g., plague or thrombosis) so that blood can flow. These new connections are referred to as collateral circulation. Coronary veins drain deoxygenated blood from the myocardium and return it to the right atrium through the coronary sinus.

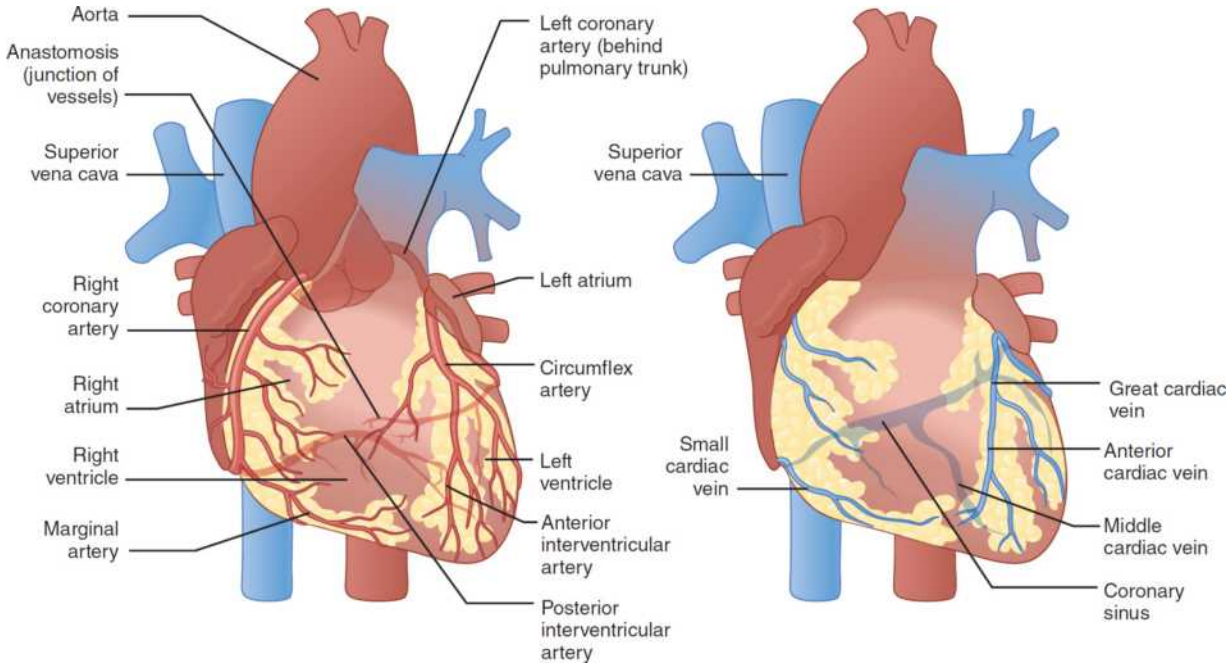
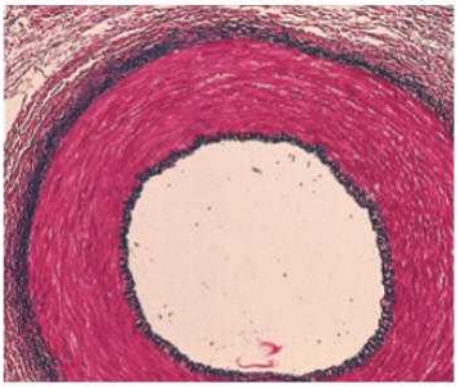


FIGURE 4-11 Coronary circulation.

Description

The walls of the blood vessels consist of three layers (**FIGURE 4-12**), whose composition varies depending on the type of blood vessel. The **tunica intima** is the smooth thin inner layer of the blood vessels. The **tunica media**, the middle layer, is composed of elastic tissue and smooth muscle that are responsible for the vessel's ability to change diameter. The outer layer, the **tunica adventitia**, consists of elastic and fibrous connective tissues that provide the necessary "give" to accommodate the rush of blood with each cardiac contraction. Arteries have an additional layer of elastic fibers in the middle and outer layers that enable them to accommodate the high pressure of the blood within these vessels. Additionally, the tunica media of arteries and arterioles is thicker than that of veins and venules because of the pressure differences. Large arteries (e.g., aorta) and veins (e.g., superior and inferior venae cavae) also contain nerve endings and a network of small blood vessels called "vasa vasorum," which provide nutrients and oxygen as well as remove waste products. Capillaries consist of a single layer of epithelial cells.



Connective tissue with elastic fibers

Circular smooth muscle

Elastic tissue

Endothelium

Artery

Arteriole

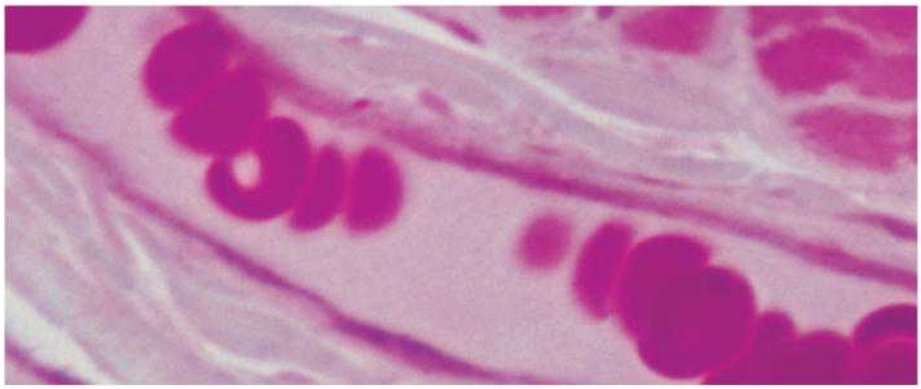
1

2

A

Capillaries

Endothelium



Capillary

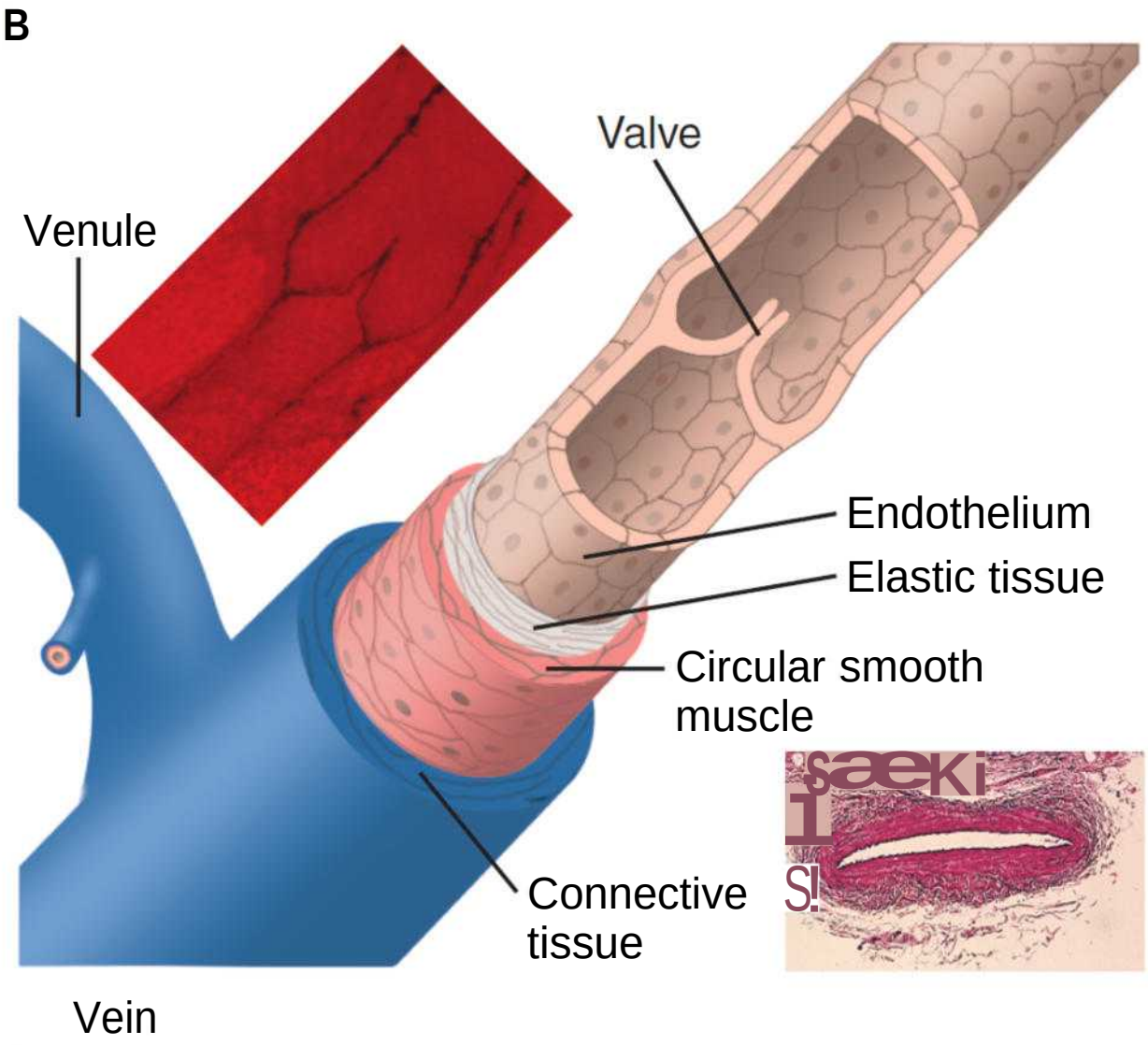


FIGURE 4-12 The walls of the blood vessels are composed of three layers of tissue: the tunica intima, the tunica media, and the tunica adventitia. **(A)** Artery; **(B)** capillary; **(C)** vein.

Artery photo: © Cabisco/Visuals Unlimited, Inc.; Capillary photo: © Ed Reschke/Photolibrary/Getty Images; Vein photos: © Carolina Biological Supply Co/Visuals Unlimited, Inc., and © Dr. John D. Cunningham/Visuals Unlimited, Inc.

Description

Lymphatic System

The lymphatic system is an extensive network of hundreds of vessels and glands that returns excess fluid in body tissue to the circulatory system and works with the immune system (see the *Immunity* chapter). Interstitial fluid surrounds cells and provides a medium through which nutrients, gases, and wastes can diffuse between the capillaries and the cells. Capillaries are continuously replenishing this fluid. Normally, the fluid outflow from the capillaries exceeds the fluid returned. Lymph capillaries absorb the excess fluid (**FIGURE 4-13**). This fluid, or **lymph**, drains from these capillaries into larger vessels and ducts that empty into large veins at the base of the neck. The movement of lymph occurs with the assistance of valves and body movement in the same way blood travels through the veins.

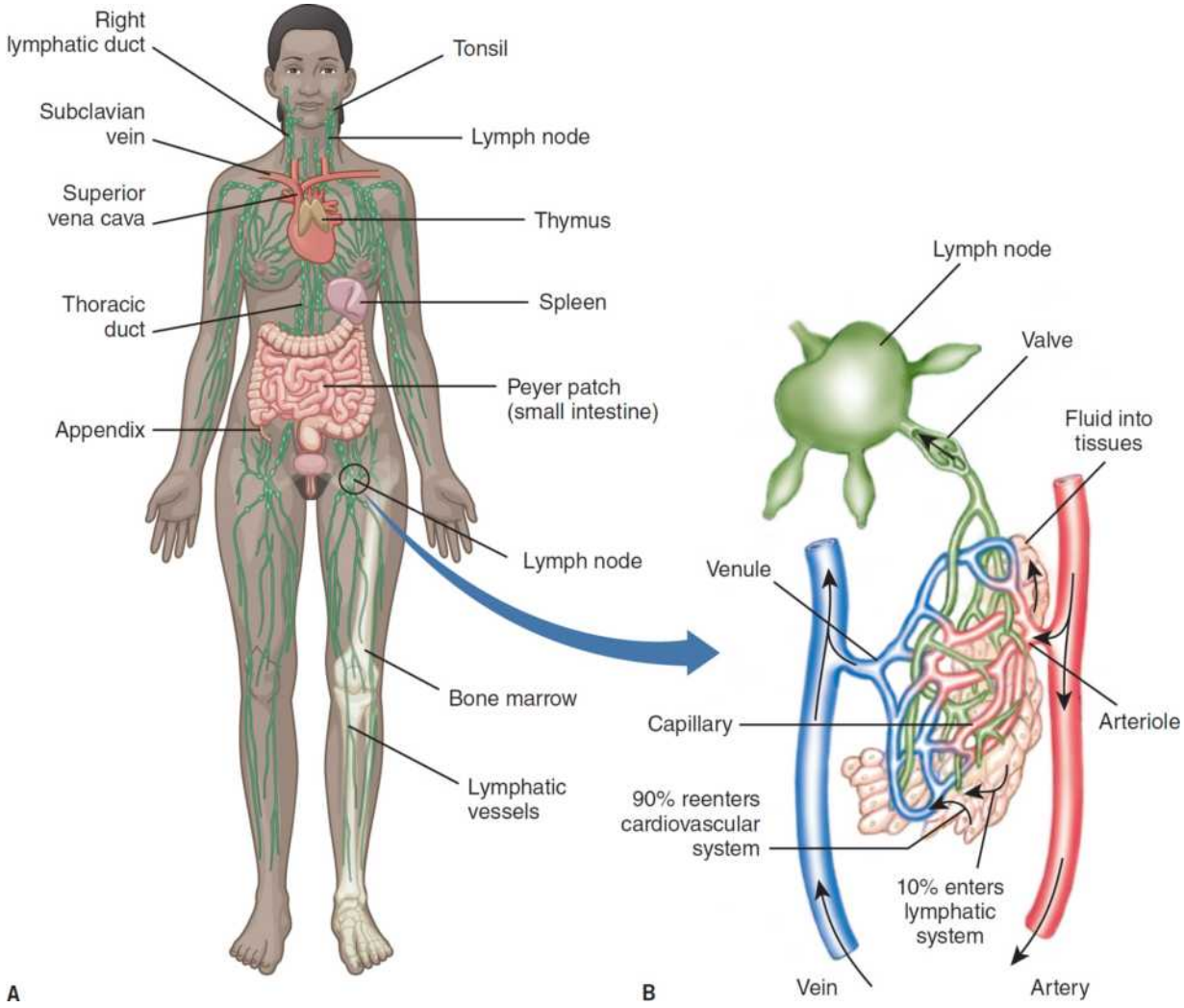


FIGURE 4-13 The lymphatic system. **(A)** The lymphatic system consists of vessels that transport lymph—that is, excess tissue fluid—back to the circulatory system. **(B)** Lymph is picked up by lymphatic capillaries that drain into larger vessels. Like the veins, the lymphatic vessels contain valves that prohibit backflow. Lymph nodes are interspersed along the vessels and serve to filter the lymph.

Description

The lymphatic system also includes several organs—lymph nodes, the spleen, the thymus, and the tonsils. These organs primarily function in the immune response (see the *Immunity* chapter). Located in clusters throughout the body, lymph nodes are a network of fibers and irregular channels that slow down the lymph flow. As lymph passes through the nodes, the fibers filter out bacteria, viruses, and cellular debris. Numerous macrophages line the channels to phagocytize microorganisms and other materials.

Normally, the rate at which lymph is produced equals the rate at which it is removed. In some bodily states, however, the amount of lymph produced exceeds the capacity of the system. For example, burns can cause extensive damage to capillaries, causing them to leak fluid into the tissues. This flooding results in excessive fluid in the tissue, or **edema**. In contrast, lymphatic vessels may sometimes become occluded, often because of infection.

Understanding Conditions That Affect the Cardiovascular System

When considering alterations in the cardiovascular system, organizing them based on the basic underlying pathophysiology can increase understanding. The two major cardiac-related nursing diagnoses are decreased cardiac output and ineffective tissue perfusion. Understanding what each of those diagnoses means facilitates understanding of the conditions that lead to their development.

Decreased cardiac output refers to states in which the amount of blood being pumped by the heart is less than normal. Decreased cardiac output can be associated with changes in preload, afterload, contractility, or dysrhythmias. Typical manifestations reflect an inability to maintain sufficient blood flow to meet the body's needs and may include fatigue, oliguria, cyanosis, fluid accumulation, and decreased peripheral pulses.

Ineffective tissue perfusion refers to a state in which there is a decrease in nutrition and oxygenation at the cellular level due to a deficit in capillary blood flow supply. Ineffective tissue perfusion can be associated with an interruption of blood flow, decreased cellular exchange, or fluid shifts. Typical manifestations reflect cellular ischemia and may include pain, skin changes, and signs of organ necrosis.

Alterations Resulting in Decreased Cardiac Output

Pericarditis

Pericarditis refers to an inflammation of the pericardium—the sac that surrounds, protects, and supports the heart. This inflammation is most commonly triggered by viral infections (usually after a respiratory infection) but may also result from other infections, thoracic trauma (e.g., surgery, radiation, accidents), myocardial infarction, malignancy, tuberculosis, uremia, and autoimmune conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis, and scleroderma). In this inflammatory process (see the *Immunity* chapter), fluid shifts from the capillaries to the space between the pericardial sac and the heart. This fluid may be serous (resulting from **heart failure**), purulent (resulting from infections), serosanguineous (resulting from neoplasms or uremia), or hemorrhagic (resulting from **aneurysms** or trauma). As the pericardial tissue becomes inflamed, the swollen pericardial tissue rubs against the swollen cardiac tissue, creating friction.

Fluid can accumulate quickly or slowly in the pericardial cavity, creating a **pericardial effusion**. Such a fluid accumulation can progress to life-threatening **cardiac tamponade** (**FIGURE 4-14**). In cardiac tamponade, the fluid accumulates in the pericardial cavity to the point that it compresses the heart. This compression prevents the heart from stretching and filling during diastole, resulting in decreased cardiac output. Arterial pressures then fall (because of the decreased cardiac output), venous pressures rise (because of the accumulation of blood within the systemic circulation), and pulse pressure narrows (because of the arterial and venous pressure changes). Additionally, the heart sounds are muffled upon auscultation because the excess fluid drowns out the sound. Sudden, acute cardiac tamponade presents much like **cardiogenic shock**, with hypotension, jugular vein distention, and muffled heart sounds—a group of symptoms referred

to as the “Beck’s triad.” More slowly developing cardiac tamponade presents much like **right-sided heart failure**, with dyspnea, tachycardia, jugular vein distention, ascites, hepatomegaly, and edema. Heart failure, cardiogenic shock, and death can result from cardiac tamponade.

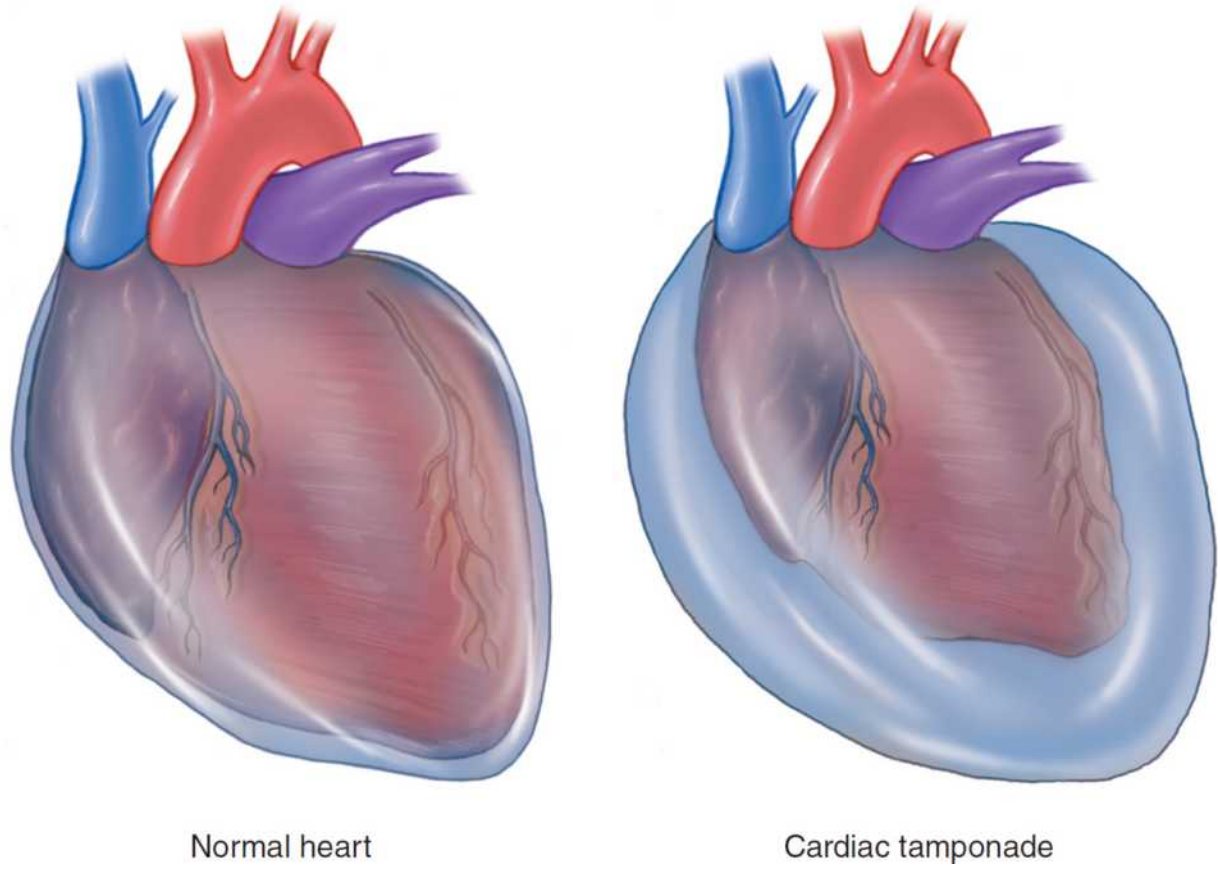


FIGURE 4-14 Cardiac tamponade.

Description

Chronic inflammation of the pericardium can lead to **constrictive pericarditis**. In this condition, the pericardium becomes thick and fibrous from the chronic inflammation and adheres to the heart. Essentially, the pericardium resembles a restrictive rubber band that has lost its elasticity. The loss of elasticity restricts cardiac filling, decreasing cardiac output and causing systemic congestion.

Clinical manifestations of pericarditis include the following signs and symptoms:

- Pericardial friction rub (a grating sound auscultated between the lower left sternal border and the cardiac apex when the breath is held) that may be intermittent
- Sharp, sudden, severe chest pain that increases with deep inspiration and decreases when the patient sits up and leans forward
- Dyspnea
- Tachycardia
- Palpitations
- Edema
- Flulike symptoms (e.g., fever, chills, and myalgia)

A diagnosis of pericarditis is accomplished through a history, physical examination, complete blood count (CBC; indications of infection or inflammation), erythrocyte sedimentation rate (ESR; elevated levels indicate inflammation), C-reactive protein levels (elevated levels indicate inflammation), EKG (ST-segment elevation), chest X-ray, echocardiogram, computed tomography (CT), and cardiac magnetic resonance imaging (MRI).

Treatment focuses on resolving the underlying cause (e.g., antibiotics for infection) and reducing the inflammation (e.g., nonsteroidal and steroidal anti-inflammatory drugs). Colchicine, an anti-inflammatory drug, can help control the inflammation as well as prevent pericarditis from reoccurring for a few months. Colchicine may have to be given for several years in cases of chronic or recurrent pericarditis even after symptoms resolve. Analgesics may be administered to manage pain. Other medications may be needed to manage symptoms or treat severe cases (e.g., diuretic, antiarrhythmic, and immunosuppressive drugs).

Additionally, bed rest is important to reduce metabolic needs and cardiac workload. Oxygen therapy can increase available oxygen. A pericardiocentesis may be performed to withdraw excess fluid from pericardium, or a pericardiectomy (a surgical procedure in which a window is created in the pericardium) may be performed to release constriction and allow excess fluid to drain into the pleural cavity.

Infective Endocarditis

Infective endocarditis (previously called "bacterial endocarditis") is an infection of the endocardium (inner layers of the heart) or heart valves. Normally, the heart is fairly resistant to infection because the endocardial surface and constant blood flow make it difficult for organisms to adhere to cardiac tissue. Thus, two factors are typically required for endocarditis to develop—abnormality of the endocardium and microorganisms in the bloodstream. *Staphylococcus aureus* and streptococci—bacteria commonly found on the skin and the upper respiratory tract—are frequent causative agents (80–90%). *Streptococcus enterococcus*, commonly found in the gastrointestinal tract, as well as *Streptococcus viridans*, commonly found in the mouth, can also cause infective endocarditis. The latter bacterium can gain access to the bloodstream during dental procedures. In addition to being an infective condition, endocarditis can arise when sterile platelet and fibrin thrombi form on the endocardium or heart valves.

The pathogenesis of this condition occurs in three stages: bacteremia, adhesion, and colonization. Once the microorganism enters the blood, it adheres to damaged endothelium, which attracts platelets and stimulates **thrombus** formation. Proliferation of the organism along with inflammation leads to vegetation (including platelets, fibrin, microorganisms, inflammatory cells, and granulomatous tissue) collecting on the internal structures because of damage from the infection. This process is similar to what occurs when a boat's anchor is placed in a body of water for an extended length of time. With each heart contraction, some of this vegetation is dislodged and ejected from the heart. These small thrombi move throughout the body, collecting in the microcirculation and creating microhemorrhages (e.g., petechiae and hematuria). The thrombi can also travel to other locations, in which case they are known as "embolisms," and become lodged there. These emboli can cause serious and often life-threatening complications, such as heart failure, myocardial infarction, stroke, seizures, and pulmonary embolism. In addition, the heart valves can become scarred and perforated

(FIGURE 4-15). If untreated, infective endocarditis is usually fatal, especially when it involves the valvular structures.

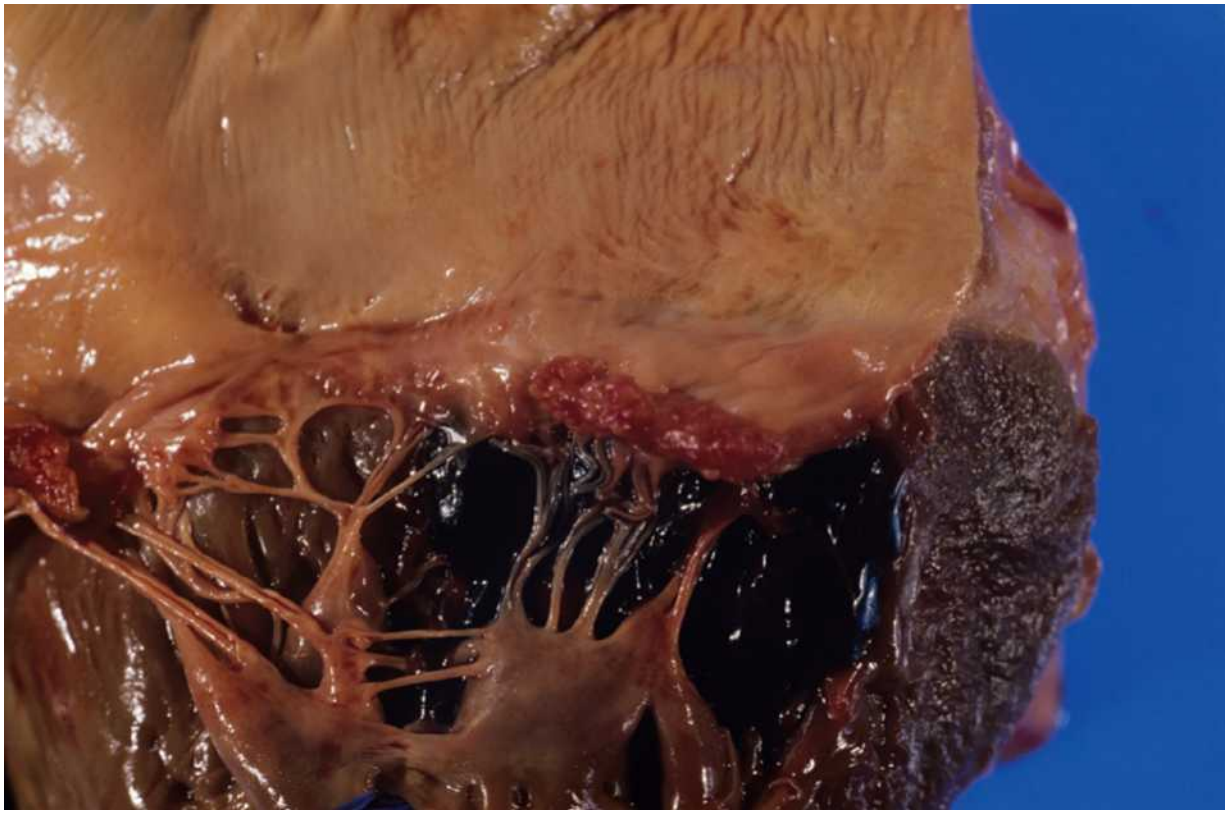


FIGURE 4-15 Infective endocarditis.

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Infective endocarditis can occur at any age but is twice as common in men as in women. Most cases occur on the left side of the heart. The following risk factors render patients more vulnerable to development of infective endocarditis:

- Intravenous drug use or presence of an intravenous catheter for an extended period
- Valvular disorders
- Prosthetic heart valves
- Implanted cardiac devices (e.g., pacemaker, internal cardioverter)
- Rheumatic heart disease

- Coarctation of the aorta
- Congenital heart defects (e.g., tetralogy of Fallot)
- Hypertrophic cardiomyopathy
- Marfan syndrome
- Immunodeficiency states

Infective endocarditis can be insidious and develop slowly (i.e., subacute), or it can develop abruptly and progress rapidly (i.e., acute). The severity of the symptoms will vary depending on the type of infective endocarditis. Clinical manifestations of infective endocarditis include the following:

- Flu-like symptoms (e.g., fever, chills, myalgia)
- Embolization (e.g., myocardial infarction, pulmonary embolism, transient ischemic attacks, stroke, splenic infarction)
- Heart murmur
- Roth spots (round hemorrhagic retinal lesions with small white centers) and conjunctival hemorrhages
- Petechiae
- Splinter hemorrhages under the nails
- Hematuria
- Osler nodes (tender raised subcutaneous lesions on the fingers and toes)
- Janeway lesions (small non-tender erythematous or hemorrhagic macular or nodular lesions on the palms or soles of the feet)
- Edema

Diagnostic procedures for infective endocarditis include a history, physical examination, blood cultures, CBC, urinalysis, serum rheumatoid factor, ESR, C-reactive protein, EKG, chest X-ray, and echocardiogram. Infective endocarditis is difficult to definitively diagnose because the endocardial vegetations are not easily obtained and examined. To aid in diagnosis, the Duke criteria were developed (Durack, Lukes, & Bright, 1994; Li et al., 2000).

If untreated, infective endocarditis is always fatal. Even with treatment, the prognosis is poor, and death is likely for older individuals. Treatment focuses on the causative agent (e.g., antibiotics or antifungals). Infective endocarditis often requires long-term anti-infective therapy (a minimum of 4 weeks). Other treatments are initiated to maintain cardiac function and treat other symptoms:

- Bed rest
- Oxygen therapy
- Antipyretics
- Surgical debridement or repair of cardiac valves
- Prosthetic valve replacement

Antibiotic prophylaxis prior to certain dental procedures may be necessary in high-risk patients (e.g., those with prosthetic cardiac valves or congenital heart disease).

Myocarditis

Myocarditis is an inflammation of the myocardium, or heart muscle. This uncommon condition is poorly understood because at least several weeks (in some cases, a decade) elapse between exposure to the causative agent and the development of symptoms. Myocarditis is usually caused by viral (e.g., influenza, coxsackie, cytomegalovirus, adenovirus, hepatitis C, herpes, HIV, or parvovirus), bacterial (e.g., *Corynebacterium diphtheriae*, *Staphylococcus aureus*, Lyme disease, *Chlamydia*, *Mycoplasma*, or *Streptococcus*), protozoal (e.g., *Babesia* or Chagas disease), or fungal (e.g., *Aspergillus*, *Candida*, *Cryptococcus*, or *Histoplasma*) infection. Other causes may include allergic reactions, chemical exposure, radiation, or inflammatory disorders (e.g., rheumatoid arthritis or sarcoidosis). Penetration of organisms, blood cells, toxins, and immune substances into the myocardium can result in muscle fiber dysfunction and degeneration that can impair contractility and conduction.

Most cases of myocarditis are benign, but some result in heart failure, **cardiomyopathy**, dysrhythmias, and thrombus development.

Myocarditis is the third leading cause of sudden death in children and young adults. This cardiac condition occurs in all age groups but most often affects otherwise healthy young athletic types, with the highest risk population being individuals ranging in age from puberty through the early 30s. It affects males twice as often as females.

Myocarditis can be classified in several ways. Because it has varying presentations, the following classification system was developed to aid in diagnosis of acute myocarditis (Saga, Liu, & Cooper, 2012):

- Possible subclinical acute myocarditis: Subclinical myocarditis without specific symptoms that can be inferred based on transient increases in troponin or EKG changes after a viral illness, adverse drug reaction, or vaccination (rarely).
- Probable acute myocarditis: Diagnosis is based on the presence of one of four clinical syndromes associated with myocarditis—chest pain, acute heart failure, presyncope or syncope, and myopericarditis (myocarditis with pericarditis).
- Definite myocarditis: Diagnosis is confirmed by histological analysis of heart tissue.

Additionally, a clinical classification system is frequently used in practice:

- Myocarditis resembling a myocardial infarction: Myocarditis can present with chest pain due to inflammation of the coronary arteries. Reversible occlusion due to vasospasm can result from an influx of inflammatory cells. The chest pain worsens with leaning backward and improves with leaning forward; this condition is classically associated with pericarditis, which often accompanies myocarditis of the outer layers of the myocardium.
- Myocarditis resembling acute or chronic heart failure: Myocarditis can present with shortness of breath, fatigue, and activity intolerance. Cardiomegaly and symptoms can present 2 weeks to a few months after a gastrointestinal or upper respiratory infection. A more chronic form of myocarditis may be seen if the immune

system continues to attack the myocardium in the absence of infection.

The patient may be asymptomatic, but when present, clinical manifestations of myocarditis include the following:

- Flulike symptoms (e.g., fever, chills, myalgia)
- Pericarditis symptoms (e.g., chest pain, friction rub)
- Heart failure symptoms (e.g., dyspnea; edema; activity intolerance; or pale, cool skin)
- Dysrhythmias
- Tachycardia
- Heart murmurs
- Cardiac enlargement
- Syncope
- Decreased urine output
- Joint pain and swelling

Diagnosis of myocarditis is accomplished through a history, physical examination, blood cultures, EKG, cardiac biomarkers (e.g., troponin and creatinine kinase), CBC, ESR, chest X-rays, echocardiogram, and endomyocardial biopsy. The endomyocardial biopsy is the gold standard for diagnosis, but it is risky and not necessary in every case.

Management centers on treating the causative agent (e.g., antibiotics for bacterial infections). Antipyretics, anticoagulants, antidysrhythmics, diuretics, and immunosuppressants (e.g., corticosteroids or nonsteroidal anti-inflammatory drugs) may be used to treat symptoms or complications. Increasing bed rest, restricting activity, and limiting fluids can reduce cardiac workload.

Valvular Disorders

Valvular disorders cause disruption of normal blood flow through the heart. These disorders are distinguished based on the valve affected

(e.g., mitral, aortic, tricuspid, or pulmonary) and the type of alteration (e.g., **stenosis** or **regurgitation**). Valvular disorders can be congenital or acquired. The mitral and aortic valves are the most commonly affected valves because of the higher pressures and workload on the left side of the heart.

Stenosis is a narrowing of a tubular structure—in this context, the heart valves. When the valves are stenosed, blood moving through the valve is reduced, causing blood to back up in the chamber just before the valve. **Atresia** refers to a lack of the valve opening that would otherwise allow blood flow. Pressures in the overfilled chambers increase to pump against the resistance of the stenosed valve. Because the heart (specifically the chamber) is working harder, hypertrophy of the chambers develops. Hypertrophy and increased workload escalate the heart's oxygen demands, but the decreased cardiac output resulting from the stenosis makes it difficult to meet these increased demands. Decreased cardiac output diminishes blood delivery to the coronary arteries that supply the heart. Without adequate blood flow, the heart deteriorates. As a result, cardiomyopathy and heart failure can develop. Aortic stenosis is the most common valvular disorder in the United States.

Regurgitation, also called "insufficiency" or "incompetence," occurs when the valve leaflets do not completely close, so blood continuously leaks through them. Normally, heart valves allow blood to flow in one direction; incompetent valves, however, allow blood to flow in both directions. This regurgitation of blood increases the amount of blood that must be pumped and, in turn, the cardiac workload. The increased workload contributes to hypertrophy developing in the affected chambers. Additionally, the increased blood volume in the heart causes the chambers to dilate to accommodate the larger volume.

application to practice

Mrs. Fulcher is a 58-year-old married homemaker who was recently discharged from the hospital because of recurrent infective endocarditis. Her most recent episodes involved a *Staphylococcus aureus* infection of the mitral valve 12 months ago and a *Streptococcus*

mutans infection of the aortic valve 1 month ago. During her most recent hospitalization, an echocardiogram showed aortic stenosis, moderate aortic insufficiency, chronic valvular vegetation, and moderate atrial enlargement. In addition, Mrs. Fulcher has a history of chronic joint pain.

After being home for 1 week, Mrs. Fulcher was readmitted to your telemetry floor with endocarditis. She reports chills, fever, fatigue, joint pain, malaise, and a headache for the past 24 hours. Upon admission, IV infusion of normal saline at 125 mL/hr and vancomycin IV every 8 hours was ordered to be continued over the next 4 weeks. Other routine medications ordered included furosemide (Lasix), amlodipine (Norvasc), and metoprolol (Lopressor). At admission, Mrs. Fulcher's blood pressure was 172/48 mm Hg (supine) and 100/40 mm Hg (sitting), her pulse was 116, her respirations were 20, and her temperature was 101.9°F. Additional assessment findings included a murmur; 2+ pitting tibial edema; no peripheral cyanosis; lung sounds clear bilaterally; orientation to person, place, and time but drowsiness; hematuria; and multiple petechiae on the skin of her arms, legs, and chest.

1. What is the significance of the orthostatic hypotension, the wide pulse pressure, and tachycardia?
2. What is the significance of the hematuria, joint pain, and petechiae?
3. For which complications of embolization should Mrs. Fulcher be assessed?

Both stenosis and regurgitation can be present simultaneously (e.g., mitral valve annulus). In these cases, stenosis usually develops first and is generally severe. As the pressure builds in the chamber pumping blood through the valve, the leaflets become damaged. These damaged valve leaflets cannot close properly, leading to regurgitation.

Valvular disorders may have a number of causes:

- Congenital defects
- Infective endocarditis
- Rheumatic fever
- Hypertension
- Myocardial infarction
- Cardiomyopathy
- Heart failure
- Aortic aneurysms
- Connective tissue disorders (e.g., Marfan syndrome)

The clinical manifestations of valvular disorders depend on the valve involved as well as the nature and severity of the alteration. Diagnostic procedures for valvular heart disease consist of a history, physical examination, heart catheterization, chest X-rays, echocardiogram, EKG, or MRI.

Learning Points

Valve Disorder Manifestations

When trying to understand the manifestations associated with the various types of valvular disorders, keep the blood flow through the heart in mind. The valve involved (e.g., mitral, aortic, tricuspid, or pulmonary) will impact the blood flow at the valve's location, and the nature of the alteration (e.g., stenosis or regurgitation) will determine the nature of that impact. *Remember: If it cannot go forward, it must go back.*

Valvular disorders in the left side of the heart (i.e., mitral and aortic) will impact cardiac output more than valvular disorders on the right side of the heart (i.e., tricuspid and pulmonary). Left-side valvular disorders will result in blood backing up into the lungs. This backup can eventually cause right-side valve disorders and blood backup into the right side of the heart. Manifestations of left-side valvular disorders start with symptoms of decreased cardiac output (e.g., **angina**, fatigue, activity intolerance, tachycardia, cyanosis, syncope). These manifestations progress to respiratory symptoms as the blood backs up in the lungs and impacts the right side of the heart (e.g., dyspnea, paroxysmal nocturnal dyspnea, orthopnea).

Right-side valvular disorders cause blood to back up into the systemic circulation. The manifestations reflect this backup, as pressures rise in the systemic circulation and the increasing pressure causes fluid to shift out of the vascular space (e.g., edema, weight gain, jugular vein distention, ascites, splenomegaly, hepatomegaly).

The degree to which the backup of blood occurs with any valvular disorder reflects the severity of stenosis and regurgitation. With both alterations, the chamber pumping blood through the valve often hypertrophies in an attempt to compensate.

Treatment is aimed at preventing or managing complications and symptoms. Medications often used to treat valvular disorders include diuretics, antidysrhythmics, vasodilators, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, and anticoagulants that decrease the workload on the heart. Additional strategies may include the following measures:

- Oxygen therapy

- Lifestyle modifications (e.g., low-sodium diet, tobacco cessation, limited alcohol consumption)
- Surgical valve repair (e.g., balloon valvuloplasty)
- Prosthetic valve replacement (e.g., mechanical or biological pig, cow, or human valve)
- Prophylactic antibiotic therapy prior to invasive procedures (e.g., dental procedures or surgery)

Cardiomyopathy

Cardiomyopathy generally refers to a group of conditions of the myocardium. In cardiomyopathy, the myocardium becomes enlarged, thick, or rigid. In rare cases, it can be replaced with scar tissue. Cardiomyopathy often goes undiagnosed, but as many as 1 in 500 adults may have this condition. As the cardiomyopathy progresses, the myocardium is weakened. The heart pumps less effectively, leading to heart failure, and has difficulty maintaining normal electrical conduction, leading to arrhythmias. Additionally, valvular disorders can develop.

Cardiomyopathy may be acquired or inherited. Most cases of cardiomyopathy develop from a genetic abnormality—more than 100 genes may be linked to the development of cardiomyopathy. Although most genetic forms of cardiomyopathy follow an autosomal dominant inheritance pattern, some types follow recessive and X-linked inheritance patterns. The large number of possible gene mutations leads to variations in clinical presentation, even among individuals with the same mutation. Additionally, other comorbidity or lifestyle choices can further influence clinical presentation.

The MOGE(S) classification (**FIGURE 4-16**) reflects the rapidly growing knowledge base regarding genetic mutations, acquired causes, and further conditions involved in the development of cardiomyopathies (**TABLE 4-1**) (Westphal et al., 2017). This classification system can be used to identify at-risk individuals, so treatment can be started prior to the development of cardiomyopathy. While classifications of the various types of cardiomyopathies have

evolved (Figure 4-16), most cardiomyopathies are classified into three groups: dilated, hypertrophic, and restrictive (**FIGURE 4-17**).

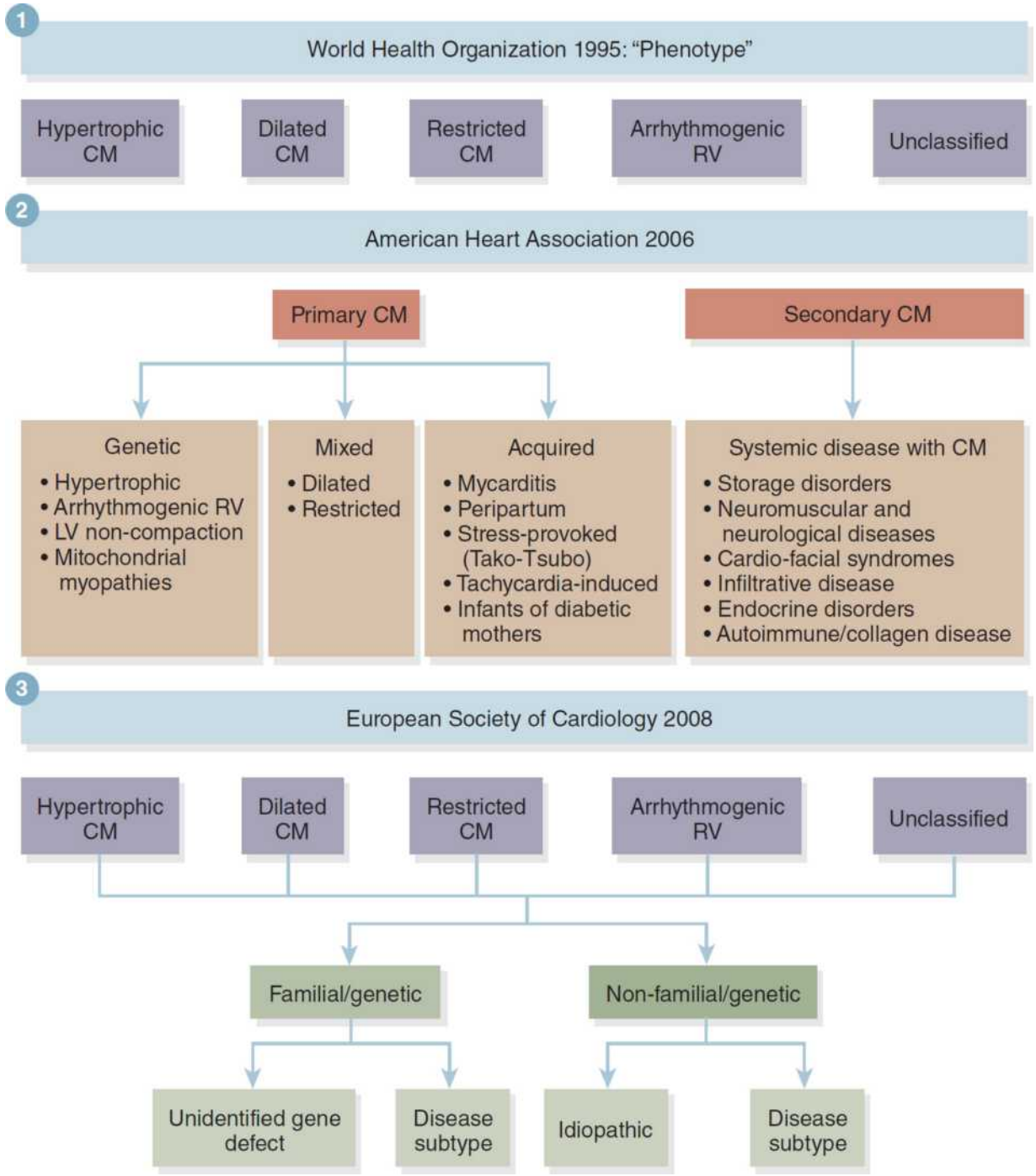


FIGURE 4-16 MOGE(S) classification for cardiomyopathy.

Abbreviations: CM: cardiomyopathy; LV: left ventricle; RV: right ventricle.

Description

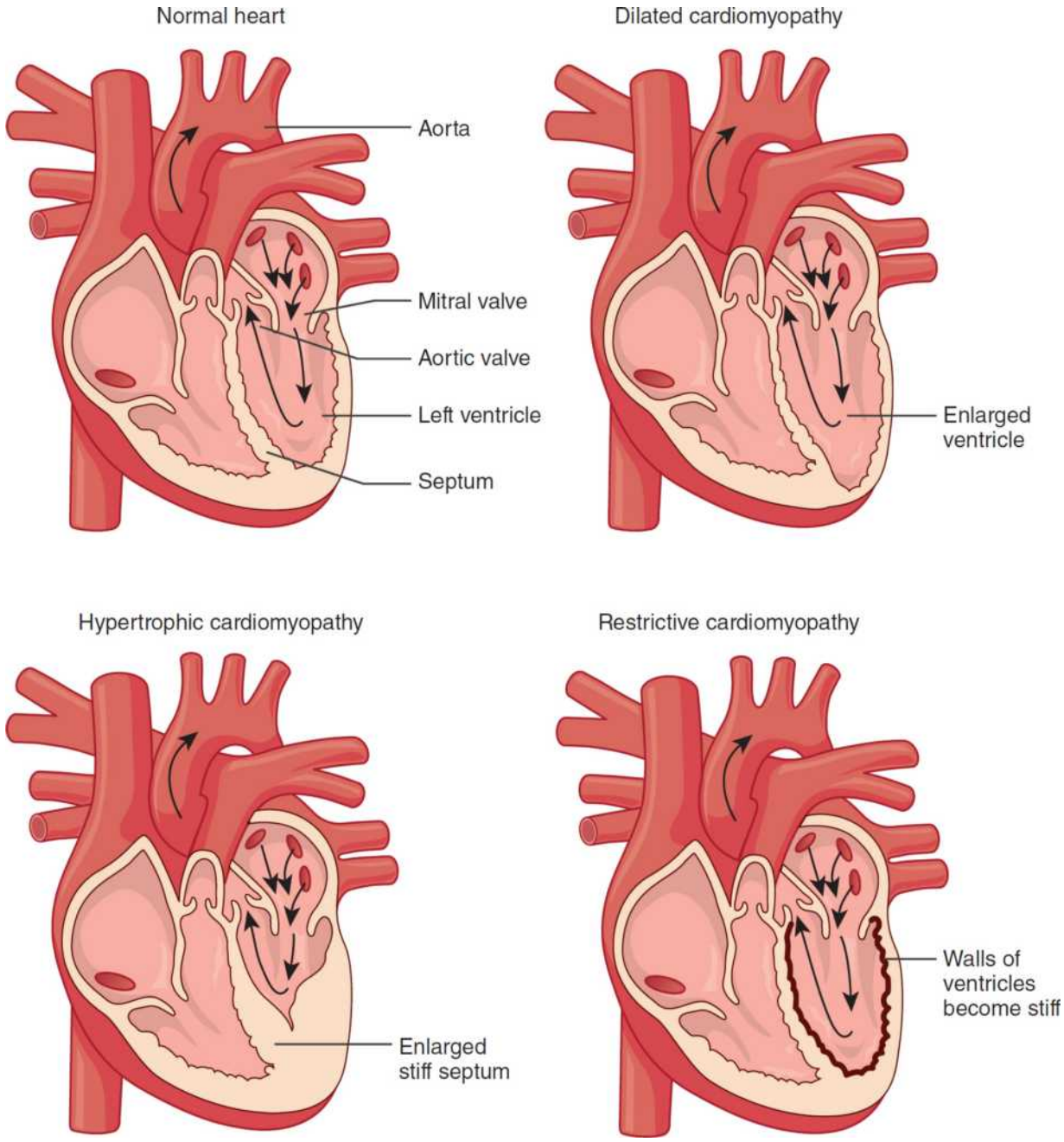


FIGURE 4-17 Comparing cardiomyopathies.

Description

TABLE 4-1 Comparison of Left- and Right-Sided Heart Failure

	Left-Sided Heart	Right-Sided Heart Failure

	Failure	
Causes	Infarction of left ventricle, aortic valve stenosis, hypertension, and hyperthyroidism	Infarction of right ventricle, pulmonary valve stenosis, and pulmonary disease (cor pulmonale)
Basic effects	Decreased cardiac output and pulmonary congestion	Decreased cardiac output and systemic congestion
Manifestations	Pulmonary congestion, dyspnea, and activity intolerance	Edema and weight gain
Forward effects (decreased output)	Fatigue, weakness, dyspnea, exercise intolerance, and cold intolerance	Fatigue, weakness, dyspnea, exercise intolerance, and cold intolerance
Compensations	Tachycardia, pallor, secondary polycythemia, and daytime oliguria	Tachycardia, pallor, secondary polycythemia, and daytime oliguria
Backup effects	Orthopnea, cough, shortness of breath, paroxysmal nocturnal dyspnea, hemoptysis, and rales	Dependent edema in feet, hepatomegaly, splenomegaly, ascites, distended neck veins, headache, and flushed face

Dilated cardiomyopathy develops when the ventricles become enlarged and weakened. Usually, this condition starts in the left ventricle and eventually affects the right ventricle. The ventricles are enlarged (dilated) as a whole, but the wall thickness is normal or thin. These stretched ventricle walls weaken cardiac contractility, resulting in **systolic dysfunction**. The systolic dysfunction, in turn, leads to decreased cardiac output and blood backing up into the pulmonary system. Additionally, blood can stagnate in the heart, causing thrombi to develop.

The risk for developing dilated cardiomyopathy increases with age, although it is the most common form of cardiomyopathy in children. This type is also more common in African Americans and men. Most cases are idiopathic. Dilated cardiomyopathy can be inherited, but secondary causes include the following:

- Chemotherapy (specifically doxorubicin and daunorubicin)
- Alcoholism
- Cocaine and amphetamine abuse
- Pregnancy, specifically the last trimester
- Infections, especially viral
- Thyrotoxicosis (hypermetabolic syndrome resulting from increased levels of thyroid hormones)
- Diabetes mellitus
- Neuromuscular diseases (e.g., muscular dystrophy)
- Hypertension
- Coronary artery disease
- Viral hepatitis
- Human immunodeficiency virus (HIV)
- Hypersensitivity to medications
- Certain toxins (e.g., poisons and heavy metals)

As dilated cardiomyopathy develops, the SNS and the kidneys attempt to compensate for the falling cardiac output by increasing both the heart rate and the blood volume. Symptoms develop as these compensatory mechanisms begin failing. Deterioration occurs rapidly once symptoms appear. The following clinical manifestations of dilated cardiomyopathy often develop insidiously:

- Dyspnea
- Fatigue
- Nonproductive cough
- Orthopnea (difficulty breathing while lying down)
- Paroxysmal nocturnal dyspnea (difficulty breathing at night)
- Dysrhythmias
- Angina (cardiac chest pain that often occurs with exertion)
- Dizziness
- Activity intolerance

- Blood pressure changes
- Tachycardia
- Murmurs
- Abnormal lung sounds (e.g., crackles and wheezes)
- Tachypnea
- Peripheral edema
- Ascites (fluid in the peritoneal cavity)
- Weak pedal pulses
- Cool, pale extremities
- Poor capillary refill
- Hepatomegaly
- Jugular vein distention

Diagnostic procedures for dilated cardiomyopathy include an echocardiogram, EKG, chest X-ray, heart catheterization, and nuclear studies. Treatment is mainly supportive, focusing on relieving heart failure symptoms by decreasing afterload and enhancing contractility. Pharmacologic treatments usually include ACE inhibitors, diuretics, digoxin (Lanoxin), beta-adrenergic blocking agents, and antidysrhythmic agents to decrease the cardiac workload. Other management strategies include an implantable cardiac defibrillator, cardioversion, pacemaker, valvular repair, and heart transplant. Additionally, lifestyle modifications include a low-fat, low-sodium diet; tobacco cessation; physical activity; and abstinence from alcohol.

Unlike dilated cardiomyopathy, which affects only systolic function, **hypertrophic cardiomyopathy** affects both systolic and diastolic function. Hypertrophic cardiomyopathy is very common, affecting 1 out of 500 people in the United States (National Institutes of Health [NIH], 2022a). This condition affects men and women equally. The acquired form is more common in persons who have a sedentary lifestyle; the inherited form appears to follow an autosomal dominant pattern. Hypertension, obstructive valvular disease, and thyroid disease increase the risk of developing this cardiac disorder.

With hypertrophic cardiomyopathy, the septum between the ventricles is most frequently affected. The hypertrophied ventricle wall becomes stiff and unable to relax during ventricular filling. With a reduction in ventricular filling, cardiac output decreases while atrial and pulmonary pressures increase. The hypertrophied myocardium compresses blood vessels, reducing tissue perfusion and causing ischemia. In addition to hypertrophy, the myocardium becomes fibrotic and forms scars. These scars do not conduct electrical impulses properly, so arrhythmias can develop. Hypertrophic cardiomyopathy is a common cause of sudden cardiac death in young people, especially young athletes.

Clinical manifestations of hypertrophic cardiomyopathy are similar to those associated with dilated cardiomyopathy:

- Dyspnea on exertion
- Fatigue
- Syncope
- Orthopnea
- Angina
- Activity intolerance
- Dysrhythmias
- Left ventricular failure
- Myocardial infarction

Diagnostic procedures for hypertrophic cardiomyopathy are similar to those for dilated cardiomyopathy. Treatment goals include reducing ventricular stiffness, improving ventricular filling, and enhancing cardiac output. Beta-adrenergic blocking agents and calcium-channel blocking agents are often included in the medication regimen. Surgical removal of excess myocardium may be necessary for those patients who do not respond well to medications. Treatment of any dysrhythmias and hypertension may also be warranted. Additionally, strenuous activity (e.g., running) should be avoided because most cases of sudden death associated with hypertrophic cardiomyopathy have occurred with this type of activity.

Restrictive cardiomyopathy is the least common of the cardiomyopathies but is endemic in parts of South and Central America, India, Asia, and Africa. This type of cardiomyopathy is characterized by rigidity of the ventricles, but the myocardium does not thicken. As a result, the ventricles do not relax and fill, leading to **diastolic dysfunction**. As restrictive cardiomyopathy progresses, the myocardium weakens, and cardiac contractility becomes ineffective. Causes of restrictive cardiomyopathy include the following conditions:

- Amyloidosis (buildup of fat and proteins in the heart muscle)
- Hemochromatosis (excessive amounts of iron in the heart)
- Radiation exposure to the chest
- Connective tissue diseases
- Buildup of scar tissue after a myocardial infarction
- Sarcoidosis (cellular growths on various organs)
- Cardiac neoplasms

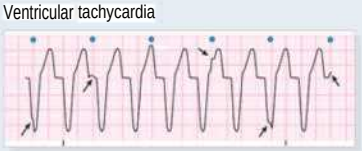
Many cases are asymptomatic, but the following clinical manifestations may also appear with restrictive cardiomyopathy:

- Fatigue
- Dyspnea
- Orthopnea
- Abnormal lung sounds
- Angina
- Hepatomegaly
- Jugular vein distention
- Ascites
- Murmurs
- Peripheral cyanosis
- Pallor

Diagnostic procedures include those for the two previously discussed cardiomyopathies. Management focuses on treating the underlying causes: dysrhythmias and heart failure. A heart transplant may be necessary when the heart can no longer meet the body's demands. The prognosis with restrictive cardiomyopathy is generally poor, with death often occurring from heart failure.

Electrical Alterations

As previously mentioned, normal myocardial contraction is accomplished by electrical impulses originating in the SA node, the natural pacemaker of the heart, which stimulates the myocardium to contract and relax in a synchronized manner. Normal electrical conduction is referred to as "sinus rhythm," whereas deviations from normal are referred to as "dysrhythmias" or "arrhythmias." Dysrhythmias vary in severity and are classified according to their origin (**FIGURE 4-18**). Their effects on cardiac output and blood pressure are partially influenced by their site of origin, which also determines the dysrhythmias' clinical significance. Causes of dysrhythmias include the following conditions:

Dysrhythmia	Features	Causes
Supraventricular Rhythms		
Sinus bradycardia 	Rate: < 60 bpm Rhythm: Regular P waves: Occur before each QRS complex; look the same in shape and size P-R interval: Normal (0.12 sec to 0.20 sec) QRS complexes: Occur after each P wave; look the same in shape and size; normal (< 0.12 sec)	Normal in a well-conditioned heart (e.g., athletes); increased intracranial pressure; increased vagal tone due to straining during bowel movement, vomiting, intubation, or mechanical ventilation; sick sinus syndrome; inferior-wall MI; may also occur with anticholinesterase, beta-adrenergic blocker, digoxin, or morphine use
Sinus tachycardia 	Rate: > 100 bpm Rhythm: Regular P waves: Occur before each QRS complex; look the same in shape and size P-R interval: Normal (0.12 sec to 0.20 sec) QRS complexes: Occur after each P wave; look the same in shape and size; normal (< 0.12 sec)	Normal physiologic response to fever, exercise, anxiety, pain, dehydration; may also accompany shock, left-sided heart failure, anemia, hypovolemia, pulmonary embolism; may also occur with atropine, epinephrine, caffeine, alcohol, and amphetamine or nicotine use
Atrial flutter 	Rate: > 100 bpm Rhythm: Regular (may vary depending on degree of AV block) P waves: Cannot be found; replaced by flutter (F) waves, which may have sawtooth pattern P-R interval: Cannot determine QRS complexes: Look the same in shape and size; normal (< 0.12 sec)	Heart failure, tricuspid or mitral valve disease, pulmonary embolism, cor pulmonale, interior-wall MI, pericarditis; digoxin toxicity
Atrial fibrillation 	Rate: > 100 bpm (grossly irregular; 350–450 bpm) Rhythm: Irregular P waves: Cannot be found P-R interval: Cannot determine QRS complexes: Look the same in shape and size	Heart failure, COPD, ischemic heart disease, sepsis, pulmonary embolism, rheumatic heart disease, hypertension, mitral stenosis; complication of coronary bypass or valve replacement surgery; nifedipine and digoxin use
Paroxysmal supraventricular tachycardia 	Rate: > 100 bpm Rhythm: Regular P waves: Occur before each QRS complex (may be hidden in preceding T wave); look the same in shape and size (but differ from normal sinus P wave) P-R interval: Normal (0.12 sec to 0.20 sec), but may differ from P-R interval associated with normal sinus beat QRS complexes: Occur after each P wave; look the same in shape and size; normal (< 0.12 sec)	Intrinsic abnormality of AV conduction system; physical/psychological stress, hypoxia, hypokalemia, cardiomyopathy, congenital heart disease, MI, valvular disease, Wolff-Parkinson-White syndrome, cor pulmonale, hyperthyroidism; digoxin toxicity, use of caffeine, marijuana, or CNS stimulants
Junctional rhythm 	Rate: Atrial rate > 60 bpm, ventricular rate usually > 60 bpm (60–100 bpm is accelerated junctional rhythm) Rhythm: Regular (irregular if escape beats occur) P waves: Cannot be found (nonexistent or hidden; usually inverted if visible) P-R interval: Cannot determine (when present, < 0.12 sec) QRS complexes: Look the same in shape and size; normal (< 0.12 sec) except in aberrant conduction	Inferior-wall MI or ischemia, hypoxia, vagal stimulation, sick sinus syndrome; acute rheumatic lever; valve surgery; digoxin toxicity
Ventricular Rhythms		
Premature ventricular contraction (PVC) 	Rate: Irregular Rhythm: Atrial rhythm regular, ventricular rhythm irregular P waves: Cannot be found P-R interval: Cannot determine QRS complexes: Wide and distorted (≥ 0.12 sec); premature QRS complexes occurring alone, in pairs, or in threes, alternating with normal beats; focus from one or more sites; ominous when clustered, multifocal, with R wave on T pattern	Heart failure; previous or acute MI, ischemia, or contusion; myocardial irritation by ventricular catheter or a pacemaker; hypokalemia; hypocalcemia; hypomagnesemia; drug toxicity (digoxin, aminophylline, tricyclic antidepressant, beta-adrenergic blocker, isoproterenol, dopamine); caffeine, tobacco, or alcohol use; psychological stress, anxiety, pain, or exercise
Ventricular tachycardia 	Rate: > 100 bpm Rhythm: Regular P waves: Cannot be found (hidden within QRS complex) P-R interval: Cannot determine QRS complexes: Look the same in shape and size; wide and bizarre (≥ 0.12 sec)	Myocardial ischemia, MI, or aneurysm; coronary artery disease; rheumatic heart disease; mitral valve prolapse; heart failure; cardiomyopathy; ventricular catheters; hypokalemia; hypercalcemia; hypomagnesemia; pulmonary embolism; digoxin, procainamide, epinephrine, or quinidine toxicity; anxiety
Ventricular fibrillation 	Rate: > 100 bpm Rhythm: Irregular, chaotic, and rapid P waves: Cannot be found P-R interval: Cannot determine QRS complexes: Wide and irregular (the ventricle is just "quivering")	Myocardial ischemia, MI, untreated ventricular tachycardia, R-on-T phenomenon, hypokalemia, hyperkalemia, hypercalcemia, hypoxemia, alkalosis, electric shock, hypothermia; digoxin, epinephrine, or quinidine toxicity

Heart Blocks		
First-degree AV block 	Rate: Varies Rhythm: Regular P waves: Occur before each QRS complex; look the same in shape and size P-R interval: Long (> 0.20 sec) QRS complexes: Occur after each P wave; look the same in shape and size; normal (< 0.12 sec)	May be seen in healthy people; inferior-wall MI or ischemia, hypothyroidism, hypokalemia, hyperkalemia; digoxin toxicity; quinidine, procainamide, beta-adrenergic blocker, calcium channel blocker, or amiodarone use
Second-degree AV block: Mobitz I (Wenckebach) 	Rate: Slow to normal Rhythm: Atrial rhythm regular, ventricular rhythm irregular P waves: Occur before each QRS complex; look the same in shape and size P-R interval: Normal (0.12–0.20 sec); progressively lengthens until there is a missed beat, then the cycle or grouping repeats itself QRS complexes: Look the same in shape and size; normal (< 0.12 sec)	Inferior-wall MI, cardiac surgery, acute rheumatic fever, vagal stimulation; digoxin toxicity; propranolol, quinidine, or procainamide use
Second-degree AV block: Mobitz II 	Rate: Slow to normal Rhythm: Atrial rhythm regular, ventricular rhythm regular or irregular, with varying degree of block P waves: Occur before each QRS complex; look the same in shape and size P-R interval: Normal (0.12–0.20 sec); normal P-R interval is key identifier of this rhythm QRS complexes: Look the same in shape and size; normal (< 0.12 sec) if the level of the block is above the bundle of His; wide (≥ 0.12 sec) if the level of the block is below the bundle of His	Severe coronary artery disease, anterior-wall MI, acute myocarditis; digoxin toxicity
Third-degree heart block: Complete heart block 	Rate: < 60 bpm Rhythm: Regular (ventricular rhythm rate slower than atrial rate) P waves: Look the same in shape and size (but some are fused into the QRS complex or T wave) P-R interval: Cannot determine QRS complexes: Look the same in shape and size (unless the P wave is fused into the QRS complex); normal (< 0.12 sec) if the level of the block is above the bundle of His; wide (≥ 0.12 sec) if the level of the block is below the bundle of His	Inferior- or anterior-wall MI, congenital abnormality, rheumatic fever, hypoxia; postoperative complication of mitral valve replacement; postprocedure complication of radiofrequency ablation in or near AV nodal tissue; Lev's disease (fibrosis and calcification that spreads from cardiac structures to the conductive tissue); digoxin toxicity
Asystole 	Rate: None Rhythm: None P waves: Not discernible P-R interval: Not discernible QRS complexes: Not discernible	Myocardial ischemia, MI, aortic valve disease, heart failure, hypoxia, hypokalemia, severe acidosis, electric shock, ventricular arrhythmia, AV block, pulmonary embolism, heart rupture, cardiac tamponade, hyperkalemia; electromechanical dissociation; cocaine overdose

Notes: AV = atrioventricular; bpm = beats per minute; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction.

FIGURE 4-18 Types of cardiac dysrhythmias.

Reproduced from *Arrhythmia recognition: The art of interpretation*, courtesy of Tomas B. Garcia, MD.

Description

- Acid–base imbalances
- Hypoxia
- Congenital heart defects
- Connective tissue disorders
- Degeneration of conductive tissues (usually as a result of aging)
- Drug toxicity

- Electrolyte imbalances (especially potassium and calcium)
- Stress
- Myocardial hypertrophy
- Myocardial ischemia or infarction

Clinical manifestations may vary according to the specific dysrhythmia. Some dysrhythmias may be asymptomatic, whereas others can cause sudden death. The danger and symptoms depend on the extent to which the dysrhythmia reduces cardiac output. Some general manifestations of dysrhythmias include the following signs and symptoms:

- Palpitations
- Fluttering sensation
- Skipped beats
- Fatigue
- Confusion
- Syncope
- Dyspnea
- Abnormal heart rate

Diagnostic procedures for dysrhythmias include a history, physical examination, EKG, and invasive electrophysiologic studies. Additional tests may be performed to identify the underlying cause. Pharmacology is the mainstay of treatment, but other interventions may include an internal cardiac defibrillator, pacemaker, cardioversion, defibrillation, and ablation. Avoiding triggers, such as caffeine, tobacco, and stress, can decrease the occurrence and severity of some dysrhythmias.

Heart Failure

Heart failure, often referred to as congestive heart failure, is a condition in which the heart is unable to pump an adequate amount of blood to meet the body's metabolic needs. In some cases, the heart

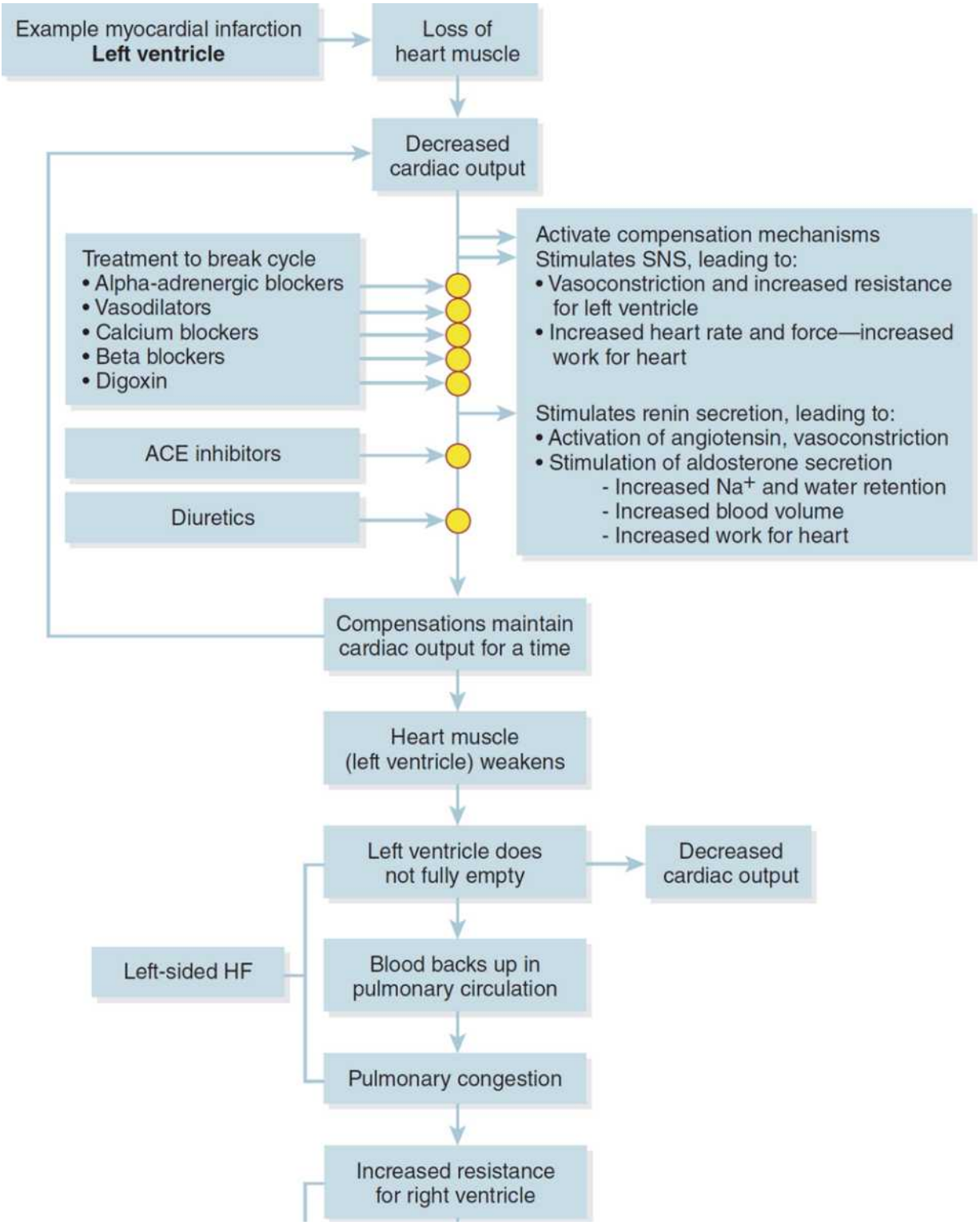
is unable to fill with blood; in other cases, cardiac contractility is ineffective. This pump inadequacy epitomizes the nursing diagnosis of decreased cardiac output, and it leads to decreased cardiac output, increased preload, and increased afterload. These three events, in turn, result in decreased contractility and stroke volume.

Heart failure is a result of structural and functional issues. Some general causes of heart failure include congenital heart defects, myocardial infarction, heart valve disease, hypertension, dysrhythmias, cardiomyopathy, diabetes mellitus, thyroid disease (either hyperthyroidism or hypothyroidism), severe anemia, alcohol abuse, drug abuse (e.g., cocaine and amphetamines), HIV/AIDS, and excessive vitamin E intake.

Heart failure is a common condition, affecting an estimated 5.7 million people in the United States. Both children and adults can have this condition, though the manifestations and treatments usually differ in these age groups. Heart failure is more common in people older than the age of 65 and those who are obese. African Americans have higher incidence and mortality rates, and manifestations are more likely to present at a younger age in this ethnic group.

Several compensatory mechanisms become activated in times of decreased cardiac output (**FIGURE 4-19**). Initially, the SNS is stimulated, which increases heart rate, contractility, vasoconstriction, and antidiuretic hormone secretion. These mechanisms increase cardiac output in the beginning, but eventually they lead to excessive preload and afterload. The compensatory mechanisms continue to struggle to meet the body's metabolic needs, until eventually excessive myocardial oxygen demand and preload result in decreased contractility and decompensation. This cycle becomes much like trying to bail water out of a sinking ship. Initially, the efforts to bail the water are able to keep the ship afloat, but over time, the flood of incoming water exceeds the amount that can be removed. Declining cardiac output also leads to decreased renal perfusion, which activates the renin–angiotensin–aldosterone system. This activation further contributes to vasoconstriction and fluid retention. Ventricular hypertrophy is another compensatory mechanism, but the demands of the enlarged myocardium eventually exceed the oxygen

supply and contractility declines. All of these compensatory mechanisms are helpful at first, but in the end, they create a vicious cycle that perpetuates the heart failure.



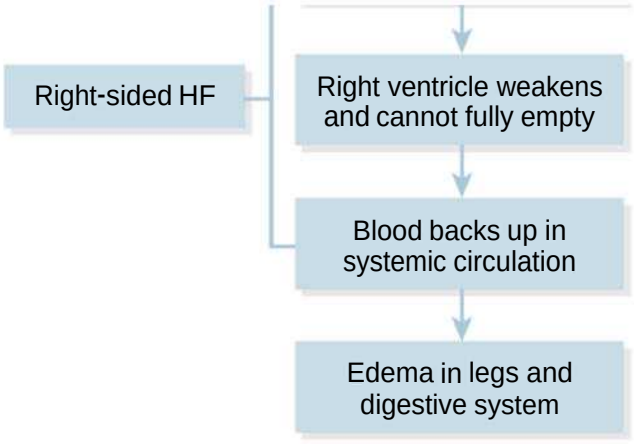


FIGURE 4-19 Course of heart failure.

Reproduced from *Arrhythmia recognition: The art of interpretation,* courtesy of Tomas B. Garcia, MD.

Description

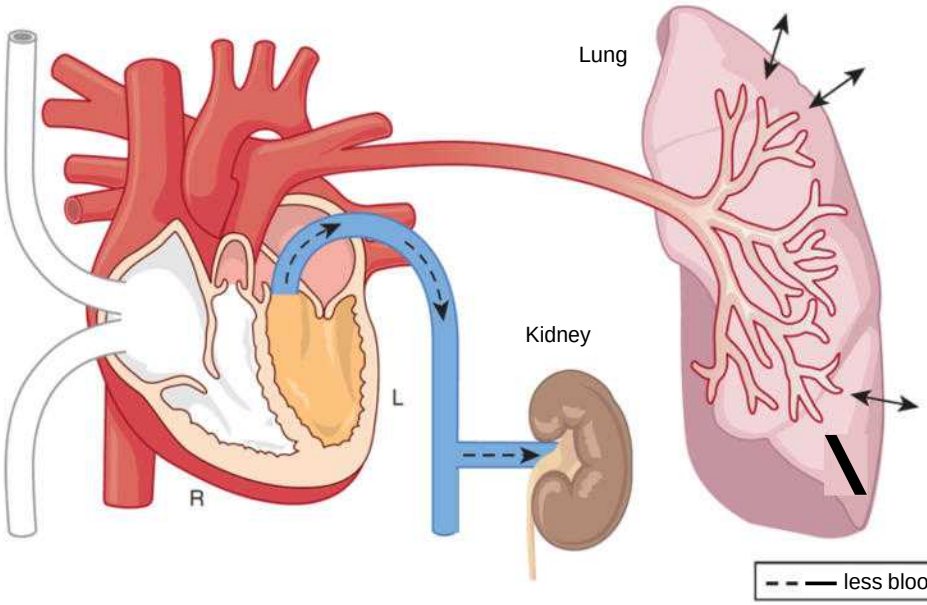
Heart failure can be categorized in several ways—systolic dysfunction, diastolic dysfunction, and mixed (see Figure 4-16). Systolic dysfunction is characterized by decreased cardiac output due to decreased contractility. The causes of this decreased contractility include chronic ischemia from coronary artery disease (most common), dysrhythmias, dilated cardiomyopathy, chronic alcohol abuse, and myocarditis. Diastolic dysfunction is characterized by decreased ventricular filling from abnormal myocardial relaxation and increased left ventricular pressure. This type of heart failure is caused by conditions that stiffen the myocardium, such as coronary artery disease, hypertrophic and restrictive cardiomyopathy, and pericardial disease. Most patients have a combination of systolic and diastolic dysfunction, known as **mixed dysfunction**.

Heart failure can be classified as left- or right-sided heart failure (**FIGURE 4-20**; see Table 4-1). **Left-sided heart failure** is a result of ineffective left ventricular contractility. As cardiac output declines, blood that is not being pumped out into the body backs up first in the left atrium and then in the pulmonary circulation. Pulmonary congestion, dyspnea, and activity intolerance develop as blood backs up in the lungs. If blood continues to accumulate, pulmonary edema and right-sided heart failure will develop. Common causes of left-

sided heart failure include left ventricular infarction, hypertension, and aortic and mitral valve stenosis. Right-sided heart failure is a result of ineffective right ventricular contractility. As a consequence of this condition, blood does not move appropriately out of the right ventricle. Blood backs up first in the right atrium, and then in the peripheral circulation, causing increased pressures in the peripheral capillary bed. The patient begins to gain weight, as the kidneys do not excrete fluid. Tissue becomes edematous, as pressures in the capillaries push fluid out of the circulatory system. The most frequent cause of right-sided failure is increased pulmonary resistance because of respiratory disease (also known as “cor pulmonale”). Additionally, pulmonic and tricuspid valve stenosis can strain the right side of the heart. Most patients have a combination of left- and right-sided heart failure.

Left-sided heart failure

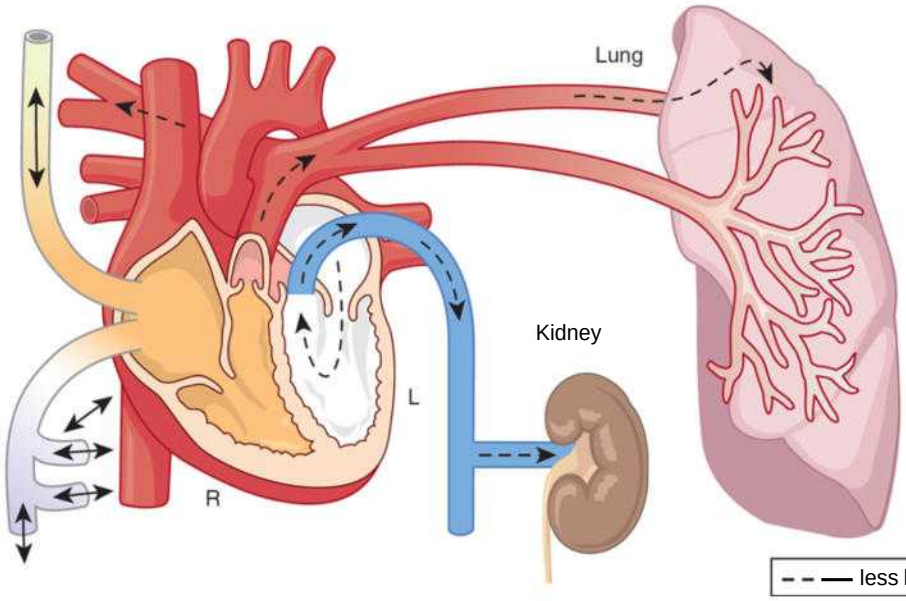
1. Left ventricle weakens and cannot empty
2. Decreased cardiac output to system
3. Decreased renal blood flow stimulates renin-angiotensin and aldosterone secretion
4. Backup of blood into pulmonary vein
5. High pressure in pulmonary capillaries leads to pulmonary congestion or edema



A

Right-sided heart failure

1. Right ventricle weakens and cannot empty
2. Decreased cardiac output to system
3. Decreased renal blood flow stimulates renin-angiotensin and aldosterone secretion
4. Backup of blood into systemic vein (venae cavae)
5. Increased venous pressure results in edema in legs and liver and abdominal organs
6. Very high venous pressure causes distended neck vein and cerebral edema



B

FIGURE 4-20 Effects of left- and right-sided heart failure.

Description

Heart failure can present as an acute or chronic problem. Acute heart failure may be related to a temporary condition and resolve with treatment of that condition. Chronic heart failure, in contrast, is a progressive condition that may have exacerbations, or an acute worsening, that will require additional treatment measures.

The clinical manifestations of heart failure depend on the side affected and on the severity. The manifestations of right-sided failure reflect systemic fluid accumulation, while left-sided failure is characterized by pulmonary fluid accumulation.

A grading system (**FIGURE 4-21**) is used to classify the severity of heart failure (I–IV, with IV being the most severe). Diagnosis and grading of heart failure are based on the following measures:

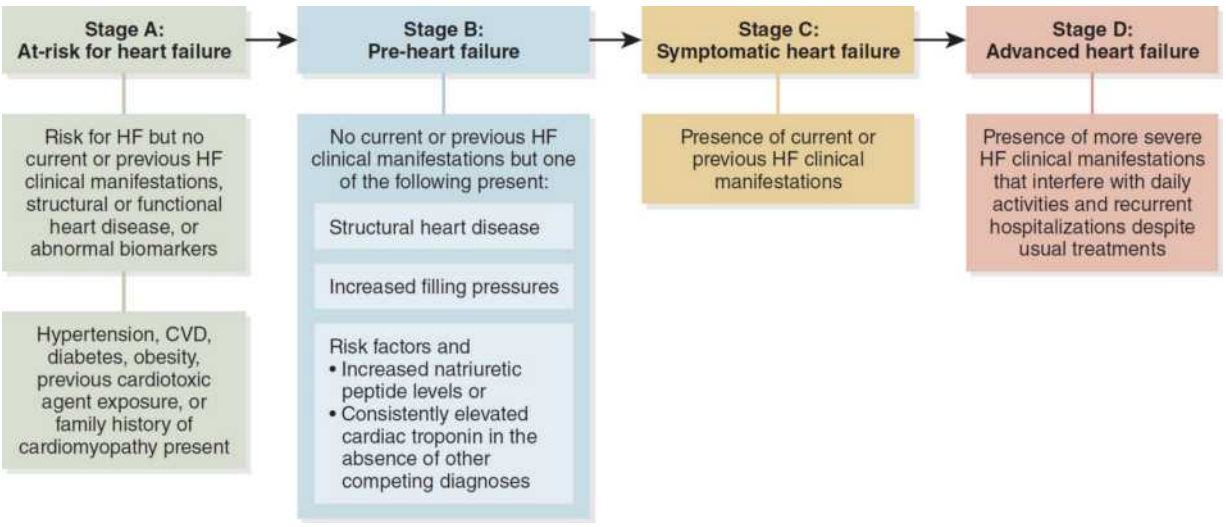


FIGURE 4-21 Stages of heart failure.

Abbreviations: ACCF/AHA: American College of Cardiology Foundation/American Heart Association; HF: heart failure; NYHA: New York Heart Association.

Description

- History
- Physical examination

- Chest X-ray
- Arterial blood gases
- Echocardiogram (including ejection fraction)
- EKG
- Brain natriuretic peptide (a hormone released by the ventricles in response to overstretching)

Management of heart failure begins with identifying and treating the underlying causes (FIGURE 4-22). Additional strategies include lifestyle modifications (e.g., weight reduction, tobacco cessation, reduced salt consumption, fluid restriction, and exercise), ACE inhibitors (to stop the renin–angiotensin–aldosterone cycle), diuretics (to remove excess fluid), aldosterone antagonists (to remove excess fluid), angiotensin receptor blockers (which vasodilate vessels, lowering blood pressure), angiotensin receptor neprilysin inhibitor (a combination drug that blocks the renin–angiotensin–aldosterone cycle as well as prevents the breakdown of helpful natriuretic peptides), cardiac glycosides (e.g., digoxin; to slow and strengthen cardiac contractions), inotropics (to increase myocardial contractility), beta-adrenergic blockers (to slow the heart rate and thereby increase diastolic filling), sinus node inhibitors (to slow the heart rate and thereby increase diastolic filling), sodium-glucose cotransporter-2 inhibitors if diabetic (to improve vascular function by directly causing vasorelaxation), biventricular pacemaker, intra-aortic balloon pump, and heart transplant.

Guideline Directed Medical Therapy Across Heart Failure Stages

Use this tool to reference guideline directed medical therapy (GDMT) across the four ACC/AHA stages of Heart Failure (HF) as outlined in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. See the guideline for specific patient population criteria.

	Stage A: At-risk for heart failure	Stage B: Pre-heart failure	Stages C & D Stage C: Symptomatic heart failure & Stage D: Advanced heart failure		
			HFrEF LVEF ≤40%	HFmrEF LVEF 41–49%	HFpEF LVEF ≥50%
GDMT of major medication classes	SGLT2i in pts with DM (1)	SGLT2i in pts with DM (1)	ARNI in NYHA II-III; ACEi or ARB in NYHA II-IV (1)	Diuretics, as needed (1)	Diuretics, as needed (1)
		ACEi (1)	Beta blocker (1)	SGLT2i (2a)	SGLT2i (2a)

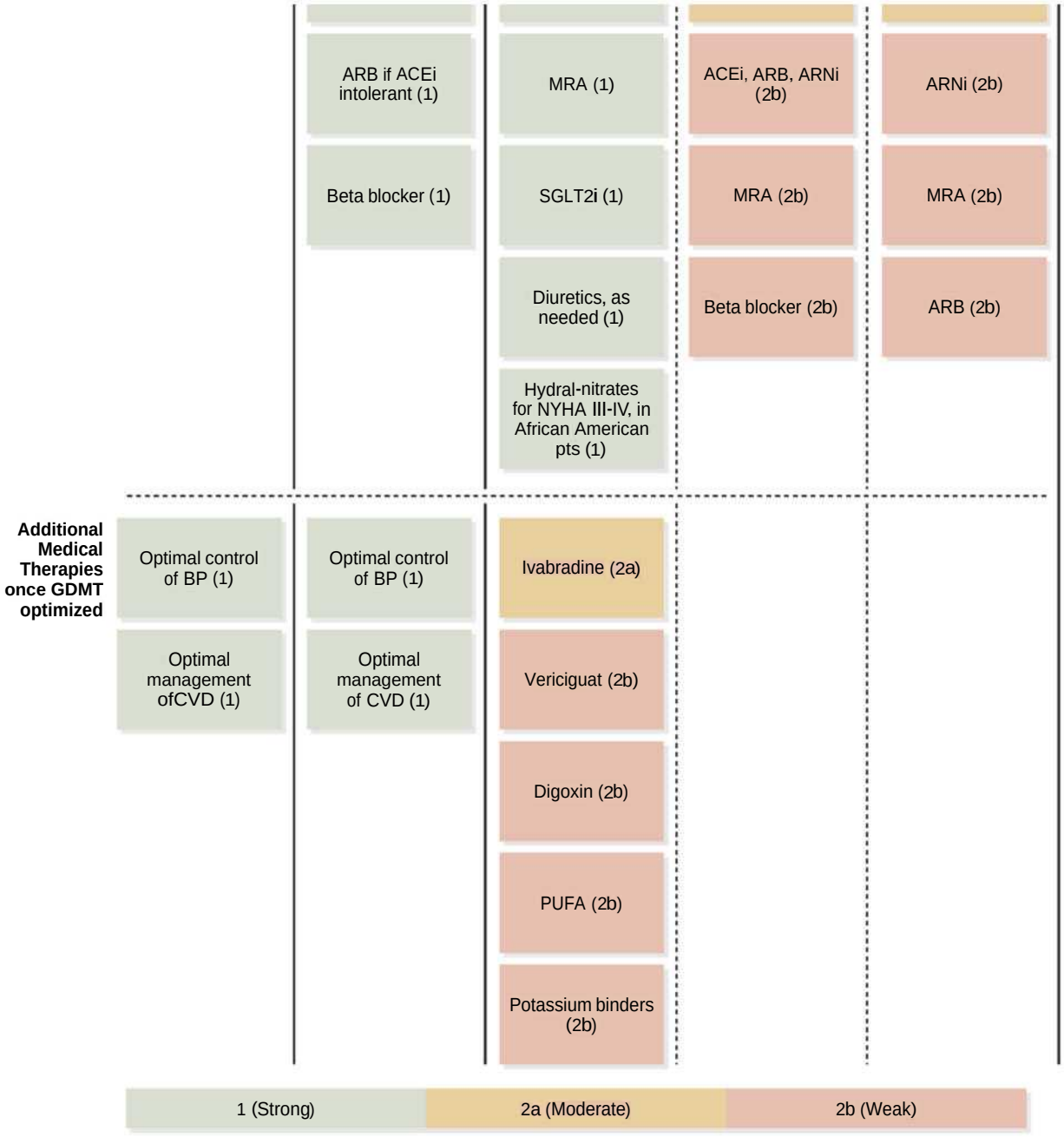


FIGURE 4-22 Guidelines for the management of heart failure.

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Description

Congenital Heart Defects

Congenital heart defects include a number of structural issues that may be present at birth, with such issues affecting 1% of live births in

the United States (NIH, 2022b). These heart defects are the most common type of birth defect. They can vary from simple to complex and involve the myocardium, heart valves, and vessels near the heart. Approximately 1 in 4 babies born with a heart defect has a critical congenital heart defect that requires surgery or other procedures in the first year of life. Some defects are apparent at birth, whereas other defects present in adulthood. Examples of congenital heart defects include the following conditions (those defects marked with an asterisk are considered critical):

- Septal defects (holes in the wall that separates the heart chambers)
- Patent ductus arteriosus (failure of the ductus arteriosus—the vessel between the aorta and the pulmonary artery—to close after birth)
- Valve disorders (e.g., stenosis, atresia, regurgitation)*
- Coarctation of the aorta (narrowing of the aorta)*
- Double-outlet right ventricle (the aorta connects to the right ventricle instead of the left ventricle)
- Dextro-transposition of the great arteries (the aorta and the pulmonary artery are switched in position)*
- Ebstein anomaly (abnormality of the tricuspid valve position and function)*
- Hypoplastic left heart syndrome (the left side of the heart does not fully develop)*
- Interrupted aortic arch (the aorta does not fully develop)*
- Single ventricle (one ventricle does not develop)*
- Tetralogy of Fallot (combination of pulmonary valve stenosis, a large ventricular septal defect, misplacement of the aorta directly over the ventricular septal defect, and right ventricular hypertrophy)*
- Total anomalous pulmonary venous return (the pulmonary veins do not connect to the left atrium)*

- Truncus arteriosus (a single common blood artery branches off the heart instead of the two usual vessels, the pulmonary artery and aorta)*

Heredity may play a role in some heart defects. In addition, some genetic disorders (e.g., Down syndrome), fetal exposure to tobacco and certain medications (e.g., ACE inhibitors or retinoic acids), and maternal health status (e.g., preexisting diabetes mellitus, phenylketonuria, rubella, and obesity) can increase the risk of these defects.

Depending on the defect, few or no manifestations may be present. When present, manifestations may include the following symptoms:

- Heart murmur
- Dyspnea
- Tachypnea
- Cyanosis
- Fatigue
- Chest pain or discomfort
- Difficulty gaining weight

Complications vary depending on the type of defect. Possible complications include arrhythmias, thrombosis, developmental disorders or delays, emotional issues (e.g., depression, anxiety, and posttraumatic stress disorder), endocarditis, endocrine disorders, kidney disease, liver disease, pneumonia, pregnancy complications, pulmonary hypertension, and stroke. In addition, heart failure may develop due to the increased cardiac workload as a result of the defect.

Diagnostic procedures for congenital heart defects include a history (including the mother's history), physical examination, fetal ultrasound, echocardiogram, EKG, chest X-ray, cardiac catheterization, and cardiac MRI. Treatment depends on the type and severity of the defect. Strategies may include repair with a heart catheterization or surgery, heart transplant, and medications to manage symptoms and

complications (e.g., diuretics, antidysrhythmic agents, antihypertensives). Ductus arteriosus normally closes within 21 days of birth.

Conditions Resulting in Ineffective Tissue Perfusion

Aneurysms

Walls of arteries can weaken because of high pressures, plaque, and infections. These weakened areas balloon outward, a condition known as an “aneurysm.” This weakening happens much like a worn spot on a tire or a bulge in an old balloon. Just like the tire and the balloon, an aneurysm can rupture when the pressure builds inside the wall or when the wall becomes too thin. When it ruptures, blood spills out of the circulatory system, a condition known as **exsanguination**. The risk for rupture increases with the size of the aneurysm, especially those equal to or greater than 4 mm. Aneurysms may also develop slow leaks rather than rupturing abruptly.

Aneurysms can occur in any artery, but they most frequently arise in the aorta, cerebral arteries, popliteal arteries, mesenteric arteries, and splenic arteries due to the higher pressures in these areas. Aortic aneurysms are the most common type. Although they can occur anywhere along the aorta, the abdominal section is the most common site. An abdominal aortic aneurysm occurs on the section that supplies the abdomen, pelvis, and legs. Abdominal aortic aneurysms are most frequent in men older than age 60 who have at least one or more risk factors (discussed later in this section). The risk for thoracic aortic aneurysms is higher with a positive family history. Rupture of an aortic aneurysm is a medical emergency, and only about 20% of patients survive. In the United States, these ruptures lead to approximately 13,000 deaths each year.

Cerebral aneurysms affect only 5% of the population and can occur on any of the arteries that supply the brain. The most common type of cerebral aneurysm is saccular. The most frequently affected sites are the anterior communicating artery in men and the posterior communicating artery in women. Cerebral aneurysms are more common in adults and in women (as compared to men). African

Americans and Hispanic Americans are twice as likely as Caucasians to experience a rupture, which is a medical emergency. **Saccular aneurysms** of the anterior communicating artery are also associated with polycystic kidney disease, which follows an autosomal dominant inheritance pattern. Most individuals do not know they have a cerebral aneurysm because these defects are often asymptomatic until they increase intracranial pressure.

The following factors increase the risk of developing aneurysm:

- Congenital weakening of the arterial wall (e.g., congenital arteriovenous malformation)
- Atherosclerosis
- Hypertension
- Dyslipidemia
- Diabetes mellitus
- Emphysema
- Tobacco usage
- Alcoholism
- Obesity
- Advanced age
- Trauma
- Infection (e.g., syphilis and tuberculosis)
- Copper deficiency (results in decreased activity of the lysyl oxidase enzyme that affects elastin in the vessel walls, causing the walls to thin)

True aneurysms are those that affect all three layers of the vessel. Two major types of true aneurysms exist—saccular and fusiform (**FIGURE 4-23**). A saccular aneurysm, also called a "berry aneurysm," is a bulge on the side of the vessel. With a **fusiform aneurysm**, the aneurysm affects the entire circumference of the vessel. A false aneurysm, in contrast, does not affect all three layers of the vessel; an example of this type is a **dissecting aneurysm**. With dissecting aneurysms, the weakening occurs in the inner layers.

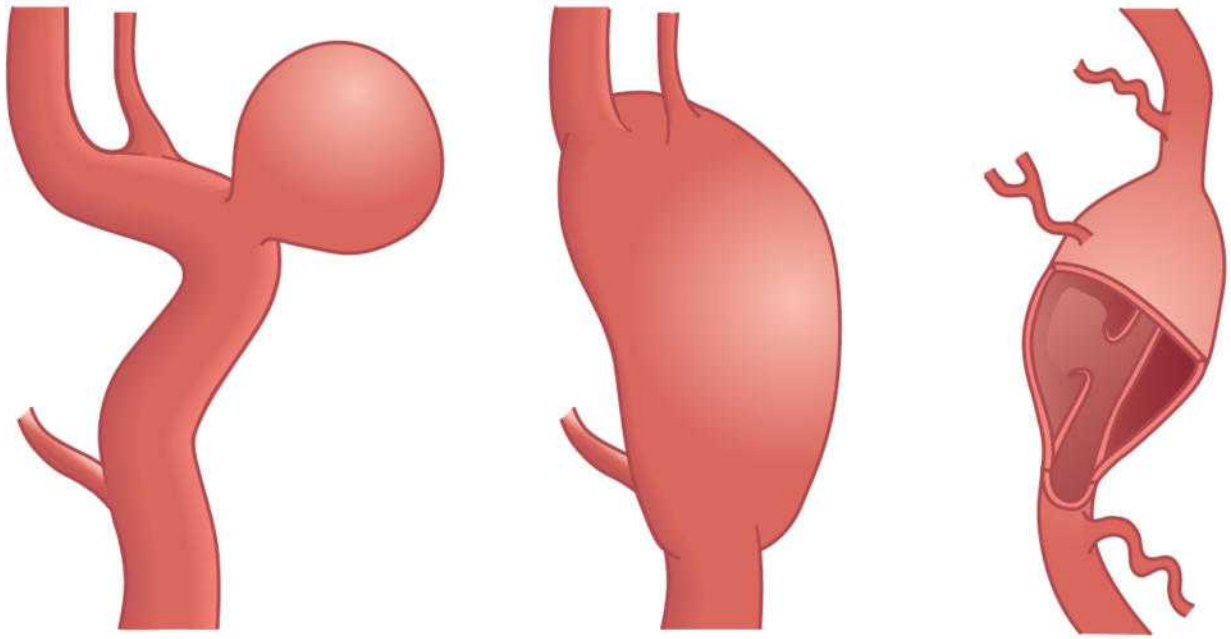


FIGURE 4-23 Types of aneurysms.

Description

Clinical manifestations of aneurysms may vary based on their location. Most aneurysms are asymptomatic until they rupture. For cerebral aneurysms, manifestations reflect increased intracranial pressure; they include headache, dizziness, vision changes, nausea, vomiting, confusion, and lethargy. Abdominal aortic aneurysms can present with a pulsating abdominal mass, abdominal or back pain, and lower-extremity cyanosis. Manifestations of thoracic aorta aneurysms can include hoarseness, dysphagia, high-pitched breathing, swelling in the neck, chest or upper back pain, and a sense of impending doom. If pain quickly subsides, rupture should be suspected, and medical attention should be sought immediately. Additionally, indications of shock may be present (e.g., tachycardia, hypotension, clammy skin, and neurologic decline). Once the rupture occurs, manifestations will quickly intensify.

Diagnosis of aneurysms often occurs incidentally during a routine physical examination or X-ray. Other diagnostic procedures include

echocardiogram, CT, MRI, and arteriograph.

The goal of treatment is to prevent rupture by eliminating or treating causes (e.g., controlling blood pressure). Beyond treating causes and managing risk factors, most aneurysms require only careful monitoring until the aneurysm grows to the point that the rupture risk outweighs the surgical risk. Surgical intervention is the only effective treatment to resolve the aneurysm; it is performed if symptoms are present or if the aneurysm's diameter is more than 5 cm in an asymptomatic patient. Surgical interventions vary depending on the location and may include an endovascular stent graft, endovascular coiling, aneurysm clipping, and bypass graft. If rupture occurs, immediate surgery is required.

Dyslipidemia

Dyslipidemia, or hyperlipidemia, refers to an elevated level of **lipids** in the blood. These lipids include cholesterol, triglycerides (fats), and phospholipids. Lipids are necessary for forming cellular membranes, providing and storing energy, producing steroid hormones (e.g., testosterone and estradiol), carrying fat-soluble vitamins (e.g., A, E, D, and K), insulating nerves, protecting organs, and insulating the body.

Lipids are insoluble in the blood, so they require a carrier protein (e.g., apolipoprotein) to be transported around the body. These bound lipids, which are termed "lipoproteins," are classified according to their density. This density reflects the amount of triglycerides in the lipoprotein, which are low in density, versus the amount of proteins, which are highly dense. The main classes of lipoproteins are chylomicrons: very-low-density lipoproteins, **low-density lipoproteins (LDLs)**, and **high-density lipoproteins (HDLs)**. The most significant of these lipoproteins are LDL and HDL.

Though cholesterol and fats are different types of lipids, the term "cholesterol" is often used as a clinical blanket term for all lipids; therefore, hypercholesterolemia is high levels of cholesterol in the blood but may or may not reflect low levels of HDL. High cholesterol is a relatively common issue in the United States. Nearly 94 million

U.S. adults aged 20 and older have total cholesterol levels higher than 200 mg/dL, and 28 million U.S. adults have total cholesterol levels above 240 mg/dL (Centers for Disease Control and Prevention, 2022). Approximately 7% of U.S. children ages 6 to 19 had high total cholesterol levels. The prevalence of hypercholesterolemia is highest among Caucasian women and Hispanic men. Increased lipid levels have been linked to multiple disease conditions, including **atherosclerosis**, peripheral vascular disease, coronary artery disease, hypertension, and stroke.

Lipids are introduced into the bloodstream in two ways—diet and liver production (**FIGURE 4-24**). Dietary cholesterol is found in animal products, and dietary triglycerides are found in saturated fats (e.g., fried foods and cakes). Bile acids solubilize ingested lipids, allowing them to be absorbed in the small intestines. Once absorbed, lipids form chylomicron, a bundle of lipoproteins that consist of triglycerides, phospholipids, cholesterol, and proteins. These chylomicrons transport the lipids to peripheral tissue. Additionally, the chylomicrons are transported to the liver for synthesis of several types of lipoproteins. Cholesterol is necessary for survival, but it is not necessary to eat it—the human liver makes more cholesterol than the body could possibly use.

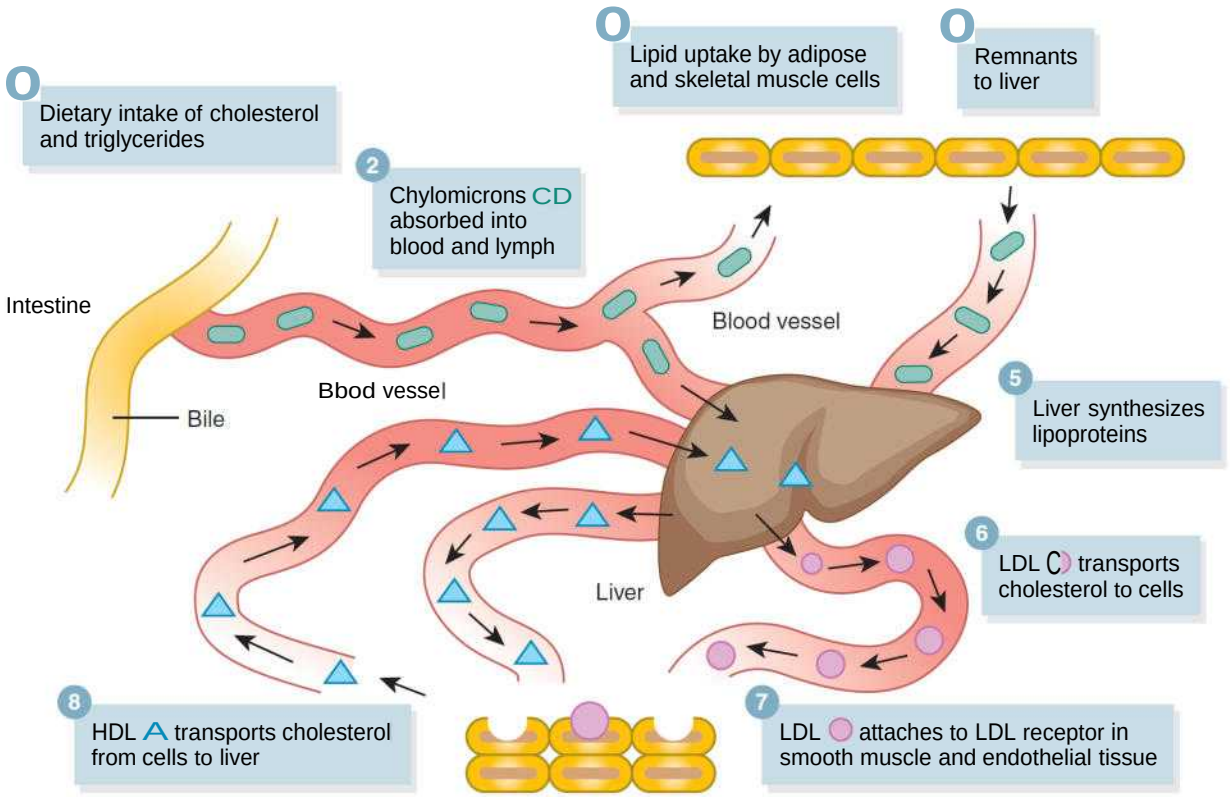


FIGURE 4-24 Transportation of lipids in the blood.

Abbreviations: HDL: high density lipoprotein; LDL: low density lipoprotein.

Description

Dyslipidemia is categorized as either primary or secondary. Primary causes include single or multiple gene mutations that result in either an overproduction or defective clearance of LDL and triglycerides or an excessive clearance of HDL. Secondary causes include lifestyle (e.g., high-cholesterol and high-fat diet, excessive alcohol consumption, smoking, sedentary lifestyle), obesity, and other factors (e.g., diabetes mellitus, hypothyroidism, liver disease, and renal disease). Additionally, medications, such as thiazides, beta-adrenergic blocking agents, retinoids, antiretroviral agents, cyclosporine, tacrolimus, estrogen, progestins, and glucocorticoids, can increase cholesterol levels.

Learning Points

Dietary Cholesterol

Dietary cholesterol comes from animal products. To keep this origin in mind, remember that this lipid *must come from something with a face*. To gauge the amount of cholesterol in the product, think of how many legs the animal has. For example, a cow with four legs has more cholesterol than a chicken with two legs, which has more cholesterol than a fish with no legs. An exception to this rule is deer. A deer has four legs but is a very lean animal; therefore, its meat has less cholesterol than beef. When considering pork, the amount of cholesterol depends on the cut of meat. Bacon has cholesterol content more like that of beef, whereas pork chops are more like chicken in terms of their cholesterol content. Finally, an egg may not have any legs yet, but one yolk contains more cholesterol than you need all day (the recommended daily allowance is less than 200 mg/day). This analogy creates an image that not only helps you remember the cholesterol in foods but is also great to use with patients because it is easy to remember.

When cholesterol is present, it moves through the bloodstream in large molecules much like cooking lard. When triglycerides are present, they move through the bloodstream in large sticky molecules, much like gum. These sticky, fatty molecules travel through the circulatory system clogging small vessels and coating larger ones, much like what happens when oils and grease are poured down a drain.

Learning Points

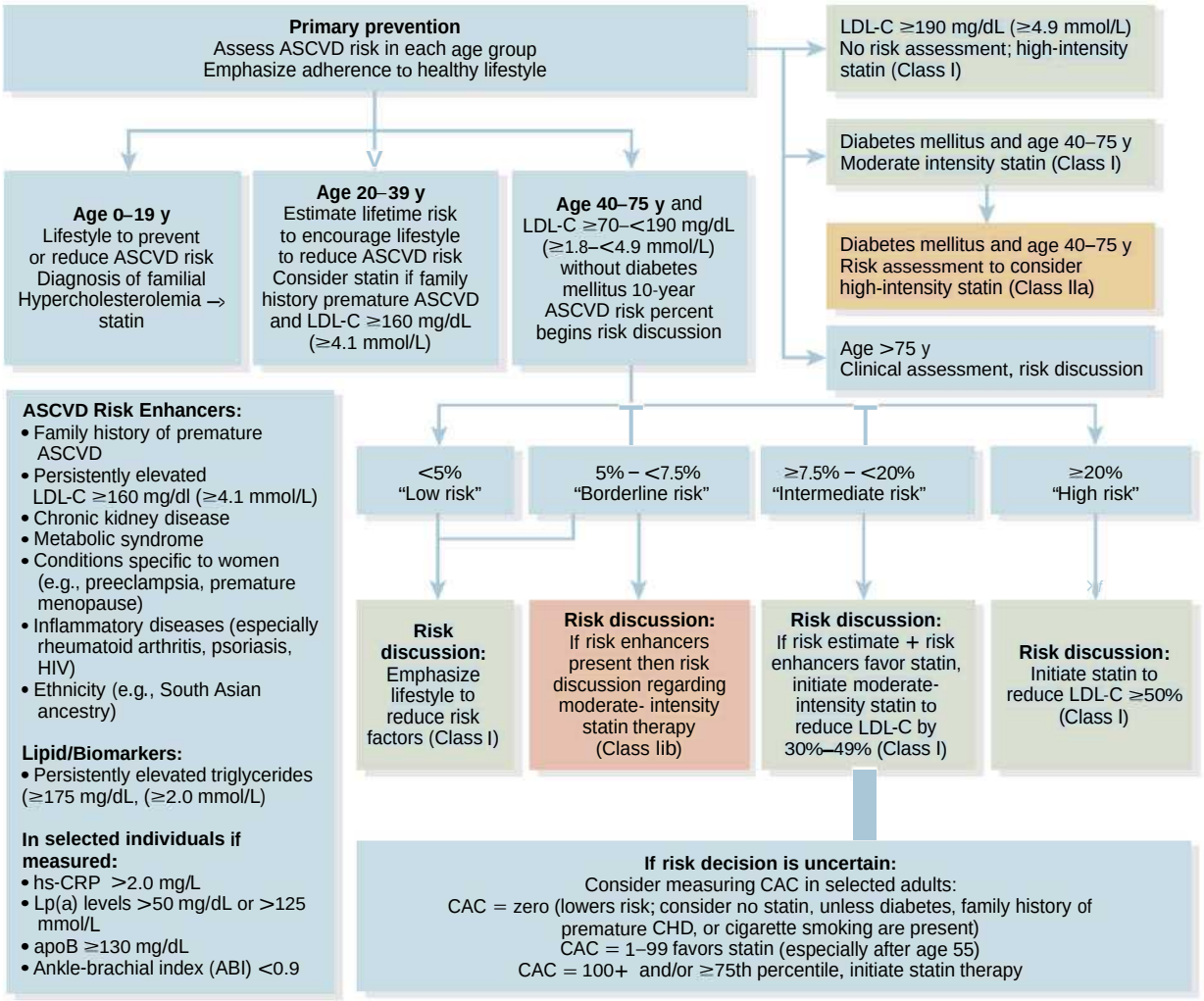
Cholesterol

LDL is known as “bad cholesterol” because most serum cholesterol is made up of LDL. The small, dense molecules of LDL are more invasive than the other lipoproteins. You can remember this point by considering it the “**l**ow-**d**own **l**ousy” cholesterol. Because it is the bad cholesterol, you want the LDL level as low as you can get it. Ways to decrease LDL through lifestyle modifications include dietary changes such as avoiding high-cholesterol and high-fat foods.

HDL is known as “good cholesterol” because it assists in removing some of the cholesterol from the bloodstream. You can remember this point by considering it the “**h**appy” cholesterol. Because it is the good cholesterol, you want the HDL level as high as you can get it. Ways to increase HDL through lifestyle modifications include tobacco cessation and exercise.

Dyslipidemia is often asymptomatic until it develops into other diseases (e.g., atherosclerosis, coronary artery disease, or stroke). At that point, the symptoms reflect the presence of those diseases. Current best practices recommend a detailed risk assessment annually using an atherosclerotic cardiovascular disease (ASCVD) risk calculator (http://static.heart.org/riskcalc/app/index.html#!/baseline-risk) (Grundy et al., 2019). Cholesterol screenings and lipid profiles can identify specific lipid abnormalities. Further testing (e.g., angiography, ultrasound, and nuclear scanning) can be conducted to determine the development of complications.

According to current best practices, primary screening and prevention strategies should be implemented for those individuals who have risk factors but have not developed ASCVD (**FIGURE 4-25**). Secondary prevention strategies should be implemented when an individual has developed ASCVD (**FIGURE 4-26**).



Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9i, PCSK9 inhibitor.
*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

FIGURE 4-25 Atherosclerotic cardiovascular disease primary prevention.

Description

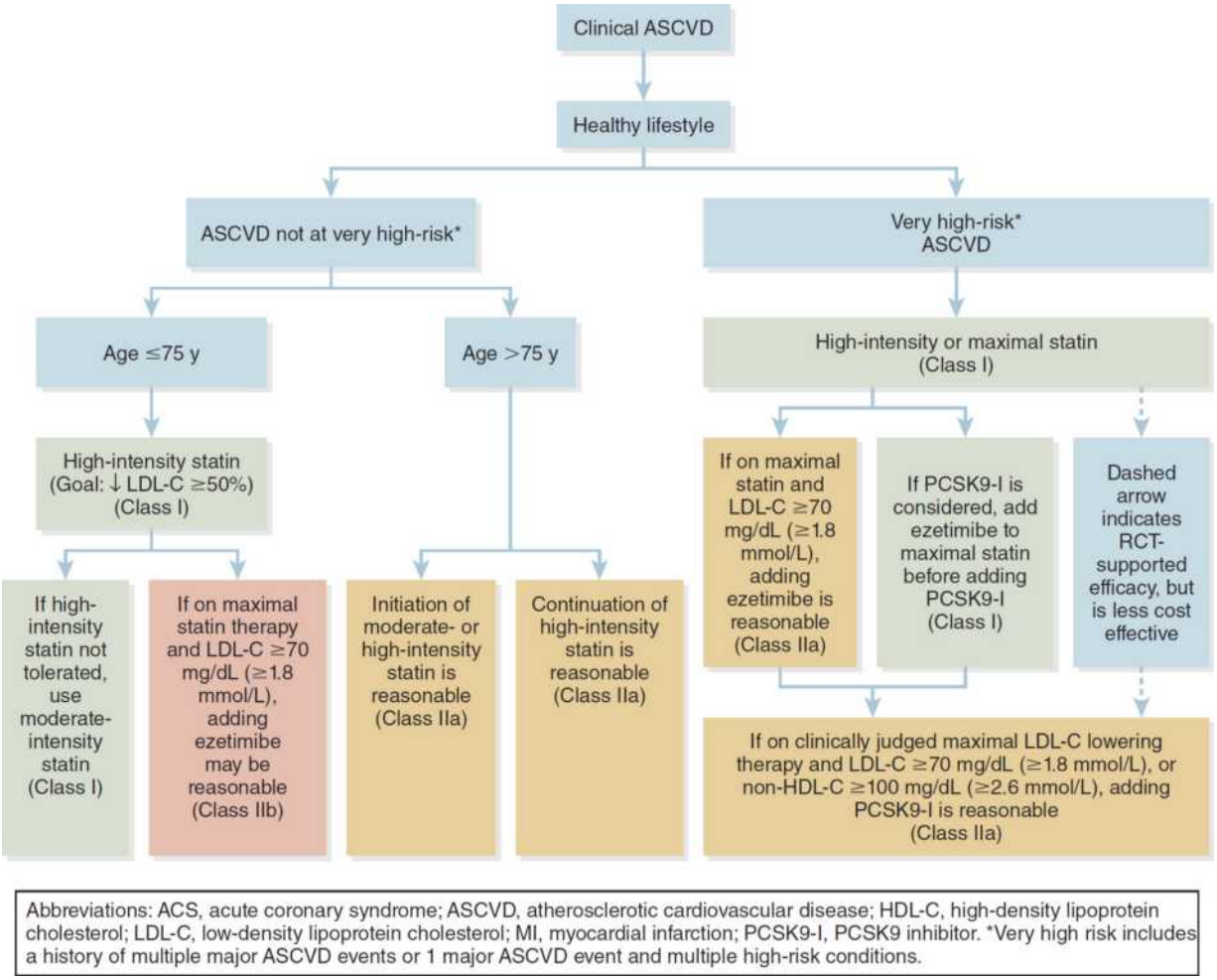


FIGURE 4-26 Secondary prevention.

Description

The goal of these strategies is to normalize lipid levels and prevent complications. These strategies take a stepwise approach, adding therapies as needed until the cholesterol is adequately lowered. Initially, treatment regimens to lower lipid levels include lifestyle modifications:

- Consumption of low-cholesterol, low-fat, high-fiber foods
- Routine exercise
- Moderate alcohol consumption
- Weight reduction (if applicable) or control
- Tobacco cessation (if applicable)

Other treatment approaches are implemented if these lifestyle modifications prove unsuccessful. While a wide range of lipid-lowering pharmacologic agents exist, pharmacologic treatment primarily focuses on HMG-CoA reductase inhibitors (also known as “statins”) (Grundy et al., 2019). Other cholesterol-lowering agents include cholesterol absorption inhibitors (e.g., ezetimibe), bile acid sequestrants, PCSK9 monoclonal antibodies (e.g., evolocumab), niacin, fibrates, and omega-3 fatty acids. Other pharmacologic agents (e.g., anticoagulants and antiplatelet agents) may be added as necessary to prevent or treat complications.

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease characterized by thickening and hardening of the arterial wall. In this condition, lesions (or plaques) composed of lipids, calcium, and other substances (e.g., cellular waste products and fibrin) develop on the vessel wall and harden over time. Development of these lesions causes platelet aggregation (collection), thrombosis, vasoconstriction, and vessel obstruction. The plaques can also break away and become embolisms, occluding vessels once they become lodged in them. The result of atherosclerosis is ineffective tissue perfusion, ischemia, and infarction, which can lead to peripheral vascular disease, coronary artery disease, renal disease, and stroke (**FIGURE 4-27**). When arteries are narrowed and hardened, the heart must work harder to pump the blood through them, resulting in hypertension.

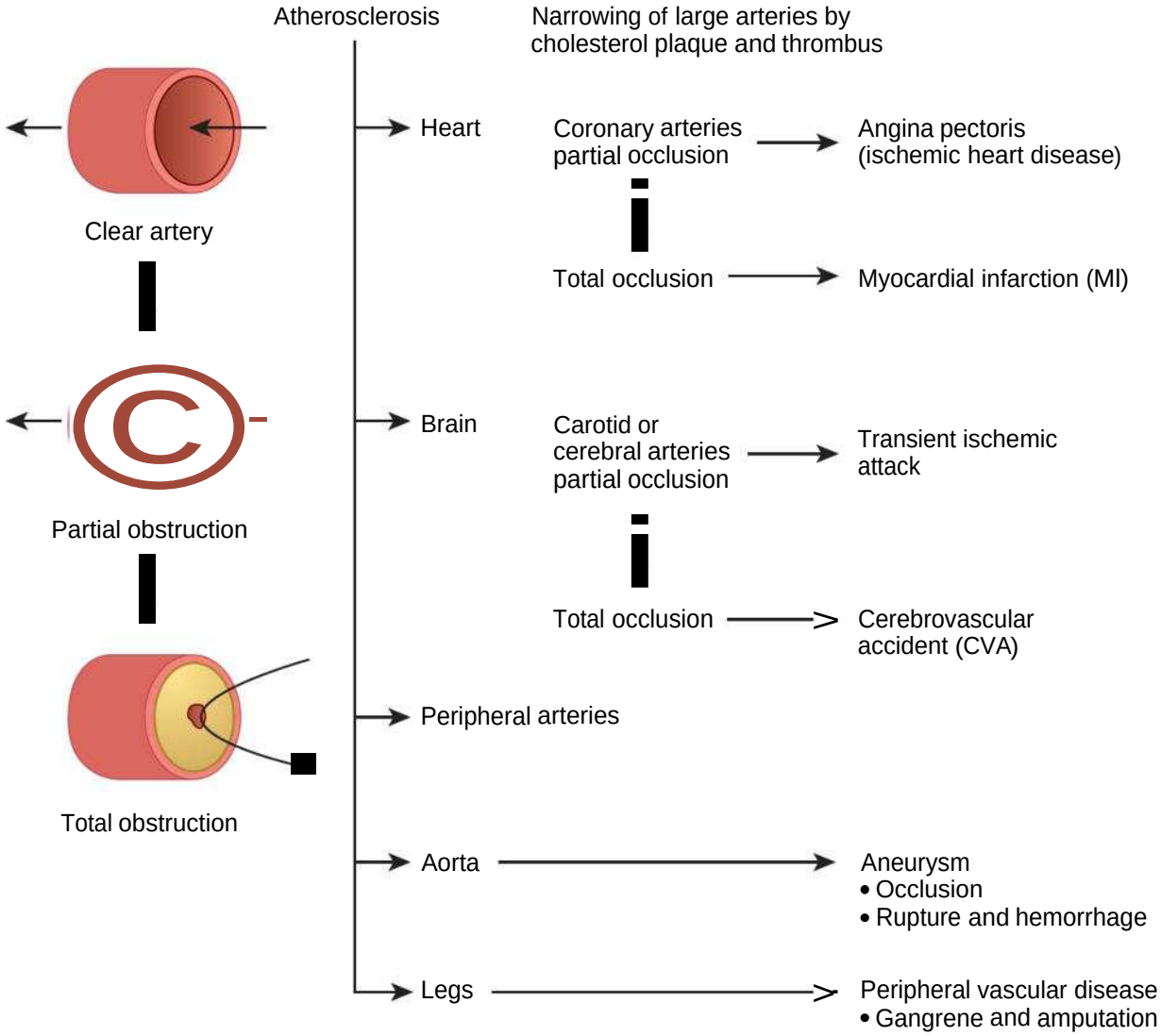


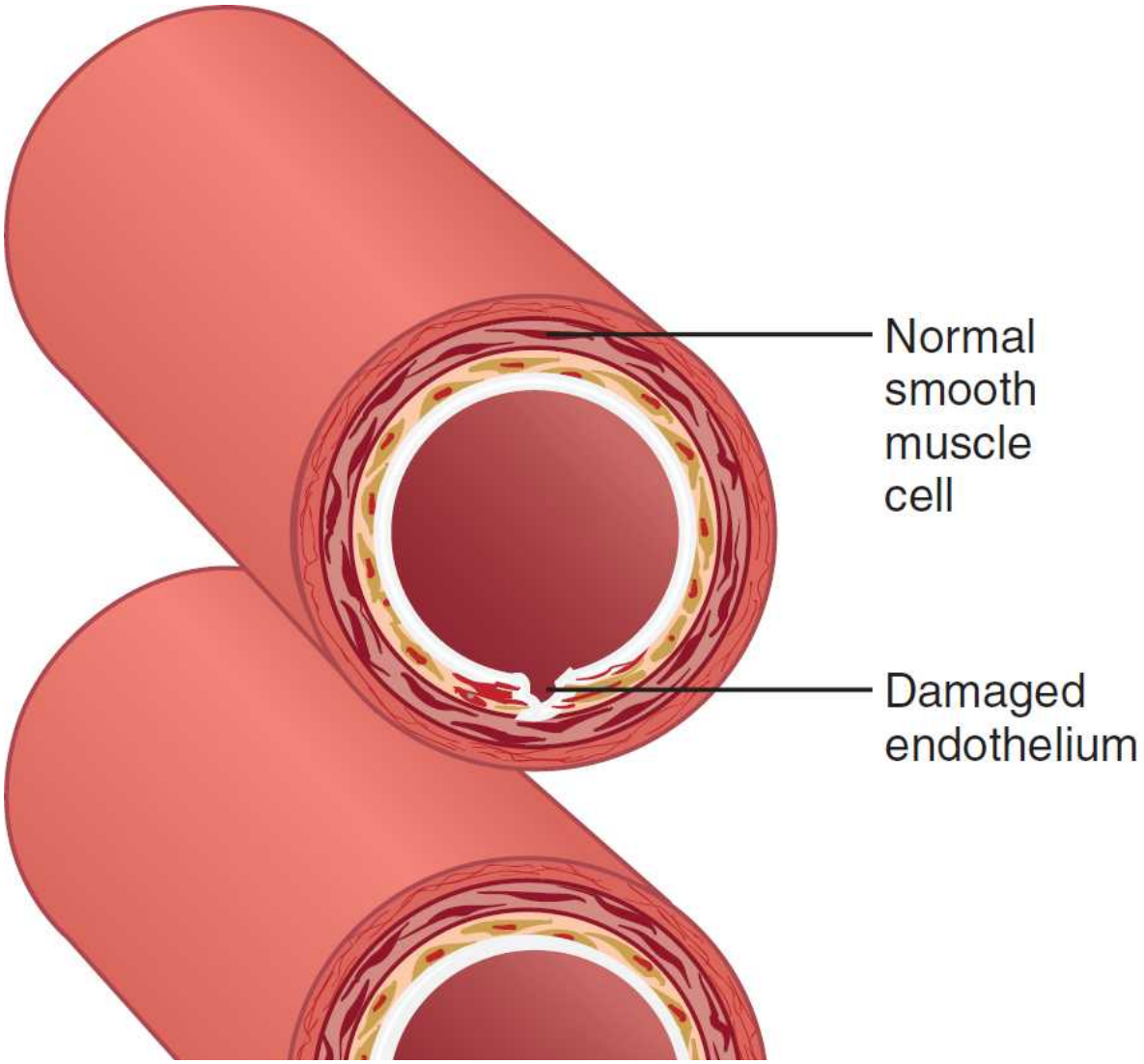
FIGURE 4-27 Possible complications of atherosclerosis.

Description

Because of its systemic involvement, atherosclerosis is the leading cause of illness and death in the United States and worldwide. In 2019, cardiovascular disease—primarily coronary artery disease and stroke as a result of atherosclerosis—caused more than 15 million deaths worldwide (World Health Organization [WHO], 2020).

Atherosclerosis is a slow, progressive disease that may start in childhood. It develops faster with age. Atherosclerosis development is initiated by endothelial injury to the vessel wall (**FIGURE 4-28**). Dyslipidemia, hypertension, tobacco use, diabetes mellitus, elevated

C-reactive protein levels (released as a result of inflammation), elevated homocysteine levels, autoimmune processes, and some infections (e.g., *Chlamydia pneumoniae* or cytomegalovirus) can cause this injury. The injured cells become more permeable, suffer from free-radical damage, become inflamed, and signal monocytes and T cells to attach to the artery wall. The monocytes and T cells move into the artery wall, where they are transformed into foam cells. These foam cells collect lipids and trigger the growth of smooth muscle cells in the artery wall. Over time, the lipid-rich foam cells accumulate, become oxidized, and form patchy deposits (or plaques) covered with a fibrous material in the artery lining. Eventually, calcium accumulates in the plaques.



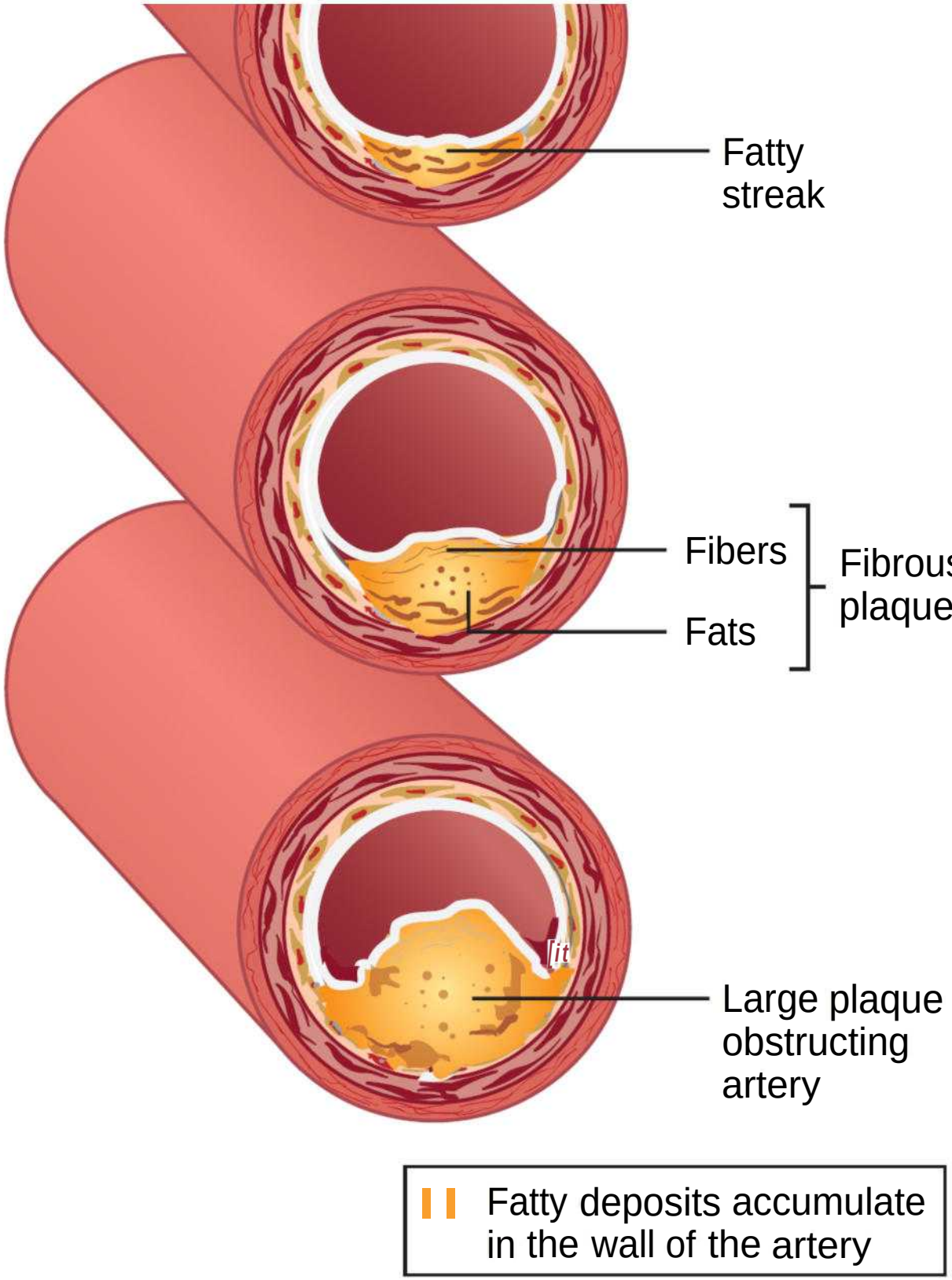


FIGURE 4-28 Development of atherosclerosis.

Description

The plaques associated with atherosclerosis typically are scattered throughout medium-size and large arteries, but they usually begin where arteries branch. Plaques can either grow into the artery lumen or into the artery wall. If the plaque grows into the artery lumen, tissue perfusion becomes compromised. In contrast, tissue perfusion is not impacted if the plaque grows into the artery wall. However, both types can rupture, exposing the material inside, which triggers thrombosis. These thrombi can suddenly occlude blood flow. Additionally, pieces of the plaque can break off, becoming emboli and suddenly occluding blood flow.

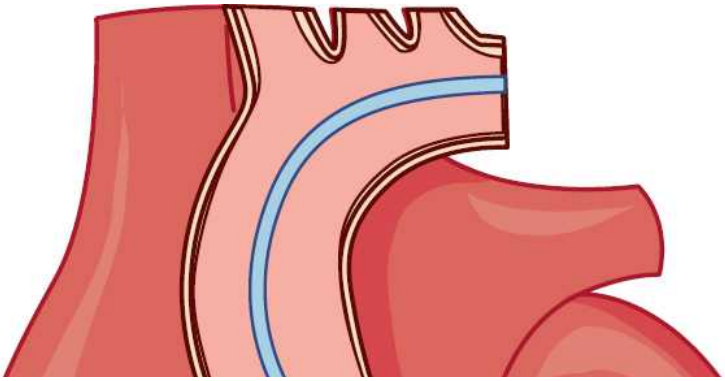
Much like dyslipidemia, atherosclerosis is often asymptomatic until the artery lumen is narrowed by more than 70% and complications develop. At that point, clinical manifestations will be related to the location and the specific complications. The first symptom of slowly progressing atherosclerosis may be pain or cramps when the blood supply is unable to meet the tissue's demands (e.g., during exercise or increased activity). The pain or discomfort usually goes away when the demand is lowered (e.g., rest). If atherosclerosis has developed in the coronary arteries, chest pain (i.e., angina) during exertion is usually the presenting symptom. If it has developed in the femoral or lower-extremity arteries, leg cramps when walking (i.e., intermittent claudication) are usually the presenting symptom. When present in the cerebral arteries, atherosclerosis can cause transient ischemic attacks, stroke symptoms that usually resolve within a few minutes without treatment. In the kidneys, atherosclerosis can cause renal failure or trigger the renin–angiotensin–aldosterone cycle, which can cause markedly high blood pressure.

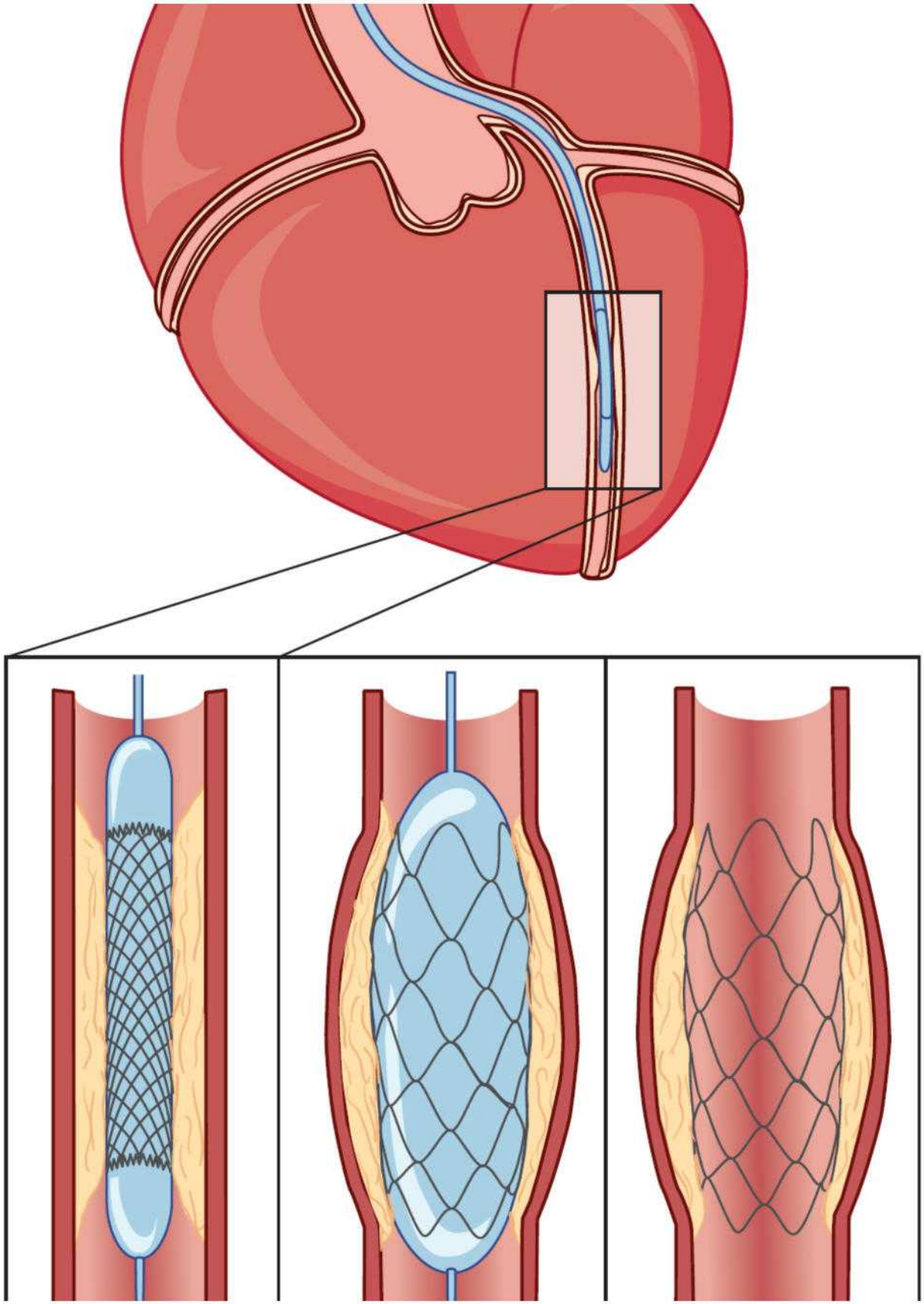
If the arteries are suddenly occluded, pain is severe and develops suddenly, usually in the absence of exertion. Additionally, this pain does not resolve with rest. In these cases, occlusions (either by plaque, thrombi, or emboli) in the coronary artery will result in a myocardial infarction. Sudden occlusions in the cerebral arteries will

result in a stroke, and sudden occlusions in leg arteries can cause gangrene distal to the occlusion (e.g., toe, foot, or leg).

Diagnostic procedures for atherosclerosis include those that identify contributing factors (e.g., lipid, C-reactive protein, homocysteine, and glucose levels). Other diagnostic procedures are used to determine whether complications have developed (e.g., EKG, cardiac markers, angiography, ankle/brachial index, ultrasound, computed tomography with angiography [CTA], and nuclear scanning). Additionally, a physical examination may reveal bruits and thrills over the affected arteries. Normally, blood flowing through an artery does not make a sound because the vessels are smooth. In contrast, turbulence is created by a vessel wall abnormality, causing the blood to create a swishing sound (i.e., bruit) that can be heard when auscultating the area with a stethoscope. This turbulence also creates a vibration sensation (i.e., thrill) when palpated. This assessment is generally possible over only larger arteries and those near the skin's surface (e.g., carotids, femoral, and aorta). Additionally, pulses may be weak or absent.

Treatment focuses on lowering risk factors (e.g., healthy lifestyle choices, lowering cholesterol levels, controlling diabetes) and preventing the development of complications (e.g., myocardial infarction, stroke). Treatment for atherosclerosis is similar to that for dyslipidemia but with the addition of angioplasty to open occluded arteries (**FIGURE 4-29**), bypass procedures to detour blood around the occlusions, laser procedures to disintegrate the plaques, and atherectomy to remove the plaques. B-complex vitamins can also help lower homocysteine levels.





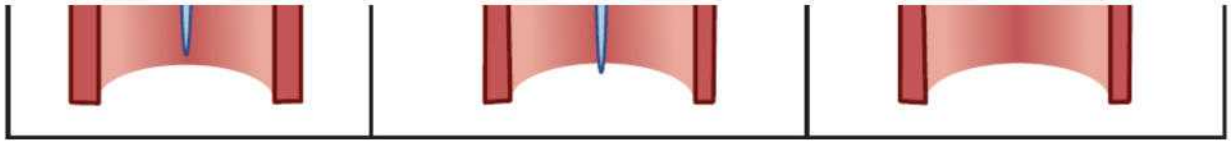


FIGURE 4-29 Angioplasty.

Description

Peripheral Vascular Disease

Peripheral vascular disease (PVD) refers to a narrowing of the peripheral vessels (arteries or veins). Most often this condition is caused by atherosclerosis that is located in the arteries, but it can also be caused by a thrombus, inflammation (e.g., **thromboangiitis obliterans**), or vasospasm (e.g., **Raynaud's disease** and Raynaud's phenomenon).

Thromboangiitis obliterans, or Buerger's disease, is a chronic inflammatory condition of the arteries (**FIGURE 4-30**). Buerger's disease can lead to thrombosis in the small- and medium-sized arteries of the arms and legs, eventually occluding them. Buerger's disease most commonly occurs in men between the ages of 20 and 40 who smoke.



FIGURE 4-30 Thromboangiitis obliterans.

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Raynaud's disease is a result of vasospasm of the arteries, most often of the hands, that occurs because of sympathetic stimulation (**FIGURE 4-31**). Raynaud's phenomenon describes the situation in which such vasospasm occurs in association with an autoimmune disease (e.g., systemic lupus erythematosus and scleroderma). This condition most commonly occurs in women between the ages of 18 and 30. As vessel occlusion increases, the ischemia to the affected tissue worsens.



FIGURE 4-31 Raynaud's phenomenon.

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Chronic venous insufficiency is a condition in which one or more veins do not return blood from the legs back to the heart due to valve damage in the veins, so blood pools in segments of the veins. Thrombophlebitis refers to a thrombus in an inflamed vein, most often in the legs.

Risk factors for developing PVD are similar to those for developing atherosclerosis but with the addition of autoimmune disease. Clinical manifestations of PVD are related to the local tissue ischemia and appear in the extremities. Most symptoms occur during activity when the oxygen demand exceeds the oxygen supply. The presence of symptoms at rest is an indicator of worsening disease. Manifestations include the following:

- Pain
- Intermittent claudication (pain that occurs in the lower legs during activity)
- Numbness, burning, or heaviness in the muscles
- Wounds that do not heal or gangrene
- Changes in skin color (pallor, cyanosis, rubor) and temperature (coolness if arteries are involved and warmth if veins are involved)
- Thin, shiny skin, especially in the lower extremities
- Hair loss, especially in areas farthest from the heart, such as the toes
- Thickened, discolored toenails
- Weak pulses, usually in the lower extremities
- Impotence

Diagnostic procedures for PVD include a history, physical examination, Duplex ultrasound, ankle-brachial index (which compares blood pressure in the arms and legs), treadmill exercise test, angiography, photoplethysmography, pulse volume recording waveform analysis, segmental blood pressure measurements, reactive hyperemia test, magnetic resonance angiography (MRA), CTA, and MRI. Additionally, laboratory testing will be similar to that for atherosclerosis and dyslipidemia (e.g., lipid, C-reactive protein, homocysteine, and glucose levels).

Emerging Research: Heart Disease Risk Factors

Most people are familiar with the traditional risk factors for heart disease—for example, hypertension, diabetes mellitus, dyslipidemia, obesity, physical inactivity, and smoking. In recent years, research has linked other health and lifestyle issues with an increased risk of developing heart disease, especially in the presence of traditional risk factors. These issues include sleep disturbances, pregnancy complications, mental health problems, and periodontal disease.

Sleep apnea has been linked with high blood pressure and arrhythmias (Kadoya et al., 2018). Sleeping less than seven hours per night can lead to increased blood pressure, truncal obesity, and stress hormones. Additionally, not getting sufficient sleep can disrupt

metabolism, causing increased lipid levels and making diabetes mellitus and hypertension more difficult to control.

Women who have a history of gestational diabetes have nearly a three times greater risk of developing coronary artery disease, hypertension, and type 2 diabetes mellitus (Daly et al., 2018). Women who have preeclampsia have a higher risk of developing hypertension and are twice as likely to develop cardiovascular disease by midlife.

Chronic mental health problems (e.g., depression, anxiety, anger, loneliness, and stress) can increase the risk of developing heart disease over time (Hegeman et al., 2018; Liu, Hernandez, Trout, Kleiman, & Bozzay, 2017). The connection between mental health and cardiovascular disease may be due in part to the fact that individuals experiencing these issues generally do not engage in healthy behaviors (e.g., regular exercise, proper diet) as well as increased levels of stress hormones.

Moderate to severe periodontal disease is associated with a significantly increased risk of developing cardiovascular disease (Holmlund, Lampa, & Lind, 2017; Singer et al., 2018).

Treatment strategies for PVD include controlling or reducing contributing factors, such as by making dietary changes or by tobacco cessation, physical activity, weight reduction, stress reduction, diabetes management, and hypertension control. In addition, direct interventions aimed at the occlusion may include angioplasty, bypass procedures, laser procedures, and atherectomy. Pharmacologic management includes antiplatelet agents (e.g., aspirin, clopidogrel, and cilostazol), hemorrhagic agents (e.g., pentoxifylline), anticoagulants, thrombolytics, and lipid-lowering medications.

Coronary Artery Disease

Coronary artery disease (CAD), also referred to as “coronary heart disease” and “ischemic heart disease,” is a narrowing or blockage of the arteries supplying the myocardium, usually caused by atherosclerosis. Along with atherosclerosis, vasospasm is another prevalent cause of CAD. Other causes of CAD include cardiomyopathy and thrombi.

CAD is the most common type of heart disease in the United States. Despite great advancements in treatment, cardiovascular disease (including CAD) remains the leading cause of death both in the United States and worldwide for men and women (WHO, 2020).

CAD is also the leading cause of myocardial infarction (Benjamin et al., 2018). Contributing factors for CAD—some modifiable and some not—are similar to those for atherosclerosis (e.g., diabetes mellitus, hypertension, stress, and tobacco) (**TABLE 4-2**).

TABLE 4-2 Risk Factors for Coronary Artery Disease

Nonmodifiable Risk Factors	Modifiable Risk Factors	Negative Risk Factors	Emerging Risk Factors
Age: men > 45 years; women > 55 years or premature menopause Family history: history of premature coronary artery disease in first-degree male relatives > 55 years or first-degree female relatives > 65 years	Tobacco use Obesity Physical inactivity Stress Diabetes mellitus Hyperlipidemia (specifically LDL and lipoprotein (a)) Hypertension Diet high in fat and calories and low in phytochemicals (found in fruits and vegetables); fiber; omega-3 fatty acids; and vitamins C, D, and E	High HDL cholesterol	Elevated C-reactive protein, homocysteine levels, and apoprotein B

Description

The three main types of CAD include obstructive, nonobstructive, and coronary microvascular disease. Obstructive CAD occurs when plaque accumulates in the large arteries, causing them to narrow gradually and reducing the blood supply to the myocardium. With this type of disease, the coronary artery is occluded more than 50%. The blood flow may eventually become completely occluded in one or more of the three main coronary arteries (e.g., right coronary artery, left anterior descending artery, and left circumflex artery).

In nonobstructive CAD, the large arteries are narrowed by plaque, but the occlusion is less than 50%. This type can also be caused by disease or injury to the lining of the coronary arteries that affects the arteries' ability to dilate in response to increased myocardial need. Damage to the inner arterial walls can cause them to spasm, leading to a temporary decrease in myocardial blood flow.

Coronary microvascular disease affects the smallest arteries of the myocardium. It may occur either alone or with one of the other two types of CAD. Coronary microvascular disease is thought to be caused by molecular changes in small vessels as a part of the normal aging processes or from damage (e.g., chronic inflammation, hypertension, or diabetes mellitus). These molecular changes affect the way genes and proteins are controlled inside the cells, such that the arteries do not respond to signals to vasodilate when myocardial need is higher.

In CAD, blood flow temporarily diminishes in the coronary arteries, causing subsequent oxygen reduction to the cardiac muscle. Myocardial ischemia is usually a result of increased demand and inadequate blood supply. The left ventricle is the most susceptible to ischemic damage because more arteries supply it to meet its increased need for oxygen. As ischemia develops, lactic acid and metabolic wastes accumulate, causing chest pain or angina. This accumulation can stimulate other nerves, causing the pain to radiate to other parts of the body. Additionally, chronic ischemia causes EKG changes (usually ST-segment depression). Reducing oxygen demand reverses ischemia and, in turn, reduces pain. **Stable angina pectoris** refers to ischemia that is initiated by increased demand (activity) and relieved with the reduction of that demand (rest). Decreased blood flow may or may not cause permanent damage to the myocardium, or infarction.

The cascade of events in which plaque ulcerates, inflammation occurs, platelets aggregate, and thrombi form further diminishes the blood supply. As a result, platelets release thromboxane A_2, a potent vasoconstrictor, causing the arteries to spasm. These spasms trigger an unrelenting cycle of more platelet aggregation and more spasms. Chest pain eventually becomes unpredictable, occurs at rest, or increases in frequency or intensity. This change in pain, which is known as **unstable angina**, is considered a preinfarction state.

In addition to causing myocardial infarctions, CAD can cause heart failure, dysrhythmias, cardiogenic shock, stroke, and sudden death. Manifestations can vary depending on the degree of the occlusion,

the location of the occlusion, and other confounding variables (e.g., presence of diabetes mellitus, history of myocardial infarction, and gender). For example, patients with diabetes mellitus usually do not experience angina in the traditional sense; because of decreased pain sensation, they may report extreme indigestion and fatigue instead of any chest pain. Clinical manifestations of CAD include the following signs and symptoms:

- Angina that can radiate to other locations (e.g., jaw, neck, arm, or back)
- Indigestion-like sensation
- Nausea and vomiting
- Cool, clammy extremities
- Diaphoresis
- Dyspnea
- Fatigue
- Weakness
- Sleep disturbances

Diagnostic procedures for CAD focus on identifying contributing factors (e.g., lipid profile, angiography, and nuclear imaging). Additionally, a history, physical examination, exercise stress test, echocardiogram, EKG, cardiac biomarkers, CT, MRI, positron emission tomography (PET), coronary calcium scan, angiography, and coronary guidewire sensor technology will be informative.

Treatment focuses on preventing myocardial infarction by reducing modifiable risk factors through the same strategies used to treat dyslipidemia and atherosclerosis—dietary changes, tobacco cessation, physical activity, weight reduction, stress reduction, diabetes management, hypertension control, angioplasty, bypass procedures, laser procedures, antiplatelet agents, anticoagulants, thrombolytics, and lipid-lowering medications. Additional medications that may be added to the regimen include nitrates, beta-adrenergic blockers, and calcium-channel blockers to vasodilate the coronary arteries and increase the oxygen supply. Ranolazine is one of a

newer class of antianginal medications that works by blocking late inward sodium currents in cardiac cells. The reductions in sodium currents, calcium overload, and diastolic wall stress lead to improved blood flow to the myocardium. Oxygen therapy may also be used to increase oxygen supply.

Thrombi and Emboli

A thrombus is a blood clot composed of platelets, fibrin, erythrocytes, and leukocytes. Such clots can form anywhere in the circulatory system (**TABLE 4-3**). Three conditions—endothelial injury, sluggish blood flow, and hypercoagulability (collectively referred to as "Virchow's triad")—promote thrombus formation (**FIGURE 4-32**). When a vessel wall is injured, the endothelial damage attracts platelets and inflammatory mediators to the site, thereby stimulating clot formation. Stagnant blood flow allows platelets and clotting factors to accumulate and adhere to the vessel wall. Hypercoagulopathy states promote clot formation inappropriately. Venous thrombi are more common than arterial thrombi because the blood in the veins moves more slowly against gravity, the pressure is lower, and valves are present.

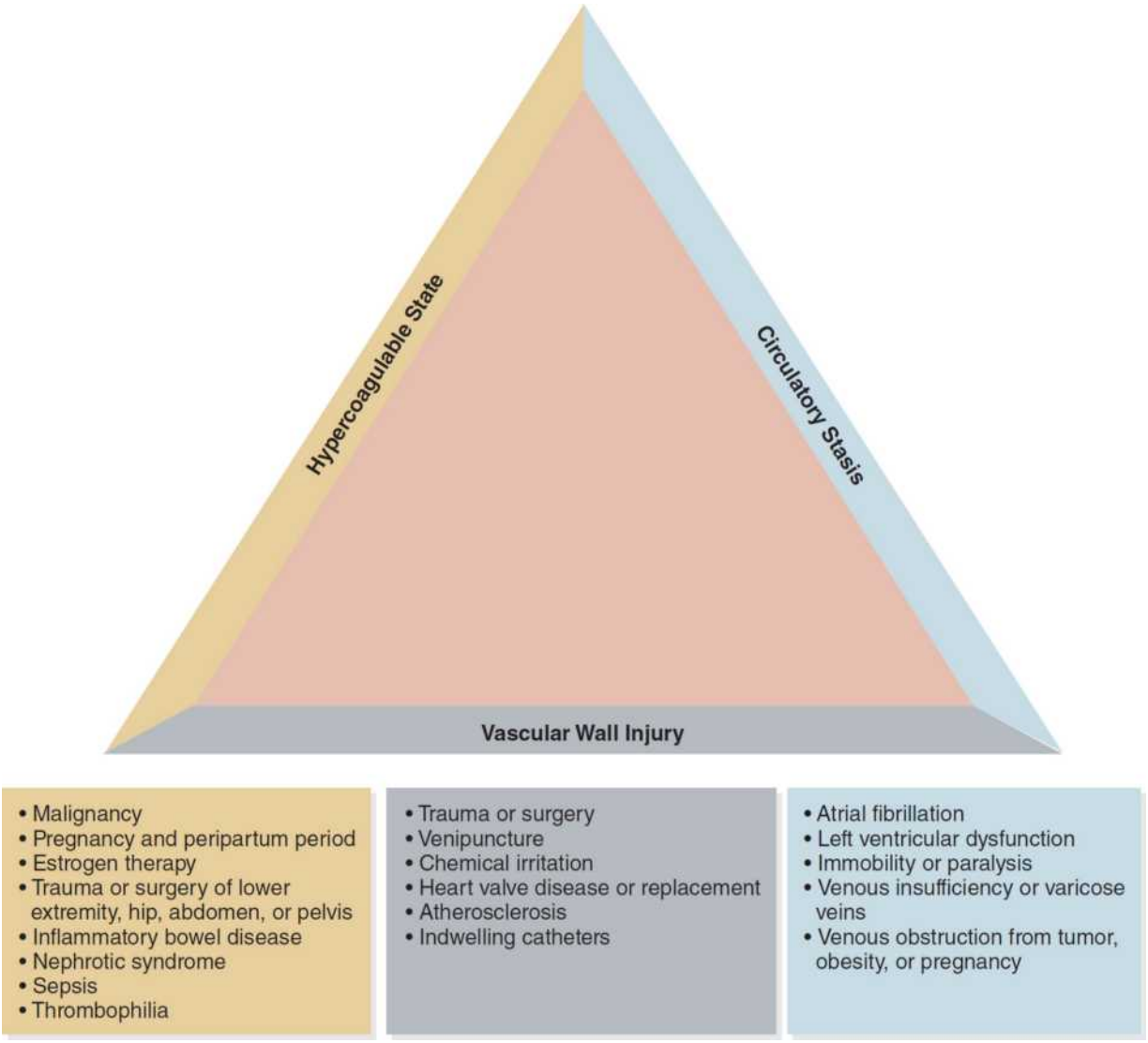


FIGURE 4-32 Virchow's triad.

Description

TABLE 4-3 Comparison of Venous and Arterial Thrombi

Manifestation	Venous Thrombus	Arterial Thrombus
Pulse	Present	Weak or absent
Skin color	Rubor	Cyanotic
Skin temperature	Warm	Cool

Manifestation	Venous Thrombus	Arterial Thrombus
Edema	Present **Venous thrombus**  © James Heilman, MD	Minimal or absent **Arterial thrombus**  © James Heilman, MD

The consequences of thrombus formation may include occlusion of a blood vessel or **embolus** development. An embolus occurs when a portion or all of the thrombus breaks loose and travels through the circulatory system, eventually becoming embedded in a smaller vessel. In addition to thrombi, any other bodies (e.g., air, fat, tissue, bacteria, amniotic fluid, tumor cells, and foreign substances) traveling through the circulatory system can become emboli.

Emboli that originate in the venous circulation, such as with deep vein thrombosis (**FIGURE 4-33**), travel to the right side of the heart and then on to the pulmonary circulation, creating a pulmonary embolism (**FIGURE 4-34**). Most emboli in the arterial system originate in the left side of the heart and travel to other organs such as the brain and heart, causing an infarction.

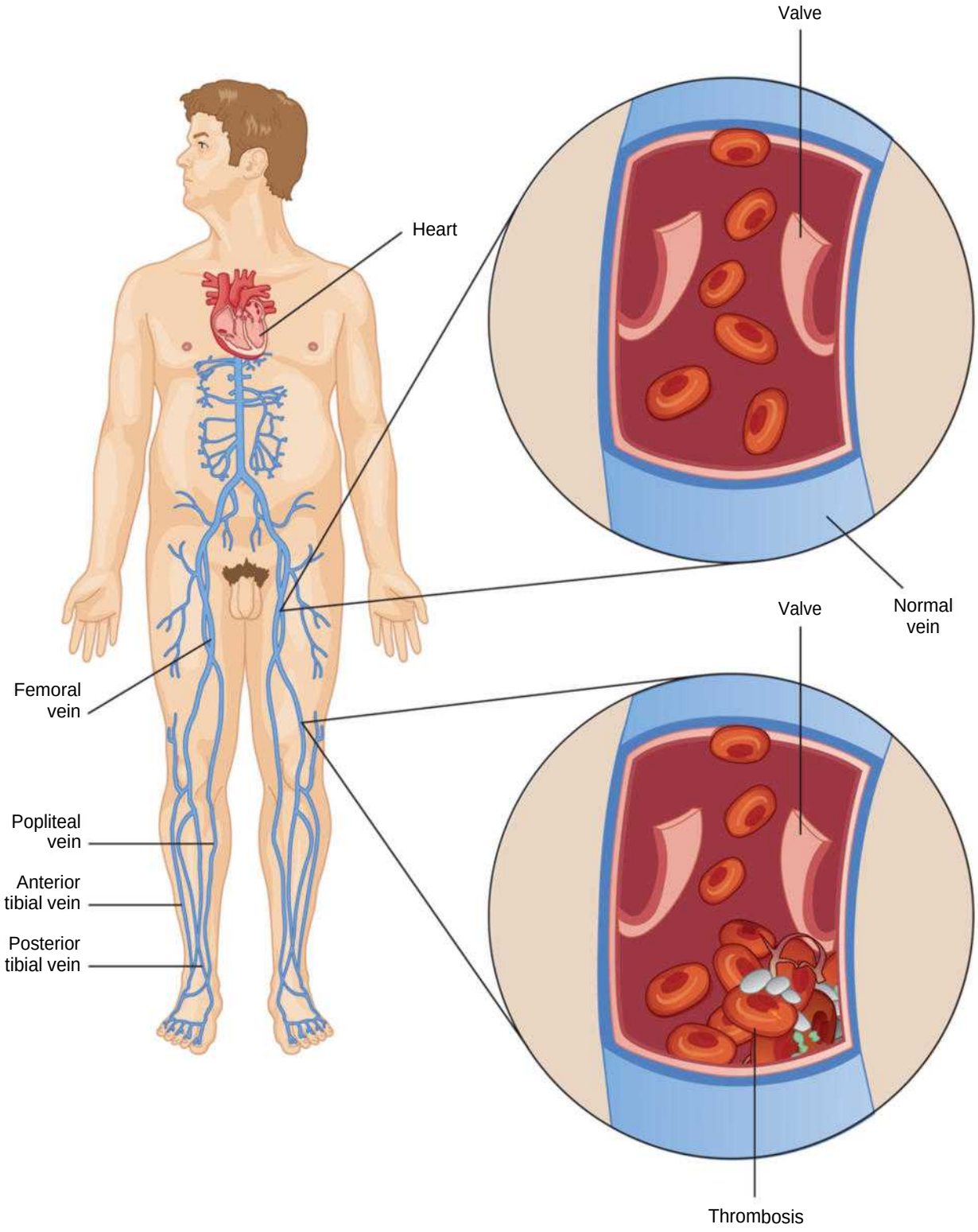


FIGURE 4-33 Deep vein thrombosis.

Description

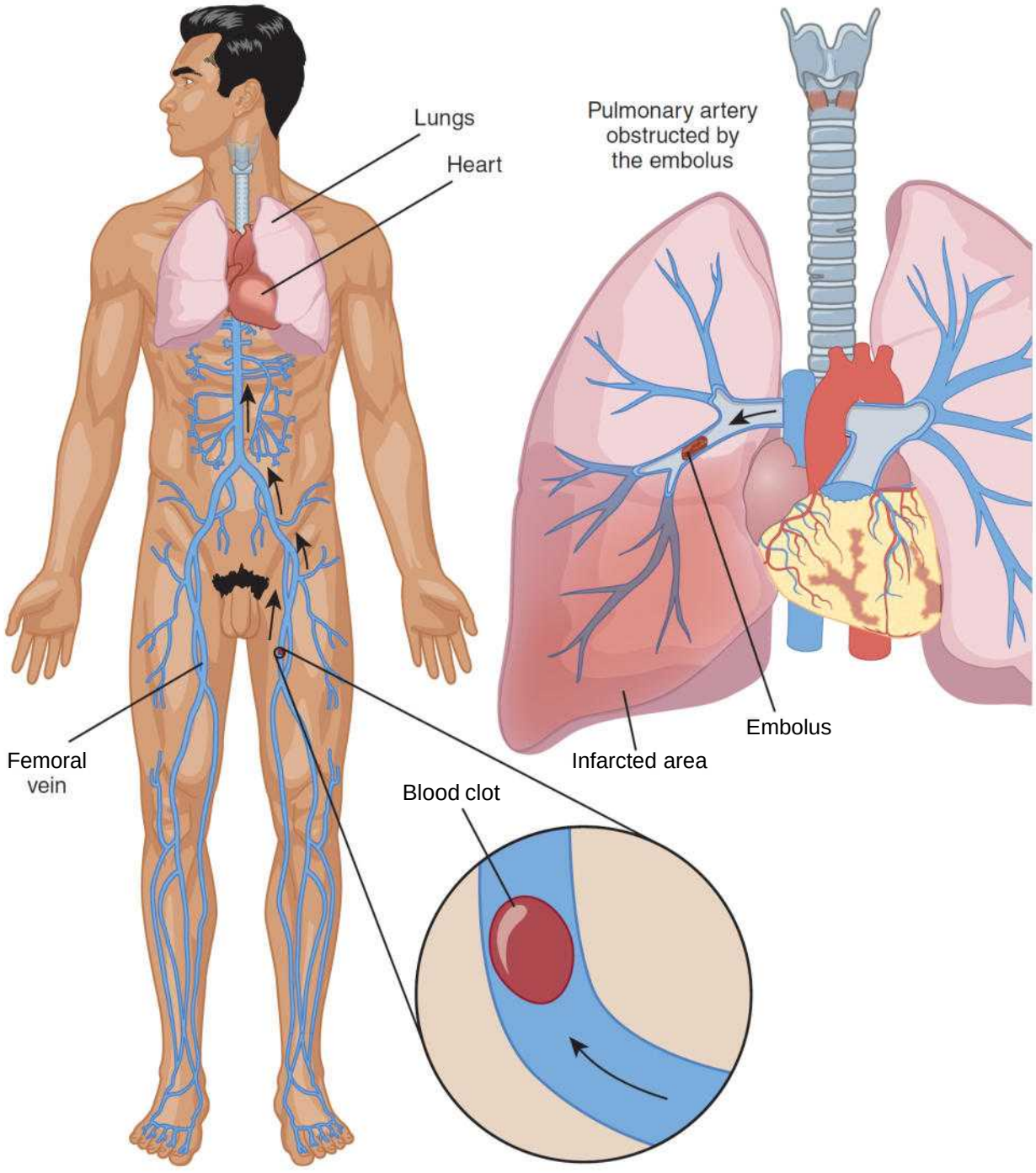


FIGURE 4-34 Pulmonary embolism.

Description

Clinical manifestations of thrombi and emboli depend on whether they are arterial or venous, as well as their location (Table 4-3). Diagnostic procedures include venous or arterial angiography (CT or

MRI), Doppler ultrasound, photoplethysmography, and echocardiogram.

Treatment of thrombi and emboli centers on prevention; thus, it includes increasing mobility, hydration, antiembolism hosiery, sequential compression devices, and medications (e.g., antiplatelet agents and anticoagulants). In the presence of active thrombi, these prevention strategies may be dangerous and should be avoided. For example, mobility and sequential compression devices may dislodge a stationary clot. Treatment of active thrombi may include anticoagulants, thrombolytic agents, or embolectomy. Once the thrombi have been treated, the prevention strategies should recommence.

Varicose Veins

Varicose veins, or varicosities, are dilated, tortuous, engorged veins that develop because of improper venous valve function (**FIGURE 4-35**). They are most commonly found in the legs but can also occur in the esophagus (esophageal varices), rectum (hemorrhoids), and testicles (varicoceles). Varicose veins are usually greater than 3 mm in diameter. Telangiectasias, also referred to as “spider veins,” are dysfunctional veins that are less than 1 mm, and reticular veins are those that are 1 to 3 mm in diameter.

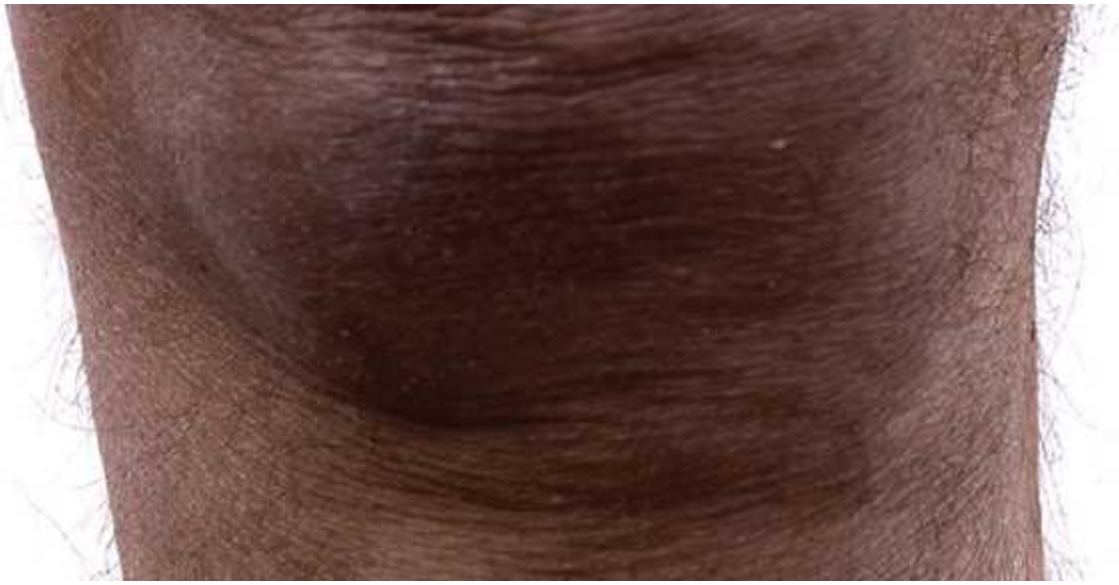




FIGURE 4-35 Varicose vein.

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Varicose veins occur when increased venous pressure and blood pooling cause the veins to enlarge, stretching the valves. The valves become incompetent, blood flow is reversed, and venous pressure and distention are further increased. Capillary pressure increases, causing fluid and pigment to leak out, leading to edema and skin discoloration. As a result, stasis pigmentation (brown skin discoloration), subcutaneous induration (thick, hardened skin), dermatitis (skin inflammation), and thrombophlebitis (vein inflammation resulting from a thrombus) can occur. The pressure caused by the edema can decrease circulation, resulting in metabolic needs not being met. Failure to meet cellular oxygen and nutrient needs can, in turn, lead to necrosis and venous stasis ulcers.

The following factors increase a person's risk of developing varicosities:

- Genetic predisposition
- Pregnancy
- Obesity
- Prolonged sitting or standing
- Alcohol abuse and liver disorders (esophageal varices)
- Constipation (hemorrhoids)

Clinical manifestations are usually minor and include the following signs and symptoms:

- Irregular purplish bulging veins
- Pedal edema
- Fatigue
- Aching in the legs
- Shiny hairless pigmented skin on the legs and feet
- Skin ulcer formation

Diagnosis of varicosities is usually accomplished through visualization during physical examination. Additional tests may include duplex ultrasound, photoplethysmography, and venogram. Treatment

ranges from conservative to invasive and includes the following measures:

- Rest with the affected leg elevated
- Compression stockings
- Avoiding prolonged standing or sitting
- Exercise
- Endovenous ablation to close off a varicose vein
- Sclerotherapy (injection of a sclerosing agent that produces fibrosis inside the vessel)
- Surgical removal

Lymphedema

Lymphedema refers to swelling, usually in the arms and legs, because of lymph obstruction (**FIGURE 4-36**). This swelling can occur on its own (primary) or because of another disease or condition (secondary). Primary lymphedema is a rare condition related to a congenital absence or decreased number of lymphatics. Secondary lymphedema is usually related to one of the following events:





FIGURE 4-36 Lymphedema.

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- Surgery (when lymph nodes and lymph vessels are removed or severed, as with a mastectomy)
- Radiation (causes scarring and inflammation of lymph nodes or lymph vessels, restricting the flow of lymph fluid)
- Cancer (occludes lymphatic vessels)
- Infection (can infiltrate lymph vessels and lymph nodes, restricting the flow of lymph fluid)
- Injury (damages lymph nodes or lymph vessels)

Lymphedema can start within a few months of injury, but it most often starts about 1 to 2 years later. Clinical manifestations of lymphedema include edema and skin changes. A staging system is used to describe the severity of the lymphedema. The edema may be unilateral or bilateral, and it usually occurs in the extremities. Skin changes include hyperpigmentation, ulceration, and thickening (referred to as brawny edema). The skin begins to appear like elephant skin, thick and rough.

Diagnostic procedures consist of a physical examination, lymphoscintigraphy, MRI, CT, Doppler ultrasound, bioimpedance spectroscopy, and nuclear imaging. Treatment of lymphedema includes the following measures:

- Sequential compression devices
- Compression stockings
- Exercise
- Manual lymph drainage (complex decongestive physiotherapy)
- Antibiotics (to treat existing infections)
- Benzopyrone agents (to increase lymphatic flow)
- Diuretics (to remove excess fluid as it returns to the circulatory system)
- Surgery (e.g., lymph node transfer, lympho-venous bypass, liposuction, or skin removal)

Myocardial Infarction

Myocardial infarction (MI) is the death of the myocardium from a sudden blockage of coronary artery blood flow (**FIGURE 4-37**; **FIGURE 4-38**). This blockage, which exemplifies the nursing diagnosis of ineffective tissue perfusion, may be caused by atherosclerosis, thrombus, or vasospasm. In most cases, tears in the plaque buildup associated with atherosclerosis trigger platelet aggregation and cause a thrombus to form. As a result of the occlusion, the myocardial oxygen supply cannot meet the body's demand for oxygen. An MI occurs in **progressive stages** as the

blood flow to the myocardium decreases. Cells die as their coronary blood and oxygen supplies dwindle. This death may occur gradually or suddenly, depending on the time frame in which the occlusion develops. The trigger for the MI is not always known, but such events may occur after physical exertion, while sleeping or resting, during outside activity in cold weather, and with severe emotional stress.

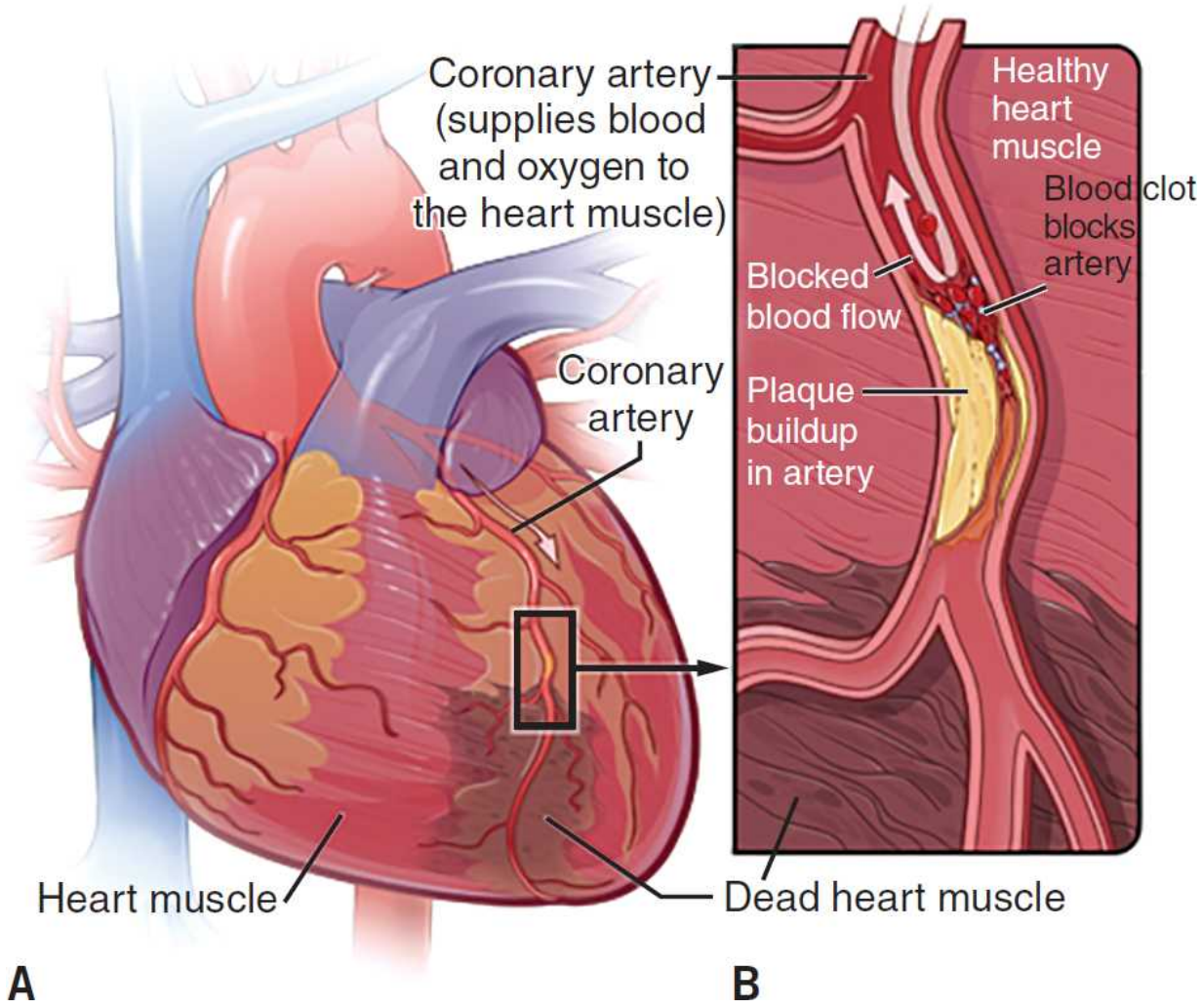


FIGURE 4-37 Myocardial infarction. **(A)** An overview of a heart and coronary artery showing damage (dead heart muscle) caused by a heart attack. **(B)** A cross-section of the coronary artery with plaque buildup and a blood clot.

Reproduced from National Heart, Lung, and Blood Institute. (2015). What is a heart attack? Retrieved from http://www.nhlbi.nih.gov/health/health-topics/topics/heartattack/

Description



A



B

FIGURE 4-38 Myocardial infarction. **(A)** Sectioned heart showing myocardial infarction of the posterior left ventricle. **(B)** Severely occluded coronary artery with calcification from an elderly woman with a fatal myocardial infarction.

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Description

Other names for MI include “heart attack” and “acute coronary syndrome.” Risk factors for such an event include the same risk factors as for atherosclerosis—for example, dyslipidemia, diabetes mellitus, hypertension, stress, and tobacco use. Cardiovascular disease (including CAD) is the leading cause of death in the United States (about 300,000 to 400,000 people annually), and death usually results from cardiac damage after an MI. Prognosis improves with early and aggressive treatment.

Some people do not experience symptoms of MI. Such an asymptomatic MI is known as a silent MI. Silent MIs generally occur in persons who have diabetes mellitus, neurologic dysfunction (e.g., neuropathy), or history of an MI because of decreased pain innervations. When clinical manifestations are present, they include the following signs and symptoms:

- Unstable angina (typically described as pressure or tightness in the arms, shoulder, neck, teeth, jaw, abdomen, or back that may radiate to other locations)
- Fatigue
- Nausea and vomiting
- Shortness of breath
- Coughing
- Diaphoresis
- Indigestion
- Elevation in cardiac biomarkers
- EKG changes (**FIGURE 4-39**)

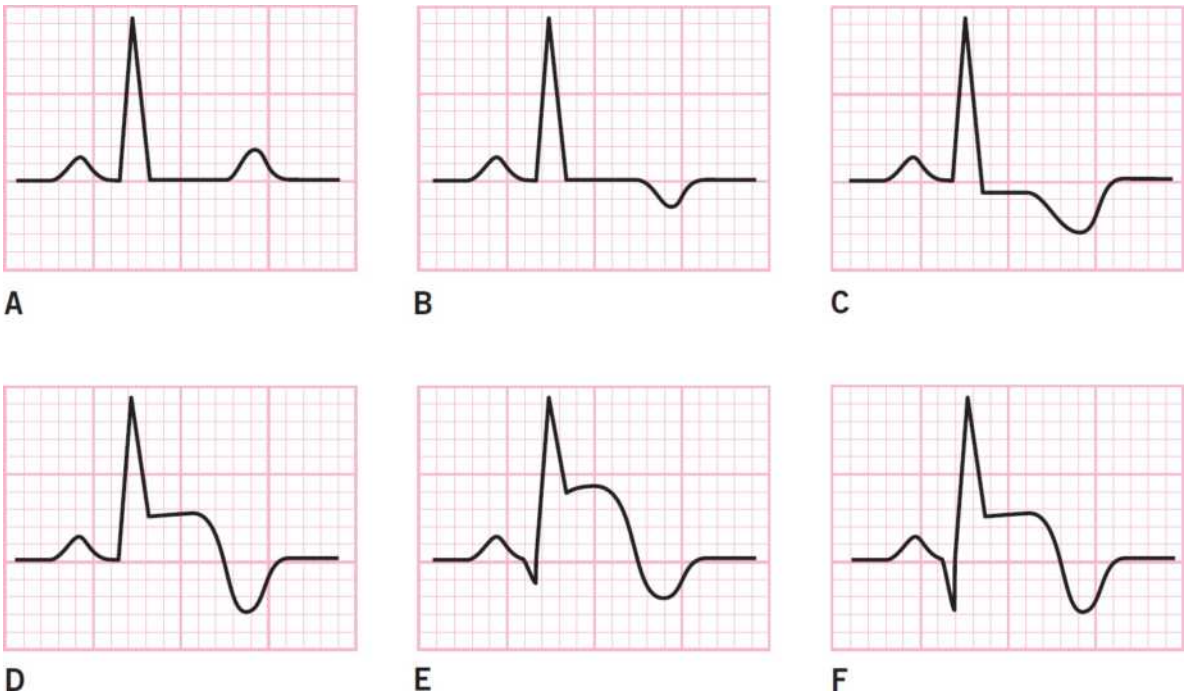


FIGURE 4-39 EKG ischemia and infarction patterns. **(A)** Normal EKG for comparison. **(B)** Mild ischemia demonstrated by inverted T wave. **(C)** Moderate ischemia demonstrated by slight ST-segment depression and inverted T wave. **(D)** and **(E)** ST-segment elevation myocardial infarction. **(F)** ST-segment myocardial infarction with prominent Q wave indicating more severe myocardial damage.

Modified from *Introduction to 12-Lead ECG: The art of interpretation*, courtesy of Tomas B. Garcia, MD.

Description

- Dysrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, and asystole)
- Anxiety
- Syncope
- Dizziness
- Sleep disturbance

Complications are more likely to occur when MIs are not treated early and aggressively. Those complications may include heart failure, dysrhythmias, cardiac shock, thrombosis, and death.

Diagnostic procedures for MIs consist of a history, physical examination, EKG, cardiac biomarkers (specifically the troponins) (**FIGURE 4-40**), stress testing, nuclear imaging, and angiography. Previously, all cardiac biomarkers were used to identify the presence of myocardial ischemia. Currently, the most important cardiac biomarkers involved in the diagnosis of an acute MI are troponin C (TnC), troponin I (TnI), and troponin T (TnT) (Park et al., 2017). The troponins have been found to be highly specific and sensitive to cardiac damage. Treatment is complex and depends on when the individual sought treatment (**FIGURE 4-41**). Prognosis hinges on initiating treatment early—ideally within 90 minutes of symptom onset. After that point, treatment options and ability to reverse damage become limited.

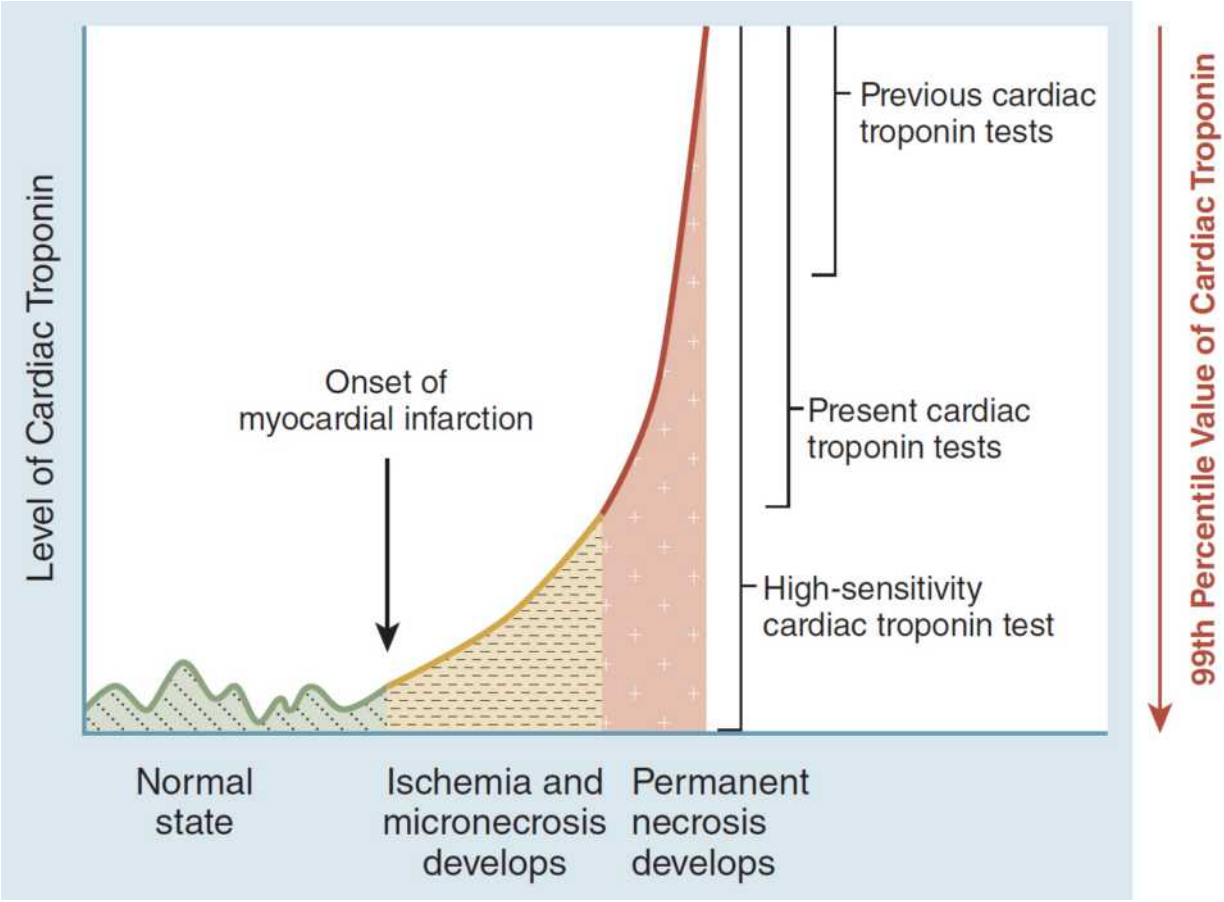
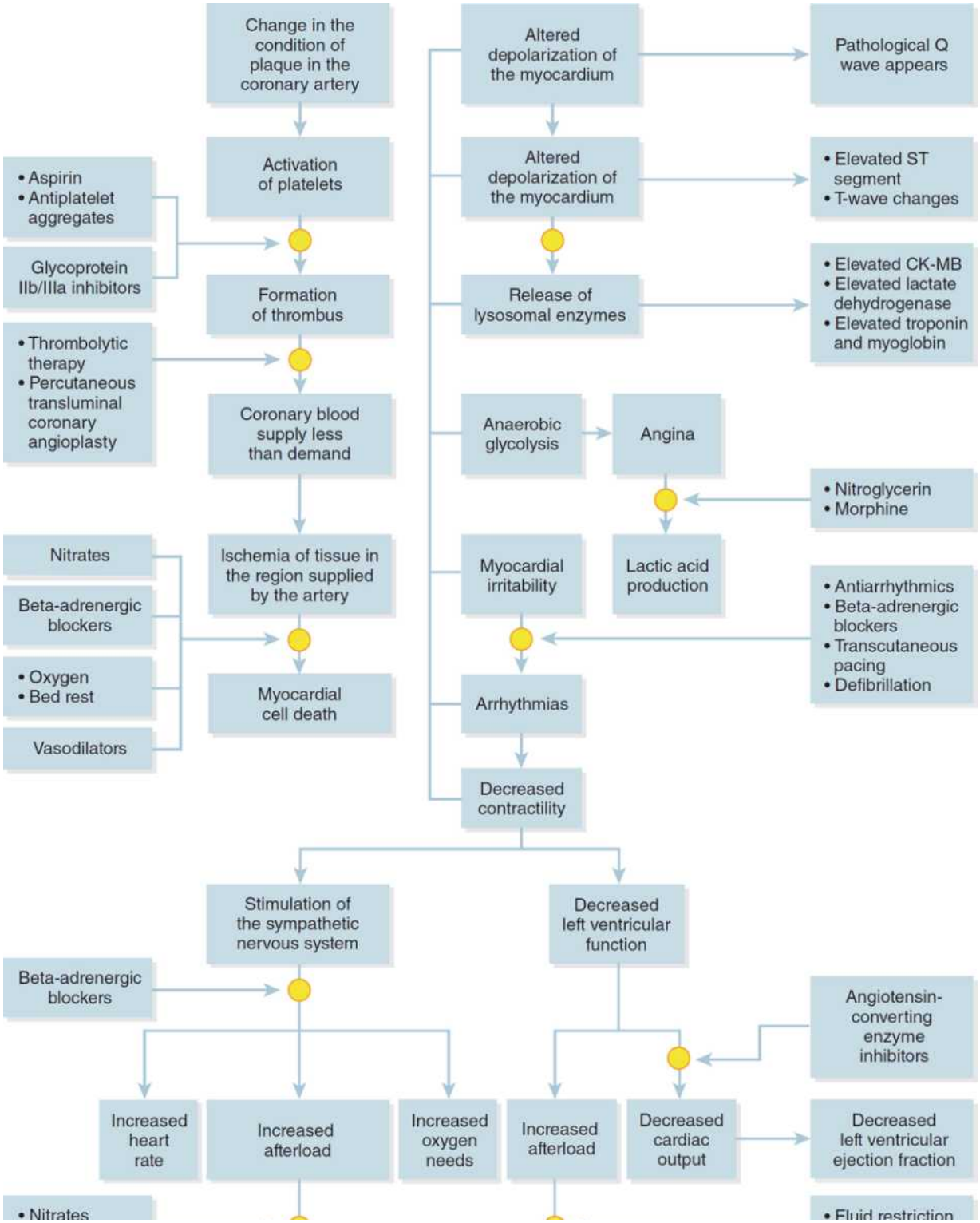


FIGURE 4-40 Cardiac biomarkers.

Data from Hochholzer W, Morrow DA, Giugliano RP. Novel biomarkers in cardiovascular disease: update 2010. Am Heart J 2010;160:583–594

Description



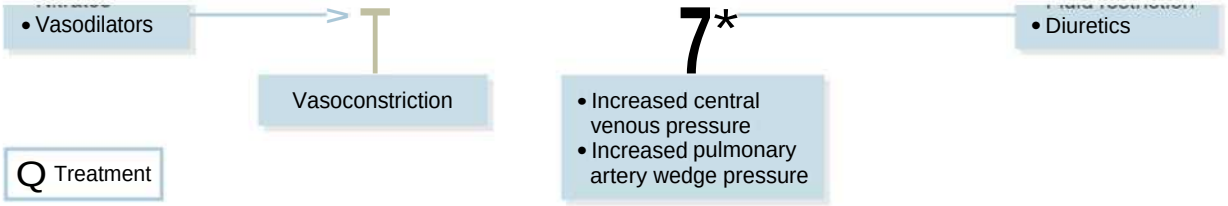


FIGURE 4-41 Treating a myocardial infarction.

Modified from *Introduction to 12-lead ECG: The art of interpretation*, courtesy of Tomas B. Garcia, MD.

Description

If a patient survives the MI, it is vital that the individual takes steps to prevent another MI through lifestyle modifications and other measures to treat atherosclerosis. Those measures may include dietary changes, tobacco cessation, physical activity, weight reduction, stress reduction, diabetes management, hypertension control, angioplasty, bypass procedures, laser procedures, antiplatelet agents, anticoagulants, thrombolytics, and lipid-lowering medications.

Conditions Resulting in Decreased Cardiac Output and Ineffective Tissue Perfusion

Hypertension

Hypertension is a prolonged elevation in blood pressure. It is one of the most prevalent chronic health conditions in the United States, affecting approximately 1 in 3 U.S. adults, or 75 million Americans (Merai et al., 2016). Only about half (54%) of these people have their hypertension under control. Although this condition was once rarely seen in younger populations, many youth are now being diagnosed because of increasing obesity in this age group. Hypertension is the leading risk factor for cardiovascular disease (e.g., CAD, MI, heart failure, and stroke). In hypertension, the heart must work harder than normal to pump the blood to all the parts of the body, in part due to vasoconstriction that increases afterload. This vasoconstriction results in decreased renal blood flow, resulting in inappropriate activation of the renin–angiotensin–aldosterone system, which further elevates blood pressure levels (**FIGURE 4-42**).

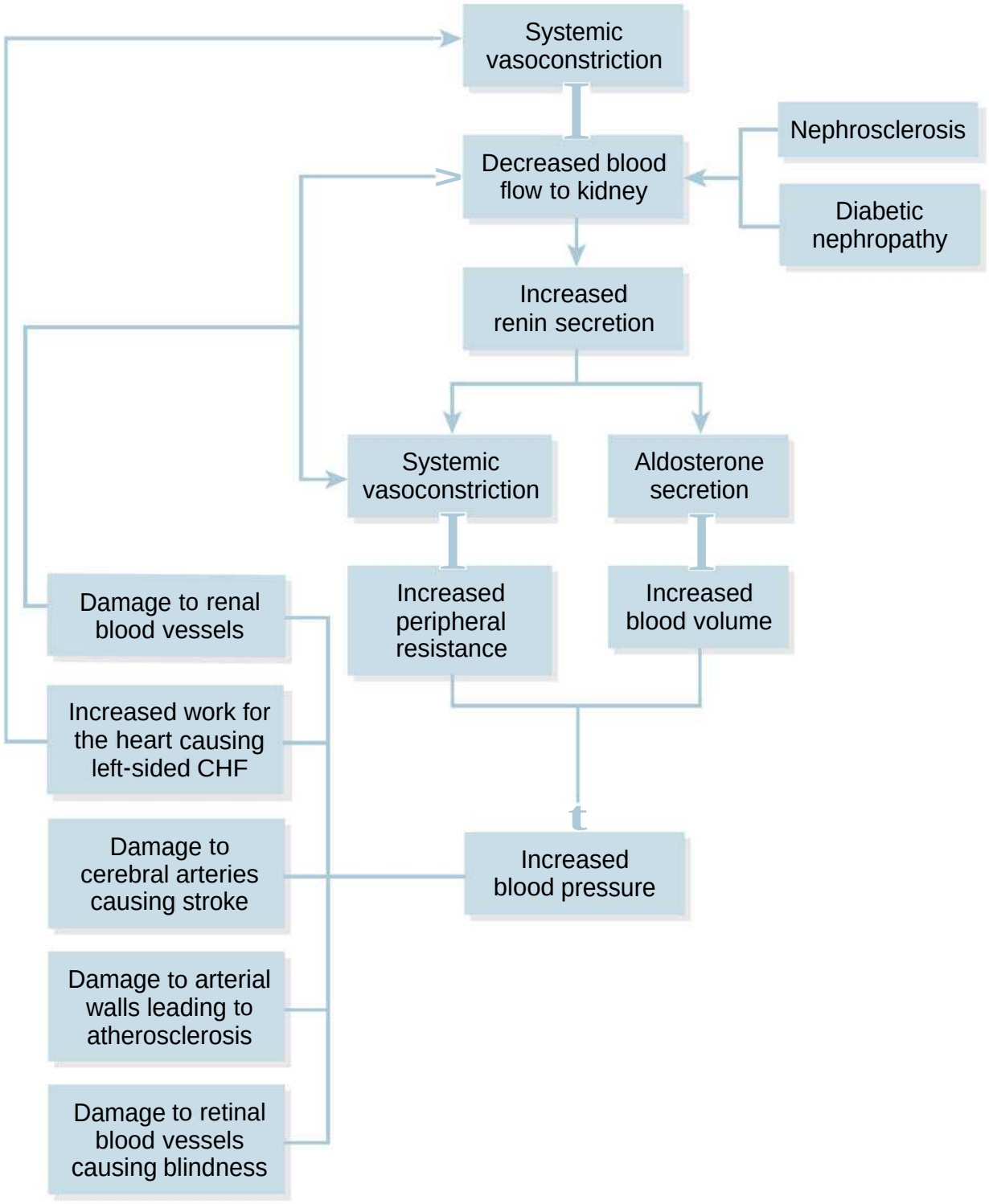


FIGURE 4-42 Development of hypertension.

Description

A new classification scheme for blood pressure has been developed to provide guidelines for classifying blood pressure levels in children, adolescents, and adults, as well as treatment based on those classifications (Flynn et al., 2017; Whelton et al., 2018). For years, hypertension was classified as a blood pressure reading of 140/90 mm Hg in adults, but the new guidelines define it as 130/80 mm Hg. In children and adolescents, diagnosing hypertension is more complicated. Factors such as age, body mass index, and gender must be considered. Additionally, the harm associated with elevated blood pressure and treatments must be weighed against the benefits from such therapy.

Risk factors for developing hypertension include the following:

- Age: Vessel compliance decreases with aging. Through early middle age, high blood pressure is more common in men, whereas women are more likely to develop high blood pressure after menopause.
- Race: Hypertension is more prevalent in African Americans.
- Family history: Many gene variations have been associated with slightly increased risk. New research suggests that certain DNA changes during fetal development may lead to hypertension later in life.
- Overweight or obesity: Excessive weight amplifies oxygen and nutrient needs; when the circulating blood volume increases to meet these greater needs, the increased volume exerts greater pressure on the artery walls.
- Physical inactivity: A sedentary lifestyle increases heart rate, which increases cardiac workload.
- Tobacco use: Ingestion of nicotine immediately raises blood pressure temporarily, and the chemicals in tobacco can damage artery walls over time.
- High-sodium diet: Too much sodium causes fluid retention, which increases blood pressure. Additionally, some individuals have a high sensitivity to sodium. This sensitivity can have a family tendency, and it is more common in African Americans, older adults, people

with elevated blood pressure, and people with chronic kidney disease, diabetes mellitus, or metabolic syndrome.

- Low-potassium, -calcium, and -magnesium diet: Potassium helps balance the amount of sodium in cells; without enough potassium, too much sodium accumulates in the blood. Deficient magnesium has a pseudo-potassium effect. Calcium controls vascular tone; calcium deficiency causes vasoconstriction.
- High vitamin D intake: This factor has an uncertain effect, though vitamin D may affect the renin–angiotensin–aldosterone system.
- Excessive alcohol consumption: Over time, heavy drinking—that is, more than two to three drinks in one sitting—can damage the heart.
- Stress: High levels of stress can lead to a temporary, but dramatic, increase in blood pressure.

Hypertension is divided into two major forms—primary and secondary. In most hypertension cases in adults (95%), there is no identifiable cause. This type of hypertension, called **primary hypertension** or **essential hypertension**, tends to develop gradually over many years. An underlying condition causes other cases of hypertension. This type of hypertension, called **secondary hypertension**, tends to appear suddenly and cause higher blood pressure than does primary hypertension. A variety of conditions and medications can lead to secondary hypertension:

- Renal disease (e.g., renal artery stenosis, polycystic kidney disease, and diabetic nephropathy)
- Diabetes mellitus
- Adrenal gland tumors
- Sleep apnea
- Endocrine disorders (e.g., Cushing syndrome, thyroid dysfunction, and hyperparathyroidism)
- Certain congenital heart defects (e.g., coarctation of the aorta)

- Certain medications (e.g., birth control pills, hormone replacement therapy, antihistamines, decongestants, and glucocorticoid steroids)
- Illegal drugs (e.g., cocaine and amphetamines)

Occasionally, hypertension is classified as systolic or diastolic, depending on which measurement is elevated. Often, elderly persons have higher systolic readings and lower diastolic readings because of aging-related changes. Diastolic hypertension is more common in younger individuals.

Hypertension can also occur during pregnancy, in which case it is referred to as **pregnancy-induced hypertension (PIH)**, toxemia, or preeclampsia. Indicators of this condition include high blood pressure, proteinuria, and edema. PIH can worsen, leading to **eclampsia**. In eclampsia, seizures often occur because of the increased blood pressure. Risk factors for developing PIH include a history of PIH, renal disease, diabetes mellitus, multiple fetuses, and maternal age younger than 20 years or older than 40 years. PIH can lead to multiple problems, including miscarriages, poor fetal development, and placental abruption. Management focuses on prevention and nonpharmacologic measures to protect the fetus. Treatment measures include bed rest and magnesium sulfate (to prevent seizures).

Hypertension is called the silent killer because many people do not have symptoms. Often by the time symptoms become evident, the hypertension is advanced or the blood pressure is remarkably high. When present, clinical manifestations include fatigue, headache, malaise, and dizziness.

Hypertension causes excessive pressure on artery walls, which damages blood vessels and organs. The higher the blood pressure and the longer it goes uncontrolled, the greater the damage. Uncontrolled high blood pressure can lead to numerous complications:

- Atherosclerosis
- Aneurysms
- Heart failure

- Stroke
- Hypertensive crisis (a severe increase in blood pressure that is a medical emergency)
- Renal damage
- Vision loss
- Metabolic syndrome (a cluster of disorders of metabolism—including increased waist circumference, high triglycerides, low HDL, high blood pressure, high blood glucose levels, and insulin resistance)
- Vascular dementia

The prognosis for persons with hypertension depends on treating any underlying causes and maintaining blood pressure control. Early detection and treatment are crucial to prevent or minimize complications. Measures to diagnose hypertension include a history, physical examination, multiple blood pressure readings at varying times of the day, EKG, and laboratory tests (e.g., urinalysis, CBC, chemistry panel, lipid panel, a creatinine test, and thyroid profile) to determine the presence of complications. Starting at 3 years of age, blood pressure readings should be measured by a healthcare provider at least annually.

The diagnosis of hypertension is based on accurate blood pressure measurement and repeated high readings (i.e., two or more readings at separate medical appointments ≥ 130/80 mm Hg in adults). However, it can also be diagnosed at an initial screening if the blood pressure is ≥ 160/100 mm Hg with target end-organ damage or if the blood pressure is ≥ 180/120 mm Hg. Hypertensive urgency describes a state in which the blood pressure is ≥ 180/120 mm Hg in an individual who is relatively asymptomatic and there is no evidence of end-organ damage. Hypertensive crisis, also referred to as a "hypertensive emergency" and formally referred to as **malignant hypertension**, describes a state in which the blood pressure is ≥ 180/120 mm Hg in an individual who is symptomatic and/or has evidence of end-organ damage. Often these excessively high blood pressures are difficult to treat. It is not recommended to decrease

the blood pressure too fast or too much because ischemic damage can occur to tissue and organs that have become accustomed to the elevated levels.

Treating any underlying causes of hypertension and maintaining blood pressure control are essential in preventing or minimizing cardiovascular risks and complications. Treatment of hypertension is based on previously mentioned guidelines, and adhering to the protocol will increase the likelihood of successful blood pressure control. Lifestyle changes are the mainstay of prevention and treatment; these changes can be implemented in those individuals at risk for developing hypertension. Dietary changes are the cornerstone of these lifestyle changes and include the Dietary Approaches to Stop Hypertension (DASH) diet (NIH, 2021). The research-driven DASH diet includes the following recommendations:

- Limiting saturated fat, cholesterol, total fat, and salt
- Focusing on fruits, vegetables, and fat-free or low-fat dairy products
- Increasing consumption of whole grains, fish, poultry, beans, seeds, and nuts
- Minimizing sweets, added sugar and sugary beverages, and red meats

Limiting salt consumption to 2,300 mg (less than a teaspoon) per day has been shown to lower blood pressure. Further restricting salt intake to 1,500 mg per day can lower blood pressure to an even greater extent. The 1,500 mg restriction is advised for individuals diagnosed with hypertension, diabetes mellitus, and chronic kidney disease as well as African Americans, middle-aged individuals, and older adults. Following these guidelines, particularly the salt recommendations, can significantly decrease the risk of developing hypertension.

Other lifestyle changes that can help prevent or treat hypertension include being active, maintaining a healthy weight, smoking cessation, stress management, and alcohol consumption (if used) in moderation. Additionally, individuals should have their blood pressure measured

regularly with a home monitor and by healthcare professionals. These readings should be documented in a blood pressure journal (including the blood pressure reading, date, time of day, activities just before the reading, and any symptoms) and brought to visits with the healthcare provider to compare readings.

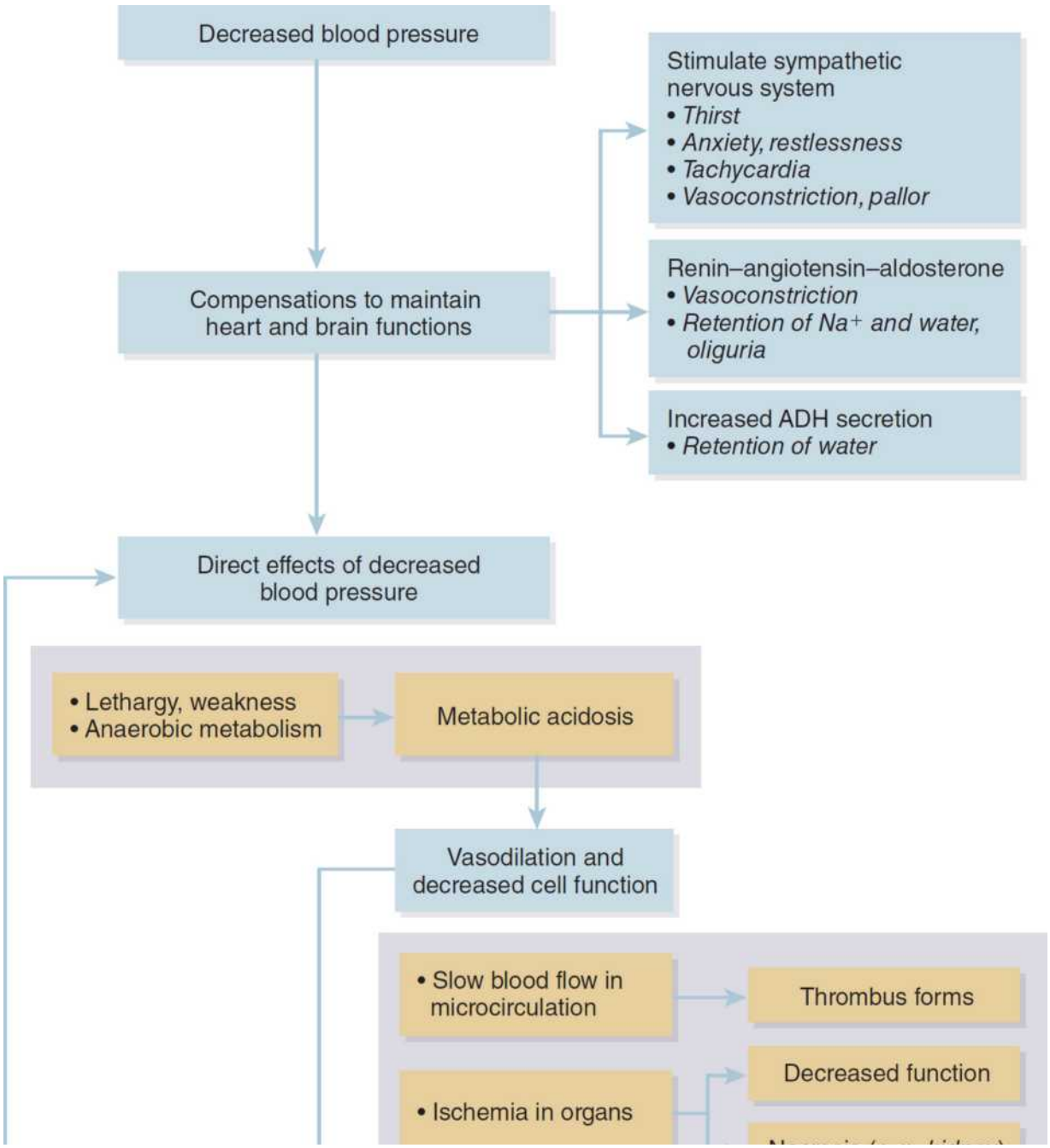
When lifestyle changes alone are not effective, or the blood pressure is markedly high, numerous pharmacologic agents are used to treat hypertension. Diuretics are generally the initial drug therapy; thiazide or thiazide-type diuretics are preferred in patients with hypertension only, and loop diuretics are preferred if heart failure is present. ACE inhibitors, angiotensin-receptor blockers, calcium-channel blockers, and direct renin inhibitors can also be used, albeit not in combination with each other. Other pharmacologic agents may include beta blockers, alpha-1 blockers, and centrally acting drugs.

Shock

Shock is a clinical syndrome resulting from inadequate tissue and organ perfusion because of decreased blood volume or circulatory stagnation. Shock occurs because of a pumping issue with the heart (e.g., decreased myocardial contractility), a vascular problem getting blood to or away from the heart (e.g., massive vasodilation), insufficient blood volume (e.g., insufficient intake or excessive loss), or a combination of these conditions. Shock can be classified into four categories based on its precipitating factors: distributive (includes neurogenic, septic, and anaphylactic), cardiogenic, obstructive, and hypovolemic.

Shock progresses through three stages that are common to all types of shock—compensatory, progressive (i.e., decompensated), and irreversible (i.e., refractory). Compensatory mechanisms are bodily responses that become activated when arterial pressure and tissue perfusion decrease; they represent the body's attempt to maintain cardiac and cerebral function. These compensatory mechanisms include the activation of the SNS and renin–angiotensin–aldosterone system. The progressive stage of shock begins when these compensatory mechanisms fail to maintain cardiac output.

Tissues become hypoxic, cells switch to anaerobic metabolism, lactic acid builds up, and metabolic acidosis develops. This acidotic state further impairs cardiac functioning, causing sluggish blood flow, and increases the risk for disseminated intravascular coagulation (see the *Hematopoietic Function* chapter). Irreversible organ damage occurs as the shock progresses, leading to respiratory and cardiac failure (**FIGURE 4-43**).



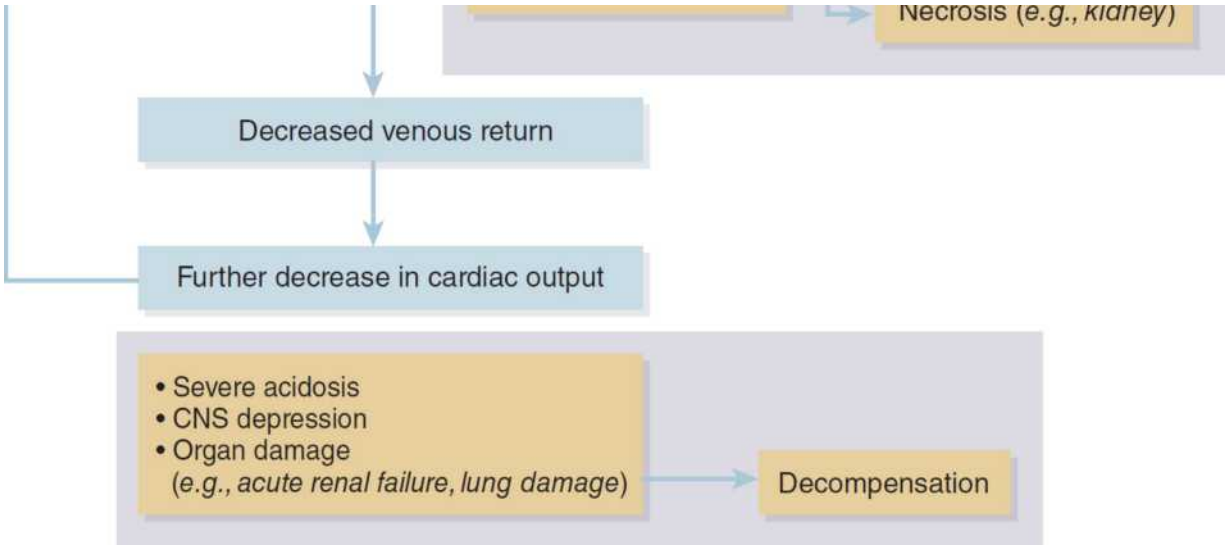


FIGURE 4-43 Progression of shock.

Description

Learning Points

Low-Salt Diet

Cutting back on salt intake can be challenging on many levels. First, eating increased amounts of salt over time decreases taste sensation on the tongue, such that foods without it will lack flavor initially. Those taste buds will wake up again in a short time, and gradually decreasing salt intake may help with this transition. For instance, have patients start by not adding salt to food once it is prepared, and then begin changing how food is prepared.

Second, salt is used in many foods of convenience as a preservative. In today's fast-paced society, these foods have become commonplace and almost a necessity. Unfortunately, processed foods (e.g., canned food, boxed meals, frozen dinners, and sandwich meats) usually contain large amounts of salt. Additionally, salt is often added to meats to preserve them, even when those meats are already naturally high in salt (e.g., pork).

Third, the practice of eating outside the home in a wide range of restaurants has increased. Salt content is difficult to control when others are preparing the food.

Finally, salt is hidden in many seasonings and condiments. As people attempt to move away from salt, they may turn to these seasonings and condiments to enhance flavor—but these items may be just as bad as using salt. Seasonings that have "salt" in their name have salt in their contents (e.g., season salt, garlic salt, and onion salt). Condiments such as hot sauce and mustard also have high salt content.

The following recommendations can help patients cut back on salt and avoid foods with hidden salt content:

- Eat at home, using fresh foods as much as possible.

- Attempt to purchase foods on the perimeter of the grocery store (where the fresh foods can be found) and avoid items in the center (where most of the processed foods can be found).
- Limit consumption of pork and cured meats.
- Use seasonings that are salt free or MSG free (e.g., garlic powder, onion powder).
- Read the labels of all products, paying attention to the sodium (salt) content and serving sizes.

In **distributive shock**, vasodilation causes hypovolemia. Three types of distributive shock are distinguished—neurogenic, septic, and anaphylactic. A loss of sympathetic tone in vascular smooth muscle and autonomic function lead to massive vasodilation in **neurogenic shock**. Blood pools in the venous system, leading to decreased venous return, cardiac output, and blood pressure. Neurogenic shock is often a result of central nervous system damage, usually the spinal cord. It is the most difficult type of shock to treat, especially if permanent spinal cord damage is the cause.

In **septic shock**, a bacterium's endotoxins activate an immune reaction. Inflammatory mediators are triggered, increasing capillary permeability and causing fluid shifts from the vascular compartment to the tissues. Falling cardiac output then leads to multisystem organ failure. Common causes of septic shock are infections with bacterial species, specifically gram-negative bacteria (e.g., *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter*). Gram-positive bacteria (e.g., pneumococci, staphylococci, streptococci) infections may also cause sepsis but are less likely to lead to shock in comparison to gram-negative infections. Other organisms that less frequently cause septic shock are fungal (e.g., *Candida albicans*, *Candida glabrata*, *Aspergillus*) and viral (e.g., *Cytomegalovirus*, influenza A and B) pathogens.

Anaphylactic shock is a consequence of an allergic reaction, usually to food, insect venom, medications, or latex. The allergic reaction leads to a cascade of events similar to those of septic shock, except that the mediators differ (see the *Immunity* chapter). Additionally, bronchospasm and laryngeal edema occur and can impair respiratory status.

Obstructive shock occurs when the blood is physically blocked in the large vessels or the heart. This blockage may be a result of thrombi, aortic stenosis, or a condition that causes an accumulation of air or fluid in the chest cavity (e.g., pneumothorax, hemothorax, or cardiac tamponade).

Cardiogenic shock results from the left ventricle's inability to maintain adequate cardiac output. This type of shock may occur because of myocardial damage (e.g., cardiomyopathy, heart failure, valve disorder, or myocardial infarction) or arrhythmias (e.g., tachycardias or bradycardias). Cardiogenic shock has the highest mortality rate. Compensatory mechanisms of heart failure are triggered, but these mechanisms increase cardiac workload and oxygen consumption, resulting in decreased contractility. Consequently, tissue and organ perfusion decreases, leading to multisystem organ failure.

Hypovolemic shock is the most common type of shock. In hypovolemic shock, venous return declines because of external blood volume losses. These losses may be a result of hemorrhage, vomiting, diarrhea, burns, diabetic ketoacidosis, or diabetes insipidus. Preload drops, decreasing ventricular filling and stroke volume. As cardiac output falls, tissue and organ perfusion decreases.

Clinical manifestations of shock reflect the decreased cardiac output and ineffective tissue perfusion but may vary depending on the type of shock. General manifestations include the following signs and symptoms:

- Thirst and dry mucous membranes
- Tachycardia (except for neurogenic shock)
- Thready pulse
- Restlessness, anxiety, and irritability
- Tachypnea progressing to Cheyne-Stokes respirations
- Cool, pale skin
- Hypotension
- Cyanosis

- Confusion
- Dizziness and syncope
- Decreased urinary output (i.e., < 30 mL/hr)
- Hyperlactatemia
- Metabolic acidosis

Complications of shock can be serious and include the following conditions:

- Acute respiratory distress syndrome (see the *Respiratory Function* chapter)
- Renal disease (see the *Urinary Function* chapter)
- Disseminated intravascular coagulation (see the *Hematopoietic Function* chapter)
- Cerebral hypoxia
- Death

Diagnostic procedures for shock focus on identifying the underlying causes and determining the severity of the condition. These procedures consist of a CBC, cultures, coagulation studies, cardiac biomarkers, natriuretic peptide levels, arterial blood gases, basic chemistry panels, renal and liver panels, chest X-ray, hemodynamic monitoring, EKG, echocardiogram ultrasounds, MRI, and CT.

Prompt treatment is crucial to ensure positive patient outcomes. Management of shock includes the identification and treatment of the underlying cause, maintaining respiratory status, cardiac monitoring, and rapid fluid replacement. Crystalloids are usually the fluid replacement of choice unless the shock is hemorrhagic. In patients with hemorrhagic shock, blood transfusions may be necessary. Oxygen or mechanical ventilation may also be necessary. Depending on the type of shock, pharmacologic agents may include vasopressors (e.g., norepinephrine or dobutamine), vasodilators, beta blockers, alpha agonists, phosphodiesterase inhibitors, steroids, antihistamines, antibiotics, and anticoagulants. Additionally, an intra-

aortic balloon pump, ventricular assist device, artificial heart, or extracorporeal membrane oxygenation may be necessary.

application to practice

Mr. Jones, a 50-year-old professor, is 5 hours post laparoscopic cholecystectomy. He is alert and oriented. His physical assessment is within normal limits, including active bowel sounds and a soft, slightly tender abdomen. He is sipping on clear liquids and conversant. The nurse is performing the final assessment and providing discharge patient education. Mr. Jones states that he feels a little tired because of all the excitement about going home and feeling so good after surgery. While checking his vital signs for the discharge form, you notice that his pulse is 110 beats/min and irregular compared to the 86–90 beats/min regular pulse that he had been having since surgery. Mr. Jones states that his higher pulse just reflects his excitement; he feels great, and his wife is waiting in the car at the patient discharge area for him.

1. What should you do?
2. Is there any significance in an irregular pulse? If yes, describe it.

The healthcare provider returns to the unit to assess the patient's current condition. The healthcare provider orders a stat EKG and chest X-ray and cancels the prior written discharge order. The EKG shows atrial fibrillation with a ventricular rate of 118, with QRS and ST patterns suggesting an old anterior-wall MI.

Mr. Jones continues to rest in a semi-Fowler position in bed. His wife has returned to his bedside. Upon auscultation, you note that Mr. Jones has fine crackles in bilateral lung bases, an occasional dry nonproductive cough, and hiccups, but he denies difficulty in breathing. As you turn to leave the room, you observe Mr. Jones getting out of bed and walking toward the restroom. He is holding onto the footboard stating, "I don't know. I feel sort of weak." He appears slightly tachypneic.

1. Why does Mr. Jones have crackles and cough at rest and tachypnea when walking?
2. Which diagnostic tests would commonly be prescribed for a patient such as Mr. Jones?

application to practice

Now that we have learned about conditions affecting the cardiovascular system, let's put that knowledge into practice. While you are working in the emergency department, the following patients come in seeking care. Which patient is the highest priority?

- An 80-year-old female with a history of atrial fibrillation complaining of tachycardia, shortness of breath, and increased pedal edema over the past 3 days

- A 67-year-old male with a history of diabetes mellitus complaining of severe indigestion for the past 2 weeks
- A 52-year-old male complaining of “not feeling right,” weakness, and severe nausea while working out in his garden yesterday
- A 28-year-old female with a history of mitral valve prolapse complaining of palpitations

Remember to go through the usual thought process—who would die first, acute versus chronic conditions, Maslow’s hierarchy of needs, and patient safety. Starting with the 80-year-old patient, atrial fibrillation is typically an irregular dysrhythmia. Occasionally, atrial fibrillation can also have a rapid ventricular response, resulting in tachycardia and decreased cardiac output. This patient should be quickly evaluated for the presence of this condition since she has other symptoms of decreased cardiac output (i.e., shortness of breath and pedal edema). Definitely keep her on your shortlist. Next, you should definitely be concerned that the patient with diabetes and severe indigestion for 2 weeks may have had or be having an MI. As we learned, individuals with diabetes are at increased risk for developing MIs because they typically also have high cholesterol and triglyceride levels, which can lead to atherosclerosis. Such patients often do not have the classic chest pain associated with MI, and it is concerning that the 67-year-old patient’s symptoms have been going on for 2 weeks. With the 52-year-old male who has no notable history, his symptoms could be caused by many things, ranging from dehydration to an active MI. Many times, patients will present with a feeling of “impending doom” or that they are “going to die” while having an MI. This man’s cardiac needs may have suddenly exceeded his blood supply while gardening. This patient should definitely stay on our radar. Finally, consider the patient having the palpitations. Mitral valve prolapse is a chronic condition that often causes dysrhythmias, most of which are not life threatening.

Although both of the male patients take high priority, the onset of these patients’ symptoms occurred 2 weeks and yesterday. Their myocardium may be permanently damaged, and treatment options may be limited. The 52-year-old may be having an active MI, but the onset is not within the optimal 90 minutes for treatment. This patient should be placed on oxygen and an EKG monitor and blood for cardiac biomarkers and other tests should be drawn. This patient is a very close runner-up in terms of priority to the patient with atrial fibrillation. This patient should be put on oxygen and an EKG monitor and immediately evaluated for whether the patient can be chemically (e.g., cardiozem) or mechanically cardioverted. In the real world, other staff would likely be available to assist with attending to her needs simultaneously, but in NCLEX questions, you are typically not given those options.

SUMMARY

The cardiovascular system is responsible for transporting the body's life fluids to maintain a delicate internal balance. This system has a reciprocal relationship with all the other systems—one in which problems in one system create problems in another system. Problems in the cardiovascular system are highly prevalent, and understanding these issues is vital for nurses to provide appropriate care. Prevention of cardiovascular issues often includes lifestyle changes. Early identification and treatment of these conditions are crucial to improve outcomes.

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CHAPTER 5

Respiratory Function

LEARNING OBJECTIVES

- Discuss normal respiratory anatomy and physiology.
- Describe and compare infectious disorders of the respiratory system.
- Describe and compare respiratory alterations that impair ventilation.
- Describe and compare respiratory alterations that impair perfusion.

KEY TERMS

active infection
acute bronchitis
acute lung injury (ALI)
acute respiratory distress syndrome (ARDS)
acute respiratory failure (ARF)
alveoli
aspiration pneumonia
asthma
atelectasis
bacterial pneumonia
bronchi (*sing.* bronchus)
bronchiole
bronchiolitis
bronchopneumonia
chronic bronchitis
chronic obstructive pulmonary disease (COPD)
cilia
community-acquired pneumonia

cystic fibrosis
diaphragm
drug-induced asthma
emphysema
epiglottis
epiglottitis
exercise-induced asthma
expiration
expiratory reserve volume
extrinsic asthma
forced expiratory volume in 1 second
forced vital capacity
infectious rhinitis
influenza
inspiration
inspiratory reserve volume
interstitial pneumonia
intrinsic asthma
laryngitis
laryngotracheobronchitis
larynx
Legionnaires' disease
lobar pneumonia
lung cancer
Middle East respiratory syndrome (MERS-CoV)
minute respiratory volume
mucus
Mycoplasma pneumoniae
nocturnal asthma
non–small-cell carcinoma
nosocomial pneumonia
occupational asthma
perfusion
pharynx
pleural effusion
pleurisy
Pneumocystis jirovecii pneumonia
pneumonia

pneumothorax
primary TB infection
residual volume
rhinosinusitis
severe acute respiratory syndrome (SARS)
sinusitis
small-cell carcinoma
spontaneous pneumothorax
status asthmaticus
surfactant
tension pneumothorax
tidal volume
trachea
traumatic pneumothorax
tuberculosis (TB)
type A influenza
type B influenza
type C influenza
ventilation
ventilation-to-perfusion ratio (VQ ratio)
viral pneumonia
vital capacity

The respiratory system includes the organs and structures associated with breathing and gas exchange. The structures of the respiratory system are grouped into two branches—the upper respiratory tract (mouth, nasal cavity, **pharynx**, and **larynx**) (**FIGURE 5-1**) and the lower respiratory tract (**trachea**, **bronchi**, **bronchioles**, and **alveoli**). This chapter focuses on both normal and abnormal states of the lungs. The respiratory tract functions automatically to provide cells with oxygen and to remove carbon dioxide waste. Disorders of the respiratory tract can become serious quickly because of the body's critical need for oxygen. Patients with these disorders will need astute nurses who respond quickly yet thoughtfully.

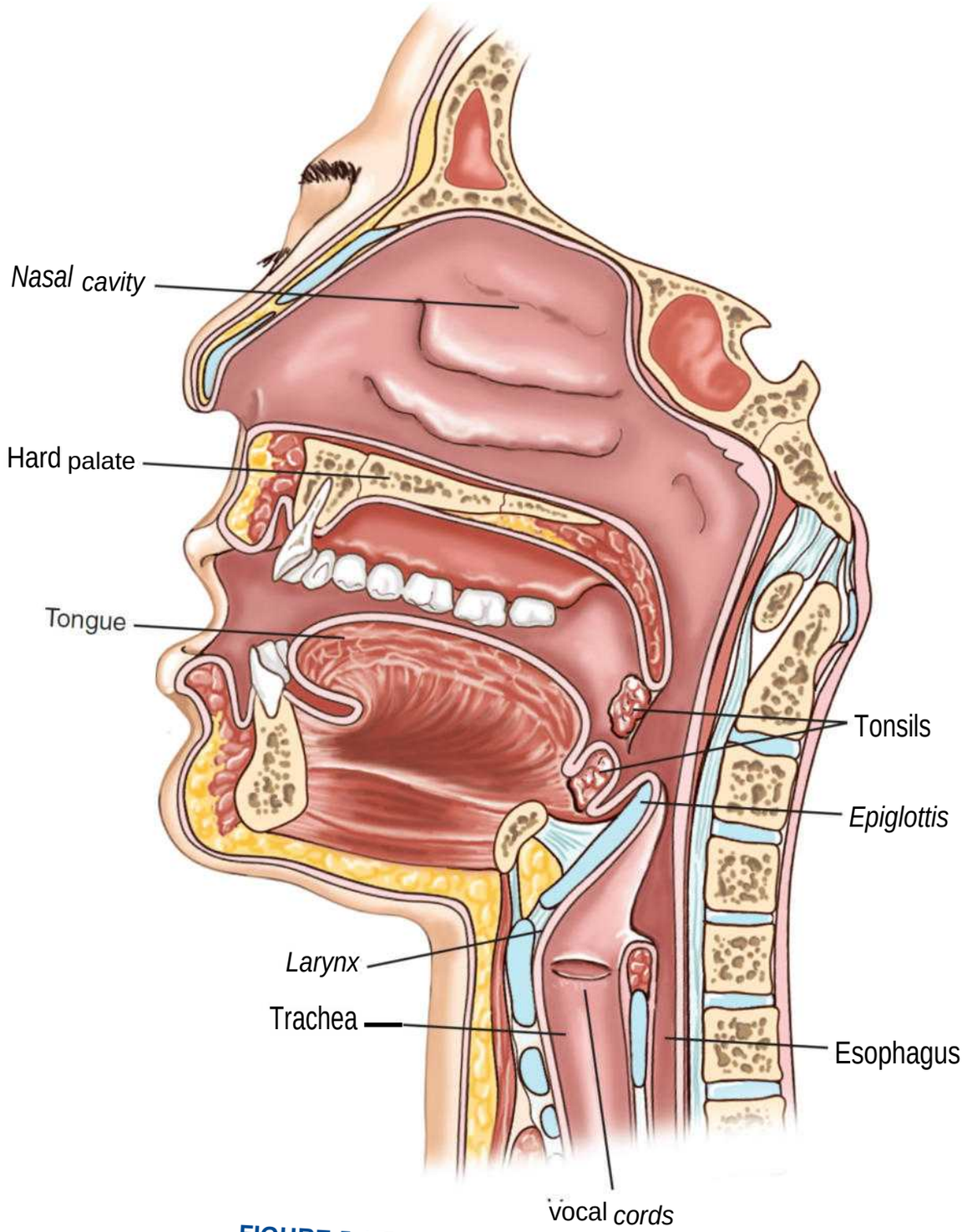


FIGURE 5-1 The upper respiratory tract.

Description

Anatomy and Physiology

The respiratory system provides vital oxygen and removes toxic carbon dioxide through the act of breathing. The respiratory tract allows a person to breathe in and out approximately 23,000 times each day. In fact, you would be a millionaire in a month and a half if you received a dollar for each breath. The act of breathing allows for gas exchange of oxygen and carbon dioxide. Oxygen is necessary for cells to produce energy through cellular metabolism; carbon dioxide is the waste product of this process. Through its gas exchange functions, the respiratory system plays a pivotal role in maintaining homeostasis.

The respiratory system consists of two basic functional divisions: an air-conducting portion and a gas-exchanging portion (**TABLE 5-1**). The air-conducting portion delivers air to the lungs, while the gas-exchanging portion allows gas exchange to occur between the air and the blood (**FIGURE 5-2**). The gas-exchanging portion of the respiratory tract includes the lungs with their millions of alveoli and capillaries (Figure 5-2).

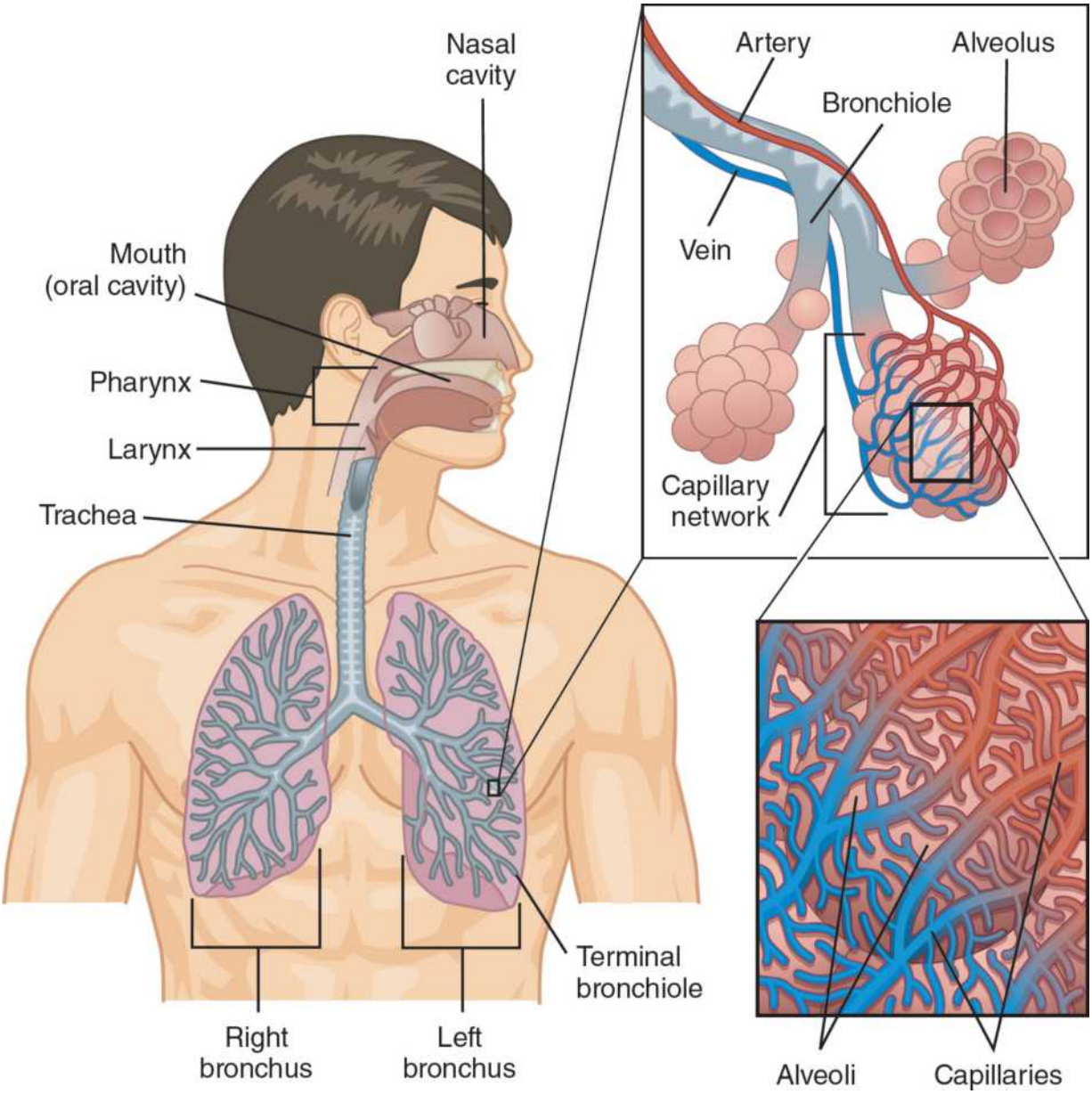


FIGURE 5-2 The respiratory system. This illustration shows the air-conducting portion and the gas-exchange portion of the human respiratory system. The insert shows a higher magnification of the alveoli where oxygen and carbon dioxide exchange occurs.

Description

TABLE 5-1 Summary of the Respiratory System

Organ	Function

Organ	Function
Air Conducting	
Nasal cavity	Filters, warms, and moistens air; also transports air to the pharynx
Oral cavity	Transports air to pharynx; warms and moistens air; helps produce sounds
Sinuses	Produce mucus; warm and moisten air
Pharynx	Transports air to the larynx
Epiglottis	Covers the opening to the trachea during swallowing
Larynx	Produces sounds; transports air to the trachea; helps filter incoming air; warms and moistens incoming air
Trachea and bronchi	Warm and moisten air; transport air to the lungs; filter incoming air
Bronchioles	Control air flow in the lungs; transport air to the alveoli
Gas Exchange	
Alveoli	Provide area for exchange of oxygen and carbon dioxide

Air enters the respiratory tract through the nose and mouth and then travels to the pharynx. Air brought in through the nose travels through the sinuses to be warmed and moistened before entering the pharynx. The pharynx joins the larynx, or voice box (**FIGURE 5-3**). The larynx, which is made of cartilage, plays a central role in swallowing and talking. When food is swallowed, the larynx rises so that it is closed by the **epiglottis**. This process prevents food and liquids from entering the lungs, where they would cause severe irritation. Even so, food does occasionally enter the lungs, often triggering the cough reflex (a primitive protective reflex). The larynx works much like the strings of a guitar or violin to produce sound—tightening and loosening to change pitch. It opens into the trachea, or windpipe. From the trachea, the air travels to the mainstem bronchi,

which then branches into the right and left bronchi, one for each lung (**FIGURE 5-4**). The left bronchus is narrow and positioned more horizontally than the right bronchus; the right bronchus is shorter and wider than the left bronchus and extends downward more vertically. Because of the difference in size between the two, objects are more easily inhaled (aspirated) into the right bronchus.

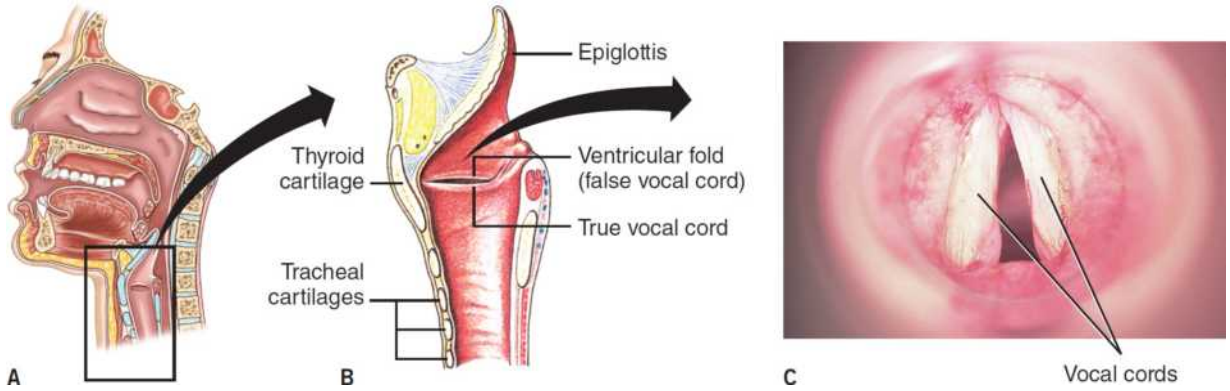


FIGURE 5-3 The vocal cords. **(A)** Uppermost portion of the respiratory system, showing the location of the vocal cords. **(B)** Longitudinal section of the larynx showing the location of the vocal cords. Note the presence of the false vocal cord, so named because it does not function in phonation. **(C)** View into the larynx of a patient showing the true vocal cords from above.

Description

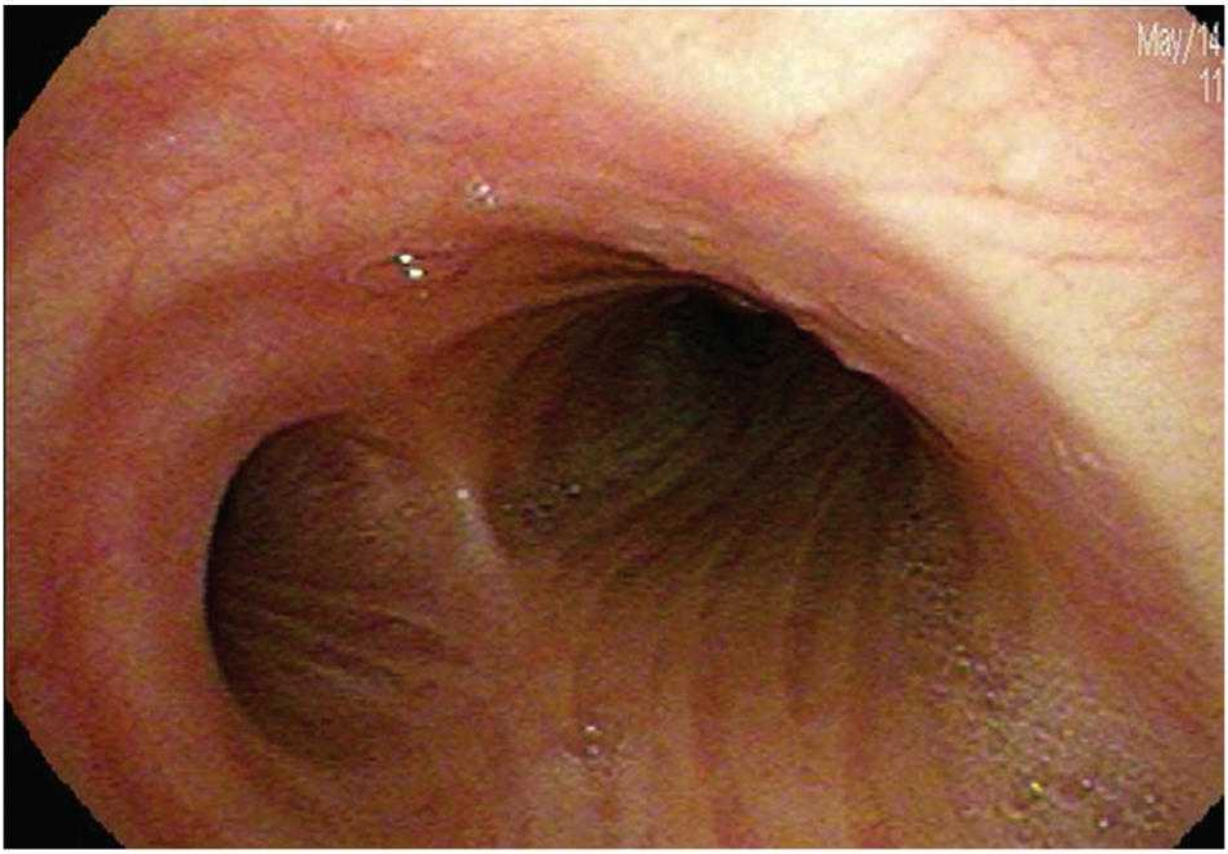


FIGURE 5-4 The bifurcation of the trachea at the carina into the right and left mainstem bronchi.

© Courtesy Dr. Scott Shofer

Inside the lungs, the bronchi branch extensively into a series of smaller and smaller tubes, or bronchioles, until they reach the alveoli. This branching from larger to smaller mimics the vessels in the cardiovascular system. The walls of the bronchioles are also like the vessel walls in that they mostly consist of smooth muscle. The smooth muscle allows for constriction and dilation of the bronchioles to control airflow. When oxygen needs are higher (e.g., during exercise or stress), the airways open more (dilate) to allow more air to enter the lungs. In times of normal or decreased oxygen needs (e.g., during sleep), the airways may narrow (constrict) slightly. Disease processes may cause constriction to the point of impeding air flow—a dangerous development.

The air entering the respiratory tract often contains particles that can be harmful—for example, infectious organisms (e.g., bacteria, viruses, and fungi) and environmental agents (e.g., dust, pollen, and pollutants). The respiratory system is equipped to filter out some of these particles as well as to protect the body against those that gain entry. The air-conducting portion of the respiratory tract filters many particles by trapping them in the mucous layer (**FIGURE 5-5**). **Mucus** is a thick, sticky substance produced by the goblet cells in the epithelial lining of the nose, trachea, and bronchi. This epithelial lining also contains many **cilia**, or hair-like projections, that move in a wavelike motion to propel the mucus and trapped particles upward to the mouth, where they can be expectorated (spit out). Cigarette smoking and air pollution can decrease mucus production and destroy cilia, increasing the risk of respiratory infections. Alcohol consumption can paralyze cilia, also increasing infection risk.

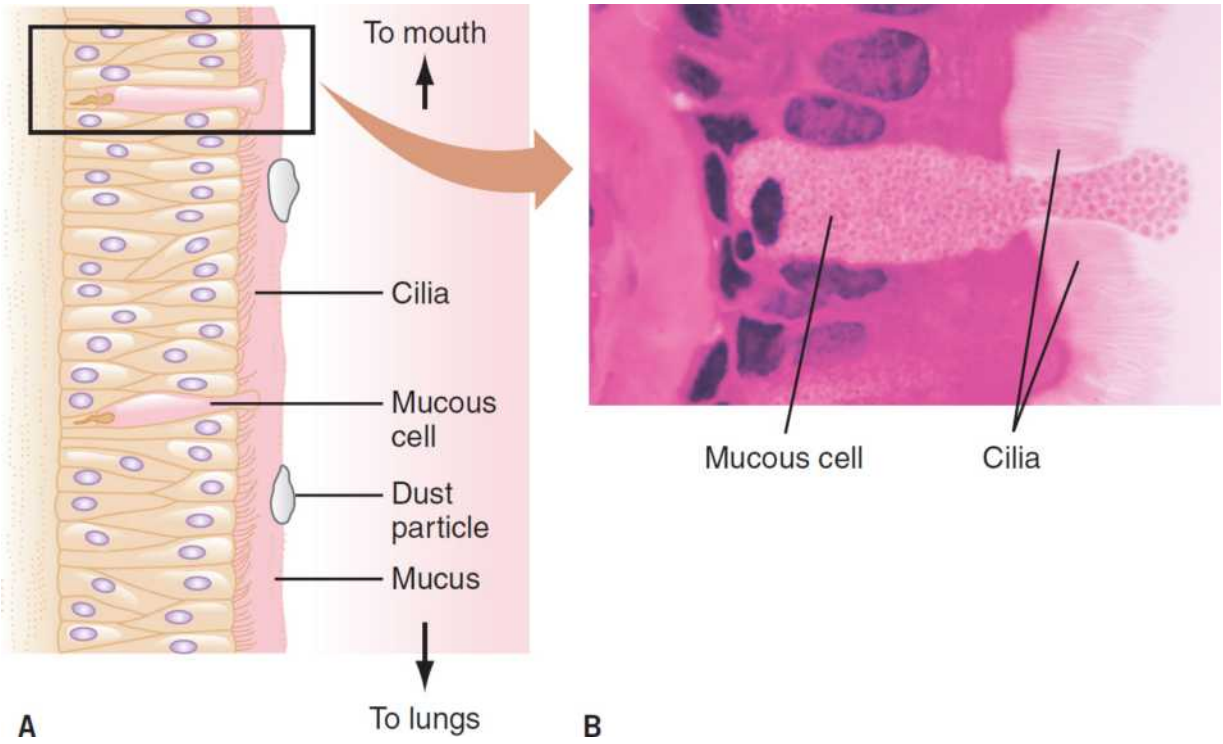


FIGURE 5-5 Mucus trap. **(A)** Drawing of the lining of the trachea. Mucus produced by the mucous cells of the lining of much of the respiratory system traps organisms and other particulates in the air. The cilia transport the mucus toward the mouth. **(B)** Higher magnification of the lining showing a mucous cell and ciliated epithelial cells.

B: © David M. Phillips/Visuals Unlimited, Inc.

Description

Additionally, the immune system is outfitted with immunoglobulin A (IgA) cells that prevent the attachment and invasion of bacteria and viruses through mucous membranes (see the *Immunity* chapter). Macrophages are also present around the alveoli in the lungs; they keep the lungs clean by phagocytizing particles that gain access to this area (**FIGURE 5-6**). Once the macrophages fill with particulates, they move into the surrounding connective tissue. When an unusually large number of particulates are present (e.g., with cigarette and marijuana smoking and when breathing in heavy pollution), the lungs become blackened by the accumulation of the particles.

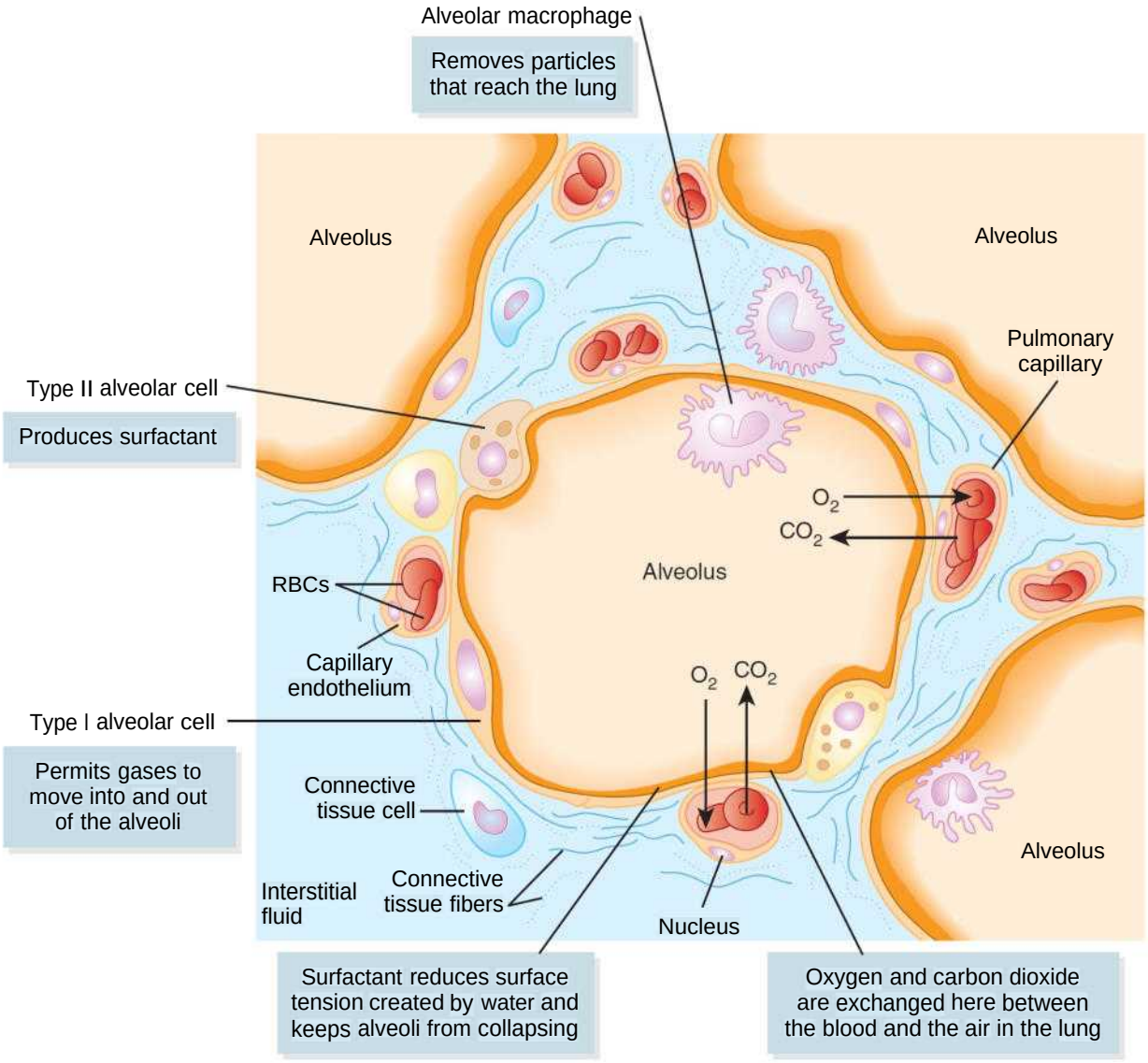


FIGURE 5-6 The alveolar macrophages.

Description

The air-conducting portion of the respiratory system also moistens and warms incoming air. An extensive network of capillaries lies beneath the epithelium of the respiratory tract. These capillaries release moisture into the incoming air, humidifying it to prevent drying of the respiratory tract. The warm blood circulating through the capillaries heats this air before it enters the lungs, thereby protecting the lungs from cold temperatures. As the air leaves the respiratory tract, much of the water that has been added to the air condenses

onto the slightly cooler lining of the nasal passages. The condensation is recycled for the next inhalation to conserve water and contributes to runny noses on cold days.

Alveoli are the sites where gas exchange with the bloodstream occurs (**FIGURE 5-7**). Oxygen is delivered to the alveoli by the air-conducting portion of the respiratory system, and carbon dioxide is brought to the lungs by the circulatory system. Each adult human lung contains approximately 150 million alveoli, which collectively create a surface area approximately the size of a tennis court for gas exchange. The alveoli and capillaries are often just a single cell layer thick, which further facilitates gas exchange. The amount of gas exchanged depends on the total surface area available and the thickness of the alveoli and capillary walls. The more surface area and the thinner the layers, the more rapidly gas diffuses. The connective tissue around the alveoli holds the capillaries in place.

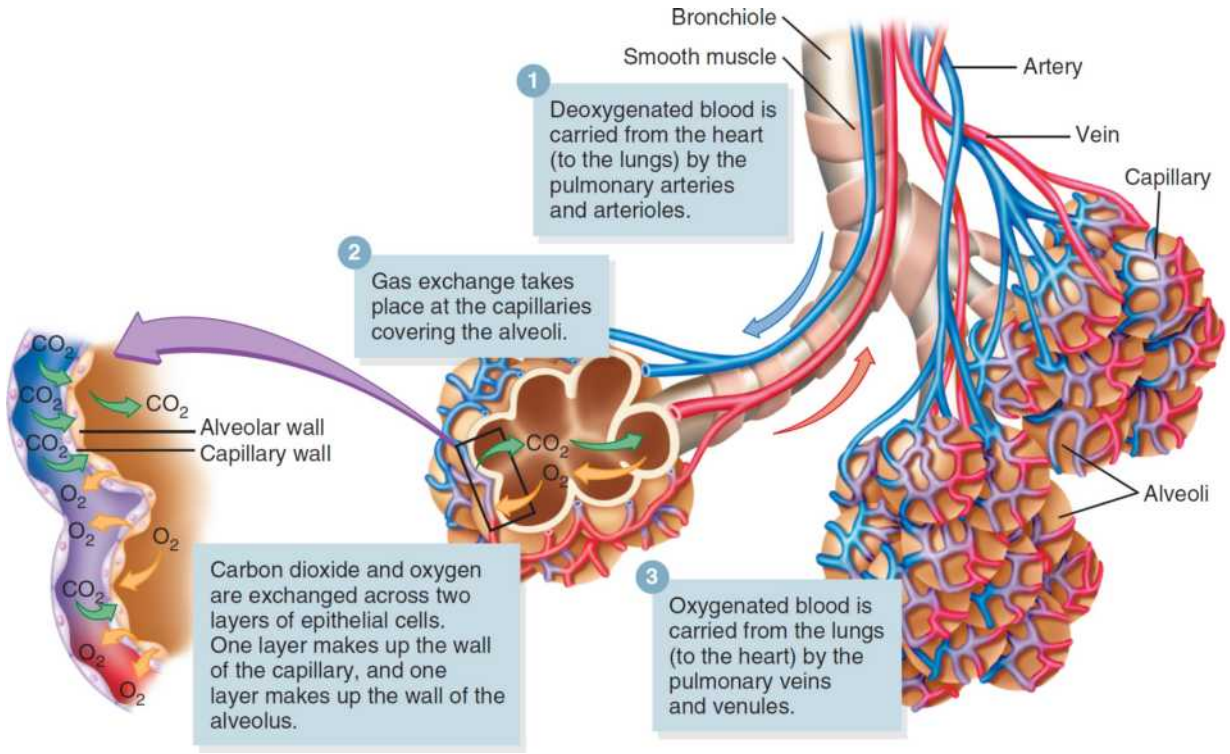


FIGURE 5-7 Gas exchange in the lungs.

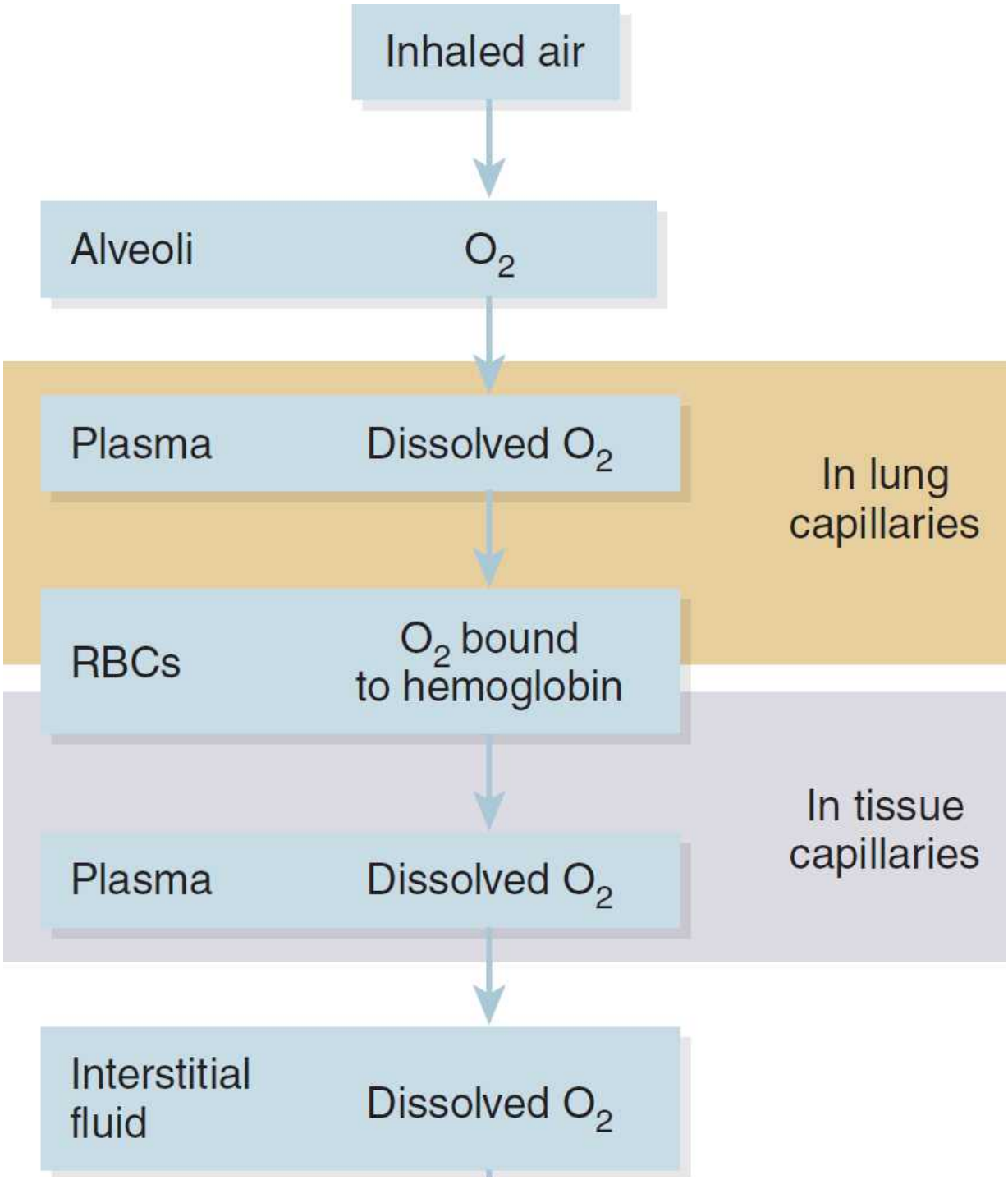
Description

Gas exchange in the alveoli requires adequate **ventilation** of air and **perfusion** of blood flow. The **ventilation-to-perfusion ratio (VQ ratio)** is a measurement of the efficacy and adequacy of these two processes. In the ideal lung, inspired air reaches all the alveoli, and all the alveoli have the same blood supply. In reality, neither alveolar ventilation nor capillary blood flow is uniform. The supply of air and blood never matches perfectly, even in healthy persons. Because of gravity, the lower parts of the lungs have greater blood flow than the upper parts. Likewise, the distribution of alveolar ventilation from the top to the bottom of the lungs is uneven. Normal ventilation is 4 liters of air per minute, and normal perfusion is 5 liters of blood per minute. This difference makes the expected VQ ratio 4:5, or 0.8. A VQ ratio higher than 0.8 indicates that ventilation exceeds perfusion, and a VQ ratio less than 0.8 indicates poor ventilation. Some respiratory disorders involve ventilation problems, whereas others result from perfusion issues. With both types of disorders, the result is impaired gas exchange.

The VQ ratio can be measured by a VQ scan—a series of two scans, performed either together or one after the other. For one scan, low-risk radioactive particles are inhaled to assess airflow (ventilation). In the other scan, radioactive particles are injected to assess blood flow (perfusion). The particles will gather in areas of abnormal air or blood flow.

When air is inhaled, gases are exchanged between the alveoli and the capillaries; that is, carbon dioxide is removed through **expiration**, and oxygen is delivered to cells by the cardiovascular system (**FIGURE 5-8**)**.** This gas exchange is a passive process. The amount of gas transferred is governed by the partial pressure of that gas in the two compartments. Atmospheric air consists of a mixture of gases (e.g., oxygen, carbon dioxide, and nitrogen). The total pressure of the atmosphere is a sum of the partial pressures of the gases in it; these partial pressures are also present in the blood (i.e., PO_2 and PCO_2). These gases exchange through diffusion based on their partial pressures, moving from an area of high pressure (or high concentration) to an area of lower pressure (or low concentration).

For example, oxygen's partial pressure is usually higher in the alveoli than in the pulmonary capillaries, so oxygen diffuses into the capillaries. In contrast, the partial pressure of carbon dioxide is usually higher in the pulmonary capillaries than in the alveoli, so carbon dioxide diffuses into the alveoli.



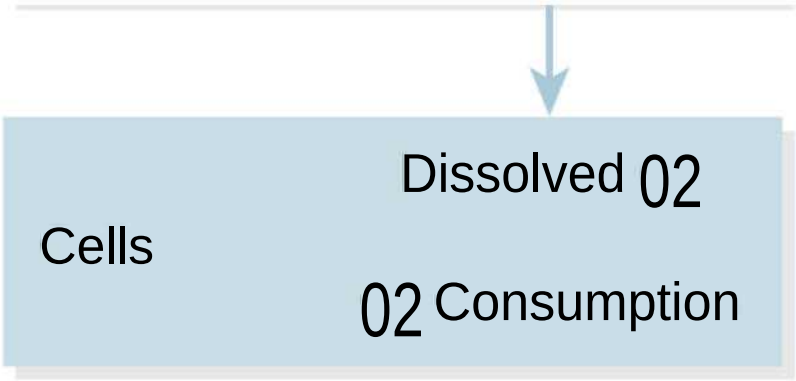


FIGURE 5-8 Oxygen diffusion. Oxygen travels from the alveoli first into the blood plasma and then into the red blood cells (RBCs), where much of it binds to hemoglobin. When the oxygenated blood reaches the tissues, oxygen is released from the RBCs and diffuses first into the plasma and then into the interstitial fluid and body cells.

Description

To facilitate gas exchange, the pulmonary circulation is a low-pressure, high-flow system with the ability to recruit unperfused vessels. At the capillary level, the pulmonary arterial pressure (PAP) is the lowest, contributing to the majority of the pulmonary vascular resistance (PVR). Changes in vascular tone or wall tension can increase PAP. The pulmonary circulation has minimal vascular tone but also minimal ability to change it. Thus, unlike most other organs, the lungs cannot control blood flow delivered to them during changing times of increased needs. However, the lungs can redistribute blood flow within their boundaries.

Once oxygen is in the blood, it binds with hemoglobin, creating a form called “oxyhemoglobin.” Oxyhemoglobin travels to the cells, where it is released. The rate at which hemoglobin binds and releases oxygen is affected by several factors, including temperature and pH, among other things (**FIGURE 5-9**). With carbon dioxide poisoning (e.g., from exposure to smoke from fire, motor [e.g., vehicle or generator] exhaust, or paint thinner), carbon dioxide’s partial pressure is higher in the alveoli than in the blood, causing more of this gas to diffuse into the blood than leaves. Hemoglobin has a higher affinity for carbon dioxide than oxygen, resulting in hypoxia.

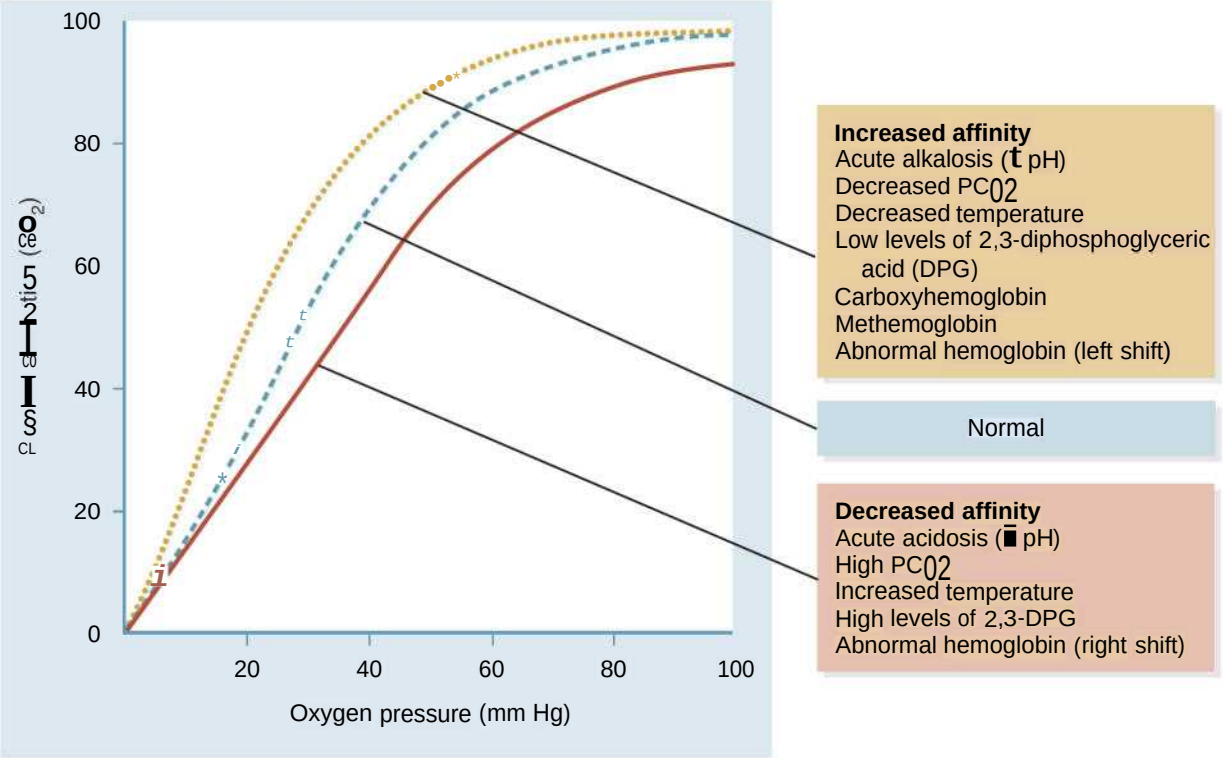


FIGURE 5-9 Oxyhemoglobin dissociation curve.

Description

The surface of the alveoli is coated with **surfactant**, a lipoprotein produced by alveoli cells that have a detergent-like quality. This watery substance produces surface tension on the alveoli, which enhances pulmonary compliance (elasticity) and prevents the alveoli from collapsing. Because the pressure in the lungs is negative compared with the atmospheric pressure, the walls of the alveoli tend to draw inward, making them collapse. This pressure is much like that seen with a vacuum-sealed pack of coffee. The pressure, and therefore the risk of collapse, further increases at the end of expiration. Surfactant promotes reinflation of the alveoli during **inspiration**. Disease states and other conditions can decrease the amount of surfactant present, leading to the collapse of the alveoli (a condition called **atelectasis**). For example, premature infants lack surfactant, and smoking impairs surfactant production. Synthetic surfactant may be administered to overcome any inadequacies in the body's production of this lipoprotein.

The respiratory drive is a system made up of three components: the neural central control system, the sensory input system, and the muscular effect system. The neural central control system, which involves the medulla oblongata in the brain, acts as an involuntary intrinsic pacemaker for the rate of ventilation and volume of breathing. This center is located in the brainstem, which controls many vital body functions (e.g., heart rate, blood pressure, and temperature). The medulla controls breathing through nerve cells that generate nerve impulses (i.e., sensory input system) that travel to the respiratory muscles (i.e., muscular effect system). When the lungs are full, these impulses cease, allowing the muscles to relax.

Chemoreceptors inside the brain and arteries also regulate breathing. Central chemoreceptors detect carbon dioxide and pH levels, and peripheral chemoreceptors detect oxygen levels. These receptors send messages to the medulla to alter breathing accordingly. Carbon dioxide and pH levels control the majority of the respiratory drive (**FIGURE 5-10**). When carbon dioxide levels go up or pH levels go down (increasing acidity), respiration depth and rate increase to remove the excess carbon dioxide, and vice versa. In disease states characterized by hypercapnia (increased carbon dioxide in the blood), the central chemoreceptors become tolerant to the high carbon dioxide levels, losing that drive.

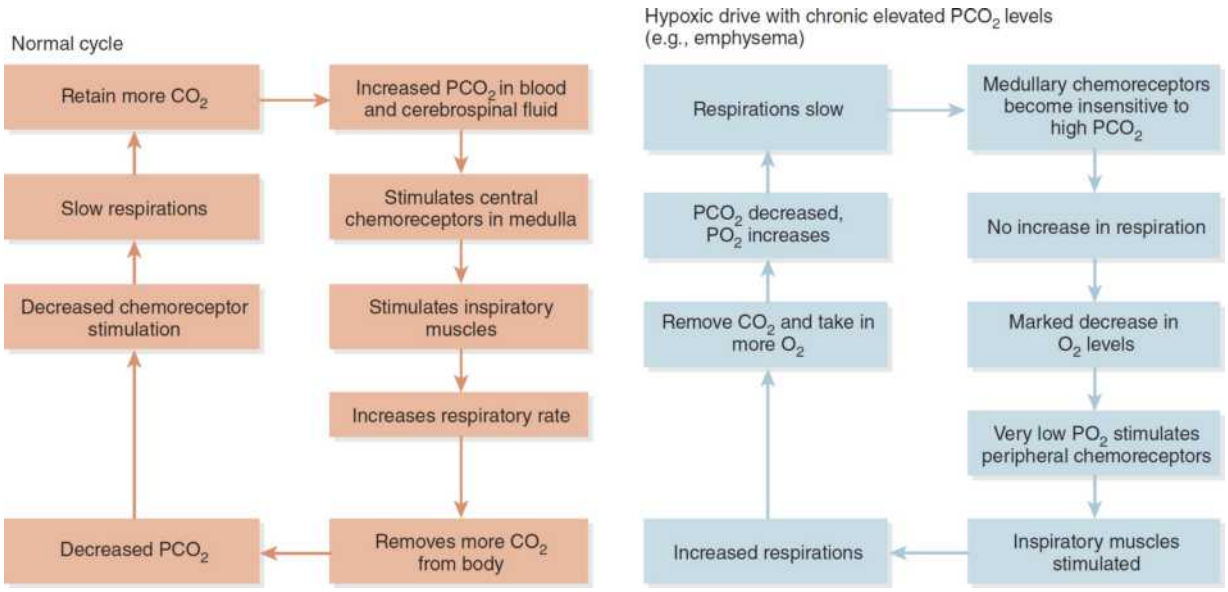


FIGURE 5-10 Normal respiratory control and hypoxic drive.

Description

Additionally, stretch receptors in the lungs aid in breathing by detecting when the lungs are full. In such a case, the stretch receptors in the lungs send a message to the medulla to cease firing. This effect, called the “Hering–Breuer reflex,” prevents overinflation of the lungs. The body also has oxygen receptors, but they are not very sensitive. These receptors do not generate impulses until oxygen levels fall to a critical point.

Along with regulating oxygen and carbon dioxide levels, the lungs aid in regulating pH by altering breathing rate and depth. Carbon dioxide is a source of acid in the body. Increasing the respiratory rate and depth will lead to the excretion of more carbon dioxide, making the blood less acidic. Conversely, decreasing the respiratory rate and depth will cause retention of more carbon dioxide, making the blood more acidic. This compensatory mechanism allows for a quick fix of pH imbalances to reestablish homeostasis (also see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter).

Breathing includes two phases: inspiration (inhalation—moving air in) and expiration (exhalation—moving air out). Inspiration is an active neural process that begins when nerve impulses travel from the brain to the **diaphragm**, the dome-shaped muscle that separates the thoracic and abdominal cavities (**FIGURE 5-11**). These impulses cause the diaphragm to contract, lower, and flatten, which draws air into the lungs. Inspiration also involves the intercostal muscles between the ribs. Nerve impulses cause the intercostal muscles to contract, lifting the ribs up and out. Contraction of the diaphragm and intercostal muscles changes the intrapulmonary pressure, causing air to flow naturally into the lungs.

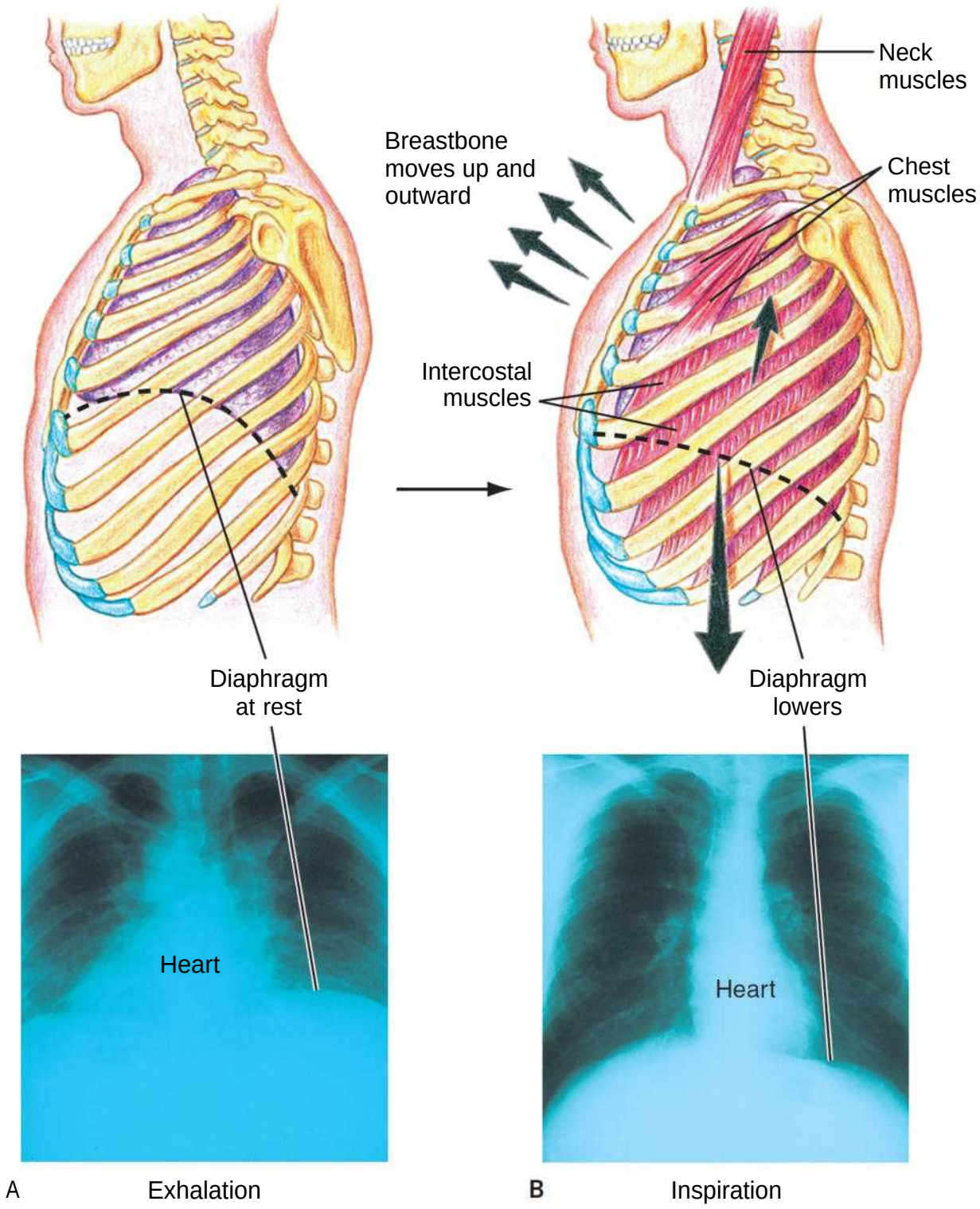


FIGURE 5-11 Breathing. The rising and falling of the chest wall through the contraction of the intercostal muscles (muscles between the ribs), illustrating the bellows effect. Inspiration is assisted by the diaphragm, which assumes a lower position in the chest. Like pulling a plunger back on a syringe, the rising of the chest wall and the lowering of the diaphragm draw air into

the lungs. Illustrations and X-rays showing the lungs in full exhalation **(A)** and full inspiration **(B)**.

A and **B:** © SIU/Visuals Unlimited, Inc.

Description

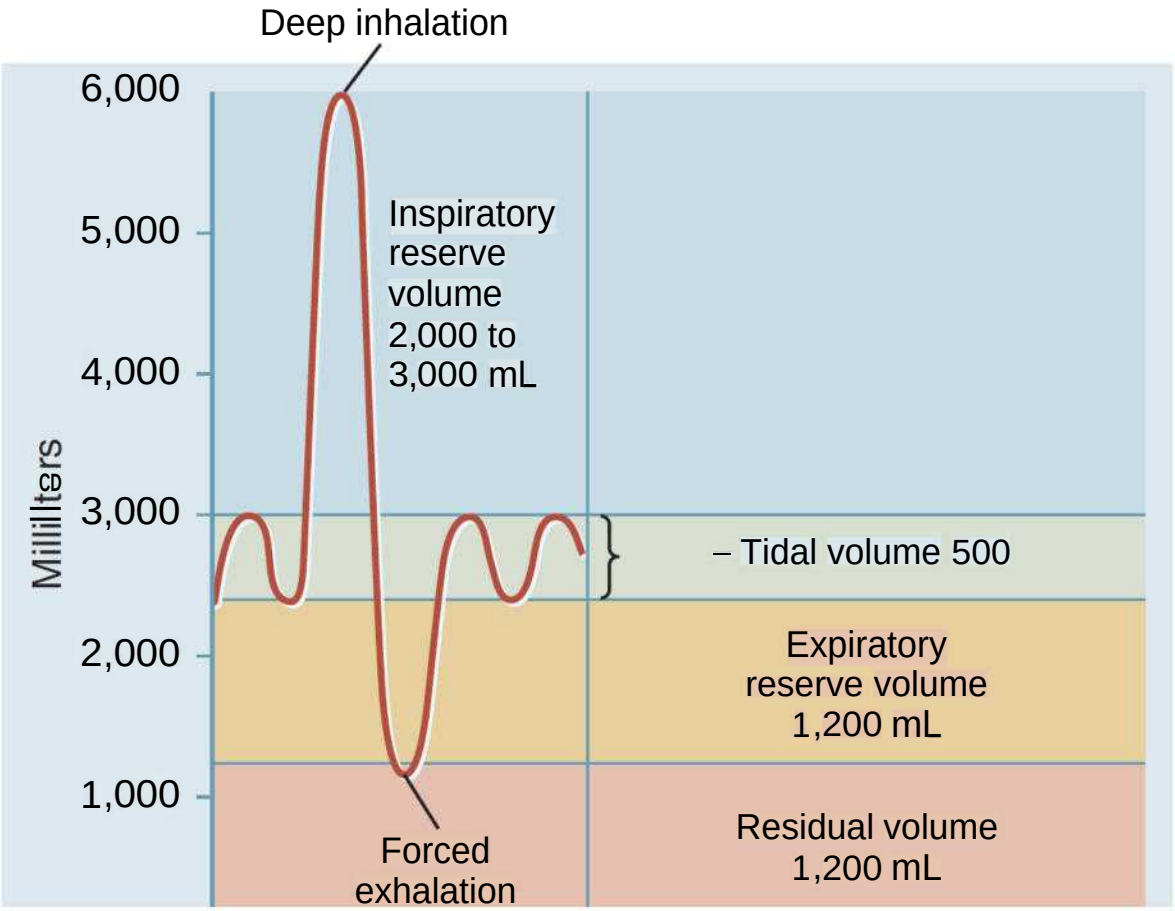
In contrast to inspiration, expiration is passive—it does not require muscle contraction. As the lungs fill with air, the diaphragm and intercostal muscles relax, returning to their previous position. Returning to their natural position decreases thoracic volume and increases intrapulmonary pressure. This greater pressure forces air out of the lungs. Elastic fibers in the lungs aid in passive expiration by causing the lungs to recoil. Expiration can also be active—that is, created by contracting the chest and abdominal muscles.

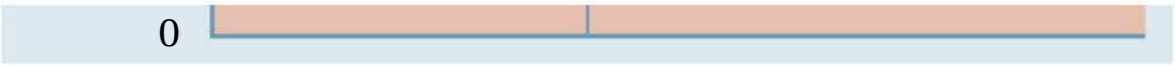
Air flow, both inspiratory and expiratory, can be measured to aid in diagnosis of respiratory disorders (**FIGURE 5-12**). Pulmonary function tests evaluate lung volumes and capacities. **Tidal volume** is the amount of air involved in one normal inhalation and exhalation. The average tidal volume is 500 mL but is smaller in shallow breathing. **Minute respiratory volume** is the amount inhaled and exhaled in 1 minute. This volume is calculated by multiplying the tidal volume by the number of respirations per minute; the average is 6 liters per minute. **Inspiratory reserve volume** is the amount of air beyond the tidal volume that can be taken in with the deepest inhalation; it averages 2 to 3 liters. **Expiratory reserve volume** is the amount of air beyond tidal volume that can be forcibly exhaled beyond the normal passive exhalation. The average expiratory reserve volume is 1 to 1.5 liters. **Vital capacity** is the sum of the tidal volume and reserves. Some air is always present in the lungs, and this amount is called **residual volume**. Even after the most forceful exhalation, 1 to 1.5 liters of air remains in the lungs, which ensures efficient and consistent gas exchange. **Forced expiratory volume in 1 second** is compared to **forced vital capacity** to diagnose pulmonary disease.





A


Deep inhalation
6,000
5,000
4,000
3,000
2,000
1,000
Milliliters
Inspiratory reserve volume 2,000 to 3,000 mL
– Tidal volume 500
Expiratory reserve volume 1,200 mL
Residual volume 1,200 mL
Forced exhalation



B

FIGURE 5-12 Measuring air flow. **(A)** This machine allows healthcare workers to determine tidal volume, inspiratory reserve volume, and other lung-capacity measurements to determine the health of an individual's lung. **(B)** This graph shows several common measurements.

Description

Age Considerations

Some age-related changes in the respiratory tract are important to understand. Lung development occurs in two phases—lung growth (structural development) and lung maturation (functional development). The fetus relies on the placenta for oxygenation until birth. During embryonic development, the lungs originate from the ectoderm, and the pulmonary circulation originates from the mesoderm. Lung development continues throughout the remainder of gestation. Progressive branching of the airways occurs until finally alveolar spaces are developed in the last trimester. Surfactant develops in the last trimester, reaching full maturation around 36 weeks' gestation.

Amniotic fluid plays a critical role in lung development, but the details of this role are not universally agreed upon. It has been widely believed that the fetus "breathes" the amniotic fluid in and out, but no evidence has been published to support this theory. More recent theories suggest that the lungs develop from the production of fetal lung fluid (some believe this fluid to be amniotic fluid) that expands the lungs. However, the fetus does practice breathing in the last trimester through fetal breathing movements to develop respiratory muscles and neural regulation (Koos & Rajaee, 2014). Exposure to drugs and adverse conditions in utero can alter these breathing movements, diminishing lung development and increasing risk for respiratory issues after birth and later in life.

At birth, the neonate's lungs are filled with fluid and are not inflated. The newborn usually takes its first breath within 10 seconds after birth. This breath sounds like a gasp as the newborn's central

nervous system reacts to the sudden change in temperature and environment. Once the newborn takes the first breath, several changes occur in the respiratory and cardiovascular systems:

- Oxygen in the lungs decreases blood flow resistance to the lungs.
- Blood flow resistance of the systemic circulation increases.
- Fluid is absorbed from the lungs.
- The lungs inflate and begin voluntarily working, exchanging gases.

Newborns typically have irregular breathing patterns, and their respiratory rate is 30 to 60 breaths per minute. This rate may slow to 20 breaths per minute when they sleep. At 6 months of age, their respiratory rate is between 25 and 40 breaths per minute; by comparison, the respiratory rate in an adult is typically 12 to 20 breaths per minute. Newborns may also take several rapid breaths and then pause for up to 10 seconds, whereas adults typically have regular breathing patterns. Babies up to 3 months of age primarily breathe through their nose and are unable to bring air in through their mouths unless they are crying; therefore, nasal congestion can significantly impair their breathing.

Lung growth continues after birth as the number of alveoli continues to increase. The lungs reach full maturity by age 25 years, but the alveoli begin to lose their shape and form by age 35. With aging, lung muscle tissue loses mass and elasticity, causing the airways to close more readily and ventilation to be impaired. The changes in the alveoli and muscles result in impaired ventilation and perfusion, which in turn decreases gas exchange.

The nervous system also goes through aging-related changes that influence functions of the respiratory system. The brainstem can experience decreased functioning, causing carbon dioxide to accumulate. The sensitivity of chemoreceptors in the respiratory tract declines, which can allow particles to accumulate in the lungs and decrease activity tolerance. Bones become thinner and change shape with aging as well. These changes in the rib cage can decrease the lungs' ability to expand and contract adequately. The diaphragm can weaken, impairing inspiration and expiration. Exposure to smoke and

pollutants can further exacerbate the effects of these changes on ventilation and perfusion. Age-related changes to the immune system diminish the effectiveness of lung defense mechanisms, resulting in more frequent and severe respiratory infections (e.g., **pneumonia** and **influenza**).

Learning Points

Normal Drive to Breathe

Carbon dioxide exerts the most control over the respiratory drive. How is this control translated into action? As carbon dioxide levels rise, the lungs exhale to expel the excess carbon dioxide. To understand how strong this drive is, consider holding your breath. If you take a deep breath and try to hold it, eventually you have to let the air out. No matter how hard you try, you cannot hold your breath past a certain point. The body can be trained to hold a breath longer and longer (as swimmers and divers do), but no matter the training, you will eventually have to let it out.

UNDERSTANDING CONDITIONS THAT AFFECT THE RESPIRATORY SYSTEM

When considering alterations in the respiratory system, it is best to organize them based on their basic underlying pathophysiology to increase understanding. Those pathophysiological concepts include conditions that are infectious in nature, problems with ventilation, and issues with perfusion. Infectious conditions may involve either the upper respiratory tract or the lower respiratory tract. The respiratory system requires both ventilation and perfusion to function properly, so problems in either of these areas will impair the respiratory system's ability to meet the body's needs. Ventilation conditions result from problems with moving air into or out of the lungs (e.g., **asthma**). Perfusion conditions result from problems that prevent gas exchange; many of these conditions are

cardiovascular in nature (e.g., pulmonary embolism). However, many conditions impact both ventilation and perfusion.

When considering these conditions, it is also important to determine which respiratory-related nursing diagnosis is in play. In respiratory disorders, the primary two nursing diagnoses involved are impaired gas exchange and ineffective airway clearance. Impaired gas exchange includes conditions that decrease gas exchange in the lungs (e.g., asthma, **emphysema**, and **chronic bronchitis**). Ineffective airway clearance includes conditions in which secretions are stagnant (e.g., pneumonia and **cystic fibrosis**). Other nursing diagnoses that may be applicable include activity intolerance, ineffective breathing pattern, fatigue, anxiety, risk for aspiration, and risk for suffocation.

Infectious Disorders

Upper Respiratory Tract Infections

The upper respiratory tract includes the mouth, nasal cavity, sinuses, pharynx, and larynx. Infections of these structures trigger the inflammatory response, which explains many of the symptoms associated with these conditions. Because of their close proximity, many infections of the upper respiratory tract are interrelated; that is, they may occur together or one may lead to another. Viruses are the most common causative organisms of primary infections, but the inflammation of the respiratory tissue increases the risk of secondary bacterial infections, especially in immunocompromised individuals.

Infectious Rhinitis

Infectious rhinitis, also referred to as nasopharyngitis and the common cold, is a viral upper respiratory infection. The most frequent culprit is one of more than 100 serotypes of rhinovirus, but many viruses (e.g., adenovirus and coronavirus) can cause this illness. In fact, more than 200 causative organisms have been identified, and their diversity makes it difficult to develop immunity. Rhinovirus infections are most common during the fall and spring and less

common during the winter. Infectious rhinitis is a significant contributor to work and school absences, with adults averaging two to three colds per year and children having even more such infections (Centers for Disease Control and Prevention [CDC], 2021)).

In infectious rhinitis, the infectious organism invades the epithelial lining of the nasal mucosa. Mild cellular inflammation leads to nasal discharge, mucus production, and shedding of the epithelial cells. This inflammation of the respiratory tract then increases vulnerability to bacterial invasions. As a consequence, secondary bacterial infections (e.g., otitis media, **rhinosinusitis**, bronchitis, and pneumonia) are commonly associated with viral infections (**FIGURE 5-13**). The risk for secondary bacterial infections is further increased in individuals who smoke because of the chronic damage done by smoke to the mucosa and cilia.

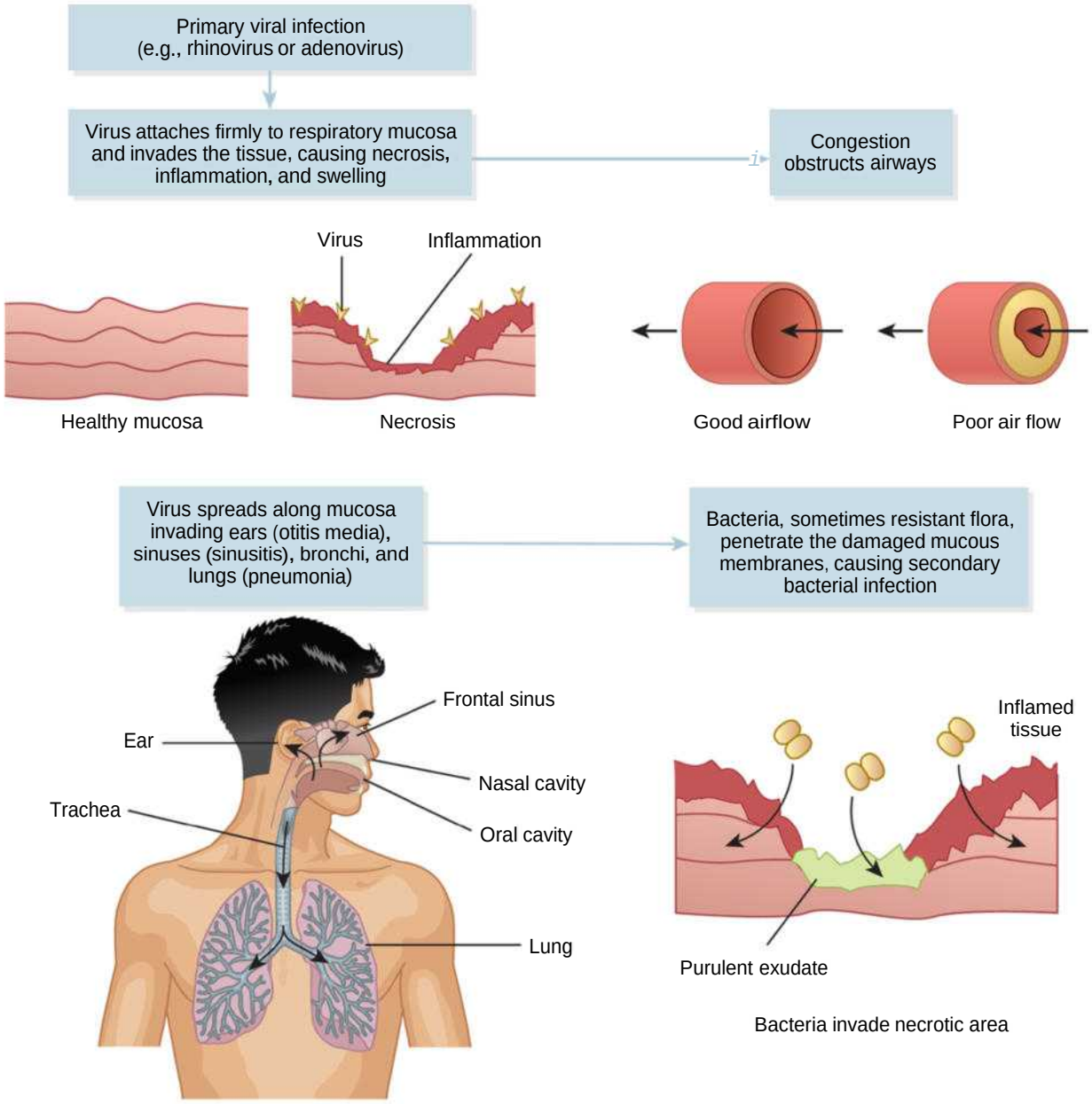


FIGURE 5-13 Complications of viral respiratory infections.

Description

Close physical contact with the virus transmits the infection through exchanges with other humans (e.g., shaking hands) and surfaces (e.g., doorknobs and telephones). Transmission most commonly occurs through direct contact (e.g., hand to hand or hand to mucous membrane) but can also occur through inhalation of large-particle aerosols. Hands are virally contaminated 60% of the time. Despite

popular misconceptions, wet and cold conditions do not cause or increase occurrences of infectious rhinitis. Instead, the apparent increase in occurrence of the infectious rhinitis during rainy and cold weather is due to increased congregation in confined spaces. Those persons in more frequent, closer contact with other people will be at higher risk for developing the infection (e.g., children in daycare centers, healthcare providers, and teachers). The virus is highly contagious because it is shed in large numbers from the nasal mucosa, and it can survive for several hours outside the body. The very young, the elderly, and immunocompromised persons are also at higher risk for both primary viral infections as well as secondary bacterial infections.

An individual who contracts infectious rhinitis usually experiences an incubation period between the invasion of the virus and the onset of symptoms that lasts approximately 1 to 3 days but can be as long as 7 days. Clinical manifestations include the following signs and symptoms:

- Clear nasal discharge (rhinorrhea) initially but may change to white, yellow, or green after 2 to 3 days (due to inflammation of the nasal tissue)
- Sneezing (triggered by nasal discharge)

Myth Busters

Myth 1: You get colds from being cold or wet.

A common misconception is that you get colds from being cold or wet. The fuel for this myth is the increased occurrence of colds during cold and wet weather. In fact, the weather conditions themselves do not make you sick—but the weather does increase congregation of people indoors to avoid those weather conditions. The congregation of people in close, closed spaces is responsible for the spread of the cold. The infectious rhinitis virus is virulent and highly contagious through close contact.

Myth 2: If nasal drainage is white, yellow, or green, you have a bacterial infection and need an antibiotic.

After 2 to 3 days, it is normal for nasal drainage to transition from clear to white, yellow, or green. This change is due to the immune cell activity (e.g., phagocytosis) and cellular by-products. Overprescribing antibiotics when a bacterial culprit has not been identified has contributed to the development of virulent bacteria that are resistant to many antibiotics. Therefore, antibiotics should be used only when a bacterial causative organism is likely or confirmed.

Misconceptions are hard to change; it usually takes multiple efforts. So do your part to educate the public about the truth of cold transmission and prevention!

- Nasal congestion or stuffiness (resulting from nasal drainage)
- Conjunctivitis with lacrimation (eye redness with tearing triggered by immune activity)
- Nonproductive cough (triggered by postnasal mucus drainage)
- Malaise (generalized discomfort caused by immune activity)
- Myalgia (muscle aches and pains caused by immune activity)
- Low-grade fever (due to immune reaction)
- Scratchy or sore throat and hoarseness (due to inflammation of the larynx triggered by mucus)
- Headache (due to inflammation of the sinuses)
- Chills (due to immune reaction)

Diagnosis of infectious rhinitis is primarily made based on the presence of symptoms. Infectious rhinitis presents similarly to the other upper respiratory infections (e.g., pharyngitis, **sinusitis**, and bronchitis), making it difficult to determine whether the etiology is viral or bacterial. Upon physical examination, the nasal passages and oropharynx are usually inflamed and erythematous, mucus may be noted, lymphadenopathy may be present in the neck, and a crease may be present on the top of the nose from an upward wiping away of drainage (nasal salute) (**FIGURE 5-14**). Due to symptoms often mimicking other infections respiratory conditions (e.g., influenza, streptococcus, and COVID-19), those conditions can easily be ruled out with quick mucosal swab tests.

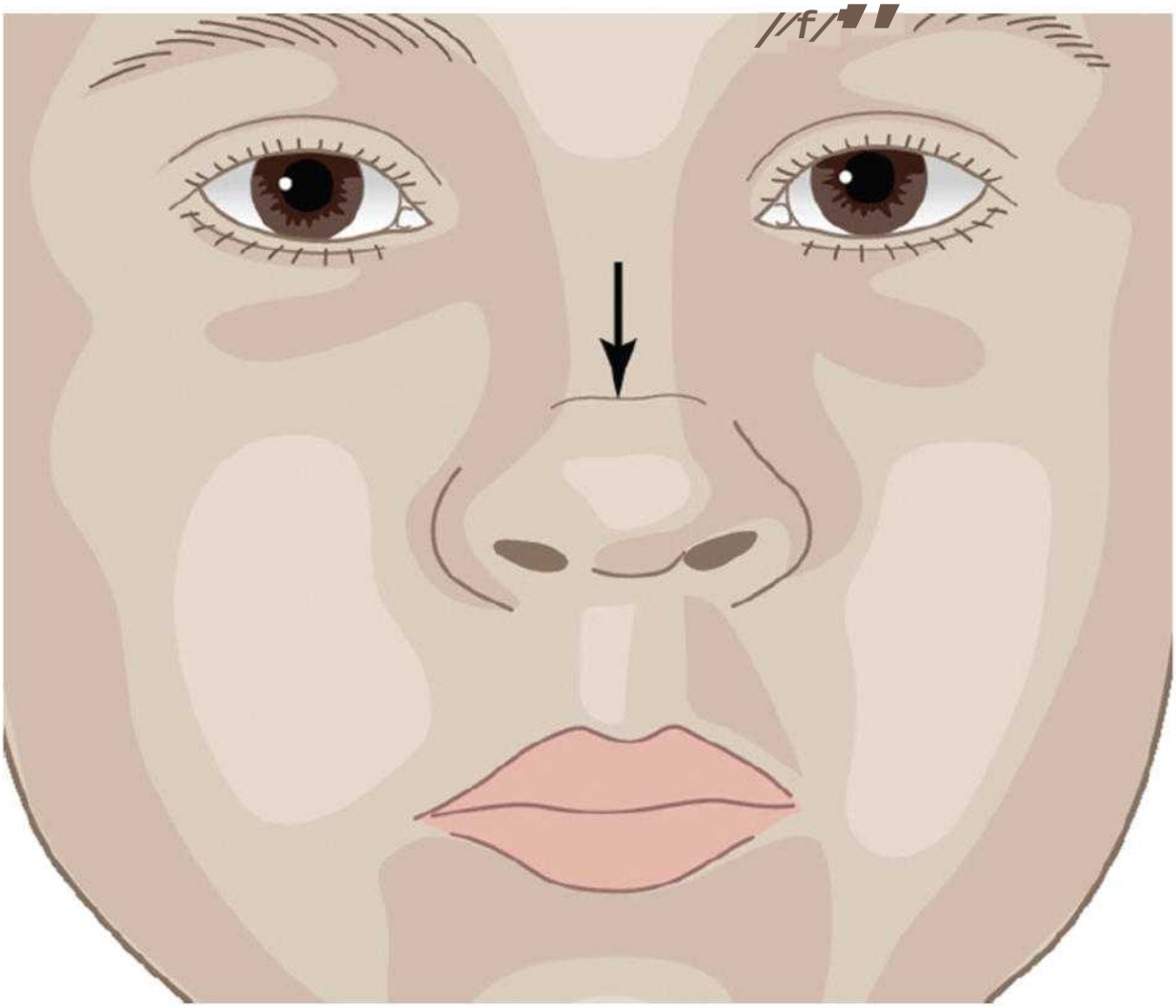


FIGURE 5-14 Nasal salute.

Treatment is symptomatic. Most over-the-counter cold preparations are ineffective in shortening the course of the infection, but they may relieve symptoms. They should be avoided in children younger than 4 years. Symptoms usually resolve within 7 to 10 days. Secondary bacterial infection should be suspected when illness is prolonged or more severe or when manifestations are localized to the sinuses. Pharmacologic therapies that may be used include antipyretics (for fever), analgesics (for discomfort), decongestants (for nasal symptoms), cough suppressants or expectorants, and antibiotics (only if a bacterial infection is present). Humidifiers can liquefy secretions to aid in expectoration. Maintaining adequate hydration can

also liquefy secretions and help manage fevers. Nasal saline can ease nasal discomfort. The benefits of vitamin C, echinacea, and zinc in prevention and treatment remain controversial.

Proper hand washing remains the long-standing cornerstone of prevention because the hands are a significant source of transmission. Hand washing entails using soap and water while rubbing hands together for at least 20 seconds. If soap and water are not available, alcohol-based sanitizer should be used. Additional prevention measures include:

- Cover your mouth when coughing and sneezing, using a tissue or the upper sleeve of your shirt, and dispose of the tissue immediately after use.
- Avoid touching your own eyes, nose, and mouth, especially with unwashed hands.
- Avoid contact with individuals who are sick.
- Disinfect frequently touched surfaces (e.g., toys, doorknobs, phones).
- Stay at home when you are sick and keep sick children out of school or daycare programs to prevent spreading the infection to others.

Rhinosinusitis

Sinusitis is an inflammation of the sinus cavities. Sinusitis rarely occurs without concurrent rhinitis; therefore, rhinosinusitis is now the preferred term for “sinusitis.” Rhinosinusitis occurs when fluid becomes trapped in the sinuses. This condition is most often caused by a viral infection (e.g., rhinovirus, influenza, or adenovirus), but other infectious causative agents include bacteria (e.g., *Streptococcus pneumoniae* or *Haemophilus influenzae*) and fungi (e.g., *Aspergillus* or mucormycosis). Environmental irritants (e.g., smoke exposure and air pollutants), allergens, barotrauma (caused by increased air or water pressure), immunocompromised status (e.g., human immunodeficiency virus [HIV] infection), conditions that increase mucus production (e.g., cystic fibrosis or asthma), nasal

structural abnormalities (e.g., nasal polyps), nasal or sinus tumors, and, among babies, use of a pacifier or drinking from a bottle while lying down can further increase risk.

Rhinosinusitis can be a result of a secondary bacterial infection associated with infectious rhinitis or allergic rhinitis in which the drainage from the sinus cavity has become blocked (**FIGURE 5-15**). The drainage accumulation provides a supportive medium for bacterial growth. *Streptococcus pneumoniae* and *Haemophilus influenzae* are commonly found in the upper airways of healthy people.

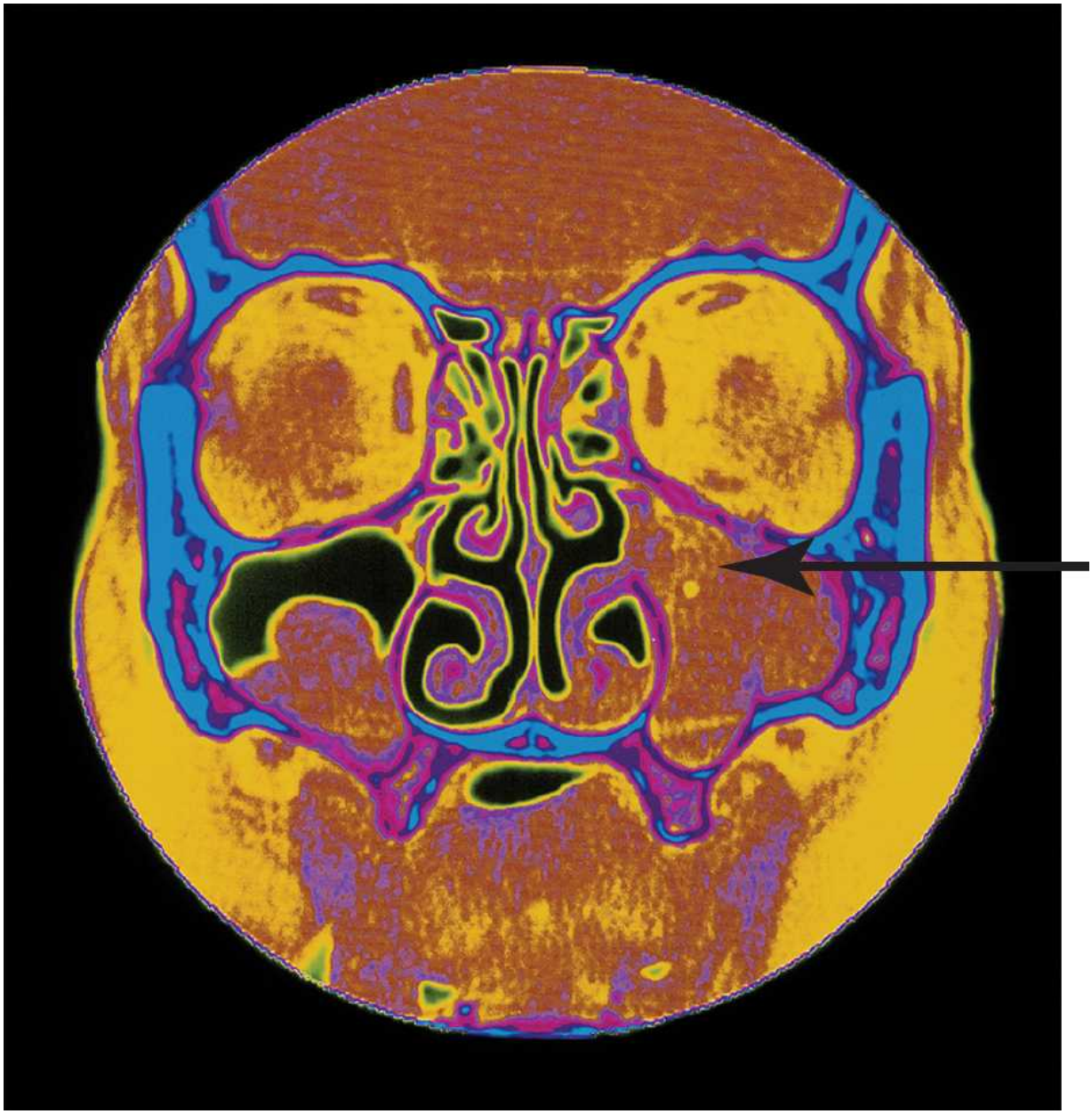


FIGURE 5-15 Blocked sinus.

© Martin Shields/Alamy Stock Photo

Rhinosinusitis can present as several different types:

- Acute, which lasts up to 4 weeks
- Subacute, which lasts 4 to 12 weeks
- Chronic, which lasts more than 12 weeks and can continue for months or even years

* Recurrent, with several attacks occurring within a year

As exudate accumulates, pressure builds in the sinus cavity, which causes facial bone pain and headache, usually described as throbbing or pressure. The location of the pain can indicate which sinus is affected. Other clinical manifestations of rhinosinusitis include nasal congestion, purulent nasal discharge, hyposmia (reduced ability to smell), halitosis (foul-smelling breath), mouth breathing, fever, sore throat, fatigue, and malaise. Complications can include otitis media (in children), orbital cellulitis, meningitis, osteomyelitis, and abscess.

Diagnostic procedures for rhinosinusitis include a history, physical examination, nasal cultures, sinus X-ray, sinus computed tomography (CT), and sinus transillumination (**FIGURE 5-16**). If the sinuses are blocked, the light will minimally appear through the hard palate. Treatment usually includes decongestants (to shrink swollen nasal membranes), analgesics, nasal irrigation with salt water or saline, and nasal corticosteroid spray (to shrink swollen nasal membranes) until the sinuses begin draining. Bacterial infections should be suspected if symptoms persist after 10 days or worsen after initially improving. Bacterial infections require antibiotic therapy to resolve. Other measures may include humidifiers (to liquefy secretions and aid in drainage), warm compresses, adequate hydration, and avoidance of irritants (e.g., smoke, chemicals, and other allergens). In children with recurrent sinusitis and other upper respiratory infections, removing the adenoids may resolve the issue.

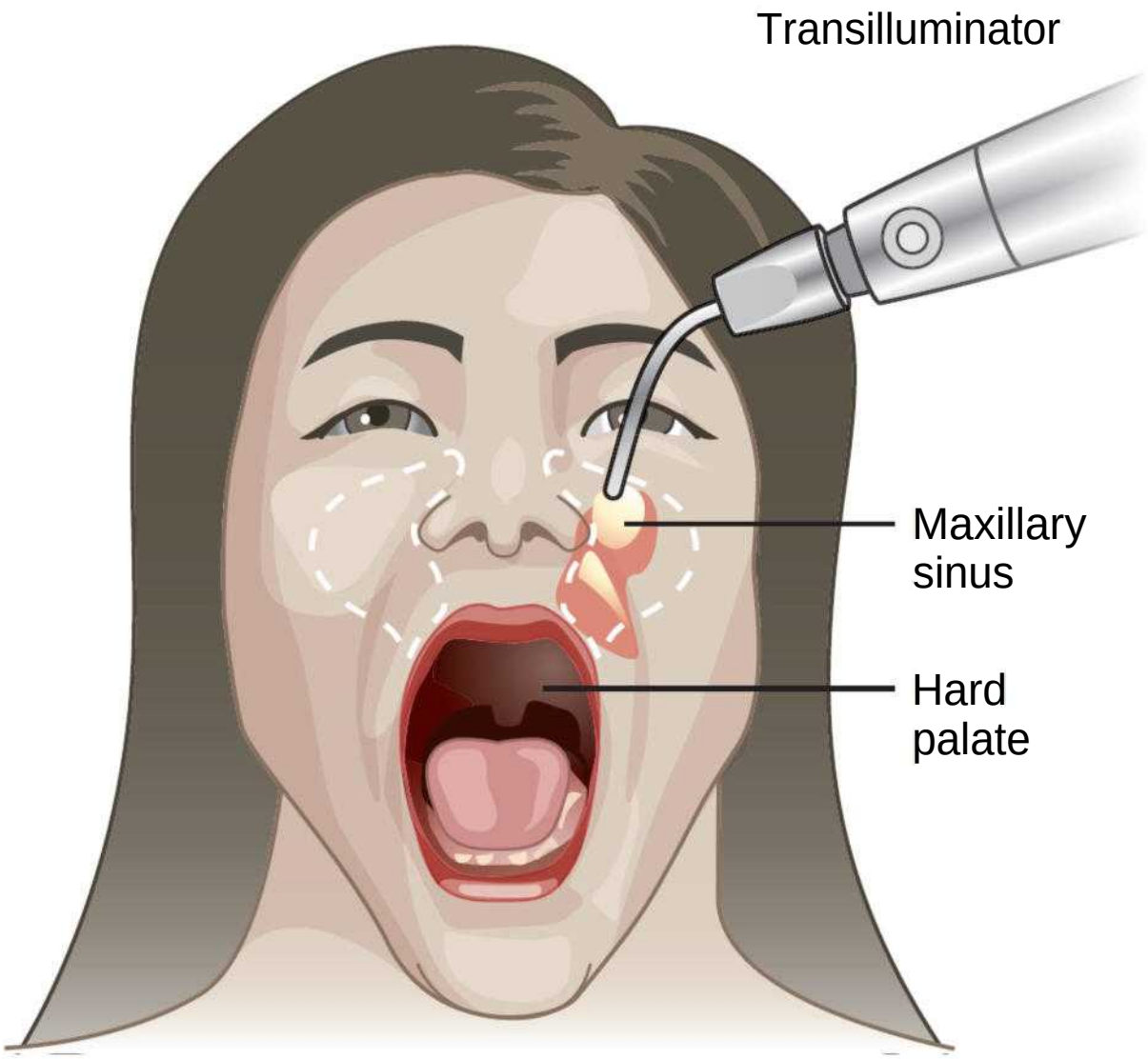


FIGURE 5-16 Transillumination of the sinuses.

Epiglottitis

Epiglottitis is a life-threatening condition of the epiglottis, the protective cartilage lid covering the tracheal opening. In the past, *Haemophilus influenzae* type b (Hib) was the most common cause of epiglottitis in the United States, but widespread use of the Hib vaccine has dramatically decreased the rate of Hib infections in recent years. With the Hib vaccine, epiglottitis is now very uncommon except in adults, who are less likely than children to receive the vaccine. Common culprits now include group A beta-hemolytic *Streptococcus*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. Other

causes include throat trauma from events, such as drinking hot liquids, swallowing a foreign object, a direct blow to the throat, or smoking crack or heroin. The inflammatory response that is triggered by these events causes the epiglottis to quickly swell and block air from entering the trachea, leading to respiratory failure. This swelling is most dangerous in children because their airways are smaller. The bacteria can also travel to the bloodstream (i.e., bacteremia), leading to life-threatening sepsis.

The onset of clinical manifestations is typically rapid in children, developing in a matter of hours, but occurs more slowly in adults, over a few days. These manifestations include the following signs and symptoms:

- High fever
- Chills and shaking
- Sore throat, hoarseness, and muffled speech
- Dysphagia (difficulty swallowing)
- Drooling with the mouth open
- Mild inspiratory stridor (a harsh, high-pitched sound made as a result of air movement restriction)
- Respiratory distress
- Central cyanosis (blue discoloration of the mouth and lips)
- Anxiety, irritability, or restlessness (a result of hypoxia)
- Pallor
- Assuming a sitting tripod position, often leaning slightly forward (a subconscious attempt to facilitate breathing, especially in children)

If epiglottitis is suspected, maintaining the airway and stabilizing respiratory status are the priorities before diagnostic procedures are performed. Efforts to preserve respiratory function include humidified oxygen therapy (likely delivered via mask), endotracheal intubation with mechanical ventilation, and tracheotomy. Additional efforts to minimize oxygen consumption should include keeping the patient calm and controlling fever (e.g., with antipyretics and hydration).

Aerosolized epinephrine and systemic steroids (often given as treatments for croup) should be avoided because they may worsen the condition. Once the patient is stabilized, diagnostic procedures include visualization of the epiglottis through a fiber-optic camera, X-rays (neck and chest), cultures (throat and blood), arterial blood gases (ABGs), and a complete blood count (CBC). The edematous epiglottitis often causes a thumbprint sign on neck X-rays (**FIGURE 5-17**).



FIGURE 5-17 Thumbprint sign.

© DrCHAMPGO/Shutterstock

Intravenous antibiotics are used to treat infections quickly. Hib vaccinations should be encouraged for children, the elderly, and immunocompromised persons so transmission rates will remain low. Other prevention strategies include proper hand washing, avoiding crowds, cleaning objects (e.g., toys), and not sharing objects (e.g., pacifiers and bottles).

Learning Points

Epiglottitis Versus Croup

Epiglottitis is often misdiagnosed as croup. One distinct difference in manifestations can assist healthcare providers in moving to appropriate life-saving treatment more quickly. With epiglottitis, patients "look worse than they sound." With croup, they "sound worse than they look" due to the seal-like barking cough. Additionally, cough is not generally seen with epiglottitis. Although severe croup can cause complete airway obstruction, it is rarely life threatening. Picking up on this significant manifestation can save the patient's life!

Laryngitis

Laryngitis is an inflammation of the larynx. With laryngitis, the vocal cords become irritated and edematous because of the inflammatory process. This inflammation distorts sounds, leading to hoarseness and in some cases making the voice undetectable. Occasionally, the airway can become blocked. Laryngitis may be acute or chronic and is usually a result of an infection, increased upper respiratory exudate, irritants (e.g., stomach acid, inhaled smoke, excessive alcohol use, or chemicals), allergic reactions, or overuse. Viral infections (e.g., influenza, rhinovirus, and adenovirus) are the most common cause. Laryngitis can also be associated with croup and epiglottitis.

Clinical manifestations of laryngitis usually last less than a week and include the following signs and symptoms:

- Hoarseness
- Aphonia (weak voice or voice loss)
- Tickling sensation and raw feeling in the throat
- Sore, dry throat
- Dry cough
- Swollen nodes of the neck
- Low-grade fever
- Leukocytosis (if bacterial)

- Difficulty breathing (especially in children)

Diagnostic procedures for laryngitis include a history, physical examination, CBC, and laryngoscopy. A biopsy may be performed if symptoms persist because throat cancer can mimic acute laryngitis. Treatment depends on the cause, and many times the laryngitis will improve without treatment. Treatment strategies aim to increase comfort or decrease the duration of the inflammation:

- Warm humidity
- Resting the voice (including whispering)
- Increasing fluid intake
- Treating the underlying cause (e.g., infection or gastric reflux)
- Analgesics
- Throat lozenges
- Gargling with salt water
- Avoidance of decongestants, antihistamines, and corticosteroids (they dry out the mucous membranes)

Laryngotracheobronchitis

Laryngotracheobronchitis, or croup, is a common viral infection in children 6 months to 6 years of age (Ernest & Khandhar, 2019). Older children and adults may also contract it. Routine causative agents include parainfluenza viruses, respiratory syncytial virus, rhinovirus, enterovirus, influenza, and adenoviruses. Other causes include bacterial infections, allergens, and irritants (e.g., stomach acid, inhaled smoke, or chemicals). Croup more commonly affects males than females. Outbreaks and epidemics occur from October to early spring, but cases can occur sporadically year-round. Croup was once a deadly disease caused by diphtheria bacteria, but the introduction of antibiotics and immunizations has improved its prevention and treatment. Today, most cases of croup are mild. Nevertheless, this disease can still be dangerous.

Croup generally affects the larynx and trachea but may sometimes extend to the bronchi. This condition usually begins as an upper

respiratory infection with nasal congestion and cough, then spreads to the subglottic space. The cricoid cartilage forms a complete cartilaginous ring that is nonexpanding. The inability of the cricoid to expand and tissue swelling from inflammation significantly narrow the subglottic region. Becoming agitated or crying can further narrow the airway below the ring. This narrowing causes the high-pitched stridor commonly associated with croup, and involvement of the bronchi can lead to abnormal breath sounds (e.g., wheezing and rales), air trapping, and tachypnea. This narrowing can lead to respiratory failure.

Clinical manifestations worsen at night and usually resolve in about a week. These manifestations vary from mild to severe, reflecting the level of respiratory distress present. Manifestations include the following signs and symptoms:

- Low-grade fever
- Nasal congestion
- Sore throat
- Seal-like barking cough (because of laryngeal swelling)
- Hoarseness
- Inspiratory stridor
- Mild expiratory wheezing or rales
- Dyspnea
- Retractions
- Anxiety
- Central cyanosis

Diagnostic procedures for croup consist of a history, physical examination, X-rays (throat), throat cultures, ABGs, and CBC. Several scoring systems are available to assess croup severity (e.g., Westley, Downes and Raphaely, and Taussig) (Johnson, 2014). The Westley score is used to determine croup severity in children younger than 6 years of age. Online calculators are available to determine this score. Diagnosis is usually made based on clinical presentation, so X-

rays are not usually necessary unless diagnosis is unclear. A throat X-ray will reveal a subglottic narrowing (often referred to as the steeple sign) in 50% of cases (**FIGURE 5-18**).



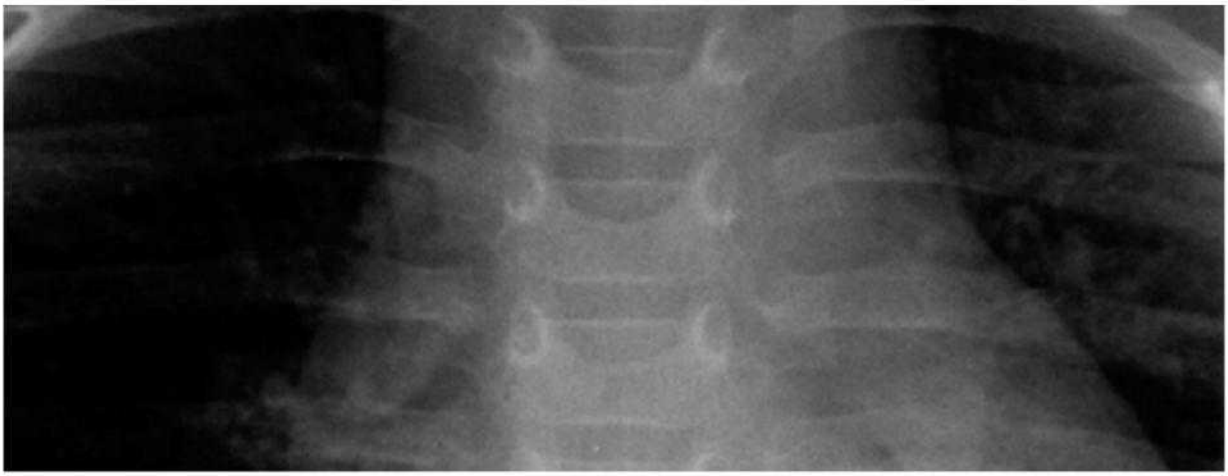


FIGURE 5-18 Steeple sign.

Courtesy of Hugh Dainer, MD, PhD.

Croup is usually self-limiting but can be life threatening without supportive therapy. Treatment strategies include cool humidity, corticosteroids (to decrease edema), humidified oxygen (e.g., an oxygen tent over an infant's crib), bronchodilators (to open the airway), hydration (to combat fever, moisten the airway, and liquefy secretions), and aerosolized epinephrine (in severe respiratory distress). Heliox, a mixture of helium and oxygen, may be used to decrease airway narrowing, but research is mixed on its efficacy (Ernest & Khandhar, 2022). Overall, heliox therapy does no harm. Cool humidity may decrease edema, but no studies have supported this treatment. This intervention should be avoided in patients with asthma because it may trigger bronchial constriction. Cool humidity can be accomplished with a cool-mist humidifier, exposure to cool outside air (especially at night), and exposure to cold shower mist in a closed bathroom. Strategies to decrease oxygen consumption include keeping the patient calm and avoiding unnecessary procedures. Intubation may be required in severe cases that do not respond to treatment, but the endotracheal tube size should be smaller than that typically used for the patient's age to avoid trauma to the already edematous airway. Additionally, educating the public regarding diphtheria vaccination compliance is critical to manage this condition.

Influenza

Influenza, or flu, is a viral infection that may affect the upper and lower respiratory tracts. Influenza viruses are classified based on their nucleoproteins and matrix proteins, of which there are three types—A, B, and C. Hemagglutinin (H) is a glycoprotein on the virus that allows the virus to bind with sialic acid, which helps keep water at the surface of cells, and fuse with the host cell membrane. Neuraminidase (NA) is another glycoprotein that enzymatically removes sialic acid, promoting viral release from the infected host cell. There are 18 H types and 11 NA types, resulting in 198 possible combinations, but only a few are human pathogens.

Influenza viruses are highly adaptive and constantly mutate, which in turn prevents the development of any long-term immune defense. Antigenic drift refers to the relatively minor progressive mutations in preexisting H and NA antigen combinations, which result in new viral strains. These new strains can cause seasonal epidemics because protection by antibodies created by exposure to previous strains is decreased. Antigenic shift refers to the relatively rare development of new H and/or NA antigen combinations, which result from the reassortment of subunits of the viral genome. These new combinations can result in pandemics because antibodies against other strains (either from vaccination or natural infection) provide little or no protection against the new strain.

Influenza types A, B, and C have the following characteristics:

- **Type A influenza**, which includes several subtypes, is highly adaptive and the most common type of influenza virus. This type is usually responsible for the most serious epidemics and global pandemics, such as those that occurred in the United States in 1918, 1957, 1968, and 2009. A subgroup of type A, H3N2, has caused most seasonal epidemics since 1968. A subgroup of type A is H1N1, colloquially referred to as “swine flu,” which was responsible for a serious pandemic that started in the United States and Mexico in 2009.

- **Type B influenza** outbreaks can also cause regional epidemics, but the disease is generally milder than that caused by type A. Type B is moderately adaptive.
- **Type C influenza** causes sporadic cases and minor local outbreaks. Type C does not usually mutate and has never been connected with a large epidemic.

Seasonal epidemics are caused by both types A and B. Current-season influenza information is available at the CDC's (2022d) FluView website, which provides a weekly surveillance report of influenza in the United States. Type A influenza viruses are found in humans and many animals (e.g., ducks, chickens, pigs, and whales). Type B is isolated primarily in humans, whereas type C is found in humans, pigs, and dogs.

Type A influenza has been found in aquatic birds for years without causing harm to them, but this frequently mutating flu virus has shown that it can jump the species barrier from wild birds to domesticated poultry and swine. Pigs can be infected by both avian and human flu, especially in areas where human contact is frequent. If a pig becomes infected with the avian and human flu simultaneously, the two types may exchange genes, causing an antigenic shift. This "reassorted" flu can sometimes spread from pigs to humans and may cause a more or less severe strain. In 1997, for the first time, scientists found that a form of avian H5N1 flu skipped the pig step and infected humans directly. Alarmed health officials feared a worldwide epidemic (a pandemic). Fortunately, the virus could not pass from person to person, so it did not spark an epidemic. In 2013, human infections with the avian H7N9 virus were reported for the first time in China. As of June 2022, there had been 1,568 confirmed human cases of avian flu H7N9 virus worldwide, which resulted in 616 deaths (Food and Agricultural Organization of the United Nations, 2023). As of February 2020, there had been 861 confirmed cases of avian flu H5N1, which resulted in 455 deaths (World Health Organization [WHO], 2023a). Most cases have been associated with direct or indirect contact with infected live or dead poultry.

Millions of Americans contract the flu each year. The flu season (i.e., when the incidence is the highest) in the United States is typically between October and March. The virus is transmitted through inhalation or contact with respiratory droplets. Children are two to three times more likely than adults to contract the flu, and children frequently spread the virus to others. The 2022–2023 U.S. flu season saw mostly influenza type A (H1N1 and H3N2) cases (CDC, 2022d). This flu season was the longest season in a decade, with two waves of influenza A activity of similar magnitude. It was moderately severe. The rate of hospitalizations for adults and children was higher compared with the 2021-2022 influenza season. Persons at greater risk of having negative outcomes because of the flu include children (especially younger than 4 years), adults older than 65, individuals who are immunocompromised, pregnant women, persons who are severely obese (with a body mass index of 40 or higher), and individuals with preexisting chronic diseases (e.g., asthma, cardiovascular disease, diabetes mellitus, kidney disease). Often deaths associated with the flu are a result of secondary **bacterial pneumonia**. Additional complications include encephalitis, myocarditis, myoglobinuria, renal failure, and Reye's syndrome (often occurs with type B influenza in children who have ingested aspirin).

The influenza virus has an incubation period of 1 to 4 days, with peak transmission risk starting approximately 1 day before the onset of symptoms and lasting 4 to 7 days afterward in adults. Children can be infectious for more than 10 days, and young children can spread the virus for 6 days before the onset of symptoms occurs. Severely immunocompromised persons can spread the virus for weeks or months. The flu differs from the common cold in that the flu usually has a sudden onset of symptoms (**TABLE 5-2**). Clinical manifestations of the flu include the following signs and symptoms:

TABLE 5-2 Comparison of Infectious Rhinitis, Influenza, COVID-19, and Respiratory Syncytial Virus Manifestations

Symptoms	Infectious Rhinitis	Influenza	COVID-19	Respiratory Syncytial Virus
Onset	Gradual	Sudden	Gradual	Gradual
Fever	Rare	Usual; high (100°F to 102°F, but occasionally higher, especially in young children); lasts 3–4 days	Common	Common
Headache	Rare	Common	Common	Common
Myalgia	Slight	Usual; often severe	Sometimes	Rare
Malaise	Sometimes	Usual; can last up to 2–3 weeks	Common	Sometimes
Exhaustion	Never	Usual; at the beginning of the illness	Common	Sometimes
Stuffy nose	Common	Sometimes	Common	Common
Loss of taste and smell	Rare	Rare	Common	Rare
Sneezing	Usual	Sometimes	Common	Common
Sore throat	Common	Sometimes	Common	Common
Chest discomfort, cough	Mild to moderate, nonproductive cough	Common; can be severe	Common; can be severe	Common; can be severe
Shortness of breath or dyspnea	Rare	Rare	Common	Sometimes
Wheezing	Rare	Rare	Sometimes	Sometimes
Diarrhea	Never	Sometimes	Sometimes	Rare
Vomiting	Never	Sometimes	Sometimes	Rare

Description

- Fever
- Headache
- Chills
- Dry cough
- Body aches
- Nasal congestion
- Sore throat
- Sweating
- Malaise

* Vomiting and diarrhea (more common in children than in adults)

Typically, fever and body aches last 3 to 5 days, while cough and fatigue may last for 2 or more weeks.

Diagnostic procedures for influenza consist of a history, physical examination, rapid flu screen, and flu culture (a nasal culture that tests for the presence of the virus). Several rapid flu tests are available that can produce results within 30 minutes (e.g., viral antigen, viral ribonucleic acid (RNA), and nucleic acid testing).

Treatment is symptomatic and supportive unless a secondary bacterial infection is present. Antiviral medications (e.g., zanamivir, oseltamivir, and peramivir) can reduce the severity and duration of the symptoms. These antivirals can also be given on a postexposure basis to decrease the likelihood of developing the flu. Adamantanes (e.g., amantadine and rimantadine) were previously used to reduce symptoms, but now more than 99% of current and recent circulating influenza viruses are resistant to them. Other strategies include increased fluid intake, adequate rest, antipyretics, and analgesics. Prevention strategies are similar to those used to prevent the common cold (e.g., hand washing and avoiding crowds) but also include vaccinations.

Currently, vaccinations exist for the seasonal flu and H1N1 flu (if warranted). A vaccine for H5N1 avian influenza has been approved for people older than 18 years at high risk of exposure. Four types of seasonal flu vaccinations are produced: regular seasonal flu vaccine (the form most commonly administered to people 6 months and older), high-dose vaccine (for people age 65 and older), intradermal vaccine (for people age 18–64), and intranasal flu vaccine (produced from a live weakened virus, unlike the other vaccines that are produced from a killed virus; approved for healthy, nonpregnant people age 2–49). Prior to each flu season (usually before the previous season is over), the CDC develops a seasonal flu vaccine based on predictions of the likely strain to be encountered. In the United States, the seasonal flu vaccine should be administered each year in October but may also be administered again in February. The vaccine is recommended to everyone age 6 months and older,

especially those in high-risk groups (e.g., persons with a chronic medical condition, persons age 65 years or older, those who are pregnant, persons living in a community setting, healthcare providers, and household contacts with anyone in these groups). When outbreaks of other types of the flu occur, as with the H1N1 influenza in 2009, the CDC develops vaccinations specific for those strains.

Vaccine development can be a lengthy process. In many cases, the vaccines are grown in fertilized chicken eggs for approximately 10 months. Therefore, flu vaccines should not be administered to persons with egg allergies. Additionally, children younger than 6 months and people with a history of Guillain-Barré syndrome should not be vaccinated. People with an active febrile illness should wait to be vaccinated until after the illness resolves.

COVID-19

In December 2019, a cluster of pneumonia cases was reported by the Wuhan Municipal Health Commission in China that was later identified as a novel coronavirus (SARS-CoV-2, coronavirus disease 2019, or COVID-19) (WHO, 2022c). Over the next several months, this new coronavirus spread across the world. Efforts to limit the transmission of this virus included hand hygiene (e.g., washing hands frequently with soap and water for at least 20 seconds, using had sanitizer containing at least 60% alcohol), avoiding touching mucous membranes (e.g., eyes, nose, and mouth), social distancing (e.g., avoiding people who are sick, staying at least 6 feet from people, avoiding crowds), covering mouth and nose with a mask or other covering when around others, covering coughs and sneezes, and cleaning and disinfecting surfaces frequently. More systemic measures to limit transmissions included variations of government shelter-in-place orders that included measures such as nonessential travel restrictions, closing some businesses (e.g., salons, tattoo shops, movie theaters, retail stores), banning social gatherings (e.g., religious services, funerals, weddings, restaurant dining), conducting education remotely, and working remotely when possible. As of early March 2023, more than 676.6 million cases of COVID-19 have been confirmed worldwide, with approximately 103.8 million cases

occurring in the United States (Johns Hopkins University and Medical, 2023). As of early March 2023, nearly 6.9 million people have died as a result of COVID-19 worldwide, with about 1.1 million deaths occurring in the United States.

Myth Busters

A common misconception is that you can get the flu from the flu vaccine. What fuels this myth is that some people may experience very mild flu-like symptoms (e.g., low-grade fever, aches, malaise) after receiving the vaccination. These symptoms do not occur because the individual has a mild case of the flu; rather, they are due to the process through which the immune system develops antibodies against the virus. An additional factor fueling this myth is the possibility that people may still get the flu even after receiving the vaccination. Since most flu vaccines use killed viruses, the infection is not typically caused by receiving the vaccine; rather, it occurs because the person encounters a strain of flu that was not covered by the vaccination. Remember—the vaccination is based on predictions. Negative outcomes from the flu vaccine are rare and minimal. So, get vaccinated and encourage others to do the same!

Research was quickly started to determine the pathogenesis and transmission as well as to identify treatments. The SARS-CoV-2 quickly mutated, creating variants that increased the transmissibility, more severe disease, or reduced response to treatments and/or vaccines. These variants were identified and tracked based on the Greek alphabet or their Pango lineage number. The Omicron variants have been the predominant strains worldwide since March 2022 (CDC, 2023b).

Transmission easily occurs through close person-to-person contact usually through respiratory droplets produced when the infected person coughs, sneezes, or talks. Less common, transmission can occur through contact with fomites on contaminated surfaces followed by contact with mucous membranes. Transmission is possible during the incubation period and when symptoms are not present. Severity varies widely from asymptomatic to acute respiratory failure and death. Advanced age, immunocompromise, comorbidity (e.g., diabetes, chronic kidney disease, heart disease, etc.), and pregnancy

increase disease severity and morbidity risk. In the United States, COVID-19 cases, hospitalization, and death rates are higher in African Americans, Hispanics or Latinos, American Indians, and Alaska Natives. Clinical manifestations vary widely and may appear 2 to 14 days after exposure. When present, manifestations may include cough, dyspnea, fever, chills, headache, sore throat, fatigue, muscle pain, nausea or vomiting, diarrhea, or loss of taste and smell. Dyspnea, hypoxia, and extensive lung involvement are common with severe disease. Severe disease can progress to respiratory failure, shock, multiorgan failure, heart disorders (e.g., arrhythmias, cardiomyopathy, acute cardiac injury), coagulation disorders (thromboembolism, disseminated intravascular coagulation, hemorrhage, and death. A postinfection inflammatory syndrome and long-term sequelae may develop and can linger for months (see *Immunity* chapter) (CDC, 2023b).

Diagnosis of COVID-19 includes real-time reverse transcriptase-polymerase chain reaction (RT-PCR), nucleic acid amplification test (NAAT), and antigen testing of respiratory secretions. Testing should be done for individuals who are symptomatic or as a screening tool (e.g., when exposure is likely or when entering communal living). People who have been in close contact with someone infected with COVID-19 but are asymptomatic should get tested at least 5 days after last contact. Wearing a mask is recommended until negative test results are achieved. Other diagnostic procedures typically include chest X-ray and chest CT.

Treatment strategies include antiviral agents (e.g., ritonavir, remdesivir, molnupiravir), dexamethasone, immunomodulators, and supportive care (e.g., fluid replacement, oxygen therapy, endotracheal intubation with mechanical ventilation, prone positioning). Vaccines have demonstrated some effectiveness in preventing transmission and very effective in preventing severe disease and mortality. Hospitalization may be required depending on the severity. People presenting with clinical manifestations should isolate until negative results are achieved.

Lower Respiratory Tract Infections

The lower respiratory tract includes the trachea, bronchi, bronchioles, and alveoli. Infections in these areas trigger inflammation and can have similar manifestations and etiology as those associated with the upper respiratory tract. Infections in the upper respiratory tract can spread to the lower tract. Lower tract infections can be life threatening.

Acute Bronchitis

Acute bronchitis is an inflammation of the tracheobronchial tree or large bronchi that frequently follows an upper respiratory infection. This inflammation is most commonly caused by a wide range of viruses (e.g., influenza, rhinovirus, respiratory syncytial virus, SARS-CoV-2, and adenovirus), but the pathogen is rarely identified. Bacterial invasions (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Chlamydia pneumoniae*), irritant inhalation (e.g., smoke, marijuana, pollution, and ammonia), and allergic reactions are less frequent causes. Young children, the elderly, smokers, and individuals with underlying chronic bronchial disorders (e.g., asthma, chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis) are at the highest risk for developing acute bronchitis.

In acute bronchitis, the bronchial lining becomes irritated, and the airways narrow due to the results of the inflammatory process (e.g., capillary dilation, edema, and exudate). Clinical manifestations of acute bronchitis are usually mild and resolve in 7 to 10 days, but coughing may linger for several weeks after the infection is resolved. Manifestations include the following:

- Nonproductive cough that may progress to a productive cough
- Sputum that may be clear, purulent, or occasionally bloody (characteristics do not correspond to a particular etiology)
- Dyspnea
- Audible wheezing

- Abnormal lung sounds (usually rales or rhonchi)
- Low-grade fever (usually suggests influenza, pneumonia, or COVID-19)
- Pharyngitis
- Malaise
- Myalgia
- Chest discomfort

Diagnosis of acute bronchitis is usually based on symptoms. Additionally, a CBC, cultures (e.g., nasal secretions, sputum, blood), and chest X-ray may be performed for differential diagnosis purposes or if complications are suspected (e.g., pneumonia).

Acute bronchitis is generally self-limiting; therefore, treatment is often supportive. Pharmacologic treatment may include antipyretics, analgesics, antihistamines, decongestants, cough suppressants (i.e., antitussives), bronchodilators, and antibiotics (in case of bacterial infection). Cough suppressants should be used cautiously, as coughing mobilizes secretions and can prevent pneumonia. Other supportive strategies include increasing fluid intake, avoiding smoke, and humidifying air.

Bronchiolitis

Bronchiolitis refers to a common acute inflammation of the bronchioles usually resulting from a viral infection, which is frequently caused by the respiratory syncytial virus (RSV). This infection most often occurs in children younger than 1 year of age, and incidence increases in the fall and winter months. According to the CDC (2022e), 2.1 million children younger than the age of 5 years seek medical attention annually for RSV infection, and nearly all children will have had an RSV infection by the time they are 2 years old. Transmission of RSV occurs through contact with or inhalation of infected respiratory droplets. Other common causes include infection with rhinovirus and parainfluenza virus type 3. Less frequently encountered infectious agents include influenza viruses A and B,

parainfluenza viruses types 1 and 2, metapneumovirus, adenoviruses, and *Mycoplasma pneumoniae.*

The virus typically spreads from an upper respiratory tract to the bronchioles, causing epithelial necrosis and triggering inflammation. These small airways become swollen, and mucus collects there, preventing air flow into and out of the alveoli. Factors contributing to the development of bronchiolitis include neonatal prematurity, asthma family history, and cigarette smoke exposure.

Clinical manifestations of bronchiolitis vary in severity but include the following signs and symptoms:

- Nasal drainage
- Nasal congestion
- Cough
- Wheezing
- Abnormal lung sounds (e.g., rhonchi or rales)
- Rapid, shallow respirations
- Labored breathing (e.g., chest retractions, nasal flaring, and grunting)
- Prolonged expiration
- Dyspnea or tachypnea
- Circumoral cyanosis
- Fever
- Tachycardia
- Malaise
- Lethargy

Diagnostic procedures include a history, physical examination, RSV antigen test, CBC, and ABGs. A routine chest X-ray is also not necessary unless complications are suspected.

Prognosis is excellent, and most children recover in 3 to 5 days. Bronchiolitis can progress to atelectasis (collapse of the alveoli) and respiratory failure without aggressive and early treatment; therefore,

airway management and respiratory stability are the treatment foci. Hospitalization is often required, and intubation may be necessary if the child decompensates or respiratory failure occurs. Other treatment strategies include oxygen therapy, cool humidity, suctioning secretions, increased fluids (either by mouth or intravenously), keeping the patient calm, bronchodilators, and corticosteroids. Antibiotics should be withheld unless a secondary bacterial infection is present. No specific treatment for RSV infection is available.

Prevention strategies are the same as those previously discussed for other infectious respiratory conditions (e.g., hand washing and avoiding crowds). Palivizumab (Synagis), a monoclonal antibody, is an injection that can be given to at-risk infants monthly during RSV season to prevent and minimize infection. It is not a vaccine; instead, palivizumab targets RSV's fusion protein, inhibiting its entry into the cell. Numerous vaccines for RSV are in development, with one recently approved for individuals 60 years and older (i.e., Arexyv).

Pneumonia

Pneumonia refers to inflammation of the lung, which may be triggered by numerous infectious agents (e.g., bacteria, viruses, and fungi) and injurious agents or events (e.g., aspiration and smoke). Pneumonia affects the portions of the lungs that are involved in gas transfer (e.g., alveoli, alveolar ducts, and bronchioles). According to the CDC (2023c), this disease accounts for 1.2 million hospitalizations and over 41,000 deaths in the United States annually. Pneumonia, along with influenza, is the ninth leading cause of death in the United States.

Streptococcus pneumoniae is responsible for 75% of all cases of pneumonia in the absence of an ongoing viral pandemic such as COVID-19, and the most common viral causes are influenza, parainfluenza, metapneumovirus, and RSV. **Viral pneumonia** and bacterial pneumonia have some notable differences (**TABLE 5-3**). Notably, viral pneumonia is usually mild and heals without intervention, but it can lead to virulent bacterial pneumonia. Microaspiration of pathogens from the upper respiratory tract is a regular occurrence, but the lung's host defenses usually deal with them without incident. Pneumonia develops when the person is immunocompromised, large

volumes of pathogens are aspirated or a particularly virulent pathogen is inhaled. Occasionally, pneumonia develops when pathogens invade the lungs from the bloodstream or surrounding tissue.

TABLE 5-3 Comparison of Viral and Bacterial Pneumonia

	Viral	Bacterial
Cough	Nonproductive	Productive
Fever	Low grade	Higher
White blood cell count	Normal (low)	Elevated
X-ray	Minimal change	Infiltrates
Severity	Less	More
Antibiotics	No	Yes

Irritating agents or events can also lead to pneumonia—for example, aspiration of gastric contents, endotracheal intubation, respiratory suctioning, and inhalation of smoke or chemicals. **Aspiration pneumonia** frequently occurs when the gag reflex is impaired because of a brain injury or anesthesia. Aspiration can also occur because of impaired lower esophageal sphincter closure secondary to nasogastric tube placement or disease (e.g., gastroesophageal reflux disease). Additionally, inappropriate gastric tube placement can lead to tube-feeding formulas entering the lungs rather than the stomach. Gastric contents and tube-feeding formulas irritate the lung tissue, triggering the inflammatory response. The inflammatory response increases mucus production, which can in turn lead to atelectasis and pneumonia. Tube-feeding formulas also contain sugar and protein, creating a superior medium in which bacteria can grow and flourish.

Finally, pneumonia can develop from the stasis of pulmonary secretions. Activities such as movement, talking, and coughing normally keep pulmonary secretions moving, and adequate hydration keeps secretions thin. When these secretions become thick and stagnate, ciliary action cannot remove the bacteria-laden mucus, leading to pneumonia.

Pneumonia is classified based on the causative agents or events, as previously discussed, and its location in the lung (TABLE 5-4). **Lobar pneumonia** is confined to a single lobe and is described based on the affected lobe (e.g., right upper lobe). **Bronchopneumonia**, the most frequent type, is a patchy pneumonia spread throughout several lobes. **Interstitial pneumonia**, or atypical pneumonia, occurs in the areas between the alveoli. Interstitial pneumonia is routinely caused by viruses (e.g., influenza type A and B) or by uncommon bacteria (e.g., *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*).

TABLE 5-4 Types of Pneumonias

	Lobar Pneumonia	Bronchopneumonia	Interstitial Pneumonia
Distribution	All of one or two lobes	Scattered small patches	Scattered small patches
Cause	*Streptococcus pneumoniae*	Multiple bacteria	Influenza virus; *Mycoplasma*
Pathophysiology	Inflammation of the alveolar wall and leakage of cells, fibrin, and fluid into alveoli, causing consolidation	Inflammation and purulent exudates in alveoli, often developing from pooled secretions or irritation	Interstitial inflammation around alveoli Necrosis of bronchial epithelium
Onset	Sudden and acute	Insidious	Variable
Signs	High fever Chills Productive cough of rusty sputum Rales progressing to absent breath sounds in affected lobes	Mild fever Productive cough of yellow-green sputum Dyspnea	Variable fever Nonproductive hacking cough Headache Myalgia

Description

Legionnaires' disease is a specific type of pneumonia that is caused by *Legionella pneumophilia*. These bacteria thrive in warm,

moist environments (e.g., air-conditioning systems, standing freshwater, respiratory therapy equipment, and whirlpools). Legionnaires' disease is not contagious. Instead, most people acquire this type of pneumonia from inhaling the bacteria as they are spread by an air-conditioning system or spa. Persons with a weakened immune system are at highest risk for developing Legionnaires' disease. Although most people who develop this type of pneumonia recover without incident, the disease can be fatal if untreated. Symptoms are similar to those of other types of pneumonia and usually appear 10 to 14 days postexposure. Additional symptoms may include nausea, vomiting, and diarrhea. Along with the usual pneumonia diagnostic procedures, a urine test can be performed to identify the presence of *Legionella* antigens. Treatment of Legionnaires' disease follows the usual pneumonia treatment protocol.

Mycoplasma pneumoniae causes a common type of pneumonia that usually affects people younger than 40 years of age. People who live or work in crowded places, such as schools, homeless shelters, and prisons, are at higher risk of developing this type of pneumonia. *Mycoplasma* infection is usually mild and responds well to antibiotics, but it can be serious. Skin rash, arthralgia, and hemolysis may also be present.

Severe acute respiratory syndrome (SARS) is a respiratory illness that presents similarly to atypical pneumonia. First identified in China, its prevalence rates remain higher in Asian countries. SARS is caused by a coronavirus, SARS-CoV. Transmission occurs through inhalation of respiratory droplets or close contact, although oral–fecal contact may also be a mechanism of transmission. SARS has high mortality and morbidity rates. The incubation period for this disease is 2 to 7 days. The first stage presents as a flulike syndrome (e.g., fever, chills, headache, myalgia, anorexia, and diarrhea) that lasts 3 to 7 days. Several days later, a dry cough and dyspnea develop as the lungs become damaged and the patient moves into the second stage of the disease. Interstitial congestion and hypoxia progress rapidly. Additionally, liver damage can occur. If the patient continues to the third stage, severe and sometimes fatal respiratory distress

can develop. Diagnostic procedures for SARS consist of a history, physical examination, and chest X-ray. Treatment focuses on maintaining oxygenation and respiratory status, with strategies including oxygen therapy, bronchodilators, and antiviral drugs. Endotracheal intubation with mechanical ventilation support may be required as hypoxia worsens.

A growing illness in the same coronavirus family is **Middle East respiratory syndrome (MERS-CoV)**. It was first reported in Saudi Arabia in 2012 and has since spread to several other countries, including the United States (CDC, 2019). Between its discovery in April 2012 and February 2023, 2,604 confirmed cases and 936 deaths from this disease were reported worldwide (WHO, 2023b). The virus is currently isolated to four countries in the Arabian Peninsula. It seems to spread through close contact, but the CDC continues to work on better understanding the virus.

Pneumonia is also classified according to where it is acquired. **Nosocomial pneumonia** refers to pneumonia that develops more than 48 hours after a hospital admission. Ventilator-associated pneumonia (VAP) is an example of nosocomial pneumonia. With this disease, the endotracheal tube provides a portal of entry for bacteria. The most common causes of nosocomial and VAP are gram-negative bacilli and *Staphylococcus aureus*. Antibiotic-resistant organisms are of particular concern with these types. In contrast, **community-acquired pneumonia** is acquired outside the hospital or healthcare setting. The most common causes of community-acquired pneumonia are *Streptococcus pneumoniae*, *Haemophilus influenzae*, atypical bacteria (e.g., *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*), and viruses.

Most healthy people do not develop pneumonia from fungal exposure. Instead, many of these illnesses occur as opportunistic infections, which can be fatal in immunocompromised individuals (e.g., children and persons with acquired immunodeficiency syndrome [AIDS] or cancer). **Pneumocystis jirovecii pneumonia**, formerly known as *Pneumocystis carinii* pneumonia, is a specific type of pneumonia that is caused by yeast-like fungus. Its diagnosis is accomplished through identification of the fungus through a sputum

culture. Aggressive and early treatment will improve outcomes in vulnerable patients. Other fungal-related pneumonias include histoplasmosis, coccidiomycosis, and cryptococcal pneumonia.

In addition to previously discussed risk factors, persons at risk for developing pneumonia and having serious complications include children, the elderly, immunocompromised individuals, those with existing chronic disease conditions, smokers, and alcoholics. Otherwise-healthy patients usually recover completely from pneumonia when treated properly. By comparison, high-risk persons are more likely to develop complications including bacteremia, septicemia, septic shock, pulmonary edema, lung abscess, **pleural effusion**, **pleurisy**, and acute respiratory distress syndrome.

Clinical manifestations of pneumonia may vary depending on type and include the following signs and symptoms:

- Productive or nonproductive cough
- Fatigue
- Pleuritic pain
- Dyspnea
- Fever
- Chills
- Abnormal lung sounds (e.g., rales)
- Pleural rub
- Tachypnea
- Mental status changes (especially in the elderly)
- Leukocytosis

Early diagnosis and treatment of pneumonia are paramount to have positive outcomes. Diagnostic procedures may include a history, physical examination, chest X-ray, sputum cultures (with antibiogram to identify antibiotic susceptibility and resistance patterns), CBC, ABGs, chest CT, and bronchoscopy. Community-acquired pneumonia can usually be managed on an outpatient basis unless the patient is in a high-risk category (e.g., children, the elderly, immunocompromised

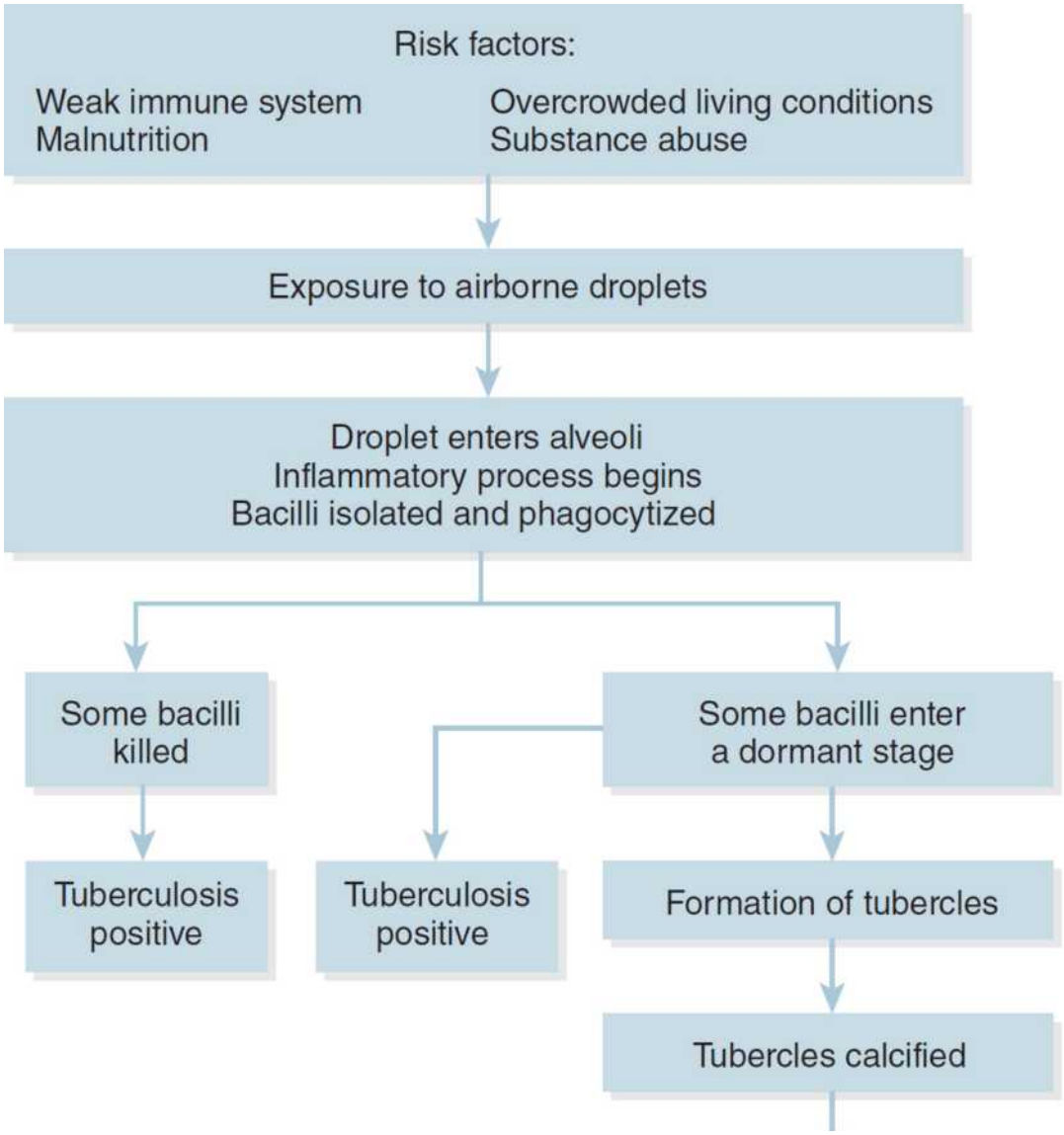
individuals, those with existing chronic disease conditions, smokers, and alcoholics). Hospitalization is necessary for severe cases in which respiratory distress or septicemia is present. Managing respiratory status is the priority, and endotracheal intubation may be necessary to provide ventilation support and maintain oxygenation. Additional treatment strategies include antibiotics (if bacterial infection is present), bronchodilators, corticosteroids, antipyretics, analgesics, humidified oxygen therapy, chest physiotherapy, increased fluids (either by mouth or intravenously), and rest. If aspiration is the cause of the pneumonia, additional treatment includes eliminating the causes and not giving the patient anything by mouth until swallowing studies can be performed. Pneumonia prevention strategies include hand washing, avoiding crowds, vaccinations (e.g., for pneumococcus, influenza, and Hib), mobilizing secretions (e.g., turning, coughing, deep breathing), and smoking cessation.

Tuberculosis

Tuberculosis (TB), an ancient disease, is one of the world's deadliest conditions. Although on the decline, TB remains a major cause of illness, with one-fourth of the world's population being infected. According to the WHO, TB was responsible for approximately 1.6 million deaths worldwide in 2021, and it is the leading cause of death for persons infected with HIV (WHO, 2022b). Nearly 8,000 TB cases were reported in the United States in 2021. TB rates are highest among Asians, followed by Native Hawaiians/Pacific Islanders, African Americans, Hispanic Americans, and American Indian/Alaska Natives (CDC, 2022f). Though the overall rate continues to decrease in the United States, 10 states (Alaska, California, Florida, Hawaii, Maryland, Massachusetts, Minnesota, New Jersey, New York, and Texas) and the District of Columbia reported incidence rates above the national average. It is estimated that between 3% and 5% of the U.S. population has latent TB infection (i.e., infected but do not have an **active infection**).

TB is caused by *Mycobacterium tuberculosis*, a slow-growing aerobic (requires oxygen) bacillus that is somewhat resistant to the body's immune efforts. Person-to-person transmission occurs through

the inhalation of tiny infected aerosol droplets (FIGURE 5-19). Only people with active TB can spread the disease to others. The bacillus is capable of surviving in dried sputum for weeks, but ultraviolet light, heat, alcohol, glutaraldehyde, and formaldehyde destroy it. Many people contract TB but do not develop the disease because of an intact, healthy immune system or early treatment. Multidrug-resistant TB strains are relatively rare in the United States but account for 1.3% of new TB cases and 1 in 3 diagnosed cases worldwide. Extensively drug-resistant TB is very rare in the United States, with only 4 known cases occurring in 2021; in contrast, this global threat occurs in 8.5% of multidrug-resistant cases worldwide.



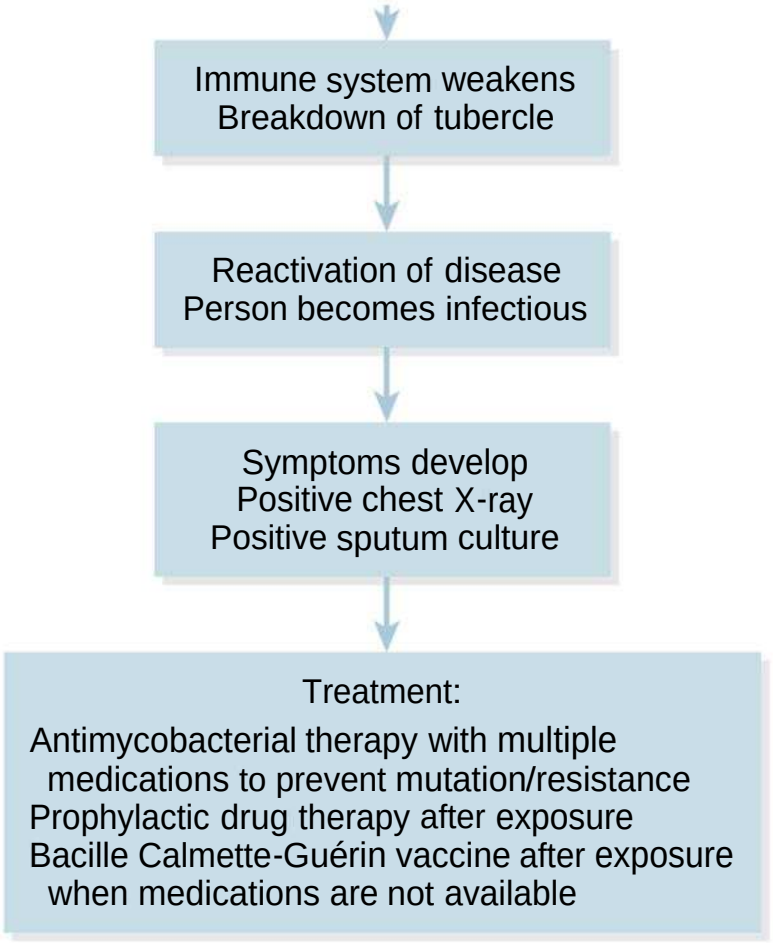


FIGURE 5-19 Tuberculosis.

Description

Although TB most frequently involves the lungs, it can also affect other organs and tissues (e.g., liver, brain, and bone marrow). TB is often considered an opportunistic infection because it is more likely to become active in someone with a weakened immune system. At-risk persons, then, include those with immune deficiency (e.g., AIDS and cancer), malnutrition, diabetes mellitus, and alcoholism. Poverty, overcrowding, homelessness, and drug abuse also increase the risk of acquiring TB.

There are three stages of TB pathogenesis—primary, latent, and active infection. **Primary TB infection** occurs when the bacillus first enters the body. In this phase, macrophages engulf the microbe, causing a local inflammatory response. Bacilli that are not killed by

the macrophages replicate inside them and ultimately kill the host macrophage. Some bacilli travel to the lymph nodes, where they access the bloodstream and activate the type IV hypersensitivity reaction (see the *Immunity* chapter). Moving through the bloodstream, the bacilli can travel to other areas of the body (i.e., miliary TB). Lymphocytes and macrophages congregate to form a granuloma (an epithelial nodule). The granuloma contains some live bacilli, forming a tubercle. Caseous necrosis, a cottage cheese–like material, develops in the center of the tubercle (see the *Cellular Function* chapter). An intact immune system can resist this development, so the lesions—referred to as Ghon complexes (**FIGURE 5-20**)—remain small, become walled off by fibrous tissue, and calcify.

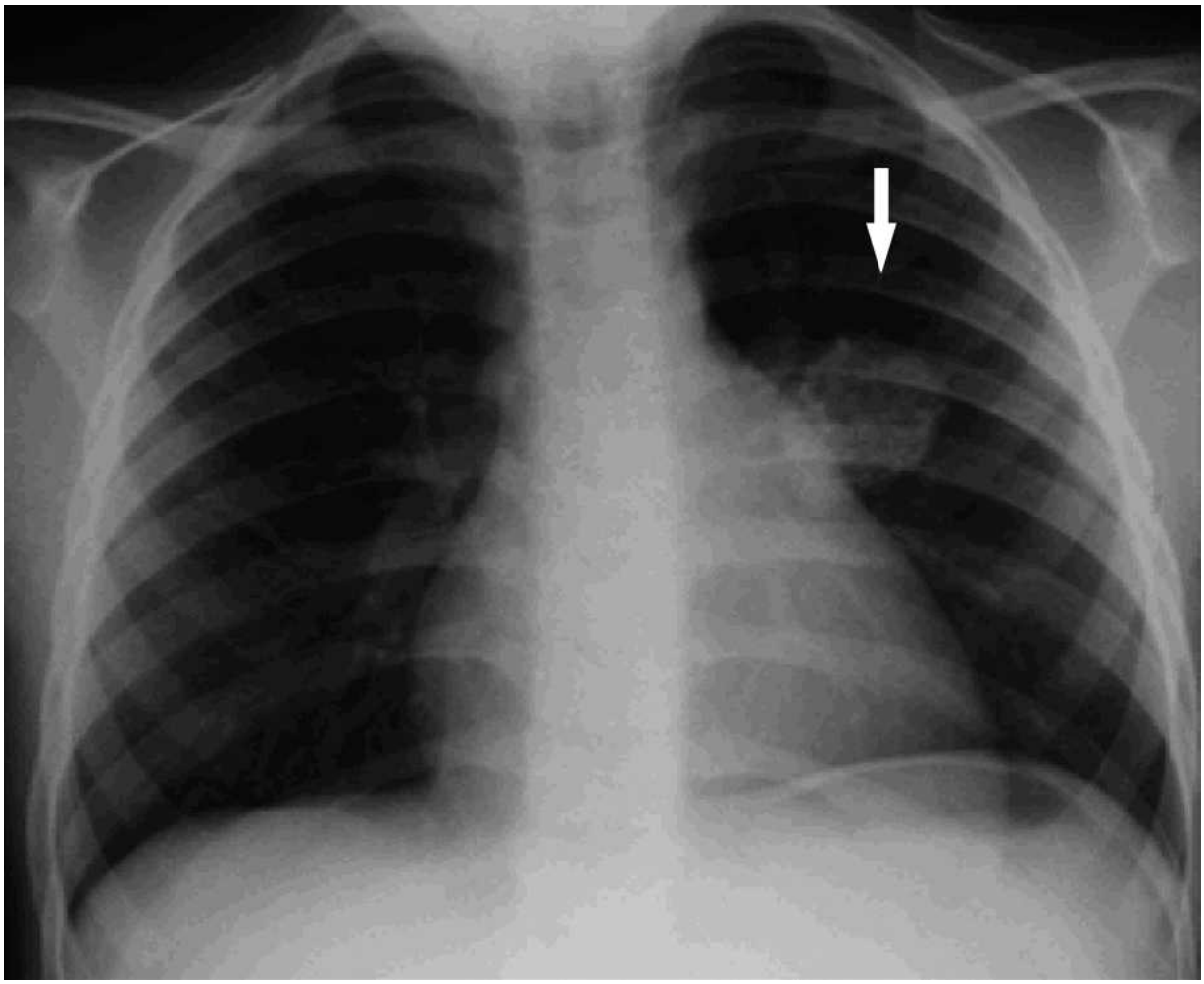


FIGURE 5-20 Ghon complexes.

Courtesy of Benjamin M. Marais.

After most primary infections, the bacilli can remain dormant (i.e., latent TB infection) and viable in the tubercle for years as long as the immune system is intact. In this phase, the individual has been infected by the bacilli and remains asymptomatic.

When the bacillus can no longer be controlled, the infection progresses to the active infection phase. Immunocompromised states often facilitate reactivation of the bacilli, but reinfection may also cause active disease to develop. During the active phase, clinical manifestations begin to appear:

- Productive cough
- Hemoptysis (coughing up blood or bloody sputum)
- Night sweats
- Fever
- Chills
- Fatigue
- Unexplained weight loss
- Anorexia
- Miscellaneous symptoms depending on other organ involvement

Diagnostic procedures for TB are multifaceted, usually beginning with a TB skin test (Mantoux test) or a blood test, the interferon-gamma release assay (IGRA). For the TB skin test, a small amount of a purified protein derivative tuberculin is injected just below the dermis. If the bacilli have infected the person, a local reaction (e.g., redness and induration) will occur (**FIGURE 5-21**). The induration (raised area) is measured to determine if the person is positive; persons will test positive once the bacilli trigger the inflammatory response. A history of bacillus Calmette-Guérin (BCG) vaccination will produce a false-positive reaction, as will a history of previously treated TB. Conversely, persons with immature (e.g., children) or

compromised (e.g., AIDS or cancer) immune systems may not generate enough of a response to test positive.



FIGURE 5-21 Positive tuberculosis skin test.

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The IGRA (e.g., QuantiFERON TB Gold and T-SPOT) measures the release of interferon-gamma by lymphocytes when exposed to TB-specific antigens. IGRAs appear to be as sensitive and more specific than TB skin tests. They are often negative after TB has been treated, and they are not affected by the BCG vaccine. However, IGRAs are often expensive.

Because of the uncertainty that the TB skin test creates, chest X-rays and sputum cultures (most definitive results) are used after a positive TB skin test is noted, either to confirm an original case or to assess reinfection. A CT scan can also be used to visualize TB lesions, because this imaging modality is more sensitive than an X-

ray. Nucleic acid amplification may be performed on the sputum to detect the presence of resistant strains.

Learning Points

TB skin testing is only useful as a screening tool to identify new TB exposure cases. Once a person's immune system has developed antibodies against TB, the person tests positive. This immunity reaction happens after the first exposure and vaccination administration. A person can be treated for TB, and he or she will continue to test positive because the antibodies are still present. Chest X-rays and sputum cultures are better diagnostic procedures once someone has tested positive. So, remember: Once positive, always positive!

Emerging Research: Lung Illness Associated with E-Cigarette Products

Beginning in 2007, e-cigarettes were marketed as a safer alternative to regular cigarettes and other smoked tobacco products. E-cigarettes are devices that deliver an aerosol to the user by heating a liquid that usually contains nicotine, flavorings, and other chemicals. E-cigarettes can also be used to deliver marijuana and other substances. While they may have a potential benefit to adult smokers, they are not safe for youth, young adults, pregnant women, or adults who do not currently smoke.

As e-cigarettes are a fairly new product, the long-term consequences of their use are not fully understood. Nevertheless, these products have raised alarms among healthcare providers. The e-cigarette aerosol that users breathe in contains harmful and potentially harmful substances (e.g., nicotine, flavoring, volatile organic compounds, cancer-causing chemicals, and heavy metals). The flavoring diacetyl has been linked to bronchiolitis obliterans, a severe, irreversible lung disease colloquially termed "popcorn lung" because it first appeared in workers who inhaled butter flavor in microwave popcorn processing facilities.

The marketing campaigns for e-cigarettes and the more than 7,000 appealing flavors (e.g., bubble gum, cherry, chocolate) of these products have served to "re-normalize" nicotine use and addiction, especially among adolescents and young adults. In 2022, 1 out of every 30 U.S. middle and high school students reported having used e-cigarettes in the past 30 days (1 out of 100 reported having smoked cigarettes) and 1 out of every 7 high school students reported having used e-cigarettes in the past 30 days (2 out of every 100 reported having smoked cigarettes). Some e-cigarettes have high levels of nicotine; such is the case with Juul, which has become popular with this age group. Nicotine is highly addictive and can harm adolescent brain development, which continues until the mid-20s. During this time, creating new memories and learning new skills builds synapses between brain cells. Nicotine changes the way these synapses are formed.

There may also be a link between e-cigarettes—especially those with higher nicotine concentrations—and seizure activity. Nicotine poisoning has occurred by swallowing, breathing, or absorbing e-cigarette liquid through the skin or eyes. E-cigarette use in individuals who did not previously use regular cigarettes or other smoked tobacco has been shown to increase regular cigarette use later in life. Additionally, using nicotine in adolescents, especially in high doses, may increase the risk of future addiction to other drugs.

In 2019, e-cigarette products were tentatively linked to a lung illness. The CDC, U.S. Food and Drug Administration (FDA), state and local health departments, and other clinical and public health stakeholders are investigating a multistate outbreak of severe lung illness associated with e-cigarette use. As of February 2020, more than 2,800 cases of lung illness associated with e-cigarette use were reported in all 50 states, 2 U.S. territories, and the District of Columbia. Sixty-eight deaths were confirmed in 29 states and the District of Columbia. No evidence of infectious disease has been identified, so lung illnesses are likely associated with chemical exposure. Evidence suggests a strong link to vitamin E acetate. Clinical manifestations of severe lung illness that have been reported include cough, shortness of breath, chest pain, nausea, vomiting, diarrhea, fatigue, fever, and weight loss. In some patients, symptoms developed over a few days, while other patients' symptoms developed over several weeks. With no real understanding of the etiology or pathogenesis, treatment is mostly supportive, with maintaining respiratory status being the priority. Many patients have required medical treatments with supplemental oxygen, endotracheal intubation with mechanical ventilation, and corticosteroids.

Until more is understood about the potential causes of this condition, e-cigarette use should be ceased and avoided. If e-cigarettes are used, the products should not be modified or substances should not be added that are not intended by the manufacturer (Data from CDC, 2022c; National Academies of Science, Engineering and Medicine, 2018; U.S. Department of Health and Human Services, 2016).

TB is often successfully treated in the home setting; however, it takes diligence to eradicate the disease. Treatment requires an average of 6 to 9 months of antimicrobial therapy: 2 months of initial intensive-phase treatment and 4 to 7 months of continuation-phase treatment. First-line drugs include isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). Combination therapy (consisting of two or more drugs) is recommended to prevent the emergence of resistant strains. The slow-growing bacilli have a high mutation rate, with those mutations often appearing when the pathogen is exposed to monotherapy. Second-line drugs available for drug-resistant TB include aminoglycosides and fluoroquinolones. Other, nonpharmacologic treatments may include surgical resection of

the persistent TB cavity or necrotic lung tissue and corticosteroids to decrease inflammation.

Because TB is a public health risk, antituberculin medications are provided free of charge by the U.S. Public Health Service. In some states, therapy noncompliance is unlawful, and imprisonment may be used to ensure adherence when other measures (e.g., direct observed therapy) fail. Compliance is a common problem in treating TB because of the length of therapy and the medication side effects (e.g., nausea, paresthesias, and discolored bodily secretions). Patient education, including an emphasis on taking the entire regimen of drugs as ordered, is crucial to maximize therapy success and prevent resistance. Individuals with latent TB infection should also be treated to prevent active infection and spread of the bacilli to other organs.

Strategies to prevent the transmission of TB include respiratory precautions (e.g., TB-approved masks, covering one's mouth when coughing, and disposing of contaminated tissues), adequate ventilation (if the patient is at home), and placing the patient in a negative-pressure isolation room (if he or she is hospitalized). The BCG vaccination is primarily used in children and in developing countries.

Alterations in Ventilation

Asthma

Asthma is a chronic pulmonary disease that produces intermittent reversible airway obstruction. It is characterized by acute airway inflammation, bronchoconstriction, bronchospasm, bronchiole edema, and mucus production (**FIGURE 5-22**). The exact cause of asthma is unknown, and the causes can vary from person to person. Asthma is not caused by a single gene mutation but rather is a polygenic, multifactorial disorder (Thomsen, 2015). Both genetics and environmental factors play a role, making asthma difficult to predict. More than 100 genes have been associated with asthma, and the list

is growing. These genes increase asthma susceptibility by affecting three main areas—functioning of the immune system, mucosal biology and function, and lung function and disease expression.

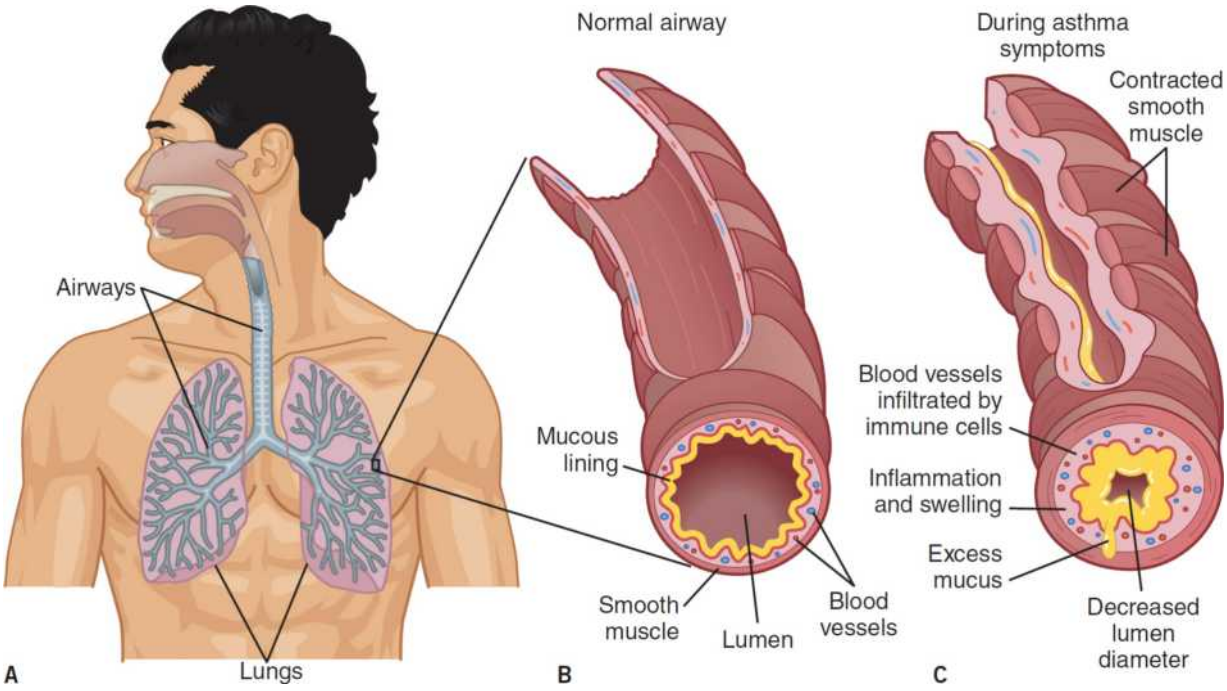


FIGURE 5-22 Asthma. **(A)** Location of the lungs and airways in the body. **(B)** Cross-section of a normal airway. **(C)** Cross-section of an airway during asthma symptoms.

Description

Regardless of the exact mechanism, asthma is often the result of a strong immune reaction to an allergen. Allergens are taken up by dendritic cells (DCs), which process antigenic molecules and present them to the naïve T-helper cells. Inhaled allergens stimulate T-helper type 2 (Th2) cell proliferation and, subsequently, the production and release of Th2 cytokines, interleukin (IL)-4, and IL-13 (Kudo, Ishigatsubo, & Aoki, 2013) (**FIGURE 5-23**). IL-4 and IL-13 promote the production of immunoglobulin E (IgE) antibodies. Consequently, the activation of allergen-specific Th2 cells occurs. Additionally, Th17 and Th9 cells are known to play a role in asthma. Th17 cells produce IL-17A, IL-17F, and IL-22. These cytokines induce airway inflammation, and IL-17A increases smooth muscle contractility.

Inflammation leads to swelling that narrows the airways and increases the production of mucus, which occludes the airways. Bronchospasm, tightening of the muscles around the airways, also makes it difficult to ventilate.

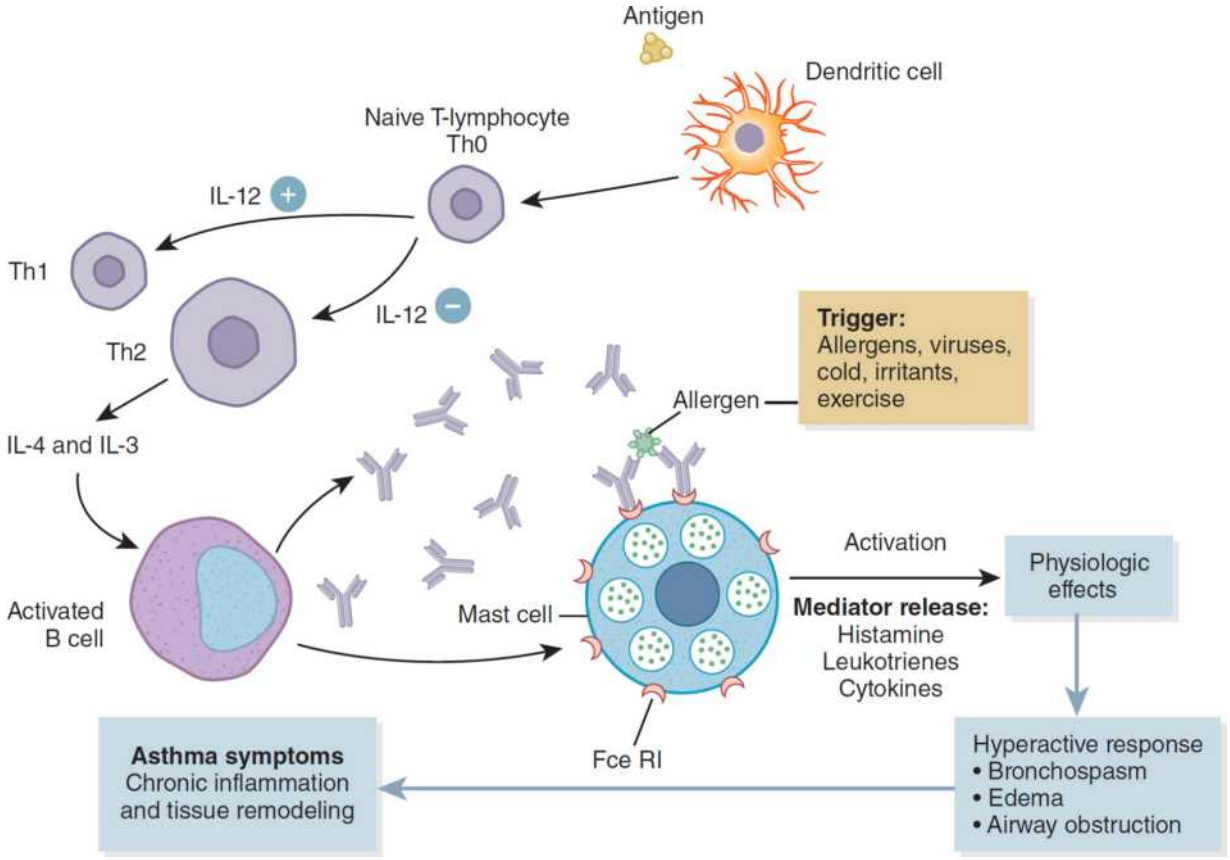


FIGURE 5-23 Pathogenesis of asthma.

Abbreviations: Fce: fragment crystallizable epsilon; IL: Interleukin; Th: T-helper.

Description

Another mechanism is modulated by Th1 cells. These cells promote cell-mediated immune responses by producing interferon-gamma, IL-2, and tumor necrosis factor beta (TNF-β). Th1-mediated responses tend to be associated with exposure early in life to certain infections (e.g., *Mycobacterium tuberculosis*, measles virus, or hepatitis A virus), increased exposure to infectious agents through contact with older siblings or attending daycare programs, and exposure to animals.

Asthma is one of the most common chronic illnesses in children in the United States; it affects more than 25 million people, including more than 4 million individuals younger than age 18 (CDC, 2023a). Prevalence rates associated with asthma remained relatively steady from 2001 to 2017, but prevalence is still higher than it was from 1980 to 1996. However, clinic visits, hospitalizations, and death rates decreased over the same period. The increased prevalence may be a result of surging urbanization and pollution. Another theory, referred to as the "hygiene hypothesis," suggests that the modern Western lifestyle's focus on hygiene and sanitation limits early childhood allergen and infection exposure, thereby rendering individuals more vulnerable when they do finally encounter allergens and infectious agents.

Women are more likely to have asthma than men, but in children, boys are more likely to have asthma than girls. African American and Puerto Rican adults and children are more likely to have asthma than Caucasian adults and children. Other risk factors include lower socioeconomic status, obesity, smoke exposure, respiratory infections early in life, presence of allergies (e.g., food, seasonal, and household), workplace exposure (e.g., chemical irritants or industrial dusts), and family history (especially maternal history).

Asthma is usually classified according to its cause (extrinsic, intrinsic, nocturnal, exercise-induced, occupational, or drug-induced) and by its severity (mild intermittent, mild persistent, moderate persistent, and severe persistent) (**TABLE 5-5**). Extrinsic triggers include allergens such as food, pollen, dust, and medications. **Extrinsic asthma** generally presents in childhood or adolescence. **Intrinsic asthma** is not an allergic reaction and usually presents after age 35 years. Intrinsic triggers include upper respiratory infections, air pollution, emotional stress, smoke, exercise, and cold exposure.

TABLE 5-5 Classification of Asthma Severity

Step/Classification*	Daytime Symptoms	Nighttime Symptoms	PEF orFEV /	PEF Variability
Step 1: Mild intermittent	≤ 2/week	≤ 2/week	≥ 80%	< 20%
Step 2: Mild persistent	> 2/week, but < daily	> 2 nights/month	> 80%	20–30%
Step 3: Moderate persistent	Daily	> 1 night/week	60–80%	> 30%
Step 4: Severe persistent	Continual	Frequent	≤ 60%	> 30%

Description

Abbreviations: FEV_1: forced expiratory volume in 1 second; PEF: peak expiratory flow (rate).

* Classification is based on symptoms and lung function before treatment. Patients should be assigned to the most severe step in which any feature occurs.

† Percentage of predicted function.

Data from National Heart, Lung, and Blood Institute. (2020). National Asthma Education and Prevention Program, Focused Update Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. NIH Publication Number 08-5846. Retrieved from https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines

Nocturnal asthma usually occurs between 3:00 and 7:00 a.m. and is thought to be related to circadian rhythms. At night, cortisol and epinephrine levels decrease, while histamine levels increase. Changes in these naturally occurring substances lead to bronchoconstriction.

Exercise-induced asthma is common and usually occurs 10 to 15 minutes after physical activity ends. Symptoms can linger for an hour with this type of asthma. The airways can become cool and dry during exercise, and asthmatic symptoms may be a compensatory mechanism to warm and moisten the airways. Following each episode of exercise-induced asthma, a refractory (symptom-free) period begins within 30 minutes and can last 90 minutes. During this time, little or no bronchospasm can be induced even if the person is rechallenged with vigorous exercise. Athletes often take advantage of this fact by warming up vigorously to induce a refractory period prior to competition.

Occupational asthma is caused by a reaction to substances encountered at work (e.g., plastic or formaldehyde). Symptoms develop over time, worsening with each exposure and improving when away from work (e.g., on weekends or during vacations).

Drug-induced asthma is frequently caused by aspirin and can be fatal. Reactions can be delayed up to 12 hours after drug ingestion.

Aspirin and other drugs (e.g., nonsteroidal anti-inflammatory drugs) prevent the conversion of prostaglandins, which stimulate leukotriene release—a powerful bronchoconstrictor.

Regardless of the classification system used, asthma attacks are the body's response to bronchial inflammation. Stage 1 of an acute asthma attack is primarily related to bronchospasm and is usually signaled by coughing. Peaking within 15 to 30 minutes, the inflammatory mediators responsible for this stage include leukotrienes, histamine, and some interleukins. Stage 2 of an asthma attack peaks within 6 hours of symptom onset. This stage is a result of airway edema and mucus production. The alveolar hyperinflation causes air trapping. Bronchospasm, smooth muscle contraction, inflammation, and mucus production combine to narrow the airways. Over time, the walls of the airways can become thicker if asthma is not controlled.

Clinical manifestations of asthma vary depending on the severity and whether it was triggered by allergens. Some individuals have symptoms daily, whereas others have symptoms only a few days a year. For some individuals, asthma may cause discomfort but does not interfere with their daily activities. Asthma can impair what the individual can do and even be life threatening in some cases. When well controlled, asthma may not cause symptoms. An asthma attack occurs when symptoms worsen. Clinical manifestations include the following:

- Wheezing
- Shortness of breath
- Prolonged expiratory phase
- Dyspnea
- Chest tightness
- Cough
- Tachypnea
- Hypoxia
- Anxiety

Status asthmaticus is a life-threatening prolonged asthma attack that does not respond to usual treatment. Maintaining a patent airway is critical in such cases, and endotracheal intubation with ventilation support may be necessary. In addition, acid–base imbalances—specifically, respiratory alkalosis from expelling too much carbon dioxide because of tachypnea—can develop. Treatment of these conditions is crucial to improve outcomes.

Diagnostic procedures can be used to identify those persons with asthma as well as to track the progression of the disease. These diagnostic procedures include a history (including the pattern of symptoms), physical examination, pulmonary function tests (see Figure 5-12), chest X-ray, ABGs, CBC, challenge testing (i.e., bronchoprovocation test), spirometry with bronchodilator test, peak expiratory flow, and allergen testing.

Asthma cannot be cured, but its symptoms can be controlled. Unless treated promptly, asthma attacks can lead to impaired gas exchange and death. Left untreated, long-term asthma can result in bronchial damage and scarring. The goals of treatment are to minimize the occurrence and severity of asthma attacks. Pharmacologic treatment includes inhaled and systemic corticosteroids, bronchodilators, beta-agonists, anticholinergics, nebulizer treatments, biologics, leukotriene mediators, mast cell stabilizers, and anticholinergics (**FIGURE 5-24**). With severe attacks that do not respond to the usual treatment, supplemental oxygen therapy and endotracheal intubation with mechanical ventilation may be needed. Bronchial thermoplasty can be performed to thin airway muscles and prevent constriction in severe or long-standing asthma. Additional strategies include the following measures:

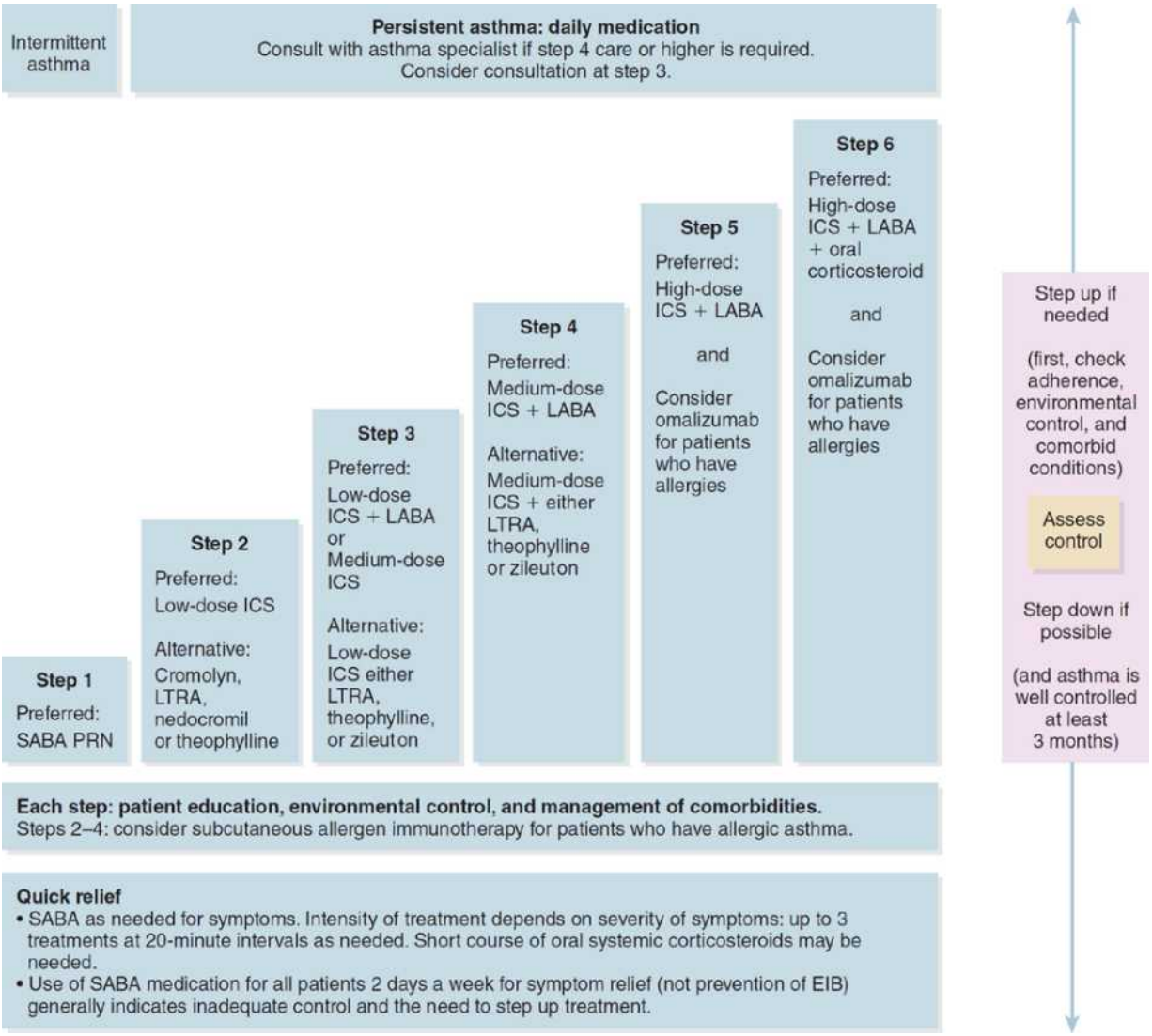


FIGURE 5-24 Treatment of asthma.

National Heart, Lung, and Blood Institute. (2020). National Asthma Education and Prevention Program, Focused Update: Guidelines for the diagnosis and management of asthma. Retrieved from https://www.nhlbi.nih.gov/resources

Description

- Develop an asthma plan (**FIGURE 5-25**) and teach it to all caregivers



GREEN ZONE

- shortness of breath during the day or night
- Can do usual activities

And, if a peak flow meter is used,

Peak flow: more than _____
(80 percent or more of my best peak flow)

My best peak flow is: _____

Before exercise	☐ _____	☐ 2 or ☐ 4 puffs	5 minutes before exercise

YELLOW ZONE

ASTHMA IS GETTING WORSE

- Cough, wheeze, chest tightness, or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities

-Or-

Peak flow: _____ to _____
(50 to 79 percent of my best peak flow)

1st Add: quick-relief medicine—and keep taking your GREEN ZONE medicine.

_____ (quick-relief medicine) _____ Number of puffs or ☐ Nebulizer, once — Can repeat every ____ minutes up to maximum of ____ doses

2nd If your symptoms (and peak flow, if used) return to GREEN ZONE after 1 hour of above treatment:

☐ continue monitoring to be sure you stay in the green zone.

-Or-

If your symptoms (and peak flow, if used) do not return to GREEN ZONE after 1 hour of above treatment:

☐ Take: _____ (quick-relief medicine) _____ Number of puffs or ☐ Nebulizer

☐ Add: _____ (oral steroid) mg per day For ____ (3-10) days

☐ Call the doctor ☐ before / ☐ within ____ hours after taking the oral steroid.

RED ZONE

MEDICAL ALERT!

- Very short of breath, or
- Quick-relief medicines have not helped,
- Cannot do usual activities, or
- Symptoms are same or get worse after 24 hours in Yellow Zone

-Or-

Peak flow: less than _____
(50 percent of my best peak flow)

Take this medicine:

☐ _____ (quick-relief medicine) _____ Number of puffs or ☐ Nebulizer

☐ _____ (oral steroid) mg

Then call your doctor NOW. Go to the hospital or call an ambulance if:

- You are still in the red zone after 15 minutes AND
- You have not reached your doctor.

DANGER SIGNS

- Trouble walking and talking due to shortness of breath
- Lips or fingernails are blue

→

- Take _____ puffs of _____ (quick relief medicine) AND
- Go to the hospital or call for an ambulance _____ (phone) NOW!

See the reverse side for things you can do to avoid your asthma triggers.

HOW TO CONTROL THINGS THAT MAKE YOUR ASTHMA WORSE

This guide suggests things you can do to avoid your asthma triggers. Put a check next to the triggers that you know make your asthma worse and ask your doctor to help you find out if you have other triggers as well. Keep in mind that controlling any allergen usually requires a combination of approaches, and reducing allergens is just one part of a comprehensive asthma management plan. Here are some tips to get started. These tips tend to work better when you use several of them together. Your health care provider can help you decide which ones may be right for you.

ALLERGENS

☐ Dust Mites

These tiny bugs, too small to see, can be found in every home—in dust, mattresses, pillows, carpets, cloth furniture, sheets and blankets, clothes, stuffed toys, and other cloth-covered items. If you are sensitive:

- Mattress and pillow covers that prevent dust mites from going through them should be used along with high efficiency particulate air (HEPA) filtration vacuum cleaners.
- Consider reducing indoor humidity to below 60 percent. Dehumidifiers or central air conditioning systems can do this.

☐ Cockroaches and Rodents

Pests like these leave droppings that may trigger your asthma. If you are sensitive:

- Consider an integrated pest management plan.
- Keep food and garbage in closed containers to decrease the chances for attracting roaches and rodents.
- Use poison baits, powders, gels, or paste (for example, boric acid) or traps to catch and kill the pests.
- If you use a spray to kill roaches, stay out of the room until the odor goes away.

☐ Animal Dander

Some people are allergic to the flakes of skin or dried saliva from animals with fur or hair. If you are sensitive and have a pet:

- Consider keeping the pet outdoors.
- Try limiting to your pet to commonly used areas indoors.

☐ Indoor Mold

If mold is a trigger for you, you may want to:

- Explore professional mold removal or cleaning to support complete removal.
- Wear gloves to avoid touching mold with your bare hands if you must remove it yourself.
- Always ventilate the area if you use a cleaner with bleach or a strong smell.

☐ Pollen and Outdoor Mold

When pollen or mold spore counts are high you should try to:

- Keep your windows closed.
- If you can, stay indoors with windows closed from late morning to afternoon, when pollen and some mold spore counts are at their highest.
- If you do go outside, change your clothes as soon as you get inside, and put dirty clothes in a covered hamper or container to avoid spreading allergens inside your home.
- Ask your health care provider if you need to take or increase your anti-inflammatory medicine before the allergy season starts.

IRRITANTS

☐ Tobacco Smoke

- If you smoke, visit smokefree.gov or ask your health care provider for ways to help you quit.
- Ask family members to quit smoking.
- Do not allow smoking in your home or car.

☐ Smoke, Strong Odors, and Sprays

- If possible, avoid using a wood-burning stove, kerosene heater, or fireplace. Vent gas stoves to outside the house.
- Try to stay away from strong odors and sprays, such as perfume, talcum powder, hair spray, and paints.

☐ Vacuum Cleaning

- Try to get someone else to vacuum for you once or twice a week, if you can. Stay out of rooms while they are being vacuumed and for a short while afterward.
- If you must vacuum yourself, using HEPA filtration vacuum cleaners may be helpful.

☐ Other Things That Can Make Asthma Worse

- Sulfites in foods and beverages: Do not drink beer or wine or eat dried fruit, processed potatoes, or shrimp if they cause asthma symptoms.
- Cold air: Cover your nose and mouth with a scarf on cold or windy days.
- Other medicines: Tell your doctor about all the medicines you take. Include cold medicines, aspirin, vitamins and other supplements, and nonselective beta-blockers (including those in eye drops).

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung,

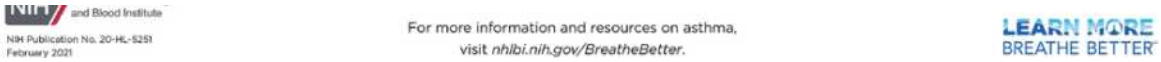


FIGURE 5-25 Example of asthma action plan.

Reproduced from National Heart, Lung, and Blood Institute. (202007). Asthma action plan: NIH Publication Number 07-5251.

Description

- Avoid triggers
- Keep the environment clean
- Limit environmental fabrics
- Filter indoor air
- Prevent respiratory infections (e.g., hand washing, avoiding crowds, vaccinations)
- Manage stress
- Maintain a healthy immune system (e.g., physical activity and proper nutrition)

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) describes a group of chronic respiratory disorders characterized by irreversible, progressive tissue degeneration and airway obstruction. These debilitating conditions can impair an individual's ability to work and function independently. The most significant contributing factor to developing COPD is cigarette smoking. Other contributing factors include the inhalation of pollution and chemical irritants.

Groups at higher risk of developing COPD include American Indians/Alaska Natives, multiracial non-Hispanics, women, individuals 65 years or older, and individuals of lower socioeconomic status. Women tend to develop COPD at a younger age and be diagnosed later than men when the COPD is more advanced and treatment is less effective. Women also seem to be more vulnerable to the effects of tobacco and other harmful substances. Moreover, women seem to respond less favorably to treatment.

Pathological changes associated with COPD are found in the airways, lung functional tissue, and pulmonary circulation. These changes include chronic inflammation, with increased numbers of specific inflammatory cells in the lungs, and structural changes resulting from repeated injury and repair. This inflammation appears to be a modification of the normal inflammatory response, though it is not fully understood. Oxidative stress and increased proteinases in the lungs likely play a role. The imbalance between proteases and antiproteases leads to a breakdown in connective tissue. COPD is characterized by increased macrophages, neutrophils, and lymphocytes (e.g., T-cell 1, Th1, Th17, and ILC3 cells) in the airways, functional lung tissue, and pulmonary vessels. In some patients, levels of eosinophils, Th2, and ILC2 cells may be increased. All of these inflammatory cells release inflammatory mediators, which then attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (pro-inflammatory cytokines), and induce structural changes (growth factors). Additionally, a local immunoglobulin A (IgA) deficiency may be associated with bacterial translocation, small-airway inflammation, and airway remodeling. This lung inflammation persists after smoking cessation through unknown mechanisms, although autoantigens and disturbances in the normal lung flora may play a role (Global Initiative for Chronic Obstructive Lung Disease, 2020).

With COPD, ventilation is impaired because of one or more of the following:

- The airways and alveoli lose elasticity.
- The walls between many alveoli are destroyed.
- The walls between the airways become thick and inflamed.
- Mucus production increases and blocks the airways.

Severe hypoxia and hypercapnia can lead to respiratory failure. The chronic hypercapnia shifts the normal breathing drive from the need to expel excess carbon dioxide to the need to raise oxygen levels (see Figure 5-10). Systemic inflammation may be present that could play a role in multiple comorbidity conditions found in patients

with COPD. Additionally, COPD can lead to cor pulmonale, a type of right-sided heart failure due to lung disease (see the *Cardiovascular Function* chapter).

Prevalence rates for COPD are likely underestimated because this disease is often asymptomatic in its early stages or is masked by smoking symptoms. According to the CDC (2022a), COPD was the sixth leading cause of death in the United States in 2021. An estimated 16 million Americans are currently diagnosed with COPD. Symptoms usually present around 60 years of age. A rare familial type of COPD (emphysema only), known as alpha-1 antitrypsin (AAT) deficiency, presents much earlier—in the 30s or 40s. ATT is a protein made in the liver, and low levels of it can lead to lung damage.

COPD is often one of or a mixture of two diseases—chronic obstructive bronchitis and emphysema (**FIGURE 5-26**). Additionally, some people who have asthma can develop COPD from the damage caused by chronic inflammation.

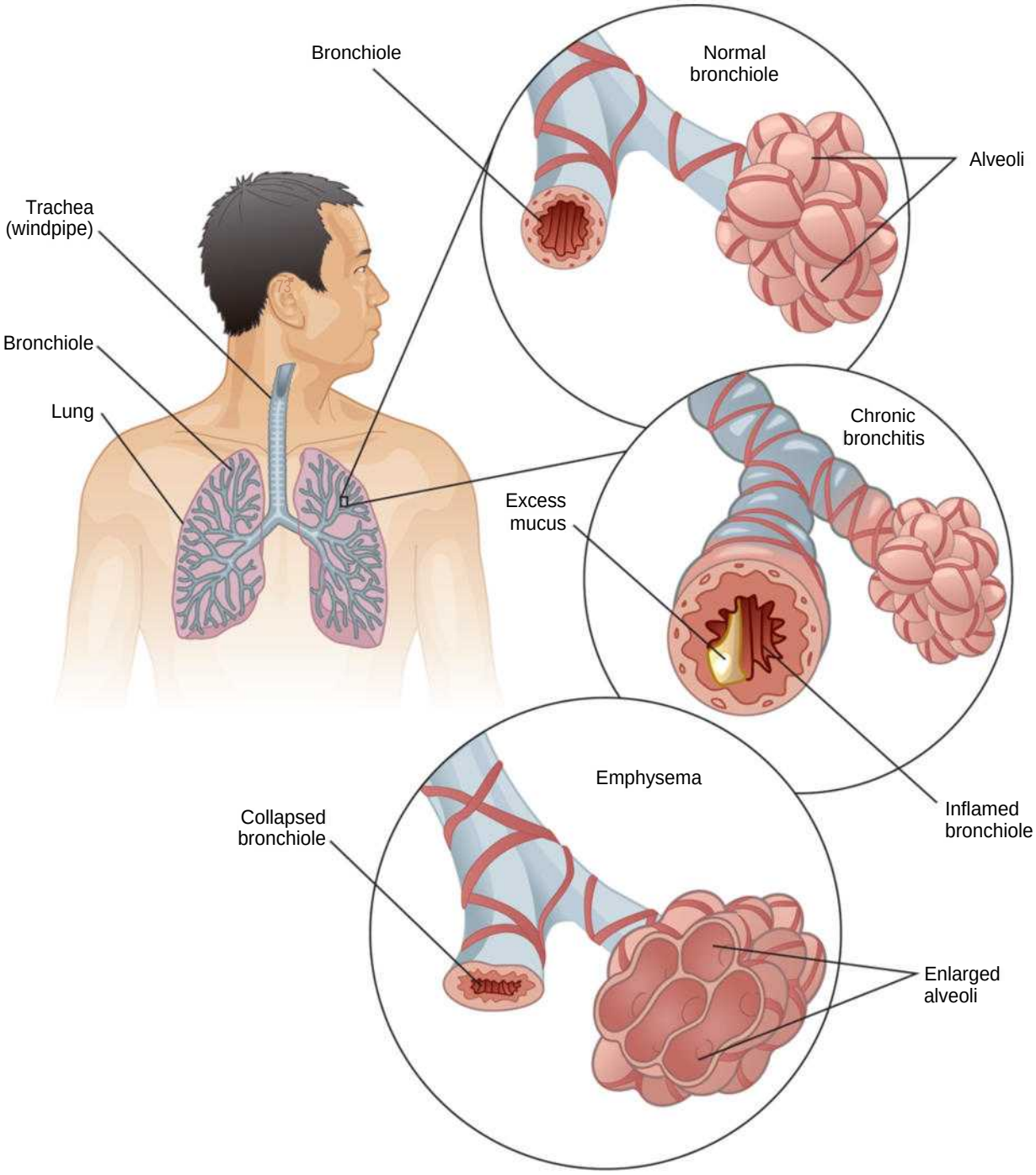


FIGURE 5-26 Chronic obstructive pulmonary disease (COPD) is often one disease or a mixture of two diseases—chronic obstructive bronchitis and emphysema.

Description

Chronic Obstructive Bronchitis

Chronic obstructive bronchitis is an obstructive respiratory disorder that is clinically defined and characterized by inflammation of the bronchi, a productive cough, and excessive mucus production. This disorder differs from acute bronchitis in that an infection does not necessarily cause the chronic type and symptoms persist longer. As previously mentioned, cigarette smoking is the greatest contributing factor to chronic bronchitis. The inflammatory response results in mucous gland hyperplasia, edema, excessive mucus production, bronchoconstriction, and cough as a defense against inhaled irritants. Airway resistance affects both inspiratory and expiratory airflow. Impaired pulmonary defenses (e.g., cilia damage and decreased phagocytic activity) result in frequent respiratory infections and, in some cases, respiratory failure.

Airway resistance leads to hypoventilation, hypoxemia, cyanosis, hypercapnia, polycythemia, clubbing of fingers, and dyspnea at rest. Additional clinical manifestations include the following signs and symptoms:

- Abnormal lung sounds (e.g., wheezing and rhonchi)
- Edema
- Weight gain
- Malaise
- Chest pain
- Fever

Diagnostic procedures for chronic obstructive bronchitis consist of a history (persistent, productive cough for at least 3 months in a year for 2 consecutive years), physical examination, chest X-ray, pulmonary function tests (see Figure 5-12), ABGs, and CBC. The goal of treatment is to maintain airway patency. Treatment strategies include oxygen therapy (in limited amounts, because too much will knock out the newly oxygen-centered drive for breathing), bronchodilators, corticosteroids, antibiotics (if bacterial infection is present), postural drainage, chest physiotherapy, and increased hydration.

Learning Points

Chronic Obstructive Bronchitis

Patients with chronic obstructive bronchitis are unable to increase ventilatory effort to maintain adequate gas exchange; therefore, they eventually develop cyanosis. This cyanosis, coupled with the edema that develops, has led to the nickname "**blue bloaters**" for these patients. Additionally, chronic obstructive bronchitis pathogenesis can be remembered by these three S's—sputum, swelling, and spasm.

Emphysema

Emphysema is an obstructive respiratory disorder that is pathologically or radiologically defined and results in the destruction of the alveolar walls, leading to large, permanently inflated alveoli. Lung tissue normally remodels during periods of growth and repair related to infections and inflammation. Enzymes are involved in this process to prevent excessive tissue damage. Enzyme deficiency, however, may result from genetic predisposition (fewer than 2% of cases) and smoking. Smoking triggers inflammation, causing changes in these enzyme levels and leading to structural changes. Emphysema gradually turns the alveoli into large, irregular pockets with gaping holes, which in turn limits the amount of oxygen entering the bloodstream. The elastic fibers and surfactant that normally keep the alveoli open are slowly destroyed, so the alveoli collapse during expiration, trapping air in the lungs. The loss of elastic recoil and hyperinflation of the alveoli narrow the terminal bronchioles, but inspiration is not affected.

Coughing is usually not a symptom of this disease. Instead, emphysema is characterized by the following clinical manifestations:

- Dyspnea upon exertion
- Diminished breath sounds
- Wheezing
- Chest tightness
- Tachypnea

- Hypoxia
- Hypercapnia
- Increased anterior–posterior thoracic diameter (from 1:2 to 1:1), giving the chest a “barrel” appearance
- Activity intolerance
- Anorexia
- Malaise

Learning Points

Emphysema

Patients with emphysema often hyperventilate, creating a pink appearance to their skin. This panting-like breathing pattern, coupled with the pink skin, has earned emphysema patients the nickname “**pink puffers**.” Additionally, the pathogenesis of emphysema is sometimes described as “lung dry rot.”

Diagnosis and progress monitoring are accomplished through the same procedures that are used for chronic bronchitis. Treatment strategies include those identified for chronic bronchitis, plus pursed-lip breathing and lung reduction surgery. Pursed-lip breathing increases expiratory resistance and produces airway backpressure, preventing the collapse of the alveoli.

Cystic Fibrosis

Cystic fibrosis is an inherited, progressive disorder of the mucus and sweat glands that primarily affects the lungs and pancreas but also impacts the liver, intestines, sinuses, sweat glands, and sex organs. According to the Cystic Fibrosis Foundation Patient Registry, approximately 1,000 new patients are diagnosed each year in the United States (Cystic Fibrosis Foundation, n.d.). Most cases (75%) are diagnosed by the age of 2. More than 30,000 Americans are living with cystic fibrosis, and more than 70,000 people worldwide are

diagnosed with the condition. Caucasians are more likely to develop cystic fibrosis than other ethnic groups.

The genetic defect that leads to cystic fibrosis has been isolated to chromosome 7, referred to as the "cystic fibrosis transmembrane conductance regulator" (*CFTR*) gene, and transmission follows an autosomal recessive pattern (see the *Cellular Function* chapter). Nearly 2,000 disease-causing mutations of the *CFTR* gene have been identified. More than 10 million Americans are carriers of this faulty gene, but many do not know about their carrier status. The genetic deficit causes the CFTR protein to be dysfunctional, resulting in an inability to move chloride to the cell surface. Without chloride to attract water to the cell surface, the mucus in various organs becomes thick and tenacious. Cystic fibrosis changes the cells that produce mucus, sweat, saliva, and digestive secretions. Instead of lubricating the respiratory tract, these secretions occlude airways, ducts, and passageways. This occlusion leads to atelectasis and permanent damage (**FIGURE 5-27**). Mucus stagnates and traps microorganisms, becoming a prime medium for bacterial growth and triggering inflammation. Infections are recurrent and contribute to progressive lung destruction. Bronchiectasis and emphysema-like changes are common as fibrosis and obstructions advance. Respiratory failure is the most common cause of death in people who have cystic fibrosis. Ultimately, cor pulmonale (right-sided heart failure) or respiratory failure occurs.

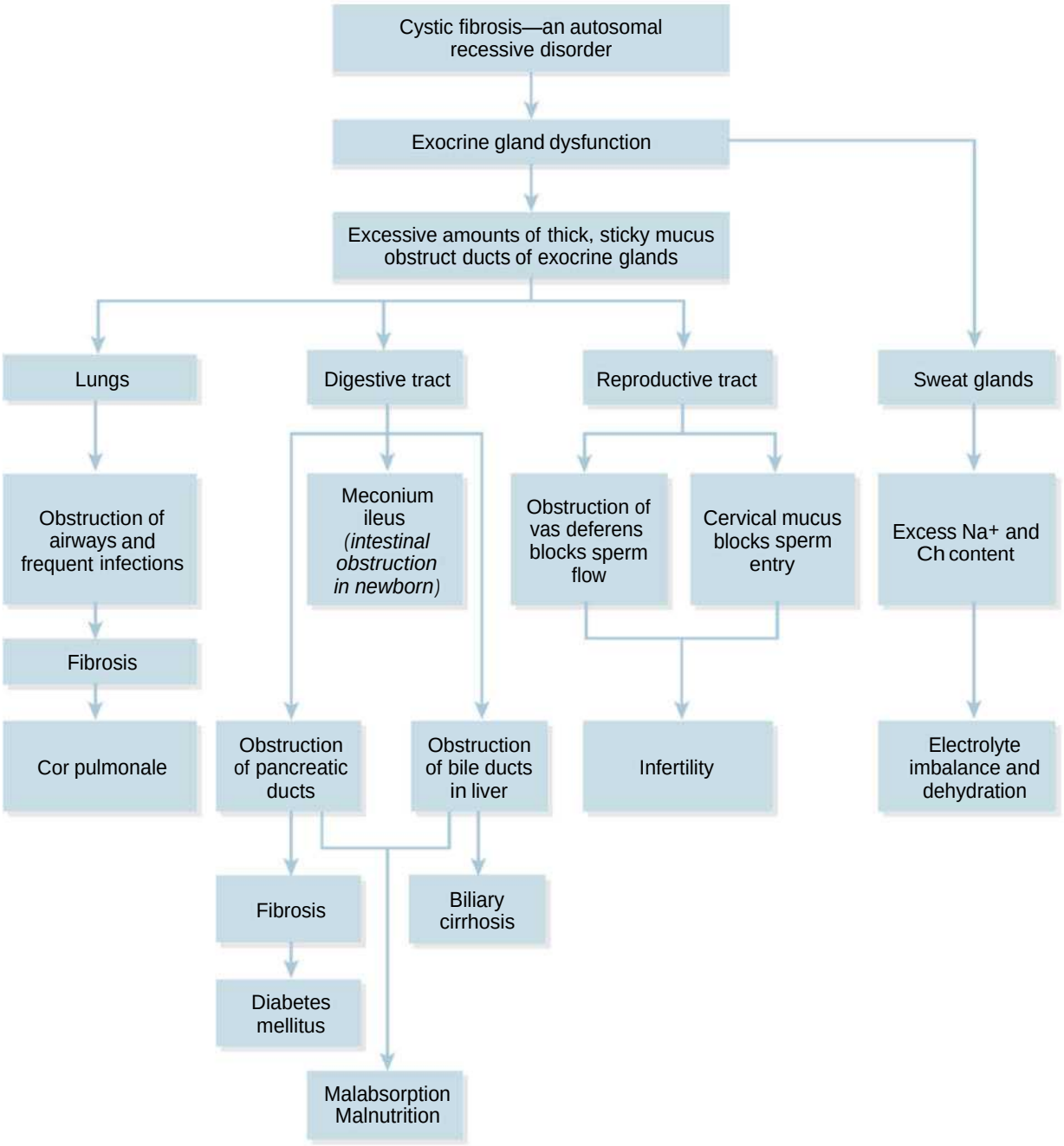


FIGURE 5-27 Cystic fibrosis.

Description

In the digestive tract, the mucus blocks the intestines, producing a meconium ileus in the newborn. It also blocks pancreatic ducts, leading to a pancreatic enzyme excretion deficit. Without these digestive enzymes, malabsorption and malnutrition develop. The

trapped digestive enzymes damage pancreatic tissue, contributing to the development of diabetes mellitus and osteoporosis. Blocked bile ducts in the liver add to the malabsorption issues and increase the risk of developing cirrhosis.

Salivary glands are only mildly affected by blockages. Sweat glands produce sweat high in sodium chloride, which can cause electrolyte imbalances in times of excessive loss (e.g., during exercise or hot weather). Obstructions in the reproductive system can lead to sterility and infertility.

Clinical manifestations of cystic fibrosis may appear at birth and progressively worsen throughout the life span. Lung function often starts declining in early childhood. These manifestations, which vary in severity, include the following signs and symptoms:

- Meconium ileus (intestinal obstruction that develops soon after birth)
- Salty skin (parents may notice that their baby's skin tastes salty when they kiss the child)
- Steatorrhea (fatty, foul-smelling stools)
- Fat-soluble vitamin deficiency (vitamins A, D, E, and K)
- Voracious appetite
- Chronic cough with tenacious sputum (may include hemoptysis)
- Frequent respiratory infections
- Hypoxia
- Audible rhonchi and wheezing
- Shortness of breath
- Dyspnea
- Fatigue
- Activity intolerance
- Digital clubbing
- Fever
- Night sweats
- Jaundice for an abnormally long time after birth

- Muscle and joint pain
- Delayed growth and development
- Development of complications (e.g., chronic bronchitis, failure to thrive, cardiomegaly, diabetes mellitus, pancreatitis, rectal prolapse, liver disease, cholelithiasis, osteoporosis, hyponatremia, metabolic alkalosis, cancers of the digestive tract, renal failure, and male infertility)

Diagnosis of cystic fibrosis is a multistep process and should include a newborn screening, a sweat test, a genetic or carrier test, and a clinical evaluation. Diagnosis can be accomplished prenatally when family history warrants testing. In the United States, all newborns are screened for cystic fibrosis regardless of family history in the first three days of life. This screening involves analysis of the newborn's blood for higher than normal levels of immunoreactive trypsinogen (IRT), a chemical released by the pancreas. IRT level may be elevated because of prematurity or a stressful delivery; therefore, other tests are used to confirm the diagnosis. Sweat analysis can be conducted at about 2 to 3 weeks of age to detect electrolyte abnormalities (particularly high levels of chloride). The delta F508 test can identify 23 of the most common disease-causing mutations of chromosome 7, and it is often used if a false-negative sweat test is suspected or to identify the carrier status of siblings. In addition, stool can be evaluated for the presence of pancreatic content. Other tests that assess lung function include chest X-rays, pulmonary function tests, and ABGs. Additional tests may be necessary to evaluate for complication development.

Cystic fibrosis treatment should be started immediately upon diagnosis. Successful management requires diligent family involvement and an interdisciplinary approach because of the progressive multisystem nature of the disease. Improved treatment regimens have improved the life expectancy for patients who have cystic fibrosis, with some people now living into their 40s or 50s. Treatment often requires a multidisciplinary team including cystic fibrosis specialists, specialized healthcare providers (e.g., expertise

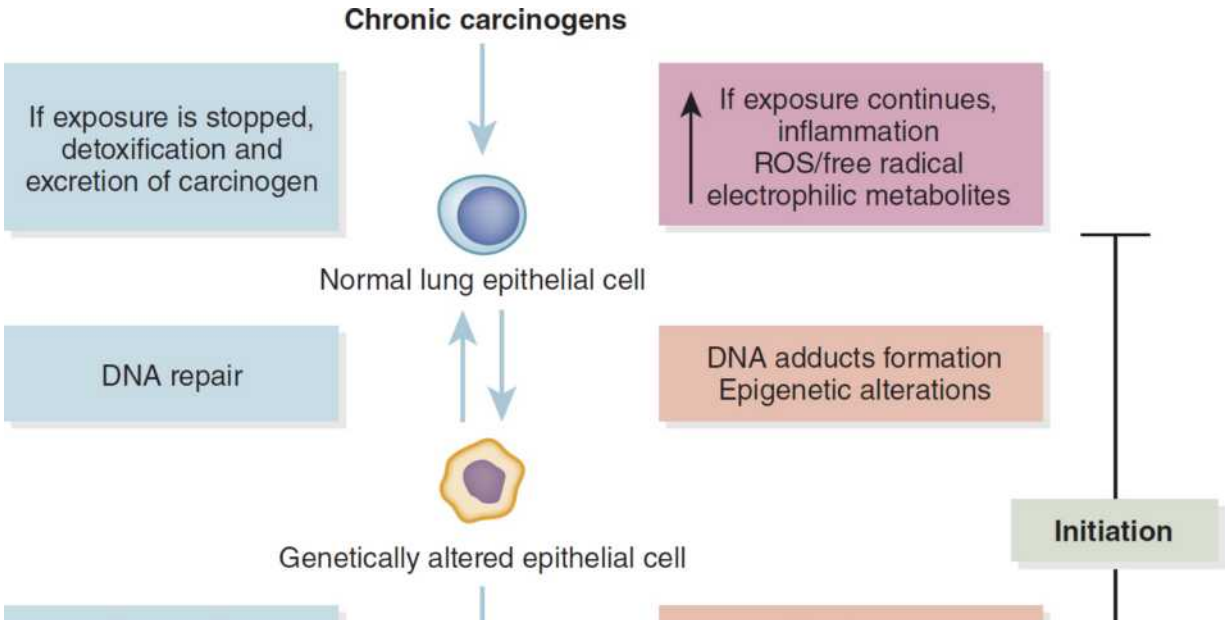
with the respiratory system, diabetes mellitus, and gastrointestinal system), nurses, respiratory therapists, dietitians, pharmacists, physical therapists, psychological counselors, social workers, and genetic counselors. Strategies include the following measures:

- Pancreatic enzyme replacement
- Bile salt replacement
- A well-balanced, high-protein, low-fat, high-sodium diet
- Fat-soluble vitamin replacement
- Increased fluid intake
- Intensive chest physiotherapy (includes chest clapping or percussion, which can be done by hand or with a mechanical percussor)
- Postural drainage
- Coughing exercises
- Humidified air
- Bronchodilators
- Mucus thinners (e.g., hypertonic saline and dornase alfa [Pulmonzyme])
- Anti-inflammatory agents
- Regular, moderate exercise
- Early, aggressive treatment of infections with antibiotics
- Oxygen therapy
- Avoidance of respiratory irritants (e.g., smoke, pollution, dust, and allergens)
- CFTR modulators (e.g., ivacaftor [Kalydeco], lumacaftor/ivacftor [Orkambi], and tezacaftor/ivacaftor [Symdeko])
- Health-promoting behaviors (e.g., frequent hand washing, proper nutrition, vaccinations, and avoiding tobacco smoke)
- Heart–lung transplant

Lung Cancer

Lung cancer is the second most frequently diagnosed cancer in men and women and the leading cause of cancer death in the United States and worldwide (American Cancer Society [ACS], 2023; WHO, 2022a). After increasing for decades, lung cancer incidence and mortality rates are now decreasing in parallel with decreases in rates of cigarette smoking in the United States. The burden is disproportionately higher in people with lower socioeconomic status. Incidence rates vary significantly by state, reflecting ongoing differences in smoking prevalence. Lung cancer rates are highest in Kentucky (67 for men and 45.3 for women per 100,000 people) and lowest in Puerto Rico (14.8 for men and 7.2 for women per 100,000 people). Frequently, other cancers—such as breast and liver, to name a few—metastasize (spread) to the lung tissue.

Smoking contributes to the majority (81%) of lung cancer cases. The more than 7,000 chemicals in cigarette smoke include at least 70 known carcinogens and chemicals that paralyze cilia (**FIGURE 5-28**). The risk of developing lung cancer is directly related to the length of time a person smokes and the number of cigarettes smoked. Cigar and pipe smoking also increases risk. Secondhand smoke can be a significant contributing factor; in fact, some research has indicated that it may be worse than firsthand smoking. Smoking cessation or removing the smoke exposure will gradually decrease risk.



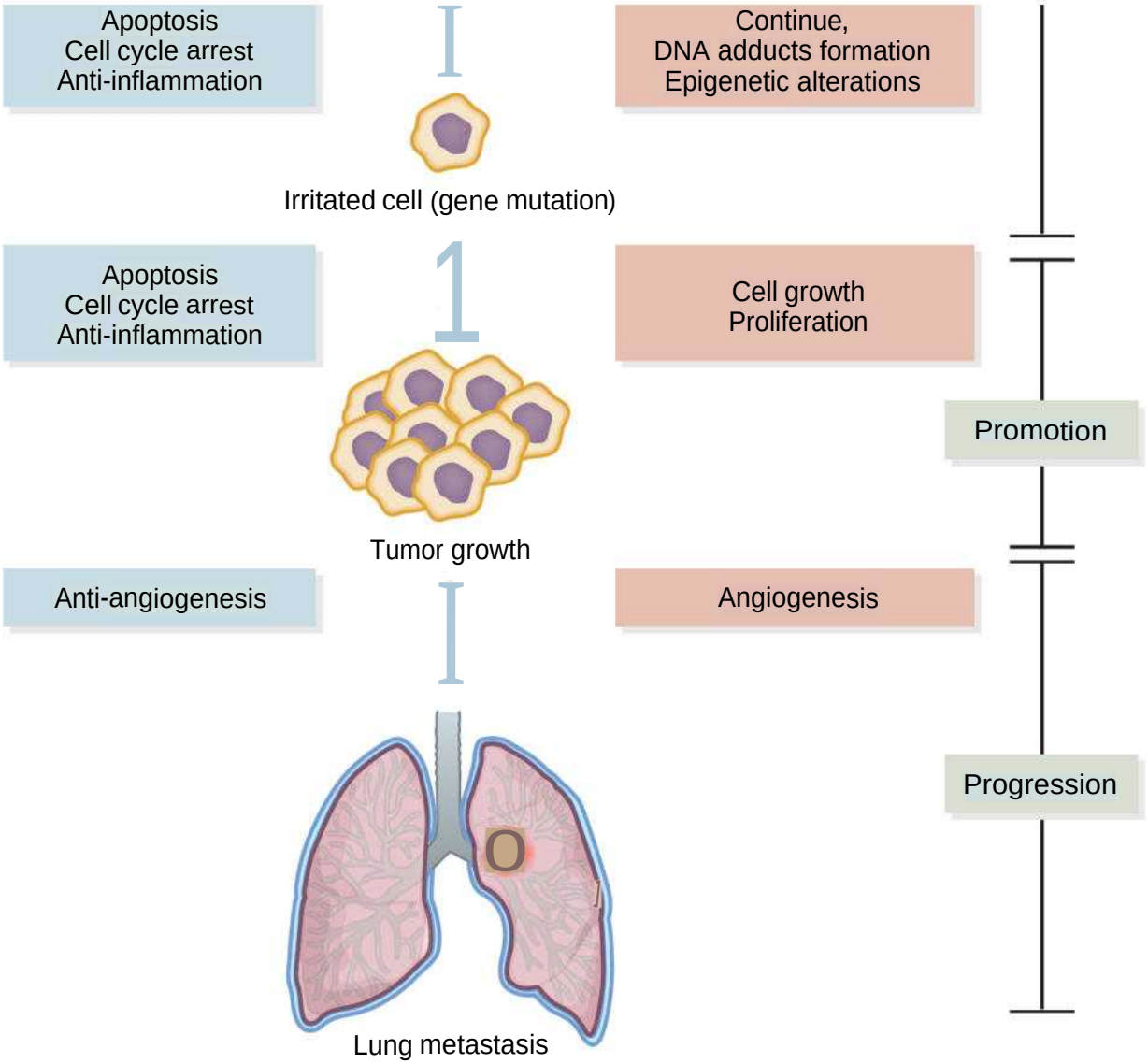


FIGURE 5-28 Lung cancer.

Description

Exposure to radon gas, which is released from soil and can accumulate in indoor air, is thought to be the second leading cause of lung cancer in the United States. Exposure to other chemicals (e.g., asbestos, tar, pollution, and diesel exhaust), certain metals (e.g., chromium, cadmium, and arsenic), or radiation, as well as the presence of chronic lung disease, can also increase risk, particularly among smokers. Specific occupational exposures that increase risk

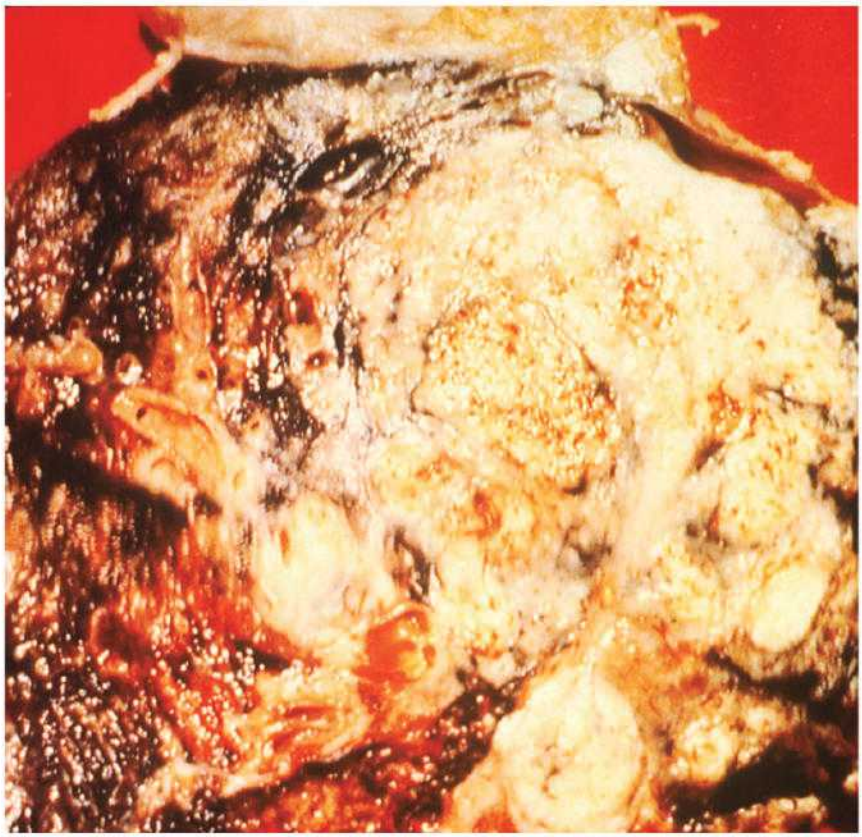
include rubber manufacturing, paving, roofing, painting, and chimney sweeping (ACS, 2023).

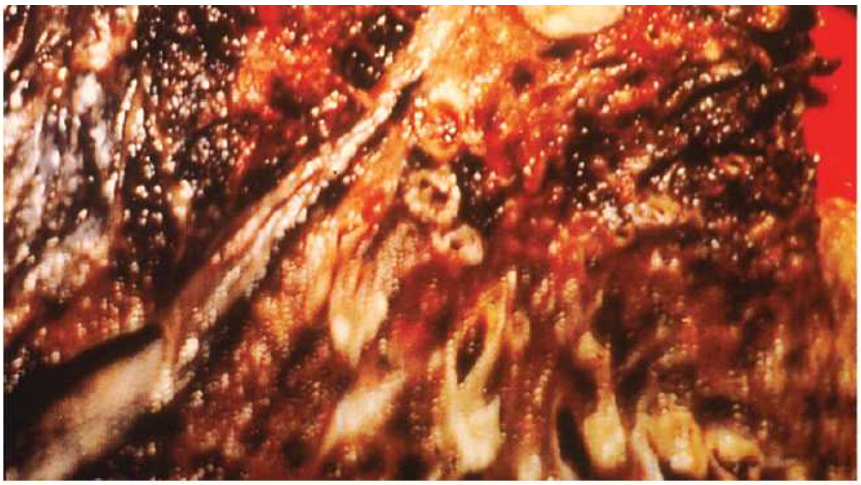
The lungs provide an optimal environment for tumor development and growth. The scores of blood vessels supplying the lungs serve as entrance points for distant cancer cells to gain access, and those vessels furnish the cancer with a rich blood source to facilitate its growth. Carcinogens can seek refuge in the many nooks and crannies of the air passages, where they have an opportunity to cause cellular changes (usually metaplasia). These carcinogens usually create somatic genetic changes, meaning they are developed over the course of a lifetime and not inherited. In rare cases, the genetic change is inherited, in the form of germline mutations. These rare inherited genetic changes follow an autosomal dominant pattern; however, not all individuals who inherit mutations will develop lung cancer.

Somatic mutations in the tumor protein 53 (TP-53), epidermal growth factor receptor (EGFR), and KRAS genes are commonly associated with lung cancers. All of these genes produce proteins. The p53 protein regulates cell growth and division by monitoring deoxyribonucleic acid (DNA) damage. When DNA is damaged, p53 determines whether it can be repaired or whether the cell will undergo apoptosis. Altered p53 proteins cannot regulate DNA damage, allowing it to accumulate in cells. This accumulation causes uncontrolled cell proliferation, leading to tumor growth (**FIGURE 5-29**). The EGFR and KRAS genes produce proteins that are embedded within the cell membrane. When activated, these proteins bind with other molecules, signaling cell proliferation. Alterations in these genes result in the proteins constantly being activated, causing the cells to continuously proliferate and form a tumor. Other mutations that have been found to be associated with lung cancer are involved in regulating gene expression, cell proliferation, cell differentiation, and apoptosis (e.g., anaplastic lymphoma kinase [ALK], BRAF, cyclin-dependent kinase inhibitor 2A [CDKN2A], MET, and ROS1, among others).



A





B

FIGURE 5-29 Normal (top) and cancerous (bottom) lungs.

Top photo: © VideoSurgery/Science Source; Bottom photo: Courtesy of National Cancer Institute.

Lung cancers are divided into two types: small cell and non-small cell. **Small-cell carcinoma**, often referred to as "oat-cell carcinoma," occurs almost exclusively in heavy smokers and is less prevalent than non-small-cell cancers. Small-cell lung cancer grows quickly and often has metastasized at the time of diagnosis. This type of lung cancer most commonly metastasizes to the liver, brain, bones, and adrenal glands. After diagnosis, most individuals with small-cell lung cancer survive for about 1 year, and fewer than 6% survive for 5 years.

Non–small-cell carcinoma, often referred to as bronchogenic carcinoma, is the most common type of malignant lung cancer, accounting for 85% of all cases of lung cancer. It is classified into several subgroups—squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma. Squamous-cell carcinoma develops from the squamous cells that line the airways. Adenocarcinoma develops from the cells that line the alveoli. Large-cell carcinoma develops from epithelial cells that line the lungs. The 5-year survival rate for people with non-small-cell lung cancer is 23%.

Tumors in the lungs lead to several issues, including the following:

- Airway obstruction

- Inflammation of lung tissue, eliciting coughing and contributing to infections
- Fluid accumulation in the pleural space (e.g., pleural effusion, hemothorax, and pneumothorax)
- Paraneoplastic syndrome (endocrine dysfunction associated with hormone secretion from the tumor)

Symptoms of lung cancer usually do not appear until the cancer is advanced. Clinical manifestations of lung cancer are insidious because they mimic signs of smoking, including:

- Persistent cough or a change in usual cough
- Dyspnea
- Hemoptysis
- Frequent respiratory infections
- Chest pain
- Hoarseness
- Weight loss with no known cause
- Anorexia
- Anemia
- Fatigue
- Other symptoms specific to the site(s) of metastasis

Diagnostic procedures for lung cancer include a history, physical examination, chest X-ray, low-dose spiral CT, MRI, bronchoscopy, sputum studies, biopsy, positron emission tomography, bone scans, and pulmonary function tests. Screening using low-dose spiral CT is recommended for people who have a history of heavy smoking (30 pack-years or more; a pack-year is smoking an average of one pack of cigarettes per day for one year), *and* smoke now or have quit within the past 15 years, *and* are between 55 and 80 years old.

Treatment is based on staging and follows the usual pattern for cancer treatment—that is, chemotherapy, surgery, and radiation (**TABLE 5-6**; **TABLE 5-7**). The treatment is generally palliative

because the tumor rarely responds favorably to treatment. Early diagnosis and treatment, however, may improve this prognosis. Other strategies include those to maintain optimal respiratory function—oxygen therapy, bronchodilators, and antibiotics (if bacterial infections are present).

TABLE 5-6 Staging and Treatment of Non-Small-Cell Lung Cancer

Stage	Description	Usual Treatment Plan
Stage I	Cancer has invaded the underlying lung tissue but has not spread to the lymph nodes.	Surgery
Stage II	Cancer has spread to neighboring lymph nodes or invaded the chest wall.	Surgery, radiation, and chemotherapy
Stage IIIA	Cancer has spread from the lung to lymph nodes in the center of the chest.	Combined chemotherapy and radiation; sometimes surgery based on results of treatment
Stage IIIB	Cancer has spread locally to areas, such as the heart, blood vessels, trachea, and esophagus—all within the chest—or to lymph nodes in the area of the collarbone or to the tissue that surrounds the lungs within the rib cage (pleura).	Chemotherapy, sometimes radiation
Stage IV	Cancer has spread to other parts of the body, such as the liver, bones, or brain.	Chemotherapy, targeted drug therapy, clinical trials, and supportive care

TABLE 5-7 Staging and Treatment of Small-Cell Lung Cancer

Stage	Description	Usual Treatment Plan
Limited	Cancer is confined to one lung and to its neighboring lymph nodes.	Combined chemotherapy and radiation, sometimes surgery
Extensive	Cancer has spread beyond one lung and nearby lymph nodes and may have invaded both lungs, more remote lymph nodes, or other organs.	Chemotherapy, clinical trials, and supportive care

Emerging Research: Lung Cancer

Research is making progress to advance our understanding of how to prevent, detect, and treat lung cancer. Progress has also been made in identifying many different genetic alterations that can increase the risk for lung cancer.

Screening Advancements

Early detection and treatment are critical to decreasing mortality rates and improving 5-year survival rates. The National Lung Screening Trial showed that low-dose CT scans can be used to screen for lung cancer in heavy smokers. Machine learning is a method that allows computers to learn how to predict certain outcomes. In lung cancer, researchers are using computer algorithms to create computer-aided programs that can identify cancer in CT scans better than radiologists or pathologists can. In one artificial intelligence study, researchers trained a computer program to diagnose two types of lung cancers with 97% accuracy as well as to detect cancer-related genetic mutations. Researchers are working to develop or refine sputum and blood tests that could detect lung cancer early. One method being researched analyzes blood samples to detect tumor cells or molecular markers; another method examines sputum samples for the presence of abnormal cells or molecular markers.

Treatment Advancements

Researchers continue to explore new treatment options for all stages of lung cancer, and studies investigating treatments for advanced-stage disease are promising. Today, immunotherapy is a major focus in lung cancer treatment. Clinical trials are ongoing to examine new combinations of immunotherapies with or without chemotherapy.

An immune checkpoint inhibitor is a drug that blocks proteins on immune cells, increasing the strength of the anticancer immune response. Several immune checkpoint inhibitors have recently been approved for advanced lung cancer, specifically those that target programmed death–ligand 1 (PD-L1) and PD-1. Immune checkpoint inhibitors

approved to treat lung cancer include atezolizumab (Tecentriq), durvalumab (Imfinzi), nivolumab (Opdivo), and pembrolizumab (Keytruda). Identifying which patients will benefit from immunotherapies is key. One marker for immunotherapy response is the tumor mutational burden (TMB), which is the total mutations present in the cancer cell DNA. Positive responses to checkpoint inhibitors have been linked with high TMB in some trials.

Targeted treatments identify and attack certain types of cancer cells while doing less harm to normal cells. Many targeted therapies have become available for advanced lung cancer, and more are in development. ALK inhibitors (e.g., ceritinib [Zykadia], crizotinib [Xalkori], alectinib [Alecensa], brigatinib [Alunbrig], and lorlatinib [Lorbrena]) target the cancer-causing alteration in the ALK gene. Recently approved ALK inhibitors have an enhanced ability to cross the blood–brain barrier, which is critical in non-small-cell lung cancer because it often metastasizes to the brain.

Epidermal growth factor receptor (EGFR) inhibitors block the EGFR protein. These receptors may be found in higher concentrations on cancer cells, causing them to grow and divide. EGFR inhibitors include afatinib (Gilotrif), dacomitinib (Vizimpro), erlotinib (Tarceva), gefitinib (Iressa), necitumumab (Portrazza), and osimertinib (Tagrisso).

The ROS1 gene produces a protein, proto-oncogene tyrosine-protein kinase ROS, involved in cell signaling and cell growth. A small percentage of patients with non-small-cell lung cancer have altered forms of the ROS1 gene. Crizotinib is a ROS1 inhibitor approved as a treatment for patients with this alteration.

The BRAF gene produces a protein, B-Raf, involved in sending signals in cells and cell growth. Alterations in this gene are seen in some patients with non-small-cell lung cancer, which can increase the proliferation and metastasis of cancer cells. A combination drug consisting of dabrafenib (Tafiniar), a BRAF inhibitor, and trametinib (Mekinist), which targets the MET protein, has been approved for selected patients with non-small-cell lung cancer.

Some patients with non-small-cell lung cancers have mutations in the nonreceptor tyrosine kinase 1 (NRTK-1) and NRTK-2 genes that can be treated with the targeted therapy larotrectinib (Vitrakvi). Inhibitors of other targets that drive some lung cancers (e.g., RET, HER2, MEK, and MET genes) are currently being tested in clinical trials (National Cancer Institute, 2021).

Pleural Effusion

A pleural effusion is the accumulation of excess fluid in the pleural cavity. Normally, a small amount of fluid (approximately 10 to 20 mL) drained from the lymphatic system is present in this space to lubricate the constantly moving lungs. Excessive fluid in the pleural cavity can compress the lungs and limit their expansion during inhalation. Effusions vary in nature and may affect both lungs or one lung.

Exudative effusions are caused by local processes that lead to increased capillary permeability, resulting in the accumulation of fluid,

protein, cells, and other serum constituents. The most frequent causes of these effusions are pneumonia, cancer, pulmonary embolisms, viral infections, and tuberculosis. Yellow nail syndrome is a rare disorder that causes chronic exudative pleural effusions, lymphedema, and yellow nails; this syndrome is thought to be a result of impaired lymphatic drainage. A combination of increased hydrostatic pressure and decreased plasma oncotic pressure causes transudative effusions. Heart failure is the most common cause, followed by cirrhosis with ascites and hypoalbuminemia, usually due to nephrotic syndrome.

Hemothorax refers to bloody fluid accumulation in the pleural space, usually due to trauma or rarely caused by coagulopathy or rupture of a major blood vessel (e.g., the aorta or pulmonary artery). Chylothorax is a milky white effusion high in triglycerides caused by traumatic or neoplastic damage to the thoracic duct; it can also occur with superior vena cava syndrome. The fluid associated with chyliform effusions is low in triglycerides and high in cholesterol. Chyliform effusions are thought to be caused by the release of cholesterol from lysed erythrocytes and neutrophils in chronic effusions.

Empyema is pus in the pleural space, usually as a complication of pneumonia, a thoracotomy, abscesses (lung, hepatic, or subdiaphragmatic), or penetrating trauma with secondary infection. Trapped lung refers to a lung encased by a fibrous peel caused by empyema or tumor. The pleural pressure becomes more negative because the lung cannot expand, increasing transudative fluid. The fluid associated with trapped lung is between a transudate and an exudate.

Iatrogenic effusions can be caused by migration or misplacement of a feeding tube into the trachea or perforation of the superior vena cava by a central venous catheter, leading to infusion of tube feeding or intravenous solutions into the pleural space. Etiology is unknown for about 15% of effusions; many of these effusions are thought to be due to viral infections.

Pleurisy, or pleuritis, can precede or follow the effusion, or it may occur independently. Pleurisy comprises inflammation of the pleural membranes, which leads to swollen and irregular tissue. This

inflammation is often associated with pneumonia and creates friction in the pleural membranes.

The consequence of a pleural effusion depends on its type, location, amount, and fluid accumulation rate. Large amounts of fluids can cause the pleural membranes to separate, preventing their cohesion during inhalation (**FIGURE 5-30**; **FIGURE 5-31**). This lack of cohesion impedes full expansion, leading to atelectasis and a **pneumothorax**. Large effusions can also impair venous return in the inferior vena cava and cardiac filling by putting pressure on those structures.

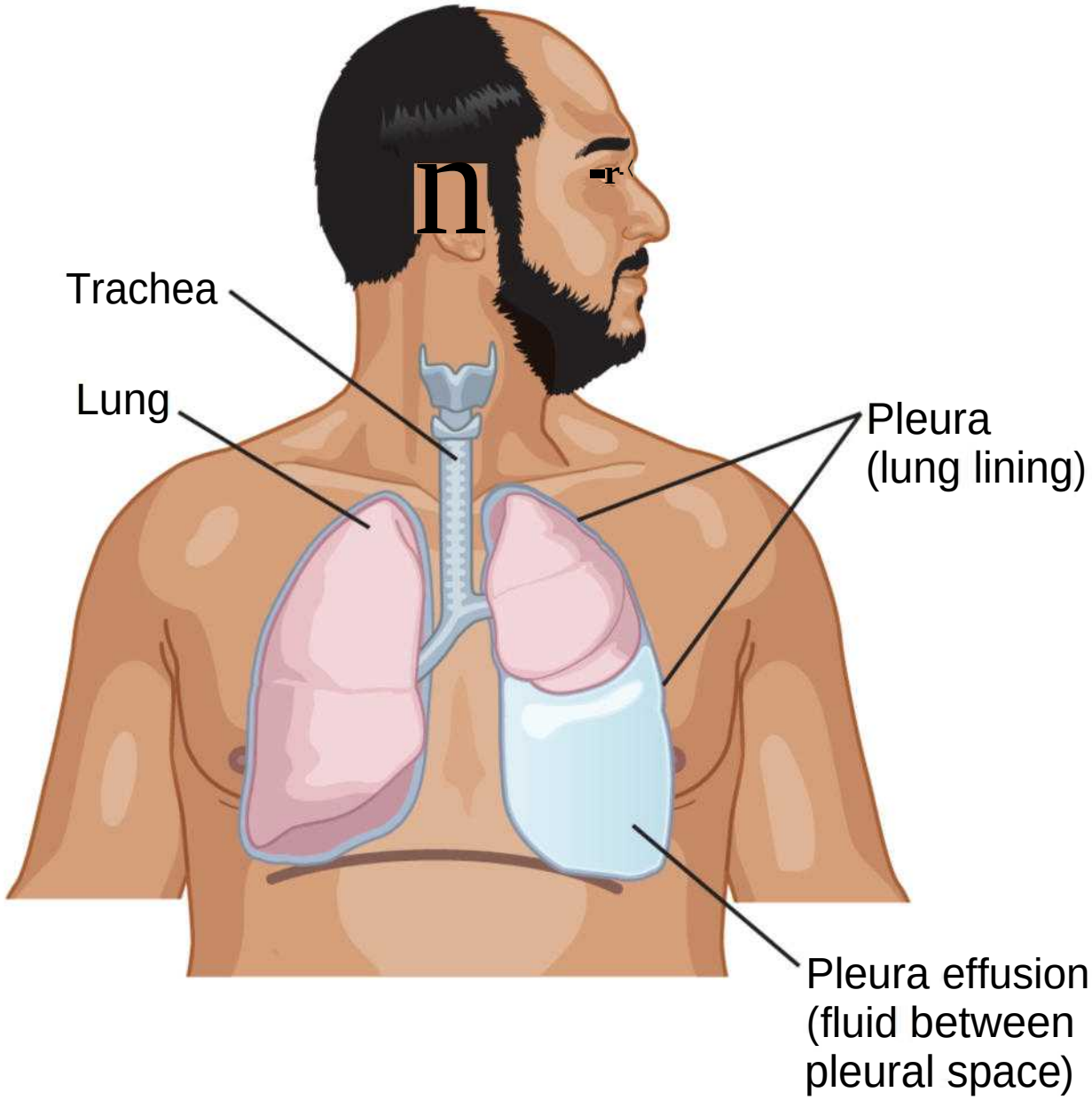


FIGURE 5-30 Pleural effusion is a buildup of fluid in the lining of the lungs.

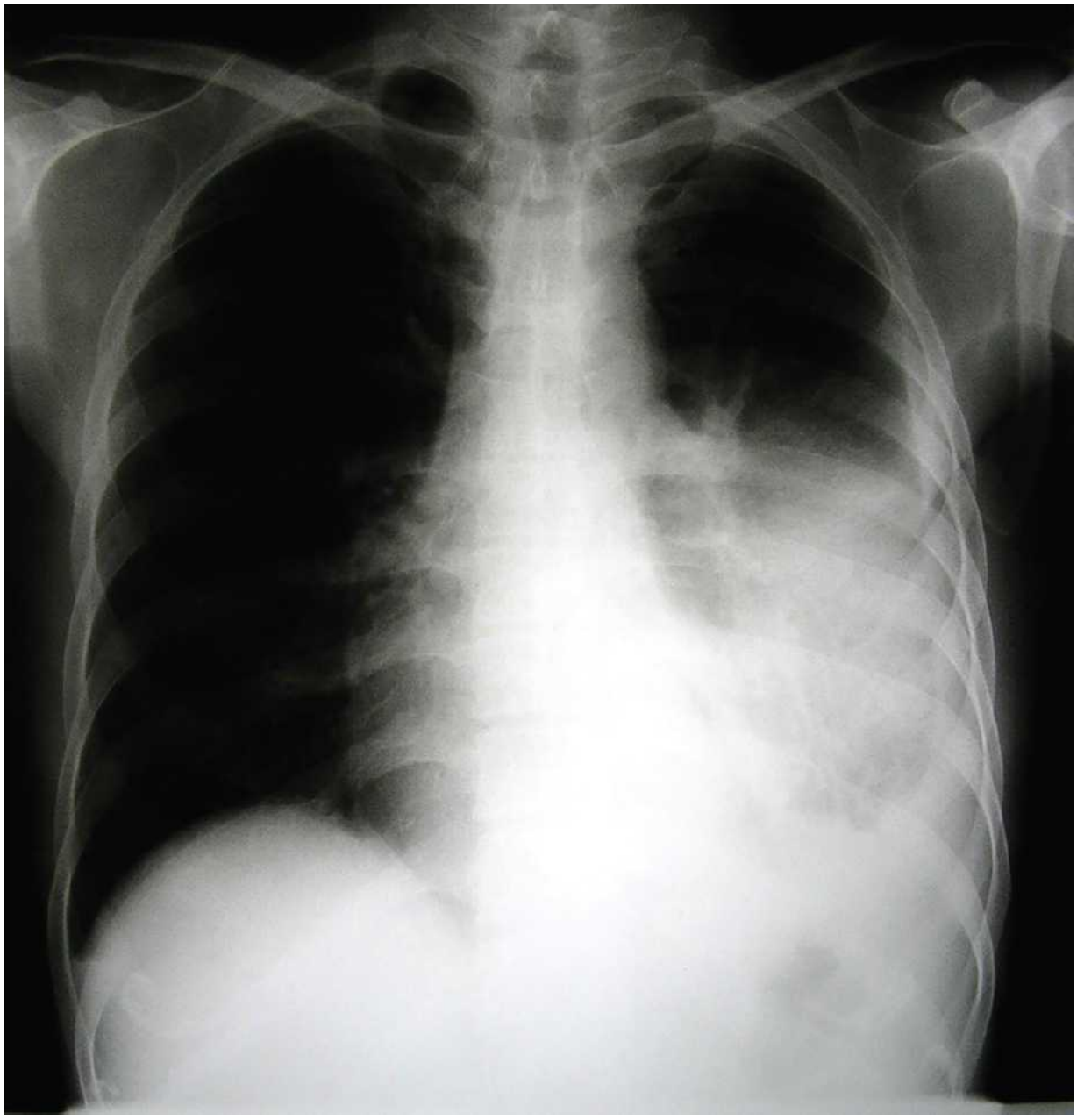


FIGURE 5-31 X-ray of pleural effusion.

Courtesy of Michael-Joseph F. Agbayani.

Some pleural effusions are asymptomatic. When present, clinical manifestations of pleural effusion include the following signs and symptoms:

- Dyspnea

- Chest pain (usually sharp and worsening with inhalation)
- Tachypnea
- Tracheal deviation (toward the unaffected side)
- Absent tactile fremitus (a palpable vibratory sensation to the chest wall) over the affected area
- Diminished or absent lung sounds over the affected area
- Dullness to percussion over the affected area
- Tachycardia
- Pleural friction rub (pleurisy)

Diagnostic procedures for pleural effusion include a history, physical examination, chest X-ray, CT, ABGs, CBC, and thoracentesis (needle aspiration of fluid) with subsequent examination of fluid. A thoracentesis should be avoided in patients with heart failure and should be delayed until heart failure is excluded.

Treatment focuses on addressing the underlying cause. Small effusions that have minimal symptoms often resolve without treatment or with correction of the underlying causes. Regardless of the etiology, removal of the fluid is often necessary to promote full expansion of the lungs. Strategies to do so may include thoracentesis, placement of a chest drainage tube, indwelling catheter drainage for chronic pleural effusion, and antibiotics.

Pneumothorax

Pneumothorax refers to air in the pleural cavity. Atmospheric air can enter into the pleural space through either the chest wall (e.g., trauma) or the functional lung tissue. The presence of atmospheric air in the pleural cavity and the separation of pleural membranes can lead to atelectasis. The resulting pressure can cause a partial or complete collapse of a lung (**FIGURE 5-32**; **FIGURE 5-33**). A small pneumothorax causes mild symptoms and may heal on its own. In contrast, a larger pneumothorax generally requires aggressive treatment to remove the air and reestablish pulmonary negative

pressure. Risk factors for developing pneumothorax include smoking, tall stature, and a history of lung disease or previous pneumothorax.

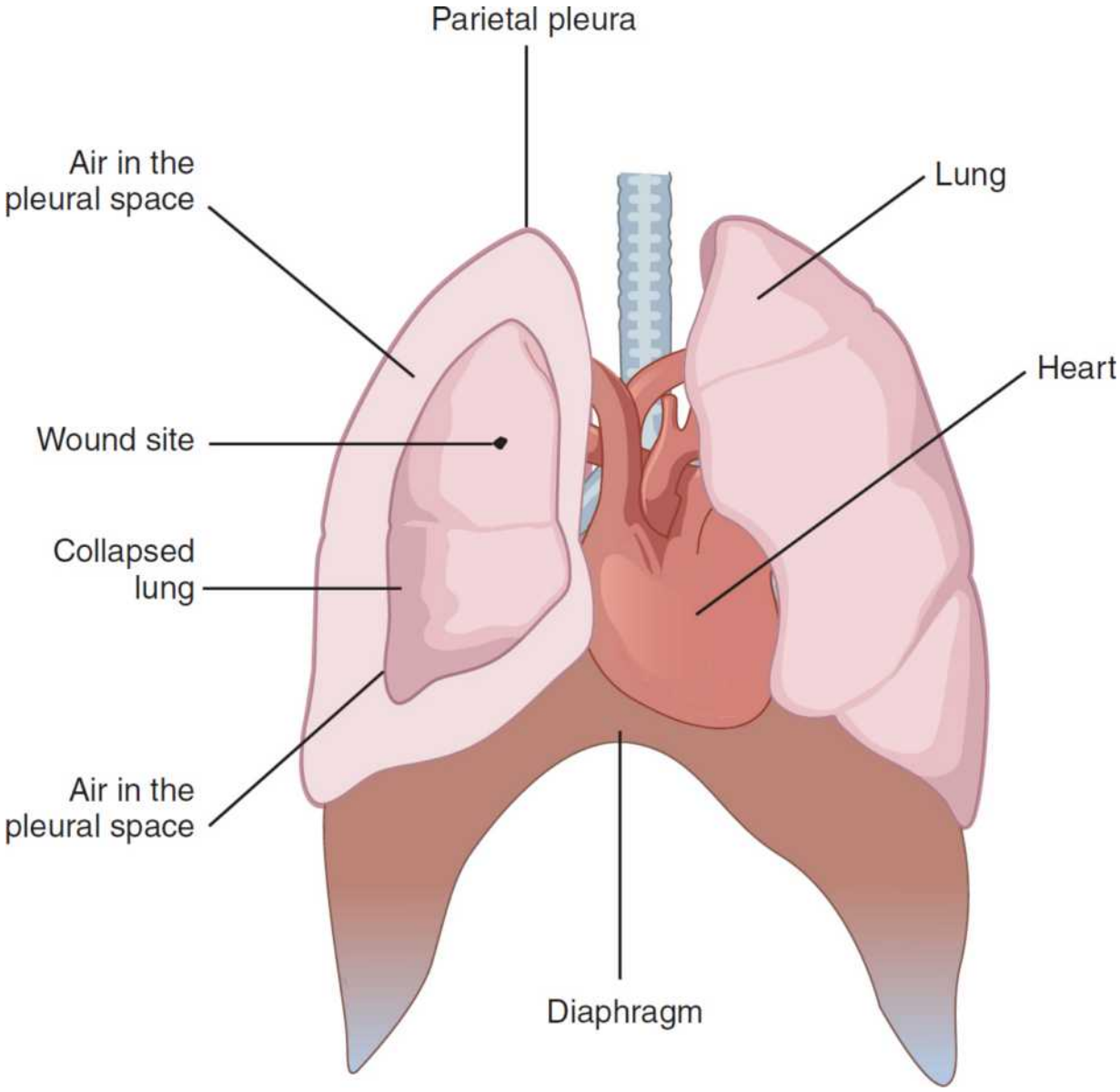


FIGURE 5-32 A pneumothorax occurs when air leaks into the pleural space between the parietal and visceral pleura. The lung collapses as air fills the pleural space, and the two pleural membranes are no longer in contact with each other.

Description

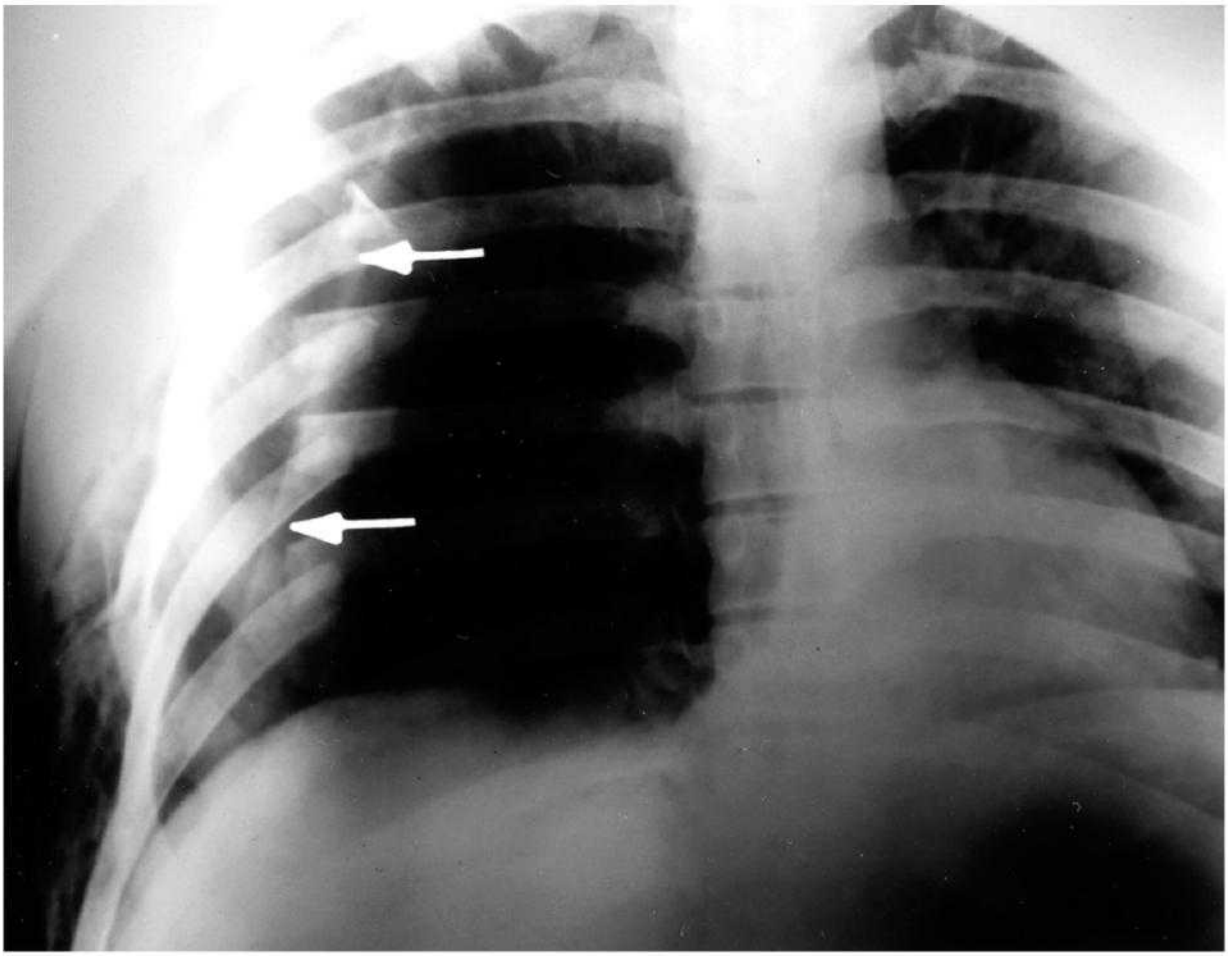


FIGURE 5-33 X-ray of pneumothorax.

Courtesy of Leonard V. Crowley, MD, Century College.

Several types of pneumothoraces are distinguished, based on their cause and the nature of their development. A **spontaneous pneumothorax** develops when air enters the pleural cavity from an opening in the internal airways. Primary spontaneous pneumothoraces occur when a small air blister (bleb) on the top of the lung ruptures in patients without any underlying lung disease. Primary spontaneous pneumothorax typically occurs in tall, thin men in their teens and 20s. Blebs are caused by a weakness in the lung tissue and can rupture from changes in air pressure, such as when scuba diving, flying, mountain climbing, or listening to extremely loud music. Additionally, a primary spontaneous pneumothorax may happen while smoking marijuana—a deep inhalation, followed by

slowly breathing out against partially closed lips, forces the smoke deeper into the lungs. Most commonly, these blebs rupture for no obvious reason, although genetic factors may play a role. In these rare cases, mutations in the *folliculin* gene, which follow an autosomal dominant inheritance pattern, have been implicated. A primary spontaneous pneumothorax is usually mild because pressure from the collapsed portion of the lung may, in turn, collapse the bleb.

A secondary spontaneous pneumothorax develops in people with preexisting lung disease (e.g., emphysema, pneumonia, cystic fibrosis, or lung cancer). In these cases, the pneumothorax occurs because the diseased lung tissue is weakened. Secondary spontaneous pneumothorax can be more severe and even life threatening because the diseased tissue can create an even larger opening, allowing more air to enter the pleural space. Additionally, pulmonary disease reduces lung reserves, making any further reduction in lung function more serious. A catamenial pneumothorax is a rare form of secondary spontaneous pneumothorax that occurs within 48 hours of the menstruation onset in premenopausal women and sometimes in postmenopausal women taking estrogen. The cause of this form is intrathoracic endometriosis, likely as a result of migration of peritoneal endometrial tissue through a diaphragmatic defect or embolism through pelvic veins.

A **traumatic pneumothorax** stems from blunt trauma (e.g., vehicle air bag deployment) or penetrating injury (e.g., knife or gunshot wounds) to the chest. These injuries can inadvertently occur during certain medical procedures (i.e., iatrogenic pneumothorax), such as transthoracic needle aspiration, thoracentesis, central venous catheter placement, mechanical ventilation, chest tube insertion, cardiopulmonary resuscitation, and lung or liver biopsy.

A **tension pneumothorax** is the most serious type of pneumothorax; it occurs when the pressure in the pleural space is greater than the atmospheric pressure. This increased pressure arises due to trapped air in the pleural space or entering air from a positive-pressure mechanical ventilator. The force of the air can cause the affected lung to collapse completely and shift the heart toward the unaffected lung (called a “mediastinal shift”), compressing

the unaffected lung and the heart (FIGURE 5-34). Tension pneumothorax progresses rapidly and is fatal if not treated quickly.

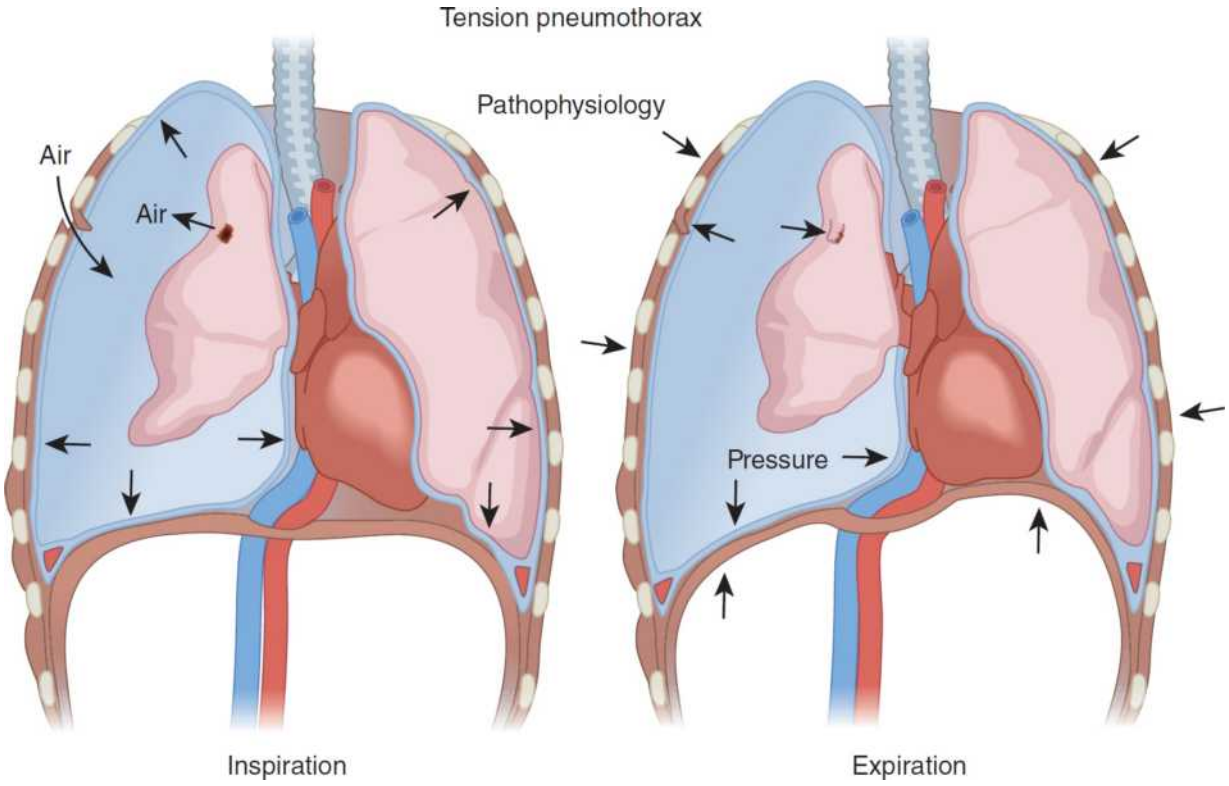


FIGURE 5-34 Tension pneumothorax. A one-way valve allows air into the pleural space during inspiration but prevents it from leaving during expiration.

Clinical manifestations vary in severity depending on the type and size of pneumothorax as well as how quickly it develops. These manifestations include the following signs and symptoms:

- Sudden chest pain over the affected lung
- Chest tightness
- Dyspnea
- Tachypnea
- Absent tactile fremitus over the affected area
- Hyperresonance to percussion over the affected area
- Decreased breath sounds over the affected area

- Asymmetrical chest movement
- Deviation of the trachea and mediastinum toward the unaffected side
- Anxiety
- Tachycardia
- Pallor
- Hypotension, particularly with tension pneumothoraces

Diagnostic procedures for pneumothorax consist of a history, physical examination, chest X-ray, CT, and ABGs. Supplemental oxygen should be started while awaiting chest X-ray results because oxygen accelerates pleural reabsorption of air. A tension pneumothorax is a medical emergency, so treatment should be initiated immediately when suspected. Treatment usually involves the removal of the air and the reestablishment of negative pressure, allowing for full expansion of the lungs. Such strategies may include thoracentesis and placement of a chest drainage tube with suction, which removes fluid and reestablishes negative pressure. Surgery may be required in some cases to correct and prevent future episodes. During surgery, the leak is repaired, and a chemical may be used to scar the area (pleurodesis). Reoccurrence is common with spontaneous pneumothoraces. Video-assisted thoracic surgery can also be performed to stabilize the blebs and remove pleurodesis (which causes the lung to adhere to the chest wall) with pleural abrasion, parietal pleurectomy, or talc insufflation.

Acute Respiratory Distress Syndrome

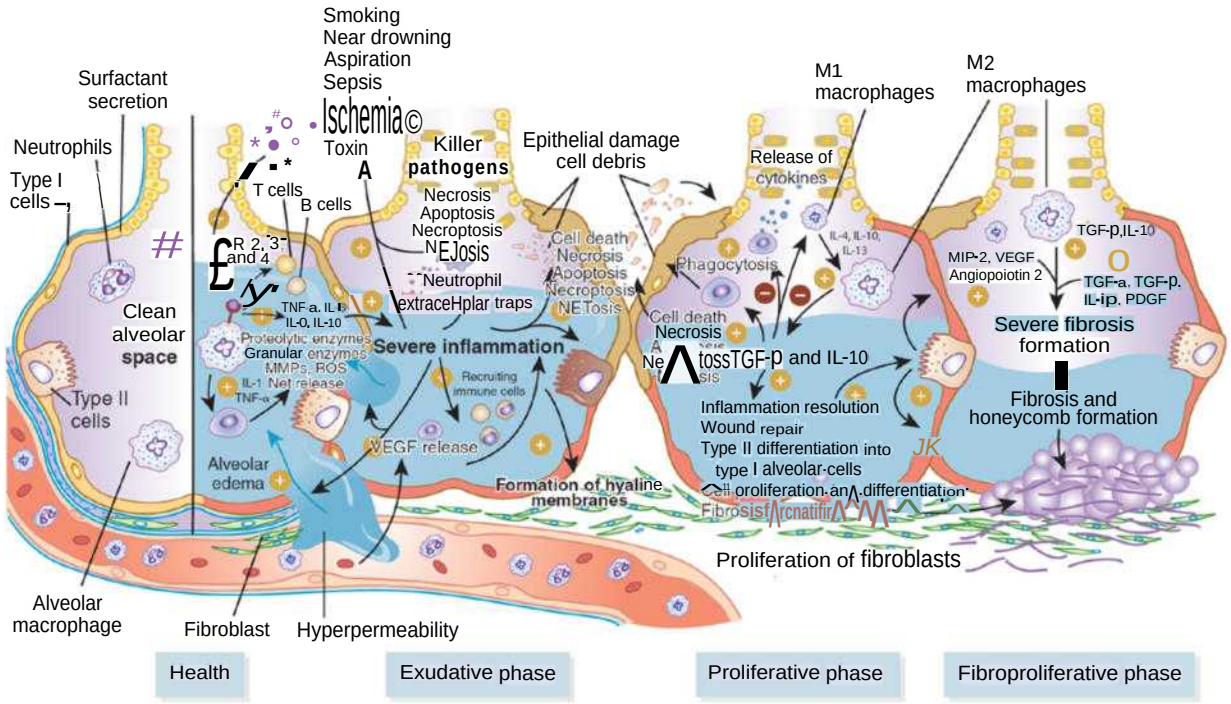
Acute respiratory distress syndrome (ARDS) is a sudden failure of the respiratory system, often as a result of fluid accumulation in the alveoli. ARDS has many other names, such as “shock lung,” “wet lung,” and “stiff lung.” **Acute lung injury** refers to a slightly less severe form of ARDS.

ARDS can be a result of direct or indirect lung injuries. Direct lung injuries may occur with acid aspiration, pneumonia, amniotic fluid

embolism, diffuse alveolar hemorrhage, fat embolism, lung transplant, pulmonary contusion, smoke inhalation, and toxic gas inhalation. Causes of indirect lung injuries include sepsis, trauma with prolonged hypovolemic shock, bone marrow transplantation, burns, cardiopulmonary bypass, drug overdose (e.g., aspirin, cocaine, opioids, phenothiazines, and tricyclics), massive blood transfusions, neurogenic pulmonary edema, pancreatitis, and preeclampsia. ARDS develops rapidly, often within 90 minutes of a systemic inflammatory response or within 48 hours of a lung injury. Other risk factors include the presence of a chronic lung disease (e.g., emphysema, chronic bronchitis, and asthma), alcoholism, age greater than 65 years, and mechanical ventilation.

ARDS is fatal in one-third of cases. Individuals who survive will fully recover, but it may take as long as a year for them to regain complete lung function.

While the overall disease progression is variable, ARDS develops through three phases: exudative, proliferative, and fibroproliferative (**FIGURE 5-35**). Initially, injury to the alveoli and the capillary membranes leads to the release of chemical inflammatory mediators (i.e., cytokines). These mediators activate alveolar macrophages and mobilize neutrophils to the lungs, which in turn release leukotrienes, oxidants, platelet-activating factors, and proteases. These substances damage the capillary–alveolar endothelium, disrupting barriers between the capillaries and the alveoli. The increased capillary permeability promotes the accumulation of fluid, protein, and cellular debris in the alveoli, which in turn causes damage to surfactant-producing cells, airway collapse, ventilation/perfusion mismatch, shunting, and pulmonary hypertension. These events result in decreased gas exchange, reduced pulmonary blood flow, limited lung expansion, and increased platelet aggregation and subsequent microembolus development. Diffuse atelectasis and reduced lung capacity ensue. A hyaline membrane—a thin layer of tissue—forms in the alveoli and causes them to become stiff. If the patient survives, scattered necrosis and fibrosis are apparent throughout the lungs. ARDS is similar in pathogenesis to disseminated intravascular coagulation (see the *Hematopoietic Function* chapter).



Abbreviations: AECC, American-European Consensus Conference; AJ, Adherens junction; APC, Antigen-presenting cell; APCs, Antigen-presenting cells; AQP, Aquaporin; ARDS, Acute respiratory distress syndrome; CPAP, Continuous positive airway pressure; FiO_2, Inspiratory oxygen fraction; IL, Interleukin; iNO, Inhaled nitric oxide; MLC, Myosin light chain; MLKL, Mixed lineage kinase domain-like protein; MLCK, Myosin light chain kinase; MLCP, Myosin light chain phosphatase; NET, Neutrophil extracellular trap; NF-KB, Nuclear factor-xb; NKA, N+-K+-adenosine triphosphatase; PaO_2, Arterial oxygen tension; PEEP, Positive end-expiratory pressure; RIP3, Receptor-interacting protein kinase 3; ROS, Reactive oxygen species; S1P, Sphingosine-1-phosphate; TGF, Transforming growth factor; TJs, Tight junctions; TNF, Tumor necrosis factor; VEGF, Vascular endothelial growth factor

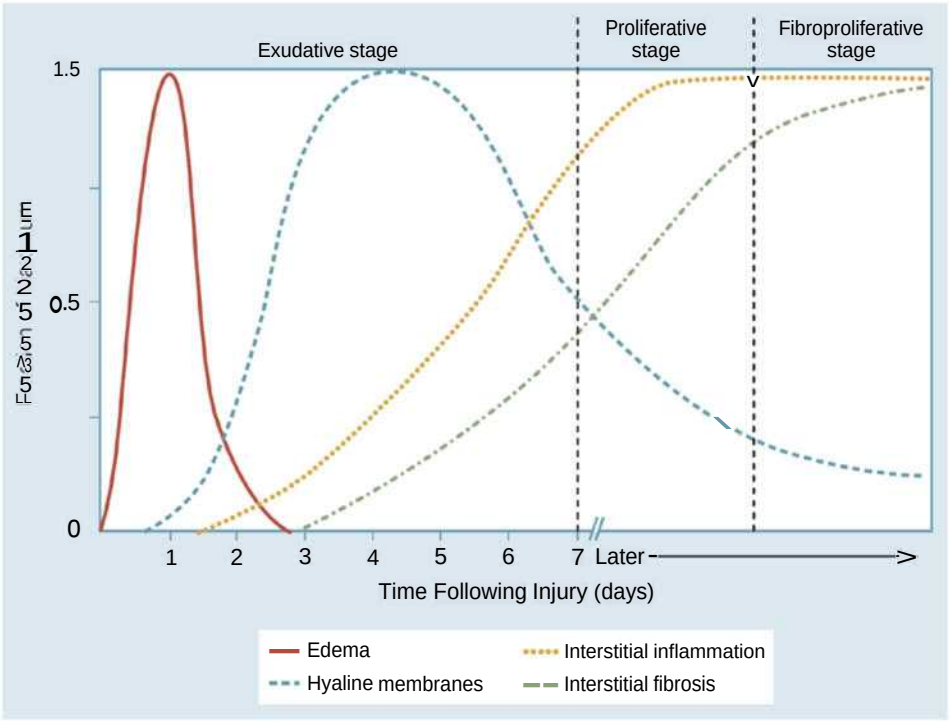


FIGURE 5-35 Phases of acute respiratory distress syndrome.

Description

ARDS is a serious condition that can lead to several complications:

- Respiratory failure
- Respiratory and metabolic acidosis
- Pulmonary fibrosis
- Pneumothorax
- Bacterial lung infections (e.g., stasis pneumonia and VAP)
- Decreased lung function
- Renal failure
- Stress ulcer
- Thromboembolism
- Muscle wasting
- Memory, cognitive, and emotional issues (due to brain damage as a result of the hypoxia)

Clinical manifestations of ARDS can develop suddenly and include the following signs and symptoms:

- Dyspnea
- Labored (requiring the use of accessory muscles), shallow respirations
- Abnormal lung sounds (e.g., rales and rhonchi)
- Productive cough with frothy sputum
- Hypoxia
- Cyanosis
- Fever
- Hypotension
- Tachycardia
- Restlessness
- Confusion

- Lethargy
- Anxiety

Diagnostic procedures for ARDS consist of a history, physical examination, ABGs, chest X-ray, CT, and CBC. The Berlin criteria are used to determine severity and predict prognosis (Ranieri et al., 2012). The main goal of treatment is to maintain adequate oxygenation and respiratory status. Strategies used to achieve this goal include endotracheal intubation with a mechanical ventilator (including positive end-expiratory pressure [PEEP]), high-dose oxygen therapy, neuromuscular blocking agents, prone positioning, inhaled nitric oxide, extracorporeal membrane oxygenation, corticosteroids, inhaled beta-agonists, and antibiotics (if bacterial infections are present), as well as prevention and treatment of emboli (e.g., embolectomy, anticoagulants, and antiplatelet agents). Other strategies include nutritional support (e.g., enteral feedings), conservative fluid therapy, sedation, and stress ulcer prophylaxis.

Alterations in Ventilation and Perfusion

Atelectasis

Atelectasis refers to incomplete alveolar expansion or collapse of the alveoli. It occurs when the walls of the alveoli stick together. Atelectasis may be caused by the following conditions:

- Surfactant deficiencies
- Bronchus obstruction (e.g., foreign objects, mucous plugs, and tumors)
- Lung tissue compression (e.g., tumor, pneumothorax, and pleural effusion)
- Increased surface tension (e.g., pulmonary edema)
- Lung fibrosis (e.g., emphysema)

When alveoli are not filled with air, they shrivel up much like raisins. This ventilation issue can, in turn, impair blood flow through the lungs. The ineffective ventilation and perfusion then impair gas exchange. Surgery and immobility increase patients' risk of developing atelectasis for this reason.

Atelectasis can occur in either small or large areas. If only a small area is affected, the respiratory rate will increase in an attempt to control carbon dioxide levels (increasing the respiratory rate will increase the excretion of carbon dioxide). The larger the area affected, the more severe the symptoms the patient will experience. Necrosis, infection (e.g., pneumonia), and permanent lung damage can occur if the alveoli are not reinflated quickly.

The clinical manifestations of atelectasis are due to impaired ventilation and perfusion:

- Diminished breath sounds
- Dyspnea
- Tachypnea
- Asymmetrical lung movement
- Anxiety
- Restlessness
- Tracheal deviation
- Tachycardia

Diagnostic procedures for atelectasis include a history, physical examination, chest X-ray (**FIGURE 5-36**), CT, bronchoscopy, ABGs, and CBC. Treatment focuses on remedying the underlying causes (e.g., antibiotics for infections or thoracentesis for pleural effusion) and reinflating the alveoli. Incentive spirometry (a device to promote ventilation) is effective in reinflating the alveoli. For more severe cases, continuous positive airway pressure or endotracheal intubation may be necessary for ventilation support. Prevention strategies include increasing mobility (e.g., turning and ambulating), coughing, and deep breathing exercises (e.g., incentive spirometry) every 1 to 2 hours. Effective pain management and postoperative incisional

splinting increase the likelihood that these interventions will be performed adequately.

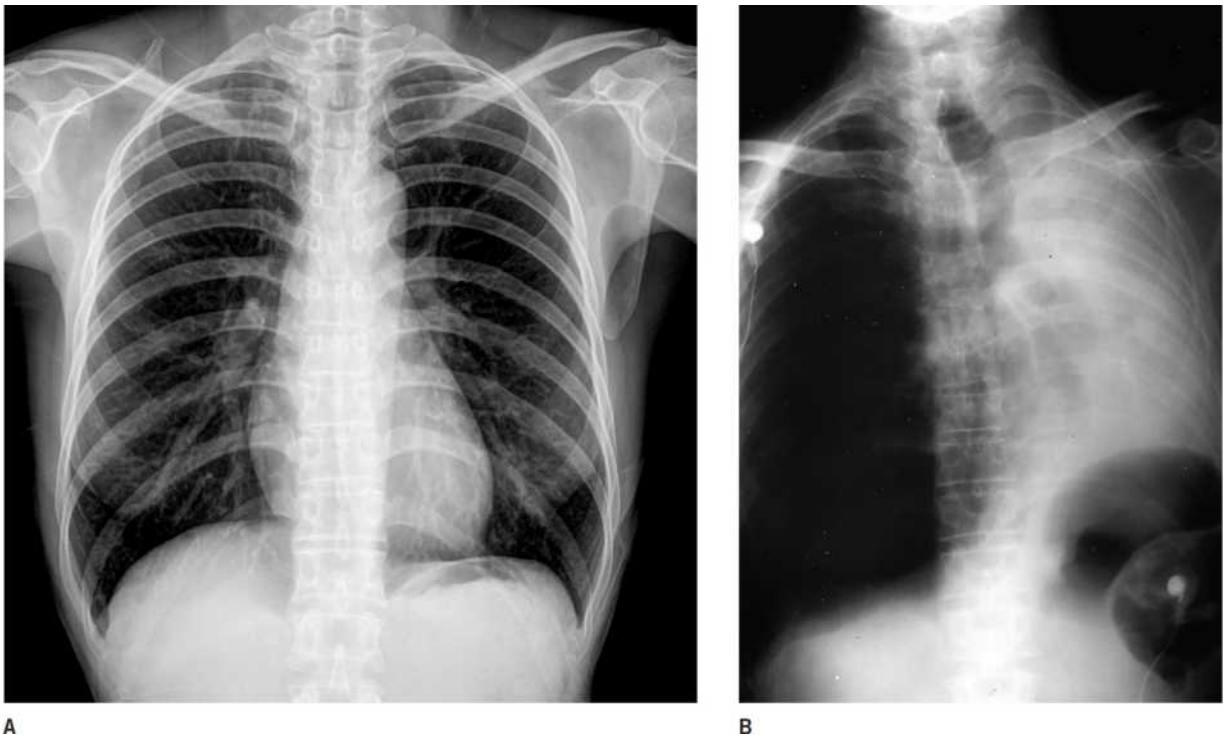


FIGURE 5-36 X-ray of atelectasis. **(A)** Normal lung. **(B)** Lung with atelectasis.

A: © Xray Computer/Shutterstock; **B:** Courtesy of Leonard V. Crowley, MD, Century College.

Acute Respiratory Failure

Acute respiratory failure (ARF) is a life-threatening condition that can result from a variety of disorders (e.g., COPD, asthma, ARDS, amyotrophic lateral sclerosis, alcohol or drug overdose, and spinal cord injury). Normally, oxygen levels are in the range of 80 to 100 mm Hg, and carbon dioxide levels are in the range of 35 to 45 mm Hg. In ARF, oxygen levels become dangerously low (less than 50 mm Hg), or carbon dioxide levels become dangerously high (greater than 50 mm Hg). The low oxygen levels observed in ARF are not sufficient to meet the body's metabolic needs, and the nervous system quickly becomes affected by the shortage of oxygen. The oxygen level becomes progressively lower as the patient's condition worsens, while respiratory acidosis develops as carbon dioxide levels rise (see

the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter). The hypoxia and acidosis trigger a reflex pulmonary vasoconstriction, further impairing gas exchange and increasing cardiac workload. The heart decompensates from the lack of oxygen, which could lead to cardiac arrest. Respiratory arrest may occur as the respiratory system ceases all activity from the strain.

Clinical manifestations are usually evident and result from the impaired gas exchange:

- Shallow respirations
- Headache
- Tachycardia
- Dysrhythmias
- Lethargy
- Confusion

Diagnostic procedures for ARF consist of a history, physical examination, ABGs, chest X-ray, electrocardiogram, and CBC. Treatment focuses on resolving the cause and maintaining adequate respiratory status. Strategies include oxygen therapy, endotracheal intubation with ventilation support (some patients may require a tracheostomy), bronchodilators, antibiotics (if bacterial infection is present), corticosteroids, and treatment of emboli (e.g., embolectomy and anticoagulants). Cardiac support (e.g., cardiopulmonary resuscitation, sympathomimetic medications, and inotropic agents) is usually inevitable as the heart arrests under the strain.

application to practice

Now that we have learned what can go wrong in the respiratory system, let's put that knowledge into practice. While working in the emergency department, the following patients need to be triaged. Which patient would have the highest priority?

- A 6-month-old female with fever, audible inspiratory stridor, and restlessness
- A 25-year-old male with nasal drainage and hoarseness
- A 40-year-old female with fever, severe body aches, and nasal congestion

- A 59-year-old male with stage III bronchogenic carcinoma who reports nausea and pain that measures a 6 on a 0 to 10 scale

Once again, you go through the usual thought process—who would die first, acute versus chronic conditions, Maslow's hierarchy of needs, and patient safety. Starting with the 6-month-old, the combination of manifestations reflects the possibility of epiglottitis or some other acute infectious respiratory process. Inspiratory stridor indicates that the child may have limited air entering the lungs due to an obstruction. The restlessness could be an indication of hypoxia. Additionally, the patient's young age increases the likelihood of her decompensating quickly. This patient definitely needs to stay on your radar. The 25-year-old is exhibiting manifestations likely due to laryngitis, which is not usually life threatening. Additionally, there is no indication that this patient is in any respiratory distress. The 40-year-old likely has the flu. Although the patient may be extremely uncomfortable, the flu is not usually life threatening in otherwise healthy adults. Also, this patient is not displaying any respiratory distress. Finally, consider the 59-year-old with lung cancer. Lung cancer is often life threatening, but this patient was admitted with pain and nausea. Although nausea and pain are uncomfortable, they are not life-threatening conditions. Furthermore, this patient is not exhibiting any manifestations indicating respiratory distress. After considering all the patients to be triaged, it becomes clear that the 6-month-old should take priority and be seen first because she is exhibiting signs of respiratory distress.

application to practice

Mr. Dan Griffith is a 65-year-old male who presented to the emergency department with shortness of breath and chest tightness of recent onset. He has a 7-year history of chronic obstructive pulmonary disease and is on oxygen at home. Physical assessment reveals a respiratory rate of 32 and slightly labored, temperature of 98.9°F, and SpO_2 of 86% while on oxygen via nasal cannula at 2 L/min.

1. Which of the following additional manifestations would be expected in a patient with emphysema?
   a. productive cough with thick sputum
   b. anterior–posterior thoracic diameter of 1:1
   c. cyanosis
   d. edema

Mr. Griffith is admitted to the pulmonary unit with acute exacerbation of emphysema. Six hours after arriving on the floor, you notice that his respiration rate has dropped from 28 to 8 breaths/min. The nurse notes that Mr. Griffith's oxygen is set at 8 L/min via nasal cannula.

1. Which action should the nurse take next?
   a. call respiratory therapy to administer an albuterol treatment
   b. auscultate the patient's breath sounds

c. change the nasal cannula to a mask

d. decrease the rate of oxygen flow

2. Which of the following nursing diagnoses would be the highest priority for Mr. Griffith?
   a. ineffective airway clearance
   b. impaired gas exchange
   c. activity intolerance
   d. self-care deficit
3. On his second day in the hospital, Mr. Griffith's morning weight indicates a 5-pound weight gain since admission. The patient's weight gain may reflect which associated complication of emphysema?
   a. metabolic acidosis
   b. respiratory alkalosis
   c. cor pulmonale
   d. pneumonia

With treatment, Mr. Griffith's condition is improving. The nurse is teaching him how to perform pursed-lip breathing, a technique that he can use when he goes home. Mr. Griffith asks the nurse to describe the purpose of this breathing technique.

1. The nurse explains that pursed-lip breathing:
   a. prolongs expiration, thereby decreasing the amount of air trapped in the alveoli.
   b. prolongs inspiration, thereby increasing oxygenation.
   c. strengthens the accessory muscles.
   d. decreases the use of accessory muscles.

SUMMARY

The respiratory system plays a crucial role by supplying the oxygen essential for cellular metabolism and excreting the carbon dioxide waste product of that metabolism. Because of this vital function, respiratory disorders can cause extensive and devastating problems throughout the body. Often the healthcare team has only a limited amount of time to identify and respond to some of these respiratory disorders to control their negative consequences. However, many of these diseases are preventable; therefore, identifying those persons at increased risk and implementing prevention strategies can limit the severity or halt the development of these debilitating conditions. Prevention, early detection, and prompt treatment will improve the outcomes of patients with these conditions.

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CHAPTER 6

Fluid, Electrolyte, and Acid–Base Homeostasis

LEARNING OBJECTIVES

- Explain normal fluid distribution and movement in the body.
- Describe and compare fluid imbalance disorders.
- Explain normal electrolyte functions in the body.
- Describe and compare electrolyte disorders.
- Explain normal pH regulation.
- Describe and compare acid–base disorders.
- Analyze arterial blood gases.
- Discuss the relationship between fluid, electrolytes, and pH.

KEY TERMS

aldosterone
anasarca
anion
anion gap
antidiuretic hormone (ADH)
arterial blood gas (ABG)
atrial natriuretic peptide
bicarbonate–carbonic acid system
calcium
cation
chloride
Chvostek sign

dehydration
depolarization
edema
extracellular fluid (ECF)
fluid deficit
fluid excess
fluid volume deficit
fluid volume excess
fully compensated
hemoglobin system
hypercalcemia
hyperchloremia
hyperkalemia
hypermagnesemia
hypernatremia
hyperphosphatemia
hypertonic solution
hypervolemia
hypocalcemia
hypochloremia
hypokalemia
hypomagnesemia
hyponatremia
hypophosphatemia
hypotonic solution
hypovolemia
interstitial
intracellular fluid (ICF)
intravascular
isotonic solution
magnesium
metabolic acidosis
metabolic alkalosis
nonvolatile acid
osmolarity
partially compensated
pH
phosphate system

phosphorus
potassium
protein system
repolarization
respiratory acidosis
respiratory alkalosis
sodium
third spacing
tonicity
transcellular
Trousseau sign
uncompensated
volatile acid
volatile gas
water intoxication

The human body requires a delicate balance, or homeostasis, to function optimally (see *Introduction to Pathophysiology*). The body continuously employs strategies to maintain this balance. Fluids, electrolytes, and **pH** all play critical roles in sustaining homeostasis. Fluids are distributed in various body compartments and move among these compartments to preserve equilibrium. Electrolytes are vital for cellular function, and they work with various fluids to maintain stability. Acid–base balance is critical for health and is achieved through a complex buffer system.

Fluids, electrolytes, and pH all share a dynamic relationship in which imbalances in one area can cause imbalances in the other two. Additionally, the other areas can serve to compensate for those imbalances. When compensatory mechanisms fail to reestablish homeostasis, many bodily functions are impaired, and serious consequences can result. In such a case, medical interventions will be necessary to reestablish stability.

Fluid Balance

Distribution

Body fluid consists of a combination of water and solutes. Water is the medium within which metabolic reactions and other processes occur. Water carries nutrients into the cells, waste products out of the cells, enzymes in digestive secretions, and blood cells around the body. Fluid also facilitates the movement of body parts (e.g., the joints, lungs, and heart). Fluid found inside the cells is referred to as **intracellular fluid (ICF)**, and fluid found outside the cells is referred to as **extracellular fluid (ECF)** (**FIGURE 6-1**). ECF is further divided into **interstitial** (ISF; between the cells) and **intravascular** (inside the blood vessels) compartments. The cell membrane serves as a barrier through which substances and water must pass to move to or from the intracellular compartment. A third compartment in which fluid is found is the **transcellular** compartment (TSF), which includes the following types of fluids:

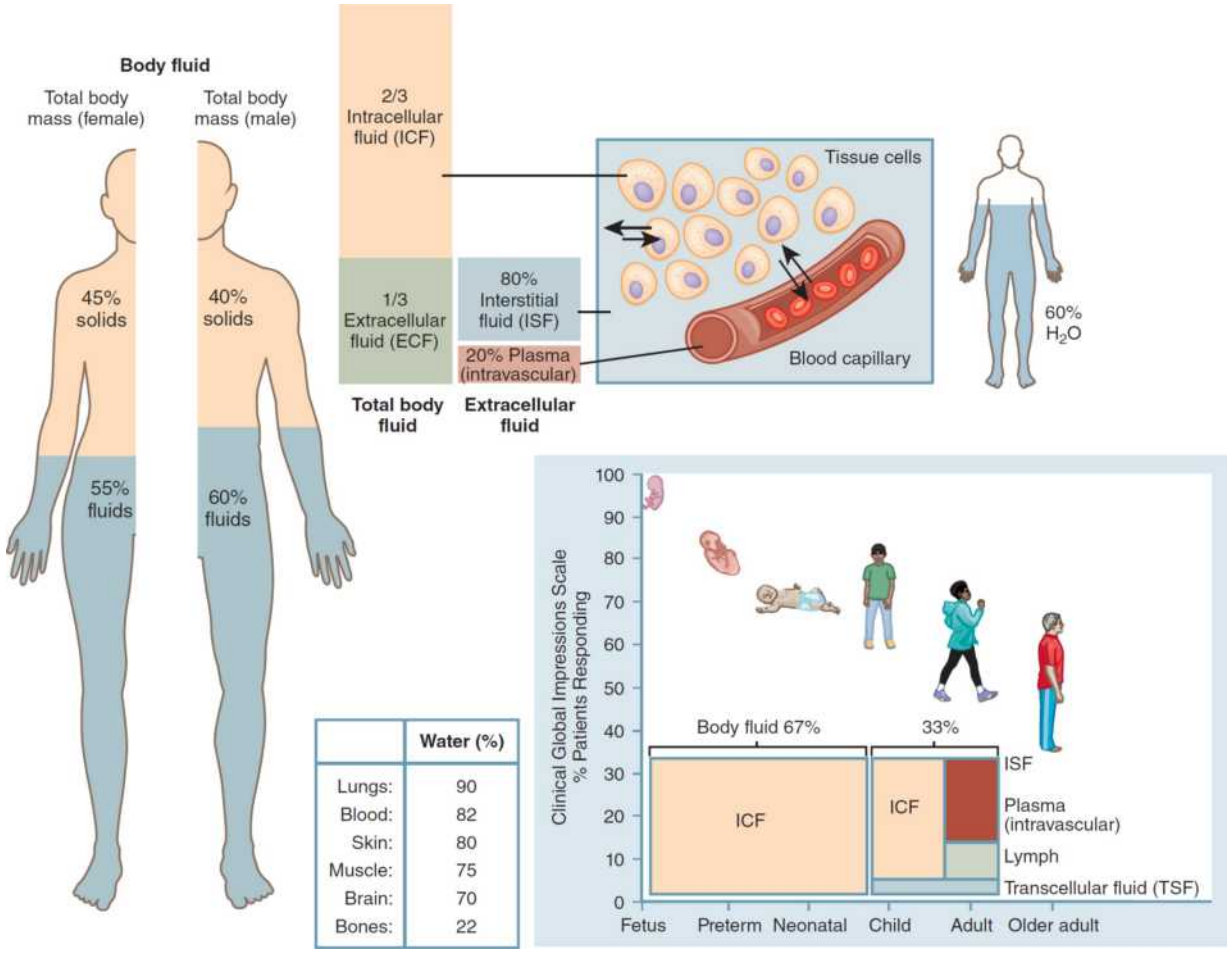


FIGURE 6-1 Fluid distribution.

Description

- Fluid in the peritoneal, pleural, and pericardial cavities
- Cerebrospinal fluid
- Fluid in the joint spaces, lymph system, eyes, and gastrointestinal tract

Collectively, the ICF accounts for approximately two-thirds of the body's water (**FIGURE 6-2**). This ICF is rich in **potassium**, **magnesium**, phosphates, and proteins. The remaining one-third of the body fluid makes up the ECF. Approximately 80% of the ECF is found in the interstitial compartment (i.e., ISF), and the remaining 20% is found in the intravascular compartment and is composed of plasma. The ECF is rich in **sodium**, **chloride**, and bicarbonate

(HCO_3^-). Blood (serum) electrolyte tests examine only intravascular electrolytes, but inferences from these tests can be made as to what is occurring in the other compartments. Transcellular fluid accounts for approximately 1% of the body's fluid.

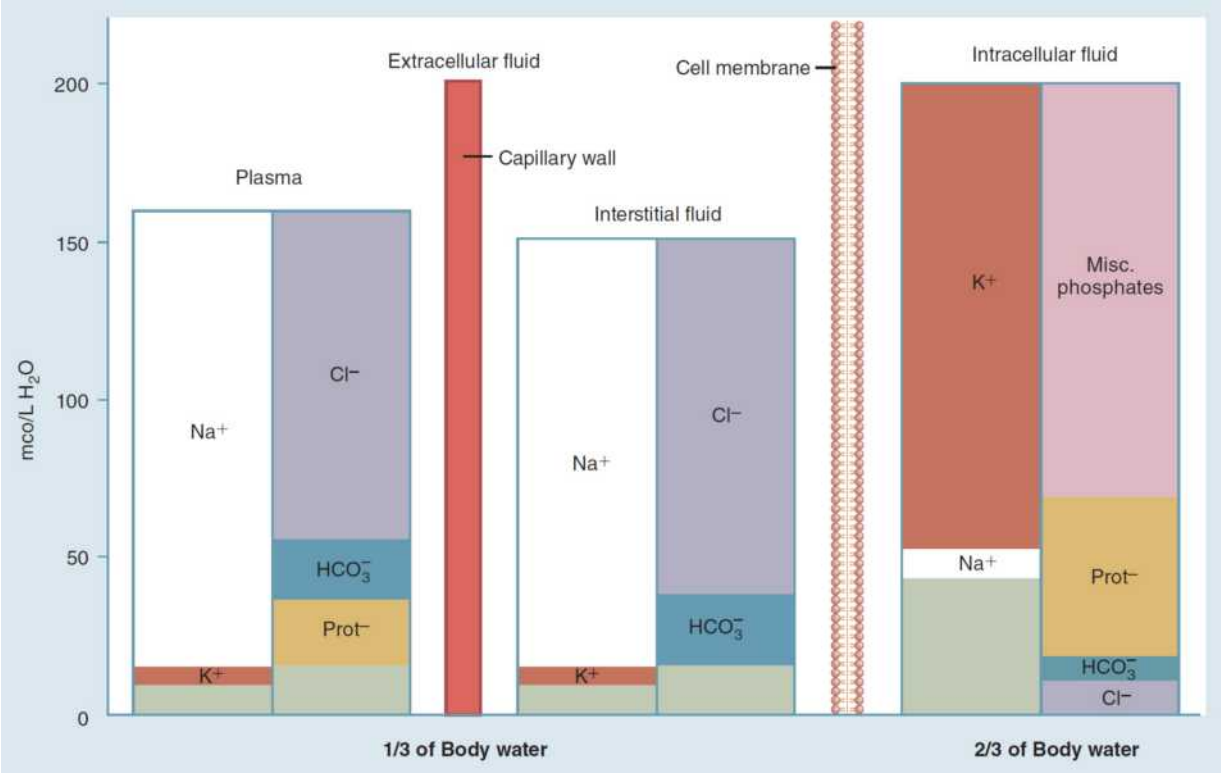


FIGURE 6-2 Intracellular fluid.

Description

Fluid distribution varies based on gender and age (see Figure 6-1). Healthy adult males are used as the reference for most percentages. However, men have more muscles and less fat than women, so they typically have higher amounts of water than women. Muscle cells store more water, while adipose cells do not store water. Newborns and infants have less body fat, so they have higher amounts of water compared to adults. While water levels may be high in this age group, their compensatory mechanisms are immature, so water losses (e.g., vomiting and diarrhea) can have serious consequences. The amount of body water decreases as the child ages until puberty, at which

time adult ratios are reached. With age, both adipose tissue and muscle mass often decrease. Additionally, compensatory mechanisms decline with age. Obesity, regardless of age, results in lower body water. Due to all of these factors, those individuals who are obese, very young, or very old are more susceptible to fluid imbalances, especially **dehydration**.

Fluid Movement

Fluids are constantly circulating throughout the body and moving among compartments to maintain homeostasis. To preserve its stability, the body exchanges solutes (e.g., ions) and water between compartments to compensate for conditions that increase or decrease losses (**FIGURE 6-3**). This movement between compartments is primarily accomplished through osmosis, the movement of fluid (specifically water) across a semipermeable membrane from an area of lower concentration to an area of higher concentration (see the *Cellular Function* chapter). Often water is overlooked as a solvent, but it also has a concentration in any solution. Consequently, water moves across the semipermeable membranes to an area of lower water concentration until equilibrium is achieved.

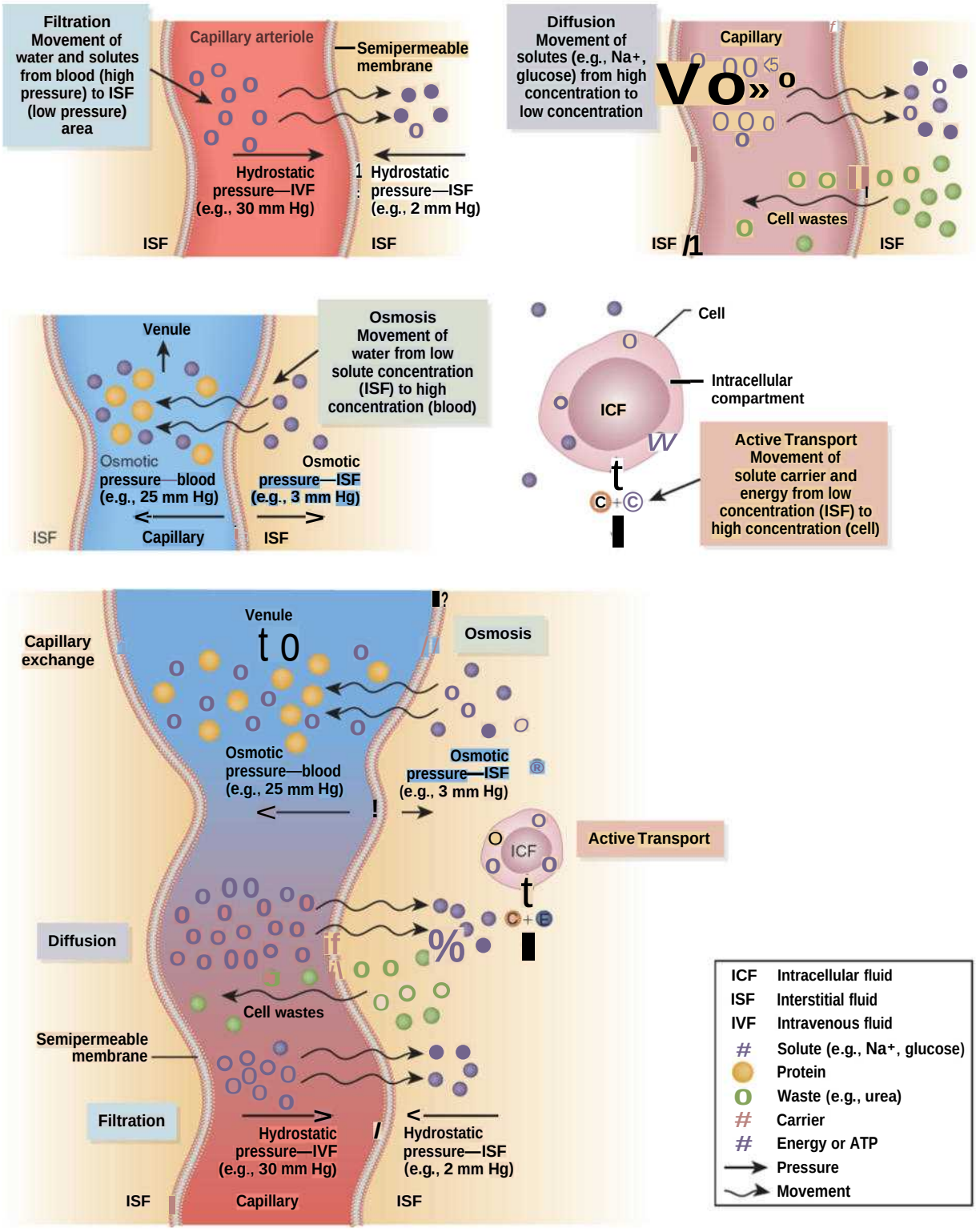


FIGURE 6-3 Fluid movement.

Description

Because water moves freely across cell membranes, equilibrium is usually easy to achieve. The movement of water depends on hydrostatic (push) and osmotic (pull) pressures (**FIGURE 6-4**). The ability of proteins and electrolytes to attract water determines the osmotic pressure of a fluid (**FIGURE 6-5**). At the arteriolar end of the capillary, the blood's hydrostatic pressure (blood pressure) exceeds the opposing interstitial hydrostatic pressure, so it moves (pushes) fluid out of the intravascular compartment and into the interstitial compartment to meet cellular needs. At the venous end of the capillary, the blood's hydrostatic pressure is decreased and the osmotic pressure is increased, so it moves (pulls) fluid from the interstitial compartment to the intravascular compartment to aid in the exchange of waste products to be excreted. To be an effective osmole, the solute must not be able to pass passively through a semipermeable membrane (e.g., protein).

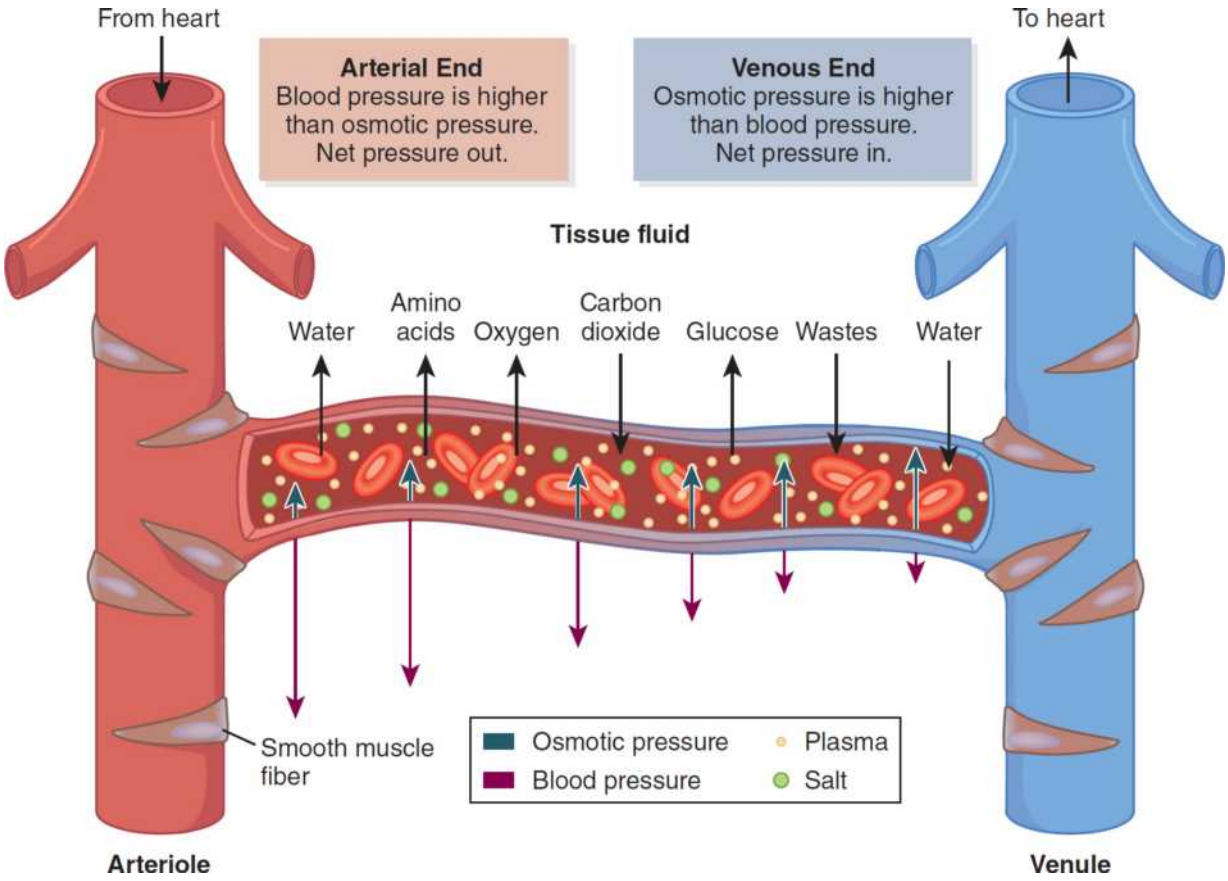
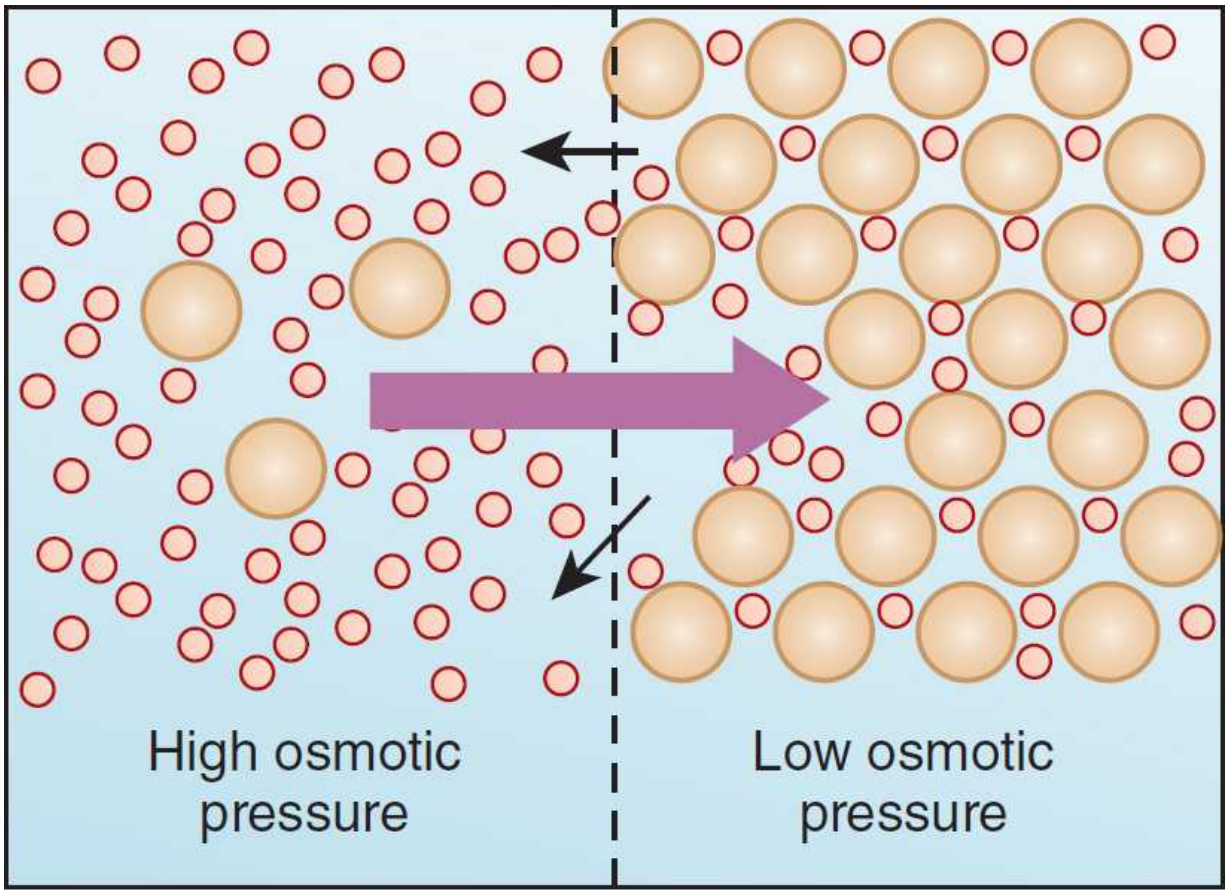
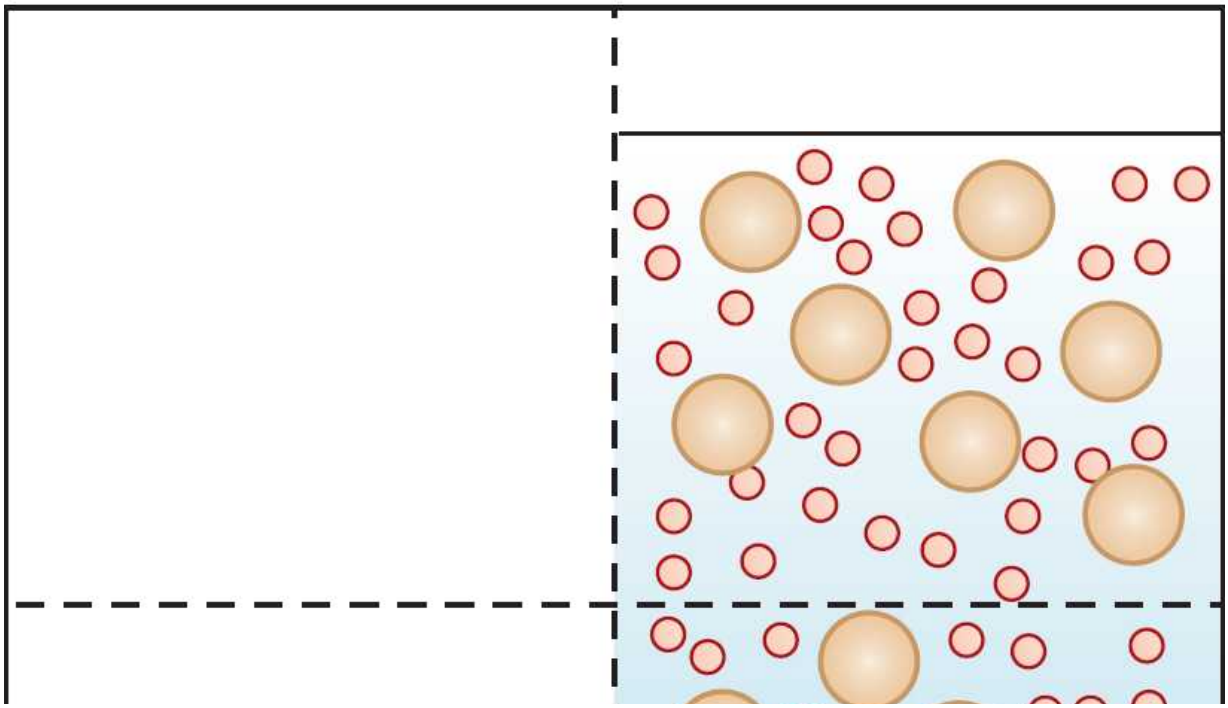


FIGURE 6-4 Pressures that control fluid balance.

Description





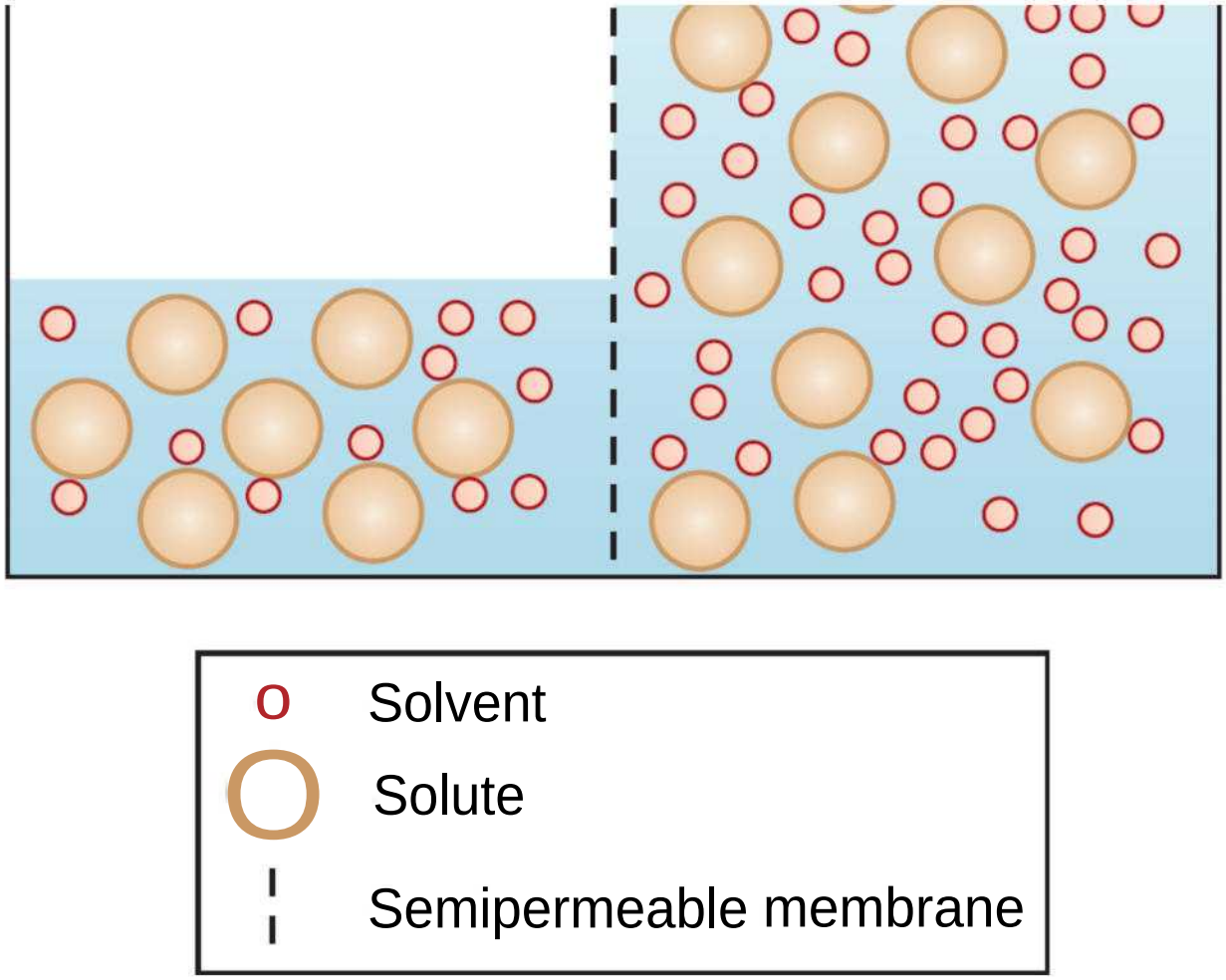


FIGURE 6-5 Osmotic pressure.

Description

Tonicity refers to the osmotic pressure of two solutions (i.e., a solvent and a solute) separated by a semipermeable membrane. This characteristic is often used to describe the cell's response to an external solution (**FIGURE 6-6**). Much like osmotic pressure, tonicity is influenced by solutes that cannot cross the membrane. In health care, the external solution described in relation to tonicity is an intravenous solution—specifically, IV solutions containing electrolytes (crystalloids) and other solutes (e.g., glucose) that are used to treat a variety of patient conditions (e.g., dehydration and shock). These solutions are classified based on their tonicity as either isotonic, hypotonic, or hypertonic. **Isotonic solutions** (e.g., 0.9% saline and lactated Ringer's solution, 5% dextrose in water) have concentrations

of solutes equal to those in the intravascular compartment. As a result of these equivalent solute concentrations, isotonic solutions move equally between all compartments and do not cause notable shifts in fluid volume. **Hypotonic solutions** (e.g., 0.45% saline) have a lower concentration of solutes than the solution in the intravascular compartment. Hypotonic solutions cause fluid to shift from the intravascular compartment to the intracellular space. **Hypertonic solutions** (e.g., 5% dextrose in 0.9% saline, 3% saline, 5% dextrose in lactated Ringer's solution) have a higher concentration of solutes than the solution in the intravascular compartment. Hypertonic solutions cause fluid to shift from the intracellular compartment to the intravascular space.

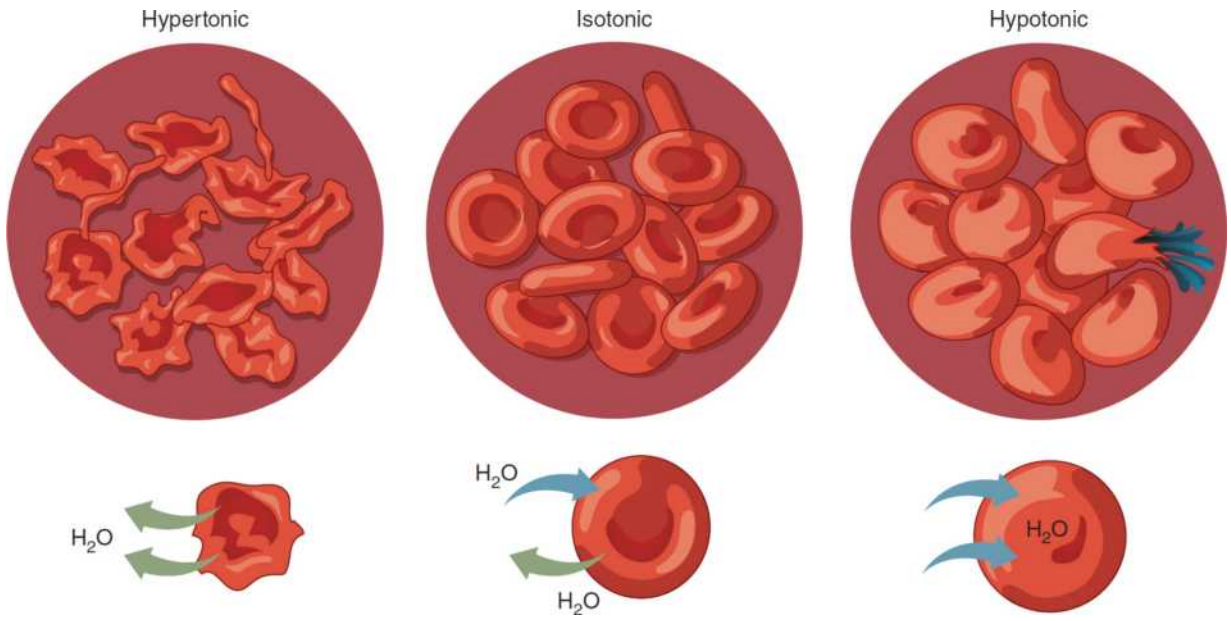


FIGURE 6-6 Cellular response to tonicity.

Courtesy of Mariana Ruiz Villarreal.

Description

Additionally, fluid is added to the body through the ingestion of food and fluids and as a cellular by-product. Approximately 100 mL of water is needed per 100 calories ingested to help with cellular metabolism and waste elimination. Therefore, most adults will require about 2,000 mL per day. Fluid is primarily lost in the urine and feces,

but additional insensible (immeasurable) losses occur through the skin (e.g., perspiration) and the respiratory tract (e.g., breathing, coughing, talking, and mechanical ventilation). The minimum urine output for an individual consuming approximately 2,000 mL per day would be 800 mL per day.

Body fluid intake and output balance are maintained through several mechanisms. The osmoreceptor cells, for example, sense intravascular fluid volume. Decreased fluid volume or increased **osmolarity** (solute concentration) triggers the thirst mechanism in the hypothalamus, which prompts the individual to increase oral intake of fluids. The thirst sensation occurs with even the smallest water losses and is one of the best regulators of water balance. This thirst sensation can decrease with age, a phenomenon called “hypodipsia.”

Antidiuretic hormone (ADH) regulates fluid volume by controlling water losses through urine. Released from the pituitary gland in times of decreased fluid volume and increased osmolarity, ADH promotes the reabsorption of water into the blood from the renal tubules. The hormone known as **aldosterone** is released to conserve more water when necessary (e.g., when a person has low blood pressure) by increasing the reabsorption of sodium and water in the renal tubules. Another hormone, **atrial natriuretic peptide**, is released when the atria of the myocardium become overstretched, indicating increased fluid volume. This peptide stimulates renal vasodilation, thereby increasing urinary output. Additionally, atrial natriuretic peptide suppresses aldosterone secretion, further increasing urinary output.

Fluid Excess

Ideally, daily fluid intake should equal the amount of fluid lost. Most significant increases in fluid accumulation occur in the interstitial, intravascular, or intracellular spaces; significant daily gains or losses do not usually occur in the transcellular compartments. Increases may occur with certain physiological conditions or traumatic events (e.g., pericarditis, pleurisy, and ascites). Significant fluid increases in the transcellular compartment are often referred to as **third spacing** because this fluid is not easily exchanged among the other ECFs.

Fluid excess is referred to by several other names, some of which reflect the compartment affected. Excess fluid in the interstitial space is generally referred to as **edema**. Edema is a problem of fluid distribution, not necessarily fluid overload. In this condition, hydrostatic and osmotic forces favor the movement of fluid from the intravascular compartment to the interstitial space; that is, hydrostatic forces are greater than osmotic forces. For example, blood stagnates in the periphery with heart failure, which increases hydrostatic pressure and pushes fluid out of the vessels (see the *Cardiovascular Function* chapter). Edema may also be localized to one area, such as the feet, or generalized throughout the body (**anasarca**). Excess fluid in the intravascular compartment is frequently referred to as **hypervolemia** or **fluid volume excess**. Often hypervolemia results from excessive sodium or water intake or insufficient losses. In such a case, the intake becomes greater than the body's compensatory mechanisms can manage. The excess fluid volume strains the left ventricle, which can cause left-sided heart failure over time (see the *Cardiovascular Function* chapter). Fluid excess can also occur in the intracellular space, a condition known as **water intoxication**. ICF excess can lead to the rupture, or lysis, of the cells. Cerebral cells are the most sensitive to lysis.

Fluid excess may result from the following conditions:

- Excessive sodium or water intake, including that caused by the following:
  - High-sodium diet (e.g., processed foods, sodas, and certain seasonings)
  - Psychogenic polydipsia (excessive water ingestion)
  - Hypertonic fluid administration
  - Free water

Learning Points

Tonicity

Tonicity reflects the relationship that certain nutrients and electrolytes have with water. Both sodium and glucose attract water—water will go wherever the higher concentrations of sodium and glucose are. In the case of intravenous fluids (IVF), the concentration of sodium and glucose in the intravascular compartment is adjusted to either attract or repel water. For example, 0.9% (isotonic) saline has a sodium concentration similar to that found in the intravascular space, so no fluid shifts between compartments when it is administered to patients. Instead, fluid is just replaced in the intravascular compartment. Hypotonic (0.45%) saline has a lower concentration of sodium than that usually found in the intravascular space, so its administration causes water to move out of the intravascular compartment and into the intracellular compartment. The same phenomenon occurs when patients receive glucose or dextrose in a solution. Finally, hypertonic (3%) saline has a higher concentration of sodium than that usually found in the intravascular space, so water moves from the intracellular compartment to the intravascular compartment when patients receive it as an intravenous formulation.

Remember: Wherever sodium and glucose are, water will follow!

  - Enteral feedings
- Inadequate sodium or water elimination, including that caused by the following:
  - Hyperaldosteronism (which increases sodium retention and, in turn, water retention)
  - Cushing syndrome (a condition characterized by excessive corticosteroids, which contain high levels of sodium; see the *Endocrine Function* chapter)
  - Syndrome of inappropriate antidiuretic hormone (excessive ADH levels, which increases fluid retention)
  - Renal failure (the kidneys are unable to eliminate fluid or waste products; see the *Urinary Function* chapter)
  - Liver failure (the liver is unable to synthesize protein, impairing colloidal pressures; see the *Gastrointestinal Function* chapter)
  - Heart failure (the heart is unable to pump blood effectively, leading to decreased blood flow to the kidneys and fluid shifts; see the *Cardiovascular Function* chapter)

Clinical manifestations of fluid excess include the following signs and symptoms:

- Peripheral edema (the skin usually indents with pressure, a condition referred to as pitting; **FIGURE 6-7**)



FIGURE 6-7 Pitting edema.

© Jones & Bartlett Learning. Photographed by Kimberly Potvin.

- Periorbital edema (swelling around the eyes)
- Anasarca (generalized edema; the skin may begin to weep fluid)
- Cerebral edema, which causes headache, confusion, irritability, anxiety, nausea, and vomiting
- Dyspnea
- Bounding pulse
- Tachycardia
- Jugular vein distention
- Hypertension
- Polyuria (large amounts of pale yellow urine)
- Rapid weight gain (3 pounds in a week or 1–2 pounds in a day; 1 pound approximately equals 500 mL of fluid)

- Crackles (abnormal lung sound)
- Bulging fontanelles (in infants)

Diagnosis of fluid excess focuses on determining the severity of the excess and the causes. Diagnostic procedures include a history, physical examination, measurements of intake and output, daily weights, urine analysis, blood chemistry, and complete blood count (CBC). When excess fluid is present, urine and blood specific gravity and osmolality will be decreased due to solute dilution. Blood cells—especially the red blood cells and platelets—may also be decreased because of the high ratio of fluid. Other procedures to determine the cause include chest X-ray, echocardiogram, duplex Doppler, and other imaging.

Management of fluid excess focuses on identifying and treating the underlying cause. Strategies may consist of wearing compression stockings, administering diuretics, restricting oral intake of sodium and fluids, and maintaining the patient in a high Fowler's position. In severe cases of intracellular and interstitial fluid excess, hypertonic solutions may be given to shift the excess fluid from these spaces to the intravascular space, where it can be excreted. To aid in excretion, a diuretic may be administered.

Fluid Deficit

Fluid deficit occurs when total body fluid levels (mostly water) are insufficient to meet the body's needs. This condition may also be referred to as dehydration. Fluid deficit of the intravascular compartment is often referred to as **fluid volume deficit** or **hypovolemia**.

Fluid deficits can occur either independently or in conjunction with electrolyte deficits, such as a sodium deficit. As fluid levels decrease, sodium levels and the levels of other blood solutes (e.g., blood cells and electrolytes) increase because of hemoconcentration. Climbing sodium levels trigger fluid shifts from other compartments as the body attempts to maintain homeostasis. When water losses are greater

than these shifts can accommodate, the cells shrink. Fluid volume levels decrease, causing hypotension.

application to practice

The serious nature of water intoxication can be seen in a story familiar to many. A radio station was having a contest, in which the contestant who could drink the most water without voiding would win a prize. Because water has limited amounts of electrolytes, such as sodium, excessive water intake in a short period can cause the sodium concentration in the vascular space to drop in relation to the water. The sodium concentration in the tissue is then higher than that in the blood, which causes water to move out of the vascular space and into the interstitial space. This fluid shift quickly caused cerebral edema (see the *Neural Function* chapter), decreased neurologic functioning, and death in the individual who consumed the most water in the contest. The sad thing is that a nurse called into the radio station to warn station officials that this contest was dangerous, yet the station went ahead with it. This seemingly harmless act had grave consequences.

Causes of fluid deficits include the following:

- Inadequate fluid intake, such as that caused by the following:
  - Poor oral intake (such as occurs in the event of stroke or dementia)
  - Inadequate IVF replacement
- Excessive fluid or sodium losses, such as those caused by the following:
  - Gastrointestinal losses (vomiting, diarrhea, and nasogastric suctioning)
  - Excessive diaphoresis (sweating)
  - Prolonged hyperventilation
  - Hemorrhage
  - Nephrosis (also called “nephrotic syndrome”— a degenerative renal disease that causes excessive protein losses, leading to fluid movement out of the intravascular compartment)

- Diabetes mellitus (which causes renal glucose excretion and, in turn, results in water losses)
- Diabetes insipidus (an inability to concentrate urine, leading to excessive water losses)
- Burns (heat denatures proteins, which disrupts colloidal pressure)
- Open wounds (increased drainage)
- Ascites
- Effusions
- Excessive use of diuretics
- Osmotic diuresis, which can occur with hypertonic tube feedings or when parenteral feedings are administered too quickly

Clinical manifestations of fluid deficits include the following signs and symptoms:

- Thirst
- Altered level of consciousness
- Hypotension
- Tachycardia
- Weak, thready pulse
- Flat jugular veins
- Dry mucous membranes
- Decreased skin turgor
- Oliguria
- Weight loss
- Sunken fontanelles (in infants)

Diagnostic procedures for fluid deficit consist of a history, physical examination, measurements of intake and output, daily weights, urinalysis, blood chemistry, and CBC. Urine- and blood-specific gravity and osmolality will be increased, indicating a high concentration of solutes. Blood cells—especially red blood cells and

platelets—may be increased because of the low ratio of fluid. Diagnostic procedures to determine the cause of the fluid deficit may also include a stool analysis.

Management focuses on identifying and treating the underlying cause of the fluid deficit. Strategies include fluid replacement—oral fluids for mild losses and IVF for greater losses (either isotonic or hypotonic).

Electrolyte Balance

Electrolytes play a crucial role in homeostasis. Electrolytes are minerals with electrical charges that are found in the blood, urine, and other body fluids. Electrolytes in the body include sodium, chloride, potassium, **calcium**, magnesium, and **phosphorus** (**TABLE 6-1**). **Cations** are positively charged, whereas **anions** are negatively charged. Electrolytes are important in muscle and neural activity and in acid–base and fluid balance.

TABLE 6-1	Electrolyte Imbalances

Electrolyte	Normal Serum Levels*	Imbalance	Causes	Consequences	Manifestations	Treatments
Sodium (Na^+)	135–145 mEq/L	Hypernatremia (>145 mEq/L)	Excessive Na^+ (e.g., sea water ingestion, hypertonic IVF, Cushing syndrome, corticosteroids) Deficient water (H_2O) (e.g., decreased water intake, vomiting, diarrhea, excessive sweating, diuretics, diabetes insipidus, hyperventilation, and burns)	Cellular dehydration Hyperchloremia	Neuromuscular dysfunction (e.g., lethargy, confusion, headache, muscle cramps, weakness, restlessness, seizures, coma) Hypovolemia (e.g., thirst, dry mucous membranes, tachycardia, hypotension, and decreased urine output)	Treat underlying cause Replace fluid (e.g., glucose-electrolyte oral solutions, and hypotonic IVF) Diuretics, if hypervolemic
		Hyponatremia (<135 mEq/L)	Deficient Na^+ (e.g., diuretics, vomiting, diarrhea, excessive sweating, Addison's disease, adrenal insufficiency, restricted Na^+ intake) Excessive H_2O (e.g., hypotonic IVF, hyperglycemia, excessive water intake, renal failure, SIADH, and heart failure)	Hypochloremia	Neuromuscular dysfunction (e.g., lethargy, confusion, headache, muscle cramps, weakness, restlessness, diminished deep tendon reflexes, seizures, coma) Gastrointestinal disturbances (e.g., anorexia, abdominal cramps, nausea, vomiting, and diarrhea) Hypovolemia (e.g., thirst, dry mucous membranes, poor skin turgor, tachycardia, hypotension, and decreased urine output) Hypervolemia (e.g., hypertension, edema, weight gain, increased urine output)	Treat underlying cause Limit fluids if hypervolemic Increase oral Na^+
Chloride (Cl^-)	98–108 mEq/L	Hyperchloremia (>108 mEq/L)	Increased Cl^- intake or exchange (e.g., hypernatremia, hypertonic IVF, metabolic acidosis, and hyperkalemia) Decreased Cl^- excretion (e.g., hyperparathyroidism, hyperaldosteronism, and renal failure)	Metabolic acidosis Hyperkalemia	No direct clinical symptoms. Symptoms generally associated with underlying cause, metabolic acidosis, or hyperkalemia	Treat underlying cause Hypotonic IVF and diuretics to correct hypernatremia HCO_3 to correct acidosis
		Hypochloremia (<98 mEq/L)	Decreased Cl^- intake or exchange (e.g., hyponatremia, excessive water intake, and hypokalemia) Decreased Cl^- excretion (e.g., diuretics, vomiting, diarrhea, and metabolic alkalosis)	Metabolic alkalosis	No direct clinical symptoms. Symptoms generally associated with underlying cause, metabolic alkalosis, or hypokalemia	Treat underlying cause Increase oral Na^+ and hypertonic IVF to correct hyponatremia Ammonium chloride Gastric lavage
Potassium (K^+)	3.5–5 mEq/L	Hyperkalemia (>5 mEq/L)	Deficient K^+ excretion (e.g., renal failure, Addison's disease, potassium-sparing diuretics, NSAIDs, ACE inhibitors, and Gordon syndrome) Excessive K^+ intake (e.g., supplemental potassium and salt substitutes) Increased K^+ release from cells (e.g., acidosis, blood transfusions, and burns)	Hyperchloremia Hyponatremia Metabolic acidosis	Cardiovascular dysfunction (e.g., peaked T wave, depressed ST segment, bradycardia, and cardiac arrest) Neuromuscular dysfunction (e.g., weakness, paresthesia, muscle cramps, flaccid paralysis, and anxiety) Respiratory dysfunction (e.g., respiratory depression) Gastrointestinal disturbances (e.g., abdominal cramping, nausea, and diarrhea)	Treat underlying cause prior to correcting the hyperkalemia Calcium gluconate to minimize dysrhythmias Decrease K^+ intake Kayexalate IVF Potassium-losing diuretics Dialysis Insulin infusion with glucose-containing IVF
		Hypokalemia (<3.5 mEq/L)	Excessive K^+ loss (e.g., vomiting, diarrhea, potassium-losing diuretics, corticosteroids, and Cushing syndrome) Deficient K^+ intake (e.g., malnutrition) Increased K^+ shift into cells (e.g., alkalosis and insulin excess)	Hypochloremia Hypernatremia Metabolic alkalosis	Cardiovascular dysfunction (e.g., flattened T wave, depressed ST segment, presence of a U wave, hypotension, irregular pulse, and cardiac arrest) Neuromuscular dysfunction (e.g., weakness, paresthesia, muscle cramps, hyporeflexia, and confusion) Gastrointestinal disturbances (e.g., anorexia, abdominal distention, nausea, constipation, and decreased bowel sounds)	Treat underlying cause oral K^+ supplements IVF with K^+

Calcium (Ca^{++})	4–5 mEq/L or 8.6–10.2 mg/dL	Hypercalcemia (>5 mEq/L or 10.2 mg/dL)	Inadequate Ca^{++} intake or release (e.g., calcium antacids, supplemental calcium, cancer, immobilization, corticosteroids, vitamin D deficiency, hypophosphatemia, and hypermagnesemia) Deficient Ca^{++} excretion (e.g., renal failure, thiazide diuretics, and hyperparathyroidism)	Hyperchloremia Hypomagnesemia Hyperphosphatemia	Neuromuscular dysfunction (e.g., personality changes, confusion, decreased memory, headache, lethargy, stupor, coma, muscle weakness, and decreased deep tendon reflexes) Cardiovascular dysfunction (e.g., short QT interval, dysrhythmias, and hypertension) Gastrointestinal disturbances (e.g., anorexia, nausea, vomiting, abdominal pain, constipation, and pancreatitis) Renal issues (e.g., renal calculi, polyuria, renal insufficiency, and dehydration)	Treat underlying cause Manage dysrhythmias Oral phosphate Increase mobility Calcitonin IVF Diuretics
		Hypocalcemia (<4 mEq/L or 8.6 mg/dL)	Excessive Ca^{++} losses (e.g., hypoparathyroidism, renal failure, hyperphosphatemia, hypomagnesemia, alkalosis, pancreatitis, diarrhea, diuretics, calcitonin, and gentamicin) Deficient Ca^{++} intake (e.g., malnutrition)	Hypermagnesemia Hypophosphatemia	Neuromuscular dysfunction (e.g., anxiety, confusion, depression, irritability, fatigue, lethargy, paresthesia, increased deep tendon reflexes, tremors, muscle spasms, seizures, laryngeal spasms) Cardiovascular dysfunction (e.g., prolonged QT interval, dysrhythmias, and hypotension) Gastrointestinal disturbances (e.g., increased bowel sounds, abdominal cramps, and diarrhea) Hematologic dysfunctions (e.g., increased bleeding tendency) Skeletal issues (e.g., osteomalacia, osteoporosis, and fractures)	Treat underlying cause Oral Ca^{++} supplements IV calcium gluconate Vitamin D supplements Limit phosphorus intake
Phosphorus (P^{-})	2.5–4.5 mg/dL	Hyperphosphatemia (>4.5 mg/dL)	Deficient P^{-} excretion (e.g., renal failure, hypoparathyroidism, adrenal insufficiency, hypothyroidism, and laxatives) Excessive P^{-} intake or cellular exchange (e.g., burns, trauma, hypocalcemia, and acidosis)	Hypocalcemia Hypermagnesemia	Similar to manifestations associated with hypocalcemia	Treat underlying cause Limit P^{-} intake Aluminum hydroxide or aluminum carbonate Treat hypocalcemia
		Hypophosphatemia (<2.5 mg/dL)	Excessive P^{-} excretion or cellular exchange (e.g., renal failure, hyperparathyroidism, and alkalosis) Deficient P^{-} intake (e.g., malnutrition, vitamin D deficiency, and hypermagnesemia)	Hypercalcemia Hypomagnesemia	Similar to manifestations associated with hypercalcemia	Treat underlying cause Oral P^{-} supplements IV potassium phosphate Treat hypercalcemia
Magnesium (Mg^{++})	1.8–2.4 mEq/L	Hypermagnesemia (>2.4 mEq/L)	Excessive Mg^{++} intake (e.g., magnesium-containing laxatives or antacids) Deficient Mg^{++} excretion (e.g., renal failure)	Hypocalcemia Hyperphosphatemia	Similar to manifestations associated with hypocalcemia	Treat underlying cause Diuretics Hypotonic IVF Dialysis IV calcium
		Hypomagnesemia (<1.8 mEq/L)	Deficient Mg^{++} intake (e.g., malnutrition) Excessive Mg^{++} excretion (e.g., diarrhea and diuretics)	Hypercalcemia Hypophosphatemia	Similar to manifestations associated with hypercalcemia	Treat underlying cause Oral Mg^{++} supplements IV Mg^{++}
Bicarbonate (HCO_3)	22–26 mEq/L	Metabolic acidosis (<22 mEq/L)	HCO_3 deficits (e.g., diarrhea and renal failure) Acid excess (e.g., tissue hypoxia, ketoacidosis, and poisonings)	Hyperchloremia Hyperkalemia Hyperphosphatemia	Neuromuscular dysfunction (e.g., headache, malaise, weakness, fatigue, lethargy, and coma) Cardiovascular dysfunction (e.g., dysrhythmias, hypotension, and shock) Gastrointestinal disturbances (e.g., anorexia, nausea, and vomiting) Respiratory dysfunction (e.g., Kussmaul respirations)	Treat underlying cause iv HCO_3 Correct electrolyte disturbances Improve oxygenation (e.g., supplemental oxygen and mechanical ventilation)
		Metabolic alkalosis (>26 mEq/L)	HCO_3 excess (e.g., antacids and hypochloremia) Acid deficits (e.g., vomiting, hypokalemia, renal failure, diuretics, hyperaldosteronism)	Hypochloremia Hypokalemia Hypocalcemia Hypophosphatemia	Neuromuscular dysfunction (e.g., confusion, hyperactive reflexes, paresthesia, tetany, seizures, and coma) Cardiovascular dysfunction (e.g., dysrhythmias) Respiratory dysfunction (e.g., respiratory depression)	Treat underlying cause IVF Correct electrolyte disturbances Diamox Arginine hydrochloride Weak hydrochloric acid solution

Description

*Values may vary slightly.

application to practice

An example of osmotic diuresis can be seen in a tragic case in which a newborn was fed concentrated formula by mistake. Often, tube feedings and baby formulas are high in glucose and other electrolytes. Many times, these formulas are concentrated for shipping purposes. The newborn's father was unaware that the formula required dilution prior to feeding it to his child. The high concentrations of glucose caused excessive urination, and the baby died because of hypertonic dehydration.

Sodium

Sodium is considered the most significant cation for the body's functioning. The most prevalent electrolyte within the ECF, sodium's primary function is to control serum osmolality and water balance. Sodium also has an affinity for chloride and helps maintain acid–base balance when combined with bicarbonate.

Sodium is regulated by the kidneys as well as by aldosterone produced by the adrenal cortex. In times of high serum osmolality or low blood volume, aldosterone is released, and the kidneys retain sodium. The opposite is true when serum osmolality decreases and fluid volume increases. The sympathetic nervous system assists the kidneys in sodium regulation by changing the glomerular filtration rate, which reflects renal blood flow. Increasing the glomerular filtration rate increases sodium excretion; decreasing the glomerular filtration rate decreases sodium excretion. The renin–angiotensin–aldosterone mechanism (see the *Cardiovascular Function* chapter) also manipulates sodium levels in the kidneys; this mechanism is triggered in times of decreased renal perfusion (e.g., hypovolemia and hypotension). Renin, a protein, converts angiotensinogen to angiotensin I; subsequently, angiotensin I is converted to angiotensin II in the lungs. Angiotensin II causes the kidneys to retain sodium and, in turn, water.

The cellular membrane is permeable to sodium, but it is dependent on the sodium–potassium pump to transport these ions (see the

Cellular Function chapter). Sodium facilitates muscle and nerve impulses through the pump. As sodium moves into the cell, potassium shifts out of the cell, resulting in **depolarization** (increasing the membrane potential or excitability) of the cell membrane. When sodium shifts out of the cell, potassium moves back into the cell, resulting in **repolarization** (restoring the resting potential) of the cell membrane.

Sodium is primarily brought into the body through dietary intake. The recommended dietary allowance (RDA) of sodium is 2–4 grams. This electrolyte can be found in many sources, such as table salt (1 teaspoon contains more than 2 grams of sodium), processed or prepackaged foods (e.g., canned foods and deli meats), snack foods (e.g., chips), condiments (e.g., ketchup and hot sauce), and certain cooking seasonings (e.g., garlic salt and seasoned salt).

Normally, sodium losses occur in the kidneys. However, excessive losses can occur through the gastrointestinal tract through vomiting, diarrhea, and nasogastric suctioning. Extensive burns can also cause sodium losses through the skin. Finally, sodium losses can occur with excessive sweating (e.g., fever and strenuous exercise).

Hypernatremia

Hypernatremia results from high serum sodium levels (greater than 145 mEq/L). The excessive sodium levels generally lead to high serum osmolality (greater than 295 mOsm/kg) because of the imbalance between sodium and water. As sodium levels rise, water shifts out of the intracellular and interstitial spaces and into the intravascular compartment.

Hypernatremia usually results from ingesting excessive sodium without consuming a proportionate amount of water or through water losses that exceed the amount of sodium being lost. Hypernatremia may be caused by a variety of conditions:

- Excessive sodium, such as that caused by the following:
  - Excessive sodium ingestion
  - Hypertonic IV saline (3% saline) administration

    - Cushing syndrome (a condition associated with excessive corticosteroids, which contain high levels of sodium)
    - Corticosteroid use
- Deficient water, such as that caused by the following:
    - Decreased water ingestion
    - Loss of thirst sensation
    - Inability to drink water (which might occur if a person is unconscious or confused)
    - Third spacing
    - Vomiting
    - Diarrhea
    - Excessive sweating
    - Prolonged episode of hyperventilation (increases insensible water losses)
    - Diuretic use
    - Diabetes insipidus (excessive water loss as a result of insufficient ADH levels)

Clinical manifestations of hypernatremia can range from subtle to serious, depending on the severity of the hypernatremia itself. They include the following signs and symptoms:

- Increased temperature
- Warm, flushed skin
- Dry and sticky mucous membranes
- Dysphagia (difficulty swallowing)
- Increased thirst
- Irritability and agitation
- Weakness
- Headache
- Seizures
- Lethargy

- Coma
- Blood pressure changes
- Tachycardia
- Weak, thready pulse
- Edema
- Decreased urine output (can be high with diabetes insipidus)

Diagnostic procedures for hypernatremia include a history, physical examination, blood chemistry, and urinalysis. Other procedures (e.g., computed tomography [CT] and magnetic resonance imaging [MRI]) may also be conducted to identify causation.

Management of hypernatremia focuses on treating the underlying cause. If the cause is related to water loss, treatment begins with replacing water and remedying any electrolyte deficits. Glucose-electrolyte solutions (e.g., sports drinks) are given orally for less severe cases. More severe cases can be corrected with intravenous hypotonic (e.g., 5% dextrose in water or 0.45% saline) solutions. The healthcare professional must use caution to avoid correcting the hypernatremia too rapidly. The brain can become accustomed to the high levels of sodium; as the levels drop with the treatment of hypernatremia, water moves into cerebral cells, causing cerebral edema. Generally, providers should not correct hypernatremia by administering water and electrolyte solutions faster than 1 mEq/L per hour. Diuretics may be necessary if the patient is hypervolemic. Additionally, seizure precautions (e.g., low lighting and decreased stimuli) and neurologic checks should be added to the patient's plan of care.

Hyponatremia

Hyponatremia results from low serum sodium levels (less than 135 mEq/L). Serum osmolality levels also fall below 275 mOsm. As sodium levels decrease, water shifts into cells. Brain cells are especially susceptible to this cellular swelling, which causes cerebral edema. Additionally, nerve conduction becomes impaired as the sodium levels fall.

Hyponatremia results from excessive sodium losses or increased water gains (referred to as dilutional hyponatremia):

- Deficient sodium, including that caused by the following:
  - Diuretic use
  - Gastrointestinal losses (e.g., vomiting and diarrhea)
  - Excessive sweating
  - Insufficient aldosterone levels (Addison's disease)
  - Adrenal insufficiency
  - Dietary sodium restrictions
- Excessive water, including that caused by the following:
  - Hypotonic intravenous saline (0.45% saline)
  - Hyperglycemia (excess glucose in the blood attracts water from the intracellular and interstitial spaces)
  - Excessive water ingestion
  - Renal failure
  - Syndrome of inappropriate antidiuretic hormone (SIADH)
  - Heart failure (circulation stagnation leads to decreased renal excretion)

Clinical manifestations of hyponatremia may vary in severity depending on the sodium level:

- Anorexia
- Gastrointestinal upset (e.g., abdominal cramps, nausea, vomiting, and diarrhea)
- Poor skin turgor
- Dry mucous membranes
- Blood pressure changes (decreased with hypovolemia and increased with hypervolemia)
- Pulse changes (weak with hypovolemia and bounding with hypervolemia)
- Edema

- Headache
- Lethargy
- Confusion
- Diminished deep tendon reflexes
- Muscle weakness
- Seizures
- Coma

Diagnostic procedures for hyponatremia are similar to those for hypernatremia. Management focuses on treating the underlying cause (e.g., administering corticosteroids for Addison's disease). In cases caused by excessive water, oral intake may be limited. In cases caused by deficient sodium, oral intake may be increased. Correction of sodium levels should be done slowly so as not to overload the heart from fluid shifting into the intravascular space. Additionally, seizure precautions (e.g., low lighting and decreased stimuli) and neurologic checks should be added to the patient's plan of care.

Chloride

Chloride is a mineral electrolyte and the major extracellular anion. Chloride assists in fluid distribution by attaching to sodium or water. Because of its negative charge, chloride can bind and travel with positively charged ions (e.g., sodium, potassium, calcium). This electrolyte is found in gastric secretions, pancreatic juices, and bile. In the stomach, chloride unites with hydrogen to form hydrochloric acid. Chloride is abundant in cerebrospinal fluid, where it binds with sodium. When bound to sodium, chloride behaves just like sodium regarding water balance. When bound to hydrogen, it plays an important role in acid–base balance. The kidneys are primarily responsible for chloride excretion, but some chloride is also lost through sweating.

Diet is the main source of chloride. The RDA for this electrolyte is 3–9 grams. Chloride is easily obtained through consumption of a balanced diet. Common sources of chloride include table salt, fruits,

vegetables, cheese, milk, eggs, fish, canned foods, and processed meats. Chloride is primarily excreted in the kidneys.

Hyperchloremia

Hyperchloremia is an excess amount of chloride in the blood (greater than 108 mEq/L). This condition usually results from an underlying condition; it does not have its own clinical manifestations, but the companion condition may cause signs and symptoms. Some causes of hyperchloremia include:

- Increased chloride intake or exchange, including that caused by the following:
  - Hypernatremia
  - Hypertonic intravenous solution
  - Metabolic acidosis
  - Hyperkalemia
- Decreased chloride excretion, including that caused by the following:
  - Hyperparathyroidism (increases calcium levels, which attracts chloride)
  - Hyperaldosteronism (increases sodium levels, which attracts chloride)
  - Renal failure (decreased chloride excretion)

Diagnostic procedures include a history, physical examination, blood chemistry, urinalysis, and measurement of arterial blood gases (ABGs). Management of hyperchloremia focuses on treating the underlying cause. Administering diuretics to assist in eliminating sodium will, in turn, assist in the removal of chloride. Administering bicarbonate can correct acidosis, if present.

Hypochloremia

Hypochloremia occurs when chloride levels fall below 98 mEq/L. This condition rarely occurs in the absence of other abnormalities;

therefore, like hyperchloremia, it does not have its own set of clinical manifestations. Causative conditions include the following:

- Decreased chloride intake or exchange, such as that accompanied by the following:
  - Hyponatremia
  - Administration of 5% dextrose in water intravenous solution
  - Water intoxication
  - Hypokalemia
- Increased chloride excretion, such as that that occurs with the following:
  - Diuretics (sodium loss, which in turn increases chloride excretion)
  - Vomiting (excessive loss of hydrochloric acid)
  - Metabolic alkalosis
  - Other gastrointestinal losses (such as those that occur with fistula, ileostomy, nasogastric suction, and diarrhea)

Diagnostic procedures for hypochloremia are similar to those for hyperchloremia. Treatment focuses on correcting the underlying cause. Some of those strategies include increasing oral sodium intake and administering sodium-containing intravenous solutions. Additionally, ammonium chloride can be given with caution to raise chloride levels. Saline solutions can also be used to irrigate gastric tubes.

Potassium

Potassium is the primary intracellular cation. It plays a crucial role in electrical conduction (e.g., nervous, musculoskeletal, and cardiac systems), acid–base balance, and metabolism (e.g., carbohydrate, protein, and glucose). Potassium is present in huge quantities in the intracellular space—a store that can be utilized if serum levels drop. However, certain conditions (e.g., cellular lysis) cause excessive amounts of potassium to shift to the intravascular space, which can be dangerous, especially within the heart. Serum potassium cannot

fluctuate very much—either up or down—without causing serious issues. The sodium–potassium pump and the kidneys regulate potassium. The diet (e.g., cantaloupes, raisins, bananas, oranges, green leafy vegetables, and lentils) is the primary source of potassium. The RDA for potassium is 40–60 mEq. In addition to potassium being excreted in the kidneys, it is lost through the gastrointestinal tract.

Hyperkalemia

Hyperkalemia refers to serum potassium levels greater than 5 mEq/L. This condition is unusual in the healthy individual and may be a medical emergency. Generally, this imbalance is caused by conditions that impair excretion, increase intake, or release potassium out of the cells:

- Deficient excretion, such as occurs with the following:
  - Renal failure
  - Addison's disease (decreased levels of aldosterone decrease potassium secretion)
  - Certain medications (e.g., potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs], and angiotensin-converting enzyme [ACE] inhibitors), which can also alter aldosterone levels
  - Gordon syndrome (a rare genetic disorder in which the kidneys are unable to respond to aldosterone)
- Excessive intake, such as occurs with the following:
  - Oral potassium supplements
  - Salt substitutes (many contain large amounts of potassium to create a "salty" taste)
  - Rapid intravenous administration of diluted potassium (administering undiluted potassium can be lethal)
- Increased release from cells, including that associated with the following:

- Acidosis (increased serum hydrogen levels cause potassium to shift out of the cells; lack of insulin in diabetic ketoacidosis impairs the transportation of potassium in the cell)
- Blood transfusions (can cause blood cell lysis, which releases intracellular potassium)
- Burns or any other cellular injuries (can cause cell lysis, which releases intracellular potassium)

Hyperkalemia can affect several body systems in which potassium plays key functions, including the nervous, cardiac, respiratory, and gastrointestinal systems. The severity of these effects depends on the extent of the hyperkalemia. Clinical manifestations of hyperkalemia include the following signs and symptoms:

- Muscle weakness
- Muscle cramps
- Paresthesia (numbness or tingling)
- Flaccid paralysis
- Anxiety
- Bradycardia
- Dysrhythmias (some of which can be fatal)
- Electrocardiogram (EKG) changes (long PR interval, wide QRS, peaked T wave, and depressed ST segment [**FIGURE 6-8**; see the *Cardiovascular Function* chapter])

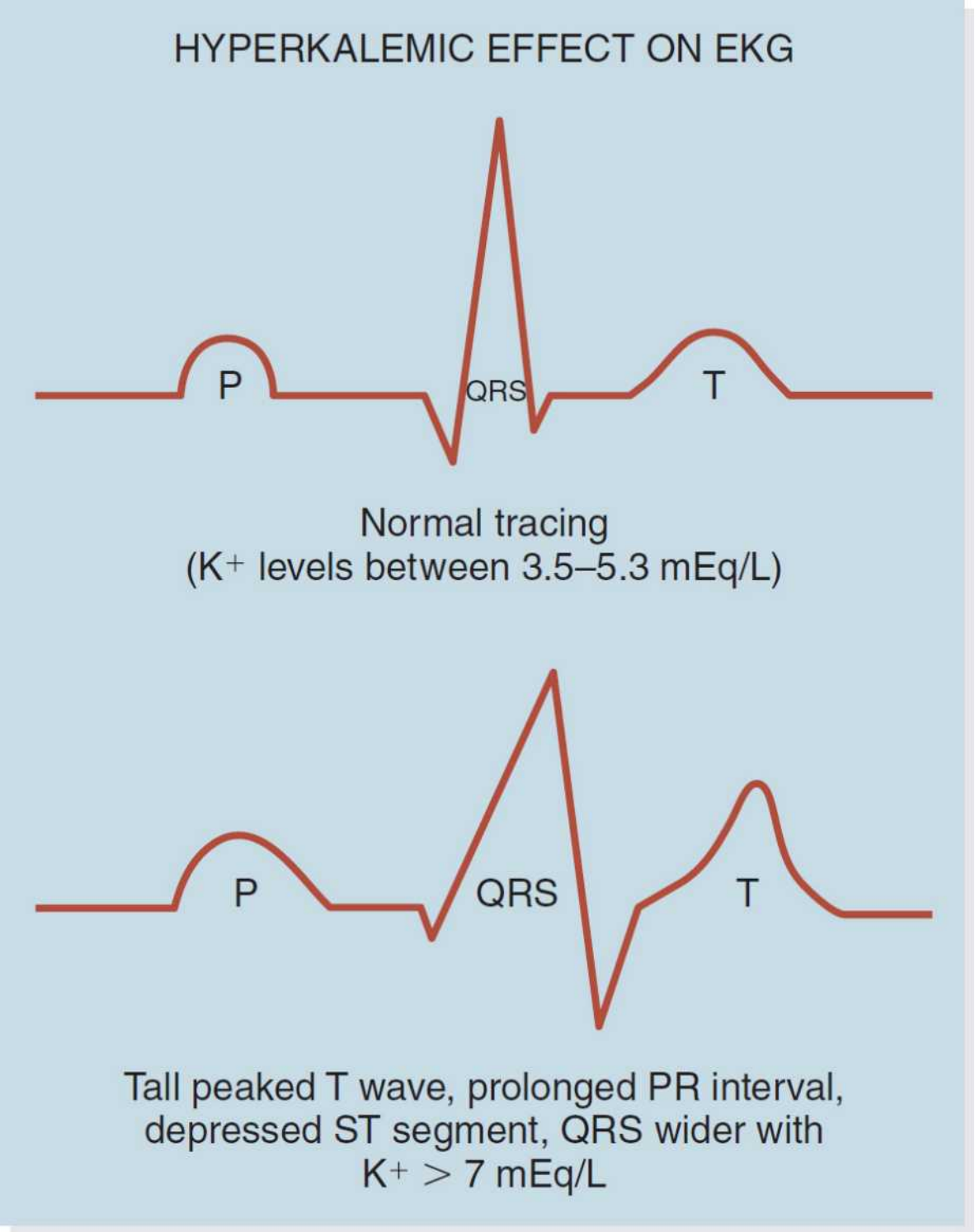


FIGURE 6-8 Hyperkalemic effects on the electrocardiogram.

Description

- Cardiac arrest

- Respiratory depression (from muscle weakness)
- Abdominal cramping
- Nausea
- Diarrhea

Diagnostic procedures for hyperkalemia include a history, physical examination, blood chemistry, 12-lead EKG, and ABGs. Management focuses on the identification and treatment of the cause (e.g., sodium bicarbonate to treat acidosis). If present, acidosis is treated prior to the hyperkalemia so that potassium can shift back into the cells and a true potassium level can be obtained. Calcium gluconate may be administered to minimize dysrhythmias. Additionally, the following measures should be taken:

- Decrease dietary potassium intake
- Increase excretion, such as by the following methods:
  - Dialysis
  - Kayexalate (sodium polystyrene sulfonate, which increases gastrointestinal potassium excretion)
  - IVF (dilutes potassium levels and increases renal excretion)
  - Potassium-losing diuretics
- Facilitate cellular exchange by administering insulin (which may be given with intravenous dextrose to prevent blood glucose drops)

Hypokalemia

Hypokalemia occurs when potassium levels drop below 3.5 mEq/L. Hypokalemia typically results from excessive loss, inadequate intake, or increased potassium cellular uptake:

- Excessive loss as a result of one or more of the following:
  - Vomiting
  - Diarrhea
  - Nasogastric suctioning
  - Fistulas

    - Laxatives
    - Potassium-losing diuretics
    - Cushing syndrome (decreases sodium excretion, which in turn increases potassium excretion)
    - Corticosteroids (decrease sodium excretion, which in turn increases potassium excretion)
- Deficient intake, such as occurs with the following:
    - Malnutrition
    - Extreme dieting
    - Alcoholism (can result in inadequate nutrition, nausea, and vomiting)
- Increased shift into the cell as occurs with the following:
    - Alkalosis (decreased serum hydrogen levels cause potassium to shift into the cells)
    - Insulin excess (increases potassium transportation into the cells)

Much like hyperkalemia, hypokalemia can affect several body systems because of potassium's expansive functions, including the nervous, cardiac, respiratory, and gastrointestinal systems. The severity of these effects reflects the extent of the hypokalemia. Clinical manifestations of hypokalemia are similar to those associated with hyperkalemia:

- Muscle weakness
- Paresthesia
- Hyporeflexia
- Leg cramps
- Weak, irregular pulse
- Hypotension
- Dysrhythmias (some of which are lethal)
- EKG changes (prolonged PR interval, depressed ST segment, flattened T wave, and a U wave [**FIGURE 6-9**; see the *Cardiovascular Function* chapter])

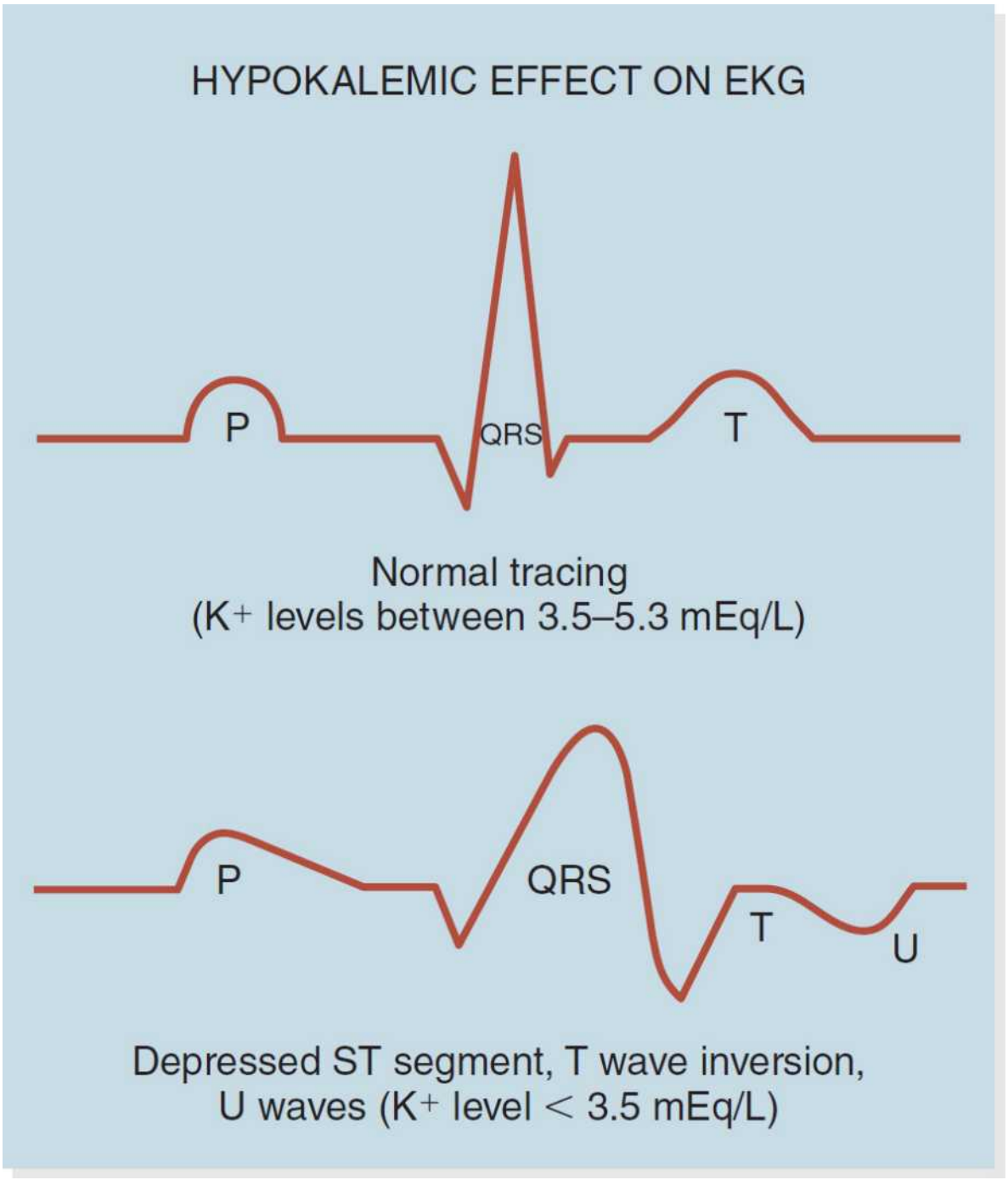


FIGURE 6-9 Hypokalemic effects on the electrocardiogram.

Description

- Decreased bowel sounds
- Abdominal distention
- Constipation or ileus

- Confusion
- Cardiac arrest

Diagnostic procedures for hypokalemia include a history, physical examination, blood chemistry, 12-lead EKG, and ABGs. Management focuses on the identification and treatment of the cause (e.g., correcting any alkalosis). Additionally, strategies are directed at increasing the amount of potassium available to the body. Oral potassium is administered for mild cases, while diluted intravenous potassium is administered for more severe deficits.

Calcium

Most of the body's calcium is found in the bones and teeth (99%). The remaining stores (1%) are largely found in an ionized (unbound) form in the blood that can be used for physiological processes—for example, blood clotting, hormone secretion, receptor functions, nerve transmission, and muscular contraction. Calcium has an inverse relationship with phosphorus and a synergistic relationship with magnesium. Thus, phosphorus levels go down when calcium levels go up, and vice versa. Calcium needs magnesium to fully function as well as to balance its effects.

Calcium is brought into the body through the absorption of dietary sources in the gastrointestinal tract, specifically the small intestines; therefore, conditions affecting intestinal absorption or surgical procedures that change the gastrointestinal tract (e.g., gastric bypass) can alter calcium absorption. Vitamin D aids in calcium absorption; it is primarily obtained through sun exposure and from fortified dairy products. Vitamin K also plays an important role in calcium regulation and bone formation (vitamin K binds to calcium in the bone); it is primarily found in green leafy vegetables. Calcium is found in large amounts in dairy products, salmon, sardines, green leafy vegetables, pinto beans, almonds, and figs, among other sources. The RDA of calcium is 800–1,200 mg/day; however, individuals' daily needs vary with certain conditions (e.g., pregnancy, childhood, and osteoporosis).

Calcium is excreted in the urine and stool. Levels of this electrolyte are regulated by the parathyroid hormones and calcitonin (a thyroid hormone). When serum calcium levels are low, parathyroid hormone mobilizes the bone calcium and pulls it into the bloodstream. To compensate for this shift, parathyroid hormone replaces this calcium by decreasing renal excretion and promoting intestinal absorption. Calcitonin, in contrast, regulates elevated calcium levels by pushing the excess calcium into the bone, decreasing intestinal absorption and increasing renal excretion.

Hypercalcemia

Hypercalcemia occurs when ionized calcium levels climb above 5 mEq/L. This imbalance may result from excessive calcium intake or calcium release from the bone as well as from inadequate excretion. Its causes include the following:

- Increased intake or release, including that caused by the following:
  - Calcium antacids (e.g., Tums)
  - Calcium supplements
  - Cancer (especially bone, but also lung, breast, ovarian, prostate, leukemia, and gastrointestinal cancers)
  - Immobilization
  - Corticosteroids
  - Vitamin D deficiency
  - Hypophosphatemia
- Deficit excretion, including that caused by the following:
  - Renal failure
  - Thiazide diuretics
  - Hyperparathyroidism

Clinical manifestations of hypercalcemia reflect decreased cell membrane excitability and are often nonspecific. The cardiac, nervous, musculoskeletal, gastrointestinal, and renal systems can all

be affected by these high calcium levels. Clinical manifestations of hypercalcemia include the following signs and symptoms:

- Dysrhythmias (some of which can be fatal)
- EKG changes (short QT interval)
- Hypertension
- Personality changes
- Confusion
- Decreased memory
- Headache
- Lethargy
- Stupor
- Coma
- Muscle weakness
- Decreased deep tendon reflexes
- Anorexia
- Nausea and vomiting
- Constipation
- Abdominal pain
- Pancreatitis
- Renal calculi (stones)
- Polyuria (high calcium levels interfere with ADH, resulting in increased water excretion)
- Dehydration
- Cardiac arrest

Diagnostic procedures include a history, physical examination, blood chemistry, and 12-lead EKG. Management of hypercalcemia focuses on the identification and treatment of the underlying cause (e.g., dialysis for renal failure). Additionally, strategies may be implemented to treat clinical manifestations (e.g., antidysrhythmic agents). Giving oral phosphate preparations, increasing mobility, and

administering calcitonin can facilitate the movement of the excessive calcium out of the bloodstream and into the bone. Increasing IVF administration can increase renal excretion of calcium. Diuretics may be necessary to enhance this excretion further.

Hypocalcemia

Hypocalcemia occurs when ionized calcium levels fall below 4 mEq/L. This condition occurs as a result of increased losses or decreased intake of calcium:

- Excessive losses, including those associated with the following:
  - Hypoparathyroidism
  - Renal failure
  - Hyperphosphatemia
  - Alkalosis (as serum hydrogen levels decrease, calcium levels decrease)
  - Pancreatitis (decreases intestinal absorption of fat; calcium binds to the fat and is excreted)
  - Laxatives (decrease absorption)
  - Diarrhea
  - Other medications (e.g., diuretics, calcitonin, and gentamicin)
- Deficient intake, including that caused by the following:
  - Decreased dietary intake
  - Alcoholism (decreased diet and poor absorption)
  - Absorption disorders (e.g., Crohn's disease)
  - Hypoalbuminemia (much of calcium is bound to protein)

As opposed to hypercalcemia, hypocalcemia increases cell membrane excitability. The low calcium levels affect the cardiac, neurologic, musculoskeletal, respiratory, and gastrointestinal systems. Clinical manifestations of hypocalcemia include the following signs and symptoms:

- Dysrhythmias (some of which can be lethal)

- EKG changes (prolonged QT interval)
- Hypotension
- Increased bleeding tendencies (e.g., bruising and petechia)
- Anxiety
- Confusion
- Depression
- Irritability
- Fatigue
- Lethargy
- Paresthesia
- Increased deep tendon reflexes
- Tremors
- Muscle spasms
- Seizures
- Laryngeal spasms
- Increased bowel sounds
- Abdominal cramping
- Diarrhea
- Decreased bone density (e.g., osteomalacia, osteoporosis, and fractures)

In addition to these clinical manifestations, two signs specific to hypocalcemia may be present—the **Trousseau** and **Chvostek signs**. To test for the Trousseau sign, arterial blood flow is occluded by using an inflated blood pressure cuff. The cuff is placed on the upper arm and inflated above the individual's usual systolic pressure measurement. The inflated cuff is left in place for approximately 3 minutes. The test is considered positive for increased neuromuscular irritability if it elicits a carpal spasm (flexed wrist and metacarpophalangeal joints, extended interphalangeal joints, and adducted thumb) (**FIGURE 6-10**). To test for the Chvostek sign, the healthcare practitioner taps the patient's facial nerve in front of the

ear. A spasm or brief contraction of the corner of the mouth, nose, eye, and muscles in the cheek is considered a positive sign and indicates increased neuromuscular irritability (**FIGURE 6-11**).



FIGURE 6-10 Trousseau sign.

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FIGURE 6-11 Chvostek sign.

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Diagnostic procedures for hypocalcemia are similar to those for hypercalcemia. Management focuses on the identification and treatment of the underlying cause. Calcium levels can be increased with oral supplements (in mild deficiencies) and intravenous calcium gluconate (in moderate to severe deficiencies). Vitamin D supplements can increase intestinal calcium absorption. Additionally, phosphorus intake may be decreased to bring calcium levels up.

Phosphorus

Most of the body's phosphorus, or phosphate, is found in the bones, with smaller quantities circulating in the bloodstream. As previously mentioned, phosphorus has an inverse relationship with calcium. Phosphorus plays a key role in bone and tooth mineralization, cellular metabolism, acid–base balance, and cell membrane formation, among other functions.

Phosphorus primarily enters the body through dietary sources, and its elimination mainly occurs in the urine. Foods with high phosphorus concentrations include dairy products, protein sources (e.g., chicken, beef, fish, and nuts), grains, and carbonated sodas. The RDA for phosphorus is approximately 1,000 mg/day. Absorption of phosphorus is decreased when it is ingested with foods containing calcium, magnesium, and aluminum—all of which bind with phosphorus.

Hyperphosphatemia

Hyperphosphatemia occurs when phosphorus levels climb above 4.5 mg/dL. It usually results from decreased excretion or increased intake of phosphorus:

- Deficient excretion, such as that caused by the following:
  - Renal failure
  - Hypoparathyroidism (decreases renal excretion)
  - Adrenal insufficiency
  - Hypothyroidism
  - Laxatives, especially those containing phosphorus (decrease calcium levels, which increases phosphorus levels)
- Excessive intake or cellular exchange, such as that caused by the following:
  - Cellular damage (e.g., burn, trauma, and chemotherapy)
  - Hypocalcemia
  - Acidosis (increased phosphorus shifts from the intracellular compartment to the intravascular compartment)

Clinical manifestations are similar to those observed with hypocalcemia and are rarely seen alone. Diagnostic procedures for hyperphosphatemia consist of a history, physical examination, and blood chemistry. Management includes identification and treatment of the underlying cause (e.g., dialysis for renal failure). Aluminum hydroxide and aluminum carbonate can bind to phosphorus and increase intestinal excretion. Additionally, treatment of hypocalcemia may be necessary.

Hypophosphatemia

Hypophosphatemia occurs when phosphorus levels drop below 2.5 mg/dL. This imbalance is usually caused by increased excretion or decreased intake of phosphorus:

- Excessive excretion or cellular exchange, such as that caused by the following:
  - Renal failure
  - Hyperparathyroidism (increases renal excretion)
  - Alkalosis (increased amounts of phosphorus shift from the intravascular compartment to the intracellular compartment)
- Deficient intake, such as that caused by the following:
  - Malabsorption
  - Vitamin D deficiency
  - Magnesium and aluminum antacids
  - Alcoholism
  - Decreased dietary intake (rare)

Clinical manifestations are similar to those associated with hypercalcemia. Diagnostic procedures include a history, physical examination, and blood chemistry. Management of hypophosphatemia focuses on the identification and treatment of the underlying cause (e.g., dialysis for renal failure). Phosphorus levels can be increased with the administration of oral supplements (in mild deficiencies) and

intravenous potassium phosphate (in moderate to severe deficiencies).

Magnesium

Magnesium is an intracellular cation that is mostly stored in the bone and muscle. This electrolyte helps maintain normal muscle and nerve function, regular cardiac rhythm, a healthy immune system, bone strength, blood glucose levels, and normal blood pressure; it is also involved in energy metabolism and protein synthesis. Magnesium has a direct relationship with calcium and an inverse relationship with phosphorus. It is obtained through dietary intake and excreted through the kidneys. Foods with a high magnesium content include green vegetables, legumes, nuts, seeds, and whole grains. The RDA for magnesium is approximately 400 mg per day.

Hypermagnesemia

Hypermagnesemia occurs when magnesium levels increase above 2.5 mEq/L. This imbalance is rare and usually results from renal failure or from excessive use of laxatives or antacids. Clinical manifestations of hypermagnesemia are similar to those of hypercalcemia. Diagnostic procedures include a history, physical examination, and blood chemistry. Treatment strategies consist of hypotonic IVF, diuretics, and dialysis to promote renal function. Additionally, administering intravenous calcium may be necessary to minimize the effects of magnesium (calcium is a direct antagonist of magnesium).

Hypomagnesemia

Hypomagnesemia results when magnesium levels drop below 1.8 mEq/L. Hypomagnesemia can result from inadequate intake, chronic alcoholism, malnutrition, pregnancy (e.g., preeclampsia), diarrhea, diuretics, and stress. Clinical manifestations of this condition are similar to those of hypocalcemia. Diagnostic procedures are the same as those used with hypermagnesemia. Treatment strategies

include magnesium oral supplements for mild deficits and intravenous magnesium for more severe cases.

Learning Points

Relationships Between Ions

Understanding ions' relationships with other ions can help you understand what is happening in the body.

- Sodium and potassium have an inverse relationship; thus, when one goes up, the other goes down.
- Calcium and phosphorus have an inverse relationship.
- Calcium and magnesium have a synergistic relationship, so one enhances the other.

Acid–Base Balance

Acid–base stability is crucial to sustaining life and maintaining health. This balance is achieved through a variety of buffer systems and compensatory mechanisms. Body fluids, the kidneys, and the lungs all play pivotal roles in maintaining this balance.

Acid–base balance is measured by examining pH, the concentration of hydrogen (H^+) ions, which has a narrow safety margin in the body (serum pH of 7.35–7.45). Acid–base imbalances can vary in severity based on the degree of pH change. Death can occur if serum pH levels fall below 6.8 or rise above 7.8. Changes in pH may be caused by a variety of conditions, including infection, organ failure, or trauma. In many cases, the acid–base fluctuations can cause more negative effects than the causative condition; therefore, the resulting acid–base imbalance is often corrected before treating the underlying condition.

pH Regulation

One way to measure serum hydrogen is by pH, which reflects acid–base status. The pH measure is a negative logarithm that reflects the hydrogen concentration: The higher the hydrogen concentration, the lower the pH number (see **FIGURE 6-12**). Hydrogen is necessary for maintaining the cellular membranes and for enzyme activities. Acids are produced as a by-product of protein, carbohydrate, and fat metabolism. The acidic by-products are found in body fluids as **volatile acids**, such as carbonic acid. Carbonic acid breaks down into hydrogen and bicarbonate. Additionally, carbon dioxide (CO_2), an acidic **volatile gas**, is produced as a by-product of cellular respiration. Carbon dioxide is expelled through breathing, and the remaining volatile acid is converted to **nonvolatile acids** (e.g., hydrochloric acid, phosphoric acid, and sulfates) that are then excreted in the urine. Three systems work together to maintain acid–base balance: the buffers, the respiratory system, and the renal system (**FIGURE 6-13**).

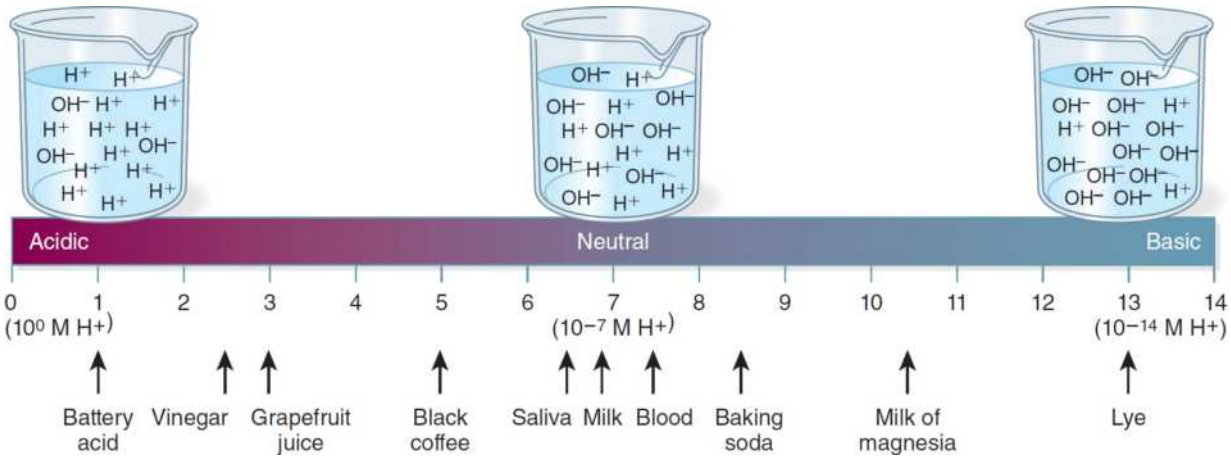


FIGURE 6-12 The pH scale.

Description

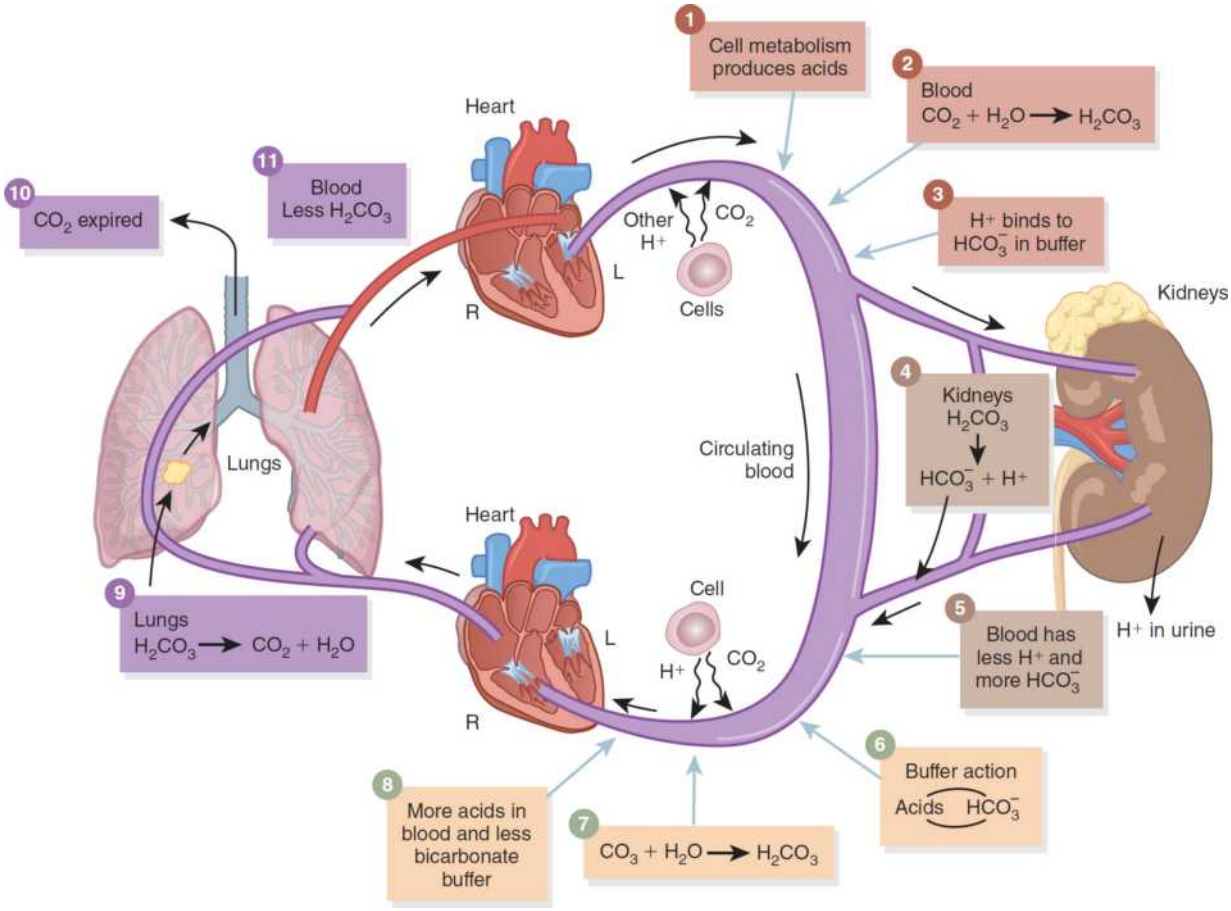


FIGURE 6-13 Buffers, the respiratory system, and the renal system in acid–base balance.

Description

Learning Points

pH Balance

The blood's pH must remain between 7.35 and 7.45 (**FIGURE 6-14**). The body's goal is to maintain a constant balance between incoming/produced acids and bases (similar to a faucet that is on) and eliminated acids and bases (similar to an open drain). Imbalances lead to acidosis (the acid sink overflows) or alkalosis (the base sink overflows). Balance can be restored by increasing elimination (by draining the sink faster) and/or by decreasing flow (by slowing down the dripping faucet).

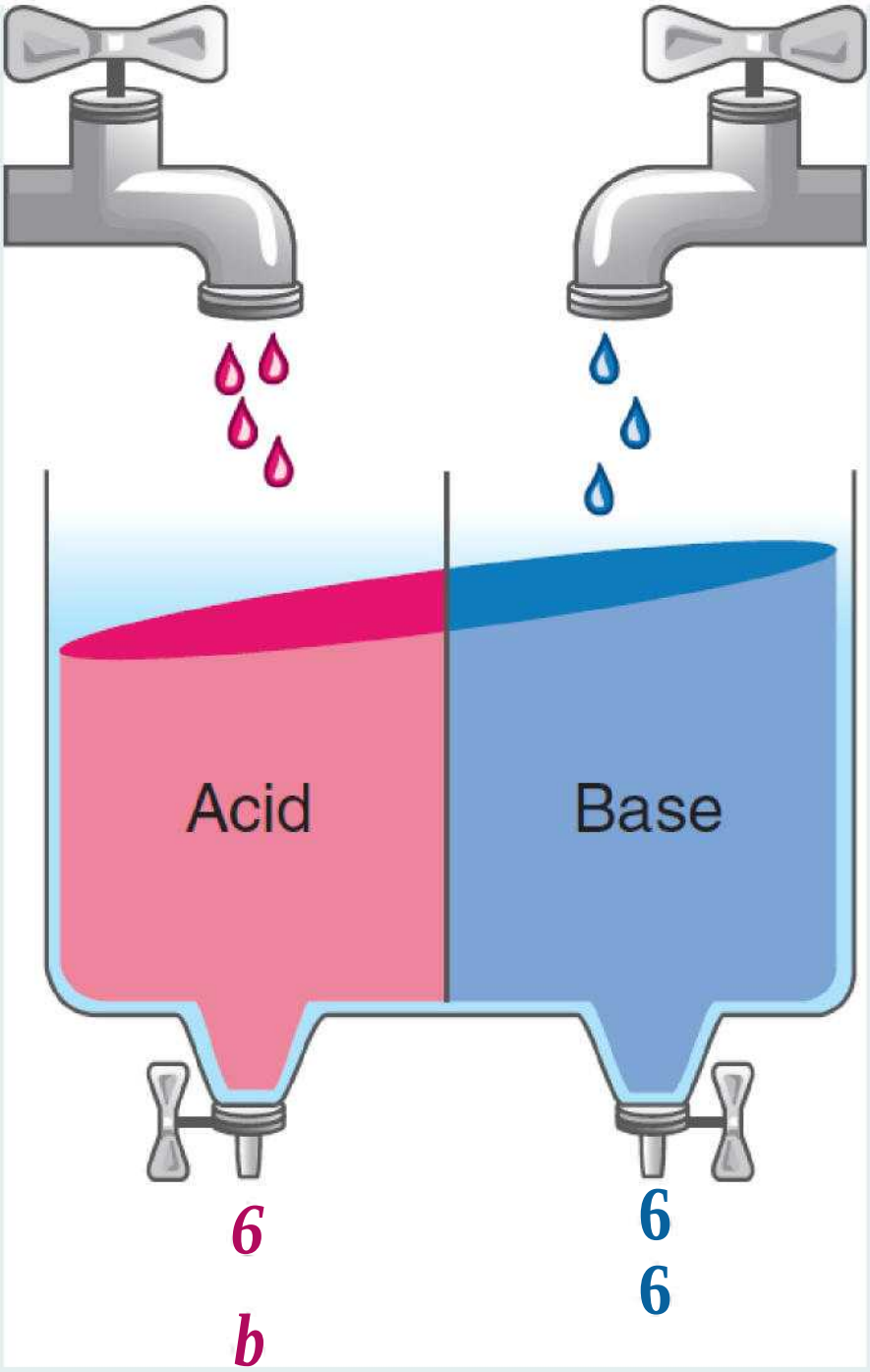


FIGURE 6-14 Acid–base balance.

Buffers

Buffers are the chemicals that combine with an acid or a base to change pH. Buffering is an immediate reaction to counteract pH variations until compensation is initiated. The body has four major buffer mechanisms: the **bicarbonate–carbonic acid system**, the **phosphate system**, the **hemoglobin system**, and the **protein system**.

The bicarbonate–carbonic acid system is the most significant buffering mechanism in the ECF. Carbonic acid and bicarbonate (base) are the key players in this system. Carbon dioxide (acid) is a by-product of cellular metabolism. Once produced, it diffuses into the interstitial fluid and blood, where it reacts with water to form carbonic acid. This carbonic acid decomposes immediately, owing to the presence of the enzyme carbonic anhydrase, to form hydrogen ions and bicarbonate. Carbonic anhydrase is present at many sites in the body, including the lungs and kidneys. In the lungs, this reaction is reversed so that carbon dioxide can be expired along with water—a process that decreases the amount of carbonic acid in the body. In the kidneys, the reaction forms hydrogen ions that are then excreted in the urine, and the bicarbonate is returned to the blood.

The phosphate system acts much like the bicarbonate–carbonic acid system. Phosphates are found in high concentrations in the intracellular fluid. Some of these phosphates act as weak acids, whereas others act as weak bases. Buffering in this system primarily takes place in the kidneys by accepting or donating hydrogen.

The hemoglobin system is a buffer found in the erythrocytes that work by binding to or releasing hydrogen and carbon dioxide. When combined with oxygen, hemoglobin tends to release hydrogen. Exposing hemoglobin to acid and lower oxygen concentrations in the capillaries causes it to release the oxygen that is bound to it (see the *Hematopoietic Function* chapter). Hemoglobin then becomes a weaker acid, taking up extra hydrogen. This change maintains the pH in the capillaries. The opposite change occurs when hemoglobin is exposed to the higher oxygen concentrations found in the lungs. As hemoglobin binds with oxygen, it becomes more acidic (more prone to release hydrogen). The hydrogen subsequently reacts with bicarbonate to form carbonic acid, which is then converted to carbon dioxide and released into the alveoli.

The protein system is the most abundant buffering system. Proteins can act as either an acid or a base by binding to or releasing hydrogen, respectively. Proteins exist in the ICF and ECF but are most abundant inside the cells. Hydrogen and carbon dioxide diffuse across the cell

membrane to bind with proteins inside the cells, while albumin and plasma are the primary buffers in the intravascular space.

In addition to these systems, two positively charged ions—potassium and hydrogen—move in opposite directions in and out of the cell to balance pH there. When there is an extracellular excess of hydrogen, hydrogen moves inside the cell for buffering purposes; in exchange, potassium moves out of the cell. When there is an extracellular deficit of hydrogen, these ions move in opposite directions. As mentioned earlier, potassium imbalances can lead to acid–base imbalances, and acid–base imbalances can lead to potassium imbalances.

Respiratory Regulation

The respiratory system manages pH deviations by changing carbon dioxide (acid) excretion. Speeding up respiration will lead to excretion of more carbon dioxide, thereby decreasing acidity. Conversely, slowing down respiration will lead to excretion of less carbon dioxide, thereby increasing acidity. Chemoreceptors that sense pH changes trigger this change in breathing pattern. The only way the lungs can remove acids is through the elimination of carbon dioxide from carbonic acid—the lungs cannot remove other acids. The respiratory system is also a mechanism that can respond quickly to pH imbalances, though its quick action is generally short lived. The respiratory system reaches its maximum response in 12–24 hours but can maintain the changes in breathing pattern for only a limited time before becoming fatigued.

Renal Regulation

The renal system is the slowest mechanism to react to pH changes, taking hours to days to achieve its buffering effect, but its actions are the longest lasting. The kidneys respond to alterations in pH by changing the excretion or retention of hydrogen (acid) or bicarbonate (base). The renal system acts to balance pH levels by permanently removing hydrogen from the body. Additionally, the kidneys can reabsorb acids or bases as well as produce bicarbonate to correct pH imbalances.

Compensation

In an effort to maintain homeostasis, the body takes actions to compensate for pH changes (**FIGURE 6-15**). The body never overcompensates; rather, the pH is adjusted so that it remains just within the normal range. The cause of the imbalance often determines the compensatory change. For instance, if pH is becoming more acidic because of lung disease that limits gas exchange (e.g., emphysema), then the renal system will kick in to compensate for this problem by releasing more bicarbonate and excreting more hydrogen. If a lung disease is increasing carbon dioxide excretion (e.g., through hyperventilation), which will increase pH, then the kidneys will compensate by decreasing bicarbonate production and hydrogen excretion. In contrast, the lungs can compensate for problems that originate outside the lungs. For example, the lungs will decrease the rate and depth of respirations to retain more carbon dioxide when a condition increases the loss of acids (e.g., vomiting). If a condition increases the loss of bases (e.g., diarrhea), then the lungs will increase the rate and depth of respirations to excrete more carbon dioxide. If the kidneys and lungs cannot compensate to restore the pH levels to normal range, cellular activities are affected, leading to disease states.

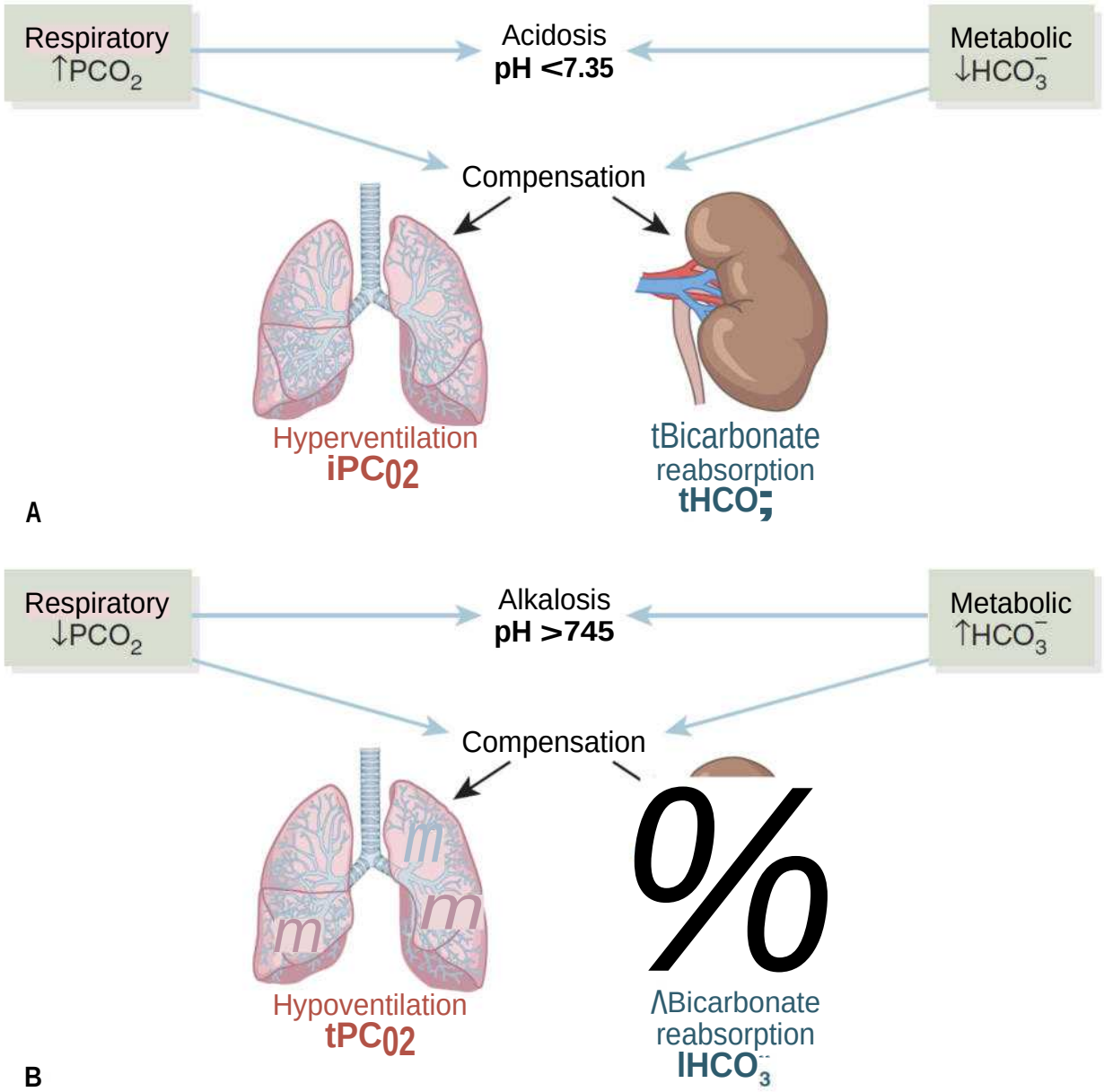


FIGURE 6-15 **(A)** Acidosis and compensatory mechanisms. **(B)** Alkalosis and compensatory mechanisms.

Description

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Metabolic Acidosis

Metabolic acidosis results from either a deficiency of bicarbonate (base) or an excess of hydrogen (acid) (**TABLE 6-2**). These conditions drop the pH below 7.35. Causes of metabolic acidosis include the following:

TABLE 6-2 Acid–Base Imbalances

	Acidosis	Alkalosis
Respiratory System		
Causes	Slow, shallow respirations Respiratory congestion	Hyperventilation
Effect	Increased $PaCO_2$	Decreased $PaCO_2$
Compensatory mechanism	Kidneys excrete more hydrogen and reabsorb more bicarbonate	Kidneys excrete less hydrogen and reabsorb less bicarbonate
Diagnostic findings	High $PaCO_2$ High bicarbonate Compensated: pH = 7.35–7.4 Decompensated: pH < 7.33	Low $PaCO_2$ Low bicarbonate Compensated: pH = 7.4–7.45 Decompensated: pH > 7.47
Metabolic System		
Causes	Diarrhea Renal failure Diabetic ketoacidosis Tissue hypoxia	Vomiting Excessive antacid use
Effect	Decreased bicarbonate	Increased bicarbonate
Compensatory mechanism	Rapid, deep respirations Kidneys excrete more hydrogen and increase bicarbonate absorption (when not involved)	Slow, shallow respirations Kidneys excrete less hydrogen and decrease bicarbonate absorption (when not involved)
Diagnostic findings	Low bicarbonate Low $PaCO_2$ Compensated: pH = 7.35–7.4 Decompensated: pH < 7.33	High bicarbonate High $PaCO_2$ Compensated: pH = 7.4–7.45 Decompensated: pH > 7.47

Abbreviations: $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen.

- Bicarbonate deficit, including that caused by the following:
  - Intestinal losses (e.g., diarrhea and fistulas)
  - Renal losses (e.g., renal failure)
- Acid excess, including that caused by the following:

- Tissue hypoxia resulting in lactic acid accumulation (e.g., shock and cardiac arrest)
- Ketoacidosis (e.g., uncontrolled diabetes, excessive alcohol consumption, starvation, and extreme dieting)
- Drugs and toxins (e.g., antifreeze, aspirin, and hyperalimentation)
- Renal retention (e.g., renal failure)

Metabolic acidosis exists when the bicarbonate and pH levels are lower than normal (TABLE 6-3). Metabolic acidosis results from an existing problem; therefore, the characteristics of that condition are manifested along with the acidosis. Clinical manifestations of metabolic acidosis are often neurologic in nature, but the gastrointestinal, cardiac, and respiratory systems can also be affected. These manifestations include the following signs and symptoms:

TABLE 6-3 Normal Serum Arterial Blood Gas Values*

Blood Gas	Normal Range
pH	7.35–7.45
PaO_2	95–100 mm Hg
$PaCO_2$	35–45 mm Hg
Bicarbonate (HCO_3)	22–26 mEq/L
Base excess	–2.4 to +2.5 mEq/L
Arterial O_2 saturation	96–98%

*Values may vary slightly.
Abbreviations: $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen.

- Headache
- Malaise
- Weakness
- Fatigue
- Lethargy

- Coma
- Warm, flushed skin
- Nausea and vomiting
- Anorexia
- Hypotension
- Dysrhythmias
- Shock
- Kussmaul respirations (deep, rapid respirations that develop in an attempt to eliminate excess acid by exhaling more carbon dioxide)
- Hyperkalemia (increased serum hydrogen levels cause potassium to shift out of the cells; lack of insulin in diabetic ketoacidosis impairs the transportation of potassium in the cell)

Learning Points

Acid–Base Compensation

Compensation can be a challenge to understand. First, make sure you understand what the acids and bases are. Carbon dioxide and hydrogen are acids; bicarbonate is a base. The body will increase or decrease the excretion of these substances in an attempt to restore pH balance. If the body excretes more acid or produces more base, then the pH will become more alkaline. If the body retains more acid or produces less base, then the pH will become more acidic.

Two body systems can compensate for pH imbalances—the renal and respiratory systems. If the cause of the imbalance originates within one of those systems, then the other system will have to perform the role of the primary compensatory mechanism. The system that is the source of the pH imbalance will not be able to resolve its own problem. Thus, if the problem originates in the lungs, the kidneys will manage it. Conversely, the lungs will manage it if the problem originates outside the lungs.

Diagnostic procedures for metabolic acidosis include a history, physical examination, ABGs, blood chemistry, and CBC. Evaluation of the **anion gap** from the ABG results can be helpful in determining the cause of metabolic acidosis. The anion gap is used to identify the anions that are not measured. Conditions that cause metabolic acidosis because of excess acid will increase the anion gap; otherwise, the anion gap will remain normal. Under normal conditions, the sum of cations is approximately equal to the sum of anions in the ECF. Sodium is the most plentiful cation in the ECF, while bicarbonate and chloride are the most abundant anions. To

determine the anion gap, the bicarbonate and chloride results are added together and subtracted from the sodium: sodium – (bicarbonate + chloride). A normal anion gap is in the range of 6–9 mEq/L.

Identifying and treating the causative condition (e.g., antidiarrheal agents or dialysis) is vital to achieving successful patient outcomes. Treatment to correct the acidosis merely stabilizes the patient until the causative condition can be managed. Strategies to correct the acidosis include the following measures:

- Administering intravenous bicarbonate
- Correcting electrolyte disturbances such as hyperkalemia
- Improving oxygenation (e.g., oxygen therapy and mechanical ventilation)
- Administering insulin (probably intravenous) to treat diabetic ketoacidosis

Metabolic Alkalosis

Metabolic alkalosis results from excess bicarbonate or deficient acid, or both (see Table 6-2). These conditions cause the pH to rise above 7.45. Causes of metabolic alkalosis include the following:

- Excess bicarbonate, such as that caused by the following:
  - Excessive antacid use
  - Use of bicarbonate-containing fluids (e.g., lactated Ringer's solution)
  - Hypochloremia (increases bicarbonate reabsorption)
- Deficient acid, such as that caused by the following:
  - Gastrointestinal loss (e.g., vomiting or nasogastric suction)
  - Hypokalemia (low potassium levels cause hydrogen to shift inside the cells)
  - Renal loss (e.g., renal failure or diuretics)
  - Hypovolemia (decreases renal perfusion)
  - Hyperaldosteronism (excessive aldosterone increases renal excretion of hydrogen)

Metabolic alkalosis exists when the bicarbonate and pH levels rise to greater than normal (Table 6-3). Much as with metabolic acidosis, metabolic alkalosis manifestations generally occur in combination with the manifestations of the causative conditions (e.g., hypovolemia). Clinical

manifestations of metabolic alkalosis are mostly neurologic in nature but may also involve the respiratory and cardiac systems:

- Mental confusion
- Hyperactive reflexes
- Paresthesia
- Tetany
- Seizures
- Respiratory depression (respirations will decrease in an attempt to hold in more carbon dioxide)
- Dysrhythmias
- Coma

Diagnostic procedures for metabolic alkalosis include a history, physical examination, ABGs, blood chemistry, and CBC. Identifying and treating the causative condition (e.g., antiemetics or cessation of antacid use) is vital to achieving successful patient outcomes. Treatment to correct the alkalosis merely stabilizes the patient until the causative condition can be managed. Strategies to correct the alkalosis include the following measures:

- Adequate hydration, likely including IVF
- Correcting electrolyte disturbances, such as hypokalemia and hypochloremia
- Cautious administration of Diamox (acetazolamide) (which increases bicarbonate excretion but may increase potassium excretion as well)
- Administering arginine hydrochloride (which increases chloride levels)
- Administering a weak hydrochloric acid solution

Respiratory Acidosis

Respiratory acidosis results from carbon dioxide retention, which increases the amount of carbonic acid present and, in turn, decreases the pH level (Table 6-2). This increase in carbon dioxide usually follows a state of hypoventilation or decreased gas exchange in the lungs. Many conditions can cause hypoventilation and/or impair gas exchange, including:

- Acute asthma exacerbations

- Chronic obstructive pulmonary disease (emphysema and chronic bronchitis)
- Airway obstruction
- Pulmonary edema
- Pneumonia
- Drug overdose
- Respiratory failure
- Central nervous system depression

Respiratory acidosis exists when the carbon dioxide levels rise and the pH levels fall below normal (Table 6-3). Manifestations generally occur in combination with the manifestations of the causative condition (e.g., asthma). Carbon dioxide easily diffuses across the blood–brain barrier, causing the neurologic manifestations. Additionally, respiratory acidosis can affect the cardiac system. Clinical manifestations of respiratory acidosis include the following signs and symptoms:

- Headache
- Blurred vision
- Tremors
- Muscle twitching
- Vertigo (an illusion of motion)
- Irritability
- Disorientation
- Lethargy
- Coma
- Tachycardia leading to bradycardia
- Blood pressure fluctuations
- Diaphoresis

Diagnostic procedures for respiratory acidosis include a history, physical examination, ABGs, blood chemistry, CBC, and chest X-ray. Treatment centers on improving respiratory status by relieving hypoxia and hypercapnia. Strategies may include the following measures:

- Oxygen therapy

- Mechanical ventilation
- Positioning the patient for optimal ventilation (high Fowler's position)
- Bronchial hygiene measures (e.g., coughing, deep breathing, and chest physiotherapy)
- Bronchodilators
- Treatment of causative conditions (e.g., antibiotics for pneumonia)

Respiratory Alkalosis

Respiratory alkalosis results from excess exhalation of carbon dioxide, which in turn leads to carbonic acid deficits and increased pH (Table 6-2). Respiratory alkalosis generally occurs because of conditions that cause hyperventilation:

- Acute anxiety
- Pain
- Fever (which causes excessive oxygen utilization, increasing respirations)
- Hypoxia (e.g., oxygen deprivation and high altitudes)
- Gram-negative septicemia (which triggers the respiratory centers in the brain to increase respirations)
- Aspirin overdose (also triggers the medulla to increase respirations)
- Excessive mechanical ventilation
- Hypermetabolic states, such as hyperthyroidism (which causes excessive oxygen utilization, increasing respirations)

Respiratory alkalosis exists when the carbon dioxide levels fall and the pH levels rise above normal (see Table 6-3). Clinical manifestations reflect central nervous system irritability. Manifestations of hypercalcemia may be present secondary to calcium binding to protein. Clinical manifestations of respiratory alkalosis include the following signs and symptoms:

- Paresthesia
- Dizziness
- Vertigo (an illusion of motion)
- Syncope
- Muscle irritability and twitching

- Tetany
- Inability to concentrate
- Seizures
- Tachycardia
- Dysrhythmias
- Dry mouth
- Anxiety
- Excessive diaphoresis
- Coma

Diagnostic procedures for respiratory alkalosis include a history, physical examination, ABGs, blood chemistry, CBC, and chest X-ray. Treatment of the underlying cause and increasing carbon dioxide levels is crucial to improve patient outcomes. Often the solution is as simple as breathing into a paper bag—an intervention that allows carbon dioxide to be recirculated back to the lungs. More aggressive strategies may be needed if the patient is unable to follow directions or is unconscious. These measures may include controlled mechanical ventilation and anxiety-reduction interventions (e.g., sedatives and therapeutic communication).

Mixed Disorders

Mixed disorders occur when respiratory and metabolic disorders result in an acidotic or alkalotic state. Such an outcome occurs when both the respiratory and renal systems demonstrate an imbalance of acid or base. The severity of the pH imbalance depends on the degree of the acid and base disturbances. Many conditions can create this synergistic effect. Such mixed disorders can make the patient critically ill and can be complex to manage.

Arterial Blood Gas Interpretation

Arterial blood gases (ABGs) are the principal diagnostic tool for evaluating acid–base balance (see Table 6-2). Unfortunately, ABG interpretation has mystified many nursing students and nurses since the invention of this measurement. Through simple steps, the ABG riddle can be solved, and the patient can receive appropriate care. First, the results

found on an ABG are, in order (some of which have already been discussed and should be reviewed again):

- The pH measures the hydrogen concentration in the plasma.
- $PaCO_2$ (the partial pressure of carbon dioxide) indicates the adequacy of pulmonary ventilation.
- HCO_3 (bicarbonate) indicates the activity in the kidneys to retain or excrete bicarbonate.
- PaO_2 (the partial pressure of oxygen) indicates the concentration of oxygen in the blood.
- Base excess/deficit indicates the concentration of buffer—in particular, bicarbonate. Positive values indicate an excess of base or a deficit of acid. Negative values indicate a deficit of base or an excess of acid.

When interpreting an ABG result, focus on the pH, $PaCO_2$, and HCO_3. Interpreting ABGs involves looking for patterns and understanding what those patterns indicate, keeping in mind the patient's total clinical picture. Recall that $PaCO_2$ is an acid and HCO_3 is a base. More acid will lower the pH, whereas less acid will raise the pH. In contrast, more base will raise the pH, whereas less base will lower the pH.

Use a systematic approach when examining the ABG results (TABLE 6-4). Make note of the patient's pH, $PaCO_2$, and HCO_3 on a piece of paper. Start by examining the pH. Is it high, low, or normal? This determination is half of the puzzle. The pH will identify whether the condition is acidosis or alkalosis. If it is high, write a *B* for "basic" beside it. If the pH is low, write an *A* for "acidic." If it is normal, which side of normal is it? For results less than 7.4, write an *A*; for results greater than 7.4, write a *B*.

TABLE 6-4 Arterial Blood Gas Interpretation

Acid–Base Disorder	pH	$PaCO_2$	HCO_3	Compensation
Respiratory acidosis	<7.4 (A)	>45 mm Hg (A)	Normal	HCO_3 > 26 mEq/L (B)
Respiratory alkalosis	>7.4 (B)	<35 mm Hg (B)	Normal	HCO_3 < 22 mEq/L (A)
Metabolic acidosis	<7.4 (A)	Normal	<22 mEq/L (A)	$PaCO_2$ < 35 mm Hg (B)
Metabolic alkalosis	>7.4 (B)	Normal	>26 mEq/L (B)	$PaCO_2$ > 45 mm Hg (A)

Description

Next, check the $PaCO_2$. Is it high, low, or normal? In respiratory disturbances, pH and CO_2 move in opposite directions. If the CO_2 goes up, the pH goes down, and vice versa. Because CO_2 is an acidic influence, write an *A* if it is high and a *B* if it is low. If it is within normal range, write an *N* beside it.

Next, examine the HCO_3. Is it high, low, or normal? With metabolic disturbances, the pH and HCO_3 move in the same direction. Because HCO_3 is a base influence, write a *B* if it is high and an *A* if it is low. If it is within normal range, write an *N* beside it.

At this point, you should have three letters written down beside your patient's ABG results. Now you just match up the *A*s and *B*s you have written down to the disturbance. Finally, determine if the body has been able to compensate. The results with the paired *A* or *B* are the primary changes. The third unpaired result indicates the compensation. If the unpaired result is still normal, then it is **uncompensated**. If the unpaired result has changed to the opposite letter of the pairs and the pH is still abnormal, then it is **partially compensated**; if the pH has returned to normal, then it is **fully compensated**.

To review, these are the steps in ABG interpretation:

1. Is the pH high, low, or normal?
   a. If pH > 7.4, write a *B* beside it for basic.
   b. If pH < 7.4, write an *A* beside it for acidic.
   c. Make a note if the pH is within normal limits (7.35–7.45).
2. Is the $PaCO_2$ high, low, or normal?
   a. If $PaCO_2$ is between 35 and 45 mm Hg, write an *N* beside it for normal.
   b. If $PaCO_2$ > 45 mm Hg, write an *A* beside it for acidic.
   c. If $PaCO_2$ < 35 mm Hg, write a *B* beside it for basic.
3. Is the HCO_3 high, low, or normal?
   a. If HCO_3 is between 22 and 26, write an *N* beside it for normal.
   b. If HCO_3 > 26 mEq/L, write a *B* beside it for basic.
   c. If HCO_3 < 22 mEq/L, write an *A* beside it for acidic.
4. Look for patterns:

a. Two *A*s indicate acidosis. If one of the *A*s is CO_2, then the disorder is respiratory. If one of the *A*s is HCO_3, then the disorder is metabolic. In both cases, the other *A* is the pH.
b. Two *B*s indicate alkalosis. If one of the *B*s is CO_2, then the disorder is respiratory. If one of the *B*s is HCO_3, then the disorder is metabolic. In both cases, the other *B* is the pH.
c. Three *A*s or *B*s indicate a mixed disorder. All *A*s indicate mixed respiratory and metabolic acidosis. All *B*s indicate mixed respiratory and metabolic alkalosis.

5. Determine compensation:
   a. If the unpaired result is within the normal range, then the disturbance is uncompensated.
   b. If the unpaired result is the opposite letter of the pairs but the pH is still abnormal, then the disturbance is partially compensated.
   c. If the unpaired result is the opposite letter and the pH has returned to normal range, then the disturbance is fully compensated.

Practice Arterial Blood Gas Interpretation

Practice 1

pH:	7.32	**A**
$PaCO_2$:	37 mm Hg	**N**ormal
HCO_3:	14 mEq/L	**A**

Practice 2

pH:	7.50	**B**
$PaCO_2$:	30 mm Hg	**B**
HCO_3:	24 mEq/L	**N**ormal

Practice 3

pH:	7.33	**A**
$PaCO_2$:	55 mm Hg	**A**
HCO_3:	28 mEq/L	**B**

Practice 4

pH:	7.47	**B**
$PaCO_2$:	48 mm Hg	**A**
HCO_3:	29 mEq/L	**B**

Practice 5

pH:	7.38	**A** (but within normal limits)
$PaCO_2$:	48 mm Hg	**A**
HCO_3:	29 mEq/L	**B**

Practice 6

pH:	7.44	**B** (but within normal limits)
$PaCO_2$:	49 mm Hg	**A**
HCO_3:	29 mEq/L	**B**

Practice 7

pH:	7.30	
$PaCO_2$:	50 mm Hg	
HCO_3:	19 mEq/L	

Practice 8

pH:	7.49	**B**
$PaCO_2$:	32 mm Hg	**B**
HCO_3:	30 mEq/L	**B**

application to practice

Now that you have learned about fluid, electrolyte, and acid–base imbalances, let's put this knowledge into practice. After receiving reports on the following patients, which patient should you go see first?

- A 76-year-old female admitted 3 days ago with pneumonia; her most recent blood gases are pH 7.35, PaO_2 90, HCO_3 35, and $PaCO_2$ 29
- A 67-year-old male admitted yesterday with vomiting and diarrhea for the last 2 days; his most recent lab results are pH 7.36, PaO_2 95, HCO_3 22, $PaCO_2$ 44, K 3.5, Na 145, and osmo 300
- A 52-year-old female admitted yesterday with acute renal failure; her most recent lab results are pH 7.3, PaO_2 94, HCO_3 15, $PaCO_2$ 44, K 6.1, Na 148, and osmo 369
- A 59-year-old male admitted 2 days ago with stage III bronchogenic carcinoma; her most recent lab results are pH 7.34, PaO_2 92, HCO_3 28, $PaCO_2$ 47, K 4.2, Na 140, and osmo 290

Once again, you go through the usual thought process—who would die first, acute versus chronic conditions, Maslow's hierarchy of needs, and patient safety. Let's start with the 76-year-old female. If you analyze the ABGs, you will find that these results are normal. This patient is relatively stable and probably can wait. Moving on to the 67-year-old male, you will notice that the metabolic acidosis, hypokalemia, hypernatremia, and fluid deficit seem to be correcting. Now consider the 52-year-old female admitted with renal failure. When you analyze her ABGs, you find that she is experiencing uncompensated metabolic acidosis. Also note that this patient's potassium is elevated. Given that both conditions can be life threatening, keep this patient on your short list. Finally, the 59-year-old male is experiencing a life-threatening cancer and partially

compensated respiratory acidosis, so this patient warrants being on the short list. Given the nature of the patient's diagnosis, these findings are likely to persist.

After considering all these patients, the two patients on your short list are experiencing life-threatening conditions. You should see the 52-year-old female with uncompensated metabolic acidosis first, because she is more acute than the 59-year-old male with lung cancer.

SUMMARY

Fluid, electrolytes, bases, and acids are constantly moving among body compartments. This movement is influenced by intake, output, cellular metabolism, and pathologic states. The body is equipped with numerous mechanisms to maintain fluid, electrolyte, and pH homeostasis among these compartments. When these mechanisms fail, conditions that threaten the individual's well-being arise. Early identification and action are crucial to improve the prognosis of the person encountering these conditions, and nurses play a pivotal role in managing this patient's plan of care.

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CHAPTER 7

Urinary Function

LEARNING OBJECTIVES

- Discuss normal urinary anatomy and physiology.
- Describe and compare renal alterations that alter urinary elimination.
- Describe and compare renal alterations that result in impaired renal function.

KEY TERMS

acute kidney injury (AKI)
afferent arteriole
ammonia
anasarca
azotemia
benign prostatic hyperplasia (BPH)
bladder
bladder cancer
Bowman capsule
calyx
chronic kidney disease (CKD)
chronic overdistention
cystitis
deamination
detrusor hyperreflexia
efferent arteriole
enuresis
erythropoietin
functional incontinence

glomerular filtration rate (GFR)
glomerulonephritis
glomerulus
gross total incontinence
hydronephrosis
intrarenal condition
micturition
mixed incontinence
nephritic syndrome
nephrolithiasis
nephron
nephrotic syndrome
neurogenic bladder
nocturnal enuresis
overactive bladder
overflow incontinence
polycystic kidney disease (PKD)
postrenal condition
prerenal condition
pyelonephritis
reflex incontinence
renal artery
renal capsule
renal cell carcinoma
renal cortex
renal hilum
renal pelvis
renal sinus
renin–angiotensin–aldosterone system
retention
stress incontinence
transient incontinence
urea
uremia
ureter
urethra
urge incontinence
uric acid

urinary incontinence
urinary tract infection (UTI)
urination
Wilms tumor

The urinary system plays a pivotal role in homeostasis. Structures of the urinary system include the kidneys, **ureters**, **bladder**, and **urethra** (**FIGURE 7-1**). This system regulates fluid volume, blood pressure, metabolic waste and drug excretion, vitamin D conversion, pH regulation, and hormone synthesis. This chapter focuses on normal and abnormal states of the urinary system. Disorders of this system can create imbalances in homeostasis quickly. Hence, these disorders require a prompt response to restore the body's delicate balance.

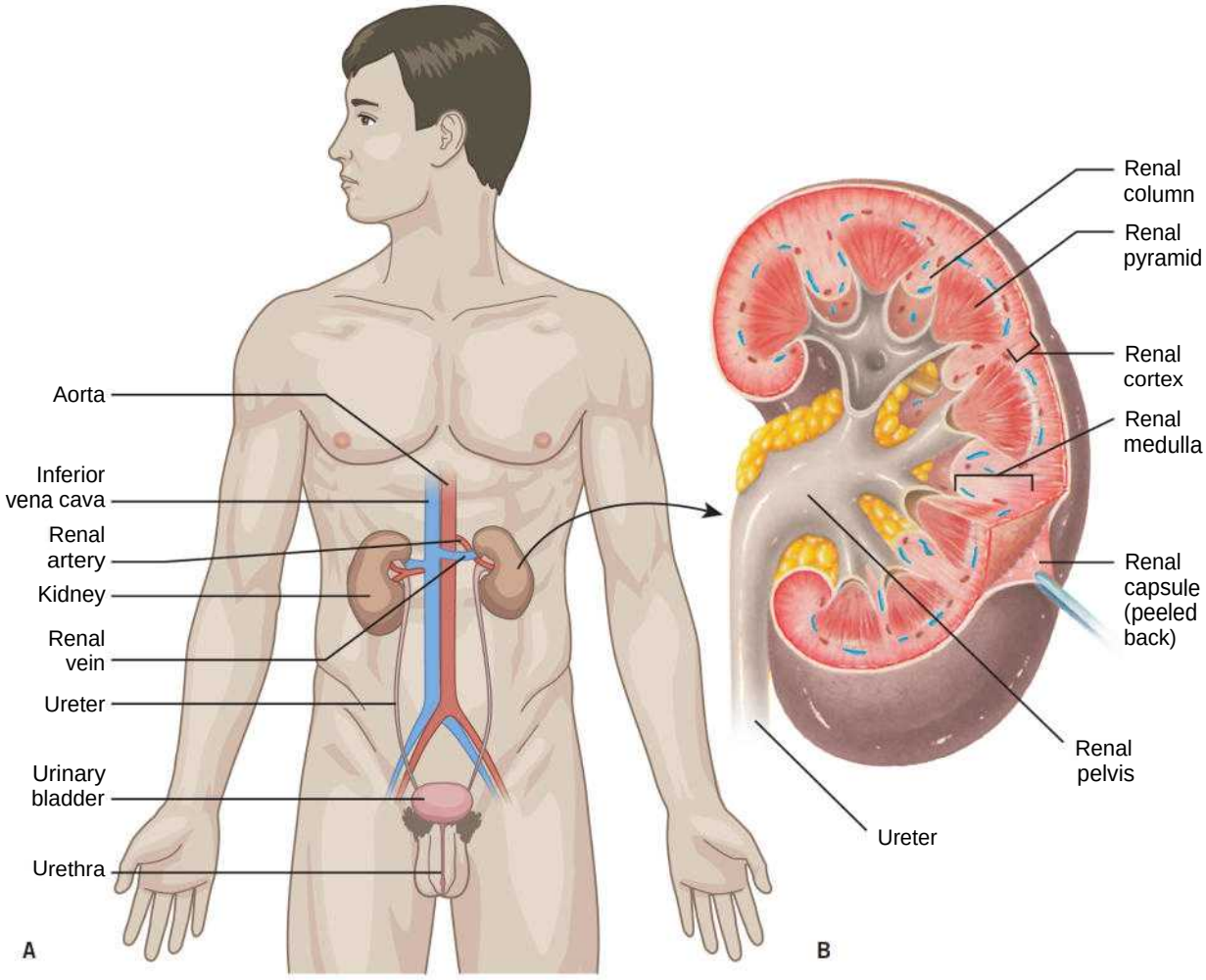


FIGURE 7-1 The urinary system. **(A)** Anterior view showing the relationship of the kidneys, ureters, urinary bladder, and urethra. **(B)** A cross section of the human kidney showing the cortex, medulla, and renal pelvis.

Description

Anatomy and Physiology

The urinary system regulates fluid volume (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter), blood pressure (see the *Cardiovascular Function* chapter), metabolic waste and drug excretion, vitamin D conversion, pH balance (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter), and hormone synthesis. The system includes the kidneys, ureters, bladder, and urethra (**TABLE 7-1**).

TABLE 7-1 Components of the Urinary System and Their Functions

Component	Function
Kidneys	Eliminate wastes from the blood; help regulate body water concentration; help regulate blood pressure; help maintain a constant blood pH
Ureters	Transport urine from the kidneys to the urinary bladder
Urinary bladder	Stores urine; contracts to eliminate stored urine
Urethra	Transports urine from the bladder to the outside of the body

The kidneys are bean-shaped organs about the size of a person's fists; they are positioned on either side of the vertebrae in retroperitoneal space. Connective tissue called the **renal capsule** surrounds each kidney. The area immediately beneath the capsule is known as the **renal cortex**; it contains the functional units of the kidney, the **nephrons**. The **renal artery** supplies each kidney with blood. The **renal hilum** is the opening in the kidney through which the renal artery and nerves enter and the renal vein and ureter exit. The hilum opens medially into a cavity called the **renal sinus**. The central

portions of the renal sinuses enlarge to form the **renal pelvis**. Urine drains similarly to a funnel into the renal pelvis through tubes called **calyces**. The calyces drain urine into the ureters, which transport the urine using peristaltic actions to the bladder for storage. The muscular bladder serves as a reservoir for urine until it can be excreted.

As the volume of urine in the bladder increases, the urine exerts pressure on the two bladder sphincters (internal and external) and stretch receptors in the bladder. A pressure of 200 to 300 mL on the sphincters and receptors sends nerve impulses to the brain, triggering the urge to urinate (**FIGURE 7-2**). **Urination**, also called **micturition**, is a voluntary act. When urination is initiated, the bladder contracts, and the external sphincter relaxes, forcing urine out through the urethra. The urethra is approximately 1.5 inches long in women and 6–8 inches long in men. The shorter urethra in women, in combination with using a sitting position for urination, increases women's risk for developing **urinary tract infections (UTIs)**.

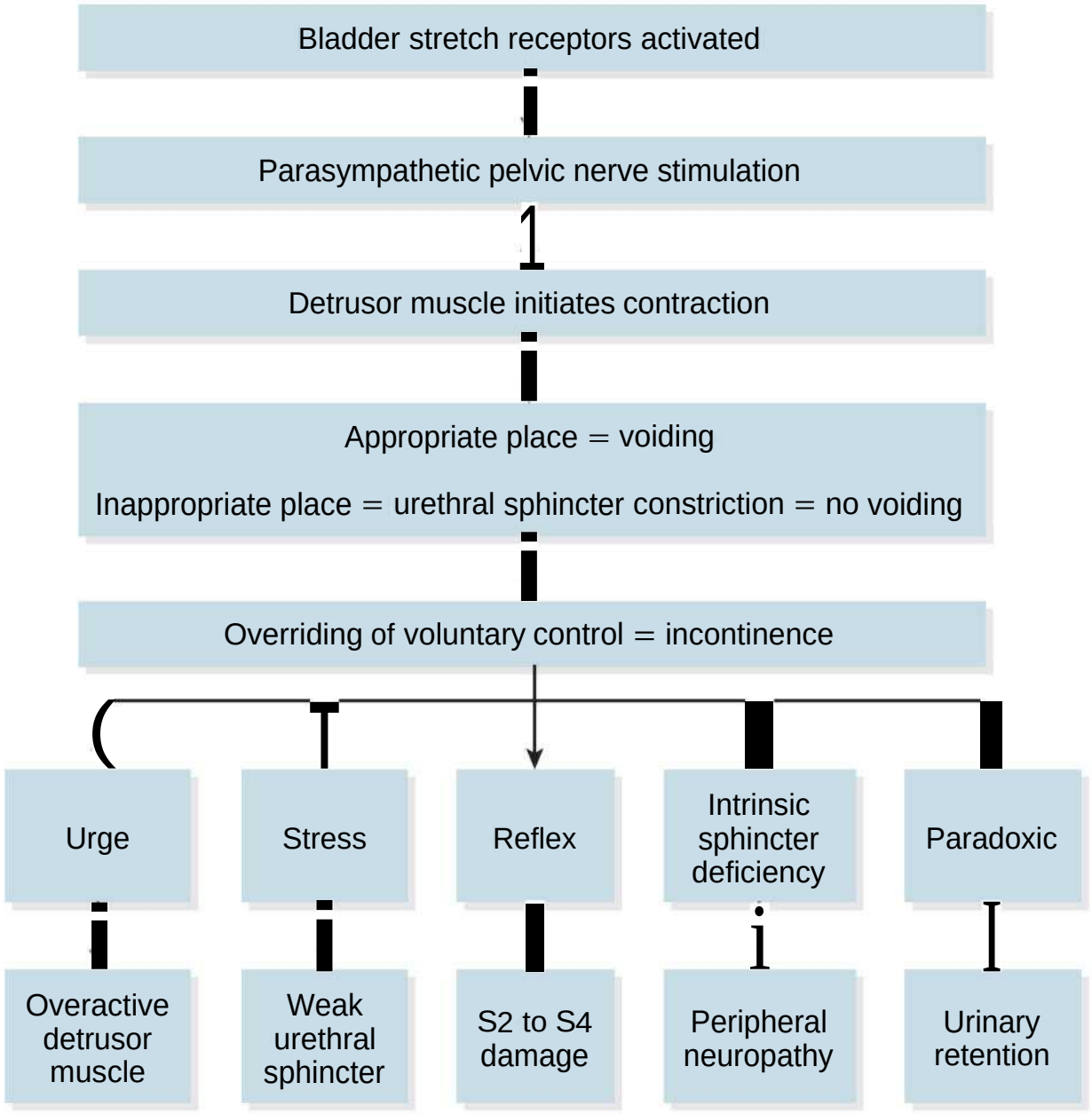


FIGURE 7-2 Urination.

Description

The kidneys are the primary site for carrying out the urinary system's functions. One kidney contains 1–2 million microscopic filtering units, or nephrons, to accomplish its functions (**FIGURE 7-3**). Each nephron is similar to a funnel with a long stem. Nephrons contain multiple sections (e.g., loop of Henle, proximal convoluted tubule, and distal convoluted tubule), and each of these sections is

responsible for excreting or reabsorbing specific substances (**TABLE 7-2**). The proximal convoluted tubule of the kidney enlarges into a double-membrane chamber called the **Bowman capsule**. The Bowman capsule surrounds a cluster of capillaries referred to as the **glomerulus**. Blood enters the glomerulus through an **afferent arteriole** and exits through an **efferent arteriole** (**FIGURE 7-4**). This blood supply to the glomerulus determines the amount of urine made and is necessary for healthy renal function. The speed at which blood moves through the glomerulus is termed the **glomerular filtration rate (GFR)**. GFR, which is the best measure of renal functioning, can be calculated using a formula that incorporates serum creatinine levels, age, gender, and ethnicity. Usually, GFR is approximately 125 mL/min, and urine output is approximately 1,500 mL/day. Urine output varies depending on age and weight, but minimum urine output for an individual consuming approximately 2,000 mL per day would be 800 mL per day.

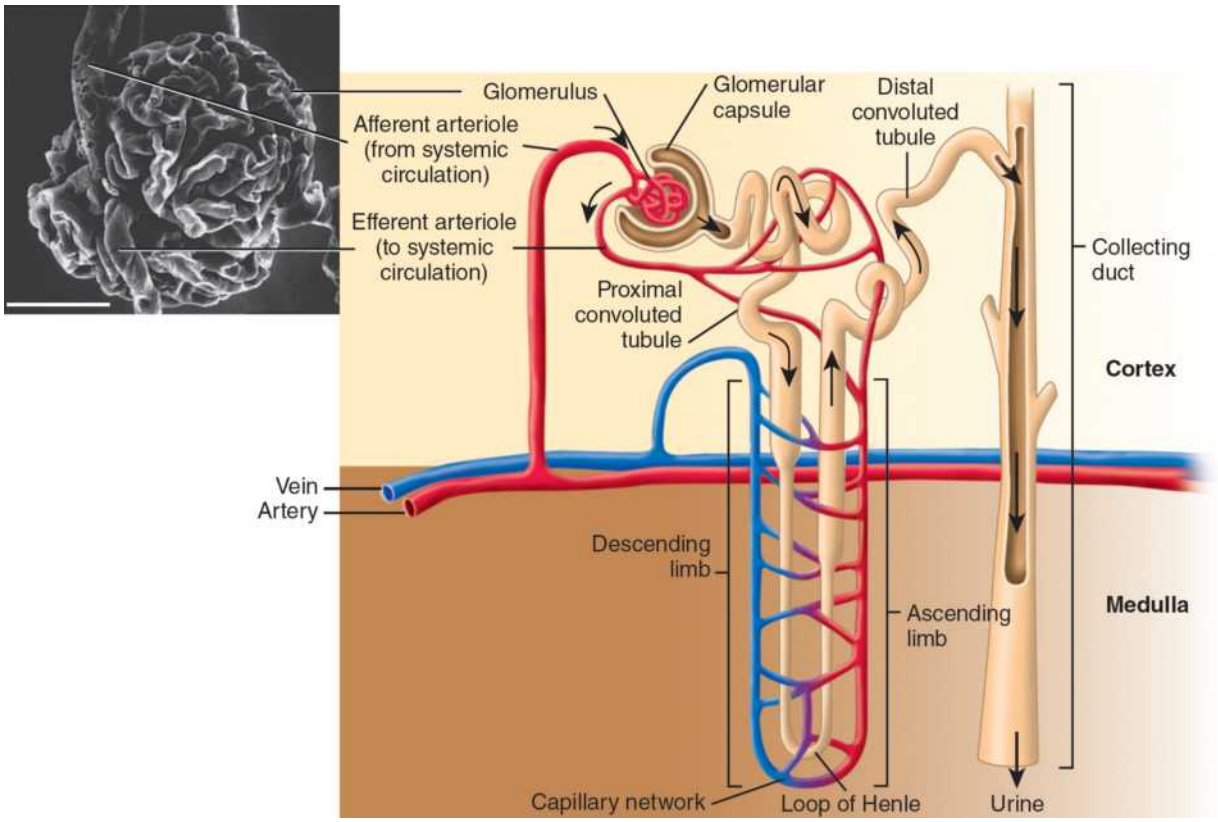
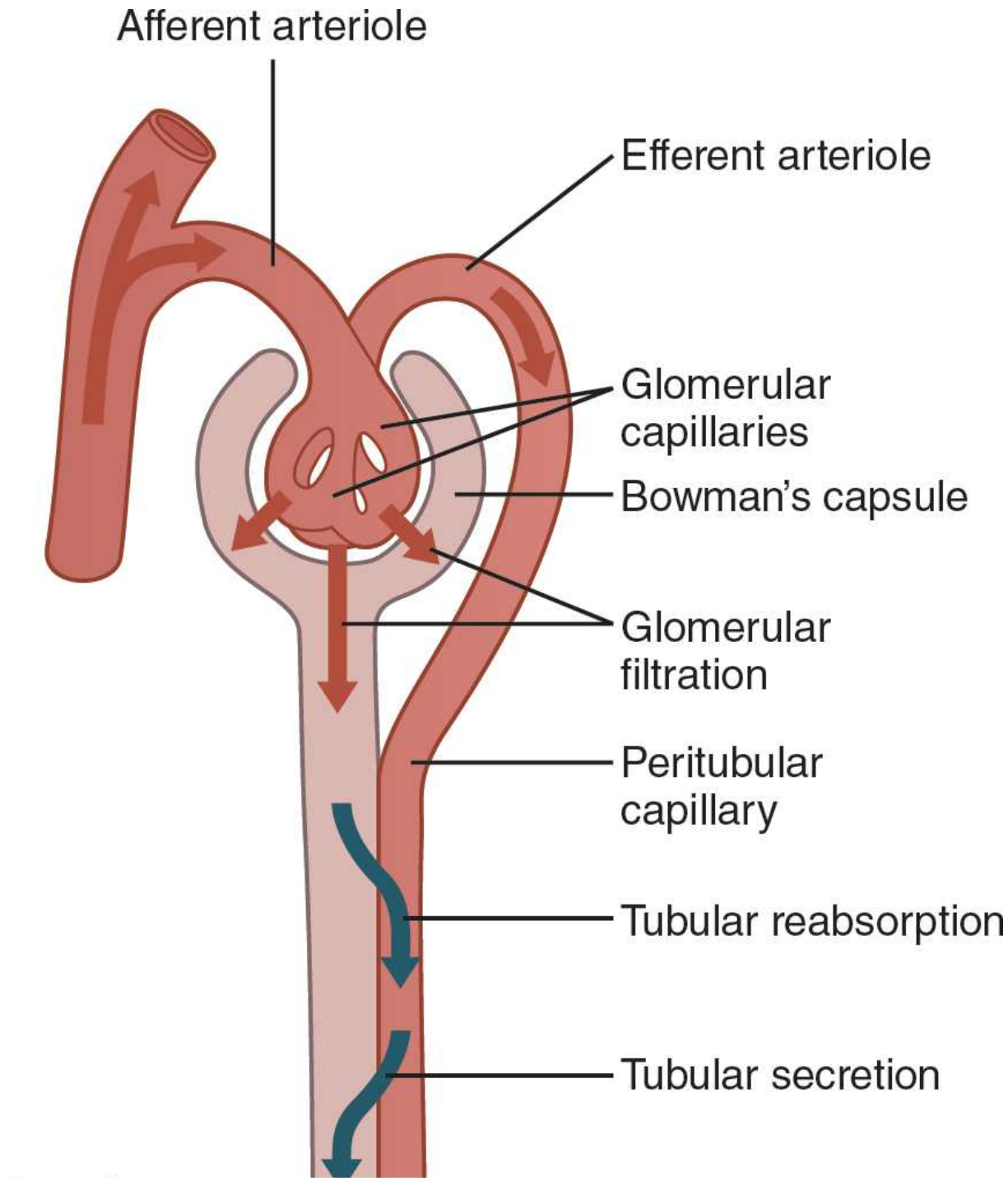


FIGURE 7-3 Nephrons of the kidney. Part of the nephron is located in the cortex, and part is located in the medulla. The electron micrograph to the left of the illustration is of a glomerulus from a human nephron.

Courtesy of Kenjiro Kimura, MD, PhD.

Description



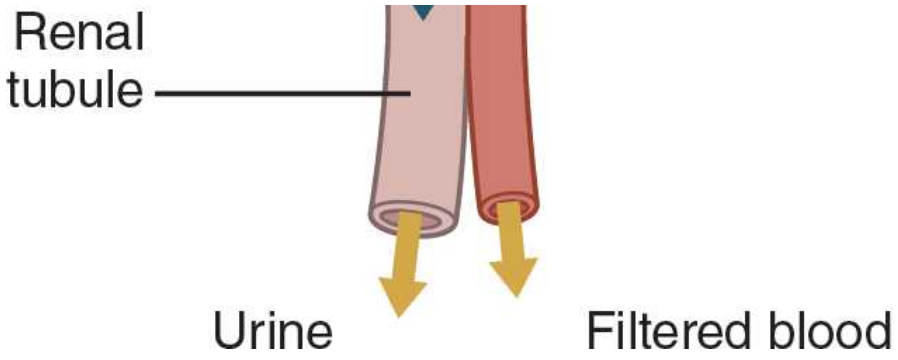


FIGURE 7-4 The glomerulus of the kidneys. The nephron carries out three processes: glomerular filtration, tubular reabsorption, and tubular secretion. All three processes contribute to the filtering of the blood.

Description

TABLE 7-2 Components of the Nephron and Their Functions

Component	Function
Glomerulus	Mechanically filters the blood
Bowman capsule	Mechanically filters the blood
Proximal convoluted tubule	Reabsorbs 75% of the water, sodium, calcium, potassium, phosphate, glucose, bicarbonate, urea, and amino acids Secretes ammonia (includes hydrogen) and creatinine
Loop of Henle (includes the thin descending limb, thin ascending limb, and thick ascending limb)	Participates in countercurrent exchange, which maintains the concentration gradient Reabsorbs water, sodium, potassium, and chloride Allows urine to be concentrated
Distal convoluted tubule	Secretes hydrogen, potassium, ammonia, and certain drugs Reabsorbs sodium and chloride Relatively impermeable to water, except in the presence of the antidiuretic hormone

Component	Function
Collecting ducts	Reabsorb hydrogen, sodium, and water Secrete potassium and hydrogen

The human body can excrete waste through the kidneys, skin, liver, and intestines, with the kidneys being the primary site for excretion. Urine is formed through glomerular filtration, tubular reabsorption, tubular secretion, and water conservation (**FIGURE 7-5**). The kidneys regulate the concentration of water and electrolytes by increasing or decreasing their excretion to maintain stability within the body (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter). Hormones, such as antidiuretic hormone and aldosterone, alter this rate of excretion (**FIGURE 7-6**). In part, this mechanism of water and electrolyte regulation aids in blood pressure management. Other renal mechanisms that contribute to blood pressure control include the **renin–angiotensin–aldosterone system** (see the *Cardiovascular Function* chapter).

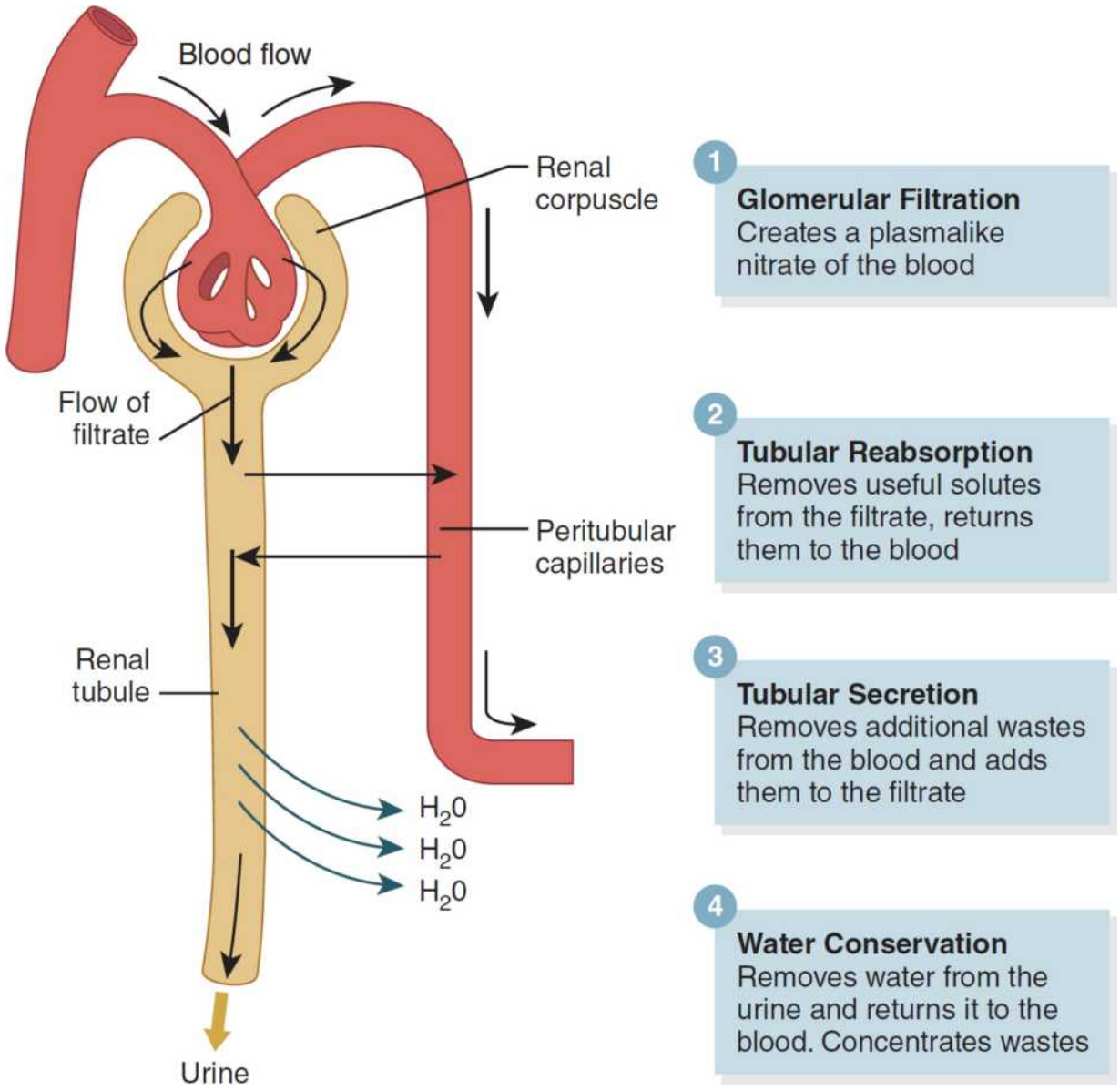
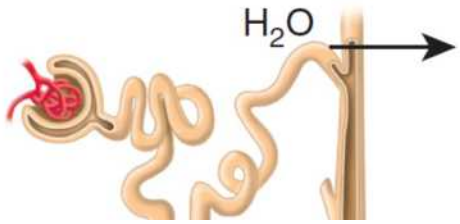
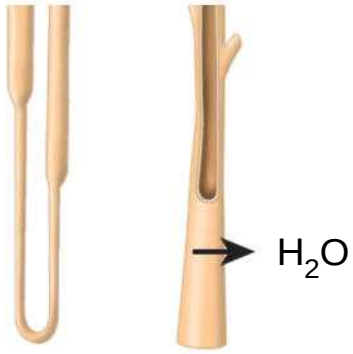
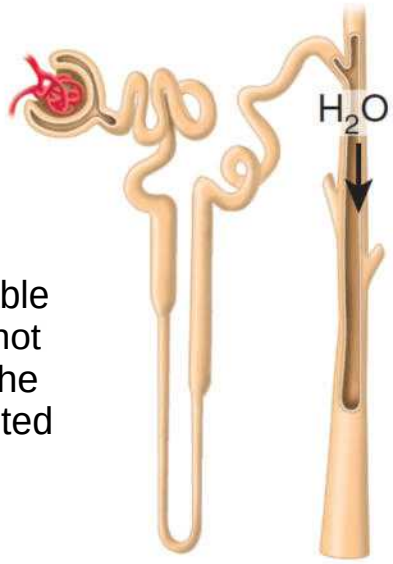


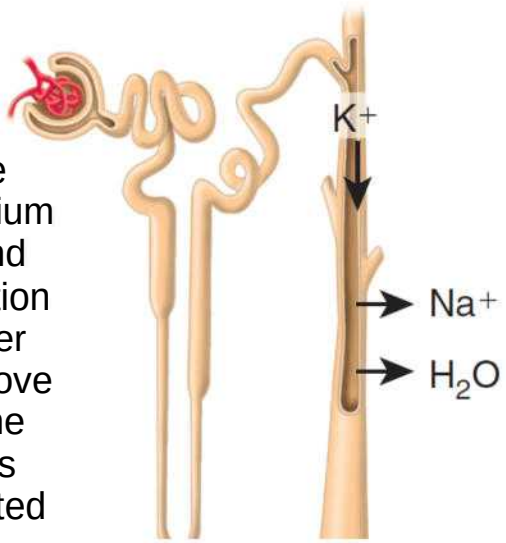
FIGURE 7-5 Formation of urine.

Description

ADH Level	Effect on Kidney
Increased	

IMUiectSfciU ADH levels	Collecting ducts and the distal convoluted tubules become permeable to water; water moves out of ducts and into blood	
Decreased ADH levels	Collecting ducts become impermeable to water; water is not reabsorbed from the filtrate and is excreted	

Aldosterone Level	Effect on Kidney
Increased aldosterone levels	Tubules increase reabsorption of sodium from the filtrate and decrease reabsorption of potassium; water and sodium thus move from filtrate into the blood, and excess potassium is excreted



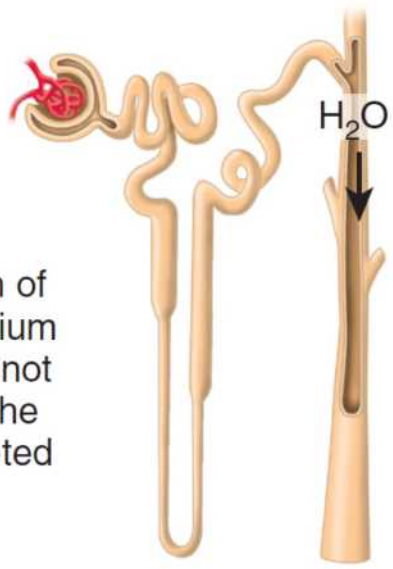
Decreased aldosterone levels	Tubular absorption of sodium and potassium is normal; water is not reabsorbed from the filtrate and is excreted 

FIGURE 7-6 Effects of antidiuretic hormone and aldosterone on the kidneys.

Description

Cells continuously produce waste products as they carry out their internal processes (**TABLE 7-3**). To maintain homeostasis, the body removes these waste products through urine formation. The three most significant metabolic wastes that the kidneys manage are **ammonia**, **urea**, and **uric acid**.

TABLE 7-3 Important Metabolic Wastes and Substances Excreted from the Body

Chemical	Source	Organ of Excretion
Ammonia	Deamination (removal of amine group) of amino acids in liver	Kidneys
Urea	Derived from ammonia	Kidneys and skin
Uric acid	Nucleotide breakdown in the liver	Kidneys

Chemical	Source	Organ of Excretion
Bile pigments	Hemoglobin breakdown in the liver	Liver (into small intestine)
Urochrome	Hemoglobin breakdown in the liver	Kidneys
Carbon dioxide	Breakdown of glucose in cells	Lungs
Water	Food and water; breakdown of glucose	Kidneys, skin, and lungs
Inorganic ions*	Food and water	Kidneys and sweat glands

*Ions are not a metabolic waste product like the other substances shown in this table. Nonetheless, ions are excreted to maintain constant levels in the body.

- Ammonia, a highly toxic chemical, results from the breakdown of amino acids in the liver. Amino acid breakdown generally occurs in the presence of an excess of protein or a deficit of carbohydrates in the diet; however, carbohydrate deficits are rare in industrialized countries except in persons on high-protein diets.
- When amino acids are broken down, the amino groups are stripped from the molecules in a process called **deamination**. These amino groups are then converted to ammonia, which is subsequently converted to urea in the liver. Liver disease can impair this process, leading to extremely high levels of ammonia in the body (see the *Gastrointestinal Function* chapter).
- Uric acid is another metabolic by-product produced by the liver. Uric acid results from the breakdown of nucleotides, the building blocks of deoxyribonucleic acid (DNA). Excess uric acid levels can lead to gout, which results in uric acid crystal deposits in the joints (see the *Musculoskeletal Function* chapter).

Along with these waste products, other substances normally found in urine include sodium, potassium, and small amounts of protein and

bacteria. Urine should be pale yellow and clear. Additional substances and changes in color or clarity can indicate renal pathology (TABLE 7-4). Multiple diagnostic tests can be performed to determine whether the kidneys are functioning properly.

TABLE 7-4 Renal Function Tests

Test	Related Physiology
Blood urea nitrogen (BUN)	The end product of protein metabolism is urea, which is excreted entirely by the kidneys. Thus, BUN is an indication of liver and kidney function.
Serum creatinine	Creatinine forms when creatinine phosphate is used in skeletal muscle contractions. Because it is entirely excreted by the kidneys, the serum creatinine level is an indication of renal function. The creatinine level is not affected by hepatic function, so it is a more precise indicator of renal function than is BUN. A 50% reduction in the glomerular filtration rate (GFR) doubles the creatinine level.
24-hour urine collection for creatinine clearance	Measures GFR and is dependent upon renal artery perfusion and glomerular filtration (GF).
Urinalysis	Cloudy, foul-smelling, white blood cells (WBCs) = urinary tract infection (UTI) Dark yellow = dehydration Acetone odor = diabetic ketoacidosis Protein = injured glomerular membrane Glucose = diabetes mellitus Ketones = fatty acid metabolism Crystals = possible renal stone formation Many hyaline casts = proteinuria Cellular casts = nephrotic syndrome
Intravenous pyelogram (IVP)	IV-administered, radiopaque dye allows the visualization of the kidneys, renal pelvis, ureters, and bladder.

Test	Related Physiology
Prostate-specific antigen (PSA)	PSA is a glycoprotein found in all prostate epithelial cells. An increase may be indicative of prostate enlargement, so this test is used to screen for prostate cancer and as an indicator of treatment success/failure.

The kidneys are also responsible for converting vitamin D into its active form. The inactive form of vitamin D is produced by the action of ultraviolet rays on cholesterol in the skin; it may also be ingested. The active form of vitamin D created by conversion aids in calcium and phosphorus absorption. People with renal disease will have issues converting vitamin D into its active form.

Additionally, the kidneys regulate pH by secreting bicarbonate and excreting hydrogen (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter). They synthesize several hormones, including atrial natriuretic peptide (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter), **erythropoietin**, and renin (see the *Cardiovascular Function* chapter). The kidneys release erythropoietin in a response to hypoxia (e.g., anemia or cardiac or pulmonary disease); erythropoietin stimulates the bone marrow to produce more red blood cells. If iron stores are adequate, an increase in red blood cells increases the body's overall oxygen-carrying capacity, thereby decreasing hypoxia.

With aging, the kidneys begin functioning less efficiently. This decreased functioning can be further exacerbated by the presence of chronic conditions (e.g., diabetes mellitus, hypertension, and arteriosclerosis). These changes result in decreased renal perfusion, fewer nephrons, and renal tissue atrophy—a condition referred to as "nephrosclerosis" (**FIGURE 7-7**). Consequently, the aging individual may experience less filtration capability, leading to waste accumulation and loss of homeostatic regulation (e.g., fluid, electrolyte, and pH balance). Additionally, renal-related complications are common with these aging changes because of impaired erythropoietin formation (e.g., anemia), renin–angiotensin system dysregulation (e.g., hypertension), and loss of vitamin D metabolism

(e.g., osteoporosis). Aging persons may require alternative medication dosing (usually a smaller dose or doses spaced further apart) to prevent drug toxicity because of this impaired filtration.

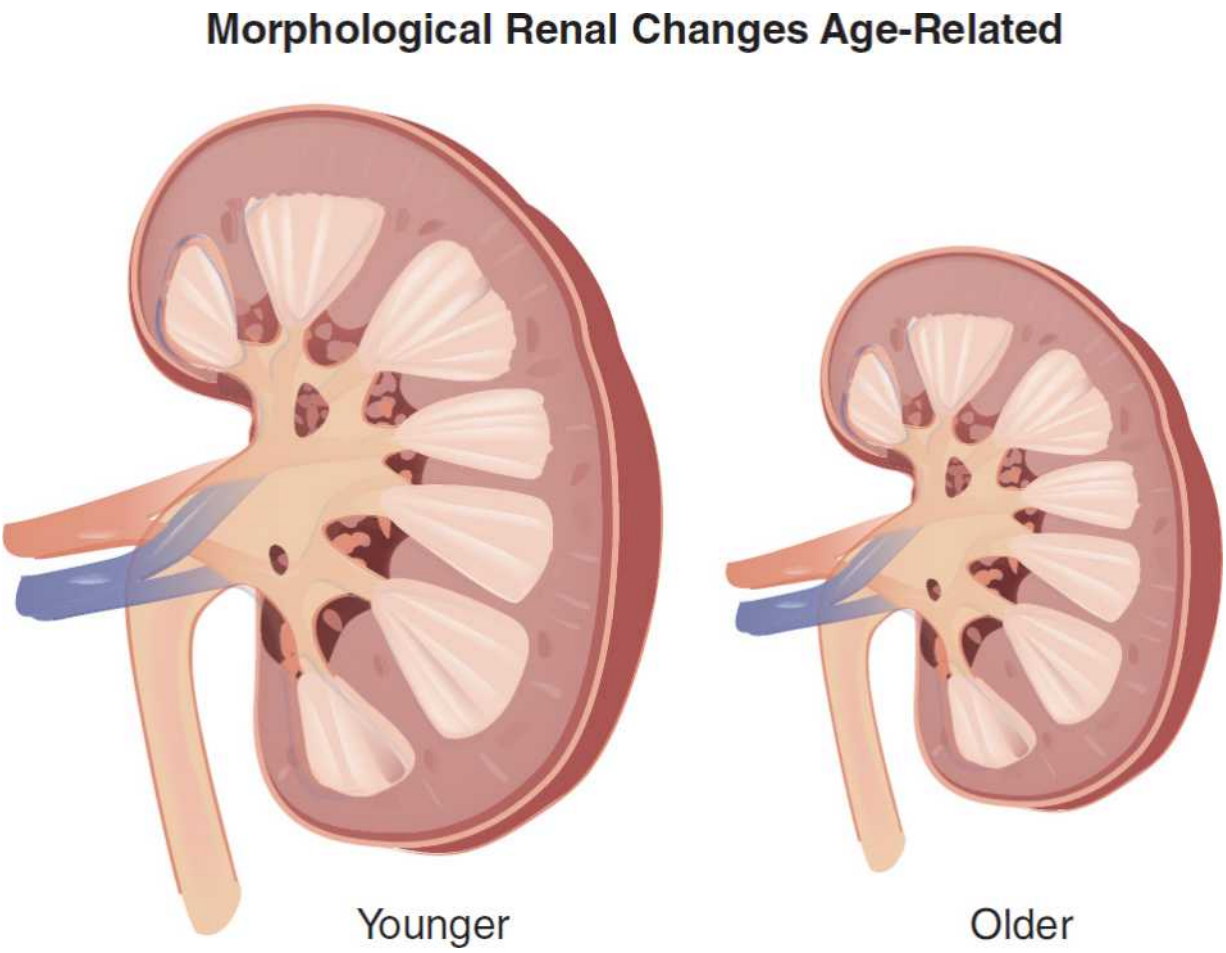


FIGURE 7-7 Age-related changes in the kidneys.

The bladder also undergoes changes with aging. It becomes less elastic, decreasing storage capacity. Bladder muscles weaken and the bladder sphincter loses tone, impairing urine control. Because of impaired bladder control and a decreased ability to concentrate urine, nocturia may increase (Ciarambino, Paolo, & Giordano, 2017; Filippo et al., 2019; O'Sullivan, Hughes, & Ferenbach, 2017).

UNDERSTANDING CONDITIONS THAT AFFECT THE URINARY SYSTEM

When considering alterations in the urinary system, it is wise to organize them based on their basic underlying pathophysiology to increase understanding—that is, whether they alter urinary elimination or impair renal function. Conditions that alter urination may include structural barriers (e.g., **nephrolithiasis**, congenital disorders, and tumors) or problems with the act of urination (e.g., incontinence). These conditions require interventions to promote urination (e.g., catheterization, bladder training, or surgery). Conditions that impair renal function include disorders that prevent the kidneys from regulating fluid and electrolytes as well as excreting waste products and other substances. These conditions require interventions to maintain homeostasis (e.g., dialysis).

Conditions Resulting in Altered Urinary Elimination

The act of urination requires (1) a functioning bladder with stretch receptors that can sense the filling of the bladder with urine, (2) an intact parasympathetic pelvic nerve to transmit the signal, and (3) working detrusor muscles to initiate bladder contractions to expel the urine (see Figure 7-2). The sympathetic nerve innervations of the detrusor muscle and internal sphincter prevent inappropriate stimulation of urination. Upper motor impulses can delay voiding by tightening the urethral sphincter. Although urination is mostly a voluntary act, voiding can be delayed only to a certain point. If the urge to void is ignored too long, bladder contractions take over the neural delaying mechanism and involuntary urination occurs.

Incontinence

Urination is a reflex in very young children, but it is controlled consciously in older children and adults. In children up to 3 years of

age, urination is completely reflexive; once the bladder expands, it empties. As children grow older, they learn to control urination. In older children and adults, the external sphincter is under conscious control—it will not relax until deliberately allowed to do so.

Older children and adults sometimes lose control over urination, resulting in a condition referred to as **urinary incontinence** (Figure 7-2). The Urology Care Foundation (2022b) estimates that one-fourth to one-third of all men and women in the United States experience urinary incontinence. Urinary incontinence is not just a medical issue; it can affect emotional, psychological, and social health.

Enuresis is the involuntary urination by a child after 4–5 years of age, when bladder control is expected. Most children have **nocturnal enuresis**, or bed-wetting, only. Nocturnal enuresis is common, affecting more than 5 million children in the United States (Urology Care Foundation, 2022a). It is slightly more frequent in boys than girls. Primary nocturnal enuresis occurs when a child has never achieved bladder control at night since potty training but typically does not have any incontinence during the day. Secondary nocturnal enuresis describes when a child has achieved nighttime bladder control for at least 6 months but has started experiencing bed-wetting. This type is usually related to a stressful event (e.g., birth of a sibling, parent divorce, development of an illness, death of a caregiver). Nocturnal enuresis can be genetic, with half of all affected individuals having a parent who also had this issue; this percentage increases to 75% when both parents experienced enuresis. Enuresis can have psychological (e.g., anxiety) and structural (e.g., smaller-than-normal bladder) origins. Additionally, the kidneys may make too much urine at night (e.g., due to type 1 diabetes mellitus, deficient antidiuretic hormone, or consuming caffeinated or carbonated beverages before bedtime). Sleep disorders, such as sleep apnea, can cause hypoxia that results in increased atrial natriuretic peptide (ANP) production by the heart; ANP causes the kidneys to increase nocturnal urine production. Constipation can cause stool to be stored in the rectum, which puts pressure on the bladder. Multiple strategies and treatments are available (e.g., motivation, support, alarm

systems, and medications to concentrate urine at night), but usually the condition resolves in time with or without treatment.

Stress incontinence describes the loss of urine from intra-abdominal pressure (stress) exerted on the bladder by coughing, sneezing, laughing, exercising, or lifting something heavy (**FIGURE 7-8**). This condition occurs when the sphincter muscle of the bladder or the pelvic floor muscles are weakened. Stress incontinence is more common in women than in men. In women, physical changes resulting from pregnancy, childbirth, and menopause can weaken the sphincter muscle. Additionally, women may develop a cystocele (bulging of the bladder through the vaginal wall; see the *Reproductive Function* chapter) because of these physical changes, which can also increase their risk for stress incontinence. In men, prostate removal can lead to this type of incontinence. Additional factors contributing to stress incontinence in both genders include obesity and chronic coughing. Obesity increases pressure on the bladder and surrounding muscles, weakening them. Chronic coughing (e.g., that caused by smoking and lung disease) can also increase stress on the urinary sphincter.

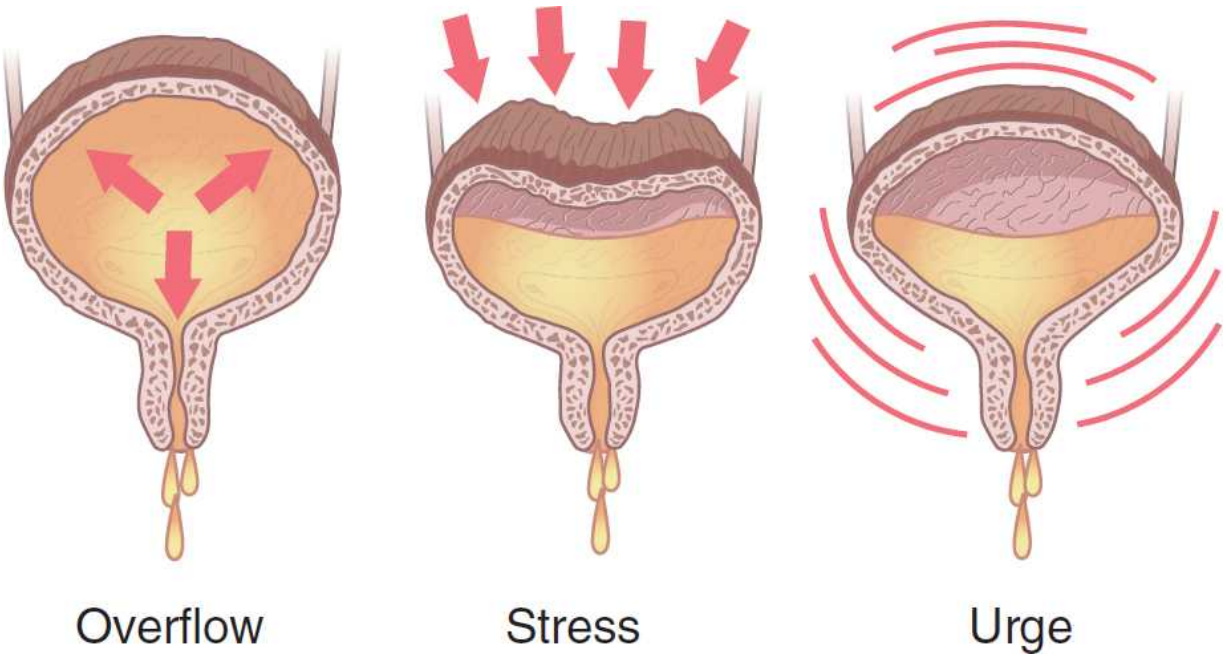


FIGURE 7-8 Types of incontinence.

Description

Overactive bladder, previously called **urge incontinence**, is a sudden, intense urge to urinate, followed by an involuntary loss of urine. The detrusor muscle in the bladder contracts and may give the individual only a few seconds' to a minute's warning before voiding. With an overactive bladder, the need to urinate is felt often, including throughout the night. Overactive bladder is more common in men than in women. It is more frequent in men with prostate issues and women after menopause. UTIs, bladder irritants, bowel conditions, smoking, Parkinson's disease, Alzheimer's disease, stroke, injury, and nervous system damage (e.g., that associated with multiple sclerosis) may all cause overactive bladder.

Reflex incontinence refers to urinary incontinence caused by trauma or damage to the nervous system (e.g., that caused by spinal cord injury above the second to fourth sacral vertebrae, multiple sclerosis, and diabetes mellitus). **Detrusor hyperreflexia** is increased detrusor muscle contractility that occurs even though there is no sensation to void. With reflex incontinence, urgency is generally absent.

Overflow incontinence is the result of an inability to empty the bladder, called **retention**. Other indications of overflow incontinence include dribbling urine and a weak urine stream. This type of incontinence may occur due to bladder damage, urethral blockage, nerve damage (e.g., that caused by diabetes mellitus), and prostate conditions. It is more common in men than in women. **Chronic overdistention**, also called "nurse's bladder" and "teacher's bladder," occurs because of a perceived inability to interrupt work to void. This chronic avoidance of emptying the bladder results in detrusor muscle areflexia and overflow incontinence.

Mixed incontinence occurs when the patient experiences symptoms of more than one type of urinary incontinence.

Functional incontinence occurs in many older adults, especially residents of nursing homes. In such a case, a physical or mental impairment prevents toileting in time. For example, a person with severe arthritis may not be able to undress quickly enough to prevent incontinence.

Gross total incontinence refers to a continuous leaking of urine, day and night, or the periodic uncontrollable leaking of large volumes of urine. In these cases, the bladder has no storage capacity. This type of incontinence can occur because of anatomic defects, spinal cord or urinary system injuries, or a fistula (abnormal opening) between the bladder and an adjacent structure, such as the vagina.

Transient incontinence refers to urinary incontinence resulting from a temporary condition. Such conditions may include delirium, infection, atrophic vaginitis, use of certain medications (e.g., diuretics and sedatives), psychological factors (e.g., depression and anxiety), high urine output (e.g., overhydration), restricted mobility, fecal impaction, alcohol, and caffeine. Transient incontinence usually resolves once the underlying condition resolves.

Learning Points

DRIPS is an easy acronym to remember the causes of acute urinary incontinence.

D = Delirium, dehydration, diapers
R = Retention, restricted mobility
I = Impaction, infection, inflammation
P = Pharmaceuticals (opiates and calcium antagonists cause urinary retention and constipation; anticholinergics cause retention; alpha-adrenergic antagonists cause reduced urethral resistance in women; diuretics increase urine production), psychological problems (e.g., depression, neurosis, or anxiety)
S = Stool impaction (constipation)

Sources: Resnick & Yalla, 1998, p. 1045.

Generally, risk factors for developing urinary incontinence include the following conditions:

- *Being female.* Women are more likely than men are to have stress incontinence. Pelvic floor muscles and decreases in vaginal connective tissue can occur with pregnancy, childbirth, and menopause. However, men with prostate conditions are at increased risk for overactive bladder and overflow incontinence.

- *Advancing age.* The muscles of the bladder and urethra lose some of their strength with age. Changes with age may also reduce bladder capacity and increase the risk of involuntary urination. However, incontinence is not inevitable with age, and incontinence is not normal at any age, except during infancy.
- *Being overweight.* Being obese or overweight increases the pressure on the bladder and surrounding muscles, weakening them and allowing urine to leak out under stress (e.g., stress caused by coughing or sneezing).
- *Smoking.* Chronic coughing associated with smoking can cause episodes of incontinence or aggravate incontinence that has other causes. Constant coughing puts stress on the urinary sphincter, leading to stress incontinence. Smokers are also at risk of developing overactive bladder.
- *Other diseases.* Renal disease or diabetes mellitus may increase the risk for incontinence because of changes in renal function and nerve innervations.

Urinary incontinence can lead to complications ranging from minor to severe in nature. Skin problems (e.g., rashes, skin infections, and ulcers) can result from the presence of constant moisture. Recurrent UTIs can develop from incomplete emptying of the bladder. Additionally, urinary incontinence can negatively affect psychological health (e.g., causing poor self-image, embarrassment, sexual dysfunction, anxiety, and depression), and changes can occur in the individual's usual activities (e.g., work and exercise).

Diagnostic procedures for urinary incontinence include a history, physical examination, bladder diary, urinalysis, urine cultures, cystourethrogram (X-ray of the bladder and urethra), cystoscopy (visualization of the bladder with a small, lighted instrument), pelvic ultrasound, postvoid residual measurement, bladder stress testing, and urodynamic testing (which measures pressures in the bladder). Other tests may be necessary to identify the underlying cause (e.g., prostate-specific antigen, renal panel, or neurologic imaging).

Treatment for urinary incontinence depends on the type, underlying cause, and severity. Treatment and management strategies range from conservative to aggressive and include:

- Bladder training
- Scheduled toileting
- Fluid and diet management (e.g., avoiding alcohol, caffeine, or acidic foods; reducing liquid consumption; losing weight; or increasing physical activity)
- Pelvic floor muscle exercises (e.g., Kegel exercises)
- Electric stimulation (electrodes are temporarily inserted into the rectum or vagina to strengthen pelvic floor muscles through gentle electric stimulation)
- Medications (e.g., anticholinergics or estrogen replacement)
- Urethral inserts (small, tampon-like disposable devices or plugs inserted into the urethra)
- Pessary (a stiff ring inserted into the vagina to hold up the bladder)
- Radiofrequency therapy (a nonsurgical procedure that uses radiofrequency energy to heat tissue in the lower urinary tract, causing it to become firmer)
- Botulinum toxin type A (Botox) injections into the bladder muscle
- Bulking material injections (e.g., collagen, carbon-coated zirconium beads, Coaptite) into tissue surrounding the urethra
- Sacral nerve stimulator (an implanted device that emits painless electrical impulses that stimulate the sacral nerve)
- Artificial urinary sphincter (a fluid-filled ring implanted around the neck of the bladder that is controlled by a manual subcutaneous valve)
- Sling procedures (a surgically constructed pelvic sling or hammock around the bladder neck and urethra created by using strips of tissue, synthetic material, or mesh)
- Bladder neck suspension (a surgical procedure to raise and support the bladder in a more normal anatomic position)

- Absorbent pads and protective garments
- Urinary catheter (usually as an intermittent self-catheterization)
- Increased perineal hygiene
- Skin barrier creams
- Safety measures (e.g., removal of any rugs or furniture from the path to the restroom, adequate lighting, widening the bathroom doorway, and installation of an elevated toilet seat)
- Acupuncture
- Hypnotherapy
- Herbal remedies (e.g., *Crataeva nurvala*, horsetail [*Equisetum*], aloe vera extract)
- Coping strategies and support

Neurogenic Bladder

Neurogenic bladder refers to all bladder dysfunction caused by an interruption of normal bladder nerve innervation. This interruption causes the bladder to be either flaccid (hypotonic) or spastic. Many factors can disrupt bladder nerve innervations, including the following conditions:

- Brain or spinal cord injury
- Nervous system tumors
- Brain or spinal cord infections
- Dementia
- Parkinson's disease
- Spina bifida
- Diabetes mellitus
- Stroke
- Medications (e.g., antidepressants, antihistamines, analgesics, antihypertensives, and antiemetics)
- Vaginal childbirth
- Multiple sclerosis

- Chronic alcoholism
- Systemic lupus erythematosus
- Heavy metal poisoning
- Herpes zoster

Urine volume is large, bladder pressure is low, and contractions are absent with flaccid neurogenic bladder. With spastic bladder, urine volume is usually normal or low, and involuntary contractions occur. Some patients may experience both conditions. Clinical manifestations of neurogenic bladder include symptoms of an overactive bladder (e.g., frequency and urgency) and an underactive bladder (e.g., hesitancy and retention). Common complications of neurogenic bladder include UTIs, renal calculi, incontinence, **hydronephrosis**, and autonomic dysreflexia.

Diagnostic procedures for neurogenic bladder consist of a history, physical examination, bladder diary, urinalysis, urine cultures, cystourethrogram, cystoscopy, pelvic ultrasound, postvoid residual measurement, and urodynamic testing. Additional procedures (e.g., computed tomography [CT], magnetic resonance imaging [MRI]) may be performed to determine the underlying cause. Treatment strategies depend on the etiology and include those therapies previously discussed for incontinence.

Interstitial Cystitis/Bladder Pain Syndrome

Interstitial **cystitis** (IC)/bladder pain syndrome (BPS) is a chronic bladder condition in which noninfectious inflammation causes pain and pressure in the suprapubic, pelvic, and abdominal area. Additional subtypes may exist, but two subtypes of IC/BPS are currently recognized—nonulcerative and ulcerative. The nonulcerative form, which accounts for 90% of cases, presents with pinpoint hemorrhages (i.e., glomerulations) in the bladder wall due to inflammation. The ulcerative form, which accounts for 5% to 10% of cases, usually presents with Hunner's ulcers or patches—that is, red, bleeding areas on the bladder wall (**FIGURE 7-9**). Approximately 5% of patients with IC/BPS will experience symptoms that persist for

more than 2 years, and 5% will develop end-stage disease in which the bladder hardens, the bladder's capacity is low, and the pain worsens.

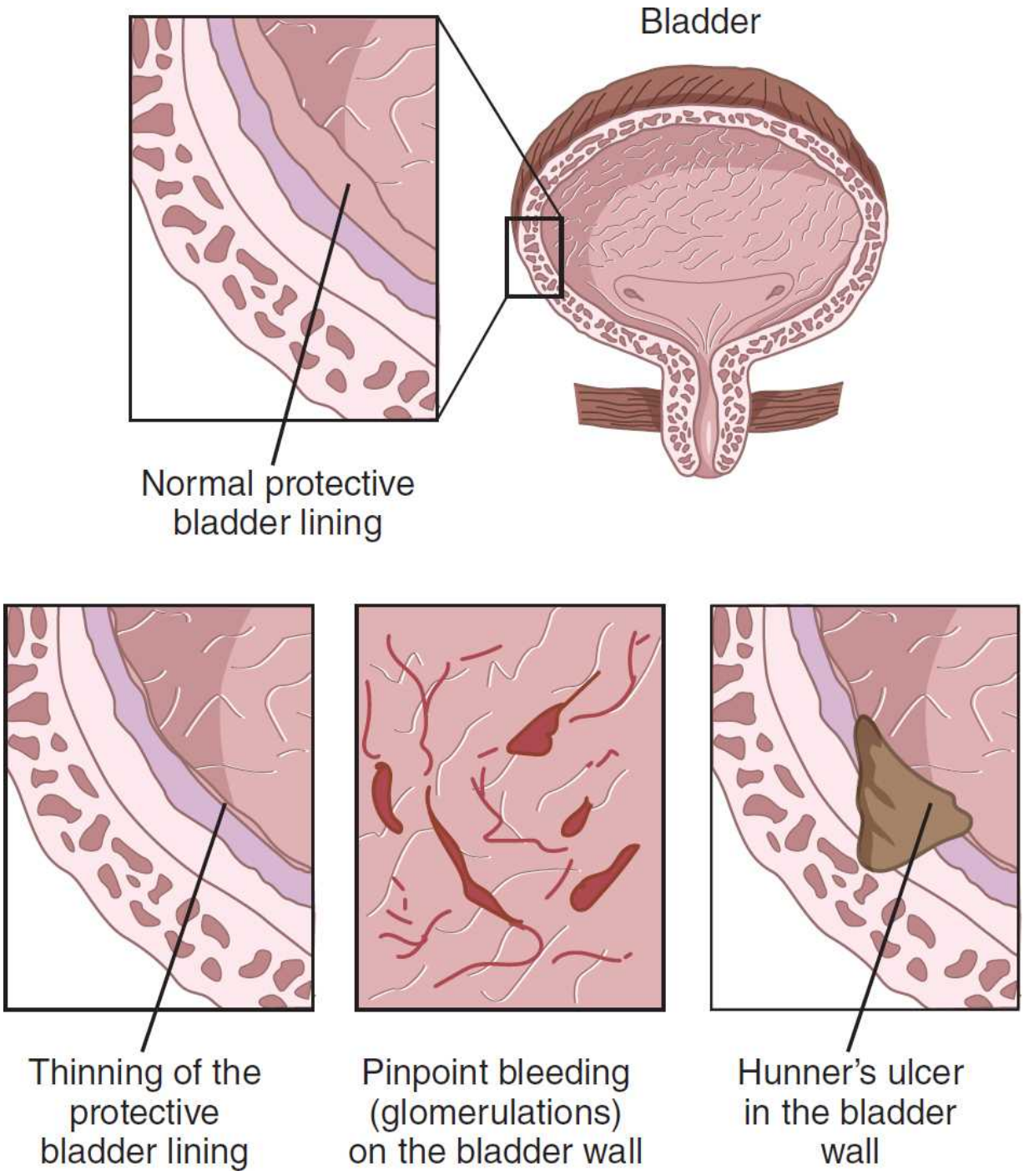


FIGURE 7-9 Interstitial cystitis.

Description

IC/BPS is more common in women than in men, and risk increases with age. Its exact cause is unknown. A bladder tissue defect may allow irritating substances in the urine to penetrate the bladder, or it may be a result of an autoimmune reaction. Other risk factors include smoking, family history of IC/BPS, and history of UTIs.

Clinical manifestations vary for each person, but the most common symptom is pain that often worsens with pressure (e.g., when the bladder is full). In addition to the bladder, pain may be experienced in the urethra, lower back, and scrotum. This pain may be intermittent or constant. Urinary frequency may be the first symptom, and nocturia may also be seen. Urgency will result as the frequency becomes more severe. This urgency can be constant, even after voiding. Stress—either physical or psychological—may worsen the urgency. In women, manifestations are worse during ovulation and menstruation, and pain can be experienced during sexual intercourse. Both men and women may experience sexual dysfunction. In men, pain is experienced during ejaculation. Urinary incontinence is uncommon. IC/BPS can be distressful, impacting the individual's social life, exercise, sleep, and work.

Diagnosis of IC/BPS includes a history, physical examination, voiding tests, urodynamic testing, and cystoscopy. Additional tests may be necessary to rule out other urinary issues.

A cure is rare, but most individuals will improve with treatment. Treatment should be individualized based on symptoms. Achieving symptom relief may require trial and error; however, most patients eventually experience significant relief. Treatment includes limiting stress, physical therapy to strengthen pelvic muscles, limiting certain foods (e.g., citrus fruits, tomatoes, chocolate, coffee, alcohol, caffeinated drinks, spicy foods, and carbonated drinks), bladder training, pentosan polysulfate (Elmiro), dimethyl sulfoxide (DMSO), hydroxyzine (Vistaril), amitriptyline (Elavil), heparin, neuromodulation therapy, bladder ulcer cauterization, intradetrusor botulinum toxin, and cyclosporine. Other procedures may include bladder hydrodistention, cystoscopic resection of a Hunner's ulcer, and sacral nerve root stimulation. Surgery (e.g., partial cystectomy, bladder augmentation,

neobladder, and urinary diversion) is generally performed as a last result because the outcome is unpredictable.

Congenital Disorders

Abnormalities of the urinary and reproductive systems are the most common congenital defects (also see the *Reproductive Function* chapter). Because of these systems' close proximity and interconnected structures, an abnormality in one system will often lead to an abnormality in the other. Numerous congenital disorders of the urinary system are possible, most of which are structural problems. Some defects cause no symptoms (e.g., both ureters draining one kidney and abnormal kidney positioning), whereas others are life threatening (e.g., renal agenesis [failure of an organ to develop in utero]). Problems with kidney development can be the most severe. The kidneys begin to develop in approximately the fifth week of gestation.

Urine formation begins at 9 to 12 weeks' gestation. Urine is the main component of amniotic fluid, which is vital for normal fetal development. Early in the pregnancy, amniotic fluid mostly consists of water, but it also contains nutrients, hormones, and antibodies. After about 20 weeks' gestation, the fluid portion is mostly made up of fetal urine.

Urinary Tract Infections

Urinary tract infections (UTIs) include any infections that begin in the urinary tract. The lower urinary tract is the most frequent site of these infections. UTIs can be more specifically classified based on location. Urethritis refers to infections in the urethra, cystitis refers to infections in the bladder, and **pyelonephritis** refers to infections in the kidneys. UTIs are extremely common, causing more than 8.1 million healthcare visits each year (Urology Care Foundation, 2022c). These infections maybe acute, recurrent, or chronic.

UTIs are caused by a direct invasion of the urinary tract by bacteria (**FIGURE 7-10**). The urinary tract is typically sterile and resistant to bacterial colonization despite frequent contamination from the large number of bacteria that grow in the vagina, rectum, and skin. Urine is

an excellent medium for microorganism growth because of its protein content. The body quickly removes most bacteria that enter the urinary tract before they cause symptoms. Notably, the urinary system includes several mechanisms to prevent infection: one-way valves (i.e., vesicoureteral valves) where the ureters attach to the bladder; urination, which washes microbes out of the body; urine acidity, which decreases bacterial growth; prostate secretions, which slow bacterial growth in men; and the general functions of the immune system. Occasionally, however, the bacteria resist the body's defenses and cause infection.

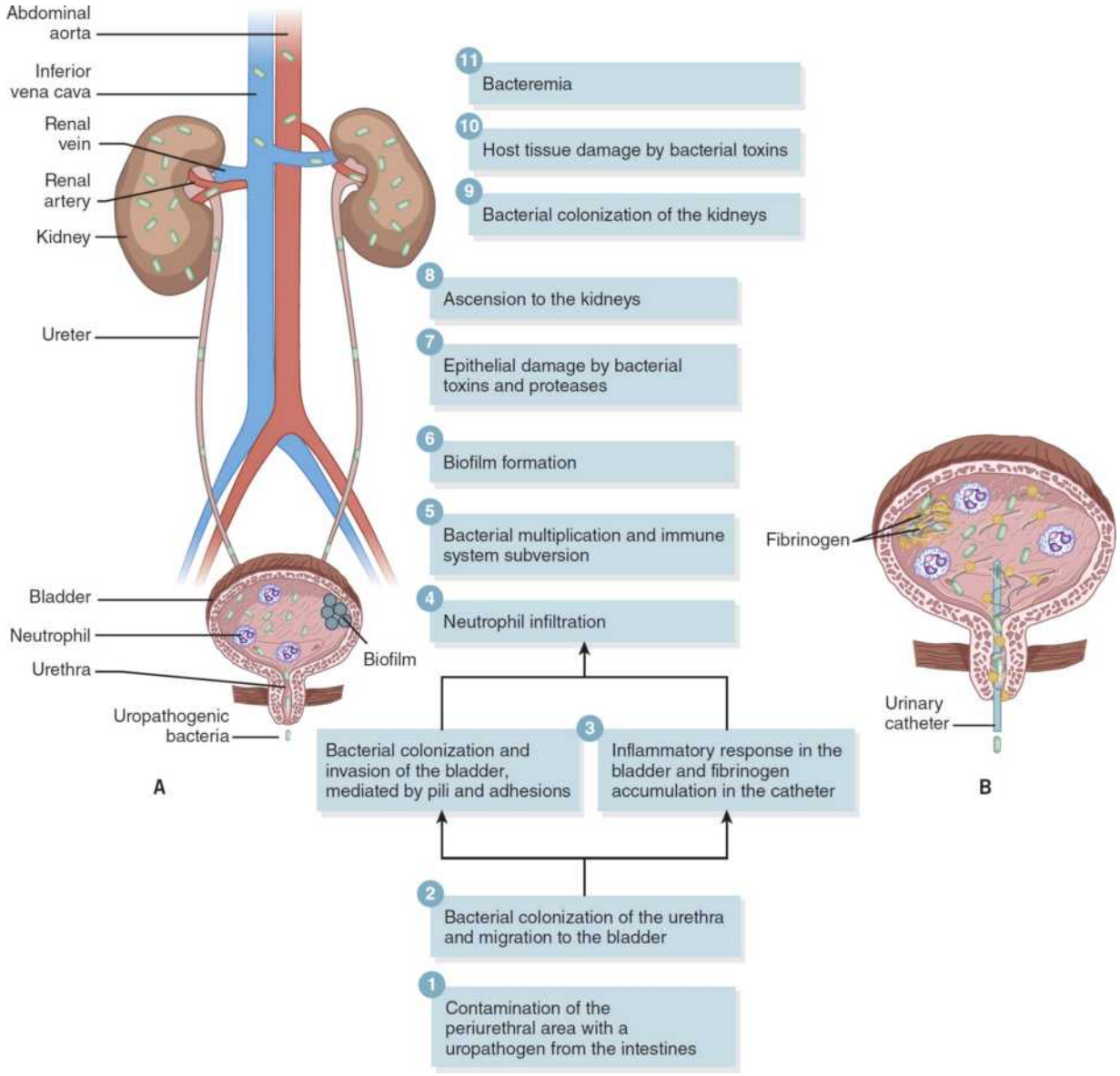


FIGURE 7-10 Pathogenesis of urinary tract infections (UTI). **(A)** Uncomplicated UTIs begin when uropathogens that reside in the intestines can colonize the urethra. **(B)** Iatrogenic UTI as a result of urinary catheterization.

Description

One way these bacteria resist the body's defenses is by collecting together and forming biofilms. Once formed, the biofilm can adhere to and invade nearby structures, causing persistent infection.

Due to the high concentration of bacteria, most infections invade the urethra from the meatus in the perineal area. The microorganisms can then ascend through the urethra to the bladder and subsequently move along the ureters to the kidneys. Occasionally, microorganisms may invade the kidneys from the blood.

Severe or untreated UTIs can lead to bacteremia or sepsis. With pyelonephritis, the kidneys become grossly edematous, and structures fill with exudate, compressing the renal artery. Abscesses and necrosis can develop in the kidneys, impairing renal function and causing permanent damage (e.g., chronic kidney disease).

Escherichia coli, a gram-negative aerobic bacterium that is a normal part of the intestinal flora, accounts for 75% to 95% of UTIs. Virulent forms of *E. coli* can avoid being washed away during urination by attaching to the mucosa along the urinary tract. This bacterium can gain access to the urinary tract due to the anus's close proximity to the urinary meatus, especially in women. In addition to this close proximity, women are more vulnerable to developing UTIs for the following reasons:

- Women have shorter urethras (so the microorganisms have a shorter distance to travel).
- Women usually urinate in a sitting position (which prevents full emptying of the bladder).
- Women may experience increased perineal tissue irritation from sexual activity, tampons, bubble baths, bathing suits, tight-fitting pants, and deodorants, as well as nylon, lace, and thong underwear.

- Women who are pregnant may experience urinary retention due to the pressure that the growing uterus puts on the bladder.
- Women who are postmenopausal experience changes in vaginal tissue and normal flora (which increases the risk for bacterial growth).
- Women are more likely to experience vesicoureteral reflux with activities that increase intra-abdominal pressure (e.g., bearing down, coughing, and sneezing).
- Women who use diaphragms, condoms with spermicidal foam, or unlubricated condoms can experience tissue irritation and increased risk for contamination.

Although men are less likely than women to experience a UTI, they are likely to have a recurrent UTI because the bacteria can hide deep inside prostate tissue. Additionally, UTIs in men can result from unprotected anal intercourse or when the penis is uncircumcised. Benign prostatic hypertrophy can increase risk because of urinary retention. Other risk factors for developing UTIs include the following:

- Congenital urinary tract abnormalities (can alter urinary flow, causing issues such as vesicoureteral reflux)
- Immobility (prevents complete bladder emptying, leading to urinary stasis)
- Urinary or bowel incontinence (can increase the potential for contamination of the urinary meatus)
- Renal calculi or tumors (obstruct urine output, leading to urinary stasis)
- Decreased cognition (increases the risk for incontinence and toileting issues)
- Impaired immune response (e.g., diabetes mellitus)
- Impaired nerve innervations (e.g., spinal cord injuries)
- Urinary catheterization (provides a direct pathway to the urinary system; the most common source of nosocomial infections)

- Invasive procedures (e.g., cystoscopy and stents) or surgery involving the urinary tract
- Antibiotic use (can disrupt normal flora and encourage the development of resistant bacterial strains)
- Improper personal hygiene (increases the number of microorganisms)

In addition to *E. coli*, other gram-negative enterobacterial causes of UTIs include *Klebsiella*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. Gram-positive bacterial causes are infrequent but can include *Staphylococcus saprophyticus*, *Enterococcus faecalis*, and *Streptococcus agalactiae*. Nosocomial and iatrogenic UTIs are often caused by multidrug-resistant organisms.

Some UTIs may be asymptomatic, and clinical manifestations, when present, may not necessarily correlate with the location of the infection within the urinary tract. General manifestations include the following signs and symptoms:

- Urgency
- Dysuria
- Frequency
- Urethral discharge
- Nocturia
- Hematuria
- Bacteriuria
- Cloudy, foul-smelling urine
- Symptoms of infection (e.g., fever, chills, and fatigue)
- Pain in the suprapubic, lower back, or flank area
- Increased blood pressure (with pyelonephritis)
- Confusion, change in mental status, or delirium (in the elderly)

Diagnostic procedures for UTIs include a history, physical examination, urinalysis, urine culture and sensitivity, renal panel, cystoscopy, cystourethrogram (X-ray of the bladder and urethra while

the bladder is full and during urination), complete blood count (CBC), and ultrasound, X-ray, CT, and MRI of the kidneys, ureters, and bladder.

Treatment for UTI focuses on eradicating the microorganism with antibiotics. Depending on the bacteria and severity of the UTI, antibiotics may be given orally or parenterally (e.g., injection or intravenous). Long-term therapy (e.g., up to 14 days) may also be necessary. Antibiotics may be used continuously; alternatively, a postcoital single dose may be used as prophylaxis. Surgery may be required if an abscess or structural abnormality is present.

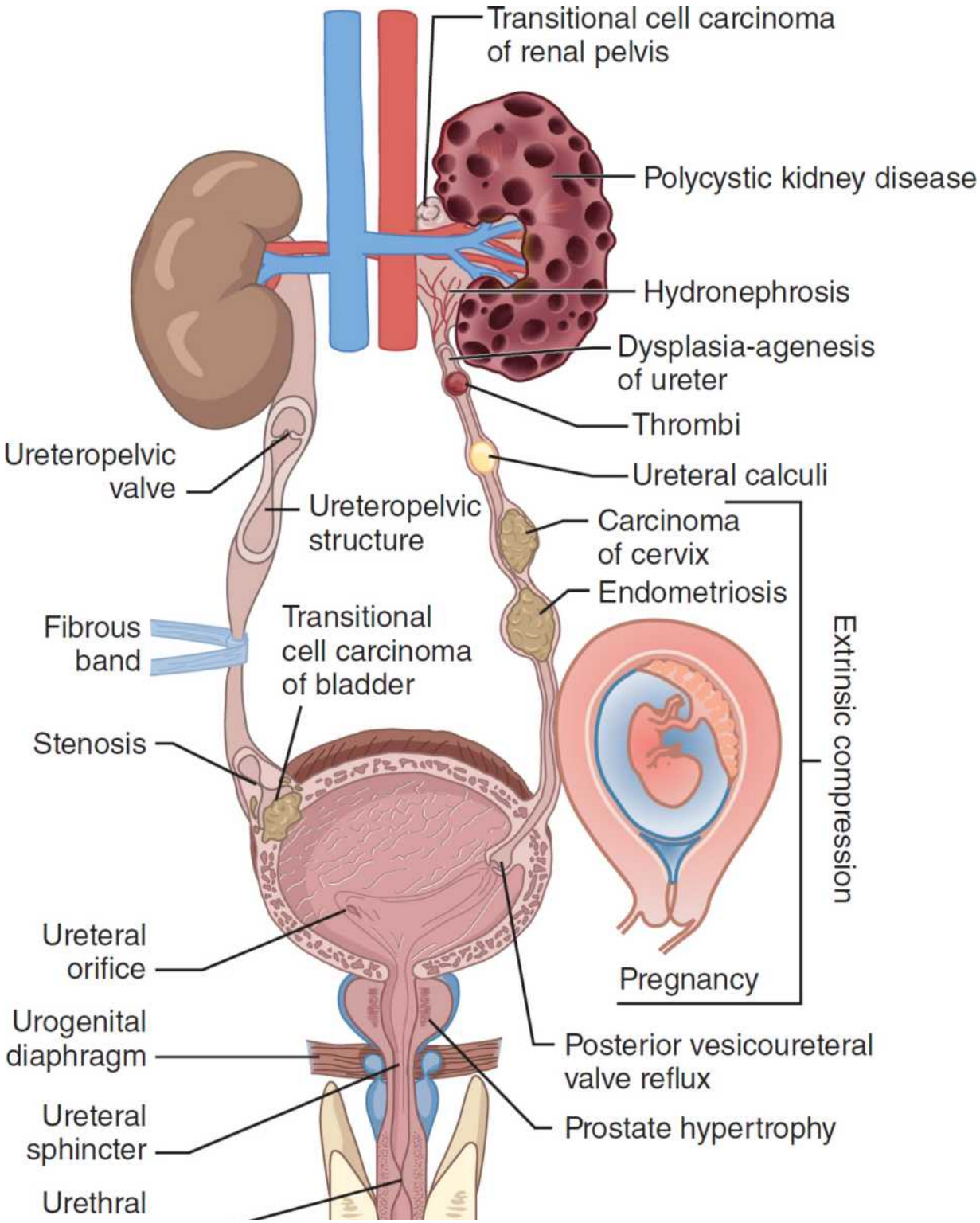
Additional strategies concentrate on the prevention of UTIs:

- Increasing hydration, especially consumption of water and juices (increases flushing of the urinary tract)
- Avoiding irritants (e.g., bubble bath, deodorants, powders, and spermicide)
- Performing proper perineal hygiene (women should clean from front to back, and uncircumcised men should retract the foreskin to clean the penis)
- Wearing cotton underwear
- Wearing loose-fitting clothing
- Not delaying urination
- Adequately emptying the bladder (especially after intercourse)
- Providing appropriate catheter care (when present)
- Probiotics (reestablish normal flora)
- Topical (vaginal) estrogen replacement in postmenopausal women

Urinary Tract Obstructions

The urinary system is similar to the basic plumbing in any house. Blockages in any part of the plumbing system will prevent the flow of the liquid, causing the system to back up. Many opportunities for blockages to occur exist throughout the urinary system, making urinary obstructions common. These blockages may be caused by collection/aggregation of particulates, growth of tumors, or structural

anomalies (**FIGURE 7-11**). Urinary tract obstructions often cause urinary stasis or reflux, which can lead to urinary infections and structural damage.



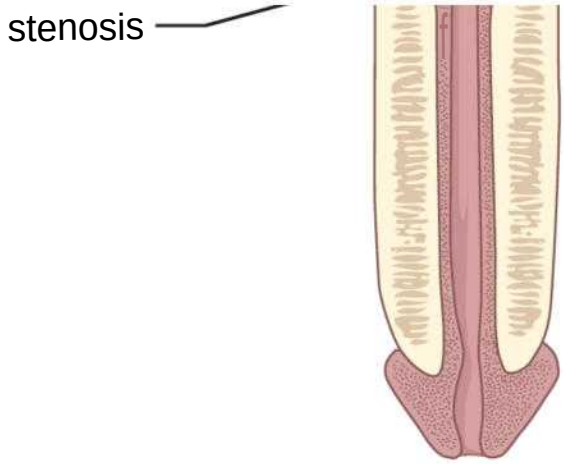


FIGURE 7-11 Urinary tract obstruction and hydronephrosis. Causes of urinary tract obstruction. Hydronephrosis, marked dilation of the renal pelvis and calyces with thinning of parenchyma.

Description

Nephrolithiasis

Nephrolithiasis refers to the presence of renal calculi (kidney stones). Calculi are hard masses of crystals composed of minerals that the kidneys normally excrete (**FIGURE 7-12**). These stones, which can vary in size from as small as a grain of sand to as large as a golf ball, are the most common cause of urinary obstruction. Nephrolithiasis is more common in men and in Caucasians. Generally, the calculi form in the renal pelvis, ureters, and bladder. Whereas nephrolithiasis refers to the calculi formed or located in the kidneys, urolithiasis refers to calculi formed or located at any point in the urinary tract.



FIGURE 7-12 Renal calculi.

© Eskimo71/Dreamstime.com

Calculi may contain various combinations of chemicals (**TABLE 7-5**). The most frequently encountered type of calculus contains calcium in combination with either oxalate (70%) or phosphate (15%). Other types of calculi include uric acid stones (10%), magnesium ammonium phosphate (struvite) stones (3%), and cystine stones (2%). The calculi may be smooth or jagged, and they are usually yellow or brown.

TABLE 7-5 Types of Renal Calculi

Type	Causes	Treatment and Prevention

Type	Causes	Treatment and Prevention
Calcium	Hereditary hypercalciuria Hypocitruia (urinary citrate < 350 mg/day; citrate normally binds to urinary calcium and inhibits calcium salt crystallization) Increased absorption of calcium from the small bowel Hyperparathyroidism Inability of renal tubules to reabsorb calcium (e.g., renal tubular acidosis) Dietary excess of calcium Chronic bowel disease that results in steatorrhea; fat then combines with calcium and renders the calcium unable to bind to oxalate, causing stone formation High doses of vitamin C (i.e., >2,000 mg/day) Rare causes of hypercalciuria (e.g., sarcoidosis, vitamin D intoxication, hyperthyroidism, multiple myeloma, metastatic cancer, and hyperoxaluria)	Cellulose phosphate or thiazide diuretics to decrease dietary absorption of calcium Surgical resection of the parathyroid gland to reduce hyperparathyroidism Thiazide diuretic therapy to correct renal tubular defects, resulting in the inability to reabsorb calcium Purine dietary restrictions to reduce uric acid production Increased fluid intake and treatment of chronic diarrhea
Uric acid	Urine pH lower than 5.5 encourages insoluble urate salt formation Rapid and dramatic weight loss and some malignancies	Large calculi can be dissolved by increasing the urine pH above 6.5 with potassium citrate (the solubility of urate salt is then increased)
Magnesium–ammonium–phosphate (struvite)	Urase-producing bacteria Urinary pH of approximately 7.2 Usually large in size Texture is relatively soft Associated with frequent UTI More common in women	Prevention of UTI Percutaneous nephrolithotomy
Cystine	Abnormal excretion of cystine (amino acid), ornithine lysine, and arginine	Prevention includes increasing fluid intake and increasing urine pH above 7.5

In a healthy individual, urine contains chemicals that prevent these crystals from forming. Once the minerals begin to precipitate, however, they grow like a snowball being rolled in the snow. Conditions that increase the likelihood of crystal formation include pH changes (e.g., as seen with a UTI), excessive concentration of insoluble salts in the urine (e.g., as seen with dehydration, bone disease, gout, renal disease, and dietary increases), and urinary stasis (e.g., immobility). Additional risk factors for developing nephrolithiasis include family history, obesity, hypertension, and diet (e.g., high-protein, high-sodium, or low-calcium diet).

Calculi usually cause symptoms only when they obstruct urine flow. This obstruction can lead to hydronephrosis (urine accumulation in the kidney) and a secondary infection. The movement of calculi through the urinary system can be quite painful and cause irritation of the urinary mucosa, increasing the risk of a UTI. Clinical manifestations of nephrolithiasis include the following signs and symptoms:

- Colicky pain (pain that fluctuates in intensity, with periods of pain lasting 20–60 minutes; often severe, this pain is due to the calculi scraping the ureter wall, and it is colicky due to ureter spasms that occur in an attempt to move the calculi along) in the flank area that radiates to the lower abdomen and groin
- Bloody, cloudy, or foul-smelling urine
- Dysuria
- Frequency
- Genital discharge
- Nausea and vomiting
- Fever and chills (if an infection is present)

Diagnostic procedures for nephrolithiasis consist of a history, physical examination, and urine examination (e.g., urinalysis, culture, 24-hour urine collection). Many calculi are viewable with a kidney–ureter–bladder X-ray, but a noncontrast, low-dose CT or ultrasound of the abdomen and pelvis can identify the presence, location, and size of calculi as well as complications (e.g., hydronephrosis).

Intravenous pyelogram may be necessary to identify smaller stones. A calculus analysis and serum studies (e.g., calcium, uric acid, and phosphate) can help identify the type of stone.

Treatment of nephrolithiasis depends on the type of calculus present (Table 7-5); therefore, determining the type of calculus is crucial to resolve the current calculus and prevent future calculus development. To determine the type of calculus, all urine is strained to capture any passed calculi. Small stones can pass through the urinary system. Strategies to assist the passing of these calculi include increasing fluid intake to 2.5–3.5 L throughout the day and engaging in physical activity (if possible). The increased presence of fluid in the urinary system will expand the diameter of the ureters and urethra, easing the passing of the calculi. Additionally, alpha-receptor blockers (e.g., tamsulosin) can facilitate calculus passage. Larger calculi can be broken up to allow for the passing of the smaller pieces. Procedures to disintegrate these calculi include extracorporeal shock wave lithotripsy (high-frequency sound waves are directed at the calculi to pulverize them), percutaneous nephrolithotomy (a laser is directed at a calculus with a fiber-optic scope), and ureteroscopy (a forceps is used to grab a calculus and remove it through a fiber-optic scope).

Surgical removal of the calculi may be indicated in the following situations:

- The calculi do not pass after a reasonable period (i.e., < 8 weeks) and cause constant pain.
- A calculus is too large to pass on its own (e.g., > 4 cm) or is lodged in a difficult location.
- The calculi obstruct urinary flow.
- The calculi cause ongoing UTIs, renal damage, or constant bleeding.
- The calculi have enlarged.

Treating the underlying cause (e.g., with antibiotics, antigout agents, or urine pH–modifying agents) of the calculi and pain

management will also be necessary. Renal colic may be relieved with opioids (e.g., morphine or fentanyl). Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) that may be administered intravenously. This drug rapidly relieves the pain and is nonsedating.

Myth Busters

Several common myths surround renal calculi and should be addressed.

Myth 1: Only men get renal calculi.

Although calculi formation is more common in men, rates among women are increasing.

Myth 2: Eating certain foods will cause calculi to form.

In general, eating certain foods will not cause calculi to form in persons who are not already susceptible to their formation.

Myth 3: Most renal calculi form from calcium, so dietary intake of calcium should be reduced.

For many years, the medical community thought a low-calcium diet was the best way to prevent renal calculi, especially in those persons who already had stones, but recent research has changed that understanding. Studies have shown that low-calcium diets are not effective and may actually be harmful because they tend to increase the likelihood of low bone density and osteoporosis. Researchers now believe that more—rather than less—calcium is better, with normal amounts being best. So, drinking that glass of milk and cutting back on the hamburgers and chips may help reduce your risk of renal calculi!

Myth 4: If a person has renal calculi, then he or she is more likely to develop cholelithiasis (gallstones).

Not even close! Cholelithiasis and nephrolithiasis are not related at all—the "stones" form in different areas of the body. Typically, those individuals who are at greater risk for developing cholelithiasis are a different group from those who have renal calculi. Women, Native Americans, Mexican Americans, people older than 60 years of age, and those on frequent diets are more likely to have gallstones.

Data from National Institutes of Diabetes and Digestive and Kidney Diseases. (2017). Kidney stones. Retrieved from www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones/definition-facts

Recurrence is common with nephrolithiasis; therefore, prevention strategies are essential. Dietary changes are the mainstay of

prevention, with the changes implemented being specific to the type of calculus (see Table 7-5). Additional prevention strategies include adequate fluid intake (2–2.5 L per day) and physical activity.

Hydronephrosis

Hydronephrosis is an abnormal dilation of the renal pelvis and the calyces of one or both kidneys that occurs secondary to a disease (**FIGURE 7-13**). Diseases that obstruct urine flow are commonly associated with this condition, including nephrolithiasis, thrombi, tumors, benign prostatic hyperplasia, strictures, and stenosis. Congenital urologic defects can also cause hydronephrosis, including reflux nephropathy, a congenital condition that causes backflow of urine into the kidneys. Unilateral renal involvement indicates an obstruction is present in one of the ureters, and bilateral renal involvement indicates an obstruction is present in the urethra.

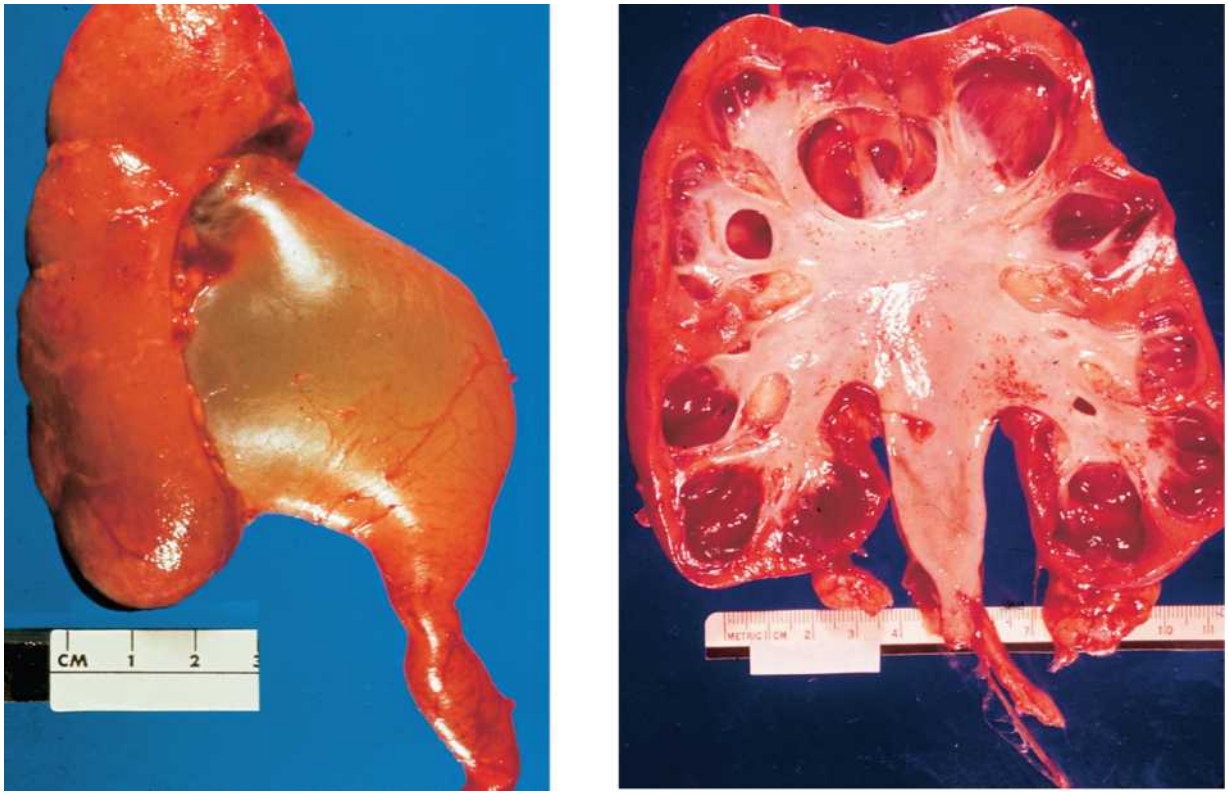


FIGURE 7-13 Hydronephrosis.

Courtesy of Leonard V. Crowley, MD, Century College.

Because urine is continuously forming, the presence and severity of clinical manifestations depend on the degree of urinary obstruction. Partial obstructions with mild hydronephrosis may not produce any initial symptoms. Complete obstruction with severe hydronephrosis, by comparison, applies direct pressure and compresses tissue and blood vessels, leading to atrophy, necrosis, and glomerular filtration cessation. When present, clinical manifestations include the following signs and symptoms:

- Colicky flank pain or pressure
- Bloody, cloudy, or foul-smelling urine
- Dysuria
- Decreased urine output
- Frequency
- Urgency
- Nausea and vomiting
- Abdominal distention
- Palpable abdominal or flank mass
- UTIs

Diagnostic procedures for hydronephrosis include a history, physical examination, urinalysis, renal panel, renal ultrasound, CT, intravenous pyelogram, and MRI. Congenital cases are often detected incidentally by routine ultrasounds performed during pregnancy.

Prognosis depends on the severity of the hydronephrosis and early treatment. Treatment focuses on resolving the underlying cause. Facilitating urine flow will be necessary; otherwise, UTIs will develop. If the hydronephrosis is prolonged, permanent renal damage can occur to one or both kidneys.

Tumors and Cysts

Masses can be found throughout the urinary tract. These masses may be cysts, a sac-like pocket of membranous tissue that contains

fluid, air, or other substances. They may also be solid tumors that are either benign (e.g., adenomas and papillomas) or malignant (e.g., **renal cell carcinoma**). Most urinary tract masses are cysts found in the kidneys. Benign tumors are rare in the urinary system; most urinary tumors are malignant. These tumors can occur at any point along the urinary system. Regardless of their location, tumors can obstruct urine flow and impair renal function in addition to leading to the consequences of cancer (e.g., metastasis, pain, and weight loss).

Renal Cysts

Cysts that form in the kidneys usually are characterized as simple cysts, meaning they have a thin wall and contain a water-like fluid. Renal cysts are relatively common with age and usually do not cause any symptoms or issues. Some renal cysts are more complex, having a thicker wall or containing solid material instead of fluid. Complications are rare and include infection, bleeding, and enlargement. Having multiple simple renal cysts is different from having polycystic kidney disease; the latter is a genetic disorder that impairs renal function.

Since most renal cysts are asymptomatic, manifestations often reflect complication development. These manifestations include fever, pain or tenderness between the ribs and pelvis, upper abdominal pain, changes in urinary patterns, and hematuria. Because renal cysts rarely cause symptoms, most cases are identified during imaging tests (e.g., ultrasound or CT) performed for other reasons. Complex renal cysts will require abdominal or pelvic ultrasound, abdominal or pelvic CT, or body MRI to distinguish benign cysts from cancer.

Renal cysts are classified and treated based on their complexity. Most do not require treatment. If treatment is required, sclerotherapy or surgery to drain the cyst may be performed.

Wilms Tumor

Wilms tumor, or nephroblastoma, is a rare kidney cancer that primarily affects children. According to the National Cancer Institute (2023c), 650 new cases of Wilms tumor are diagnosed each year. Wilms tumor is the most common malignant tumor in children, with its

peak incidence occurring around age 3–4 years. This tumor usually occurs in one kidney, but it can affect both (in 4% to 5% of cases). A second tumor may appear later in the remaining kidney. Wilms tumor usually grows as a solitary mass that can become quite large.

The exact cause of Wilms tumor is unknown, but it is thought to arise in utero when the cells that normally form the kidneys fail to develop properly. This development issue can occur spontaneously or as a result of genetic changes. Wilms tumor has been associated with several genetic mutations, including those on chromosome 3 (usually *CTNNB1*), chromosome 11 (usually deletion of Wilms tumor suppressor genes *WT1* or *WT2*), and the X chromosome (usually inactivation of the *WTX* gene, also called *AMER1*). This type of cancer often occurs in conjunction with several congenital defects, including aniridia (absence of the iris of the eye), hemihypertrophy (enlargement of one side of the body), and genitourinary abnormalities (e.g., cryptorchidism and hypospadias). WAGR syndrome is the combination of Wilms tumor (with *WT1* deletion), aniridia, genitourinary malformations, and intellectual disability. Denys-Drash syndrome is characterized by **nephrotic syndrome**, gonadal dysgenesis, and an increased risk of Wilms tumor (with *WT1* mutation).

Even though it is rare, Wilms tumor tends to run in families (10%), usually following an autosomal dominant inheritance pattern. The risk of developing this tumor also seems to be higher in females and African Americans. In contrast, Asian Americans have a lower risk of developing Wilms tumor than other ethnic groups.

Wilms tumors are grouped into two major types based on their histology—favorable histology and anaplastic histology. With favorable histology, the tumor cells show mutation, but anaplasia is not present. With anaplastic histology, the tumor cells vary widely and the cells' nuclei are large and distorted.

Because of improved diagnostic procedures, Wilms tumor can now be detected early, leading to an improved prognosis for children affected by this disease. The long-term survival rate is excellent with early detection and treatment. Unfortunately, Wilms tumor may sometimes go undetected early because the tumor can grow quite

large without causing pain; nevertheless, most of these tumors are diagnosed before they have metastasized.

Clinical manifestations of Wilms tumor are similar to those of other cancers:

- Asymptomatic abdominal mass
- High blood pressure
- Hemihypertrophy
- Hematuria
- UTIs
- Abdominal pain (late)
- Nausea and vomiting
- Anorexia
- Bowel pattern changes (often constipation)
- Weight loss
- Fatigue

Diagnostic procedures for Wilms tumor include a history, physical examination, abdominal X-ray, renal ultrasound, BUN, creatinine, creatinine clearance, CBC, abdominal CT with contrast or MRI, urinalysis, and biopsy. Once diagnosed, the following staging system guides treatment:

Emerging Research: Wilms Tumor

The past few decades have seen advances in research that have significantly increased cure rates for patients with Wilms tumor. In the United States, the Children's Oncology Group coordinates most of the research on Wilms tumor. A National Cancer Institute–supported clinical trials group, the Children's Oncology Group is the world's largest organization devoted exclusively to childhood and adolescent cancer research. It brings together more than 9,000 childhood cancer experts at more than 200 leading children's hospitals, universities, and cancer centers across North America, Australia, New Zealand, and Europe.

Research continues to unravel how genetic mutations cause Wilms tumors and affect how aggressive these tumors are likely to be. For example, studies have shown that Wilms tumors with mutations on chromosomes 1 or 16 have an increased incidence of

recurrence, so research is being conducted to determine whether children with such tumors would benefit from more intensive treatment. Research is also underway to determine which genetic changes cause Wilms tumor cells to grow and spread; this research may lead to more targeted treatments. Targeted drugs work differently from standard chemotherapy agents. In particular, targeted drugs can work when chemotherapy agents do not, and they often have different and less severe side effects.

Researchers are also working to identify when less treatment is possible to minimize side effects. For example, studies are exploring whether young children with a favorable Wilms tumor need any treatment other than surgery. Additionally, recent research suggests that some children with Wilms tumor that has spread to only one area in the lung might not need radiation therapy to the lungs—an important consideration given that such therapy can cause long-term side effects.

Other research is investigating new approaches for tumors that are more difficult to treat, such as anaplastic Wilms tumors. Newer chemotherapy drugs (e.g., topotecan and irinotecan) are being tested. Additionally, studies are exploring stem cell transplants (i.e., bone marrow transplants), which would allow higher doses of chemotherapy to be administered in cases that do not respond to standard treatments or have a poor outlook.

Research has also looked at how to treat bilateral Wilms tumors while preserving as much kidney function as possible. Studies now in progress are seeking more effective ways of reducing symptoms and side effects of current Wilms tumor treatment to improve children's comfort and quality of life (American Cancer Society, 2018; Cancer.Net, 2022).

- *Stage I:* The cancer is in only one kidney and generally can be completely removed with surgery.
- *Stage II:* The cancer has metastasized to the tissues and structures near the kidney, but it can still be completely removed by surgery.
- *Stage III:* The cancer has metastasized beyond the kidney area to nearby lymph nodes or other structures within the abdomen and may not be completely removed by surgery.
- *Stage IV:* The cancer has metastasized to distant structures, such as the lungs, liver, or brain.
- *Stage V:* Cancer cells are found in both kidneys.

The standard treatment for Wilms tumor is surgery (e.g., simple, partial, or radical nephrectomy) and chemotherapy, but radiation therapy may be used if warranted by tumor histology or with higher staging. After completion of treatment, a renal transplantation may be performed if the child remains cancer-free for 1–2 years. Coping strategies and support interventions (e.g., allowing play time and local

support groups) will be beneficial for the family and child. Additionally, palpation of the abdomen should be avoided.

Renal Cell Carcinoma

Renal cell carcinoma is the most frequently occurring kidney cancer in adults (most common in those 50–70 years of age). The National Cancer Institute (2023b) estimated that more than 76,000 new cases of renal cancer were diagnosed in 2021, with almost 14,000 deaths attributed to this cancer.

Renal cell carcinoma is usually a primary adenocarcinoma arising from the renal tubule (**FIGURE 7-14**). Its exact cause is unknown. Risk factors for developing this type of cancer include smoking, obesity, being male, dialysis treatment (i.e., acquired cystic disease), family history, hypertension, excessive use of phenacetin (an analgesic/antipyretic agent banned in 1983), exposure to certain chemicals (e.g., radiopaque contrast agents, asbestos, cadmium, and leather tanning and petroleum products), and other kidney disease (e.g., horseshoe kidney and polycystic kidney disease). Metastasis to the liver, lungs, bone, lymph nodes, adrenal glands, or brain is common at the time of diagnosis. Renal cell carcinoma can also trigger thrombus formation in the renal vein, which can travel to the vena cava.

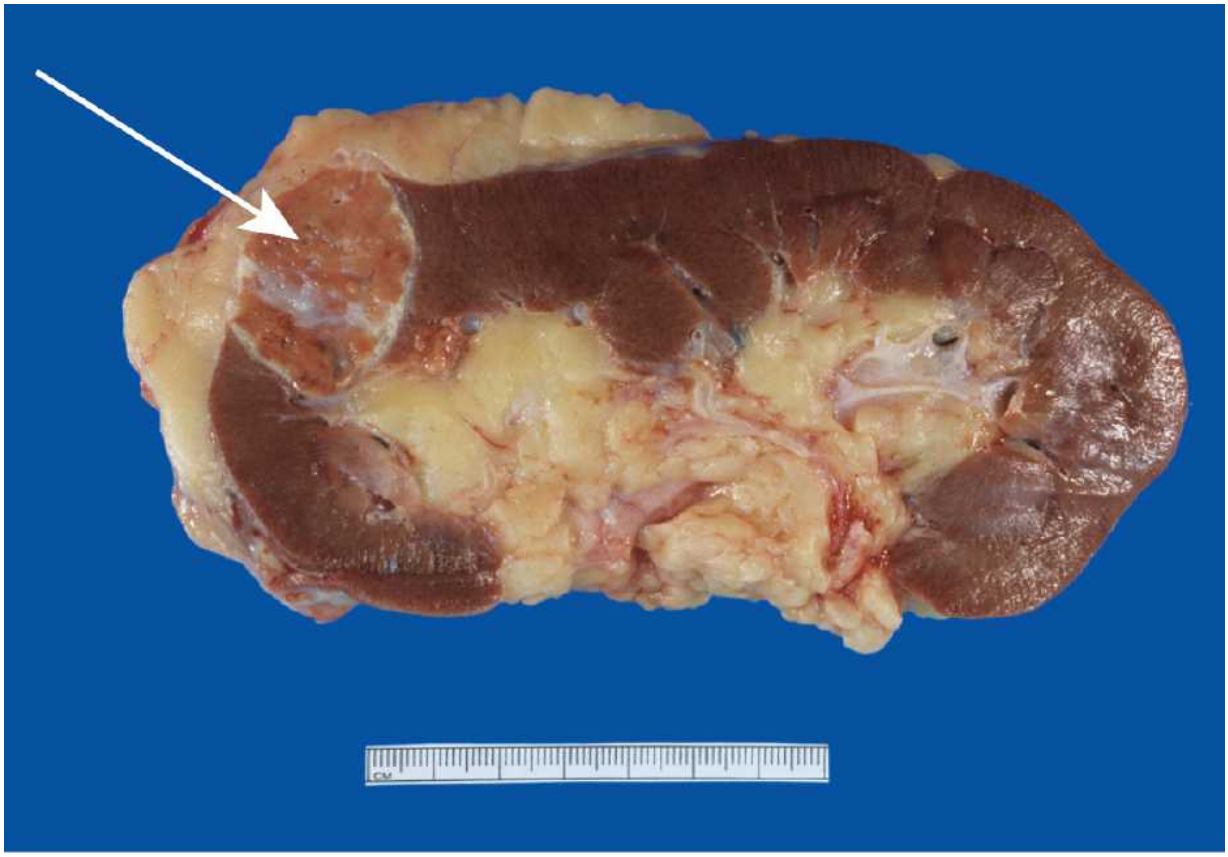


FIGURE 7-14 Renal cell carcinoma.

© Dr. Gladden Willis/Visuals Unlimited, Inc.

Renal cell carcinoma is typically asymptomatic in its early stages. When present, clinical manifestations include the following signs and symptoms:

- Dull, achy flank pain
- Palpable mass over the affected kidney
- Fever of unknown origin
- Painless hematuria (gross or microscopic)
- Abnormal urine color (dark, rusty, or brown)
- Urinary retention
- Unexplained weight loss
- Anemia (if the tumor suppresses hormone secretion)

- Polycythemia (if the tumor secretes erythropoietin or an erythropoietin-like substance)
- Hypertension
- Paraneoplastic syndromes, such as hypercalcemia (due to ectopic parathyroid hormone production by the tumor or bone metastasis) or Cushing syndrome (increased adrenocorticotropic hormone)

Diagnostic procedures for renal cell carcinoma are used to identify the presence of a tumor and determine whether metastasis has occurred. These procedures include a history, physical examination, urinalysis, CT, MRI, positron emission tomography (PET) scan, bone scan, chest X-ray, intravenous pyelogram, cystoscopy, renal arteriogram, biopsy, liver function panel, CBC, and blood chemistry.

Interestingly, renal cell carcinoma is one of the few tumors in which well-documented cases of spontaneous tumor regression in the absence of therapy exist, but such outcomes occur very rarely and may not lead to long-term survival (National Cancer Institute, 2023b). Partial or complete surgical removal of the kidney (nephrectomy) is recommended because the cancer is generally unresponsive to radiation or chemotherapy, although some newer chemotherapy agents (e.g., multikinase inhibitors) have shown promise. Hormone therapy and immunotherapy may have modest effects in shrinking the tumor. Prognosis is better when the condition is diagnosed prior to metastasis of the cancer.

Bladder Cancer

Bladder cancer refers to any cancer that forms in the tissue of the bladder. Most (more than 90%) bladder cancers are urothelial or transitional cell carcinomas (cancer beginning in the cells that make up the inner bladder lining). Transitional cell carcinomas tend to be noninvasive, meaning they have not grown into the deep layers. Many of these transitional cell carcinomas are papillary carcinomas, which tend to be superficial, well differentiated, and grow outward. Other transitional cell carcinomas are sessile tumors, which are more insidious, tend to invade early, and metastasize. Other types of

bladder cancers include squamous cell carcinoma (cancer beginning in thin, flat cells), adenocarcinoma (cancer beginning in the cells that make and release mucus and other fluids), small-cell carcinoma (cancer beginning as nerve-like cells called “neuroendocrine cells”), and sarcoma (cancer beginning in the muscle cells of the bladder). The cells that form squamous-cell carcinoma and adenocarcinoma develop in the inner lining of the bladder because of chronic irritation and inflammation. Squamous-cell carcinomas tend to occur in the presence of parasitic bladder infections or chronic mucosal irritation. Adenocarcinomas usually occur as a primary tumor but can rarely occur as a result of metastasis from intestinal carcinoma. Squamous-cell carcinomas and adenocarcinomas usually evolve as multiple invasive tumors that extend through the bladder wall and surrounding structures. Small-cell carcinomas often grow quickly and usually are treated with chemotherapy used to treat small cell carcinoma in the lung. Sarcoma in the bladder is extremely rare.

Bladder cancers tend to grow either as papillary or flat tumors (**FIGURE 7-15**). Papillary carcinomas grow as a slender finger-like projection from the inner surface toward the hollow center. Flat carcinomas do not grow toward the hollow center of the bladder.

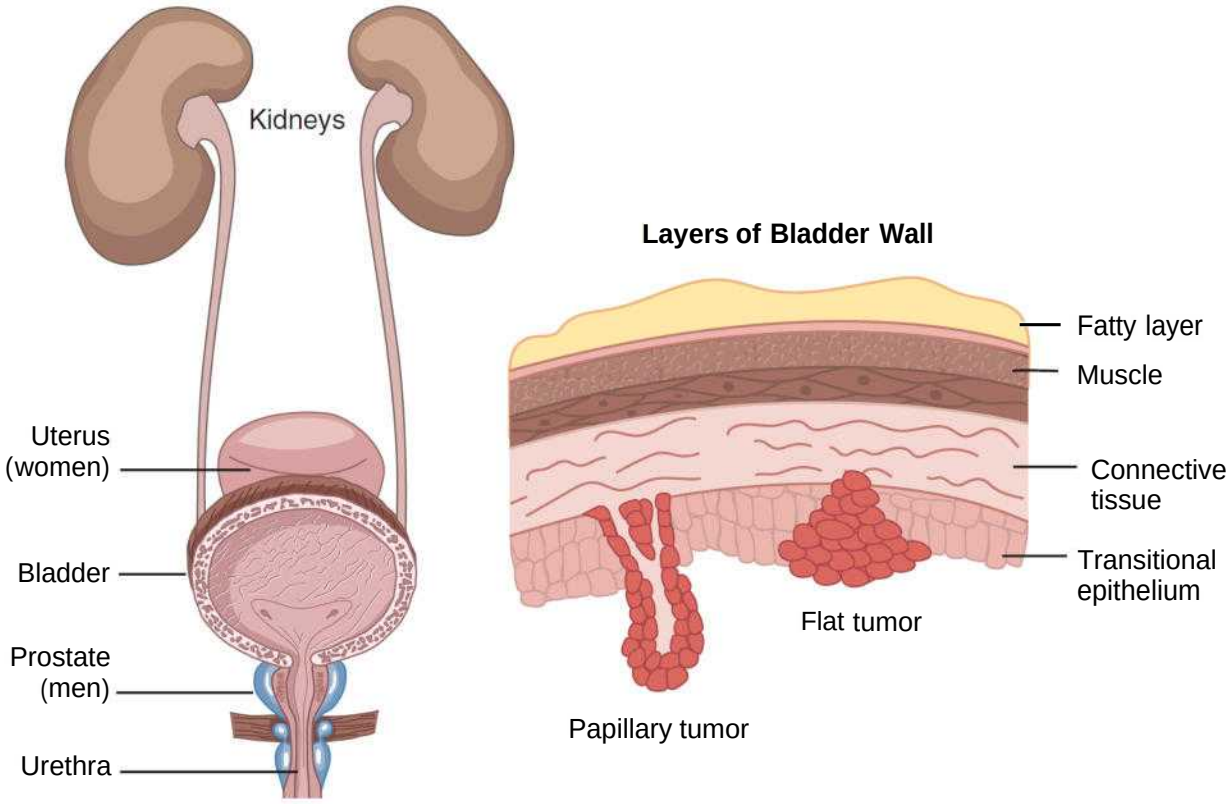


FIGURE 7-15 Bladder cancer.

Description

Recurrence at the same or another location in the bladder happens in about 40% of cases, especially in patients with large or poorly differentiated tumors. Metastasis to the pelvic lymph nodes, liver, and bone is common. Prognosis is generally good but depends on the type and stage of the bladder cancer at the time of diagnosis (see Figure 7-15). Mutations in tumor gene *p53* may be associated with progression and chemotherapy resistance.

The National Cancer Institute (2023a) estimated that more than 82,000 new cases of bladder cancer were diagnosed in 2023, with nearly 17,000 deaths being attributed to this cancer. Although bladder cancer most frequently occurs in older adults, it can arise at any age, and it is more common in men and in Caucasians. Other persons at increased risk include those who smoke cigarettes (most common risk factor), work with chemicals (e.g., dye, rubber, hairdressing chemicals, arsenic, and aluminum), have excessive use of analgesics,

use cyclophosphamide and pioglitazone on a long-term basis, experience recurrent UTIs, have chronic bladder irritation (e.g., long-term catheter placement and bladder calculi), and have received chemotherapy or radiation. Genetic mutations associated with increased risk for bladder cancer include *HRAS* (codes for the H-Ras protein, which regulates cell division) mutations, *Rb1* (codes for the retinoblastoma tumor suppressor protein) mutations, *PTEN/MMAC1* (codes for a tumor suppressor protein) mutations, *N*-acetyltransferase 2 (*NAT2*) slow acetylator phenotype (changes drug metabolic rates), and glutathione *S*-transferase M1 (*GSTM1*) null phenotype (increases susceptibility to carcinogens and toxins) (National Cancer Institute, 2023a).

Clinical manifestations of bladder cancer include the following:

- Painless hematuria (gross or microscopic)
- Abnormal urine color (dark, rusty, or brown)
- Frequency
- Dysuria
- Urge incontinence
- Nocturia
- UTIs
- Back, abdominal, or pelvic pain
- Anemia

Diagnostic procedures are used to identify the presence of a tumor and determine whether metastasis has occurred. These procedures consist of a history, physical examination, urine cytology, urinalysis, CT, MRI, PET scan, bone scan, chest X-ray, ultrasound, intravenous pyelogram, cystoscopy, biopsy, and liver function panel.

Even with early diagnosis and treatment, bladder cancer often recurs. Treatment strategies are based on staging and include surgical removal of the tumor (e.g., transurethral resection or cystectomy), radiation, chemotherapy (e.g., intravesical or intravenous), and immunologic agents (e.g., intravesical immunotherapy). Urinary diversion that routes urine through an ileal

conduit to an abdominal stoma and external collecting bag or some alternative (e.g., orthotopic neobladder or continent cutaneous diversion) will be required following cystectomy. Patients should be monitored every 3 to 6 months for progression or reoccurrence.

Benign Prostatic Hyperplasia

Although the prostate is a structure of the male reproductive system, diseases of the prostate can cause significant issues in the urinary system because of this gland's close proximity to those structures (**FIGURE 7-16**). **Benign prostatic hyperplasia (BPH)**, also called "benign prostatic hypertrophy," is a common, nonmalignant enlargement of the prostate gland that occurs as men age, usually appearing by age 50. Its exact cause is unknown, but declining testosterone, increasing estrogen, and rising dihydrotestosterone levels are thought to cause prostatic stromal cell proliferation. This increase in proliferation enlarges the prostate gland. A second theory postulates that stem cells in the prostate do not mature and die as they are programmed to do (apoptosis) (see the *Cellular Function* chapter), such that the resulting imbalance between dying cells and reproducing cells enlarges the prostate over time. As the prostate expands, it presses against the urethra like a clamp on a hose. Clamping the urethra obstructs urine flow, leading to urinary stasis and UTIs. The bladder wall becomes thick and irritated as urine overfills this organ. The bladder begins to contract with even small amounts of urine and, over time, loses its ability to empty completely.

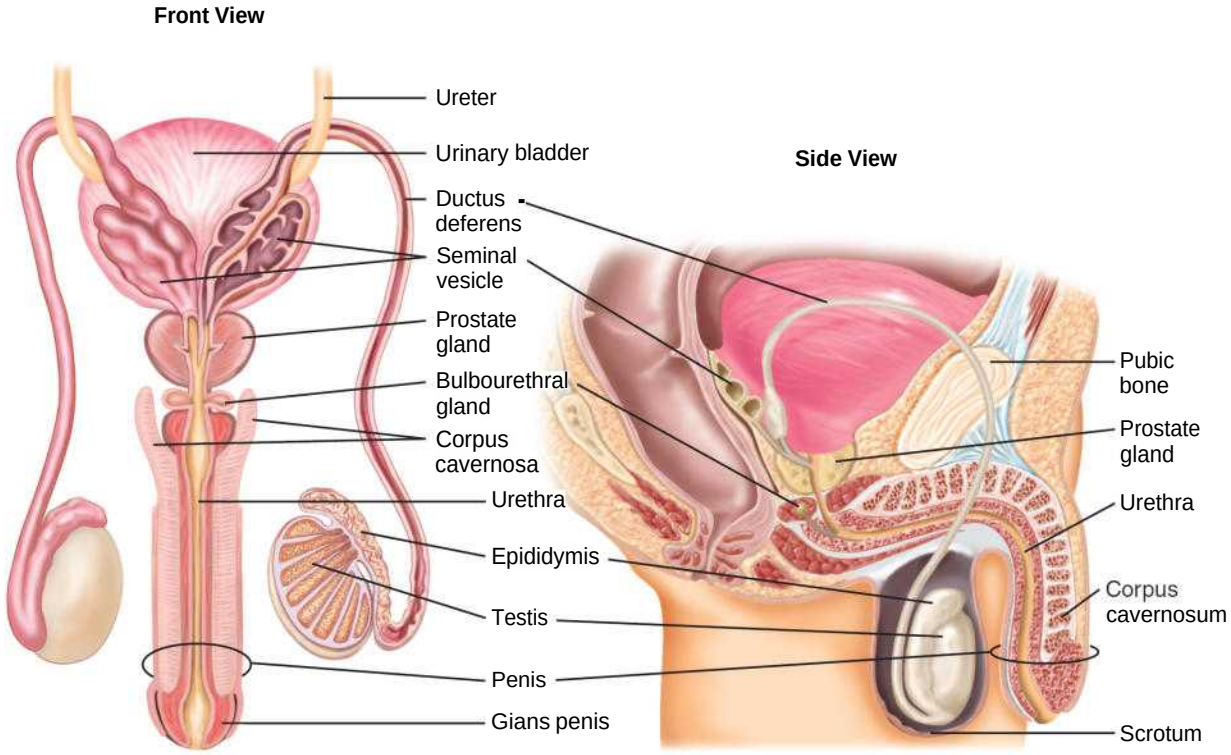


FIGURE 7-16 Urethra and prostate gland.

Courtesy of Dr. Edwin P. Ewing, Jr./CDC.

Description

In addition to age, other risk factors for BPH include a family history of BPH, obesity, cardiovascular disease, type 2 diabetes mellitus, physical inactivity, and erectile dysfunction. Complications from BPH may include UTIs, bladder calculi, bladder damage, hydronephrosis, and renal impairment. Clinical manifestations of BPH are primarily urinary in nature, with the severity of these symptoms depending on the size of the prostate:

Emerging Research: Bladder Cancer

Bladder cancer research is ongoing to advance our understanding of the disease's etiology, diagnostic practices, and treatment protocols. Studies are currently exploring how these cancer cells grow and metastasize. Identifying genetic mutations associated with cancer cells can help predict prognosis and recurrence as well as aid providers and patients in choosing the best treatment.

New diagnostic tests are in development that detect substances in the urine that can be used for initial diagnosis as well as for monitoring for recurrence. Some tests now in development may be able to screen for bladder cancer earlier, even prior to symptoms developing.

Treatments under investigation include robotic cystectomy, which could decrease recovery time and minimize surgical risks. Some studies are exploring combinations of treatments that would be effective as well as preserve the bladder. New drugs for intravesical instillation are being tested, along with the use of these medications in combination with existing drugs. These drugs are being tested not only for their effectiveness in treating bladder cancer but also as a means to prevent recurrence.

Photodynamic therapy is being explored with early-stage bladder cancers. With photodynamic therapy, a light-sensitive drug is injected into the blood. This drug collects in the cancer cells over a few days, and then a laser is focused on the bladder's inner lining using a cystoscope. The light transforms the drug in the cancer cells into a new chemical that kills these cells while causing little harm to nearby normal cells.

Additionally, targeted therapies (e.g., rogaratinib, lapatinib [Tykerb], and erlotinib [Tarceva]) are being developed and tested. Other drugs that target the blood vessels supporting tumors, called "anti-angiogenesis drugs," are also under development. Examples include bevacizumab (Avastin), sorafenib (Nexavar), cabozantinib (Cometriq), and pazopanib (Votrient), which are currently being used for other cancer types. These drugs are typically used in combination with chemotherapy.

Gene therapy is being explored as a new bladder cancer treatment. This therapy involves adding or changing cancer cell genes and other host cells. One approach to gene therapy involves injecting viruses that have been altered in the laboratory into the bladder, where they are expected to infect the cancer cells. The viruses inject a gene into the cell that can assist the immune system in attacking the cancer (American Cancer Society, 2019).

- Frequency
- Urgency
- Urinary retention
- Difficulty initiating urination
- Weak urinary stream
- Dribbling urine
- Nocturia
- Bladder distention
- Overflow incontinence
- Erectile dysfunction

BPH does not increase prostate cancer risk, but its clinical presentation is very similar to that of prostate cancer. Diagnostic procedures can determine whether the prostate enlargement is due to BPH or prostate cancer (see the *Reproductive Function* chapter). These procedures consist of a history, physical examination (including digital rectal examination), urine flow measures, urinalysis, urine culture, prostate-specific antigen (PSA), transrectal ultrasound, biopsy, urodynamic tests, cystoscopy, BUN, and creatinine. The American Urological Association Symptom Score for BPH is used to diagnose, determine severity, and monitor progression. Scores of 1 to 7 indicate mild symptoms, scores of 8 to 19 indicate moderate symptoms, and scores of 20 to 35 indicate severe symptoms (Barry et al., 1992).

Treatment centers on relieving the urinary obstruction and reestablishing sexual function (if possible). Strategies to improve urine flow include pharmacologic agents (e.g., alpha-blockers and $alpha_5$-reductase inhibitors) to shrink or limit the growth of the prostate. Combination therapy including alpha-blockers and $alpha_5$-reductase inhibitors has been shown to be more effective than single-agent therapy. Herbal remedies (e.g., saw palmetto) have also been used, although only limited evidence supports their effectiveness. Other strategies to improve BPH symptoms include minimally invasive procedures, such as prostatic urethral lift (PUL), convective water vapor ablation, transurethral microwave thermotherapy (TUMT), catheterization, and transurethral water vapor thermal therapy. More invasive surgical procedures include transurethral incision of the prostate (TUIP), photoselective vaporization of the prostate (PVP), transurethral resection of the prostate (TURP), holmium laser enucleation of the prostate (HoLEP), thulium laser enucleation of the prostate (ThuLEP), transurethral electrovaporization of the prostate (TUVP), and transurethral water-jet ablation (TWJA).

Prostate artery embolization (PAE) is an experimental therapy under investigation, but its efficacy has not been established. In PAE, small particles are injected into the blood vessels supplying the

prostate using a catheter. The particles obstruct blood flow, causing the prostate to shrink.

Other treatments include hyperthermia, high-density forced ultrasound (HIFU), intraurethral stents, and transurethral balloon dilation. Partial or complete surgical removal of the prostate gland may be necessary.

Lifestyle modifications can often improve BPH symptoms or improve functioning after or along with treatment. Suggested lifestyle modifications include limiting fluid intake, restricting caffeine, avoiding certain medications (e.g., decongestants, antihistamines, antidepressants, and diuretics), bladder training, pelvic floor exercises, preventing constipation, and abstaining from alcohol. Phosphodiesterase-5 inhibitors can be used to treat erectile dysfunction.

Learning Points

The urinary system is basically the human septic system. The kidneys remove wastes and unneeded substances from the blood and ready them for excretion. The kidneys collect these products in the form of urine much like a toilet, and flushing the toilet is much like what the kidneys do in sending the urine to the bladder. The bladder acts like a septic tank, holding the waste until the tank is full. When full, the bladder (and the septic tank) must be emptied.

When obstructions occur at any point in the urinary system, urine backs up, much like the septic system would do if it were obstructed. This backflow can cause severe damage in both cases. In the urinary system, the kidneys become damaged by the irritation and pressure of the excess urine; in the septic system, the house becomes damaged by the corrosive septic contents.

Conditions Resulting in Impaired Renal Function

Both disorders and trauma can damage the kidney structures. The nephrons are particularly vulnerable to such damage. Injury to the nephrons impairs renal function by altering regulatory mechanisms in the kidneys. This impairment often results in issues with urination formation and accumulation of waste products.

Polycystic Kidney Disease

Polycystic kidney disease (PKD) is an inherited disorder characterized by numerous, grape-like clusters of fluid-filled cysts in both kidneys (**FIGURE 7-17**). These cysts enlarge the kidneys while compressing and eventually replacing the functional kidney tissue. The exact trigger for the formation of the cysts is unknown, but genetic mutations are thought to play a role.

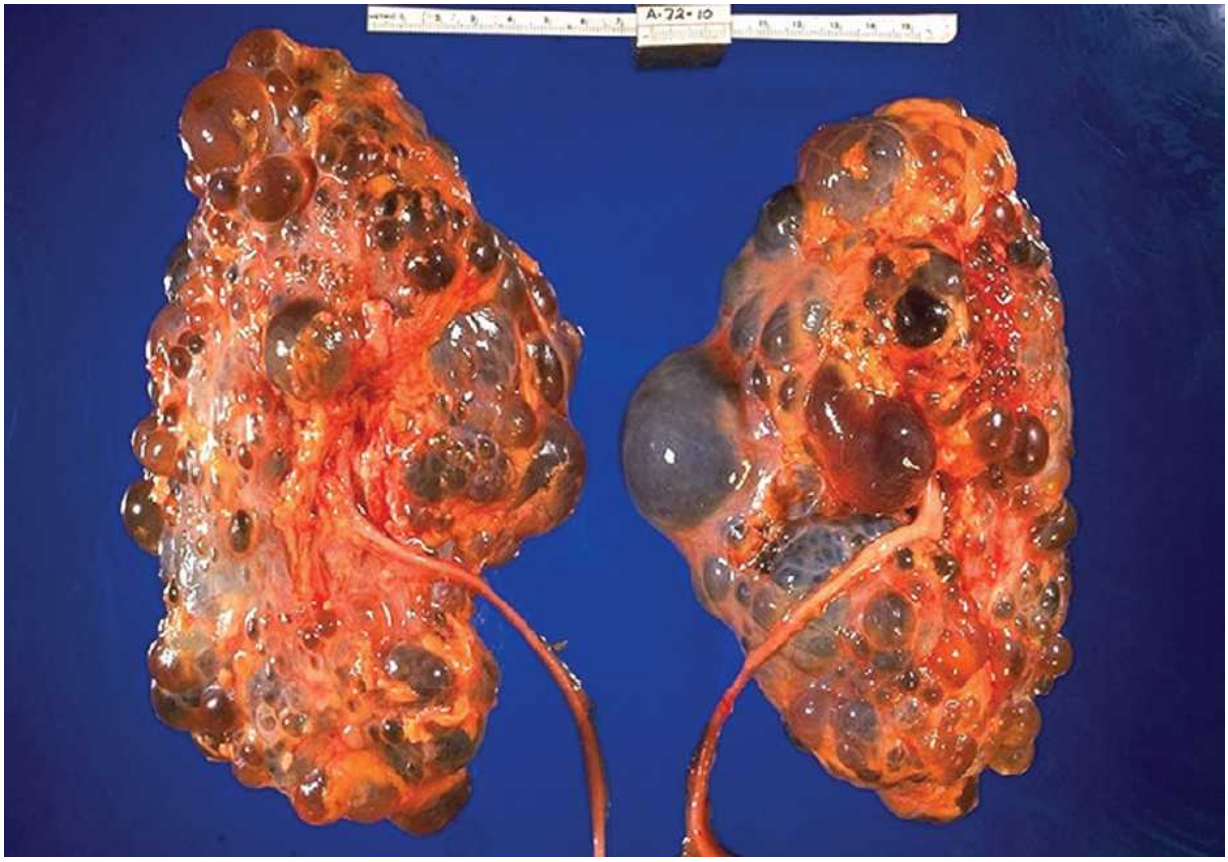


FIGURE 7-17 Polycystic Kidney Disease.

Courtesy of Dr. Edwin P. Ewing, Jr./CDC.

Prognosis and progression of the disease vary widely, depending on the type of PKD. Autosomal dominant (see the *Cellular Function* chapter) PKD is the most common type, and this form can further be divided into type 1 and type 2. Type 1 has been mapped to mutations on the short arm of chromosome 16 (*PKD1* gene), and type 2 has been mapped to mutations on the short arm of chromosome 4 (*PKD1*

gene). Autosomal PKD occurs in both children and adults but is much more common in adults, with symptoms often not emerging until middle age. Like most recessive conditions (see the *Cellular Function* chapter), autosomal recessive PKD is far less common. Recessive PKD has been mapped to a mutation on chromosome 6 (*PKHD1* gene). This type appears in infancy or childhood, tends to be extremely serious, and progresses rapidly, resulting in renal failure and generally causing death in infancy or childhood. PKD affects males and females equally.

Clinical manifestations depend on the individual's age and the type of PKD. These manifestations reflect the structural changes associated with the disease and the resulting renal impairment. In neonates, manifestations include the following signs and symptoms:

- Potter facies—pronounced epicanthic folds (skin folds at the corner of the eyes on either side of the nose), pointed nose, small chin, and floppy, low-set ears
- Large, bilateral, symmetrical masses on the flanks
- Respiratory distress (caused by fluid accumulation from renal impairment)
- Uremia (waste accumulation due to renal impairment)

In adults, manifestations include the following signs and symptoms:

- Hypertension (due to activation of the renin–angiotensin–aldosterone system)
- Lumbar pain
- Increased abdominal girth
- Swollen, tender abdomen
- Grossly enlarged palpable kidneys

Some other symptoms may affect both groups:

- Hematuria (due to impaired glomerular filtration)
- Nocturia (related to an inability to concentrate urine)

- Drowsiness (because of waste accumulation)

Other conditions that may occur in conjunction with PKD include brain aneurysms, cysts in other organs (especially the liver), and colon diverticula. Because of the renal impairment associated with this condition, PKD can lead to critical complications such as pyelonephritis, cyst rupture, retroperitoneal bleeding, and chronic kidney disease. Other, less serious complications include anemia, hypertension, and renal calculi.

Diagnostic procedures for PKD consist of a history, physical examination, genetic testing, urinalysis, blood chemistry, urography (kidney X-ray), abdominal ultrasound, CT, MRI, and intravenous pyelogram (X-ray of the kidneys, ureters, and bladder with the use of radioactive contrast media). Genetic testing can be confirmatory or used to screen individuals with a family history.

PKD often progresses slowly, leading to end-stage renal disease. Treatment strategies focus on controlling symptoms and preventing complications:

- Pharmacology, including the following agents:
  - Antibiotics (when infections are present)
  - Analgesics (for pain)
  - Antihypertensive agents
  - Diuretics
- Adequate hydration
- Low-salt diet
- Surgically draining cystic abscesses or retroperitoneal bleeding
- Dialysis
- Kidney transplant

Glomerular Diseases

The glomerulus, the filtering unit of the kidney, is a collection of capillaries surrounded by the Bowman capsule. The glomerulus and tubules form the nephron. The glomerulus filters the blood to form

urine. Many diseases affect renal function by damaging the glomeruli. Glomerular disease may be idiopathic, but it can also be caused by infections (e.g., streptococcal, human immunodeficiency virus [HIV], hepatitis B or C), drugs or chemical toxins, diabetes mellitus, hypertension, autoimmune conditions (e.g., systemic lupus erythematosus, Goodpasture syndrome, immunoglobulin A [IgA] nephropathy), and genetic conditions (e.g., Alport syndrome). Damage can be diffuse, involving all or most of the glomeruli, or focal, involving fewer than half of the glomeruli. The entire glomerulus (i.e., global) or only a portion can be affected.

The damage associated with glomerular diseases can affect any of the layers or structures of the glomerulus. The inner endothelial lining has openings or holes. The middle layer or glomerular basement membrane prevents the passage of large molecules, thereby acting as a filter. The outer layer is composed of parietal epithelial cells, or podocytes. An interglomerular matrix consisting of mesangial cells inside the glomerulus removes trapped residues and proteins, keeping the filter free of debris. Injury can increase the production of glomerular cells (i.e., proliferative disease) that form lesions, referred to as crescents, consisting of macrophages, fibroblasts, and other cells (**FIGURE 7-18**). These crescent lesions accumulate in the Bowman capsule, causing it to rupture. The damage can also cause scar formation (i.e., sclerosing) or necrotic cell death.

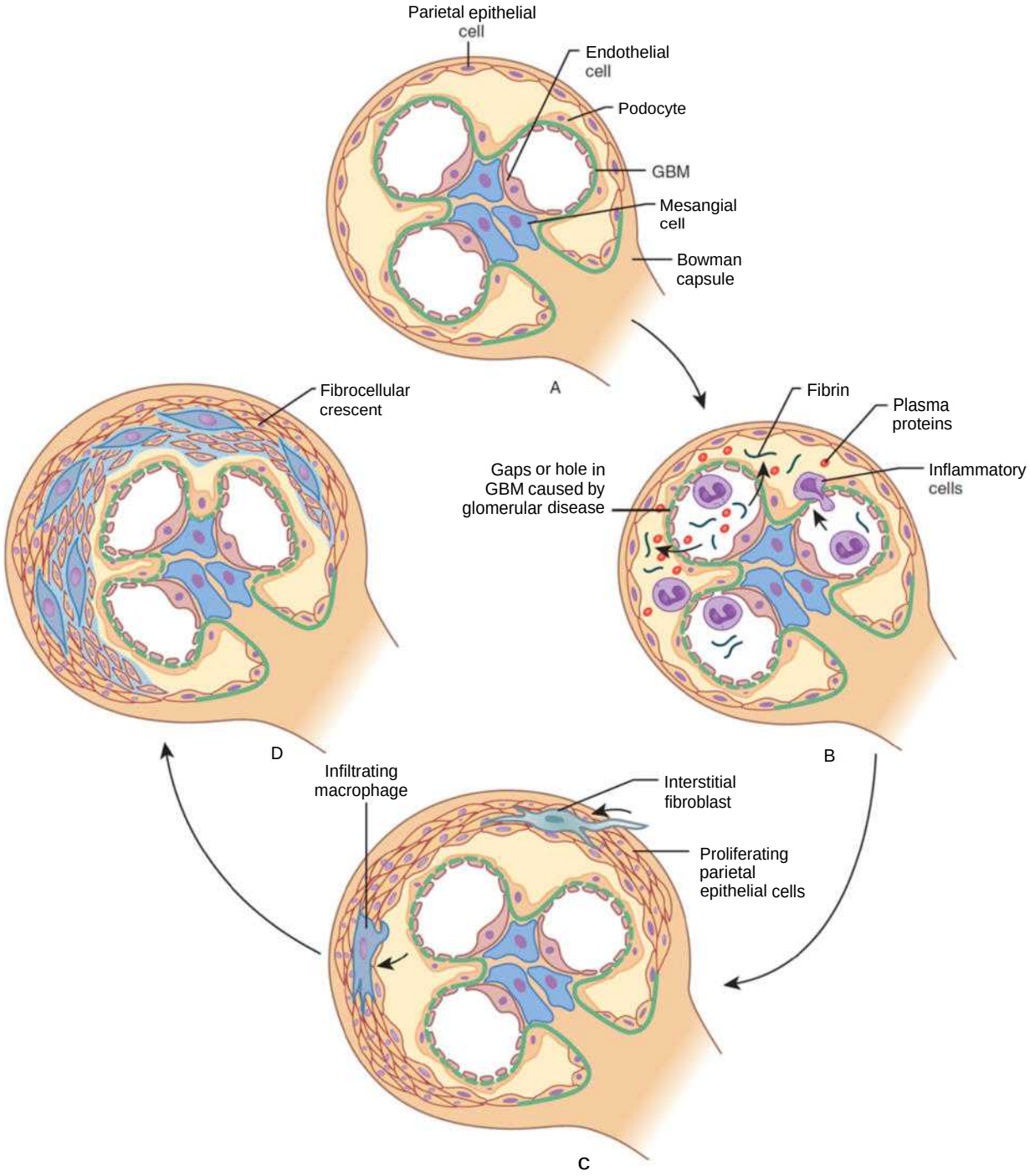


FIGURE 7-18 A simplified cross-sectional view illustrating the events leading to crescent formation. **(A)** Normal glomerulus. **(B)** Glomerular disease leads to gaps or holes in the glomerular basement membrane (GBM), resulting in **(C)** proliferation of parietal epithelial cells and ultimately **(D)** fibrocellular crescent formation.

Description

Glomerular diseases include **glomerulonephritis** and glomerulosclerosis, either of which can lead to renal failure. The damage associated with glomerular disease can cause protein and erythrocyte loss in the urine while preventing waste products in the blood from being filtered.

Glomerulonephritis

Glomerulonephritis refers to renal conditions typically affecting both kidneys, most of which are characterized by inflammation of the glomeruli. Presentation depends on the specific disease because of varying pathogenesis (e.g., nonproliferative and proliferative) (**FIGURE 7-19**). Risk factors include infections (e.g., streptococcal, *Staphylococcus*, *Pneumococcus*, varicella, malaria, and HIV) and the presence of chronic inflammatory conditions (e.g., systemic lupus erythematosus, IgA nephropathy, or Goodpasture syndrome). Glomerulonephritis can also be inherited (e.g., Alport syndrome). Affecting men more than women, glomerulonephritis is a leading cause of chronic kidney disease in the United States; the inflammatory changes (e.g., congestion and cell proliferation) impair the kidneys' ability to excrete waste and excess fluid. Glomerulonephritis can be acute or chronic. Many forms of glomerulonephritis have been identified, with nephrotic and **nephritic syndromes** being the most prevalent (**FIGURE 7-20**).

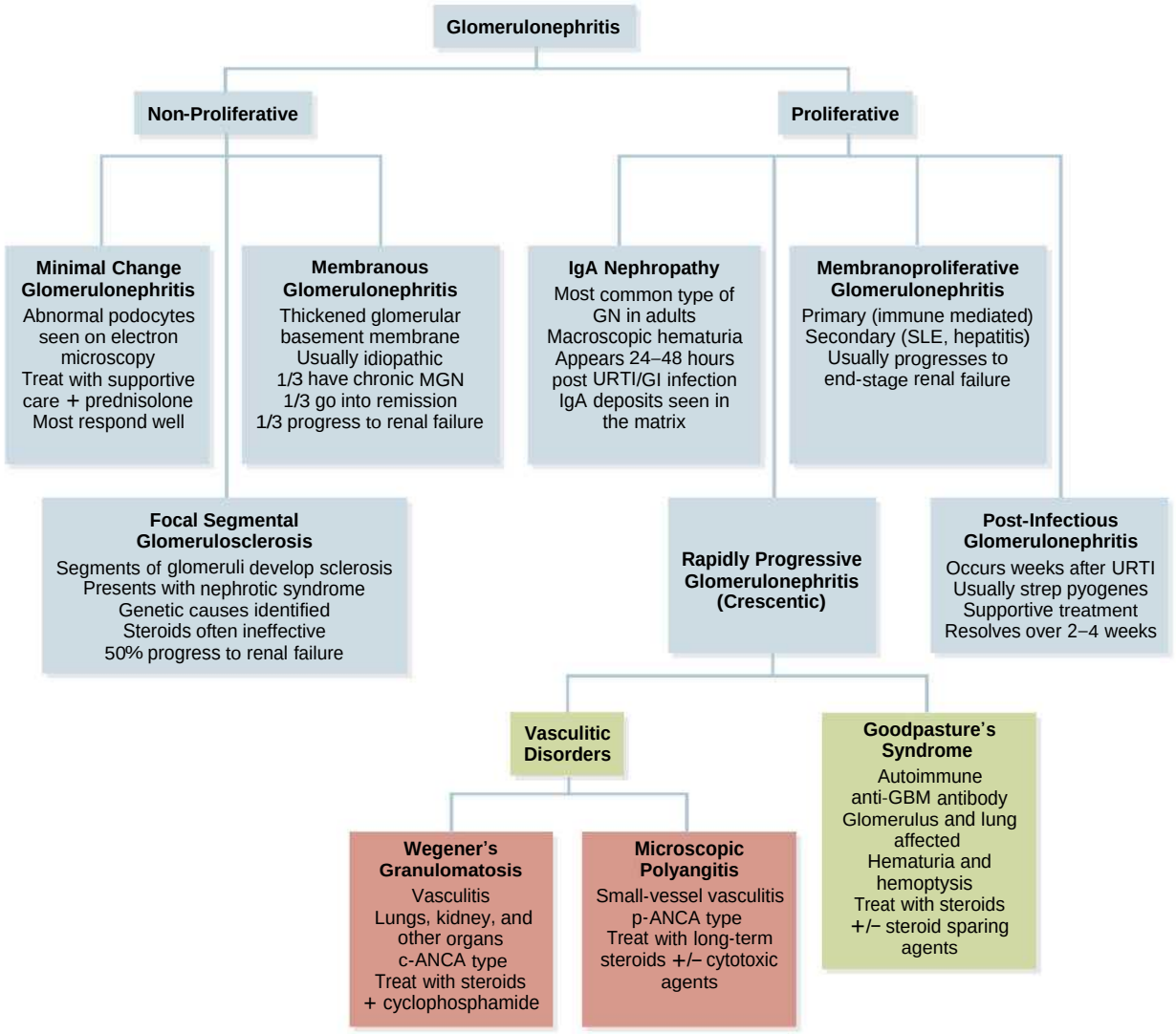


FIGURE 7-19 Glomerulonephritis.

Abbreviations: c-ANCA: cytoplasmic antineutrophil cytoplasmic antibodies; GBM: glomerular basement membrane; GI: gastrointestinal; GN: glomerulonephritis; IgA: immunoglobulin A; MGN: membranous glomerulonephritis; SLE: systemic lupus erythematous; p-ANCA: perinuclear antineutrophil cytoplasmic antibodies; URTI: upper respiratory tract infection.

Description

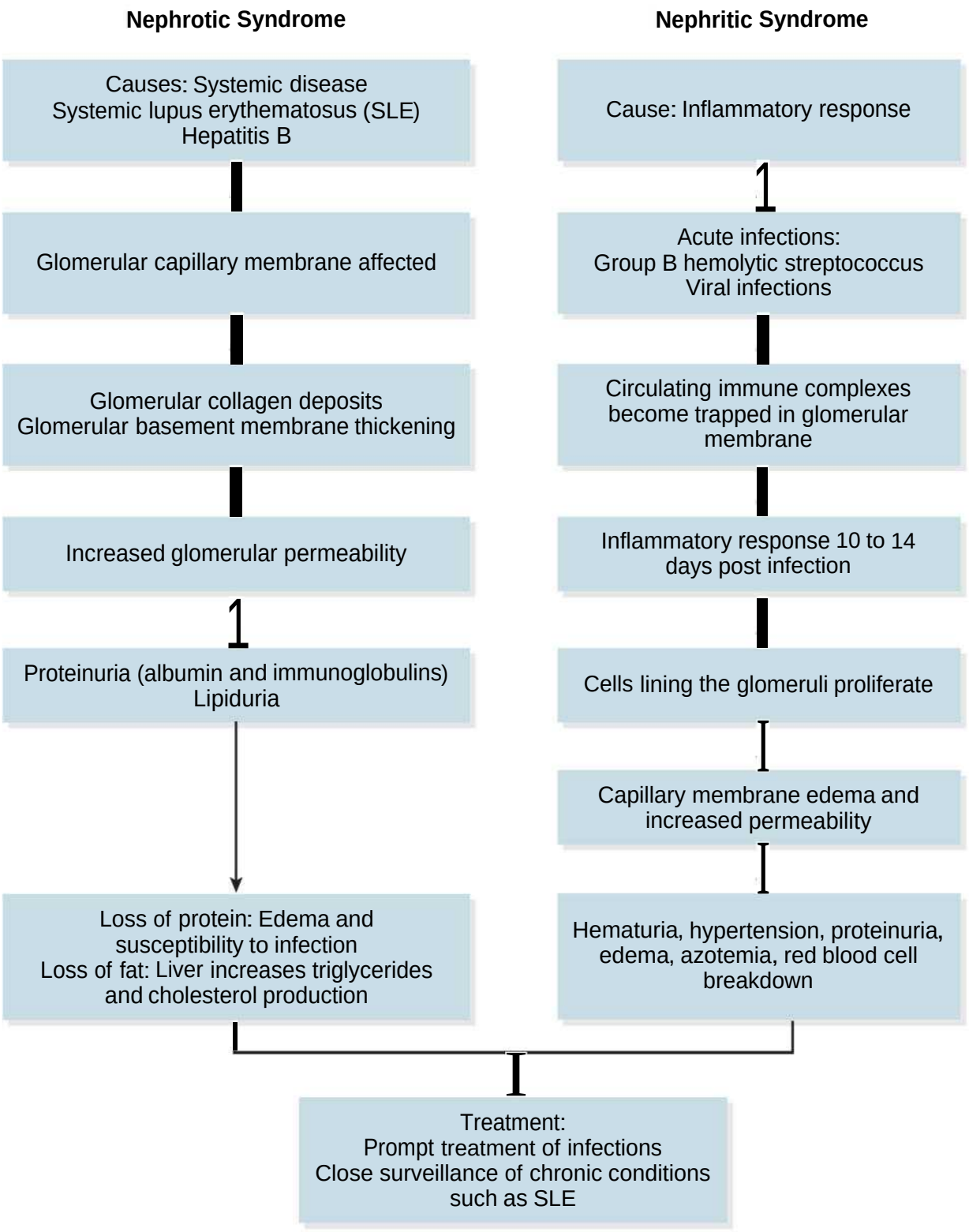


FIGURE 7-20 Nephrotic and nephritic syndrome.

Description

Nephrotic Syndrome

Nephrotic syndrome is a form of glomerulonephritis that results in excretion of excessive amounts of protein. The most common forms of primary nephrotic syndrome are nonproliferative (e.g., minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy). Secondary causes include systemic diseases that damage the kidneys (e.g., systemic lupus erythematosus, hepatitis B, and diabetes mellitus), infections (e.g., streptococcal infections and mononucleosis), medications (e.g., gold therapy and NSAIDs), and idiopathic sources. The exact mechanism of the damage is unknown, but T cells may upregulate a circulating permeability factor or downregulate an inhibitor of the permeability factor in response to unidentified immunogens and cytokines. Other possible factors include hereditary defects in proteins that are essential for filtration openings in the glomeruli, activation of the complement system that damages epithelial cells, and loss of the negatively charged substances on the GBM and epithelial cells. The damage results in increased glomerular capillary permeability, leading to marked proteinuria, lipiduria, hypoalbuminemia, and massive generalized edema (**anasarca**).

A high level of protein in the urine indicates impaired glomerular filtration. The loss of protein in the urine contributes to low serum levels (hypoalbuminemia) and gives the urine a dark and cloudy (smoky or coffee-colored) appearance. Additionally, immunoglobulins are excreted in the urine; this loss of immune cells, in turn, increases the individual's risk for infection. To compensate for the loss of protein in the urine, the liver increases albumin, triglyceride, and cholesterol production—a response that puts the individual at increased risk for atherosclerosis (see the *Cardiovascular Function* chapter). The loss of protein also decreases colloidal pressure, leading to massive edema.

Nephritic Syndrome

Nephritic syndrome refers to proliferative, inflammatory injury to the glomeruli that can occur when antibodies interact with normally

occurring antigens in the glomeruli. Typical forms of nephrotic syndrome include IgA nephropathy, membranoproliferative glomerulonephritis (e.g., primary or secondary to systemic lupus erythematosus or hepatitis), postinfectious (e.g., streptococcal) glomerulonephritis, and rapidly progressive glomerulonephritis (e.g., vasculitic disorders and Goodpasture syndrome).

Clinical manifestations of nephritic syndrome include gross hematuria, urinary casts and leukocytes, low GFR, **azotemia** (buildup of waste products), oliguria (decreased urine output), and high blood pressure. The inflammatory injury results in erythrocytes being excreted in the urine, which changes circulatory pressures. Changes in these pressures result in a low GFR and, in turn, impair renal function.

Diagnostic procedures for glomerulonephritis consist of a history, physical examination, urinalysis, blood chemistry, serum antibody levels (e.g., antinuclear antibody and rheumatoid factor), erythrocyte sedimentation rate (ESR), CT, and renal biopsy. Treatment depends on the type, cause, and severity of the glomerulonephritis. In many cases, recovery occurs with minimal residual damage. Children tend to have the best prognosis. Treatment strategies may include antibiotic therapy, corticosteroids, blood pressure management (e.g., diuretics, angiotensin-converting enzyme inhibitors), and temporary dialysis.

Kidney Injury and Disease

The pivotal role that the kidneys play in maintaining homeostasis (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter) becomes clear when these organs stop performing that role. *Renal failure* refers to the kidneys' inability to function adequately; it is classified as either acute or chronic.

Acute Kidney Injury

Acute kidney injury (AKI), formerly known as "acute renal failure," refers to a sudden loss of renal function over a period of days to weeks. This loss, which is generally reversible, most commonly occurs in critically ill, hospitalized patients. AKI usually results from

inadequate renal perfusion as a result of severe trauma, illness, or surgery, but it can also be caused by rapidly developing intrinsic renal disease. AKI has a mortality rate ranging from 10% to 60% depending on the underlying etiology. Its causes are divided into three categories:

1. **Prerenal conditions**, which disrupt blood flow on its way to the kidneys:
   - Extremely low blood pressure or blood volume (e.g., hemorrhage, sepsis, dehydration, shock, and traumatic injury)
   - Heart dysfunction (e.g., myocardial infarction and heart failure)
2. **Intrarenal conditions**, which directly damage the structures of the kidneys:
   - Reduced blood supply within the kidneys (e.g., atherosclerosis), which usually results in acute tubular injury or necrosis
   - Hemolytic uremic syndrome (associated with infection with certain strains of *E. coli*, in which bacterial toxins damage small blood vessels; it is the leading cause of AKI in children)
   - Renal inflammation (e.g., glomerulonephritis and acute interstitial nephritis [usually associated with an allergic reaction to certain nephrotoxic medications])
   - Toxic injury (usually from alcohol, cocaine, heavy metals, solvents, fuels, chemotherapy drugs, and contrast dyes)
3. **Postrenal conditions**, which interfere with the urine excretion:
   - Ureter obstruction (e.g., nephrolithiasis and tumors)
   - Bladder obstruction and dysfunction (e.g., BPH, tumors, and nerve innervation disruption)

In addition to these causes, other factors that can increase the risk of developing AKI include advanced age, autoimmune disorders, and liver disease.

AKI has an abrupt onset (usually over a period of 48 hours) and progresses through four phases. The individual is usually asymptomatic in the initial (prodromal) phase. Although renal damage is occurring, the nephrons that are still functioning compensate for

those that are not. During the second (oliguric) phase, impaired glomerular filtration leads to solute and water reabsorption. This reabsorption decreases daily urine output to approximately 400 mL or less, such that waste products begin to accumulate (**uremia**). The second phase can last a few days to a few weeks. In the third (diuretic) phase, renal function gradually returns as healing and cellular regeneration occur. Diuresis occurs due to tubular damage that impairs the kidneys' ability to concentrate the urine. Daily urine output in this phase can be as much as 5 L. The excessive urine output can lead to dehydration and electrolyte imbalances. The third phase can last days to weeks. In the recovery stage, glomerular function gradually returns to normal. This final stage can persist for 3–12 months. Depending on the individual's age and overall health, full renal function may be regained.

As previously mentioned, the initial phase of AKI is asymptomatic. As renal function is lost, however, symptoms appear. Clinical manifestations vary depending on the AKI phase. In the oliguric phase, manifestations are as follows:

- Decreased urine output
- Electrolyte disturbances (usually increased levels)
- Fluid volume excess

application to practice

A 13-year-old boy presented to the clinic complaining of a sore throat that persisted for 2 days. After those 2 days, he developed fever, nausea, and malaise. A throat culture revealed the presence of group A beta-hemolytic streptococci, and the child was started on antibiotic therapy. The child's symptoms gradually improved, but approximately 2 weeks later, he returned to the clinic because the fever, nausea, and malaise had returned. He became tachypneic and short of breath. The mother noted that his eyes were puffy, his ankles were swollen, and his urine was dark and cloudy.

On examination, the child's blood pressure was 148/100 mm Hg, his pulse was 122 beats/min, and his respirations were 35/min. Orbital and ankle edema were present. Rales (abnormal breath sounds) were auscultated bilaterally in the chest, but no heart murmurs were found. Slight tenderness to percussion over the flank areas was noted.

A chest X-ray showed evidence of congestion and edema in the lungs. The patient's hematocrit was 37%, and his WBC was 11,200/mm^3. Blood urea nitrogen was 48

mg/dL (normal is less than 20 mg/dL). Urinalysis results showed that the patient's protein was 2+ (24-hour excretion was 0.8 g), specific gravity was 1.012, and there were moderate amounts of RBCs and WBCs in the urine. Serum albumin was 4.1 g/dL (normal is 3.5–4.5).

- Which evidence supports the conclusion that this patient has a kidney disease?
- Which clinical pattern of kidney disease does this patient have? Can you explain the symptoms?
- Which morphological changes would you expect in the kidney?
- What is the prognosis? What are the possible short- and long-term complications of this disease? Is it necessary to hospitalize the patient?

- Azotemia
- Metabolic acidosis

In the diuretic phase, manifestations include:

- Increased urine output
- Electrolyte disturbances (usually decreased levels)
- Dehydration
- Hypotension

In the recovery phase, symptoms begin resolving.

Diagnostic procedures for AKI include those to identify both the renal injury and its underlying cause. These procedures consist of a history, physical examination, BUN, creatinine, blood chemistry, arterial blood gases, urinalysis, CBC, renal ultrasound, and biopsy. The Kidney Disease: Improving Global Outcomes Guidelines (KDIGO, 2012a) define AKI as follows: (1) increase in serum creatinine ≥ 0.3 mg/dL within a 48-hour period; or (2) increase in serum creatinine to ≥ 1.5 times baseline, which has occurred in the past 7 days; or (3) urine volume < 0.5 mL/kg/hour for 6 hours. A gradual increase in serum creatinine daily (as much as 2 mg/dL/day) is indicative of AKI. Urea nitrogen may increase by 10–20 mg/dL/day, but BUN can be misleading because it is often elevated in conditions causing increased protein catabolism (e.g., surgery, trauma, corticosteroids, burns, transfusion reactions, parenteral nutrition, or

gastrointestinal or other internal bleeding). Other findings include acidosis, hyperkalemia, hyponatremia, hyperphosphatemia, hypocalcemia, and anemia.

Treatment strategies for AKI vary depending on the phase and cause. For instance, different fluid and electrolyte disturbances occur in the second and third phases, requiring different strategies for these phases. Some patients with AKI may require temporary dialysis until renal recovery occurs. Other supportive strategies include the following measures:

- A diet that is high in calories and carbohydrates but restricted in protein, sodium, potassium, and phosphates
- Hypertension management
- Anemia treatment with synthetic erythropoietin
- Infection prevention strategies (e.g., hand washing, limiting visitors, and aseptic technique)

Chronic Kidney Disease

Chronic kidney disease (CKD) involves a gradual, irreversible loss of renal function. During the disease process, nonoperational scar tissue replaces injured nephrons. More than 37 million adults are living with CKD in the United States (CDC, 2021). Several conditions, including those in the following list, can initiate the slow, progressive destruction of the nephrons:

- Diabetes mellitus (type 1 and type 2) is the leading cause of CKD in the United States because of the vascular damage it produces (see the *Endocrine Function* chapter).
- Hypertension is another common cause of CKD in the United States; it can damage the glomeruli and ultimately cause the damaged nephrons to lose their ability to filter waste from the blood.
- Urine obstructions (e.g., nephrolithiasis and BPH) can block urine flow, increasing pressure in the kidneys and reducing their function.

- Renal diseases (e.g., polycystic kidney disease, pyelonephritis, and glomerulonephritis) damage nephrons in a variety of ways.
- Renal artery stenosis (narrowing or blockage of the artery that supplies the kidneys) impairs blood flow and leads to kidney damage.
- Ongoing exposure to toxins (e.g., fuel, solvents, and lead) and nephrotoxic medications (e.g., many antibiotics, chemotherapy, and NSAIDs) can cause direct damage as these agents circulate through the kidneys.
- Sickle cell disease can damage the kidneys by impairing renal blood flow as the sickled blood cells clump together in the renal arteries.
- Systemic lupus erythematosus causes direct damage to the renal tissue as the autoantibodies destroy the body's own cells.
- Smoking hardens the blood vessel walls throughout the body, especially in the tiny vessels of the kidney, and triggers vasoconstriction; both changes cause chronic ischemia and necrosis.
- With aging, the kidneys generally become less efficient and are exposed to more conditions that can cause damage.

Regardless of the etiology, renal function gradually diminishes as nephrons are increasingly damaged. In turn, the kidneys progressively lose the ability to regulate fluid volume, blood pressure, metabolic waste and drug excretion, vitamin D conversion, pH regulation, and hormone synthesis. Fluid and electrolyte imbalances occur as the ability to concentrate urine declines early, followed by decreases in the ability to excrete phosphate, acid, and potassium. As the disease progresses, the ability to effectively dilute or concentrate urine is lost. Serum potassium is usually controlled through distal nephron secretion until renal failure is advanced. Serum sodium levels usually remain normal because the kidneys increase sodium excretion in the urine (i.e., fractional sodium). Decreased renal production of calcitriol contributes to hypocalcemia, while

decreased renal excretion of phosphate leads to hyperphosphatemia. Secondary hyperparathyroidism commonly develops.

Renal osteodystrophy refers to abnormal bone mineralization resulting from hyperparathyroidism, calcitriol deficiency, elevated serum phosphate, or low or normal serum calcium. This condition can lead to increased bone turnover, causing osteopenia or osteomalacia. Metabolic acidosis triggers muscle wasting due to protein catabolism, bone loss due to bone buffering of acid, and accelerated progression of kidney disease.

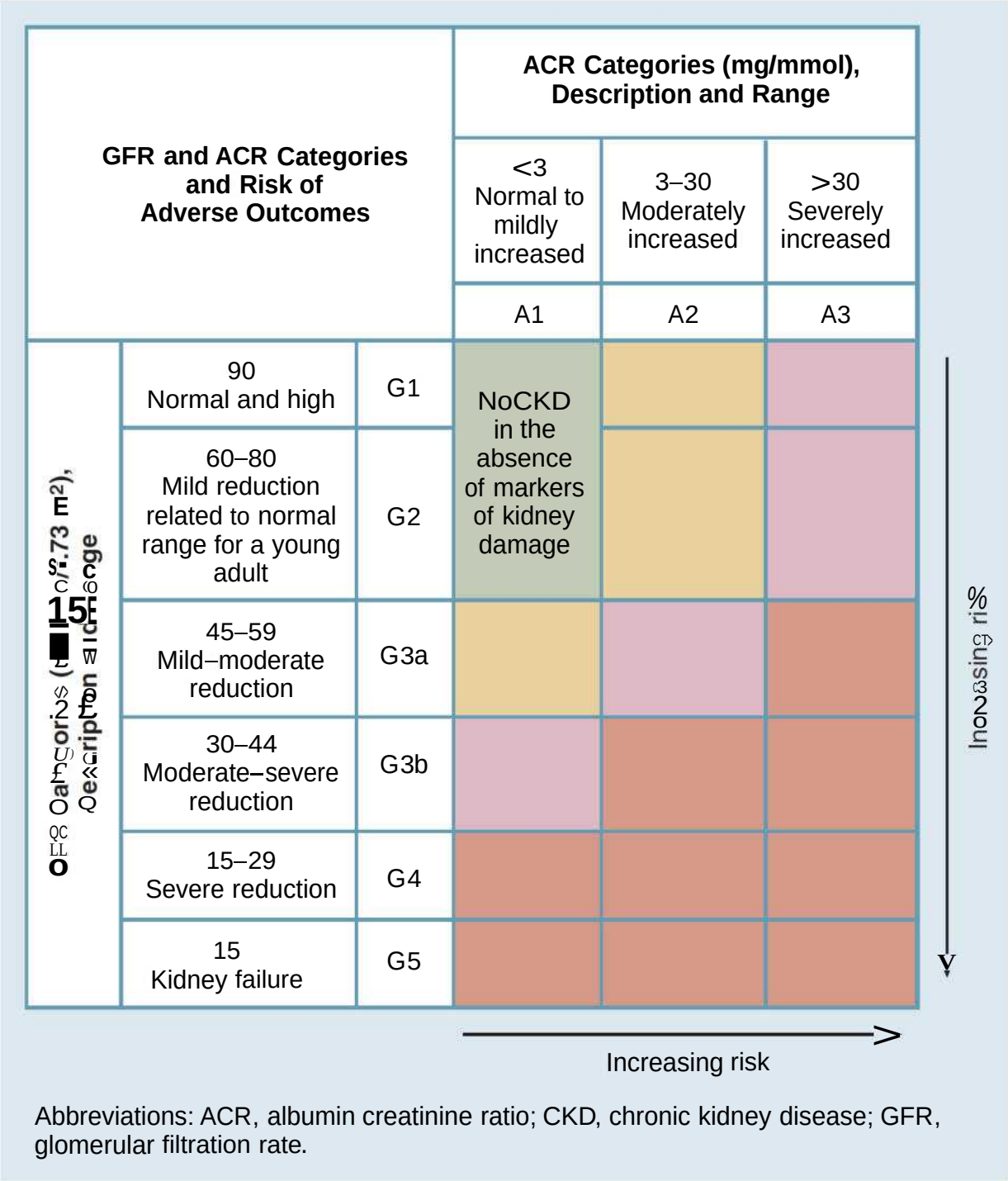
Changes in serum creatinine and urea levels are minimal early, as compensatory mechanisms increase as GFR diminishes. As the disease progresses, serum urea and creatinine climb, causing many of the systemic manifestations associated with CKD. Anemia develops as erythropoietin production declines with disease progression.

CKD can develop from several different types of injuries, all of which result in a common syndrome characterized clinically by systemic hypertension, proteinuria, and a gradual decline in GFR as well as pathophysiologically by progressive interstitial fibrosis, peritubular capillary loss with hypoxia, and destruction of functioning nephrons due to tubular atrophy (Metcalfe, 2007). The rate at which GFR declines—that is, the rate of CKD progression—may primarily reflect secondary factors that are mostly unrelated to the initial disease. Two of these nonmodifiable factors are age and race.

Other factors include compensatory glomerular hyperfiltration, glomerular hypertrophy, and intraglomerular hypertension. Initially, compensatory hyperfiltration by undamaged nephrons is triggered to maintain overall GFR; however, the hyperfiltration causes glomerular injury and glomerulosclerosis. Glomerular cell proliferation, macrophage infiltration, and accumulation of extracellular matrix (ECM) contribute to the sclerosis and stretching the capillaries and mesangial cells, which trigger mesangial proliferation. Cytokines are thought to be responsible for some of these changes. The proliferation results in glomerulus hypertrophy, and the sclerosis leads to intraglomerular hypertension. The intraglomerular hypertension and hypertrophy increase capillary wall stress and glomerular diameter,

which causes the glomerular epithelial cells to detach from the capillary walls. Water and solutes can pass more freely through these areas, but large circulating macromolecules (e.g., immunoglobulin M, fibrinogen, and complement metabolites) cannot cross the GBM and become trapped in the subendothelial space (i.e., hyaline deposits). Their accumulation slowly narrows the capillary lumens, decreasing glomerular perfusion and filtration. Increased synthesis and decreased breakdown of ECM result in tubulointerstitial injury and fibrosis.

CKD generally evolves through five stages that are identified based on GFR as well as urine albumin levels (**FIGURE 7-21**) (KDIGO, 2012b). In the first stage, kidney damage is present, but the GFR is normal or high (>90). The GFR begins falling as the patient progresses through stage II (GFR 60–89), stage III (GFR 30–59), and stage IV (GFR 15–29). Eventually, the patient reaches kidney failure in stage V, as the GFR drops to less than 15 or the patient begins dialysis. Clinical manifestations begin to appear slowly as the renal function declines by 50%. The definition and diagnosis of CKD based on albuminuria is based on the following criteria: (1) kidney damage for longer than 3 months, as defined by structural or functional kidney abnormalities with or without decreased GFR, and (2) GFR < 60 for longer than 3 months, with or without kidney damage. Kidney damage is further specified as albuminuria (albumin clearance rate > 30 mg/24 hours), urine sediment abnormalities, electrolyte imbalances as a result of tubular disorders, kidney disease based on histology or structural abnormalities, and history of kidney transplant.



Abbreviations: ACR, albumin creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate.

FIGURE 7-21 Classifications of chronic kidney disease using glomerular filtration rate (GFR) and albumin clearance rate (ACR) categories.

Description

Clinical manifestations are complex and depend on the degree of renal function lost. These manifestations also reflect the complications associated with CKD (TABLE 7-6). In addition to complications resulting from declining functioning, increased albumin levels have been associated with increased mortality, cardiovascular events, and progressive CKD. As mentioned, CKD is often asymptomatic initially because the remaining nephrons compensate for those lost to the disease. Clinical manifestations develop insidiously as 50% of the nephrons are destroyed. These manifestations include the following signs and symptoms:

TABLE 7-6 Complications of Chronic Kidney Disease

System	Etiology	Treatment
General appearance	Tired, weak, sallow skin color due to anemia and toxins	Dialysis and epoetin alfa
Integumentary	Itching (uremic frost) occurs in an attempt to remove toxins (e.g., phosphate and urea) from the body Dryness and decreased sweating as a result of decreased oil and sweat gland activity	Dialysis and palliative care
Sensory	Metallic taste in mouth and fishy breath odor (uremic fetor) due to toxins	Dialysis
Cardiopulmonary	Hypertension	
	Related to salt and water retention, supplemental erythropoietin (20% of patients on this therapy develop CKD), or increased renin production Accelerated renal damage if not controlled Development of heart failure	Limiting salt and fluids ACE inhibitors, angiotensin II receptor blockers, calcium-channel blockers, and beta blockers Blood pressure goal is 120/80 mm Hg
	Pericarditis	

System	Etiology	Treatment
	Result of metabolic toxins	Hemodialysis
	Chest pain, fever, friction rub, and decreased cardiac output	
	Heart failure (in 75% of patients needing dialysis), ischemic heart disease, and cardiomyopathy	
	Result of increased workload of the heart (left ventricular hypertrophy) secondary to anemia, dialysis (shunting of blood), fluid overload, hypertension, and atherosclerosis	Salt and fluid restriction Diuretics (loop) ACE inhibitors and angiotensin II receptor blockers
Hematologic	Coagulopathy	
	Platelet dysfunction due to abnormal aggregation and adhesion Increased bleeding time Platelet count slightly decreased May have petechiae or purpura Increased thrombosis risk	Desmopressin (causes release of factor VIII from endothelial cells)—used before surgery
	Anemia	
	Related to decreased erythropoietin production (occurs when glomerular filtration rate falls below 20–25 mL/min), iron deficiency, and bone marrow suppression secondary to uremia Erythrocyte destruction due to hemodialysis	Epoetin alfa if hematocrit < 33% (hemoglobin levels should increase no more than 1 g/dL every 3–4 weeks so hypertension does not develop) Intravenous iron for patients on dialysis (oral absorption of iron is poor)
Gastrointestinal	Anorexia, nausea, vomiting, hiccups, ulcerations—related to metabolic toxins	Dietary protein restriction Dialysis
Endocrine	Decreased libido, impotence, and infertility	

System	Etiology	Treatment
	Decreased estrogen levels in women—prevents ovulation and causes menorrhagia and amenorrhea Decreased testosterone levels in men	Dialysis and a healthy diet may restore fertility
	Glucose intolerance	
	Peripheral insulin resistance	
	Serum insulin high	
	Kidneys cannot clear insulin from bloodstream	Patients with diabetes may require lower doses of hypoglycemic agents
Mineral metabolism	Renal osteodystrophy (disorder of calcium, phosphorus, and bone) leading to bone pain, fractures, muscle weakness, and calcium deposits in the blood vessels, soft tissue, heart, and lungs	
	Low glomerular filtration rate leads to slower phosphorus excretion and increased calcium excretion Increased parathyroid hormone secretion, leading to a high bone turnover rate In stage V, buffering of excess hydrogen ions by leaching of large stores of calcium phosphate and calcium carbonate from the bones (i.e., bone demineralization)	Dietary phosphorus restriction Administer phosphorus-binding drugs such as calcium carbonate Vitamin D (suppresses parathyroid hormone)
Neurologic	Uremic encephalopathy	

System	Etiology	Treatment
	Appears when glomerular filtration rate falls below 10–15 mL/min or because of hyperparathyroidism Symptoms: poor concentration (first sign) that progresses to confusion, asterixis, weakness, nystagmus, and hyperreflexia Peripheral neuropathy (restless legs syndrome, distal pain, and loss of deep tendon reflexes), usually symmetrical and in the lower extremities Impotence and autonomic dysfunction	Dialysis
Metabolic	Hyperkalemia	
	Glomerular filtration rate < 10–20 mL/min Hemolysis, trauma, and acidosis Diet high in citrus fruits/juices Medications such as ACE inhibitors and NSAIDs	Monitor cardiac status Administer calcium chlorides, insulin, glucose (insulin moves potassium into cells), bicarbonate, or an exchange resin Dietary potassium restriction
Acid–base disorders	Damaged kidneys	
	Cannot produce enough ammonia or buffer hydrogen ions Arterial pH generally between 7.33 and 7.37 Buffering of excess hydrogen ions by large stores of calcium phosphate and calcium carbonate from the bones	Maintain serum bicarbonate > 21 mEq/L by giving alkali supplements, such as sodium bicarbonate, calcium bicarbonate, or sodium citrate

Abbreviations: ACE: angiotensin-converting enzyme; CKD: chronic kidney disease; NSAIDs: nonsteroidal anti-inflammatory drugs.

- Hypertension (see the *Cardiovascular Function* chapter)
- Polyuria with pale urine (early)
- Oliguria or anuria (absent urine output) with dark-colored urine (late)

- Anemia
- Bruising and bleeding tendencies
- Electrolyte imbalances, specifically hyperkalemia, hypocalcemia, hypomagnesemia, and hyperphosphatemia
- Muscle twitches and cramps (related to hypocalcemia and hyperphosphatemia; see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter)
- Pericarditis, pericardial effusion, pleuritis, and pleural effusion (secondary to uremia)
- Heart failure (see the *Cardiovascular Function* chapter)
- Respiratory distress and abnormal breath sounds (due to pulmonary edema associated with heart failure; see the *Cardiovascular Function* chapter)
- Sudden weight change (usually increased because of fluid retention)
- Edema of the feet and ankles (due to fluid retention)
- Azotemia
- Peripheral neuropathy, restless legs syndrome, and seizures
- Nausea and vomiting
- Anorexia
- Malaise
- Fatigue and weakness
- Headaches that seem unrelated to any other cause
- Sleep disturbances
- Decreased mental alertness
- Flank pain
- Jaundice
- Persistent pruritus
- Recurrent infections (due to an impaired immune response because of uremia)

Diagnosis of CKD is often difficult because the initial symptoms are vague and nonspecific. Additionally, distinguishing CKD from AKI can be challenging (TABLE 7-7). Diagnosis is based on KDIGO (2012a, 2012b) criteria, and diagnostic procedures focus on identifying the disease and any complications that have developed as a result of its development. These procedures include a history, physical examination, urinalysis, quantitative urine protein, blood chemistry (especially electrolytes, creatinine, and BUN), CT, MRI, renal ultrasound, biopsy, CBC, and arterial blood gases.

TABLE 7-7 Distinguishing Acute Kidney Injury from Chronic Kidney Disease

Finding	Comment
Decreased kidney function (eGFR < 60 mL/min/1.73 m^2) for ≥ 3 months	Most reliable evidence of CKD
Renal sonogram showing small kidneys	Usually CKD
Renal sonogram showing normal or enlarged kidneys	May be AKI or some forms of CKD (diabetic nephropathy, acute hypertensive nephrosclerosis, polycystic kidney disease, myeloma, rapidly progressive glomerulonephritis, infiltrative diseases [e.g., lymphoma, leukemia, amyloidosis], obstruction)
Oliguria, daily increases in serum creatinine and BUN	Probably AKI or AKI superimposed on CKD
No anemia	Probably AKI or CKD due to polycystic kidney disease
Severe anemia, hyperphosphatemia, and hypocalcemia	Possibly CKD but may be AKI

Finding	Comment
Subperiosteal erosions on radiography	Probably CKD
Chronic symptoms or signs (e.g., fatigue, nausea, pruritus, nocturia, hypertension)	Usually CKD

Abbreviations: AKI: acute kidney injury; BUN: blood urea nitrogen; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

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The main goal of CKD treatment is to stop or slow disease progression, usually by controlling the underlying cause. Additionally, strategies to treat and prevent complications will be necessary (see Table 7-6). Doses of any medications will likely need adjustments; with limited excretion capability, medication toxicity is probable when the usual doses are given. Without treatment, CKD has a mortality rate of 100%. Conservative management strategies are employed early but evolve into more aggressive measures as renal function declines.

application to practice

Now that we have discussed conditions of the urinary system, let's put this knowledge into practice. After receiving reports on the following patients, which patient should you assess first?

- A 32-year-old female admitted yesterday with recurrent UTI who is not responding to therapy and complains of dysuria and hesitancy
- A 48-year-old male admitted yesterday with nephrolithiasis who complains of pain rated as a 5 on a 0–10 scale
- A 38-year-old female admitted 2 hours ago who was involved in a motor vehicle accident and has hematuria

» A 62-year-old male 2 days post TURP

Once again, you go through the usual thought process—who would die first, acute versus chronic conditions, Maslow's hierarchy of needs, and patient safety. Let's start with the 32-year-old patient. UTI is acute but not generally life threatening. Keep her on the short list, though. Moving on to the 48-year-old patient, nephrolithiasis is not life threatening, but it is acute. Additionally, this patient is experiencing some moderate pain. We should keep him on the short list, too. For the 38-year-old patient, hematuria can be concerning because she was in a motor vehicle accident. The kidneys likely experienced trauma that could lead to AKI, which can be life threatening. This patient would likely take priority over the first two but take a look at the last patient before you make your final decision. The 62-year-old patient is 2 days postoperative. The critical time period is likely passed, and the TURP procedure is generally minimally invasive. Prostate issues would not likely be life threatening in the short term. After considering all the patients to be assessed, you should see the 38-year-old female first.

application to practice

Mrs. Ester Hudson, a 72-year-old female, presents to the emergency department with slurred speech and her family stating she has "not been acting like herself" since she woke up this morning. Her gait is unsteady. She responds appropriately to questions, but her response is delayed. She is alert and oriented to person, place, time, and situation. She has no specific complaints other than feeling "tired."

Vital signs: blood pressure 80/50, pulse 70, respiration rate 22, temperature 98.4°, oxygen saturation 89% on room air.

Medical history: hypertension, systemic lupus erythematous, and osteoporosis

Medications: Metoprolol ER 50 mg once daily, Lisinopril 20 mg once daily, hydrochlorothiazide 50 mg once daily, and diclofenac 50 mg twice daily

1. What information would be important to assess as a part of Mrs. Hudson's history?
2. What physical assessments should you perform based on her presenting information?
3. Based on this available information, what diagnostic tests should be performed?

SUMMARY

The urinary system maintains homeostasis through a complex filter (kidney) that can regulate pH, fluid, electrolytes, and blood glucose. Additionally, the urinary system is the main site for excreting waste products and other harmful substances obtained from the food and water ingested orally. A functioning urinary system is crucial to maintaining health, and disease in this system can have detrimental effects on other systems and the body as a whole. Prevention and early treatment of these diseases are paramount to avoiding these consequences. Maintaining a healthy lifestyle (e.g., drinking plenty of fluids, avoiding harmful chemicals, preventing sexually transmitted infection, exercising, and smoking cessation) can help preserve urinary health.

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CHAPTER 8

Reproductive Function

LEARNING OBJECTIVES

- Discuss normal reproductive anatomy and physiology.
- Describe congenital reproductive disorders.
- Describe issues with fertility.
- Describe and compare common menstrual disorders.
- Discuss various disorders of the reproductive structures.
- Describe and compare infectious disorders of the reproductive system.
- Describe and compare cancers of the reproductive system.

KEY TERMS

amenorrhea
ampulla
anteflexed
areola
areolar gland
ascending testicle
Bartholin gland
breast cancer
candidiasis
cervical cancer
cervix
chancre
chlamydia
chordee
clitoris

condylomata acuminatum
Cowper gland
cryptorchidism
cystocele
dysmenorrhea
ectopic pregnancy
ectopic testis
ejaculation
ejaculatory duct
endometrial cancer
endometriosis
endometrium
epididymis
epididymitis
epispadias
erectile dysfunction (ED)
fallopian tube
fibrocystic breast mass
foreskin
genital herpes
gestation
gonorrhea
herpes simplex virus (HSV)
human papillomavirus (HPV)
hydrocele
hymen
hypospadias
impregnation
infertility
labia majora
labia minora
lactation
latent herpes genitalis
latent syphilis
leiomyoma
mammary gland
mastitis
meatus

menopause
menstrual cycle
menstruation
mons pubis
myometrium
nipple
oogenesis
orgasm
ovarian cancer
ovarian cyst
ovary
ovulation
paraphimosis
parturition
pelvic inflammatory disease (PID)
penile cancer
penis
perimetrium
phimosis
placenta
polycystic ovary syndrome
premenstrual dysphoric syndrome (PMDS)
premenstrual syndrome (PMS)
priapism
primary herpes genitalis
primary syphilis
prodrome
prolactin
prostate cancer
prostate gland
prostatitis
rectocele
recurrent herpes genitalis
retractile testicle
retroflexed
scrotum
secondary syphilis
semen

seminal vesicle
sexually transmitted infection (STI)
shedding herpes genitalis
Skene gland
smegma
spermatic cord
spermatocele
spermatogenesis
syphilis
tertiary syphilis
testes
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vulva
zygote

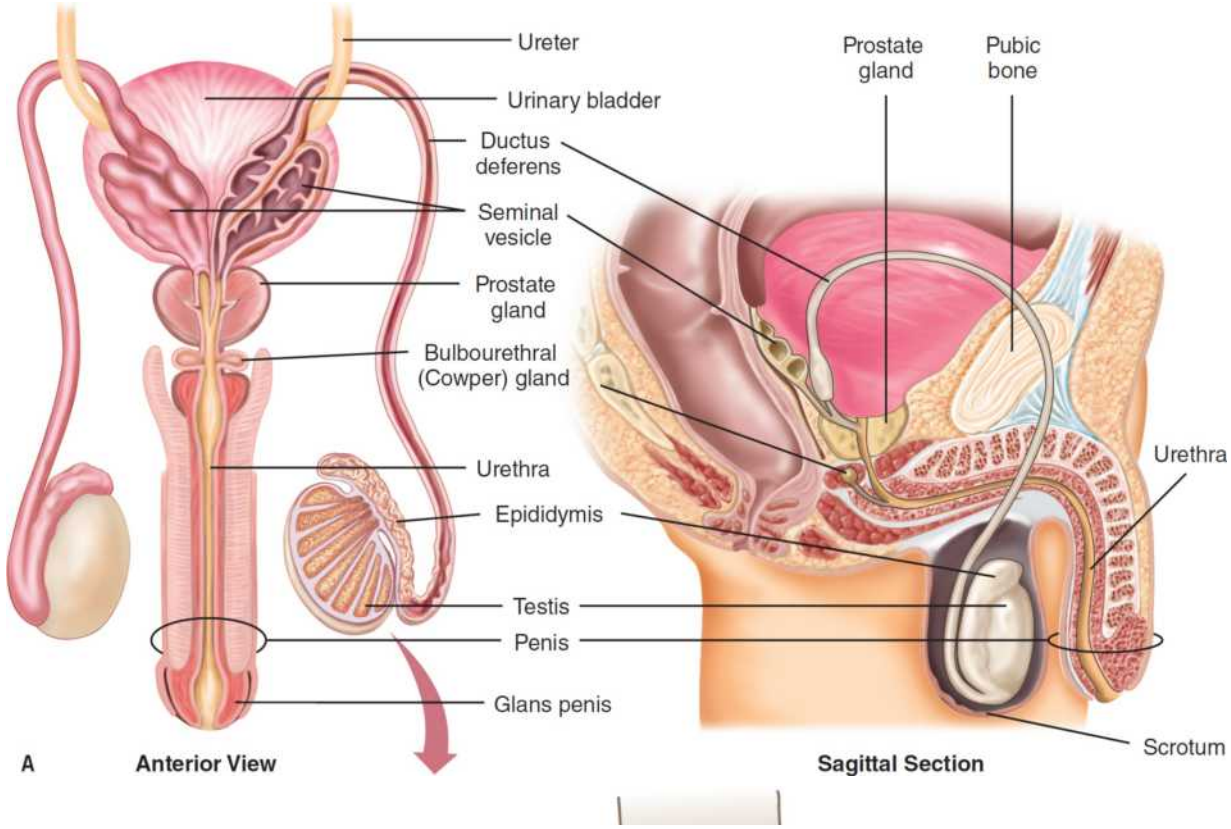
The reproductive system is composed of the structures responsible for procreation; therefore, a healthy reproductive system is necessary for the survival of the species. This system is responsible for transmitting genetic material to offspring (see the *Cellular Function* chapter). The male reproductive system generates sperm and transports it to the female reproductive system. The female reproductive system produces ova. When a sperm fertilizes an ovum, the female reproductive system nurtures and safeguards the embryo as it develops into a fetus, with this process lasting until birth. The primary difference between the two systems is the varying hormone levels, which cause the reproductive system to

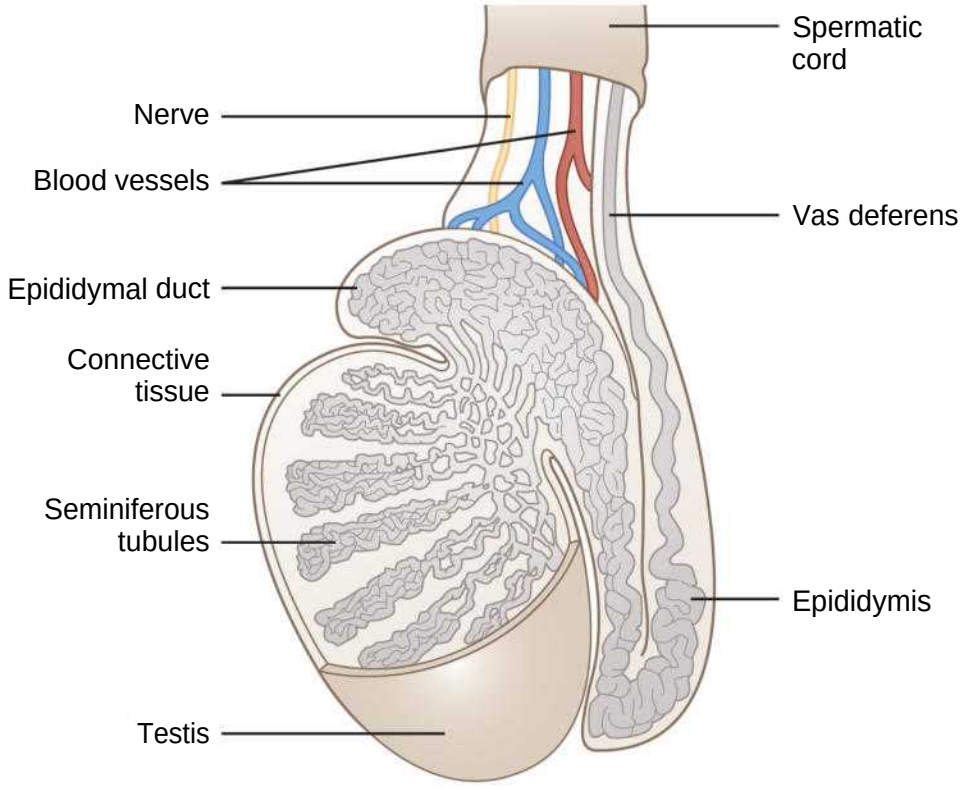
develop differently. The male reproductive system is generally external, whereas the female reproductive system is internal.

Anatomy and Physiology

Normal Male Reproductive System

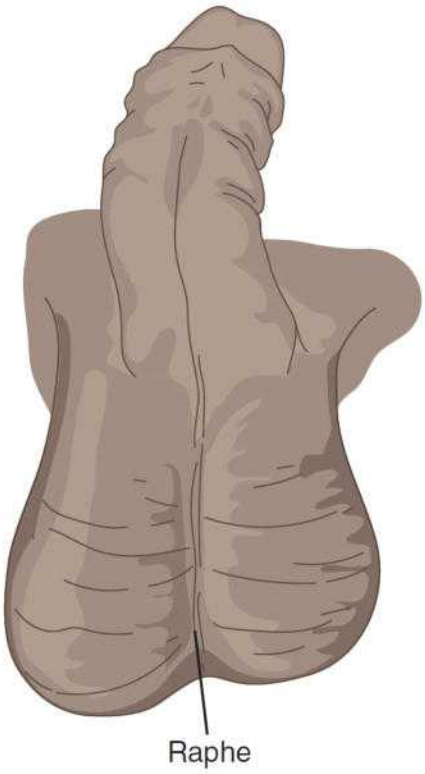
The male reproductive system includes organs involved in the generation (**spermatogenesis**) and transportation of sperm—the **penis**, **scrotum**, **testes**, duct system, and accessory glands (**FIGURE 8-1**; **TABLE 8-1**). In addition to producing sperm, the male reproductive system produces sex hormones (mostly **testosterone**) that give males their distinct characteristics (e.g., facial hair, increased muscle mass, and low voice pitch). Parts of the male reproductive system work with the urinary system to aid in urinary elimination (e.g., the urethra). Because the male reproductive and urinary systems are integrated, disorders in one system generally affect the other system (see the *Urinary Function* chapter for more discussion of the urinary system).





B

External View of Scrotum



Muscle Layer/Deep Tissues

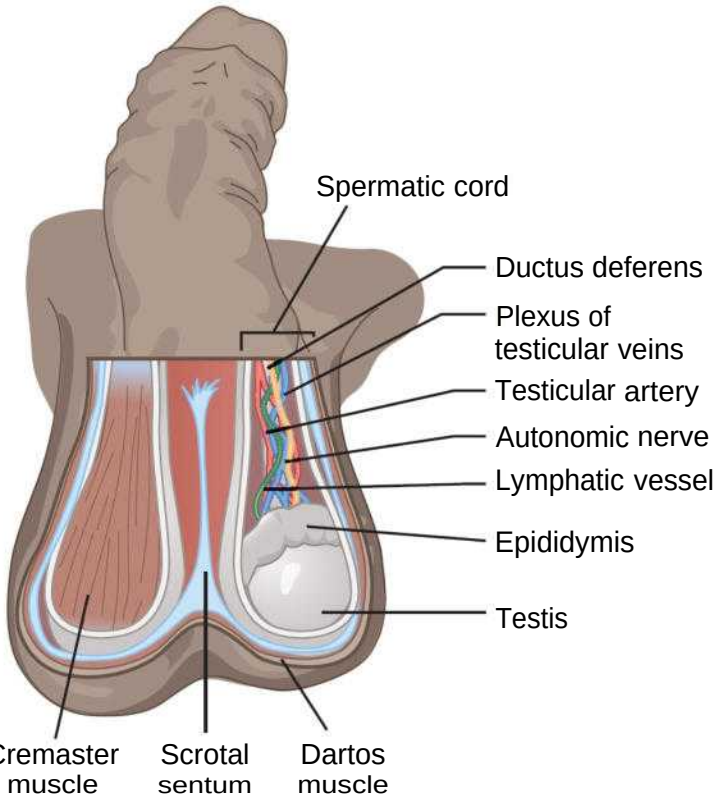




FIGURE 8-1 The male reproductive system. **(A)** Organs of the male reproductive system. **(B)** Interior view of the testis. **(C)** Muscle layer and deep tissues of the scrotum.

Description

TABLE 8-1 The Male Reproductive System

Component	Function
Testes	Produce sperm and male sex steroids
Epididymides	Transport and store sperm; site for sperm maturation
Vas deferens	Transport sperm to urethra
Sex accessory glands	Produce seminal fluid that nourishes sperm
Urethra	Carries sperm to the outside of the male body
Penis	Organ of copulation
Scrotum	Provides protection and proper temperature for testes

Penis

The penis is part of the male external genitalia; it contains erectile tissue that fills with blood during sexual arousal. The penis deposits sperm in the female reproductive system during sexual intercourse. The penis consists of three cylinders—the corpus spongiosum (which contains the urethra) and two corpora cavernosa (**FIGURE 8-2**). The penis structure includes the root, shaft, and glans (enlarged tip). Penis length can vary considerably, but the average length is 2–5 inches when flaccid and 4–7 inches when erect. Penis appearance can also vary from person to person (**FIGURE 8-3**).

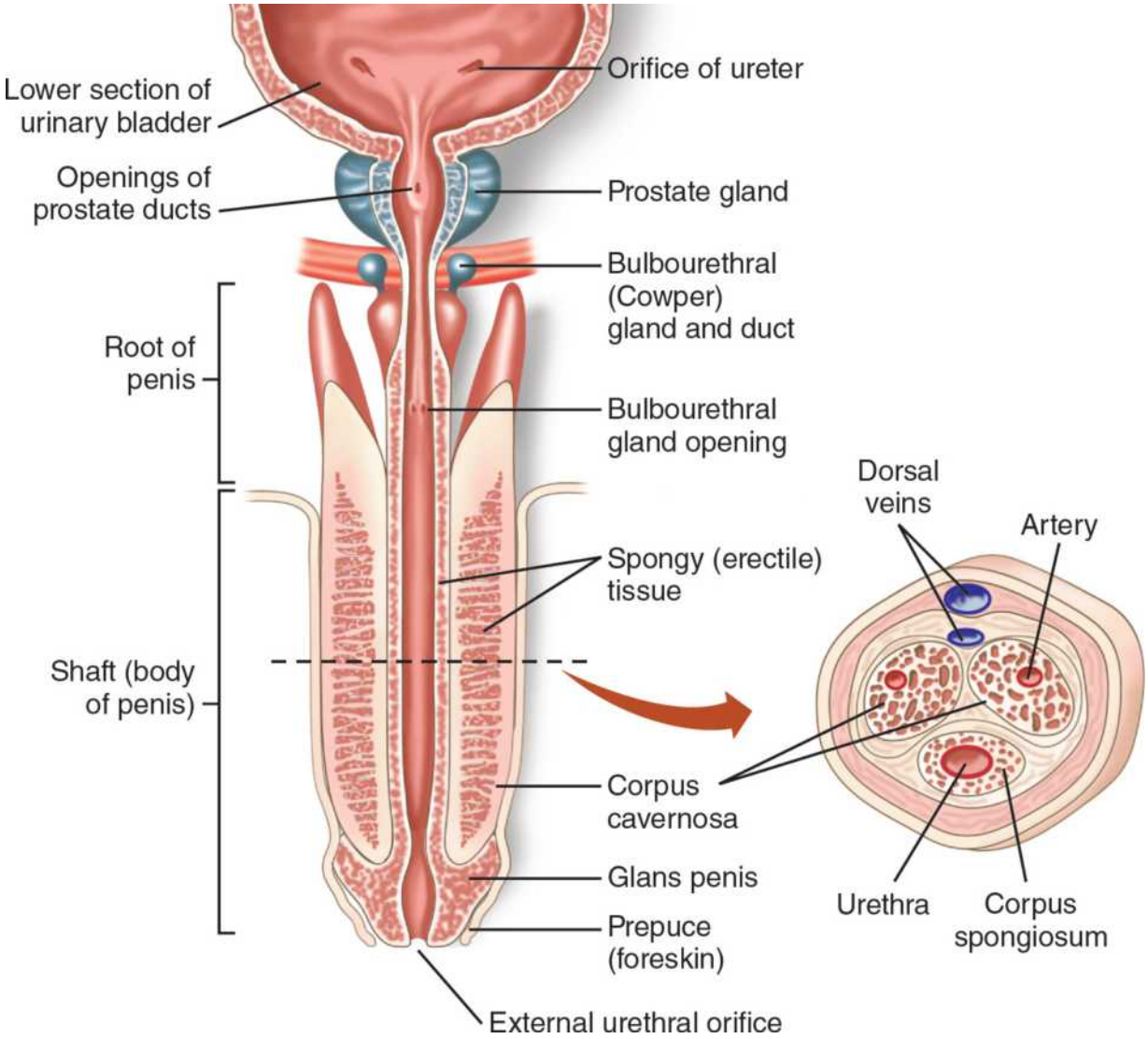


FIGURE 8-2 Anatomy of the penis.

Description



FIGURE 8-3 Variations of the male genitalia.

A: © Publiphoto/Science Source; **C:** © John Henderson/Alamy Stock Photo

A sheath of loose skin, called the **foreskin**, covers the glans penis at birth; it is fully attached to the penis at this point. The foreskin is often surgically removed (i.e., circumcision) shortly after birth for hygienic, cultural, or religious reasons. If the foreskin is not surgically removed, it separates and can be retracted (pulled back) by two years of age. The glans produces an oily secretion that can combine with dead skin to form a cheesy substance called **smegma**. If the smegma is not regularly removed from under the foreskin, the penis can become irritated and infected. The glans also has an opening, or **meatus**, that allows for **ejaculation** (propulsion of sperm-containing fluid) and urination.

Scrotum

The scrotum is a sac of skin just below the penis that contains the testes, epididymides, and lower **spermatic cords** (see Figure 8-1). The scrotal wall is a thin layer of skin lined with smooth muscle. The scrotum is divided into two compartments, each containing one testicle and **epididymis**. The two compartments are distinguished externally by a middle ridge called a “raphe.” Internally, the raphe connects to a muscular divider called the “septum.” The scrotum maintains the proper testicular temperature for spermatogenesis by contracting to draw the testes closer to the body to warm them and relaxing to drop the testes farther from the body to cool them.

Testes

The testes, or gonads, produce sperm and the sex hormones. Spermatogenesis develops in most males by 16 years of age and continues over the male’s lifetime. The testes form in the abdominal cavity in utero and descend into the scrotum in approximately the seventh month of **gestation** when stimulated by rising testosterone levels. Occasionally, they will descend shortly after birth (usually by 3 months of age). The seminiferous tubules produce sperm, and the

epididymis stores sperm until ejaculation (up to 6 weeks). Sertoli cells —somatic cells found in the seminiferous tubules—nourish the sperm as they mature during storage, making them capable of swimming. The testes can produce approximately 50,000 sperm per minute; the sperm's maturation takes approximately 70–80 days.

Most male sex hormones (especially testosterone) are produced by the Leydig cells of the testes. The adrenal gland in both sexes produces small amounts of these hormones (i.e., androgens). The number of Leydig cells is controlled by two hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH also regulates the amount of hormones produced by these cells. The hypothalamic–pituitary–testicular axis regulates the amount of hormones produced (**FIGURE 8-4**). When testosterone levels are low, gonadotropin-releasing hormone (GnRH) is released by the hypothalamus, which stimulates the pituitary gland to release LH and FSH. LH and FSH then stimulates testosterone synthesis. This mechanism is a negative feedback loop, so it inhibits testosterone synthesis when levels are high.

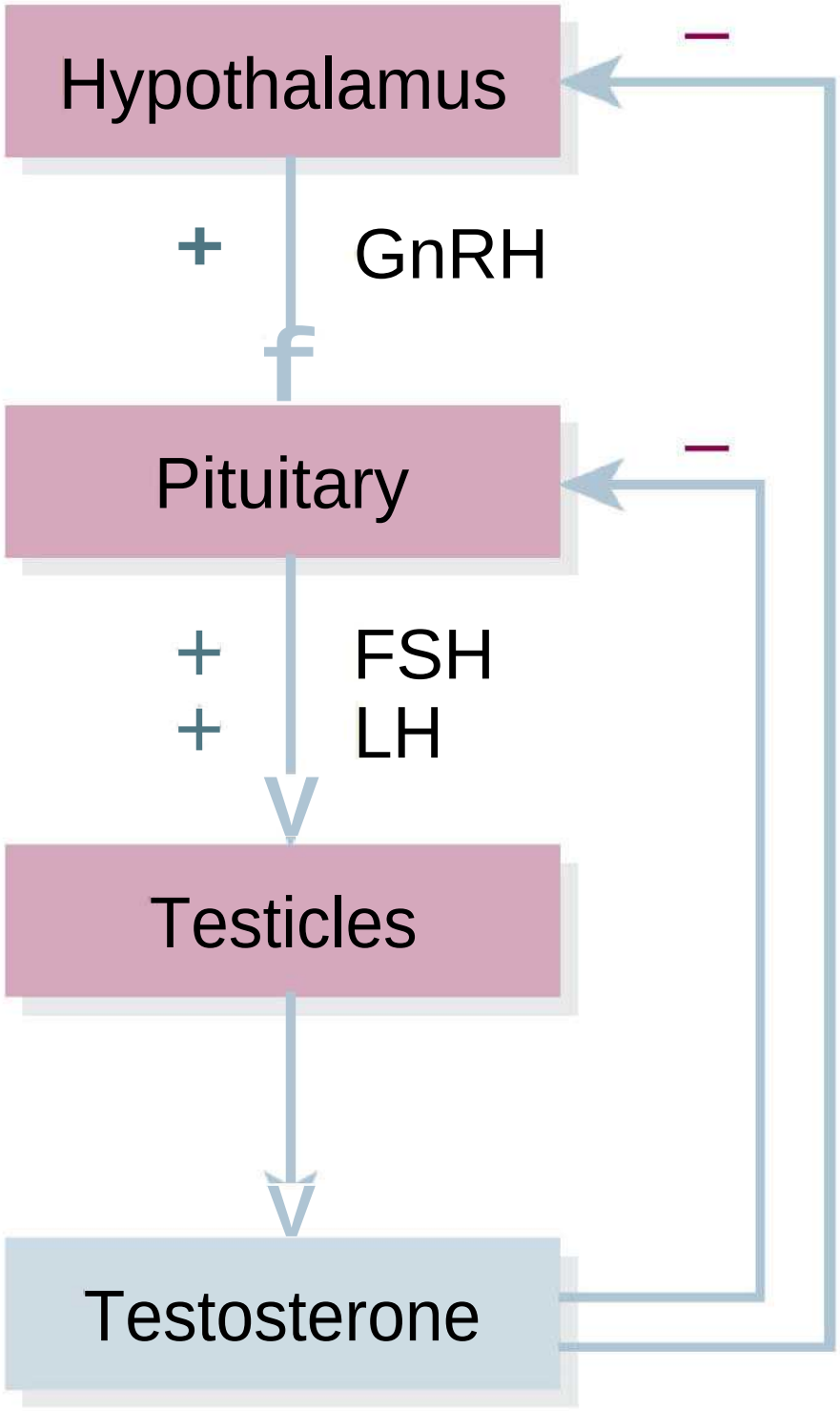


FIGURE 8-4 The hypothalamic–pituitary–testicular axis.

Description

Exposure to increased testosterone levels gives males their classic secondary sex characteristics (e.g., facial hair and deep voice) and sex drive. Testosterone also regulates metabolism and protein anabolism (encourages skeletal growth and muscle development), inhibits pituitary secretion of the gonadotropins (FSH and interstitial cell–stimulating hormone), and promotes potassium excretion and renal sodium reabsorption. Additionally, testosterone contributes to male pattern baldness and acne in some men.

Duct System

The male reproductive system contains a complex tube structure to deliver sperm from the testes to the female reproductive system. This duct system includes the epididymis, **vas deferens**, spermatic cord, **ejaculatory duct**, and urethra. Once they are mature, sperm leave the epididymis and travel to the vas deferens. The testicular artery and venous plexus, lymph vessels, nerves, connective tissue, and cremaster muscle (which contracts or relaxes the scrotum) surround the vas deferens; together, these structures make up the spermatic cord. The vas deferens widens at the prostate, forming a pouch called the **ampulla**. The ampulla joins the **seminal vesicles** (a pair of pouches that secrete an alkaline ejaculatory fluid containing sugar, protein, and prostaglandins to nurture and protect the sperm) to form the ejaculatory duct. In the vesicles, the sperm and the ejaculatory fluid join to form **semen**. Semen flows from the ejaculatory duct to the urethra, where it is propelled from the penis during sexual intercourse.

Accessory Glands

The primary function of the accessory reproductive glands is to facilitate ejaculation. Sexual stimulation initiates the ejaculatory process. When a male is sexually stimulated, his sperm travel first from the epididymis to the vas deferens, and then to the seminal vesicles and ejaculation duct. Fluid from the **prostate gland** (a chestnut-shaped gland located at the base of the urethra) mixes with the sperm and secretions of the seminal vesicles. This prostate fluid further decreases the ejaculatory fluid's acidity, increases sperm

motility, and prolongs sperm life. The alkaline medium counteracts the acidity of vaginal secretions that would otherwise kill the sperm. The **Cowper glands** (two pea-sized glands found adjacent to the urethra) secrete another alkaline fluid into the urethra to neutralize the acidity caused by urine transportation. The Cowper gland secretions can sometimes be seen at the meatus before ejaculation. They aid in lubrication of the penis during sexual intercourse and may contain some sperm left over from a previous ejaculation; therefore, these secretions can cause pregnancy even if the penis is withdrawn prior to ejaculation.

The actual expulsion of semen from the penis is the result of motor neurons stimulating muscular contractions of the glands and ducts of the reproductive system—particularly the ampulla, seminal vesicles, and bulbocavernosus muscle (the muscle surrounding the corpus spongiosum). During ejaculation, a valve at the bladder closes to prevent urine from entering the urethra and killing the sperm. An **orgasm**, the climax of pleasurable sensations, usually accompanies the ejaculation. Ejaculated semen contains sperm (about the volume of a pinhead) and secretions (about a tablespoon) from the seminal vesicles, prostate, and Cowper glands. One ejaculation contains approximately 300 million sperm.

Normal Female Reproductive System

The female reproductive tract is a complex system that includes organs to manage the generation of eggs (**oogenesis**), transportation of eggs (**ovulation**) for fertilization (**impregnation**), support of fetal development (gestation), birth of the fetus (**parturition**), and feeding of the offspring (through **lactation**). To accomplish all these functions, the female reproductive system requires a delicate hormone balance and operational organs. These organs include the ovaries, **fallopian tubes**, **uterus**, **vagina**, external genitalia, and **mammary glands** (**FIGURE 8-5**; **FIGURE 8-6**; **FIGURE 8-7**; **FIGURE 8-8**). In addition to facilitating the system's function, the hormones produced by the female reproductive system —specifically estrogen and progesterone—give females their distinct

characteristics (e.g., enlarged breasts, wide hips, and high-pitched voice).

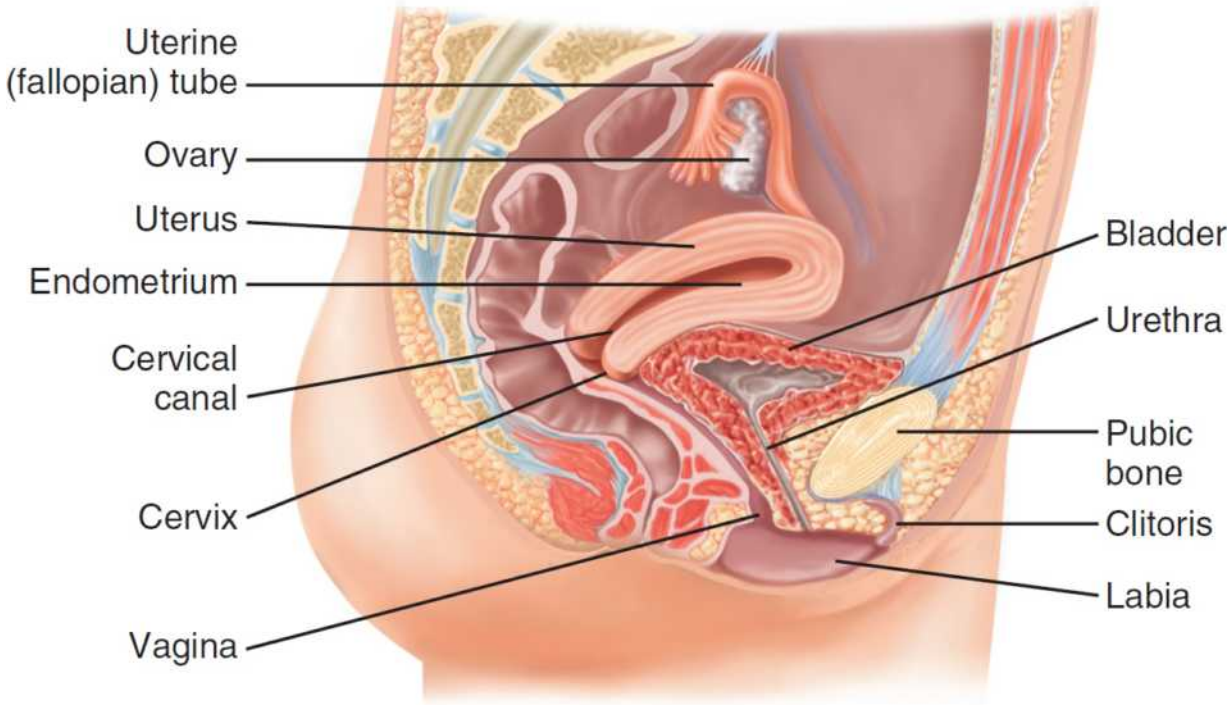


FIGURE 8-5 Side view of the female reproductive system.

Description

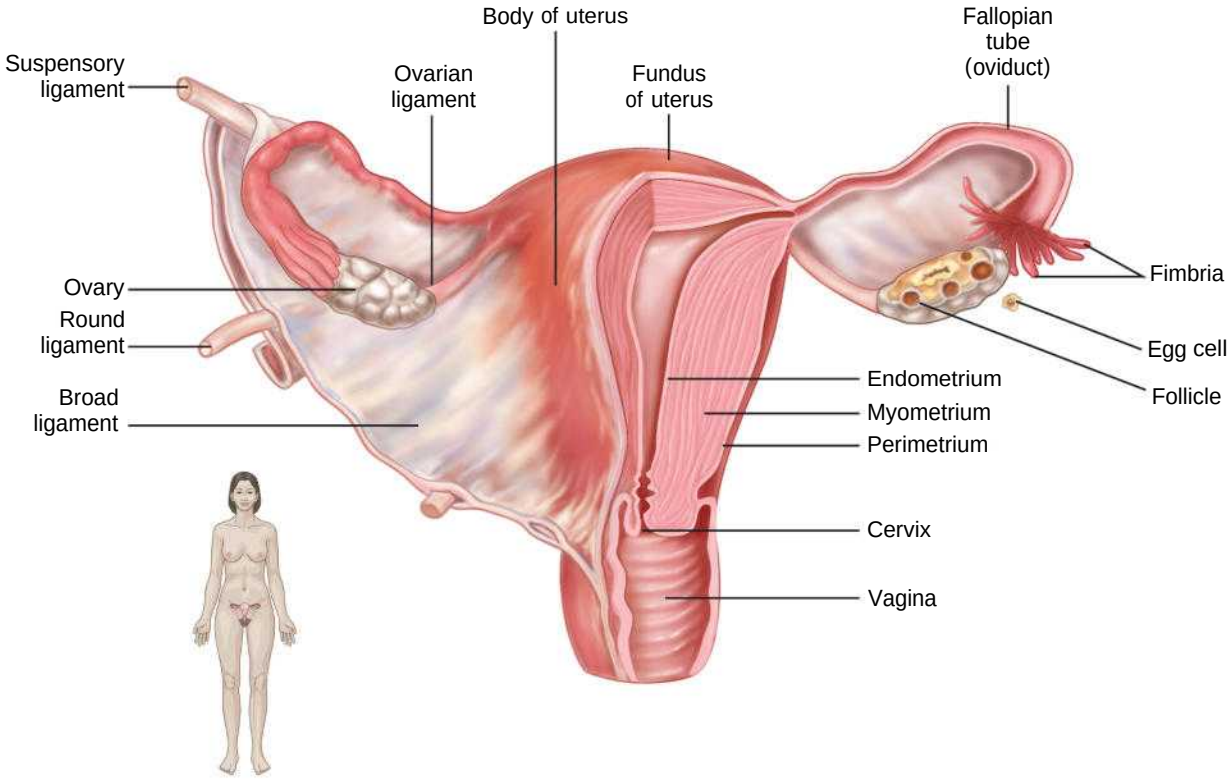


FIGURE 8-6 Front view of the female reproductive system.

Description

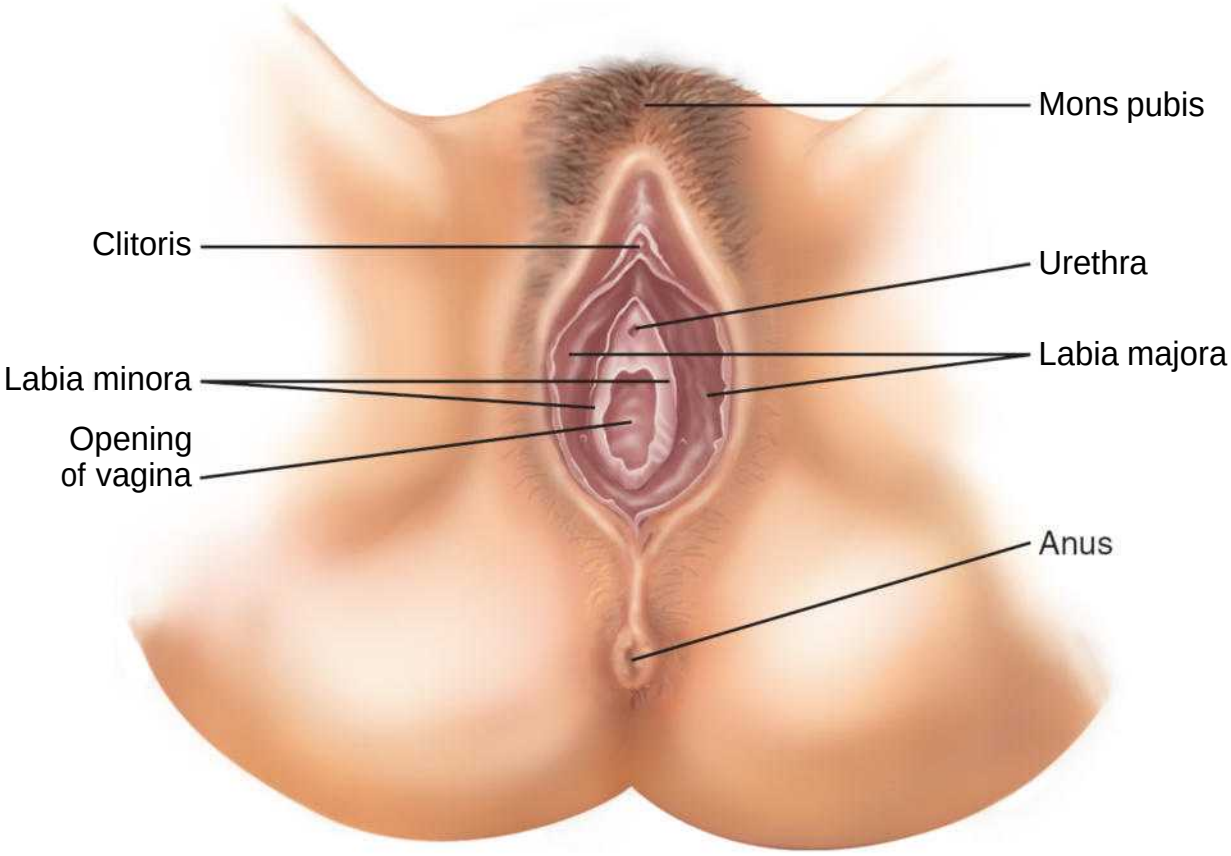


FIGURE 8-7 The female external genitalia.

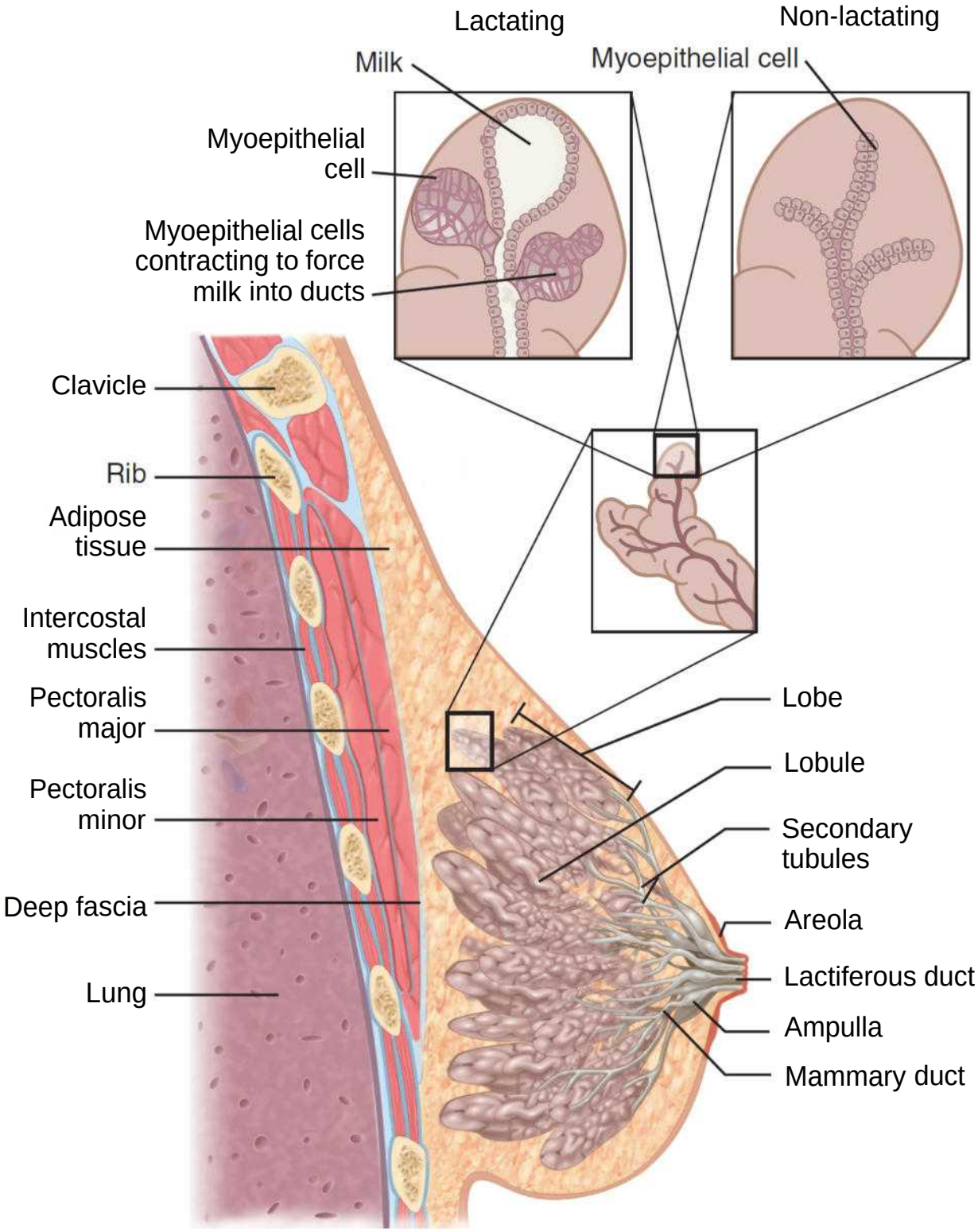


FIGURE 8-8 The female mammary glands.

Description

The female reproductive system is located in a hub of activity in the body. This system is intimately intertwined with the physiologic functions of nearby structures in the female pelvis. The female pelvis contains organs of the urinary and gastrointestinal systems along with organs for reproduction; thus, the female pelvis is the site for urination, defecation, **menstruation**, ovulation, copulation (sexual intercourse), impregnation, pregnancy, and parturition. Because of the close proximity of these three systems, problems in one system can lead to problems in the others.

Ovaries

The ovaries are paired almond-shaped organs located on each side of the uterus (Figure 8-6; **FIGURE 8-9**). The suspensory and ovarian ligaments along with the mesovarium (fold in the peritoneum) hold the ovaries in place. The ovaries produce hormones (primarily estrogen and progesterone) that regulate reproductive function and secondary sex characteristics (e.g., enlarged breasts, wide hips, and high-pitched voice). FSH stimulates hormone production in the ovaries, whereas LH inhibits this production. Small amounts of these hormones are also produced by adipose cells and the adrenal gland in both sexes. During pregnancy, the **placenta** produces both estrogen and progesterone. The ovaries also produce testosterone and other androgens, albeit at lower levels than the testicles in men.

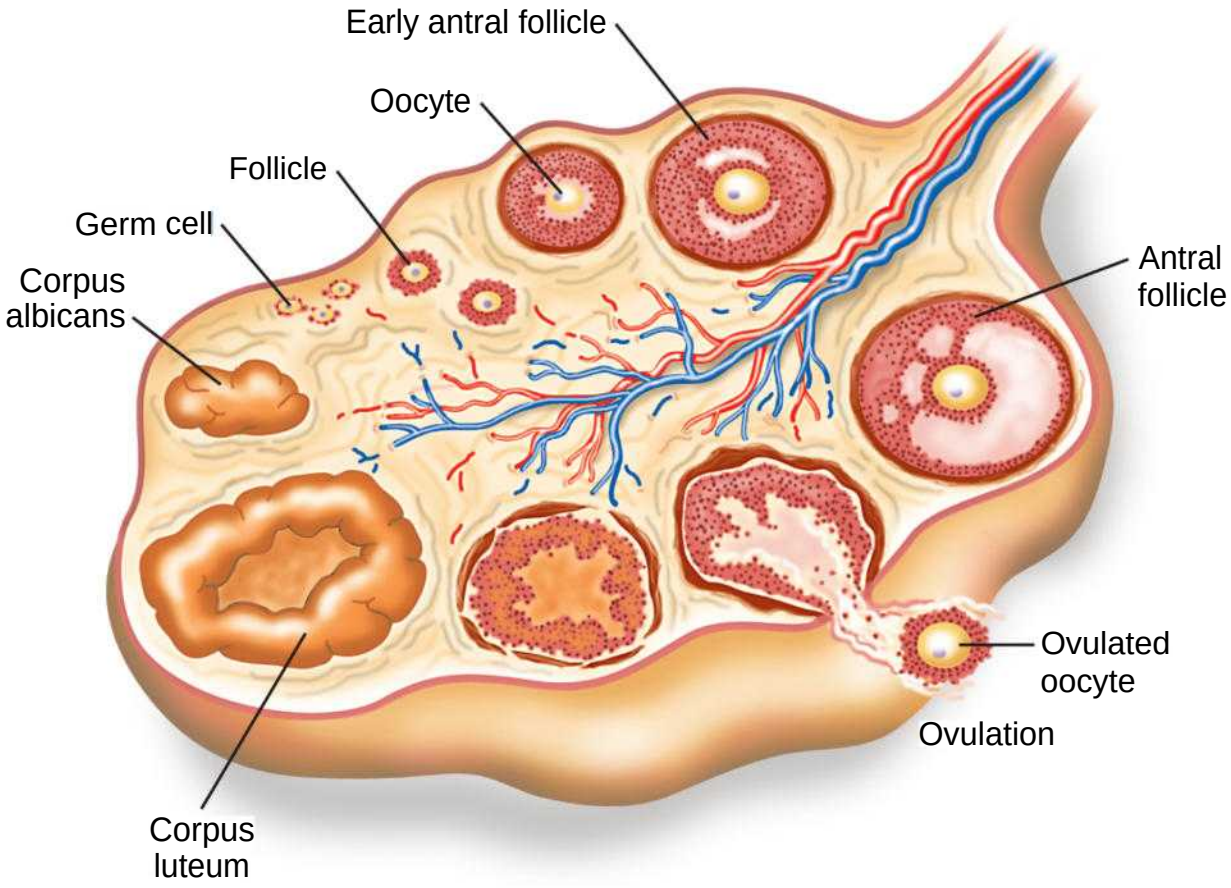


FIGURE 8-9 Structure of the ovary.

Description

Estrogen regulates the **menstrual cycle**, controlling uterine growth during the first part of the cycle. Along with its effects on the reproductive system, estrogen has systemic effects including increased metabolism, adipose storage, collagen production, protein synthesis, and bone formation. Estrogen affects the cardiovascular system by altering coagulation (e.g., increases plasminogen level and platelet aggregation and decreases antithrombin III) and lipids (e.g., increases high-density lipoprotein and triglycerides and decreases low-density lipoprotein) as well as by causing sodium and water retention. Estrogen also has a positive effect on cognition and mental health.

The corpus luteum, a temporary gland formed in the **ovary**, secretes progesterone after ovulation during the second half of the menstrual cycle. Progesterone prepares the **endometrium** for

potential pregnancy after ovulation. If pregnancy does not occur, the corpus luteum breaks down, which lowers progesterone levels in the body. If conception occurs, progesterone levels remain higher to stimulate blood supply to the endometrium, enabling it to accept the fertilized egg and support the growing fetus. Once formed, the placenta secretes progesterone to prevent egg production during the pregnancy and prepare the breast for lactation. Progesterone is a neurosteroid, meaning that it is also synthesized within the nervous system by neurons and glial cells. In the nervous system, progesterone plays a role in myelination and myelin repair, protecting the brain from damage, and enhancing the function of serotonin receptors in the brain, promoting mood stability.

The ovaries also contain the precursors to mature eggs (oocytes). During oogenesis, the oocytes mature into ova (mature eggs). By the 30th week of gestation, the female fetus has approximately 7 million follicles (biological units, each containing a single oocyte). These 7 million follicles degenerate to approximately 2 million follicles by birth. By puberty, only approximately 400,000 follicles remain, and no new ova are produced.

During the reproductive years, the follicles mature as they are exposed to pituitary hormones—specifically, FSH and LH. During the ovulation phase of the menstrual cycle, the mature follicle ruptures, releasing the mature ovum into the fallopian tubes (**FIGURE 8-10**). The ovum travels to the uterus for fertilization by the sperm. Fewer than 500 of each woman's ova mature and become potentially fertile. Although approximately a dozen follicles begin developing during each cycle, usually only one makes it to ovulation. Multiple births (e.g., twins or triplets) may occur when more than one ovum is produced, released, and fertilized.

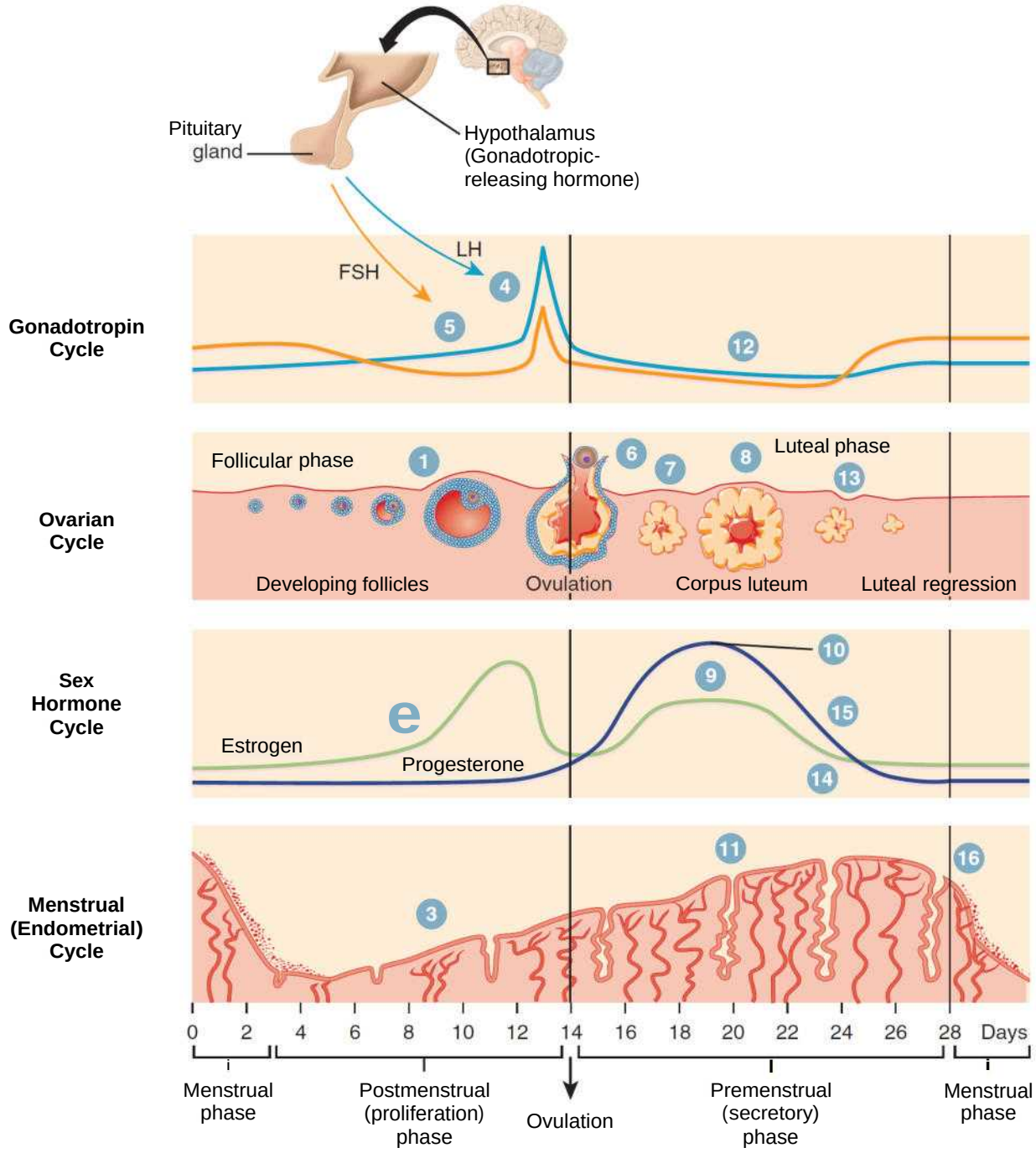


FIGURE 8-10 The menstrual cycle.

Description

Once the mature follicle releases the ovum, the empty follicle (called the corpus luteum) secretes progesterone to signal the

endometrium to prepare for fertilization. If pregnancy does not occur, the corpus luteum disintegrates.

Ovulation becomes less frequent and ova quality declines over time, which can increase the risk for **infertility** and for chromosomal abnormalities and congenital diseases in offspring. Eventually, the ovaries stop producing hormones and stop releasing ova, a stage referred to as **menopause**.

Fallopian Tubes

The fallopian tubes are two cylindrical structures that extend from the fundus of the uterus to near the ovaries. The ends of the tubes near the ovaries are fimbriated (fringe-like) to capture the ovum after ovulation. The tubes use a ciliary and muscular action to move the ovum toward the uterus as well as to assist sperm in moving from the uterus toward the ovum that is likely still in one of the tubes. If fertilization occurs, the same ciliary and muscular action moves the fertilized egg (**zygote**) from the tube to the uterus for implantation (**FIGURE 8-11**). Occasionally, the zygote does not reach the uterus but rather becomes implanted outside the uterus, leading to an **ectopic pregnancy**. The most common site for ectopic pregnancies is the fallopian tubes. Ectopic pregnancies cannot develop normally and can be life threatening.

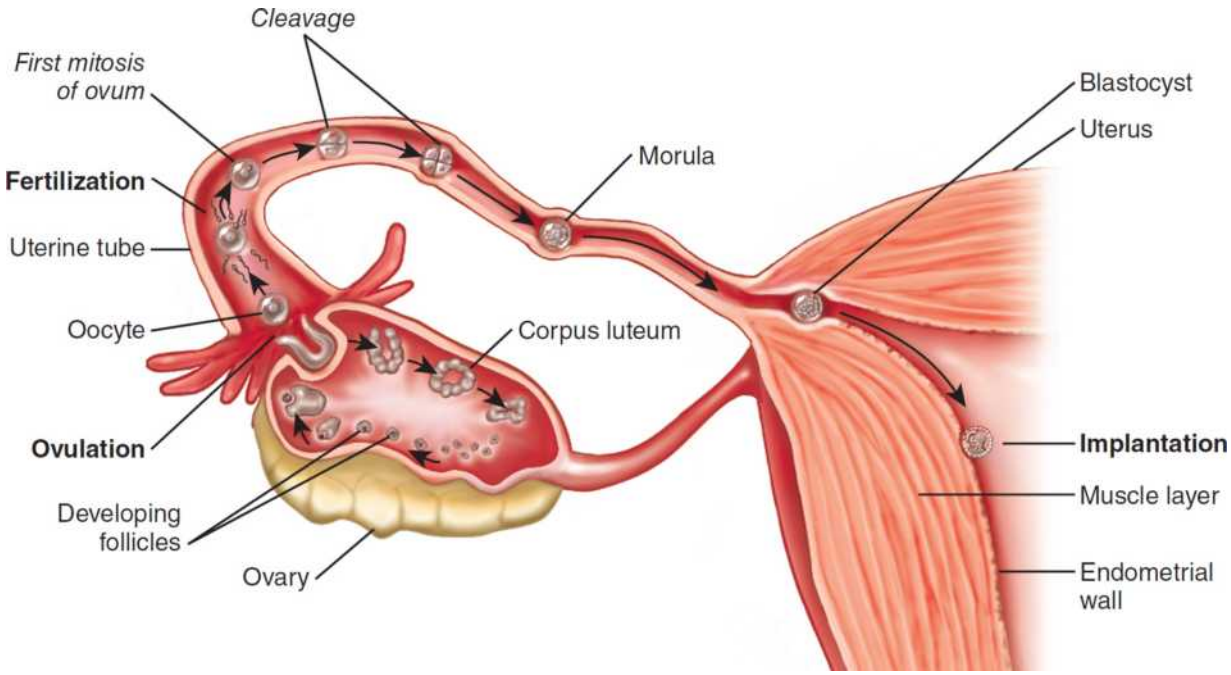


FIGURE 8-11 Fertilization and implantation of the embryo.

Description

Uterus

The uterus is a hollow pear-shaped organ held in place by the broad, round uterosacral ligaments. Usually, the uterus is tilted forward (**anteflexed**) over the bladder, but it is tilted backward (**retroflexed**) in approximately 20% of women. Women with retroflexed uteruses are more likely to experience discomfort during menstruation and sexual intercourse but usually do not have fertility issues.

During pregnancy, the fetus grows and develops inside the uterus. The thick uterine wall consists of three layers that serve to carry, nurture, and deliver the fetus.

- The endometrium is the inner mucosal lining of the uterus, which undergoes hormonal changes to facilitate and maintain pregnancy. The placenta, a vascular organ, develops during pregnancy to nourish the fetus through the umbilical cord, which contains two arteries and one vein. The placenta attaches to the endometrium on one side and surrounds the fetus on the other side (**FIGURE 8-12**). The uterus expels the placenta within a few minutes after birth.

If pregnancy does not occur, the lining of the endometrium is shed during menses.

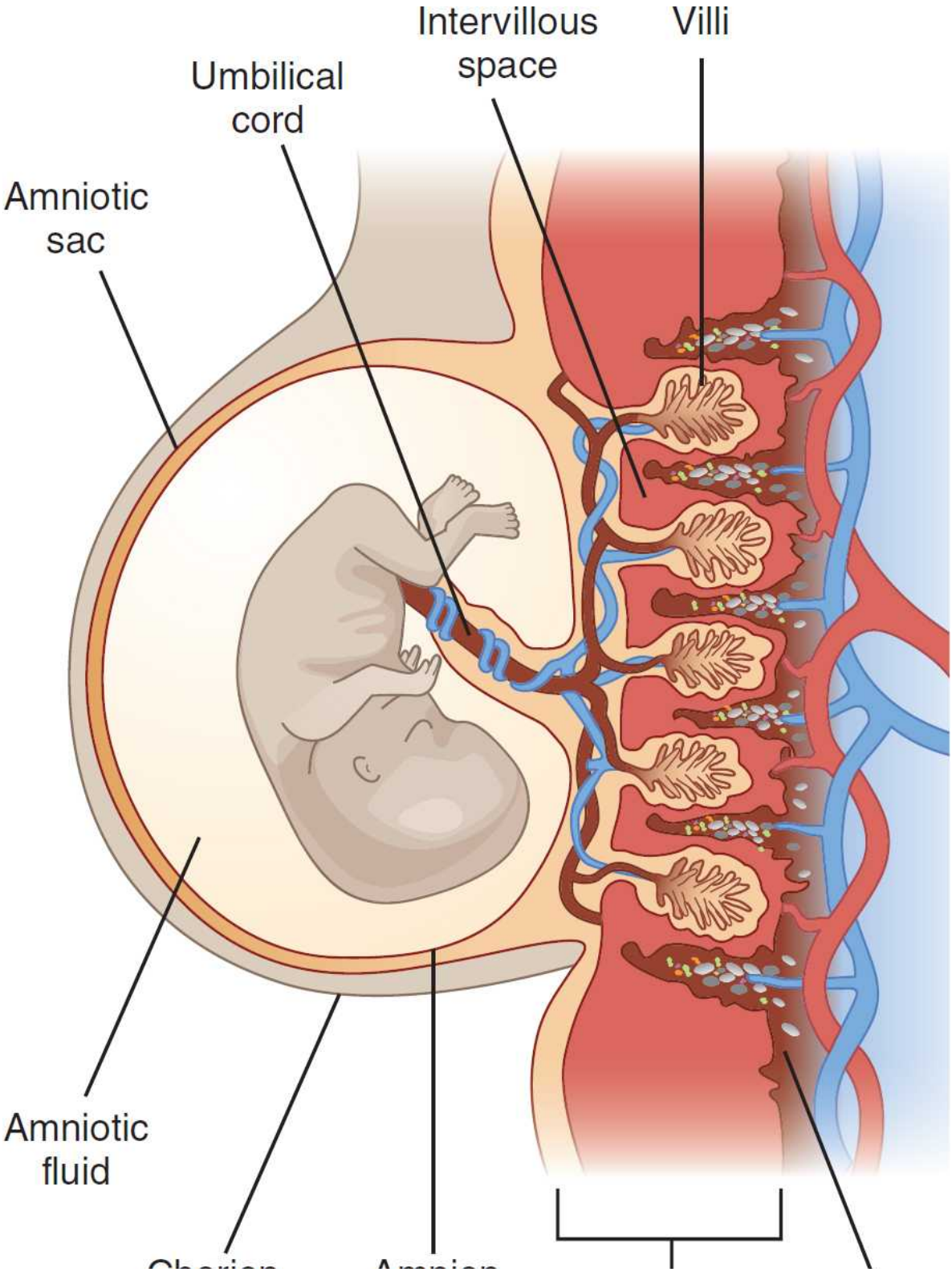




FIGURE 8-12 The developing placenta and embryo.

Description

- The **myometrium** is the middle layer of the uterus; it consists of smooth muscle and a vascular system. During pregnancy, the vascular system radically increases to support the fetus. During childbirth, the myometrium contracts to push the fetus out through the vaginal canal. After childbirth or abortion (spontaneous or induced pregnancy termination), this layer contracts to constrict blood vessels and control bleeding.
- The **perimetrium** is the outer, serous layer that covers the entire fundus and part of the corpus but none of the **cervix** (the narrow opening from the uterus to the vagina). In this layer, several hundred glands produce 1 to 4 mL of cervical mucus daily. The amount, color, and consistency of this cervical mucus vary throughout the menstrual cycle (e.g., less after menses, more before ovulation, thicker after ovulation, and thin during ovulation). The mucus provides lubrication for the vagina, prevents infection, and protects and nourishes the sperm. The incomplete coverage of this layer allows for surgical access into the uterus without requiring an incision into the peritoneum (the membrane that lines the abdominal cavity).

The menstrual cycle is a series of monthly changes that begin at puberty and continue through the reproductive years. The average age of onset of menstruation (menarche) is approximately 12 to 13 years. Hypothalamus maturation and subsequent hormone increases trigger the menstrual cycle. Initiation of this cycle is marked by the onset of menstruation (shedding of the endometrium). The menstrual cycle is usually a 28-day cycle that consists of four phases: the

menstrual, ovulatory, proliferative (estrogen-dominated), and secretory (progesterone-dominated) phases.

At the end of the secretory phase, the uterus is ready to receive and nourish a zygote. If fertilization does not occur, estrogen and progesterone levels increase, while FSH and LH levels decrease. Lower FSH and LH levels cause the corpus luteum to atrophy, reducing estrogen and progesterone production. The uterine lining thickens and sloughs off, signaling the beginning of menstruation. Menstruation expels the unfertilized ovum and maintains a healthy uterine lining that is prepared for fertilization.

If fertilization and pregnancy occur, the endometrium thickens and vascularization develops. After implantation of the zygote (5–6 days after fertilization), the placenta secretes human chorionic gonadotropin (hCG) to stimulate the corpus luteum to continue estrogen and progesterone production. The continued estrogen and progesterone production will suppress FSH and LH production, preventing further ovulation and menstruation. Human chorionic gonadotropin secretion continues until the placenta fully develops and begins making its own estrogen and progesterone, a phase that usually begins by the end of the first trimester.

The menstrual cycle continues to be repeated throughout a woman's reproductive years until estrogen levels begin to decline with age. As a result of the decreased estrogen levels, ovulation and menstruation become less frequent and more erratic. This change in the menstrual cycle usually begins between 45 and 55 years of age and occurs in phases (perimenopause, menopausal transition, and postmenopause). Menopause refers to the complete cessation of the menstrual cycle. In addition to changes in the menstrual cycle, the declining estrogen levels associated with menopause can cause the following manifestations:

- Atrophy of the breasts and internal reproductive organs
- Decreased vaginal secretions (which can make sexual intercourse painful)
- Urinary issues (e.g., urgency, incontinence, urinary tract infections)

- Neuropsychiatric changes (e.g., poor concentration, memory loss, irritability, anxiety, and depression)
- Insomnia
- Hot flashes
- Night sweats
- Decreased bone density
- Dyslipidemia
- Exacerbation of menstrual migraines
- Thinning skin and less adipose tissue

These manifestations can vary in severity, but in most women are mild and improve with time. Hormone replacement therapy can decrease the severity of the symptoms, but careful consideration should be given prior to initiating such therapy because it is associated with an increased risk of **breast cancer**, thrombus (blood clot), and stroke.

Vagina

The vagina is a hollow, tunnel-like structure located between the bladder and the rectum, which extends from the cervix to the external genitalia. This muscular canal is usually 2–4 inches in length, and it can expand in width (e.g., during parturition). The vagina serves as a passageway for sperm to travel to the fallopian tubes, for the body to discharge menstrual fluid, and to birth the fetus. Sperm enter the vagina when the male partner inserts his penis during sexual intercourse. Ejaculation propels the semen into this canal, where the sperm begin their journey to the fallopian tubes. In the mucosal lining of the vagina, **Skene glands** secrete a protective lubricating fluid during sexual intercourse. Tactile stimulation of the vagina is generally thought to produce the female orgasm; however, orgasms may sometimes require clitoral stimulation, either manually or through vaginal intercourse. Orgasms can also occur as a result of cervical stimulation. The normal bacterial flora of the vagina primarily includes

lactobacilli that produce lactic acid. This acidic environment prevents infection but can impair viability and motility.

The vagina may contain a thin connective tissue that covers the external vaginal opening to some degree, called the **hymen** (**FIGURE 8-13**). All hymens have openings large enough to permit menstrual flow passage or tampon insertion, but the openings are generally too small to permit an erect penis to enter without tearing. Tearing of the hymen does not usually cause significant discomfort, but it may cause a few drops of blood to be noticed. In addition to sexual intercourse, physical activity can partially or completely tear the hymen; therefore, the absence or presence of the hymen is not a reliable indicator of virginity.

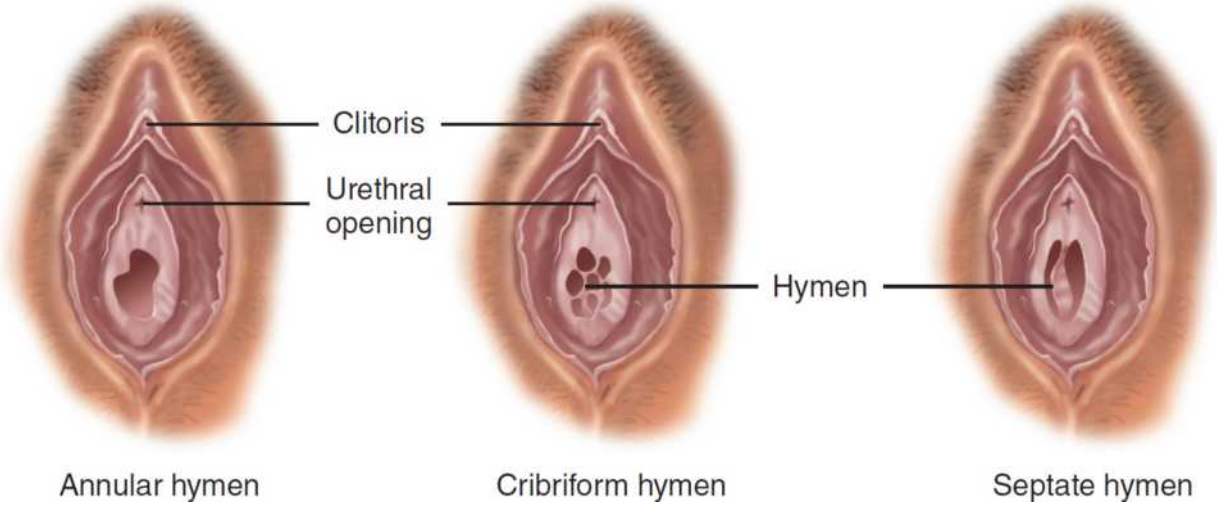


FIGURE 8-13 The various types of hymens.

External Genitalia

The external female genitalia contain several structures that are collectively referred to as the **vulva**. These structures include the **mons pubis**, **labia majora**, **labia minora**, **clitoris**, and **vestibule**. The size, color, and shape of these structures as well as hair distribution and skin texture can vary significantly from person to person (**FIGURE 8-14**). The mons pubis is the pad of fat over the pubic bone (symphysis pubis) that becomes covered with hair after puberty. The labia majora are the two large, fatty skin folds that

protect the perineum and aid in lubrication; they become prominent and darkened after puberty. The labia minora are two small, firm skin folds just inside the labia majora; they have a rich blood and nerve supply. The two labia minora connect at their upper portion to form the clitoris. The clitoris is very sensitive to stimulation and becomes filled with blood during sexual arousal. It contains two corpora cavernosa, similar to the penis. **Bartholin glands** lie just within the labia minora and provide lubrication during sexual intercourse. The vestibule refers to the area that contains the urethral and vaginal opening.



FIGURE 8-14 Variations of the female genitalia.

A: © Daniel Sambraus/Science Source; **B:** © John R. Foster/Science Source; and **C:** © Medical Images RM/Ansell Horn

Mammary Glands

The mammary glands are in the breasts. Although both males and females have mammary glands, they are functioning structures only in females. The mammary glands are not a reproductive organ per se, but they can have a role in sexual arousal and provide nourishment to the newborn. Each breast contains 15–20 clusters of milk-secreting mammary glands that open into the **nipple**. The mammary glands do not make milk unless stimulated to do so. **Prolactin**, a hormone released by the anterior pituitary gland, prompts milk production. During pregnancy, increased estrogen levels trigger prolactin

secretion, which matures the mammary glands and prepares them for milk production. After childbirth, prolactin secretion initially decreases as the estrogen levels return to nonpregnancy levels, but the newborn's suckling then stimulates increased prolactin production.

Each breast in both sexes contains a nipple surrounded by an **areola** (area of pigmentation). The **areolar glands** produce secretions that protect and lubricate the nipple and areola during breastfeeding.

Congenital Disorders

Abnormalities of the urinary and reproductive systems are the most common congenital defects. Because of these systems' close relationship, an abnormality in one system will often lead to an abnormality in the other. Additionally, fetal development of both systems is intertwined. The reproductive system continues its development until birth. Although this system is formed at birth, it remains incapable of reproduction until it matures during puberty. Numerous congenital disorders of the reproductive system are possible, most of which involve structural problems. Some disorders cause mild symptoms (e.g., **epispadias** and **hypospadias**), whereas others may cause infertility and gender ambiguity (e.g., testicular or ovarian agenesis).

Epispadias

Epispadias refers to an abnormality involving the urethral meatus. In males with this condition, the urethra opens on the dorsal (upper) surface of the penis instead of the tip (**FIGURE 8-15**). In some cases, the urethral opening may extend the entire length of the penis. Additionally, the penis may be shorter, be wider, or have an abnormal curve (i.e., dorsal **chordee**). In females with epispadias, the urethra opens toward the clitoris or abdomen, resulting in the external genitalia and urethra not forming or functioning well.



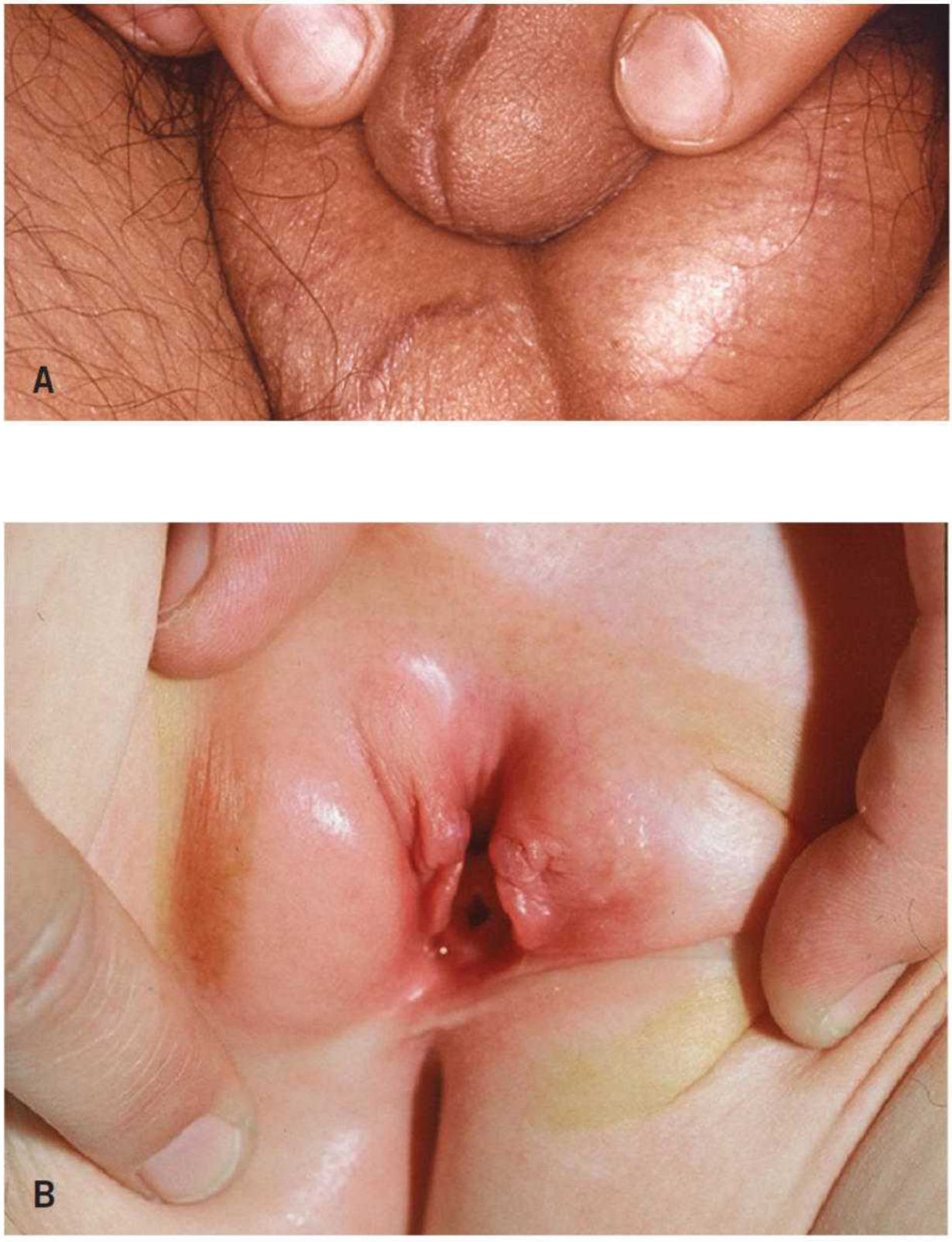


FIGURE 8-15 Epispadias. **(A)** Male. **(B)** Female.

A: Courtesy of Dr. Gavin Hart/CDC; **B:** Reproduced from Ebert, A., Reutter, H., Ludwig, M., & Rosch, W.H. (2009). The exstrophy-epispadias complex. *Orphanet Journal of Rare Diseases, 4*, 23. doi:10.1186/1750-1172-4-23. Creative Commons license available at http://creativecommons.org/licenses/by/2.0

Epispadias is rare (1 in 117,000 newborn males; 1 in 484,000 newborn females) and usually develops during the first month of gestation (Jayachandran, Bythell, Platt, & Rankin, 2011). The position of the meatus (e.g., head, shaft, or near the pubic bone) can predict the presence and severity of secondary issues. Epispadias is more likely to cause urination problems (e.g., incontinence) in men and sexual dissatisfaction in women. Men with epispadias are not necessarily infertile, but they may have trouble propelling the semen adequately during ejaculation. Both males and females with epispadias are at increased risk for urinary tract infections.

Urinary defects, such as bladder exstrophy (in which part or all of the bladder is present outside the body) (**FIGURE 8-16**), often occur with this type of congenital condition. Classic bladder exstrophy occurs in 3.3 per 100,000 births. Exstrophy–epispadias complex (EEC) refers to a spectrum of congenital abnormalities that includes epispadias, classic bladder exstrophy, cloaca exstrophy (the bladder and intestines are exposed at birth), and several variations. EEC occurs due to a rupture of fetal tissue (the cloacal membrane) during the first trimester. The prevalence of this condition ranges from 1 per 10,000 births (EEC involving classic exstrophy) to 1 per 200,000 births (EEC involving cloaca exstrophy). With exstrophy, defects may also be present in the reproductive organs, intestines, pelvic bones, and abdominal muscles.





FIGURE 8-16 Bladder exstrophy.

© Scott Camazine/Alamy Stock Photo

The exact cause of epispadias and EEC is unknown, but these defects are thought to result from an event occurring early in pregnancy. Risk factors include parental history of epispadias or exstrophy (500 times greater risk than in the general population) and maternal factors including young age, high parity, and smoking.

Diagnosis of epispadias is typically made through a physical examination at birth. Other procedures may be used to identify associated conditions and to determine the severity of this congenital defect, including intravenous pyelogram (X-ray of the kidneys, bladder, and ureters using radioactive isotopes), pelvic X-ray, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound of the urinary system and genital structures. Diagnosis can also be made prenatally with an ultrasound.

In males, surgical procedures may use the foreskin to repair the defect. Reconstruction is less complex in females. In patients with EEC, the goal is to protect the external structures (e.g., prevent injury, cover with plastic wrap, and use mist tents) until repair can be performed. Surgical repair of EEC may also include closure of the abdominal wall and urinary or intestinal diversions. With advancements in surgical repair at birth, some children achieve urinary control without other procedures, but multiple procedures may be required to achieve the desired cosmetic outcome, urine flow control, and sexual function.

Hypospadias

Hypospadias refers to another abnormality involving the urethral meatus. In males, the urethral meatus is on the ventral (under) surface of the penis instead of the end (**FIGURE 8-17**). In addition, the foreskin is not completely formed on the underside, leaving the penis tip exposed. According to the Centers for Disease Control and Prevention (CDC, 2022), hypospadias is a commonly occurring congenital defect (1 out of 200 babies).



FIGURE 8-17 Hypospadias.

Courtesy of CDC/ Robert S. Craig.

Like epispadias, hypospadias can vary in severity, and the opening can extend along the length of the penis. Males with this condition may also have a downward curvature of the penis, called “chordee,” that becomes apparent with an erection. Males often will also have one testicle that has not fully descended into the scrotum. In females with hypospadias, the urethral opening is usually located on the anterior wall within the vaginal opening. Hypospadias does not usually affect females, but it can be the cause of gender ambiguity. This ambiguity may lead to inappropriate surgical gender assignment. Genetic studies prior to any gender assignment procedures can minimize this risk.

The exact cause of hypospadias is unknown, but it is thought to result from a combination of environmental exposure (e.g., medication exposure in utero) and genetic vulnerability. Risk increases with maternal factors such as age greater than 35 years, obesity, use of fertility treatments, and hormone therapy just before or during pregnancy.

Diagnosis of hypospadias is made through a physical examination at birth. Imaging tests (e.g., MRI, CT, X-rays, and ultrasound) may be performed to identify other congenital defects. Surgical repair (often in stages) can improve the penis' appearance as well as urinary and sexual function. Surgery can be performed as early as 4 months of age but should be undertaken before 18 months of age.

Cryptorchidism

Cryptorchidism is a condition in which one or both testes do not descend from the abdomen to the scrotum prior to birth (**FIGURE 8-18**). Normally, the testes develop at 7 to 8 weeks' gestation; they remain anterior to the internal inguinal ring until they begin the first phase of descent around 8 to 15 weeks' gestation guided by the gubernaculum (a mesenchymal cord that extends between the caudal pole of the fetal testis and the scrotum). The testes mediate this stage through its secretion of insulin-like 3 (a peptide hormone) and its G protein–coupled receptor (i.e., relaxin receptor 2). The second phase begins between 25 and 35 weeks' gestation and is primarily driven by androgens. The descent is also initiated by physical (e.g., gubernacular regression and intra-abdominal pressure) and environmental factors (e.g., maternal exposure to estrogen or antiandrogenic substances). In some males, the testicle may be absent in the scrotum because it never developed or it atrophied. With cryptorchidism, the undescended testes usually remain along the path of descent, but they can also deviate from that path (**ectopic testes**).

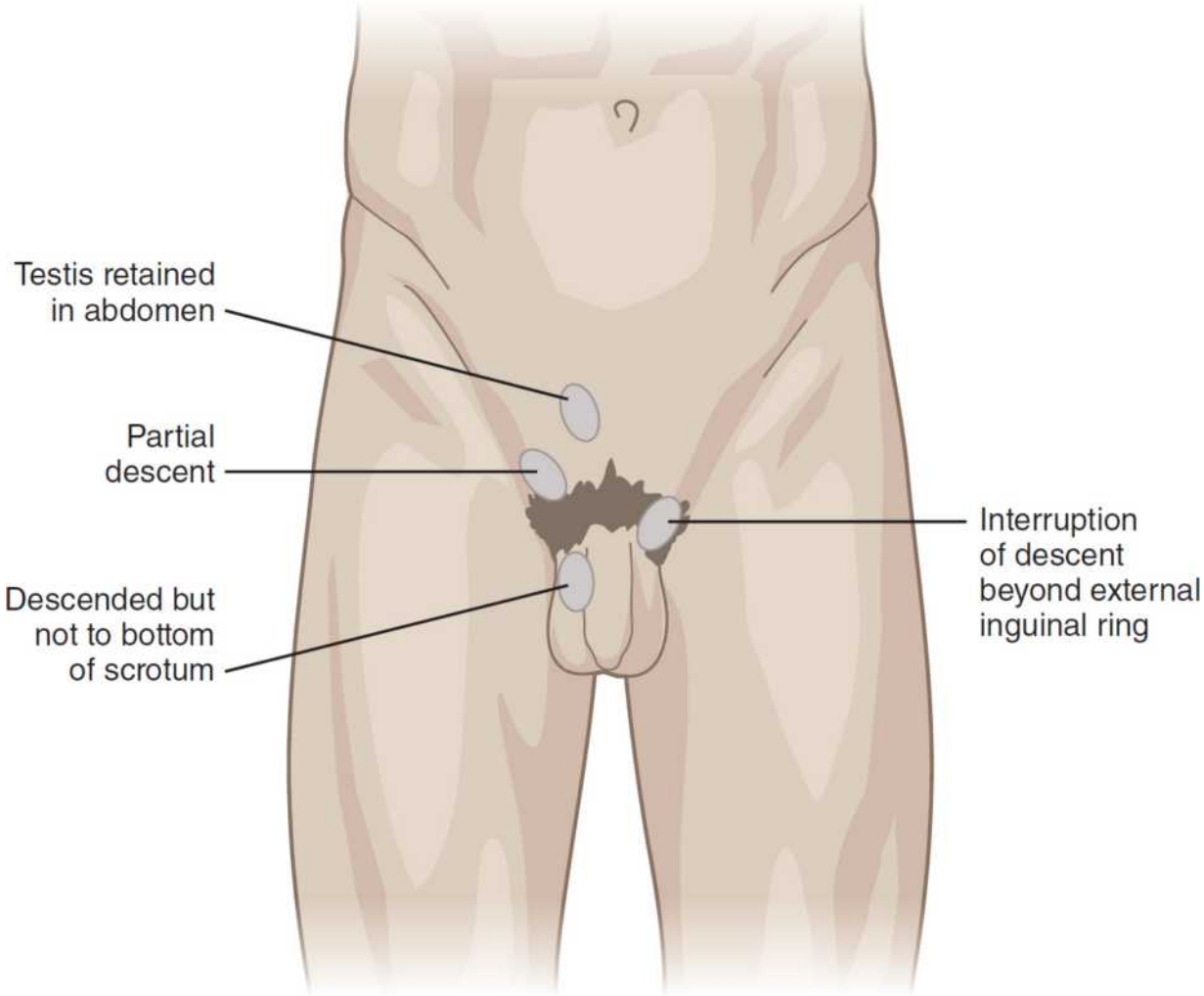


FIGURE 8-18 Potential sites for cryptorchidism.

Description

Cryptorchidism is the most common birth defect involving male genitalia, with approximately 3% of full-term males and 30% of premature males being born with one or two undescended testicles (Leslie, Sajjad, & Villanueva, 2023). The right testicle is most commonly affected. The testes descend by 3 months of age in about 80% of cases. Rarely, both testes are undescended. Risk factors for cryptorchidism include:

- Prematurity (before 37 weeks' gestation)
- Low birth weight
- Small size for gestational age

- Multiple fetuses (e.g., twins)
- Family history of cryptorchidism or other problems of genital development
- Maternal estrogen exposure during the first trimester
- Maternal alcohol use during pregnancy
- Maternal cigarette smoking or secondhand smoke exposure during pregnancy
- Maternal diabetes (type 1 diabetes, type 2 diabetes, or gestational diabetes)
- Maternal obesity
- Preeclampsia (the more severe the preeclampsia, the greater the risk)
- Maternal use of ibuprofen during pregnancy
- Parental exposure to some pesticides
- In vitro fertilization

Occasionally, a testicle that descended normally by birth may disappear later in childhood, often due to muscular reflexes that develop in puberty. A **retractile testicle** moves back and forth between the scrotum and the lower abdomen. In this case, the testicle is easily returned to the scrotum through gentle manipulation. An **ascending testicle**, or acquired undescended testicle, refers to a testicle that has returned to the lower abdomen and cannot easily be guided back into the scrotum.

If a testicle does not descend, it is unable to produce sperm and hormones normally. Even if the other testicle descends and functions normally, the individual is at risk for fertility issues because of low sperm quantity and quality due to structural, cellular, and hormonal changes. Males with a history of cryptorchidism also have an increased risk of **testicular cancer**. The cancer risk is not directly related to the testicle not descending but rather is thought to be linked to the underlying etiology. Treatment can lower infertility and cancer risk; however, some risk remains.

Cryptorchidism is diagnosed at birth in most cases, but some males with this condition are not diagnosed until childhood or early adolescence. Diagnostic procedures for cryptorchidism include a history, physical examination, self-testicular examinations (the condition places the individual at increased risk for testicular cancer later in life), laparoscopy (visualization using a small camera through a small abdominal incision), abdominal ultrasound, MRI, and open abdominal exploratory surgery. Additionally, hormone levels and genetic studies can distinguish potential causes and complications.

In most cases, the testes descend by 9 months of age without treatment; however, cryptorchidism should be treated if it persists at 6 months of age because the testes are unlikely to descend on their own after this time. Early treatment prevents permanent damage to the testicles and improves fertility during later life. Testes that do not naturally descend into the scrotum before birth are considered abnormal, and the individual should be screened and monitored for testicular cancer and infertility even with repair. The American Urology Association (2018) does not recommend using hormonal therapy to induce testicular descent. Treatment strategies include the following measures:

- Manual manipulation
- Surgical repair (either laparoscopic or open) such as orchidopexy
- Orchiectomy (testicle removal)
- Testicle implants

Infertility Issues

Infertility describes a biological inability to contribute to reproduction. The ability to conceive and support a fetus requires functioning male and female reproductive systems. Frequent unprotected intercourse usually results in conception for 50% of couples within 3 months, 75% within 6 months, and 90% within 1 year. Infertility is defined clinically as not being able to conceive after 1 year of regular, unprotected intercourse or after 6 months if the woman is older than 35 years of age. Infertility also includes cases in which women are able to conceive but unable to carry a pregnancy to term because of spontaneous abortion (i.e., miscarriage; pregnancy ends or fetus dies before 20 weeks' gestation), recurrent pregnancy loss, or fetal demise (i.e., stillbirth; death of a fetus at or after 20 weeks' gestation).

Approximately 9% of men and 11% of women of reproductive age in the United States have experienced fertility issues. The issue is with the male in one-third of cases, with the female in one-third of cases, and with both or unknown in the remaining one-third of cases. Fertility declines with age in both males and females, but females are more significantly affected. Infertility can have multiple causes that are often overlapping. Nutrition, age, weight (overweight and underweight), exercise (excessive), physical and psychological stress, environmental and occupational exposures (e.g., radiology), substance and drug use and abuse (e.g., androgens, tobacco, marijuana, heavy alcohol consumption, heroin, cocaine), and medications (e.g., chemotherapy) can affect fertility in both males and females (National Institutes of Health [NIH], 2017).

Male problems that can lead to infertility include decreased sperm or sperm abnormalities, hormone deviations, blockages or absence of ducts that carry sperm, and physical impediments (e.g., erectile dysfunction). Along with hormonal imbalances, hypertension can change the shape of the sperm. Despite common misconceptions,

infertility is not correlated with the type of underwear a man wears. Diagnostic procedures for infertility in males include a history, physical examination, sperm analysis, complete blood count (CBC), cultures of penal drainage (if infection is suspected), hormone analysis (e.g., FSH, LH, thyroid-stimulating hormone [TSH], testosterone, and prolactin), imaging studies (e.g., ultrasound and vasography), and genetic testing.

Female infertility problems include ovulation dysfunction (e.g., **polycystic ovary syndrome**), hormone deviations, physical obstructions (e.g., stenosis or tumors of the fallopian tubes or cervix), uterine defects (e.g., positioning or placenta development), abnormal cervical mucus, and severe reproductive tract infections. Diagnostic procedures for infertility in females include a history, physical examination (including pelvic exam and Papanicolaou [Pap] smear), ovulation testing, hysterosalpingography (X-ray of the uterus with radioactive isotopes), ovarian reserve testing (determines the quality and quantity of eggs available), hormone analysis (e.g., FSH, LH, TSH, prolactin, estrogen, and progesterone), imaging studies (e.g., ultrasound and hysterosonography), and genetic testing.

Treatment for infertility includes the following measures:

- Lifestyle modifications (e.g., weight management, stress reduction, and smoking cessation)
- Endocrinopathy therapy
  - hCG, GnRH, testosterone, and estrogen supplements
  - Estrogen receptor blockers (increase GnRH secretion)
  - Dopamine antagonists (inhibit prolactin release)
  - Gonadotropins (stimulate gonadal steroid hormones)
- Immunotherapy for males who have antisperm antibodies
- Alpha-sympathomimetics for males with retrograde ejaculation (closes bladder neck)
- Collagen injections to the bladder neck
- Sperm treatment to wash and concventrate sperm
- Antimicrobial therapy (if infection is present)

- Coenzyme Q (may increase sperm quantity and quality)
- Metformin (decreases insulin resistance, making ovulation more likely to occur)
- Intrauterine insemination
- In vitro fertilization
- Fertility preservation (e.g., sperm, embryo, and oocyte cryopreservation; gonadal shielding; and ovarian transposition)
- Surgical repair of structural issues

Erectile Dysfunction

Erectile dysfunction (ED), or impotence, refers to a male's inability to attain or maintain a penile erection sufficient to complete sexual intercourse. ED affects as many as 30 million men (Urology Care Foundation, 2018). Although ED can occur at any age, this problem is most common in older men. This condition can be transient or permanent, depending on the etiology. ED can be primary, meaning an erection has never been achieved or sustained, or secondary, acquired later in life after erections were previously achieved.

An erection results from psychological, neurologic, and vascular processes; thus, ED can result from dysfunctions in any of these areas.

Psychological causes include the following:

- Anxiety
- Depression
- Guilt
- Stress
- Feelings of inadequacy
- Relationship issues

Physiologic causes include the following:

- Circulatory impairment (e.g., arteriosclerosis)

- Diabetes mellitus
- Multiple sclerosis
- Prostate disease (e.g., benign prostatic hypertrophy or prostate cancer)
- Hypertension
- Neurologic dysfunction (e.g., spinal cord injury, Parkinson's disease, or cerebral trauma)
- Certain medications (e.g., antihypertensive and antipsychotic agents)
- Low testosterone levels
- Alcohol and tobacco use
- Liver cirrhosis
- Obesity

Diagnostic procedures for ED consist of a history, physical examination, hormone analysis (e.g., testosterone, LH, TSH, and prolactin), ultrasound (e.g., penis, testicles, transrectal), dynamic infusion cavernosometry and cavernosography (X-ray of the penis after injecting contrast dye into penile blood vessels), and specific tests for chronic diseases (e.g., diabetes mellitus, hypertension, and arteriosclerosis). A variety of treatment options are available, some of which are costly and are not covered by most insurance plans. When ED has a physiologic origin, identifying and resolving the cause is the priority. Treatment strategies include the following measures:

- Psychological counseling
- Testosterone replacement
- Phosphodiesterase inhibitors (e.g., sildenafil [Viagra], tadalafil [Cialis], and vardenafil [Levitra])
- Other medications (e.g., adrenergic antagonists)
- Herbal remedies (e.g., ginkgo, ginseng, saw palmetto)
- Prostaglandin E injections directly into the corpus cavernosum or through the urethra

- Penis pumps (or vacuum devices)
- Surgical penile implants
- Vascular surgery

Phimosis

Phimosis occurs when the foreskin cannot be retracted from the glans penis. Not being able to retract the foreskin is common during the first 3 years of age, but the foreskin should become retractable as the child grows. Scarring resulting from poor hygiene, infections, and inflammation can all cause phimosis. Elderly men are at risk of this condition due to loss of skin elasticity and infrequent erections. Phimosis can lead to urinary obstruction, urinary tract infections, inflammation of the glans penis (i.e., balanitis), and pain.

Paraphimosis is a condition in which the foreskin is retracted and cannot be returned over the glans penis. Paraphimosis may occur when the foreskin is forcibly retracted or when the patient or caregiver forgets to replace the foreskin during hygiene. In paraphimosis, the penis becomes constricted and the glans becomes edematous. If this condition is not resolved, the lack of blood flow can lead to gangrene, making it a medical emergency.

Treatment strategies for paraphimosis include manual circumferential compression as well as surgery (e.g., dorsal slit and circumcision). Phimosis can be treated with topical steroid cream, foreskin stretching, and circumcision.

Priapism

Priapism is a prolonged (usually longer than 4 hours), painful erection. The unwanted, unrelenting erection is not a result of sexual stimulation. Priapism usually results from either too much blood shunting within the corpus cavernosum (referred to as nonischemic or high-flow priapism) or blood becoming trapped in the penis (referred to as ischemic or low-flow priapism). Stuttering priapism refers to a recurrent form of ischemic priapism characterized by periods of exacerbations and remissions.

Priapism is most commonly seen in boys between 5 and 10 years old and in men 20 to 50 years of age. It occurs in conjunction with a variety of blood, circulatory, and nervous dysfunctions caused by the following issues:

- Sickle cell anemia (the most common cause in pediatric cases)
- Leukemia
- Trauma to the genitalia
- Tumors (e.g., prostate, bladder, and renal carcinomas; melanoma)
- Diabetes mellitus
- Spinal cord injuries
- Neurologic diseases (e.g., multiple sclerosis and stroke)
- Medications (e.g., phosphodiesterase inhibitors, anticoagulants, and antianxiety agents)
- Alcohol and illicit drugs (e.g., cocaine, ecstasy, and marijuana)
- Poisonous venom (e.g., from a scorpion or black widow spider)

Diagnostic procedures can identify the type of priapism. These procedures include a history, physical examination, abdominal and penile ultrasound, intracavernosal arterial blood gases (ABGs), CBC, urinalysis, urine culture, toxicology tests, Doppler ultrasound, MRI, and CT. An erection lasting more than 4 hours is considered a urologic emergency, warranting immediate medical attention. Without medical attention, priapism can lead to ischemia, necrosis, ED, and infertility.

Priapism treatment is challenging to resolve even when the etiology is known. A urologist should be consulted to manage the case, and treatment should be initiated quickly. Treatment focuses on managing the underlying cause and varies depending on the type of priapism. Priapism often resolves, and reoccurrence is minimized once the underlying cause is treated.

Strategies for ischemic (low-flow) priapism include the following:

- Needle aspiration of blood from the base of one of the corpora cavernosa

- Injection of medications (e.g., alpha-adrenergic sympathomimetic agents to produce vasoconstriction) directly into the penis veins
- Saline irrigation of the penis veins to remove oxygen-depleted blood
- Surgical placement of a shunt (if priapism lasts longer than 48 hours)

Strategies for nonischemic (high-flow) priapism include the following:

- Cold application
- Lower abdominal pressure
- Surgical repair of trauma

Additional interventions may also be prescribed regardless of the type of priapism:

- Analgesics
- Sedation
- Hydration
- Urinary catheterization

Disorders of the Testes and Scrotum

Disorders of the testes and scrotum are usually structural in origin, and some can cause infertility (e.g., cryptorchidism). These disorders can be acquired or congenital, and most can be resolved with minimal residual effects.

Hydrocele

A **hydrocele** is an accumulation of fluid between the layers of the tunica vaginalis (the membrane covering the testes) or along the spermatic cord (**FIGURE 8-19**). This condition can affect one or both testes. A hydrocele often occurs as a congenital defect, affecting approximately 10% of newborn males. In this case, the vas deferens does not close properly as the testes descend into the scrotum and fluid drains from the abdomen. A congenital hydrocele usually disappears without treatment by 1 year of age. An inguinal hernia—a condition in which a section of the intestine passes through the abdominal wall—commonly occurs in infants with hydroceles. Adult men can acquire a hydrocele because of inflammation, infection, trauma, and tumors.

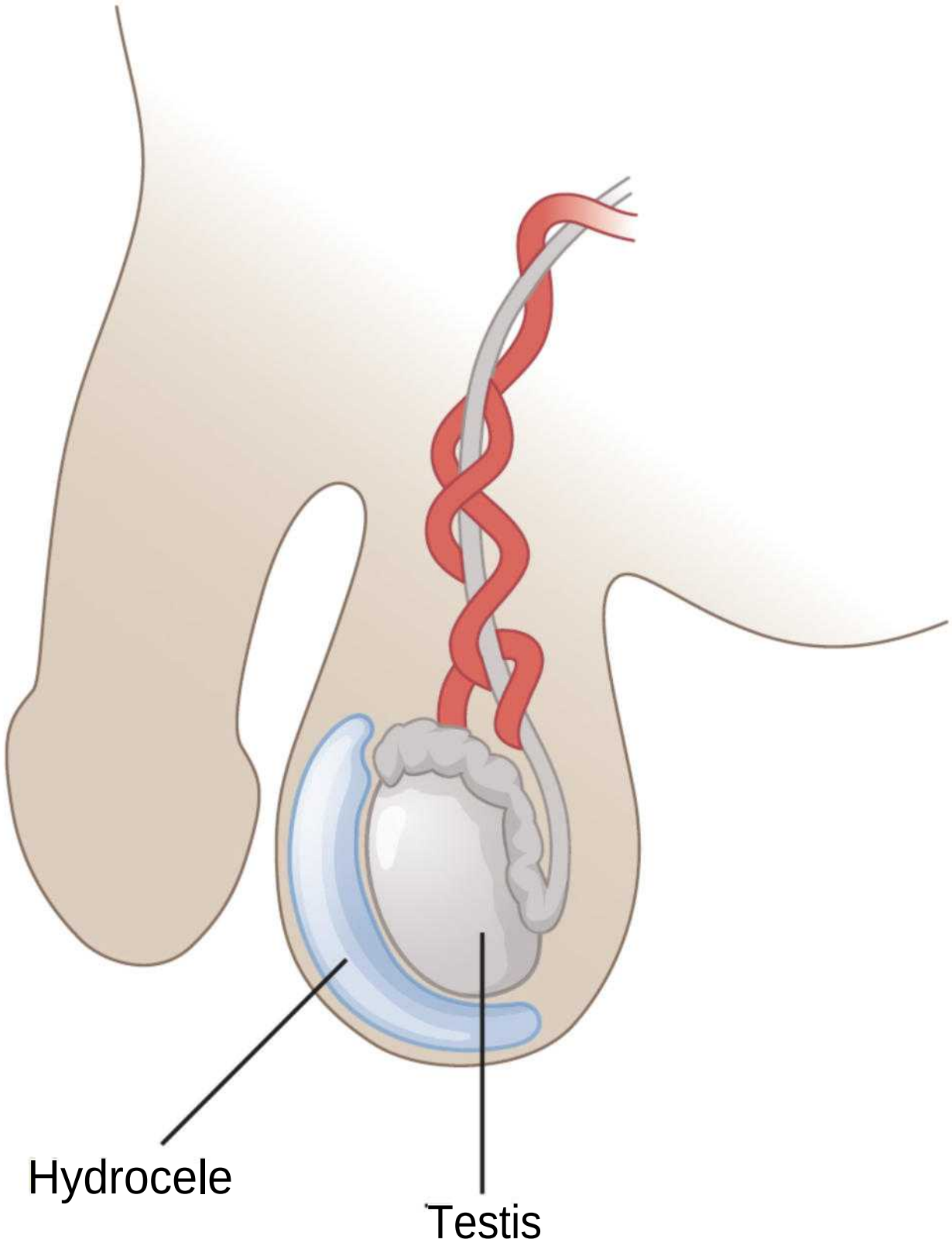


FIGURE 8-19 Hydrocele.

Hydroceles are usually painless, but the scrotum feels heavy. The swelling generally worsens over the course of the day. This scrotal enlargement can be differentiated from other testicular disorders (e.g., testicular cancer) using transillumination (transmission of light through tissue). Hydroceles will transilluminate light, whereas solid tumors will not (**FIGURE 8-20**).

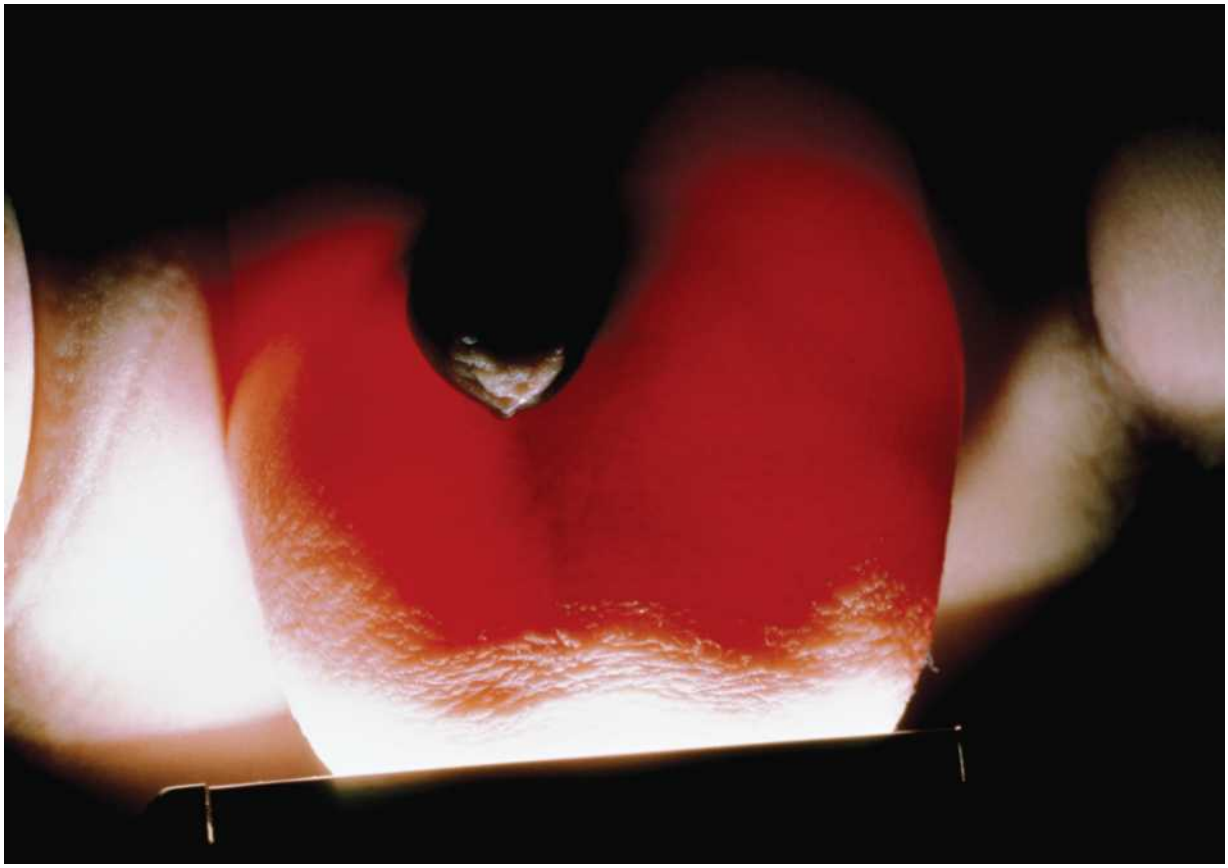


FIGURE 8-20 Transillumination of hydrocele.

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Diagnostic procedures for hydroceles consist of a history, physical examination (including transillumination), and ultrasound. In most cases, the hydrocele resolves without any action other than treating the underlying cause. Strategies to encourage reabsorption of the fluid include scrotal elevation (on a rolled towel), sitz baths (warm-water treatments for the perineum), and heat/cold application. Large

amounts of fluid can compromise testicular blood flow, requiring aspiration or surgical removal (hydrocelectomy) of the fluid.

Spermatocele

A **spermatocele** is a benign sperm-containing cyst that develops between the testis and the epididymis (**FIGURE 8-21**). Usually, the cyst is painless and small, but it can grow quite large, leading to increased discomfort. Additionally, the cyst is moveable and may transilluminate light. The exact cause of this common condition is unknown, but it is thought to be caused by a blockage of the duct system, infection, inflammation, or trauma. Diagnostic procedures are similar to those for hydroceles. Such a cyst rarely needs treatment because it usually does not cause pain or problems; however, the cyst may require surgical removal (spermatocelectomy) if it is large.

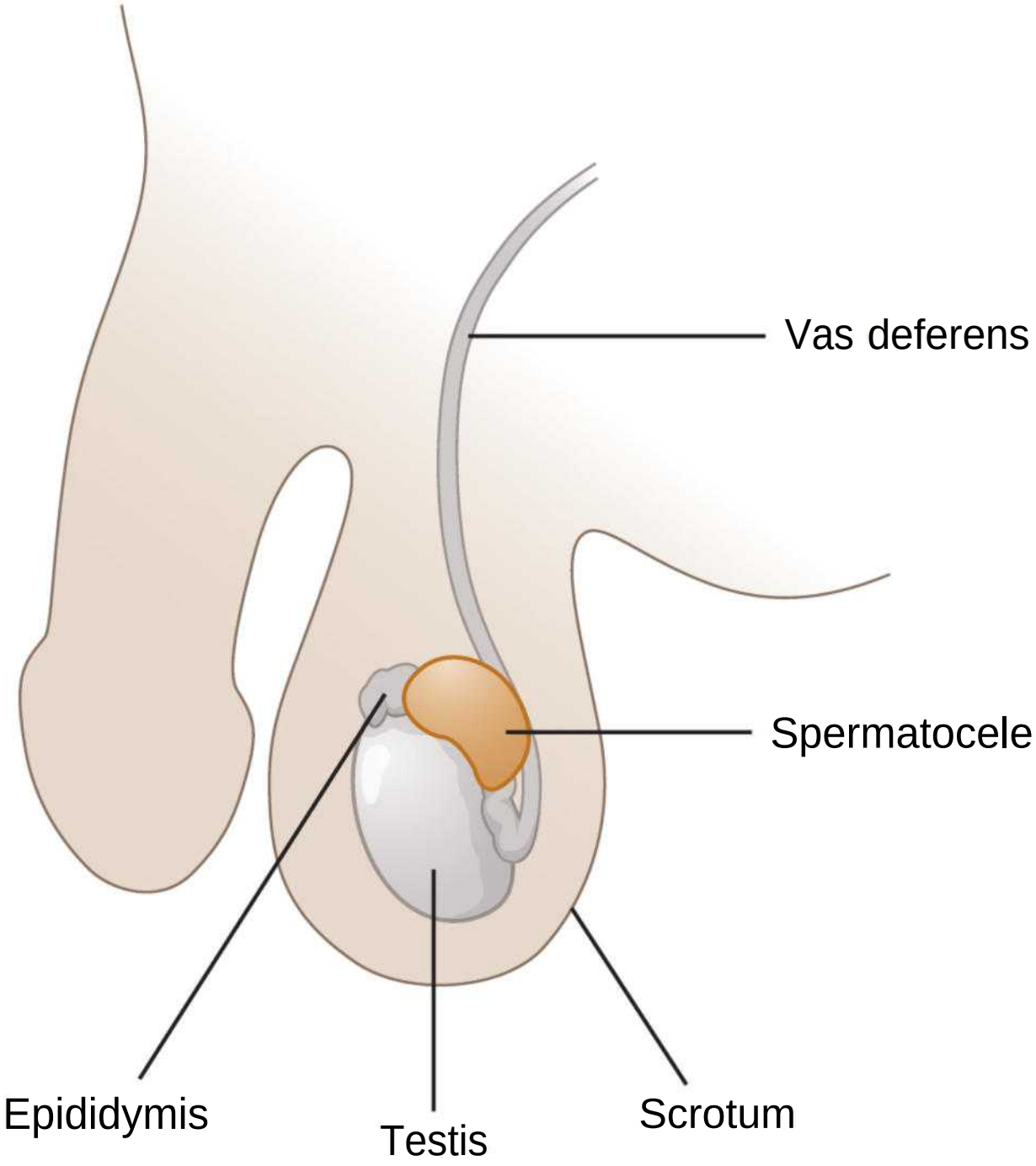


FIGURE 8-21 Spermatocele.

Varicocele

A **varicocele** is a dilated vein in the spermatic cord (**FIGURE 8-22**). Much like varicose veins in the leg (see the *Cardiovascular Function* chapter), this condition results from valve issues that allow blood to

pool in the veins. These valve issues can be caused by congenital defects (e.g., incompetent or absent valves) or obstructions (e.g., tumors and thrombi). Varicoceles are more common in men ages 15–25 and are typically seen on the left side of the scrotum. For unknown reasons, they occur more frequently in infertile men (approximately 40% greater risk). Additionally, varicoceles are the most common cause of low sperm counts and decreased sperm quality because of testicular ischemia. Varicoceles that appear suddenly in an older man may be caused by a renal tumor that has blocked blood flow.

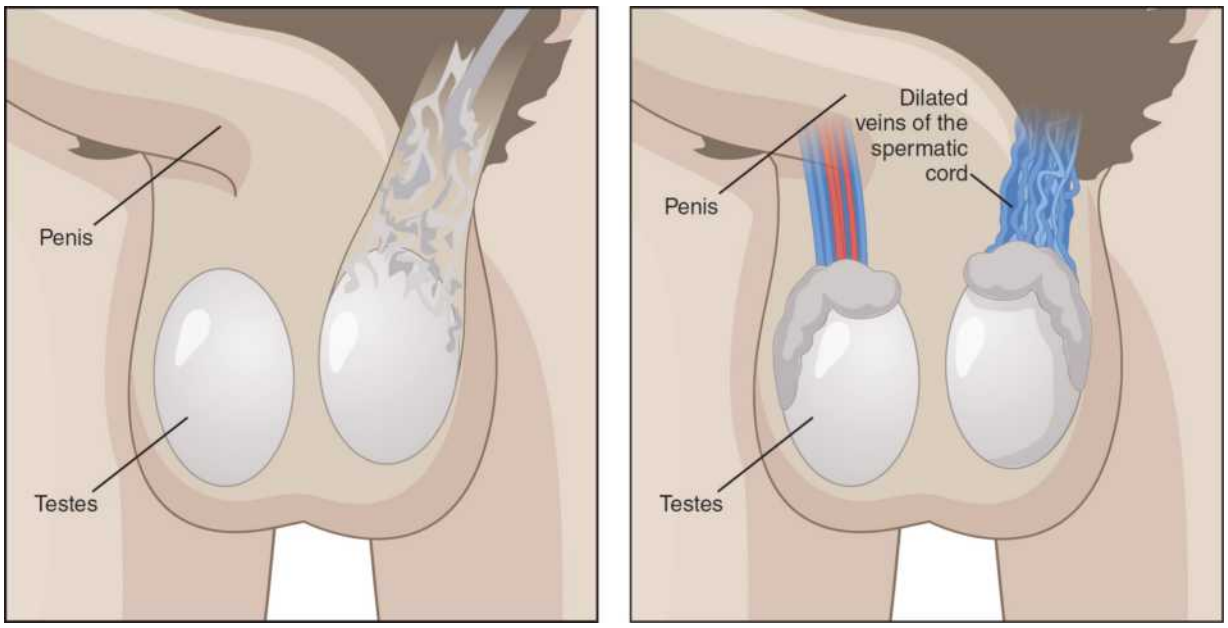


FIGURE 8-22 Varicocele.

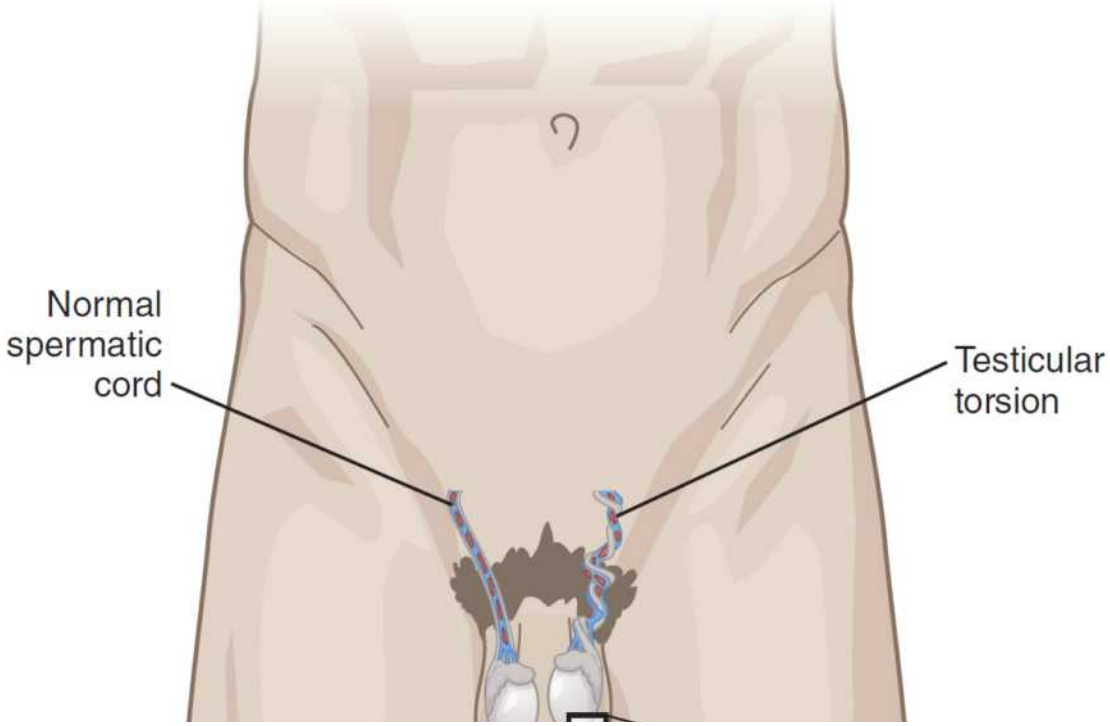
Varicoceles are much more common (approximately 80% to 90% of cases) in the left testicle than in the right testicle because of several anatomic factors. These factors include the angle at which the left testicular vein enters the left renal vein, a lack of effective antireflux valves at the left testicular and renal vein juncture, and increased renal vein pressure. Bilateral varicoceles are rare. Some varicoceles may be mild and asymptomatic, whereas extensive varicoceles can be tender and painful. The dilated veins give the scrotum a bag-of-worms feeling upon palpation, and the blood pooling may give a sense of heaviness in the scrotum. Varicoceles

can cause the testicle to develop more slowly or atrophy. Additionally, men with varicoceles may experience fertility issues.

Diagnostic procedures for varicoceles are similar to those for hydroceles. Additionally, the physical examination should include having the patient stand, take a deep breath, hold it, and bear down while palpating the scrotum, referred to as the "Valsalva maneuver." Treatment is often unnecessary unless the varicocele causes discomfort, testicular damage, or infertility. Treatment strategies include scrotal support (e.g., wearing briefs or a jockstrap), surgical repair (open or laparoscopic), embolectomy, and sclerotherapy (injection of an irritant into the vein that causes the vessel to harden and fade).

Testicular Torsion

Testicular torsion refers to an abnormal rotation of the testes on the spermatic cord (**FIGURE 8-23**). Sudden scrotal edema and pain develop as the twisting compresses the blood vessels, leading to ischemia and necrosis. Immediate treatment is required to restore blood flow and minimize testicular damage.



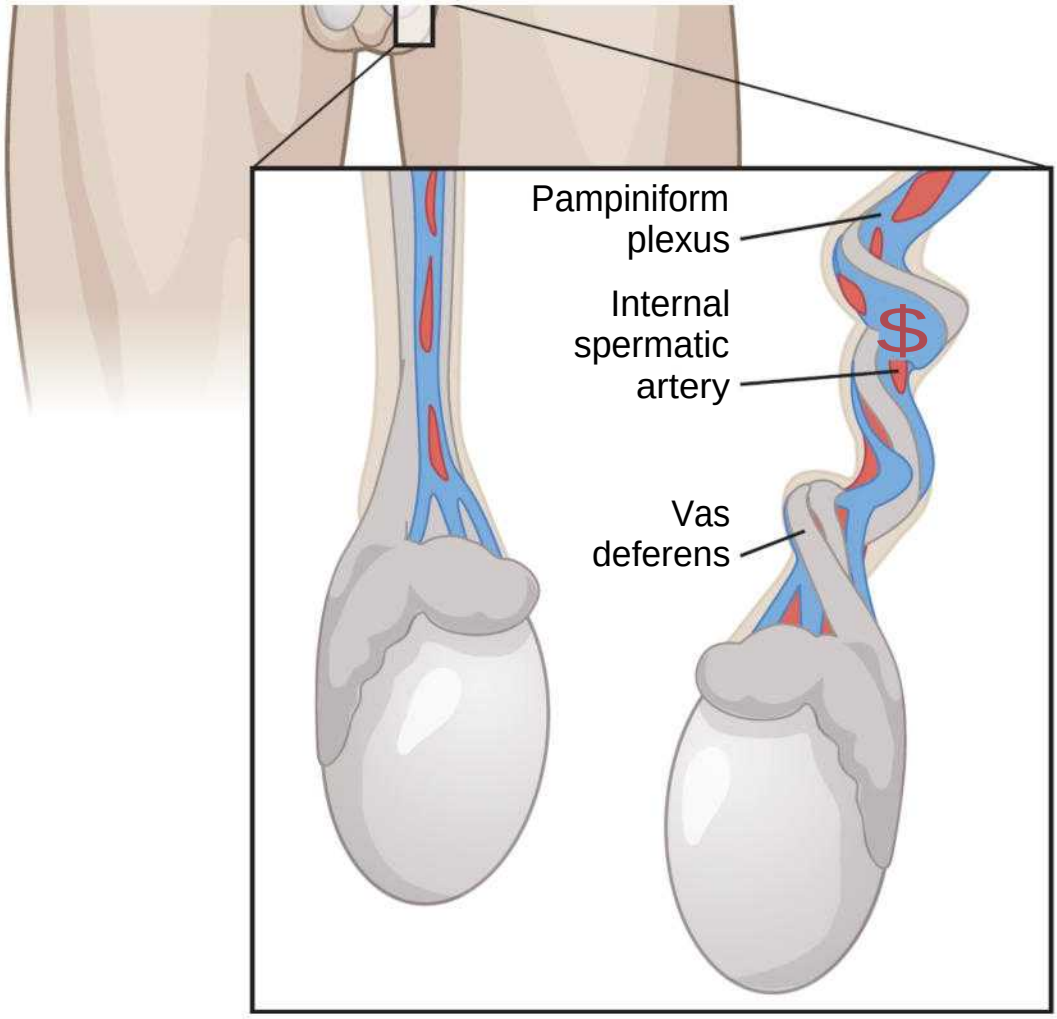


FIGURE 8-23 Testicular torsion.

Description

Testicular torsion is more common during the first year of life and at the beginning of puberty. It affects the left testicle more often than the right. This condition is most frequently caused by trauma but can also occur after strenuous exercise or spontaneously, especially in males whose testicles are not secured in the scrotum due to congenital differences. The primary manifestation is sudden, severe testicular pain (usually unilateral) with or without a predisposing event. Other manifestations may include scrotal edema, nausea, vomiting, dizziness, hematospermia (bloody semen), and a testicular mass. The cremasteric reflex (testicular contraction when the inner thigh is stroked) is usually absent on the affected side.

Diagnostic procedures include a history, physical examination, testicular Doppler ultrasound (to determine blood flow), and scrotal ultrasound. Testicular torsion may spontaneously resolve and recur. Surgery will be required to treat testicular torsion and should be performed within 6 hours to prevent testicular necrosis. Manual manipulation (i.e., detorsion) may be used to untwist the testes, but surgery may be required to secure the testicle and prevent reoccurrence.

Menstrual Disorders

The menstrual cycle can vary from woman to woman. The duration and the amount of menstrual bleeding fluctuate to some degree, but a standard pattern can be expected. The usual duration of menstruation is 4–6 days, and the usual amount of bleeding for the entire menstruation is approximately 80 mL. Irregular or abnormal bleeding may be harmless, merely uncomfortable, or an indication of serious problems. These conditions may or may not require treatment.

Abnormal Uterine Bleeding

Abnormal uterine bleeding (AUB) is a broad term that describes irregularities in the menstrual cycle involving frequency, regularity, duration, and volume of flow outside pregnancy. Previous terms such as “oligomenorrhea,” “menorrhagia,” and “dysfunctional uterine bleeding” are no longer used. Nearly one-third of women will experience AUB in their life, usually at menarche and at perimenopause. AUB can be acute or chronic. Acute AUB is a single episode of excessive bleeding that requires immediate medical attention, whereas chronic AUB refers to abnormal menstrual bleeding (frequency, regularity, duration, and/or volume) for most of the previous 6 months. Heavy menstrual bleeding (HMB) refers to increased menstrual daily or monthly volume, and intermenstrual bleeding (IMB) describes menstrual bleeding between regular menses (Davis & Sparzak, 2022; Munro et al., 2018).

The acronym PALM-COEIN is used to describe the underlying etiologies of AUB. The PALM (polyp, adenomyosis, **leiomyoma**, and malignancy and hyperplasia) part of this acronym describes structural issues, and the COEIN (coagulopathy, ovulatory dysfunction, endometrial disorders, iatrogenic, and not otherwise classified) part describes nonstructural issues. AUB not otherwise classified includes rare conditions, including arteriovenous malformations, myometrial

hyperplasia, and endometritis (Davis & Sparzak, 2022; Munro et al., 2018).

Diagnostic procedures include a history (including menstrual, sexual, and reproductive history), physical examination (including a pelvic examination), Pap smear, **sexually transmitted infection (STI)** screening, endometrial biopsy, pregnancy test, CBC, ferritin, coagulation panel, thyroid function tests, hormone levels (e.g., gonadotropins and prolactin), transvaginal ultrasound, MRI, and hysteroscopy. Treatment varies depending on the underlying cause (e.g., surgical removal of polyps). Intravenous fluids or blood products may be needed to treat or replace acute blood loss. Iron supplements and erythropoietin may be administered to counteract chronic blood loss.

Amenorrhea

Amenorrhea refers to the absence of menstruation. With this condition, menstruation may have never occurred or may have ceased. Amenorrhea is considered primary if menstruation has not occurred by 16 years of age. Genetic disorders (e.g., Turner syndrome) and congenital defects (e.g., uterine agenesis and hypothalamic conditions) can result in failure of menstruation to start when expected. Hypothalamic tumors, stress, sudden weight loss, extreme reduction in body fat (such as caused by eating disorders or incurred by athletes), anemia, and chemotherapy can also halt menstruation (i.e., secondary amenorrhea) by changing hormone levels. Normal causes of amenorrhea include pregnancy, lactation, and menopause.

Diagnostic procedures include a history (including menstrual, sexual, and reproductive history), physical examination (including pelvic examination), pregnancy test, thyroid function test, hormone levels (e.g., FSH, prolactin, and androgens), hormone challenge test (administering hormones in an attempt to trigger menses), pelvic ultrasound, CT, MRI, and hysteroscopy. Management of amenorrhea focuses on the identification and treatment of the underlying cause.

Dysmenorrhea

Dysmenorrhea is painful menstruation. Most women experience some mild lower abdominal discomfort during menstruation, but with dysmenorrhea, the cramping pain impairs usual daily activities. The pain begins at the conclusion of ovulation and continues through menstruation. Primary dysmenorrhea may appear at the first menstrual cycle and often has no known etiology. Dysmenorrhea may also appear later in life secondary to a number of conditions (e.g., **endometriosis** or reproductive cancers). In many cases of dysmenorrhea (especially the primary type), the condition resolves following childbirth.

In dysmenorrhea, excessive prostaglandin secretion produces strong uterine muscle contractions and blood vessel constriction, intensifying the normal uterine ischemia associated with menstruation. These contractions and ischemia generate strong, intermittent abdominal pain that can radiate to the back, legs, and perineum. Excessive prostaglandins can also cause nausea, vomiting, diarrhea, headaches, and dizziness.

Diagnostic procedures may be performed to identify the dysmenorrhea and underlying cause—specifically, a history, physical examination, pelvic ultrasound, laparoscopy, and hysteroscopy. Treatment strategies focus on relieving the discomfort and resolving the underlying etiology. These strategies include analgesics (especially nonsteroidal anti-inflammatory drugs [NSAIDs], which inhibit prostaglandin secretion), oral contraceptives (which prohibit ovulation), and heat application.

Premenstrual Syndrome

Premenstrual syndrome (PMS) refers to a group of physical and emotional symptoms that affect many women for reasons not fully understood. Most females who menstruate suffer from some degree of PMS. The exact cause of PMS is unclear, but it occurs more often in women between their late 20s and late 40s who have at least one child, a personal or family history of major depression, and a history

of postpartum depression or affective mood disorder. Clinical manifestations of PMS include irritability, depression, mood swings, fatigue, headache, abdominal bloating, changes in bowel pattern, joint pain, breast tenderness, weight gain, and sleep disturbances; these symptoms usually begin 5–11 days before menstruation.

Premenstrual dysphoric syndrome (PMDS) is a severe form of PMS that is characterized by severe depression, tension, and irritability. With this condition, symptoms interfere with daily activities or functioning. PMDS generally occurs only during the second half of the menstrual cycle with menses or shortly afterward.

Diagnostic procedures for PMS center on a thorough history (focusing on gynecologic complaints) and physical examination. Diagnostic criteria for PMS require the presence of at least one symptom during the five days before menses in each of the three previous menstrual cycles; diagnostic criteria for PMDS include the presence of at least five symptoms the final week before a majority of menses, which improve a few days after menses onset and become minimal or absent the week following menses (Hofmeister & Bodden, 2016). Additionally, at least one of the following symptoms must be present with PMDS: marked affective liability (e.g., mood swings), marked irritability, marked depression, and marked anxiety.

Treatment strategies are individualized and often include hormone therapy, diuretics, antidepressants (especially selective serotonin reuptake inhibitors), analgesics (specifically NSAIDs), and comfort measures (e.g., heat application, warm baths, rest, and light exercise). Additional measures include the following:

- Decreasing consumption of caffeine, soda, chocolate, fat, processed sugars, and alcohol
- Increasing consumption of fluids, specifically water and juice

Myth Busters

Menstruation has long been a source of myths, misconceptions, and old wives' tales. Because of their history, these misconceptions are often difficult to change.

Myth 1: You should not wash your hair or take a bath during menstruation.

There is absolutely no reason why you should not wash your hair or take a bath during menstruation! In fact, a warm bath may actually decrease discomfort by relaxing uterine muscles.

Myth 2: You cannot get pregnant if you have sex during menstruation.

Do not bet on it! While the odds of becoming pregnant are the highest near ovulation, pregnancy can occur at any time during the menstrual cycle.

Myth 3: You should not get your feet wet during menstruation.

This old wives' tale has no medical basis. This myth was made popular by some historical educational materials.

Myth 4: Sex is unhealthy during menstruation.

Some women may feel uncomfortable having sexual intercourse during menstruation, but there is no medical reason not to have sex during menstruation. In fact, sexual intercourse may relieve discomfort.

Myth 5: Women who are menstruating can catch colds easily and should avoid cold water or iced drinks.

Being cold may make abdominal cramping worse, but the incidence of colds does not increase during menstruation.

Numerous other myths surround menstruation; these myths are just the more popular ones.

- Eating frequent small meals that are high in whole grains, vegetables, and fruit but low in sodium and sugar
- Supplementing vitamin B_6, calcium, and magnesium

Pelvic Organ Prolapse

Muscles, ligaments, and fascia normally support the bladder, uterus, and rectum in the female pelvis. These supportive structures weaken with age, excessive stretching (e.g., childbirth), and trauma. Decreasing hormone levels at the onset of menopause can further atrophy these structures. With weakened support, the organs can

shift out of normal position. In many women, more than one organ is affected.

Vaginal Wall Prolapse

Anterior and posterior vaginal wall prolapse refers to the protrusion of an organ into the vaginal canal. Anterior vaginal wall prolapse is commonly referred to as **cystocele** or urethrocele. A cystocele occurs when the bladder protrudes into the anterior wall of the vagina. For this reason, a cystocele may be identified as a prolapsed bladder. A urethrocele is when the urethra is involved. The weakened pelvic support that results in this condition often results from excessive straining (e.g., childbirth, chronic constipation, and heavy lifting). The abnormal positioning prevents the bladder from completely emptying; therefore, recurrent cystitis (bladder infection) is common. Cystoceles vary in severity, and mild cases can be asymptomatic. Clinical manifestations of a cystocele include the following:

- Visualization of the bladder from the vaginal opening (**FIGURE 8-24**)



FIGURE 8-24 Cystocele.

© Dr. P. Marazzi/Science Source

- Feeling of fullness in the pelvis or vagina
- Stress incontinence
- Urinary retention, frequency, and urgency
- Pain or urine leakage during sexual intercourse

Diagnostic procedures for cystoceles consist of a history, physical examination (including pelvic examination), and voiding cystourethrogram (X-ray of the bladder during urination). The Pelvic Organ Prolapse Quantification (POPQ) system is often used to grade the prolapse based on the level of protrusion (**FIGURE 8-25**). Treatment strategies include pessary devices (vaginally inserted rings that support the bladder), surgical repair, estrogen therapy (if the woman is postmenopausal), incontinence interventions (e.g., bladder training and protective garments), Kegel exercises (isometric

exercises to strengthen the pelvic muscles), and avoidance of straining.

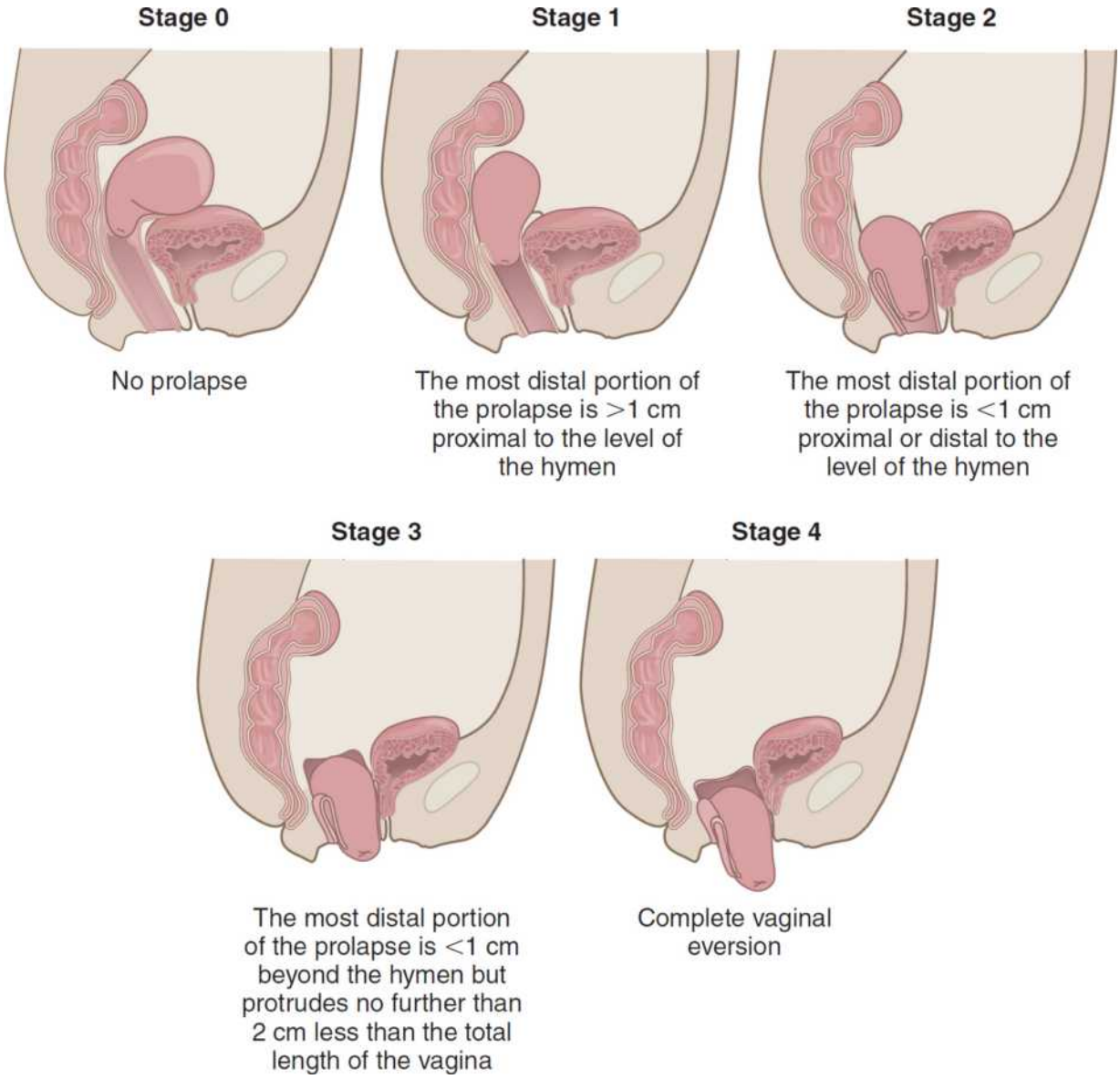


FIGURE 8-25 Pelvic Organ Prolapse Quantification system.

Description

Posterior vaginal wall prolapse is commonly referred to as a **rectocele** or enterocele. A rectocele occurs when the rectum protrudes through the posterior wall of the vagina. The rectocele may be large enough to bulge through the vaginal opening. An enterocele

is when the small intestine and peritoneum are involved. Although any condition that strains the fascia can contribute to rectoceles, most occur after menopause because of decreasing levels of estrogen. Rectoceles may be uncomfortable, but they are rarely painful. Mild cases are usually asymptomatic, but when present, clinical manifestations include the following:

- Visualization of the rectum from the vaginal opening
- Feeling of fullness in the pelvis or vagina
- Difficulty defecating
- Rectal pressure
- Bowel incontinence

Diagnostic procedures for rectoceles are similar to those used for cystoceles. The POPQ system is often used to grade the prolapse based on the level of protrusion. Treatment strategies include surgical repair, estrogen therapy (if postmenopausal), bowel training, and avoidance of straining.

Uterine and Apical Prolapse

Uterine prolapse refers to the descent of the uterus or cervix into the vagina. Uterine prolapse results from conditions that stretch or weaken the pelvic support (e.g., childbirth, aging, obesity, chronic cough, and chronic constipation). Apical (vaginal) prolapse refers to the descent of the vaginal vault after a hysterectomy.

Uterine and apical prolapse is usually asymptomatic in its early stages, but as the uterus descends, clinical manifestations appear:

- Visualization of the cervix or uterus from the vaginal opening
- Feeling of fullness in the pelvis or vagina
- Difficult or painful sexual intercourse (i.e., dyspareunia)
- Vaginal bleeding
- Difficulty with urination and defecation
- Urinary incontinence

Diagnostic and treatment strategies for uterine and apical prolapse are similar to those used for cystoceles and rectoceles.

Disorders of the Uterus

The uterus is a crucial organ for reproduction in females. Conditions that affect the uterus include benign or malignant tumors (e.g., leiomyomas and **cervical cancer**), congenital disorders (e.g., abnormal uterine positioning), infections (e.g., pelvic inflammatory disease), and hormonal imbalances that may affect menstruation and fertility.

Endometriosis

With endometriosis, the endometrium begins growing in areas outside the uterus. Such ectopic endometrial tissue most commonly occurs in the fallopian tubes, ovaries, and peritoneum, but it can be found anywhere in the body. The abnormal endometrial tissue continues to act as it normally would during menstruation (e.g., thickening, breaking down, and bleeding) even though it is outside the uterus. Without an outlet, the blood becomes trapped and irritates the surrounding tissue. Pain, cysts, scarring, and adhesions (fibrotic tissue that binds organs together) develop because of the inflammation, with the scarring and adhesions often resulting in infertility.

The exact cause of endometriosis is unclear, but numerous theories have been proposed. One theory holds that menstrual blood containing endometrial cells flows back through the fallopian tubes (retrograde menstruation), takes root, and grows. Another theory proposes that the bloodstream carries endometrial cells to other sites in the body. Other theories speculate that a predisposition toward endometriosis may be carried in the genes of certain families, or an inappropriate immune response may contribute to endometriosis development. Still other theories suggest that certain cells that are responsible for embryonic reproductive development are present within the abdomens of some women and retain their ability to

become endometrial cells with genetic or environmental influences later in life.

Risk factors for endometriosis include early onset of menstruation, late onset of menopause, delayed childbearing or nulligravida, menses cycle less than 27 days, and heavy menstrual bleeding. Clinical manifestations depend on the severity of the endometriosis but often worsen as the endometriosis progresses (**FIGURE 8-26**). Endometriosis begins developing at the onset of menstruation and advances over time. Most cases are diagnosed in patients between 25 and 35 years of age. Clinical manifestations of endometriosis include the following symptoms:

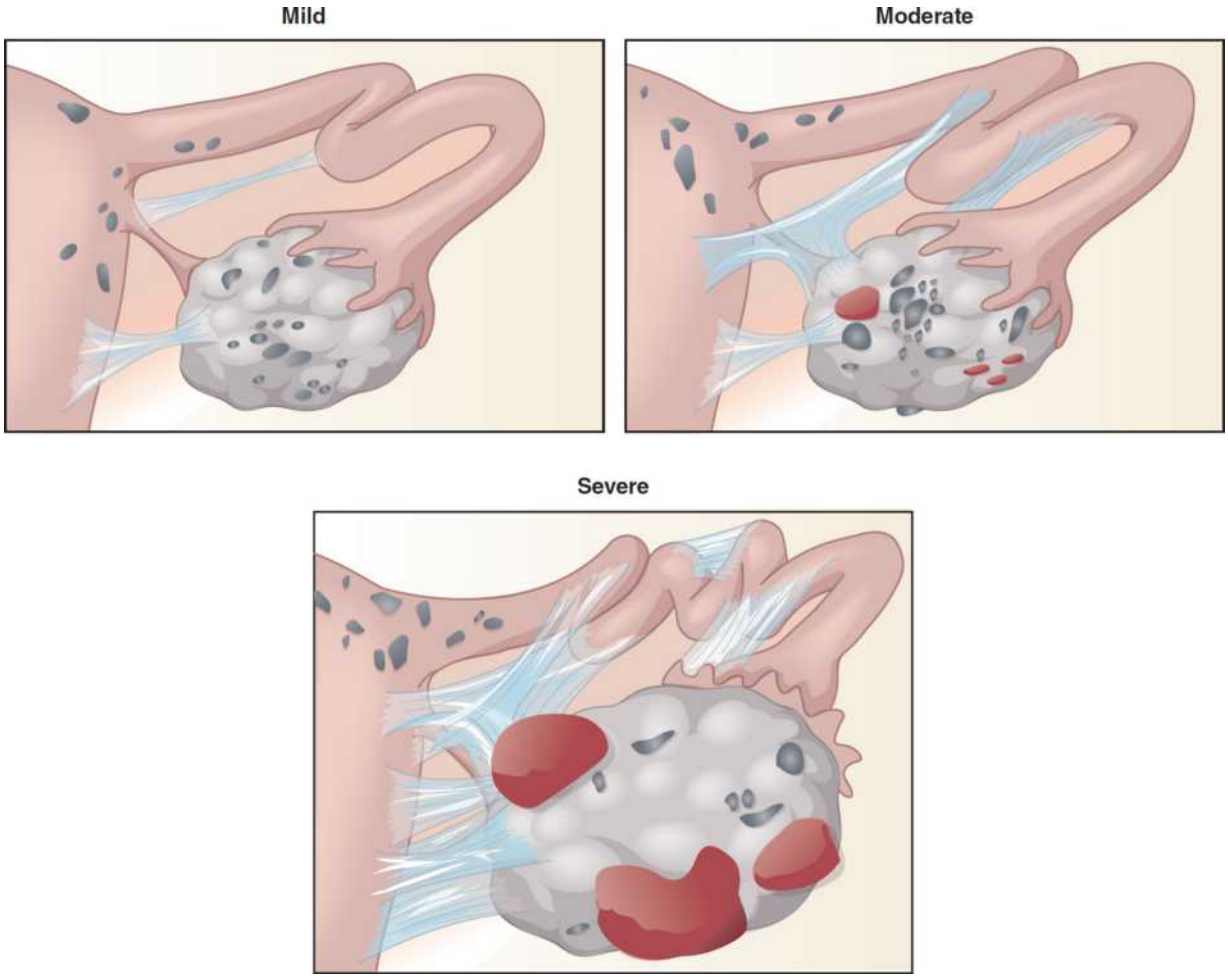


FIGURE 8-26 Stages of endometriosis.

Description

- Dysmenorrhea
- Pelvic pain
- Dyschezia (pain with bowel movements)
- Pain during or after sexual intercourse
- Interstitial cystitis
- Infertility
- Intermenstrual bleeding

Diagnostic procedures for endometriosis consist of a history, physical examination (including pelvic examination), pelvic laparoscopy, and pelvic ultrasound. The severity of the endometriosis is described using a staging system based on the number, location, and depth of lesions as well as the presence of adhesions. The endometriosis fertility index is used to predict pregnancy based on the woman's age, the number of years she has been infertile, history of pregnancies, function of reproductive organs, and endometriosis stage.

Treatment strategies focus on minimizing discomfort and maximizing childbearing potential (if desired):

- Analgesics (particularly NSAIDs)
- Hormone therapy (e.g., contraceptive agents, GnRH agonists and antagonists, and androgens)
- Surgical repair (laparoscopy or hysterectomy)

Leiomyomas

A leiomyoma, or uterine fibroid, is a firm, rubbery growth of the myometrium consisting of smooth muscle cells, fibroblasts, and other material that grows in or on the uterine wall (**FIGURE 8-27**). The exact cause of leiomyomas is unknown, but multiple factors are thought to play a role. The following genetic mutations have been associated with leiomyomas:



FIGURE 8-27 Leiomyomas.

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- *MED12* (mediator complex subunit 12)—codes for the mediator complex subunit 12 protein that is essential for activating CDK8 kinase
- *HMGA2* (high mobility group AT-hook 2)—codes for nonhistone chromosomal high mobility group proteins that are essential structural components of enhanceosomes that aid in regulating transcription
- *COL4A5* (collagen type IV alpha 5 chain) and *COL4A6* (collagen type IV alpha 6 chain)—code for a type of collagen that is the major structural component of basement membrane
- *FH* (fumarate hydratase)—codes for a protein that is an enzymatic component of the Krebs cycle and catalyzes the formation of L-malate from fumarate

Other factors that contribute to the development of leiomyomas include hormone levels (e.g., estrogen, progesterone, and growth hormones), micronutrients (e.g., iron and vitamin D), and major stresses.

Leiomyomas are the most common benign tumors in women and are more frequent in African Americans. In African American women, leiomyomas usually develop at a younger age, grow larger, and cause more severe symptoms. Other risk factors include obesity, advancing age, hypertension, nulligravida, vitamin D deficiency, food additive consumption, and ingestion of soybean milk. Most leiomyomas seem to grow during the menstruation years in the presence of estrogen but then shrink after menopause. Research indicates that leiomyomas are more likely to shrink in postmenopausal Caucasian women than in postmenopausal African American women. Tumor growth was thought to increase during pregnancy, but recent research suggests that growth actually levels off during pregnancy (NIH, 2018).

Although leiomyomas can grow as a single tumor, they more typically occur as multiple well-defined, unencapsulated masses of varying sizes. These tumors are classified based on their location (**FIGURE 8-28**). Submucosal leiomyomas grow just underneath the uterine lining and into the endometrial cavity. Intramural leiomyomas grow between the uterine muscles. Subserosal leiomyomas grow outside the uterus (e.g., broad ligaments, fallopian tubes, or cervix). Pedunculated leiomyomas are stalk-like growths attached to the outer or inner uterine surface.

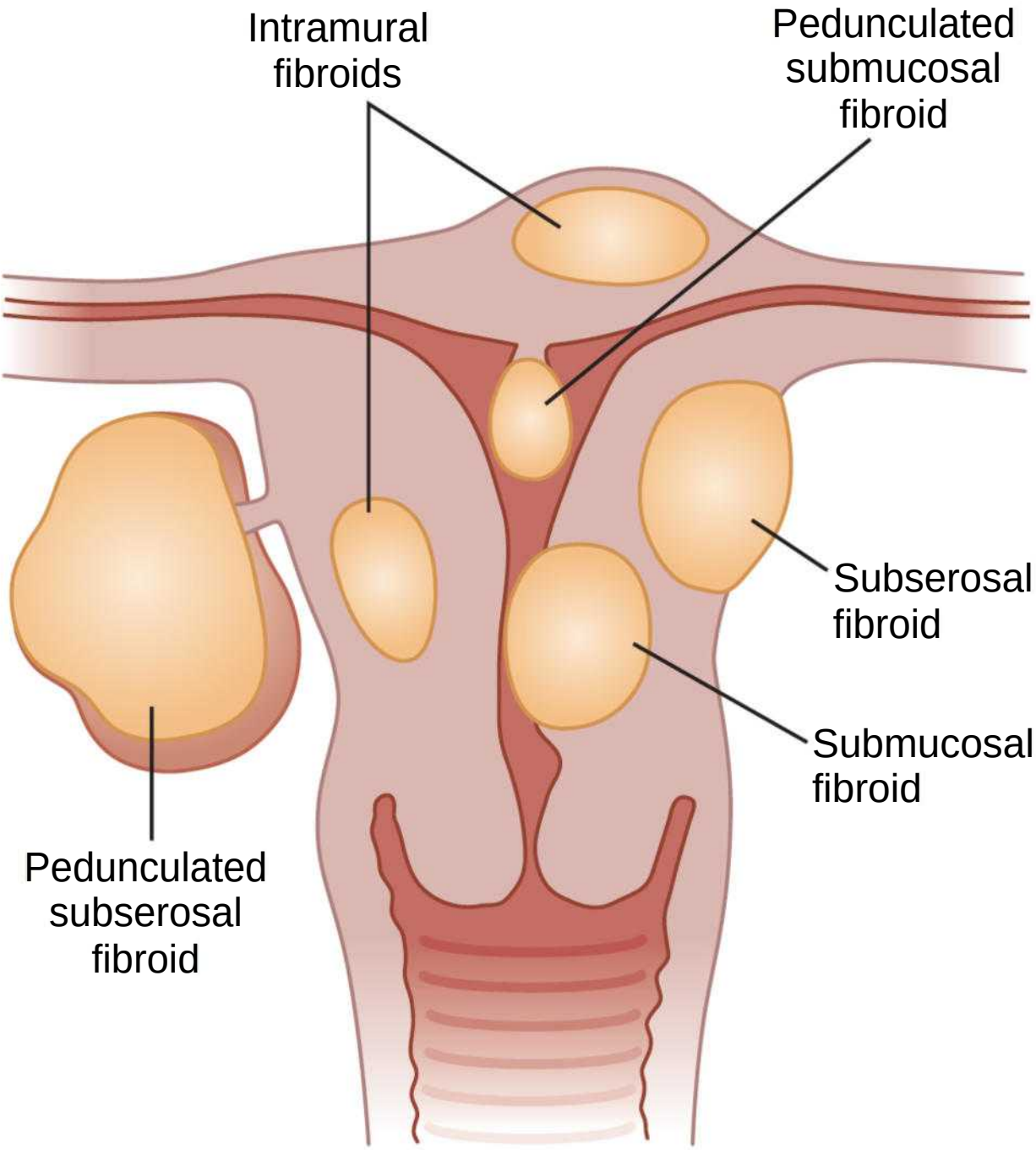


FIGURE 8-28 Leiomyoma classification.

Description

Leiomyomas can outgrow their blood supply and degenerate, usually as a result of rapid growth associated with pregnancy. This degeneration can cause severe pain, fever, or leukocytosis. Although they do not usually interfere with fertility, these tumors do increase

the risk of spontaneous abortion, preterm labor slightly, and postpartum hemorrhage. The risk for fertility and pregnancy problems increases as the tumor size increases. Leiomyomas rarely undergo cancerous changes.

Most leiomyomas are asymptomatic and go undetected. Clinical manifestations do not seem to be related to the leiomyoma size, which can range from microscopic to weighing several pounds. Even small leiomyomas can cause considerable symptoms. When present, clinical manifestations include the following symptoms:

- Dysmenorrhea
- Heavy menstrual bleeding
- Intermenstrual bleeding
- Pain in the pelvis, lower back, or legs
- Pelvic pressure or feeling of fullness
- Abdominal distention
- Urinary frequency and retention
- Urinary tract infections
- Constipation
- Pain during sexual intercourse
- Anemia

Diagnostic procedures for leiomyomas consist of a history (including menstrual history), physical examination (including pelvic examination), abdominal and transvaginal ultrasound, saline infusion sonography (injection of saline solution into the uterus to create an ultrasound image), hysteroscopy (uterine endoscopy), biopsy (to rule out malignancy), laparoscopy, CT, MRI, and CBC. Generally, most leiomyomas are harmless and do not require treatment. Symptom severity and childbearing intentions should be considered when choosing treatment options.

Treatment strategies include simple monitoring, hormone therapy (e.g., oral contraceptives, GnRH agonists, progesterone-releasing intrauterine devices, and selective progesterone receptor

modulators), analgesics (e.g., NSAIDs), surgery (e.g., myomectomy [removal of the fibroid] or hysterectomy), myolysis (laparoscopic laser treatment), endometrial ablation (using heat to destroy the uterine lining), MRI-guided focused ultrasound (use of high-intensity ultrasound to destroy the leiomyomas), and uterine artery embolization (which obstructs uterine blood supply). Additionally, anemia treatment (e.g., iron supplements and blood transfusions) may be necessary.

Disorders of the Ovaries

A variety of benign and malignant conditions can affect the ovaries. Ovarian disorders can be congenital (e.g., hypogonadism and Turner syndrome) or acquired (e.g., **ovarian cancer**), but many have a genetic basis. These disorders can affect the women's hormonal balance and fertility status.

Ovarian Cysts

Ovarian cysts are benign fluid-filled sacs on the ovary. Often the functional cyst forms during the ovulation process. Two types of functional cysts can develop based on their location—follicular and corpus luteum. With follicular cysts, the fluid stays in the follicle instead of the follicle releasing the egg. Cysts can also develop from the corpus luteum.

Most functional cysts are less than 1.5 cm in diameter, but some can exceed 5 cm. In most cases, these cysts are harmless and disappear over days or weeks without treatment. On occasion, they rupture, causing discomfort. This common condition most frequently occurs during the childbearing years and is uncommon after menopause. Complications are rare, but ovarian cysts can lead to hemorrhage, peritonitis, infertility, and amenorrhea. Most ovarian cysts are benign, but some cysts can become cancerous, especially when present in postmenopausal women.

Most ovarian cysts are asymptomatic. When present, abdominal pain or discomfort is the most prevalent clinical manifestation. Pain occurs when the cyst bleeds, ruptures, twists, or exerts pressure on nearby structures. Pain may also be associated with bowel movements and sexual intercourse. Other clinical manifestations include AUB and abdominal distention.

Polycystic ovary syndrome is a condition in which the ovary enlarges and contains numerous cysts. Although the exact cause is unknown, this condition is associated with hormone (e.g., androgen,

estrogen, and LH increases; FSH decreases) and endocrine (e.g., hypothalamus and pituitary) abnormalities. Some evidence suggests a link to genetic mutations in cytochrome P450c17 that affect 17-hydroxylase, an enzyme that limits androgen production (Reyes-Muñoz et al., 2018; Rocha et al., 2019). Clinical manifestations include AUB, amenorrhea, and symptoms of androgen excess (e.g., hirsutism, acne, and male-pattern baldness). Polycystic ovary syndrome increases the risk of developing obesity, infertility, metabolic syndrome, diabetes mellitus, cardiovascular disorders (particularly hypertension and hyperlipidemia), cancer (especially endometrial and breast cancers), and fatty liver disease.

Diagnostic procedures for ovarian cysts consist of a history, physical examination, transvaginal ultrasound, abdominal ultrasound, hormone levels (including LH, FSH, estradiol, and testosterone), pregnancy test (to rule out ectopic pregnancy), CT, MRI, laparoscopy, CA-125 levels (to screen for ovarian cancer), and biopsy (to rule out ovarian cancer). Most cysts will resolve in 8–12 weeks and only require follow-up monitoring. When warranted, treatment strategies include the following measures:

- Hormone therapy (e.g., oral contraceptives)
- Analgesics (e.g., NSAIDs)
- Management of metabolic (e.g., diabetes mellitus) and other disorders
- Weight control
- Surgery (e.g., laparoscopic cystectomy or oophorectomy)

Disorders of the Breasts

Breast disorders can be benign (e.g., **fibrocystic breast masses**) or malignant (e.g., breast cancer). Most breast disorders are not life threatening; however, malignancies should always be ruled out when breast symptoms are noted. These conditions can affect lactation, breastfeeding, and self-image.

Benign Breast Masses

Breast masses refer to lesions arising from mammary epithelium or in other mammary tissue and may be linked to vascular, inflammatory, or traumatic etiologies. The most common causes of these benign masses include fibrocystic changes, fibroadenomas, and galactoceles.

Fibrocystic breast masses (previously referred to as “fibrocystic breast disease”) refer to cysts and nondescript masses that are usually bilateral. Breasts become nodular and dense, often feeling heavy and uncomfortable, and there may occasionally be nonbloody nipple discharge. These masses become more prominent and painful during menstruation because of hormone fluctuations. This kind of change in breast tissue is so common (affecting more than 60% of women) that many healthcare professionals consider it a normal variation. Although its exact cause is unknown, this condition is thought to result from repeated estrogen and progesterone stimulation. Fibrocystic breast masses are more frequent during the childbearing years and are rare after menopause. Some contributing factors may be family history, a high-fat diet, consumption of chocolate, and excessive caffeine intake, although no scientific evidence has been obtained to confirm these links. These fibrocystic changes are not associated with increased cancer risk.

Fibroadenomas are usually smooth, round, moveable, painless masses that are often mistaken for cancer. These masses usually develop during the childbearing years and may shrink over time.

Three types of fibroadenomas are juvenile, simple, and complex. Juvenile fibroadenomas occur in adolescents and continue to grow over time. Simple fibroadenomas do not seem to increase breast cancer risk, whereas complex fibroadenomas may increase risk slightly.

Galactoceles refer to milk-containing cysts that are usually round and moveable. These cysts typically occur up to 10 months after lactation ceases. Galactoceles rarely become infected.

Diagnostic procedures for benign breast masses consist of a history, physical examination, mammogram, breast ultrasound, and biopsy (to rule out breast cancer). Usually, no treatment is required. When necessary, treatment strategies are largely symptomatic and include needle aspiration of fluid, surgical removal of cysts or masses, analgesics (e.g., NSAIDs or acetaminophen), a supportive bra, heat/cold application, limitation of dietary fat, and avoidance of caffeine and chocolate (although research is inconclusive about this strategy). Vitamin E, vitamin B_6, magnesium, and evening primrose oil may improve symptoms, but the use of these supplements remains controversial. Additionally, oral contraceptives can minimize symptoms.

Mastitis

Mastitis refers to an inflammation of the breast tissue that can be associated with infection and lactation. This condition usually develops within 6 weeks of childbirth. In most cases, a staphylococcal or streptococcal bacterium is introduced to the nipple through the breastfeeding process, but mastitis can also occur in the absence of lactation or breastfeeding. Impaired nipple or skin integrity increases the likelihood of mastitis developing. The infection usually invades the breast's fatty tissue, triggering an inflammatory response (e.g., edema, redness, and warmth). The edema puts pressure on the milk ducts, causing pain and palpable lumps. Despite popular belief to the contrary, breastfeeding can occur in the presence of mastitis, although it may be uncomfortable. In some cases, milk flow may become blocked, and abscesses can develop.

Clinical manifestations usually appear suddenly and include the following signs and symptoms:

- Breast tenderness, swelling, redness, and warmth (**FIGURE 8-29**)



FIGURE 8-29 Mastitis.

Courtesy of Sarah Coulter-Danner.

- Breast lumps
- Pain or a burning sensation continuously or while breastfeeding
- Flulike symptoms (e.g., fever, malaise, chills, nausea, and vomiting)
- Nipple discharge (usually purulent)
- Enlarged nearby axillary lymph nodes

Diagnostic procedures for mastitis include a history, physical examination, and cultures (drainage and/or breastmilk). Treatment strategies consist of antibiotic therapy, adequate hydration, rest, analgesics (e.g., acetaminophen and NSAIDs), a supportive bra, heat/cold application, adequate milk expression, and needle aspiration. During treatment, breastfeeding is safe and should be encouraged (except if the mother is human immunodeficiency virus [HIV] positive).

Miscellaneous Infectious and Inflammatory Disorders

Infections can occur at any point along the reproductive tract. Such infections often originate in the urinary tract, but reproductive tract infections can also migrate to the urinary system. Many of these infections are easily resolved, but if untreated, some can have detrimental effects (e.g., infertility). Additionally, inflammatory processes can be triggered as a result of a variety of stressors or trauma. Edema and irritation as a result of these processes can cause significant discomfort but rarely result in serious complications.

Prostatitis

Prostatitis refers to inflammation of the prostate, which can be either acute or chronic. Prostatitis may be caused by a variety of conditions (e.g., bacteria, sperm, trauma, stress, and urinary catheter) that trigger the inflammatory process. The prostate has protective mechanisms to prevent ascending infection such as the flushing action of urination and ejaculation. Additionally, it produces secretions that have an antimicrobial action (possibly attributable to their zinc content). Owing to its close proximity to the urinary system, the prostate is often invaded by a pathogen from this system. Prostatitis is more common in young and middle-aged men, and immune-compromised states and a history of STIs (especially **chlamydia** and **gonorrhea**) increase the risk of this condition.

Prostatitis is classified into four categories:

- Category 1: Acute bacterial prostatitis
  - Usually seen in younger men
  - Usually results from a urinary tract infection (often *Escherichia coli*)
  - Least common

    - Easiest to diagnose and treat but can be life threatening
- Category 2: Chronic bacterial prostatitis
    - Usually results from recurrent urinary tract infections
    - Relatively uncommon
    - Persists longer than 3 months
    - Indolent (causes little to no pain)
- Category 3: Chronic prostatitis/chronic pelvic pain
    - Can be inflammatory or noninflammatory
    - No bacteria are present, but immune cells can be found
    - Most common and least understood
    - Manifestations last longer than 3 months; can disappear and reappear without warning
- Category 4: Asymptomatic inflammatory prostatitis
    - No clear etiology
    - No bacteria are present, but immune cells can be found
    - May be associated with infertility

Clinical manifestations of prostatitis vary depending on the type. These manifestations include the following signs and symptoms:

- Dysuria
- Difficulty urinating, such as dribbling or hesitancy
- Urinary frequency and urgency
- Nocturia
- Pain in the abdomen, groin, lower back, perineum, or genitals
- Painful ejaculation
- Indications of infection, such as fever, chills, and myalgia (with acute bacterial prostatitis)
- Recurrent urinary tract infections (with chronic bacterial prostatitis)

Diagnostic procedures for prostatitis consist of a history, physical examination (including a digital rectal examination), urinalysis, sperm

analysis, cultures (urine and prostate discharge), cystoscopy, and transrectal ultrasound. Treatment varies depending on the type. Typical strategies include long-term organism-specific antibiotic therapy, analgesics (e.g., NSAIDs and acetaminophen), antipyretics, adequate hydration, sitz bath, and prostatic massage.

Epididymitis

Epididymitis describes an inflammation of the epididymis, the duct connecting the testes to the vas deferens. Ascending bacterial infections or STIs usually initiate this inflammatory process. Bacteria, most commonly *E. coli*, frequently spread to the epididymis from the urinary system. *E. coli* can also cause epididymitis when men engage in insertive anal sex. Gonorrhea and chlamydia are the typical sexually transmitted culprits. Urinary tract infections are the most frequent etiology in older men, whereas STIs are more frequent in younger men. Rare triggers of this type of inflammation include tuberculosis and the antidysrhythmic medication amiodarone (Cordarone). Risk factors for developing epididymitis include the following conditions:

- Being uncircumcised
- Recent surgery or a history of structural problems in the urinary tract
- Urinary catheterization
- Sexual intercourse with more than one partner and failure to use condoms

The inflammatory and infectious processes can lead to abscesses, fistulas (cutaneous scrotal type), infertility, testicular necrosis, and chronic epididymitis. Clinical manifestations of epididymitis reflect these inflammatory and infectious processes:

- Indicators of infection (e.g., fever, chills, and myalgia)
- Scrotal tenderness, erythema, and edema (which can become severe)

- Prehn's sign (elevating the scrotum relieves pain)
- Penile discharge
- Bloody semen
- Painful ejaculation
- Dysuria
- Groin pain

Diagnostic procedures for epididymitis focus on identifying the causative agent and consist of a history, physical examination, ultrasound, urinalysis, cultures (urine and penile discharge), and STI testing (e.g., gonorrhea and chlamydia). Treatment strategies center on eliminating the infection and decreasing discomfort. These interventions include the following measures:

- Antibiotic therapy
- Analgesics (especially NSAIDs)
- Bed rest
- Scrotal support (wearing briefs instead of boxers) and elevation (with a jock strap when upright and with a rolled towel when lying down)
- Cold application
- Screening and treatment of sexual partners

Candidiasis

Candidiasis is a yeast infection caused by the common fungus *Candida albicans*. This condition usually occurs as an opportunistic infection (see the *Immunity* chapter) that can arise anywhere in the body (especially the skin and the gastrointestinal tract), but the focus of the discussion here is the infection's effects on the reproductive system.

In the reproductive system, candidiasis most frequently occurs in the vagina and is a common cause of vaginitis (inflammation of the vagina). *Candida* and many other microorganisms are part of the

normal flora present in the vagina that usually exist in a balanced state. Imbalance may occur in the presence of vaginal pH changes; normally, the vagina is slightly acidic as a result of lactobacillus in the vaginal flora that breaks down glycogen into lactic acid. Antibiotic therapy can increase vaginal pH (making it more alkaline), leading to yeast overgrowth. Bubble baths and the use of feminine products can also alter the delicate pH balance. Other factors contributing to such imbalance include decreased immune response (e.g., due to corticosteroid medications or HIV) and increased glucose in the vaginal secretions (e.g., pregnancy, oral contraceptives, diabetes mellitus, and obesity).

Candidiasis is not sexually transmitted, but men may develop mild symptoms after having sexual intercourse with an infected partner. Men may develop inflammation of the glans penis, or the foreskin may become infected if uncircumcised. Small white spots, redness, or dry peeling rash may occur on the penis, along with itching, irritation, or burning. These symptoms in males will usually resolve without treatment.

Clinical manifestations of candidiasis in women include the following signs and symptoms:

- A thick, white vaginal discharge that resembles cottage cheese
- Vulvular erythema and edema
- Vaginal and labial itching (can be intense) and burning
- White patches on the vaginal wall
- Dysuria
- Dyspareunia

Candidiasis can mimic other vaginal infections; therefore, diagnostic procedures are used as part of the differential diagnosis. Diagnostic procedures include a history, physical examination (including a pelvic examination), and discharge analysis (including vaginal pH and wet mount).

Treatment focuses on reestablishing the normal floral balance, minimizing tissue irritation, and increasing comfort. Most cases of

candidiasis can be treated at home and without medical supervision. However, self-management is not recommended in the following situations:

- Symptoms are moderate or severe
- Fever or pelvic pain is present
- The patient has a negative history of candidiasis
- Pregnancy
- Immunosuppression or uncontrolled diabetes mellitus
- Candidiasis is recurrent (at least four episodes in one year)
- Other vaginal infections are present

If self-management strategies are not successful, a healthcare provider should be consulted. The following treatment strategies can also be used to prevent candidiasis:

- Antifungal agents (available in oral, parenteral, and vaginal cream or suppository forms; some are available without a prescription)
- Perineum care (including cleaning from front to back, keeping the perineum area clean and dry, avoiding soap and rinsing with water only, and taking warm—not hot—baths)
- Avoidance of douching
- Resisting the urge to scratch
- Practicing safe sex (tissue irritation increases the risk of contracting STIs)
- Avoiding the use of feminine hygiene sprays, fragrances, or powders in the genital area
- Not wearing extremely tight-fitting clothing (which may cause irritation)
- Wearing cotton underwear or cotton-crotch pantyhose and avoiding underwear made of silk or nylon (these materials are not very absorbent and restrict airflow, increasing sweating in the genital area and irritation)
- Using feminine pads instead of tampons during menstruation

- Controlling blood glucose (if diabetic)
- Eating yogurt with live cultures or taking *Lactobacillus acidophilus* tablets (these can also be taken with antibiotics to prevent candidiasis)

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is a clinical syndrome that refers to a polymicrobial infection of the female reproductive system. According to the CDC (2021a), PID diagnoses have declined in recent years, but an estimated 2.5 million U.S. women will have PID in their lifetime. Changes in STI rates, advances in screening technologies, and improvements in antimicrobial therapies may be responsible in part for the decline in incidence. Risk factors for PID include those associated with STIs, such as younger age, having new or multiple sex partners, having a sex partner who has other concurrent sex partners, and inconsistent use of condoms during sex. Other risk factors include a history of STIs or prior PID, vaginal douching, and intrauterine device use (primarily the first 3 weeks after insertion).

In this infection, bacteria usually ascend to the upper reproductive tract from the cervix and vagina. PID can be either acute or chronic and most commonly results from an STI (usually gonorrhea or chlamydia). Endogenous microorganisms (e.g., gram-positive and -negative anaerobic organisms and aerobic/facultative gram-positive and -negative rods and cocci) associated with bacterial vaginosis have also been implicated in PID development. *Mycoplasma genitalium* may also play a role. Acute bacterial invasions are more likely to occur immediately following menstruation when the endometrium is more vulnerable.

Whatever its source, the infection triggers the inflammatory response, resulting in mucosal irritation, edema, and purulent exudate. The edema and exudate can obstruct the reproductive structures, and the exudate can migrate to the peritoneal cavity, increasing the risk of peritonitis (see the *Gastrointestinal Function* chapter). Abscesses and septicemia (bacterial blood infection) can

develop and become life threatening. Adhesions and strictures frequently result from PID, leading to chronic pelvic pain, ectopic pregnancies, infertility, and problems with surrounding structures. Fitz-Hugh-Curtis syndrome is a rare complication involving inflammation of the liver and peritoneal surfaces that leads to adhesion development. Infrequently, death from PID can occur usually as a result of abscess rupture or ectopic pregnancy. Recurrent episodes of PID and more severe inflammation are associated with a greater risk of complications, particularly infertility; however, subclinical (i.e., cases not severe enough to produce symptoms) PID has also been associated with infertility.

Clinical manifestations of PID vary from subtle to severe, depending on whether the infection is acute or chronic. These manifestations include the following signs and symptoms:

- Indications of infection such as fever, chills, myalgia, and leukocytosis (with acute forms or when complications develop)
- Pain or tenderness in the pelvis, lower abdomen, lower back, or pelvic organs (sudden and severe with acute forms or when complications develop)
- Abnormal or increased vaginal and cervical discharge (usually purulent)
- Postcoital bleeding (after sexual intercourse)
- Dyspareunia
- Urinary frequency
- Dysuria
- Dysmenorrhea
- Amenorrhea
- AUB
- Anorexia
- Nausea and vomiting

Mild cases of PID can go unrecognized. Diagnostic procedures for PID consist of a history (including menstrual and sexual history),

physical examination (including pelvic examination), discharge analysis (including nucleic acid amplification test [NAAT], culture, and wet mount), Pap smear, CBC, inflammatory markers (e.g., C-reactive protein and erythrocyte sedimentation rate), endometrial biopsy, pelvic ultrasound, transvaginal sonography, MRI, CT, and laparoscopy. Histologic evidence of endometritis is usually demonstrated in women with subclinical PID. PID manifestations are nonspecific, so other reproductive, urinary, and gastrointestinal tract illnesses or diseases should be ruled out. Pregnancy (including ectopic pregnancy) should also be excluded, and HIV screening is recommended.

Aggressive treatment is necessary to prevent complications. Presumptive treatment should be initiated in sexually active young women and other women at risk for STIs if they are experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified, and if one or more of the following minimum clinical criteria are present on pelvic examination:

- Cervical motion tenderness
- Uterine tenderness
- Adnexal (space occupied by the uterus, ovaries, and fallopian tubes) tenderness (CDC, 2021a)

Additional criteria used to enhance the specificity of the diagnosis, ensure proper diagnosis, and prevent complications include one or more of the following:

- Fever greater than 101°F
- Abnormal cervical mucopurulent discharge or cervical friability (bleeds easily when touched)
- Abundant numbers of leukocytes in vaginal fluid
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Confirmation of *N. gonorrhoeae* or *C. trachomatis* infection (CDC, 2021a)

Treatment strategies specific to PID include the following measures:

- Antibiotic therapy
- Screen and treat sexual partners (to prevent spreading and reinfection)
- Practice safe sex (to prevent spreading and reinfection)
- Avoid douching (which spreads the infection to the upper reproductive tract)
- Treat abscesses (needle aspiration or surgical removal)
- Follow-up reexamination (to ensure that infection is completely resolved)
- Infertility evaluation

Screening for and treatment of STIs (especially gonorrhea or chlamydia) should also be initiated promptly to prevent PID.

Sexually Transmitted Infections

Sexually transmitted infections (STIs), sometimes referred to as sexually transmitted diseases (STDs), encompass a broad range of infections that can be contracted through sexual contact (including oral–genital contact, anal contact, and vaginal intercourse). More than 30 different sexually transmissible bacteria, viruses, and parasites have been identified; some of these pathogens can also be transmitted from mother to child during pregnancy and childbirth as well as through blood contact (e.g., HIV [see the *Immunity* chapter] and **syphilis**). Some STIs are easily eradicated with appropriate treatment (e.g., chlamydia and gonorrhea), whereas others persist for a lifetime (e.g., **genital herpes** and **condylomata acuminata**).

Federal laws mandate that cases of three STIs be reported to the CDC: chlamydia, gonorrhea, and syphilis. Other STIs are not required to be reported (e.g., genital herpes and condylomata acuminata); therefore, their actual prevalence may be much higher than the CDC's estimates. The CDC (2021b) estimates that approximately 20 million new STIs are diagnosed each year in the United States—almost half of them among people 15–24 years of age. More than 110 million men and women are estimated to be living with an STI across the nation. However, it is worth noting that the COVID-19 pandemic led to disruptions in STD-related screening, prevention, and care, especially in 2020 and 2021. Yet still, the rates for gonorrhea and syphilis increased from 2019 to 2020 10% and 7% respectively, but cases of chlamydia decreased 5% from 2019 to 2020. Concerningly, rates of syphilis increased 24% among reproductive-aged women from 2019 to 2020, resulting in a 15% increase in congenital syphilis. These trends continued into 2021.

STI prevalence rates vary depending on the geographic region within and outside the United States. These rates continue to increase in the United States despite education efforts directed

toward their prevention. Multiple factors have been identified in the overall increase in STIs, including:

- Drug use, poverty, stigma, and unstable housing, which can reduce access to STI prevention and care
- Decreased condom use among vulnerable groups, including young adults and gay and bisexual men
- Funding cuts to STI programs at the state and local levels (CDC, 2021b)

Bacterial STIs

Bacterial STIs are common and are usually treated with minimal residual effects. Screening generally focuses on identifying the causative organism through cultures of exudate, rapid assay tests, and fluorescent antibody tests. Treatment of most bacterial STIs requires a simple course of antibiotics. If taken properly, the antibiotics will resolve the infection. However, these infections can lead to a wide range of issues (e.g., epididymitis and pelvic inflammatory disease). Reinfection is common, but it can be minimized by refraining from sexual activity until bacteria are eradicated, by practicing safe sex (e.g., using condoms and dental dams), and by treating sexual partners.

Chlamydia

Chlamydia is caused by *Chlamydia trachomatis*, an intracellular parasite that requires a host cell to reproduce. Eighteen different strains of this pathogen have been identified. Chlamydia is the most commonly reported STI in the United States; more than 1.6 million cases were reported to the CDC in 2021. Chlamydia prevalence rates have been steadily increasing in the United States for the past 20 years until 2019, likely due to the influence of the COVID-19 pandemic on screening (**FIGURE 8-30**). However, reported chlamydia cases increased from 2020-2021. According to the CDC (2021b), chlamydia rates are high across all groups and regions in the United States, but the burden of chlamydia is the highest in young women;

African Americans; and persons living in the District of Columbia, Alaska, the U.S. Virgin Islands, and the South.

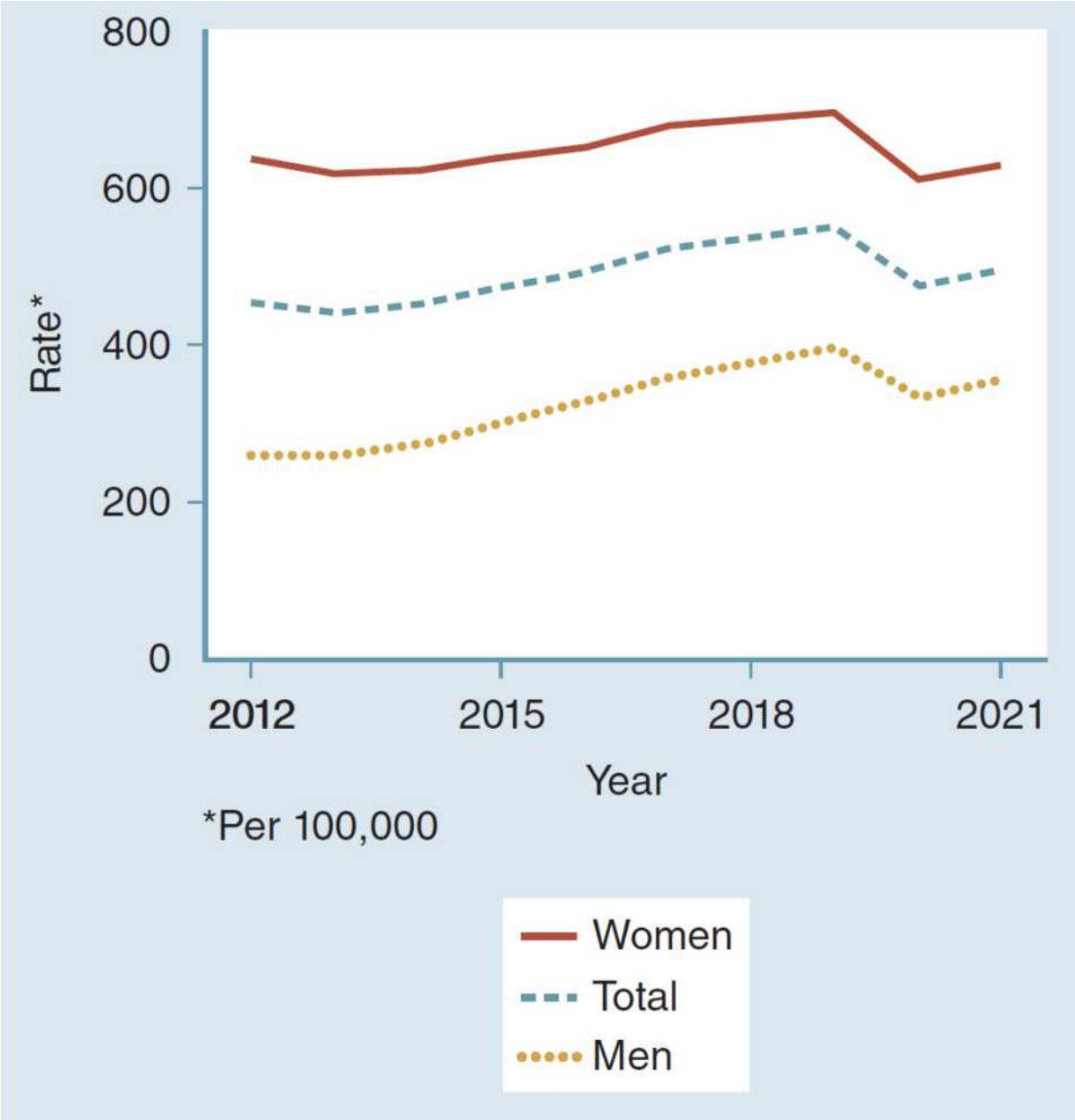


FIGURE 8-30 U.S. chlamydia prevalence rates.

Reproduced from Centers for Disease Control and Prevention. (2021b). Sexually transmitted disease surveillance 2021. Retrieved from from https://www.cdc.gov/std/statistics/2021/default.htm

Description

Chlamydia can be transmitted through sexual contact and from mother to child during childbirth. In the initial contact, a metabolically inactive form of the bacterium (i.e., elementary body) is taken up by the epithelial cells of the urogenital tract, rectum, or conjunctiva. Once in the host cell, the elementary body begins to differentiate into the metabolically active form (i.e., reticulate body). The reticulate body then uses the host's energy sources and amino acids to replicate and form new elementary bodies, which then infect additional cells. Many times, this infection is transmitted to the child in the form of neonatal conjunctivitis (an eye infection that can lead to blindness). Complications of chlamydia can include PID, epididymitis, prostatitis, infertility, neonatal conjunctivitis, and ectopic pregnancy. In addition, the bacterium's invasion of the reproductive tract epithelial lining causes inflammation that can increase the individual's risk for contracting other STIs, and exposure to the bacterium though oral sex can cause laryngitis.

Chlamydia's incubation period varies from days to months after the initial exposure, but the average time from exposure to symptom development is about 1 to 3 weeks. The pathogen is usually detectable 1 to 5 days after exposure, but it is unclear when the individual becomes contagious after exposure during the incubation period.

Often called the silent STI, chlamydia is usually asymptomatic in both males and females. When present, clinical manifestations include the following signs and symptoms:

- Dysuria
- Penile, vaginal, or rectal discharge (usually purulent)
- Testicular tenderness or pain
- Rectal pain
- Dyspareunia
- Postcoital bleeding
- Intermenstrual bleeding
- Pharyngitis

Because of this STI's high prevalence and potential to cause neonatal complications, it is recommended that all pregnant women be screened for chlamydia and receive treatment if they are found to be infected. Additionally, screening should be performed in individuals who are sexually active and younger than 25 years of age, have a history of STIs, engage in high-risk sexual behavior (e.g., engage in unprotected sexual intercourse, have multiple sex partners, have new sex partners, or engage in sex work), or have a partner who has had an STI or engages in high-risk behavior. Diagnostic procedures include a history (including menstrual and sexual history), physical examination (including pelvic examination), and discharge analysis (including NAAT). Additionally, other tests may be performed if complication development is suspected (e.g., CBC for PID).

Treatment usually consists of antibiotics such as azithromycin (Zithromax), doxycycline, or erythromycin. Sexual partners should also be screened and treated. Uncomplicated chlamydia is usually no longer contagious 7 days after initiating treatment. Antibiotic resistance is uncommon, but reinfection occurs frequently. Therefore, follow-up testing is unnecessary unless testing for a new infection or reinfection. Pregnant women are usually retested prior to birth. Additionally, avoiding vaginal childbirth by electing to have a cesarean section delivery may decrease the chances of mother-to-child transmission rates.

Gonorrhea

Gonorrhea (referred to colloquially as "the clap") is caused by *Neisseria gonorrhoeae*, an aerobic bacterium that has developed many drug-resistant strains. Rates of gonorrhea have been increasing for 20 years (**FIGURE 8-31**); more than 710,000 cases of gonorrhea were reported to the CDC in 2021, the highest number recorded since 1991. Gonorrhea rates have increased 118% since its historic low in 2009. According to the CDC (2021b), gonorrhea rates are highest in men; African Americans; and persons living in the District of Columbia, Alaska, and the South. Gonorrhea can quickly develop resistance to the typical antibiotics used to treat the infection. In

2021, more than half of all gonorrhea infections were estimated to be resistant to at least one antibiotic.

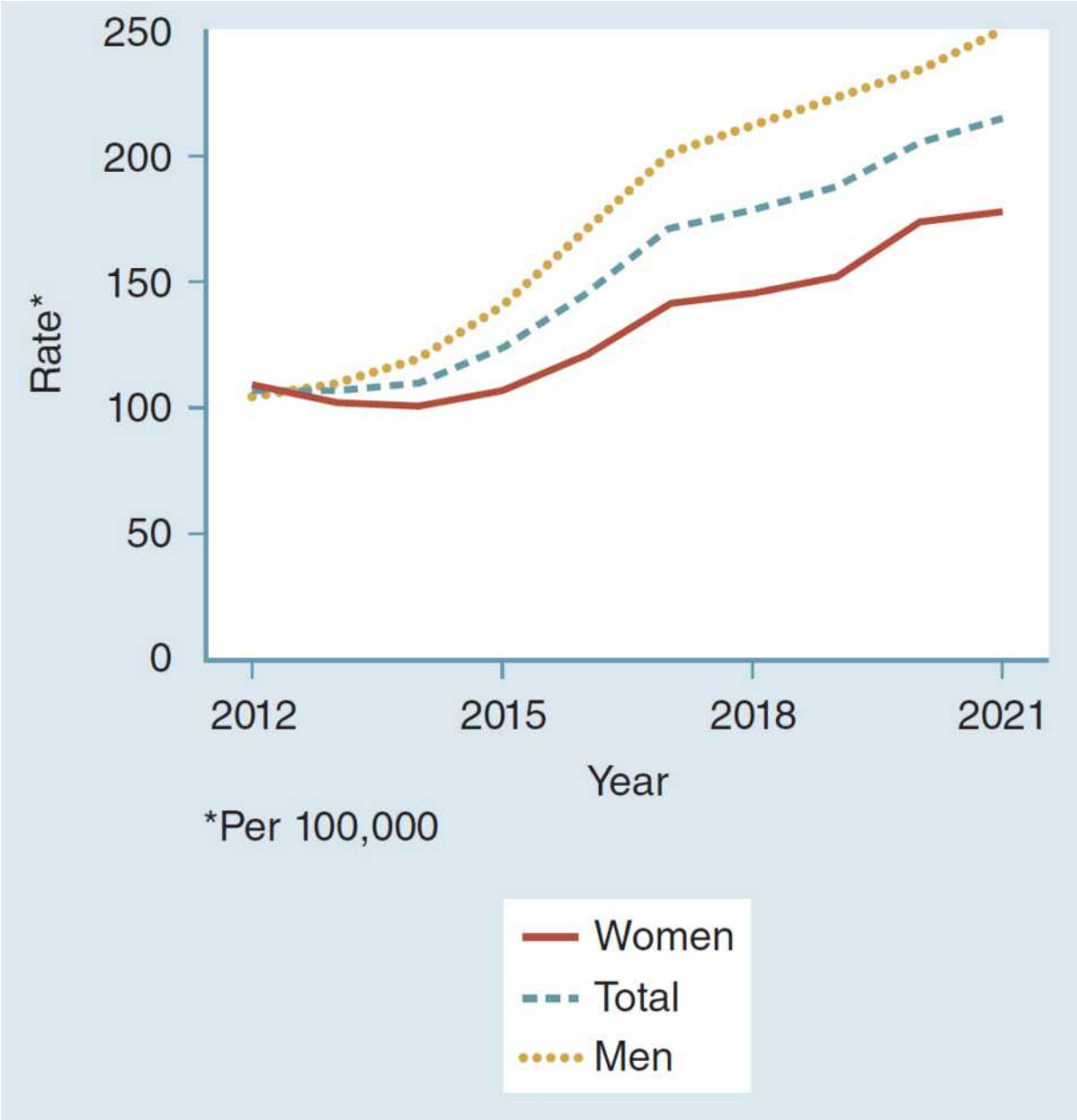


FIGURE 8-31 U.S. gonorrhea prevalence rates.

Reproduced from Centers for Disease Control and Prevention. (2021b). Sexually transmitted disease surveillance 2021. Retrieved from from https://www.cdc.gov/std/statistics/2021/default.htm

Description

The *N. gonorrhoeae* bacterium infects the epithelia of the vagina, mouth, anus, pharynx, or conjunctivae, causing irritation and inflammation. After the bacterium attaches to the epithelia, microvilli surround it and draw it into the surface of the mucosal cell. Gonorrhea is transmissible through sexual contact and from mother to infant during childbirth. Mother-to-child transmission usually results in neonatal conjunctivitis. Outside the body, the bacterium dies within a few seconds.

Complications of gonorrhea include PID, epididymitis, prostatitis, infertility, neonatal conjunctivitis, ectopic pregnancy, and Fitz-Hugh-Curtis syndrome. Inflammation of the epithelial lining caused by the infection can increase the risk of contracting other STIs. Rarely, gonorrhea can spread to other locations in the body (i.e., disseminated gonococcal infection); in such a case, complications may include arthritis (usually of the hands, wrists, ankles, knees, and elbows), dermatitis (usually of the hands and lower extremities), and endocarditis.

Gonorrhea is often asymptomatic. Clinical manifestations, if they occur, usually do not appear until 2–10 days after the infection. Although gonorrhea is usually detectable 1 to 5 days after exposure, it is unclear when the individual becomes contagious after exposure during the incubation period. Men are more likely than women to experience symptoms. When present, clinical manifestations are similar to those of chlamydia and include the following signs and symptoms:

- Dysuria
- Urinary frequency or urgency
- Penile, vaginal, or rectal discharge (white, yellow, or green) (colloquially referred to as “the drip”) (**FIGURE 8-32**)



FIGURE 8-32 Characteristic lesions and discharge associated with gonorrhea.

Courtesy of Joe Miller/CDC.

- Penile, scrotal, rectal, or lower abdominal pain and tenderness
- Redness or edema at the urinary meatus (in men)
- Dyspareunia
- Postcoital bleeding
- Intermenstrual bleeding
- AUB
- Pharyngitis
- White blisters that darken and disappear (see Figure 8-32)

Because of this STI's high prevalence and potential to cause neonatal complications, it is recommended that all pregnant women be screened for gonorrhea and receive treatment if they are found to

be infected. Additionally, screening should be performed in individuals who are sexually active and younger than 25 years of age, have a history of STIs, engage in high-risk sexual behavior (e.g., engage in unprotected sexual intercourse, have multiple sex partners, have new sex partners, or engage in sex work), or have a partner who has had an STI or engages in high-risk behavior. Diagnostic procedures include a history (including menstrual and sexual history), physical examination (including pelvic examination), and discharge analysis (including NAAT, Gram staining, culture, and sensitivity).

Since antibiotic resistance can occur with gonorrhea, the culture and sensitivity can ensure the appropriate antibiotic is selected. Single-drug therapy is no longer recommended. Instead, treatment for gonorrhea usually consists of a combination of antibiotics, such as ceftriaxone (cephalosporin), azithromycin (Zithromax), doxycycline, or gemifloxacin (Factive). Sexual partners should also be screened and treated. Uncomplicated gonorrhea is usually no longer contagious 7 days after initiating treatment. Retesting may be necessary if resistance or reinfection is suspected. Pregnant women are usually retested prior to birth. Additionally, avoiding vaginal childbirth by electing to have a cesarean section delivery may decrease the chances of mother-to-child transmission rates.

Syphilis

Syphilis is an ulcerative infection caused by *Treponema pallidum*, a spiral-shaped (spirochete) bacterium that requires a warm, moist environment and cannot survive long outside the human body (**FIGURE 8-33**). Syphilis is transmitted through skin or mucous membrane contact with infected, ulcerative lesions (**chancres**). Chancres can be present on or near the penis, vagina, anus, rectum, lips, or mouth. The spirochete reaches nearby lymph nodes within hours and rapidly spreads throughout the body. Additionally, the spirochete can cross, through the placental barrier, from a mother to her fetus after the fourth month of gestation (congenital syphilis). Syphilitic lesions also provide an opportunity for other STIs to invade.



FIGURE 8-33 Treponema pallidum, the spirochete that causes syphilis.

Courtesy of Bill Schwartz/CDC.

Syphilis occurs in several stages, each with its own clinical manifestations. Long asymptomatic periods are usually seen between each stage. Treatment during any stage will prevent disease progression to the next stage.

- **Primary syphilis** is the first stage. Painless chancres (usually one) form at the site of infection about 2–3 weeks after the initial infection is acquired (**FIGURE 8-34**). Additionally, lymphadenopathy develops in the region as the spirochete travels to nearby lymph nodes. The chancres often go unnoticed and disappear about 4–6 weeks later, even without treatment, because of the body's immune response. However, this response is not sufficient to eradicate the spirochete or keep it from spreading. The spirochete becomes dormant, and no other symptoms are present. Because the individual may not test positive during this stage, the test should be repeated at a later date. Even if he or she tests negative, the infected individual is contagious during this stage.



FIGURE 8-34 Chancre characteristic of primary syphilis.

Courtesy of Dr. Gavin Hart and Dr. N.J. Fiumara/CDC.

- **Secondary syphilis** occurs about 2–8 weeks after the first chancres form. Approximately 33% of those individuals with infection who do not receive treatment for primary syphilis will develop this second stage, which is characterized by a generalized, nonpruritic, brown-red rash that may be raised (popular) or flat (macular) (i.e., syphilitic dermatitis or condyloma lata) (**FIGURE 8-35**). Other symptoms include malaise, fever, patchy hair loss, lymphadenopathy, sore throat, headaches, weight loss, myalgia, and fatigue. These symptoms will often go away without treatment, and again, the spirochete becomes dormant. Secondary syphilis can affect other organs, including the eyes (uveitis), bones (periostitis), joints, meninges (meningitis), kidneys (glomerulitis), liver (hepatitis), or spleen. The individual will test positive (if untreated) and is contagious during this stage, especially through direct contact with the rash.



FIGURE 8-35 Skin rash characteristic of secondary syphilis.

Courtesy of J. Pledger, BSS/VD/CDC.

- **Latent syphilis** describes asymptomatic periods. The early latency stage begins when the secondary symptoms disappear and lasts 1–4 years. This stage can last for years as the infection spreads to the eyes, brain, nervous system, heart, blood vessels, skin, and bones.
- Late or **tertiary syphilis** is the final stage of syphilis. Most people with untreated syphilis do not progress to this stage. Tertiary syphilis may not develop for 10–30 years. When tertiary syphilis does develop, it is serious and can affect many different organs. Soft growths, called "gummas," develop in the organs. These granulomatous growths are benign and localized but are destructive because they trigger the inflammatory process. The infection can cause ocular syphilis (vision changes or blindness), neurosyphilis (severe headache, ataxia, paraesthesia, paralysis, and dementia), cardiovascular syphilis (aorta dilation, aortic valve regurgitation, or coronary artery disease), pathological fractures, and death. The individual will test positive if untreated.

Syphilis prevalence rates in the United States have remained constant for the past 50 years but have recently started to increase (**FIGURE 8-36**). More than 176,000 cases were reported to the CDC in 2021. Syphilis rates have increased nearly every year since its historic low in 2000, with rates increasing 28.6% from 2020 to 2021. These rates have increased in both men and women, in all regions of the United States, and in all age groups. Rates increased in all racial/Hispanic ethnicity groups, with the greatest increase among non-Hispanic Indian or Alaska Native persons. According to the CDC (2021b), syphilis rates are highest in men (especially men who have sex with men [MSM]); African Americans; and persons living in the District of Columbia, Alaska, and the West.

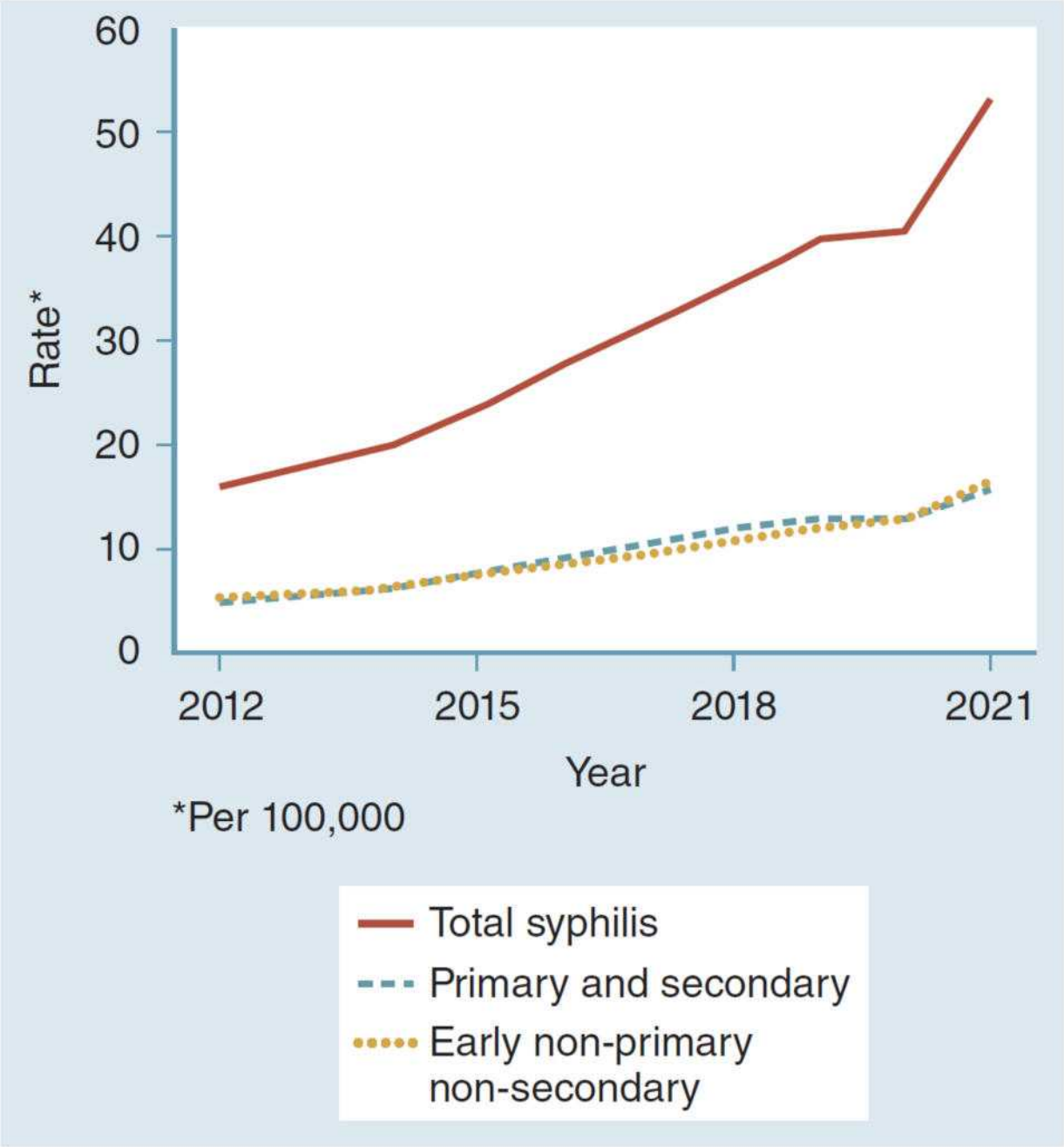


FIGURE 8-36 U.S. syphilis prevalence rates.

Reproduced from Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2021. Atlanta: U.S. Department of Health and Human Services; 2023.

Description

For the first 4 months of the pregnancy, the fetus is protected from maternal syphilis by a membrane known as the “Langhans layer.” The

risk of transmission in utero increases significantly in the second half of the pregnancy. Consequently, screening and treating the mother prior to the fourth month of gestation can significantly decrease the likelihood that the fetus will contract the infection. Untreated early maternal syphilis infections lead to fetal demise in approximately 40% of cases. Congenital syphilis can lead to multiple defects affecting the bones, teeth, liver, lungs, and nervous system.

Diagnostic procedures include a history (including sexual history), physical examination, serum screening antibody tests (e.g., Venereal Disease Research Laboratory [VDRL] test or rapid plasma reagin [RPR]), and serum confirmatory antibody tests (e.g., fluorescent treponemal antibody absorption [FTA-ABS]). Positive (if treated) and high-risk women should be retested for syphilis in the last trimester of the pregnancy. For nonpregnant women and men, treatment should begin early—at the first sign of a suspicious lesion. Treatment usually consists of antibiotics, such as penicillin (preferred), a penicillin derivative, doxycycline, azithromycin, or ceftriaxone.

Viral STIs

Viruses cause many STIs. In terms of their severity, these infections can range from minor (e.g., condylomata acuminata) to life threatening (e.g., HIV). Viral STIs can also lead to several reproductive cancers (e.g., human papillomavirus). These types of infections are the most difficult STIs to treat because viruses are highly adaptive and elusive. Treatment options for the various infections depend on the causative virus.

Genital Herpes

Genital herpes is an infection that causes blisters (vesicles) on the genitals and in the reproductive tract. It is caused by the **herpes simplex virus (HSV)**, which belongs to a family containing more than 70 herpes viruses. Other viruses in this family include cytomegalovirus (which can cause mental disability and fetal demise with maternal infections), varicella-zoster virus (which causes chickenpox and shingles), and Epstein-Barr virus (which can cause lymphoma).

HSV occurs in two forms—type 1 and type 2. Generally, HSV type 1 infections occur above the waist, whereas HSV type 2 infections occur below the waist. HSV type 1 infection most frequently manifests as a cold sore (a small blister on the mouth or nose). Most cases of genital herpes (70%) are caused by HSV type 2. HSV type 2 infections can also spread above the waist, and HSV type 1 infections can spread below the waist through oral–genital sexual contact. HSV type 2 is also transmissible through direct skin-to-skin contact. Although the risk of transmission is greatest when lesions are present, HSV can be spread when lesions are not apparent. HSV type 2 is also transmissible from mother to child.

Contracting genital herpes during pregnancy creates the greatest risk to the fetus (e.g., spontaneous abortion). HSV can also be transmitted to the infant during childbirth if an active genital herpes infection is present at the time of delivery. Transmission of this infection during childbirth can result in encephalitis and brain damage. If lesions are present at the time of birth, a cesarean section should be performed to minimize these risks. Rarely, HSV can be transmitted to the fetus through the placenta, causing an infection prior to birth. Pregnant women should be monitored for genital herpes throughout their pregnancy.

Genital herpes is not a reportable disease to the CDC; however, HSV is one of the most prevalent STIs (**FIGURE 8-37**). In 2018, the CDC estimates there were 572,000 new genital herpes infections in the United States among people aged 14 to 19. Most cases of genital herpes are subclinical and have not been diagnosed. According to the CDC (2021b), rates of genital herpes are highest in young adults, women, and African Americans.

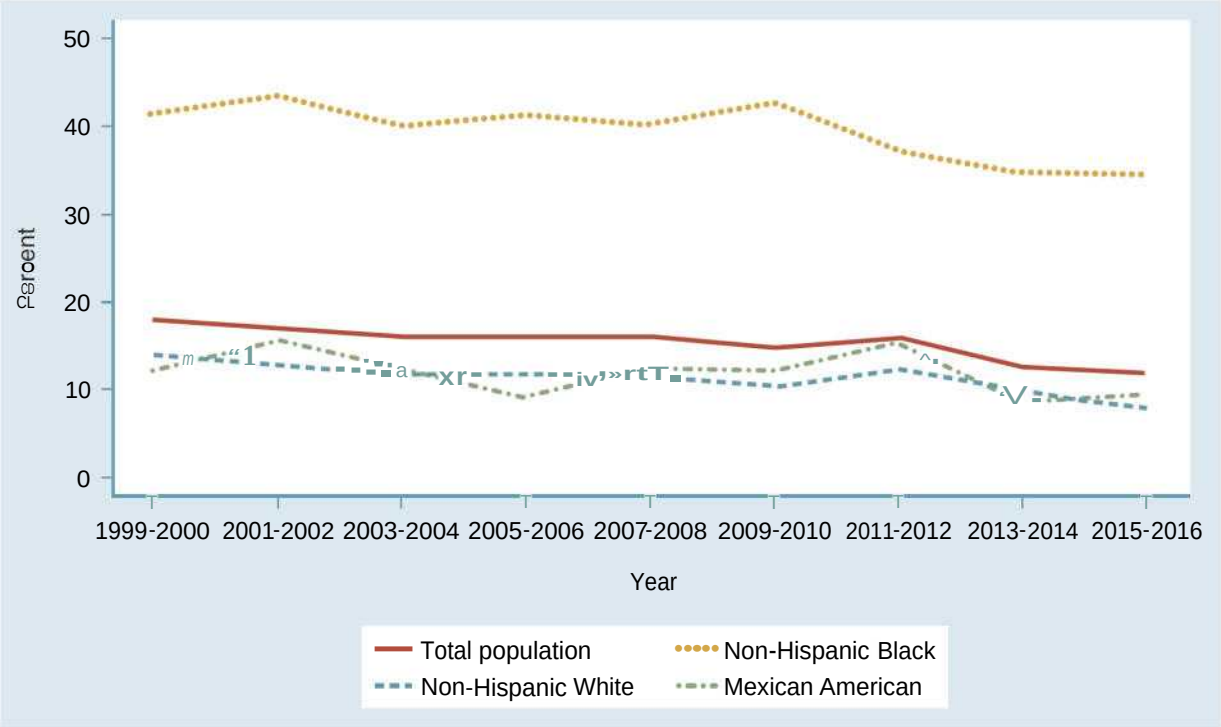


FIGURE 8-37 Genital herpes prevalence rates.

Reproduced from Centers for Disease Control and Prevention. (2021b). Sexually transmitted disease surveillance 2021. Retrieved from from https://www.cdc.gov/std/statistics/2021/default.htm

Description

Both types of HSV infections are characterized by recurrent episodes of the lesions. Most people with HSV type 2 will experience recurrence of the lesions; however, recurrence is much less frequent with HSV type 1. The virus causes an initial infection at the entry site but then travels along the dermatome to the nerve root, where it remains protected and dormant until the next outbreak (recurrence), which will occur at the same site. With both types 1 and 2, the lesions appear and progress similarly. Recurrent episodes begin with a tingling or burning sensation at the site just before the lesion appears (**prodrome**). The lesions first appear as vesicles surrounded by erythema. These vesicles rupture, leaving behind a painful ulcerative lesion with watery exudate (**FIGURE 8-38**). Ultimately, a crust forms over the ulcer, and it heals spontaneously in 3–4 weeks. Because

genital herpes creates an opening in the skin, the individual is at risk for contracting other STIs.







FIGURE 8-38 Genital herpes blisters on the external genitalia.

A: © Dr P. Marazzi/Science Source; **B:** © Mediscan/Visuals Unlimited, Inc.

Genital herpes progresses through four stages:

1. **Primary herpes genitalis** is the first stage. This stage begins at the actual time of infection and antibody development. The time from exposure to this primary infection can range from 2 to 20 days. This first occurrence of the infection can be either very painful or completely asymptomatic (75% of cases). When present, clinical manifestations associated with this stage include painful lesions, malaise, low-grade fever, groin lymph node enlargement, and urinary issues (e.g., dysuria and hesitancy). The lesions are vesicles located anywhere on the penis, external female genitalia (e.g., labia, clitoris, or perineum), vagina, cervix, anus, or rectum that usually erode to form ulcers and may coalesce. Viral shedding is high during this stage, making transmission more likely.

2. **Latent herpes genitalis** begins once the antibodies are formed. Antibodies do not protect an individual against reinfection, but they do tend to make the recurrent episodes less severe. During this phase, the virus travels up the nerve root and becomes dormant (**FIGURE 8-39**). The individual is asymptomatic while the virus is dormant.

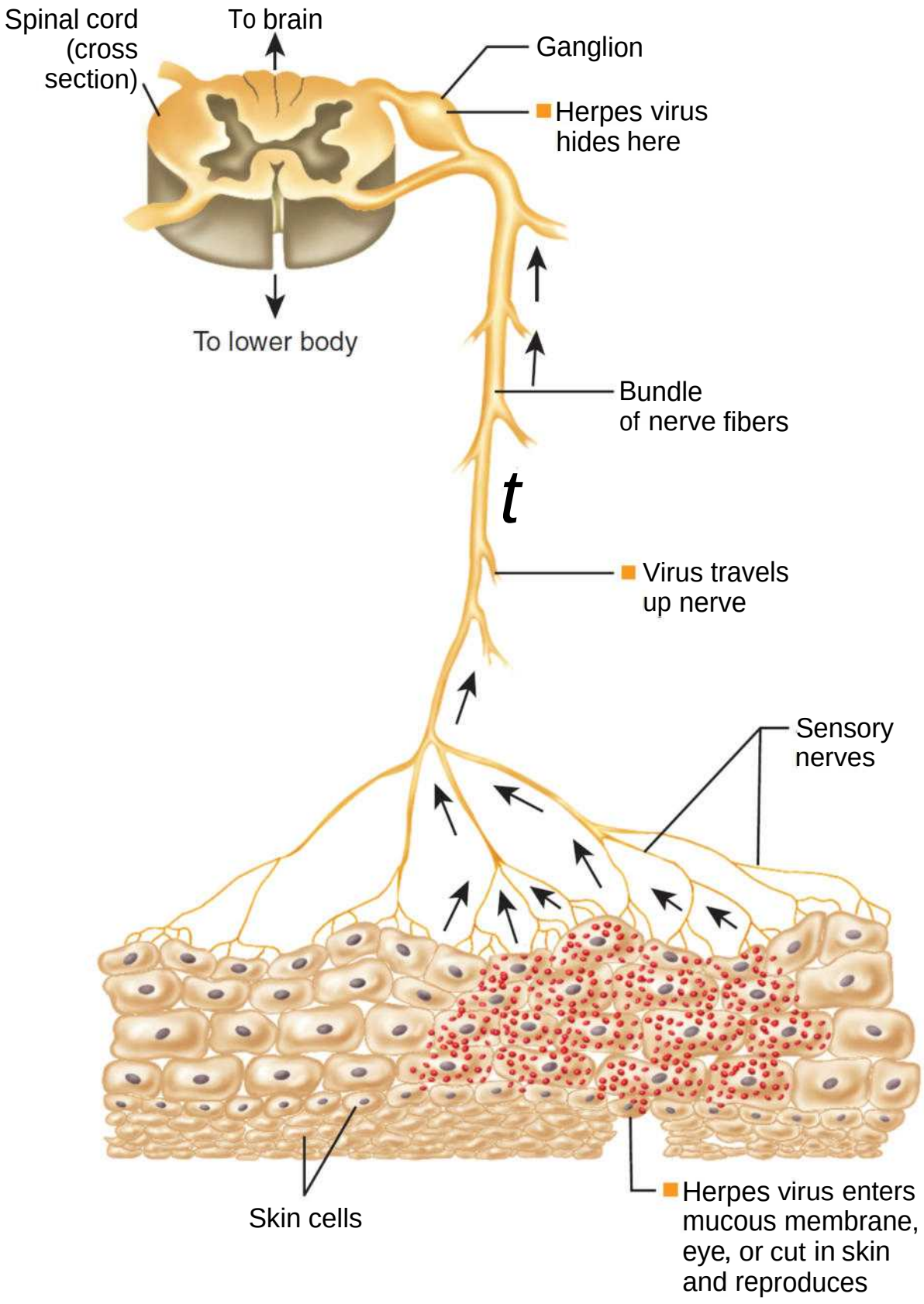

Spinal cord (cross section)
To brain
Ganglion
Herpes virus hides here
To lower body
Bundle of nerve fibers
t
Virus travels up nerve
Sensory nerves
Skin cells
Herpes virus enters mucous membrane, eye, or cut in skin and reproduces

FIGURE 8-39 Herpes simplex virus movement in the nervous system.

Description

3. **Shedding herpes genitalis** is the third stage. During this stage, the virus is reactivated but produces no symptoms. It is being excreted from the body and can be transmitted to another person through sexual contact. This stage occurs infrequently—in fewer than 1% of cases.
4. **Recurrent herpes genitalis** is characterized by the reactivation of the virus and clinical manifestations. During this stage, the virus travels back down the nerve root to the skin and causes a blister at the same site as with the first stage. The lesions usually last less than 10 days, and viral shedding can occur for up to 5 days. The number of reoccurrences varies from none to many in a lifetime. Factors that can trigger a reoccurrence include stress, menstruation, and illness.

Diagnostic procedures for genital herpes include a history (including sexual history), physical examination (including pelvic examination), tissue and secretion cultures, Pap smears, polymerase chain reaction test (which detects the presence of HSV and determines the type in serum or secretions), and serum HSV antibodies. Genital herpes is a significant public concern because the lesions and symptoms are not always apparent, transmission can occur with or without symptoms, and no cure exists. It can cause a great deal of psychological stress for patients because of the ongoing fear of outbreaks and the need to disclose the information about their infection status to partners. Universal pregnancy screening for HSV is not recommended, nor has it been shown to be an effective means to prevent neonatal transmission.

Treatment options including antiviral medications (e.g., acyclovir, valacyclovir, and famciclovir) that can suppress the number of outbreaks as well as minimize the severity and duration of recurrences are available. Avoiding recurrence triggers, especially stress, can also prevent outbreaks. Implementing stress-reduction strategies (e.g., yoga, meditation, journaling, and distraction) is

advised. Secondary bacterial infections can develop from the lesions, so proper hygiene (e.g., washing the area with soap and water several times a day, keeping the area dry, and wearing loose-fitting clothing and cotton underwear) is advised during outbreaks. Additionally, genital herpes increases the risk for reproductive cancers in women (especially cervical cancer), so Pap smears should be performed every 6–12 months. Because the risk of transmission is highest when lesions are present, sexual activity should be avoided during outbreaks.

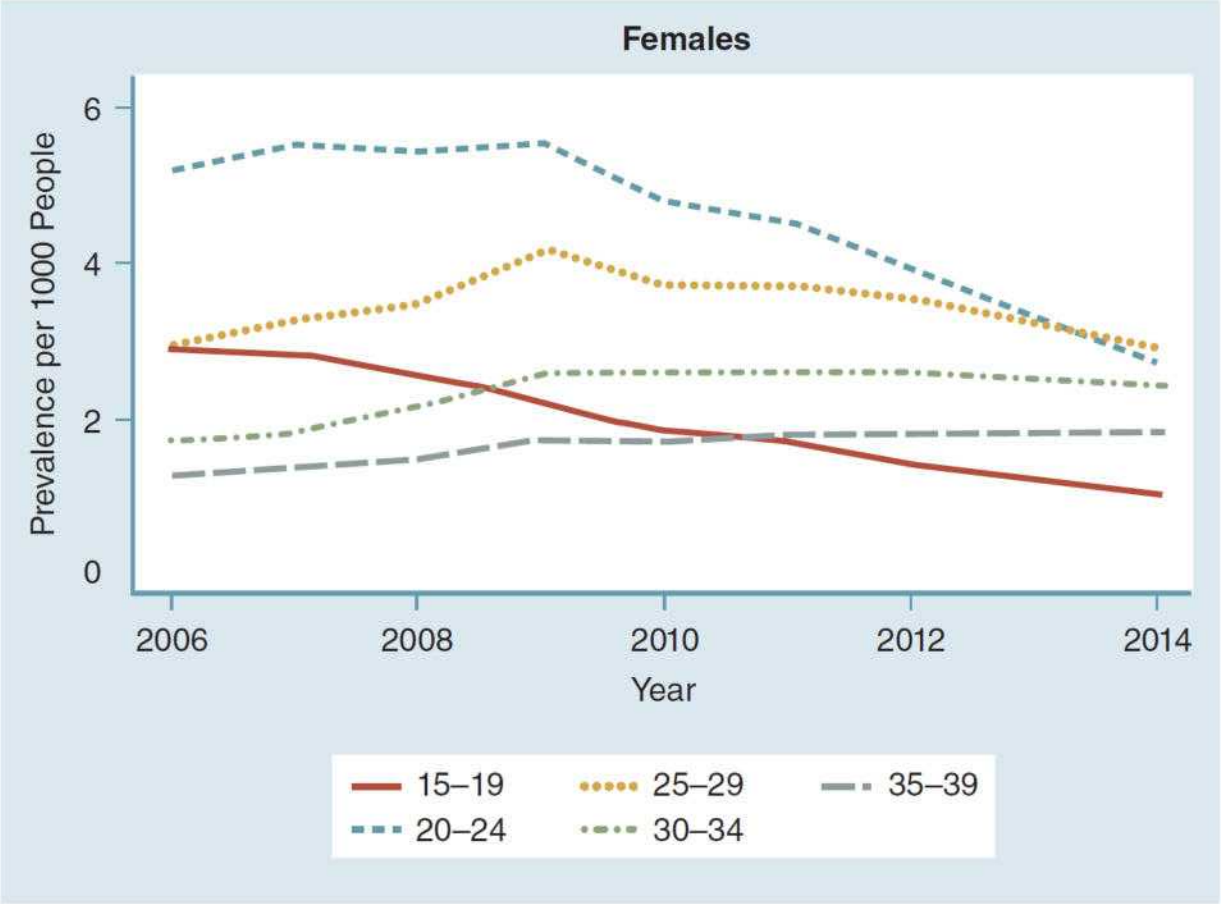
Due to the lifelong implications of genital herpes, prevention is the best treatment strategy. Prevention strategies center on safe sex practices (e.g., using condoms, limiting sexual partners).

Pregnant women should be educated regarding the dangers of contracting genital herpes while pregnant. If herpes symptoms are present when labor begins, cesarean delivery is recommended. Pregnant women can be given acyclovir starting at 36 weeks' gestation to reduce the risk of recurrence and, therefore, the need for cesarean delivery.

Condylomata Acuminata

Condylomata acuminata, or anogenital warts, are benign growths caused by **human papillomavirus (HPV)**. More than 70 different types of HPVs exist, several of which can cause condylomata acuminata (usually types 6 and 11). The lesions can occur on the external genitals, vaginal wall, cervix, anus, thighs, lips, mouth, and throat. In addition to condylomata acuminata, virtually all reproductive (e.g., cervical and penile) and anal cancers are caused by HPV (usually types 16 and 18). HPV can have an incubation period that lasts up to 6 months. The immune system clears most HPV within 2 years (in about 90% of cases), though some infections persist.

Most sexually active men and women will contract HPV at some point in their lives. Transmission of the virus can occur through mere skin contact with the lesion as well as from mother to fetus. Condylomata acuminata are not reportable to the CDC; however, an estimated 43 million Americans, most in their late teens and early 20s, are infected with HPV (**FIGURE 8-40**).


Females
Prevalence per 1000 People
0
2
4
6
2006
2008
2010
2012
2014
Year
15–19
20–24
25–29
30–34
35–39

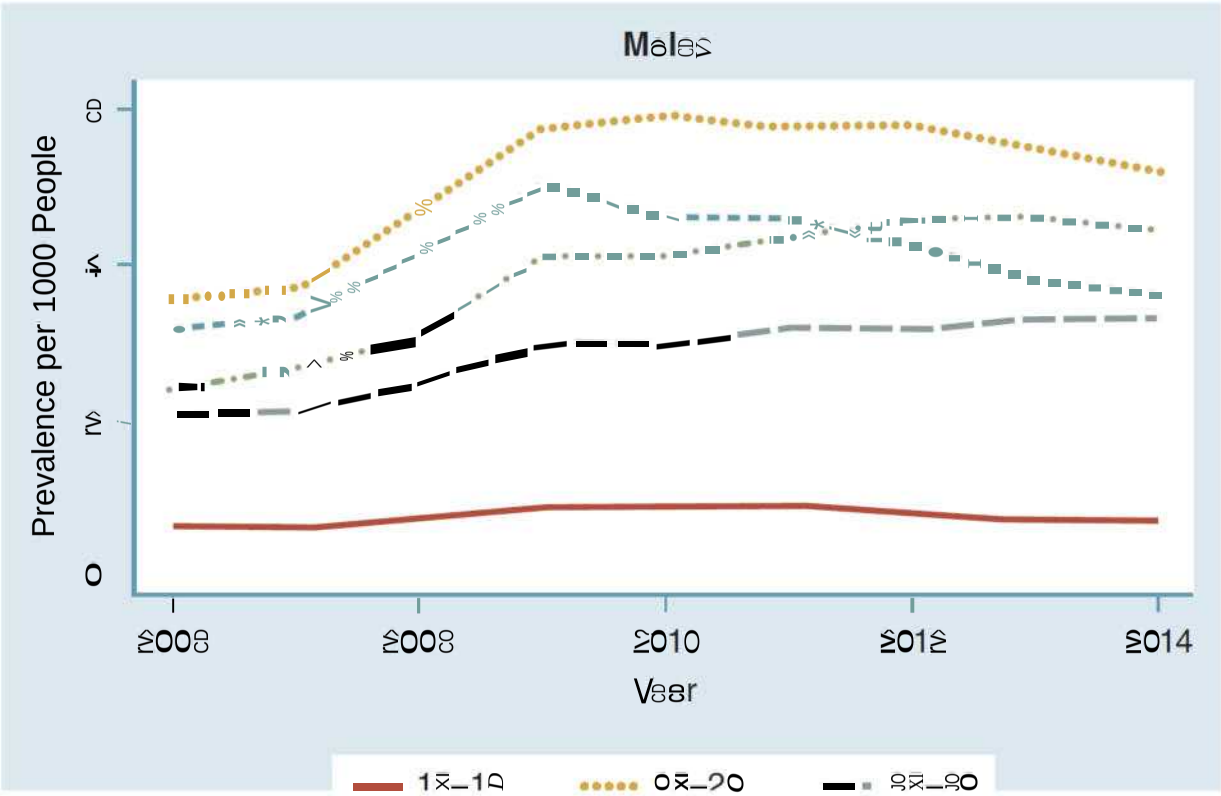

Prevalence per 1000 People
Year



FIGURE 8-40 Genital warts prevalence rates.

Reproduced from Centers for Disease Control and Prevention. (2021b). Sexually transmitted disease surveillance 2021. Retrieved from from https://www.cdc.gov/std/statistics/2021/default.htm

Description

Condylomata acuminata may be asymptomatic, depending on their location. The lesions vary in appearance, texture, and size (**FIGURE 8-41**). Growths can be raised or flat; rough or smooth; flesh-colored, white, gray, or pink; cauliflower-like, large, or barely visible. Additional symptoms may include abnormal bleeding, discharge, or itching.




A





FIGURE 8-41 **(A)** Genital warts on the penis. **(B)** Genital warts on the vagina.

A: Reproduced from Centers for Disease Control and Prevention. (2021b). Sexually transmitted disease surveillance 2021. Retrieved from from https://www.cdc.gov/std/statistics/2021/default.htm; **B:** Courtesy of Joe Millar/CDC.

Diagnostic procedures for condylomata acuminata include a history (including sexual history), physical examination (including pelvic examination), Pap smear, tissue biopsy, and polymerase chain reaction test. While there are no treatments for HPV itself, treatments exist for the serious conditions that HPV can cause (e.g., cancer). A vaccine is available to prevent the types of HPVs that are the most common sources of infections. Because of the cancer risk associated with HPV infection, this vaccine is recommended for both males and females (ideally to be administered around 11 or 12 years of age, before sexual activity is initiated). Use of condoms and dental dams can also reduce the risk of HPV transmission.

Most condylomata acuminata are harmless, but they can be removed for aesthetic purposes. Removal of the growths will not cure the underlying condition, so the growths may reappear. Condylomata acuminata can be removed using chemicals (e.g., podophyllin), cryosurgery (freezing the tissue with liquid nitrogen), electrocauterization (heating the tissue with electricity), laser therapy (burning the tissue with a light), or surgical excision.

As is the case with other STIs, sexual partners of individuals with HPV infection should also be screened and treated. Condylomata acuminata can be fatal if transmitted to infants at birth, so cesarean section deliveries are advised for pregnant women with this STI.

Protozoan STIs

Like candidiasis infections, protozoan infections often arise when the body's natural defenses are altered; unlike candidiasis, however, some of these infections can be transmitted through sexual contact. Protozoan STIs are usually easily treated and resolve with minimal issues.

Trichomoniasis

Trichomoniasis (colloquially referred to as "trich") is caused by *Trichomonas vaginalis*, a one-celled anaerobic organism. This extracellular parasite can burrow under the mucosal lining. In men, the organism primarily resides in the urethra and causes no symptoms. In women, the organism resides in the vagina, and the infection becomes symptomatic when vaginal microbial imbalance occurs. The *T. vaginalis* organism cannot survive in the mouth or the rectum. Coinfection with other STIs is common. Complications include female infertility, PID, prostatitis, and epididymitis. Pregnant women with trichomoniasis are more likely to have preterm and low-birth-weight infants.

In addition to sexual contact, trichomoniasis can be contracted through prolonged moisture exposure (e.g., bathing suits and protective garments). Trichomoniasis is not reportable to the CDC, but an estimated 2 million Americans have trichomoniasis (**FIGURE 8-42**). Risk is highest among women and African Americans.

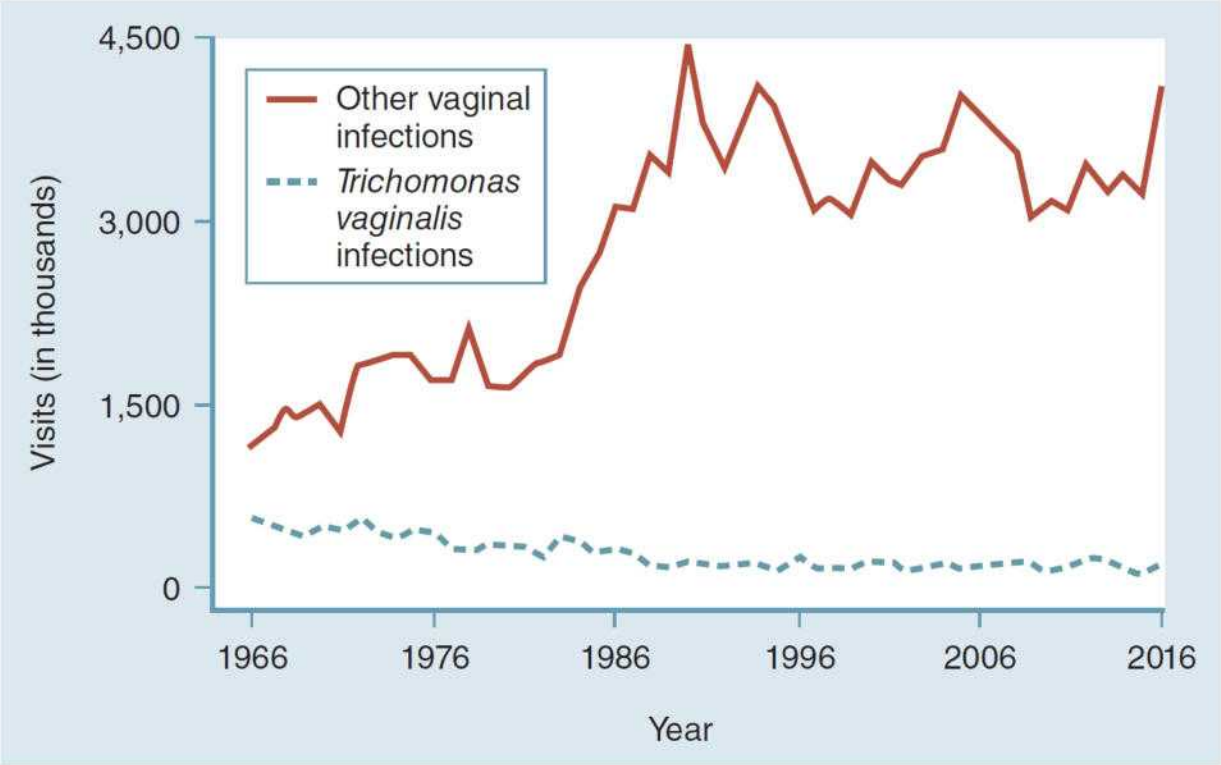


FIGURE 8-42 Initial visits to physicians' offices for trichomoniasis and other vaginal infections among females.

Reproduced from Centers for Disease Control and Prevention. (2021b). Sexually transmitted disease surveillance 2021. Retrieved from from https://www.cdc.gov/std/statistics/2021/default.htm

Description

In men, trichomoniasis does not usually generate symptoms and resolves in a few weeks without treatment. In women, the primary clinical manifestation is copious amounts of odorous, frothy, white or yellow-green vaginal discharge. This discharge can irritate the vagina and vulva. The cervix can develop petechiae, giving it a strawberry appearance. Additional symptoms may include itching, dyspareunia, and dysuria.

Diagnostic procedures for trichomoniasis include a history (including sexual history), physical examination (including pelvic examination), Pap smear, and discharge analysis (e.g., NAAT, wet mount, and cultures). Trichomoniasis is easily treated with metronidazole (Flagyl), an antibiotic that treats bacterial and parasitic infections. Sexual

partners should also be treated to prevent reinfection. Follow-up testing is recommended because the risk of reinfection is high. Additionally, sexual intercourse should be avoided for 7–10 days after the individual and the partner(s) have been treated. Untreated or prolonged infections can increase the risk of cervical cancer.

Myth Busters

A common misconception is that condoms protect users against all STIs. While condoms are highly effective against most STIs, some of these infections have been known to spread despite condom use. STIs that can spread through skin-to-skin contact even with a condom in place include HPV, HSV, and syphilis. Additional strategies, such as obtaining the HPV vaccine, receiving genital herpes suppression therapy, and treating syphilis early, can decrease the likelihood of contracting and spreading these infections.

Cancers

Malignancies of the reproductive system may either originate in the reproductive tract or spread there from other sites. Some of these cancers have high rates of successful treatment (e.g., testicular cancer), whereas others have high mortality rates (e.g., ovarian cancer). Typical cancer diagnosis, staging, and treatments are generally utilized with these tumors (see the *Cellular Function* chapter).

Penile Cancer

Penile cancer is a rare malignancy. Most penile cancers are squamous-cell carcinomas. Their exact cause is unknown, but HPV (specifically types 16 and 18) likely plays a role in these cancers' development. Risk is thought to be increased by the presence of smegma, being uncircumcised, poor hygiene, phimosis, and HPV infections. Penile cancer appears as a thick, gray-white lesion (Bowen lesion) or a red, shiny lesion (erythroplasia of Queyrat) (**FIGURE 8-43**). Lesions can be superficial or deep and are usually painless. Inguinal lymphadenopathy may also be present. Prognosis is good with early diagnosis (e.g., biopsy) and treatment, but a penectomy (removal of the penis) may be required if the cancer is extensive or does not respond to the usual cancer treatments (e.g., chemotherapy, radiation, and surgical excision).





FIGURE 8-43 Penile cancer.

Courtesy of William R. Smart/Susan Lindsley/CDC.

Prostate Cancer

Prostate cancer is the most common cancer among men—particularly African American men, for unknown reasons (American Cancer Society, 2023). Prostate cancer usually occurs as an adenocarcinoma, but it can rarely occur as sarcoma, primarily in children. This kind of slow-growing tumor often remains confined to the prostate or nearby region (90% of cases are diagnosed while the cancer is still confined to the prostate), improving the prognosis. Prostate cancer is the second leading cause of cancer deaths in the United States, but the 5- and 10-year survival rates for this disease are improving. Prognosis improves with early diagnosis and treatment and worsens with advancing age. Increased screening with prostate-specific antigen (PSA) and prostate biopsy for those men with elevated PSA have contributed to these newly improved survival rates. The exact cause of prostate cancer remains unknown, but men's risk is thought to increase with age, a history of STIs, family history, and certain inherited genetic conditions (e.g., Lynch syndrome and *BRCA1* and *BRCA2* mutations), consumption of a high-fat diet, cigarette smoking, and androgen hormone replacement (some tumors are androgen dependent).

As the tumor grows, the prostate enlarges and impedes the urethra; therefore, prostate cancer presents with clinical manifestations similar to those associated with benign prostatic hyperplasia (e.g., urinary difficulty and erectile dysfunction; see the *Urinary Function* chapter). However, many men are asymptomatic at diagnosis. Additional manifestations may include bloody semen and hematuria. Late-stage prostate cancer commonly metastasizes to the bones, causing pain in the hips, spine, ribs, or other areas.

In addition to the usual cancer diagnostic procedures (e.g., biopsy), measurements of PSA (whose level is elevated in any prostate enlargement), free PSA (which can differentiate between benign prostatic hypertrophy and prostate cancer), and prostatic acid phosphatase (which is high in prostate cancer) may be performed. Routine screening is not recommended except in high-risk men. Additionally, a digital rectal examination can reveal prostate abnormalities.

Prostate cancer treatment follows the path of the usual cancer treatments and can vary depending on the cancer stage. If the cancer is diagnosed in an early stage, careful observation (called “active surveillance”) instead of immediate treatment is appropriate for many patients. Treatment includes a combination of a radical prostatectomy (complete prostate removal), radiation, and orchiectomy (removal of the testes) or anti-testosterone drug therapy. These treatments often impact the patient’s quality of life due to their side effects or complications (e.g., urinary and erectile dysfunctions), which may be short or long term in duration. Researchers are exploring new biological markers in an effort to improve the differential diagnosis between indolent and aggressive prostate cancer so as to minimize unnecessary treatment of the indolent variant (American Cancer Society, 2023).

Emerging Research: Prostate Cancer

With prostate cancer being so common, a significant amount of funding dollars is being focused on finding cures and improving outcomes. The American Cancer Society (2023a) has two large, ongoing cancer prevention studies within their Population Science department. Some findings from these studies have indicated that:

- Prostate cancer survivors who eat more chicken and less steak may live longer
- Men who have obesity or gain 10+ pounds after prostate cancer diagnosis are more likely to die from all causes
- Access to Medicaid alone does not improve the diagnosis and treatment of prostate cancer

In 2008, the U.S. Preventative Services Task Force (USPSTF) recommended against regular PSA screening for men age 75 and older, and in 2012, they recommended against routine PSA screening for all men. Since then, studies have reported that incidence rates for localized prostate cancer have declined, but incidence of metastatic prostate cancer have increased. Future studies are needed to understand this phenomenon.

Testicular Cancer

Testicular cancer is an uncommon cancer. In the United States, more than 9,200 new cases and 470 deaths occur each year (American

Cancer Society, 2023). Men age 15–35 years old and Caucasian men are at higher risk of developing this type of cancer compared to other groups. Most cases of testicular cancer originate in germ cells and take the form of a slow-growing (seminoma) tumor, but some cases manifest as a fast-growing (nonseminoma) tumor. Risk for developing testicular cancer is thought to be increased by family history, infection, trauma, tobacco use, testicular abnormalities (e.g., atrophy or dysgenesis), and cryptorchidism. This cancer usually affects one testicle but can affect both. Metastasis, when it happens, usually occurs in the nearby lymph nodes, lungs, liver, bone, and brain.

Testicular cancer is often asymptomatic. When present, clinical manifestations usually include a hard, painless, palpable mass that does not transilluminate; testicular discomfort or pain; testicle enlargement; and gynecomastia (female-like breast).

Testicular cancer is highly curable even when it has metastasized to other sites. Early diagnosis and treatment enhance prognosis. Monthly self-testicular examinations are the cornerstone of early detection. Other diagnostic procedures include measurement of tumor markers, such as alpha-fetoprotein, beta human chorionic gonadotropin, and lactate dehydrogenase. Abdominal, pelvic, and chest CT is used to determine clinical staging. In most cases, an orchiectomy is advised, but chemotherapy and radiation may also be used to treat this disease. Prior to treatment, sperm banking may be available for men who wish to retain reproductive capacity. Testicular cancer can reoccur in the remaining testicle, so self-testicular examinations and follow-up are crucial.

Breast Cancer

Breast cancer is the most common malignancy in women and the second-leading cause of cancer death in women (American Cancer Society, 2023a). While breast cancer can occur in men, its rates are highest in Caucasian women, although African American women are most likely to die from it. Other factors that increase the risk of this type of cancer include advancing age, early menarche, nulligravida,

delayed menopause, family history (although not always present), genetic predisposition (defects on the *BRCA1* and *BRCA2* genes), obesity, chest-wall radiation, excessive alcohol consumption (more than one to two drinks per day), and physical inactivity. Exogenous estrogen exposure (e.g., oral contraceptives, hormone replacement therapy) may increase the risk for breast cancer, although current formulations have minimized this risk. The Breast Cancer Risk Assessment Tool (https://bcrisktool.cancer.gov/) can be used to calculate a woman's 5-year and lifetime risk for developing breast cancer. Notably, many cases do not possess any risk.

Most breast cancers originate in the glandular breast cells of the ducts or lobules (structures that produce milk). A tumor can infiltrate the surrounding tissue and adhere to the skin, causing dimpling. In its early stages, the tumor moves freely, but it becomes fixed as the cancer progresses. Most tumors are estrogen dependent, and metastasis usually occurs to nearby axillary lymph nodes. Because metastasis can occur early, in most cases several nodes are affected at the time of diagnosis. Widespread metastasis quickly follows to the lungs, brain, bone, and liver.

In its early stages, breast cancer is often asymptomatic. Symptoms arise as the tumor grows. In men, symptoms usually include a breast mass and breast tenderness or pain. Clinical manifestations of breast cancer in women include the following signs and symptoms:

- Mass in the breast or axillary that is hard, has uneven edges, and is usually painless

Myth Busters

Several misconceptions about breast cancer warrant discussion.

Myth 1: Breast implants, use of antiperspirant, and wearing underwire bras increase breast cancer risk.

There is *no* evidence that links these factors to breast cancer. Breast implants can make it more difficult to detect tumors with a self-breast examination depending on the

surgical technique used to insert the implants. Placing the implants behind the muscle wall can improve the ability to detect any tumors. Nevertheless, breast implants, antiperspirant, and underwire bras do *not* increase breast cancer risk.

Myth 2: Only older women need to worry about breast cancer.

Breast cancer risk does increase with age, but women of *all* ages can develop breast cancer.

Myth 3: Breast cancer always runs in families.

Family history does increase the likelihood of developing breast cancer, but *most* women who develop breast cancer *do not* have a family history of breast cancer.

Myth 4: There is no need to worry about breast cancer if no *BRCA1* and *BRCA2* mutation is present.

BRCA1 and *BRCA2* mutations do increase breast cancer risk, but 90% to 95% of women who are diagnosed with breast cancer *do not* have either a family history or this genetic mutation.

Data from American Cancer Society. (2023). Breast cancer risk and prevention. Retrieved from https://www.cancer.org/cancer/types/breast-cancer/risk-and-prevention.html

- Change in the size, shape, or feel of the breast or nipple (e.g., redness, dimpling, or puckering that looks like the peel of an orange) (**FIGURE 8-44**)

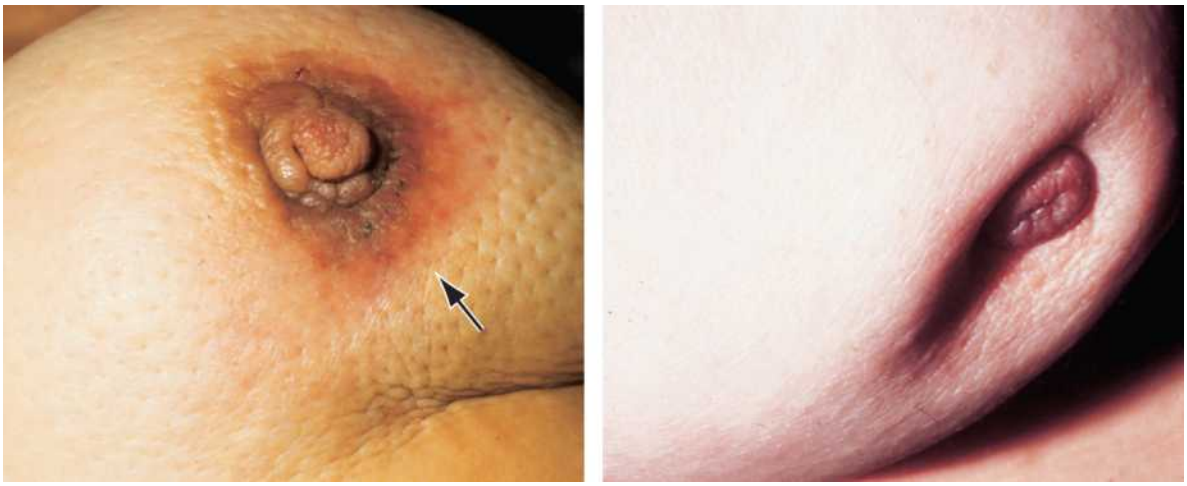


FIGURE 8-44 Changes in the breast caused by advanced breast cancer.

Courtesy of Leonard V. Crowley, MD, Century College.

Description

- Nipple drainage that may be bloody, clear to yellow, green, or purulent

Indications that the cancer has metastasized include bone pain, skin ulcers, edema in the arm next to the affected breast, and weight loss.

Early diagnosis and treatment are crucial to positive outcomes. Monthly breast self-examinations are the cornerstone of early detection; in fact, women discover most tumors during this examination. Another diagnostic procedure specific to breast cancer is the mammogram, but like other screening tools, it is not perfect. Most (95%) of the 10% of women who have abnormal mammograms do not have cancer (American Cancer Society, 2023a). Currently, the American Cancer Society's (2023a) recommendations are that women at average risk who are 40–44 years of age should be given the choice for an annual mammogram; those 45–54 years of age should have annual mammograms; and those 55 years of age and older should have biennial or annual mammograms. Women in high-risk groups should start annual mammograms sooner (typically age 30), in addition to receiving annual MRI. Men at high risk for breast cancer should do self-examinations monthly and have clinical examinations annually.

Recent advances in breast cancer treatments (especially in chemotherapies) have significantly increased survival rates for this disease. Treatment strategies vary depending on the stage, but usually breast cancer requires an aggressive, multimethod treatment (e.g., chemotherapy, radiation, surgery, and hormone therapy) to improve outcomes. The life-threatening nature of breast cancer, along with the changes in body image that result from treatment, can increase the need for coping and support interventions (e.g., support groups and counseling). Breast reconstruction surgery may be performed at the time of the tumor or breast removal or as a second procedure later.

Cervical Cancer

Cervical cancer rates have been declining in recent years with advancements in screening. The Pap smear—the long-standing cervical screening method—can now detect precancerous changes (dysplasia). Procedures can be performed to remove these precancerous cells, limiting the likelihood of these changes progressing to permanent malignant changes (**FIGURE 8-45**). The precancerous cells are 100% treatable; however, malignant changes can return if carcinogen exposure continues. Almost all cervical cancers are caused by HPV infection (usually types 16 and 18); therefore, most risk factors for cervical cancer are the same as those that increase the risk of contracting HPV (e.g., having multiple sex partners and not practicing safe sex) as well as younger age at first intercourse, cigarette smoking, and immunodeficiency.

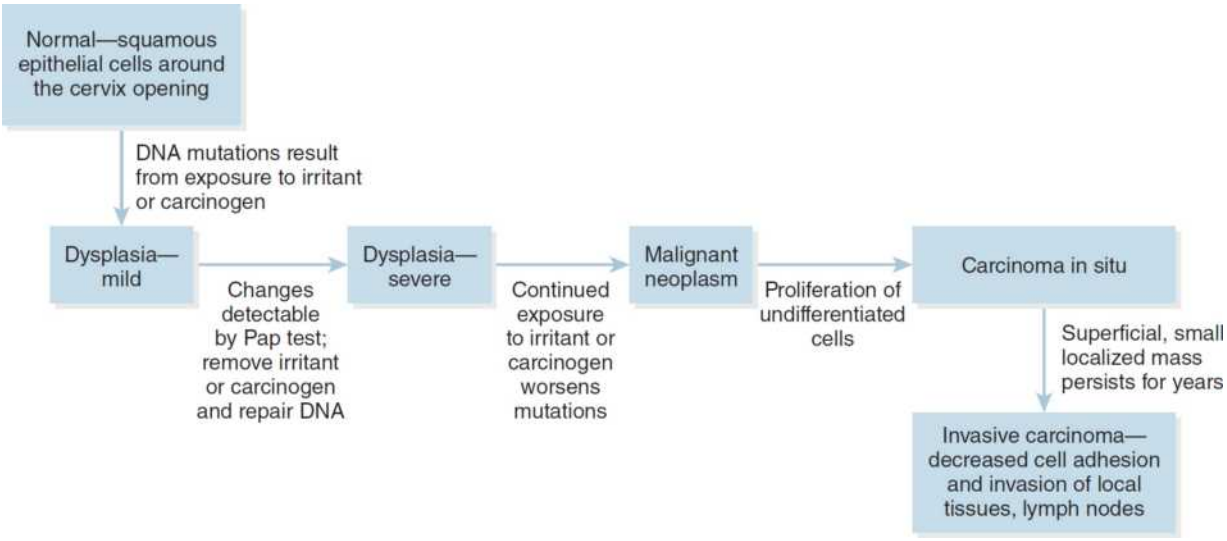


FIGURE 8-45 Development of cervical cancer.

Based on Gould, B. (2014). *Pathophysiology for the health professions* (5th ed.). Philadelphia, PA: Elsevier. Copyright Elsevier 2015.

Description

Early-stage cervical cancer is usually asymptomatic. When present, clinical manifestations include the following signs and symptoms:

- Continuous vaginal discharge, which may be pale, watery, pink, brown, bloody, or foul smelling
- Intermenstrual, postcoital, and postmenopausal bleeding
- AUB

Indications of advanced cervical cancer include the following conditions:

- Anorexia
- Weight loss
- Fatigue
- Pelvic, back, or leg pain
- Unilateral lower-extremity edema
- Heavy vaginal bleeding
- Leaking of urine or feces from the vagina
- Bone fractures

The Pap smear remains the cornerstone of early cervical cancer detection. Administration of the HPV vaccine may prevent the cancer. Precancerous and early malignant changes can be treated using a loop electrosurgical excision procedure, cryotherapy, and laser therapy. Advanced cancer will require chemotherapy, radiation, and surgery (usually a hysterectomy). The survival rate is usually 100% when cervical cancer is treated early, but the rate decreases as the disease advances.

Endometrial Cancer

Endometrial cancer, or cancer of the lining of the uterus, is a common malignancy in women. According to the American Cancer Society (2023a), endometrial cancer is the fourth most frequent cancer in women and the sixth leading cause of cancer death in women, with a 5-year survival rate of approximately 84% in most cases. Caucasian women have the highest prevalence rates, but African American women have the highest mortality rates. The exact

cause of this disease is unknown, but excessive estrogen exposure may be a major factor in its development. Additional risk factors for developing endometrial cancer include obesity, physical inactivity, diabetes mellitus, estrogen exposure, and hypertension.

The most significant finding indicating the possible presence of endometrial cancer is abnormal painless uterine bleeding (the cancer erodes the endometrium), especially after menopause. Additional clinical manifestations include nonbloody vaginal discharge, pelvic pain, weight loss, palpable abdominal mass, and dyspareunia.

The Pap smear does not detect cancers above the cervix; however, a Pap smear showing the presence of endometrial cells in a postmenopausal woman or atypical endometrial cells in any woman suggests endometrial cancer. Biopsy is the diagnostic procedure of choice when this malignancy is suspected. If diagnosed early, endometrial cancer can be successfully treated with chemotherapy, radiation, surgery (hysterectomy), and hormone therapy.

application to practice

Now that we have discussed conditions of the reproductive system, let's put that knowledge into practice. While working in the emergency department, the following patients need to be triaged. Which patient would have the highest priority?

- A 55-year-old man with a chancre on his genitals
- A 20-year-old man with a swollen, painful scrotum who has a history of a recent mumps infection
- A 65-year-old man with a history of prostate cancer and palpable bladder distention
- A 19-year-old man who has had an erection for "10 or 11 hours" and is complaining of severe pain

Once again, you go through the usual thought process—who would die first, acute versus chronic conditions, Maslow's hierarchy of needs, and patient safety. Most of the conditions affecting the reproductive are not immediately life threatening; however, many conditions can be medical emergencies because they threaten bodily function.

Let's start with the 55-year-old man with a chancre on the penis. Chancres may indicate the presence of any of several STIs, none of which is life threatening. STIs are acute, however, so keep this patient on your short list. Now consider the 20-year-old man with the swollen scrotum. Mumps often causes inflammation of the testes (orchitis). Neither condition is life threatening, but they are acute. Keep this patient on the short list, too. Next, consider the 65-year-old man with prostate cancer and bladder distention. Cancer is chronic, but the bladder distention is an acute change. Urinary retention is

common with prostate problems, but it is not life threatening. Even so, this person should remain on the short list. Finally, consider the 19-year-old man with the prolonged erection. Priapism is a medical emergency because the penis may develop necrosis. Although all of these patients are experiencing acute problems, the 19-year-old is experiencing the most severe issue and should be seen first to have a chance to save bodily functioning.

Emerging Research: Ovarian Cancer

Ovarian cancer is often advanced at diagnosis and difficult to treat because there are no reliable screening tools. When ovarian cancer is diagnosed before it has spread, more than 90% of women live longer than 5 years after diagnosis. Therefore, ovarian cancer research often focuses on early diagnosis and treatment efforts. One research team discovered that carbon nanotubes, tiny fluorescent particles, can respond to proteins in the blood and give a diverse set of signals. Machine learning algorithms are used to interpret these signals. These nanosensors have been found to detect ovarian cancer. The hope is that this technology will be further developed so that it can be used for rapid screening for early-stage ovarian cancer and many other cancers (American Cancer Society, 2023b).

Ovarian Cancer

Ovarian cancer is a relatively common cancer in women. According to the American Cancer Society (2023a), ovarian cancer incidence rates have declined, but this disease remains the fifth leading cause of cancer death in women. Prevalence and mortality rates are the highest in Caucasian women. Ovarian cancer causes concern because there is no reliable screening test for this disease, it is difficult to treat, and it has often metastasized at the time of diagnosis. However, advances in treatment are improving the survival rates (5-year survival rates are approximately 50%). Risk factors for developing ovarian cancer include genetic predisposition (defects on the *BRCA1* and *BRCA2* genes), advancing age, infertility, nulligravida, early menarche, delayed menopause, excessive estrogen exposure, obesity, and androgen hormone therapy. Most cases originate in the epithelium as a serous cystadenocarcinoma; the remaining cases involve invasive mucinous carcinomas or originate in germ or stromal cells.

Early clinical manifestations of ovarian cancer are vague and include abdominal distention, pelvic pain, and eating disturbances. An asymptomatic adnexal mass that is solid, irregular, and fixed may be palpated. Additional symptoms consist of bowel pattern changes, gastrointestinal discomfort (e.g., gas, indigestion, and nausea), pain during sexual intercourse, malaise, urinary frequency, and menstruation changes.

CA-125, a protein that is produced in response to several conditions, including ovarian cancer, is often examined as a part of the diagnostic and treatment process. Because this marker is not specific to ovarian cancer, a biopsy is still required for definitive diagnosis. During treatment, a declining CA-125 level is considered a favorable response to interventions. Surgery and chemotherapy are the preferred treatment strategies. Surgery may include a bilateral salpingo-oophorectomy (removal of both ovaries and fallopian tubes) and a hysterectomy.

SUMMARY

The reproductive systems in males and females are responsible for procreation and hormone balance. Disorders of the reproductive system range from harmless to life threatening. These disorders are most often infections or tumors (benign and malignant). Reproductive function is closely connected with the endocrine, cardiovascular, and nervous systems and, therefore, can affect those systems. Maintaining reproductive health can decrease the likelihood of issues within this system. Strategies to promote reproductive health include practicing safe sex; abstaining from alcohol, smoking, and illicit drug use; maintaining a healthy weight; and limiting exposure to radiation and chemicals.

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CHAPTER 9

Gastrointestinal Function

LEARNING OBJECTIVES

- Discuss normal gastrointestinal anatomy and physiology.
- Describe and compare congenital defects of the gastrointestinal system.
- Compare and contrast disorders of the upper gastrointestinal system.
- Describe and compare disorders of the gallbladder, liver, and pancreas.
- Compare and contrast disorders of the lower gastrointestinal system.
- Describe and compare cancers of the gastrointestinal system.

KEY TERMS

achlorhydria
acute gastritis
appendicitis
appendix
ascites
aspiration
atrophic gastritis
bile
cecum
celiac disease
cholecystitis
cholelithiasis
chronic gastritis
chyme
cirrhosis
cleft lip

cleft palate
colon
colorectal cancer
constipation
Crohn’s disease
Curling ulcer
Cushing ulcer
defecation
diarrhea
diverticula
diverticular disease
diverticulitis
diverticulosis
duodenal ulcer
dysphagia
emesis
esophageal cancer
esophagus
feces
frank blood
gallbladder
gastric cancer
gastric ulcer
gastritis
gastroenteritis
gastroesophageal reflux disease (GERD)
hematemesis
hepatic artery
hepatitis
hepatobiliary system
hiatal hernia
infantile hypertrophic pyloric stenosis
inflammatory bowel disease (IBD)
intestinal obstruction
irritable bowel syndrome (IBS)
jaundice
large intestine
liver

liver cancer
lower esophageal sphincter (LES)
mastication
melena
mesentery
mucosa
mucus
muscle layer
nausea
occult blood
oral cancer
pancreas
pancreatic cancer
pancreatitis
paralytic ileus
parietal peritoneum layer
peptic ulcer disease (PUD)
peristalsis
peritoneal cavity
peritoneum
peritonitis
portal hypertension
portal vein
pyloric sphincter
pyloric stenosis
rectum
retching
rugae
serosa
small intestine
stomach
stress ulcer
submucosa layer
ulcerative colitis
visceral peritoneum layer
vomiting
vomitus

The gastrointestinal (GI) system, or digestive system, consists of structures responsible for consumption, digestion, and elimination of food (**FIGURE 9-1**). These processes provide the essential nutrients, water, and electrolytes required for the body's physiologic activities. Structures of the GI system include an alimentary canal through which food is passed and accessory organs that aid digestion (**FIGURE 9-2**). The alimentary canal includes the oral cavity, pharynx, esophagus, **stomach**, **small intestine**, **large intestine**, and anus. The accessory organs include the salivary glands, **liver**, gallbladder, **bile** ducts, and **pancreas**.

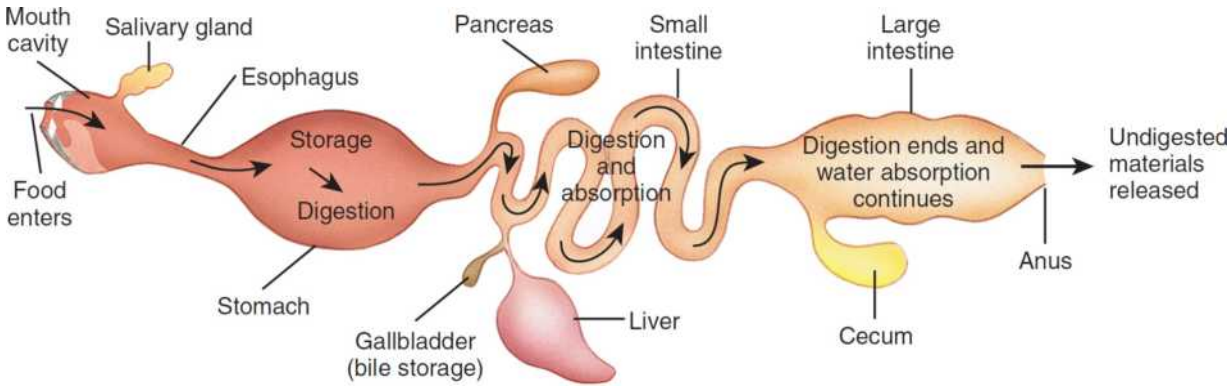


FIGURE 9-1 Functions of the gastrointestinal system.

Description

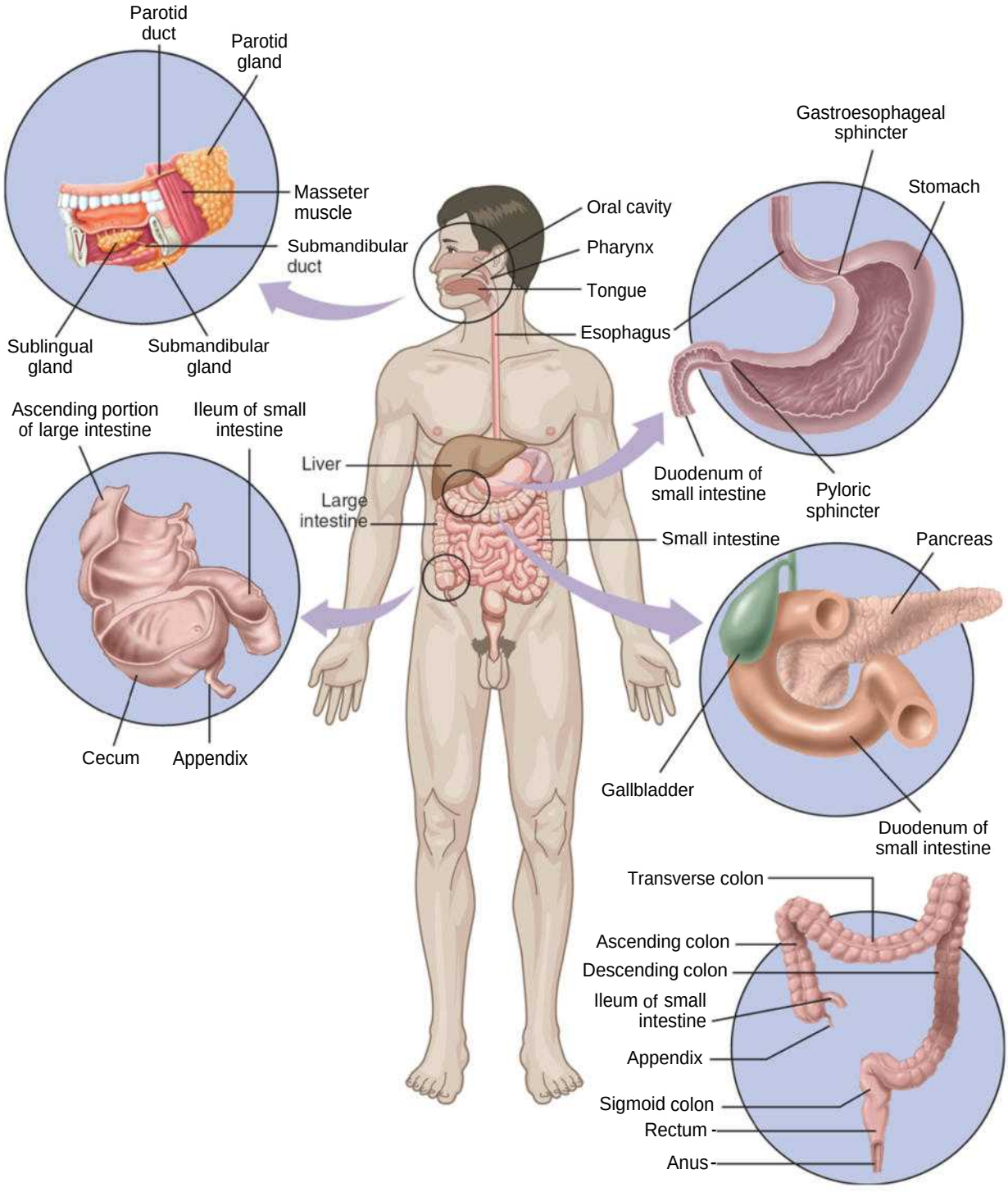


FIGURE 9-2 Structures of the gastrointestinal system.

Description

Disorders of the GI system can result in nutritional deficits and metabolic imbalances. These conditions vary from mild (e.g.,

constipation) to life threatening (e.g., **pancreatitis**) in severity, and often present as vague, nonspecific manifestations that reflect a disruption in the system's normal functioning.

Anatomy and Physiology

The GI tract is divided into upper and lower divisions, which will be further discussed in upcoming sections. Additionally, the liver, gallbladder, and pancreas are collectively referred to as the **hepatobiliary system** because of their close proximity to each other and their complementary functions.

The walls of the GI tract have four layers (**FIGURE 9-3**). The **mucosa** is the innermost layer that produces **mucus**. Mucus facilitates movement of the GI contents and protects the GI tissue from the extreme pH conditions of the GI tract (the stomach's pH is in the range of 1–2) necessary for digestion. The epithelial mucosa cells have a high turnover rate because of erosion associated with food passage and the highly acidic environment. The **submucosa layer** consists of connective tissue that includes blood vessels, nerves, lymphatics, and secretory glands. The **muscle layer** includes both circular and longitudinal smooth muscle layers. This layer contracts in a wavelike motion to propel food through the GI tract, an action called **peristalsis**. The **serosa** is the outer layer of the wall.

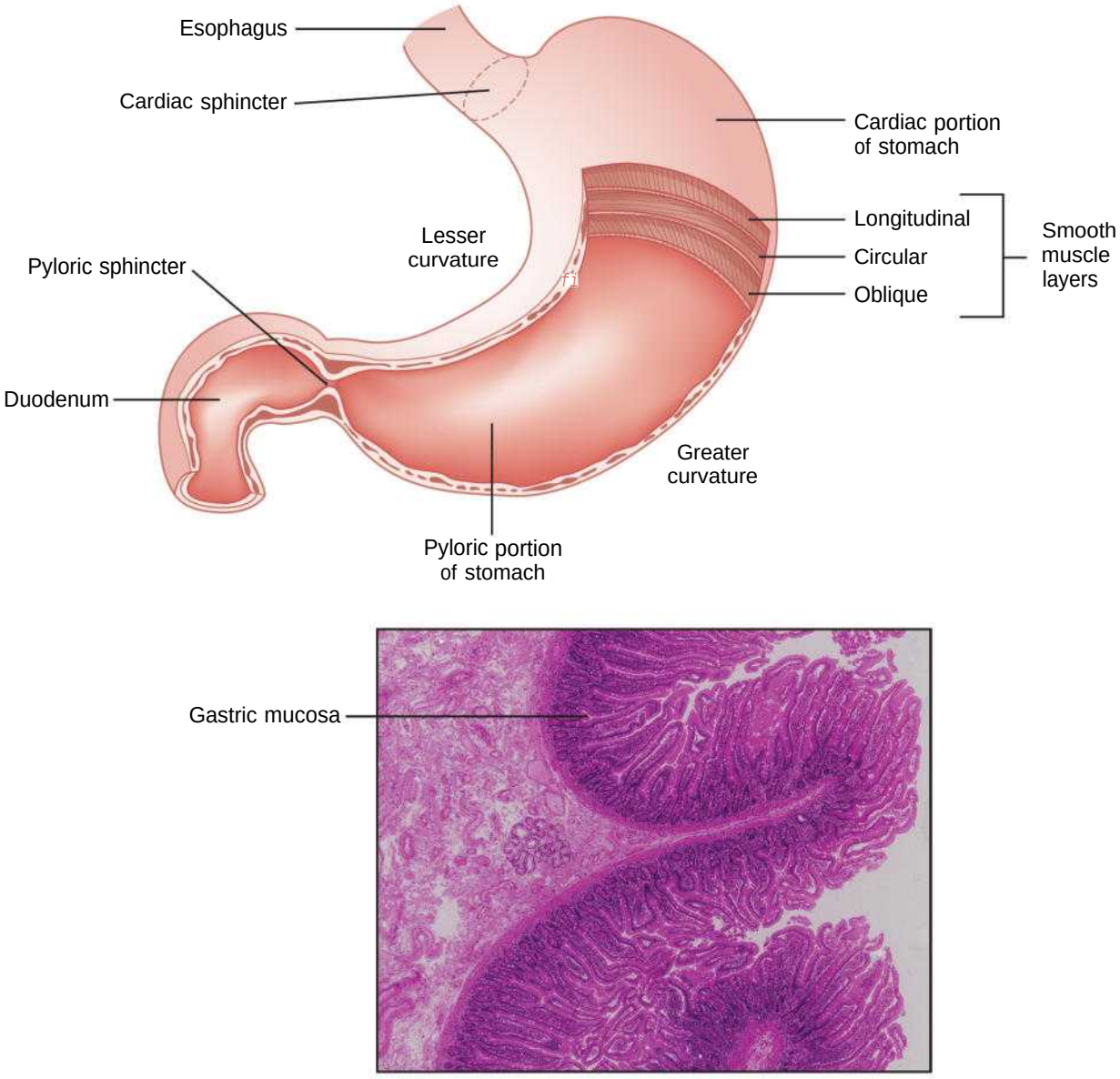


FIGURE 9-3 The layers of the gastrointestinal tract.

Photo: © Donna Beer Stolz, PhD, Center for Biologic Imaging, University of Pittsburgh Medical School.

Description

The **peritoneum** is the large serous membrane that lines the abdominal cavity. The outer **parietal peritoneum layer** covers the abdominal wall as well as the top of the bladder and uterus. The inner **visceral peritoneum layer** encases the abdominal organs. This double-walled membrane is similar to the pericardial sac (see the

Cardiovascular Function chapter) and the pleural membrane (see the *Respiratory Function* chapter). The **peritoneal cavity** is the space between these two layers; it contains serous fluid that decreases friction and facilitates movement. The **mesentery** is a double-layer peritoneum containing blood vessels and nerves that supply the intestinal wall. It supports the intestines while allowing flexibility to accommodate peristalsis and varying content volumes.

Upper Gastrointestinal Tract

The upper GI tract includes the oral cavity, pharynx, esophagus, and stomach (see Figure 9-2). Food usually enters the GI tract through the mouth (consumption), where chemical and mechanical digestion begins. Issues with the mouth or swallowing can create a need to bypass the mouth and esophagus and introduce the food or a food supplement directly into the stomach or small intestine. Chewing, or **mastication**, pulverizes the food into small pieces, and saliva from the salivary glands moistens and further breaks down the food (**TABLE 9-1**). Saliva contains enzymes and antibodies that can kill or neutralize bacteria. The smell, taste, feel, and thought of food trigger saliva secretion. Healthy teeth and gums play a key role in maintaining adequate nutrition.

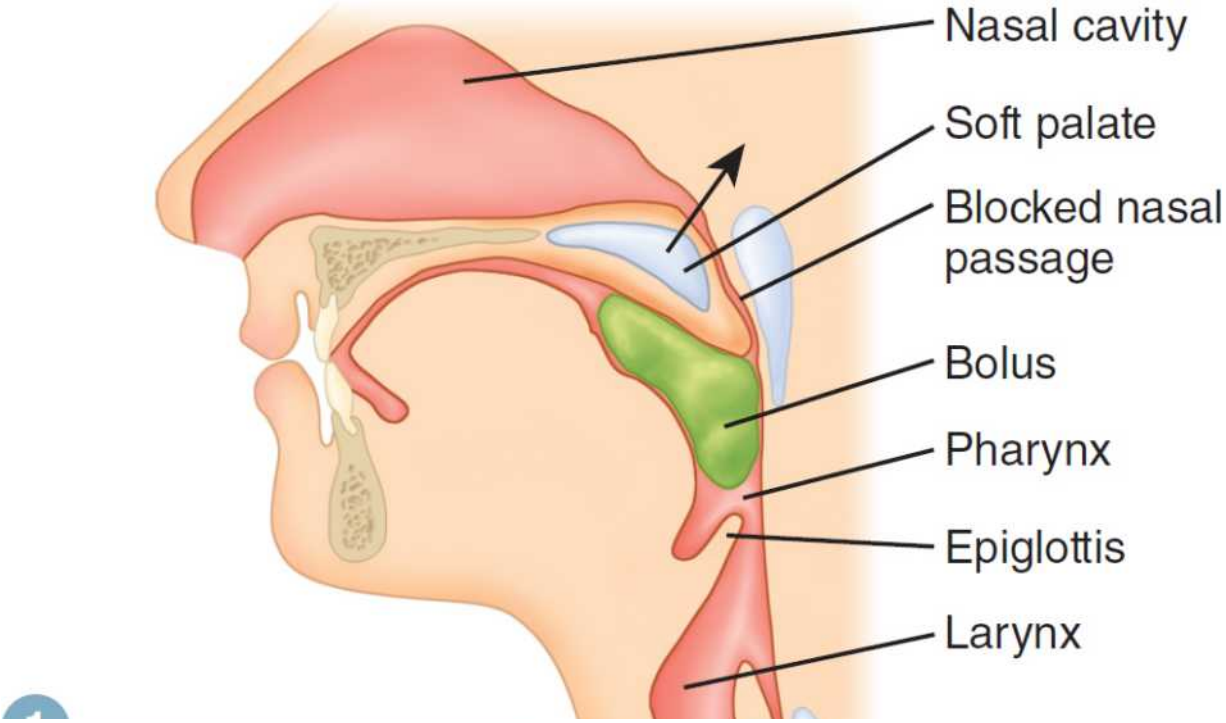
TABLE 9-1 Digestive Juices and Actions

Source	Type	Action
Salivary glands	Bicarbonate	Moistens food
	Salivary lipase	Digests fat
	Amylase	Digests starch

Source	Type	Action
Stomach	Hydrochloric acid	Digests protein Kills bacteria
	Protease (pepsin)	Digests protein Digests fat
	Gastric lipase	Aids in absorption of vitamin B_{12} in the small intestine
	Intrinsic factor	Protects stomach lining
	Mucus	Aids in triggering hydrochloric acid production
	Histamine	Stimulates appetite
	Ghrelin	Inhibits gastrin and histamine release
	Somatostatin	Inhibits motility
Liver	Bile acids	Dissolve fats
	Cholesterol	Excreted in bile
	Phospholipids	Aid in absorption of fats
	Immunoglobulins	Act as antibodies
Small intestine	Peptidases	Hydrolyze (break down using water) peptides (proteins) into free amino acids and smaller peptides
	Sucrase	Hydrolyzes sucrose into fructose and glucose
	Lactase	Breaks down lactose into glucose and galactose
	Maltase	Hydrolyzes maltose into glucose
	Motilin	Stimulates gastric emptying
	Cholecystokinin	Increases intestinal peristalsis
	Serotonin	Stimulates the gallbladder to release bile and pancreas to secrete enzymes
	Glucagon	Stimulates intestinal peristalsis
	Gastric inhibitory peptide	Regulates intestinal motility Stimulates insulin secretion Inhibits gastric secretion and motility Inhibits water and electrolyte absorption
Pancreas	Bicarbonate	Protects digestive enzymes
	Water	Neutralizes acid
	Amylase	Carries enzymes
	Lipases	Digests starch and glycogen
	Proteases (trypsin)	Digest fats Digest protein
	Glucagon	Stimulates the breakdown of glycogen and gluconeogenesis in the liver
	Somatostatin	Decreases production of gastric and pancreatic secretions Inhibits secretion of pancreatic hormones (e.g., lipase, insulin, and glucagon)

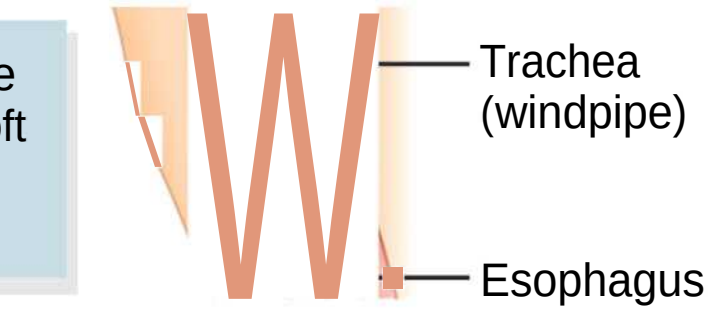
Source	Type	Action
Liver	Bile	Aids in digestion of lipids in the small intestines

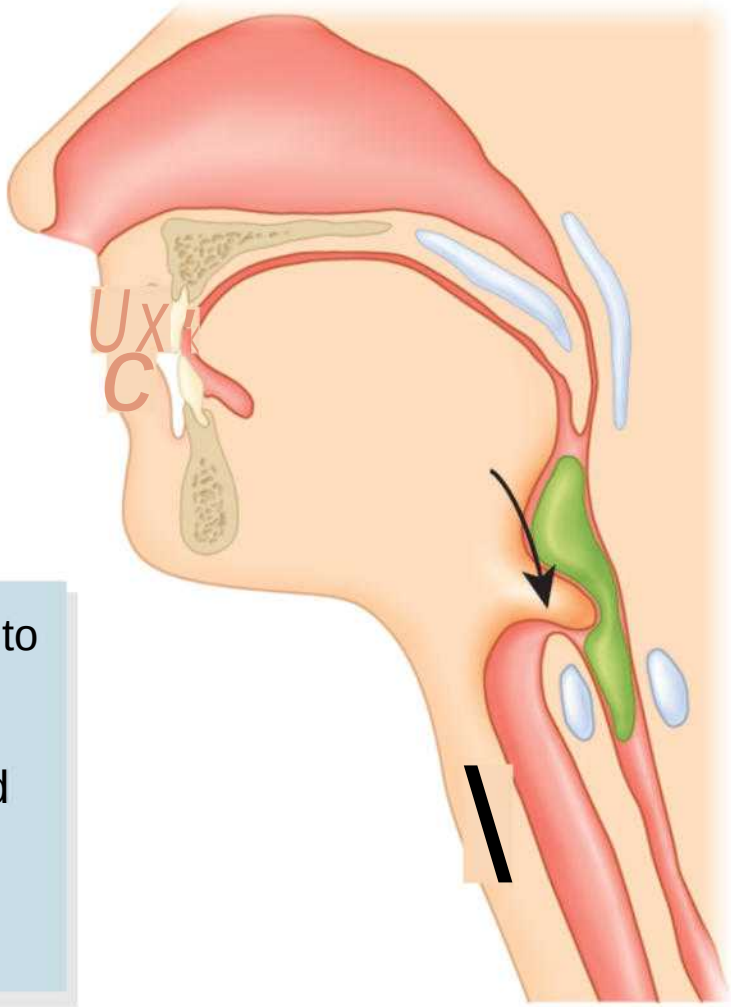
The tongue pushes the semisolid food mass (bolus) to the back of the throat, where it is swallowed (i.e., deglutition) (**FIGURE 9-4**). Food passing by the trigeminal and glossopharyngeal nerves (i.e., cranial nerves V and IX) initiates the swallowing reflex. These nerves relay information to the swallowing center in the medulla; the swallowing center then coordinates the movement of the food from the mouth through the esophagus to the stomach with the trigeminal, glossopharyngeal, vagus (i.e., cranial nerve X), and hypoglossal (i.e., cranial nerve XII) nerves. This orchestrated movement prevents food from entering the nearby trachea and lungs (a phenomenon called **aspiration**). The esophagus has muscular rings to move the food toward the stomach (**FIGURE 9-5**). As the food nears the stomach, the closed **lower esophageal sphincter (LES)** relaxes to allow the food to enter the stomach. The LES also prevents the stomach contents from refluxing into the esophagus.



V

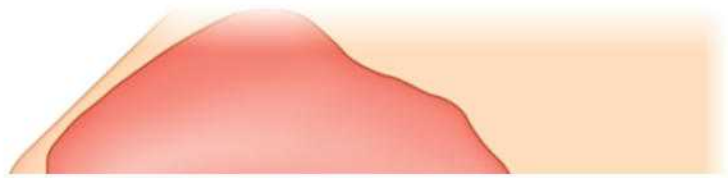
The bolus enters the pharynx, and the soft palate closes the nasal cavity.





O

The larynx rises up to meet the epiglottis. The bolus presses on the epiglottis and bends it downward, closing the opening to the windpipe.



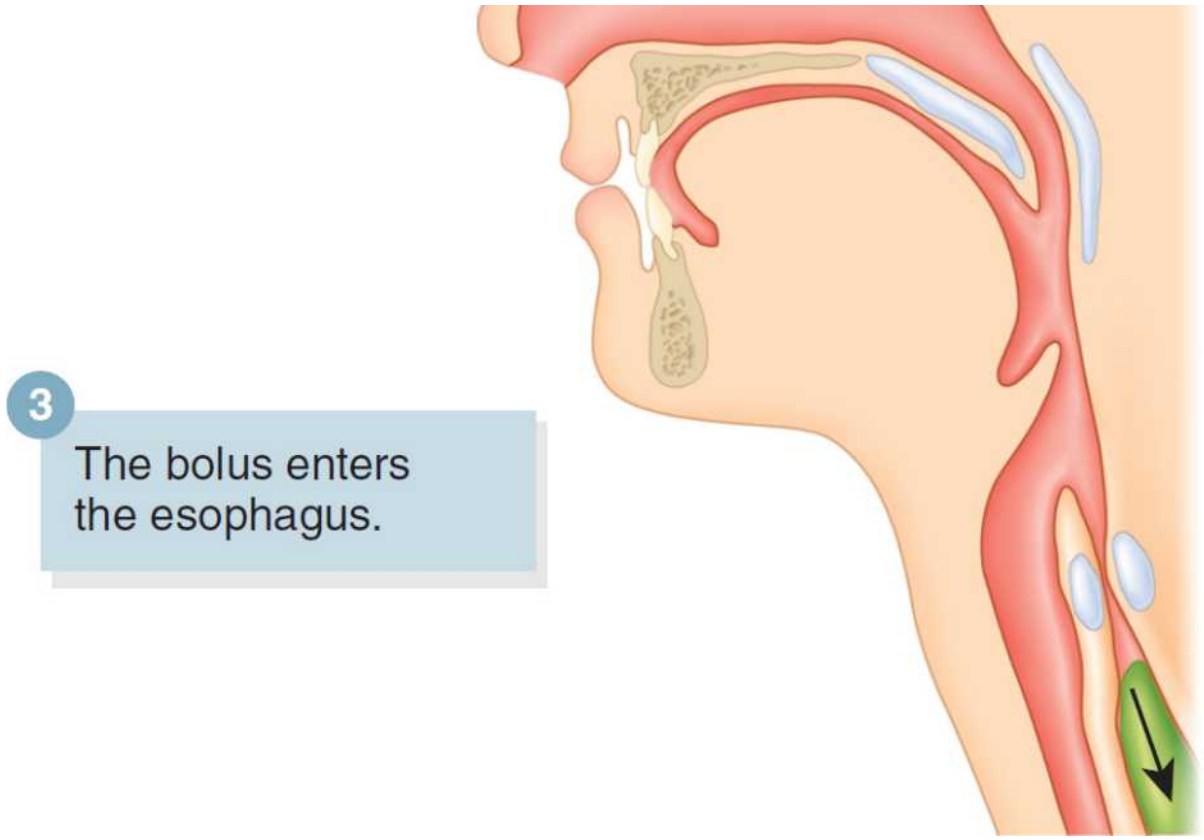
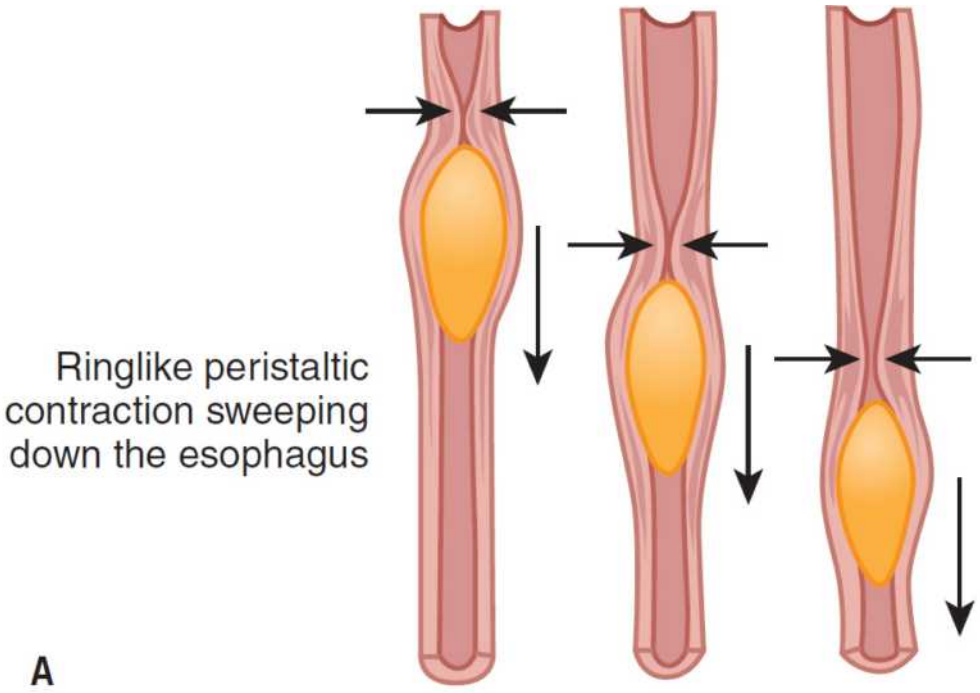


FIGURE 9-4 Swallowing.

Description



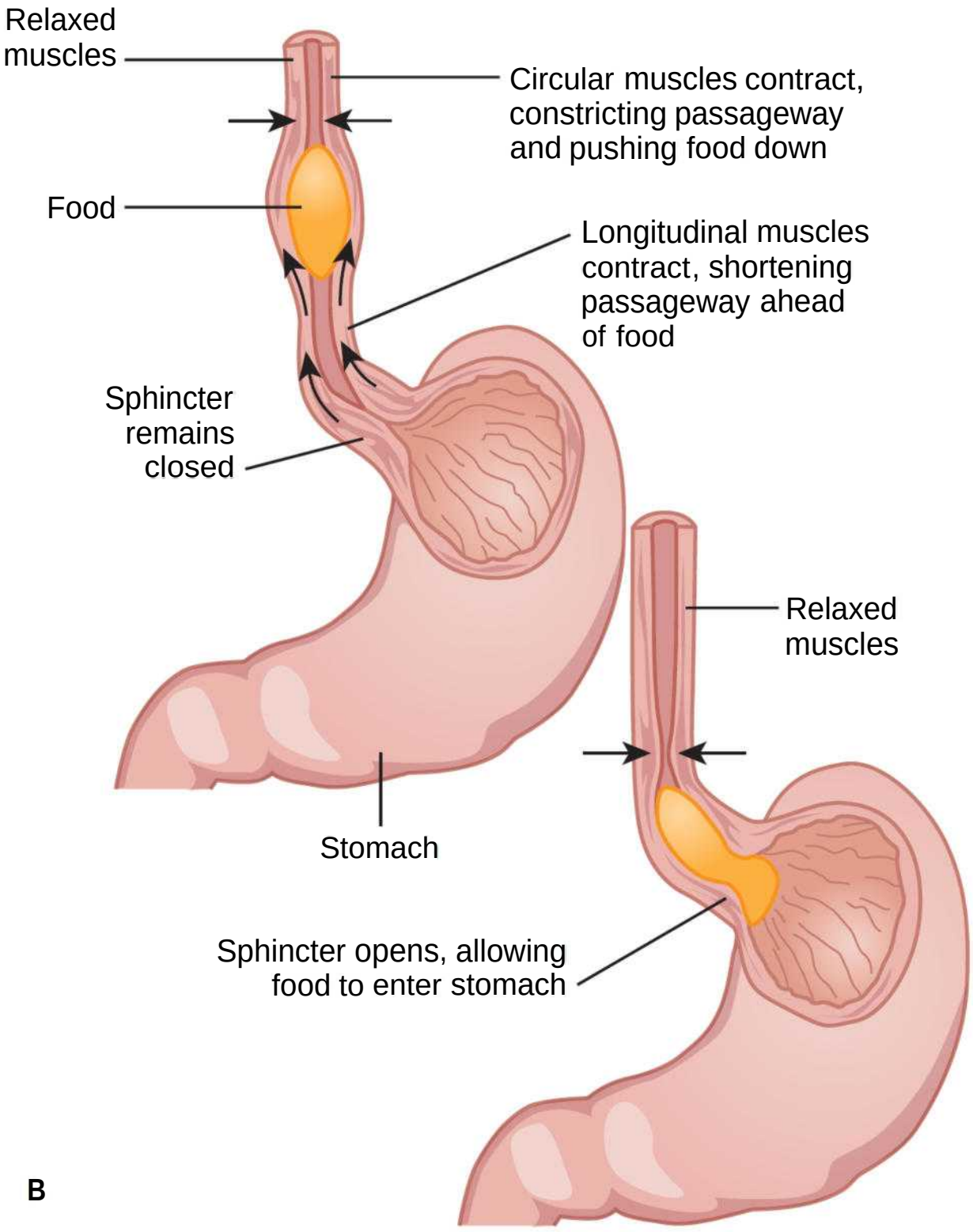


FIGURE 9-5 Peristalsis. **(A)** Peristaltic contractions in the esophagus propel food into the stomach. **(B)** When food reaches the stomach, the gastroesophageal sphincter opens,

allowing food to enter.

Description

The stomach is an expandable food and liquid reservoir. When it is empty, the stomach wall shrinks, forming wrinkles called **rugae** (**FIGURE 9-6**). As the stomach fills, the rugae unfold and the wall stretches to accommodate a volume of up to 4 L. Inside the stomach, hydrochloric acid and enzymes (see Table 9-1) further chemically digest the food, and peristaltic churning further mechanically digests the food. The highly acidic nature of this new food mixture, called **chyme**, aids in digestion and destroys bacteria. The epithelial cells of the stomach's inner lining are densely packed together to prevent damage to the tissues through contact with the acidic stomach contents. For additional protection, numerous glands are located in the stomach that coat the inner lining with a thick layer of mucus. Nutrients are not absorbed in the stomach; instead, the food is simply prepared for absorption. However, alcohol is absorbed in the stomach. Chyme leaves the stomach through the **pyloric sphincter** in small (1–3 mL), intermittent amounts. As it passes through the pyloric sphincter into the duodenum, liver and pancreatic secretions (see Table 9-1) are added to continue the digestion process. Much like the LES, the pyloric sphincter prevents reflux of bile from the small intestines into the stomach.

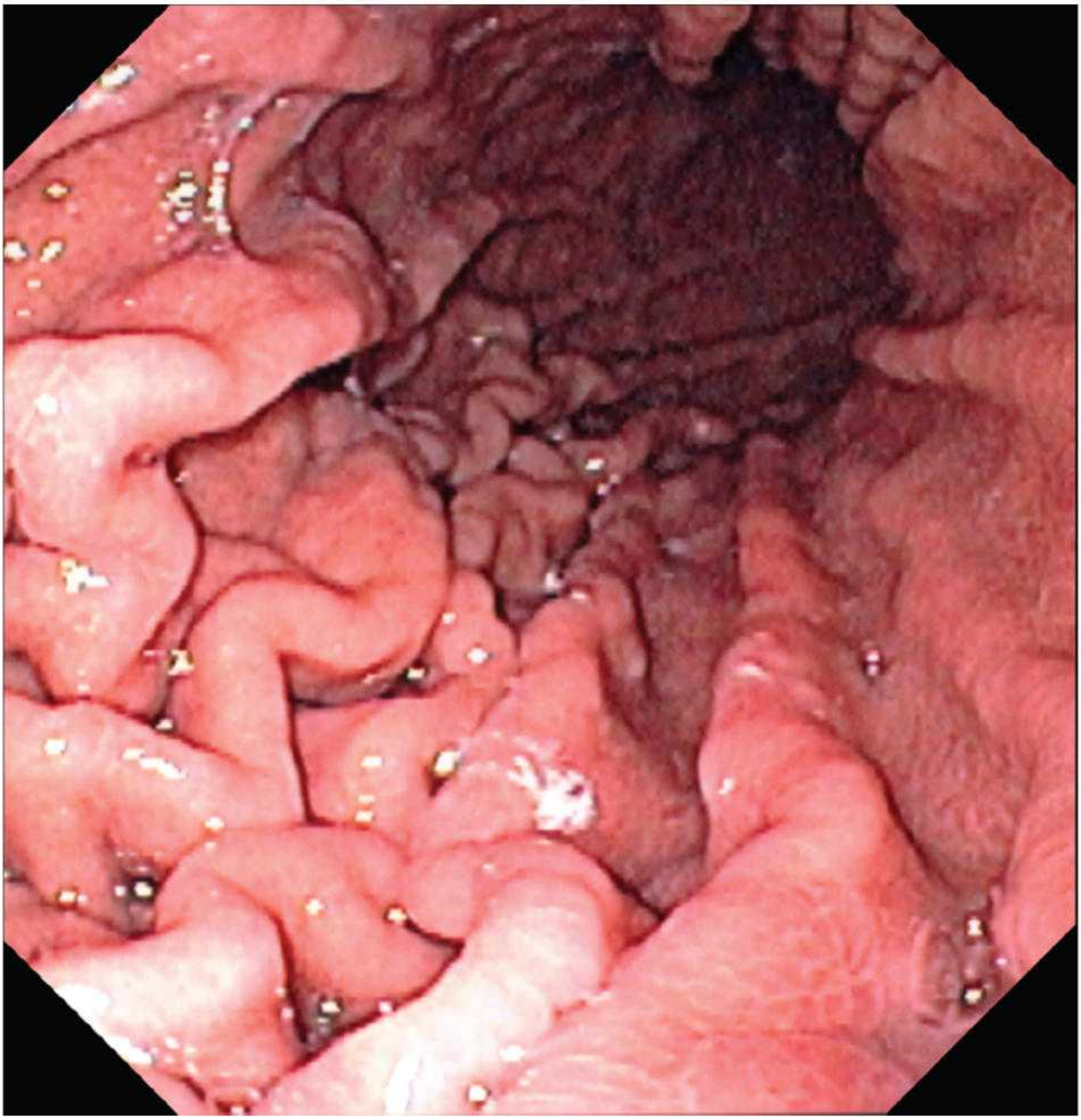


FIGURE 9-6 Rugae of the stomach.

© David M. Martin, MD/Science Source

Liver

The liver is an organ that is a hub of activity. This large organ performs as many as 500 different functions. Some of the liver's primary roles are vital for homeostasis and include the following:

- Metabolize carbohydrates, protein, and fats
- Synthesize glucose, protein (albumin), cholesterol, triglycerides, and clotting factors
- Store glucose (glycogen), fats (lipids), and micronutrients (e.g., iron, copper, and vitamin B_{12}) and release them when needed
- Detoxify the blood of potentially harmful chemicals (e.g., alcohol, nicotine, and medications)
- Maintain intravascular fluid volume through the production of circulating proteins (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter)
- Metabolize medications to prepare them for excretion
- Produce bile (necessary for emulsification of fat and fat-soluble vitamins)
- Inactivate and prepare hormones for excretion
- Remove damaged or old erythrocytes from blood to recycle iron and protein
- Serve as a blood reservoir (stores approximately 450 mL of blood that can be used when needed)
- Convert fatty acids to ketones

A tough membrane (Glisson capsule) protects this crucial organ. The liver has a dual blood supply. The **hepatic artery** carries oxygenated blood from the general circulation to the liver at a rate of approximately 300 mL per minute to nourish the liver. The **portal vein** carries partially deoxygenated blood from the stomach, pancreas, and spleen, as well as from the small and large intestines to the liver at a rate of approximately 1,000 mL per minute so that the liver can process nutrients and digestion by-products.

The liver is one of the body's few organs that can regenerate. As much as 75% of the liver tissue can be lost or removed, yet the remaining liver tissue can slowly regenerate into a whole liver again. This regeneration occurs primarily due to certain liver cells (hepatocytes) that act as stem cells. A single hepatocyte can divide into two daughter cells. During regeneration, steps should be taken to

protect the liver from damage (e.g., avoiding hepatotoxic medications and substances).

In addition to providing regeneration capabilities, the hepatocytes produce bile and perform most of the liver's other activities. The hepatocytes constantly produce bile at a rate of approximately 600–1,200 mL per day. Bile is a green or yellowish liquid that contains water, bile salts (formed from cholesterol), conjugated bilirubin, cholesterol, and electrolytes (including bicarbonate). Bile salts are necessary to emulsify fats and fat-soluble vitamins (A, D, E, and K) so that they can be absorbed in the small intestine. The distal ileum reabsorbs most of the bile and returns it to the liver through the portal vein for recycling. The bicarbonate ions in the bile neutralize the acidic gastric contents so that the intestinal and pancreatic enzymes can perform their functions.

The bile flows from the liver through a duct system to either the gallbladder for storage or to the duodenum. The gallbladder is a small (usually no larger than a golf ball), saclike organ located on the under-surface of the liver that serves as a reservoir for bile. In addition to storing the bile, the gallbladder concentrates it by removing water. The presence of chyme in the small intestine triggers the gallbladder to contract, releasing bile into yet another duct system, where it travels to the small intestine. If the gallbladder requires surgical removal, the bile constantly flows directly from the liver to the small intestine.

Pancreas

The pancreas is an organ that is nestled underneath the stomach and liver. It has exocrine and endocrine functions. The exocrine functions include producing enzymes, electrolytes (e.g., bicarbonate ions), and water necessary for digestion (see Table 9-1). A duct system carries these substances to the duodenum to join the chyme. The endocrine functions (see the *Endocrine Function* chapter) include producing hormones (e.g., insulin and glycogen) to help regulate blood glucose, thereby maintaining homeostasis.

Lower Gastrointestinal Tract

The lower GI tract comprises the small intestine (duodenum, jejunum, and ileum), large intestine (**cecum**, **colon**, **rectum**), and anus (see Figure 9-2). The small intestine is the longest section of the GI tract (approximately 20 feet long in adults). This length allows for adequate nutrient absorption as the small intestine continues the digestion process. In the small intestine, the enzymes that have been secreted into the GI tract break the large food molecules into smaller molecules, which are then absorbed. These smaller molecules are transported to the circulatory and lymphatic systems. Muscular rings slowly move the food mixture through the small intestine using a peristaltic wave motion. The wall of the small intestine contains numerous circular folds (plicae circulars) covered with villi and microvilli (**FIGURE 9-7**). These projections increase the surface area available for absorption of nutrients. Each villus contains capillaries, nerves, and lymphatic vessels that play key roles in this absorption. Intestinal glands (i.e., intestinal crypts or crypt of Lieberkühn) in the epithelia of the villi contain Paneth cells that play a role in defense, endocrine cells that secrete digestive juices, and stem cells that can differentiate into several types of cells (e.g., enterocytes or absorptive cells, goblet cells, Paneth cells, and neuroendocrine cells). The small intestine also contains cells that secrete fluid to neutralize pH and enzymes to facilitate digestion. Much like the stomach, the small intestine produces a large amount of protective mucus. The muscular layer of the intestines, particularly the ileum, contains lymphoid tissue (i.e., Peyer patches) that plays a role in monitoring normal intestinal flora and preventing pathogenic bacterial growth.

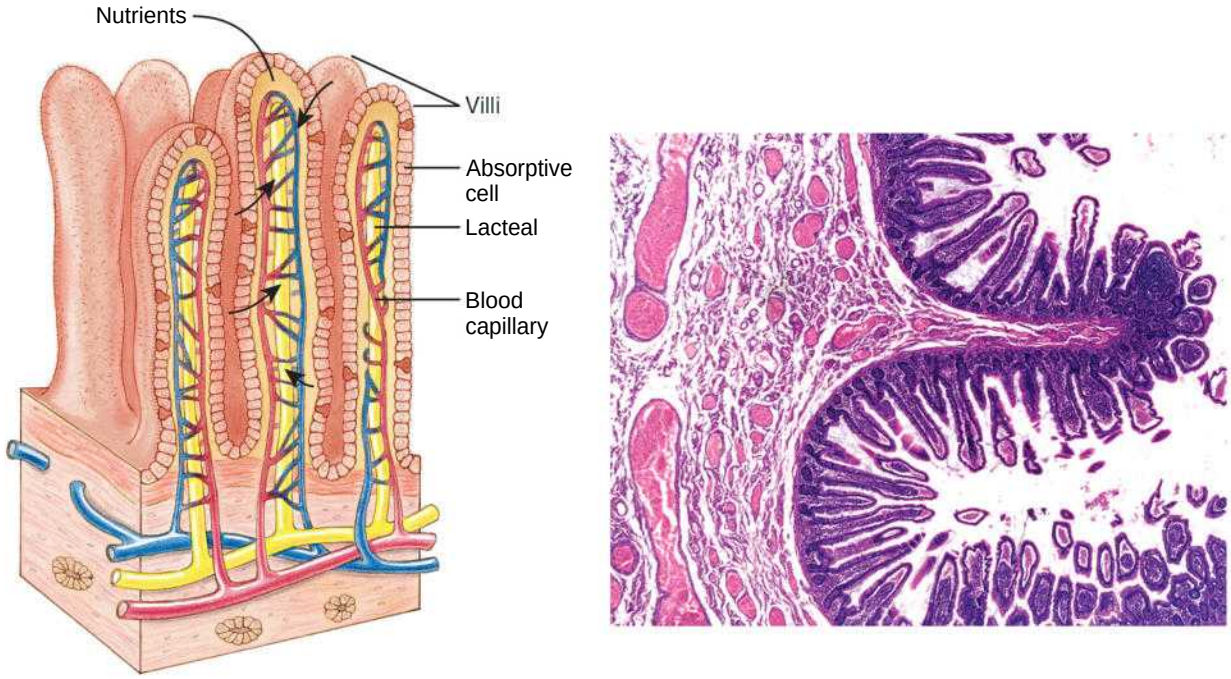


FIGURE 9-7 Villi of the small intestines.

Photo: © Donna Beer Stolz, PhD, Center for Biologic Imaging, University of Pittsburgh Medical School.

Description

After making its long journey through the small intestine, the chyme ultimately reaches the large intestine (in approximately 3–5 hours). The small intestine ends in a pouch called the “cecum.” The **appendix** is also attached to the cecum. This small, wormlike structure seemingly has no function, but it does have plenty of potential to cause harm.

The large intestine is approximately 5 feet long and does not contain villi, but it does contain deep crypts. Absorptive cells (e.g., goblet cells, endocrine cells, and basal stem cells) form the thick epithelium, but no Paneth cells are present. The muscular layer is arranged into bands called “taenia coli.” The colon makes up most of the large intestine. Unlike the coiled small intestine, the colon has three relatively straight sections—termed the “ascending,” “transverse,” and “descending” colons. The descending colon transitions to the sigmoid colon, a curved section just before the rectum.

The mixture entering the colon from the small intestine includes water, unabsorbed food molecules, indigestible food remnants (e.g., cellulose), and electrolytes (sodium and potassium). The colon absorbs 90% of the water and electrolytes, and *Escherichia coli* feed off the undigested or unabsorbed food remnants. *E. coli* organisms constitute a large population of bacteria normally found in the GI tract. These bacteria synthesize several key vitamins (e.g., vitamins B_{12}, B_1, B_2, and K) that are later absorbed by the large intestine. As the chyme moves through the colon, it changes into feces. Feces contain the remaining undigested or unabsorbed remnants along with bacteria (one-third of the feces). Feces also introduce mucus (approximately 300 mL daily) to aid in bowel movements, even in times of decreased dietary intake. Because the feces are denser than the contents in the small intestines, the colon's muscular rings must be thicker to propel the feces until they reach the rectum (this usually takes approximately 18 hours). The rectum serves as a reservoir to store the feces.

Much like the bladder (see the *Urinary Function* chapter), the rectum expands when feces enter this area, stimulating the stretch receptors in the rectal wall. These receptors send an impulse through the spinal cord to elicit the **defecation reflex**. During defecation, the internal and external anal sphincters relax, and the rectum contracts to expel the feces. Defecation is consciously controlled (except in infants) and may require assistance from abdominal muscles. Defecation control requires both appropriate muscular and nervous functions. The urge to defecate can be delayed up to a point, but the longer the feces remain in the large intestine, the more water from them will be absorbed, making the feces more difficult to expel.

In addition to the nerves that control defecation, the sympathetic and parasympathetic nervous systems innervate the GI tract. Activation of the sympathetic nervous system slows digestive activity, whereas activation of the parasympathetic nervous system increases digestive activity.

Gastrointestinal Changes Associated with Aging

The GI system undergoes a few, usually minor, changes with aging. The stomach lining may shrink and become inflamed, leading to **atrophic gastritis**. Stomach acid production can decrease (**achlorhydria**), occasionally because of atrophic gastritis. Achlorhydria can cause vitamin B_{12} deficiency and slow digestion. Changes in the liver associated with age include reduced blood flow, delayed drug clearance, and a diminished capacity to regenerate damaged liver cells. Additionally, changes in the metabolism and absorption of lactose, calcium, and iron can occur. In particular, the small intestine absorbs less calcium with advancing age, so increased calcium intake is needed to prevent bone mineral loss and osteoporosis. The production of some enzymes, such as lactase (which aids in the digestion of lactose, a sugar found in dairy products), also declines with age. Likewise, peristalsis decreases with age, increasing the risk of constipation.

Learning Points

The GI tract is another system in the body that is analogous to basic household plumbing. Normally, food enters the tubular system and moves in one direction until the waste products are expelled. Peristaltic movement keeps the system flowing in the right direction, but conditions can sometimes slow, cease, or reverse this movement. Problems can occur when food moves too rapidly or too slowly through the system. Much like household plumbing, the whole system backs up, and overall health can be significantly impacted if an occlusion occurs. If the system is backing up, intake should cease until functioning returns. Remember, *what goes in must come out!*

UNDERSTANDING CONDITIONS THAT AFFECT THE GASTROINTESTINAL SYSTEM

hen considering alterations in the GI system, organizing them based on their basic underlying pathophysiology can increase understanding. These concepts are based on the two major underlying pathological

issues—altered nutrition and impaired elimination. Conditions that alter nutritional status include issues with consuming (e.g., **cleft lip**), digesting (e.g., pancreatitis), and absorbing (e.g., **celiac disease**) food. Regardless of the cause of the altered nutrition, the end result is similar—inadequate nutritional states in which individuals may be underweight and vitamin deficient. Conditions impairing elimination generally result in constipation or **diarrhea**. These issues may be either the primary condition or a symptom of another condition. Additionally, conditions that cause altered nutrition may cause issues with elimination.

Disorders of the Upper Gastrointestinal Tract

Disorders of the upper GI tract generally cause issues with nutrition and range in severity from mild to life threatening. These disorders can be congenital (e.g., cleft lip/palate or **pyloric stenosis**) or acquired (e.g., peptic ulcers). Depending on their severity, most of these disorders can be resolved or managed with minimal residual effects.

Congenital Defects

Congenital defects of the digestive system often affect the upper GI tract. These congenital disorders are common and not usually life threatening, but they may cause nutritional and self-image issues.

Cleft Lip and Palate

Cleft lip and **cleft palate**, collectively referred to as "oral clefts," are relatively common congenital defects of the mouth and face that are apparent at birth. The Centers for Disease Control and Prevention (CDC, 2022a) estimates that a cleft palate without a cleft lip occurs in 1 in every 1,600 births in the United States, and a cleft lip with or without a cleft palate occurs in 1 in every 2,800 births. These conditions usually develop between the fourth and seventh weeks of gestation and are multifactorial in origin—that is, they involve a combination of environmental and hereditary factors. Such defects have been associated with genetic mutations, maternal diabetes,

drugs (e.g., anticonvulsants), toxins, viruses, vitamin deficiencies (e.g., folate), alcohol, and cigarette smoking. Having one child with an oral cleft increases the risk of having a second child with this condition. Oral clefts are most frequent in children of Native American, Hispanic, and Asian descent, whereas African American children are the least likely to have a cleft. Males are twice as likely as females to have a cleft lip. Females, however, are twice as likely as males to have a cleft palate.

A cleft lip and palate can affect the appearance of an individual's face and may lead to feeding issues, speech problems, ear infections (otitis media), and hearing problems. The conditions may vary in severity from a small notch in the lip to a complete groove that runs into the roof of the mouth and nose (**FIGURE 9-8**). These defects may occur either separately or together.

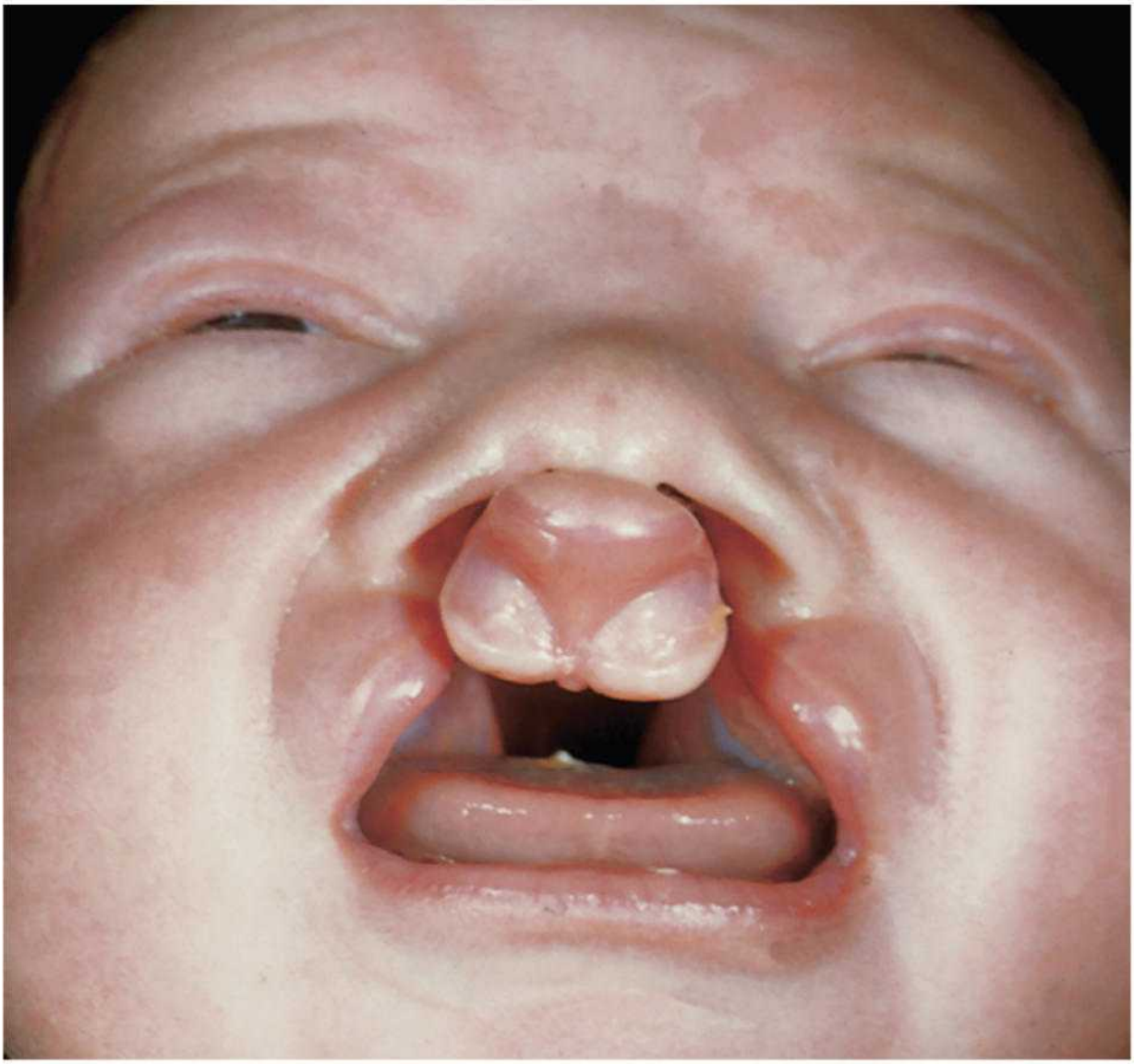


FIGURE 9-8 Cleft lip and palate.

Courtesy of Leonard V. Crowley, MD, Century College.

Syndromic oral clefts may occur in tandem with congenital syndromes or with multiple congenital defects. These clefts are usually a result of a chromosomal abnormality. Nonsyndromic or isolated oral clefts occur without the presence of other anomalies or developmental delays. These clefts have been associated with genetic mutations, including some of the same mutations associated with syndromic oral clefts.

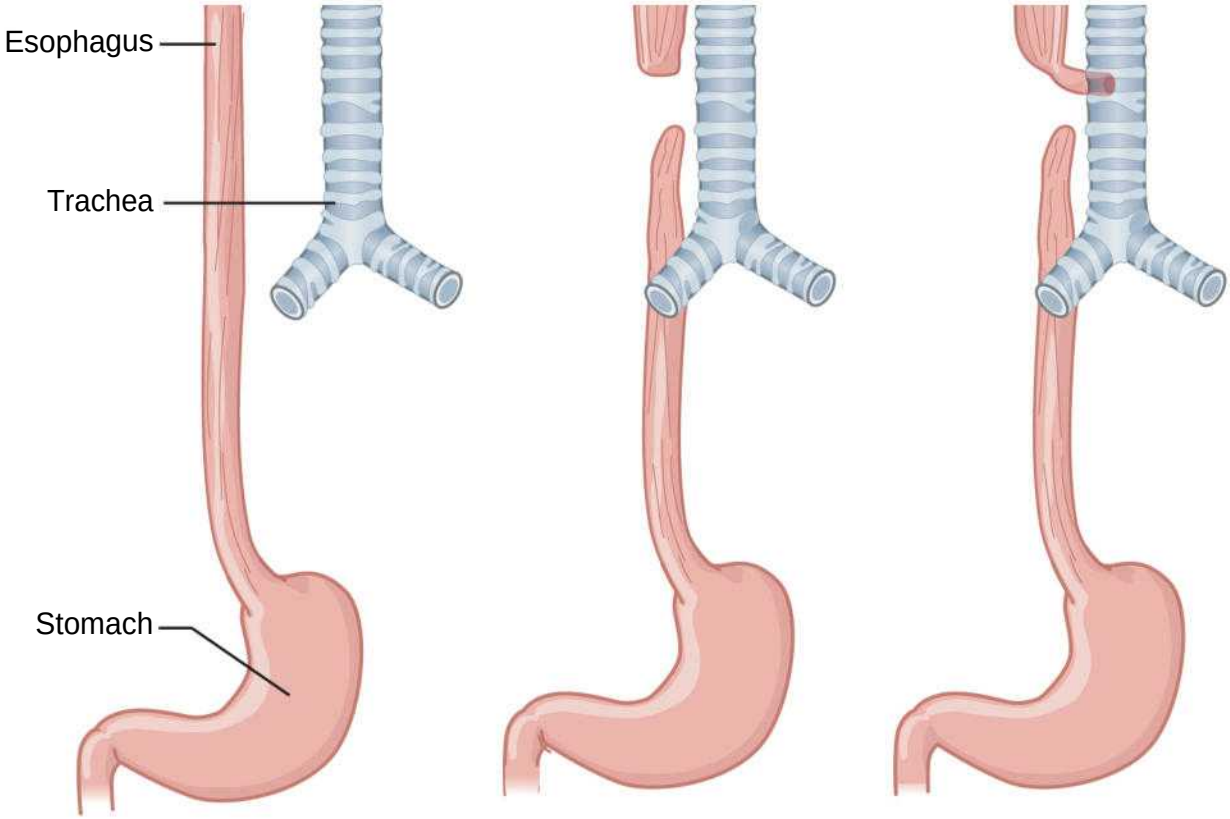
Cleft lip may appear unilaterally or bilaterally (on either side of the midline of the upper lip). This defect results from failure of the maxillary processes and nasal elevations or upper lip to fuse during development. A cleft palate results from the failure of the hard and soft palates to fuse in development, creating an opening between the oral and nasal cavities. In addition to lip and palate deformities, teeth and nose malformations may be present. Feeding problems result from these deficits due to the infant's insufficient ability to suck. An infant with a cleft lip and/or palate is also at high risk for aspiration when the nasal cavity is open. Moreover, the inability to make sounds using the lips and tongue impairs speech development.

Diagnostic procedures for oral clefts consist of a history, physical examination, and prenatal ultrasound. Treatment strategies for oral clefts include temporary measures (e.g., special nipples or dental appliances) until surgical procedures are recommended. Surgical repair of the defect is necessary to close the gap. Cleft lip repair is recommended before age 3 months, and cleft palate repair is recommended by 18 months of age. Follow-up procedures are often necessary from 2 years through the adolescent years. Cosmetic plastic surgery can improve the appearance of the defect. Surgical repair in utero is currently being explored. The major advantage of surgical repair before birth is little or no scarring. Speech therapy, including language and eating interventions, and orthodontist consultation can promote normal growth and development. Additionally, a multidisciplinary team (including an audiologist and a pediatrician) is frequently required to manage severe cases.

Esophageal Atresia

Esophageal atresia refers to an incomplete formation of the esophagus. This fairly common congenital defect affects approximately 1 in every 4,100 births in the United States (CDC, 2022b). Five major types of esophageal atresias are distinguished (**FIGURE 9-9**). Type C is the most common form, and type D is the rarest, but most severe form.

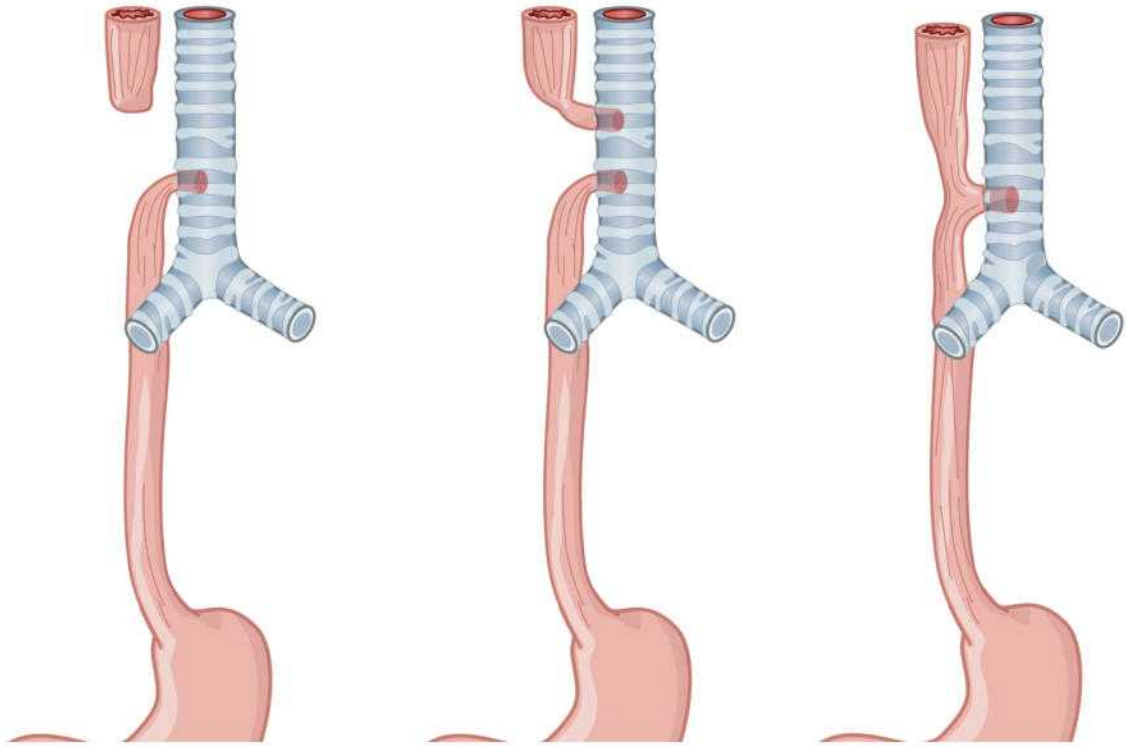




Typical anatomy

Type A: isolated esophageal atresia

Type B: atresia with proximal fistula





Type C: atresia with distal fistula | Type D: atresia with double fistula | Type E: isolated fistula (H type)

FIGURE 9-9 Types of esophageal atresias.

Description

The exact cause is unknown, but esophageal atresia is often associated with other congenital malformations. One syndrome associated with esophageal atresia is VACTERL (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, esophageal atresia, renal anomalies and radial aplasia, and limb anomalies). CHARGE (coloboma, heart defects, atresia of the choanae, retardation of mental and/or physical development, genital hypoplasia, and ear abnormalities) is another syndrome associated with esophageal atresia. Risk factors for this condition include the older age of the father and maternal use of assisted reproductive technology.

Clinical manifestations characteristic of esophageal atresia include excessive secretions, coughing, **vomiting**, and cyanosis after feeding. Aspiration pneumonia in the infant may also be noted. Type C can cause abdominal distention as air from the trachea enters into the esophagus and stomach. In utero, polyhydramnios (excessive amniotic fluid) may be present.

Esophageal atresia is rarely diagnosed in utero; instead, it is most commonly identified after birth when feeding is attempted. Diagnostic procedures include a history, physical examination, prenatal ultrasound, and postnatal nasogastric or orogastric tube placement with X-ray.

Surgical repair is the primary treatment for esophageal atresia to ensure the infant's respiratory and nutritional status is maintained. Multiple surgeries may be required. Oral feedings are withheld until surgery can be performed. Continuous suction with a nasogastric tube in the upper esophageal pouch prevents aspiration of saliva. The infant should be placed in a prone position with the head elevated 30

to 40 degrees and the right side down to facilitate gastric emptying and minimize aspiration of gastric contents. A gastrostomy tube may be placed to decompress the stomach if surgical repair must be significantly delayed.

Pyloric Stenosis

Pyloric stenosis, also known as **infantile hypertrophic pyloric stenosis**, is a narrowing and obstruction of the pyloric sphincter. The pyloric sphincter muscle fibers become thick and stiff, making it difficult for the stomach to empty food into the small intestines. This condition can be present at birth, or it may develop later in life (rarely in children older than 6 months). Most cases present at approximately 3 weeks of life.

The exact cause of pyloric stenosis is unknown, but it is thought to be multifactorial. Genetics likely plays a role because risk is higher among those infants with siblings (especially with monozygotic twins) or parents who have a history of pyloric stenosis. Proposed mechanisms include a lack of neuronal nitric oxide synthase, abnormal innervation of the muscular layer, and hypergastrinemia. Recently, exposure to macrolides in early infancy has been demonstrated to have a strong association with increased pyloric stenosis risk. Evidence also suggests that use of azithromycin and erythromycin in infants increases this risk. Other risk factors may include prematurity, maternal smoking during pregnancy, and bottle feeding. Although it is the most common cause of **intestinal obstructions** in infancy, pyloric stenosis is relatively uncommon, occurring in 2–4 infants per 1,000 births. Pyloric stenosis is most common in Caucasians and in males.

Clinical manifestations of pyloric stenosis usually appear within several weeks after birth. In the congenital form, the hypertrophied pyloric muscle can be palpated as a hard olive-shaped mass in the abdomen (right upper quadrant), and vomiting (usually after every feeding, often projectile, and sometimes with hematemesis being noted) is usually the first symptom. Additional manifestations include the following signs and symptoms:

- Regurgitation
- Persistent hunger (often wants to eat soon after vomiting)
- Irritability (caused by persistent hunger)
- Belching
- Wavelike stomach contractions (result from the increased peristaltic effort to pass food through the narrowed areas)
- Small, infrequent stools
- Abdominal pain
- Failure to gain weight
- Dehydration, electrolyte imbalances, and pH disturbances (usually metabolic alkalosis)
- Jaundice (yellowing of the skin)

Diagnostic procedures for pyloric stenosis include a history, physical examination, abdominal ultrasound, barium X-ray, endoscopy, arterial blood gases (ABGs; to identify and monitor pH disturbances), and blood chemistry (to identify and monitor fluid and electrolyte imbalances). Surgical repair called “pyloromyotomy” is recommended to open the sphincter, but balloon dilation may be used in high-surgical-risk infants. Additionally, fluid, electrolyte, and pH imbalances may need correction. Signs and symptoms usually resolve within 24 hours of surgical repair. In most cases, feedings are restarted within 8 hours of surgery.

Learning Points

Abdominal Pain

Abdominal pain can indicate a wide range of disorders in multiple systems, including the cardiovascular, gastrointestinal, reproductive, and renal systems. Identifying and treating serious issues such as myocardial infarction, **appendicitis**, and **peritonitis** are critical to positive patient outcomes. The location (**FIGURE 9-10**) and description (**TABLE 9-2**) of the abdominal pain are critical parts of that identification.

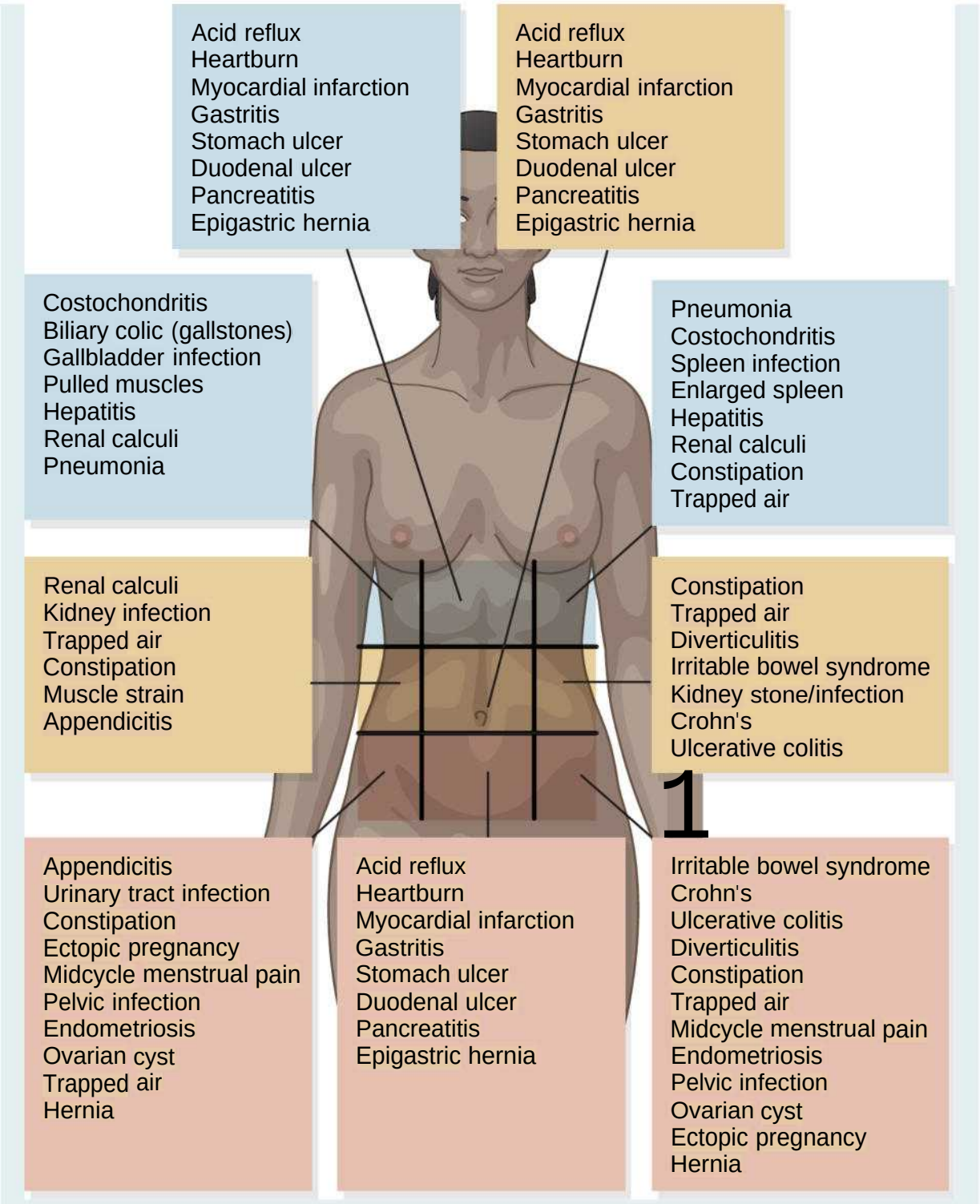


FIGURE 9-10 Common causes of abdominal pain.

Description

TABLE 9-2 Causes of Abdominal Pain

Causes	Onset	Location	Characteristics	Description	Radiation	Intensity
Appendicitis	Usually gradual but can be sudden	Periumbilical early; RLQ late	Diffuse early, localized late	Ache	None	++ to +++
Cholecystitis	Sudden	RUQ or MUQ	Localized	Cramping	Back or right shoulder	++
Acute pancreatitis	Sudden	Epigastric, upper abdominal	Localized	Blunt	Back	++ to +++
Diverticulitis	Gradual	LLQ	Localized	Ache	None	+ to ++
Perforated peptic ulcer	Sudden	Epigastric	Localized early, diffuse late	Burning sensation	None	+++
Small bowel obstruction	Gradual	Periumbilical	Diffuse	Cramping	None	++
Ruptured abdominal aortic aneurysm	Sudden	Abdominal back, flank	Diffuse	Tearing	None	+++
Gastroenteritis	Gradual	Periumbilical, epigastric	Diffuse	Cramping	None	+ to ++
Pelvic inflammation disease	Gradual	LQ, pelvic	Localized	Blunt	Upper thigh	++ to +++
Ruptured ectopic pregnancy	Gradual	LQ, pelvic	Localized	Sharp	None	++

Description

Abbreviations: LLQ: left lower quadrant; LQ: left quadrant; MUQ: middle upper quadrant; RLQ: right lower quadrant; RUQ: right upper quadrant.

Data from Abdullah, M., & Firmansyah, M.A. (2012). Diagnostic approach and management of acute abdominal pain. *Acta Medica Indonesiana, 44*(4), 344–350.

Dysphagia

Dysphagia, or difficulty swallowing, usually develops secondary to a condition that causes mechanical obstruction of the esophagus or impaired esophageal motility (**FIGURE 9-11**). Numerous conditions can lead to dysphagia:

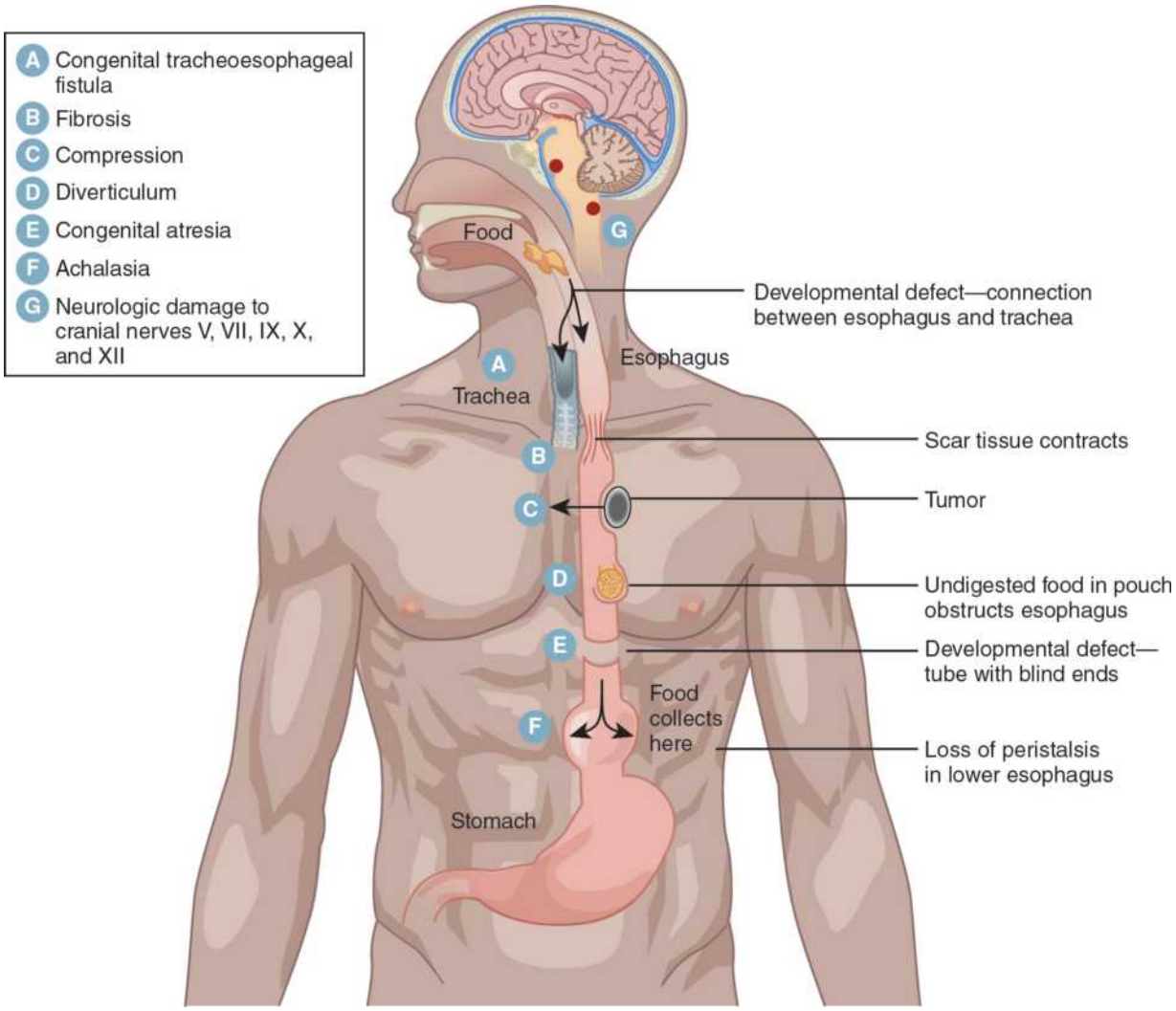


FIGURE 9-11 Causes of dysphagia.

Description

- Mechanical obstructions, including those caused by the following:
  - Congenital atresia (congenital separation of the upper and lower esophagus)
  - Esophageal stenosis or stricture (may be developmental or acquired)
  - Esophageal diverticula (outpouching of the esophageal wall)
  - Tumors (esophageal or of nearby structures)
- Neurologic disorders, including those caused by the following:
  - Stroke

- Cerebral damage (e.g., traumatic brain injury)
- Achalasia (failure of the LES to relax because of loss of innervations)
- Parkinson's disease
- Alzheimer's disease
- Huntington disease
- Cerebral palsy
- Multiple sclerosis
- Amyotrophic lateral sclerosis
- Guillain-Barré syndrome

- Muscular disorders, including those caused by muscular dystrophy

Dysphagia can also have iatrogenic causes, resulting from many head and neck surgeries and procedures (e.g., laryngectomy, tracheostomy, endotracheal intubation, esophageal dilatation, radiation) as well as medications. Medications that relax the muscles, suppress the nervous system, or damage the mucosa may cause dysphagia (e.g., sedatives, narcotics, antipsychotics, nonsteroidal anti-inflammatory drugs [NSAIDs], or potassium chloride tablets). Dysphagia has likewise been associated with several psychiatric conditions, including anxiety, depression, somatoform disorders, hypochondriasis, conversion disorders, and eating disorders.

Clinical manifestations include a sensation of food being stuck in the throat, choking, coughing, pocketing food in the cheeks, difficulty forming a food bolus, delayed swallowing, and painful swallowing (odynophagia). Dysphagia may also include difficulty swallowing liquids. This condition not only causes alterations in nutrition but also poses an aspiration risk.

Diagnostic procedures focus on identifying the underlying cause. They consist of a history, physical examination, barium swallow, chest and neck X-rays, esophageal pH measurement, esophageal manometry (pressure measurement), flexible endoscopic evaluation of swallowing with sensory testing (FEESST; uses a small lighted camera to view the mouth and throat while examining how the

swallowing mechanism responds to such stimuli as a puff of air, food, or liquids), videofluoroscopic swallow study (VFSS; a videotaped X-ray of the entire swallowing process in which foods or liquids along with the mineral barium are consumed), and esophagogastroduodenoscopy (EGD; visualization of the esophagus, stomach, and duodenum using a small lighted camera).

Treatment strategies are specific for the causative condition but usually include speech therapy. Additionally, interventions are employed to maintain nutritional status and prevent aspiration (e.g., soft or pureed foods, thickened liquids, small bites, no use of straws, or gastrostomy tube).

Vomiting

Vomiting, or **emesis**, is the involuntary or voluntary forceful ejection of chyme from the stomach up through the esophagus and out the mouth. Vomiting is a common event that results from a wide range of conditions. It may be protective (e.g., with drug overdose or infections) or result from reverse peristalsis (e.g., with intestinal obstructions). Increased intracranial pressure (see the *Neural Function* chapter) can cause sudden projectile vomiting. Additionally, vomiting may be associated with other symptoms such as severe pain (e.g., migraines or renal calculi). The medulla coordinates vomiting, and drugs, toxins, and chemicals can stimulate this vomiting center.

Regardless of the cause, vomiting requires the collaboration of several structures (**FIGURE 9-12**). Involuntary vomiting occurs through the following sequence:

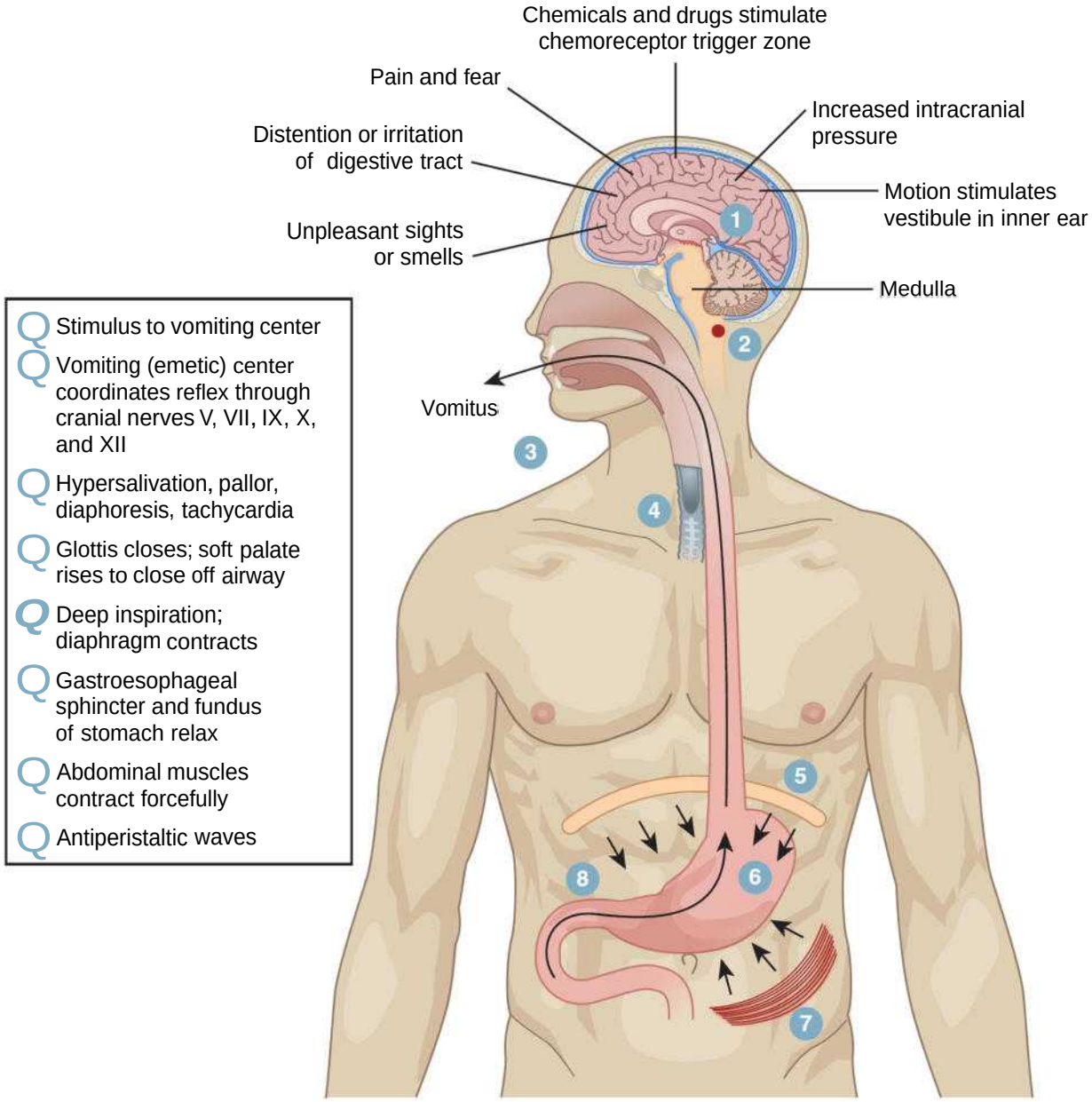


FIGURE 9-12 Vomiting reflex.

Description

1. A deep breath is taken.
2. The glottis closes, and the soft palate rises.
3. Respirations cease to minimize the risk of aspiration.
4. The gastroesophageal sphincter relaxes.

5. The abdominal muscles contract, squeezing the stomach against the diaphragm and forcing the chyme upward into the esophagus.
6. Reverse peristaltic waves eject chyme out of the mouth.

Vomiting may be preceded by **nausea** (a subjective urge to vomit) or **retching** (a strong unproductive effort to vomit). Recurrent vomiting can be exhausting because of the strong muscular contractions. Additionally, recurrent vomiting can lead to fluid, electrolyte, and pH imbalances (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter). Aspiration of chyme into the lungs can cause serious damage and inflammation. This event can occur if the individual is supine or unconscious when vomiting occurs. Aspiration can also occur when the vomiting or cough reflex is suppressed by drugs (e.g., anesthesia or narcotics) or disease (e.g., stroke).

The characteristics of the contents vomited (called **vomitus**) are significant and can illuminate the underlying cause of the vomiting event. Hematemesis describes the condition in which blood is present in the vomitus. Blood in vomitus has a characteristic brown granular appearance similar to coffee grounds. This appearance results from protein in the blood being partially digested in the stomach. Blood in the stomach is irritating to the gastric mucosa, so the stomach attempts to expel it. Hematemesis can occur from several conditions that can cause upper GI bleeding (e.g., gastric ulcers and esophageal varices). Yellow- or green-colored vomitus usually indicates the presence of bile. This type of vomitus can occur as a result of a GI tract obstruction. A deep brown color of vomitus may indicate content from the lower intestine, possibly fecal. This type of vomitus frequently results from intestinal obstruction. Conditions that impair gastric emptying (e.g., pyloric stenosis) can cause recurrent vomiting of undigested food.

The force with which the vomiting occurs is important. Projectile vomiting occurs when the vomitus exits the mouth with such force that it is propelled over a short but significant distance. It is often sudden, with excessive vomitus with each attack, and not preceded by nausea. Projectile vomiting is associated with intestinal obstructions,

delayed gastric emptying, increased intracranial pressure, poisoning, and overeating.

Diagnostic procedures for vomiting focus on identifying causative agents as well as fluid, electrolyte, and pH imbalances (usually metabolic alkalosis). These procedures vary and may include a history, physical examination, and blood chemistry, among others.

Treatment strategies center on the cessation of vomiting, maintaining hydration, restoring acid–base balance, and correcting electrolyte alterations. These strategies may vary depending on the severity of the vomiting:

- Antiemetic medications (e.g., dimenhydrinate [Dramamine], ondansetron [Zofran], and promethazine [Phenergan])
- Oral or intravenous fluid replacement
- Correcting any electrolyte imbalances (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter)
- Restoring acid–base balance (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter)

Hiatal Hernia

A **hiatal hernia** occurs when a section of the stomach protrudes upward through an opening (hiatus) in the diaphragm toward the thoracic cavity (**FIGURE 9-13**). The main types of hernias include sliding, rolling (i.e., paraesophageal), and mixed. In sliding hernias—the most common type—the gastroesophageal junction and portion of the stomach are above the diaphragm. With rolling hernias, a portion of the stomach is next to the esophagus, but the gastroesophageal junction is in the normal location.

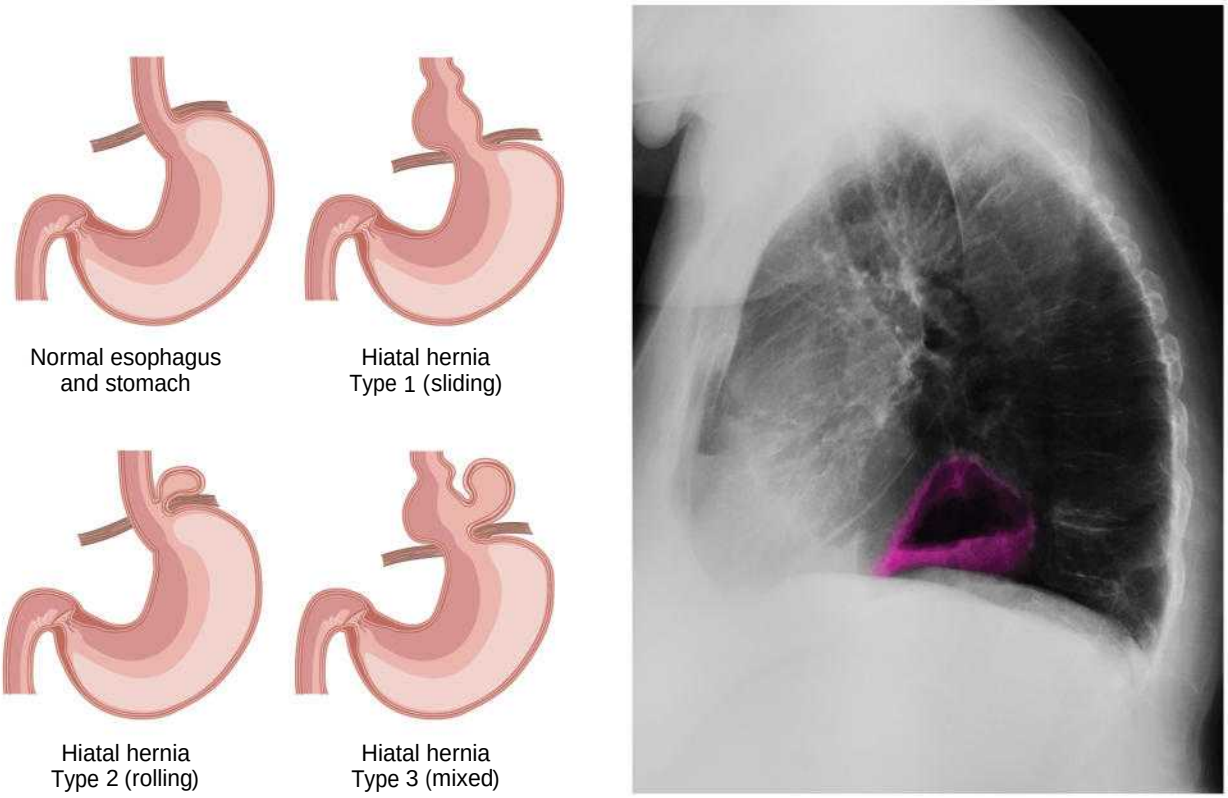


FIGURE 9-13 Hiatal hernia.

B. © Scott Camazine/Alamy Stock Photo

Description

The hiatus develops from the weakening of the diaphragm muscle, frequently resulting from increased intrathoracic pressure (e.g., coughing, vomiting, or straining to defecate) or increased intra-abdominal pressure (e.g., pregnancy and obesity). Other causes of a hiatus include trauma and congenital defects. Risk factors associated with hiatal hernias include advancing age and smoking. Small hiatal hernias may go undetected and rarely cause problems. In contrast, large hiatal hernias can cause chyme to reflux into the esophagus, irritating the mucosa. When the stomach protrudes through the diaphragm, it creates a pouch. Chyme collects in this pouch, causing mucosal inflammation. Complications include ulcer development, ischemia, perforation, hemorrhage, and obstruction.

A hiatal hernia by itself rarely causes symptoms. Clinical manifestations reflect inflammation of the esophagus and stomach

due to reflux of gastric acid, air, or bile. These manifestations include indigestion, heartburn (pyrosis), frequent belching, nausea, chest pain, strictures, and dysphagia. Manifestations worsen with recumbent positioning, eating (especially after large meals), bending over, and coughing. Conversely, these symptoms often improve when standing. Additionally, a soft upper abdominal mass (protruding stomach pouch) may be visualized especially when intra-abdominal pressure is increased (e.g., coughing, laughing, straining).

Diagnostic procedures for hiatal hernia consist of a history, physical examination, barium swallow, upper GI tract X-rays, manometry (measures the movement and pressure in the esophagus and stomach through a small nasogastric tube), and EGD. Treatment strategies focus on relieving inflammation by decreasing regurgitation of chyme and healing the mucosa. Such strategies include eating small frequent meals (six small meals per day), avoiding alcohol, assuming a high Fowler's position after meals, sleeping with the head of the bed elevated 6 inches, smoking cessation, losing weight (if overweight), reducing stress (stress increases gastrointestinal ischemia), as well as taking antacids, acid-reducing agents (e.g., histamine$_2$ blockers and proton pump inhibitors), and mucosal barrier agents. Surgical repair may be necessary for hiatal hernias not relieved by these strategies.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a condition where chyme periodically backs up from the stomach into the esophagus. Occasionally, bile can back up into the esophagus. The presence of these gastric secretions irritates the esophageal mucosa (**FIGURE 9-14**). This gastric backflow occurs because the LES relaxes abnormally or weakens. Factors that increase the risk for GERD or that can worsen GERD include:

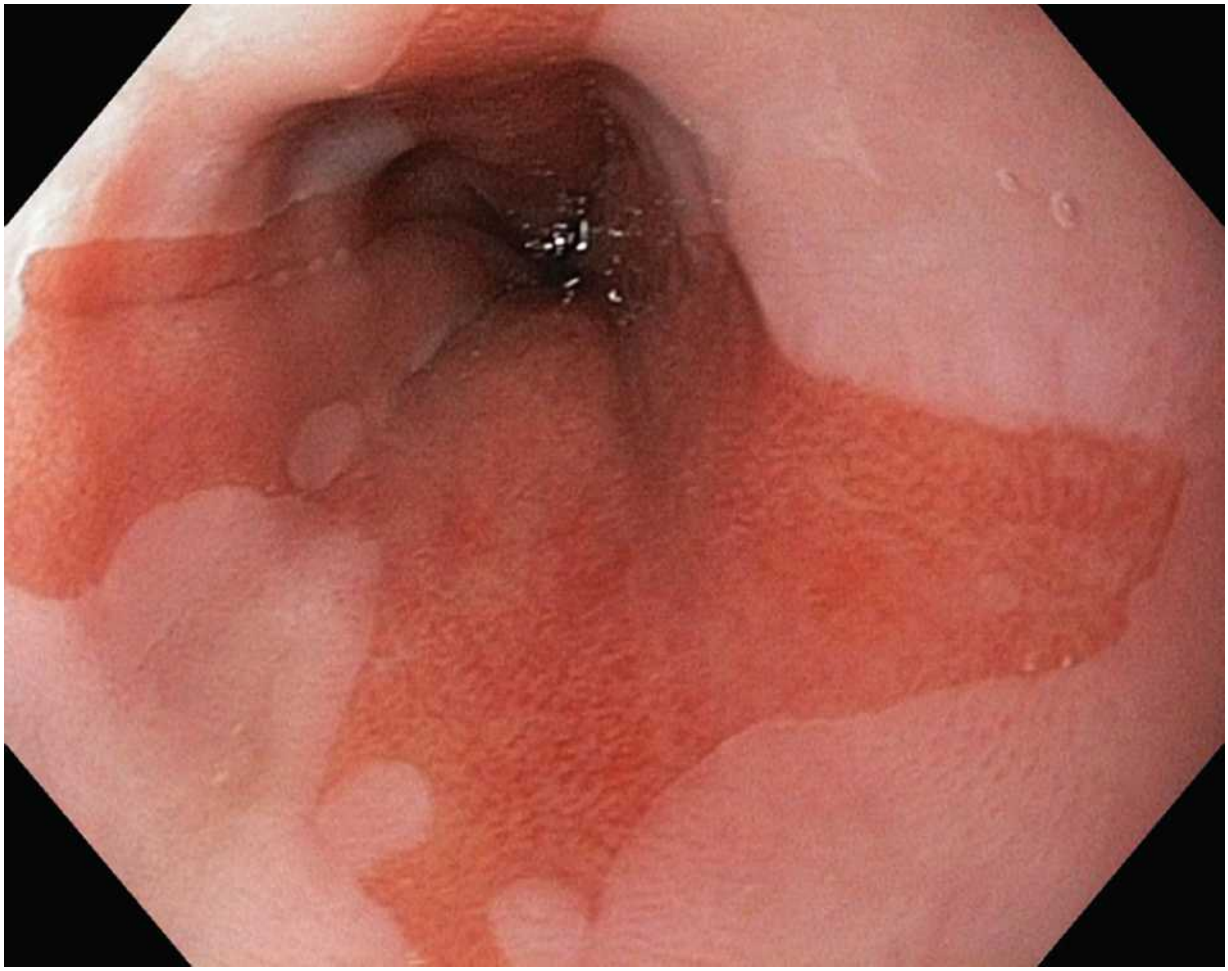


FIGURE 9-14 Gastroesophageal reflux disease.

© Gastrolab/Science Source

- Certain foods (e.g., chocolate, caffeine, carbonated beverages, citrus fruit, tomatoes, spicy or fatty foods, and peppermint)
- Alcohol consumption
- Nicotine
- Hiatal hernia
- Obesity
- Pregnancy
- Certain medications (e.g., nitrates, sedatives, beta-blockers, calcium-channel blockers, and anticholinergics)
- Nasogastric intubation

- Delayed gastric emptying

GERD varies in severity depending on the degree of LES weakness. Clinical manifestations include heartburn (early), epigastric pain (usually after a meal or when recombinant), dysphagia, odynophagia, nausea (usually after eating), dry cough, laryngitis, pharyngitis, regurgitation of food, and sensation of a lump in the throat. The pain associated with GERD is often confused with angina (see the *Cardiovascular Function* chapter) and may warrant steps to rule out cardiac disease. GERD can result in esophagitis, strictures, ulcerations, esophageal hemorrhage, Barrett esophagus (precancerous changes), esophageal cancer (usually adenocarcinoma), and chronic pulmonary disease (e.g., asthma).

Diagnostic procedures for GERD consist of a history, physical examination, barium swallow, EGD, esophageal pH monitoring, and esophagus manometry. Treatment strategies focus on balancing pressures and reducing acid, including:

- Avoiding triggers (e.g., precipitating foods, alcohol, coffee, and nicotine)
- Avoiding medications that cause gastric irritation (e.g., aspirin and NSAIDs)
- Avoiding clothing that is restrictive around the waist
- Eating small, frequent meals and avoiding eating 2–3 hours before bedtime
- Assuming a high Fowler's position for 2–3 hours after meals
- Losing weight
- Reducing stress
- Elevating the head of the bed approximately 6 inches
- Antacids (e.g., Maalox and Tums)
- Acid-reducing agents (e.g., proton pump inhibitors and histamine$_2$ blockers)
- Mucosal barrier agents
- Herbal therapies (e.g., licorice, slippery elm, and chamomile)

* Surgery (e.g., Nissen fundoplication or implantation of a Linx device)

Gastritis

Gastritis refers to an inflammation of the stomach's mucosal lining. The inflammation can involve the entire stomach or a region.

Gastritis can be either acute or chronic; each type has its own presentation. **Acute gastritis** can be a mild, transient irritation, or it can be a severe ulceration with hemorrhage. It usually develops suddenly and is typically accompanied by nausea and epigastric pain. Acute gastritis is characterized by the presence of polymorphonuclear leukocytes (PMNs) in the mucosa. **Chronic gastritis**, in contrast, develops gradually and can last for months to years. Some degree of atrophy or metaplasia is usually seen with chronic gastritis. It is likely to be accompanied by a dull epigastric pain and a sensation of fullness after minimal intake. In some cases, chronic gastritis can be asymptomatic.

Gastritis can be further categorized as erosive (resulting from an imbalance between the aggressive and defensive factors that maintain the integrity of the gastric mucosa) or nonerosive (generally caused by *Helicobacter pylori* infections). Gastroenteritis refers to inflammation of the stomach and intestines usually resulting from an infection or allergic reaction.

H. pylori infection is the most common cause of chronic gastritis. Although this bacterium readily spreads from person to person, the majority of those individuals infected do not experience gastritis. In other cases, *H. pylori* embeds itself in the mucosal layer, activating toxins and enzymes that cause inflammation (**FIGURE 9-15**). *H. pylori* is equipped with flagella that help it move, molecules that help it adhere, and enzymes that neutralize the gastric acid in its immediate vicinity. Why some people experience complications from *H. pylori* infections and others do not is not clear; however, genetic vulnerability and lifestyle behaviors (e.g., smoking and stress) may increase susceptibility to the bacterium's effects. Other organisms that can be transmitted through food and water contamination and cause gastritis include *E. coli*, *Salmonella*, rotavirus, and amoebas.

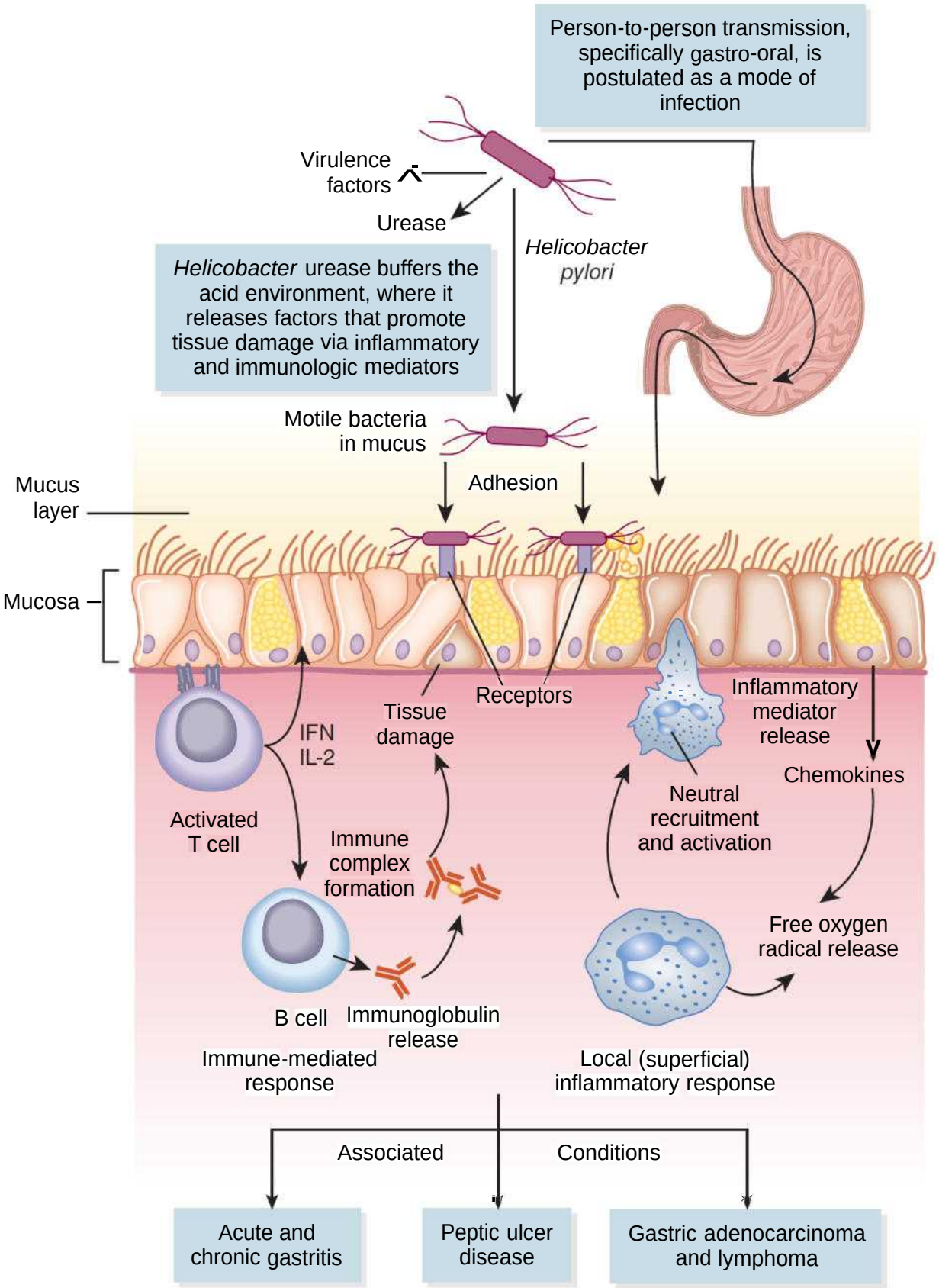

Person-to-person transmission, specifically gastro-oral, is postulated as a mode of infection
Virulence factors
Urease
Helicobacter pylori
Helicobacter urease buffers the acid environment, where it releases factors that promote tissue damage via inflammatory and immunologic mediators
Motile bacteria in mucus
Adhesion
Mucus layer
Mucosa
Receptors
Tissue damage
IFN
IL-2
Activated T cell
Immune complex formation
B cell
Immunoglobulin release
Immune-mediated response
Inflammatory mediator release
Chemokines
Neutral recruitment and activation
Free oxygen radical release
Local (superficial) inflammatory response
Associated Conditions
Acute and chronic gastritis
Peptic ulcer disease
Gastric adenocarcinoma and lymphoma

FIGURE 9-15 Pathogenesis of Helicobacter pylori.

Description

Long-term use of NSAIDs (e.g., ibuprofen [Advil, Motrin], naproxen [Aleve]) can cause acute and chronic gastritis by reducing cyclooxygenase, a key substance that helps preserve the mucosal lining. Excessive alcohol consumption can also irritate and erode the mucosal lining. Severe stress due to major surgery, traumatic injury, burns, or severe infections can cause acute gastritis because of tissue ischemia and decreased gastric motility resulting from the stress response (see the *Immunity* chapter). Autoimmune conditions (e.g., Hashimoto disease, Addison's disease, type 1 diabetes, and pernicious anemia) can create autoantibodies that attack the cells of the stomach lining. Other chronic diseases (e.g., human immunodeficiency virus, acquired immunodeficiency syndrome, **Crohn's disease**, parasitic infections, scleroderma, and liver or renal failure) may be associated with chronic gastritis.

The clinical manifestations of gastritis reflect inflammation of the mucosal lining. These symptoms include indigestion, heartburn, epigastric pain, abdominal cramping, nausea, vomiting, anorexia, fever, and malaise. The presence of hematemesis and dark, tarry stools can indicate ulceration and bleeding. Chronic gastritis increases the risk of peptic ulcers, gastric cancer, anemia, and hemorrhage.

Diagnostic procedures for gastritis consist of a history, physical examination, upper GI tract X-ray, EGD, serum *H. pylori* antibody levels, *H. pylori* breath test, complete blood count (CBC; to identify anemia), and stool analysis (*H. pylori* and **occult blood**). Acute gastritis is often self-limiting and resolves within 3 days. Treatment strategies vary depending on the underlying etiology. For instance, bacterial infections require antibiotic therapy. Chronic disease management is important to limit any complications associated with this inflammation. In addition to etiology-specific interventions, pharmacologic management may include antacids, acid-reducing agents, and mucosal barrier agents.

Peptic Ulcers

Peptic ulcer disease (PUD) refers to erosive lesions affecting the muscularis mucosae of the stomach or duodenum (which accounts for approximately 80% of cases) (see Figure 9-15; **FIGURE 9-16**). Ulcers vary in size and severity, ranging from superficial erosions to complete penetration through the GI tract wall.

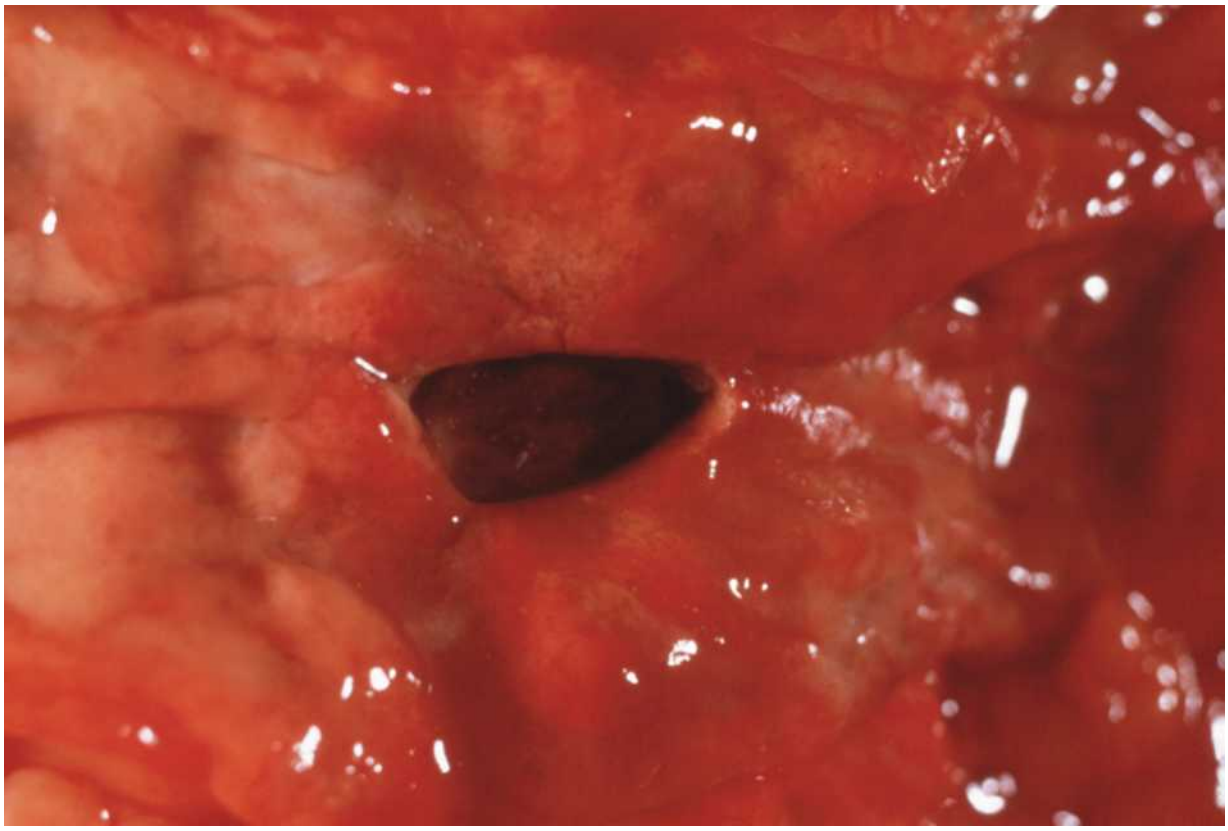


FIGURE 9-16 Peptic ulcer.

© CNRI/Science Source

The incidence of PUD has been declining in recent years, but it remains a common condition that affects approximately 4.6 million people in the United States each year (Anand, 2021). The most common risk factors for developing PUD are NSAID use and *H. pylori* infections. Other risk factors include chronic disease (especially pulmonary and renal), certain gastric tumors (e.g., those associated with Zollinger-Ellison syndrome), stress (acute or chronic), cigarette

smoking, alcohol use, family history, and certain medications (e.g., bisphosphonate derivatives, anticoagulants, selective serotonin reuptake inhibitors, and chemotherapy). Peptic ulcers can occur at any age but are most common among adults starting in middle age. Regardless of its etiology, PUD develops because of an imbalance between destructive forces (e.g., excess acid production) and protective mechanisms (e.g., decreased mucus production) induced by a secondary process rather than an innate defect.

Duodenal ulcers, the most common peptic ulcers, are usually associated with excessive acid or *H. pylori* infections. Individuals with duodenal ulcers typically present with epigastric pain that is usually absent when they awaken, appears mid-morning, and arouses them at night. This epigastric pain is relieved in the presence of food but returns 2–3 hours after eating. Hemorrhage may be the first manifestation in infants and young children.

Gastric ulcers (stomach ulcers), by comparison, are less frequent but deadlier. These ulcers are often associated with malignancy and NSAID use. In contrast to duodenal ulcers, the pain experienced with gastric ulcers typically worsens with eating.

Stress ulcers is a term used to describe PUD that develops because of a major physiological stressor on the body (e.g., large burns, trauma, sepsis, surgery, or head injury). Stress ulcers associated with burns are generally called **Curling ulcers**, whereas stress ulcers associated with head injuries are generally called **Cushing ulcers**. These types of ulcers develop due to local tissue ischemia, tissue acidosis, entry of bile salts into the stomach, and decreased GI motility. They most frequently develop in the stomach, and multiple ulcers can form within hours of the precipitating event. Often hemorrhage is the first indicator of a stress ulcer because the ulcer develops rapidly and tends to be masked by the primary problem. General complications of PUD may involve GI hemorrhage, obstruction, perforation, peritonitis, and gastric cancer.

PUD is often asymptomatic, with as few as half of individuals presenting with characteristic symptoms. When present, clinical manifestations are chronic and recurrent and resemble those

associated with other conditions of GI inflammation (e.g., gastritis and GERD):

- Epigastric or abdominal pain
- Abdominal cramping
- Heartburn
- Indigestion
- Chest pain
- Nausea and vomiting (may include hematemesis)
- Melena (dark, tarry stools)
- Fatigue
- Unexplained weight loss

Diagnosis relies on procedures to identify the presence of the ulcer, the underlying etiology, and complication development. These procedures include a history, physical examination, upper GI tract X-ray (i.e., barium swallow), EGD (including analysis for *H. pylori*), serum *H. pylori* antibody levels, urea breath test (determine the presence of *H. pylori)*, CBC (to identify anemia), stool analysis (*H. pylori* and occult blood), and serum gastrin levels (to rule out gastrinoma).

Treatment strategies include those discussed for gastritis. Additionally, surgical repair may be necessary if complications develop or the ulcer does not respond to drug therapy. Surgery may include procedures to reduce acid secretion combined with a procedure to ensure gastric drainage (e.g., vagotomy, antrectomy, hemigastrectomy, or partial gastrectomy). In cases of perforation, repair may include a laparoscopic surgical patch (e.g., omental) along with a thorough abdominal lavage to prevent peritonitis. Prevention is crucial with stress ulcers to improve outcomes. Prophylactic medications (e.g., acid-reducing agents) are administered to persons at risk for developing stress ulcers.

Cholelithiasis

Cholelithiasis, or gallstones, is a common condition (affecting 6% of men and 9% of women in the United States) in which stones (calculi) of varying sizes and shapes form inside the gallbladder (Tanaja, Lopez, & Meer, 2022) (**FIGURE 9-17**). Cholelithiasis is more common in fair-skinned women and Native American populations. Other risk factors include advancing age, obesity, diet (high fat, high cholesterol, and low fiber), rapid weight loss (like that associated with bariatric surgery), pregnancy, hormone replacement, certain chronic diseases (e.g., diabetes mellitus, hyperlipidemia, and liver disease), and long-term parenteral nutrition.



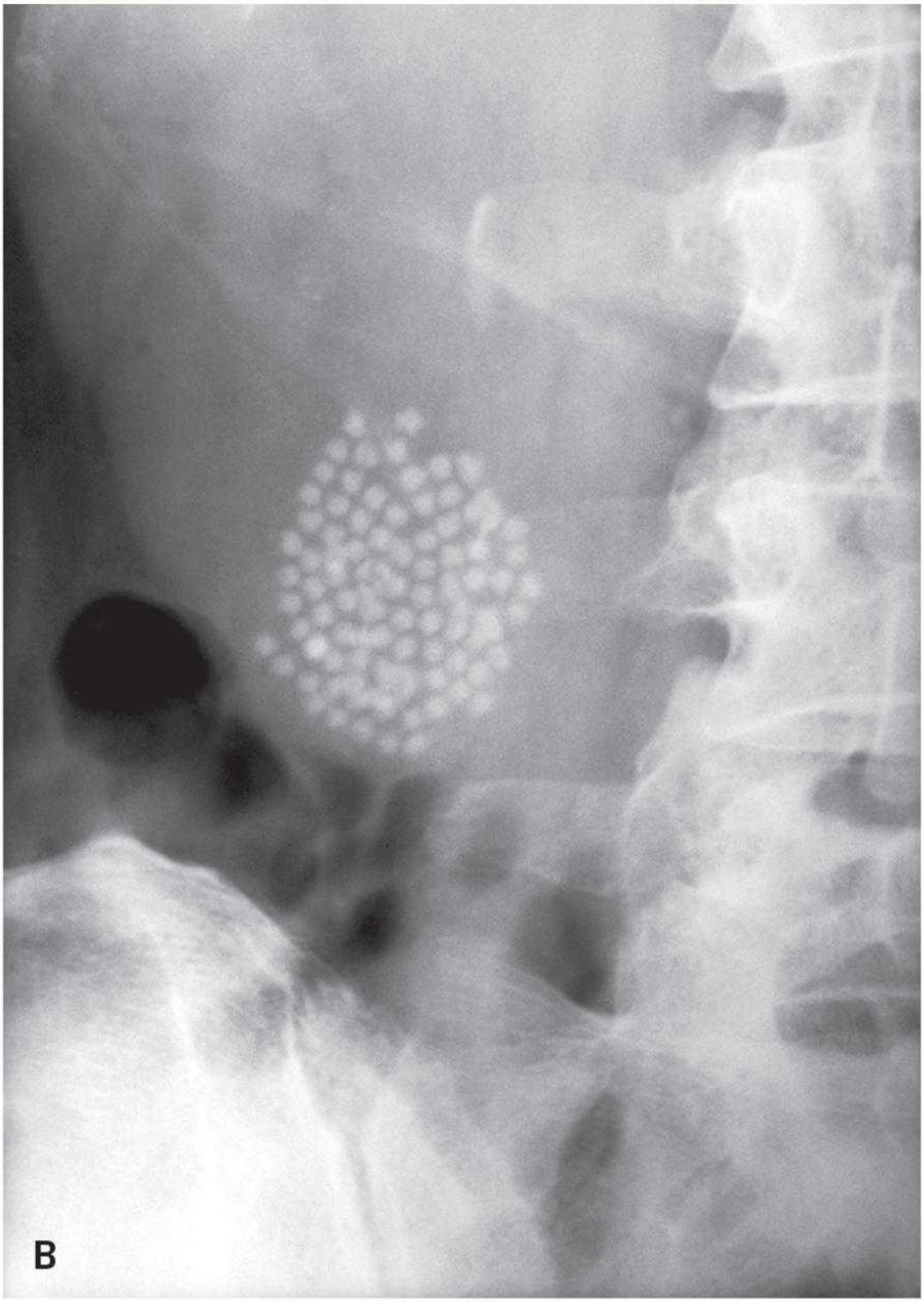


FIGURE 9-17 Cholelithiasis.

A: Courtesy of Leonard V. Crowley, MD, Century College; **B:** © Mediscan/Alamy Stock Photo

Three types of calculi can develop in the gallbladder or nearby ducts (**TABLE 9-3**; **FIGURE 9-18**), and the presence of calculi can cause inflammation or infection in the biliary system (**cholecystitis**). Biliary sludge as a result of gallbladder stasis often precedes cholelithiasis; it consists of calcium bilirubinate (main bile pigment), cholesterol microcrystals, and mucin (a family of large, heavily glycosylated proteins). Biliary sludge is usually asymptomatic and resolves without treatment; however, it can develop into calculi or obstruct ducts, leading to biliary colic, cholangitis (bile duct inflammation), or pancreatitis. Cholesterol calculi are usually a result of an overproduction of cholesterol by the liver and hypomotility or impaired emptying of the gallbladder. Bilirubin can crystalize, forming stones, in high concentrations.

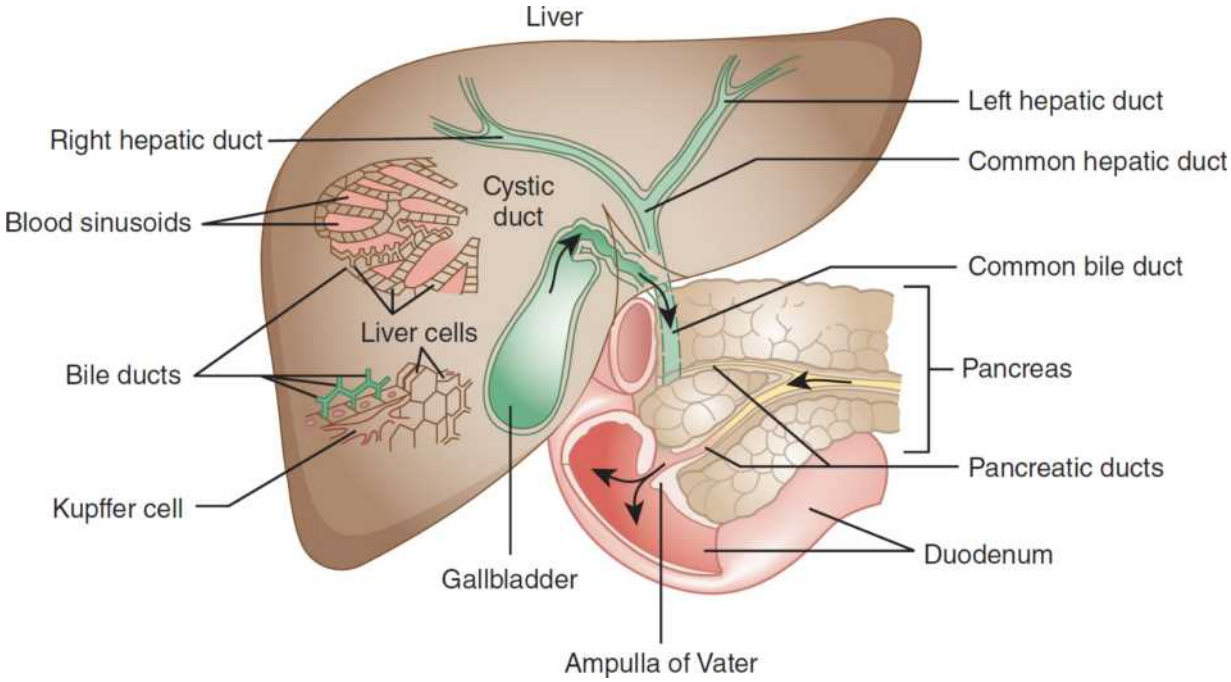


FIGURE 9-18 Location of cholelithiasis.

Description

TABLE 9-3	Types of Cholelithiasis

Type	Characteristics
Cholesterol	Most common Can be small or large, single, or multiple Can cause obstruction, pain (biliary colic), and jaundice Strong association with female hormones Increased incidence with obesity, extreme dieting, and hypercholesterolemia
Bilirubin (pigmented)	Usually multiple, small, black stones More common in Asians and in persons with chronic diseases that cause hemolysis (e.g., sickle cell anemia)
Mixed	Usually found in large numbers Bilirubin center surrounded by cholesterol and calcium

Small calculi are often asymptomatic and excreted with the bile. Larger calculi are likely to obstruct bile flow and cause clinical manifestations. Prolonged obstruction of bile flow can lead to acute cholecystitis (gallbladder inflammation), gallbladder rupture, fistula formation, gangrene, **hepatitis**, pancreatitis, and carcinoma. Gallstone disease is responsible for approximately 10,000 deaths annually in the United States—7,000 are attributed to acute complications and 3,000 are attributed to gallbladder cancer (Heuman, 2019). Manifestations of cholelithiasis include the following signs and symptoms:

- Biliary colic (abdominal cramping and pain that worsens after a fatty meal)
- Abdominal pain (especially in the right-upper and middle-upper quadrants; may radiate to the back or right shoulder)
- Abdominal distention
- Nausea and vomiting
- Jaundice (yellowing of the skin)
- Clay-colored stools (due to the lack of bile)
- Fever

- Leukocytosis
- Tachycardia
- Hypotension

Diagnostic procedures for cholelithiasis consist of a history, physical examination, abdominal ultrasound (most effective), abdominal X-ray, abdominal computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), percutaneous transhepatic cholangiogram (PTCA), bilirubin levels, liver function tests, CBC, pancreatic enzymes, and laparoscopy. Treatment strategies focus on removing the calculi, restoring bile flow, and preventing reoccurrence:

- Low-fat diet
- Medications to dissolve the calculi (e.g., bile acids)
- Antibiotic therapy (if infection is present)
- Nasogastric tube with intermittent suction (to facilitate abdominal decompression in the presence of an obstruction)
- Lithotripsy (e.g., extracorporeal shock wave)
- Surgically created opening for drainage (choledochostomy)
- Surgical removal, usually laparoscopically, of calculi or gallbladder (cholecystectomy)

Disorders of the Liver

Disorders of the liver are usually serious and often life threatening. The liver's involvement in so many of the body's activities results in a situation that can be complex to manage when this organ's functions become disrupted. Liver disorders are often acquired through ingestion of hepatotoxic substances (e.g., medications or alcohol) or infections.

Hepatitis

Hepatitis is an inflammation of the liver that can be caused by infections (usually viral), alcohol, medications (e.g., acetaminophen

[Tylenol], antiseizure agents, and antibiotics), or autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis, and scleroderma). Hepatitis can be acute, chronic, or fulminant (such as in liver failure). Additionally, this disease can be active or nonactive. Most individuals with nonviral hepatitis recover, but some develop liver failure, **liver cancer**, or **cirrhosis**. Nonviral hepatitis is not contagious, whereas viral hepatitis is contagious. Like individuals with nonviral hepatitis, those with viral hepatitis usually recover in time with no residual damage. However, advancing age and comorbidity increase the likelihood of liver failure, liver cancer, or cirrhosis in these patients. Both viral and nonviral hepatitis can result in hepatic cell destruction, necrosis, autolysis, hyperplasia, and scarring (fibrosis).

Viral hepatitis accounts for approximately 50% of all cases of acute hepatitis in the United States (Buggs & Dronen, 2017). Five types of viral hepatitis have been identified, each with its own characteristics (**TABLE 9-4**). In the United States, viral hepatitis is most commonly caused by hepatitis A, hepatitis B, and hepatitis C. According to the CDC (2022c), rates of hepatitis A decreased more than 95% from 1995 to 2011 as a result of vaccine development, but then rates increased by 140% from 2011 to 2017. The rates of hepatitis A then decreased from 2019 to 2020; however, the number of viral hepatitis cases reported in 2020 may be lower than in years before due to the COVID-19 pandemic. Until 2017, occasional outbreaks usually linked to imported food accounted for most of the hepatitis A rates; at that time, however, large person-to-person outbreaks began emerging among persons who use drugs and experience homelessness. Hepatitis B rates declined from 1990 to 2014 due to changes in vaccination recommendations, when rates started increasing again. After a decade of stable rates, acute hepatitis B abruptly decreased by 32% from 2019 to 2020, again likely due to the COVID-19 pandemic. Hepatitis C cases have rapidly increased since 2000, doubling since 2013 (124% increase), and increased 15% from 2019 to 2020. Following the 2020 surveillance report, the CDC worked to improve the viral hepatis outcomes by 2025 (CDC, 2022d). These efforts have started improving these outcomes and progress has been made in reaching the goals set.

TABLE 9-4 Types of Viral Hepatitis

Characteristic	Type A	Type B	Type C	Type D	Type E
Mode of transmission	Waterborne	Perinatal	Venereal	Venereal	Waterborne
	Fecal–oral	Blood/skin	Blood/skin	Blood	Fecal–oral
	Venereal	Venereal			Perinatal
Incubation period (range in days)	15–42	42–160	14–160	28–180	14–56
Onset	Abrupt	Insidious	Insidious	Insidious	Abrupt
Symptoms					
Fever	Common	Uncommon	Uncommon	Common	Common
Nausea/vomiting	Common	Common	Common	Common	Common
Jaundice	More common in adults than in children	Occasionally	Uncommon	Common	Common
Outcome					
Severity	Mild	Moderate	Mild	Moderate to severe	Severe
Fulminating hepatitis	< 0.5%	> 1%	Rare	3–4% with coinfection with hepatitis B	0.3–3% 20% in pregnant women
Mortality rate	Low (< 1%)	Low (1–3%)	Low (2%)	High (5%)	Moderate; high with pregnancy
Chronic hepatitis	No	Yes (5–10%)	Yes (80%)	< 5% with coinfection 80% with superinfection	Rare (usually associated with immunodeficiency)
Carrier state	No	Yes (1 million in United States)	Yes	Yes	No
Relapse	Yes	Yes	Persistent	Unknown	Unknown
Carcinoma	No	Yes (25–40%)	Yes (25–30%)	No increase above that for hepatitis B	Unknown but not likely
Develop cirrhosis	No	40%	30%	Yes, with superinfection	Rare
Source of virus	Feces	Blood/blood-derived body fluids	Blood/blood-derived body fluids	Blood/blood-derived body fluids	Feces
Chronic infection	No	Yes	Yes	Yes	Yes
Prevention	Pre-/post-exposure immunization	Pre-/post-exposure immunization	Blood donor screening; risk behavior modification	Pre-/post-exposure immunization; risk behavior modification	Ensure safe drinking water

Description

Injection drug use has been associated with the climbing rates of hepatitis B and C. Rare in the United States, the hepatitis D virus

requires the hepatitis B virus for replication. Hepatitis E is rare in the United States and more common in countries with poor sanitation.

Acute hepatitis proceeds through four distinct phases—an asymptomatic incubation phase and three symptomatic phases. Clinical manifestations for each symptomatic phase include the following signs and symptoms:

- Prodromal phase: Starts 2 weeks after exposure to the virus; includes viral symptoms, such as nausea, vomiting, malaise, anorexia, low-grade fever, and headache
- Icteric phase: Begins 1–2 weeks after the prodromal phase and lasts up to 6 weeks; includes jaundice, dark tea-colored urine (bilirubinuria) or clay-colored stools (due to lack of bilirubin), hepatomegaly, and right upper quadrant pain
- Recovery phase: Resolution of jaundice approximately 6–8 weeks after exposure; the liver may remain enlarged for as long as 3 months

Chronic hepatitis is characterized by continued hepatic disease lasting longer than 6 months. Its symptom severity and disease progression vary depending on the degree of liver damage. An individual can live with chronic hepatitis for years, but his or her health can quickly deteriorate with declining liver integrity. Fulminant hepatitis is an uncommon, rapidly progressing form that can quickly lead to liver failure, hepatic encephalopathy, or death within 3 weeks.

Diagnostic procedures for hepatitis include a history, physical examination, serum hepatitis profile, liver function tests, clotting studies, liver biopsy, and abdominal ultrasound. The enhanced liver fibrosis (ELF) serological panel includes hyaluronic acid, tissue inhibitor of matrix metalloproteinase-1, and amino-terminal propeptide of type III procollagen. The ELF panel is effective in detecting liver fibrosis present in liver diseases such as hepatitis (Fernandes et al., 2015).

Treatment strategies focus on prevention, with vaccinations being the cornerstone of hepatitis prevention. Vaccinations are available for hepatitis A and B. Hepatitis A vaccination is recommended for all

children starting at age 1 year, travelers to certain countries, men who have sex with men (MSM), intravenous drug users, persons with long-term liver disease, persons requiring repeated blood transfusions (e.g., those with hemophilia), and others at risk for exposure (e.g., living with someone who is hepatitis A positive). Hepatitis B vaccination is recommended for all infants beginning at birth, older children and adolescents who were not vaccinated previously, and adults at risk of contracting this form of hepatitis (e.g., healthcare workers, MSM, and intravenous drug users) as well as those at risk for contracting hepatitis D. Prevention also includes limiting exposure to the virus (e.g., by limiting exposure to blood, body fluids, and feces).

Once viral hepatitis is contracted, there is no method of destroying the virus. Thus, treatment is mostly supportive. Most cases of hepatitis A and E will resolve with no treatment. The other types of viral hepatitis can be treated with interferon injections to improve the immune response (see the *Immunity* chapter) and antiviral medications to decrease viral replication. Additional strategies include rest, adequate nutrition (a diet high in carbohydrates, protein, and vitamins), increased hydration, paracentesis (needle aspiration of fluid accumulation in the abdomen), and liver transplant. Education should include modes of transmission and strategies to decrease spread to self and others (e.g., good personal hygiene, cooking foods properly, treating water, not sharing needles).

Cirrhosis

Cirrhosis refers to chronic, progressive, irreversible, diffuse damage to the liver resulting in decreased liver function (**FIGURE 9-19**). With cirrhosis, regenerative nodules surrounded by fibrotic bands develop. In the United States, cirrhosis is estimated to affect 1 in 400 adults, but the actual numbers are thought to be higher because many people are not diagnosed (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], n.d.c). Cirrhosis is more common in adults ages 45 to 54, men, and persons with type 2 diabetes. This condition can be caused by hepatitis and all those factors that can lead to hepatitis (e.g., alcohol abuse, hepatotoxic

medications, and autoimmune conditions). Hepatitis C infection and chronic alcohol abuse are the most frequent causes of cirrhosis in the United States (Wolf, 2020). Hepatitis B often causes cirrhosis in Asia and Africa. Eventually, the damage leads to fibrosis, nodule formation, impaired blood flow, and bile obstruction that can result in liver failure. The rate of disease progression varies. Cirrhosis may take as long as 40 years to develop, and it can occur even with the removal of the underlying cause.



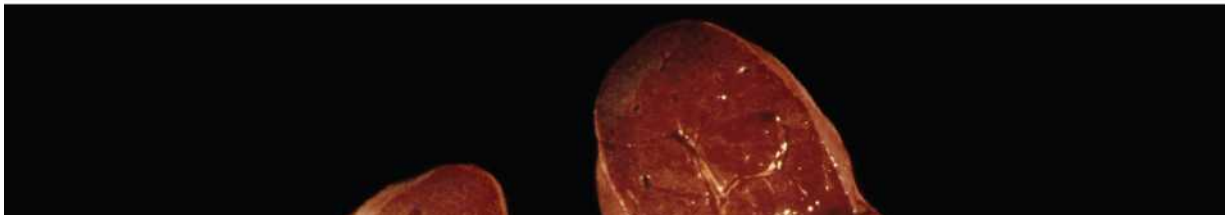




FIGURE 9-19 **(A)** Cirrhosis. **(B)** A normal liver.

A. © Martin M. Rotker/Science Source; **B.** © Prof. Ren?? Abelanet/CNRI/Science Source

Clinical manifestations of cirrhosis are similar regardless of the underlying cause. These manifestations reflect a failure of the liver to accomplish its many functions (**FIGURE 9-20**). The underlying mechanisms are complex given the diverse functions of the liver (**FIGURE 9-21**). Pressures rise as the hepatic artery and the portal vein become constricted by scar tissue (**portal hypertension**). Veins become engorged and varicosities (see the *Cardiovascular Function* chapter) commonly develop in the esophagus (**FIGURE 9-22**) and abdomen. Nearby organs utilizing the same circulation (e.g., the spleen, pancreas, and stomach) enlarge as pressures rise. Bleeding, either slow or severe, can occur along these overstretched vessels—particularly in the esophagus. Esophageal bleeding has a high mortality and reoccurrence rate. Fluid accumulates in the peritoneal cavity (a condition referred to as **ascites**) as the portal hypertension pushes fluid back into the abdominal cavity and the damaged liver can no longer produce sufficient amounts of albumin (a protein responsible for maintaining colloidal pressure and fluid balance in the vessels; see the *Fluid, Electrolyte, and Acid–Base Homeostasis*

chapter). Changes in protein metabolism result in decreased protein clotting factors, muscle wasting, and hyperlipidemia. Changes in glucose metabolism can lead to hyperglycemia or hypoglycemia.

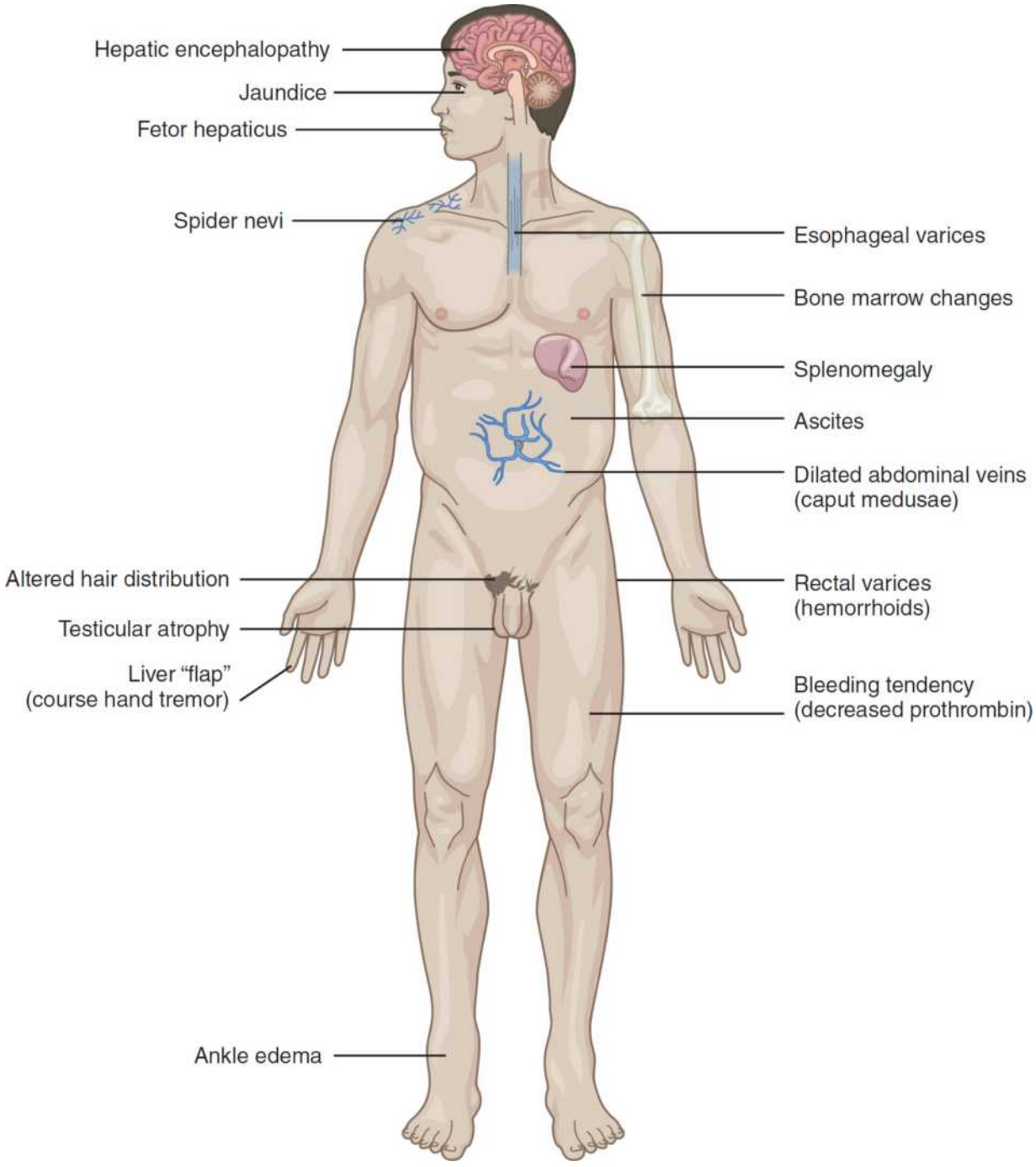


FIGURE 9-20 Effects of cirrhosis.

Description

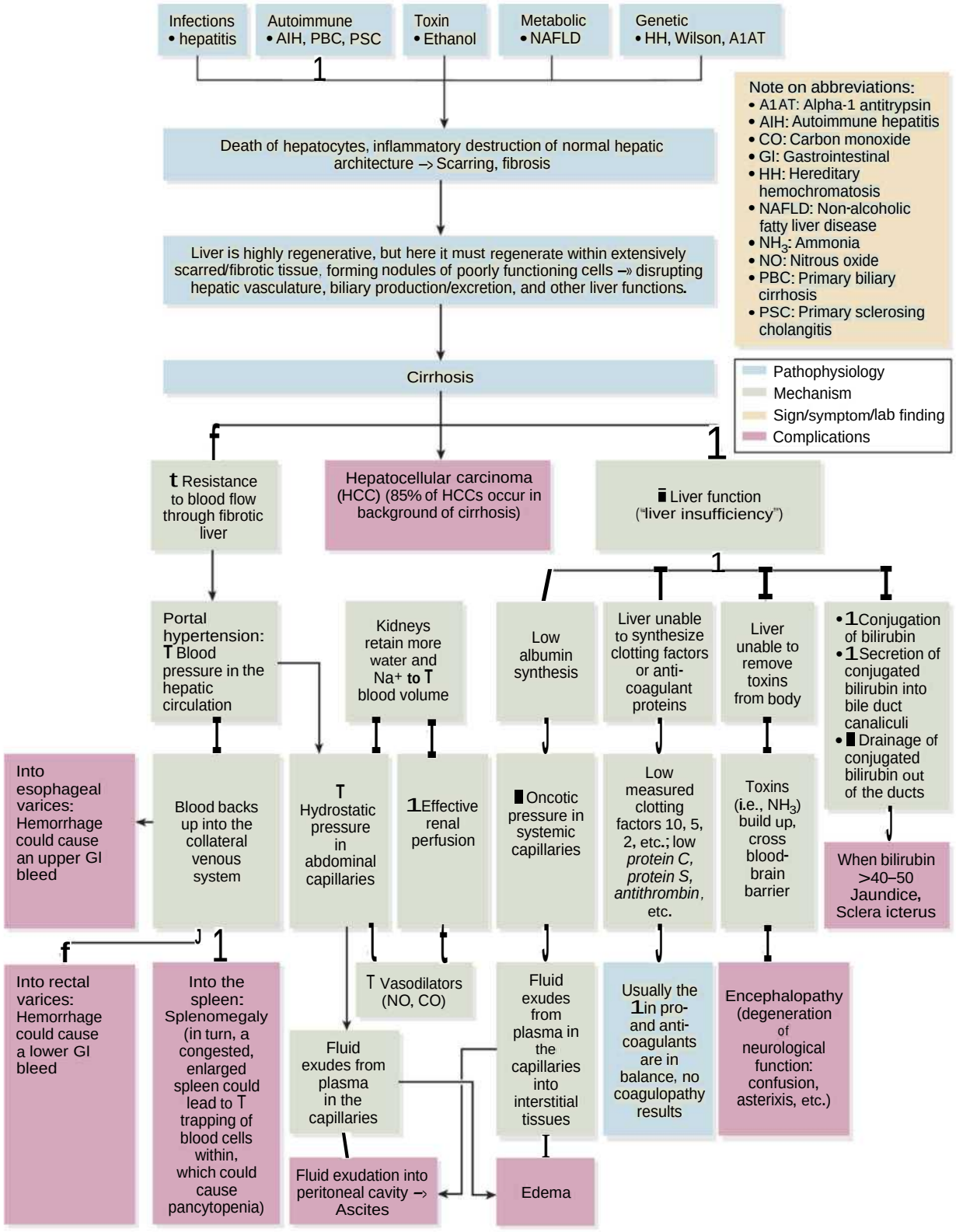


FIGURE 9-21 Pathogenesis and complications of cirrhosis.

Description

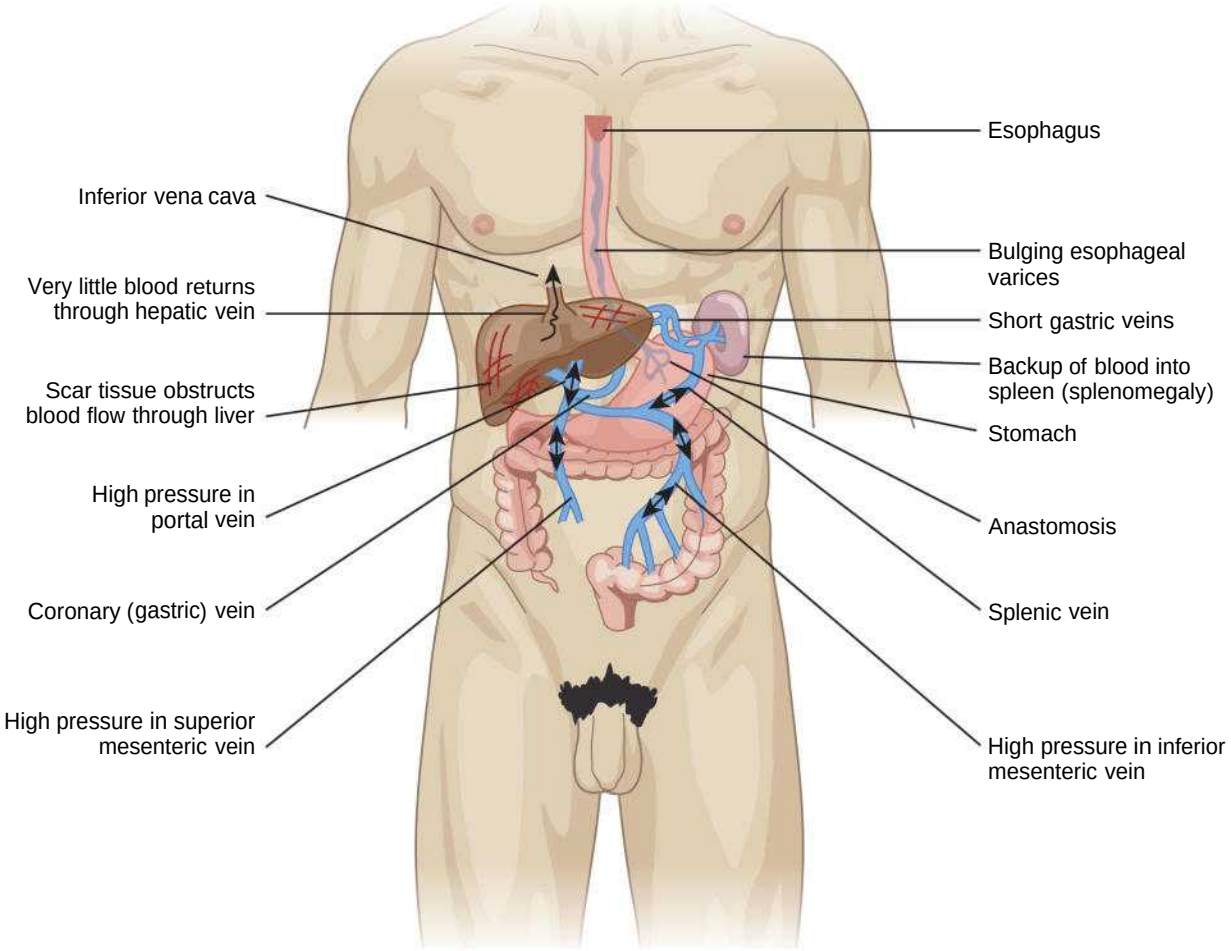


FIGURE 9-22 Development of esophageal varices.

Description

application to practice

K.S. is a 35-year-old man who has been homeless for the past 5 years. He presents to the health department complaining of flu-like symptoms and abdominal pain. K.S. has multiple tattoos and piercings. He admits to intravenous drug use and unprotected sexual behavior with multiple partners. Blood tests reveal that K.S.'s liver enzymes are elevated. The healthcare provider suspects some type of hepatitis.

1. Considering K.S.'s lifestyle, which type or types of hepatitis has he most likely contracted?
   a. Hepatitis A
   b. Hepatitis B
   c. Hepatitis C
   d. Hepatitis B or hepatitis C
2. How would you expect a differential diagnosis of hepatitis to be confirmed?

a. Presence of viral particles in the stool
b. Presence of the specific hepatitis virus in the blood
c. Presence of the specific hepatitis antibodies in the blood
d. Development of jaundice

Tests confirm that K.S. has hepatitis B, and treatment is initiated. K.S. returns to the health department 2 weeks later with his girlfriend, who is exhibiting similar symptoms.

1. Which of the following factors likely explains the onset of the girlfriend's symptoms?
   a. They probably ate the same food.
   b. They likely obtained the virus from contaminated water.
   c. They probably infected each other through sexual contact or drug activity.
   d. They likely became infected because of poor living conditions (Offord, 2017).

Bile accumulation in the liver causes inflammation and necrosis. Because it cannot flow through the duct system to the intestine, bile enters the bloodstream and causes **jaundice**. Fats cannot be digested, and fat-soluble vitamins cannot be absorbed without the presence of bile. Additionally, the stools become clay colored without the presence of bile. The kidneys attempt to compensate for the excessive bile in the blood by increasing excretion, causing the urine to become dark. The excessive bile is also excreted in the sweat, causing bile salts to accumulate on the skin; these bile salts cause intense itching.

Estrogen builds up in both sexes, as the liver can no longer inactivate the hormone. Excessive estrogen produces female characteristics in men and irregular menstruation in women. Numerous toxins and waste products also accumulate as the liver fails to detoxify the blood. In particular, the buildup of ammonia produces neurologic impairment that presents as confusion, disorientation, and hand tremors.

Ulcers and GI bleeding occur as the excessive bile and inflammation impair the mucosa. GI bleeding, in combination with a high-protein diet, renal failure, and infection, can cause protein levels to increase. In turn, these excessive protein levels lead to the rapid onset of encephalopathy. Spontaneous bacterial peritonitis may also occur because of the compromised host defenses and bacterial

overgrowth common in persons with cirrhosis. Cirrhosis also increases the risk of other bacterial infections, such as urinary tract infections and pneumonia. Other complications include liver cancer and failure, osteoporosis, cholelithiasis, malnutrition, mediation issues (e.g., sensitivity and toxicity), insulin resistance, and type 2 diabetes.

Diagnostic procedures for cirrhosis include those to identify the condition, as well as the underlying cause and complication development to guide treatment. These procedures entail a history, physical examination, liver biopsy, abdominal X-ray, abdominal ultrasound, abdominal CT, abdominal magnetic resonance imaging (MRI), CBC, liver enzyme panel, EGD, clotting studies, serum hepatitis profile, autoimmune panel (e.g., antinuclear antibody, anti-smooth muscle antibody, and anti-mitochondrial antibody tests), stool examination (for occult blood), and endoscopy (to identify esophageal varices). The ELF panel can also be used to identify the presence of fibrosis.

Treatment strategies for cirrhosis are complex and focus on slowing the progression and managing complications. Hepatitis-related cirrhosis is treated with antiviral agents and interferon. Alcohol, drugs, and hepatotoxic medications should be completely avoided. If hepatotoxic medications are necessary, dosing may need to be adjusted to prevent further damage. Hepatitis vaccinations should be administered to prevent the patient from contracting conditions that could worsen liver damage. Nutritional imbalances (usually treated with total parenteral nutrition [TPN]) and metabolic dysfunctions are corrected to manage complications and promote optimal health. Bile acid–binding agents can aid bile excretion. Portal hypertension is treated with a surgically implanted shunt. Fluid restriction, a low-sodium diet, diuretics, paracentesis, and shunts may be used to treat ascites. Esophageal varices are treated with endoscopic bands, shunts, or sclerotherapy. Antacids and acid-reducing agents can minimize GI inflammation. Strategies to treat encephalopathy are directed at eliminating the source of protein breakdown. Lactulose, a type of laxative, can promote ammonia excretion in the stool. Antibiotics can be given to suppress intestinal flora and decrease endogenous ammonia production.

A liver transplant usually offers the best outcome for individuals with cirrhosis, but not all patients are candidates for this therapy. Alcoholics must refrain from all alcohol consumption for a minimum of 6 months to be considered for transplant. Some hepatitis infections (hepatitis B more than hepatitis C) can return after transplant, so patients with such infections may not be considered as good candidates for this treatment. Additionally, patients with any evidence of cancer are not considered transplant candidates.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) describes a condition where fat accumulates in liver cells (hepatocytes) but not as a result of alcohol consumption. The liver normally contains some fat, but if more than 5% to 10% of the liver's weight is fat, then the liver is considered fatty (i.e., steatosis). The two types of NAFLD include simple fatty liver and nonalcoholic steatohepatitis (NASH). Simple fatty liver, also called "nonalcoholic fatty liver" (NAFL), is the most common form and involves the presence of fat in the liver but little or no inflammation or liver damage. NAFL does not progress to liver damage or complications. The more severe form, NASH, can cause the liver to swell and become damaged as a result of lipotoxicity and inflammation (i.e., hepatitis). The inflammation and damage can cause fibrosis, potentially leading to cirrhosis and liver cancer.

NAFLD is one of the most common causes of liver disease in the United States, affecting an estimated 100 million individuals (NIDDK, n.d.d). Although it can occur at any age, risk increases with age. Between 30% and 40% of adults have NAFLD, and NAFLD is the most common form of liver disease in children, with rates more than doubling over the past 20 years. Approximately 20% of all patients with NAFLD have NASH. NAFLD is more common in individuals who are obese (affecting 30% to 90% of these individuals) and/or have type 2 diabetes (affecting 40% to 80% of these patients). NAFLD is most common in Hispanics, followed by Caucasians; it is less common in African Americans. Asian Americans are more likely to develop NAFLD in the absence of obesity. Other risk factors include dyslipidemia, rapid weight loss, and use of certain medications (e.g.,

antiarrhythmic agents, glucocorticoids, antiretroviral therapy, and hormone modulators).

The pathogenesis of NAFLD is poorly understood but seems to be linked to insulin resistance, such as that seen with obesity or metabolic syndrome. Possible mechanisms for steatosis include reduced synthesis of very low-density lipoprotein (VLDL) and increased hepatic triglyceride synthesis, possibly due to decreased oxidation of fatty acids or increased free fatty acid delivery to the liver. Inflammation is thought to result from lipid peroxidative damage to cell membranes. These changes stimulate hepatic stellate cells that store vitamin A and likely help maintain the normal basement membrane–type matrix, resulting in fibrosis. Genetics may also play a role.

Most patients are asymptomatic. When present, clinical manifestations of NAFLD include fatigue, malaise, anorexia, nausea, and right upper quadrant abdominal discomfort. Hepatomegaly, splenomegaly, portal hypertension, and cirrhosis may develop.

Diagnosis of NAFLD includes procedures to identify the condition, rule out other liver diseases (e.g., hepatitis and cirrhosis), and determine complication development. Distinguishing NAFLD from alcoholic hepatitis is difficult. Alcohol use should be ruled out during a history. Additionally, differentiating NAFL from NASH is challenging, and elevated liver enzymes are not a sensitive predictor of NASH. The presence of metabolic syndrome (obesity, dyslipidemia, hypertension, and glucose intolerance) as well as elevated ferritin (iron stores) increases the likelihood that the individual has NASH as opposed to NAFLD. Other diagnostic procedures include a physical examination, serum hepatitis profile, ELF, abdominal ultrasound, abdominal CT, abdominal MRI, and liver biopsy.

Treatment strategies for NAFLD focus on eliminating and managing the underlying cause and risk factors. These strategies include weight loss, healthy diet (e.g., low fat, cholesterol, and calories; smaller portions), physical activity, avoiding alcohol, managing dyslipidemia, and controlling diabetes. Although no specific medications have been approved to treat NAFLD, some may improve the condition. For example, thiazolidinediones (e.g., pioglitazone [Actos])—medications

used to treat type 2 diabetes—have been found to improve NASH in people who do not have diabetes. Other diabetes medications have not demonstrated similar results. Vitamin E, especially in addition to Actos, has also been found to improve NASH.

Disorders of the Pancreas

Disorders of the pancreas are frequently grave. The pancreas has a significant role in maintaining homeostasis by regulating electrolytes, water, and glucose. Consequently, conditions affecting the pancreas can have a global impact on the individual's health. Most often, the gallbladder is affected by pancreatic disorders because of the intricate relationship between these two organs.

Pancreatitis

Pancreatitis is an inflammation of the pancreas that can be either acute or chronic. Causes of pancreatitis include cholelithiasis (the most common acute cause), alcohol abuse (the most common chronic cause), biliary dysfunction, hepatotoxic drugs, metabolic disorders (e.g., hypertriglyceridemia and hyperglycemia), trauma, acute kidney injury, endocrine disorders (e.g., hyperthyroidism), pancreatic tumors, and penetrating peptic ulcer. Pancreatitis is more common in men, African Americans, those with a family history of pancreatitis, and smokers.

Emerging Research: Nonalcoholic Fatty Liver Disease

As the exact mechanisms that underlie nonalcoholic fatty liver disease (NAFLD) are not completely understood, treatment is mostly supportive and not curative. In recent years, new drugs that act on various pathophysiological processes involved in nonalcoholic steatohepatitis (NASH), the most severe form, have been developed. These drugs improve metabolic activity, suppress the inflammatory process, and minimize fibrosis development. They include peroxisome proliferator-activated receptor-alpha, glucagon-like peptide-1 modulators, and farnesoid X receptor ligands. These new therapies have the potential to resolve the NASH as well as reverse preexisting fibrosis (Geier & Rau, 2017;

NIDDK, n.d.d). A daily dose of the natural form of vitamin E (found in food sources as opposed to synthetically made) improved NASH in multiple clinical trials (NIDDK, n.d.d).

When the pancreas is injured or its function is disrupted, pancreatic enzymes (e.g., phospholipase A, lipase, and elastase) leak into the pancreatic tissue, initiate autodigestion, and activate the complement system and the inflammatory process. Trypsin and elastase are activated proteases that, along with lipase, break down tissue and cell membranes, resulting in edema, vascular damage, hemorrhage, and necrosis. Pancreatic tissue is replaced by fibrosis, which causes exocrine and endocrine changes and dysfunction of the islets of Langerhans. Pancreatic enzymes and cytokines can enter the peritoneal cavity, causing a chemical burn and third spacing of fluid. These enzymes and cytokines can also enter the systemic circulation.

Acute pancreatitis is considered a medical emergency (**FIGURE 9-23**). The mortality rate from this condition is approximately 15%, but the rate increases with advancing age and comorbidity. The following serious complications can also develop with acute or chronic pancreatitis:

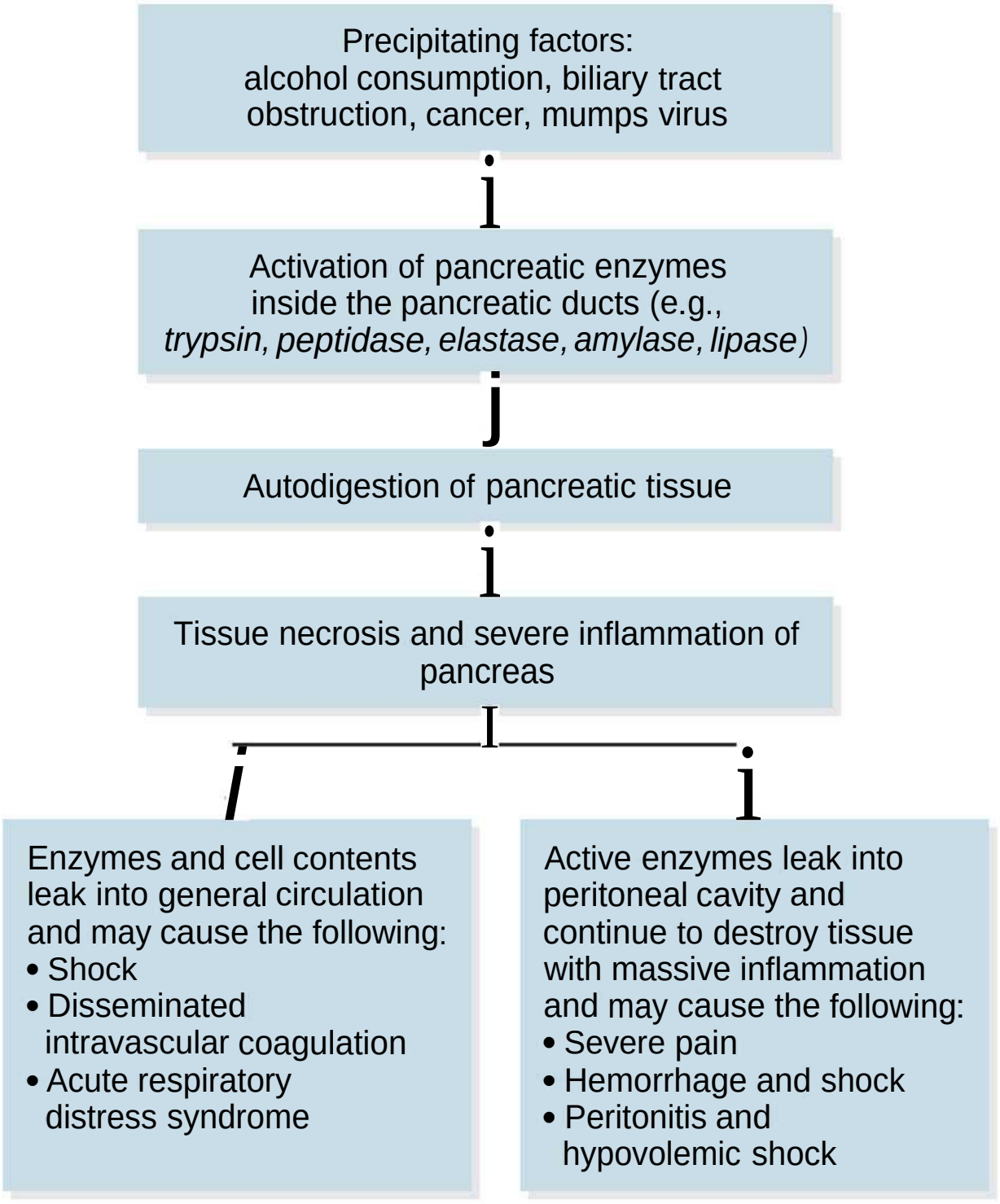


FIGURE 9-23 Effects of acute pancreatitis.

Description

- Acute respiratory distress syndrome (ARDS; see the *Respiratory Function* chapter): Acute pancreatitis can trigger the release of chemicals that lead to this life-threatening event.
- Diabetes mellitus (see the *Endocrine Function* chapter): Chronic pancreatitis can damage insulin-producing cells in the pancreas.
- Infection: Acute pancreatitis can make the pancreas vulnerable to bacteria and infection; pancreatic infections are serious and require intensive treatment such as surgery to remove the infected tissue.
- Shock (see the *Cardiovascular Function* chapter): Infection and the release of miscellaneous immune mediators can trigger shock in patients with acute pancreatitis.
- Disseminated intravascular coagulation (DIC; see the *Hematopoietic Function* chapter): DIC can be triggered by similar pathways as those that trigger ARDS and shock.
- Renal failure (see the *Urinary Function* chapter): Shock and activation of the renin–angiotensin system lead to decreased renal perfusion.
- Malnutrition: Both acute and chronic pancreatitis can decrease pancreatic enzyme production, and these enzymes are necessary for digestion and absorption; malnutrition and weight loss may occur, even when food intake remains stable.
- Pancreatic cancer: Long-standing inflammation caused by chronic pancreatitis can initiate cellular mutations.
- Pseudocyst or abscess: Acute pancreatitis can cause pancreatic fluids and necrotic debris to collect in cyst-like pockets; a large pseudocyst or abscess that ruptures can cause complications such as internal bleeding and infection (e.g., peritonitis).

Additionally, repeated episodes of acute pancreatitis can lead to chronic pancreatitis. Clinical manifestations vary depending on whether the pancreatitis is acute or chronic. Manifestations of acute pancreatitis are usually sudden and severe; in contrast, manifestations of chronic pancreatitis tend to be insidious. Clinical manifestations of acute pancreatitis include the following symptoms:

- Upper abdominal pain that radiates to the back, worsens after eating, and is somewhat relieved by leaning forward or pulling the knees toward the chest
- Nausea and vomiting
- Mild jaundice
- Fever
- Blood pressure and pulse changes (may be increased or decreased)

Clinical manifestations of chronic pancreatitis include these symptoms:

- Upper abdominal pain
- Indigestion
- Losing weight without trying
- Steatorrhea (oily, fatty, odorous stools)
- Flatulence

Diagnostic procedures for pancreatitis include those to verify the pancreatitis and those to identify complications. These procedures may consist of a history, physical examination, serum amylase and lipase levels, serum calcium levels, CBC, liver enzyme panel, serum bilirubin level, ABGs, pancreatic function tests, stool analysis (lipid and trypsin levels), abdominal X-ray, abdominal CT, abdominal MRI, abdominal ultrasound, and ERCP. Laboratory tests (e.g., amylase and lipase levels) may be normal with chronic pancreatitis; pancreatic function tests are the most reliable tool to identify chronic pancreatitis. Monitoring for the development of complications is crucial to achieve positive patient outcomes.

Management of acute pancreatitis requires early treatment and aggressive strategies to prevent complications. Patients will likely need to be closely monitored in an intensive care unit. This monitoring should include frequent measurement of vital signs (temperature, pulse, blood pressure, and respiration rate) and strict measurement

of intake and output (usually hourly). Treatment strategies include the following measures:

- Resting the pancreas by fasting, administering intravenous nutrition (e.g., TPN), and gradually advancing the diet from clear liquids as tolerated to a low-fat diet
- Pancreatic enzyme supplements when the diet is resumed
- Maintaining hydration status with intravenous fluids
- Inserting a nasogastric tube with intermittent suction for persistent nausea and vomiting
- Antiemetic agents (if vomiting is present)
- Pain management (usually includes intravenous narcotic agents and analgesics)
- Antacids and acid-reducing agents
- Anticholinergic agents (which reduce vagal stimulation, decrease GI motility, and inhibit pancreatic enzyme secretion)
- Antibiotic therapy (if infection is present)
- Insulin (which treats hyperglycemia secondary to temporary or permanent pancreatic damage and TPN administration)
- Identifying and treating complications early (e.g., blood transfusions for hemorrhage, dialysis for renal failure, airway management for ARDS, surgical drain for abscesses, and laparotomy for biliary obstruction)

Lifestyle modification (e.g., limiting alcohol consumption, smoking cessation, healthy diet) once the individual has recovered from acute episodes can prevent progression to chronic pancreatitis. Long-term pain management will likely be needed for individuals with chronic pancreatitis. Individuals with unexplained or worsening symptoms, especially after treatment, should be evaluated for **pancreatic cancer**.

Disorders of the Lower Gastrointestinal Tract

Disorders of the lower GI tract can alter nutrition or impair elimination. These conditions range in severity from mild (e.g., diarrhea and constipation) to life threatening (e.g., appendicitis and peritonitis) and can be either congenital (e.g., celiac disease) or acquired (e.g., intestinal obstruction). Depending on their severity, most of these disorders can be resolved or managed with minimal residual effects.

Diarrhea

Diarrhea refers to a change in bowel pattern characterized by an increased frequency, amount, and water content of the stool. This condition can result from an increase in fluid secretion (it is secretory), a decrease in fluid absorption (it is osmotic), or an alteration in GI peristalsis (motility is affected). Diarrhea can be acute (three or more loose or watery stools in 24 hours) or chronic (lasting longer than 4 weeks) and may be attributed to many conditions. Acute diarrhea is often caused by viral (e.g., norovirus and rotavirus) or bacterial (e.g., *Salmonella, Clostridium difficile*, *Shigella*, *Campylobacter*, and *E. coli*) infections (i.e., gastroenteritis), but can also be triggered by certain medications (e.g., antibiotics, antacids, and laxatives). Parasitic infections (e.g., *Giardia*, *S. dysenteriae*, and *V. cholerae*) are causes of diarrhea for individuals who live or travel to undeveloped countries. Depending on the cause, acute diarrhea is usually self-limiting. Causes of chronic diarrhea include inflammatory bowel diseases (e.g., Crohn's disease and **ulcerative colitis**), malabsorption syndromes (e.g., celiac disease), endocrine disorders (e.g., thyroid disorders), chemotherapy, and radiation.

Clinical manifestations of diarrhea vary depending on the underlying etiology. Stools are large, loose, and provoked by eating when this condition originates in the small intestine. Diarrhea originating in the small intestine is usually accompanied by pain in the right lower quadrant of the abdomen. When diarrhea originates in the large intestine, stools are small and frequent. Diarrhea originating in the large intestine is frequently accompanied by pain and cramping in the left lower quadrant of the abdomen. Acute diarrhea is generally infectious in origin and accompanied by cramping, fever, chills,

nausea, and vomiting. Blood, pus, or mucus may be present in the stool, which can aid in diagnosis. Blood in the stool may present as frank blood (bright red blood on the surface of the stool), occult blood (small amounts of blood hidden in the stool), or **melena** (dark tarry stool from a significant amount of bleeding higher up in the GI tract). Additionally, bowel sounds may be hyperactive. Fluid, electrolyte, and pH (usually metabolic acidosis) imbalances frequently develop regardless of whether the diarrhea is acute or chronic (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter).

Diagnostic procedures for diarrhea focus on identifying the underlying cause and any complications. These procedures may include a history (including usual bowel pattern and completion of the Bristol stool chart [**FIGURE 9-24**]), physical examination, stool analysis (including cultures and occult blood), CBC, blood chemistry, ABGs, abdominal ultrasound, and abdominal CT.

Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on its surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges (passed easily)
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces; Entirely liquid

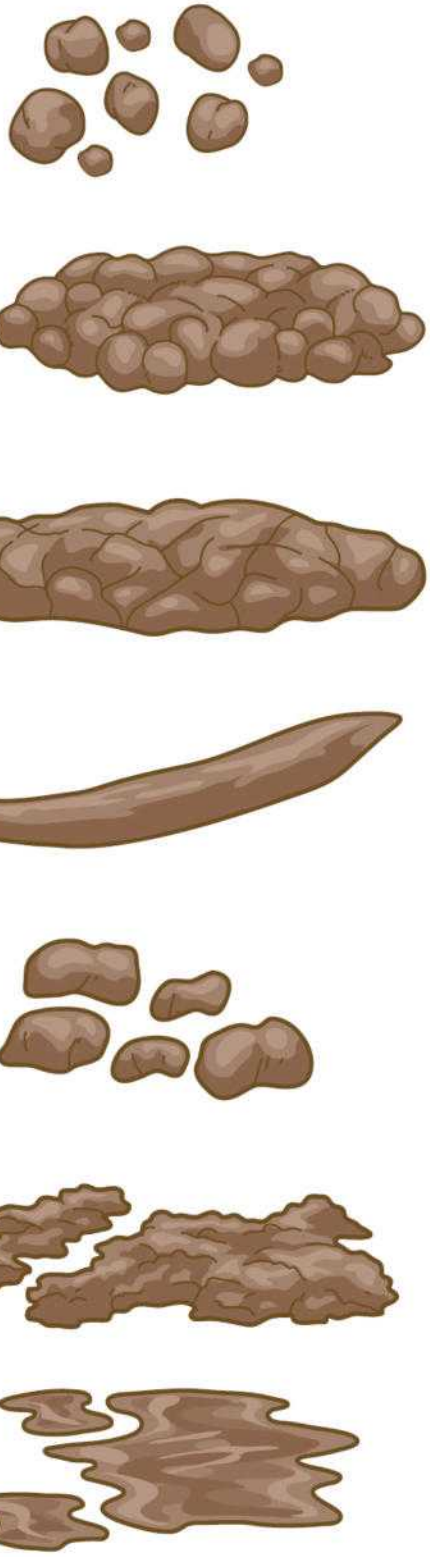


FIGURE 9-24 Bristol stool chart.

Data from Lewis, S., & Heaton, K. (1997). Stool form scale as a useful guide to intestinal transit time. *Scandinavian Journal of Gastroenterology, 32*(9), 920–924.

Description

Treatment strategies vary depending on the underlying etiology. Acute diarrhea with infectious origins usually improves with fasting. Generally, food consumption slows GI motility, allowing bacterial and viral toxins to increase. As toxin levels rise, diarrhea can become more severe. In addition to avoiding food consumption, antidiarrheal agents may be withheld for the same reason. Antibiotics may be necessary depending on the infectious agent. In noninfectious diarrhea, antidiarrheal agents slow GI motility and increase fluid absorption. Some additional medications that may be administered include anticholinergic and antispasmodic agents. When oral intake is recommended, a clear liquid diet is usually ordered until the diarrhea subsides. At that time, the diet is advanced to a regular diet as tolerated.

Probiotics are live bacteria and yeast normally found in normal flora, especially in the GI tract. Probiotics can be found in yogurt, buttermilk, kimchi, sauerkraut, and supplements. Consuming probiotics helps reestablish normal flora, which can become disrupted during episodes of diarrhea. Dietary fiber can be used to manage chronic diarrhea; the fiber acts like a sponge to absorb the excess water and increase bulk in the stool.

Maintaining hydration status and correcting electrolyte and pH imbalances are crucial to managing acute or chronic diarrhea (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter). Meticulous skin care can maintain skin integrity, especially in cases of bowel incontinence.

Constipation

Constipation refers to a change in bowel pattern characterized by infrequent passage of stool. Bowel patterns vary from person to person, so the decrease in frequency is in reference to the individual's typical bowel pattern. With constipation, the stool remains in the large

intestine longer than usual. The longer the stool remains in the large intestine, the more water is removed from the stool. Consequently, the stool becomes hard and difficult to pass. Constipation is often caused by a low-fiber diet, inadequate physical activity, insufficient fluid intake, delaying the urge to defecate, or laxative abuse (which smooths intestinal rugae). Stress (sympathetic nervous system stimulation slows GI motility) and travel can also contribute to constipation or other changes in bowel habits. Diseases of the bowel (e.g., irritable bowel syndrome), pregnancy, certain medications (e.g., narcotics, anticholinergic agents, and iron supplements), mental health problems (e.g., depression), neurologic diseases (e.g., stroke, Parkinson's disease, and spinal cord injuries), and colon cancer can cause constipation as well. In addition, constipation is common in children who are toilet training, especially if they are not ready for training or are scared of toileting.

Constipation may involve pain during the passage of a bowel movement, inability to pass stool after straining or pushing for more than 10 minutes, or no bowel movements for more than 3 days. Additionally, bowel sounds may be hypoactive. The passage of large, wide stools may tear the mucosal membrane of the anus, especially in children. This tearing can cause bleeding and an anal fissure to develop. Chronic constipation can lead to pH disturbances (usually metabolic alkalosis; see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter), hemorrhoids (swollen, inflamed veins in the rectum or anus), **diverticulitis**, impaction, intestinal obstruction, and fistulas.

Diagnostic procedures for constipation focus on identifying the underlying cause. These procedures consist of a history (including usual bowel pattern and completion of the Bristol stool chart [Figure 9-24]), physical examination (may include a digital examination), abdominal X-ray, upper GI series, barium swallow, colonoscopy (for visualization of the large intestine), and proctosigmoidoscopy (for visualization of the lower bowel).

Treatment strategies focus on reestablishing the individual's usual bowel pattern and preventing future constipation episodes. These strategies may involve managing or removing any underlying causes.

Strategies to treat and prevent constipation may include the following measures:

- Increasing dietary fiber (e.g., vegetables, fruit, and whole grains) with concomitant increase in hydration, specifically water and juices
- Avoid constipating foods (e.g., processed sugar, white flour, and red meat)
- Increasing physical activity
- Defecating when the initial urge is sensed
- Taking stool softeners (incorporates lipids and water into the stool)
- Limiting the use of laxatives and enemas
- Digitally removing an impaction (if present)

Intestinal Obstruction

An intestinal obstruction refers to a blockage of intestinal contents in the small intestine (where it is most common) or the large intestine. Intestinal obstructions have two types of causes—mechanical and functional. Mechanical obstructions consist of physical barriers, whereas functional obstructions result from GI tract dysfunction. These types of obstructions can occur due to foreign bodies, tumors, adhesions, hernias, intussusception (telescoping of a portion of the intestine into another portion), volvulus (twisting of the intestine), strictures, Crohn's disease, diverticulitis, Hirschsprung's disease (also known as "congenital megacolon"), and fecal impaction (**FIGURE 9-25**). Tumors, adhesions, and hernias account for approximately 90% of all mechanical small intestine obstructions. Tumors, diverticulitis, and volvulus are the most common causes of mechanical large intestine obstructions. A functional obstruction, also called **paralytic ileus**, usually results from neurologic impairment (e.g., spinal cord injury); intra-abdominal surgery complications; chemical, electrolyte, and mineral disturbances; intra-abdominal infections (e.g., peritonitis and pancreatitis); abdominal blood supply impairment; renal and lung disease; and use of certain medications (e.g., narcotics).

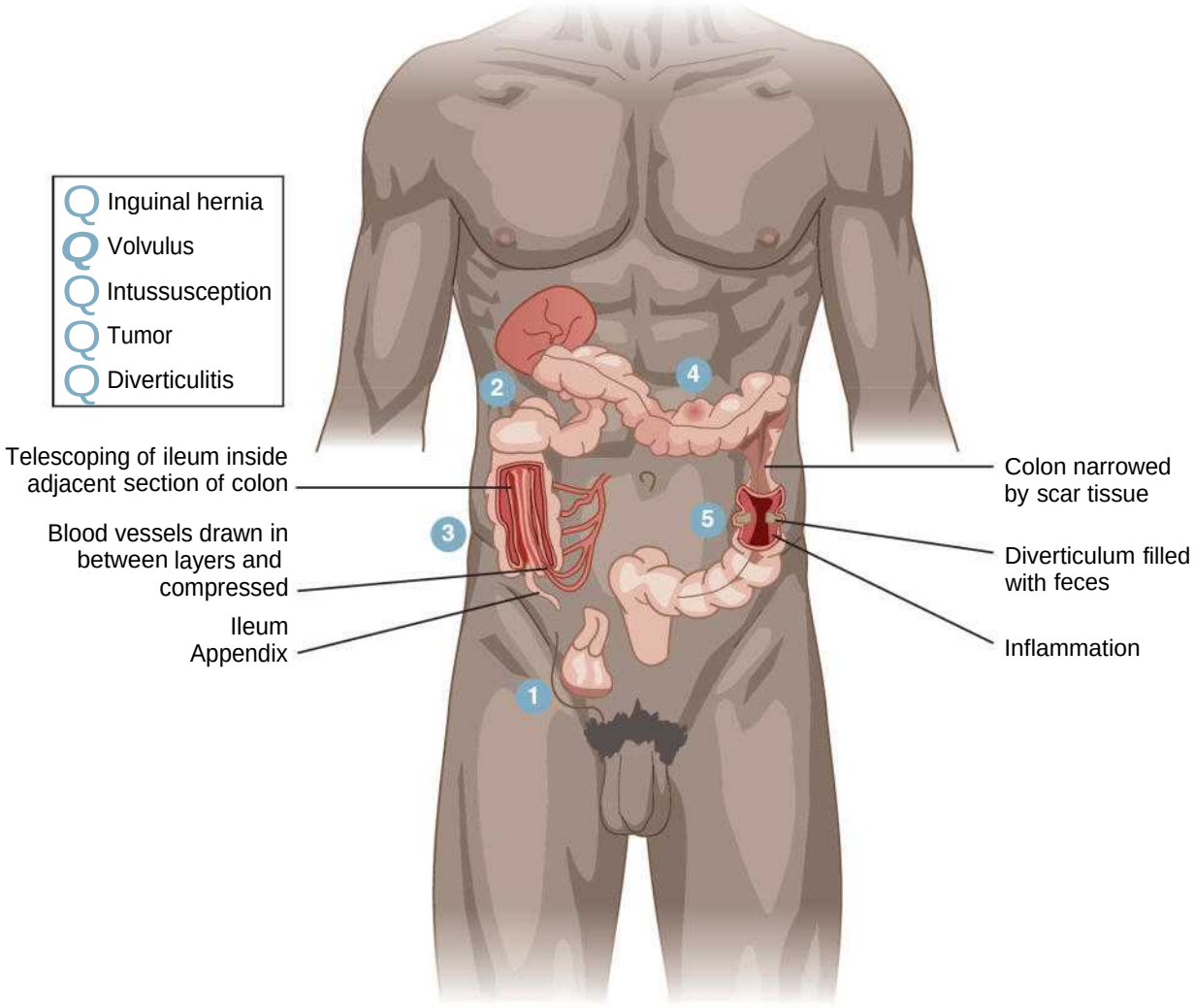


FIGURE 9-25 Causes of intestinal obstruction.

Description

Depending on the cause and location, intestinal obstructions can develop either suddenly or gradually. Additionally, the obstruction can be either partial or complete. Chyme and gas initially accumulate at the site of the blockage. Over time, saliva, gastric juices, bile, and pancreatic secretions begin to collect as the blockage lingers. This GI fluid buildup increases serum electrolytes and protein and causes abdominal distention and pain. Intestinal blood flow can become impaired, leading to strangulation and necrosis. Intestinal contents begin to seep into the abdomen as the pressure at the blockage increases. These complications are more likely to develop with a

complete obstruction. If a complete obstruction goes untreated, death can occur within hours due to shock and cardiovascular collapse. Other complications may include perforation, pH imbalances, and fluid disturbances.

The following manifestations are a result of the GI tract blockage (**FIGURE 9-26**):

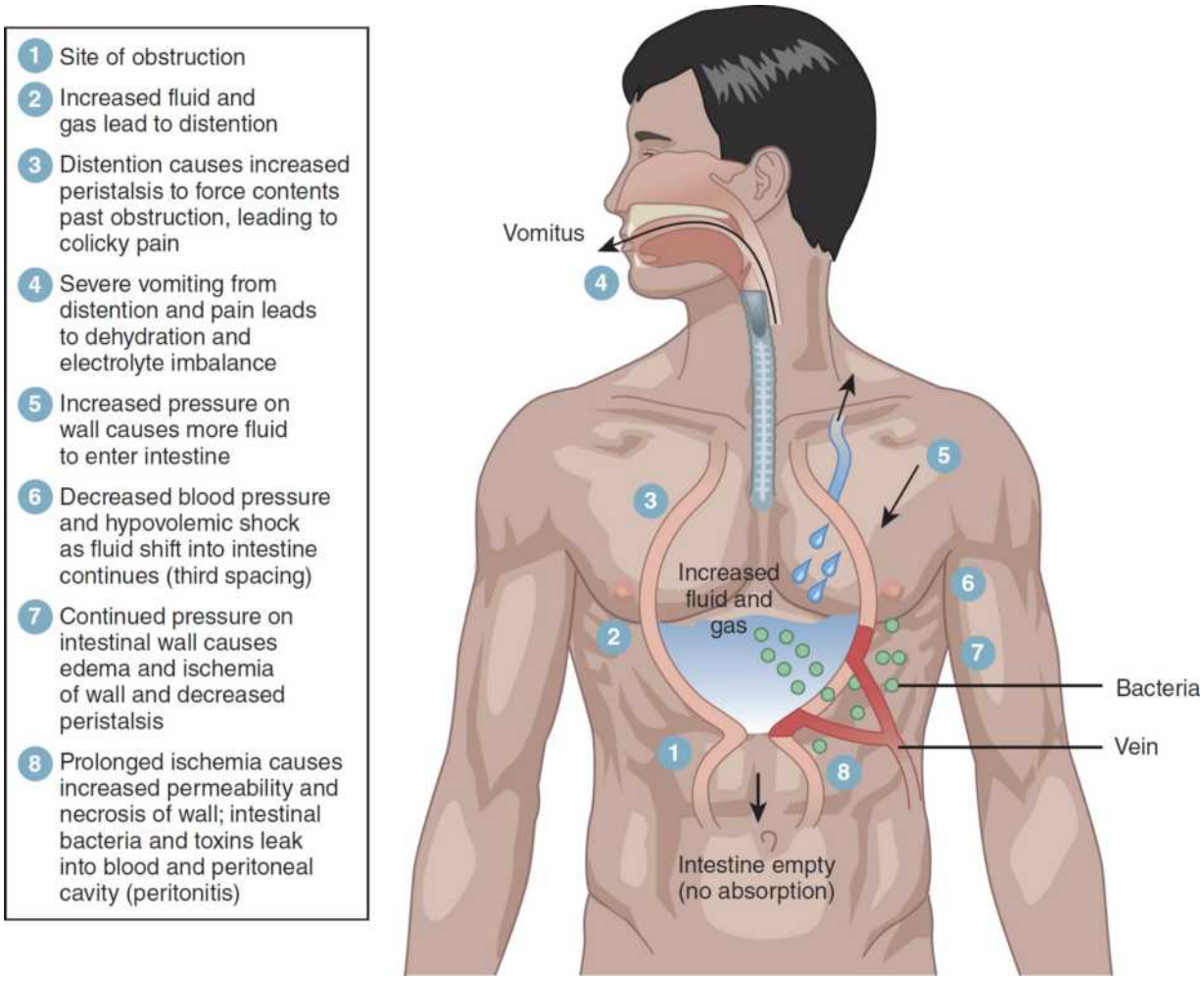


FIGURE 9-26 Effects of intestinal obstruction.

Description

- Abdominal distention
- Abdominal cramping and colicky pain
- Nausea and vomiting (usually gastric or bile contents)

- Constipation
- Inability to pass flatus
- Diarrhea (some of the intestinal liquid passes around the obstruction)
- Borborygmi (audible bowel sounds; associated with mechanical obstruction)
- Intestinal rushes (forcible intestinal contractions; associated with mechanical obstruction)
- Decreased or absent bowel sounds
- Anorexia
- Restlessness, diaphoresis, tachycardia progressing to weakness, confusion, and shock

Diagnostic procedures for intestinal obstruction are directed at identifying the obstruction, the underlying etiology, and complications. These procedures consist of a history (including the usual bowel pattern), physical examination, blood chemistry, ABGs, CBC, abdominal CT, abdominal X-ray, and abdominal ultrasound.

Treatment strategies depend on the underlying cause. Such strategies generally focus on correcting fluid, electrolyte, and pH imbalances (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter); decompressing the bowel; and reestablishing bowel movements. A nasogastric tube with intermittent suctioning is inserted to decompress the bowel and relieve vomiting. The patient should fast and receive TPN until bowel function is restored. Ambulation can help restore peristalsis. Laxatives should not be used in most cases until the obstruction is resolved. Surgery is frequently necessary to relieve mechanical obstruction.

Appendicitis

Appendicitis refers to an acute inflammation of the vermiform appendix (**FIGURE 9-27**). More than 5% of the population in the United States will develop appendicitis at some point (NIDDK, n.d.a).

Appendicitis can occur at any age but most commonly affects adolescents and individuals in their 20s.



FIGURE 9-27 Appendicitis.

Courtesy of Leonard V. Crowley, MD, Century College.

Appendicitis occurs when an obstruction arises inside the appendix (i.e., appendiceal lumen). The obstruction is usually caused by lymphoid hyperplasia but can also result from a fecalith (a stone made of feces), foreign body, intestinal parasites, or tumors. The obstruction leads to distention, bacterial overgrowth, inflammation, and ischemia. The inflammation process triggers local tissue edema, which obstructs the small structure. As fluid builds inside the appendix, microorganisms proliferate. The appendix fills with purulent exudate, and the stretched, edematous wall compresses area blood vessels. With blood flow compromised, ischemia and necrosis

develop. The pressure inside the appendix escalates, forcing bacteria and toxins out to surrounding structures. Abscesses and peritonitis can develop as bacteria escape, and gangrene can result from the worsening necrosis. The pressure inside the appendix continues to intensify until the appendix ruptures or perforates, releasing its contents. This release can accelerate peritonitis, which can be life threatening.

Clinical manifestations reflect the pathogenetic characteristics of appendicitis. These manifestations vary significantly in severity, from asymptomatic to sudden and severe. The first symptom is often pain near the umbilicus. As swelling increases, the pain tends to move to the lower right quadrant of the abdomen (McBurney's point). The pain gradually intensifies over approximately 12–24 hours. It is often aggravated by movement, so patients tend to guard their abdomen. Due to normal anatomic variations, this pain may occur anywhere in the abdomen. The pain will temporarily subside if the appendix ruptures but then will return and escalate as peritonitis develops. Anorexia, nausea, vomiting, abdominal distention, and bowel pattern changes can also be associated with appendicitis. Other manifestations reflect the inflammation and infectious process (e.g., fever, chills, and leukocytosis). Additionally, the patient should be monitored for signs and symptoms of peritonitis (e.g., abdominal rigidity, tachycardia, and hypotension).

Urgent diagnosis and treatment are crucial for positive patient outcomes. Diagnostic procedures include a history, physical examination, CBC, abdominal ultrasound, abdominal X-ray, abdominal CT, and laparoscopy. Because of the life-threatening nature of appendicitis, surgery remains the cornerstone of treatment. In fact, appendicitis is the most common cause of acute abdominal pain requiring surgery in the United States. Performing the surgery prior to rupture of the appendix is paramount. Prior to rupture, the surgery can be performed through laparoscopy with minimal risk. If the appendix ruptures, an open surgical procedure is necessary to ensure all the appendix fragments and infectious materials are removed. Extensive irrigation of the abdominal cavity is performed to flush out any remaining bacteria. The wound may be left open to heal by

secondary intention to decrease the risk of infection. Tubes may be inserted to drain any abscesses. Long-term antibiotic therapy may be necessary to prevent and resolve any infections. Analgesics will be necessary to manage pain before and after surgery. Additionally, the patient should avoid activities that increase intra-abdominal pressure (e.g., straining and coughing).

Peritonitis

Peritonitis is an inflammation of the peritoneum, the membrane that lines the abdominal wall and abdominal organs. Peritonitis usually presents as an acute condition, and treatment centers on resolving the underlying cause. The inflammation may result from chemical irritation (e.g., ruptured gallbladder or spleen) or direct organism invasion (e.g., appendicitis and peritoneal dialysis) (**FIGURE 9-28**). Chemical irritation will lead to a bacterial invasion if not quickly treated. The inflammatory response triggered by the chemical increases intestinal wall permeability. In turn, the increased permeability allows for the passage of enteric bacteria. Necrosis or perforation of the intestinal wall also creates an opportunity for an enteric bacteria invasion. Multiple bacteria are usually present with peritonitis, making it difficult to manage. Commonly present are *E. coli*, *Klebsiella pneumoniae*, gram-positive *Streptococcus pneumoniae*, and *Bacteroides fragilis*.

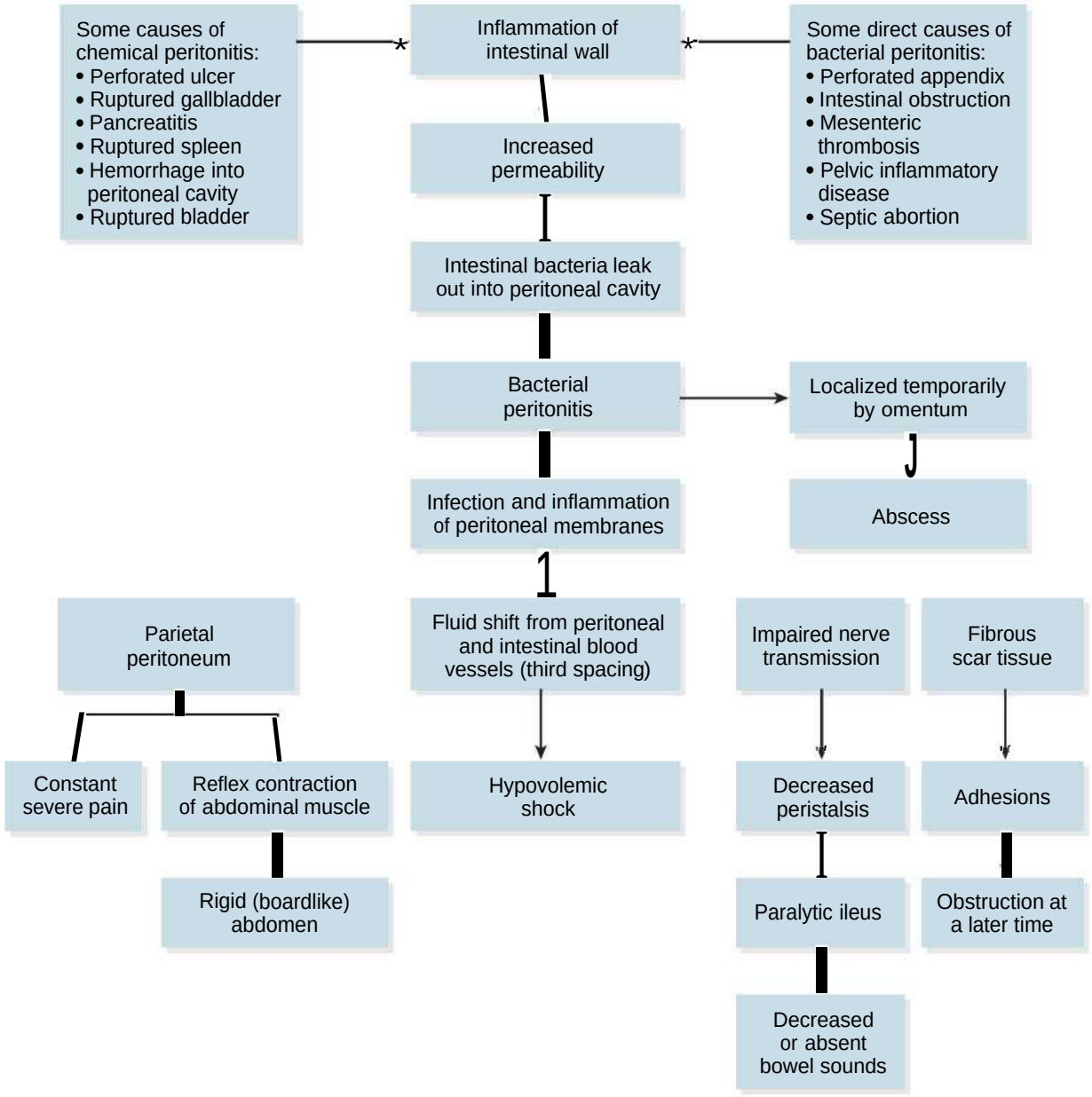


FIGURE 9-28 Development of peritonitis.

Description

Several protective mechanisms are activated along with the inflammatory response in an attempt to localize the problem. These mechanisms include the production of a thick, sticky exudate that bonds nearby structures and temporarily seals them off. Abscesses may form as the body attempts to wall off the infections. Peristalsis may slow down as a response to the inflammation, decreasing the

spread of toxins and bacteria. These mechanisms merely slow the progression, however. If the underlying cause is not treated, the condition can become critical as sepsis and shock develop, leading to multisystem organ failure.

Clinical manifestations reflect the inflammatory and infectious processes underway; these manifestations tend to be sudden and severe. The classic manifestation of peritonitis is abdominal rigidity. A rigid, boardlike abdomen develops because of a reflexive abdominal muscle spasm that occurs in response to the peritoneal inflammation. Inflamed tissue creates abdominal tenderness and pain that worsen with movement (e.g., increased intrathoracic pressure, flexing hips, or applying abdominal pressure and then quickly removing it [i.e., rebound tenderness]). Large volumes of fluid can leak into the peritoneal cavity (a phenomenon called third spacing), leading to hypovolemic shock (see the *Cardiovascular Function* chapter). This fluid contains protein and electrolytes, making it an optimal medium for bacterial growth. Nausea and vomiting are common responses to the intestinal irritation. Persistent inflammation impairs nerve conduction, which decreases peristalsis. This decreased peristalsis can, in turn, lead to intestinal obstruction. Sepsis develops as the bacteria and toxins migrate to the circulatory system through the inflamed membranes. Fever, malaise, and leukocytosis occur because of the infectious process. Additionally, the patient should be monitored for signs of sepsis and shock (e.g., tachycardia, hypotension, restlessness, and diaphoresis).

Diagnostic procedures for peritonitis consist of a history, physical examination, CBC, abdominal X-ray, abdominal ultrasound, abdominal CT, paracentesis with peritoneal fluid analysis, and laparotomy. Treatment strategies vary based on the underlying cause. The patient's prognosis depends on the underlying cause along with the implementation of early and aggressive treatment. Management often includes surgical repair of the chemical leak and draining of the infected fluid. Long-term antibiotic therapy specific to the causative organisms will be required. In addition, correction of any fluid and electrolyte imbalances may be required. Insertion of a nasogastric tube with intermittent suction can relieve abdominal distention and

treat intestinal obstructions. TPN will be necessary to maintain nutritional status until the peritonitis is resolved.

Celiac Disease

Celiac disease (also known as "celiac sprue" or "gluten-sensitive enteropathy") is an inherited autoimmune malabsorption disorder of the small intestines. Although its etiology is not completely understood, celiac disease results from a combination of the immune response to an environmental factor (gliadin) and genetic predisposition. Nearly all individuals diagnosed with celiac disease have at least one mutation of the two genes coding for HLA-DQ, a cell surface receptor protein found on antigen-presenting cells that helps the immune system distinguish self from non-self and coordinate T cells' activity (Offord, 2017). Approximately 40% of all people have this genetic predisposition, but not all individuals with these mutations develop celiac disease.

One hypothesis proposes that a gluten-rich diet may be the stimulus for disease development. Gluten is an ingredient of grains (e.g., wheat, barley, rye, and oats). In addition to the quantity of gluten consumed, evidence suggests that characteristics of the gluten and the age at which it is introduced into the individual's diet may influence celiac disease development.

Another hypothesis proposes that alterations in the intestinal microbiome's composition may change how these microbes interact with gluten. For example, individuals with celiac disease have shown to have higher proportions of gram-negative bacteria in their intestinal flora (e.g., *Bacteroides*, *E. coli*, and *H. pylori*). Whether this change is a cause or a consequence of celiac disease is unclear, but these changes remain after elimination of gluten from their diet.

Celiac disease is different from gluten sensitivity or wheat intolerance. The symptoms are similar, but consuming gluten will not damage the small intestines with these conditions. In genetically susceptible individuals, gluten-sensitive T cells are activated when gluten-derived peptide epitopes are present (**FIGURE 9-29**). The inflammatory response causes mucosal villous atrophy in the small intestines. The villi atrophy and flatten, resulting in decreased enzyme

production and making less surface area available for nutrient absorption (Figure 9-29). Regardless of the source of the celiac disease, it cannot be wholly reversed. Removing gluten from the diet, however, will allow for some healing and minimize symptoms.

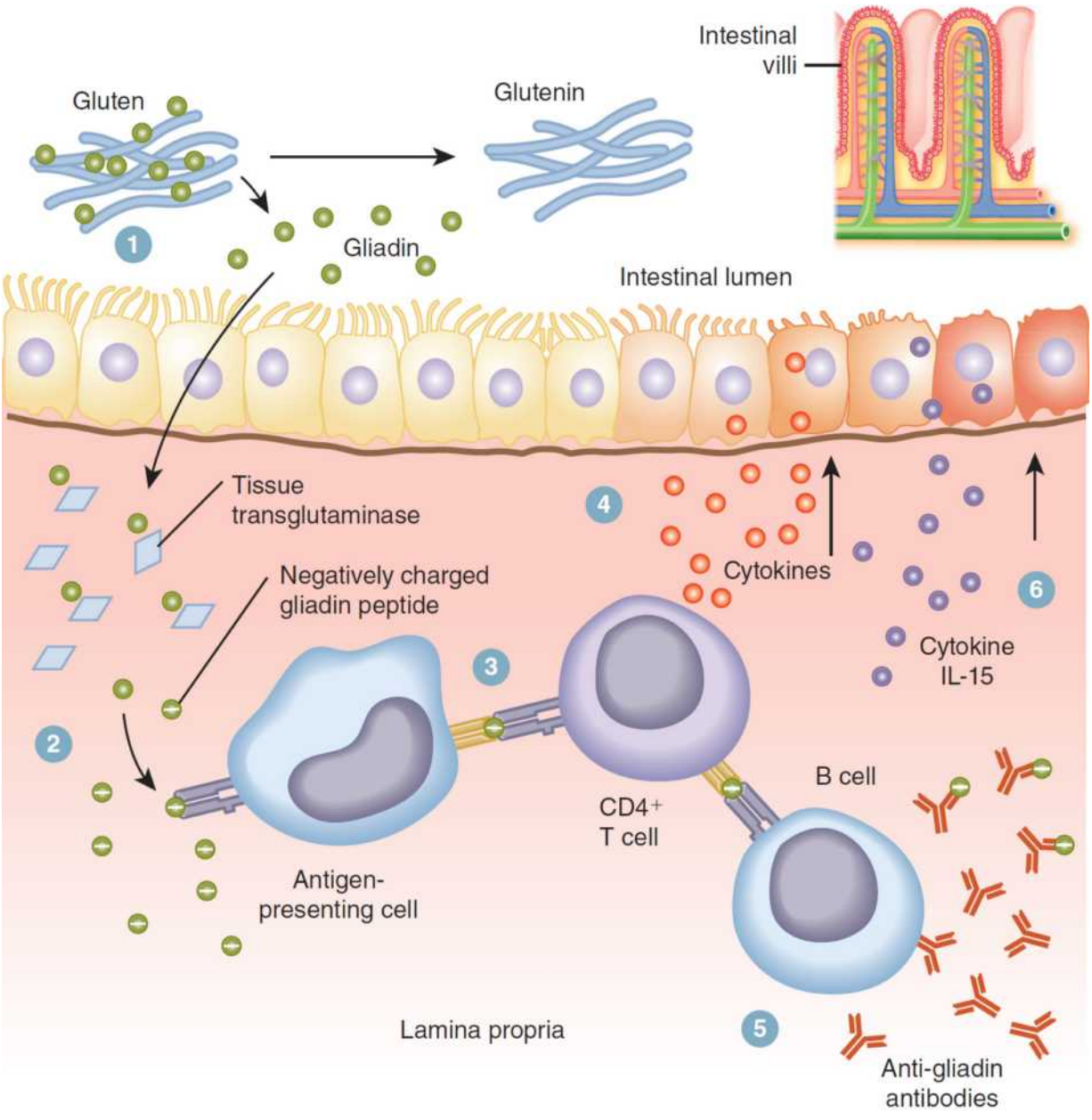






FIGURE 9-29 Effects of celiac disease on intestinal villi.

© Biophoto Associates/Science Source

Description

Worldwide, celiac disease affects an estimated 1 in 100 people. Global rates have significantly increased in recent years for reasons that are not completely understood. In the United States, it affects about 2 million people. This condition can develop at any age but is most common in Caucasians, females, and those with a family history. Celiac disease is also more common in individuals with Down syndrome, Turner syndrome, type 1 diabetes, and Hashimoto thyroiditis. Mortality risk in individuals with celiac disease is twice that for the general population (Offord, 2017).

Tropical sprue is a related disorder that occurs in tropical regions, especially India, Southeast Asia, Central America, South America, and the Caribbean. Tropical sprue can affect natives and visitors to these areas. This rare, acquired disease is thought to be caused by a bacterial, viral, parasitic, or amoebic infection. Tropical sprue is characterized by malabsorption and megaloblastic anemia. It can be resolved with antibiotic therapy, unlike celiac disease, which is a lifelong condition.

Celiac disease can be serious, causing long-lasting digestive problems. Eventually, the malnutrition associated with this disease can cause vitamin deficiencies that deprive the brain, peripheral nervous system, bones, liver, and other organs of vital nourishment. Malabsorption can continue even after following a strict gluten-free diet (i.e., refractory celiac disease) because of severe intestinal damage. These nutritional deficits, in turn, can lead to other illnesses:

- Anemia
- Arthralgia (bone and joint pain)
- Myalgia (muscle pain)
- Bone disease (e.g., osteomalacia, osteoporosis, kyphoscoliosis, and fractures)
- Dental enamel defects and discoloration
- Intestinal cancers
- Depression and anxiety
- Failure to thrive in infants
- Growth and development delays in children
- Delayed puberty
- Hair loss
- Hypoglycemia
- Mouth ulcers, stomatitis (inflammation of the mouth and lips), and glossitis (red, smooth tongue)
- Increased bleeding tendencies (e.g., bruising and nosebleeds)
- Neurologic disorders (e.g., seizures and peripheral neuropathy)
- Skin disorders (e.g., dermatitis herpetiformis and eczema)
- Vitamin or mineral deficiency, of either a single or multiple nutrients (e.g., iron, folate, vitamin B_{12}, and vitamin K)
- Endocrine disorders (e.g., abnormal uterine bleeding, infertility, thyroid disease, type 1 diabetes, and adrenal insufficiency)

Clinical manifestations of celiac disease vary significantly from person to person—a factor that often delays diagnosis. In infants, clinical manifestations generally appear as cereals are added to their diet (usually around 4–6 months of age). Most of the clinical manifestations are GI in nature, but occasionally a patient has no GI symptoms other than nutritional deficits. Sometimes surgery, pregnancy, childbirth, bacterial gastroenteritis, a viral infection, or severe mental stress can trigger symptoms. The GI clinical manifestations may include the following symptoms:

- Abdominal pain
- Abdominal distention, bloating, gas, and indigestion
- Anorexia
- Weakness
- Constipation or diarrhea (may be chronic or occasional)
- Changes in appetite (usually decreased)
- Lactose intolerance (common upon diagnosis; usually goes away following treatment)
- Nausea and vomiting
- Steatorrhea
- Unexplained weight loss (although people can be overweight or of normal weight upon diagnosis)
- Signs of vitamin deficiencies (e.g., bruising, fatigue, hair loss, paresthesia, and mouth ulcers)
- Headaches
- Fatigue

Manifestations that are not GI in nature may include irritability, lethargy, malaise, and behavioral changes. Additionally, the individual with celiac disease should be monitored for the development of complications. Notably, celiac disease increases the risk of developing other autoimmune conditions (e.g., Addison's disease, Hashimoto thyroiditis, type 1 diabetes, and multiple sclerosis), primary biliary cirrhosis, and coronary artery disease.

Diagnostic procedures for celiac disease consist of a history, physical examination, celiac blood panel, and EGD with duodenal biopsy. The celiac blood panel includes the immunoglobulin A antibody–endomysium antibodies, immunoglobulin A antigliadin antibodies, deaminated gliadin peptide antibody, immunoglobulin A antitissue transglutaminase, lactose tolerance test, and d-xylose test. Genetic testing can be performed if the blood panel and biopsy are not conclusive (Rubio-Tapia et al., 2013).

Dietary management is the only available treatment. A strict gluten-free diet may lessen symptoms, although some symptoms can persist, and accidental consumption of gluten is inevitable. A gluten-free diet involves avoiding wheat and wheat products—rice and corn can be substituted. Gluten is commonly found in bread, pasta, cookies, and cake. Many prepackaged foods, lip balms and lipstick, hair and skin products, toothpastes, vitamins and nutritional supplements, and some medications (although rare) contain gluten. Once gluten is removed from the diet, the intestinal mucosa will begin to heal but will not return to the predisease state. Intravenous nutritional supplements (e.g., TPN) may be needed, especially if symptoms persist after following a strict gluten-free diet. Even when symptoms are controlled with diet, the individual with celiac disease remains at risk for intestinal cancers; consequently, he or she should be periodically monitored for cancer development. Additionally, long-term support may be necessary for children and parents of children with celiac disease.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) describes chronic inflammation of the GI tract, usually the intestines. IBD is chiefly seen in women, Caucasians, persons of Jewish descent, and smokers. This disease can affect people of all ages but usually appears before age 30. It encompasses two disorders: Crohn's disease and ulcerative colitis. Both conditions are characterized by periods of exacerbations and remissions that can vary in severity. In some cases, IBD may be painful, debilitating, and life threatening.

The exact cause of IBD is unknown, and its pathogenesis is not completely understood. Recent evidence indicates that genetic susceptibility, environmental influences, the intestinal microbiome, and the immune system are all involved (**FIGURE 9-30**). Inflammation results from a cell-mediated immune response in the intestinal mucosa. The normal intestinal microbiome is thought to trigger an abnormal immune response in people with genetic vulnerabilities, likely those resulting in abnormal epithelial barriers and mucosal immune defenses. More than 300 genes have been identified as

potentially playing a role in susceptibility to IBD (Loddo & Romano, 2015). Immune cells located in the intestinal mucosa are stimulated to release inflammatory mediators (e.g., histamine, prostaglandins, leukotrienes, and cytokines). These mediators alter the function and neural activity of the secretory and smooth muscle cells in the GI tract.

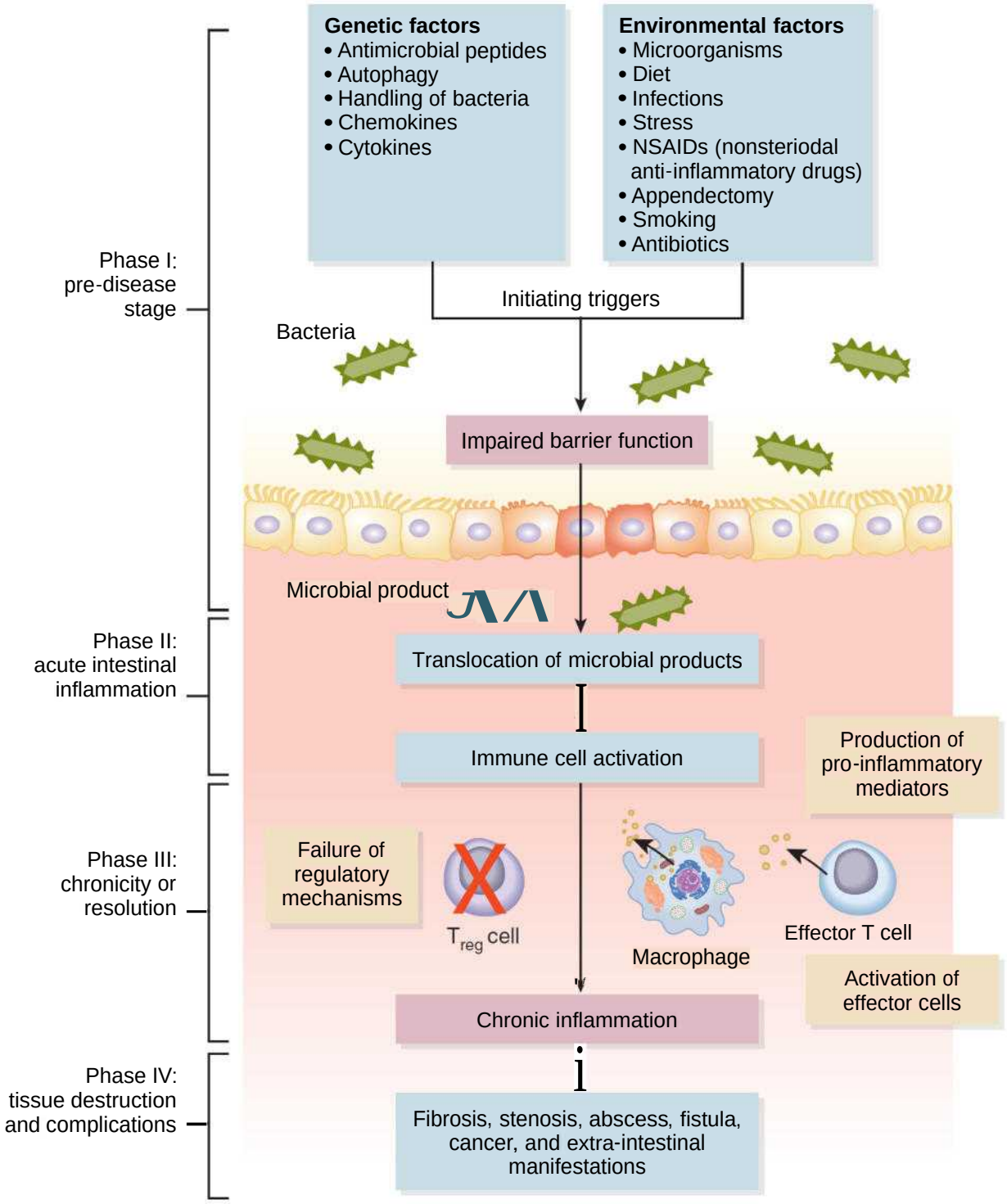


FIGURE 9-30 Pathogenesis of inflammatory bowel disease.

Description

Environmentally, cigarette smoking increases the risk of Crohn's disease but decreases the risk of ulcerative colitis. Having an appendectomy to treat appendicitis appears to lower the risk of ulcerative colitis. Conversely, the use of oral contraceptives and a high-fat diet may increase the risk for Crohn's disease. NSAIDs, perinatal illness, and antibiotic use in childhood may also increase the risk for IBD. Fluid, electrolyte, and pH imbalances develop.

Even though the two forms of IBD are similar, some differences between them warrant discussion. Additionally, IBD is similar to irritable bowel syndrome, so differences should be noted.

Crohn's Disease

Crohn's disease is an insidious, slow-developing, progressive condition that often emerges in adolescence. Its exact cause is unknown, but T-cell activation leading to tissue damage has been implicated. This condition usually affects the intestines, especially the distal ileum and colon; however, it may occur anywhere along the GI tract. Crohn's disease begins with crypt inflammation and abscesses that progress to small focal aphthoid ulcers. These ulcers progress deeper into the mucosa, producing characteristic patchy areas of inflammation involving the full thickness (transmural) of the intestinal wall. These patchy areas and ulcerations, often called "skip lesions," are separated by areas of normal tissue (**FIGURE 9-31**). The ulcers combine to form fissures divided by nodules (thickened elevations), giving the intestinal wall a cobblestone appearance. Eventually, the entire wall becomes thick and rigid, and the intestinal lumen becomes narrowed and potentially obstructed. Granulomas—nodules consisting of epithelial and immune cells—develop on the intestinal wall and nearby lymph nodes because of the chronic inflammation. Over time, the damaged intestinal wall loses the ability to process and absorb food. The inflammation also stimulates intestinal motility, decreasing digestion and absorption.



FIGURE 9-31 Crohn's disease.

Courtesy of Leonard V. Crowley, MD, Century College.

Emerging Research: Celiac Disease

In recent years, a rapid global increase in cases of celiac disease has occurred that some countries and researchers have labeled an epidemic. This alarming surge has put pressure on the scientific community to understand the cause of this trend and identify solutions. The increase in case numbers may be due in part to advances in screening and diagnosis that make celiac disease easier to detect. However, multiple environmental factors (e.g., changes in quantity, characteristics, or early introduction of gluten consumed or alterations in intestinal microbiome composition) are likely driving this trend. Celiac disease has been studied for decades, yet little is understood about what causes people to develop it. Understanding why some genetically suspectable individuals develop celiac disease, while others do not, is important in slowing this trend (Offord, 2017).

The Environmental Determinants of Diabetes in the Young (TEDDY) study examines factors that affect the development of type I diabetes and celiac disease in children who have a genetic vulnerability. Reovirus infections may also trigger celiac disease in those individuals with genetic risks. Additionally, one study found that people in the United States living north of 35° north latitude were more likely to have celiac disease than people living south of 35° north latitude (NIDDK, n.d.b).

A gluten-free diet is the only treatment available for celiac disease, but evidence regarding its effectiveness is not encouraging. The intestinal mucosa does not completely heal even when gluten is completely removed from the diet. Accidental gluten ingestion is inevitable, and a gluten-free diet is costly and often unrealistic.

Currently, researchers are exploring ways to address the intestines' response to gluten and potentially restore tolerance. For example, a vaccine, to be administered as a series of injections, is being evaluated that would help desensitize patients to gluten. The vaccine is composed of three peptides—the components of gluten acquired from wheat, barley, and rye. Oral medications are also under investigation that could be used in conjunction with a gluten-free diet to minimize the reaction to accidental exposure. These medications contain a synthetic peptide known as larazotide acetate that inhibits zonulin, a protein that regulates epithelial cells' tight junctions. Zonulin is thought to increase the permeability of intestinal mucosa and is unregulated in individuals with celiac disease. Another medication under investigation is a mixture of two gluten-targeting proteases—one derived from plants and one derived from bacteria. The proteases cut the gluten molecules into smaller pieces, thereby reducing intestinal damage when small amounts of gluten are ingested (Celiac Disease Foundation, 2019; Offord, 2017).

Since many of these treatments are years from becoming available for general use, improvements in diagnosis are also a priority. The gluten-free diet trend is complicating the scientific community's efforts to gain a deeper understanding of the increase in celiac disease prevalence, pathogenesis, and treatment. Many individuals are self-prescribing this diet for various reasons without being evaluated for celiac disease. Many people report symptoms after ingesting gluten, including abdominal pain and other GI symptoms.

In addition to celiac disease, numerous less well-understood conditions are related to gluten, including dermatitis herpetiformis, gluten ataxia, wheat allergy, and gluten sensitivity. While their symptoms are similar to those associated with celiac disease, these conditions do not usually cause intestinal damage. Some evidence suggests that gluten may not be the actual issue with some of these conditions. For example, some individuals diagnosed with gluten sensitivity and placed on a gluten-free diet do not experience symptoms when gluten is reintroduced into their diet. Other dietary components are being explored as possible causes of the symptoms, including a group of carbohydrates called "fermentable oligosaccharides," "disaccharides," "monosaccharides," and "polyols." Other studies have found that another component of wheat, amylase trypsin inhibitors, can trigger an innate immune response that could explain the GI symptoms in what appears to be a gluten sensitivity.

The medical community should discourage people from self-treating gluten-related symptoms. Evaluation to identify the underlying condition contributing to the symptoms is important (Offord, 2017).

Complications of Crohn's disease include the following conditions:

- Malnutrition
- Anemia (especially iron-deficiency anemia because of the malnutrition)

- Fistulas
- Adhesions
- Abscesses
- Intestinal obstruction
- Perforation
- Anal fissure
- Fluid, electrolyte, and pH imbalances
- Delayed growth and development (in children)
- Intestinal cancer (colon and small intestines)

Clinical manifestations of Crohn's disease reflect the inflammatory process and the digestive dysfunction. These manifestations, which intensify during exacerbations, include the following symptoms:

- Abdominal cramping and pain (typically in the right lower quadrant and may occur with defecation)
- Diarrhea (usually watery)
- Steatorrhea
- Constipation (as the intestinal lumen narrows)
- Palpable abdominal mass (thickened intestinal wall)
- Hematochezia (gross, red blood; rare unless ulcers begin bleeding)
- Anorexia
- Mouth ulcers
- Weight loss
- Indications of inflammation (e.g., fever, fatigue, arthralgia, and malaise)

Diagnostic procedures for Crohn's disease consist of a history, physical examination, stool analysis (including cultures and occult blood), CBC, blood chemistry, C-reactive protein levels, erythrocyte sedimentation rate, abdominal X-ray, abdominal CT, abdominal MRI, barium studies (swallow and enema), sigmoidoscopy, colonoscopy, capsule endoscopy, and biopsy. Additionally, serological antibodies

can help distinguish Crohn's disease from ulcerative colitis. Anti–*Saccharomyces cerevisiae* antibodies are fairly specific to Crohn's disease, whereas perinuclear antineutrophil cytoplasmic antibodies are more specific to ulcerative colitis. These tests can be unreliable and not recommended for routine diagnosis.

Crohn's disease is rarely cured, but the number and severity of exacerbations can be minimized. Treatment strategies focus on nutritional support, symptom relief, and complication minimization. Dietary management usually includes (1) a low-residue, high-calorie, high-protein diet; (2) oral nutritional supplements (e.g., Ensure and Sustacal); (3) multivitamin supplements; and (4) TPN as the disease progresses. Pharmacologic management usually includes (1) antidiarrheal agents (e.g., loperamide); (2) aminosalicylates (5-ASAs) to treat mild to moderate inflammation; (3) glucocorticoids to treat moderate to severe inflammation; (4) immune modulators (e.g., cyclosporine and methotrexate) to suppress inflammatory response; (5) biologic agents (e.g., infliximab or adalimumab) to treat severe unresponsive Crohn's disease; (6) analgesics; and (7) antibiotics if infection is present. Surgical intestine resection may be necessary as the disease progresses and complications develop. Additional strategies involve stress management (e.g., exercise, meditation, deep breathing, biofeedback, and acupuncture) and support (e.g., group involvement and counseling).

Ulcerative Colitis

Ulcerative colitis is a progressive condition of the rectum and colon mucosa that usually develops in the second or third decade of life. Inflammation triggered by T-cell accumulation in the colon mucosa causes epithelium loss, surface erosion, and ulceration (**FIGURE 9-32**). The ulceration begins in the rectum and extends in a continuous segment to involve the entire colon; it rarely affects the small intestine. The mucosa becomes inflamed, edematous, and frail. Necrosis of the epithelial tissue (specifically at the base of the crypts of Lieberkühn) can result in abscesses, known as "crypt abscesses." As the body attempts to heal, granulation tissue forms, but the tissue remains fragile and bleeds easily. The ulcers merge together,

creating large areas of stripped mucosa. In severe cases, the muscularis is involved, and large ulcers produce copious purulent exudate. Areas of relatively normal or hyperplastic inflammatory mucosa (pseudopolyps) protrude above areas of ulcerative mucosa. Fistulas and abscesses do not occur.

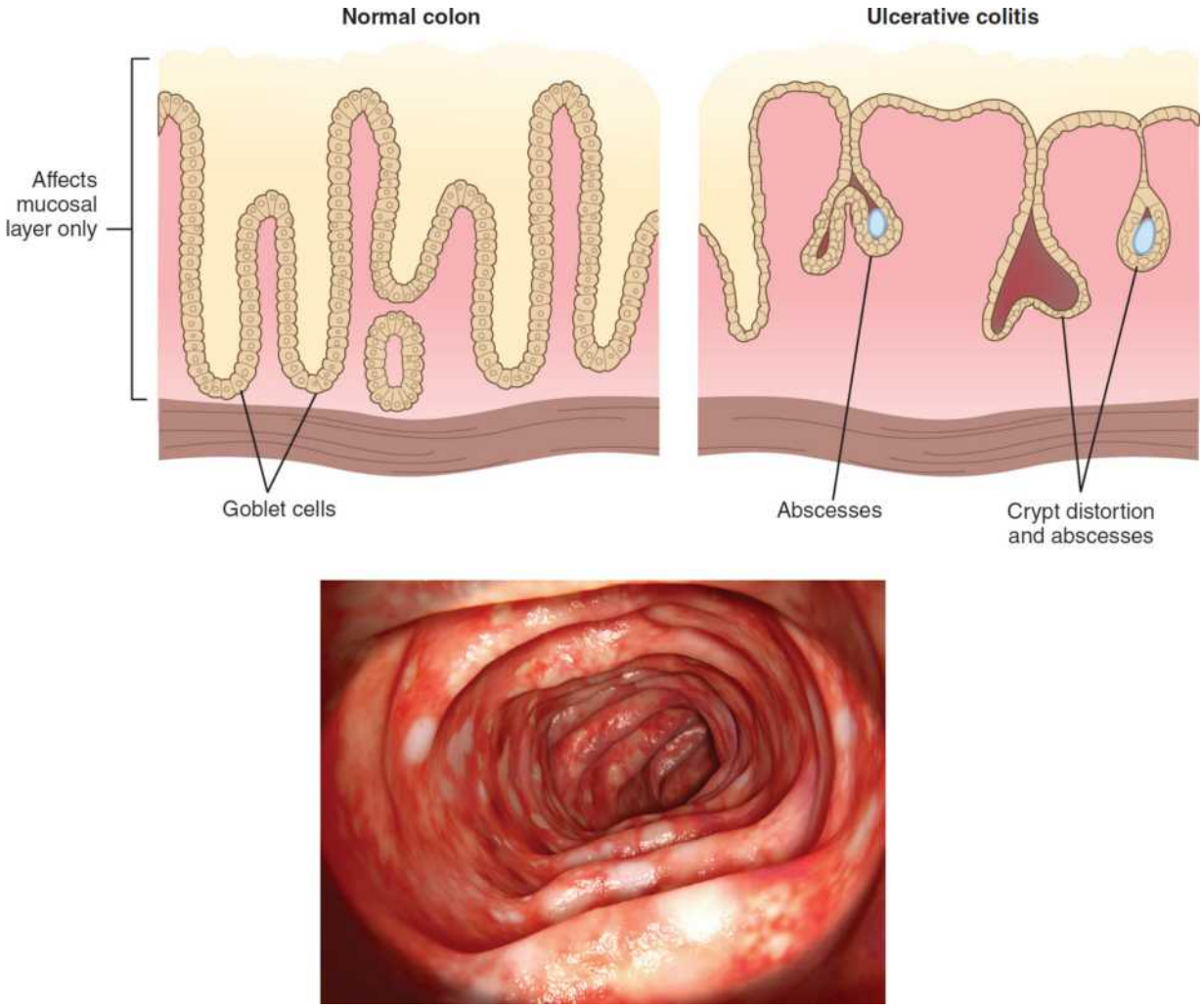


FIGURE 9-32 Ulcerative colitis.

© Juan Gaertner/Shutterstock

Description

Over time, nutritional, fluid, electrolyte, and pH imbalances develop due to the lack of an adequate surface area for absorption. Other complications of ulcerative colitis may include the following conditions:

- Malnutrition
- Anemia
- Hemorrhage
- Perforation
- Strictures
- Fistulas
- Pseudopolyps
- Toxic megacolon (life-threatening condition caused by rapid dilation of the large intestine)
- Colorectal carcinoma
- Liver disease (because of inflammation and scarring of the bile ducts)

Clinical manifestations of ulcerative colitis reflect the inflammatory process and digestive dysfunction. As is the case with Crohn's disease, these manifestations intensify during exacerbations. Manifestations usually include the following symptoms:

- Diarrhea (usually frequent [as many as 20 daily], watery stools containing blood and mucus)
- Tenesmus (persistent rectal spasms associated with the need to defecate)
- Proctitis (inflammation of the rectum)
- Abdominal cramping
- Nausea and vomiting
- Weight loss
- Indications of inflammation (e.g., fever, fatigue, arthralgia, and malaise)

Diagnostic procedures are the same as those for Crohn's disease. During severe exacerbations, healthcare providers should avoid performing a colonoscopy or barium enema because of perforation risk.

Similar to Crohn's disease, treatment strategies focus on nutritional support, symptom relief, and complication minimization. Dietary management usually includes (1) a high-fiber, high-calorie, high-protein diet; (2) oral nutritional supplements (e.g., Ensure or Sustacal); (3) multivitamin supplements; and (4) TPN as the disease progresses. Pharmacologic management usually includes (1) antidiarrheal agents; (2) antispasmodics; (3) anticholinergics; (4) aminosalicylates to treat mild to moderate inflammation; (5) glucocorticoids to treat moderate to severe inflammation; (6) immune modulators to suppress inflammatory response; (7) biologic agents; (8) analgesics; and (9) antibiotics if infection is present. Surgical intervention (e.g., ileostomy or colostomy) may be necessary as the disease progresses and complications develop. Additional strategies involve stress management (e.g., exercise, meditation, deep breathing, biofeedback, and acupuncture) and support (e.g., group involvement and counseling).

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) refers to a chronic functional GI condition characterized by exacerbations associated with stress. This condition is characterized by alterations in bowel pattern and abdominal pain not explained by structural or biochemical abnormalities. IBS is similar to IBD but is less serious than IBD, is noninflammatory, and does not cause permanent intestinal damage (**TABLE 9-5**). IBS is more common in women than in men. Its exact cause is unknown, but three theories of its etiology include altered GI motility, visceral hyperalgesia, and psychopathology. IBS is thought to be an intensified response to stimuli featuring increased intestinal motility and contractions. People with IBS may have a low tolerance for stretching and pain in the intestinal smooth muscle, causing them to respond to stimuli to which people without IBS do not respond. Complications of IBS include hemorrhoids, nutritional deficits, social issues, and sexual discomfort.

TABLE 9-5 Comparison of Inflammatory Bowel Disease and Irritable Bowel Syndrome

	Inflammatory Bowel Disease		Irritable Bowel Syndrome
	Ulcerative Colitis	**Crohn's Disease**	
Epidemiology	Gradual, progressive onset Peak ages 15–30 Caucasian > African American Female > male	Insidious onset Ages 15–40 Female > male	Late teens/early adulthood Female > male
Pathology	Possible autoimmune infection may precipitate familial tendency Continuous, irregular superficial inflammation of mucosal layer of colon and rectum Strictures/fistulas uncommon	Possible autoimmune infection may precipitate genetic predisposition Skipping ulcerations involving mucosal and submucosal layers along the entire GI tract; 50% involve small intestine/colon Strictures/fistulas common	Cause unknown Increased bowel response to stimuli and visceral hypersensitivity Altered perception of central nervous system
Signs and Symptoms			
Abdominal pain	Intermittent, mild, crampy tenderness	Crampy or steady Periumbilical or right lower quadrant	Sharp, burning; may be diffuse or affect only left lower quadrant
Mass present	No	Common	No
Bleeding	Common	Occasionally	No
Diarrhea	Frequent watery stools with blood and mucus	Chronic, recurrent; may have some blood	Intermittent, predominant Symptom varies with individual
Perianal lesions	No	One-third develop perianal abscesses or fistulas	No
Weight loss	With severe diarrhea	Common	No
Fever/malaise	During severe exacerbation	With exacerbation and abscess formation	No
Psychological	As a result of long-standing disease	As a result of long-standing disease	Exacerbation with stressful situations
Course/prognosis	75–80% relapse after first attack Most have mild to moderate disease Routine colonoscopy with biopsy after having the disease for 7–8 years because of increased colon cancer risk	Recurrent, progressive Typically need surgery after 7 years to treat/repair fistulas or abscesses Shortened life span	Chronic, intermittent Rare functional limitations

Description

Clinical manifestations vary from person to person. Stress, mood disorders (e.g., anxiety and depression), food (e.g., chocolate, alcohol, dairy products, carbonated beverages, vegetables, and fruits), and hormone changes (e.g., menstruation) often worsen symptoms. These manifestations usually include the following symptoms:

- Abdominal distention, fullness, flatus, and bloating
- Intermittent abdominal pain exacerbated by eating and relieved by defecation
- Chronic and frequent constipation, usually accompanied by pain
- Chronic and frequent diarrhea, usually accompanied by pain
- Alternating constipation and diarrhea that may or may not be separated by periods of normal bowel movements
- Nonbloody stool that may contain mucus
- Bowel urgency and tenesmus (rectal pain)
- Sensation of incomplete stool evacuation
- Intolerance of certain foods (usually gas-forming foods and those containing sorbitol, lactose, and gluten)
- Emotional distress
- Anorexia

Diagnosis is based on clinical presentation (TABLE 9-6) and is often made by excluding other GI and psychological disorders. Diagnostic procedures consist of a history (including bowel pattern and Rome IV criteria), stool analysis (including cultures and occult blood), celiac blood panel, abdominal X-ray, abdominal CT, abdominal MRI, barium studies (swallow and enema), sigmoidoscopy, colonoscopy, and biopsy.

TABLE 9-6 Rome IV Criteria

Recurrent abdominal pain on average at least 1 day/week in the past 3 months, associated with two or more of the following features:

1. Related to defecation
2. Changes in stool frequency
3. Changes in stool form (appearance)

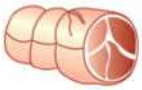
Symptoms That Support Diagnosis of IBS

Abnormal stool frequency (> 3/day or < 3/week)
Abnormal stool form (lumpy and hard or watery and loose)
Abnormal stool passage (straining, urgency, feeling of incomplete evacuation)
Passage of mucus
Bloating or feeling of abdominal distention

Adapted from: Saps, M., Malcom, A., Pasricha, P. J., Toner, B. B., Elsenbruch, S., Schechter, N. L...Miwa, H. (2016). *Rome IV Functional Gastrointestinal Disorders: Disorders of the Gut-Brain Interaction* (4th Ed.) Volume 2. United States: Rome Foundation.

Treatment focuses on management of symptoms and may vary depending on those symptoms. Pharmacologic strategies may include antidiarrheal agents, laxatives, chloride-channel activators (e.g., lubiprostone [Amitiza]), guanylate cyclase C agonists (e.g., linaclotide [Linzess]), antispasmodics, and antidepressants. Diet recommendations include maintaining adequate fiber intake, limiting gluten, avoiding gas-producing foods (e.g., beans, cabbage, and broccoli), and following a low FODMAP (fermentable oligo-, di-, and monosaccharides, and polyols) diet (**FIGURE 9-33**). Probiotics may also improve symptoms. Other strategies involve avoiding triggers, stress management (through techniques such as exercise, meditation, deep breathing, biofeedback, and acupuncture), and support (e.g., group involvement, counseling, and psychotherapy).

Low-FODMAP Diet Food Choices

Fruit	Vegetables	Grains	Dairy	Meat and seafood
Banana, blueberry, cantaloupe, clementine, cranberry, grapes, grapefruit, honeydew, kiwi, lemon, lime, orange, pineapple, papaya, raspberry, rhubarb, strawberry, tangelo  Note: if fruit is dried, eat in small quantities	Alfalfa, bamboo shoots, bok choy, carrot, celery, chives, cucumber, eggplant, green beans, lettuce, leeks, parsnip, potato, red/orange bell peppers, pickle, radish, scallions, seaweed, spinach, yellow squash, tomato, zucchini  **Herbs** Basil, coriander, marjoram, mint, oregano, parsley, rosemary, thyme	**Cereals** Gluten-free bread or cereal products **Rice** White, brown, wild  **Oats corn chips and corn tortilla** **Other** Amaranth, millet, quinoa, tapioca, cornmeal/polenta	**Milk** Lactose-free milk rice or coconut milk Lactose-free ice cream **Butter** Yogurt Lactose- free  Cheese Cheddar, swiss, parmesan, feta, lactose-free cottage cheese	 **Sweeteners** Sugar*, Splenda, aspartame, 100% maple syrup* **Fats** Oil, nuts/seeds* (no pistachios or cashews), mayo **Drinks** Water, coffee* Black/green tea, (avoid chamomile, fennel, and oolong) *Small amounts

Avoid or Reduce These Foods Containing FODMAPS

Fructose	Lactose	Fructans	Polyols	Galactans
Fruit Apple, mango, pear, watermelon, juice, large amounts of dried fruit  **Sweeteners** Honey, high fructose corn syrup, molasses	**Milk** Milk from cows/goats/sheep, custard, ice cream, yogurt, egg nog Cheese Soft, unripened cheese (ex: cottage, cream, mascarpone, ricotta), American, gouda *small amounts of sour cream is okay	**Vegetables** Asparagus, beet, broccoli, brussel sprouts, cabbage, fennel, garlic, onion, chicory root  **Other** Wheat, rye, barley, couscous, (regular bread, pasta), inulin	**Fruit** Apricot, avocado, blackberry, cherry, nectarine, peach, plum, prune, fig **Vegetables** Cauliflower, corn, mushrooms, sweet potato **Sweeteners** Ending in "ol" (i.e., xylitol, sorbitol) and isomalt	**Legumes** Beans, chickpeas, lentils  **Other** Soy and almond milk, soy beans, pistachios *However, tofu is low FODMAP

FIGURE 9-33 Low-FODMAP diet food choices.

Description

Diverticular Disease

Diverticular disease refers to conditions related to the development of **diverticula**. Diverticula (singular, *diverticulum*) are outwardly bulging pouches of the intestinal wall that develop when mucosa sections or large intestine submucosa layers herniate through a weakened muscular layer (**FIGURE 9-34**). Diverticula may be congenital or acquired. Their exact etiology is multifactorial and not completely understood. Evidence indicates that environmental factors (e.g., a diet low in fiber or high in red meat), heritable factors, and alterations in the intestinal wall structure or motility may contribute to diverticular disease development. The muscular wall can become weakened from the prolonged effort of moving stools. Pressure increases in the intestine in an attempt to propel the stool, forcing the mucosa through areas of weakness. Diverticular disease is rare in developing countries where high-fiber diets are typical but is more common in developed countries where processed foods and low-fiber diets are widely consumed. In addition to diet, poor bowel habits (e.g., straining and delaying defecation) can contribute to the development of diverticula.

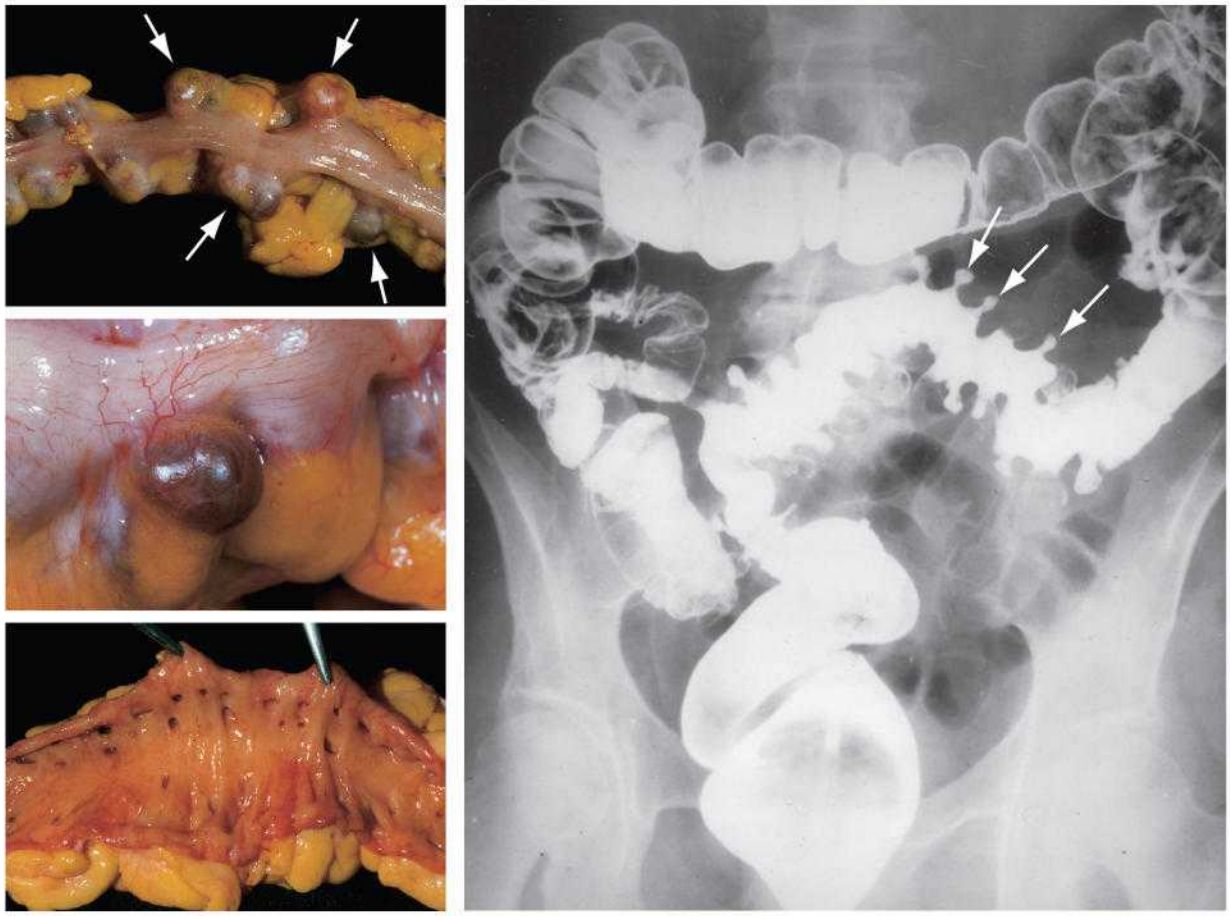


FIGURE 9-34 Diverticula. **(A)** Exterior of the colon illustrating several diverticula projecting through the wall of the colon. **(B)** A closer view of the diverticulum. **(C)** Interior of the colon, illustrating openings of multiple diverticula. **(D)** Diverticula of the colon demonstrated by injection of barium contrast material into the colon.

Courtesy of Leonard V. Crowley, MD, Century College.

Description

Most cases of diverticular disease are asymptomatic and are discovered incidentally. **Diverticulosis** refers to asymptomatic diverticular disease, usually with multiple diverticula present. In diverticulitis, diverticula have become inflamed, usually because of retained fecal matter. This condition can result in potentially fatal obstructions, infection, abscess, perforation, peritonitis, hemorrhage, and shock. Diverticulitis often remains asymptomatic until the condition becomes serious. When they appear, clinical manifestations usually include abdominal cramping, followed by passing a large

quantity of frank blood. Bleeding may last hours or days before spontaneously ceasing. Most people with diverticulitis (approximately 80%) will experience only a single episode of bleeding and require no further treatment. Persistent or recurrent bleeding, however, requires further actions. In addition to bleeding, other clinical manifestations that may be present include a low-grade fever, abdominal tenderness (usually in the left lower quadrant), abdominal distention, constipation, obstipation (severe constipation usually caused by an intestinal obstruction), nausea, vomiting, a palpable abdominal mass, and leukocytosis.

Diagnostic procedures for diverticular disease consist of a history, physical examination, stool analysis (including that for occult blood), abdominal ultrasound, abdominal CT, abdominal MRI, colonoscopy, barium enema, and biopsy. Treatment strategies include consumption of a high-fiber diet, adequate hydration, proper bowel habits (e.g., defecating when the urge is sensed and not straining), stool softeners, antibiotics (if infection is present), analgesics, and colon resection. A low-residue diet (i.e., avoiding foods with seeds, nuts, and corn) is thought to help, but no evidence supports this notion. Food intake is usually decreased when active bleeding is present, and blood transfusions may be necessary depending on the amount of blood loss.

Cancers

Malignancies of the GI system may either originate in the GI tract or spread there from other sites. These cancers can lead to altered nutrition as well as impaired elimination depending on their location. Some GI cancers have moderate treatment success rates (e.g., **colorectal cancer**), whereas others have high mortality rates (e.g., oral and pancreatic cancer). Typical cancer diagnosis, staging, and treatments are usually employed with cancers involving the GI system (see the *Cellular Function* chapter).

Oral Cancer

Oral cancer can occur anywhere in the mouth, but most cases involve squamous cell carcinomas of the tongue and mouth floor; however, 50% of cases occur on the tongue or tonsils (**FIGURE 9-35**). Approximately 75% of cases can be attributed to the use of smoked and smokeless tobacco. Alcohol consumption also significantly increases the risk of developing oral cancer. Combined alcohol and tobacco use can increase this risk by as much as 100 times. Additional risk factors include chewing areca nuts, viral infections (especially human papillomavirus), immunodeficiencies, inadequate nutrition, poor dental hygiene, chronic irritation (e.g., from dentures), and exposure to ultraviolet light (as in cancer of the lips).

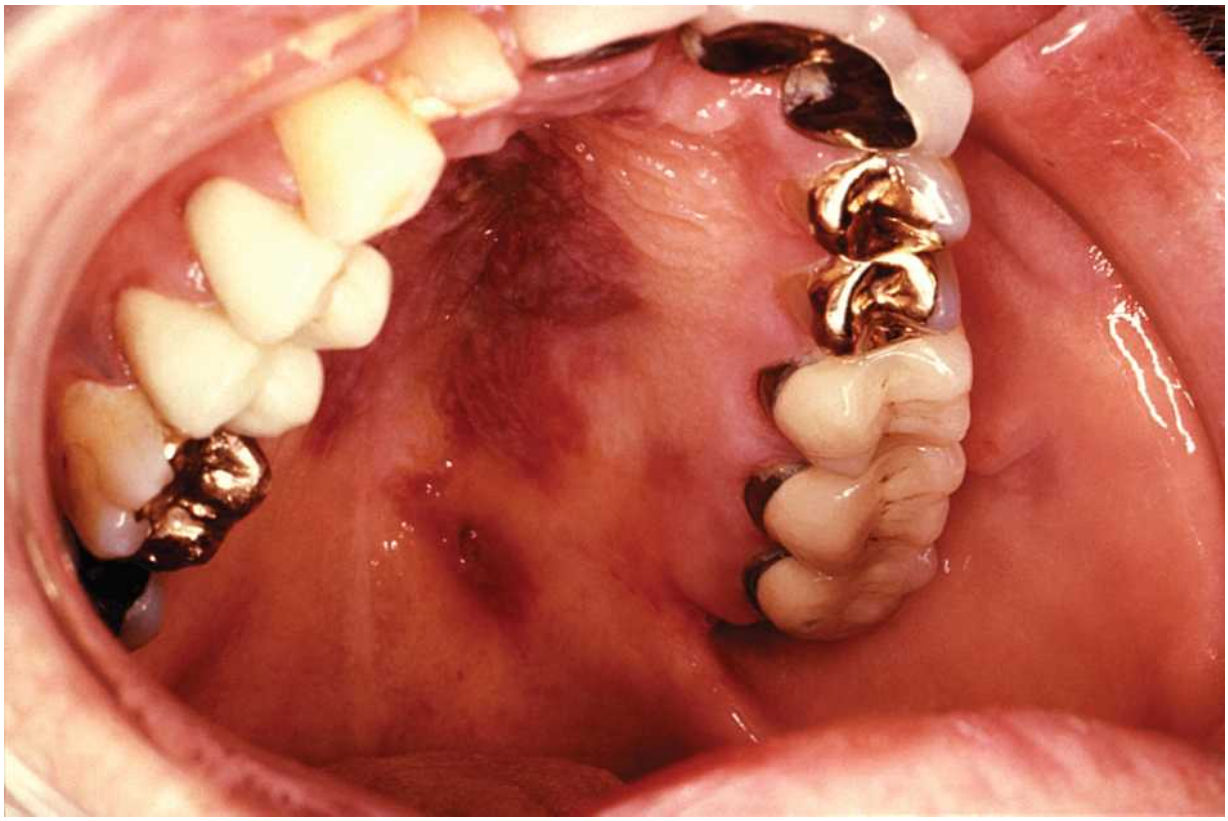


FIGURE 9-35 Oral cancer.

Courtesy of CDC/Sol Silverman, Jr., DDS, University of California, San Francisco.

Incidence rates of oral cancer have slightly decreased since 1980. Men are twice as likely as women to develop oral cancer. According to the American Cancer Society (2023), oral cancer is the eighth

most frequent cancer in men, and incidence rates are twice as high in men as in women. After years of declines, overall mortality rates increased 0.4% each year from 2009 to 2020.

In its early stages, oral cancer is very treatable. Unfortunately, most cases are advanced by the time the diagnosis is made because the cancer tends to be hidden. Oral cancer has a 5-year survival rate of 68%—a rate that has significantly improved since 1990; however, it is much lower in African Americans (52%) than Caucasians (70%).

Oral cancer usually appears initially as a painless whitish thickening (leukoplakia) that develops into a nodule or a red patch (erythroplakia). Multiple lesions may be present. These lesions develop into nodules or ulcers that persist, do not heal, and bleed easily. Additional manifestations include a lump, thickening, or soreness in the mouth, throat, or tongue as well as difficulty chewing or swallowing food. Oral cancer often metastasizes to the neck lymph nodes and the esophagus.

Treatment primarily consists of surgery and radiation, but surgery may be difficult depending on the location. Chemotherapy may be added for patients with advanced disease. Speech therapy is often necessary after treatment to improve chewing, swallowing, and speech.

Esophageal Cancer

Much like oral cancer, esophageal cancer is usually a squamous cell carcinoma or adenocarcinoma, and it most often affects men. The incidence rates of esophageal cancer have remained steady, but the mortality rates have increased since 1980. According to the American Cancer Society (2023), esophageal cancer is the seventh leading cause of cancer death in men, even though it did not make the list of top 10 cancers in men. Esophageal cancer is more common in African Americans than in Caucasians.

The distal esophagus is the most common site at which this cancer develops. Esophageal cancer is associated with chronic irritation (e.g., GERD, achalasia, hiatal hernia, alcohol abuse, and use of smoked and smokeless tobacco), obesity, Barrett esophagus, and human papillomavirus infections. These tumors can grow to match the

circumference of the esophagus, creating a stricture, or they can grow out into the lumen of the esophagus, creating an obstruction. Complications include esophageal obstruction, respiratory compromise, and esophageal bleeding.

Esophageal cancer is usually asymptomatic in its early stages, delaying its diagnosis and treatment. Because of the usually late diagnosis, the prognosis is poor for patients with esophageal cancer. Clinical manifestations, when present, typically include dysphagia, odynophagia, chest pain (not related to eating), weight loss, hematemesis, and halitosis. Iron deficiency may develop because of chronic blood loss. Diagnosis is confirmed using endoscopy with a biopsy.

Surgery is the treatment of choice, but chemotherapy and radiation are also frequently included in management. Speech therapy will likely be necessary following treatment.

Gastric Cancer

Gastric cancer occurs in several forms, but adenocarcinoma (an ulcerative lesion) is the most frequently encountered type. Incidence and mortality rates of gastric cancer in the United States have declined since 1980. Nevertheless, gastric cancer remains extremely prevalent worldwide (it is the sixth most common type of cancer) and is the fourth most deadly cancer worldwide (World Health Organization [WHO], 2022). Japan has particularly high rates of gastric cancer. Gastric cancer is more prevalent in men and in Asians and Pacific Islanders, but mortality rates are highest among African American men. Gastric cancer has a 5-year survival rate of approximately 33%.

Gastric cancer risk is associated with *H. pylori* infections, autoimmune atrophic gastritis, gastric polyps, and cigarette smoking. Dietary factors are not proven causes, but increased intake of salted, cured, pickled, preserved (containing nitrates and nitrites), and smoked meats has been correlated with gastric cancer. A low-fiber diet and constipation can increase the risk of developing this cancer because they prolong the time over which the intestinal wall is exposed to potentially harmful substances.

Gastric cancer is asymptomatic in its early stages, which often delays its diagnosis and treatment. When present, clinical manifestations include the following symptoms:

- Abdominal pain and fullness
- Epigastric discomfort
- Palpable abdominal mass
- Dark stools, possibly melena
- Dysphagia that worsens over time
- Excessive belching
- Anorexia
- Nausea and vomiting
- Hematemesis
- Premature abdominal fullness after meals
- Unintentional weight loss
- Weakness and fatigue

Diagnosis is confirmed using endoscopy with a biopsy. Surgical removal of the stomach (gastrectomy) is the only curative treatment. Chemotherapy and radiation are also used as curative and palliative measures. Nutritional support (e.g., TPN) and supplements (e.g., vitamin B_{12} and iron) will be needed before, during, and after treatment.

Liver Cancer

Liver cancer most commonly occurs as a secondary tumor that has metastasized from the breast, lung, or other GI structures (**FIGURE 9-36**). Incidence and mortality rates of liver cancer in the United States have tripled since 1980. According to the American Cancer Society (2023), liver cancer is the fifth deadliest cancer in men, but it did not make the top 10 cancers in men. Worldwide, liver cancer is the third most common cancer (WHO, 2022). Most primary tumors are caused by chronic cirrhosis or hepatitis. Liver cancer is most prevalent among men as well as among Asians and Pacific Islanders.

Additional risk factors include obesity, type 2 diabetes, chronic hepatitis B and C virus infection, heavy alcohol consumption, and cigarette smoking. Emerging evidence suggests that coffee consumption may reduce risk. Liver cancer has a 5-year survival rate of approximately 18%.



FIGURE 9-36 Liver cancer.

© Dr. E. Walker/Science Source

Liver cancer may either be asymptomatic or produce mild symptoms initially. Clinical manifestations are similar to those of other liver diseases:

- Anorexia
- Fever
- Jaundice
- Nausea and vomiting

- Abdominal pain (usually in the upper right quadrant)
- Hepatomegaly
- Splenomegaly
- Portal hypertension
- Edema, third spacing (accumulation of fluid in tissue or body cavities), and ascites
- Paraneoplastic syndrome (manifestations and diseases that result from cancer)
- Diaphoresis
- Weight loss

Diagnosis is confirmed using a liver biopsy guided by imaging. Treatment strategies vary depending on the primary site and progression of the cancer. Chemotherapy is used systemically when metastasis is evident; alternatively, it may be injected directly into localized tumors. Common sites of metastasis are the heart, lungs, brain, kidney, and spleen. If the tumor is small, a section of the liver may be surgically removed (a procedure called a “hepatectomy”). If the cancer has spread throughout the liver or caused significant damage, a liver transplant will be the best option if metastasis has not occurred.

Several nontraditional cancer treatment procedures are also available to treat liver cancer. Cryoablation is a procedure that uses extreme cold to destroy cancer cells by injecting liquid nitrogen into the tumor. Radiofrequency ablation uses electric current to heat and destroy cancer cells. Pure alcohol can also be injected into the tumor to dry and eventually kill the cancer cells.

Pancreatic Cancer

Pancreatic cancer is an aggressive malignancy (most commonly adenocarcinoma) that can quickly spread to nearby structures (e.g., stomach, intestines, spleen, liver, and kidneys). Its incidence and mortality rates have remained steady since 1980. According to the American Cancer Society (2023), pancreatic cancer is the tenth most

common cancer in men and eighth most common cancer in women, and it is the fourth leading cause of cancer deaths in both men and women. Pancreatic cancer occurs most frequently in men and in African Americans. Other risk factors include family history, obesity, chronic pancreatitis, long-standing diabetes mellitus, cirrhosis, heavy alcohol consumption, tobacco use, genetic syndromes (e.g., Lynch syndrome), and *BRCA1* and *BRCA2* mutations.

The overall 5-year survival rate for this disease is a mere 12%. This dismal prognosis is due largely to the asymptomatic nature of pancreatic cancer and the lack of a reliable early detection method. Clinical manifestations do not generally develop until the cancer is well advanced and has metastasized, delaying diagnosis and treatment. These manifestations may include the following signs and symptoms:

- Upper abdominal pain that may radiate to the back (pain worsens as cancer progresses)
- Jaundice
- Dark urine and clay-colored stools
- Indigestion
- Anorexia
- Weight loss
- Depression
- Malnutrition
- Hyperglycemia or recent onset of diabetes mellitus
- Increased clotting tendencies

Diagnosis is usually confirmed with an abdominal helical CT using pancreatic technique, magnetic resonance cholangiopancreatography, endoscopic ultrasonography, and percutaneous needle aspiration. No effective treatment has been developed for pancreatic cancer. Surgical removal of the tumor (called a “Whipple procedure”) is recommended, but few pancreatic tumors can be surgically removed. Chemotherapy and radiation are often used as palliative treatment or

in combination with surgery. Biliary blockages that develop will require repair through surgery or endoscopy. Other treatment strategies usually include pain management and nutritional support.

Colorectal Cancer

Colorectal cancer most often develops from an adenomatous polyp. According to the WHO (2022), colorectal cancer is the fourth most common and second most fatal cancer worldwide. According to the American Cancer Society (2023), colorectal cancer is the third most common and most fatal cancer in men and women in the United States, although its rates have been declining since 1980. Incidence and mortality rates are the highest among men and among African Americans. It is the second leading cause of cancer death worldwide (WHO, 2022). The 5-year survival rate for colorectal cancer is a robust 65%.

Dietary factors that have been associated with colorectal cancer include excessive intake of fat, calories, red meat, processed meat, and alcohol as well as deficient intake of fiber and calcium. Other risk factors involve family history, advancing age, obesity, tobacco use, physical inactivity, IBD, type 2 diabetes, and long-term NSAID use.

Like many other GI cancers, colorectal cancer remains asymptomatic until it is well advanced. When present, clinical manifestations may include the following symptoms:

- Lower abdominal pain and tenderness
- Blood in the stool (occult or frank)
- Diarrhea, constipation, or other changes in bowel habits
- Intestinal obstruction
- Narrow stools
- Unexplained anemia (usually iron-deficiency anemia)
- Unintentional weight loss

Routine screening can dramatically improve prognosis. The 5-year survival rate for colorectal cancer, if detected when it is localized to the large intestine, is approximately 90%. The American Cancer

Society (2023) recommends regular colorectal screening beginning at 45 years of age for both sexes (earlier if risk factors are present). The screening tests and recommended intervals are identified here:

- A high-sensitivity fecal occult blood test (which checks for hidden blood in three consecutive stool samples) should be administered every year.
- A fecal immunochemical test (which is more accurate than the fecal occult blood test) should be administered every year.
- Flexible sigmoidoscopy should be administered every 5 years.
- CT colonography (i.e., virtual colonoscopy) should be administered every 5 years.
- Colonoscopy should be administered every 10 years.

Myth Busters

Several myths regarding the GI system merit discussion.

Myth 1: Smoking a cigarette helps relieve heartburn.

Actually, cigarette smoking may contribute to heartburn. Heartburn occurs when the lower esophageal sphincter relaxes, allowing the acidic contents of the stomach to reflux into the esophagus. Esophagitis occurs more frequently in people who smoke, presumably as a result of increased acid reflux. The increased reflux is thought to occur because cigarette smoking relaxes the LES.

Myth 2: After ostomy surgery, men have erectile dysfunction and women have impaired sexual function and are unable to become pregnant.

Ostomy surgery does not, in general, interfere with a person's sexual or reproductive capabilities. In this procedure, the diseased part of the small or large intestine is removed, and the remaining intestine is attached to an opening in the abdomen. Stool is collected in a bag adhered to the skin over the opening (i.e., stoma) or in an internal pouch. Although some men who have had radical ostomy surgery lose the ability to achieve and sustain an erection, most do not. Temporary erectile dysfunction may be experienced because of damage to the nerves innervating the penis. In women, ostomy surgery does not damage sexual or reproductive organs, so it is not a direct cause of sexual problems or sterility. Factors such as pain and the adjustment to a new body image may create temporary sexual problems, but these problems can usually be resolved with time and, in some

cases, counseling. Unless a woman has undergone a hysterectomy, she can still bear children.

Myth 3: Bowel regularity means a bowel movement every day.

The frequency of bowel movements among normal healthy people varies from three a day to three a week, and some perfectly healthy people fall outside both ends of this range. Nevertheless, even three bowel movements a day can be abnormal in someone who usually has one bowel movement a day. The key to determining normality is comparing current bowel activities to the individual's usual patterns.

Myth 4: Spicy foods can increase your risk for ulcers or cause them.

Certain foods can irritate the stomach, but eating spicy foods neither increases your risk for ulcers nor causes them.

Colonoscopy is also used as a diagnostic test when symptoms are present, and it can be used as a follow-up test when the results of another colorectal cancer screening test are unclear or abnormal. Additionally, early (stage 0) cancer cells can be removed during the colonoscopy.

Cancers at stages I through III require extensive surgery (colon resection). Chemotherapy and radiation use varies depending on the cancer stage. A colostomy (a colon diversionary procedure in which the colon is brought to the abdominal wall to drain into an externally attached pouch) is rarely needed because of the colon resection. Because colorectal cancer often recurs, lifestyle changes (e.g., diet and physical activity) and follow-up screenings are crucial to long-term survival.

application to practice

Now that we have discussed conditions of the GI system, let's put that knowledge into practice. While working in the clinic, you encounter the following patients. Which patient would be at greatest risk for developing an intestinal obstruction?

- An adult diagnosed with cirrhosis of the liver
- An individual eating a low-fiber, high-fat diet

- A Jewish patient who smokes and consumes large amounts of caffeine
- An elderly patient who is on bed rest because of postoperative abdominal surgery

When determining who is at greatest risk, just start counting risk factors—the patient with the most risk factors “wins.” Here, we start with the adult with cirrhosis. This patient has no risk factors for developing an intestinal obstruction. The patient with a low-fiber, high-fat diet may be at risk because consuming a low-fiber diet can put individuals at risk for constipation. Keep this patient on the short list. Next, consider the Jewish patient. This patient does not have any risk factors, so eliminate this individual. Finally, the elderly patient has three risk factors—advancing age, immobility, and abdominal surgery. With three risk factors, the elderly patient is at the greatest risk for developing an intestinal obstruction.

SUMMARY

The GI system is responsible for ingestion, absorption, and removal of food. These functions obtain the essential nutrients, water, and electrolytes the body needs to maintain many physiologic activities and homeostasis. Disorders of the GI tract range in severity from harmless to life threatening. These disorders can be congenital, infectious, structural, or cancerous in nature. Regardless of the pathogenesis, GI disorders often create short- or long-term nutritional deficits or elimination issues that can affect the individual's overall health. Promoting GI health focuses primarily on dietary strategies that include following a well-balanced diet. Additional lifestyle behaviors include limiting alcohol consumption, maintaining a healthy weight, eliminating tobacco use, regular physical activity, and stress reduction.

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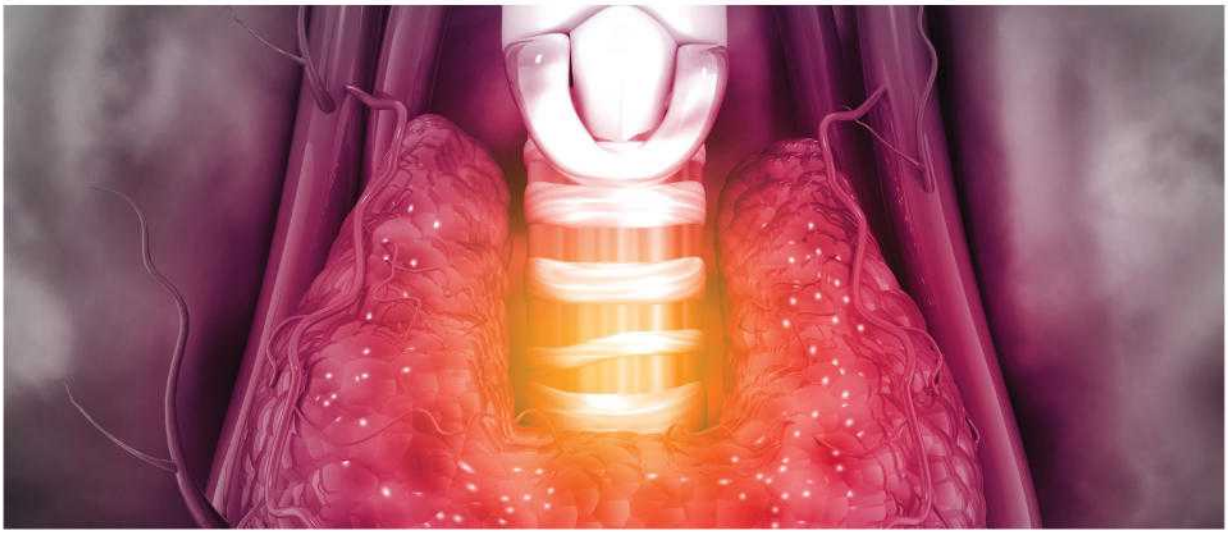
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CHAPTER 10

Endocrine Function

LEARNING OBJECTIVES

- Discuss normal endocrine anatomy and physiology.
- Compare and contrast disorders of the parathyroid gland.
- Describe and differentiate the types of diabetes mellitus.
- Compare and contrast disorders of the thyroid gland.
- Compare and contrast disorders of the adrenal glands.

KEY TERMS

acromegaly
Addison's disease
adrenal gland
aldosterone
alpha cell
amylin
beta cell
calcitonin
cortex
cortisol
Cushing syndrome
delta cell
diabetes insipidus
diabetes mellitus (DM)
diabetic ketoacidosis
dwarfism
epinephrine

epsilon cell
exophthalmos
follicle
gestational diabetes
ghrelin
gigantism
glucagon
glucocorticoid
goiter
gonadocorticoid
Graves' disease
Hashimoto's thyroiditis
hyperglycemia
hyperparathyroidism
hyperpituitarism
hyperprolactinemia
hyperthyroidism
hypoglycemia
hypoparathyroidism
hypopituitarism
hypothalamic–pituitary axis
hypothalamus
hypothyroidism
insulin
islets of Langerhans
isthmus
medulla
metabolic syndrome
mineralocorticoid
myxedema
negative feedback system
norepinephrine
pancreas
pancreatic polypeptide
pancreatic polypeptide cell
panhypopituitarism
parathyroid gland
parathyroid hormone (PTH)

pheochromocytoma
pituitary gland
polydipsia
polyphagia
polyuria
positive feedback system
somatostatin
syndrome of inappropriate antidiuretic hormone (SIADH)
T_3
T_4
thyroid gland
thyroid-stimulating hormone (TSH)
thyrotoxicosis
type 1 diabetes
type 2 diabetes

The endocrine system consists of glands located throughout the body (**FIGURE 10-1**) that are responsible for producing and secreting a wide range of hormones and chemical transmitters. These hormones serve as chemical messengers, traveling to various sites to regulate several processes, including (1) growth and development, (2) metabolism, (3) sexual function, (4) reproduction, and (5) mood stability. Hormones influence these processes by binding to receptors on the surface or within their target cells. Only small amounts of these potent substances are required to make a significant impact at the cellular and organism levels. Consequently, even subtle fluctuations in hormone levels can disrupt the body's delicate balance. Disorders of the endocrine system can result from insufficient or excessive amounts of these hormones that alter their specific function. Causes of these disorders vary but include genetic alterations, lifestyle behaviors, and tumors. The severity of these endocrine disorders can range from mild conditions that are easily managed to life-shortening or life-threatening conditions.

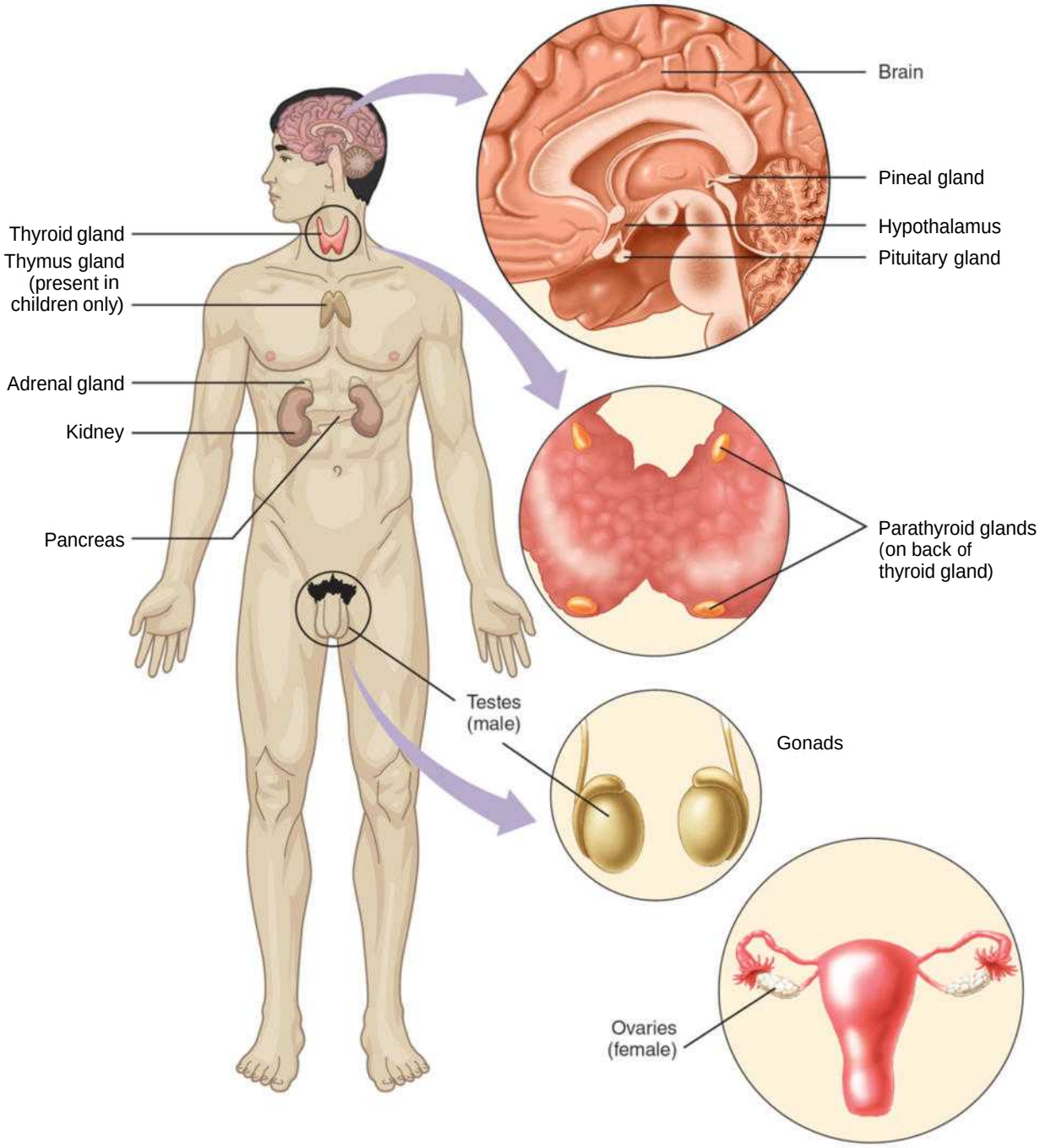
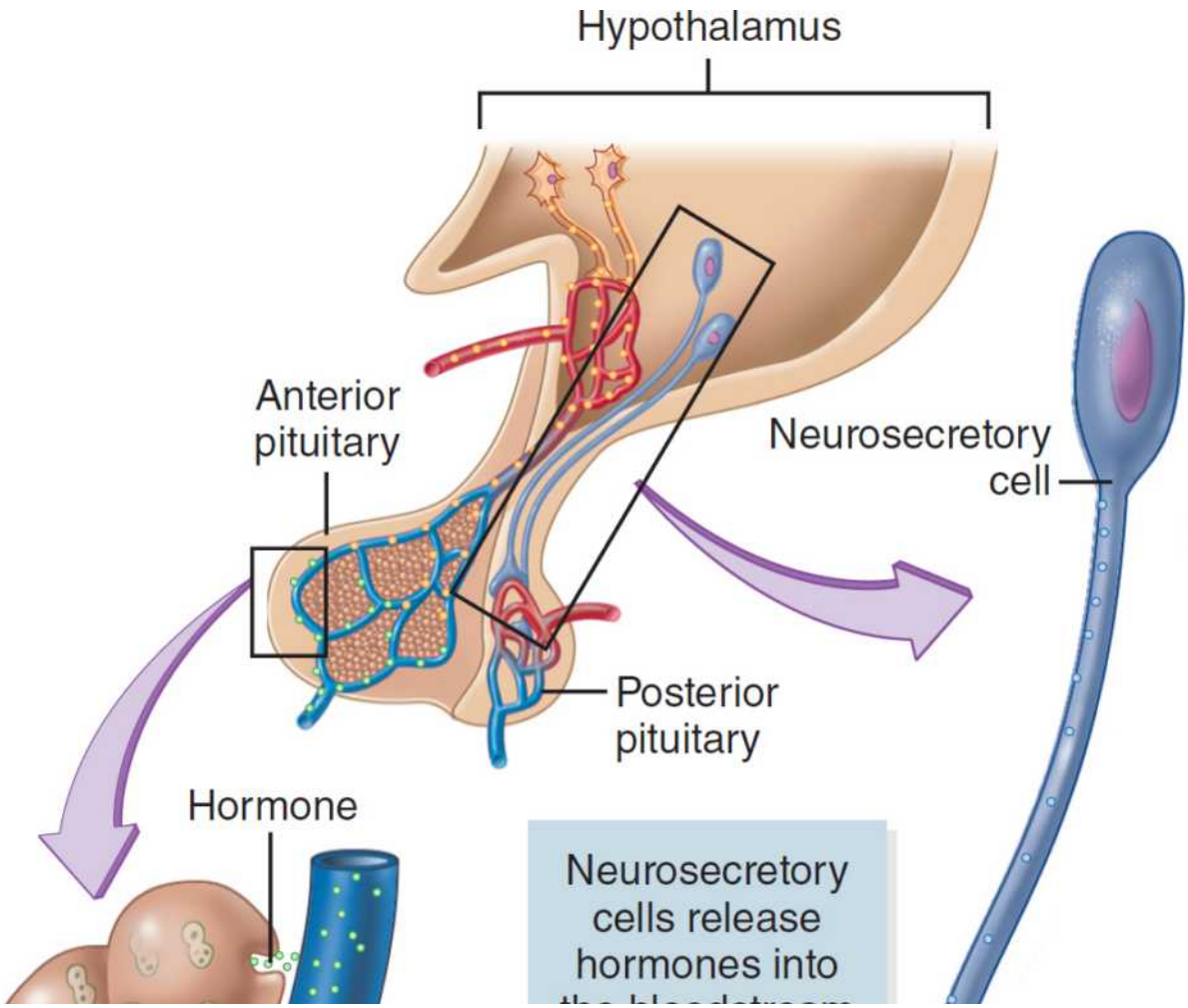


FIGURE 10-1 The human endocrine system.

Description

Anatomy and Physiology

The endocrine system is a complex messaging and control system that interacts with several body functions, using hormones to orchestrate these multifaceted communication and control operations. Endocrine glands located throughout the body produce and secrete these hormones. The term *endocrine* refers to the act of secreting substances directly into the bloodstream (**FIGURE 10-2**) rather than in a duct (like the exocrine glands of the gastrointestinal tract; see the *Gastrointestinal Function* chapter). In addition to these structures, reproductive glands (e.g., testes and ovaries) produce hormones (see the *Reproductive Function* chapter).



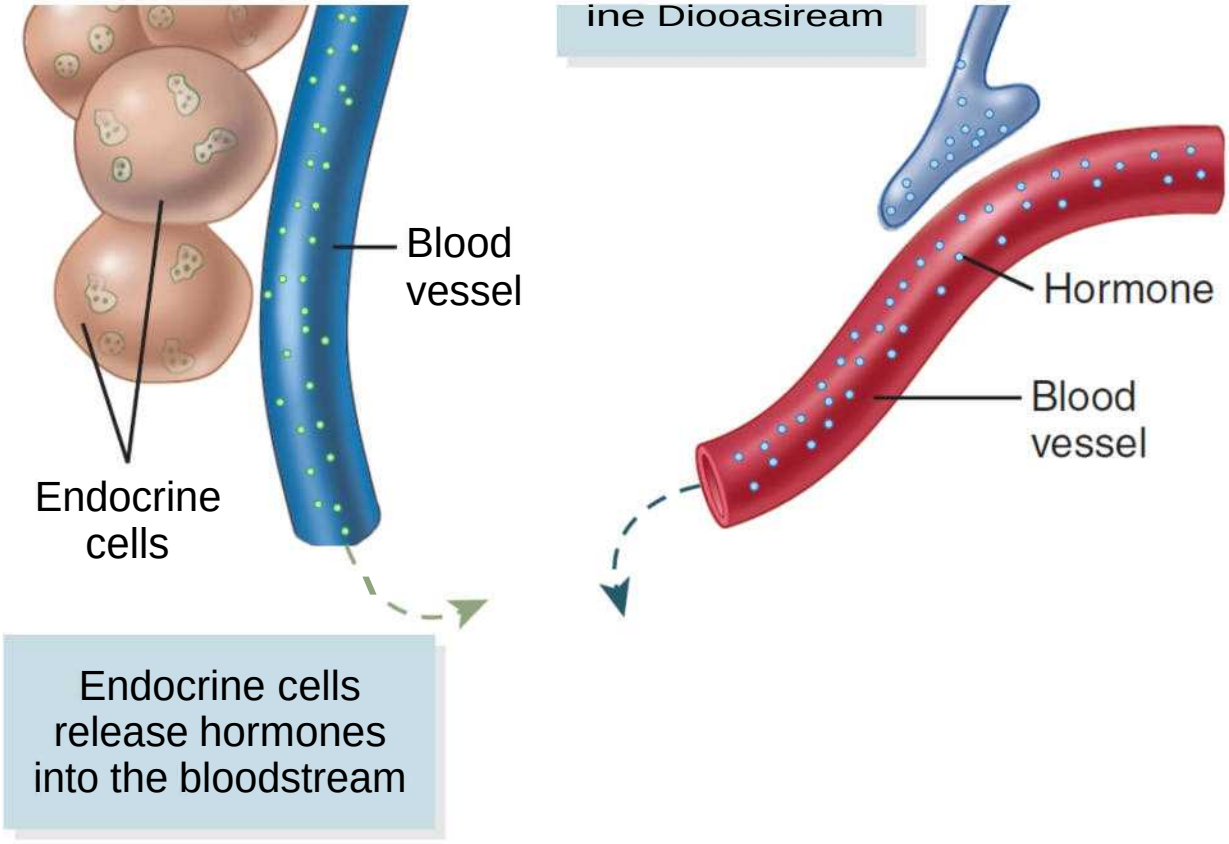


FIGURE 10-2 Endocrine release of hormones.

Description

Hormones can be classified or described regarding their action (e.g., altering serum and glucose levels), source (e.g., anterior **pituitary gland**), or chemical structure. They can also be divided into four categories based on chemical composition: (1) steroids (e.g., androgens, **glucocorticoids**, and thyroid hormones), which are lipid soluble; (2) proteins or polypeptides (e.g., **insulin** and growth hormone [GH]), which are water soluble; (3) amines and amino acids (e.g., **epinephrine**), which are water soluble; and (4) fatty acid derivatives (e.g., prostaglandins).

Release of these hormones from their respective glands is primarily controlled by a **negative feedback system** but may occasionally be influenced by a **positive feedback system** (see the *Cellular Function* chapter). The nervous system, other substances, and circadian rhythm can all influence these systems. In a negative

feedback loop, the end product (in this case, a hormone) of a biochemical process inhibits its own production—the hormone is released only when its levels decline, and production stops when its levels rise (e.g., insulin is released in response to changes in serum glucose levels). In the endocrine system, a positive feedback loop is rare; it occurs when one hormone product stimulates the production of another (e.g., the release of oxytocin during childbirth). Tropic hormones regulate endocrine glands to produce other hormones (e.g., thyroid-stimulating hormone), whereas nontropic hormones directly stimulate cellular metabolism and other activities.

Once released from an endocrine gland, hormones travel through the circulatory system to their target cells in other glands and tissues. Multiple hormone signals continuously interact with these target cells, but the cells respond only to their specific hormone. This selective response is due to protein receptors located in the cell membrane or the cytoplasm. Once the hormone has acted on the target cells, the liver metabolizes the hormone, and the kidneys excrete it to prevent an accumulative effect.

Hypothalamus and Pituitary Gland

Roughly the size of a pea, the pituitary gland is located at the base of the brain. This gland consists of two parts—the anterior and the posterior pituitary gland. The pituitary gland is often referred to as the master gland because, despite its small size, it secretes several hormones that influence many different body functions (**FIGURE 10-3**; **TABLE 10-1**). The **hypothalamus**, which is the basal (bottom) portion of the diencephalon, regulates the pituitary gland by sending signals to release or inhibit hormone production. The hypothalamus connects the nervous and endocrine systems. It contains receptors that monitor hormone, nutrient, and ion levels. When activated, these receptors stimulate neurosecretory neurons in the hypothalamus to synthesize and secrete various types of releasing and inhibiting hormones (see Figure 10-2). These hypothalamus hormones, in turn, regulate the hormones produced by the anterior pituitary gland (a relationship known as the **hypothalamic–pituitary axis**). In contrast

to the anterior pituitary, the posterior pituitary gland contains nerve cells connected directly to the hypothalamus. The hypothalamus sends hormones to the posterior pituitary gland through these nerves.

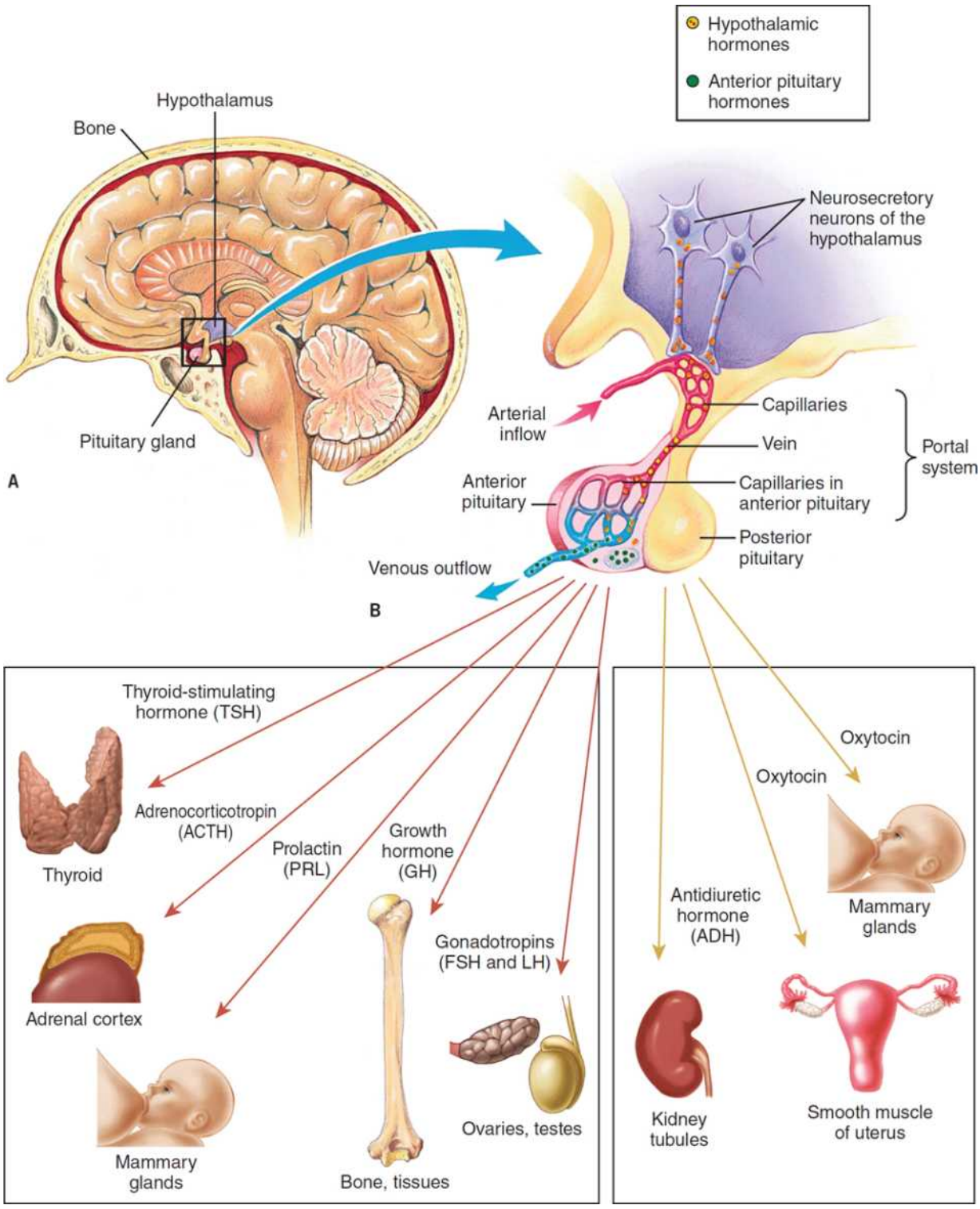


FIGURE 10-3 The pituitary gland. **(A)** A cross section of the brain showing the location of the pituitary and the hypothalamus. **(B)** The structure of the pituitary gland. Releasing and inhibiting hormones travel via the portal system from the hypothalamus to the anterior pituitary, where they affect hormone secretion.

Description

TABLE 10-1 Hormones Secreted by the Hypothalamus and Pituitary Gland

Hormone	Function
Hypothalamus	
Antidiuretic hormone (ADH)	Stimulates water reabsorption by nephrons of the kidney.
Corticotropin-releasing hormone (CRH)	Signals the anterior pituitary gland to stimulate the adrenal glands to release corticosteroids.
Gonadotropin-releasing hormone (GnRH)	Signals the anterior pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
Growth hormone–releasing hormone (GHRH) or growth hormone–inhibiting hormone (GHIH), also known as somatostatin	GHRH stimulates the anterior pituitary gland to release growth hormone (GH). GHIH inhibits the release of GH.
Oxytocin	Stimulates the breasts to release milk and uterine contractions during birth.
Prolactin-releasing hormone (PRH) or prolactin-inhibiting hormone (PIH), also known as “dopamine”	PRH signals the anterior pituitary gland to stimulate prolactin production postpartum. PIH inhibits the release of prolactin.
Thyrotropin-releasing hormone (TRH)	Stimulates the release of thyroid-stimulating hormone (TSH).
Anterior Pituitary Gland	

Hormone	Function
GH	Stimulates cell growth and fat breakdown. Primary targets are muscle and bone, where GH stimulates amino acid uptake and protein synthesis.
TSH	Stimulates the release of thyroxine and triiodothyronine by the thyroid.
Adrenocorticotropic hormone (ACTH)	Stimulates secretion of hormones by the adrenal cortex, especially glucocorticoids.
Gonadotropins: FSH and LH	Stimulate gamete production and hormone production by the gonads (i.e., ovaries and testes).
Prolactin	Stimulates milk production by the breast postpartum.
Melanocyte-stimulating hormone	Stimulates the production and release of melanin by melanocytes in skin and hair, causing the pigment to be darker and protecting against ultraviolet rays.
Posterior Pituitary Gland	
ADH	Stimulates water reabsorption by nephrons of the kidney.
Oxytocin	Stimulates the breasts to release milk and uterine contractions during birth.

Pancreas

The **pancreas** is an organ with both exocrine digestive functions (see the *Gastrointestinal Function* chapter) and endocrine functions. More than 90% of its cells focus on carrying out the digestive functions. The pancreas lies underneath the liver and between the two kidneys in the retroperitoneum (the space behind the peritoneum) (**FIGURE 10-4**). Its endocrine functions are carried out by the **islets of Langerhans**,

which are situated among the many small acini (cell clusters that produce digestive enzymes) in the pancreas. The human pancreas contains approximately 1 million islets of Langerhans, and each islet of Langerhans contains five types of cells: (1) **alpha cells**, which secrete **glucagon**; (2) **beta cells**, which secrete insulin and **amylin**; (3) **delta cells**, which secrete **somatostatin**; (4) **pancreatic polypeptide cells**, which secrete a **pancreatic polypeptide**; and (5) **epsilon cells**, which secrete **ghrelin**. Glucagon is released when serum glucose levels fall, insulin levels decline, or glucose needs increase. This hormone stimulates the breakdown of glycogen to glucose in the liver, which raises serum glucose levels. Insulin is released when serum glucose levels increase. Insulin stimulates cellular uptake of glucose, which in turn decreases serum glucose levels. Amylin is released from the beta cells along with insulin. It has a synergistic relationship with insulin in controlling glucose by suppressing glucagon, slowing gastric emptying, and promoting satiety (feeling of fullness). Somatostatin in the pancreas regulates insulin and glucagon. Pancreatic polypeptide is thought to regulate some of the other pancreatic activities. Finally, ghrelin stimulates hunger.

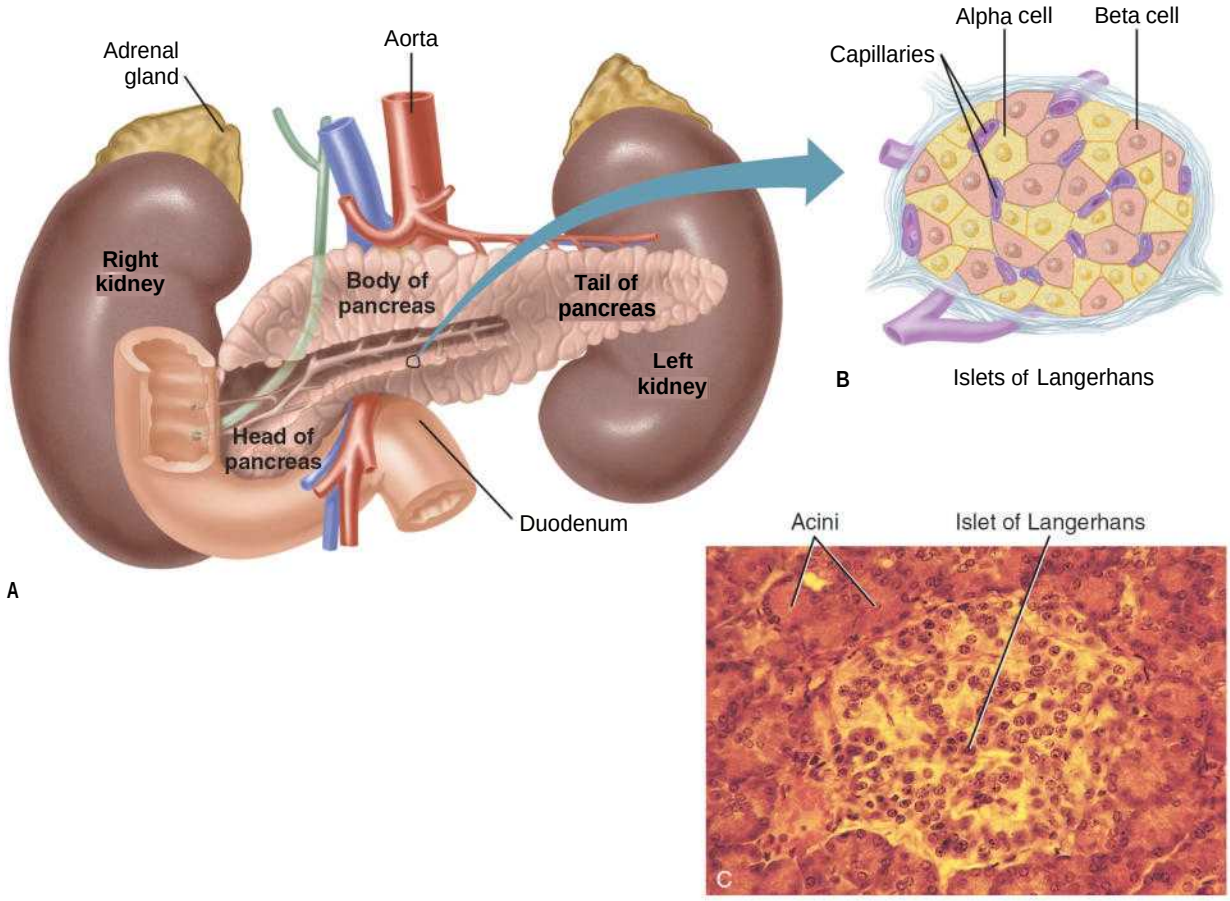


FIGURE 10-4 The pancreas. **(A)** The pancreas produces two hormones, insulin and glucagon, as well as digestive enzymes. **(B)** Hormones are produced by specialized cells within the islets of Langerhans. **(C)** The islets of Langerhans are located among the acini, very small groups of digestive enzyme–producing cells of the pancreas.

C: © Dr. John D. Cunningham/Visuals Unlimited, Inc.

Description

Thyroid Gland

The **thyroid gland** (**FIGURE 10-5**) is located at the base of the neck below the larynx. This gland consists of two lobes, one on either side of the trachea, which are connected by a thin band of tissue (**isthmus**) that extends across the anterior aspect of the trachea. A highly vascular gland, the thyroid contains several functional units called **follicles**. These follicles produce three hormones: (1) thyroxine, or T_4; (2) triiodothyronine, or T_3; and (3) thyrocalcitonin, or **calcitonin**.

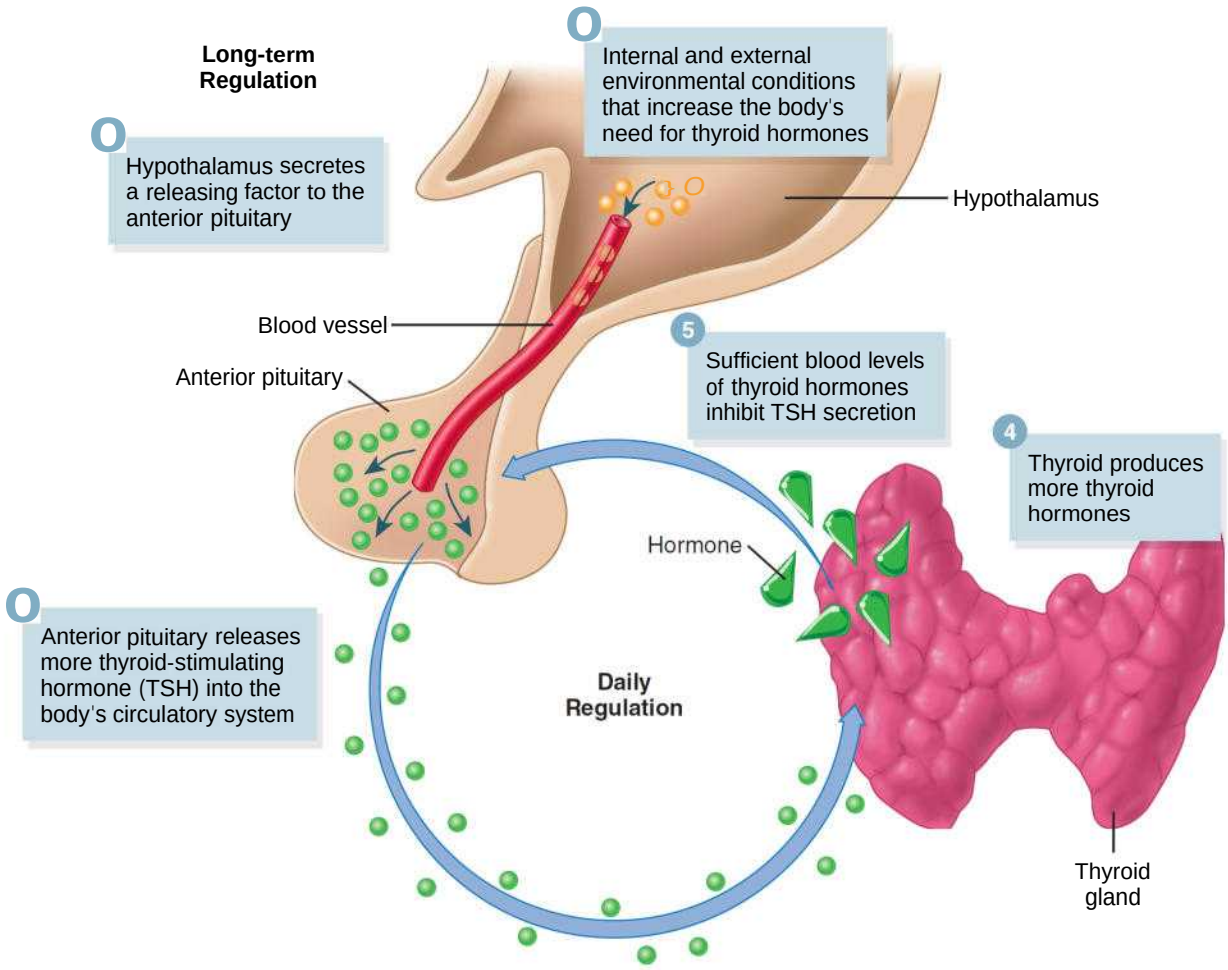


FIGURE 10-5 The thyroid gland.

Description

Together, T_3 and T_4 account for 95% of all circulating thyroid hormones; they regulate cellular metabolism as well as growth and development. The hypothalamus releases thyrotropin-releasing hormone (TRH) to stimulate the pituitary gland to produce **thyroid-stimulating hormone (TSH)** using a negative feedback system. TSH, in turn, drives the thyroid to produce T_3 and T_4. To synthesize these hormones, the thyroid requires iodine. The hypothalamus releases somatostatin to inhibit the release of TSH. Thyroid hormone secretion declines with age—but the rate at which the hormones are cleared from the blood also slows as a result of aging, so the body is usually able to maintain a balance.

Calcitonin, along with parathyroid hormone, regulates serum calcium levels. Calcitonin alters serum calcium levels by inhibiting osteoclast activity (which decreases calcium release from the bone) and stimulating osteoblast activity (which increases calcium deposits in the bone). Calcitonin also regulates calcium and phosphate by inhibiting or promoting urinary excretion through the renal tubules. This hormone is regulated by a negative feedback system, such that it is secreted when serum calcium levels are high.

Parathyroid Glands

The **parathyroid glands**, usually four in number, are located on the posterior surface of the thyroid. Each parathyroid gland secretes **parathyroid hormone (PTH)**. PTH works in the opposite way to calcitonin to regulate serum calcium levels. Specifically, PTH is secreted when serum calcium levels drop. This hormone increases serum calcium levels by increasing osteoclast activity (which increases calcium release from the bone) as well as by increasing absorption of calcium in the gastrointestinal tract and kidneys. PTH also regulates phosphate levels by reducing renal reabsorption of phosphate in the proximal tubule as well as increasing the uptake from the intestines and bones into the blood.

Adrenal Glands

The **adrenal glands** are located on each kidney. Each adrenal gland has an inner portion, or **medulla**, and an outer portion, or **cortex**. The hypothalamus influences both portions of the adrenal glands, albeit by different mechanisms. The hypothalamus secretes corticotropin-releasing hormone (CRH) to stimulate the pituitary gland to release adrenal corticotropic hormone (ACTH). ACTH alerts the adrenal glands to produce corticosteroid hormones.

The adrenal cortex is regulated by a negative feedback system involving the hypothalamus and adrenocorticotropic hormones; the medulla is regulated by nerve impulses from the hypothalamus. The medulla produces epinephrine and **norepinephrine** during times of

stress. Epinephrine and norepinephrine mediate the fight-or-flight response of the sympathetic nervous system (see the *Immunity* chapter).

The cortex has three separate regions that produce different steroids. The outermost region of the adrenal cortex secretes **mineralocorticoids**. The principal mineralocorticoid is **aldosterone**, which acts to conserve sodium and water in the body. Aldosterone is primarily regulated by the renin–angiotensin–aldosterone system, which is normally activated in times of decreased renal perfusion (e.g., hypotension, hypovolemia, and shock). The middle region of the adrenal cortex secretes glucocorticoids during times of stress. The principal glucocorticoid is **cortisol**, which increases serum glucose levels. Glucocorticoids also act on the immune system, metabolic processes, growth and development, and body fluid homeostasis. Last, the innermost region of the cortex secretes **gonadocorticoids**, or sex hormones. The adrenal cortex secretes minimal amounts of male hormones (e.g., androgen) and female hormones (e.g., estrogen) in both sexes, but the hormones from the testes and ovaries usually mask their effects. In females, the masculinization effect of androgen secretion may become evident after menopause, when estrogen levels from the ovaries decrease.

UNDERSTANDING CONDITIONS THAT AFFECT THE ENDOCRINE SYSTEM

When considering alterations in the endocrine system, organizing them based on their basic underlying pathophysiology can increase understanding. These concepts focus on inadequate (hypo) or excessive (hyper) functioning of the glands. Once you understand the normal function of the glands and the hormones they produce, it becomes clear that those functions can be either insufficient or exaggerated. In most cases of hypofunctioning, something has destroyed the gland (e.g., aging or

autoimmune conditions). Treatment for hypofunctioning usually centers on hormone replacement. In most cases of hyperfunctioning, something is overstimulating the gland or secreting hormone-like substances (e.g., tumors). Treatment for hyperfunctioning usually centers on giving medications to block hormone production, removing the cause (e.g., a tumor), or removing part or all of the gland.

Disorders of the Pituitary Gland

Disorders of the pituitary gland can have significant consequences because of the many hormones and processes that this gland influences. These disorders can originate in the hypothalamus or pituitary gland. Like most endocrine disorders, pituitary gland disorders result in either increased or decreased levels of the hormones associated with the gland (Table 10-1). These conditions can be caused by tumors (most common), infection, trauma, and necrosis.

Hypopituitarism

Hypopituitarism is a rare, complex condition in which the pituitary gland does not produce sufficient amounts of some or all (**panhypopituitarism**) of its hormones (e.g., TSH, GH, ACTH, follicle-stimulating hormone [FSH], luteinizing hormone [LH], prolactin, melanocyte-stimulating hormone, antidiuretic hormone [ADH], and oxytocin). As a result, the gland or process that the hormone controls is impaired. Hypopituitarism may result from primary (originating in the pituitary gland) or secondary (originating in the hypothalamus) causes, including the following:

- Congenital defects (e.g., pituitary hypoplasia or aplasia)
- Cerebral or pituitary trauma (may be a result of surgery, infections, stroke, radiation, or injury)
- Autoimmune conditions (e.g., hypophysitis)
- Infections of the brain and tissues that support the brain
- Tuberculosis

- Pituitary tumors (e.g., adenoma and craniopharyngioma)
- Hemochromatosis (a condition resulting in excessive iron absorption)
- Histiocytosis X (an abnormal immune condition that results in tissue damage)
- Sarcoidosis (an abnormal inflammatory condition that results in tissue damage)
- Hypothalamic dysfunction or tumors (e.g., craniopharyngioma, meningioma, or metastatic tumor)

Hypopituitarism is a progressive disorder that can occur suddenly, though it usually develops slowly. It can result in several different conditions depending on the hormones involved. The severity of these conditions reflects the degree of hormone deficit. Clinical manifestations vary greatly depending on the hormones affected and the severity of those alterations. Usually GH is lost first, followed by gonadotropins, and then TSH and ACTH. The lack of GH is usually asymptomatic and clinically undetectable in adults, but it can cause fatigue. Decreased LH and FSH levels in children cause delayed puberty. Premenopausal women experience amenorrhea, decreased libido, regression of secondary sex characteristics, and infertility. In men, a lack of LH and FSH causes erectile dysfunction, testicular atrophy, decreased libido, regression of secondary sex characteristics, and decreased spermatogenesis. Decreased TSH levels lead to **hypothyroidism** (e.g., weight gain, bradycardia, and cold intolerance). ACTH deficiency results in hypoadrenalism (e.g., fatigue, hypotension, stress intolerance, and infection). Hypothalamic causes of hypopituitarism can also result in appetite disturbances (e.g., anorexia or hyperphagia). Deficient levels of GH, somatotropin, or somatotropin-releasing hormone cause **dwarfism**, which results in short stature (**FIGURE 10-6**). **Diabetes insipidus** refers to excessive fluid excretion in the kidneys caused by deficient ADH levels.

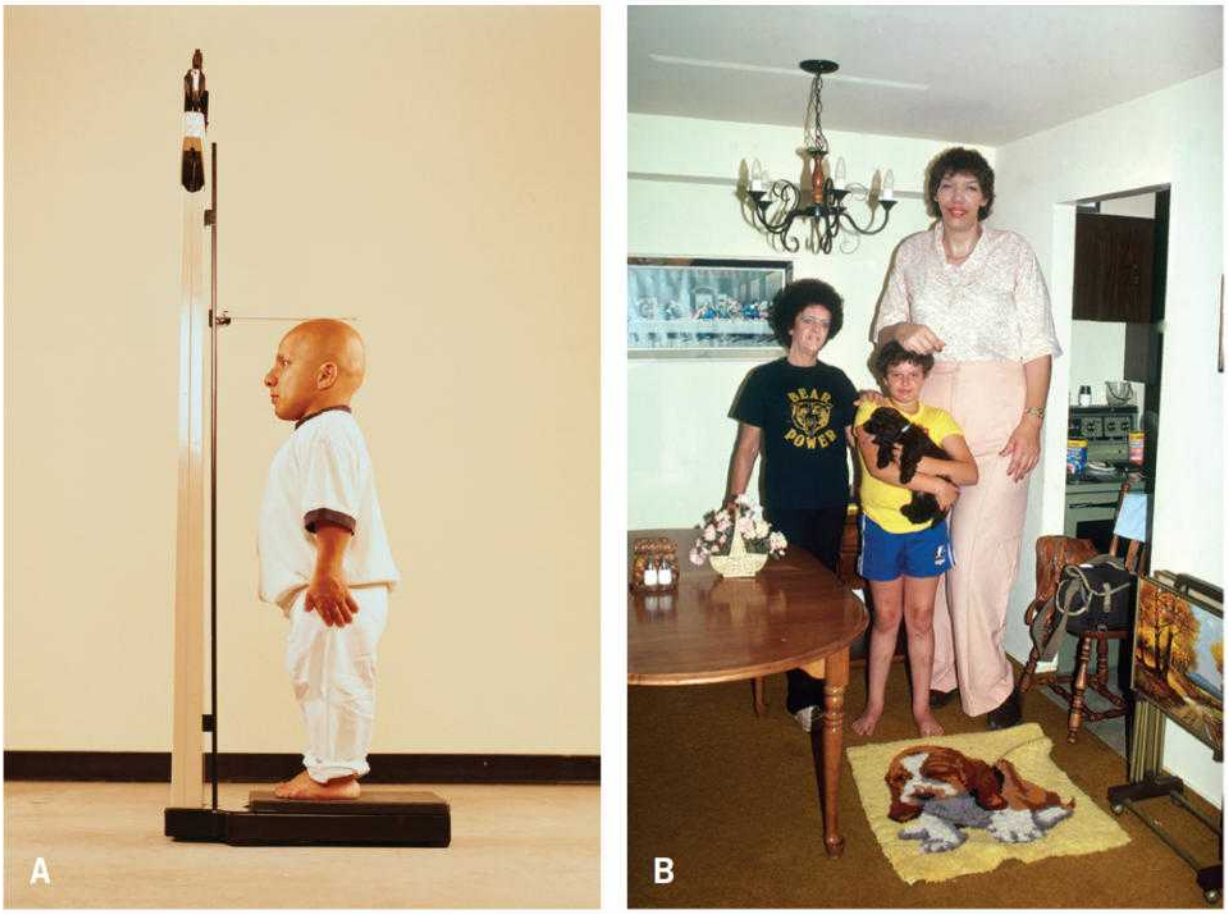


FIGURE 10-6 **(A)** Dwarfism and **(B)** gigantism.

A: Patrik Giardino/Getty Images; **B:** © Bettina Cirone/Science Source

Description

Diagnosis of hypopituitarism is often delayed because of its variable presentation and nonspecific clinical features. Definitive diagnosis is critical before treatment is initiated. Diagnostic procedures usually include a history, physical examination, serum hormone levels, brain computed tomography (CT), pituitary magnetic resonance imaging (MRI), vision testing, and X-rays (to identify any bone abnormalities).

Lifelong hormone replacement therapy is the cornerstone of treatment. Resolving and treating the underlying cause is also important when possible (e.g., cancer treatment). Additional strategies depend on the specific hormones affected (e.g., infertility

treatments and counseling). The patient will likely require monitoring by an endocrinologist and will need to wear a medical alert bracelet.

Hyperpituitarism

Hyperpituitarism is a condition in which the pituitary gland secretes excessive amounts of one or all of the pituitary hormones. The most common causes are tumors (e.g., adenoma) that secrete hormones or hormone-like substances.

Hyperpituitarism is a progressive disorder that can occur suddenly but usually develops slowly. It can result in several different conditions depending on the hormones involved. The severity of these conditions reflects the degree of hormone excess. Clinical manifestations vary greatly depending on the hormones affected and the severity of those alterations. Prolactin-secreting pituitary tumors (i.e., prolactinomas) are the most frequent secretory pituitary tumors. **Hyperprolactinemia** results in menstrual dysfunction and galactorrhea (inappropriate lactation). **Gigantism** refers to tall stature caused by excessive GH levels prior to puberty (see Figure 10-6). **Acromegaly** describes increased bone size caused by excessive GH levels in adulthood (**FIGURE 10-7**). In rare cases, acromegaly can be a result of increased levels of GHRH from a hypothalamic tumor. Excessive ACTH production results in **Cushing syndrome**. Increased TSH production is rare, but it usually occurs with GH and prolactin excess. **Syndrome of inappropriate antidiuretic hormone (SIADH)** results from increased renal water retention caused by excessive ADH levels. **Hyperthyroidism** is a hypermetabolic state caused by excessive thyroid hormones that result from increased TSH levels.



FIGURE 10-7 A woman with acromegaly **(A)** as a child, **(B)** as a teenager, and **(C)** as an adult.

Courtesy of Tanya Angus and Karen Strutynsky (www.tanyaangus.com).

Description

Clinical manifestations are similar to those noted with hypopituitarism:

- Headache
- Visual field loss or double vision
- Excessive sweating
- Hoarseness
- Galactorrhea (spontaneous lactation unassociated with childbirth or nursing)
- Sleep apnea
- Carpal tunnel syndrome
- Joint pain and stiffness
- Muscle weakness
- Paresthesia

Diagnosis of hyperpituitarism is often delayed because of its varying presentation. Diagnostic procedures usually include a history, physical examination, serum hormone levels, brain CT, pituitary MRI, vision testing, and X-rays (to identify any bone abnormalities).

Treatment strategies depend on the underlying etiology and the hormone affected. Tumors will likely require surgery, radiation, and chemotherapy, but they often reoccur. Additionally, analogues that inhibit hormone production may be given.

Diabetes Mellitus

Diabetes mellitus (DM) refers to a group of conditions characterized by **hyperglycemia** (high serum glucose levels) resulting from defects in insulin production, insulin action, or both. Glucose is a vital energy source for the body, but insulin is required for glucose to travel into the cell, where it can be used. Insulin acts like a key that unlocks the cell membrane and allows the glucose to enter. In individuals with DM, amylin levels are deficient. Without sufficient amylin, glucagon secretion increases, gastric emptying speeds up, and satiety decreases. Impaired insulin production or action results in abnormal carbohydrate, protein, and fat metabolism because of the glucose transportation issue. However, some cells, such as those in the brain, gastrointestinal tract, and skeletal muscles, can use glucose without insulin to some degree.

DM can occur in three main forms—type 1, type 2, and **gestational diabetes**; each of these variants has its own pathogenesis. Other forms of DM can also occur due to miscellaneous causes, such as monogenic diabetes syndrome (e.g., neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (e.g., cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (e.g., glucocorticoid use) (American Diabetes Association [ADA], 2023).

An estimated 422 million people worldwide have DM (World Health Organization, 2018). This disease is extremely common in the United States; in the past 20 years, the number of adults diagnosed with DM has more than doubled as the population has aged and become more overweight. Approximately 37 million Americans have diabetes and another 96 million have prediabetes, but one in five of these people do not know they have it (Centers for Disease Control and Prevention [CDC], 2022, 2023). Although DM incidence is relatively equal across

genders, this disease is most common in people older than 65 years of age, with nearly 27% of this population having DM. DM is most prevalent among African Americans, American Indians, Alaska Natives, and Hispanics. Some Pacific Islanders and Asian Americans are also at higher risk. DM accounts for $327 billion in medical costs and lost wages in the United States yearly. Although DM was only the eighth most common listed cause of death on U.S. death certificates in 2021, it likely played a role in many more deaths, as this disease contributes to numerous serious complications (e.g., heart disease, stroke, and kidney disease).

DM can result in an array of acute and chronic complications. Acute complications may include the following conditions:

- Hyperglycemia—may be a result of excessive dietary carbohydrate intake as well as insufficient or inappropriate diabetic pharmacologic therapy.
- **Diabetic ketoacidosis**—pH imbalance characterized by increased ketones in the urine caused by insufficient insulin. If cells are starved for energy, the body may begin to break down fat-producing toxic acids (ketones).
- **Hypoglycemia** (low serum glucose level)—may result from insufficient dietary intake, increased physical activity, and excessive diabetic pharmacologic therapy.

Chronic complications are a direct result of long-term excessive glucose levels, especially when DM is not adequately managed. Over time, increased glucose levels contribute to the thickening and hardening of vessel walls (much in the same way that the sugar in icing hardens on a cake), causing diffuse ischemia and necrosis. DM complications reflect these circulatory changes, with the risk of these complications increasing the longer an individual has DM and when the disease is not well controlled. Adequate DM management is the best strategy to prevent chronic complications, which include the following problems:

- Heart disease: Heart disease death rates are 2 to 4 times higher in people with DM.
- Stroke: Incidence rates are 2 to 4 times higher in people with DM.
- Hypertension: An estimated 75% of people with DM also have hypertension.
- Hypercholesterolemia.
- Diabetic retinopathy.
- Blindness: DM, as a result of diabetic retinopathy, is the leading cause of blindness.
- Kidney disease: DM is the leading cause of kidney disease.
- Diabetic neuropathy: Approximately 70% of people with DM have neuropathy (pain and numbness in the hands and feet).
- Amputations: Approximately 60% of nontraumatic amputations occur in persons with DM.
- Periodontal disease: Incidence rates are approximately 2 times higher in people with DM.
- Pregnancy complications (e.g., birth defects and high birth weight).
- Increased susceptibility to infections and delayed healing.
- Erectile dysfunction.
- Depression: Incidence rates are 2 times higher in people with DM.

Clinical manifestations of DM may vary depending on the type. These manifestations, which include the following symptoms, are a direct result of the excess glucose levels:

- Hyperglycemia
- Glucosuria (glucose is excreted in the urine in an attempt to lower serum levels)
- **Polyuria** (increased urine output because of the osmotic effects of the glucosuria)
- **Polydipsia** (increased thirst because of the dehydration caused by the increased urine output)

- **Polyphagia** (increased appetite because of the energy loss as glucose is excreted)
- Weight loss (from increased fat catabolism)
- Blurred vision (excessive glucose changes the shape and flexibility of the lens of the eye, distorting the ability to focus and causing blurred vision)
- Fatigue (because of a lack of an energy source)
- Nausea, vomiting, and abdominal pain (associated with sudden onset of type 1 diabetes)

Diagnostic procedures for DM are complex. These procedures are used for diagnosing DM and complications as well as for assessing the effectiveness of DM management (**TABLE 10-2**). Diagnostic procedures include a history, physical examination, urinalysis (to detect the presence of glucose), fasting blood glucose test, oral glucose tolerance test, random blood glucose test, hemoglobin A_{1c} ($HgbA_{1c}$; an average of glucose control for the previous 2–3 months), autoantibody levels, blood pressure measurement, and cholesterol panel.

TABLE 10-2 Diagnostic Procedures and Treatment Goals for Diabetes Mellitus

Criteria for Diagnosis of Prediabetes
$HgbA_{1c}$ 5.7–6.4%
OR
Impaired fasting glucose 100–125 mg/dL (fasting plasma glucose)
OR
Impaired glucose tolerance 140–199 mg/dL (2-hour post 75 g glucose challenge)

Criteria for Diagnosis of Prediabetes

Criteria for Diagnosis of Diabetes

$HgbA_{1c}$ > 6.5%

OR

Fasting plasma glucose > 126 mg/dL[a]

OR

2-hour plasma glucose > 200 mg/dL[a] post 75 g glucose challenge

OR

Random plasma glucose > 200 mg/dL with symptoms (polyuria, polydipsia, and unexplained weight loss)

Treatment Goals for the ABCs of Diabetes

$HgbA_{1c}$

Should be less than 7% for patients in general.

Preprandial (after a meal) capillary plasma glucose should be 70–130 mg/dL.

Peak postprandial capillary plasma glucose should be less than 180 mg/dL (usually 1–2 hours after the start of a meal). Be alert to the impact of hemoglobin variants on $HgbA_{1c}$ values.

Blood Pressure

Systolic < 130 mm Hg

Diastolic < 80 mm Hg

Cholesterol: Lipid Profile

LDL cholesterol < 100 mg/dL

Criteria for Diagnosis of Prediabetes

HDL cholesterol

- Men > 40 mg/dL
- Women > 50 mg/dL

Triglycerides < 150 mg/dL

[a]Repeat to confirm on subsequent day unless symptoms are present.

Data from American Diabetes Association. (2023). American Diabetes Association standards of medical care. *Diabetes Care, 46* (Suppl 1), S1–S204.

Treatment strategies for DM vary depending on the type, but dietary changes (American Diabetic Association recommendations) and exercise are the first line of treatment. Management also includes glucose self-monitoring, weight loss (if the patient is overweight), oral hyperglycemia medications (which usually increase insulin sensitivity), supplemental insulin, adjunctive amylin, and complication management. In addition, bariatric and metabolic surgeries have shown promise as potential cures for DM.

Emerging Research: Diabetes

Diabetes mellitus (DM) affects more than 37 million people in the United States and is the eighth leading cause of death. DM's scope and impact on human life and the healthcare system make research into this disease a priority. Basic clinical and translational research is being conducted to combat DM and its complications. A better understanding of how DM develops and progresses is important for both prevention and treatment.

The Diabetes Prevention Program (DPP) and DPP Outcomes Study (DPPOS) are major studies that changed the way type 2 DM prevention is approached worldwide (National Institute of Diabetes and Digestive and Kidney Disease [NIDDK], n.d.). Conducted from 1996 to 2002, the DPP was a clinical trial carried out in 27 clinical centers (N = 3,234) around the United States, which demonstrated that a modest weight loss and lifestyle changes (primarily dietary changes and increased physical activity) can prevent type 2 DM in high-risk individuals. The DPP also indicated that taking metformin (Glucophage) can prevent type 2 DM, albeit to a lesser degree.

Starting in 2002, the DPPOS continued following most of the DPP participants (N = 2,776). To date, the DPPOS has shown that participants who followed the DPP Lifestyle

Change Program or are taking metformin continue to prevent or delay type 2 DM as well as that these strategies are cost-effective and easily accessible. The DPPOS is currently monitoring the study participants for other health issues (e.g., cancer, cardiovascular disease, nerve damage, kidney disease, and eye disease). As participants age, DPPOS is also assessing them for age-related health problems, such as physical and cognitive difficulties.

Researchers are also working to identify genetic and environmental factors that contribute to DM development and progression. Fundamental cellular and molecular pathways underlying the development of DM and its complications are being investigated. Other researchers are exploring ways to preserve insulin-producing cells in the pancreas. Glucose monitoring is critical for adequate DM management, so researchers are also working to identify new methods to improve blood glucose monitoring as well as insulin delivery in patients with type 1 DM.

Much of the current research is focused on treatment. Nevertheless, studies are examining behavioral approaches to prevent type 2 DM as well as to enhance diabetes self-management. Clinical trials are currently testing new prevention and treatment strategies. For example, one trial is comparing different type 2 medications, and other trials are testing ways to prevent type 1 DM in those individuals with a family history. Early weight-loss surgery has also shown promise in improving **type 2 diabetes** and blood pressure outcomes (NIDDK, 2022).

The Diabetes Research Institute (DRI, 2022) is leading research focused on finding a DM cure; it is housed at the University of Miami and supported mostly through private funding. The DRI is seeking to develop a biological cure by restoring natural insulin production and normalizing blood glucose without imposing other risks. Its research has already demonstrated that islet transplantations can eliminate the need for insulin therapy for people with type 1 DM. Research is building on this work to address the major challenges that have limited this type of cell replacement therapy to the most severe cases. The DRI has focused on developing BioHub, a bioengineered “mini organ” that mimics the pancreas, containing insulin-producing cells and other vital components for keeping the cells healthy and functioning over the long term. DRI researchers are also working to develop strategies to eliminate the need for antirejection drugs, shield the islets from or stop the autoimmune attack that triggers DM onset without harsh drugs, and create an unlimited supply of insulin-producing cells or regenerate a patient’s own islets.

Type 1 Diabetes

Type 1 diabetes was previously called insulin-dependent DM and juvenile-onset DM, but these terms are no longer used (**TABLE 10-3**). Type 1 DM develops when the body’s immune system destroys pancreatic beta cells. The exact cause of type 1 DM is unknown, but most likely a viral or environmental trigger in genetically susceptible people causes an autoimmune reaction. Susceptible genes include those within the major histocompatibility complex (e.g., human leukocyte antigen [HLA]-DR3,DQB1*0201, and HLA-

DR4,DQB1*0302). Other vulnerable genes include those that regulate insulin production (e.g., insulin growth factor genes). The autoantigens thought to be responsible for the autoimmune reaction include glutamic acid decarboxylase, insulin, proinsulin, insulinoma-associated protein, zinc transporter ZnT8, and other beta-cell proteins. These substances are released during normal beta-cell turnover and beta-cell injury, triggering a T-cell–mediated immune response that results in beta-cell destruction. For unknown reasons, the autoantigens seemingly spare the other pancreatic cells. Viruses that have been linked to the onset of type 1 DM include coxsackievirus, rubella virus, cytomegalovirus, Epstein-Barr virus, and retroviruses. These viruses may directly infect and destroy beta cells or cause these cells' destruction through autoantigen activation. For unknown reasons, exposure to dairy products during infancy, increased nitrates in drinking water, and decreased vitamin D consumption also increase risk.

TABLE 10-3 Comparison of Type 1 and Type 2 Diabetes

	Type 1	Type 2
Age	Usually in children or young adults	Usually after age 40, and incidence increases with age
Onset	Generally abrupt Often diagnosed after infection Diabetic ketoacidosis	More often insidious Patients often obese Nonketotic coma resulting from dehydration
Treatment	Insulin	Diet, exercise, oral medication Insulin may be required as disease progresses
Complications	Occur early, often severe	Full range of complications may be present at diagnosis
Insulin levels	Low or absent	Frequently normal or high

The destruction progresses subclinically for months or years until the remaining beta cells are unable to compensate for the loss. At this point, insulin concentrations are no longer adequate to control serum glucose levels. This form of DM usually strikes children and young adults, although its onset can occur at any age.

In adults, type 1 DM accounts for 5% of all diagnosed DM cases. Referred to as “latent autoimmune diabetes” in adulthood, type 1 DM in adults initially appears to be type 2 and is often misdiagnosed. Some cases of type 1 DM in adults, particularly in non-Caucasian populations, do not seem to be autoimmune in origin and are considered idiopathic.

Type 1 DM cannot be prevented, and people with this disease must obtain insulin delivered by injection or a pump to survive. Pramlintide (Symlin) is a new adjunct medication to treat type 1 or 2 DM. This injectable synthetic amylin delays gastric emptying, suppresses appetite, slows intestinal absorption, and reduces hepatic glucagon production. Pramlintide is always used with insulin, and because of its synergistic effects, severe hypoglycemia can occur, especially in individuals with type 1 DM.

Prediabetes

Prediabetes refers to a state where blood glucose levels are higher than normal but have not reached the threshold at which the individual would be diagnosed with type 2 DM. In prediabetes, cells become resistant to insulin, meaning they prevent insulin from transporting glucose into the cells. Although not completely understood, this resistance is thought to develop in part because of hormones called “adipokines” (e.g., resistin, adiponectin, and leptin) secreted by adipose cells (i.e., adipocytes) (Dasari & Raghunath, 2018). These adipose cells also secrete immune and inflammatory substances (e.g., tumor necrosis factor-alpha and interleukin-6, among others) that impair insulin sensitivity and glucose metabolism. Low levels of adiponectin have been found in obesity. Adiponectin is a protective adipokine that reduces free fatty acids and is associated with glucose control, reduced inflammation, and improved lipid levels. High levels of resistin have been found with obesity; this hormone is also released

from leukocytes during the subclinical chronic low-grade inflammatory response that accompanies obesity. As a pro-inflammatory adipokine, resistin is thought to contribute to atherosclerosis development as well.

In individuals with prediabetes, glucose levels in the blood increase as a result of insulin resistance. The resulting hyperglycemia causes the pancreas to increase insulin production to compensate. A vicious cycle begins as the pancreas continues to increase insulin production in response to the hyperglycemia until this organ can no longer keep up with the demand. Hyperglycemia itself may also desensitize or destroy beta cells (glucose toxicity), resulting in decreased insulin secretion.

Intrauterine growth restriction and low birth weight have been associated with insulin resistance later in life. In both children and adults, lifestyle changes (e.g., weight loss, healthy diet, and physical activity) can prevent or delay type 2 DM and its complications.

Type 2 Diabetes

Type 2 diabetes was previously called “non-insulin-dependent DM” and “adult-onset DM,” but those terms are no longer used. In adults, type 2 DM accounts for approximately 90% to 95% of all newly diagnosed DM cases.

This form of DM usually begins as insulin resistance (see the “Prediabetes” section). Insulin resistance in the liver leads to the inability to suppress glucose production, further contributing to excessive hyperglycemia. Insulin levels are often markedly high, especially early in the disease. Over time, the pancreas may gradually lose its ability to produce insulin.

Type 2 DM is associated with advancing age, obesity, family history of DM, history of gestational DM, impaired glucose metabolism, and physical inactivity. African Americans, Hispanics, Native Americans, Asians, Native Hawaiians, and other Pacific Islanders are at particularly high risk for type 2 DM and its complications. Asian populations tend to develop type 2 DM at a younger age and with a normal weight. Type 2 DM in children and adolescents, although still rare, is being diagnosed more frequently

because of increasing rates of childhood obesity. Additionally, type 2 DM has been associated with depression and schizophrenia.

Postprandial (after a meal) serum glucose levels are generally higher in older adults with type 2 DM than in young adults, especially after consuming high-carbohydrate meals. Glucose levels also take longer to return to normal in the former group.

Type 2 DM is usually managed initially with oral antidiabetic medications that increase insulin production and action. Some of these medications also have an anti-inflammatory property (e.g., thiazolidinediones). As the condition progresses, supplemental insulin often becomes necessary as pancreatic production declines. Pramlintide (Symlin) can also be used along with insulin.

Gestational Diabetes

Gestational diabetes is a form of glucose intolerance diagnosed during pregnancy, usually in the second or third trimester. For many years, gestational DM was defined as any degree of glucose intolerance that was first identified during pregnancy, but evidence suggests that many cases may actually represent undiagnosed preexisting (pregestational) DM (ADA, 2023).

Many metabolic, biochemical, physiological, hematological, and immunological changes occur during pregnancy, though these changes usually reverse after delivery. Normally, the development of insulin resistance during pregnancy represents an attempt to ensure adequate glucose is available to meet the increased maternal energy needs but, more importantly, to ensure the growing fetus can meet its metabolic needs. This physiological insulin resistance leads to more use of fats than carbohydrates for energy by the mother, sparing the carbohydrates for the fetus. This change is mediated by several factors, including increased levels of estrogen, progesterone, human placental lactogen, GH, and prolactin, among others. Gestational DM occurs when the pancreas is unable to function effectively to overcome this insulin-resistant state.

Gestational DM occurs most frequently among African Americans, Hispanics, and Native Americans. Other risk factors include obesity and a family history of DM. DM during pregnancy (whether

pregestational or gestational) increases the risk for preeclampsia (high blood pressure during pregnancy along with organ damage), fetal demise (e.g., abortion and stillbirth), major congenital malformations, increased birth weight, as well as neonatal respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, and increased blood viscosity. The risk of these conditions increases when blood glucose is poorly controlled. Additionally, DM during pregnancy increases the risk of a cesarean section.

During pregnancy, gestational DM requires treatment (usually lifestyle changes and insulin) to normalize maternal blood glucose levels to avoid fetal complications. Gestational DM usually indicates underlying beta-cell destruction, which increases the risk of the woman developing DM later. Immediately after pregnancy, 5% to 10% of women with gestational DM are diagnosed with DM, usually type 2. Women who have had gestational DM have a 40% to 60% chance of developing DM within 5–10 years. Additionally, children born to women who had DM while pregnant with them have an increased risk of developing DM later in life.

Diabetes Due to Other Causes

Diabetes may also be caused by genetic defects affecting beta-cell function, insulin action, and mitochondrial deoxyribonucleic acid (DNA) (e.g., maturity-onset diabetes of youth). Individuals with maturity-onset diabetes in youth are often misdiagnosed as having type 1 DM. Pancreatic conditions (e.g., cystic fibrosis, pancreatitis, hemochromatosis, and pancreatectomy), endocrine dysfunction (e.g., Cushing syndrome and acromegaly), exposure to toxins (e.g., rodenticides), and long-term use of certain medications (e.g., glucocorticoids, beta blockers, protease inhibitors, and niacin) may all lead to DM in some individuals, though these other causes account for only a small number of cases of DM. Although the underlying pathology varies, the treatment follows the usual DM management (e.g., lifestyle changes, oral antidiabetic medications, and supplemental insulin and amylin). Identifying and treating the

underlying cause (e.g., discontinuing causative medications), when possible, can also aid in disease control and possible reversal.

Metabolic Syndrome

Metabolic syndrome, also referred to as "syndrome X" or "insulin resistance syndrome," is a cluster of risk factors that occur together—specifically, hyperglycemia (particularly fasting), hypertension, dyslipidemia, and increased waist circumference due to excess abdominal fat (apple-shaped). Metabolic syndrome is not a form of DM, but it is related to DM because this syndrome increases the risk of cardiovascular disease, DM, and stroke. Metabolic syndrome is common in developed countries, especially in people aged 50 or older. It is less common among people with excessive fat distribution around the hips (pear-shaped) and a low waist-to-hip ratio. Excessive abdominal fat leads to increased free fatty acids in the portal vein and increasing fat accumulation in the liver (i.e., nonalcoholic steatohepatitis). Fat also accumulates in the muscle cells. Insulin resistance develops, resulting in impaired glucose metabolism. Hyperglycemia promotes dyslipidemia and hypertension development. Increased serum uric acid levels, hypercoagulopathy, and systemic inflammation may be present as well.

The diagnostic criteria for metabolic syndrome include the presence of three or more of the risk factors. Treatment strategies focus on lifestyle changes (e.g., weight loss, dietary changes, regular physical activity, and smoking cessation) to prevent the development of complications. Occasionally, metformin (Glucophage) or a thiazolidinedione may be used to decrease insulin resistance.

Disorders of the Thyroid

Because of the thyroid hormones' responsibilities, disorders of the thyroid have a significant impact on metabolic activities. These disorders result in either an increase or a decrease in the thyroid hormones. Several etiologies can give rise to these conditions, including tumors, congenital defects, damage (e.g., from surgery,

radiation, or infections), and aging. These conditions are usually easily managed with medications and surgery.

Goiter and Thyroid Nodules

A **goiter** refers to an abnormal enlargement of the thyroid gland (**FIGURE 10-8**). This enlargement is usually painless but may affect the respiratory and gastrointestinal systems. It is not necessarily malignant. Goiters can occur in hyperthyroidism, hypothyroidism, and normal thyroid states. Thyroid nodules are (single or multiple) benign or malignant growths within the thyroid gland. Benign causes include cysts, thyroiditis, and thyroid adenomas. Risk for developing these nodules increases with age. These nodules occasionally produce excessive thyroid hormones, leading to hyperthyroidism.

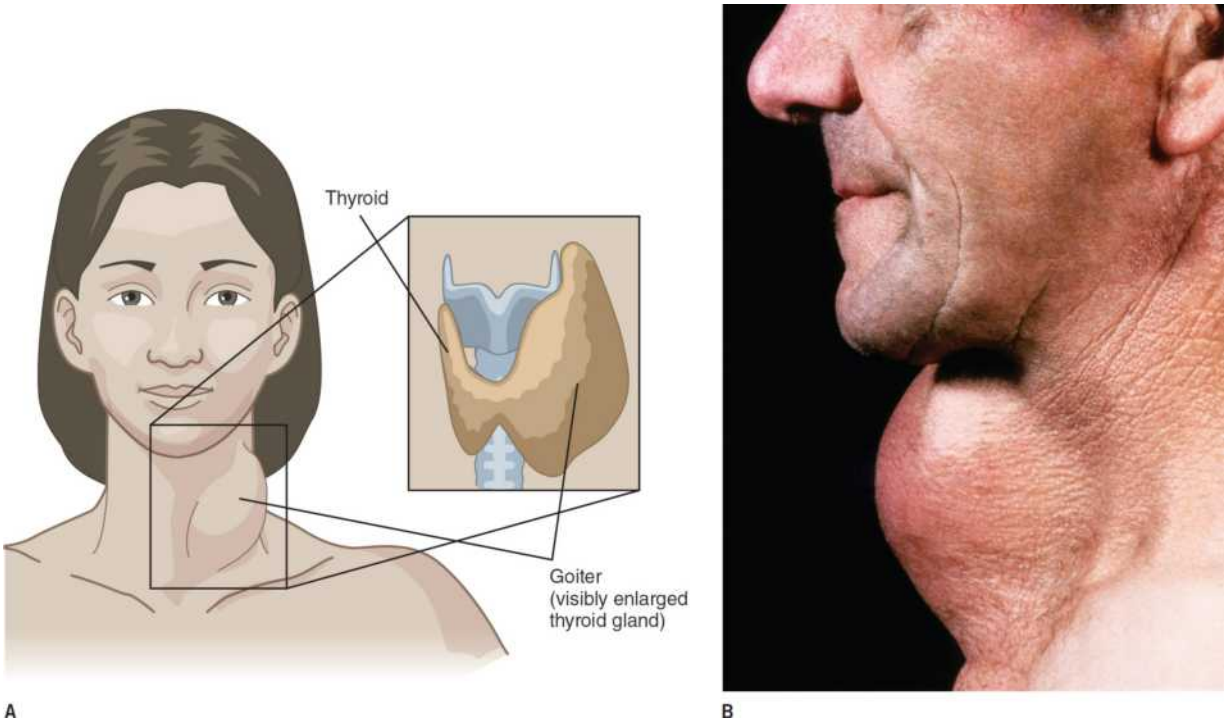


FIGURE 10-8 Goiter.

B: © Biophoto Associates/Science Source

Description

Iodine deficiency is the most common cause of goiters worldwide. Iodine deficiency is rare in the United States, so goiters in this country

more often result from thyroid nodules and autoimmune thyroid disorders. Iodine deficiency leads to decreased T_3 and T_4 production, and TSH production increases in an attempt to compensate for the low levels of these thyroid hormones. Increased levels of TSH lead to thyroid hyperplasia and hypertrophy. A similar reaction occurs in both hyperthyroidism and hypothyroidism states.

Hypothyroidism

Hypothyroidism refers to a condition in which the thyroid does not produce enough thyroid hormones. This endocrine disorder is relatively common, affecting 5 out of 100 Americans. Hypothyroidism can be congenital or acquired as a result of hypothalamus, pituitary, or thyroid (the most common) dysfunction. Several conditions can result in hypothyroidism. Women are more likely to develop hypothyroidism than men, and risk increases with age, especially in persons older than 50 years.

In many cases, a previous or current inflammation of the thyroid gland (i.e., thyroiditis) leaves a large percentage of thyroid cells damaged and incapable of producing sufficient hormone amounts. The most common cause of this kind of thyroid gland failure is called "chronic autoimmune thyroiditis" (also called **Hashimoto's thyroiditis**). Subclinical hypothyroidism refers to elevated serum TSH in individuals with absent or minimal symptoms and normal serum T_4. Subclinical hypothyroidism is fairly common, especially in individuals with chronic autoimmune thyroiditis. Additional causes of thyroiditis include infections, trauma, and following childbirth or abortion. Thyroid autoantibodies are often detected after pregnancy and persist after birth. The inflammation often resolves, and the thyroid can begin to function normally again. However, the hypothyroidism can persist or develop permanently in the future.

The second major cause of hypothyroidism is iatrogenic (resulting from medical treatments). The treatment of many thyroid conditions, such as hyperthyroidism, warrants partial or complete surgical removal of the thyroid gland. If the total remaining thyroid hormone-producing cells are not able to meet the needs of the body,

hypothyroidism develops. This result is often the goal of surgery for thyroid cancer. Similarly, goiters and some other thyroid conditions can be treated with radioactive iodine therapy. The aim of this therapy (for benign conditions) is to kill a portion of the thyroid and thereby prevent goiters from growing larger or developing into hyperthyroidism. Occasionally, the radioactive iodine treatment can damage too many cells, but this consequence is usually preferred over the original problem. Hypothyroidism can also result from the use of certain medications (e.g., lithium and amiodarone). Lithium inhibits the release of thyroid hormones, and amiodarone contains iodine.

Myth Busters

Several myths regarding diabetes mellitus (DM) in the community merit discussion.

Myth 1: People with diabetes cannot eat sweets or chocolate.

If chocolate and other sweets are eaten as part of a healthy meal plan, or combined with exercise, people with DM can eat them. There are no more off-limit foods for people with DM than there are for people without DM.

Myth 2: Eating too much sugar causes diabetes.

DM is caused by a combination of genetic and lifestyle factors, not by eating too much sugar. However, being overweight does increase your risk for developing type 2 DM. If there is a family history of DM, following a healthy meal plan and getting regular exercise are recommended to manage weight.

Myth 3: Pills for DM provide oral insulin.

Oral medications for DM affect the ability of the body to produce insulin and use insulin better—they are not oral insulin. Going through the gastrointestinal system would destroy the insulin; therefore, insulin must be injected.

Myth 4: Drinking water can excrete the extra sugar in the blood.

Extra glucose in the blood cannot be excreted by drinking extra water. However, DM can be controlled by eating healthy food, being physically active, managing weight, receiving routine examinations, taking prescribed medications, and monitoring blood glucose often.

Myth 5: Fruit is a healthy food, so it is acceptable to eat large quantities of it.

Fruit is a healthy food, containing fiber and lots of vitamins and minerals. Because fruit contains carbohydrates that break down quickly into simple sugars, it needs to be included in a healthy meal plan, but amounts should be controlled because fruit will raise blood glucose levels.

Myth 6: When taking oral diabetic medications or insulin, people with DM can eat anything they want.

The oral medications or insulin taken for DM are more effective when they do not have to work as hard to lower blood glucose. Combining medicines with a healthy meal plan and physical activity gives better glucose control.

Myth 7: Once a person begins taking oral diabetic medications or insulin for type 2 diabetes, they must be taken for life.

Sometimes, temporary circumstances may cause elevated glucose levels (e.g., glucocorticoid therapy and total parenteral nutrition administration), and diabetic medications will be needed only during those events. Some people who have been started on oral diabetic medications and/or insulin find that they can control their blood glucose without medications with weight loss, exercise, and healthy dieting.

Myth 8: If I have to start taking insulin after being on diabetic pills for my type 2 diabetes, then my type 2 diabetes has progressed to type 1.

This myth is a common misconception and why the term “non-insulin-dependent diabetes” is no longer used for type 2 DM. With type 2 DM, insulin resistance can lead to a progressive decrease in insulin production as pancreatic destruction advances and failure develops. The lack of insulin production does not make it type 1 or type 2; instead, the underlying pathology determines the type of diabetes.

The Global Diabetes Community. (2023). Diabetes myths. Retrieved from http://www.diabetes.co.uk/diabetes-myths.html

Secondary hypothyroidism, a relatively uncommon condition, occurs when the hypothalamus produces insufficient TRH or the pituitary gland produces too little TSH. Deficient TRH can also lead to deficient TSH, referred to as “tertiary hypothyroidism.”

The clinical manifestations of hypothyroidism vary widely, depending on the severity of the hormone deficiency. Generally, these symptoms tend to be insidious and develop slowly, often over a number of years. In contrast, manifestations can develop suddenly after a thyroidectomy, abrupt cessation of thyroid hormone replacement, or widespread thyroid damage. The clinical

manifestations reflect the decreased thyroid activity (e.g., metabolism):

- Fatigue
- Sluggishness
- Increased sensitivity to cold
- Constipation
- Pale, dry skin
- Edema in the face, hands, and feet
- Effusions (pericardial, pleural, or abdominal)
- Hoarseness
- Hypercholesterolemia
- Unexplained weight gain
- Myalgia
- Arthralgia
- Muscle weakness
- Paresthesias of the hands and feet
- Abnormal uterine bleeding
- Infertility
- Brittle fingernails
- Hair loss or thinning
- Bradycardia
- Hypotension
- Hypothermia
- Forgetfulness, personality changes, depression, dementia, or psychosis
- Goiter

Advanced hypothyroidism, known as **myxedema**, is rare. When it occurs, however, myxedema can be life threatening. Myxedema is usually triggered by an illness, infection, trauma, central nervous system suppressants, and exposure to cold. Clinical manifestations

include marked hypotension, respiratory depression, extreme hypothermia, areflexia, seizures, lethargy, and coma.

Diagnostic procedures for hypothyroidism include a history, physical examination, serum thyroid hormone levels, serum TSH, serum antithyroid antibody levels, liver function tests, complete blood counts (CBC), cholesterol panel, and electrocardiogram (EKG). Primary hypothyroidism results in high serum TSH and low T_3 and T_4 levels. High serum TSH and normal T_3 and T_4 levels indicate subclinical hypothyroidism. Secondary hypothyroidism results in low serum TSH (occasionally normal with less bioactivity) and low thyroid hormones.

Hypothyroidism is easily managed with thyroid hormone replacement (e.g., levothyroxine [Synthroid]). However, the therapy should not be initiated in patients with secondary hypothyroidism until adequate cortisol levels are verified because it could precipitate an adrenal crisis. Additional strategies are implemented to manage symptoms and may include weight management (e.g., a low-calorie diet and increased physical activity), constipation measures (e.g., stool softener and increase in dietary fiber and fluid intake), and avoidance of cold temperatures.

Learning Points

Hypothyroidism and hyperthyroidism present very differently. When considering the clinical manifestations of these disorders, think about what increasing or decreasing thyroid hormones would do in the body. With hypothyroidism, the hormone levels are decreased and so are all the clinical manifestations (e.g., bradycardia, hypotension, depression, and constipation), except for weight. With hyperthyroidism, the hormone levels are increased and so are all the clinical manifestations (e.g., tachycardia, hypertension, anxiety, and diarrhea), except for weight.

Hyperthyroidism

Hyperthyroidism refers to a condition characterized by excessive levels of thyroid hormones. This overabundance of thyroid hormones results in a hypermetabolic state. Hyperthyroidism is relatively

common, affecting about 1 in 100 Americans. Women are more likely to develop hyperthyroidism than men, and risk increases with age. Hyperthyroidism can result from a variety of conditions, including the following:

- Excessive iodine (usually from iodine-containing medications)
- **Graves' disease** (an autoimmune condition that stimulates thyroid hormone production)
- Nonmalignant thyroid tumors (which produce thyroid or thyroid-like hormones)
- Goiter
- Thyroid inflammation (increased capillary permeability resulting from the inflammatory process causes additional thyroid hormones to be released in the bloodstream)
- Taking large amounts of thyroid hormone replacement medications
- High levels of serum human chorionic gonadotropin (e.g., molar pregnancy, choriocarcinoma, and hyperemesis gravidarum; it is a weak thyroid stimulator)
- Metastatic thyroid cancer (rare)

A nonautoimmune form of hyperthyroidism can develop as a result of mutations in the TSH receptor gene. This form follows an autosomal dominant inheritance pattern. Hyperthyroidism can also mimic other health problems, and its clinical manifestations can vary, making diagnosis difficult. These clinical manifestations reflect increased thyroid activity:

- Sudden weight loss
- Tachycardia
- Dysrhythmias (especially atrial fibrillation)
- Hypertension
- Increased appetite
- Nervousness, anxiety or anxiety attacks, and irritability
- Difficulty concentrating

- Tremor (usually a fine trembling in the hands)
- Diaphoresis
- Abnormal uterine bleeding
- Increased sensitivity to heat
- Diarrhea
- Goiter
- Difficulty sleeping
- Exophthalmos (protruding eyes with decreased blinking and movement) (**FIGURE 10-9**)

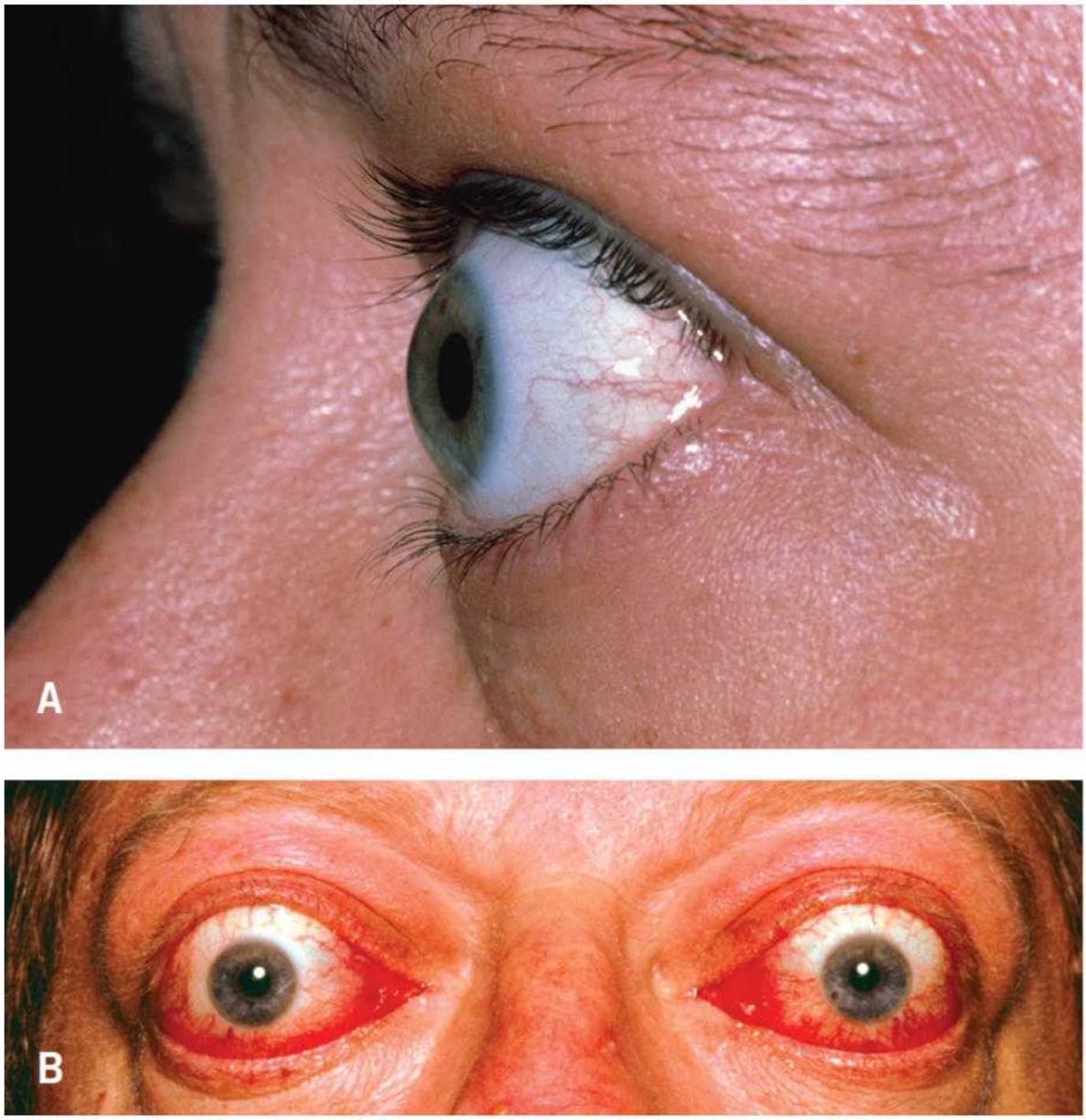


FIGURE 10-9 Exophthalmos.

A: © Dr. P. Marazzi/Science Source; **B:** © SPL/Science Source

Description

Thyroid crisis (storm), also called **thyrotoxicosis**, is a sudden worsening of hyperthyroidism symptoms that may occur with infection or stress. This medical emergency is characterized by fever, decreased mental alertness, and abdominal pain. Additional

complications of hyperthyroidism include cardiomyopathy, heart failure, and osteoporosis.

Diagnostic procedures for hyperthyroidism include a history, physical examination, serum thyroid hormone levels, serum TSH, radioactive iodine uptake test, thyroid autoantibody levels, liver function tests, EKG, and thyroid scan. In hyperthyroidism, serum T_3 usually increases more than T_4; in fact, only T_3 is elevated in some cases. TSH will be low except in rare instances where the etiology is a TSH-secreting pituitary adenoma.

Hyperthyroidism can usually be easily managed with medication and surgery. Pharmacologic treatment usually includes radioactive iodine (which shrinks the gland), antithyroid agents (to decrease hormone production), and beta blockers (to treat cardiac symptoms). Surgical removal of the thyroid (thyroidectomy) with subsequent hormone replacement is warranted when the patient does not respond to or tolerate medications. Even with treatment, **exophthalmos** usually remains. Strategies to improve the discomfort associated with exophthalmos include cool compresses, wearing sunglasses, eye lubricants, and elevating the head of the bed. Increasing caloric and calcium intake is crucial to maintain weight and prevent bone loss.

Disorders of the Parathyroid Glands

Parathyroid disorders result in an increase or decrease in PTH. Because of PTH's actions, disorders of the parathyroid have a significant impact on calcium balance, which then has a domino effect on other electrolytes (phosphorus and magnesium; see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter). Several etiologies can result in these conditions, including tumors, congenital defects, damage (e.g., from surgery, radiation, or infections), and renal failure. These conditions are usually easily managed with medications and surgery.

Hypoparathyroidism

Hypoparathyroidism refers to an uncommon state of decreased secretion or activity of PTH. Deficient PTH secretion occurs when there is too little or a complete absence of parathyroid tissue, such that inadequate amounts of PTH are produced. The most common cause of deficient secretion is accidental removal or damage of the parathyroid glands during thyroid surgery. The parathyroid and thyroid glands not only reside close in proximity but also share the same blood supply. Even with a successful thyroid surgery, a transient decrease in PTH secretion can be experienced for several days following. Decreased PTH secretion can also occur with parathyroid surgical removal (i.e., parathyroidectomy) to treat **hyperparathyroidism**. Hyperparathyroidism is often caused by tumors, so removal of the tumor is necessary. Leaving at least half of one parathyroid gland that is functioning usually can provide sufficient PTH.

Deficient PTH secretion can also be caused by congenital defects. These defects can be a result of altered genes that encode abnormal forms of PTH or its receptors, prevent normal conduction of cell signals from PTH receptor to the nucleus, or prevent normal gland development before birth. Hypoparathyroidism that appears within the first few months of life can be permanent or temporary with spontaneous resolution.

If a woman with overactive parathyroid glands and high calcium levels becomes pregnant, the excess calcium can cross the placenta and suppress the fetus's parathyroid gland development. Parathyroidectomy before the middle of the second trimester can decrease the risk of poor parathyroid gland development.

Radiation can also damage the parathyroid glands. In addition, hypothyroidism can develop as a result of an autoimmune response. An antibody that binds to the calcium sensor in the parathyroid glands has been identified in individuals with this form. The parathyroid glands are thought to interpret the binding of these antibodies as high calcium levels, which in turn leads them to decrease PTH secretion.

Magnesium is required for the production and release of PTH. Hypomagnesemia from conditions, such as chronic alcoholism or malabsorption, can suppress PTH secretion and cause calcium levels

to drop. PTH levels usually return to normal once magnesium levels are corrected. Increased pH levels, as occur with metabolic alkalosis, can also suppress PTH secretion and cause calcium levels to drop. Increased pH causes albumin and the globulins to become more negatively charged and bind more to calcium, decreasing circulating calcium.

In hypoparathyroidism caused by resistance to PTH, the parathyroid glands produce sufficient PTH, but the bones and kidneys do not respond to this hormone appropriately. These individuals appear to have hypoparathyroidism but really do not. Consequently, this rare form is referred to as pseudohypoparathyroidism. Hypoparathyroidism can also be idiopathic.

PTH deficiency results in hypocalcemia and a subsequent increase in phosphorus levels. Clinical manifestations reflect these electrolyte and pH imbalances, particularly hypocalcemia, and vary from mild to severe. Hypocalcemia results in increased nerve and muscle excitability. Thus, manifestations of hypoparathyroidism include the following symptoms:

- Paresthesias of the fingertips, toes, and lips
- Muscle twitching or spasms (tetany)
- Seizures
- Fatigue or weakness
- Dysrhythmias
- Hypotension
- Abdominal cramping
- Diarrhea
- Painful menstruation
- Patchy hair loss
- Dry, coarse skin
- Brittle nails
- Anxiety or nervousness
- Headaches

- Depression or mood swings
- Memory loss

Diagnostic procedures for hypoparathyroidism include a history, physical examination, serum PTH levels, blood chemistry (includes electrolyte levels), EKG, X-rays, and bone density studies. Serum calcium and PTH will be low, and serum phosphate levels will be high; PTH levels will be normal or high with pseudohypoparathyroidism.

Treatment regimens rarely include PTH replacement, but it is indicated if calcium levels are not maintained. Strategies generally focus on correcting electrolyte and pH imbalances (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter). Calcium supplements for a few days after thyroid surgery can prevent symptoms from the transient decrease in PTH secretion.

Hyperparathyroidism

Hyperparathyroidism refers to a condition of excessive PTH production by one or more of the parathyroid glands, regardless of the calcium level. This imbalance may be caused by tumors, hyperplasia, or chronic hypocalcemia (e.g., kidney disease, malabsorption, and vitamin D deficiency). In most cases, one of the parathyroid glands has developed a benign tumor (usually an adenoma) that secretes all the hormone, and the other three glands are small and respond appropriately to the high calcium levels by becoming dormant. Although parathyroid tumors are rarely malignant, they can grow large, potentially causing respiratory issues. In rare cases, hyperparathyroidism is caused by enlargement of all four parathyroid glands (i.e., hyperplasia).

Regardless of etiology, hyperparathyroidism will result in hypercalcemia. The excessive calcium levels can lead to decreases in phosphorus levels, increases in magnesium levels, and metabolic acidosis (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter). The clinical manifestations of hyperparathyroidism reflect these electrolyte and pH imbalances, particularly hypercalcemia, and vary from mild to severe. Hypercalcemia results in decreased nerve

and muscle excitability. Thus, manifestations of hyperparathyroidism include the following symptoms:

- Osteoporosis
- Bone pain
- Pathological fractures
- Renal calculi
- Polyuria
- Abdominal pain
- Constipation
- Fatigue or weakness
- Flaccid muscles
- Dysrhythmias
- Hypertension
- Depression or forgetfulness
- Nausea and vomiting
- Anorexia

Diagnostic procedures for hyperparathyroidism include a history, physical examination, serum PTH levels, blood chemistry (includes electrolyte levels), EKG, X-rays, and bone density studies. Serum calcium and PTH will usually be high, and serum phosphate levels will be low. Low serum calcium and high PTH levels indicate hyperparathyroidism secondary to chronic hypocalcemia.

Treatment varies depending on the underlying etiology. Tumors will likely require surgery (usually minimally invasive parathyroid surgery) and radiation. Calcitonin may be administered to shift the calcium from the bloodstream to the bones. Calcimimetic agents may be administered to mimic calcium circulating in the blood and, in turn, may lead to decreased PTH production. Bisphosphates can decrease the loss of calcium from the bone and lessen osteoporosis. Phosphates may be administered to correct phosphorus deficits, which will decrease calcium levels (see the *Fluid, Electrolyte, and*

Acid–Base Homeostasis chapter). Increasing fluid intake (either oral or intravenous) will increase renal excretion of calcium. Additionally, magnesium and pH imbalances may need correction (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter). If these efforts are unsuccessful, minimally invasive parathyroid surgery can be performed to target the overactive area using radioactive isotopes, with minimal risk of damage to the healthy parathyroid glands.

Disorders of the Adrenal Gland

Adrenal gland disorders may affect one or both areas of the adrenal gland. These disorders result in an increase or a decrease in one or more adrenal hormones. Depending on the hormone affected and the severity of the condition, adrenal gland disorders can have serious consequences. Several etiologies can result in these conditions, including tumors, congenital defects, medications (e.g., corticosteroids), and damage (e.g., from surgery, radiation, or infections). These disorders are usually easily managed with medications and surgery, but they can become life threatening if not managed promptly.

Pheochromocytoma

Pheochromocytoma is a rare tumor of the chromaffin cells located in the adrenals. Most tumors occur in the adrenal medulla, but some may be located in other tissues derived from neural crest cells (embryonic ectoderm cells that give rise to melanocytes, craniofacial cartilage and bone, smooth muscle, and peripheral and enteric neurons and glia). The tumor excretes catecholamines (e.g., epinephrine, norepinephrine, dopamine, and dopa) and can be life threatening because of the effects of these hormones (e.g., increased blood pressure and tachycardia). Pheochromocytoma can occur as a single tumor or as multiple tumors in one or both adrenal glands, though it is malignant in only about 10% of cases. Tumors can vary in size but average 5 to 6 cm in diameter. Infrequently, they can grow large enough to be palpated.

The exact cause is unknown, but half of cases are thought to be due to germline mutations. Some cases may be due to mutations in genes that encode the enzyme succinate dehydrogenase or other signaling molecules. Pheochromocytomas may sometimes be a part of a syndrome of familial multiple endocrine neoplasia types 2A and 2B, in which other endocrine tumors (e.g., parathyroid or medullary carcinoma of the thyroid) occur together or develop afterward. Pheochromocytomas are also associated with neurofibromatosis, hemangioblastomas, and renal cell carcinoma. The tumors can occur at any age but are more common in early to middle adulthood.

Clinical manifestations reflect the fight-or-flight response and occur in unpredictable attacks that usually last 15 to 20 minutes. These attacks can be triggered by palpation of the tumor, postural changes, abdominal compression or massage, anesthesia, or emotional stress. Manifestations include the following symptoms:

- Hypertension or postural hypotension
- Tachycardia
- Dysrhythmias
- Forceful palpitations
- Angina
- Profound diaphoresis
- Tachypnea or dyspnea
- Hyperglycemia
- Abdominal or epigastric pain
- Nausea and vomiting
- Sudden onset of severe headaches
- Visual disturbances
- Anxiety
- Feeling of extreme fright or impending doom
- Pale, cool, and clammy skin
- Paresthesias
- Weight loss

- Difficulty sleeping
- Constipation

Diagnostic procedures for pheochromocytoma include a history, physical examination, serum catecholamines and metanephrine levels, serum glucose level, urine catecholamine and metanephrine analysis, EKG, abdominal CT, abdominal MRI, *m*-iodobenzylguanidine scintiscan (a nuclear scan to confirm pheochromocytoma), and biopsy. Genetic testing is suggested if familial multiple endocrine neoplasia is suspected. Provocative tests with histamine, glucagon, or tyramine are dangerous and should be avoided.

If not promptly treated, pheochromocytoma can lead to hypertensive crisis, stroke, kidney disease, psychosis, and seizures. Surgical removal (usually laparoscopically) of the tumor or adrenal gland is the cornerstone of treatment. Administration of antihypertensive medications (e.g., alpha blockers and beta blockers) is often necessary until surgery can be performed. Administer alpha-blockers first before beta blockers. Giving beta blockers first or alone can cause a paradoxical increase in blood pressure by blocking beta-mediated vasodilatation. Radiation may be used in cases of malignant pheochromocytoma; chemotherapy may also be used but is rarely effective.

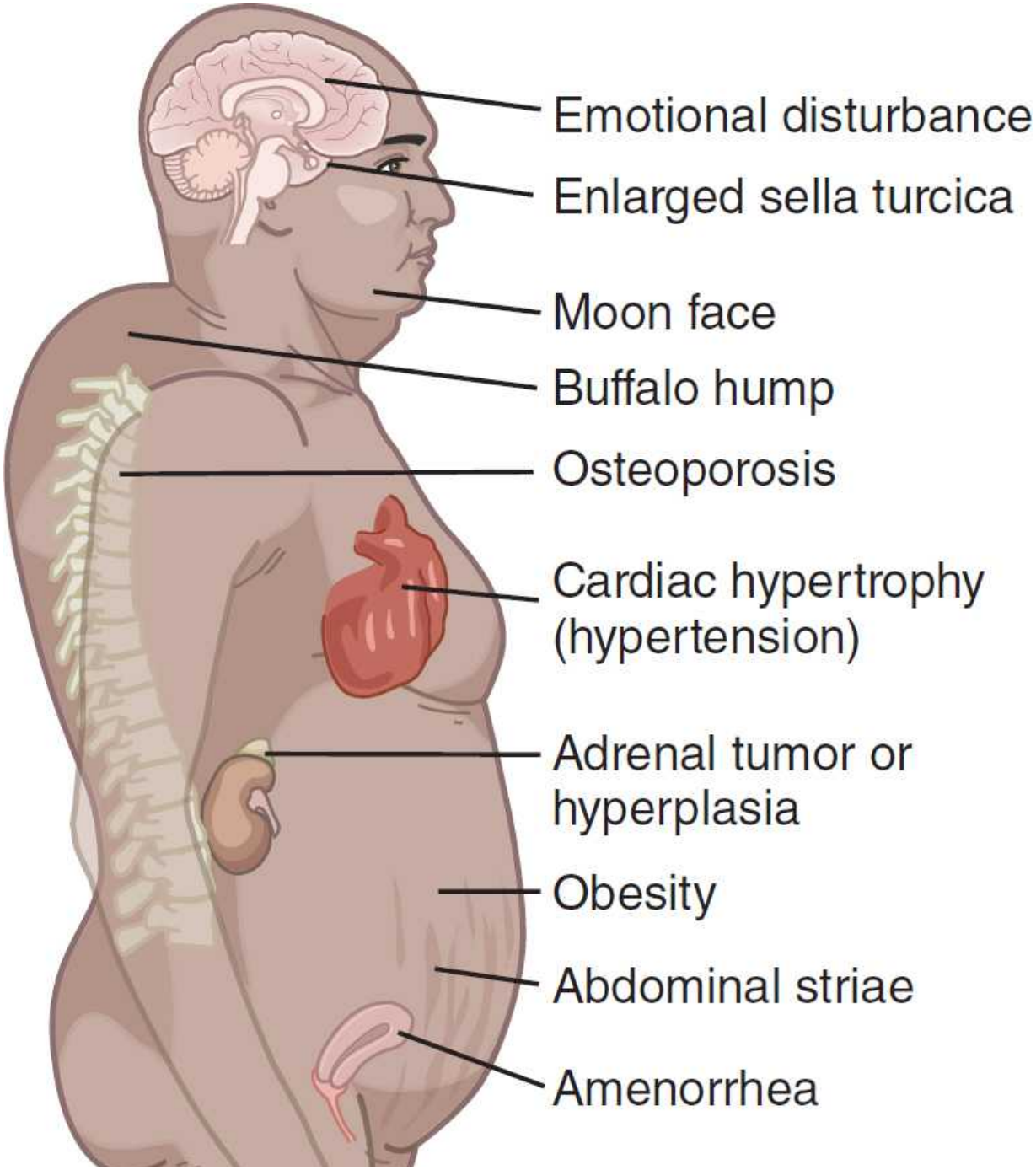
Cushing Syndrome

Cushing syndrome is a group of clinical abnormalities caused by chronic high levels of glucocorticoids, usually cortisol. Cushing disease is Cushing syndrome that results from increased pituitary production of ACTH, typically as a result of a pituitary adenoma. Cushing syndrome refers to the clinical picture resulting from the excess of cortisol, whereas Cushing disease refers to hyperfunction of the adrenal cortex from pituitary ACTH excess.

The most common cause of Cushing syndrome is iatrogenic, resulting from ingestion of glucocorticoid medications, which mimic the body's own hormones. Cushing syndrome can also be caused by adrenal tumors that secrete glucocorticoids. Additionally, these adrenal tumors can secrete androgens. Paraneoplastic syndrome

resulting from cancers outside the endocrine system can also cause Cushing syndrome by increasing production of ACTH and cortisol.

Glucocorticoids are essential for life but can produce serious effects when present in increased amounts (**FIGURE 10-10**). The clinical manifestations of Cushing syndrome are a direct result of the excessive amounts of glucocorticoids:



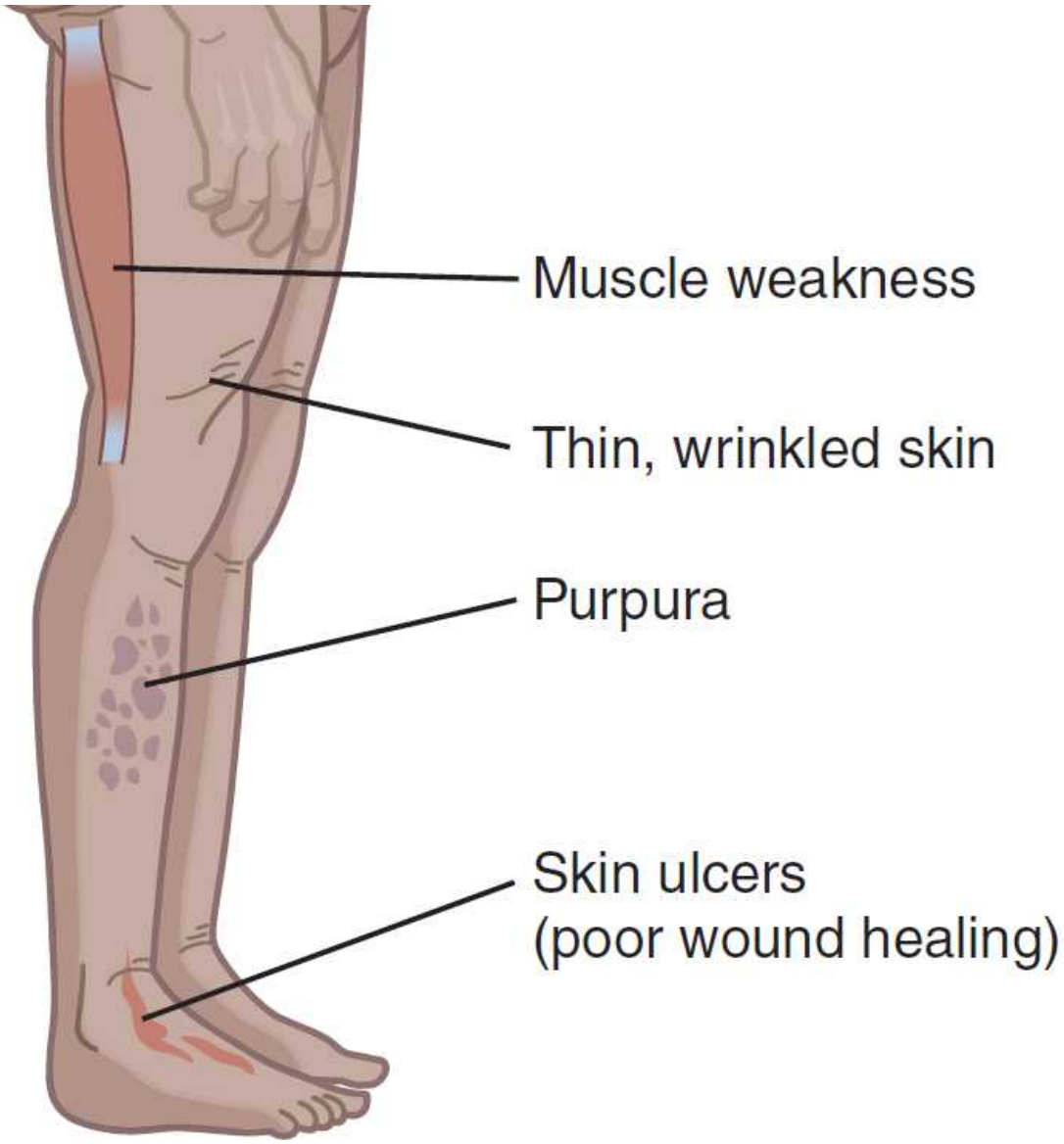


FIGURE 10-10 Signs and symptoms of Cushing syndrome.

Description

- Round, full, red face (“moon” face) (**FIGURE 10-11**)



FIGURE 10-11 Cushing syndrome before and after treatment. **(A)** Full, rounded face ("moon face") prior to treatment. **(B)** Normal facial appearance after treatment.

Courtesy of Leonard V. Crowley, MD, Century College.

Description

- Obesity (especially around the trunk) (**FIGURE 10-12**)



FIGURE 10-12 Cushing syndrome before and after treatment. **(A)** Before treatment, front and side views of subject, illustrating trunk obesity with relatively thin extremities. **(B)** After treatment, illustrating normal body configuration.

Courtesy of Leonard V. Crowley, MD, Century College.

Description

- Fatty pad between the shoulders (“buffalo hump”)
- Muscle weakness and wasting
- Delayed growth and development
- Acne
- Broad purple striae (marks) on the abdomen, thighs, and breast
- Thin skin that bruises easily
- Hyperpigmentation (due to increased ACTH)
- Delayed wound healing
- Increased rate and severity of infections
- Osteoporosis

- Hirsutism (abnormal hair growth from increased androgen production)
- Abnormal uterine bleeding
- Decreased libido
- Erectile dysfunction
- Glucose intolerance (because of insulin resistance)
- Hypertension
- Dyslipidemia
- Edema
- Hypokalemia
- Mood changes and psychosis

Diagnostic procedures for Cushing syndrome include a history, physical examination, serum hormone levels (e.g., cortisol and ACTH), urinary cortisol levels, serum glucose level, CBC, blood chemistry, urine cortisol, bone density studies, adrenal and pituitary CT and MRI, and biopsy. Treatment varies depending on the underlying cause. Gradual tapering of any glucocorticoids being administered is crucial. If these medications are suddenly discontinued, the adrenal gland does not have the opportunity to initiate its own production of hormones, leading to an adrenal crisis. Tumors will likely require surgical removal and radiation. Medications can be used to control cortisol production (e.g., ketoconazole [Nizoral], mitotane [Lysodren], metyrapone [Metopirone]), control the effects of cortisol (e.g., mifepristone [Korlym]), and decrease ACTH production (e.g., pasireotide [Signifor]). High-protein diets are recommended to counteract the catabolic effects of the glucocorticoids. Interventions may be necessary to manage specific complications as they develop (e.g., hypokalemia, osteoporosis, DM, and hypertension).

Addison's Disease

Addison's disease refers to a deficiency of adrenal cortex hormones (glucocorticoids, mineralocorticoids, and androgens), usually as a

result of an insidious, progressive hypofunctioning of the adrenal cortex. It can be caused by damage resulting from autoimmune conditions (the most common cause), infections (e.g., tuberculosis, human immunodeficiency virus, fungal infections, and meningitis), hemorrhage, and tumors. Additionally, Addison's disease may result from pituitary dysfunction that results in insufficient ACTH levels. This disease may occur with DM or hypothyroidism in polyglandular deficiency syndrome as well.

Addison's disease tends to become clinically apparent during metabolic stress, infection, or trauma. Clinical manifestations reflect the deficiency of the hormones and usually develop slowly over weeks to months. Because mineralocorticoids stimulate sodium reabsorption and potassium excretion, deficiency results in increased sodium excretion and decreased potassium excretion, primarily in the urine as well as in sweat, saliva, and the gastrointestinal tract. Glucocorticoid deficiencies contribute to hypotension and cause severe insulin sensitivity and metabolism disturbances. Adrenal crisis refers to an onset of severe symptoms usually triggered by an acute infection, trauma, surgery, or sodium loss. Manifestations of Addison's disease include the following symptoms:

- Hypotension
- Changes in heart rate
- Hypoglycemia
- Chronic diarrhea
- Patchy hyperpigmentation
- Pallor
- Extreme weakness and fatigue
- Anorexia
- Mouth lesions on the inside of a cheek (buccal mucosa)
- Nausea and vomiting
- Salt craving
- Slow, sluggish movement

- Unintentional weight loss
- Mood changes and depression
- Electrolyte disturbances (particularly hyperkalemia, hyponatremia, and hypochloremia)

Diagnostic procedures for Addison's disease include a history, physical examination, serum hormone levels (e.g., cortisol, ACTH, and androgens), serum glucose levels, CBC, blood chemistry, urine cortisol, adrenal and pituitary CT and MRI, and biopsy. Treatment of this disease requires lifelong hormone replacement therapy. Hydrocortisone or prednisone can be used to replace glucocorticoids, and fludrocortisone (Florinef) can be used to replace mineralocorticoids. Increases in hormone doses may be required during times of infections, stress, and trauma. The patient should wear a medical alert bracelet and always carry extra medication.

application to practice

A 68-year-old woman with an 8-year history of DM presents to the clinic for worsening dyspnea and cough. She had COVID-19 (see the *Respiratory Function* chapter) in 2020 and has had some lingering respiratory symptoms. She now has dyspnea from walking one-third of a block, as well as a persistent cough. She has managed her type 2 DM with diet and exercise. Her last glycosylated hemoglobin ($HgbA_{1c}$), which was measured 1 month ago, was 6.8% (normal range is 4–6%). Physical examination reveals an anxious woman with blood pressure of 134/70 mm Hg, pulse of 116, respiratory rate of 24 breaths per minute, and weight of 190 pounds. Expiratory wheezing is present bilaterally. No accessory muscles are being used. No cyanosis is present. The lab evaluation results are as follows: arterial blood gas (ABG) 7.46; PaO_2 60; $PaCO_2$ 40; O_2 sat 88% (see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter).

The patient is started on albuterol (bronchodilator) and a course of prednisone (glucocorticoid) at 40 mg/day for 3 days, then tapering over 2 weeks. On day 3, she calls back to the clinic to report that her blood glucose level is 358 mg/dL at 4:00 p.m.

1. Which of the following is the most likely cause of this patient's acute loss of glucose control?
   a. An acid–base imbalance
   b. Prednisone therapy
   c. COPD exacerbation
   d. Albuterol

2. All of the following actions are important for this patient to learn regarding glucocorticoid therapy, but which one is the most important?
   a. Monitor cuts for healing
   b. Take the medication with food
   c. Do not stop taking the medication abruptly
   d. Contact her healthcare provider if she has any manifestations of infection
3. Which of the following endocrine conditions is this patient at risk of developing?
   a. Hyperthyroidism
   b. Pheochromocytoma
   c. Addison's disease
   d. Cushing syndrome
4. Given this patient's acute loss of glucose control, which of the following interventions would the nurse expect to be ordered for this patient?
   a. Insulin as needed per routine sliding scale (dosing based on blood glucose levels)
   b. Increase exercise
   c. Decrease caloric intake
   d. Decrease prednisone dose

application to practice

Now that we have discussed conditions of the endocrine system, let's put that knowledge into practice. While working in a clinic, you have the following patient messages. Which patient would you call back first?

- A 58-year-old male diagnosed with diabetes, reporting a fasting blood glucose of 112 and requesting prescription refills for his diabetic medication
- A 64-year-old female diagnosed with Cushing syndrome, reporting a pulse of 74, blood pressure of 150/90 mm Hg, and blood glucose of 290
- A 72-year-old female diagnosed with hypothyroidism, reporting a pulse of 78 and blood pressure of 128/70 mm Hg, and requesting prescription refills for her thyroid medication
- A 45-year-old female diagnosed with hyperthyroidism, reporting a pulse of 89 and blood pressure of 130/78 mm Hg

You will want to treat these callbacks in the same way you treat other priority questions, such as "who would you see first"—that is, by considering who would die first, acute versus chronic conditions, Maslow's hierarchy of needs, and patient safety. Start with the 58-year-old man diagnosed with diabetes. The fasting blood glucose is not alarming; the prescription refills are important but can wait. Now, move on to the 64-year-old woman diagnosed with Cushing syndrome. Her pulse is normal, but her blood pressure and glucose readings are high. Keep this patient on the short list. Then, consider the 72-year-old woman diagnosed with hypothyroidism. Her pulse and blood pressure are normal, and

the prescription refills can wait. Finally, consider the 45-year-old woman diagnosed with hyperthyroidism. Her pulse and blood pressure are on the high end of normal, but they are still normal. After considering all the patients, the 64-year-old patient with Cushing syndrome should be called back first.

SUMMARY

The endocrine system is responsible for producing a wide range of hormones necessary for a variety of processes. Endocrine disorders are often caused by congenital defects, tumors, or gland damage. These conditions vary from harmless to life threatening, and most are managed easily with medications and surgery. Clinical manifestations of these conditions reflect the hormones affected and the degree of deviation. Regardless of the disorder and the severity, lifelong management is necessary to prevent significant complications or death.

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CHAPTER 11

Neural Function

LEARNING OBJECTIVES

- Discuss normal neural anatomy and physiology.
- Describe and compare congenital neurologic disorders.
- Compare and contrast traumatic neurologic disorders.
- Compare and contrast infectious neurologic disorders.
- Describe and compare vascular neurologic disorders.
- Describe and compare headache disorders.
- Compare and contrast types of seizure disorders.
- Compare and contrast chronic degenerative neurologic disorders.
- Compare and contrast types of dementias.
- Compare and contrast psychiatric disorders.
- Describe and compare cancers of the nervous system.

KEY TERMS

action potential
acute stress disorder
addictive disorder
adjustment disorder
afferent nerve
afferent tract
AIDS dementia complex
Alzheimer's disease (AD)
amyotrophic lateral sclerosis (ALS)
anorexia nervosa
antisocial personality disorder

anxiety disorder
arachnoid layer
ascending fiber
attention-deficit/hyperactivity disorder (ADHD)
aura
autism spectrum disorder (ASD)
automatism
autonomic hyperreflexia
autonomic nervous system
autoregulation
avoidant personality disorder
axon
basal ganglia
basilar skull fracture
binge-eating disorder
bipolar disorder
borderline personality disorder
brain
brainstem
bulimia nervosa
cauda equina
cauda equina syndrome
central nervous system (CNS)
cephalalgia
cerebellum
cerebral aneurysm
cerebral contusion
cerebral palsy (CP)
cerebrospinal fluid (CSF)
cerebrovascular accident (CVA)
cerebrum
chorea
cluster headache (CH)
comminuted skull fracture
communication disorders
compound skull fracture
concussion
conduct disorder

contrecoup
conversion disorder
coup
cranial nerve
Creutzfeldt-Jakob disease (CJD)
Cushing reflex
Cushing triad
dementia
dementia with Lewy bodies (DLB)
dendrite
depersonalization/derealization disorder
depolarization
depressed skull fracture
depressive disorder
dermatome
descending fiber
diencephalon
disruptive mood dysregulation disorder
dissociative amnesia
dissociative disorder
dissociative identity disorder
dorsal root
dura mater
efferent nerve
efferent tract
encephalitis
epidural hematoma
epilepsy
epithalamus
factitious disorder
flexor reflex
focal seizure
foramen magnum
frontal lobe
frontotemporal dementia (FTD)
gender dysphoria
generalized anxiety disorder (GAD)
generalized seizure

global developmental delays
gyrus
headache
hematoma
hemorrhagic stroke
herniation
histrionic personality disorder
Huntington's disease (HD)
hydrocephalus
hypersomnolence disorder
hypothalamus
illness anxiety disorder
increased intracranial pressure
insomnia disorder
intellectual disability
intermittent explosive disorder
interneuron
intracerebral hematoma
ischemic stroke
kleptomania
linear skull fracture
lobe
longitudinal fissure
major depressive disorder
mania
medulla
meninges
meningitis
meningocele
midbrain
migraine
Monro-Kellie hypothesis
motor nerve
multiple sclerosis (MS)
Munchausen syndrome
myasthenia gravis
myasthenic crisis
myelin sheath

myelinated cell
myelomeningocele
narcissistic personality disorder
narcolepsy
nerve
neuroglia
neuromelanin
neuron
neurotransmitter
node of Ranvier
obsessive–compulsive disorder (OCD)
obsessive–compulsive personality disorder
occipital lobe
oppositional defiant disorder
panic disorder
paralysis
paranoid personality disorder
paraphilic disorder
paraplegia
parasomnia
parasympathetic nervous system
parietal lobe
Parkinson’s disease
pedophilic disorder
peripheral nerve
peripheral nervous system (PNS)
persistent depressive disorder
personality disorder
phobia
pia mater
pica
plexus
pons
postictal period
postsynaptic cell membrane
posttraumatic stress disorder (PTSD)
presynaptic terminal
prion

pyromania
quadriplegia
reactive attachment disorder
resting potential
reticular activation system
reticular formation
rootlet
rumination disorder
schizophrenia
schizotypal personality disorder
schwann cell
seizure
sensory nerve
separation anxiety disorder
sexual sadism disorder
sleep disorder
social anxiety disorder
somatic disorder
somatic symptom disorder
spina bifida
spina bifida occulta
spinal cord
spinal cord injury (SCI)
spinal reflex arc
spinal shock
status epilepticus
subarachnoid hemorrhage
subdural hematoma
substance-related disorder
substantia nigra
subthalamus
sulcus
sympathetic nervous system (SNS)
synapse
synaptic cleft
temporal lobe
tension-type headache (TTH)
terminal bouton

thalamus
transient ischemic attack (TIA)
transsexualism
traumatic brain injury (TBI)
trigeminal autonomic cephalalgias (TACs)
vascular dementia
ventral root
ventricle
vertebral canal
voyeuristic disorder
white matter
Zika virus disease

The nervous system consists of complex structures that control many body functions and cognition. The functions managed by this system include (1) structures such as muscles, glands, and organs; (2) heart rate; (3) blood flow; (4) breathing; (5) digestion; (6) urination; and (7) defecation. The nervous system works with other systems to maintain homeostasis by receiving and responding to input from the environment. Disorders of the nervous system may be acute or chronic; regardless of their severity, these conditions often have grave or life-altering effects on the body. Causes of these disorders include congenital defects, trauma, infections, tumors, chemical imbalances, and vascular changes.

Anatomy and Physiology

The nervous system is an intricate network of specialized cells and tissue that receive and react to environmental stimuli on physiologic and cognitive levels. To communicate this input, these structures conduct electric impulses between the **brain** and the rest of the body. The nervous system consists of three main components—the brain, the **spinal cord**, and the **nerves**. The brain and spinal cord make up the **central nervous system (CNS)**, and the nerves make up the **peripheral nervous system (PNS)**.

Central Nervous System

The skull and vertebral column house and protect the brain and spinal cord. Additionally, a set of three tough membranes, called the **meninges**, encase the CNS (**FIGURE 11-1**). The **dura mater** is the outer and toughest layer. The **arachnoid layer** is the middle layer, named for its spider weblike vascular system. The **pia mater** is the innermost layer that rests directly on the brain and spinal cord.

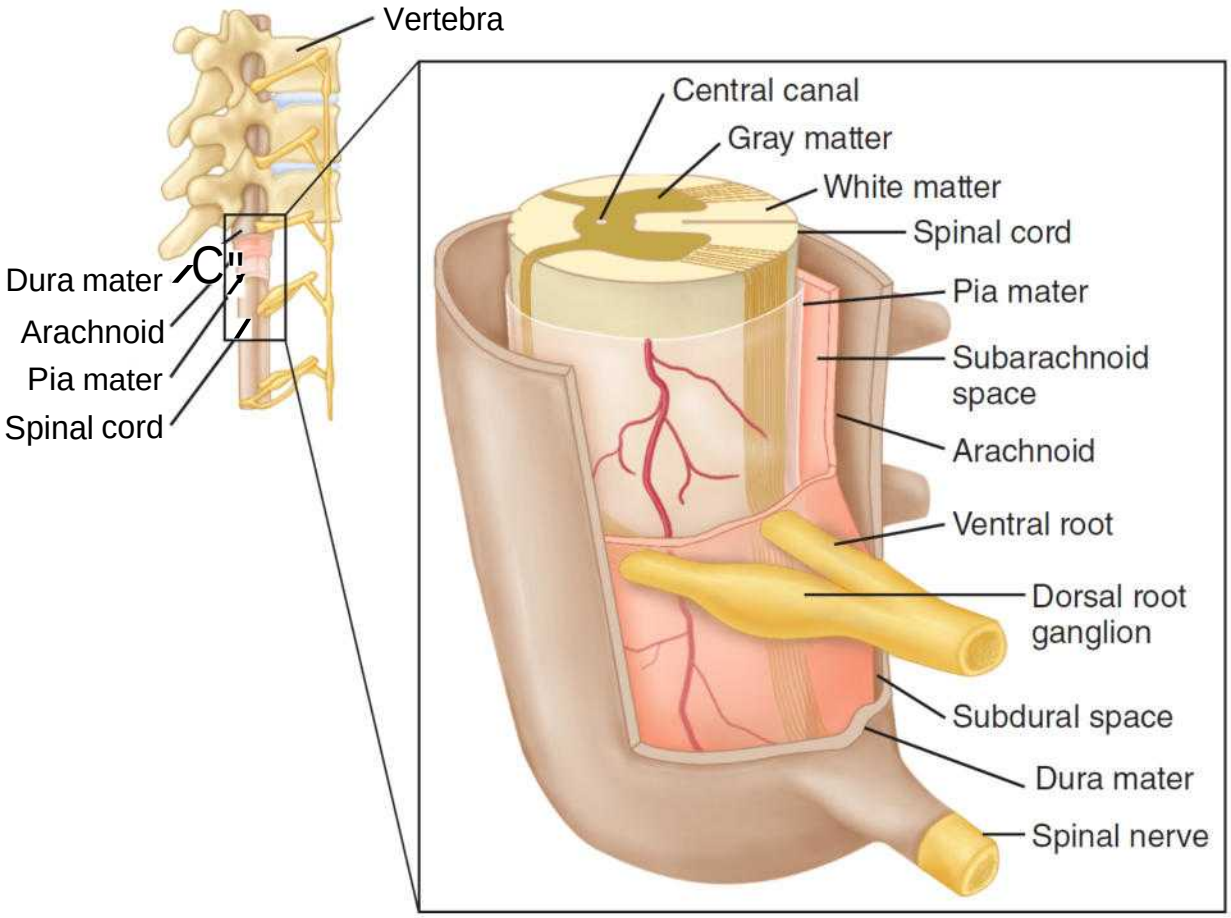


FIGURE 11-1 The meninges enclose the brain and the spinal cord.

Description

Cerebrospinal fluid (CSF) is a plasmalike liquid that fills the space between the arachnoid and pia mater layers to provide additional cushioning and support to the CNS. The choroid **plexus** cells in the brain's **ventricles** continuously produce this fluid. Adults produce approximately 600–700 mL of CSF daily, with about 125–270 mL circulating at any one time. CSF volume is age dependent, and children reach adult volumes by the age of 5 years. CSF contains plasma protein (e.g., albumin and gamma globulins), glucose, and mononuclear cells (e.g., lymphocytes and monocytes). Normal CSF pressure, measured with a lumbar puncture, is 100–180 mm H_2O or 8–15 mm Hg lying on the side and 200–300 mm H_2O sitting up. The four ventricles are interconnected hollow areas of the brain that the

CSF fills and where it flows freely between them through foramens. Excess CSF drains into the bloodstream.

The brain is located within the skull and contains billions of **neurons**. Neural tissue consists of two basic types of cells—**neuroglia** and neurons. Neuroglia cells, the most plentiful type, play several important supportive roles in the nervous system. In particular, these cells scaffold neural tissue as well as isolate and protect neuron cell membranes. Additionally, neuroglia cells regulate interstitial fluid, defend the neurons against pathogens, and assist with neural repair. In the CNS, neuroglia cells include ependymal cells, oligodendrocytes, astrocytes, and microglia (**FIGURE 11-2**). Ependymal cells line the spinal cord and ventricles in the brain. Oligodendrocytes produce myelin that surrounds and insulates **axons** of neurons. Astrocytes maintain a neuron's work environment by controlling **neurotransmitter** levels and ion (e.g., potassium) concentrations around the **synapses** and providing metabolic support. Astrocytes also regulate neuron communication. Microglia are phagocytic immune cells that protect the brain against injury and disease by removing toxins and dead cells. Additionally, microglia remove weaker and unneeded synapses in the developing brain, leaving only the strongest and most critical synapses. In the PNS, neuroglia cells include satellite and **Schwann cells**. Satellite cells surround neurons in the sensory, sympathetic, and parasympathetic ganglia and regulate the chemical environment. Schwann cells myelinate neurons in the PNS.

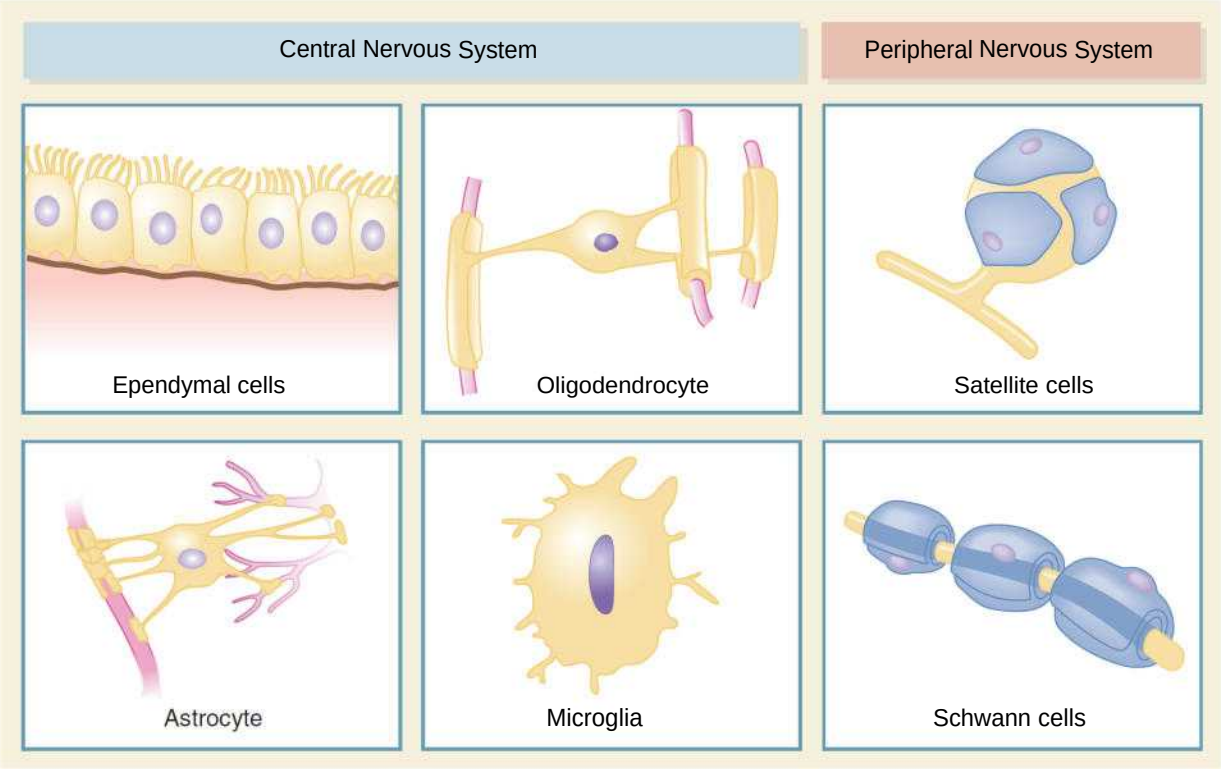


FIGURE 11-2 Types of neuroglia.

Description

Neurons are the fundamental units of the nervous system; they generate bioelectrical impulses and transmit these signals from one area of the body to another. Neurons occur in several sizes and shapes, but all share similar characteristics. Because neurons do not have the ability to divide, these cells cannot be replaced when they are lost due to aging or injury. Not all cell deaths result in loss of functioning, however. If neurons become damaged in one area of the brain, neurons in other areas can eventually assume responsibility for those functions. In the PNS, severed nerves can regenerate to a point so that they can reestablish connections with the tissue they once supplied. In the brain or spinal cord, severed axons cannot be repaired. Thus, severed spinal cord nerves result in **paralysis** and loss of sensation below the area of damage. In addition to being unable to divide, nerve cells require a constant supply of oxygen and glucose. This characteristic makes neurons vulnerable to the effects

of hypoxia and hypoglycemia—neurons can begin dying within minutes of these events.

Most neurons have a spherical cell body that houses the nucleus, most of the cytoplasm, and organelles. Neurons contain projections called axons and **dendrites** that make connections with nearby cells (**FIGURE 11-3**). Axons transmit impulses away from the cell body, whereas dendrites transmit impulses toward the cell body. When the axon reaches its destination, it often branches into several small fibers that terminate in minuscule bulges, called **terminal boutons**. These terminal boutons communicate with neurons, muscle fibers, or glands. Axons may be surrounded by a **myelin sheath**, which increases the rate of impulse transmission (i.e., conduction velocity) to approximately 400 times faster than is possible in unmyelinated nerves (**FIGURE 11-4**). **Myelinated cells** are separated by **nodes of Ranvier**. Nutrient exchange occurs at the nodes, where myelin is not present. Because of the myelin, impulses move at greater speeds down the axon, jumping from one node to the next, much like stones skipping across water. Bundles of these myelinated nerves are referred to as **white matter**. In unmyelinated nerves, impulses move in a slow, wavelike pattern. Conduction velocity increases as the axon diameter increases. Gaps between the neurons are referred to as synapses. Each of these gaps includes a **presynaptic terminal** (e.g., a terminal bouton or some similar structure), a **synaptic cleft** (the space between neurons), and a **postsynaptic cell membrane** (**FIGURE 11-5**). The presynaptic and postsynaptic terminals are opposite ends of the nerve.

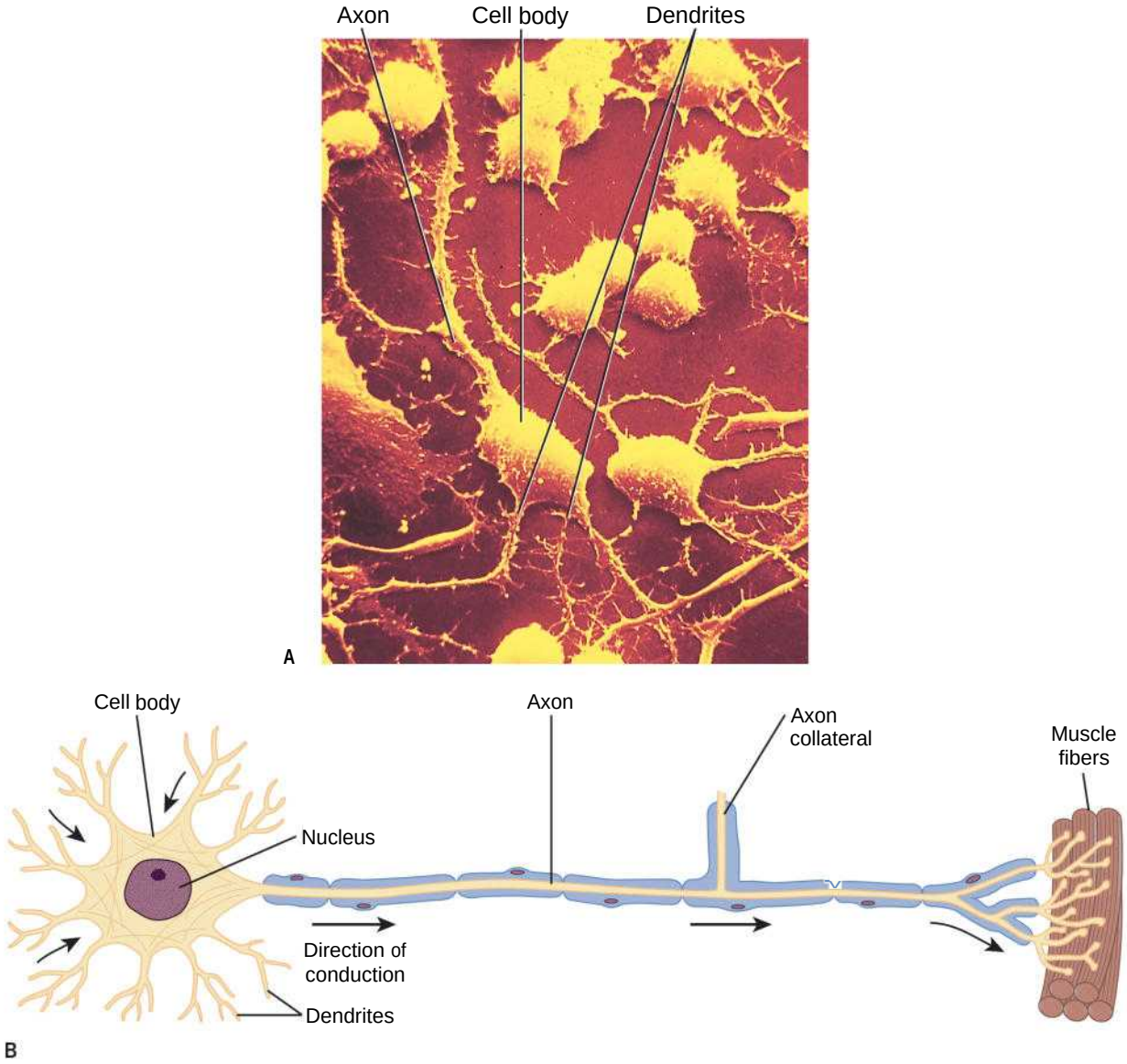


FIGURE 11-3 A neuron. **(A)** A scanning electron micrograph of the cell body and dendrites. **(B)** Collateral branches may occur along the length of the axon. In motor neurons, when the axon terminates, it branches many times, ending in individual muscle fibers.

A: © David M. Phillips/Visuals Unlimited, Inc.

Description

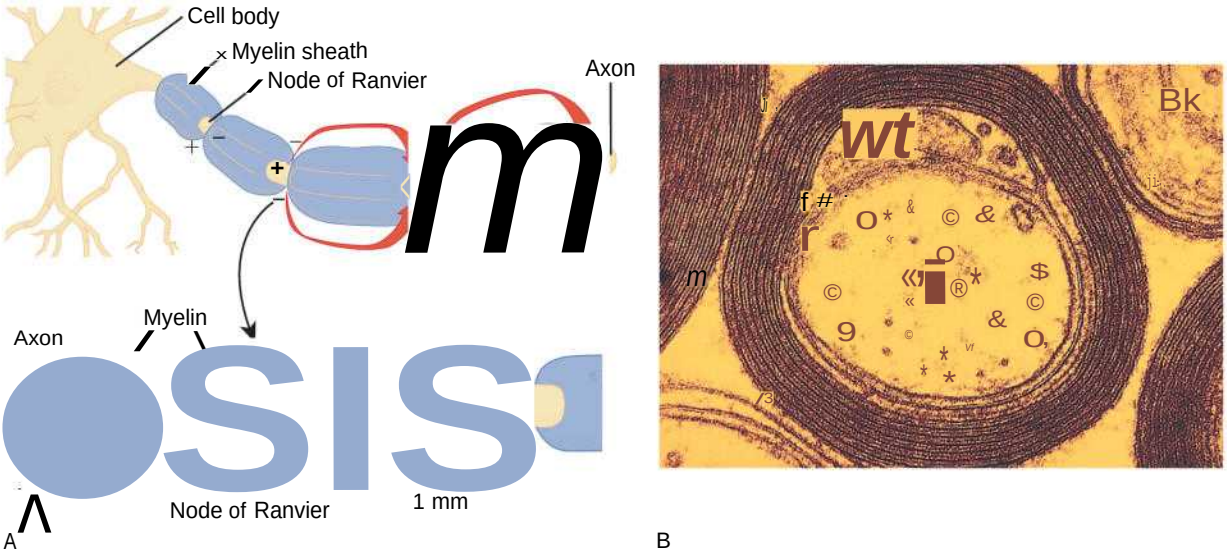


FIGURE 11-4 A myelinated nerve. **(A)** The myelin sheath allows impulses to "jump" from node to node, greatly accelerating the rate of transmission. **(B)** A transmission electron micrograph of an axon in the cross section, showing a myelin sheath.

B: © C. Raine/Science VU/Visuals Unlimited, Inc.

Description

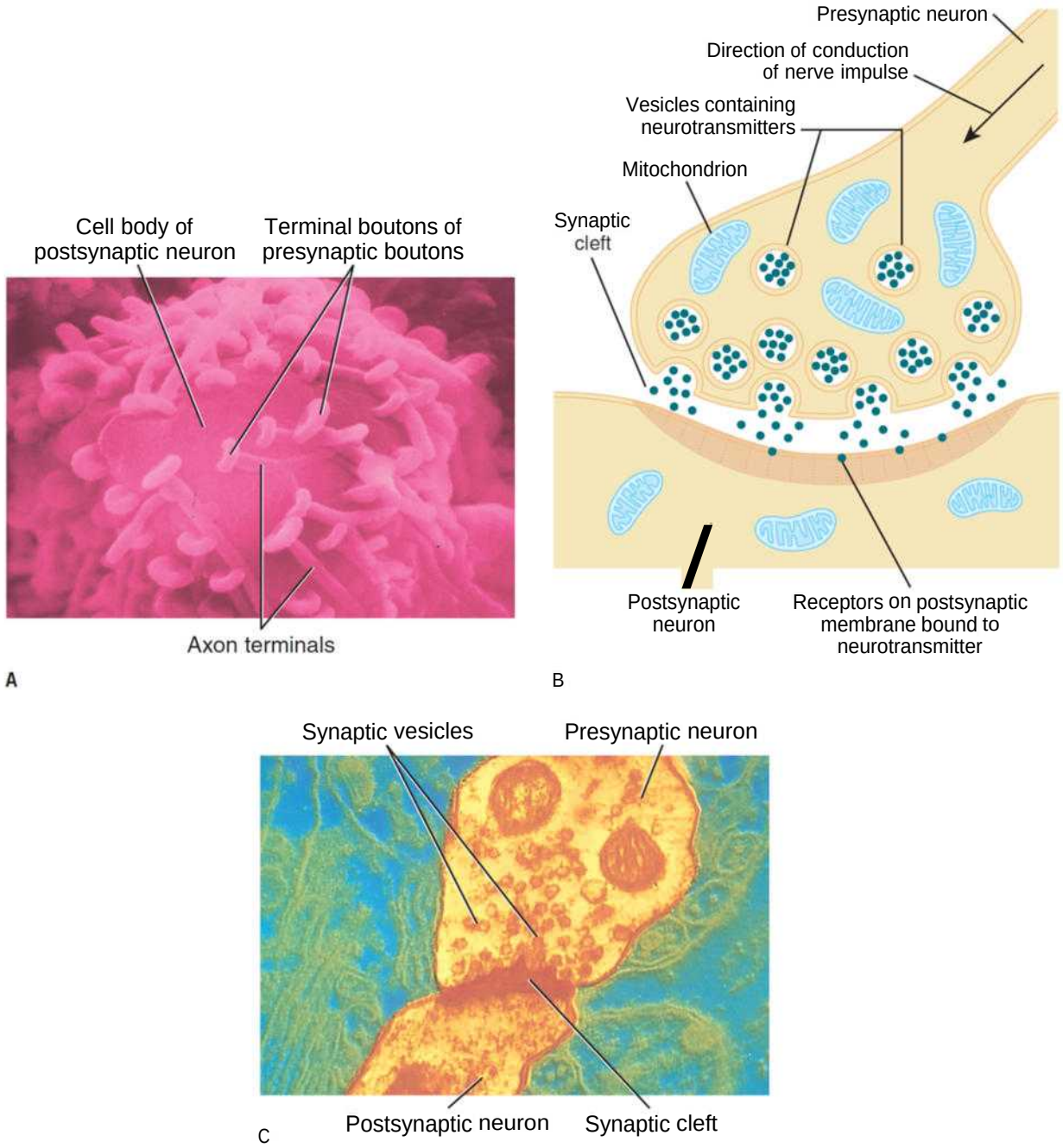


FIGURE 11-5 The function of neurotransmitters in the synaptic cleft. **(A)** A scanning electron micrograph showing the terminal boutons of an axon ending on the cell body of another neuron. **(B)** The arrival of the impulse stimulates the release of neurotransmitters held in synaptic vesicles in the axon terminals. The neurotransmitter diffuses across the synaptic cleft and binds to the postsynaptic membrane, where it elicits another action potential that travels down the dendrite to the cell body. **(C)** A transmission electron micrograph showing the details of the synapse.

A: © Lewis-Everhart-Zeevi/Science VU/Visuals Unlimited, Inc.; **C:** © T. Reese, DW Fawcett/Visuals Unlimited, Inc.

Description

Electrical impulses of the nervous system are not like the electrical current that powers appliances, which is formed by the flow of electrons. Instead, small ionic changes (e.g., potassium and sodium ions moving across cell membranes) generate neural impulses. The charge created by these changes is referred to as an **action potential** (**FIGURE 11-6**). The plasma side of the neuron membrane has a slight charge at rest, or **resting potential**, because of the sodium ions concentrated on the outside of the cell. When the neuron is stimulated, protein gates open and sodium flows into the cell. The rapid inflow of positively charged sodium ions increases the charge—a process called **depolarization**. Immediately following depolarization, the cell membrane returns to its resting state through the rapid outflow of the positively charged potassium ions. When generated, these neural impulses travel down the nerve to trigger the release of neurotransmitters from vesicles in the presynaptic terminal. The neurotransmitters cross the synaptic cleft, albeit only in one direction, to stimulate an electrical reaction in nearby neurons. Synaptic transmission of the impulse takes a mere millisecond. This electrical reaction passes through those neurons to the next synapse, where the process is repeated. At each synaptic transmission, a small burst of neurotransmitters is released and then removed. These neurotransmitters are either destroyed by enzymes or reabsorbed by the postsynaptic membrane to be recycled for the next transmission. Whereas some neurotransmitters stimulate the action potentials of neurons, other neurotransmitters inhibit action potentials. Some common neurotransmitters include acetylcholine, dopamine, norepinephrine, serotonin, glutamate, gamma aminobutyric acid (GABA), and endogenous opioids (**TABLE 11-1**).

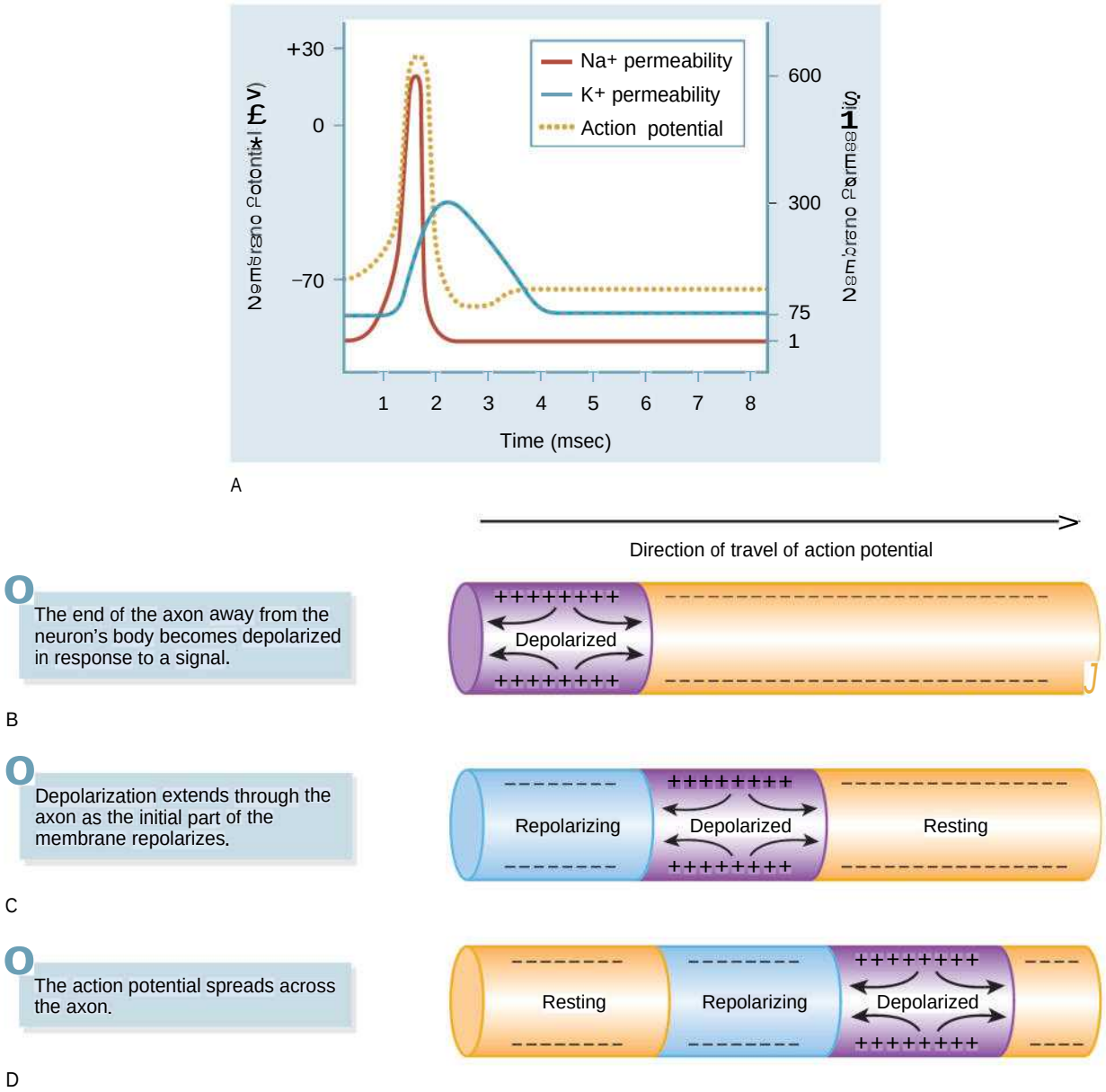


FIGURE 11-6 Action potential. **(A)** Stimulating the neuron creates a bioelectric impulse, which is recorded as an action potential. The resulting potential shifts from 270 millivolts to 130 millivolts, and the membrane is said to be depolarized. This graph shows the shift in potential and the change in the permeability of sodium (Na+) and potassium (K+) ions, which are largely responsible for the action potential. **(B)** The influx of Na+ ions and the depolarization that occur at the point of stimulation. **(C)** The impulse travels along the membrane as a wave of depolarization. **(D)** The efflux of K+ ions restores the resting potential, allowing the neuron to transmit additional impulses almost immediately.

Description

TABLE 11-1 Common Neurotransmitters

Neurotransmitter	Effects or Diseases Associated with These Neurotransmitters
Acetylcholine	Learning and memory; Alzheimer's disease; muscle movement in the peripheral nervous system
Dopamine	Reward circuits; motor circuits involved in Parkinson's disease; schizophrenia
Norepinephrine	Arousal; depression
Serotonin	Depression; aggression; schizophrenia
Glutamate	Learning; major excitatory neurotransmitter in the brain
Gamma aminobutyric acid (GABA)	Anxiety disorders; epilepsy; major inhibitory neurotransmitter in the brain
Endogenous opioids	Pain; analgesia; reward

One of the largest and most complex organs in the human body, the brain contains more than 100 billion nerves that communicate to trillions of synapses. The brain is responsible for a variety of physiologically vital functions and cognitive activities. Its major regions include the **cerebrum** (including the cerebral cortex), **diencephalon** (**thalamus** and **hypothalamus**), **brainstem** (**pons**, **midbrain**, and **medulla**), and **cerebellum** (**FIGURE 11-7**). The cerebrum, the largest of the regions (accounting for 80% of the brain's total mass), controls the higher thought processes (**FIGURE 11-8**). A thin layer of gray matter, referred to as the cerebral cortex, surrounds the cerebrum. A thick central core of white matter lies beneath the gray matter. This white matter contains bundles of axons that transmit impulses from the cerebral cortex to the spinal cord, enhancing communication and coordination of activities. The cerebrum is divided into right and left hemispheres by a **longitudinal fissure**. Although minor shifts of one hemisphere into the other may occur, impinging

one hemisphere on the other can have significant—even life-threatening—effects. Numerous folds, or gyri, increase the surface area of the cerebrum. The grooves in between the gyri are called **sulci**. At birth, only a minimal set of gyri is present, but these folds increase as the brain develops into adulthood.

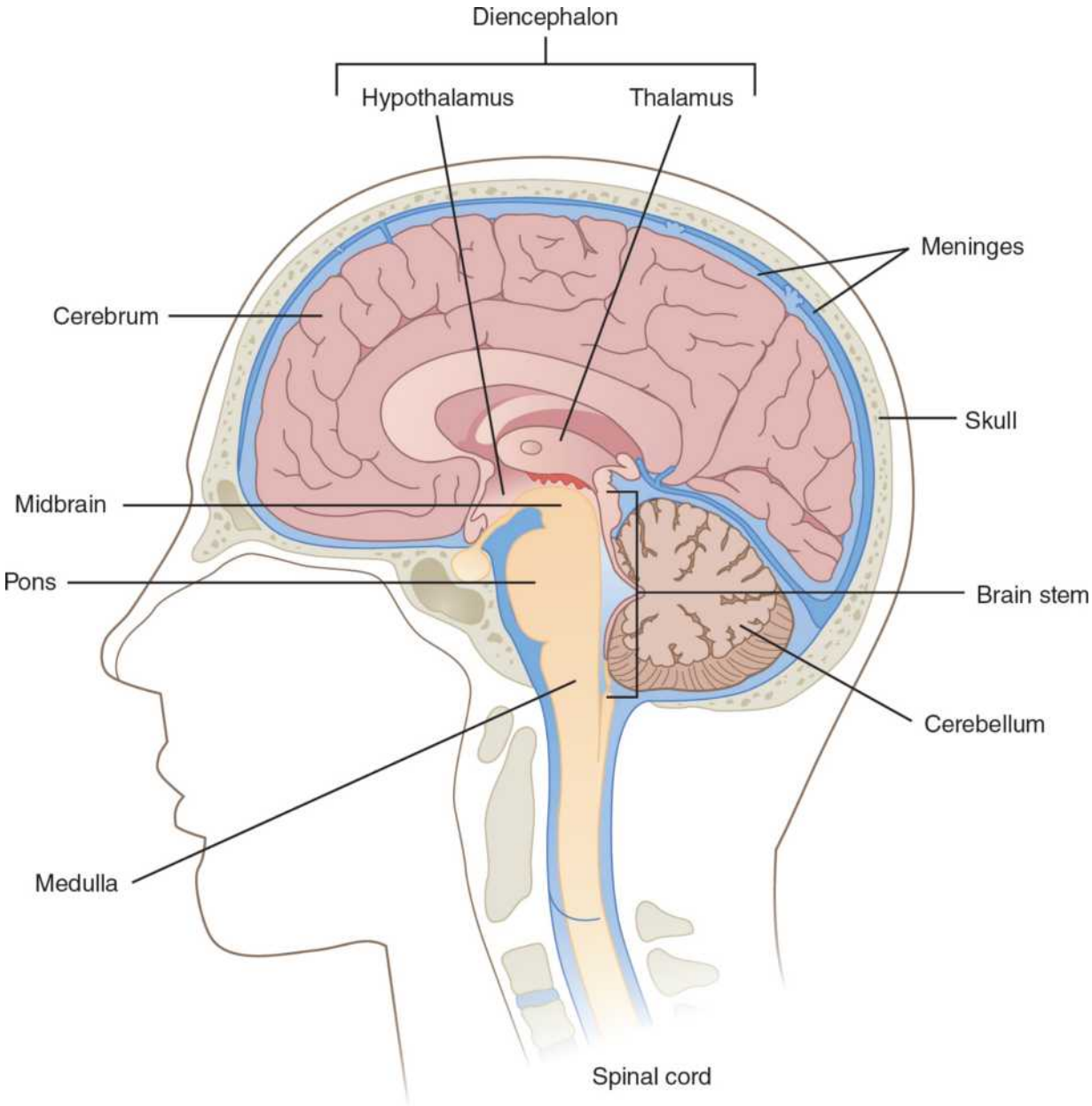


FIGURE 11-7 The major regions of the brain.

Description

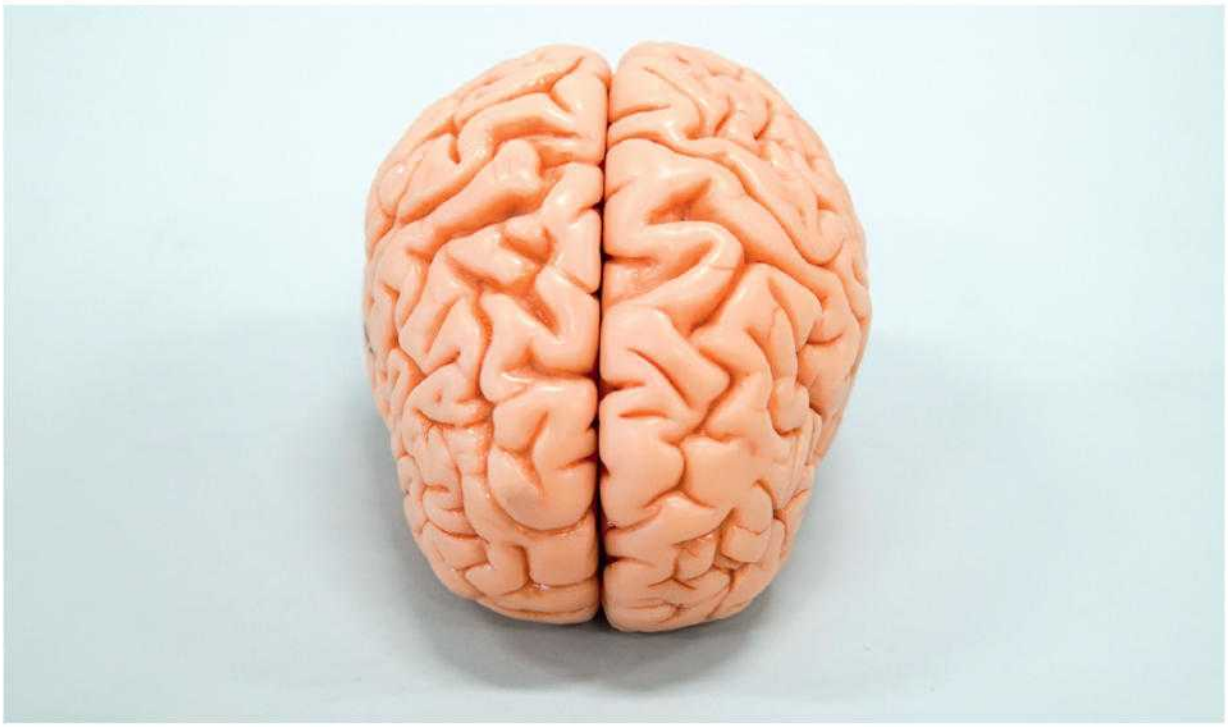


FIGURE 11-8 The cerebrum.

© Choksawatdikorn/Shutterstock

Within each hemisphere of the brain are subdivisions called **lobes**; each lobe is named for the bone of the skull that covers it (**FIGURE 11-9**). The **frontal lobe** facilitates voluntary motor activity and plays a role in personality traits. The **parietal lobe** receives and interprets sensory input, except for smell, hearing, and vision stimuli. The **occipital lobe** processes visual information. The **temporal lobe** plays an essential role in hearing and memory. Areas within and across these lobes can be classified as three types: motor (which stimulates muscle activity), sensory (which receives sensory information), and association (which integrates information and initiates coordinated responses).

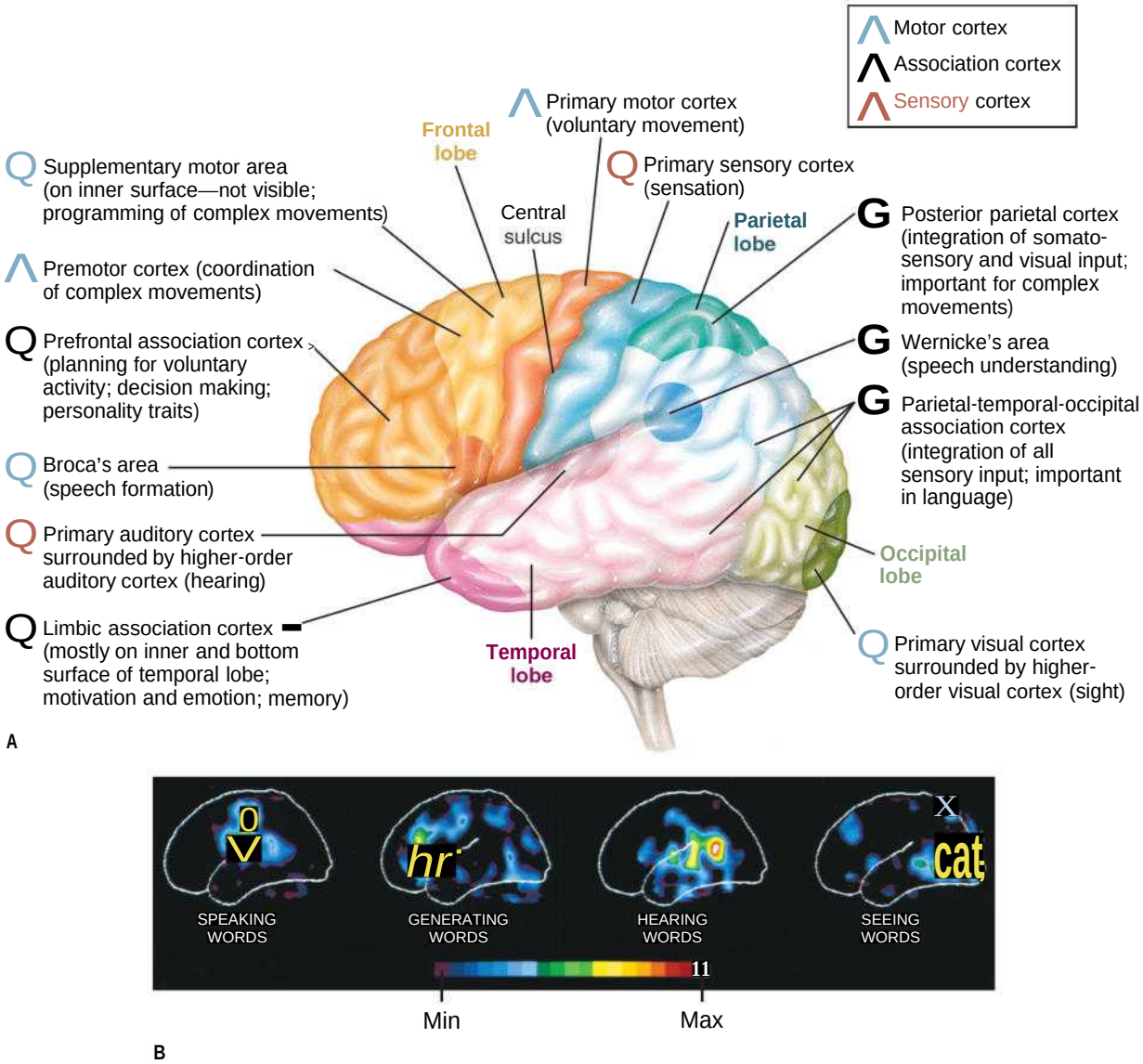


FIGURE 11-9 The lobes of the cerebrum. **(A)** The cerebral cortex has three principal functions: receiving sensory input, integrating sensory information, and generating motor responses. Special sensory areas handle vision, smell, taste, and hearing. **(B)** A positron emission tomography (PET) scan reveals the locations of increased blood flow in the brain during the performance of certain tasks.

B: Photo: Courtesy of Marcus Raichle, MD, Mallinckrodt Institute of Radiology, Washington University in St. Louis School of Medicine.

Description

The diencephalon includes the thalamus and hypothalamus (**FIGURE 11-10**). The thalamus receives and relays most of the

sensory input, affects mood, and initiates body movements, especially those associated with fear or anger. The **subthalamus** participates in motor activities, but the functions of the **epithalamus**—especially the pineal body—are unclear. The hypothalamus is the most inferior portion of the diencephalon; it regulates many bodily functions (see the *Endocrine Function* chapter).

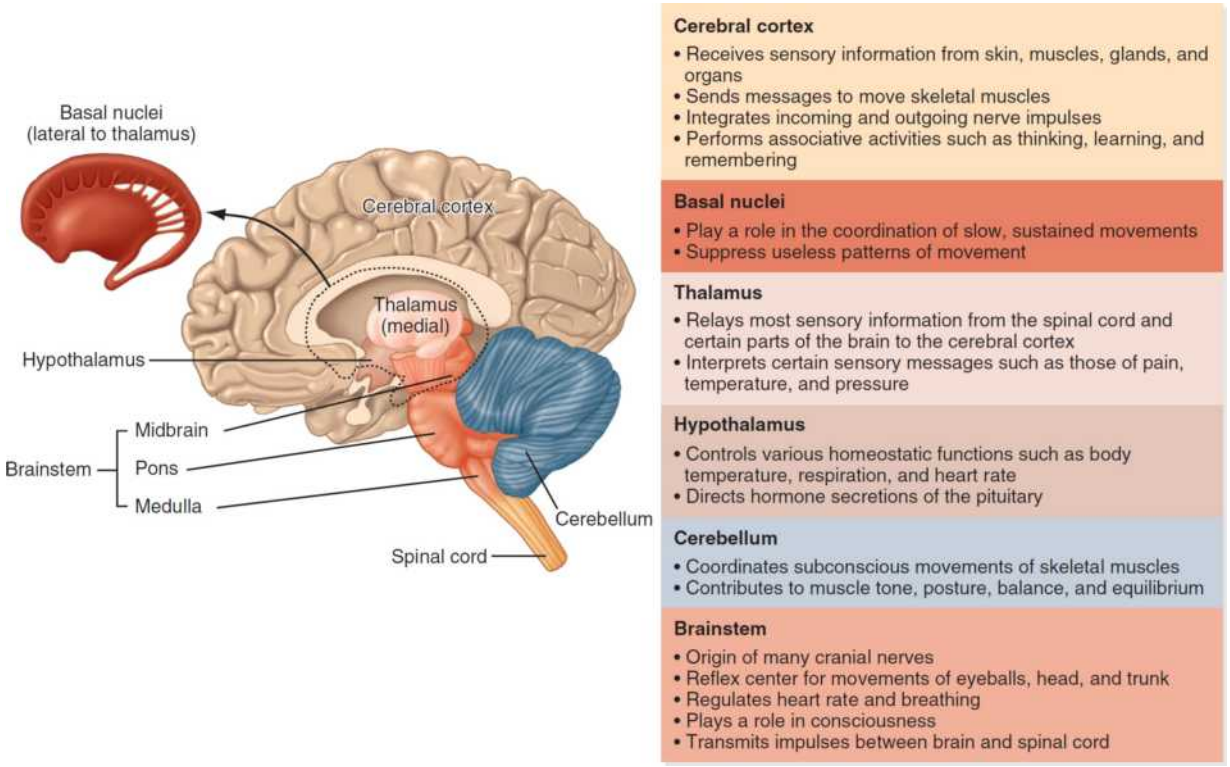


FIGURE 11-10 The regions of the brain and their functions.

Description

The brainstem (including the pons, cerebellum, and medulla) connects the brain to the spinal cord. This structure is crucial for many basic body functions (e.g., maintaining heart rate, blood pressure, and respiration), and injury to the brainstem can easily result in death. The brainstem collaborates with the hypothalamus to regulate these vital activities. In addition to containing control regions, the brainstem serves as the main thoroughfare for information traveling to and from the brain. Of the 12 **cranial nerves**, 10 exit from the brainstem. The pons contains nerves that regulate sleep and

breathing. The midbrain, which is the smallest region of the brain, acts as a sort of relay station for auditory and visual information. It controls the visual and auditory systems as well as eye movement. The medulla is a conduction pathway for ascending and descending nerve tracts. It coordinates heart rate, peripheral vascular resistance, breathing, swallowing, vomiting, coughing, and sneezing.

Most of the many nerve fibers passing through the brainstem have branches that terminate in a region of the brainstem called the **reticular formation**. The reticular formation acts like a gatekeeper, receiving all incoming and outgoing information. It sends impulses to the cerebral cortex through specialized nerve fibers. These fibers, in turn, make up the **reticular activation system** (**FIGURE 11-11**). The reticular formation and the reticular activation system are responsible for alertness during the day, and their ongoing activation can prevent sleeping at night.

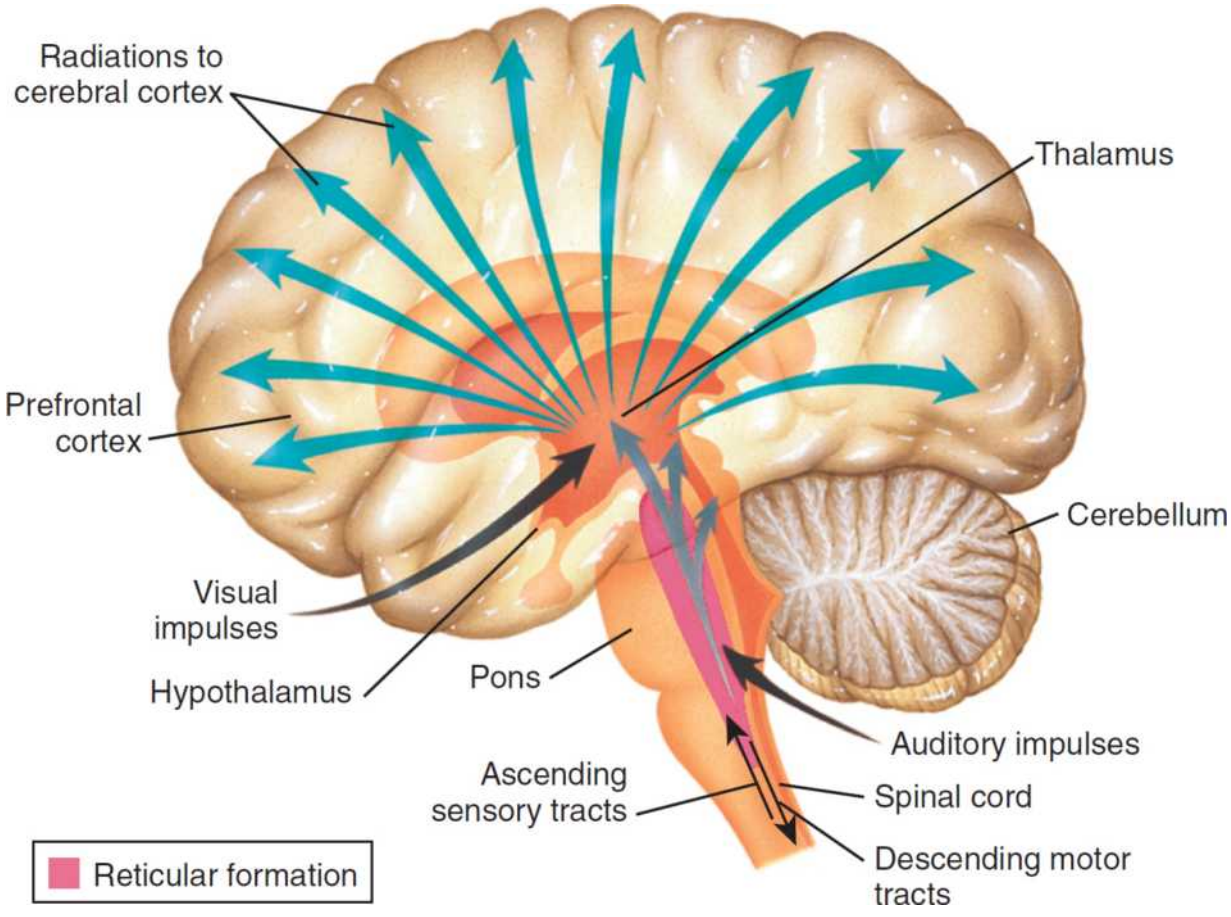


FIGURE 11-11 The reticular activation system.

Description

The cerebellum communicates with other regions of the brain to coordinate the synergistic motion of muscle movement and balance as well as cognition. Deep within the cerebrum, diencephalon, and midbrain is a set of key structures called the **basal ganglia**. The basal ganglia play a pivotal role in coordination, motor movement, and posture. The **substantia nigra** is a small region in the midbrain that is considered part of the basal ganglia. It plays an important role as the center for dopamine production, a neurotransmitter that is responsible for movement and reward.

The limbic system comprises the area where the subcortical structures meet the cerebral cortex (**FIGURE 11-12**). The limbic system works to influence instinctive behavior, emotions, motivation, mood, pain, and pleasure. Its primary structures include the amygdala (controls emotion), hippocampus (supports memory formation), thalamus (relays information), hypothalamus (maintains homeostasis), basal ganglia, and cingulate **gyrus** (processes emotions, regulates behavior, and controls autonomic motor function).

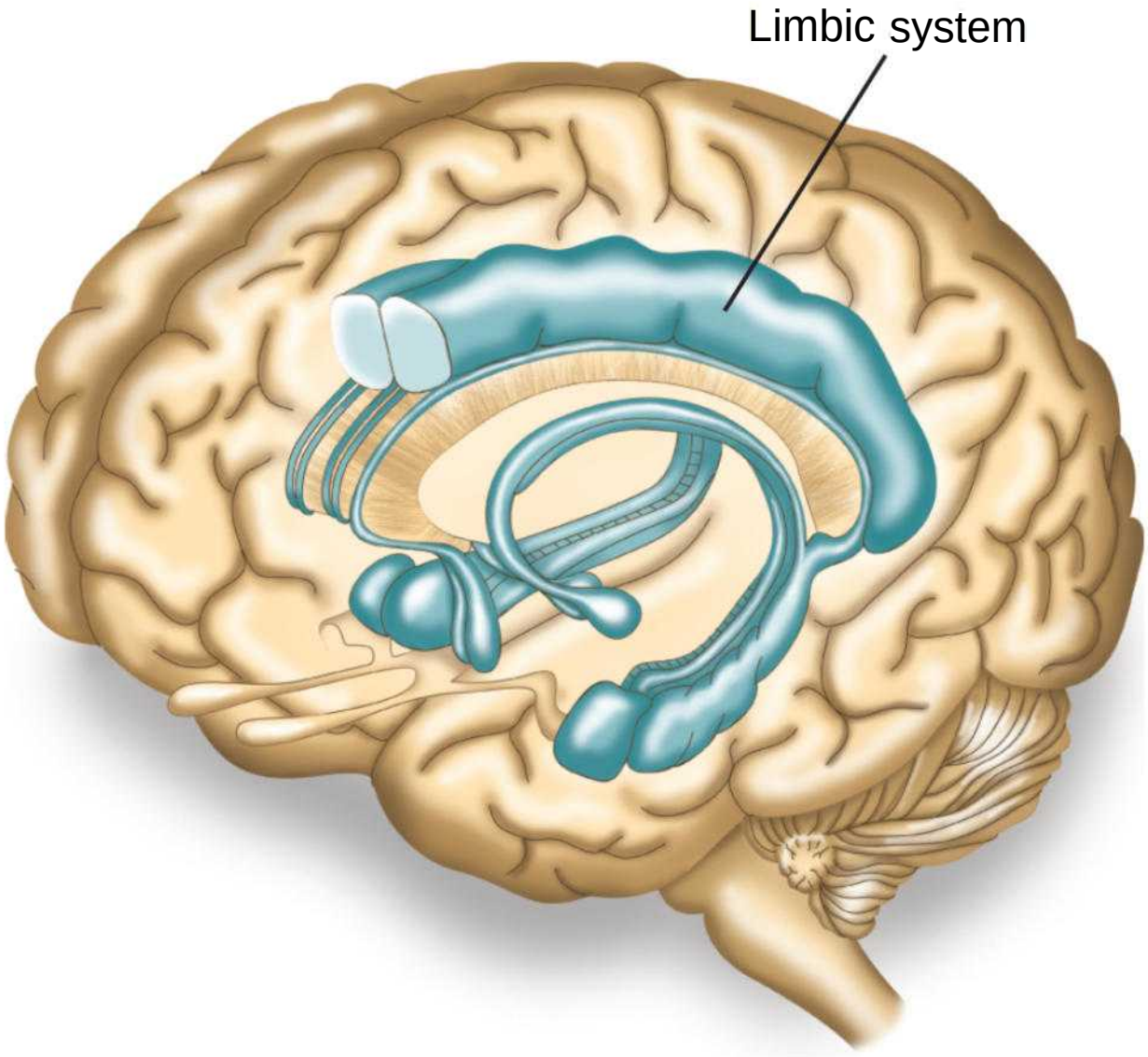
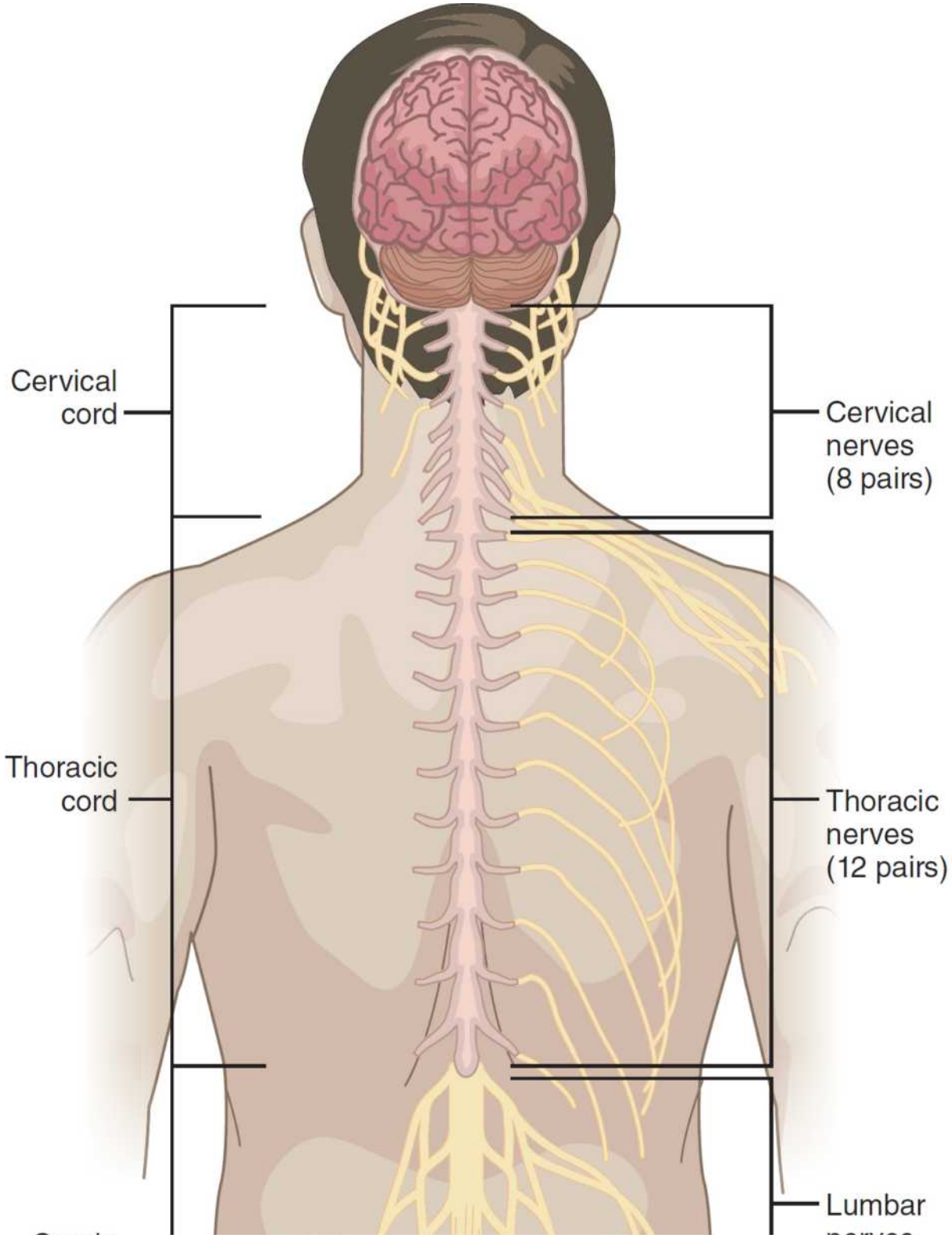


FIGURE 11-12 The limbic system. The odd assortment of structures shown in blue is the limbic system. The limbic system is the seat of emotions, such as joy and instincts; it is home to other functions as well.

The spinal cord is a long, thin, tubular structure composed of nervous tissue that extends from the medulla in the brainstem and exits the skull through the large (and only) opening in the skull, called the **foramen magnum**. The spinal cord extends through the **vertebral canal** to the second lumbar vertebra. At this point, the spinal cord transitions into individual nerve roots referred to as the

cauda equina. The spinal cord consists of 31 pairs of spinal nerves that branch off at regular intervals (**FIGURE 11-13**).



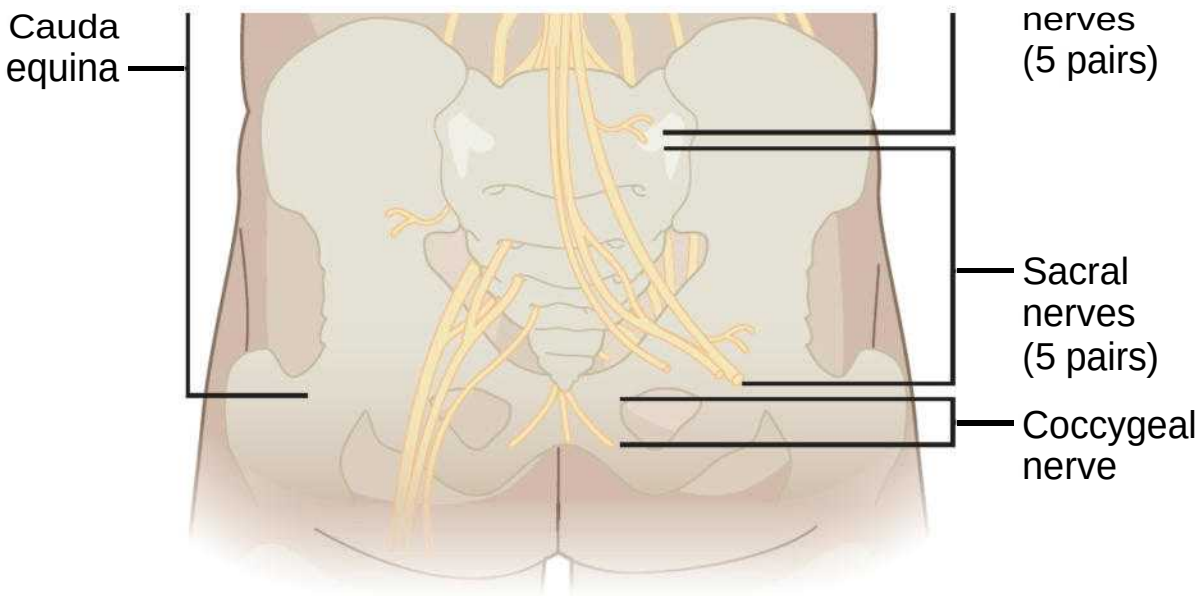


FIGURE 11-13 The spinal cord.

Description

The central portion of the spinal cord is an H-shaped area of gray matter, which contains nerve cell bodies. White matter consisting of nerve fiber tracts, or pathways, surrounds the gray matter (**FIGURE 11-14**). **Ascending fibers**, also known as **afferent tracts**, carry sensory information in the form of action potentials from the periphery back to the brain. **Descending fibers**, also known as **efferent tracts**, carry motor impulses in the form of action potentials from the brain to the PNS. The ascending fibers contain a variety of tracts that communicate specific sensory input:

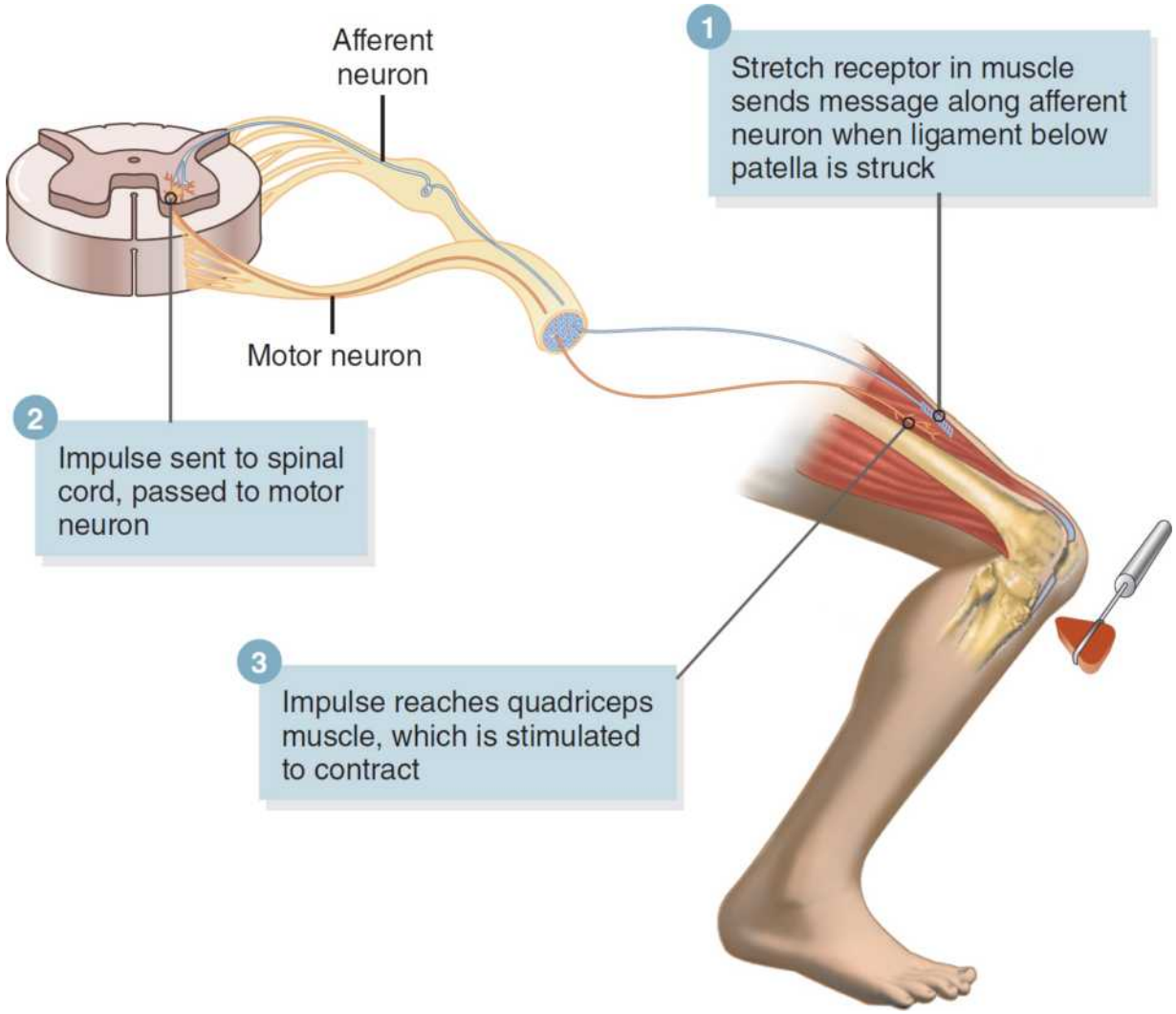


FIGURE 11-14 Spinal cord nerve tracts.

Description

- Anterior spinothalamic tracts permit sensations of light touch, pressure, tickling, and itching.
- Lateral spinothalamic tracts allow the sensations of pain and temperature.
- Spinocerebellar tracts establish the body's position in relation to the cerebellum.
- Corticospinal tracts coordinate movements, especially in the hands.
- Vestibulospinal tracts are responsible for involuntary movements.

- Reticulospinal tracts are also responsible for involuntary movements.

The **spinal reflex arcs** are part of the process that creates an unconscious response to stimuli (**FIGURE 11-15**). An example of this arc can be seen by tapping the patella gently with a reflex hammer. The tendon stretch reflex is elicited when the patella is tapped, causing the lower leg to sharply move first forward (called "extension") and then backward (called "flexion"). The **flexor reflex** is a withdrawal reflex that occurs in response to touching an unpleasant stimulus (e.g., extreme heat). This reflex causes the muscles of a limb to withdraw the limb from the source of the stimulus without any conscious action. The tracts of the spinal cord and brain regulate these impulses.

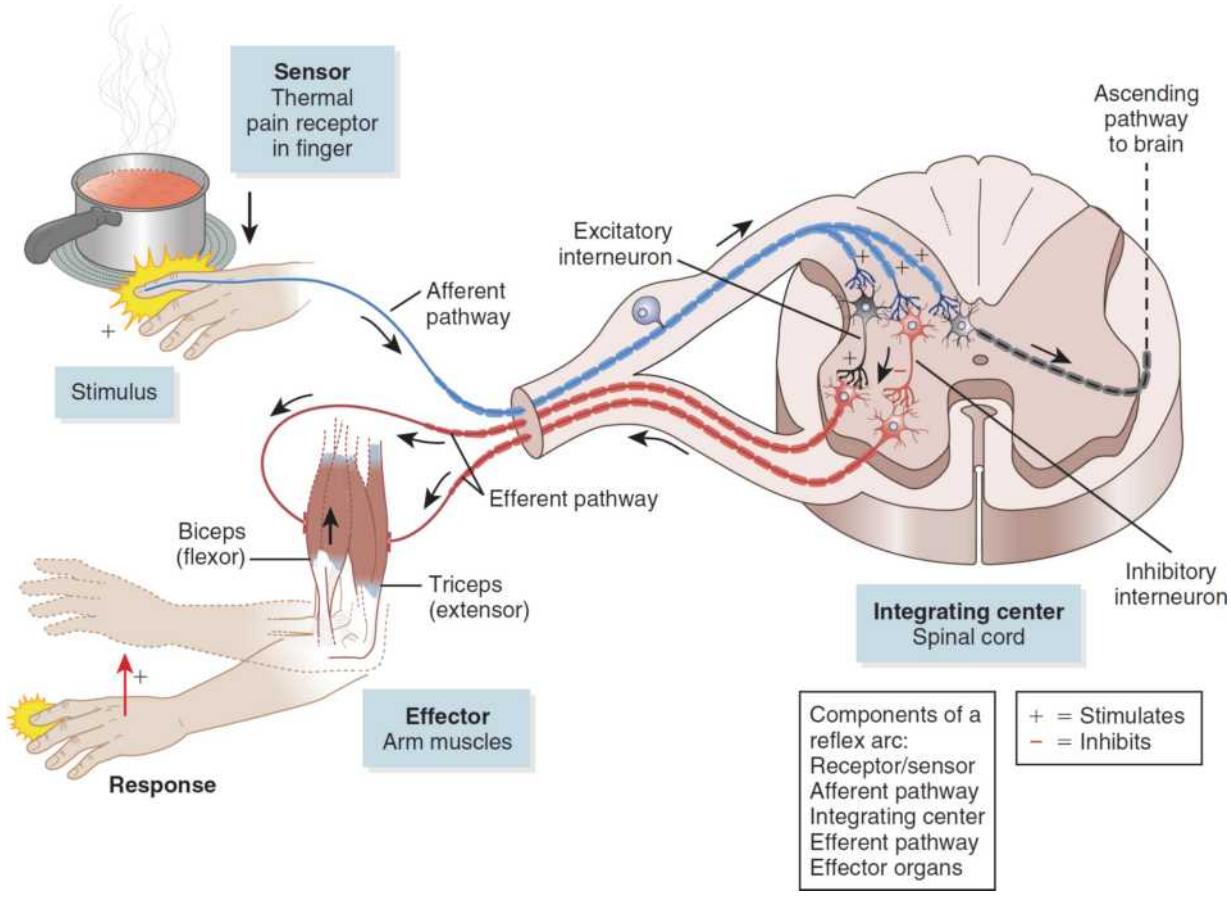


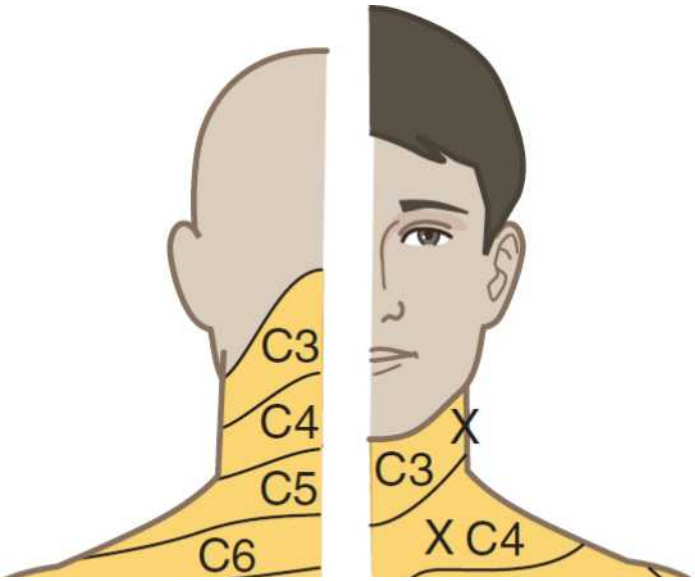
FIGURE 11-15 The spinal reflex arc. When you accidentally touch a hot pan on the stove, you withdraw your hand before your brain even knows what is happening. This reaction occurs

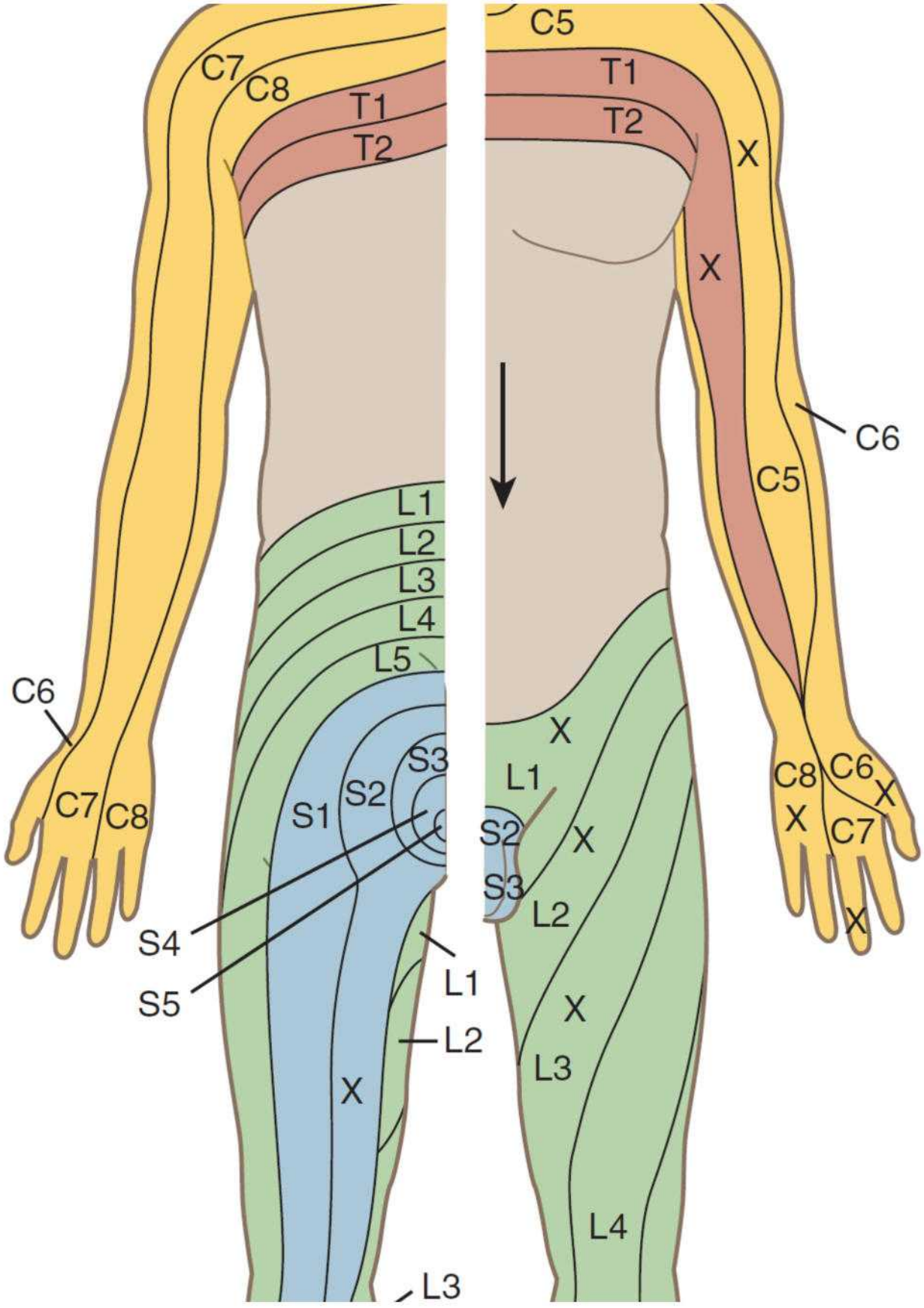
because of a reflex arc. Sensory fibers send impulses to the spinal cord, which stimulate motor neurons in the spinal cord. This stimulation (1) causes muscle contraction in the flexor muscles and (2) inhibits muscle contraction in the extensor muscles, allowing you to withdraw your hand. Nerve impulses also ascend to the brain to let it know what is happening.

Description

Peripheral Nervous System

The nerves of the PNS consist of bundles of nerve fibers, with each fiber being part of the neuron. These spinal and cranial nerves transport messages to and from the CNS. The nerves end on receptors that respond to a variety of internal and external stimuli. The 31 spinal nerve pairs (8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal) branch directly off the spinal cord to make up the PNS. Each spinal nerve pair is named for the vertebral level at which it exits the spinal cord (e.g., C3 is the 3rd cervical nerve, and T12 is the 12th thoracic nerve) and innervates specific areas of the body (**FIGURE 11-16**). Ganglia comprise collections of nerve cell bodies outside the CNS. Spinal nerves arise from several small nerves called **rootlets** along the dorsal and ventral surfaces of the spinal cord (**FIGURE 11-17**). Approximately 6–8 rootlets combine to form each **dorsal root** and **ventral root**. These roots, in turn, come together to form the spinal nerve.




C7
C8
T1
T2
C5
T1
T2
X
X
C6
C5
L1
L2
L3
L4
L5
C6
C7
C8
S1
S2
S3
S4
S5
X
L1
S2
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X
X
C7
X

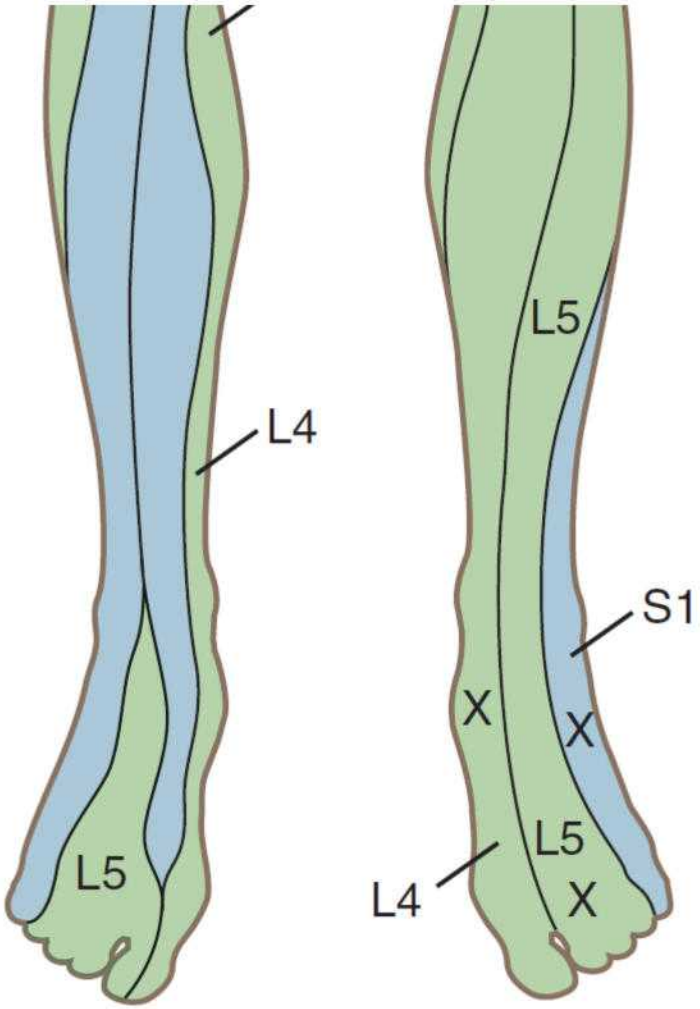


FIGURE 11-16 Spinal nerve innervation.

Description

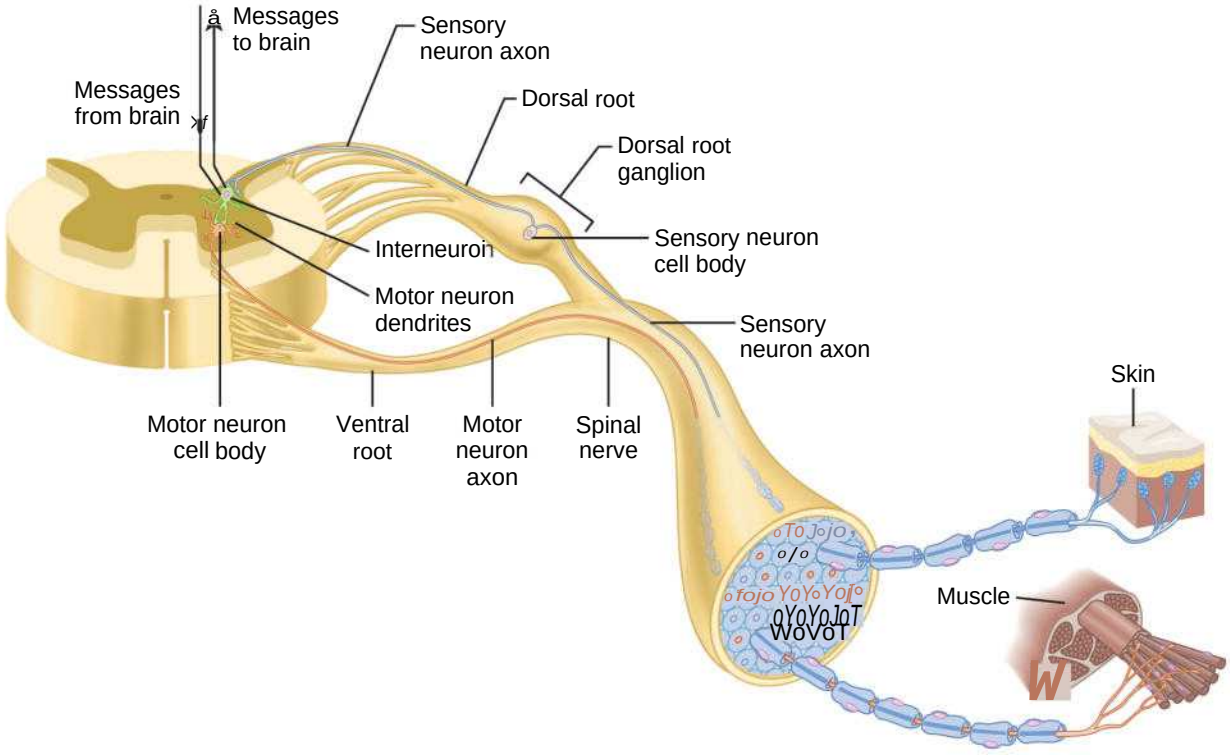


FIGURE 11-17 The dorsal root ganglion.

Description

Each spinal nerve of the PNS comprises two types of nerves—sensory and motor. The **sensory nerves**, or **afferent nerves**, carry impulses (regarding information) from the body to the brain. A **dermatome** is the area of the skin innervated by a given pair of spinal sensory nerves. Each spinal nerve, except for C1, has a specific body surface area from which it obtains sensory information. The **motor nerves**, or **efferent nerves**, carry impulses regarding action from the brain to the corresponding muscle receptor, resulting in muscle contraction and movement. **Interneurons** connect the sensory and motor neurons in the spinal cord.

Sometimes several nerves intersect to form an organized collaboration, or plexus. Four plexuses occur in the body: cervical (located at C1 to C4), brachial (located at C5 to T1), lumbar (located at L1 to L4), and sacral (located at L4 to S4). These plexuses branch into the **peripheral nerves**, which supply sensory and motor functions to many areas of the body. The thoracic nerves do not form

a plexus but instead pass through the intercostal spaces to innervate the thorax.

Twelve pairs of cranial nerves branch directly from the base of the brain (**FIGURE 11-18**). Some cranial nerves carry only sensory fibers (I, II, and VIII), others carry only motor fibers (III, IV, VI, XI, and XII), and a few carry both types of fibers (V, VII, IX, and X). Each nerve travels from the brain through the foramen to its destination.

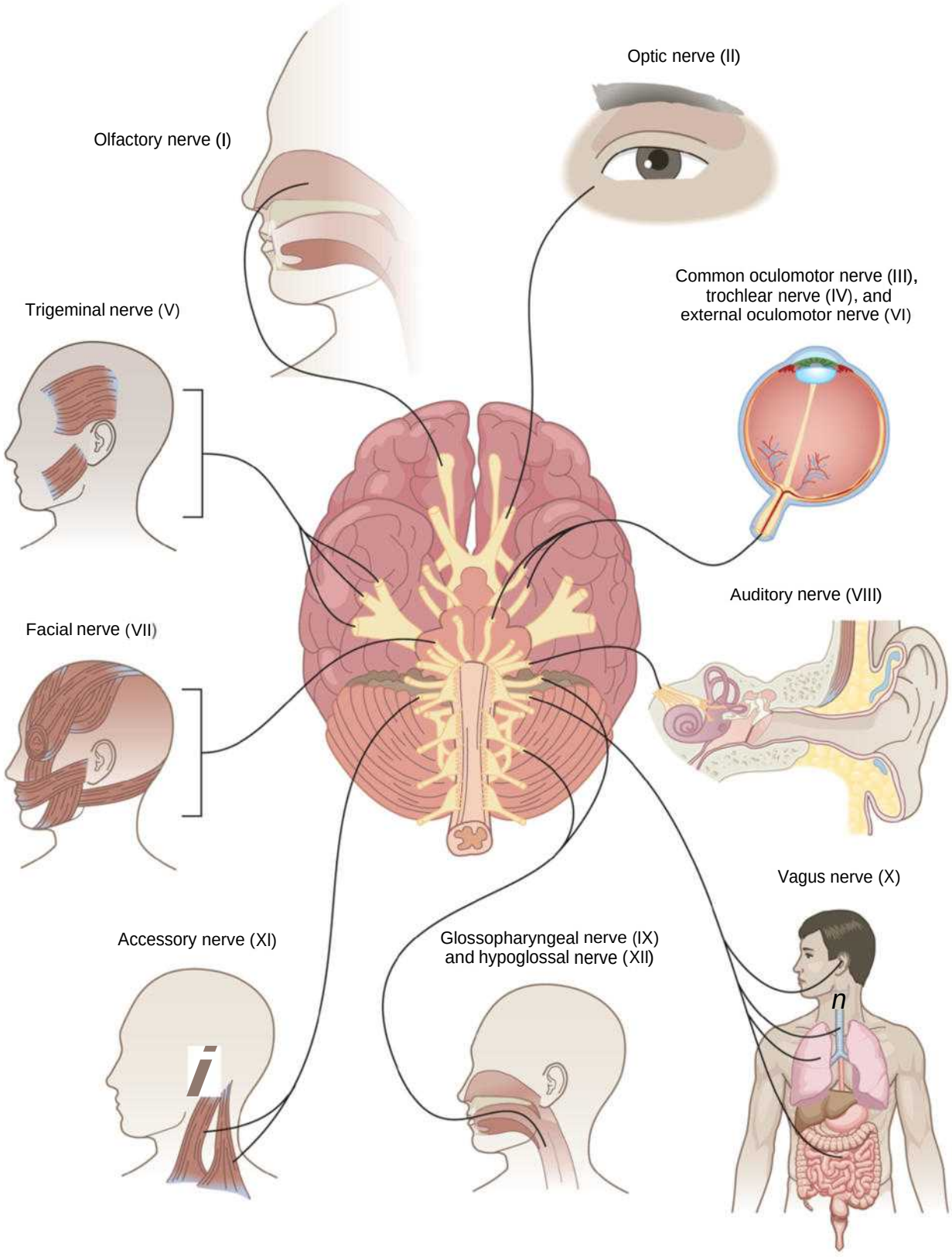


FIGURE 11-18 The cranial nerves.

Description

Autonomic Nervous System

The **autonomic nervous system** controls smooth muscles and is responsible for the fight-or-flight response (see the *Immunity* chapter). The autonomic nervous system, which is not under conscious control, affects such bodily activities as heart rate, blood pressure, and intestinal motility. This system has two subdivisions—sympathetic and parasympathetic. The two divisions have an antagonistic effect on each other that aids in maintaining homeostasis (**FIGURE 11-19**). The **sympathetic nervous system (SNS)** is responsible for the fight-or-flight response; this response is initiated when a person is startled or faced with danger and is augmented by secretions of the adrenal medulla. In contrast, the **parasympathetic nervous system** is responsible for the rest-and-digest response. Neurotransmitters and receptors are important in the autonomic nervous system because the SNS and the parasympathetic nervous system will either stimulate or inhibit them, leading to the physiologic response (**TABLE 11-2**). The SNS stimulates the adrenergic receptors, while the parasympathetic nervous system stimulates the cholinergic receptors. Some medications can also stimulate or inhibit these receptors.

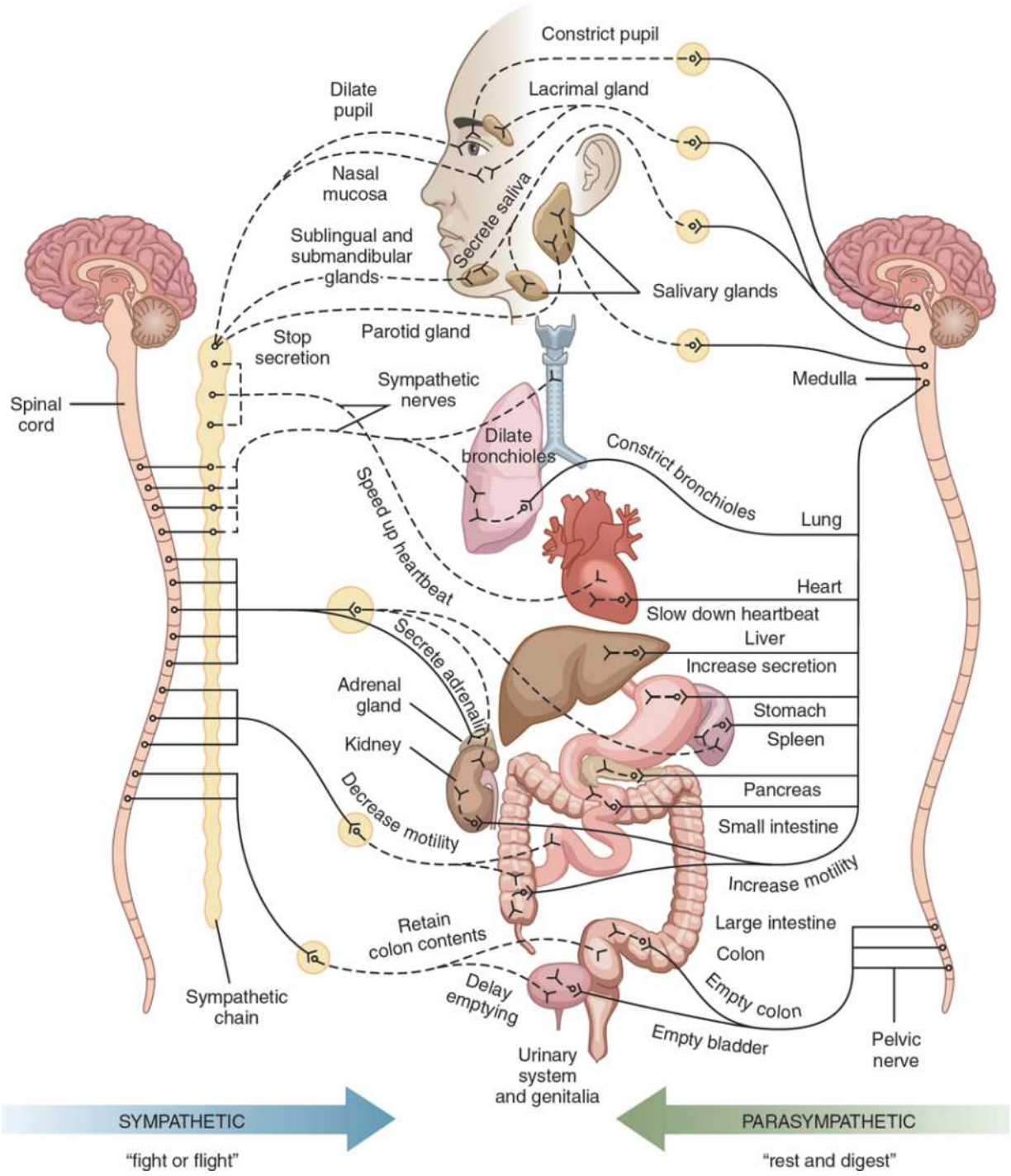


FIGURE 11-19 Comparison of the two divisions of the autonomic nervous system.

Description

TABLE 11-2 Types of Autonomic Receptors

Neurotransmitter	Receptor	Primary Locations	Responses
Acetylcholine (cholinergic)	Nicotinic	Postganglionic neurons	Stimulation of smooth muscle and gland secretions
	Muscarinic	Parasympathetic target: organs other than the heart	Stimulation of smooth muscle and gland secretions
		Heart	Decreased heart rate and force of contraction
Norepinephrine (adrenergic)	$Alpha_1$	All sympathetic target organs except the heart	Constriction of blood vessels, dilation of pupils
	$Alpha_2$	Presynaptic adrenergic nerve terminals	Inhibition of release of norepinephrine
	$Beta_1$	Heart and kidneys	Increased heart rate and force of contraction; release of renin
	$Beta_2$	All other sympathetic target organs	Dilation of bronchial passages; vasodilation in muscles and liver; relaxation of uterine muscle; release of insulin

Description

Learning Points

Memories

How do we learn and store memories? Learning is the acquisition and retention of new information, and memory is the storage and recall of information. Both learning and memory depend on proper nutrition and adequate sleep. Newly acquired memory is first stored in the short-term memory, where it is held for seconds to hours. For example, cramming for tests puts most of the information into short-term memory. Unfortunately, this information fades soon after the test ends—a good reason not to cram! Long-term memory, by comparison, holds information for days to years.

Transferring information from short- to long-term memory requires special efforts, such as using repetition, mnemonics, and rhymes. Recalling information in short-term memory is often faster than recalling information in long-term memory. When information is lost from short-term memory, it is usually lost forever. Information you cannot recall from long-term memory, in contrast, is often still there; it just requires time or stimuli to extract. However, not all information in long-term memory is stored forever.

Memories are stored in neurons throughout the cerebral cortex (especially the temporal lobe), cerebellum, and limbic system. The hippocampus seems to be crucial in transferring information from short- to long-term memory.

You can use this knowledge to help you study—for example, by not cramming but instead moving information from short- to long-term memory by paying attention, making the information memorable, and relating new information with facts you already know. Do not forget that you still have to get plenty of rest and eat a balanced diet to optimize your learning potential!

Myth Busters

Some myths surrounding the brain warrant discussion.

Myth 1: The brain is gray.

The living, pulsing brain currently residing in your skull is not just a dull, bland, gray organ like the image often depicted in movies; instead, the brain is also white, black, and red. Like many myths, this one has a grain of truth, because much of the brain *is* gray. Sometimes the entire brain is referred to as gray matter. However, the brain also contains white matter, which comprises nerve fibers that connect the gray matter. The black component is called "substantia nigra," which is Latin for "black substance." The substantia nigra has a black color because of **neuromelanin**, a specialized type of pigment. Finally, the brain is red in some areas because of the many blood vessels it contains.

Myth 2: Listening to classical music, especially by Mozart, increases intelligence.

How did this myth get started? In the 1950s, a physician named Albert Tomatis claimed he had successfully used Mozart's music to help people with speech and auditory disorders. In the 1990s, 36 students in a study at the University of California at Irvine listened to 10 minutes of a Mozart sonata before taking an IQ test. The study reported that the students' IQ scores went up by about 8 points—and thus the Mozart effect was born. Multiple products have been sold based on this assumption. However, the original University of California at Irvine study remains controversial within the scientific community. Other scientists have been unable to replicate the original results, and current scientific evidence does not support the contention that listening to Mozart—or any other classical music, for that matter—increases intelligence. However, some evidence indicates that learning an instrument improves concentration, self-confidence, and coordination. Mozart's music certainly cannot hurt you, and you might even enjoy it if you try listening to this music; however, you will not get any smarter because of this activity.

Myth 3: You use only 10% of your brain.

This myth is probably one of the most well-known legends about the brain. This assumption seems puzzling at first glance. We have the biggest brain in proportion to our bodies of any animal, so why would we not use all of it? Many people have jumped on this idea, writing books and selling products that claim to tap into the other 90%. Believers in psychic abilities cite this claim as proof, suggesting that people with these abilities have tapped into the rest of their brains.

In fact, this myth is false. In addition to 100 billion neurons, the brain is full of other types of cells that are continually in use. Significant neurologic deficits can occur from even minor damage depending on the location, so it is highly unlikely that we could function with only 10% of our brain in use. Brain scans have shown that no matter what we are doing, our brains are always active. Some areas are more active at any one time than others, but unless we have brain damage, no one part of the brain is completely turned off. Thus, there is no hidden, extra potential you can tap into, in terms of actual brain space.

Myth 4: Games like Sudoku and Brain Age keep your brain young.

There is some truth to this myth! Continued mental engagement has benefits, and puzzles can help you get good at a specific skill, such as memorizing grocery lists or hand–eye coordination. Most evidence, however, suggests that practicing a task helps you get better only at that particular task. Far better for mental function is physical exercise. Regular physical exercise is especially effective in the elderly, who may suffer from gradual problems with cognitive function, such as planning ahead and abstract thinking.

UNDERSTANDING CONDITIONS THAT AFFECT THE NERVOUS SYSTEM

When considering alterations in the nervous system, organizing them based on their basic underlying pathophysiology can increase understanding. Conditions of the nervous system are usually complex, affecting many areas of function. For example, these disorders may lead to impaired physical mobility, chronic pain, disrupted social interaction, altered thought process, incontinence, risk for injury, and self-care deficit, just to name a few possibilities. Each of these nursing diagnoses requires its own set of interventions. Patients experiencing these neurologic conditions often require vigilance to manage the complexity of the situation.

Congenital Neurologic Disorders

Congenital defects of the nervous system are often serious, with lifelong consequences. These disorders often have limited treatment options and require long-term management of complications.

Hydrocephalus

Hydrocephalus is a condition in which excess CSF accumulates, dilating the ventricles and compressing the brain and blood vessels (**FIGURE 11-20**). The pressure from the excess CSF thins the cortex, causing severe brain damage. CSF accumulates when the flow of this

fluid is disrupted (referred to as “noncommunicating” or an “obstructive hydrocephalus”) or when too much CSF is made or not properly absorbed by the bloodstream (referred to as “communicating hydrocephalus”).

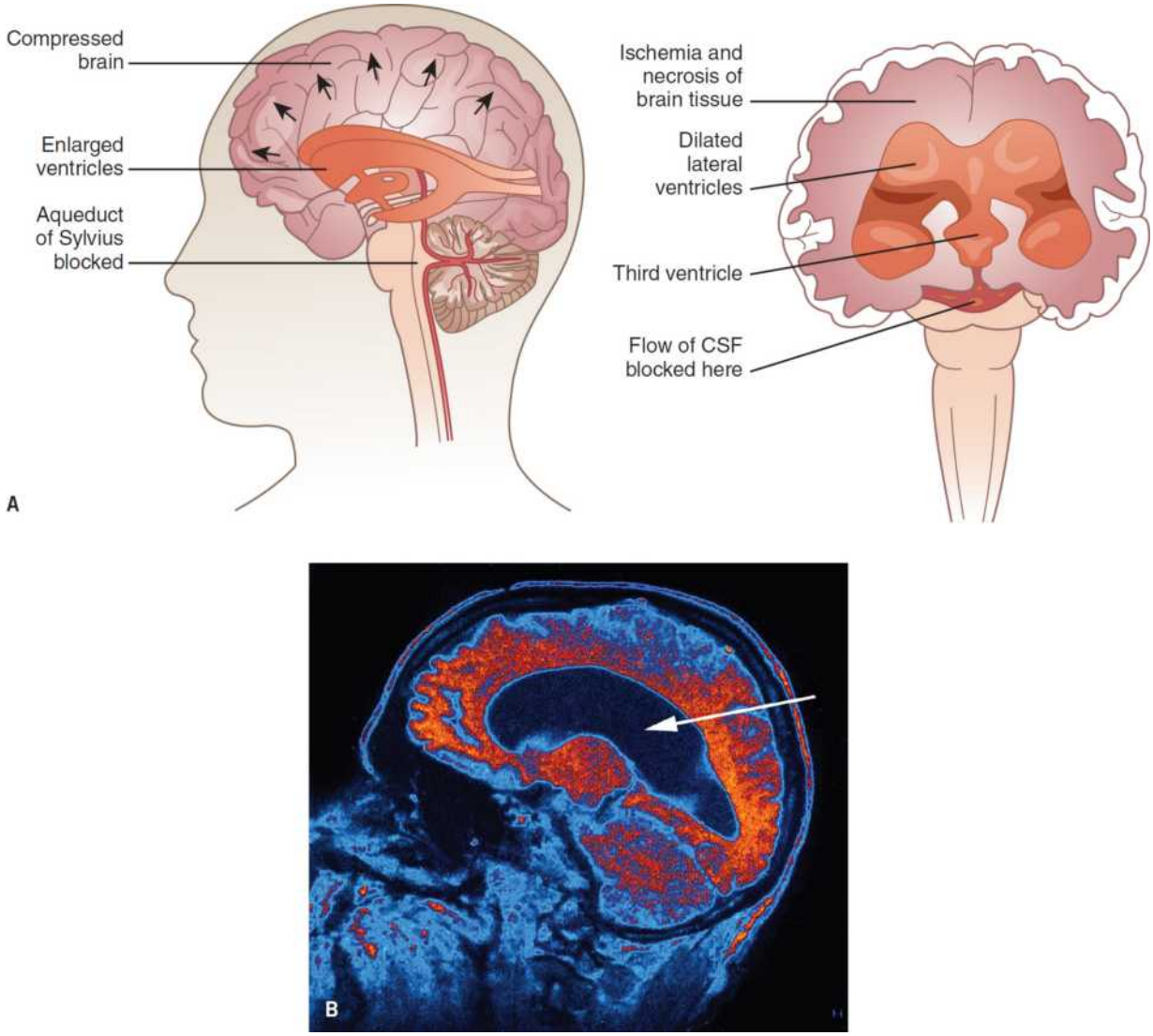


FIGURE 11-20 Hydrocephalus development.

B: © Cavallini James/BSIP/age fotostock

Description

Hydrocephalus is a common condition that may be present at birth (in an estimated 1 out of 500 births) or develop later in life (another 6,000 children younger than 2 years of age develop it each year)

(National Hydrocephalus Foundation, 2018). Congenital hydrocephalus has been associated with four genes (Shaheen et al., 2017). *LICAM1* and *AP1S2* are X-linked, and *CCDC88C* and *MPDZ* are autosomal recessive. In adults, hydrocephalus is most common after the age of 60 and usually results from enlarged ventricles without increased cerebral pressure. This kind of normal-pressure hydrocephalus may contribute to a small number of **dementia** cases. Risk factors for hydrocephalus at any age include prematurity, pregnancy complications, other congenital defects (especially nervous system defects, such as **spina bifida**), nervous system tumors, CNS infections, cerebral hemorrhage, and severe head injuries. If left untreated, hydrocephalus is often fatal (60% mortality rate). The prognosis depends on early treatment and comorbidity.

Clinical manifestations of hydrocephalus reflect the **increased intracranial pressure (ICP)**. These manifestations vary by age group, underlying etiology, and disease progression. In infants, clinical manifestations often include the following:

- An unusually large head (**FIGURE 11-21**)

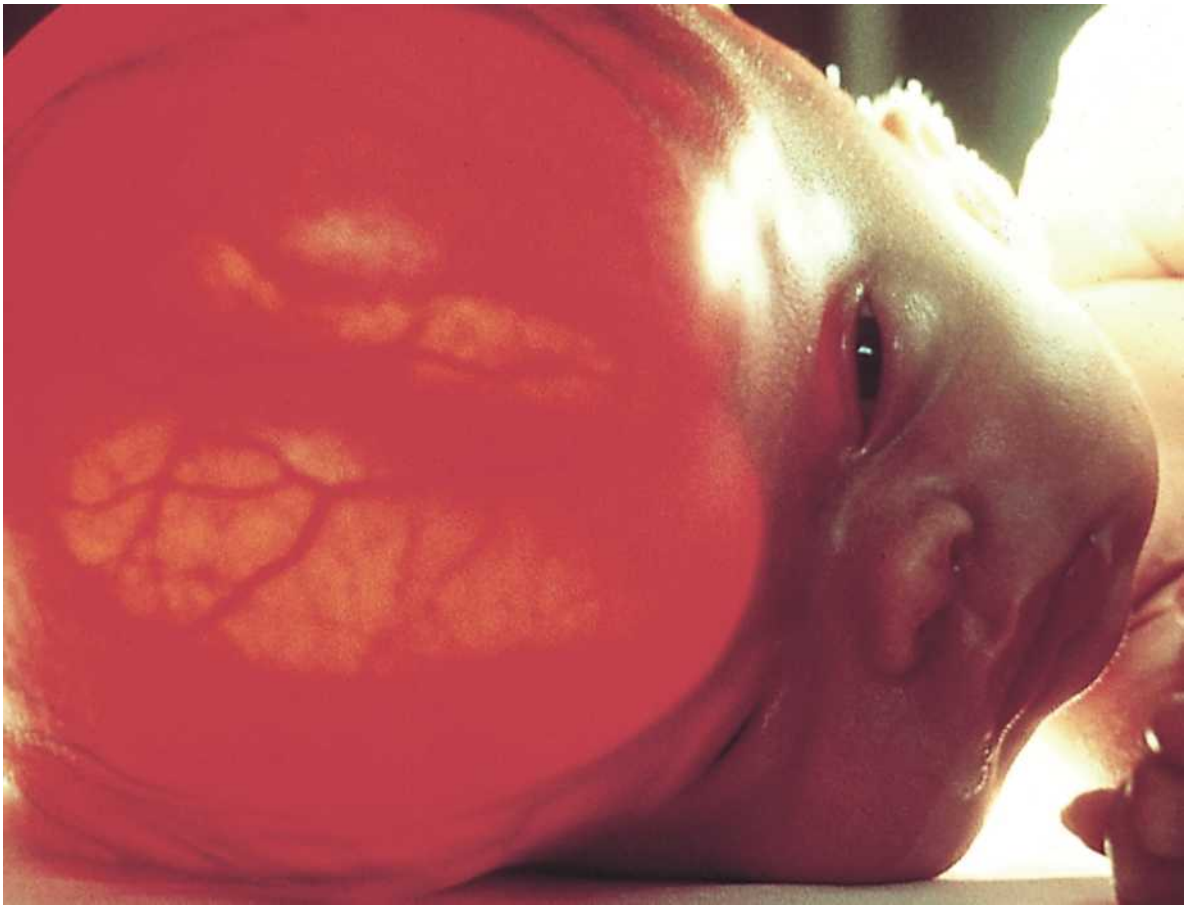


FIGURE 11-21 Hydrocephalus.

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- A rapid increase in the head size
- A bulging fontanelle, or soft spot, on the top of the head
- Vomiting (often projectile)
- Lethargy
- Irritability
- High-pitched cry
- Feeding difficulties
- Seizures
- Eyes that gaze downward (setting-sun appearance)
- Developmental delays

In older children and adults, the head cannot enlarge because the sutures have closed. Thus, clinical manifestations of hydrocephalus in these groups may include the following signs and symptoms:

- Headache followed by vomiting (usually absent in normal-pressure hydrocephalus)
- Nausea
- Blurred vision or diplopia (double vision)
- Sluggish pupil response to light; eyes that gaze downward (setting-sun appearance)
- Problems with balance, coordination, or gait
- Extreme fatigue
- Slowing or regression of development
- Memory loss
- Confusion
- Urinary incontinence
- Irritability
- Personality, memory, or cognition changes
- Impaired performance in school or work

Diagnostic procedures for hydrocephalus may be performed during pregnancy or after birth. These procedures consist of a history, physical examination (including head circumference measurement and a neurologic assessment), head computed tomography (CT), head magnetic resonance imaging (MRI), skull X-ray, cranial ultrasound, and prenatal ultrasound.

The goal of treatment is to minimize brain damage by reducing CSF accumulations. Blockages are surgically removed, if possible. If the blockage cannot be removed, a shunt (flexible tube) may be placed within the brain to allow CSF to flow around the blocked area. The shunt tubing travels to another part of the body, such as the peritoneal cavity (ventriculoperitoneal) or right atrium (ventriculoatrial), where the extra CSF can be drained and absorbed. Shunt replacement may be needed periodically as a child grows or if the

shunt becomes blocked or infected. Antibiotic therapy will treat hydrocephalus caused by an infection or if a shunt infection develops. An endoscopic third ventriculostomy can also be performed to relieve pressure without replacing the shunt. Additionally, the area producing too much CSF may be cauterized. Follow-up examinations generally continue throughout a child's life to monitor developmental progress and to manage any intellectual, neurologic, or physical problems. A multidisciplinary team (e.g., nurses, occupational therapists, educational specialists, social services personnel, and support groups) can provide emotional support and assistance with the care of those patients who have significant brain damage.

Spina Bifida

Spina bifida, meaning "cleft spine," is a neural tube defect that can vary in severity from mild to debilitating. Neural tube development begins early in pregnancy, starting at the cervical area and progressing toward the lumbar area, and the neural tube usually closes by 4 weeks' gestation. In spina bifida, the posterior spinous processes on the vertebrae fail to fuse (i.e., spinal dysraphism). This opening permits the meninges and spinal cord to herniate, resulting in neurologic impairment. The lumbar area of the vertebrae is most commonly the site of the defect, but in rare cases, it can occur in the thoracic and cervical areas.

Spina bifida rates have decreased in the United States over the past 20 years in part due to mandates to enrich grains with folic acid as well as recommendations for childbearing-age women to consume 400 mcg of folic acid daily. Currently, about 1,427 babies are born with spina bifida each year in the United States (Centers for Disease Control and Prevention [CDC], 2020c). Worldwide, the incidence is highest in Ireland and Wales. Spina bifida is most common in Hispanic and Caucasian populations, with females being more affected than males. Additional maternal risk factors for the development of this defect in a child include family history of neural defects (although most are sporadic), folate deficiency (thought to be a key factor), certain medications (e.g., antiseizure agents), diabetes mellitus,

prepregnancy obesity, and increased body temperature (e.g., from fever, hot tubs, saunas, and tanning beds).

The etiology of spina bifida is complex. The exact cause is unknown, but this condition is thought to be caused by interactions of multiple genetic and environmental factors. Changes in dozens of genes influence the risk of developing spina bifida. The best-studied gene is *MTHFR* (methylenetetrahydrofolate reductase), which provides the instructions for making a protein involved in processing folate (National Institutes of Health [NIH], 2019).

The estimated lifetime cost of care of persons with spina bifida is nearly $800,000 (CDC, 2020c). Complications of spina bifida include physical and neurologic impairments as well as hydrocephalus and **meningitis**. Syringomyelia, a dilation of the normally small fluid-filled central canal of the spinal cord, and other congenital anomalies and soft-tissue masses around the spinal cord may be present. Children with spina bifida are usually of normal intelligence, but they may have learning problems because of the chronic nature of the condition.

Spina bifida occurs in three forms, each varying in severity (**FIGURE 11-22**):

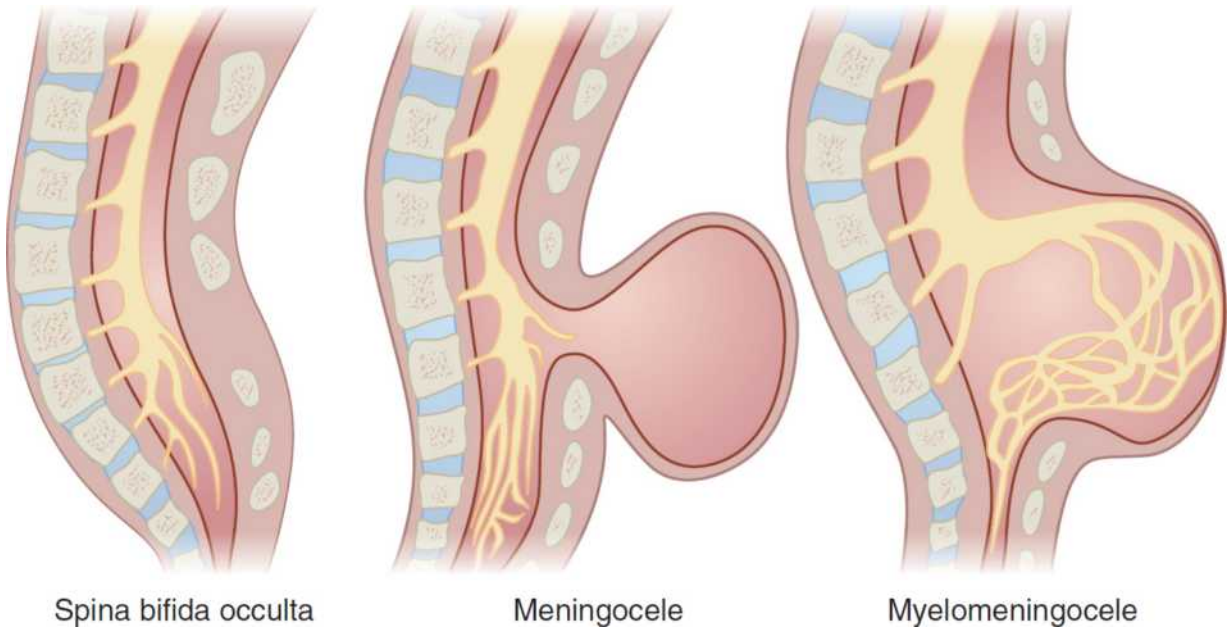


FIGURE 11-22 Most common types of spina bifida.

Description

- **Spina bifida occulta** (i.e., occult spinal dysraphism) is the mildest and most common form. It results in a small gap in one or more of the vertebrae. The spinal nerves and meninges do not usually protrude through the opening, so most children with this form have no clinical manifestations and experience no neurologic deficits. The defect may not be diagnosed until late childhood or adulthood because only a dimple, birthmark, or tuft of hair over the site may be present.
- **Meningocele** is a rare form that involves the same bony defect as in spina bifida occulta, but the meninges protrude through the vertebral opening. The meninges and CSF form a sac (i.e., cystica) on the surface of the infant's back. Transillumination (shining a light through the tissue) can confirm the absence of nerve tissue in the sac. Because the spinal cord develops normally, neurologic impairment is usually not present, and these membranes can be removed by surgery with little or no damage to nerve pathways. However, infection or rupture of the sac can lead to neurologic impairment.
- **Myelomeningocele**, also known as open spina bifida, is the most severe form. In this variant, the spinal canal remains open along several vertebrae in the lower or middle back. The meninges, spinal cord, spinal nerves, and CSF protrude through this large opening at birth and form a sac on the infant's back (**FIGURE 11-23**). Skin covers the sac in some cases. However, tissues and nerves are exposed in most cases, making the infant vulnerable to life-threatening infections. Neurologic impairment (often including paralysis), bowel and bladder problems (e.g., incontinence, urinary tract infections, and constipation), **seizures**, and other medical complications (e.g., skin conditions and latex allergies) are common.



FIGURE 11-23 Myelomeningocele.

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Clinical manifestations depend on the type and severity of spina bifida. Diagnostic procedures may be performed during pregnancy or after birth. These procedures may include a history, physical examination, check of maternal serum and amniotic fluid alpha-fetoprotein levels (high levels indicate a possible neural tube or other congenital defect), prenatal ultrasound, spinal X-ray, spinal CT, and spinal MRI.

application to practice

M.S. is a 26-year-old woman pregnant with her first child. Her husband accompanied her to all her prenatal visits. An ultrasound during a routine visit at 34 weeks' gestation revealed that the baby had hydrocephalus and a myelomeningocele. The parents were initially devastated but remained very excited about the birth of their first child. M.S. was scheduled for a cesarean section at 38 weeks' gestation, and the couple was anxious about their child's condition and care following birth.

M.S. delivered a baby boy by cesarean section; he was transferred to the pediatric intensive care unit. On admission to the nursery, the baby's vital signs and weight were within normal limits, but his head circumference was large. He had bulging fontanelles and a high-pitched cry. The nurse noted a saclike projection in the lumbar region of his spine.

1. Discuss the rationale for delivering the infant by cesarean section.
2. Explain the significance of the infant's clinical manifestations.
3. Describe the complications associated with myelomeningocele.
4. Identify short- and long-term treatment strategies for the infant.

Treatment strategies vary depending on the type and severity. For instance, spina bifida occulta often requires no treatment. Surgery is the mainstay of treatment for the other two types; however, the appropriate timing of the surgery (in utero, immediately after birth, or delayed) remains a topic of debate. Surgery usually includes replacing the meninges and closing the vertebral opening. A shunt may be placed during surgery to control hydrocephalus. Early correction of the defect may improve outcomes. Intrauterine exposure to amniotic fluid may be toxic to the vulnerable spinal nerve tissue and bone. Although the procedure cannot restore lost neurologic function, it may prevent further loss. Additional risk may be incurred with this procedure, including premature delivery and death. If spina bifida is diagnosed before birth, cesarean delivery is preferred to prevent rupture of the sac or damage to any exposed nerves. Long-term support from a multidisciplinary team (e.g., a nurse, physical therapist, social worker, and education specialist) will be necessary to limit complications and promote positive outcomes.

Cerebral Palsy

Cerebral palsy (CP) refers to a group of nonprogressive disorders that appear in infancy or early childhood and permanently affect motor movement and muscle coordination. In addition to motor dysfunction, other cerebral functioning may be affected (e.g., cognition and communication). CP usually results from damage to the cerebellum during the prenatal period (often during childbirth), but it can also occur at any time during the first 3 years of life, when the

brain is developing. In addition, this disorder can occur because of brain abnormalities. In the United States, CP is the leading cause of childhood disability, affecting approximately 1 to 4 out of every 1,000 births (CDC, 2022a). CP is more common in males, in African Americans, and in persons of lower socioeconomic status.

Although CP is not curable, the right treatment can make a significant impact on the child's prognosis. Unfortunately, these therapies are costly. According to the CDC (2022a), the average lifetime costs (direct and indirect) for one person with CP are estimated to be nearly $1 million (in 2003 dollars). The estimated lifetime costs (direct and indirect) for all people with CP who were born in 2000 will total $11.5 billion (in 2003 dollars).

The etiology of CP is multifactorial, and a specific cause is often difficult to identify. Hypoxia during the birth process was once thought to be the primary cause of this condition, but it likely causes only a small number of cases. The following factors contribute to the development of CP:

- Prematurity
- Low birth weight
- Breech births (feet first, rather than head first)
- Multiple fetuses
- Hypoxia during birth (e.g., placental abruption, uterine rupture, or umbilical cord compression)
- Hypoglycemia (in either the mother or the child)
- Cerebral hemorrhage
- Neurologic infections (e.g., meningitis and encephalitis)
- Head injury
- Maternal infections (e.g., rubella and varicella) during pregnancy resulting in cytokine-related brain damage
- Maternal exposure to toxins during pregnancy (e.g., mercury)
- Severe jaundice resulting in kernicterus

CP is classified according to the movement disorder involved, which reflects the area of the brain affected: spasticity (stiff muscles), dyskinesia (uncontrolled movements), or ataxia (poor balance and coordination). Spasticity is present in 80% of cases. In most patients, one or more movement disorders are present.

Clinical manifestations of CP may or may not be evident at birth. These manifestations vary from mild to severe in their effects. CP may affect the entire body (resulting in **quadriplegia**) or just one area (resulting in diplegia); it may affect one side or both sides of the body. Manifestations may include the following signs and symptoms:

- Persistence of early reflexes (e.g., Moro reflex)
- Developmental delays
- Ataxia
- Spasticity
- Flaccidity (weak, limp muscles)
- Hyperreflexia (exaggerated reflexes)
- Asymmetrical walking gait, with one foot or leg dragging
- Unusual positioning of limbs when resting or when held up (e.g., scissors position of the legs)
- Excessive drooling
- Difficulties swallowing, sucking, or speaking
- Facial grimaces
- Tremors
- Difficulty with precise motions (e.g., writing and buttoning a shirt)

Complications of CP result because of these clinical manifestations:

- Balance and coordination issues
- Contractures (shortening of a muscle, which causes severe limitations in movement)
- Atrophy below the waist
- Scoliosis

- Malnutrition
- Communication issues and speech delays
- Learning or cognition difficulties
- Seizures (occur in approximately 50% of patients)
- Vision and hearing issues
- Urinary incontinence
- Constipation
- Osteoporosis
- Chronic pain
- Injury

Diagnosis cannot be confirmed during early infancy, and the specific form of CP may not be identified until 2 years of age. High-risk children should be followed closely because diagnosis at an early age is important so that treatment can be initiated to improve outcomes. Diagnostic procedures for CP include a history, physical examination, developmental monitoring and screening, head CT, head MRI, and electroencephalogram (EEG), as well as hearing and vision screening.

Treatment strategies focus on maximizing functioning and minimizing complications. Management is long term in nature and requires a multidisciplinary team (e.g., the primary care provider, nurses, a social worker, a physical therapist, an occupational therapist, a speech therapist, a dietitian, and education specialists). Therapeutic strategies often include the following measures:

- Muscle relaxants (usually intrathecal baclofen)
- Botulinum toxin type A (Botox) injections directly into spastic muscles
- Antiseizure medications
- Pain management (e.g., massage therapy and analgesics)
- Physical therapy
- Occupational therapy

- Speech therapy
- Nutritional support
- Home safety (e.g., remove rugs)
- Braces and orthopedic devices (e.g., splints)
- Ambulation devices (e.g., walker and wheelchair)
- Constipation prevention (e.g., high-fiber diet, adequate water intake, and stool softeners)
- Glasses and hearing aids
- Surgical procedures to relieve contractures or to sever nerves of spastic muscles
- Support groups (especially for caregivers)
- Individualized education program

Infectious Neurologic Disorders

Nervous system infections can have serious effects by triggering the infectious and inflammatory response (see the *Immunity* chapter). These infections can be caused by a number of bacterial, viral, and fungal pathogens. Regardless of the causative agent, neurologic compromise (either temporary or permanent) can result. Early diagnosis and treatment are imperative for positive outcomes.

Meningitis

Meningitis refers to an inflammation of the meninges and subarachnoid space, usually resulting from an infection. The CSF may also become affected. Meningitis is most often caused by viral infections associated with enterovirus, West Nile virus, influenza, human immunodeficiency virus [HIV], and herpes. Bacterial meningitis tends to be more severe; its causes include group B *Streptococcus*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. These infectious agents invade the meninges through the blood or nearby structures (e.g., respiratory tract) or by direct access (e.g., wounds). Additional causes of meningitis include chemical irritants, tumors, fungi (e.g., *Cryptococcus*

and *Histoplasmosis*), parasites (e.g., *Angiostrongylus cantonensis*, *Baylisascaris procyonis*, and *Gnathostoma spinigerum*), amoebas (e.g., *Naegleria fowleri*), allergens, systemic lupus erythematosus, trauma (e.g., head injury or brain surgery), and certain medications. The infection or irritant triggers the inflammatory process, leading to swelling of the meninges and increased ICP.

Risk factors for developing meningitis include age younger than 25 years, living in a community setting (e.g., a college dormitory), pregnancy, working with animals, and immunodeficiency. Depending on the cause of the infection, meningitis can be self-limiting (as with viral meningitis) or life-threatening (as with acute bacterial meningitis). Complications of meningitis may include permanent neurologic damage, seizures, hearing loss, blindness, speech difficulties, learning disabilities, behavior problems, paralysis, acute renal failure, adrenal gland failure, cerebral edema, shock, and death.

Clinical manifestations of meningitis result from the inflammation of the meninges. Initially, these manifestations mimic those associated with an influenza infection (e.g., fever, chills, and malaise). Severity varies depending on the type of meningitis. For example, bacterial meningitis is more severe than viral meningitis; while amebic causes are rare, this type of meningitis is typically fatal. The clinical manifestations, which usually arise suddenly, include the following signs and symptoms:

- Fever and chills
- Mental status changes (e.g., confusion and lethargy)
- Nausea and vomiting
- Photophobia
- Severe headache
- Stiff neck (meningismus)
- Agitation
- Bulging fontanelle
- Decreased consciousness

- Opisthotonos (abnormal positioning that involves rigidity and severe arching of the back with the head thrown backward)
- Poor feeding or irritability in children
- Tachypnea (increased breathing)
- Tachycardia (increased heart rate)
- Rash

Diagnostic procedures for meningitis include a history, physical examination, throat cultures, lumbar puncture with CSF analysis, polymerase chain reaction test, and head CT. Treatment varies depending on the underlying etiology. Strategies may include antibiotics (if the infection is bacterial in origin), corticosteroids (if the infection is bacterial in origin), antivirals (usually reserved for those cases caused by a herpes virus), hydration, and fever management. Additional strategies are geared toward managing complications as they develop (e.g., seizures, cerebral edema, and shock). Vaccinations, including those for *H. influenzae*, pneumococcal, and meningococcal infections, are the cornerstone of meningitis prevention.

Encephalitis

Encephalitis refers to an inflammation of the brain, and encephalomyelitis refers to inflammation of the brain and spinal cord. The inflammation is usually a result of an infection. A virus (e.g., coxsackievirus, echovirus, poliovirus, adenovirus, herpes virus, cytomegalovirus, Eastern equine encephalitis virus, West Nile virus, St. Louis virus, measles, or mumps) most frequently causes this infection. Viral exposure may occur through respiratory inhalation of droplets, ingestion of contaminated food or beverages, insect bites (especially mosquitoes and parasites), and skin contact. Encephalitis can also result from bacterial infections, such as Lyme disease, tuberculosis, and syphilis. Noninfectious causes of encephalitis include allergic reactions (especially to vaccinations) and autoimmune conditions. The infection or other etiologic process triggers the inflammatory response, which then causes vasodilation, increased

capillary permeability, and leukocyte infiltration. This inflammatory process can also lead to nerve cell degeneration and diffuse brain destruction.

Encephalitis is classified as either primary or secondary. Primary encephalitis involves a direct infection of the brain and spinal cord. In secondary encephalitis, an infection first occurs elsewhere in the body and then travels to the brain.

Most cases of encephalitis are mild and self-limiting, but in rare cases, this condition can be severe and life threatening. Those individuals who are particularly vulnerable to more severe progression of encephalitis include immunocompromised persons (e.g., those with acquired immunodeficiency syndrome [AIDS]), young children, older adults, persons living in high-incidence areas, and persons who are frequently outdoors. Complications of encephalitis include cerebral edema, cerebral hemorrhage, and brain damage.

Clinical manifestations of encephalitis result from the meningeal irritation and neurologic damage associated with the inflammatory response. These manifestations resemble those noted in meningitis but have a more gradual onset. In most cases, clinical manifestations are mild and go undetected. When present, manifestations of encephalitis may include the following signs and symptoms:

- Flulike symptoms (e.g., fever, lethargy, and joint pain)
- Headache
- Neck rigidity
- Confusion and hallucinations
- Personality changes (e.g., flat affect, impaired judgment, and withdrawal from social interactions)
- Diplopia and photophobia
- Seizures
- Muscle weakness
- Ataxia
- Paresthesia or paralysis
- Loss of consciousness

- Tremors
- Abnormal deep tendon reflexes
- Rash
- Bulging fontanelle (in infants)

Diagnostic procedures for encephalitis include a history, physical examination, head CT, head MRI, EEG, lumbar puncture with CSF analysis, polymerase chain reaction test, and serum viral antibodies. Encephalitis is usually self-limiting, so treatment is largely supportive. Treatment strategies often include the following measures:

- Rest
- Adequate nutrition, including plenty of fluids
- Respiratory support (e.g., oxygen therapy or endotracheal intubation with mechanical ventilation, for severe cases)
- Reorientation and emotional support
- Analgesics and antipyretics to relieve headaches and fever
- Antiviral agents (if the origin is viral)
- Antibiotic therapy (if the origin is bacterial)
- Corticosteroids to reduce cerebral edema
- Antiseizure agents
- Sedatives to treat irritability and restlessness
- Physical, speech, and occupational therapy as necessary for any residual neurologic dysfunction

Infection by many of the encephalitis-causative organisms can be prevented. Prevention strategies include vaccinations, wearing protective clothing when outside (e.g., long-sleeve shirts), using mosquito repellant, and eliminating water sources around the home (e.g., standing water in containers).

Zika Virus Disease

A growing worldwide health concern, **Zika virus disease** is a condition caused by a flavivirus that is transmitted primarily by

mosquitoes (Navalkele, Chandrasekar, & Levine, 2021). In 1952, this virus was first discovered in Uganda and the United Republic of Tanzania (World Health Organization [WHO], 2022). Since then, several outbreaks—usually involving a mild illness—have been recorded in Africa, the Americas, Asia, and the Pacific. In 2015, Brazil reported a large outbreak causing more severe neurologic complications. Within a short period of time, cases of Zika virus disease were noted in Florida (tracked to foreign travel to Zika-affected regions), and then the virus spread across the southeastern United States. Currently, ongoing local transmission of Zika virus remains active in many countries, but no cases of Zika virus disease have been reported in the United States since 2019 (CDC, 2022b).

In addition to being carried by mosquitoes, the Zika virus can be transmitted from mother to fetus, through sexual contact, and via blood transfusions. The virus persists much longer in semen than in vaginal secretions, blood, and other body fluids. It can also be transmitted through sexual contact with exposed sex toys when shared.

In most cases, Zika virus infection causes a mild, self-limiting illness. In fact, more than 80% of the cases go unnoticed. The incubation period is thought to range from 3 to 12 days. Most individuals will not experience any manifestations, but even when they do, manifestations are usually mild. Manifestations may include the following signs and symptoms:

- Flu-like symptoms (e.g., fever, lethargy, and joint pain)
- Maculopapular rash
- Conjunctivitis
- Retro-orbital pain
- Muscle and joint pain
- Headache

In rare cases, complications of Zika infection can be severe. The most severe complications occur with maternal–fetal transmission and may include ocular lesions, congenital contractures (e.g.,

clubfoot), miscarriage, and microcephaly (FIGURE 11-24). Additionally, the Zika virus can cause Guillain-Barré syndrome.



FIGURE 11-24 Microcephaly.

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Diagnostic procedures for Zika virus disease include a history, physical examination, and body fluid examination (e.g., blood, urine, saliva, and semen). The CDC requires confirmed cases of Zika infection to be reported. Blood examination can include enzyme-linked immunosorbent assay (ELISA) for immunoglobulin M (IgM), the plaque reduction neutralization test (PRNT) for Zika virus antibodies, and real-time reverse-transcription polymerase chain reaction (RT-PCR) to detect viral RNA.

Treatment is primarily supportive and includes rest, hydration, analgesics, and antipyretics. Prevention is paramount. It includes wearing protective covering, minimizing outdoor exposure, using an

insect repellant containing DEET (*N*,*N*-diethyl-meta-toluamide), using condoms, and abstaining from sex while pregnant if there is risk of exposure. Brain development should be closely monitored for at least 2 years in all infants born to infected mothers whether the infant does or does not have obvious effects (e.g., microcephaly, ocular lesions, or congenital contractures).

Traumatic Neurologic Disorders

Traumatic neurologic disorders vary significantly in severity and presentation depending on the location and extent of damage. Even minor injuries to the nervous system can have substantial effects on neurologic functioning. Traumatic injuries to the nervous system can result from a number of events that cause physical damage (e.g., motor vehicle accidents, gunshot wounds, and falls). Commonly, a number of these traumatic conditions overlap and occur concurrently (e.g., **subdural hematoma** and increased intracranial pressure).

Brain Injuries

A **traumatic brain injury (TBI)** is usually caused by a sudden and violent blow or jolt to the head (called a closed injury) or a penetrating head wound (known as an open injury) that disrupts normal brain function. With such injuries, the brain collides with the skull (**FIGURE 11-25**) and any penetrating objects (**FIGURE 11-26**). Structural changes may be gross or microscopic, depending on the mechanism and forces involved. These events can bruise the brain, damage nerve fibers, and cause hemorrhaging. However, not all blows or jolts to the head result in a TBI.

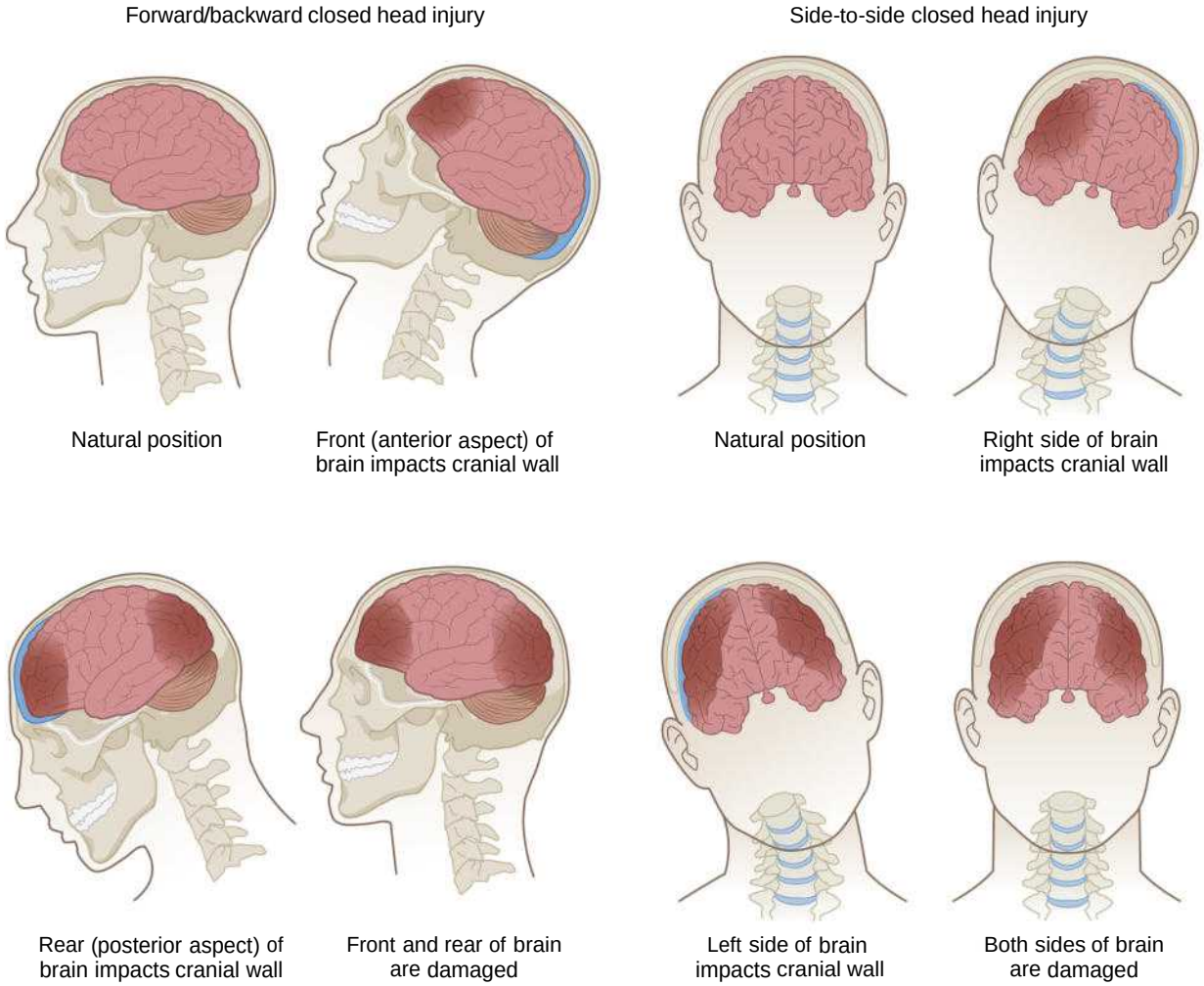
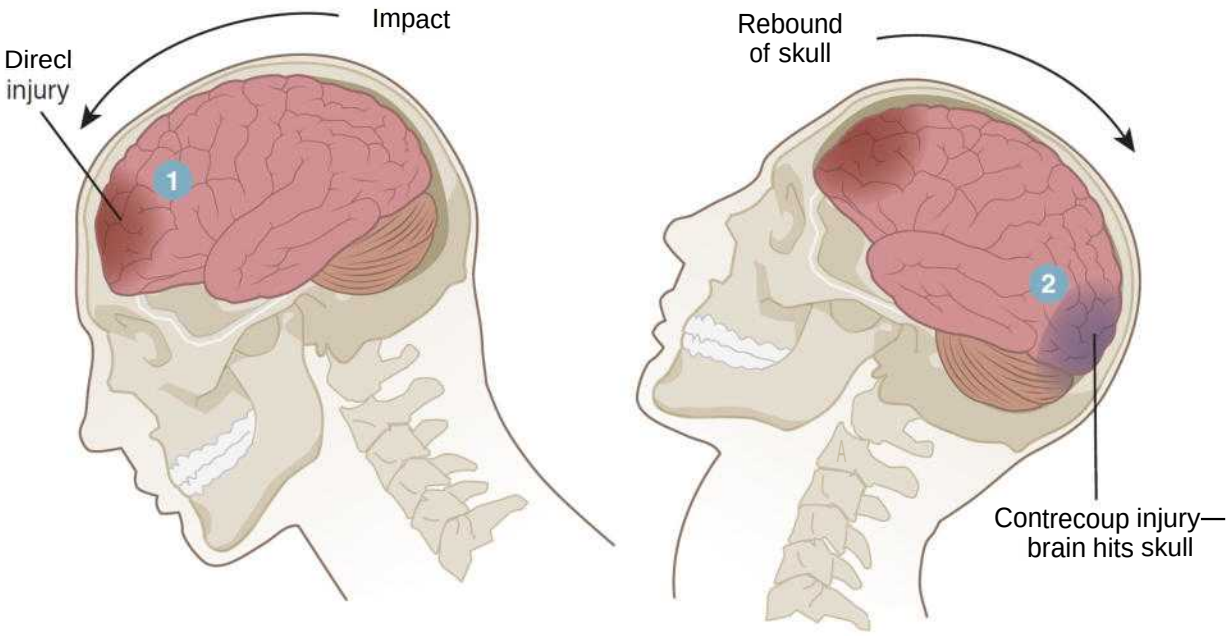


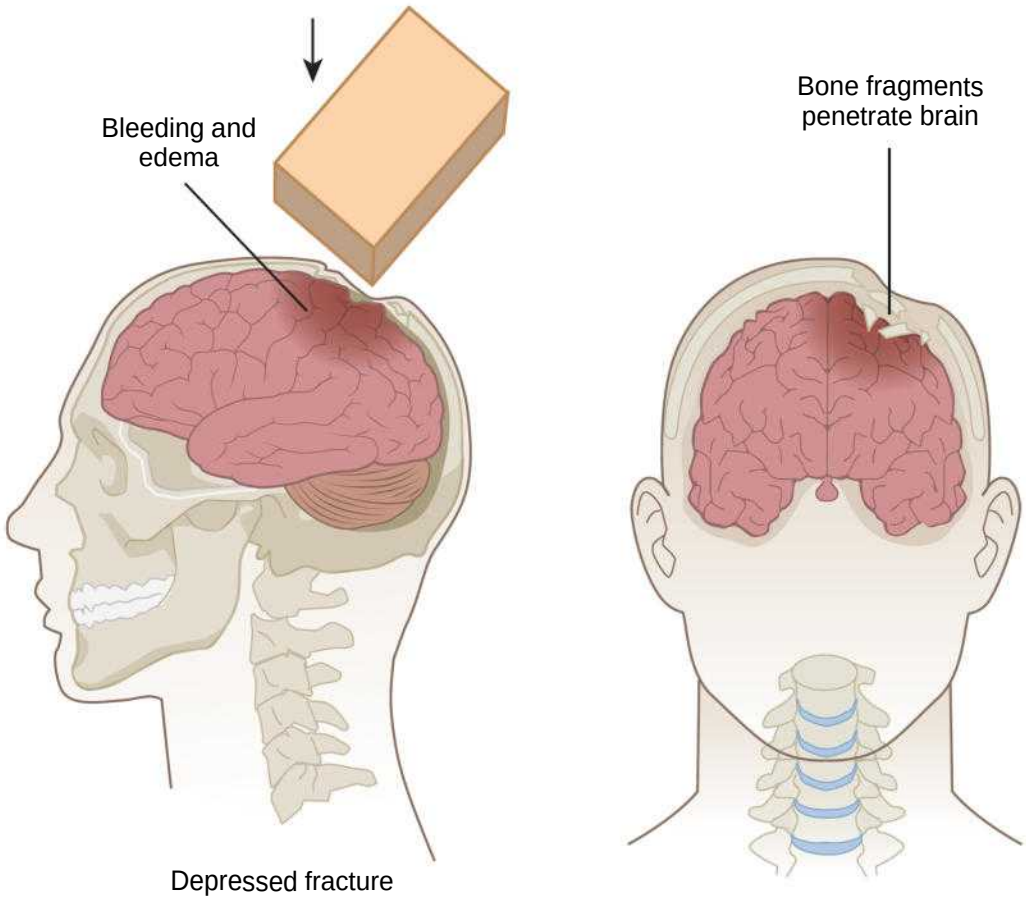
FIGURE 11-25 Closed traumatic brain injury.

Description

Closed injury—direct and contrecoup injury



Open injury



Depressed fracture

FIGURE 11-26 Comparison of closed and open traumatic brain injury.

Description

According to the CDC (2023b), TBI is a major cause of death and disability in the United States. In 2017, over 1 million TBI-related emergency department visits, hospitalizations, and deaths occurred. Nearly 8% of these events involved children. TBIs contributed to 69,473 deaths in 2021, including 2,303 deaths among children. The main causes of TBI are falls (nearly half), firearm-related suicide (most common cause of TBI-related deaths in the United States), motor vehicle accidents, and assault. TBIs range from mild (e.g., a brief change in mental status or consciousness) to severe (e.g., an extended period of unconsciousness or amnesia after the injury). Persons at highest risk for experiencing a TBI include the following groups:

- Males (nearly two times as likely as females to have a TBI and three times as likely to die from a TBI)
- Adults 75 years of age or older (account for 32% of TBI-related hospitalizations and 28% of TBI-related deaths)
- Certain military personnel (e.g., paratroopers)
- Individuals in correctional or detention facilities (almost half have a history of TBI)
- People who experience homelessness (2 to 4 times more likely to have a history of TBI)
- Survivors of intimate partner violence
- American Indian/Alaska Natives

Additionally, individuals living in rural areas, with lower incomes, and without insurance are less likely to access needed and timely TBI care. Many TBIs result in a wide range of long-term and potentially life-altering complications, such as changes in thinking, sensation, language, or emotions. These injuries can increase the risk for seizures, **migraine headaches**, Alzheimer's disease, and **Parkinson's disease**. Multiple mild TBIs can have an accumulative

effect and result in neurologic dysfunction, cognitive deficits, and death. This damage, referred to as "chronic traumatic encephalopathy" (CTE), has especially been noted in football players. These athletes—especially those who encounter routine impacts (e.g., cornerbacks, linemen, wide receivers, and quarterbacks)—have higher rates of cognitive deficits (e.g., memory and attention impairment) and neurologic diseases (e.g., Alzheimer's disease, Parkinson's disease, depression, and anxiety). Damage tends to be mild in high school football players, but most college, semi-professional, and professional players experience severe damage and symptoms. Other athletes at higher risk for these injuries include soccer players because of the repetitive impact of the head with the ball.

Closed TBIs often result in a variety of conditions. **Concussion** describes a momentary and reversible interruption of brain function. Concussions usually result from a mild blow to the head that causes sudden movement of the brain, disrupting neurologic functioning. Concussions may or may not lead to a loss of consciousness. Amnesia, confusion, sleep disturbances, and headaches may follow a concussion for weeks or months.

Cerebral contusion refers to a bruising of the brain accompanied by rupture of small blood vessels and edema. Most contusions result from a blunt blow to the head that causes the brain to make sudden impact with the skull. The initial area where the brain impacts the skull is referred to as the **coup**. The brain then rebounds and impacts the opposite side of the skull, causing another area of damage referred to as the **contrecoup** (Figure 11-26). Contusions vary in severity depending on the extent of damage and the amount of bleeding. Focal or diffuse axonal injury may be present. Larger contusions may result in cerebral edema and ICP. Contusions may enlarge in the days following the initial injury, leading to ongoing neurologic deterioration.

Hematomas, a collection of blood in or around the brain, can occur with closed or open injuries. The presence and severity of residual effects depend on these factors.

Open TBIs can also result in serious issues. In addition to the tissue damage from the impact of the brain with the skull, such

injuries can cause damage owing to the penetrating object and skull fragments. The skull fractures as the object breaches it. Much like when an egg is broken, the skull usually ends up in multiple pieces when it is struck by an external force. The resulting fracture may take the form of a **linear skull fracture** (a simple crack), a **comminuted skull fracture** (several fracture lines), a **compound skull fracture** (a fracture where the brain tissue is exposed), a **depressed skull fracture** (displacement of the bone fragments into the brain), or a **basilar skull fracture** (located at the base of the skull and usually accompanied by CSF leakage). In addition to the brain damage from impact and penetrating objects, open TBIs carry a higher risk for developing infections because they permit direct access to the brain by infectious organisms (see the *Immunity* chapter). As discussed in previous sections, infections of the nervous system can have serious consequences.

Clinical manifestations of TBIs may be vague and develop slowly, or they may be sudden and severe. Sometimes symptoms may improve and then suddenly worsen. The outward appearance of the head is not an indication of the injury severity—serious injuries can occur even while the skin and the skull remain intact. When a TBI is suspected, the individual should be asked to give an account of the accident. Not being able to recall details is an indication of a TBI. Additional clinical manifestations may include the following signs and symptoms:

- Indications of a concussion (e.g., amnesia, confusion, and headache)
- Changes in or unequal size of pupils
- Seizures
- Asymmetrical facial features
- Fluid draining from the nose, mouth, or ears (may be clear or bloody, likely CSF)
- Fracture in the skull or face, bruising of the face, swelling at the site of the injury, or scalp wound
- Impaired hearing, smell, taste, speech, or vision

- Inability to move one or more limbs
- Irritability (especially in children), personality changes, or unusual behavior
- Loss of consciousness (usually for seconds or minutes)
- Bradypnea (slowed breathing)
- Hypotension
- Restlessness
- Lack of coordination
- Lethargy
- Stiff neck
- Vomiting

Diagnostic procedures for TBI consist of a history, physical examination (including using the Glasgow Coma Scale [GCS; **FIGURE 11-27**]), head CT, head MRI, and ICP monitoring. Initially, an overall assessment should include airway adequacy, breathing status, and a rapid, focused neurologic evaluation. Originally developed in 1974, the GCS has been used worldwide to assess and document the level of consciousness in patients with head trauma (Teasdale et al., 2014). An evaluation of the GCS revealed that how the scale was applied varied. Clinicians were using different methods to apply stimuli to patients and using different standards in interpreting the responses. As a result, a team from the Institute of Neurological Sciences updated the GCS and developed a structured approach to assessment to minimize variation. This revised scale is referred to as the GCS-40.



For factors Interfering with communication, ability to respond and other injuries	Eye opening, content of speech and movements of right and left sides	Sound: spoken or shouted request Physical: Pressure on fingertip, trapezius or supraorbital notch	Assign according to highest response observed

Eye opening

Criterion	Observed	Rating	Score
Open before stimulus	✔	Spontaneous	4
After spoken or shouted request	✔	To sound	3
After fingertip stimulus	✔	To pressure	2
No opening at any time, no interfering factor	✔	None	**1**
Closed by local factor	✔	Non testable	NT

Verbal response

Criterion	Observed	Rating	Score
Correctly gives name, place and date	✔	Orientated	5
Not orientated but communication coherent	✔	Confused	4
Intelligible single words	✔	Words	3
Only moans / groans	✔	Sounds	2
No audible response, no interfering factor	✔	None	**1**
Factor interfering with communication	✔	Non testable	NT

Best motor response

Criterion	Observed	Rating	Score
Obeys 2-part request	✔	Obeys commands	6
Brings hand above clavicle to stimulus on head / neck	✔	Localising	5
Bends arm at elbow rapidly but features not predominantly abnormal	✔	Normal flexion	4
Bends arm at elbow, features clearly predominantly abnormal	✔	Abnormal flexion	3
Extends arm at elbow	✔	Extension	2
No movement in arms / legs, no interfering factor	✔	None	**1**
Paralysed or other limiting factor	✔	Non testable	NT

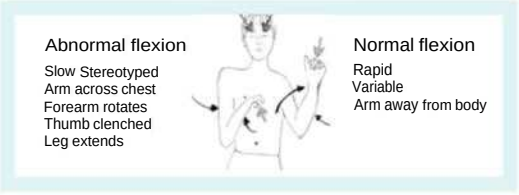
Sites For Physical Stimulation

Fingertip pressure | Trapezius inch | Supraorbital notch



Features of Flexion Responses

Modified with permission from Van Der Naalt 2004
Ned Tijdschr Geneeskd



visit www.glasgowcomascale.org - available in more than 25 languages

Graphic design by Margaret Fre based on layout and Mustrabons from MeOcal Illustration M I • 268093
(c) Sir Graham Teasdate 201S

FIGURE 11-27 Glasgow Coma Scale-40.

https://www.glasgowcomascale.org/downloads/GCS-Assessment-Aid-English.pdf?v=3

Description

Treatment strategies vary depending on the severity and the time since injury. Immediate emergency care for TBI focuses on limiting

brain damage. Mild injuries usually require no treatment other than rest, analgesics (specifically, acetaminophen [Tylenol]) if headache is present, and 24-hour observation in the hospital or at home if a reliable caregiver is available. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen (Motrin), should be avoided because they can increase bleeding risk. Cold compresses can be applied to any outward edema.

Severe brain injuries usually require hospitalization, and patients with such damage often need intensive care. Controlling blood pressure and maintaining cerebral perfusion are important to prevent further injury. Hypertonic saline solutions (e.g., 2% or 3% saline) may be given to reduce cerebral edema. Endotracheal intubation with mechanical ventilation may be needed to maintain adequate oxygenation and control hypercapnia. Sedation can be used to prevent agitation, excessive muscular activity, and pain, all of which can decrease oxygen needs and ICP. Severe TBIs also usually require opioids to adequately control pain. Additionally, antiseizure agents may be needed. Surgery can be performed to remove blood or repair fractures. Physical, speech, and occupational therapy may be required after the acute injury phase to minimize residual neurologic dysfunction.

Prevention strategies for TBIs include wearing a seat belt when driving or riding in a motor vehicle, using appropriate child safety seats, wearing a helmet when appropriate (e.g., when playing sports, riding a bicycle, or skating), making the home safe (e.g., removing tripping hazards, having adequate lighting, and using safety gates), storing firearms in locked cabinets, never driving impaired, and supervising children when playing.

Increased Intracranial Pressure

Increased intracranial pressure describes increased volume in the limited space of the cranial cavity. Increased ICP may occur because of a TBI and other conditions that increase the volume in the skull (e.g., tumor, hydrocephalus, cerebral edema, and hemorrhage). The delicate pressure–volume relationship among ICP; volume of CSF, blood, and brain tissue; and cerebral perfusion is explained by the

Monro-Kellie hypothesis (**FIGURE 11-28**). The Monro-Kellie hypothesis states that the cranial cavity cannot be compressed, and the volume inside the cavity is fixed (normal ICP is 60–200 mm H_2O or 4–15 mm Hg). The skull and its components (blood, CSF, and brain tissue) create a state of volume equilibrium, such that any increase in the volume of one component must be compensated for by a decrease in the volume of another component. This compensation is primarily accomplished by shifts in the CSF and, to a lesser extent, blood volume, as brain tissue volume remains relatively constant. These fluids respond to increases in the volume of the remaining components. For example, an area of bleeding into the brain tissue (e.g., **epidural hematoma**) will be compensated for by the downward displacement of CSF and venous blood. Transient increases in ICP routinely occur with position changes, coughing, or sneezing. These compensatory mechanisms can maintain a normal ICP for changes in volume up to a point (approximately 100–120 mL of volume increases).

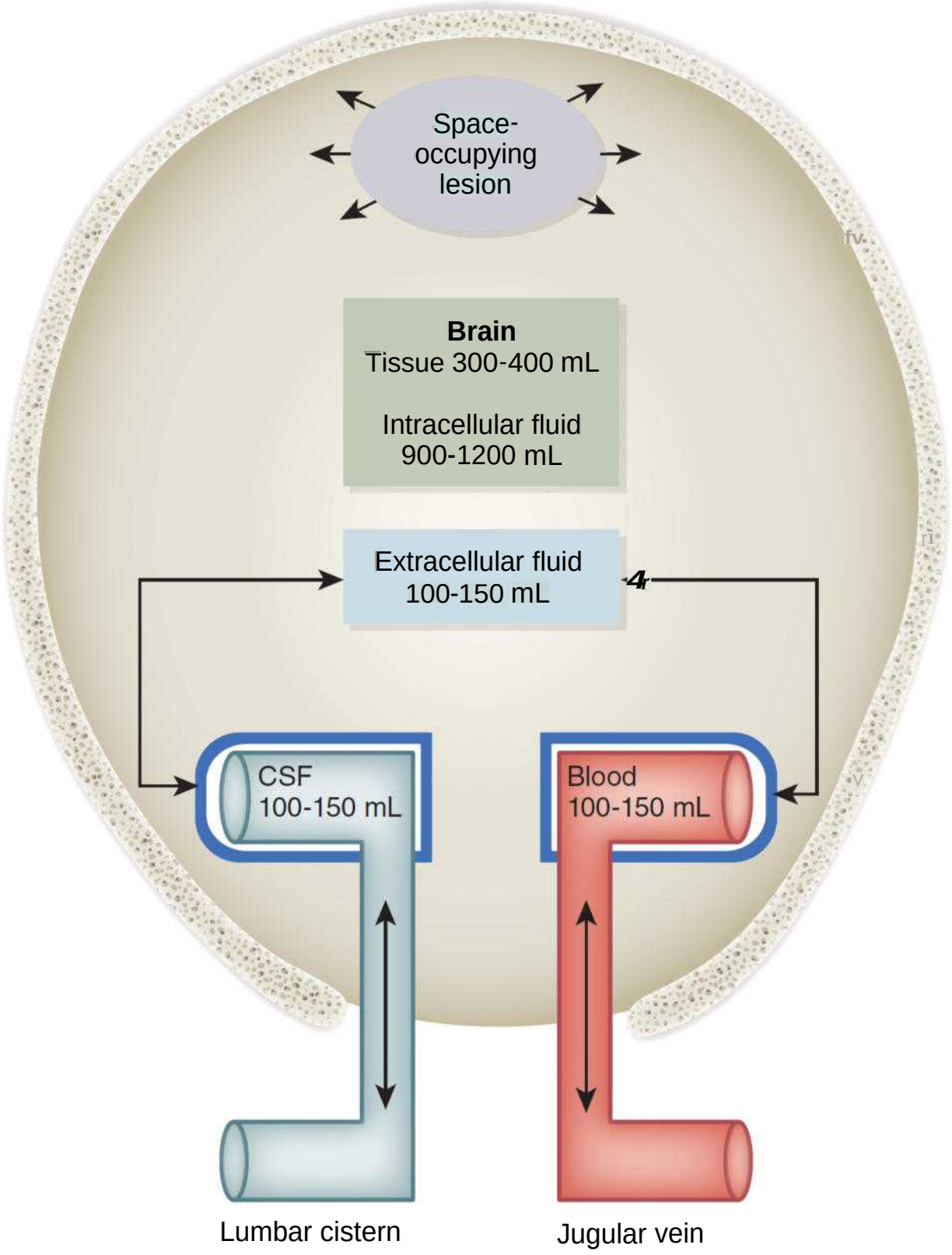


FIGURE 11-28 Monro-Kellie hypothesis.

Data from Leffert, L. R., & Schwamm, L. H. (2013). Neuraxial anesthesia in parturients with intracranial pathology: A comprehensive review and reassessment of risk. *Anesthesiology, 119*, 703–718. Retrieved from doi: 10.1097/ALN.0b013e31829374c2

Description

In addition to shifting volumes, the brain has two other compensatory mechanisms to maintain tissue perfusion—**autoregulation** and the **Cushing reflex**. With autoregulation, the blood vessels dilate to increase blood flow and constrict if the ICP is increased. The Cushing reflex is a complex cascade of events that results in increased blood pressure. When the mean arterial pressure (average blood pressure) drops below the ICP, the hypothalamus increases sympathetic stimulation. This stimulation causes vasoconstriction, increased cardiac contractility, and increased cardiac output. If unresolved, the increased ICP eventually leads to a trio of effects known as **Cushing triad**—increased blood pressure, bradycardia, and changes in respiratory pattern (**FIGURE 11-29**). Baroreceptors in the carotid arteries detect the increase in blood pressure, triggering a parasympathetic response through vagal stimulation that induces bradycardia. Bradycardia may also be stimulated by the increased ICP impinging on the vagal nerve, causing a parasympathetic response. As pressure increases inside the skull, space becomes limited, and the brain tissue shifts downward. An irregular respiratory pattern, called “Cheyne-Stokes respiration” (characterized by progressively deeper, sometimes faster, breathing followed by a gradual decrease, which results in periods of apnea), and bradypnea typically result from increased pressure on the brainstem due to swelling or from brainstem **herniation**.

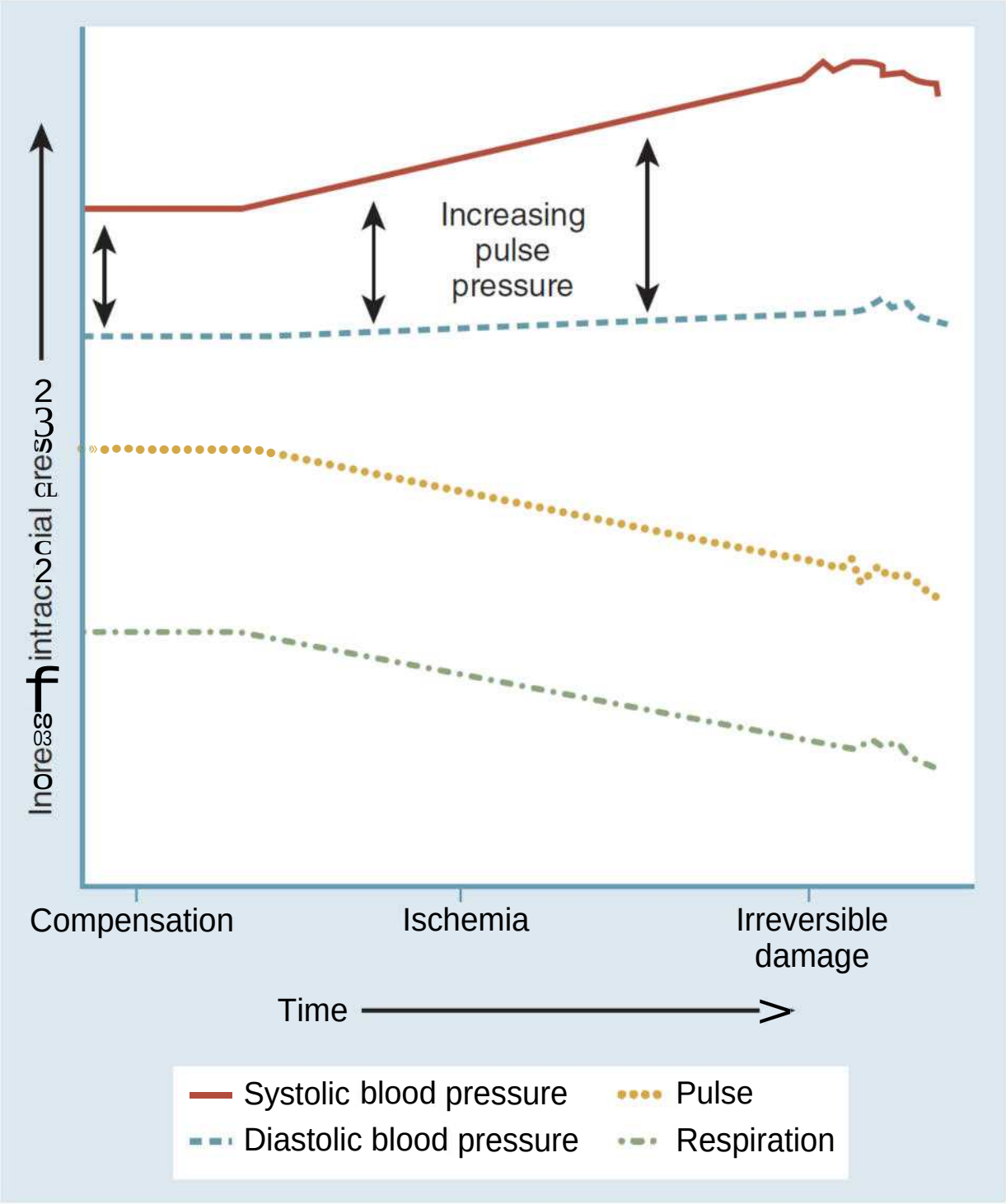


FIGURE 11-29 Vital sign changes with increased intracranial pressure.

Description

Herniation—a feared complication of increased ICP—involves the displacement of brain tissue. Several types of herniations are possible (**FIGURE 11-30**). In transtentorial (central) herniation, the cerebral hemispheres, diencephalon, and midbrain are displaced downward. The pressure created by this type of herniation impairs the cerebral blood flow, CSF, reticular activation system, and respirations. Uncal (uncinate) herniation occurs when the uncus (the hooklike anterior end of the hippocampal gyrus) of the temporal lobe shifts downward past the tentorium cerebelli (the extension of the dura mater that separates the cerebellum from the inferior portion of the occipital lobes). This type of herniation creates pressure on cranial nerve III, the posterior cerebral artery, and the reticular activation system. Cerebellar, or tonsillar (infratentorial), herniation occurs when the cerebellar tonsils (the rounded lobules on the undersurface of each cerebellar hemisphere) are pushed downward through the foramen magnum. This type of herniation compresses the brainstem and vital centers, causing death.

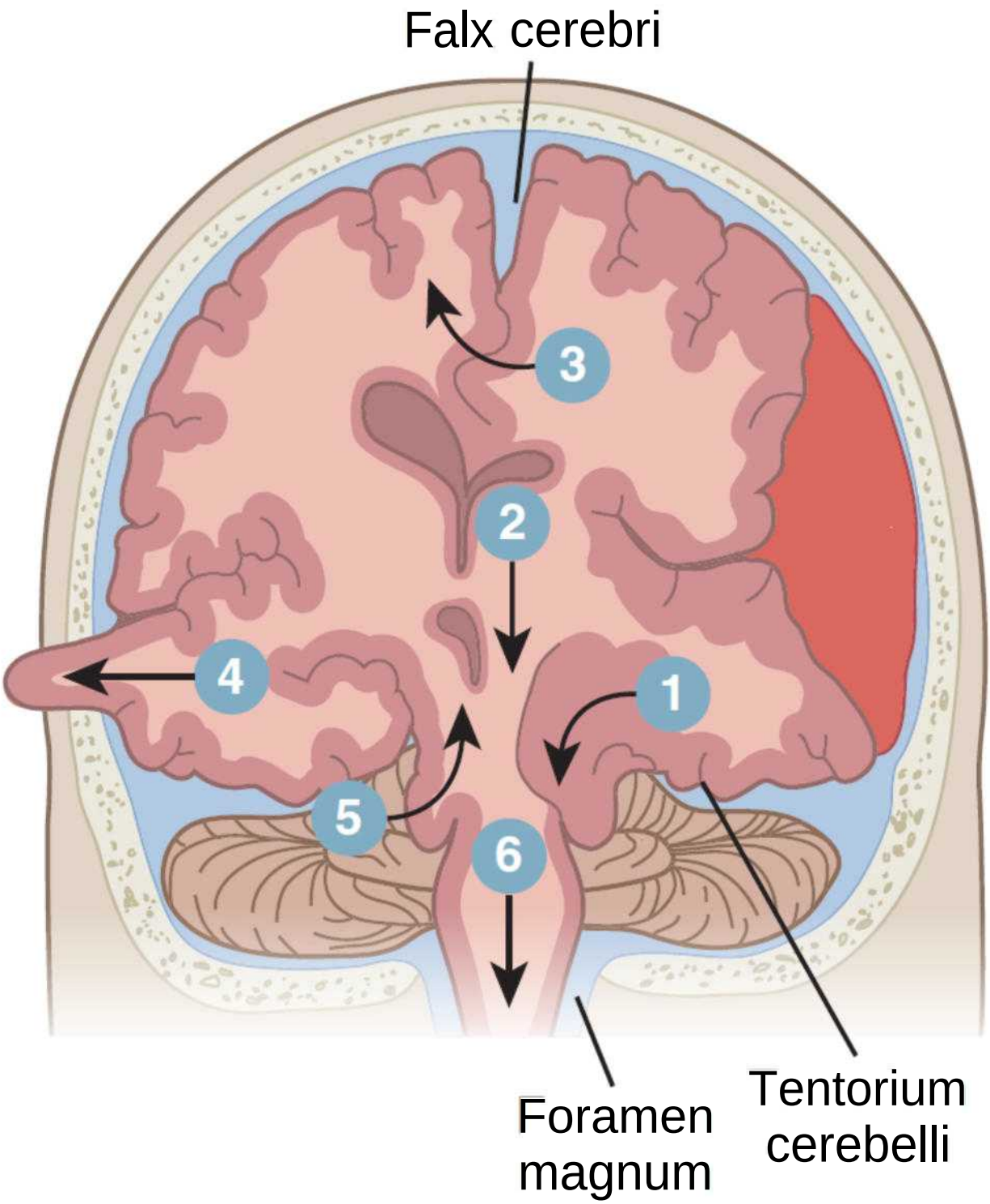


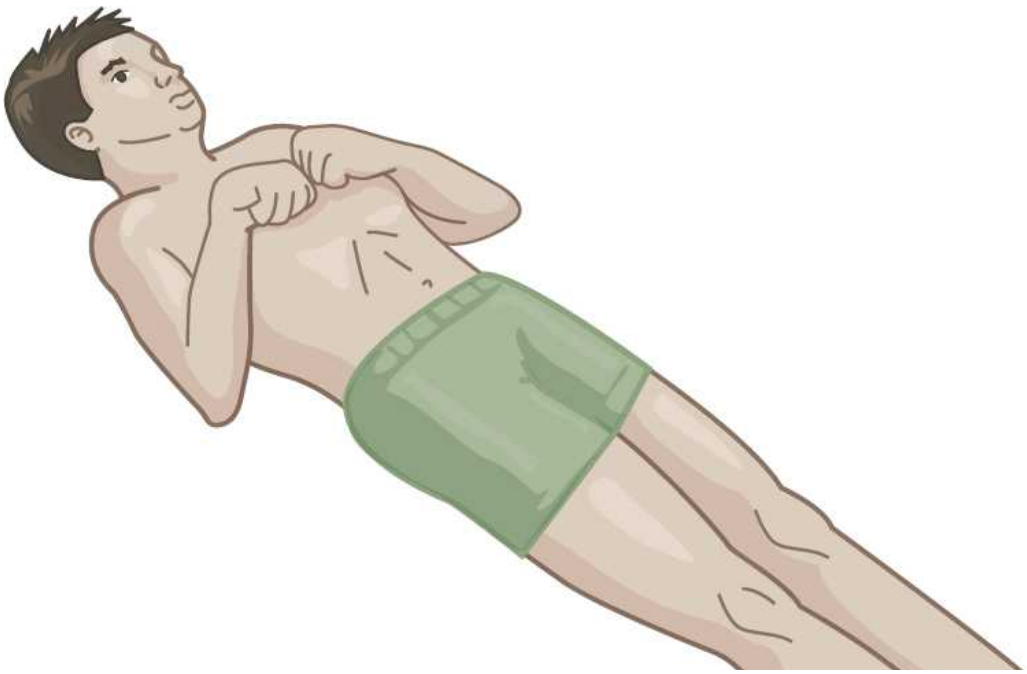
FIGURE 11-30 Types of herniations.

Description

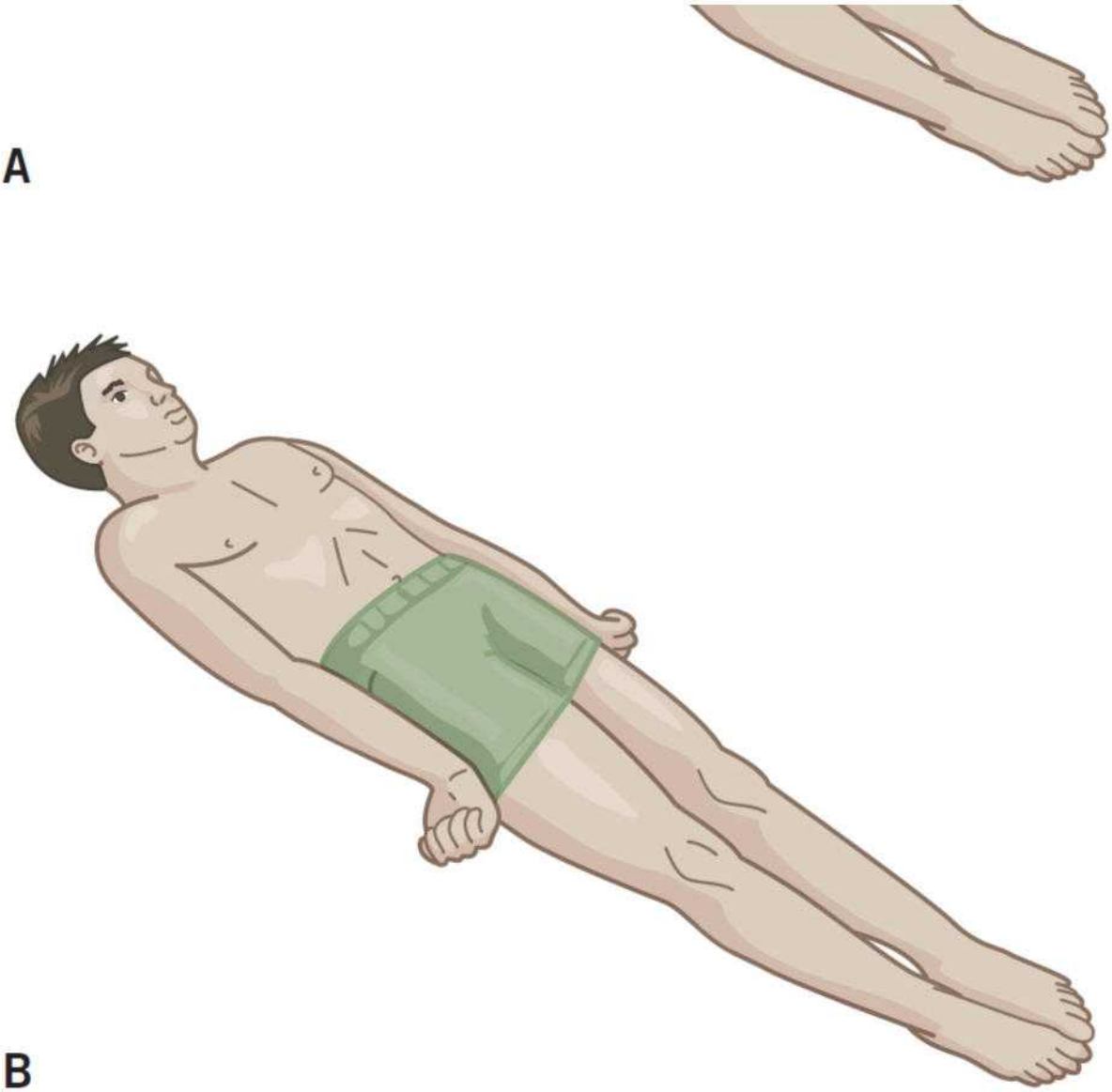
Regardless of the cause, increased ICP past the point of compensation compresses cerebral blood vessels and other structures as the brain's contents shift. Eventually, brain tissue dies. Thus, increased ICP is a life-threatening situation that requires prompt treatment. If left unresolved, it causes declining neurologic function, leading to death.

The clinical manifestations of increased ICP vary depending on the patient's age and reflect the effects of the rising pressures:

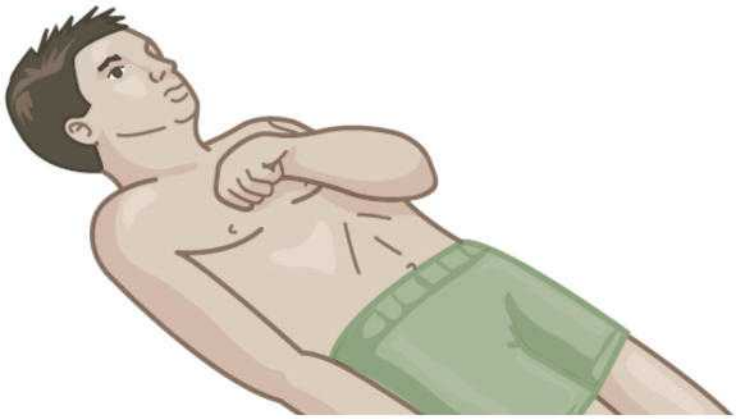
- Decreasing level of consciousness (results from pressure on the brainstem and cerebral cortex)
- Vomiting, often projectile (results from pressure on the medulla)
- Increasing blood pressure with increasing pulse pressure (the difference between the systolic and diastolic pressures) (results from the Cushing reflex)
- Bradycardia (response to the increasing blood pressure)
- Papilledema (results from increased pressure exerted by CSF, which causes swelling around the optic disk)
- Fixed and dilated pupils (results from pressure on cranial nerve III)
- Posturing (**FIGURE 11-31**)

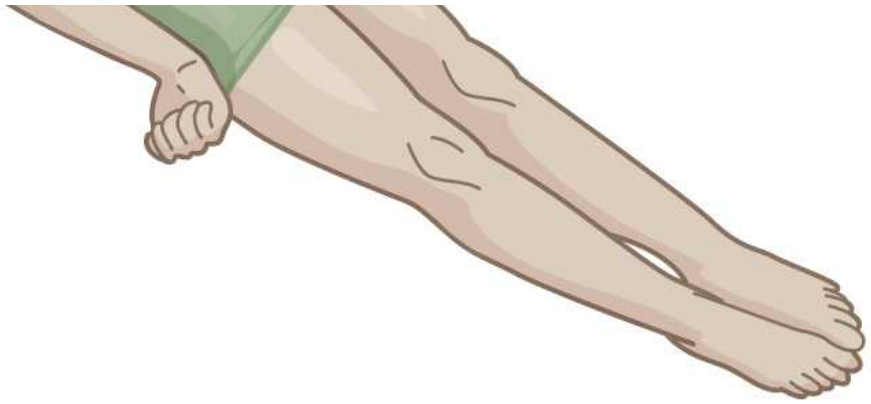


A



B





C

FIGURE 11-31 Decorticate and decerebrate posturing. **(A)** Decorticate response: flexion of the arms, wrists, and fingers with adduction in the upper extremities; extension, internal rotation, and plantar flexion in the lower extremities. **(B)** Decerebrate response: all four extremities in rigid extension with hyperpronation of the forearms and plantar extension of the feet. **(C)** Decorticate response on the left side of the body and decerebrate response on the right side of the body.

Description

Two manifestations of increased ICP are unique to infants:

- Separated sutures
- Bulging fontanelle

Manifestations in older children and adults include the following symptoms:

- Behavior changes
- Severe headache (results from stretching of the dura and walls of the large blood vessels)
- Lethargy
- Neurologic deficits
- Seizures

Diagnostic procedures for increased ICP consist of a history, physical examination (including completing the GCS), head CT, head MRI, and ICP monitoring. Increased ICP requires prompt diagnosis and treatment for optimal patient outcomes. Treatment strategies

vary depending on the underlying etiology, and attempts should be made to resolve the source of the increased pressure if possible (e.g., remove a tumor or accumulated blood). Additional strategies are similar to those for TBIs and may include respiratory support (e.g., oxygen therapy or endotracheal intubation with mechanical ventilation), semi-Fowler positioning, draining excess CSF, hypertonic saline solutions, seizure precautions (e.g., low lighting and minimal stimulation), antiseizure agents, sedatives, stool softeners (because straining increases ICP), antiulcer agents (for those patients at high risk for stress ulcers), thermoregulation, and glucose management. Hypertonic saline solutions are more effective than osmotic diuretics such as mannitol for controlling ICP. In the past, high-dose corticosteroids were recommended to decrease cerebral edema and ICP, but corticosteroids have since been determined not to be useful in controlling ICP and can increase the risk of mortality and severe disability in survivors (Edwards et al., 2005). While controlling hyperthermia is important, therapeutic systemic hypothermia has not proven to be helpful. Rarely, surgical removal of a skull segment may be performed.

Hematomas

Secondary brain damage can be caused by additional injurious factors, such as hemorrhaging. A hematoma is a collection of blood in the tissue that develops from ruptured blood vessels. Hematomas, which can develop immediately or slowly because of a TBI or surgery, are classified by their location (**FIGURE 11-32**).

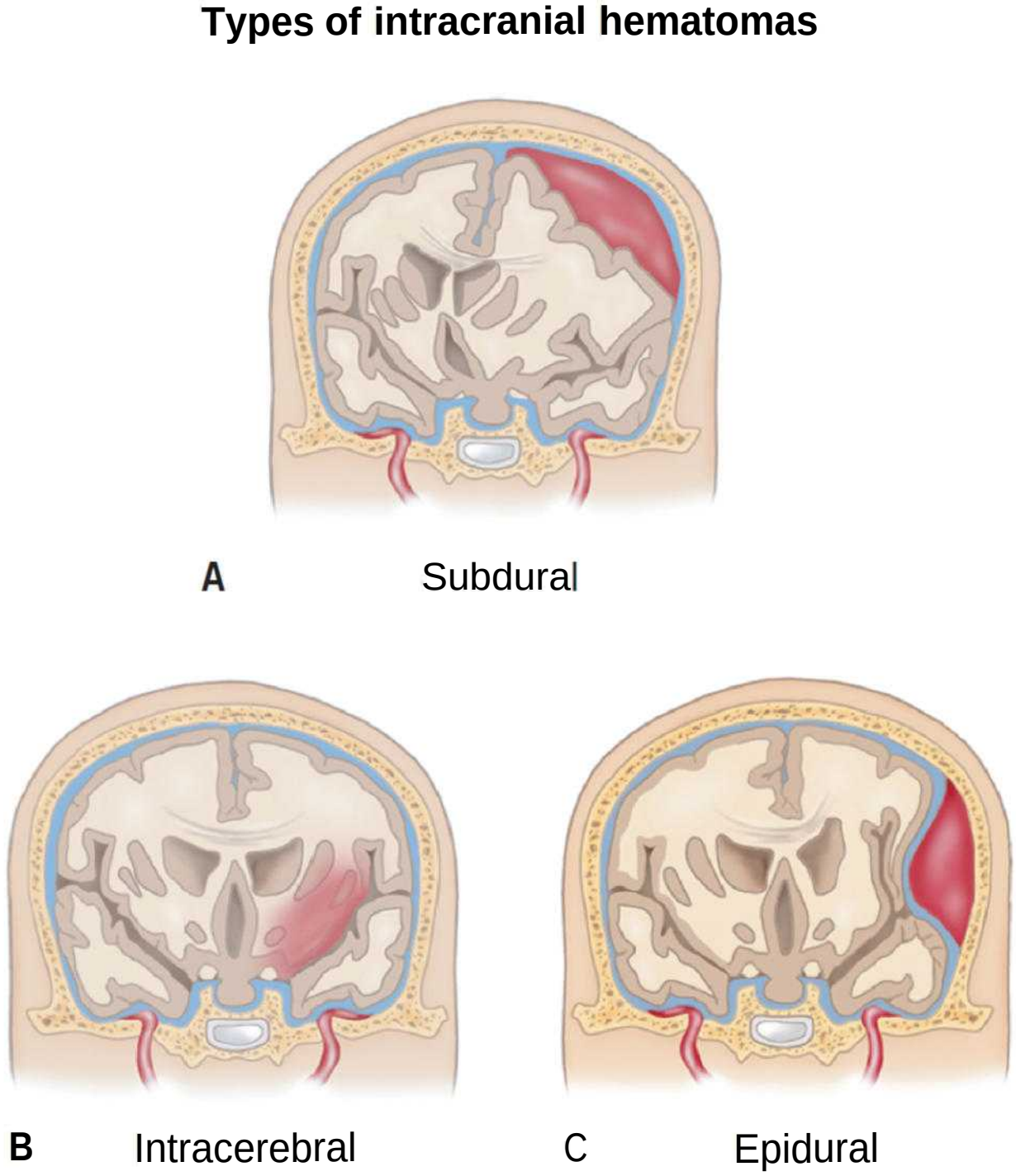


FIGURE 11-32 Types of hematomas. **(A)** Beneath the dura but outside the brain (subdural hematoma). **(B)** Within the brain tissue (intracerebral hematoma). **(C)** Outside the dura and under the skull (epidural hematoma).

- Epidural hematomas result from bleeding between the dura and skull, usually caused by an arterial tear. Epidural hematomas are less common than subdural hematomas. Epidural hematomas caused by arterial bleeding can be large and typically more severe, whereas those caused by venous bleeding tend to be small and are rarely lethal. Clinical manifestations of epidural hematomas include marked neurologic dysfunction that usually develops within a few hours of injury. The typical symptom pattern of an epidural hematoma is a brief loss of consciousness, followed by a short period of alertness, then loss of consciousness again. This pattern may not appear in all people.
- Subdural hematomas develop between the dura and the arachnoid and are frequently caused by a small venous tear (**FIGURE 11-33**). Because they are usually the result of a venous tear, these types of hematomas generally develop slowly. Subdural hematomas follow several patterns. With acute subdural hematomas, manifestations of neurologic deficits present within 24 hours of an injury. This type of hematoma progresses rapidly and has a high mortality. With subacute subdural hematomas, ICP increases over a period of about a week after the injury. With chronic subdural hematomas, manifestations develop several weeks after the injury because of a slow leak. Chronic subdural hematomas are more common in elderly adults because of the brain atrophy that occurs with age, which gives the hematoma more space to develop.



FIGURE 11-33 Midline shift associated with right-sided subdural hematoma.

Courtesy of Dr. Jason W. Schroeder, MD.

- **Intracerebral hematomas** result from bleeding in the brain tissue itself. These types of hematomas are caused by contusion or shearing injuries but can also result from hypertension,

cerebrovascular accidents (i.e., strokes), **cerebral aneurysms**, or cerebral vascular abnormalities.

- **Subarachnoid hemorrhages** result from bleeding in the space between the arachnoid and the pia. These types of hematomas are typically caused by the rupture of cerebral aneurysms and vascular abnormalities. Their primary clinical presentation is a severe headache that has a sudden onset and is worse near the back of the head.

In all types of hematomas, the bleeding exerts localized pressure on nearby tissue and increases ICP. Blood may coagulate and form a solid mass. The hematoma becomes encapsulated by fibroblasts, and blood cells within the capsule lyse. The fluid from the hemolysis exerts osmotic pressure, drawing more fluid into the capsule. This edema increases the size of the mass, applying pressure on the surrounding tissue and increasing ICP. Bleeding can trigger vasospasms, worsening ischemia. Additionally, increasing ICP can result in herniation.

Diagnostic procedures for all types of hematomas and hemorrhaging consist of a history, physical examination (including completing the GCS), head CT, head MRI, cerebral angiogram, and intracranial pressure monitor. Treatment strategies depend on the location and severity of the bleeding. No treatment may be required in mild cases in which the volume is small and the bleeding has ceased. For many patients, surgical removal of the blood through a burr hole or a craniotomy is required. In some cases, however, removal of the blood may not be possible. In these situations, patients may experience significant residual neurologic deficits that require physical, speech, and occupational therapy. Additionally, strategies similar to those used for TBIs and increased ICP (e.g., respiratory management, seizure precautions, and thermoregulation) may be required.

Learning Points

Head Injury

mmediately following a head injury, some key actions should be *avoided*:

- Do *not* apply direct pressure to a bleeding site; cover the wound with sterile gauze.
- Do *not* wash a head wound that is deep or bleeding profusely.
- Do *not* remove any object sticking out of a wound.
- Do *not* move the person unless it is absolutely necessary.
- Do *not* shake the person if he or she seems dazed.
- Do *not* remove a helmet if you suspect a serious head injury.
- Do *not* pick up a fallen child with any sign of a head injury.
- Do *not* drink alcohol within 48 hours of a serious head injury.

Spinal Cord Injuries

Spinal cord injuries (SCIs) result from direct injury to the spinal cord or indirectly from damage to surrounding bones, tissues, or blood vessels as a result of blunt or penetrating physical forces. Not including cases in which the individual dies, an estimated 17,730 new SCI cases occur each year (National Spinal Cord Injury Statistical Center [NSCISC], 2019). SCIs are most common in Caucasians (60%) and in males (78%). The average age for experiencing SCI has increased from 29 years in the 1970s to 43 years today. These injuries are often caused by motor vehicle accidents (39%), falls (32%), violence (14%, primarily gunshot wounds), and sports injuries (8%). Minor injuries to the spinal cord can occur because of weakening vertebral structures (e.g., rheumatoid arthritis or osteoporosis). Direct damage can occur if the spinal cord is pulled, pressed sideways, or compressed (**FIGURE 11-34**). Such damage may occur if the head, neck, or back twists abnormally during an accident or injury.

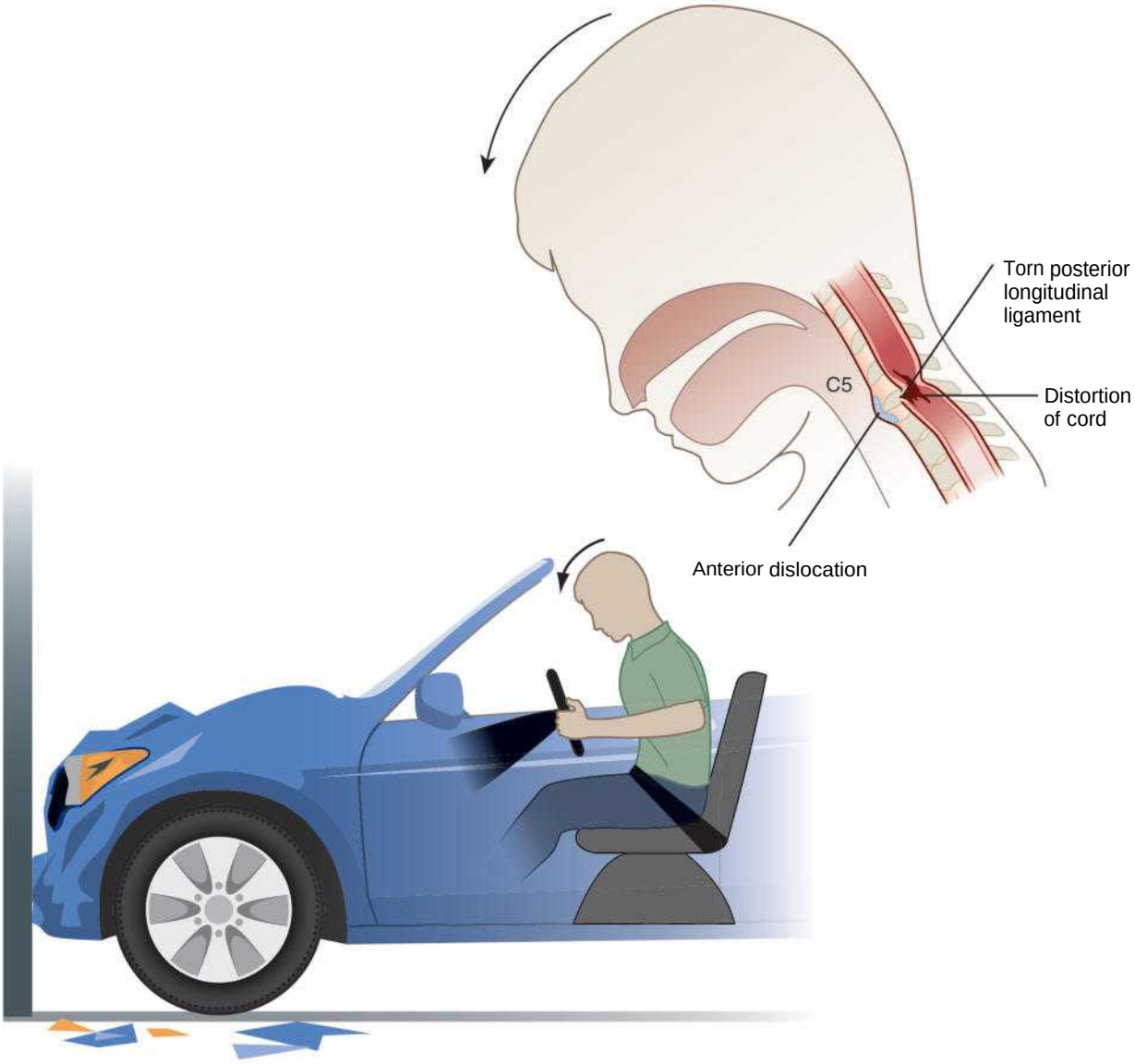


FIGURE 11-34 Spinal cord injuries.

Description

The initial mechanical forces exerted on the spinal cord inflict the primary injury. This structural injury occurs as displaced bone fragments, disk material, and/or ligaments bruise or tear into the spinal cord. Most injuries do not completely sever the spinal cord. Four mechanisms of primary injury have been identified—impact plus persistent compression, impact alone with transient compression, distraction, and laceration/transection. Impact plus persistent compression is the most common form, typically occurring through

burst fractures with bone fragments compressing the spinal cord or through fracture-dislocation injuries. Impact alone with transient compression is usually associated with hyperextension injuries. Distraction injuries occur when two adjacent vertebrae are pulled apart, causing the spinal column to stretch and tear horizontally. Laceration and transection injuries can occur as a result of penetrating injuries, severe dislocation, or sharp bone fragments (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019).

Damage to the spinal cord can continue for months regardless of the initial injury mechanism, referred to as the "secondary injury." These secondary injuries, which can be more serious than the primary injury, include **spinal shock**, systemic hypotension, vasospasm, ischemia, ionic imbalance, and neurotransmitter accumulation (Alizadeh et al., 2019; Fehlings, 2019). In addition to the initial structural injury, nearby glial and nerve cells become damaged and prevent tissue perfusion. Glial cells normally provide nutrients and other support to nerve cells. This cellular damage triggers the secondary injury cascade, a series of changes that begin within hours after the SCI and typically develop one after another (**FIGURE 11-35**). First, injured glial and nerve cells in the spinal cord begin to die. Blood supply is reduced due to microvascular damage in the area of the injury, resulting in ischemia. The blood vessel injury can also cause hemorrhaging, triggering the inflammatory response. The inflammatory response results in edema at the injury site. Hemorrhage and edema can occur either inside or outside the spinal cord (but within the spinal canal). The accumulation of blood or fluid can compress the spinal cord, further decreasing tissue perfusion and oxygenation. Ischemia causes excessive release of neurotransmitters from injured glial and nerve cells, which triggers the release of cytokines, opens calcium channels, activates destructive enzymes, leads to the accumulation of free radicals, and initiates apoptosis. Cytokines secrete destructive enzymes, causing further glial and nerve cell death. Opening calcium channels results in the influx of calcium and the activation of more destructive enzymes. Free radicals cause cell membrane and mitochondrial DNA damage, leading to the buildup of toxic metabolites and cell death. As more cells die, tissue

perfusion further decreases, and inflammation escalates. Injured cells also release intracellular potassium, weakening depolarization and reducing impulse transmission. Spinal cord compression and potassium shifts can temporarily suppress neurologic function, a condition referred to as spinal shock. In spinal shock, neurologic function gradually returns.

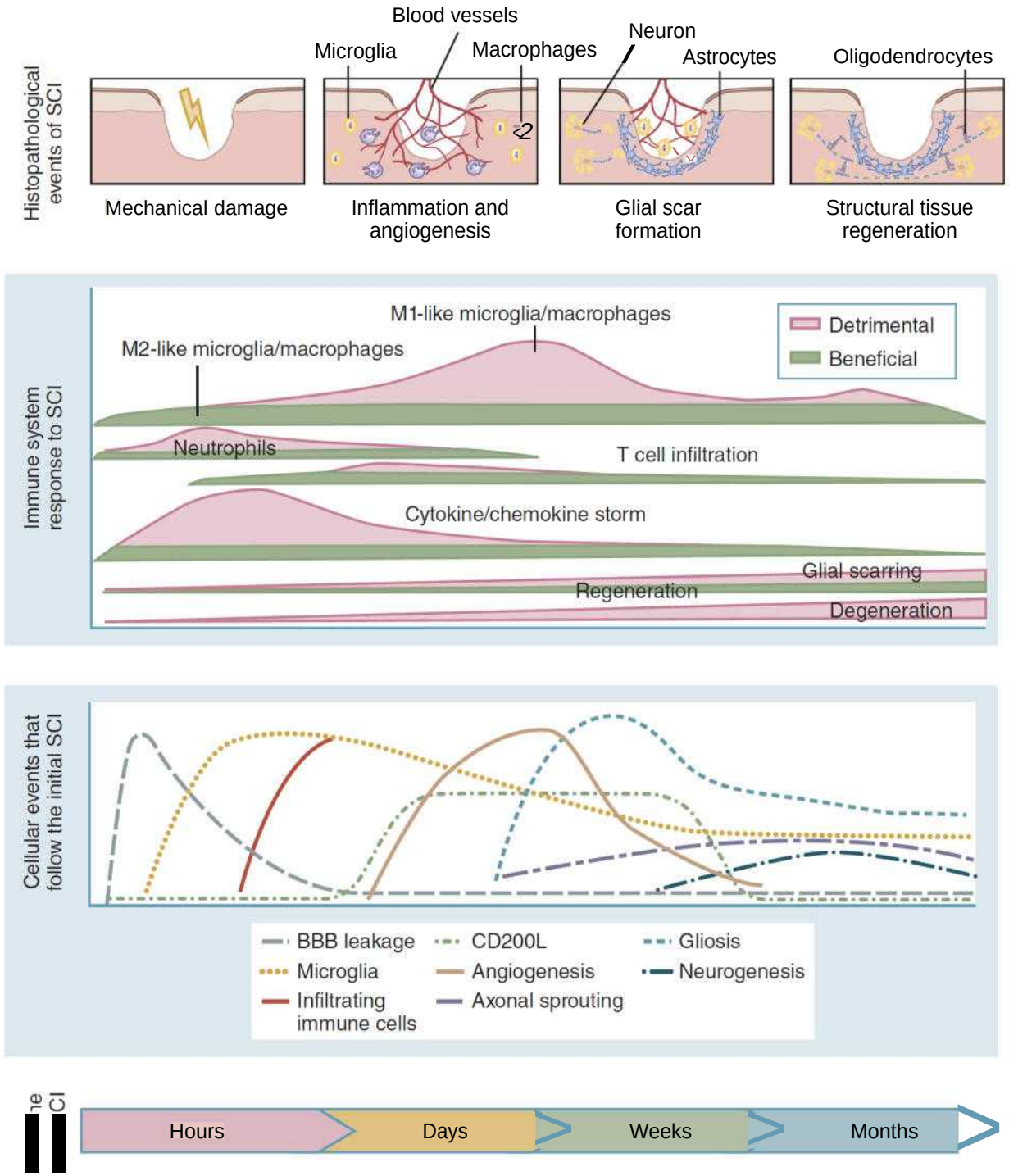


FIGURE 11-35 Stages of spinal cord injuries (SCIs).

Description

The spinal cord attempts to repair itself by forming cystic cavities and glial scars. Cystic cavities appear after a significant number of

cells die, resulting in a loss of tissue volume. These cavities contain fluid, connective tissue, and leukocytes. The cystic cavities form a barrier that promotes nerve cell and pathway regeneration. Glial scars can be protective as well as problematic. Glial scars form a barrier around the site to allow for repair, prevent infection, reestablish tissue perfusion, and minimize further damage; however, these scars can also prevent nerve cells and pathways from regenerating. The surviving nerve cells create new myelin sheaths (i.e., remyelination). The spinal cord can also internally repair some damage from the secondary injury. In particular, the nerve cells within the spinal cord can adapt and promote sustained recovery (i.e., plasticity), and other precursor glial cells can create new glial and nerve cells to support the regeneration process for years after the initial injury (Fehlings, 2019).

An estimated 291,000 Americans are living with a SCI (NSCISC, 2019). Prognosis, healthcare burden, and life expectancy can vary greatly depending on the level of injury and age at the time of injury. SCIs result in a significant loss of neurologic functioning, often requiring extensive long-term management. These injuries can also result in death, either immediately due to the injury or because of subsequent complications (e.g., pneumonia, embolism, or septicemia).

The degree of dysfunction depends on the severity of the injury and its location (see Figure 11-16), as such an injury may result in a partial or complete disruption of the neurons and neural tracts anywhere along the spinal cord. SCIs are classified based on the location of damage (e.g., C4, T12) and the degree of function lost. An injury to one of the eight cervical segments of the spinal cord causes quadriplegia (tetraplegia)—loss of all or most function in all four limbs. Injury to the thoracic, lumbar, or sacral regions causes **paraplegia**—loss of lower-extremity function. Some individuals may experience complete paralysis (no voluntary use of the affected limbs) or incomplete paralysis (some voluntary use of the affected limbs). Incomplete quadriplegia is the most frequently occurring injury, accounting for approximately 48% of SCIs. The spinal cord does not extend beyond the first lumbar vertebra, so injuries at and below this

level do not cause SCIs. However, they may cause **cauda equina syndrome** (injury to the nerve roots in the area of the cauda equina). In addition to injury to the spinal cord, vertebral injuries may be present (e.g., fracture, dislocation, or subluxation).

Numerous complications of SCIs can contribute to the mortality associated with SCIs:

- **Autonomic hyperreflexia**—a massive sympathetic response that can cause headaches, hypertension, tachycardia, seizures, stroke, and death; most commonly associated with injuries above T6 and triggered by noxious stimuli
- Neurogenic shock—an abnormal vasomotor response secondary to disruption of sympathetic impulses
- Respiratory failure (caused by paralysis of the respiratory muscles)
- Effects of immobility (e.g., constipation, pulmonary infections, urinary infections, thrombus, impaired skin integrity, and contractures)
- Changes in bowel and bladder function (e.g., urinary retention, incontinence, and constipation)
- Sexual dysfunction (e.g., erectile dysfunction)
- Chronic pain

Clinical manifestations of SCIs depend on the level of injury. Neurologic function will be intact above the level of injury, whereas function is absent or notably diminished below the injury. If vertebrae are damaged, pain may also be present depending on any other injuries that may be present or changes in level of consciousness. Cervical injuries can affect both the upper and lower extremities. Manifestations of such injuries include the following symptoms:

- Breathing difficulties resulting from paralysis of the respiratory muscles
- Loss of normal bowel and bladder control (e.g., constipation, incontinence, and bladder spasms)
- Paresthesia

- Sensory changes
- Spasticity
- Pain
- Weakness or paralysis
- Blood pressure instability
- Temperature fluctuations
- Diaphoresis

Thoracic injuries affect the lower extremities, and the symptoms can be similar to those for cervical injuries. Lumbar sacral injuries can affect the lower extremities to varying degrees. Manifestations of lumbar sacral injuries are similar to those of cervical injuries, with the exception of breathing difficulties.

Diagnostic procedures for SCIs consist of a history, physical examination (including a neurologic assessment), spinal CT, spinal MRI, spinal X-ray, somatosensory evoked potential testing or magnetic stimulation, and spinal myelogram (X-ray using contrast dye). These injuries are always medical emergencies requiring immediate treatment. Therapeutic strategies include both immediate interventions to minimize residual effects and long-term interventions to limit complications. Immediate strategies may include the following measures:

- Immobilization of the spine
- Spinal traction to reduce fractures and immobilize the spine
- Surgical repair of vertebral fractures or surgical removal of the fluid compressing the spinal cord (decompression laminectomy)
- Respiratory management (e.g., oxygen therapy and endotracheal intubation with mechanical ventilation)
- Thromboembolism prophylaxis (e.g., anticoagulation therapy, intermittent pneumatic compression, compression stockings, and inferior vena cava filter)
- Bed rest

Long-term strategies may include the following interventions:

- Physical, occupational, speech, and recreational therapy
- Mobility assistive devices (e.g., a wheelchair, walking assistance system)
- Electronic devices (e.g., brain–computer interface, functional electronic stimulation systems, and electronic aids for daily living)
- Long-term respiratory management (e.g., mechanical ventilation)
- Meticulous skin care
- Bowel and bladder training or management (e.g., catheterization and stool softeners)
- Antispasmodic agents and botulinum toxin type A (Botox) injections to treat muscle spasms
- Pain management
- Nutritional support
- Prompt treatment of infections (pneumonia is the leading cause of death)
- Vocational rehabilitation

Vascular Neurologic Disorders

Vascular neurologic disorders generally involve ischemic injuries to the brain resulting from occlusion of blood flow or hemorrhage. These disorders vary significantly in their severity and presentation depending on the location and extent of damage. Often, they result in some degree of neurologic dysfunction. These conditions may occur due to congenital abnormalities or chronic diseases, such as hypertension, hypercholesterolemia, and atherosclerosis.

Emerging Research: Spinal Cord Injury

Given the long-term residual effects and healthcare burden of spinal cord injuries (SCIs), identifying ways to support the spinal cord's internal repair processes is a priority. Clinical trials are in various stages to explore and determine the efficacy of medications, cellular

transplantation, spinal cord stimulation, robotic devices, robotic-guided surgery, and biosensing. Advancements are largely categorized as neuroprotective and neuroregenerative therapies. Neuroprotective treatments include a drug (Minocycline) that may protect nerves, a drug (Riluzole) that may prevent cell swelling and death, basic fibroblast growth factor that may improve functional recovery, and hospital-induced systemic hypothermia to safely control inflammation. Neuroregenerative treatments include a drug (Cethrin) to promote cell regeneration, anti-Nogo antibodies to block a protein that interferes with functional recovery, and implantable bioengineered scaffolds or matrices designed to mimic lost cells and help regulate cell migration and regeneration. Since the spinal cord cannot repair all the tissue lost due to an injury, cell transplantation can help replace lost cells, regulate cell function at the injury site, and improve cell regeneration. Cell transplantation has shown promise in promoting motor and bladder function when implanted 1 month after the injury. Spinal cord stimulation uses surgically implanted electrical current in the epidural space to improve functional and walking-related outcomes in patients with an SCI longer than 1 year. A wearable robotic exoskeleton for people with paraplegia after SCI was first approved by the U.S. Food and Drug Administration in 2014. This device fits around the legs and back to allow the individual to stand, walk, and move. Eventually, these advancements may be used together to minimize the injury and long-term effects to improve patient outcomes (Fehlings, 2019).

For individuals with even long standing and severe paralysis from spinal cord injuries or other neurological issues (e.g., amyotrophic lateral sclerosis), OpenBCI (https://openbci.com) is working on technology that protects the individual's agency and mental health. A neurotechnologist, Conor Russomanno, and the team at OpenBCI have been working to develop technology in which the brain interfaces with computers through a closed-loop system. Their latest innovation, Galea, is a hardware and software platform that merges biometrics with mixed reality. This innovative device integrates EEG, EMG, electrodermal activity (a sensitive psychophysiological index of changes in autonomic sympathetic arousal that integrates with emotional and cognitive states), preproglucagon neurons (regulate energy balance and general autonomic homeostasis), and eye-tracking into a single, multi-modal, sensor system headset. This headset can allow for better interface with and control of the world around the person through augmented and virtual reality by creating a virtual joystick of sorts. Even more astonishing is that OpenBCI is an open source neurotechnology company that invites other neuroscientists and neurohackers to contribute and advance the technology, meaning the technology is freely available for others to use and improve upon in order to make what has been impossible possible.

Transient Ischemic Attack

A **transient ischemic attack (TIA)** is a temporary episode of cerebral ischemia that results in symptoms of neurologic deficits. TIAs are often called "ministrokes" because these neurologic deficits mimic a **cerebrovascular accident (CVA)**, or stroke, except that the deficits resolve within 24 hours (1–2 hours in most cases). TIAs may

occur singly or in a series. They serve as warning signs that a CVA may be impending; approximately 1 in 3 people who experience a TIA will eventually have a stroke, with about half of these CVAs occurring within one year of the TIA. However, not all CVAs are preceded by a TIA.

This type of ischemia can occur because of a cerebral artery occlusion (e.g., thrombus, embolus, or plaque), cerebral arterial narrowing (e.g., atherosclerosis or spasms), or cerebral artery injury (e.g., inflammation or hypertension). Additional risk factors for TIAs include migraines, smoking, diabetes mellitus, advancing age, inadequate nutrition, hypercholesterolemia, oral contraceptive usage, excessive alcohol consumption, and illicit drug use. Complications of TIAs include permanent brain damage from the lack of oxygen and glucose, injury from falls, and CVA from the ischemia.

Clinical manifestations of TIAs begin suddenly and last for a short period (2–30 minutes). Within 24 hours, symptoms disappear completely. Although TIAs are not strokes, they have the same manifestations as CVAs. These manifestations reflect the location of the ischemia and may include the following symptoms:

- Muscle weakness or paralysis of the face, arm, or leg (usually unilateral)
- Paresthesia on one side of the body
- Aphasia (difficulty speaking) or receptive aphasia (difficulty understanding spoken language)
- Dysphagia (difficulty swallowing)
- Dysgraphia (difficulty writing)
- Difficulty reading
- Vision issues (e.g., diplopia, nystagmus, and partial or complete loss of vision)
- Changes in sensation (e.g., touch, pain, temperature, pressure, hearing, and taste)
- Change in levels of consciousness (e.g., lethargy, unconscious, or coma)

- Personality, mood, or emotional changes
- Confusion
- Agnosia (inability to recognize or identify sensory stimuli)
- Ataxia
- Vertigo (abnormal sensation of movement) or dizziness
- Bowel or bladder incontinence

Because these clinical manifestations often resolve prior to the patient reaching a healthcare facility, diagnosis may be made based on a history alone. Additional diagnostic procedures consist of a physical examination (including a neurologic assessment and blood pressure), head CT, head computed tomography angiography (CTA), head MRI, head magnetic resonance angiography (MRA), carotid ultrasound, cerebral arteriogram, EEG, serum clotting studies, blood chemistry, complete blood count (CBC), erythrocyte sedimentation rate test (can identify inflammatory process), and serum lipids test.

Treatment strategies for TIAs focus on preventing the occurrence of a CVA. These strategies typically include managing any underlying conditions (e.g., hypertension, atherosclerosis, and diabetes mellitus). Medications, such as antiplatelet aggregation agents (e.g., aspirin and clopidogrel [Plavix]) or anticoagulants (e.g., warfarin [Coumadin]), may be used to prevent clotting. Angioplasty (balloon dilation) can be undertaken to open narrowed arteries, or a carotid endarterectomy (surgical removal of plaque) may be performed to increase cerebral blood flow. Lifestyle management includes smoking cessation, minimizing dietary cholesterol and fat, increasing dietary fruits and vegetables, exercising regularly, limiting alcohol consumption, and eliminating illicit drug use.

Cerebrovascular Accident

Cerebrovascular accident (CVA), or stroke, refers to an interruption of the cerebral arterial blood supply (**FIGURE 11-36**). The chief difference between a CVA and a TIA is that CVA damage is permanent. A CVA is an infarction of the brain, so it is often referred to as a "brain attack." This kind of interruption in the brain's blood

flow may result from either a total vessel occlusion (e.g., thrombus, embolus, or plaque) or cerebral vessel rupture (e.g., cerebral aneurysm, arteriovenous malformation, or hypertension). Thus, there are two major types of CVAs—ischemic and hemorrhagic, respectively. **Ischemic strokes** are the most common (87%), but **hemorrhagic strokes** are the deadliest. Even 5 minutes (sometimes less) of altered tissue perfusion can lead to irreversible cell damage from the lack of oxygen and glucose. CVA can result in significant neurologic dysfunction and death; in fact, it is the chief cause of long-term disability and fifth leading cause of death in the United States (CDC, 2023a).

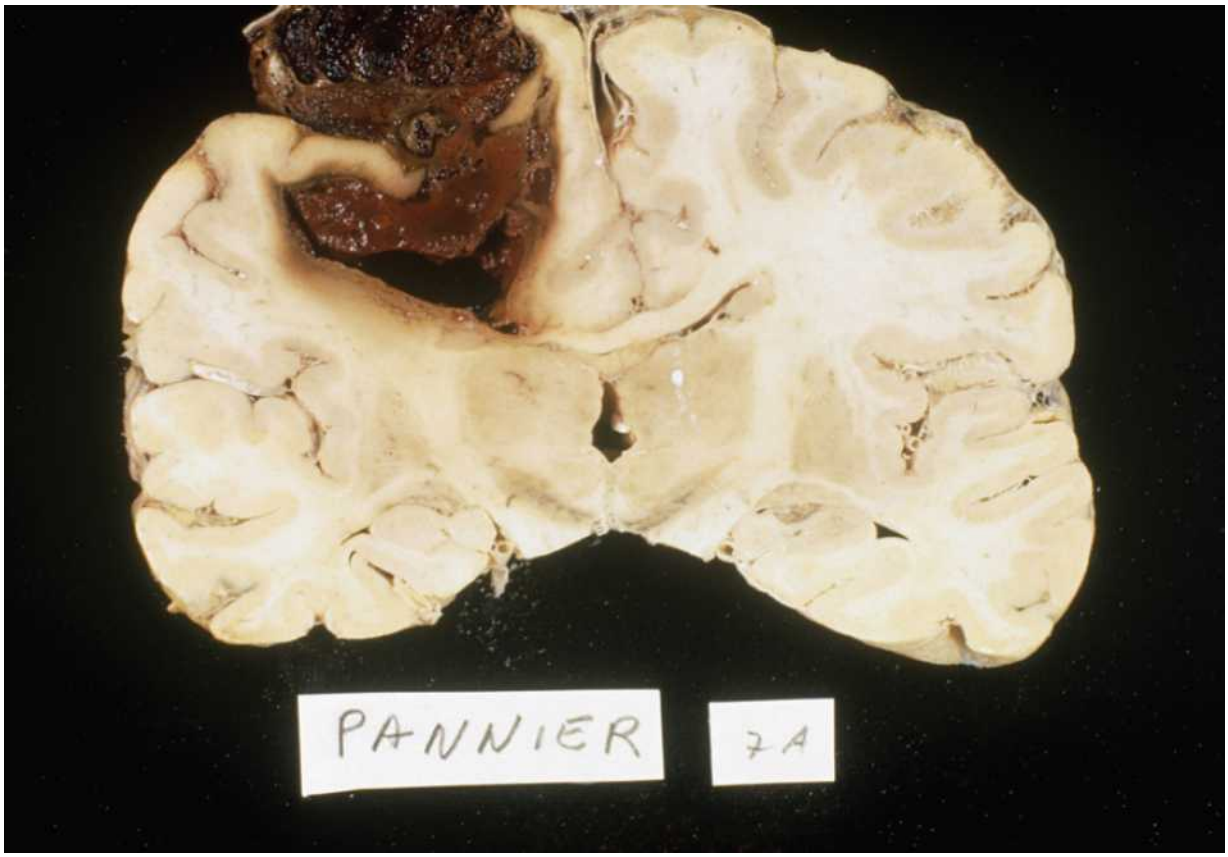


FIGURE 11-36 Cerebrovascular accident, or stroke.

© BSIP/age fotostock

CVA incidence and mortality rates are highest in the southeastern United States, often referred to as the “Stroke Belt.” In the United

States, someone experiences a CVA every 40 seconds and dies from a CVA every 4 minutes. The costs associated with this widespread problem and its extensive consequences are estimated at $56.5 billion annually in the United States (CDC, 2023a). In this country, CVA prevalence and mortality are highest among African Americans. Additional risk factors include physical inactivity, psychosocial stress, obesity, hypertension, smoking, dyslipidemia, diabetes mellitus, atherosclerosis, oral contraceptive usage, excessive alcohol consumption, illicit drug use (especially cocaine and amphetamines), and advancing age.

application to practice

Sally Stubbs, a 58-year-old African American female, is brought to the emergency room by her daughter, Pat. Ms. Stubbs complains of right-sided weakness, a severe headache, and not feeling well for the last couple of days. Upon assessment, she is alert but has trouble answering questions. Her speech is slurred, and she appears frightened.

1. Which additional clinical manifestations would the nurse expect to find if Ms. Stubbs' symptoms have been caused by a stroke?
   a. A carotid bruit
   b. Hypertension
   c. Increased deep tendon reflexes
   d. Decreased bowel sounds
2. While assessing Ms. Stubbs every 15 minutes, which of the following findings warrants immediate action?
   a. Glasgow Coma Scale score increasing from 11 to 14
   b. Bilateral grip strength is unequal
   c. Responding only to painful stimuli
   d. Negative Babinski reflex
3. Due to her deteriorating condition, Ms. Stubbs is immediately referred to the neurologist. This patient has likely suffered a left-sided cerebrovascular accident. Which clinical manifestation further supports this conclusion?
   a. Visual field deficit on the left side
   b. Spatial–perceptual deficits
   c. Paresthesia of the left side
   d. Global aphasia

Clinical manifestations of CVA are similar to those of a TIA, except that CVA symptoms do not resolve in the same way as TIA symptoms. TIA symptoms disappear in less than 24 hours; in contrast, CVA manifestations may improve with time and therapy, but they may also persist, creating complications. Complications include increased ICP, sleep disturbances, confusion, depression, incontinence, dysphagia, aspiration, atelectasis, pneumonia, dehydration, malnutrition, hemiparalysis, immobility, and self-care deficits. In addition to the manifestations of neurologic impairment associated with TIAs, headaches may be present with hemorrhagic strokes because of increasing ICP.

Diagnostic procedures for CVA consist of a history, physical examination (including a neurologic assessment), head CT, head MRI, carotid ultrasound, cerebral arteriogram, serum clotting studies, blood chemistry, and CBC. A CVA is a medical emergency that requires prompt treatment to minimize brain damage. Determining whether the CVA is ischemic or hemorrhagic in origin prior to treatment is crucial because the interventions vary depending on the type. Additionally, some interventions for ischemic strokes can worsen hemorrhagic strokes (e.g., thrombolytic agents).

The differential diagnosis should be made as soon as possible because early treatment will improve outcomes. Optimally, treatment should be delivered within 3 hours of symptom onset; therefore, persons or family members of persons who seem to be experiencing a CVA should make note of when the symptoms began. Stabilizing the patient may be needed prior to complete evaluation. Such stabilization measures can include airway support, ICP monitoring, and measures to reduce cerebral edema (e.g., hypertonic saline, sedation, CSF drainage).

Ischemic strokes are treated with thrombolytic agents (to dissolve any clots) and aspirin (to limit platelet activity). This treatment is contraindicated in persons with a recent history of bleeding issues. Additionally, procedures such as angioplasty or carotid endarterectomy may be necessary in patients with ischemic strokes. Surgical repair of aneurysms or arteriovenous malformations and blood removal may be required in patients with hemorrhagic strokes.

Hypertonic saline (usually 2% to 3% saline) may also be administered with either type of CVA to reduce cerebral edema, and antihypertensive agents may be used cautiously to reduce blood pressure slowly. A multidisciplinary approach (using a team consisting of a nurse, physical therapist, speech therapist, occupational therapist, dietitian, and social worker) should be initiated as soon as the patient is stable and may be required on a long-term basis to minimize or prevent complications. Depending on the degree of dysfunction, strategies may be necessary to prevent complications of immobility (e.g., constipation, impaired skin integrity, contractures, thromboembolism, and infections).

Cerebral Aneurysm

A cerebral aneurysm is a localized outpouching of a cerebral artery (see the *Cardiovascular Function* chapter, as well as **FIGURE 11-37** and **FIGURE 11-38**). This weakening of the artery may occur as a congenital defect, or it may develop later in life because of conditions such as hypertension, diabetes mellitus, dyslipidemia, connective tissue disease (e.g., Marfan syndrome), arterial wall infection (i.e., mycotic aneurysm), polycystic kidney disease, arteriovenous malformations, cigarette smoking, illicit drug use (e.g., cocaine and amphetamines), TBI, and brain tumor. Cerebral aneurysms are most common in adults between the ages of 30 and 60 and in women compared to men. The bulging artery segment can put pressure on surrounding tissues. Additionally, the aneurysm may leak (i.e., sentinel bleed) or rupture, causing a CVA or death. Several types of aneurysms are possible, but most cerebral aneurysms are berry or saccular forms. Cerebral aneurysms most frequently form at the base of the skull, usually as multiple aneurysms on the circle of Willis.

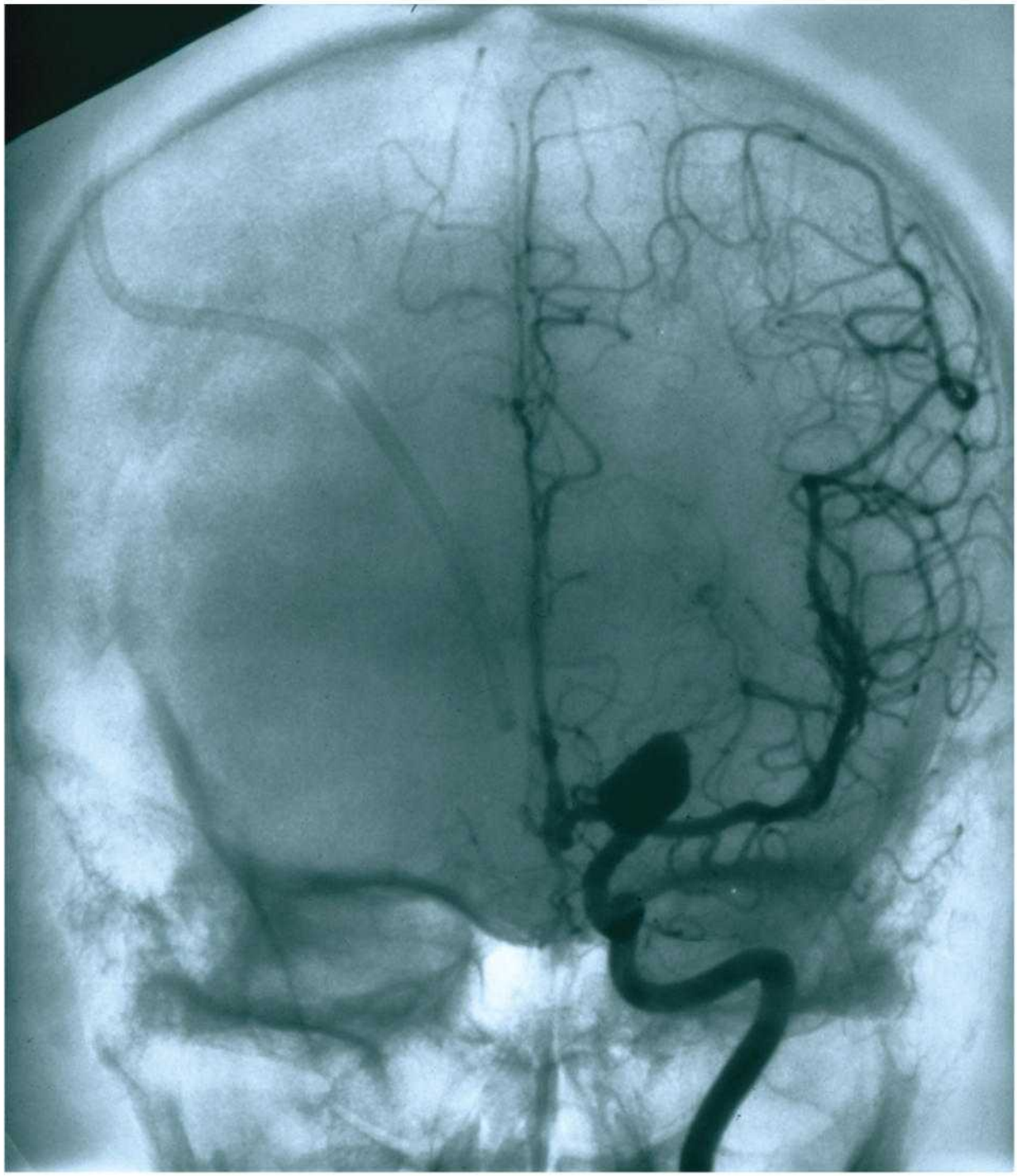


FIGURE 11-37 Cerebral aneurysm.

Courtesy of Michael Hart.

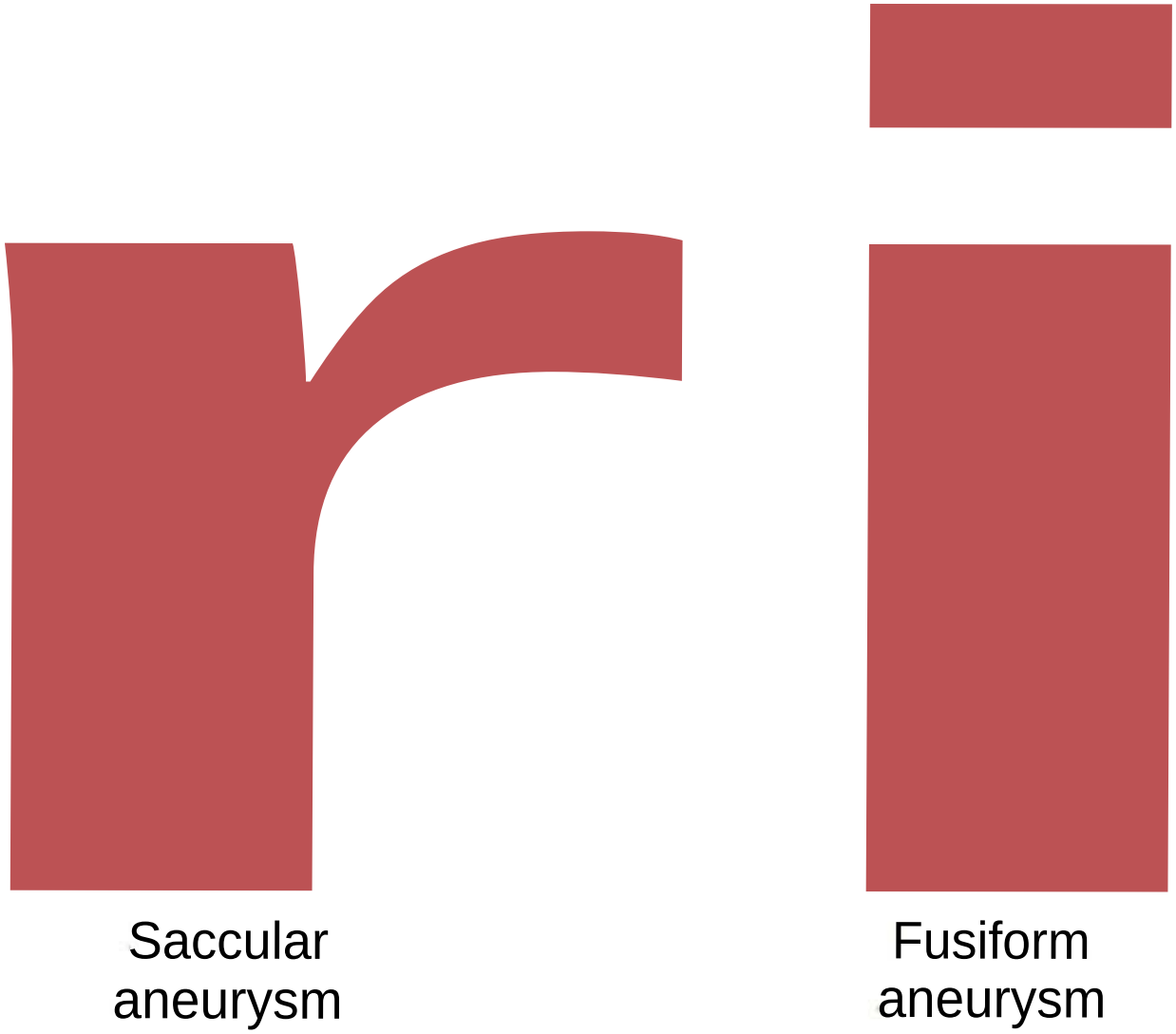


FIGURE 11-38 Types of cerebral aneurysms.

Many cerebral aneurysms remain asymptomatic until they grow large enough to compress surrounding structures or they rupture. Clinical manifestations that may appear as the aneurysm compresses nearby structures include vision issues (e.g., diplopia and loss of vision), headache, eye pain, or neck pain. A sudden, severe headache is an indication that the aneurysm has ruptured. Additional manifestations resemble those associated with increased ICP and CVA.

Often diagnosis occurs inadvertently with a head CT or MRI. Additional diagnostic procedures include a history, physical examination, cerebral arteriography, and EEG. If discovered prior to

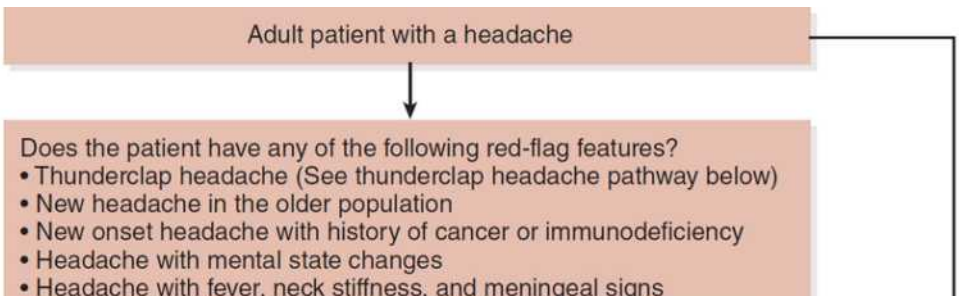
rupture, treatment strategies include surgical repair (if possible), managing contributing factors (e.g., hypertension), and close monitoring. Rupture is a medical emergency that requires immediate surgical repair. Additional strategies are similar to those for a CVA and subarachnoid hemorrhage.

Headache Disorders

A **headache**, or **cephalalgia**, refers to pain in any region of the head; headache disorders are characterized by recurrent headache. The pain can occur on one or both sides of the head, be isolated to a specific area, radiate across the head from one point, or have a viselike quality. A headache may appear as a sharp pain, a throbbing sensation, or a dull ache. Headaches can develop gradually or suddenly and may last from less than an hour to several days. Other symptoms may be present, such as vomiting and visual disturbances. All of these qualities can assist in identifying the type and cause of the headache.

Headache is an extremely common symptom, and headache disorders are collectively among the most frequently occurring neurologic conditions. Approximately half of the world's adult population has had a headache in the past year (WHO, 2016). Headache disorders are often underdiagnosed and undertreated, and they are associated with disability, poor quality of life, financial burden, and increased risk of comorbidity (e.g., anxiety and depression).

Diagnosis for headaches generally includes a history and physical examination. Additional tests may be required to rule out causes of secondary headache disorders (**FIGURE 11-39**).



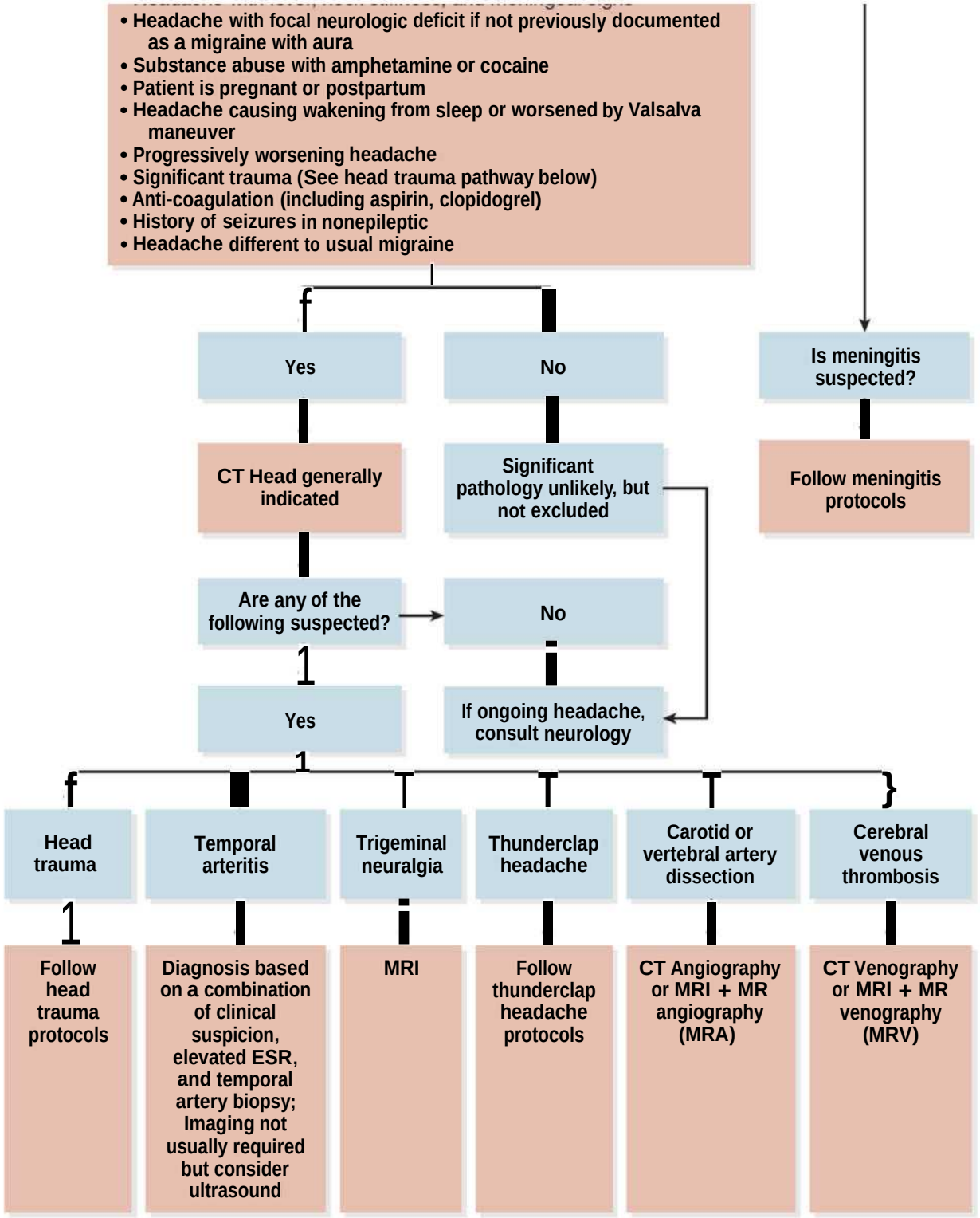


FIGURE 11-39 Diagnostic pathways for secondary headache disorder.

Description

Treatment for headaches includes avoiding triggers, yoga, behavioral interventions (e.g., biofeedback, stress management, and psychotherapy), supplemental oxygen, analgesics (usually acetaminophen), NSAIDs, intranasal or subcutaneous triptans (i.e., serotonin agonists), dihydroergotamine, dopamine antagonist antiemetics, Botox injections, topiramate (Topamax), tricyclic antidepressants, and antiemetics (if nausea or vomiting is present). Analgesics containing opioids, caffeine, or butalbital may be used for infrequent mild attacks, but they are prone to overuse and can lead to a daily headache syndrome called "medication-overuse headache (MOH)." Opioids should be used as a last resort for severe headaches when other measures are ineffective. Triptans are not a direct analgesic, but they block the release of vasoactive neuropeptides that trigger migraine pain. Triptans are most effective when taken at the onset of symptoms, and they are available in oral, intranasal, and subcutaneous forms. Overuse of triptans can lead to MOH. Intravenous fluids may be needed in patients who are dehydrated from vomiting. Triptans and dihydroergotamine are contraindicated in patients with coronary artery disease or uncontrolled hypertension because of their action on the vascular system. Botox and Topamax can be used to prevent headaches.

Primary Headache Disorders

Headaches are generally classified as primary or secondary based on the underlying cause. Primary headaches have no apparent underlying cause, so they are not a symptom of another disorder. Primary headaches include migraines, **tension-type headaches (TTH)**, **trigeminal autonomic cephalalgias (TACs)**, and other miscellaneous headaches (Headache Classification Committee of the International Headache Society [HCCIHS], 2018). The etiology of primary headaches is not completely understood but is thought to involve a combination of genetic and environmental factors. Chemical activity, nerves, blood vessels, or muscles of the brain, head, or neck likely play a role.

Due to the complexity of these disorders, isolating the genetic factors involved in primary headaches has proven difficult. Evidence

suggests that genes involved in vascular, neuronal, and endocrine functions may have a significant role (Rainero et al., 2013). Several genes involved in vascular function have been studied, with methylenetetrahydrofolate reductase (*MTHFR*) being most significantly associated with primary headaches, such as migraines. The *MTHFR* gene codes for a crucial enzyme involved in purine and thymidylate biosynthesis, methylation of DNA and amino acids, and neurotransmitter synthesis. As a result of this genetic mutation, spontaneous trigeminal cell firing increases and cortical neurons are predisposed to hyperexcitability.

Mutations in neuronal genes that code for ion channels or pumps have also been implicated. These genes include the potassium channel family, subfamily K member 18 (*KCNK18*), transient related potential vanilloid type 1 (*TRPV1*), and transient related potential vanilloid type 3 (*TRPV3*) (Rainero et al., 2013). These genes are important for cellular channel functioning, membrane surface expression, intracellular calcium signaling, and membrane potential.

Several endocrine abnormalities have been identified in patients with primary headaches. The hypothalamus has a significant role in primary headaches, especially migraines and **cluster headaches (CHs)**, because of its control of the endocrine system and interactions with the central and autonomic nervous systems. Neuroendocrine genes that have been associated with primary headaches include hypocretin (orexin) receptor 1 (*HCRTR1*) and hypocretin (orexin) receptor 2 (*HCRTR2*) (Rainero et al., 2013). Hypocretins, also called “orexins,” are peptides derived by proteolytic cleavage from the same 130-amino-acid precursor peptide called “prepro-hypocretin.” A single gene located on chromosome 17q21 is responsible for encoding prepro-hypocretin. Hypocretins are involved in pain modulation within the CNS.

Migraines

Migraine is a common disabling primary headache disorder. There are two major types of migraines—with and without **aura**. An aura occurs in approximately 25% of patients. An aura is a transient focal neurologic symptom that can affect sensation, balance, muscle

coordination, speech, or vision; lasts minutes to an hour; and usually precedes but sometimes accompanies a headache. Most frequently, auras are visual disturbances involving lights. Individuals may also experience a prodromal phase, occurring hours or days prior to the headache, and/or a postdromal phase following headache resolution. Prodromal and postdromal symptoms may include hyperactivity, hypoactivity, depression, food cravings, repetitive yawning, fatigue, and neck stiffness and pain.

The headache associated with migraines varies from moderate to severe and lasts from 4 hours to several days. The pain is often unilateral, throbbing, worse with exertion, and accompanied by nausea and sensitivity to light, sound, or odors. Symptoms are usually variable in frequency and severity over time. Migraines are more common in women, adolescents and young adults, those with a family history, those with mild TBI, and those with chronic traumatic encephalopathy. These headaches are thought to be neurovascular in origin, involving altered central neuronal processing (activation of brainstem nuclei, cortical hyperexcitability, and spreading cortical depression) and the trigeminovascular system (triggering neuropeptide release, which causes painful inflammation in cranial vessels and the dura mater). Migraines may be triggered by drinking red wine, skipping meals, excessive neurologic stimuli (e.g., flashing lights, loud noises, and strong odors), sleep deprivation, stress, hormonal fluctuations (e.g., menstruation or oral contraceptives), foods specific to the individual, weather changes, and head or neck trauma or pain (HCCIHS, 2018).

Tension-Type Headaches

The pain associated with TTHs is mild and not disabling. These headaches are usually described as “viselike” and originate in the occipital or frontal region bilaterally and spread over the entire head. Nausea and photophobia are absent. Physical activity, light, sounds, or smells do not make these headaches worse.

TTHs may be episodic or chronic. Episodic TTHs are extremely common and occur fewer than 15 days each month. These headaches can last 30 minutes to several days. They typically start

several hours after waking and worsen over the course of the day but rarely awaken patients from sleep. Most patients obtain relief with over-the-counter analgesics and do not seek medical attention. Chronic TTHs occur more than 15 days in a month. These headaches vary in intensity throughout the day but are almost always present. Triggers for TTHs may include sleep disturbances, stress, temporomandibular joint dysfunction, neck pain, and eye strain (HCCIHS, 2018).

Trigeminal Autonomic Cephalalgias

Headaches associated with TACs are characterized by unilateral trigeminal distribution pain occurring in association with ipsilateral (occurring on the same side) cranial autonomic symptoms. TACs include CHs, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection (i.e., hyperemia) and tearing. These disorders have been described as the most painful conditions known to humankind and, as such, are highly disabling (Lambru & Matharu, 2012).

Cluster headaches are the most prevalent type of TACs. Headaches associated with CHs are short in duration, strictly unilateral, and associated with autonomic features (e.g., lacrimation, rhinorrhea, conjunctival injection, and ptosis). CHs are more common in young men who smoke. The pain is excruciating and often described as “suicidal headaches.” The CH attacks last between 15 minutes and 3 hours and occur from once every other day up to eight times a day (usually at the same times every day). Restlessness, agitation, and profuse diaphoresis are also usually present. CHs are usually episodic, with attacks occurring daily up to a few months, followed by a symptom-free period that can last up to a few years. Individuals with chronic CHs experience continuous attacks for a year or longer with no symptom-free period or a remission that lasts less than a month. Alcohol most often triggers the attack. The other forms of TACs are extremely rare (Ahmed, 2012; HCCIHS, 2018).

Other Miscellaneous Primary Headaches

Other primary headaches include those associated with physical exertion, excessive coughing, straining, sexual activity, external application of a cold stimulus to the head, ingestion or inhalation of a cold stimulus, compression of the head, and external traction of the head. This category also includes thunderclap (intense, exploding, and hyperacute onset), stabbing, nummular (small, localized, circular area), hypnic (occurs with an awakening jerk during sleep), and new daily persistent headaches. These headaches are poorly understood. Treatment, if needed, varies and is often based on anecdotal response (HCCIHS, 2018).

Secondary Headache Disorders

Secondary headaches are uncommon, but their recognition is important for timely and potentially lifesaving intervention (Ahmed, 2012). Some common causes of secondary headaches include intracranial tumors, CNS infections (e.g., meningitis or encephalitis), intracranial hemorrhage, giant-cell arteritis, cerebral venous thrombosis, cerebral aneurysm, cerebral arteriovenous malformation, acute sinusitis, otitis media, concussion, dehydration, dental problems, glaucoma, hangovers, idiopathic intracranial hypertension, carbon monoxide poisoning, monosodium glutamate ingestion, low CSF pressure or volume (as with CSF leakage and spinal anesthesia), and skull deformities (e.g., Chiari malformation). The following "red-flag" symptoms are associated with secondary headaches:

- Thunderclap headache
- New-onset headaches in patients older than age 50 or younger than age 10, with a history of cancer, or with a history of HIV infection
- Persistent morning headache with nausea
- Progressive headache, worsening over weeks
- Headaches associated with postural changes
- Aura symptoms that last longer than an hour, include motor weakness, are different from previous aura, or occur for the first

time while using oral contraceptives

Seizure Disorders

A seizure is a transient physical or behavioral alteration that results from abnormal electrical activity in the brain. Mechanisms that may be responsible for this abnormal electrical activity include altered membrane ion channels, altered extracellular electrolytes, and imbalances in excitatory and inhibitory neurotransmitters. Some neurons are hypersensitive or remain in a partial state of depolarization, increasing excitability.

Symptomatic **epilepsy** refers to seizures provoked by a known cause, such as brain tumors, CVA, and CTE. Head trauma, metabolic disorders (e.g., hypoglycemia, electrolyte disorders, and acidosis), CNS infection, fever, chemical ingestion (e.g., medications, illicit drugs, and alcohol), drug withdrawal (e.g., alcohol, anesthetics, barbiturates, and benzodiazepines), cerebral ischemia or hypoxia (e.g., carbon monoxide poisoning and near drowning), and increased ICP (e.g., cerebral edema and hemorrhage) can all provoke isolated seizure activity, referred to as "nonepileptic seizures." Psychogenic nonepileptic seizures (i.e., pseudoseizures) are symptoms associated with psychiatric disorders that stimulate seizures but do not involve abnormal electrical activity. Additionally, seizures can be unprovoked and recurrent, referred to as "epilepsy." Epilepsy results from spontaneous firing of abnormal neurons and is characterized by at least 2 seizures that occur more than 24 hours apart for which there is no underlying or correctable cause. According to the CDC (2020b), epilepsy affects approximately 3.4 million Americans. Cryptogenic epilepsy describes seizures that are assumed to be due to a specific cause that has not been identified yet. Reflex epilepsy is a rare disorder in which seizures are predictably triggered by an external stimulus (e.g., repetitive sounds, flashing lights, video games, music, or touch). Complications of seizures may include brain damage, TBIs, aspiration, mood disorders, and **status epilepticus** (seizures that last longer than 5 minutes or subsequent seizures that occur before the individual has fully regained consciousness).

Seizures can be classified into two broad categories—focal and generalized. **Focal seizures**, also called “partial seizures,” occur in just one part of the brain. Approximately 60% of people with epilepsy have focal seizures. These seizures vary depending on the area of the brain affected, and they are frequently described by the area of the brain in which they originate (**FIGURE 11-40**). In a focal aware seizure (formally called a “simple partial” or “focal” seizure), the individual remains conscious but experiences unusual feelings or sensations that can take many forms. For example, the person may experience sudden and unexplainable feelings of joy, anger, sadness, or nausea. Additionally, he or she may hear, smell, taste, see, or feel things that are not real. In a focal impaired-aware seizure (formally called a “complex partial” or “focal” seizure), the individual has changes in or loss of consciousness and memory, producing a dreamlike experience. People having a complex focal seizure may display strange, repetitious behaviors (e.g., blinking, twitching, moving the mouth, walking in a circle) called **automatisms**. These seizures usually last just a few seconds. Some people with focal seizures, especially complex focal seizures, experience auras (unusual sensations just prior to an impending seizure). An aura is actually a simple focal seizure in which the person maintains consciousness. Responsiveness may or may not be intact with focal seizures depending on whether awareness is impaired. The symptoms an individual has and the progression of those symptoms tend to be similar with every seizure. Because the symptoms of focal seizures can easily be confused with other disorders (e.g., migraine headaches, **narcolepsy**, syncope, and psychiatric disorders), those disorders should be ruled out as part of the differential diagnosis.

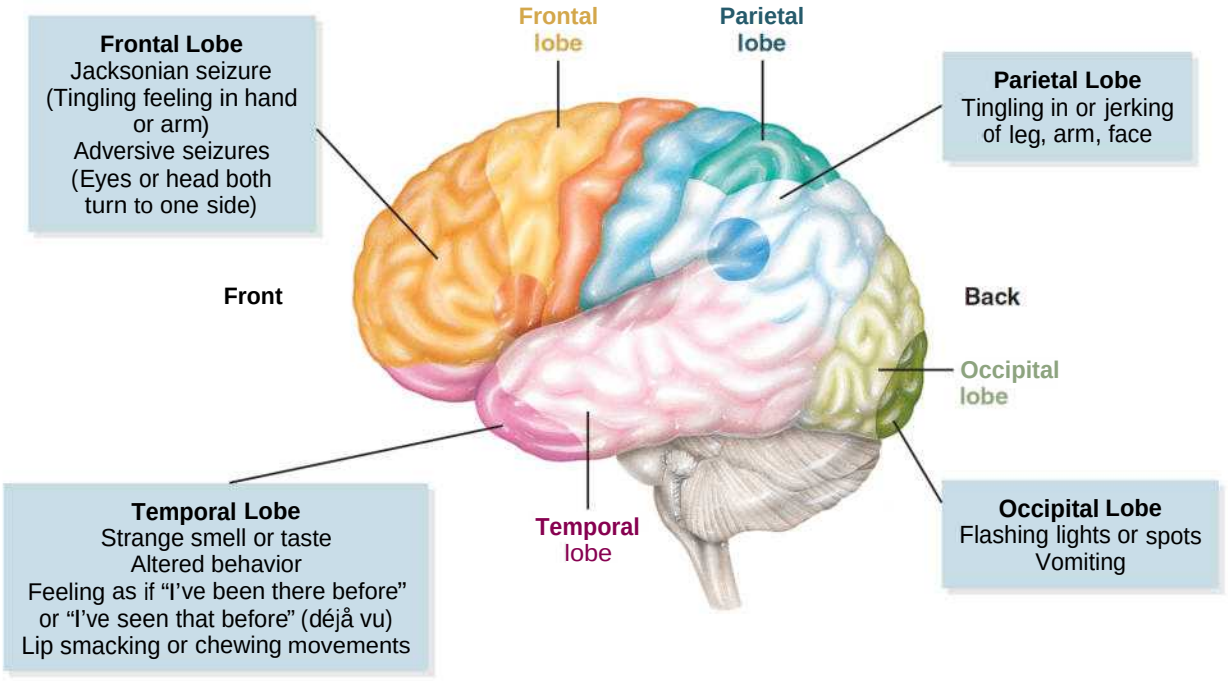


FIGURE 11-40 Manifestations of focal seizures depend on the region of the brain involved.

Description

Generalized seizures are a result of abnormal neuronal activity on both sides of the brain. These seizures may cause loss of consciousness, falls, or massive muscle spasms. Many kinds of generalized seizures are possible. A person having a nonmotor or absence seizure (previously called a "petit mal" seizure) may appear to be staring into space and/or have jerking or twitching muscles. These seizures usually are brief, lasting less than 15 seconds. Tonic seizures cause stiffening of muscles of the body, generally those in the back and extremities, without rhythmic jerking. Clonic seizures cause repeated jerking movements of muscles on both sides of the body. Myoclonic seizures cause jerks or twitches of the upper body, arms, or legs not preceded by stiffening (**FIGURE 11-41**). Atonic seizures cause a loss of normal muscle tone, such that the affected person will fall or may drop his or her head involuntarily. Tonic–clonic seizures (previously called "grand mal" seizures) cause a mixture of symptoms, including stiffening of the body and repeated jerks of the arms and/or legs as well as loss of consciousness (**FIGURE 11-42**). The individual having a generalized seizure may be confused or

fatigued, have a headache, experience muscle soreness, and fall into a deep sleep in the period following the seizure, referred to as the **postictal period**. A transient neurologic deficit, usually weakness of a limb contralateral to the seizure focus—referred to as “Todd’s paralysis”—may also be noted during this time. This postictal period may last minutes to hours.

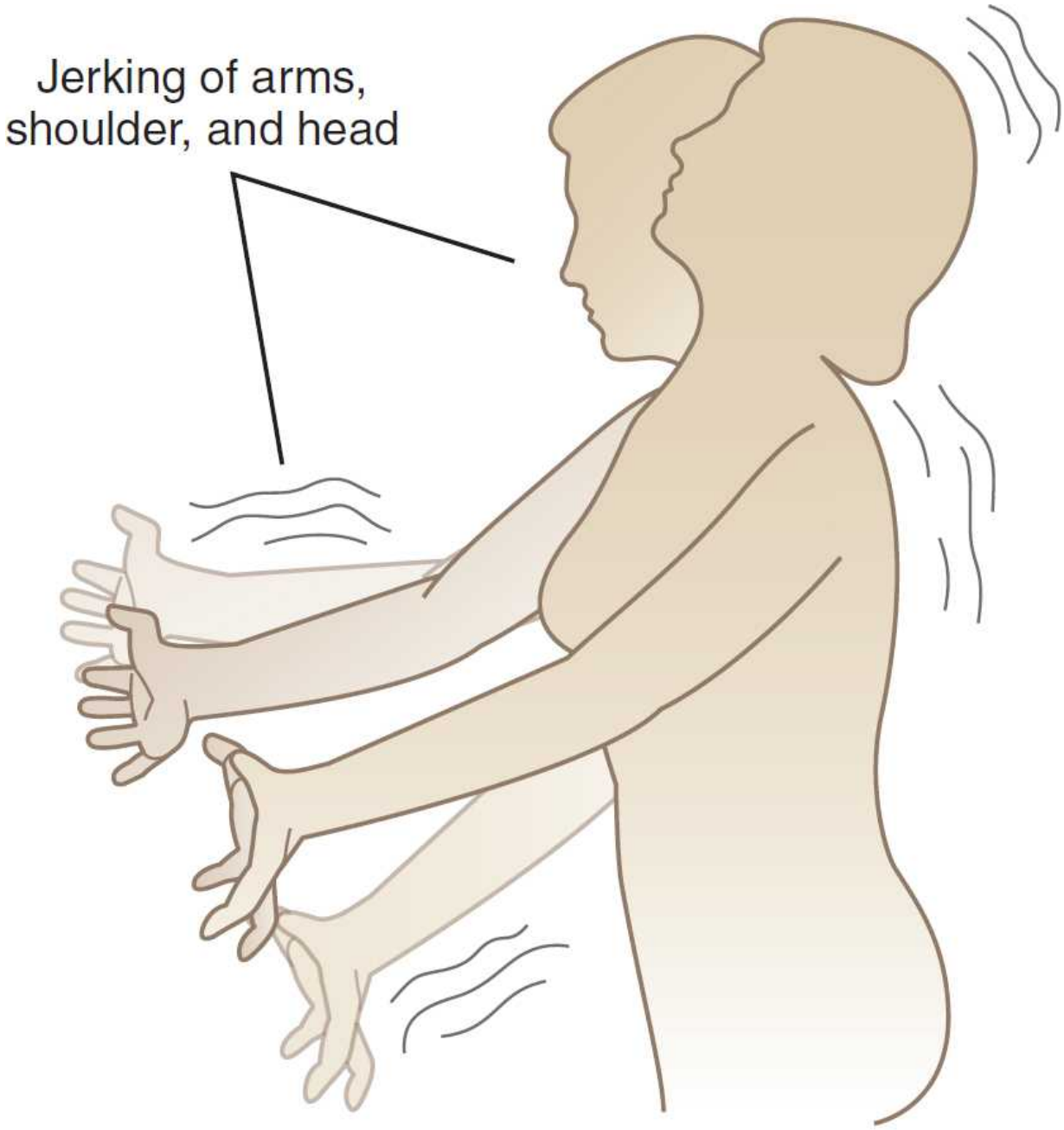
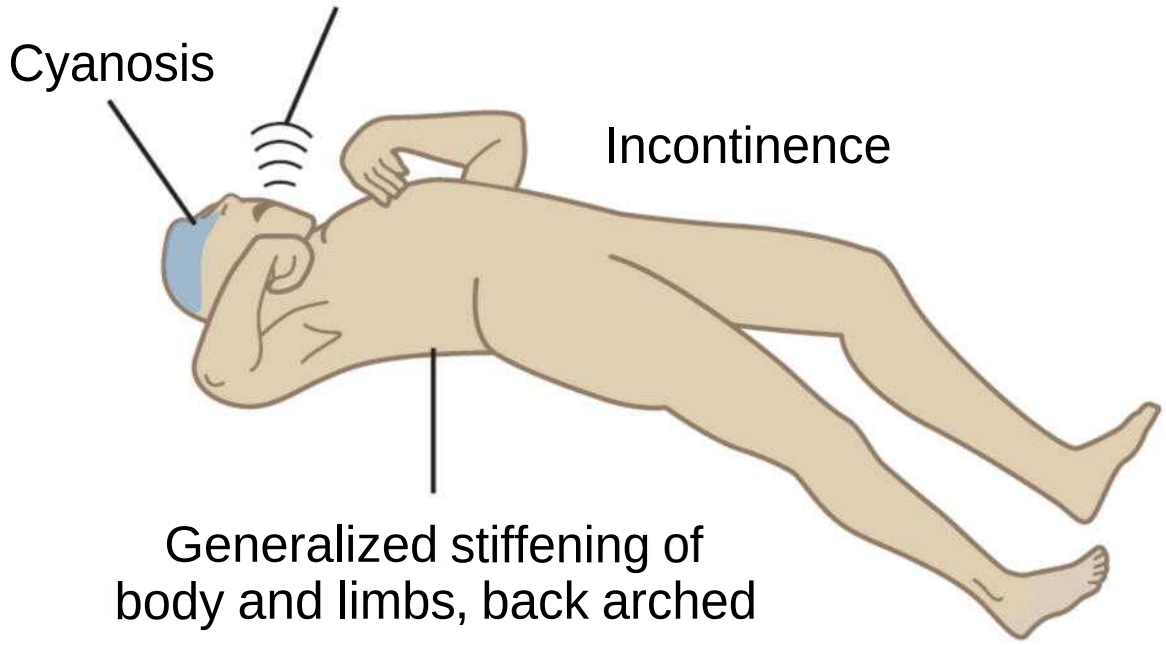


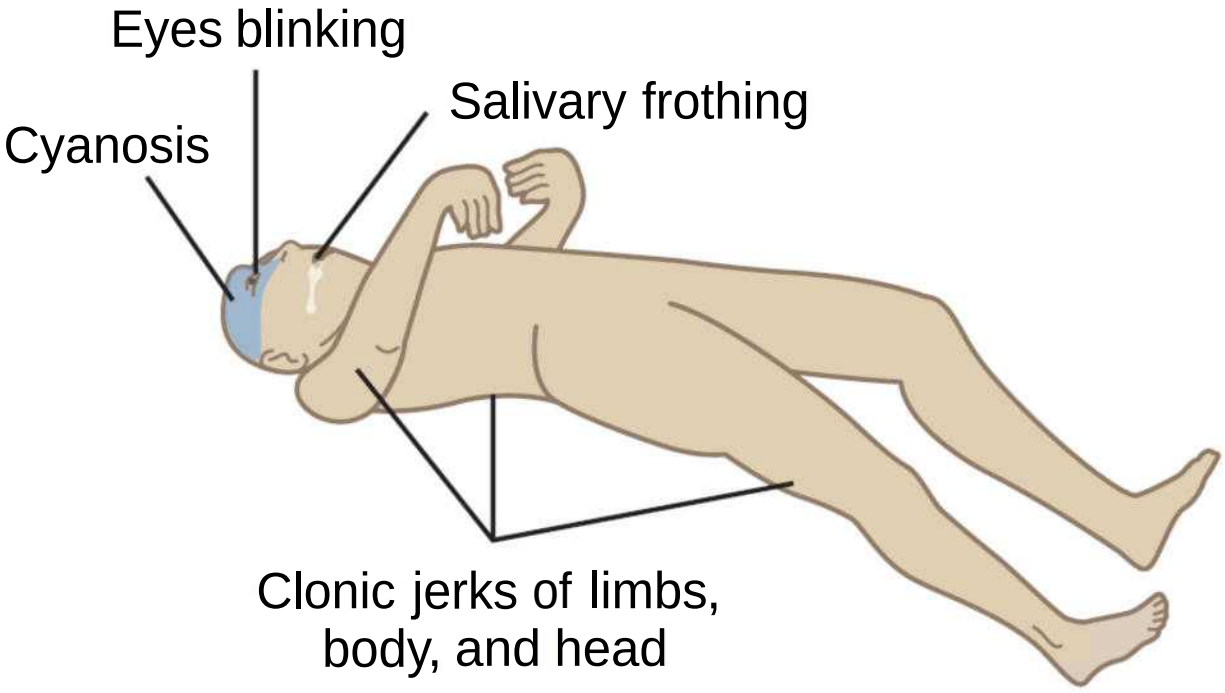
FIGURE 11-41 Myoclonic seizures.

Tonic phase

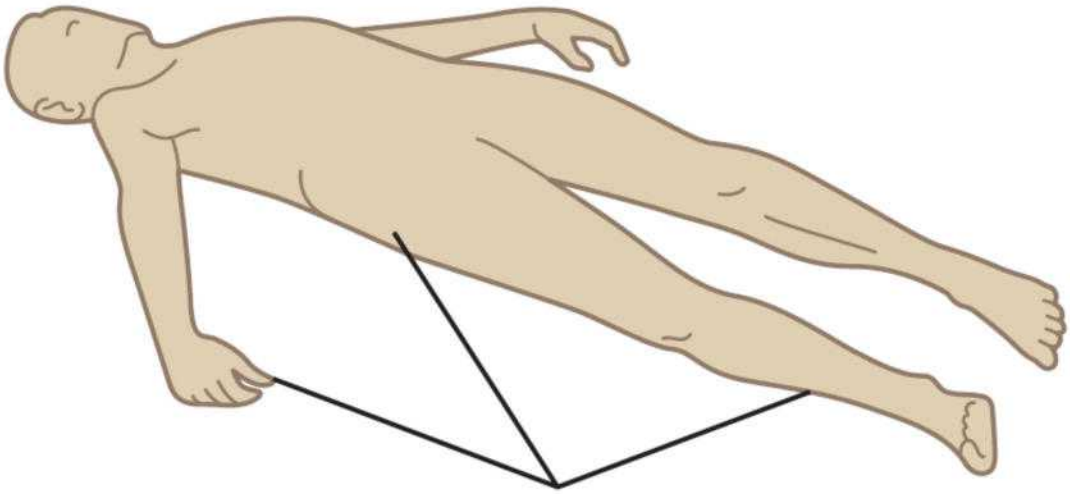
Epileptic cry



Clonic phase



Postictal confusional fatigue



Limbs and body limp

FIGURE 11-42 Tonic–clonic seizures.

Description

Not all seizures can be easily defined as either focal or generalized. Some people have seizures that begin as focal seizures but then spread to the entire brain. Other people may have both types of seizures but with no clear pattern.

Diagnostic procedures for seizure disorders consist of a history (including a description of the seizure activity if possible), physical examination, head CT, head MRI, head PET, EEG, blood chemistry, and liver function tests. Treatment focuses on preventing the occurrence and limiting the duration of the seizure activity. Treatment strategies can be grouped into two categories—those to manage acute seizures and those to prevent seizures. Most seizures resolve spontaneously within 1 to 2 minutes, but employing safety precautions can prevent injury. During a seizure, positioning the individual on his or her side can prevent aspiration (vomiting is common). Additionally, the head should be protected. Items should not be forced in between the individual's teeth; doing so is more likely to cause harm than to help.

Attempts should not be made to restrain the individual; this also is more likely to cause injury. Airway management and oxygen therapy may be necessary to minimize hypoxia. If status epilepticus develops, medication (e.g., muscle relaxants or antiseizure agents) will often be administered intravenously to stop the seizure. Following a seizure, the individual should be allowed to sleep as desired.

For patients with epilepsy, antiseizure agents will be administered daily to minimize the frequency and duration of seizure activity. These medications require close monitoring and accurate administration to ensure therapeutic dosing and limit side effects. If medications are not successful in controlling seizure activity, surgical resection or transaction of the region in which the abnormal electrical activity originates might be necessary. Intermittent electrical vagus nerve stimulation with an implanted pacemaker-like device or focal stimulation with a brain-responsive neurostimulation system can also be used for seizures not controlled by medication. Additionally, persons with seizure disorders should wear a medical alert bracelet and avoid precipitating factors (e.g., sleep deprivation, alcohol, illicit drugs, and excessive stimuli).

Emerging Research: Cannabidiol as a Treatment for Seizure Disorders

Cannabidiol (CBD), a noneuphoric compound found in cannabis, has been found to reduce multiple forms of seizures in children; however, the exact mechanism remains unclear. One leading theory is that CBD acts at the glutamatergic axon terminals, blocking the pro-excitatory actions of an endogenous membrane phospholipid, lysophosphatidylinositol (LPI), at the G-protein-coupled receptor GPR55. However, the role of LPI-GPR55 signaling at inhibitory synapses and seizure activity had not been established. LPI was recently found to briefly increase hippocampal CA3-CA1 (the principal neuron types of the hippocampus) excitatory presynaptic release and evoke synaptic strength in mice while reducing inhibitory postsynaptic strength by decreasing GABAARγ2 and gephyrin puncta (Rosenberg et al., 2023). The LPI effects at excitatory and inhibitory synapses were eliminated by CBD pretreatment and absent GPR55 deletion. In summary, this study confirmed previous findings that suggested CBD blocks the ability of LPI to amplify nerve signals in the hippocampus. The findings also indicated that LPI also weakens signals that counter seizures, further justifying the use of CBD

treatment. These same imbalances are found in autism and **schizophrenia**, so these findings may have broader implications.

Chronic Degenerative Disorders

Chronic degenerative disorders of the nervous system include those conditions in which neurologic function deteriorates over time. These conditions usually result in significant neurologic dysfunction that requires lifelong management. Such disorders are not usually preventable, and often treatment options are limited.

Multiple Sclerosis

Multiple sclerosis (MS) is a debilitating neuroinflammatory disease that involves an abnormal immune-mediated process directed against the CNS, causing progressive and irreversible demyelination of brain, spinal cord, and cranial nerve neurons (**FIGURE 11-43**). This inflammatory damage occurs in diffuse patches throughout the nervous system and slows or stops nerve impulses. As the disease progresses, the brain's cortex atrophies, and scar tissue (plaques) develops throughout the white matter (**FIGURE 11-44**). The progression of this damage varies from person to person.

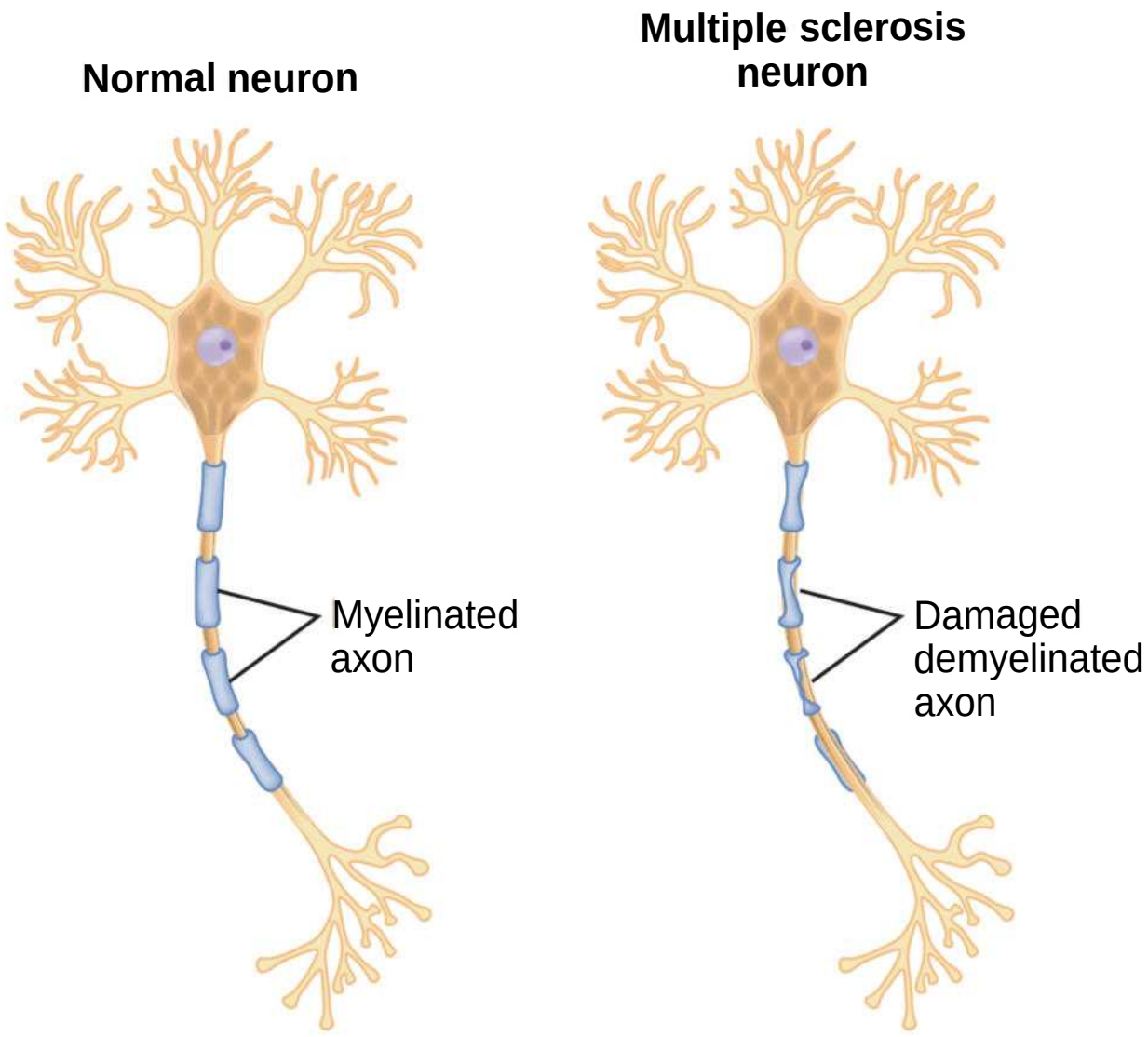


FIGURE 11-43 Multiple sclerosis.

Description

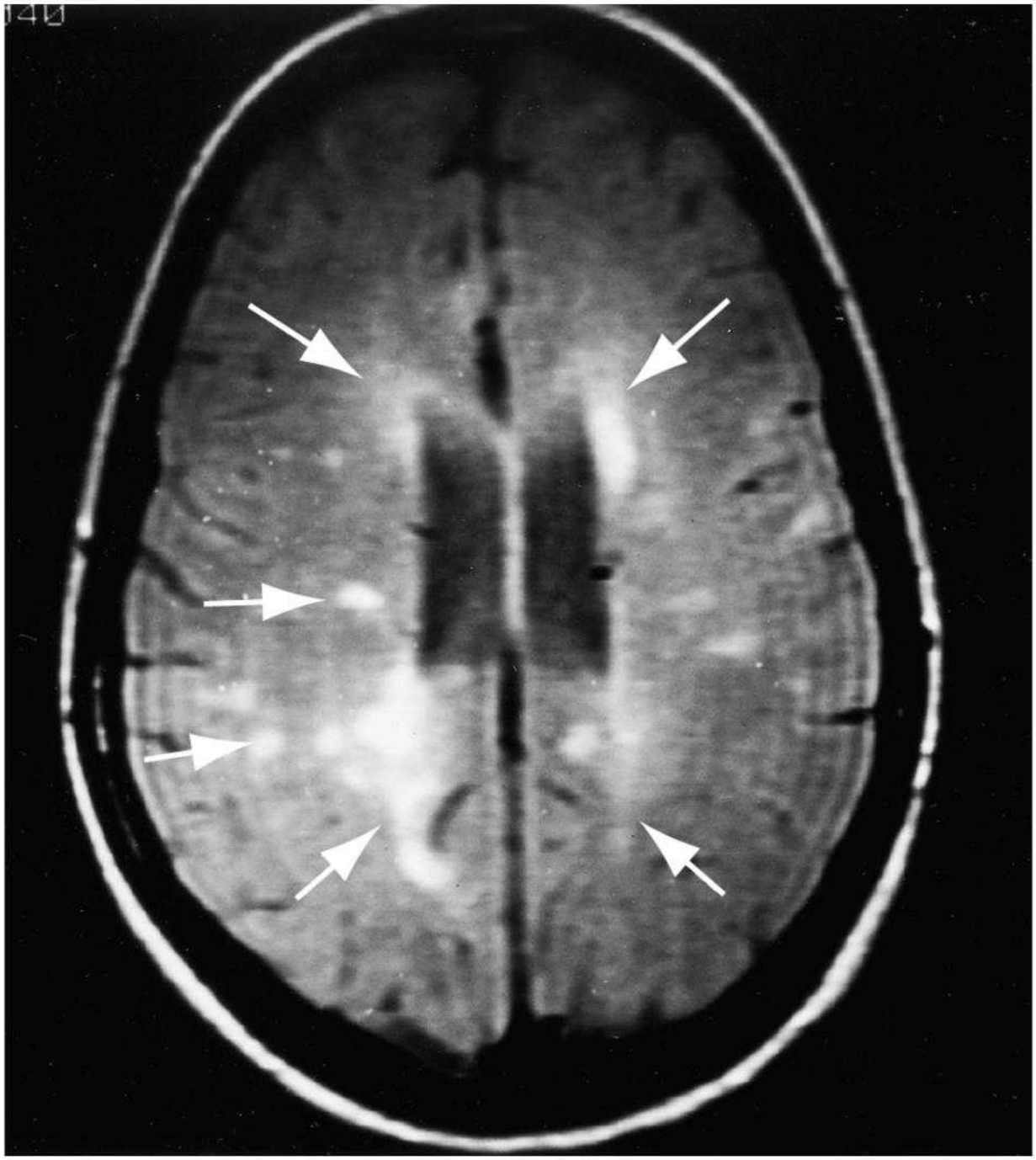


FIGURE 11-44 Multiple sclerosis demonstrated by magnetic resonance imaging (MRI).

Courtesy of Leonard V. Crowley, MD, Century College.

The exact cause of MS is unknown but is thought to involve genetic susceptibility, abnormalities in the immune system, and environmental factors. MS is not an inherited disease; however, the genetic risk may

be inherited. The risk of developing MS is about 1 in 750–1,000 in the general population. In identical twins, the risk increases to 1 in 4 if one twin has the condition. To a lesser degree, the risk increases in individuals with a first-degree relative (i.e., parents, siblings, and children) who has MS. Approximately 200 genes have been identified that each contribute a small amount to the overall risk of developing MS—for example, the presence of human leukocyte antigen allotypes (HLA-DR2). Many of the genes associated with MS are also identified in people with autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis, or systemic lupus erythematosus.

Several viruses and bacteria have been investigated for their possible role in the development of MS. A growing body of evidence suggests that a previous infection with the Epstein-Barr virus increases the risk of developing MS. One theory suggests that a latent infection with the virus becomes activated, triggering a secondary autoimmune response. Both T cells and B cells are involved in the abnormal immune response that occurs with MS. T cells release chemicals in the CNS that cause the inflammation and damage. Additionally, T regulatory cells do not function correctly, so inflammation is not turned off appropriately. Cytotoxic or “killer” T cells also directly attack and destroy nerve cells. The T cells activate B cells, which then produce antibodies and stimulate other proteins, further damaging the CNS.

No single environmental factor has been identified as triggering MS, but several factors are believed to contribute to the overall risk. These factors include living farther away from the equator, low vitamin D levels, cigarette smoking, and obesity. Previous theories about MS’s etiology that have been disproven include environmental allergies, exposure to household pets, exposure to heavy metals (e.g., mercury, lead, or manganese), and consumption of aspartame.

According to the NIH (2022), approximately 400,000 Americans have MS. The prevalence rates are the highest among women and Caucasians. MS is the most common disabling neurologic disease among young adults, often presenting in persons between 20 and 40 years of age.

The course of MS is unpredictable. However, four basic MS disease courses (also called “types” or “phenotypes”) have been defined: clinically isolated syndrome, relapsing–remitting, secondary progressive, and primary progressive (Lublin et al., 2014). Some patients will have a mild course with little to no disability, whereas others will experience a steady deterioration with increasing disability. The clinically isolated syndrome form of MS is a first episode of neurologic symptoms caused by inflammation and demyelination in the CNS. This episode lasts at least 24 hours and is characteristic of MS but does not quite meet the criteria for an MS diagnosis. Relapsing–remitting MS is the most common course and is characterized by clearly defined attacks of new or increasing neurologic symptoms. During remissions, all symptoms disappear or diminish, and there is no apparent progression of the disease during these periods. In contrast, symptoms become active during exacerbations. Most individuals diagnosed with relapsing–remitting MS will eventually transition to a secondary progressive course, in which there is a progressive worsening of neurologic function. Thus, secondary progressive MS follows an initial relapsing–remitting course. Primary progressive MS is characterized by worsening neurologic function from the onset of symptoms, without early relapses or remissions.

Clinical manifestations of MS vary depending on the degree of damage and the specific nerves affected; however, the disease is typically characterized by remissions and exacerbations. Exacerbations may last for days to months and can occur every 1 to 2 years. Infections, vaccines, childbirth, and vitamin D deficiency can trigger or worsen these episodes. Although remissions and exacerbations are common, the disease may continue to progress in some individuals without remissions. Clinical manifestations include the following symptoms:

- Fatigue
- Ataxia
- Muscle spasms

- Paresthesia or abnormal sensation in any area
- Difficulty moving arms or legs
- Weakness in one or more arms or legs
- Unsteady gait
- Lack of coordination
- Tremor in one or more arms or legs
- Constipation and stool leakage
- Urinary frequency, urgency, hesitancy, or incontinence
- Vision issues (e.g., diplopia and vision loss)
- Decreased attention span, poor judgment, and memory loss
- Difficulty reasoning and solving problems
- Dizziness
- Hearing loss
- Sexual dysfunction
- Slurred speech
- Dysphagia

Some patients experience transverse myelitis, a condition caused by inflammation of the spinal cord that causes a loss of cord functioning that can last several hours to several weeks. Transverse myelitis usually begins as a sudden onset of lower back pain, muscle weakness, or paresthesia of the toes and feet, and it can rapidly progress to more severe symptoms, including paralysis. In most cases of transverse myelitis, people recover at least some function within the first 12 weeks after an attack begins. Transverse myelitis is also associated with neuromyelitis optica, a type of optic nerve inflammation. Other complications of MS include epilepsy, paralysis (most often the legs), and depression.

No definitive test is available for MS, which can delay diagnosis of this condition. Instead, other potential conditions must be systematically excluded. Diagnostic procedures for MS may consist of a history, physical examination (including a neurologic assessment), MRI studies (brain and spinal cord), lumbar puncture

with CSF analysis (this often shows high levels of protein, gamma globulin, and lymphocytes), nerve conduction studies, and autoimmune testing (e.g., erythrocyte sedimentation rate, antimyelin titers, and antinuclear antibody). Diagnostic criteria for MS include evidence of neurologic damage in at least two separate areas of the CNS, evidence that the damage occurred at different points in time, and ruling out all other possible causes.

No cure for MS exists, but treatment can often slow its progression. Treatment strategies focus on minimizing symptoms and maximizing quality of life. These strategies include medications, such as corticosteroids (treat exacerbations), interferons (slow damage), plasmapheresis (used for unresponsive exacerbations), disease-modifying agents, and immunomodulators (suppress immune response). Other medications may be used to manage symptoms (e.g., antispasmodics, cholinergics, laxatives, and antidepressants). Additionally, physical and occupational therapy, along with assistive devices (e.g., wheelchairs, walkers, and handrails), can maximize functioning. Coping strategies, support, proper nutrition, and adequate rest can promote and maintain overall health.

Parkinson's Disease

Parkinson's disease is a progressive condition involving the destruction of pigmented neurons in the substantia nigra, locus coeruleus (nucleus in the pons of the brainstem involved in physiologic responses to stress and panic), and other brainstem dopaminergic cells. This destruction results in a lack of dopamine, a chemical messenger that allows for smooth, coordinated muscle movement. When approximately 80% of the dopamine-producing cells are destroyed, movement issues develop—which typically include tremors (involuntary shaking) of the hands and head. These tremors may disappear or decrease when the body part is moved intentionally. Recent evidence suggests that norepinephrine-producing cells may also be destroyed, explaining the issues with blood pressure regulation and fatigue noted in Parkinson's disease. Additionally, Lewy bodies (unusual deposits of the alpha-synuclein protein) have been identified in most cases, although their role in the disease is not

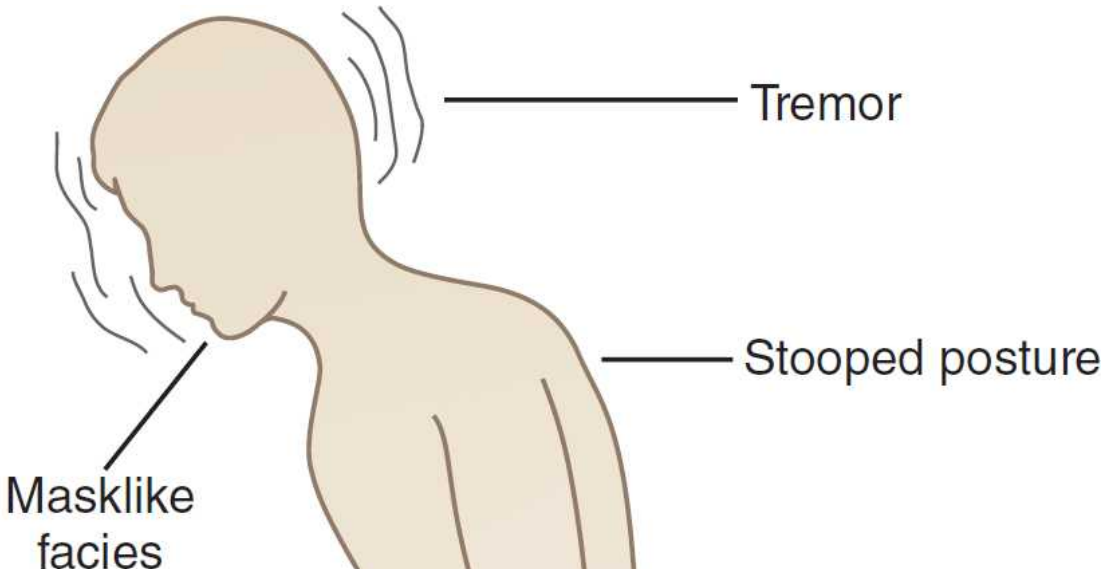
yet understood. Some researchers speculate that these deposits may be part of the body's unsuccessful attempt to protect cells from the toxicity of synuclein accumulation.

The exact cause of Parkinson's disease is unknown. Although some cases are inherited, most cases are sporadic. The same genetic mutations and proteins seen with the inherited cases may also be altered in the sporadic cases as a result of environmental toxins or other factors. Genes definitively linked to Parkinson's disease include those responsible for the following proteins: alpha-synuclein, parkin, DJ-1, PTEN (e.g., *PINK1* gene), and dardarin (e.g., *LRRK2* gene). Evidence suggests that mitochondria may also play a role in development of the disease (NIH, 2023d). Mitochondria produce energy for cells, and mitochondrial abnormalities can result in free radicals (i.e., oxidative stress). Oxidative stress–related changes have been detected in the brains of individuals with Parkinson's disease. Additionally, some genetic mutations that affect mitochondrial function have been identified in these individuals. Environmental causes of Parkinson's disease or parkinsonism symptoms may include viruses, certain drugs (e.g., chlorpromazine, haloperidol, reserpine, and valproate), and toxins (e.g., MPTP). Symptoms in these cases may or may not remain if the environmental cause is removed.

According to the NIH (2023d), approximately 50,000 Americans are diagnosed with Parkinson's disease each year, and it has been estimated that up to 1 million people in the United States are living with the condition. Parkinson's disease is the most common nervous system disorder of the elderly. Genetically driven cases tend to have a younger onset, but the course in such patients is usually less severe than in patients with later-onset, likely sporadic Parkinson's disease. The average age at onset of Parkinson's disease is 60 years. Rarely, parkinsonian symptoms may appear in people before 20 years of age, referred to as juvenile parkinsonism. For unknown reasons, prevalence rates for the disease are twice as high in men as in women. Some evidence suggests that Parkinson's disease is more common in developing countries and in rural areas, but the risks associated with these characteristics are not fully understood.

Several disorders can cause symptoms similar to Parkinson's disease, including multiple system atrophy, dementia with Lewy bodies, progressive supranuclear palsy, and corticobasal degeneration. People with symptoms that resemble Parkinson's disease due to other causes are considered to have parkinsonism. These diseases are sometimes referred to as "Parkinson-plus" because they have symptoms of Parkinson's disease plus additional features. Parkinsonism symptoms can also result from neurologic disorders, such as CVA, TBI, normal-pressure hydrocephalus, Wilson disease, Huntington's disease, Alzheimer's disease, spinocerebellar ataxias, and Creutzfeldt-Jakob disease. Parkinsonism–dementia complex of Guam refers to a disease occurring in the Chamorro populations of Guam and the Mariana Islands. This rapidly progressing form typically causes death within 5 years and may also be accompanied by a motor neuron disease resembling amyotrophic lateral sclerosis (i.e., Lou Gehrig's disease).

Clinical manifestations of Parkinson's disease vary depending on the degree of dopamine deficit. Early symptoms may be subtle and advance gradually. Symptoms typically begin on one side of the body and progress to affect both sides. Even when the symptoms are present on both sides, one side is typically more severely affected than the other. Parkinson's disease manifestations often include the following signs and symptoms (**FIGURE 11-45**):



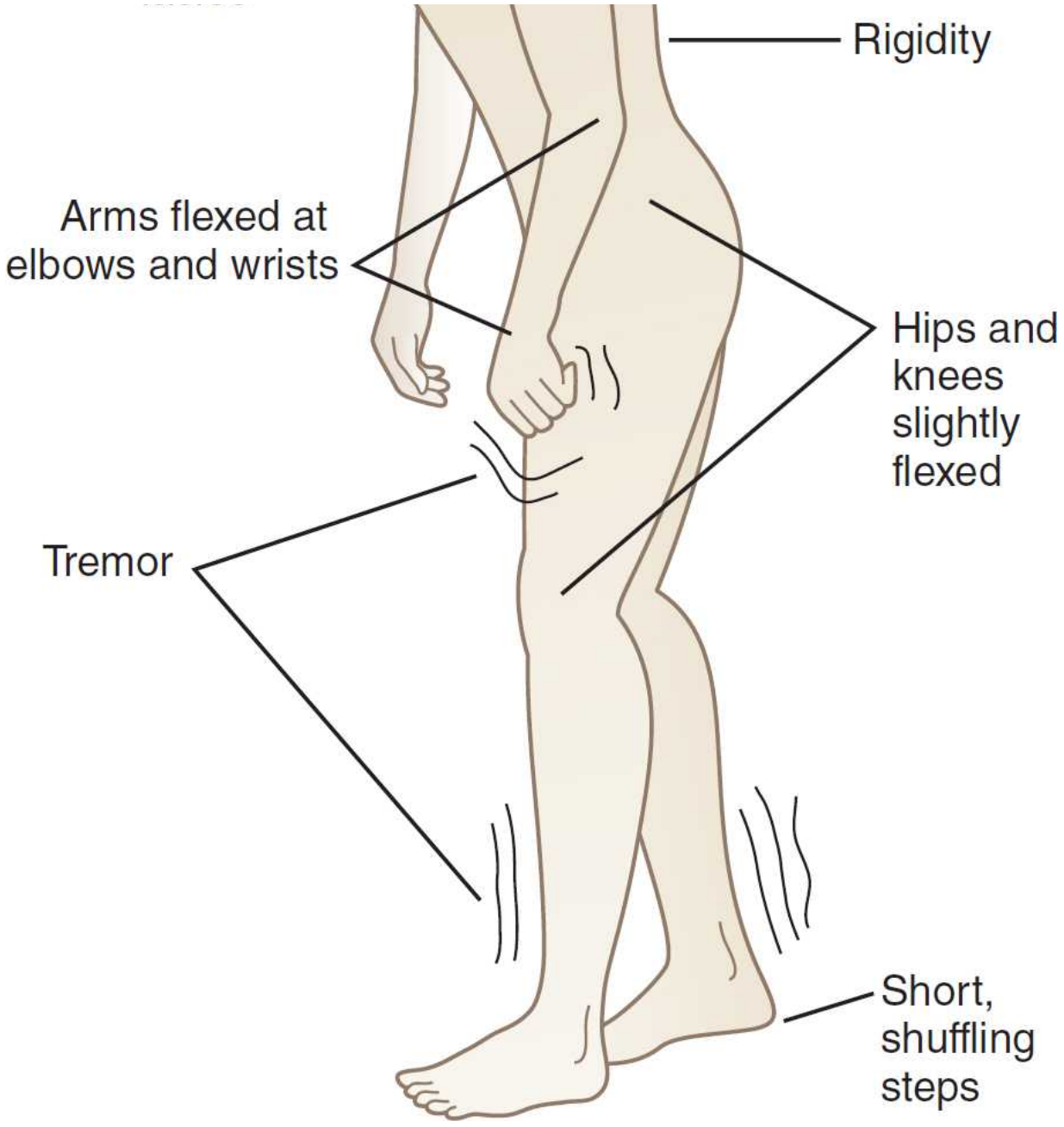


FIGURE 11-45 Clinical presentation of Parkinson's disease.

Description

- Slowing or stopping of automatic movements (e.g., blinking)
- Constipation
- Urinary hesitancy and/or urgency, leading to incontinence
- Dysphagia

- Drooling
- Anosmia (loss of sense of smell)
- Masklike appearance to face
- Myalgia (muscle aches or soreness)
- Muscle cramps and dystonia (sustained muscle contraction that causes forced or twisted position)
- Problems with movement, including the following:
  - Difficulty initiating or continuing movement (e.g., walking or getting out of a chair)
  - Loss of fine hand movements (writing may become small and difficult to read; eating can become more difficult)
  - Shuffling gait
  - Unsteady gait
  - Bradykinesia (slowed movements)
  - Rigid or stiff muscles (often beginning in the legs)
- Tremors
  - Usually occur in the limbs at rest or when the arm or leg is held out
  - Stop during purposeful movement
  - Eventually can be seen in the head, lips, tongue, and feet
  - May be worse when the affected individual is tired, excited, or stressed
  - Finger-thumb rubbing (called “pill-rolling” tremor) may be present
- Slowed, quieter speech with monotone voice
- Stooped position
- Anxiety, stress, and tension
- Emotional changes (e.g., fearful, insecure, irritable, or pessimistic)
- Confusion
- Dementia
- Depression

- Syncope
- Hallucinations
- Memory loss
- Sleep disturbances (e.g., difficulty staying asleep, restless sleep, nightmares, emotional dreams, drowsiness or sudden sleep during the day, and REM behavior disorders [acting out dreams])
- Seborrhea (oily skin)
- Orthostatic hypotension

As the disease progresses, the individual may have difficulty with daily activities. Additionally, patients are at risk for falls, injuries, nutritional deficits, and aspiration. Eventually, most become severely disabled and immobile.

Much like MS, Parkinson's disease does not have a definitive test available for its diagnosis. Diagnostic procedures consist of a history, physical examination (including neurologic assessment), and other tests to rule out other conditions. Early diagnosis can be difficult because the initial symptoms can be subtle and are often dismissed as normal aging effects. Several rating scales are used to stage Parkinson's disease, including the Hoehn and Yahr scale (Goetz et al., 2014; Hoehn & Yahr, 1967) and Unified Parkinson's Disease Rating Scale (Fahn & Elton, 1987; Goetz et al., 2008).

There is no cure for Parkinson's disease; instead, the goal of treatment is to control symptoms. Medications (e.g., levodopa, dopamine agonists, monoamine oxidase B [MAO-B] inhibitors, catechol *O*-methyltransferase [COMT] inhibitors, and anticholinergic agents) can increase the levels of dopamine, but the effects of the medications often diminish over time, requiring increased doses to maintain effectiveness. Medications may eventually reach maximum dosing, at which point symptom control will be lost. Deep brain stimulation with an implanted pacemaker-like device and lesional surgery (e.g., pallidotomy and thalamotomy) may be performed if medications become ineffective or the patient has intolerable adverse effects. However, these procedures are contraindicated in patients with cognitive impairment, dementia, or psychiatric disorders because

they can worsen these conditions. Medications that can cause or worsen symptoms (e.g., antipsychotics) should be avoided. Additionally, physical and occupational therapy, along with assistive devices (e.g., wheelchairs, walkers, and handrails), can maximize functioning. Coping strategies, support, adequate nutrition, physical activity, and sufficient rest can promote and maintain overall health.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS)—also called Lou Gehrig's disease, after the famous baseball player who died from this condition—is a progressive disease that involves damage to the upper motor neurons of the cerebral cortex and lower motor neurons of the brainstem and spinal cord that control voluntary muscle movement (e.g., chewing, walking, and talking) (**FIGURE 11-46**). Sensory neurons, cognitive function, and cranial nerves III, IV, and VI are not affected. The nerves lose their ability to trigger muscle movement, resulting in muscle weakness, disability, paralysis, and death usually as a result of respiratory failure (typically within 3 to 5 years of onset of symptoms). ALS may also increase the risk for dementia. In most cases, the cause of ALS is undetermined, but genetics plays a role in 10% of cases.

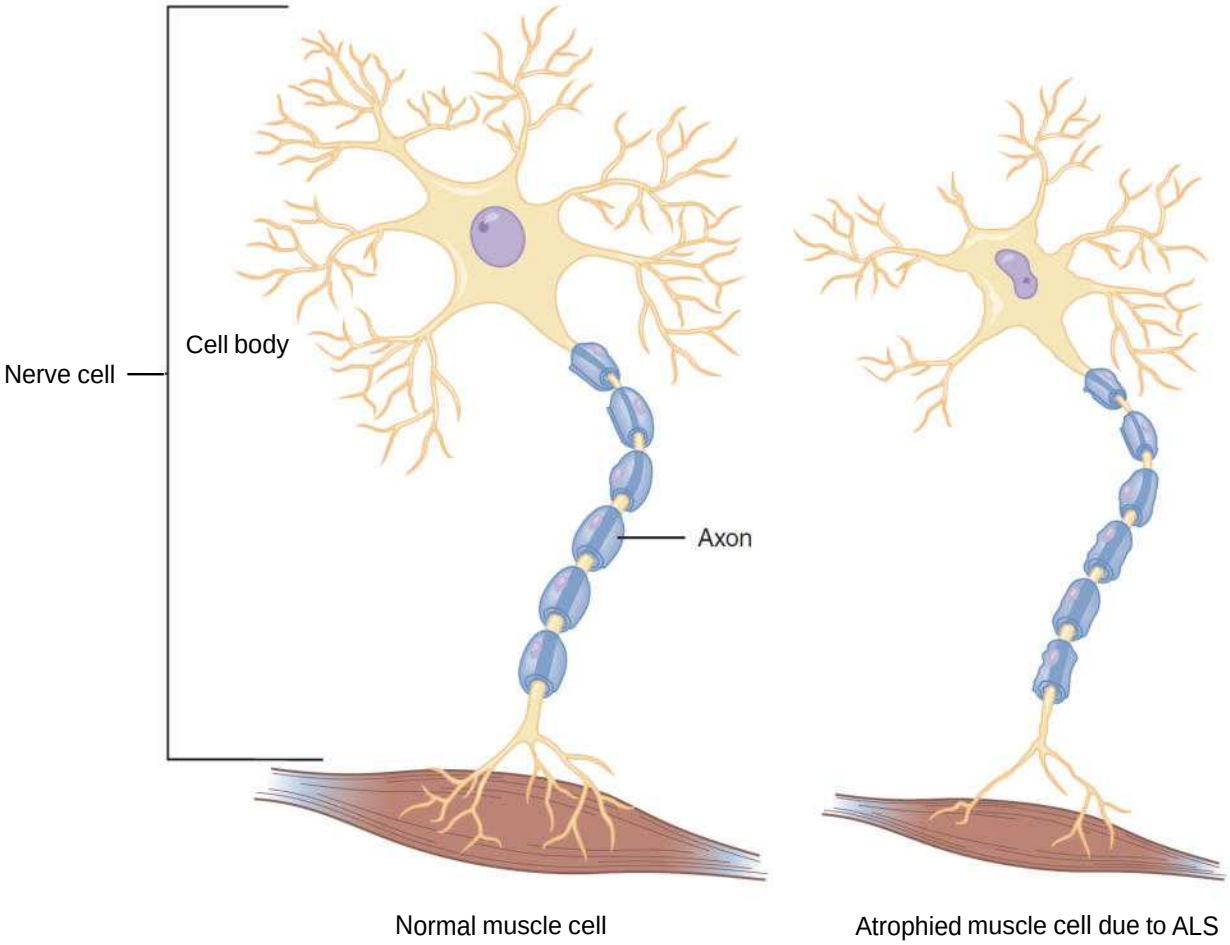


FIGURE 11-46 Effects of amyotrophic lateral sclerosis (ALS).

Description

The exact cause and pathogenetic mechanisms of ALS are unknown, but it is likely a result of both genetic and environmental influences. Most cases (approximately 90%) are considered sporadic; the remaining cases are thought to be inherited. Mutations in more than 20 genes have been linked to familial ALS. Familial ALS can have an autosomal dominant (most common), autosomal recessive, or X-linked pattern of inheritance. One possible cause of ALS is free radical damage. The inherited form of ALS often involves a mutation in a gene responsible for producing a strong antioxidant enzyme that protects cells from damage caused by free radicals. Another possible cause being explored is glutamate's influence. People who have ALS typically have higher than normal levels of

glutamate, a chemical messenger in the brain, in their CSF. Too much glutamate is toxic to some nerve cells. Finally, autoimmune responses are being studied as a possible trigger for ALS. A number of environmental factors (e.g., smoking, high physical fitness, lower body mass index, exposure to toxins, viral infections, TBI, metabolic diseases, and autoimmune conditions) have been hypothesized as playing a role in the development of ALS, but more research is needed to clarify their contributions.

The exact number of cases in the United States is unknown, but the NIH (2023a) estimates that 32,000 Americans have ALS. Although this condition is not necessarily common, it is a public concern because there is no way to prevent the continuous and rapid decline in motor function. In 2010, a National ALS registry was launched to collect, manage, and analyze data about people with ALS. This registry is intended to provide information that will illuminate the scope and epidemiology of the problem as well as guide practice and research.

Although ALS can occur at any age, the symptoms most commonly develop between ages 55 and 75. Men are slightly more likely than women to develop ALS, but this difference diminishes with age. Caucasians and non-Hispanics are most likely to develop ALS in comparison to members of other racial and ethnic groups. For unclear reasons, some evidence suggests that military veterans are up to two times more likely to develop ALS than the general population.

Clinical manifestations of ALS become progressively worse as more motor neurons are damaged. The loss of upper motor neurons results in spastic paralysis and hyperreflexia, and the loss of lower motor neurons results in flaccid paralysis. Patients typically present with random, asymmetric symptoms. Early manifestations of ALS include the following symptoms:

- Footdrop (difficulty lifting the front of the foot and toes)
- Lower extremity weakness
- Hand weakness or clumsiness

- Slurred speech or dysphagia
- Muscle cramps and twitching (i.e., fasciculations) in the upper extremities and the tongue

The disease frequently begins in the upper or lower extremities and then spreads to other parts of the body. As it advances, muscles become progressively weaker, until eventually they are paralyzed. ALS eventually affects chewing, swallowing, speaking, and breathing.

As is true for the other degenerative neurologic disorders, there is no definitive test for ALS. Instead, diagnostic procedures are used to rule out other conditions (e.g., spinal muscular atrophies, polymyositis, dermatomyositis, thyroid disorders, adrenal disorders, electrolyte abnormalities, various infections, and autoimmune-mediated motor neuropathies). These procedures consist of a history, physical examination (including a neurologic assessment), electromyogram (in which an electrode is inserted into the muscles to measure electrical activity), nerve conduction studies, MRI studies (head and spinal cord), lumbar puncture with CSF analysis, muscle biopsy, and laboratory tests (e.g., CBC, electrolytes, creatine kinase, thyroid function tests, antibodies, and venereal disease tests).

ALS has no cure. Treatment strategies focus on slowing the progression and controlling symptoms. For many years, riluzole (Rilutek), a benzothiazole, was the only medication approved by the Food and Drug Administration (FDA) for slowing ALS. This drug appears to slow the disease's progression in some people, perhaps by reducing levels of glutamate. Recently, edaravone (Radicava) was also approved to treat ALS. This neuroprotective drug slows the progression of ALS by removing free radicals. Additionally, stem cell therapy is being explored as a possible treatment. Antispasmodic agents may be given to treat muscle spasms. Physical, occupational, and speech therapy, along with assistive devices (e.g., wheelchairs and braces), can maximize muscle function. Because of risk for aspiration and dysphagia, nutritional support (e.g., high-caloric foods, soft or pureed foods, thickened liquids, and parenteral feedings) becomes critical to maintaining optimal health as the patient's muscles weaken. Likewise, respiratory management (e.g., oxygen

therapy, pulmonary hygiene, respiratory treatments, and mechanical ventilation) becomes necessary as muscle weakness progresses. Coping strategies and support for the patient and caregivers can be helpful as the condition worsens.

Myasthenia Gravis

Myasthenia gravis is an autoimmune condition in which acetylcholine receptors are impaired or destroyed by immunoglobulin G (IgG) autoantibodies. This acetylcholine receptor compromise leads to a disruption of normal communication between the nerve and the muscle at the neuromuscular junction. The result is weakness of the voluntary skeletal muscles because of inadequate nerve stimulation. Muscle weakness typically increases during periods of activity and improves after periods of rest. Muscles that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often—but not always—involved in the disorder. Muscles that control breathing and neck and limb movements may also be affected.

Myasthenia gravis is common (2–3 cases per 10,000 people) and affects all gender, ethnic, and age groups equally. The exact trigger for the autoimmune response is unclear, but the disorder is associated with thymus abnormalities (e.g., hyperplasia and tumors), autoimmune hyperthyroidism, and other autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, and pernicious anemia). Precipitating factors for myasthenia gravis include infection, surgery, and certain medications (e.g., aminoglycosides, quinine, magnesium sulfate, procainamide, calcium-channel blockers, and immune checkpoint inhibitors). Several factors can worsen myasthenia gravis and cause **myasthenic crisis**, including fatigue, illness, stress, extreme heat, alcohol consumption, and certain medications (e.g., beta blockers, calcium-channel blockers, quinine, and some antibiotics). Myasthenic crisis is a potentially life-threatening complication that occurs when the muscles become too weak to maintain adequate ventilation.

Emerging Research: Amyotrophic Lateral Sclerosis

Researchers continue to work to better understand the cellular mechanisms involved in the development and progression of the disease, investigate genetic influences and risk factors, identify biomarkers, and develop new treatments.

Studies are seeking to understand the mechanisms that selectively cause motor neurons to degenerate in ALS with the hopes to stop this process. Evidence suggests that motor neuron death is caused by various cellular defects, including those involved in protein recycling and gene regulation as well as motor neuron structural impairments. Evidence is also growing that indicates that glial support cells and nervous system inflammation cells may also play a prominent role in ALS.

In 2021, a unique form of genetic ALS was identified that affects children as young as 4 years of age. This childhood form is linked to the gene SPTLC1 that plays a role in the body's fat production and may be caused by changes in the way the body metabolizes lipids.

Other studies are (1) exploring how ALS symptoms change over time in people with C9ORF72 mutations; (2) working to identify additional genes that may cause or increase risk for either familial or sporadic ALS; (3) using novel gene editing tools to rapidly identify new genes involved in ALS and other neurodegenerative diseases; (4) determining the potential role of epigenetics in ALS development; (5) developing biomarkers to identify the presence, rate of progression, or effectiveness of treatments; (6) testing new drug-like compounds, gene therapy approaches, antibodies, and cell-based therapies (NIH, 2023a).

Clinical manifestations of myasthenia gravis reflect the muscle weakness that is characteristic of this disease:

- Breathing difficulty
- Dysphagia
- Difficulty climbing stairs, lifting objects, or rising from a seated position
- Dysarthria
- Drooping head
- Facial paralysis or weakness
- Fatigue
- Hoarseness or changing voice
- Eye and vision issues (e.g., diplopia, ptosis, blurred vision, and difficulty maintaining gaze)

Diagnosis of myasthenia gravis is primarily made based on the clinical presentation. Diagnostic procedures consist of a history, physical examination (including a neurologic assessment), edrophonium test (a short-acting anticholinesterase inhibitor called edrophonium is injected, and a sudden, albeit temporary, improvement in muscle strength indicates possible myasthenia gravis), serum antibody levels, nerve conduction study, electromyogram, thymus CT or MRI, and autoimmune testing (e.g., erythrocyte sedimentation rate, acetylcholine receptor antibodies, and antinuclear antibody).

There is no cure for myasthenia gravis, but treatment strategies can be employed to manage its symptoms. Medications used to treat this disorder include anticholinesterase agents, which improve neuromuscular transmission and increase muscle strength. Immunosuppressive drugs may improve muscle strength by suppressing the production of abnormal antibodies. Other therapies include thymectomy, plasmapheresis (removal of abnormal antibodies from the blood), and high doses of immunoglobulins. Additional self-care strategies to maximize health and functioning include proper nutrition, adequate rest, assistive devices, coping strategies, and support.

Huntington's Disease

Huntington's disease (HD), or Huntington **chorea**, is a condition caused by a genetically programmed degeneration of neurons in the brain. According to the NIH (2023b), more than 30,000 Americans have HD. HD is an autosomal dominant disorder (see the *Cellular Function* chapter) involving a defect on chromosome 4. This defect causes a segment of DNA, called a cytosine–adenine–guanine (CAG) repeat, to occur many more times than usual. Normally, this section of DNA is repeated 10–35 times within the DNA coding sequence, but it is repeated 36–120 times in persons with HD. This defect leads to progressive atrophy of the brain, particularly in the corpus stratum in the basal ganglia and the frontal cortex (**FIGURE 11-47**). The ventricles dilate and levels of GABA, substance P, and acetylcholine decrease. As the gene is transmitted from one generation to the next,

the number of repeats (called “CAG repeat expansion”) tends to increase. With a larger number of repeats, the chance of developing symptoms at an earlier age increases. As the disease is transmitted in families, it becomes evident at younger and younger ages. The earlier the HD symptoms appear, the faster the disease progresses. Most cases of HD appear in persons between 30 and 40 years of age, but the disease may appear in childhood or adolescence in a small number of cases. In general, the duration of the illness ranges from 10 to 30 years. The most common causes of death for persons with HD are infection (most often pneumonia), injuries related to a fall, or other complications (e.g., suicide).

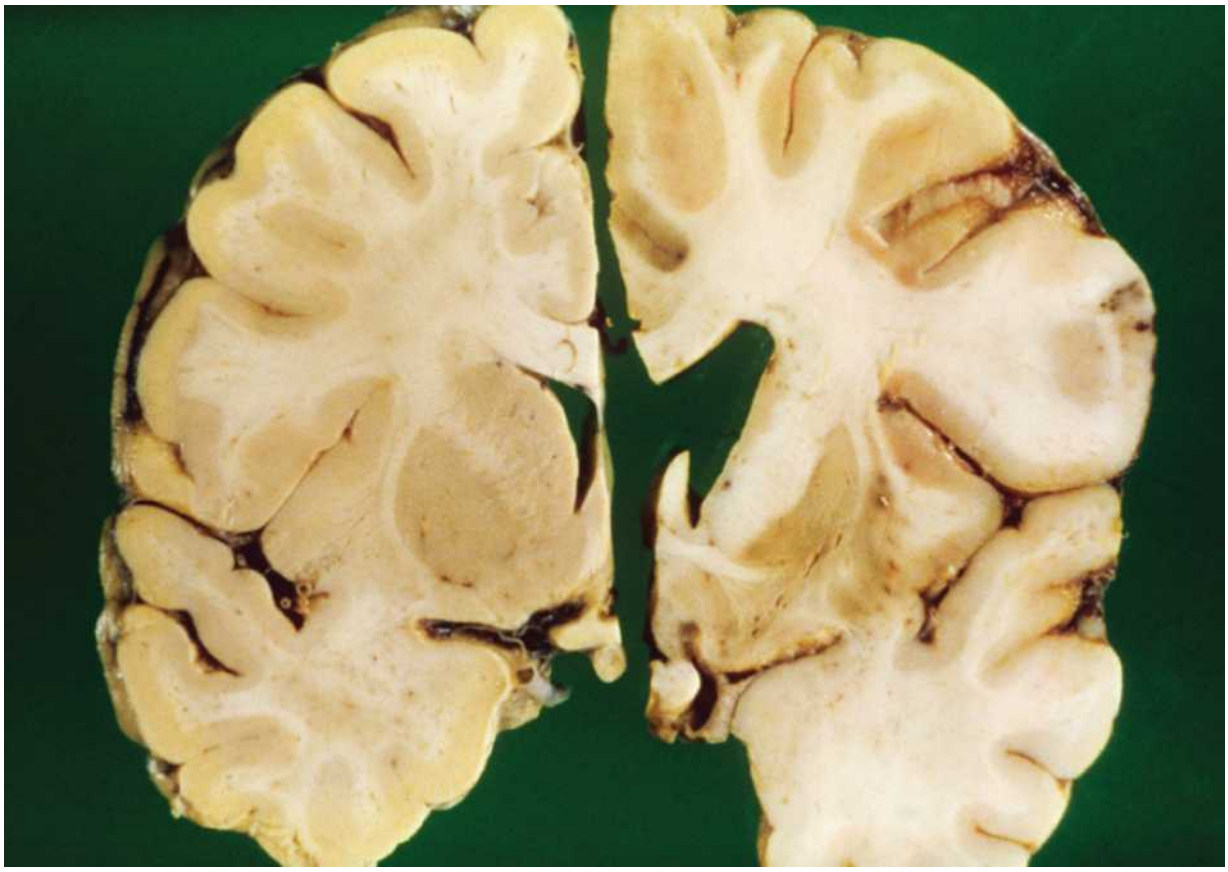


FIGURE 11-47 Neurologic changes of Huntington’s disease.

© Biophoto Associates/Science Source

Clinical manifestations of HD reflect the cerebral atrophy caused by neural degeneration. Initially, manifestations are insidious and vary from person to person. Family members may first notice that the individual experiences mood swings or becomes uncharacteristically irritable, apathetic, passive, depressed, or angry. Other behavioral symptoms may include antisocial behavior, hallucinations, paranoia, and psychosis. These symptoms may lessen as the disease progresses or, in some individuals, may persist and expand to include aggression or severe depression. HD may produce dementia as the individual's judgment, memory, and other cognitive functions become affected. Early signs often include having trouble driving, learning new things, remembering facts, answering questions, or making decisions. Some people may even display changes in handwriting. As the disease progresses, concentration on intellectual tasks becomes increasingly difficult.

In some people, the disease may initially manifest with uncontrolled rapid, jerky movements (chorea, Greek for "dance")—for example, tremors, grimaces, and twitching—in the fingers, feet, face, or trunk. These movements often intensify when the person is anxious. HD can also begin with mild clumsiness, unsteady gait, and rigidity. Some people develop chorea manifestations later, after the disease has progressed. Chorea often creates serious problems with ambulation, increasing the likelihood of falls. As the disease progresses, speech becomes slurred, and other functions (e.g., swallowing, eating, speaking, and walking) continue to decline. Many people with HD remain aware of their environment and can express emotions, but some cannot recognize their family members.

Because of its psychological manifestations, HD is often mistaken for various psychiatric disorders. Diagnostic procedures for this disease include a history, physical examination, psychiatric evaluation, genetic testing for the defective gene (either before or after the onset of symptoms), head CT, head MRI, and head PET.

There is no cure for HD and no treatment to stop its progression. Treatment strategies focus on slowing the progression and managing symptoms to maximize functioning. Tetrabenazine (Xenazine) is the first medication specifically approved by the FDA for the treatment of

HD signs and symptoms. This agent reduces the involuntary jerky movements associated with HD by increasing the amount of dopamine available in the brain. Additionally, deuterabenazine (Austedo) can be given to treat the chorea associated with HD. It depletes the levels of presynaptic dopamine by blocking VMAT2, which is responsible for the uptake of dopamine into synaptic vesicles in monoaminergic neurons and exocytotic release. Tranquilizers and antipsychotic agents can control movements, violent outbursts, and hallucinations. Antidepressant agents can control depression and the obsessive–compulsive rituals that some people with HD develop. Some evidence suggests that coenzyme Q10 may also slow the course of the disease. Physical, occupational, and speech therapy can maximize function. Coping strategies, support, adequate hydration, proper nutrition, and regular exercise for both the patient and caregivers can support optimal health. New therapies are currently under investigation, including stem cell therapy, new medications, and new combinations of existing medications.

Dementia

Dementia refers to a group of conditions in which cortical function is decreased, impairing cognitive skills (e.g., language, logical thinking, judgment, and learning) and motor coordination. Issues with memory are common with dementia and include short-term memory losses as well as confusion of historical events. Behavioral and personality changes may interfere with relationships, work, and activities of daily living. Vascular disease (e.g., atherosclerosis), infections, toxins, and genetic conditions may cause dementia.

Several types of dementias have been identified (TABLE 11-3), each of which has only limited treatment options. Although great strides have been made in recent years, most types of dementias remain poorly understood.

TABLE 11-3	Types of Dementias

Type of Dementia	History	Clinical Manifestations	Pathophysiology
Alzheimer's disease (50–80% of all dementia cases)	Gradual, progressive onset	Memory loss, especially for names and recent events Language deficits Rapid forgetting Impaired visuospatial skills Normal gait and neurologic exam early Later affective disturbances; behavioral symptoms, such as aggression	Generalized atrophy (e.g., medial temporal) Beta-amyloid plaques Neurofibrillary tangles
Vascular (20–30%)	Abrupt or gradual onset	Focal neurologic signs Signs of vascular disease	Strokes Lacunar infarcts White matter lesions Vulnerable to cerebrovascular events
Lewy body (10–25%)	Insidious onset; progressive without fluctuations	Fluctuating cognition Visual hallucinations Neuroleptic sensitivity Shuffling gait Increased tone Tremors Falls	Generalized atrophy Lewy bodies in cortex and midbrain
Frontotemporal (10–15%)	Insidious onset; typically in 50s to 60s; rapid progression	Disinhibition Socially inappropriate behavior Poor judgment Apathy, decreased motivation Poor executive function	Frontal and temporal atrophy Pick cells and Pick bodies in cortex

Description

Data from Psychiatry Report, T. (2014). Types of dementia. *Psych Central*. Retrieved August 19, 2020, from https://pro.psychcentral.com/6467/

Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia among older adults. In AD, healthy brain tissue degenerates and atrophies (**FIGURE 11-48**), causing a steady decline in memory and mental abilities. The exact etiology of AD is unknown, but at least five distinct genetic loci located on chromosomes 1, 12, 14, 19, and 21 influence its initiation and progression.

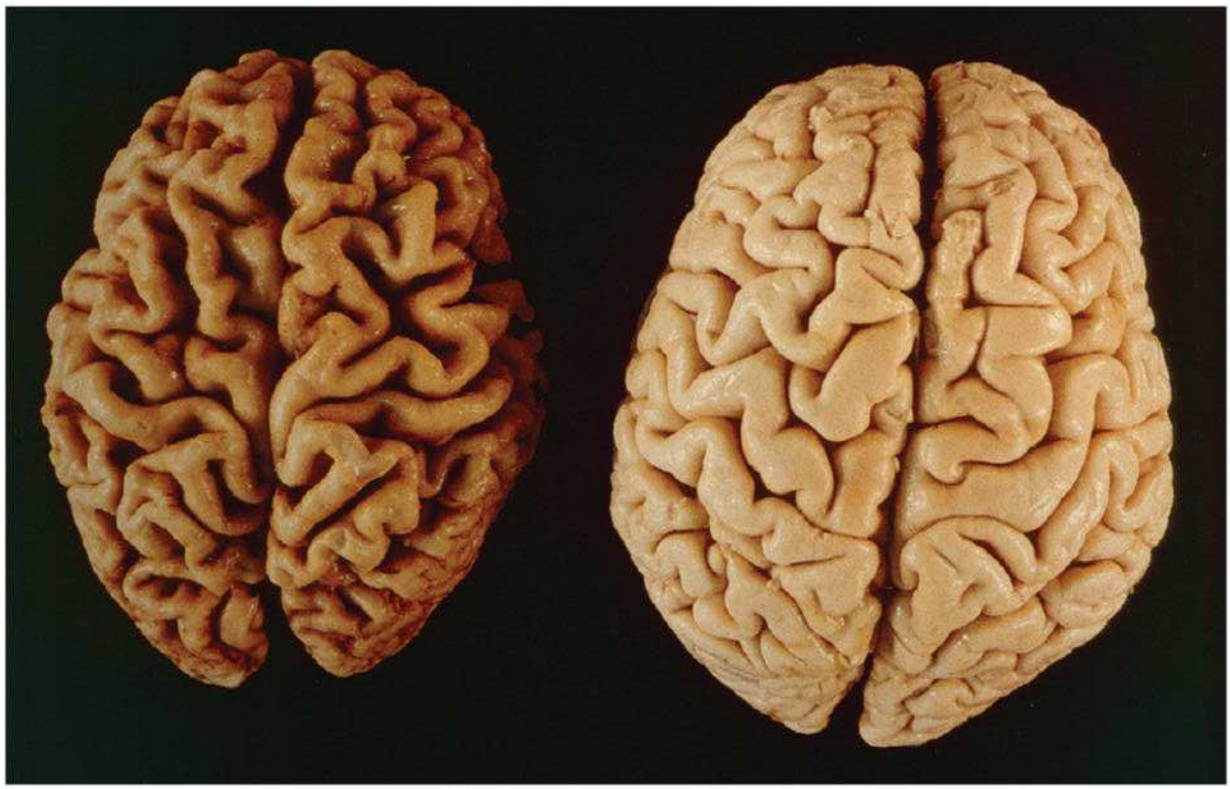


FIGURE 11-48 Brain with Alzheimer's disease (left) compared to a normal brain (right). Courtesy of Michael Hart.

Three pathologic characteristics are associated with AD. First, amyloid plaques, which contain fragments of a protein called "beta-amyloid peptide," mix with a collection of additional proteins, neuron remnants, and other nerve cell pieces. Second, neurofibrillary tangles, found inside neurons, form as abnormal collections of a protein called "tau." Normal tau is required for healthy neurons; however, in AD, tau clumps together. For unclear reasons, neurons fail to function normally and eventually die as a result. In AD, beta amyloid in cerebral amyloid deposits and tau in neurofibrillary tangles are thought to have prion-like, self-replicating properties. In **prion** disease, a normal cell-surface brain protein called "prion protein" becomes misfolded in a pathologic form (i.e., prion). The prion causes other prion proteins to misfold, resulting in increases in the abnormal proteins. Third, connections among the neurons responsible for memory and learning are lost. Neurons cannot survive when their

connections to other neurons are lost. As neurons die throughout the brain, the affected regions begin to atrophy. By the final stage of AD, damage is widespread, and brain tissue has atrophied significantly.

Although AD is not a part of normal aging, the risk for developing this disease does increase with age (onset is usually after 60 years of age). Prevalence rates are higher in women, in part because of their longer life expectancy relative to men. Some evidence suggests that AD rates are higher in those persons with less education, but the precise reason for this association remains unknown. Some researchers theorize that the more the brain is used, the more synapses are created, which provides a greater reserve with aging. Additional risk factors include family history, hypertension, hypercholesterolemia, diabetes mellitus, and history of TBI. According to the CDC (2020a), nearly 6 million Americans have AD, and the number of people living with this disease is projected to nearly triple to 14 million by 2060. AD is the seventh leading cause of death in the United States. Complications such as infections (primarily pneumonia and urinary tract infections), injuries related to falls, malnutrition, dehydration, and decubitus ulcers contribute to the mortality associated with AD.

The onset of AD tends to be insidious. Clinical manifestations may start with mild memory loss and confusion, but AD eventually leads to irreversible mental impairment that destroys a person's ability to remember, reason, learn, and imagine. This course may extend 10–20 years. Clinical manifestations may include the following symptoms:

- Memory loss (e.g., the person might repeat things, forget conversations or appointments, misplace things, and eventually forget the names of family members and everyday objects)
- Problems with abstract thinking (e.g., trouble balancing a checkbook, a problem that progresses to trouble recognizing and dealing with numbers)
- Difficulty finding the right word to express thoughts or even follow conversations
- Difficulty reading and writing

- Disorientation, even in familiar surroundings
- Loss of judgment (e.g., not knowing what to do if food on the stove is burning)
- Difficulty performing familiar tasks (e.g., driving, cooking, bathing, dressing, and eating)
- Personality changes (e.g., mood swings, paranoia, stubbornness, withdrawal, depression, anxiety, and aggression)
- Hallucinations
- Bowel or bladder incontinence

Diagnosis of AD is often difficult and involves ruling out other conditions. Diagnostic procedures consist of a history, physical examination (including a neurologic assessment and mental status evaluation), CSF analysis, head CT, head MRI, and head PET. The National Institute on Aging–Alzheimer's Association diagnostic guidelines (Jack et al., 2011; McKhann et al., 2011) include the following criteria:

- Dementia established clinically and documented by a formal mental status examination
- Deficits in at least two areas of cognition
- Gradual onset and progressive worsening of memory and other cognitive functions
- No disturbances of consciousness
- Onset after age 40, most often after age 65
- No systemic or brain disorder that could account for the progressive memory and cognition deficits
- A low level of beta-amyloid in the CSF
- Beta-amyloid deposits in the brain detected by PET imaging using a radioactive tracer that binds specifically to beta-amyloid plaques
- Elevated levels of tau protein in the CSF
- Decreased cerebral metabolism in the temporoparietal cortex measured using PET with fluorine-18-labeled deoxyglucose

* Local atrophy in the medial, basal, and lateral temporal lobes and the medial parietal cortex detected by MRI

There is no cure for AD, nor are there any therapies that will slow its progression. Medications can, however, manage symptoms and maximize functioning. Cholinesterase inhibitors (e.g., donepezil [Aricept], rivastigmine [Exelon], and galantamine [Razadyne]) can improve neurotransmitter levels in the brain in some cases. Memantine (Namenda) is specifically approved to treat AD; it blocks *N*-methyl-d-aspartic acid receptors, which are glutamate receptors. Memantine may be given in combination with a cholinesterase inhibitor. Other medications may be given to control aggression. Alternative therapies that may improve symptoms include vitamin B_6, vitamin B_{12}, vitamin E, ginkgo, and huperzine A, although the research evidence is mixed regarding their efficacy. Other strategies may include memory aids (e.g., calendars), nutritional support, physical exercise, cognitive activities, safety precautions (e.g., supervision and removing clutter), maintaining a calm environment, and social interactions (e.g., adult day care). Coping strategies and support for both the patient and the caregiver can decrease stress and anxiety.

Vascular Dementia

Vascular dementia is acute or chronic cognitive deterioration due to diffuse or focal cerebral infarction, most often related to cerebrovascular disease. Vascular dementia is the second most common cause of dementia among older people. It typically occurs when multiple small cerebral infarctions, or occasionally hemorrhages, cause sufficient neuronal or axonal loss to impair brain function due to inadequate oxygen and nutrients. This condition is more common among men and usually begins after age 70. Vascular dementia occurs more often in people who have vascular risk factors (e.g., hypertension, diabetes mellitus, dyslipidemia, and smoking) and in those who have had several CVAs. Many people have both vascular dementia and AD.

Clinical manifestations of vascular dementia are similar to the signs and symptoms of other forms of dementia—for example, memory

loss, impaired decision making, slowed thinking, personality and mood changes, and language deficits. However, vascular dementia tends to cause memory loss later and affect decision making earlier as compared to AD. Unlike with other dementias, intellectual declines are typically seen following each infarct episode with vascular dementia. As the disease progresses, focal neurologic deficits often develop, including:

- Exaggerated deep tendon reflexes
- Extensor plantar response
- Gait abnormalities
- Extremity weakness
- Hemiplegias (paralysis of one side of the body)
- Pseudobulbar palsy with pathologic laughing and crying
- Other signs of extrapyramidal dysfunction (e.g., dystonia, akathisia [motor restlessness], parkinsonism, bradykinesia, tremors, and tardive dyskinesia [irregular jerky movements])
- Aphasias (loss of the ability to understand or express speech)

Diagnostic procedures are similar to those tests used in CVA or AD. Treatment includes management of vascular risk factors (e.g., blood pressure control, cholesterol-lowering therapy, blood glucose regulation, proper diet, physical activity, smoking cessation). Managing vascular risk factors may slow the progression and prevent future CVAs. Other strategies include safety (e.g., supervision and removing clutter) and supportive measures (e.g., memory aids, cognitive activities, maintaining a calm environment, social interactions, and caregiver support) similar to those used with other dementias.

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is chronic cognitive deterioration characterized by cellular inclusions called “Lewy bodies” in the cytoplasm of cortical neurons. DLB is the third most common dementia. Lewy bodies are spherical, eosinophilic, neuronal

cytoplasmic inclusions composed of aggregates of alpha-synuclein, a synaptic protein whose function is unclear. For unknown reasons, these Lewy bodies accumulate in individuals with DLB. Neurotransmitter levels and neuronal pathways between the striatum and the neocortex also become abnormal. Lewy bodies also occur with Parkinson's disease and in some patients with AD. There is considerable overlap among the three conditions; however, the relationship among these conditions is unclear.

The onset of DLB typically occurs after the age of 60, with death following, on average, about 8 years after the onset of symptoms. The initial cognitive deterioration associated with DLB is similar to that associated with other dementias. However, DLB frequently manifests with early and prominent deficits in attention, decision making, and visuoperceptual ability. Prominent or persistent impairments tend to occur as the DLB progresses. Extrapyramidal and cognitive symptoms usually begin within 1 year of each other. Fluctuating cognitive function (e.g., periods of being alert, coherent, and oriented, alternating with periods of being confused and unresponsive) is a characteristic feature of this disease. Excessive daytime drowsiness, visual hallucinations, autonomic dysfunction, sleep disturbances, and frequent falls are common.

Diagnostic procedures include a history and physical examination (including a neurologic assessment and mental status evaluation). Other diagnostic tests (e.g., head CT, MRI, and PET) may be performed to rule out other causes of dementia.

No cure is available for DLB. Treatment strategies include supportive measures (e.g., memory aids, cognitive activities, maintaining a calm environment, social interactions, and caregiver support) similar to those used with other dementias. Pharmacologic agents used to manage Parkinson's disease and AD (e.g., cholinesterase inhibitors, memantine, and levodopa) may be administered to patients with DLB as well. Antipsychotics should be avoided due to the severe sensitivity that is present in many patients with DLB. Melatonin may be used to treat sleep disturbances.

Frontotemporal Dementia

Frontotemporal dementia (FTD) refers to an uncommon group of sporadic and hereditary disorders that affect the frontal and temporal lobes. “Pick disease” is a term used to describe pathologic changes in FTD, including severe atrophy, neuronal loss, gliosis, and presence of abnormal neurons (i.e., Pick cells) containing inclusions (i.e., Pick bodies). About half of FTDs are inherited and involve mutations on chromosome 17q21-22. These mutations result in abnormalities of the microtubule-binding tau protein.

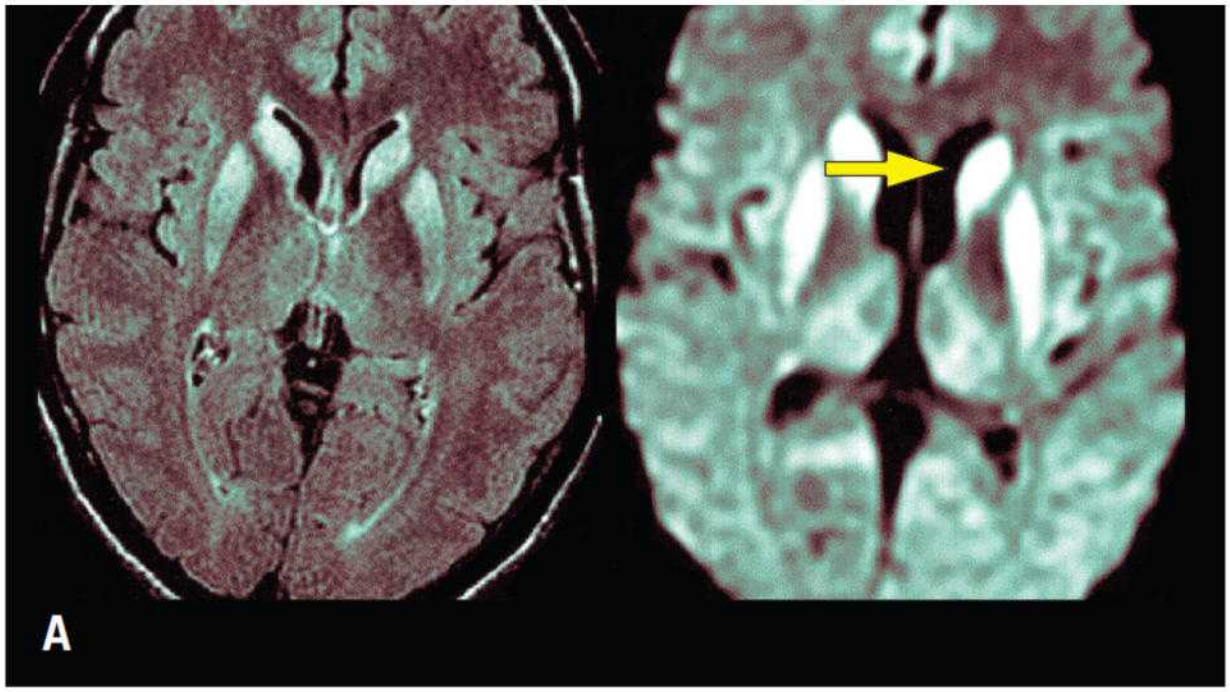
Clinical manifestations of FTD vary from one individual to the next and progressively worsen over years. The most common feature of FTD is extreme changes in behavior and personality. Orientation and motor skills are usually preserved, but abstract thinking, attention, and retrieval of information may be impaired. Other manifestations include language difficulties, movement-related issues (e.g., tremors, rigidity, muscle spasms, poor coordination, dysphagia, muscle weakness, and inappropriate laughing or crying).

Diagnostic procedures include a history, physical examination (including a neurologic assessment and mental status evaluation), and neurologic testing (e.g., CT, MRI, and PET). There is no cure. Instead, treatment strategies include supportive measures (e.g., memory aids, cognitive activities, maintaining a calm environment, social interactions, and caregiver support) similar to those used with other dementias.

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease (CJD) is a rare but rapidly progressive form of dementia caused by an infectious prion. A prion is an abnormal protein particle that causes proteins to fold abnormally, especially in nervous tissue. The prion, which is resistant to common methods of sterilization and disinfection, renders the protein dysfunctional, creating plaques and vacuoles (empty spaces) (**FIGURE 11-49**).




A

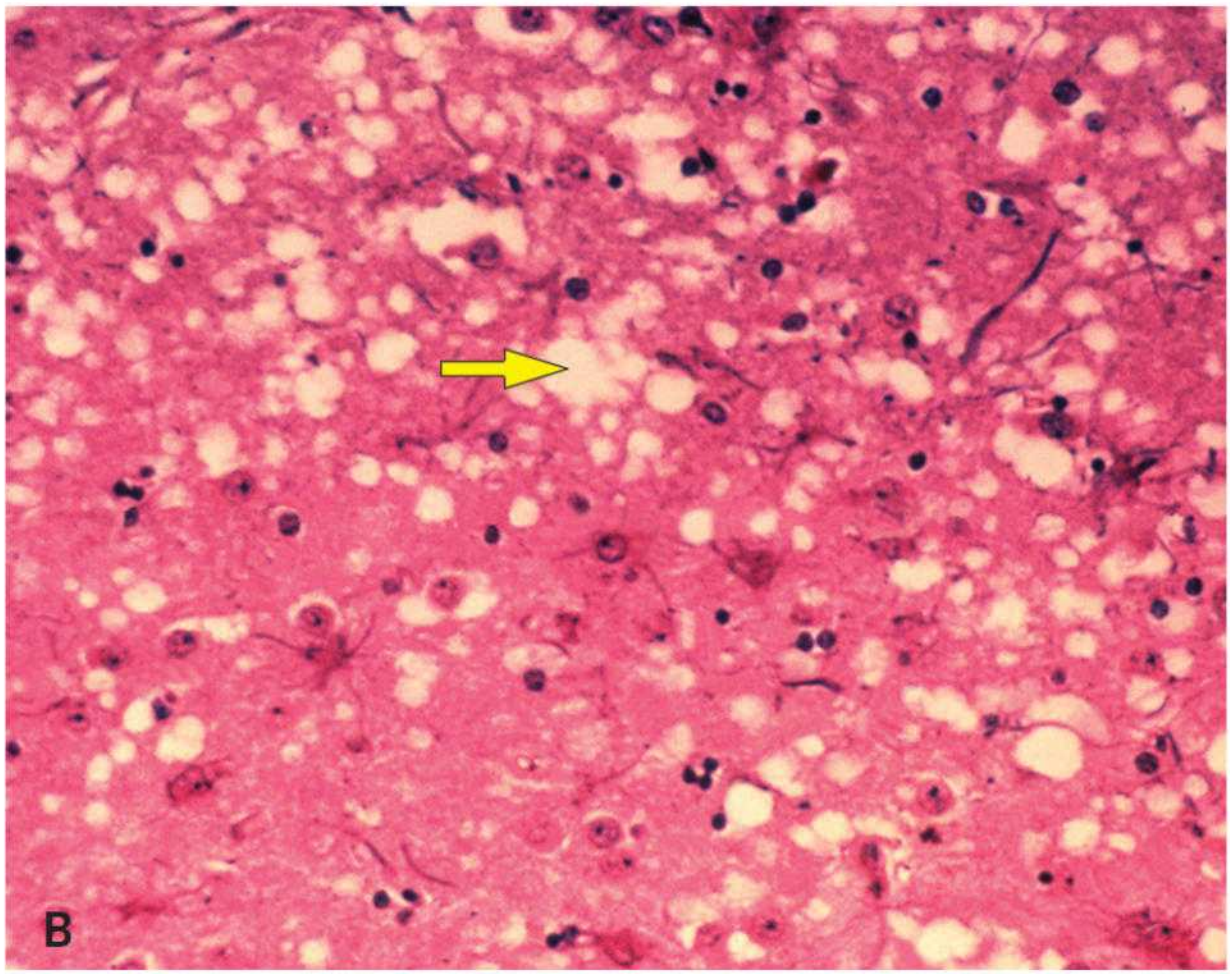

B

FIGURE 11-49 Creutzfeldt-Jakob disease.

A: © BSIP/Science Source; **B:** Courtesy of Dr. Al Jenny/CDC.

CJD may be classified into two types (classic and variant) and three main categories (sporadic, hereditary, and acquired). Although also caused by a prion, classic CJD is not related to bovine spongiform encephalopathy (commonly known as "mad cow disease"). However, the new variant is related to bovine spongiform encephalopathy. The most common form of classic CJD occurs sporadically, caused by the spontaneous transformation of normal prion proteins into abnormal prions. This sporadic disease occurs worldwide, including in the United States, at an annual rate of approximately 1 to 2 case per 1 million people (CDC, 2021). Hereditary CJD is rare and occurs when the gene coding for the abnormal protein is inherited. Finally, acquired CJD is rare (accounting for fewer than 1% of all cases worldwide); it occurs when the individual is exposed to infected materials (e.g., via tissue transplants and ingestion).

CJD has a long incubation period (up to 40 years) after being introduced into the brain. However, it progresses rapidly and is always fatal (usually within 1 year of onset) when the disease becomes activated. Clinical manifestations develop rapidly and include the following symptoms:

- Blurred vision
- Ataxia
- Hallucinations
- Lack of coordination
- Muscle twitching
- Myoclonic jerks or seizures
- Spasticity
- Anxiety
- Personality changes

- Profound confusion or disorientation
- Lethargy
- Speech impairment

Diagnostic procedures for CJD consist of a history, physical examination (including a neurologic assessment and mental status evaluation), EEG, diffusion-weighted MRI of the head, and other tests (e.g., lumbar puncture and serum tests) to rule out other forms of dementia. CJD should be considered in elderly patients with rapidly progressing dementia, especially if accompanied by myoclonus and ataxia.

There is no known cure for CJD, although interleukins and other immunomodulator agents may slow its progression. Custodial care (nonmedical care that assists with activities of daily living) may be required early in the course of the disease. Medications may be needed to control aggressive behaviors, spasticity, pain, and seizure activity. Providing a safe environment, controlling aggressive or agitated behavior, and meeting physiologic needs may require monitoring and assistance in the home or in an institutionalized setting. Family counseling may help in coping with the changes required for home care.

AIDS Dementia Complex

Dementia is common in later stages of acquired immunodeficiency syndrome (AIDS) (see the *Immunity* chapter), a condition referred to as **AIDS dementia complex** or "human immunodeficiency virus (HIV)-associated encephalopathy." When HIV invades the brain tissue, its effects may be exacerbated by the other infections and tumors that are frequently associated with AIDS. Clinical manifestations include encephalitis, behavioral changes, and a gradual decline in cognitive function (e.g., trouble with concentration, memory, and attention). Persons with AIDS dementia complex also show progressive slowing of motor function with a loss of dexterity and coordination. In children with congenital HIV infection, the brain is often affected, causing **intellectual disability** and delayed motor development.

Diagnostic procedures for AIDS dementia complex consist of a history, physical examination (including a neurologic assessment and mental status evaluation), head CT, head MRI, and biopsy. The staging system used to describe the condition's progression ranges from 0 (normal) to 4 (nearly vegetative). When left untreated, AIDS dementia complex can be fatal. Aggressive antiretroviral therapy is the cornerstone of treatment.

Psychiatric Disorders

Psychiatric disorders encompass a number of mental illnesses that alter thinking, mood, and/or behavior. These disorders can also have physical symptoms, most often pain, and can lead to disability, impaired social interaction, and death. Suicide can be a devastating consequence of these conditions. The underlying etiology of most psychiatric disorders is not completely understood, but often genetic and environmental factors are involved.

Many people experience mental health issues from time to time, such as depression following the death of a family member. These issues are typically time-limited, and eventually individuals improve. With psychiatric disorders, in contrast, the symptoms are ongoing and are frequently disturbing to the affected individuals and people around them. A large number of psychiatric disorders have been identified, whose severity ranges from mild to severe.

Psychiatric disorders are common in the United States, with nearly one in five adults living with one of these conditions, equating to about 57.8 million adults in 2021 (NIH, 2023c). They affect persons of all ages, though the highest prevalence is among young adults (18–25 years), with prevalence then decreasing. For unknown reasons, psychiatric disorders are generally more common in women and in those individuals who report being of two or more races, followed by American Indian/Alaskan Native.

Diagnosis of psychiatric disorders is often complex and challenging. Factors such as developmental, cultural, social, and familial norms must be considered to avoid misdiagnosis. The *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (*DSM-5*; American

Psychiatric Association, 2013), is one of the mostly widely used systems for classifying psychiatric disorders and provides standardized diagnostic criteria.

Treatment for these conditions is a long-term endeavor, and each condition has specific strategies. Evidence suggests that only half of people with psychiatric disorders receive treatment. These strategies typically include medications and psychotherapy.

More than 100 psychiatric disorders have been identified. This chapter will provide a brief overview of the more common disorders, focusing on the pathogenesis of these conditions when known.

Neurodevelopmental Disorders

Neurodevelopmental disorders are a group of conditions that usually appear in infancy or childhood. Often manifestations begin when the child starts school. Examples include intellectual disability (or intellectual developmental disorder), global developmental delay, **communication disorders**, **autism spectrum disorder (ASD)**, **attention-deficit/hyperactivity disorder (ADHD)**, and learning disorders.

Learning Point

Neurodivergent and neurodiversity is a growing idea or framework that describes people whose brain differences affect how their brain processes, learns, and behaves from what is often considered "typical." This paradigm suggests that the intrinsic diversity of the human brain are differences but not necessarily pathological. That means they have different strengths and challenges from people considered "neurotypical." The concept first emerged in the late 1990s and grew out of the autism rights movement and the social model of disability, which contends that disabilities partly arise from societal barriers. Neurodivergent individuals may or may not have a developmental disorder. Some conditions that have been considered neurodivergent include ASD, learning disorders, ADHD, dyspraxia, obsessive-compulsive disorder, and Tourette syndrome. The neurodiversity concept remains controversial with opponents arguing it risks downplaying the impact of these conditions and may result in the acceptance of some aspects individuals wish to treat (Happé & Frith, 2020).

Intellectual disability originates prior to the age of 18 and is characterized by limitations in both intellectual functioning and adaptive behaviors (i.e., behaviors involving practical everyday skills, such as self-care, social interaction, and living skills). Such disabilities are often identified through intelligence quotient (IQ) testing; an IQ score less than 70 often indicates a limitation. Intellectual disability can be a result of a multitude of genetic (e.g., Down syndrome) and environmental (e.g., congenital infections and lead exposure) factors. However, a specific genetic mutation has not been identified as causing intellectual disability.

Global developmental delays include developmental disabilities in children younger than the age of 5. Such delays relate to cognition, social functioning, speech, language, and motor skills. This condition is generally considered a temporary diagnosis, applying to children who are too young to take standardized IQ tests. Once children reach the appropriate age for IQ testing, the diagnosis may be changed to intellectual disability. Treatment for intellectual disability and global developmental delays includes individualized early intervention programs and multidisciplinary team support (e.g., speech therapy, physical therapy, and education programs).

Communication disorders affect the ability to use, understand, or detect language and speech. More than 10% of children have a communication disorder. Subtypes of communication disorders include language disorder, speech-sound disorder, childhood-onset fluency disorder (stuttering), and social (pragmatic) communication disorder. Causes of communication disorders vary greatly and may include neurologic (e.g., TBI and ASD), structural (e.g., cleft palate and hearing damage), and environmental (e.g., neglect or abuse) issues. All communication disorders may interfere with academic performance and social relationships. Early diagnosis and treatment are critical to maximize outcomes.

ASD is characterized by persistent deficits in social interactions and communication in multiple life areas as well as restricted and repetitive patterns of behaviors. *DSM-5* specifies that the symptoms of ASD must be present during the early developmental period and that these symptoms must cause significant impairment in important

areas of life, including social and occupational functioning. Autism is known as a "spectrum" disorder because there is a wide variation in the type and severity of symptoms individuals experience. A great deal of controversy exists regarding possible etiologies of this disorder, but evidence is inconclusive regarding the cause. Some cases have occurred with congenital rubella syndrome, cytomegalic inclusion disease, phenylketonuria, tuberous sclerosis complex, and fragile X syndrome. Strong evidence supports a genetic component—most likely involving genes related to two neurotransmitter receptors, serotonin and GABA, and genes involved in CNS structural control. Environmental causes have not been proven, and strong evidence suggests that vaccinations do not cause ASD. Changes in brain structure and function probably underlie much of the ASD etiology. Some children have enlarged ventricles, some have hypoplasia of the cerebellar vermis, and some have abnormalities of the brainstem nuclei. ASD occurs in people of all genders, races, ethnicities, and economic backgrounds; therefore, the American Academy of Pediatrics recommends screening all children (NIH, 2023c). Early diagnosis is critical so that treatment can be initiated as soon as possible. ASD can usually be reliably diagnosed by the age of 2 years. Diagnosis in young children usually includes general developmental screening during routine wellness check-ups and more extensive diagnostics if ASD is suspected. In older children and adolescents, ASD may be first recognized by caregivers or teachers. Diagnosis in adults may be difficult due to symptoms mimicking other mental health disorders (e.g., **anxiety disorder** or ADHD). Treatment is multidisciplinary and generally includes behavior and speech therapy. Physical and occupational therapy may be needed in some cases. Medications may be used to relieve symptoms, including atypical antipsychotics (e.g., risperidone and aripiprazole), antidepressants (usually selective serotonin reuptake inhibitors), and mood stabilizers (e.g., valproate). Dietary interventions (e.g., multivitamins and a gluten-free and casein-free diet) may be helpful, but evidence is inconclusive regarding their effectiveness.

ADHD is characterized by a persistent pattern of hyperactivity–impulsivity and/or inattention that interferes with functioning and

presents itself in two or more settings, such as home, work, school, and social situations. *DSM-5* specifies that several symptoms must have been present prior to the age of 12 and that these symptoms must have a negative impact on social, occupational, or academic functioning. The number of children diagnosed with ADHD increased by 42% between 2003 and 2011, with males being most frequently affected (NIH, 2023c). While sources vary, it is estimated that approximately 6 million children ages 3 to 17 are diagnosed with ADHD. However, some experts suggest that ADHD is overdiagnosed largely because the criteria are applied incorrectly. Nearly 9% of individuals will experience ADHD in their lifetime. ADHD is most frequently diagnosed in childhood but persists into adulthood in approximately half of all cases. It has no known single specific cause but rather is thought to be due to genetic, biochemical, sensorimotor, physiologic, and behavioral factors. Some risk factors include low birth weight, head trauma, iron deficiency, obstructive sleep apnea, lead exposure, and prenatal exposure to alcohol, tobacco, and cocaine. Increasing evidence suggests affected individuals have differences in their dopaminergic and noradrenergic systems, with decreased activity or stimulation in their upper brainstem and frontal-midbrain tracts. Treatment typically includes both behavioral therapy and medications, as behavioral therapy alone is less effective. Stimulant drug therapy (e.g., methylphenidate or dextroamphetamine) is the mainstay of pharmacologic treatment. These medications are thought to act by stimulating the underactive area of the upper brainstem and frontal-midbrain tracts.

Schizophrenia Spectrum and Other Psychotic Disorders

Psychotic disorders cause detachment from reality. People with these conditions experience delusions, hallucinations, and disorganized thinking and speech. **Schizophrenia** is probably the best known of these illnesses. This complex, chronic condition disrupts thought processes, perceptions, emotional responsiveness, behaviors, and social interactions.

Diagnostic criteria for schizophrenia specify that two or more symptoms must be present for a least 1 month. One symptom *must*

be one of the following:

- Delusions (beliefs that conflict with reality)
- Hallucinations (seeing or hearing things that are not present)
- Disorganized speech (words do not follow language rules and may be incoherent)

The second symptom may be one of the following:

- Grossly disorganized or catatonic behavior (confused thinking and bizarre behavior or movements)
- Negative symptoms (inability to initiate plans, speak, express emotions, or feel pleasure)

Diagnosis also requires significant impairments in social or occupational functioning for at least 6 months.

The onset of schizophrenia usually occurs in the late teens to early 20s, with men usually experiencing symptoms earlier. Early symptoms may include poor motivation, difficult relationships, and poor school performance. Evidence suggests that multiple factors likely play a role in causing schizophrenia, including genetics, neurochemistry (e.g., dopamine and glutamate transmission), environmental factors (e.g., urban living, poverty, childhood trauma, neglect, and prenatal infections), and substance misuse. Fewer than 1% of individuals will develop schizophrenia and psychotic disorders; however, these disorders are associated with significant health, social, and economic concerns (NIH, 2023c). Schizophrenia increases the risks for disability, comorbidity (e.g., heart disease, liver disease, and diabetes mellitus), and early mortality (due to comorbidity and suicide).

No cure is available for schizophrenia, but treatments are available that can improve symptoms. Strategies typically include antipsychotic medications, psychotherapy, self-management, education, and social support.

Bipolar and Related Disorders

Bipolar disorder is characterized by dramatic shifts in mood, activity, and energy levels. Affected individuals experience episodes of **mania** (periods of excessive excitement, activity, and energy) alternating with periods of depression. During periods of mania, feelings of distraction, irritability, excessive confidence, and insomnia may also be experienced. People experiencing mania are more prone to engage in risky behavior that may have long-term consequences (e.g., gambling, excessive shopping, substance misuse). During periods of depression, feelings of guilt, fatigue, and irritability may be experienced. People experiencing depression may lose interest in activities they previously enjoyed, experience sleep difficulties, and have suicidal thoughts. Suicide risk in patients with bipolar disorder is approximately 15 times higher than in the general population.

Episodes typically last from a few weeks to 6 months. The term *cycle* is used to refer to the time from the onset of one episode to that of the next. Cycles vary in length among patients, from a few over a lifetime to four episodes a year.

Bipolar disorder affects males and females equally, and more than 4% of adults in the United States will experience this disorder at some time in their lives (NIH, 2023c). The exact etiology of bipolar disorder is unknown, but heredity plays a significant role. Evidence also suggests dysregulation of serotonin and norepinephrine may be a factor. Triggers for exacerbations include sympathomimetics (e.g., cocaine and amphetamines), alcohol, and certain antidepressants (e.g., tricyclics and monoamine oxidase inhibitors).

application to practice

Sonny, a 20-year-old male college student, was brought to the campus clinic by his girlfriend, Abby, because she was concerned about changes in his behaviors that have escalated over the last 6 months. Abby states that Sonny recently stopped going to class because he started hearing voices telling him that his faculty was “out to fail him.” She also stated that he has unpredictable episodes of rage and crying. Sonny’s past medical history is unremarkable, but he does report having a first cousin who “had mental problems.” Both deny any current drug use, but he does often binge drink on the weekend. His physical exam reveals a thin, anxious, disheveled male who randomly stops

talking and tilts his head as though he is listening to something. He does not make eye contact, and his speech is fast and disjointed.

1. Based on these findings, Sonny likely has which of the following:
   a. Attention deficit hyperactivity disorder
   b. Autism spectrum disorder
   c. Schizophrenia
   d. Bipolar disorder
2. Explain the role genetics plays in this suspected diagnosis, if any.
3. Which of the following neurotransmitters, if any, are thought to play a substantial role in the development of this condition?
   a. Dopamine and glutamine
   b. Acetylcholine and serotonin
   c. γ-Aminobutyric acid, or GABA, and norepinephrine
   d. Neurotransmitters do not play a direct role

Treatment usually includes mood stabilizers (e.g., lithium and certain anticonvulsants [e.g., valproate]), second-generation antipsychotics (e.g., aripiprazole, lurasidone, and risperidone), combination pharmacology therapy, psychotherapy, and support. Electroconvulsive therapy and phototherapy may be helpful in some cases.

Depressive Disorders

Depressive disorders are characterized by feelings of extreme sadness and worthlessness, along with reduced interest in previously enjoyable activities. These disorders can occur independently or as a result of other psychiatric and medical conditions. The exact cause of depressive disorders is unknown, but genetic and environmental factors contribute to their development. In fact, heredity is believed to account for about half of cases. Some theories suggest changes in neurotransmitter levels (e.g., cholinergic, catecholaminergic, glutamatergic, and serotonin) and neuroendocrine dysregulation (e.g., hypothalamic–pituitary–adrenal axis, hypothalamic–pituitary–thyroid axis, and growth hormone) may play a role. Additionally, psychosocial factors may be involved, including major life stressors. Examples include **disruptive mood dysregulation disorder**, **major**

depressive disorder, persistent depressive disorder, and premenstrual dysphoric disorder (see the *Reproductive Function* chapter). These conditions vary in terms of their duration, timing, and presumed etiology.

Disruptive mood dysregulation disorder (DMDD) is characterized by extreme anger and irritability in children. Affected children display frequent and intense outbursts of temper. DMDD symptoms are severe and go beyond typical moodiness. Children with DMDD often experience significant difficulties at home, at school, and with peers. These children are also more likely to develop other mood disorders, and DMDD may be seen with ADHD as well. DMDD first appeared in the *DSM-5* in 2013, developed because children were being misdiagnosed with pediatric bipolar disorder. Although the exact incidence is unknown, it is estimated that 2 to 5% of children are affected by DMDD.

Major depressive disorder involves a loss of interest in activities and depressed mood, which leads to significant impairments to function. An estimated 21 million adults in the United States have had at least one major depressive episode (NIH, 2023c). Major depressive disorders are most frequent in females and adults reporting two or more races. Diagnosis requires an individual to have five or more of the following symptoms over the same 2-week period:

- Depressed mood for most or all of the day
- Decreased or lack of interest in activities the individual previously enjoyed
- Significant weight loss or gain, or decreased or increased appetite
- Sleep disturbances (insomnia or hypersomnia)
- Feelings of slowed physical activity or restlessness
- Lack of energy or fatigue that lasts most or all of the day
- Feelings of guilt or worthlessness
- Difficulty thinking or concentrating
- Preoccupation with death or thoughts of suicide

Persistent depressive disorder (i.e., dysthymia) refers to an ongoing chronic depression characterized by other symptoms of depression that are often less severe but last longer. Diagnosis requires experiencing depressed mood on most days for a period of at least 2 years. Persistent depressive disorder typically appears in childhood to early adulthood. Family history of any depressive disorder, traumatic or stressful events, certain personality traits (e.g., negativity, low self-esteem, increased dependency on others), and the presence of other psychiatric disorders increases the risk of developing this disorder.

Anxiety Disorders

Anxiety disorders are characterized by excessive and persistent fear, worry, anxiety, and related behavioral disturbances. Fear refers to an emotional response to a threat, whether real or perceived. Anxiety involves the anticipation of a future threat that may arise. Approximately 31% of adults in the United States will experience an anxiety disorder at some time in their lives (NIH, 2023c), with these disorders occurring most frequently in females. The causes of anxiety disorders are not fully understood, but both psychiatric and medical factors are involved. Anxiety disorders can be directly caused by hyperthyroidism, pheochromocytoma, heart failure, arrhythmias, asthma, and chronic obstructive pulmonary disorders. In addition, use of corticosteroids, cocaine, amphetamines, and caffeine can directly cause anxiety, as can withdrawal from alcohol, sedatives, and some illicit drugs (e.g., opioids). Treatment for anxiety disorders usually includes disease-specific psychotherapy and medications (e.g., benzodiazepines and selective serotonin reuptake inhibitors). Examples of anxiety disorders include **generalized anxiety disorder (GAD)**, **social anxiety disorder**, **panic disorder**, **separation anxiety disorder**, and phobias.

GAD involves excessive worry about everyday events that is present more days than not for at least 6 months. Some stress and worry are normal, but with GAD, the worry becomes so excessive that it interferes with a person's well-being and functions. The cause

of GAD is unknown, but it commonly coexists in people who have alcohol abuse, major depression, and panic disorder.

Social anxiety disorder is a fairly common psychological disorder that involves an irrational fear of being watched or judged. **Panic disorder** is characterized by periods of intense discomfort, anxiety, or fear accompanied by somatic and/or cognitive symptoms (i.e., panic attacks) that often seem to strike for no reason. Because of its unpredictability, people with panic disorder often experience anxiety and preoccupation over the possibility of having another panic attack.

Separation anxiety disorder involves persistent, intense, and developmentally inappropriate fear or anxiety related to being separated from attachment figures (usually the mother). While often associated with younger children, older children and adults can experience it as well. These individuals may avoid moving away from home, going to school, or getting married to remain in close proximity to the attachment figure. When separation is forced, these children are distressfully preoccupied with reunification.

Phobias involve an extreme fear of a specific object or situation. The four main types of specific phobias involve natural events (e.g., thunder, lightning, or tornadoes), medical (e.g., medical procedures, dental procedures, or medical equipment), animals (e.g., dogs, snakes, or bugs), and situations (e.g., small spaces, leaving home, driving, or heights).

Obsessive–Compulsive and Related Disorders

People with **obsessive–compulsive disorder (OCD)** experience repeated and unwanted urges, thoughts, or images (i.e., obsessions) and feel driven to take repeated actions in response to them (i.e., compulsions or rituals). To warrant a diagnosis of OCD, the obsessions and compulsions must be time consuming (taking up to an hour or more each day), cause significant distress or functional impairment, must not be attributable to another medical condition or substance use, and must not be better explained by another psychiatric condition (e.g., GAD). OCD is most frequent in females, and more than 2% of adults in the United States will develop OCD in their lifetime (NIH, 2023c). Other related disorders include hoarding

disorder, body-dysmorphic disorder, excoriation disorder (i.e., skin picking), and hair-pulling disorder (i.e., trichotillomania). Treatment for OCD usually focuses on a combination of cognitive-behavioral therapy and medications (e.g., antidepressants).

Trauma- and Stress-Related Disorders

Trauma- and stress-related disorders develop during or after stressful or traumatic life events. Examples include **acute stress disorder**, **adjustment disorders**, **posttraumatic stress disorder (PTSD)**, and **reactive attachment disorder**.

Acute stress disorder is characterized by the emergence of severe anxiety for up to 1 month after exposure to a traumatic event (e.g., natural disaster, war, an accident, or witnessing a death) and lasting a minimum of 3 days. As a result, the individual may experience dissociative symptoms (e.g., sense of altered reality, inability to recall important details, and vivid flashbacks). Other symptoms can include reduced emotional responsiveness, distressing memories of the trauma, and difficulty experiencing positive emotions.

Adjustment disorder is a common condition that can occur as a response to a sudden life change, such as divorce, job loss, end of a close relationship, a move, or some other loss or disappointment. This disorder, which can affect both children and adults, is characterized by anxiety, irritability, depressed mood, worry, anger, hopelessness, and feelings of isolation.

PTSD can develop after an individual has experienced exposure to actual or threatened death, serious injury, or sexual violence. Symptoms typically include episodes of intrusive recollections of the event, avoiding reminders of the events, feeling on edge, having negative thoughts, nightmares, flashbacks, anger outbursts, difficulty concentrating, exaggerated startle response, and difficulty remembering aspects of the events. Recollections last longer than 1 month and begin within 6 months of the event. Approximately half of all adults in the United States will experience at least one traumatic event in their lives, but most do not develop PTSD. Nearly 7% of adults will experience PTSD in their lifetime. The prevalence of PTSD is significantly higher in females.

Reactive attachment disorder can occur when children do not form normal healthy relationships and attachments with adult caregivers during the first few years of childhood. Symptoms may include being withdrawn from adult caregivers as well as social and emotional disturbances that result from patterns of insufficient care and neglect.

Dissociative Disorders

Dissociative disorders are psychological conditions in which a person's sense of self is disrupted. This disruption involves aspects of the consciousness, including identity and memory. Everyone occasionally experiences failure of normal automatic integration of memories, perceptions, identity, and consciousness; however, individuals with dissociative disorders may not be able to recall behaviors occupying minutes to weeks. The exact etiology is not known, but dissociative disorders are often precipitated by trauma. Examples include **dissociative identity disorder**, **dissociative amnesia**, and **depersonalization/derealization disorder**.

Dissociative identity disorder, formerly known as multiple personality disorder, involves the presence of two or more different identities or personalities that alternate control over the person's consciousness. Each personality has its own way of perceiving and interacting with the environment, but how overt the different identities are varies. The separation of the identities usually leads to asymmetric amnesia—that is, what is known by one identity may or may not be known by another. Some identities seem to know and interact with the others in an elaborate inner world, and some identities interact more than others. Dissociative identity disorder causes changes in behavior, memory, perceptions, emotional response, and consciousness.

Dissociative amnesia is characterized by a temporary memory loss as a result of dissociation. The memory loss may last for a brief period or many years and is often the result of psychological trauma. More than just having simple forgetfulness, individuals who experience this disorder may remember some details about events but have no recall of other details around a particular time period. Rarely,

dissociative amnesia is accompanied by purposeful travel or wandering (i.e., fugue). Memories may return quickly, or memory loss may persist for an extended time.

Depersonalization/derealization disorder involves a persistent or recurrent sense of being outside of one's own body (i.e., depersonalization) and being disconnected from reality (i.e., derealization). People with this disorder often feel a sense of unreality and involuntary disconnection from their own memories, feelings, and consciousness.

Somatic Symptom and Related Disorders

Somatic disorders, formerly called "somatoform disorders," comprise conditions that can cause distressing and incapacitating physical symptoms with no clear medical causes. The word somatic means "of the body." The focus of these conditions is not the fact that there is no medical explanation for the physical symptoms; rather, emphasis is placed on the abnormal thoughts, feelings, and behaviors that occur in response to these symptoms. Examples include **somatic symptom disorder** (previously known as "hypochondriasis"), **illness anxiety disorder**, **conversion disorder**, and **factitious disorder**.

Somatic symptom disorder involves a preoccupation with physical symptoms that make it difficult to function normally. This preoccupation results in emotional distress and difficulty coping. It is important to note that the somatic symptoms do not indicate that the individual is faking the physical pain, fatigue, or other symptoms. The symptoms are not the significant cause of the disruption, but rather the extreme reaction and resulting behaviors create the difficulties.

Illness anxiety disorder is a psychological condition characterized by excessive concern about having an undiagnosed medical issue. Affected individuals experience intense worry that bodily functions and sensations are a result of a serious disease and are not reassured when medical tests are negative. Their preoccupation with illness causes significant anxiety and distress as well as leads to changes in behavior (e.g., seeking medical attention or avoiding unhealthy situations).

Conversion disorder is characterized by motor or sensory symptoms that lack a compatible neurologic or medical explanation. For example, individuals may present with impaired coordination, weakness, paralysis, numbness, seizures, unresponsiveness, blindness, diplopia, deafness, aphonia, dysphagia, or urinary retention. Individuals may have a single episode, sporadic repeated episodes, or chronic symptoms. Episodes are typically brief. Many cases of conversion disorder follow a real physical injury or stressful event, which then results in a psychological and emotional response.

Factitious disorder refers to falsification of physical or psychologic symptoms in oneself or others without an obvious external incentive. **Munchausen syndrome** is a severe form that occurs when people pretend to have an illness to attract attention.

Substance-Related and Addictive Disorders

Substance-related disorder and **addictive disorders** are often associated with excessive use or misuse of alcohol, opioids (e.g., oxycodone and morphine), illicit drugs (e.g., methamphetamine), hallucinogens, and other types of drugs (e.g., inhalants and excessive nicotine). This group also includes gambling disorder. Individuals with these disorders usually progress from experimentation to occasional use and then to heavy use. This progression is complex and only partially understood. The process depends on the interaction between the specific drug (e.g., route of administration, rate at which the drug crosses the blood–brain barrier and stimulates the reward pathway, time of onset, and ability to induce tolerance and/or withdrawal symptoms), the user (e.g., physical qualities, personal characteristics, circumstances, and coexisting disorders), and the setting (e.g., cultural and social factors). Substance-related disorders are also associated with intoxication, withdrawal, psychosis, anxiety, and delirium.

Feeding and Eating Disorders

Feeding and eating disorders are characterized by obsessive concerns with weight and disruptive eating patterns that negatively impact physical and mental health. These serious disorders, which

are sometimes fatal, occur more frequently in females. Examples include **anorexia nervosa**, **bulimia nervosa**, **rumination disorder**, **pica**, and **binge-eating disorder**.

Anorexia nervosa involves restricted food consumption that leads to weight loss and an extremely low body weight. Affected individuals experience a preoccupation and fear of gaining weight as well as a distorted view of their own appearance and behavior.

Bulimia nervosa is characterized by bingeing (consuming large amounts of food) and then taking extreme steps to compensate for these binges. These compensatory behaviors may include self-induced vomiting, laxative or diuretic abuse, fasting, and excessive exercise.

Rumination disorder involves recurrent regurgitation of previously chewed or swallowed food so as to either spit it out or re-swallow it. This disorder is often present in children and adults who also have a developmental delay or intellectual disability. Additional issues associated with rumination disorder include dental decay, esophageal ulcers, and malnutrition.

Pica describes persistent cravings and consumption of nonfood substances, such as dirt, paint, or soap. This disorder most commonly affects children and individuals with developmental disabilities, but it is not diagnosed in children younger than the age of 2 years because of developmental norms.

Binge-eating disorders are the most common type of eating disorder; they are characterized by the individual consuming an unusually large amount of food over the course of a few hours. These individuals not only overeat but also feel as if they have no control over their eating. The binge-eating episodes are followed by inappropriate compensatory behaviors and are sometimes triggered by emotions, boredom, or stressful events.

Gender Dysphoria

Gender dysphoria stems from the distress that can occur when a person desires to be a different gender. This distress can result in anxiety, depression, and irritability. For most people, their biological sex, gender identity, and gender role are congruent. However,

individuals with gender dysphoria experience some incongruity between their birth sex and their gender identity (i.e., transgender) and often have an intense desire to live as a gender different from the sex assigned at birth. Both biological and societal factors influence gender identity, but evidence suggests transgender identity has a heritable component. **Transsexualism** refers to the most extreme form of gender dysphoria. Rarely, transsexualism is associated with genital ambiguity or a genetic abnormality (e.g., Turner syndrome and Klinefelter syndrome).

Gender dysphoria often becomes apparent by age 2. Manifestations may include cross-dressing, insistence that they are the other sex, preferring to participate in stereotypical activities of the other sex (e.g., a girl may stand to urinate, or boys may play with dolls), and negative feelings toward their genitals. Diagnostic criteria differ among children, adolescents, and adults.

Disruptive, Impulse-Control, and Conduct Disorders

Disruptive, impulse-control, and **conduct disorders** encompass conditions in which the individual has difficulty with emotional and behavioral self-control. These emotions and behaviors often involve violating the rights of others (e.g., destroying property or physical aggression); conflict with societal norms, authority figures, and laws; and harm to oneself or others. Examples include **kleptomania**, **pyromania**, **intermittent explosive disorder**, conduct disorder, and **oppositional defiant disorder**.

With **kleptomania**, the individual is unable to control the urge to steal. Often individuals will steal items that they do not need or have no real monetary value. Individuals with kleptomania experience escalating tension prior to committing a theft and feel relief and gratification after the act is complete.

Pyromania involves a fascination with fire that results in acts of fire-starting, which endanger both the affected individual and others. **Intermittent explosive disorder** is characterized by brief outbursts of anger and violence that are disproportionate to the situation (e.g., everyday annoyances or disappointments).

Conduct disorder is diagnosed in children and adolescents younger than age 18 who regularly violate social norms and the rights of others. These children may display aggression toward people and animals, destroy property, steal and deceive, and violate other rules and laws. These behaviors can significantly impact academic, work, and social functioning. The etiology of conduct disorder involves a complex interaction of genetic and environmental factors. Parents of adolescents with conduct disorder often have engaged in substance misuse and antisocial behaviors. Frequently, these parents have been diagnosed with ADHD, mood disorders, schizophrenia, or **antisocial personality disorder**. However, conduct disorders can also occur in children from high-functioning, healthy families.

Oppositional defiant disorder begins prior to the age of 18 and is characterized by a recurrent or persistent pattern of defiance, irritability, anger, aggression, and vindictiveness. While occasional defiance is common in children, children with oppositional defiant disorder refuse to comply with adult requests nearly all the time and engage in behaviors to deliberately annoy others. The etiology is unknown, but this disorder is most common among children from families in which adults engage in loud, argumentative, interpersonal conflicts.

Personality Disorders

A **personality disorder** involves a persistent pattern of emotional instability and unhealthy behaviors that seriously disrupt daily living and relationships. More than 9% of adults in the United States have a personality disorder (NIH, 2023c). Such disorders usually present in late adolescence or early adulthood. Examples include antisocial, avoidant, borderline, histrionic, narcissistic, obsessive–compulsive, paranoid, schizoid, and **schizotypal personality disorders**.

Antisocial personality disorder is characterized by a long-standing disregard for rules, social norms, the rights of others, and consequences. Individuals typically begin displaying symptoms during childhood, have difficulty feeling empathy for others, and lack remorse for destructive behaviors. Comorbidities are common with antisocial personality disorder, including substance use disorder,

impulse control disorder, ADHD, or **borderline personality disorder**. Genetic and environmental factors (e.g., childhood abuse) contribute to the development of antisocial personality disorder. Abnormal serotonin transporter function is a possible mechanism.

Avoidant personality disorder involves severe social inhibition and sensitivity to rejection, criticism, or humiliation. These feelings of insecurity result in significant issues with daily functioning.

Borderline personality disorder is associated with symptoms including emotional instability, unstable and intense interpersonal relationships, unstable self-image, and impulsive behaviors. Childhood stresses or trauma may contribute to the development of this disorder in genetically vulnerable individuals.

Histrionic personality disorder is characterized by pervasive patterns of extreme emotionality and attention-seeking behaviors. Individuals with this disorder feel uncomfortable when they are not the center of attention, have rapidly changing emotions, and may engage in socially inappropriate behaviors designed to attract attention from others. They often use their physical appearance in inappropriately seductive or provocative ways to gain the attention of others.

Narcissistic personality disorder refers to an enduring pattern of exaggerated self-image (i.e., grandiosity), self-centeredness, and low empathy. Individuals tend to be more focused on themselves than on others. Little is known about the biological factors that contribute to narcissistic personality disorder, but it appears both to have a heritable component and to be affected by childhood environmental influences (e.g., overly critical or excessively praising, admiring, or indulging behaviors).

Obsessive–compulsive personality disorder is not the same as OCD. Obsessive–compulsive personality disorder is a pervasive pattern of preoccupation with orderliness, perfectionism, inflexibility, and mental and interpersonal control. Affected individuals are excessively dedicated to work and productivity but not out of financial necessity. As a result, leisure activities and relationships are neglected.

Paranoid personality disorder is characterized by a distrust of others, even family, friends, and romantic partners. Individuals

perceive others' intentions as malevolent, even without any evidence or justification.

Schizotypal personality disorder is characterized by symptoms of feeling detached from social relationships. Individuals are often directed inward, are indifferent to relationships, and lack emotional expression. Schizotypal personality disorder involves eccentricities in speech, behaviors, appearance, and thoughts. Individuals may experience odd beliefs, "magical thinking," or difficulty forming relationships. The etiology of schizotypal personality disorder is thought to be primarily biological, similar to those characteristics associated with schizophrenia.

Paraphilic Disorders

Paraphilic disorders include sexual-interest conditions. These disorders are characterized by recurrent, intense, sexually arousing fantasies, urges, or behaviors that are distressing or disabling. Such behaviors may involve inanimate objects, children or nonconsenting adults, or suffering or humiliation of oneself or a partner. Examples include **sexual sadism disorder**, **voyeuristic disorder**, and **pedophilic disorder**.

Sexual sadism disorder refers to the infliction of physical or psychological suffering on another person to stimulate sexual excitement and orgasm. The infliction of suffering causes significant distress or functional impairment or is acted on with a nonconsenting person.

Voyeuristic disorder refers to the achievement of sexual arousal by observing nonconsenting people who are naked, disrobing, or engaging in sexual activity. The behaviors associated voyeuristic urges or impulses cause significant distress or functional impairment.

Pedophilic disorder is characterized by recurrent, intense sexual arousal involving prepubescent or young adolescents.

Sleep Disorders

Sleep disorders involve interruptions in sleep patterns that lead to distress and affect daytime functioning. These disorders can occur independently or as a result of other psychiatric and medical

conditions. In the latter case, the sleep disorder warrants independent clinical attention apart from those conditions. Examples include narcolepsy, **insomnia disorder**, hypersomnolence, and **parasomnias**.

application to practice

Now that we have discussed conditions of the nervous system, let's put that knowledge into practice. While working in the clinic, you encounter the following patients. Which patient would be at greatest risk for developing Alzheimer's disease (AD)?

- A young Caucasian woman with rheumatic heart disease
- A middle-aged African American woman with a history of several head injuries
- A middle-aged Hispanic man with diabetes mellitus
- An older Caucasian man who consumes a diet high in red meat

When determining who is at greatest risk, remember to start by counting risk factors, with the patient with the most risk factors being the "winner." First, consider the young woman. Ethnicity does not increase risk for AD. Women are at greater risk of AD, but rheumatic heart disease does not further increase this risk. Thus, this patient has one risk factor. Now consider the middle-aged African American woman. She is reaching the age at which AD is more likely to appear, and TBIs increase the risk for developing AD. Including gender, this patient has three risk factors. Moving on to the middle-aged Hispanic man, his risk factors include age and diabetes. Finally, consider the older Caucasian man. Red meat is high in cholesterol, which can be a contributing factor in AD development. Including his age, he has two risk factors. After considering all the patients, the middle-aged African American woman is at the highest risk for AD owing to her three risk factors.

Narcolepsy refers to a condition in which people experience an irrepressible need to sleep. Individuals may experience a sudden loss of muscle tone.

Insomnia disorder involves being unable to obtain sufficient sleep to feel rested. Everyone experiences sleeping difficulties and interruptions at some point, but insomnia is considered a disorder when it is accompanied by significant distress or impairment over time.

Hypersomnolence disorder is characterized by excessive sleepiness despite an adequate sleep period. Individuals may fall asleep during the day at inappropriate times (e.g., at work or school).

Parasomnia refers to disorders that feature abnormal behaviors that occur during sleep. These behaviors include sleepwalking, sleep terrors, sleep talking, and sleep eating.

Cancers of the Nervous System

Nervous system malignancies can originate in the brain or spinal cord, or they may spread there from other sites. Regardless of the etiology, these cancers can result in significant neurologic dysfunction and death. Typical cancer diagnosis, staging, and treatments are utilized in such cases (see the *Cellular Function* chapter).

Brain Tumors

Brain tumors, whether malignant or benign, can be life threatening because they often increase ICP and are difficult to access (**FIGURE 11-50**). Although brain tumors may represent primary cancers, most are secondary tumors. Any cancer can spread to the brain, but the types that most commonly do so include breast cancer, colon cancer, kidney cancer, lung cancer, melanoma, and sarcoma. Primary tumors are thought to arise from genetic mutations. The risk for such mutations increases with age and exposure to radiation and occupational chemicals.

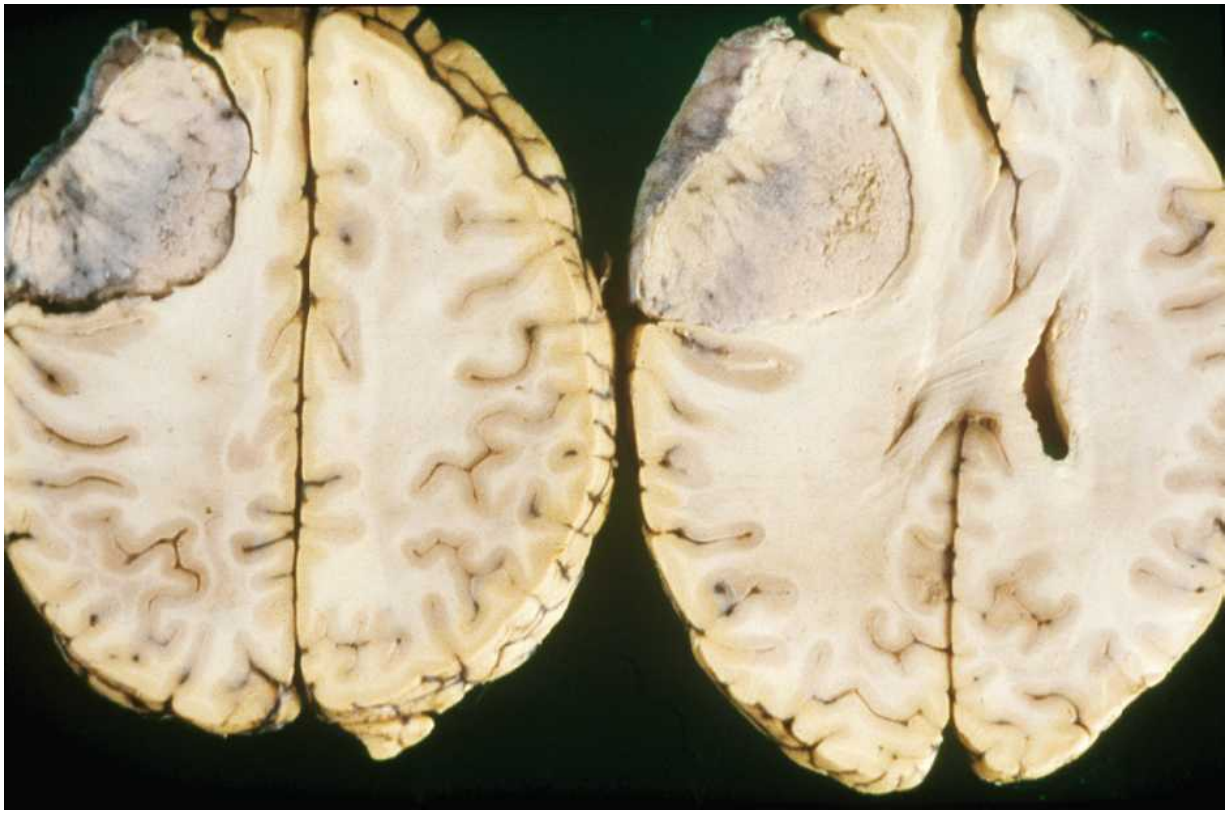


FIGURE 11-50 Brain tumor.

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In the United States, the prevalence and mortality rates of brain tumors are highest among Caucasians and males (National Cancer Institute, 2023). Complications of brain tumors include neurologic deficits, seizures, personality changes, and death. The 5-year survival rate for brain tumors is nearly 34%.

Clinical manifestations of brain tumors vary depending on their size and location. These manifestations reflect the increased ICP associated with such tumors:

- New onset or change in pattern of headaches
- Headaches that gradually become more frequent and more severe
- Unexplained nausea or vomiting
- Vision problems (e.g., blurred vision, diplopia, or loss of peripheral vision)

- Gradual loss of sensation or movement in an extremity
- Balance difficulties
- Speech difficulties
- Confusion
- Hearing problems
- Hormonal (endocrine) disorders

Diagnostic procedures consist of a history, physical examination (including a neurologic assessment), head MRI, biopsy, and other tests to determine cancer histology. Treatment of brain tumors depends on the size and location of the originating cancer, if any. If possible, surgical removal of the tumor is recommended. Additional treatment options include radiation (external and radiosurgery), chemotherapy (e.g., temozolomide [Temodar]), and targeted drug therapy (e.g., bevacizumab [Avastin]). Regardless of the strategy, rehabilitation will be necessary to minimize residual neurologic dysfunction. Rehabilitation will likely require physical, occupational, and speech therapy.

SUMMARY

The nervous system is a complex network that receives, organizes, and responds to internal and external stimuli—functions that are vital for achieving and maintaining homeostasis. The nervous system controls all sensory and motor functions. Damage to this system—even when minor—can result in significant neurologic deficits. The nature and severity of those deficits depend on the location and extent of damage. Such damage can result from trauma, infections, tumors, chemical imbalances, or genetic conditions. Regardless of the neurologic disorder, an affected individual may experience impaired social functioning, significant neurologic dysfunction, negative physical health consequences, and even death. Supporting neurologic health involves strategies such as observing safety precautions (e.g., wearing safety equipment), avoiding illicit drug use, minimizing alcohol consumption, getting vaccinations, and maintaining adequate nutrition.

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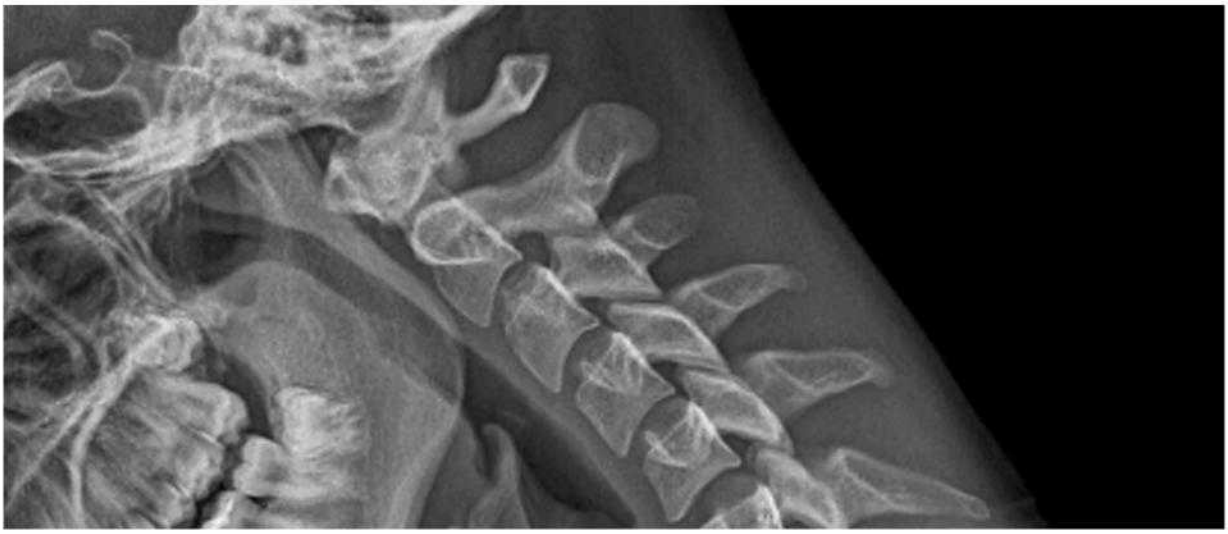
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CHAPTER 12

Musculoskeletal Function

LEARNING OBJECTIVES

- Discuss normal musculoskeletal anatomy and physiology.
- Compare and contrast congenital musculoskeletal disorders.
- Compare and contrast traumatic musculoskeletal disorders.
- Compare and contrast metabolic bone disorders.
- Compare and contrast inflammatory joint disorders.
- Describe and discuss chronic muscle disorders.
- Describe and discuss bone cancers.

KEY TERMS

actin
amphiarthrosis
ankylosing spondylitis
ankylosis
appendicular skeleton
axial skeleton
bone
bone marrow
callus
cardiac muscle
cartilage
chondrosarcoma
closed fracture
comminuted fracture
compact bone

compartment syndrome
complete fracture
compression fracture
crepitus
depressed fracture
diaphysis
dislocation
epiphysis
Ewing sarcoma
fascia
fat embolism
fibromyalgia
flat bone
fracture
gout
greenstick fracture
herniated intervertebral disk
hyaline cartilage
impacted fracture
incomplete fracture
irregular bone
joint
joint capsule
kyphosis
lamella
ligament
long bone
lordosis
matrix
muscle fiber
muscular dystrophy (MD)
myofibril
myofilament
myosin
oblique fracture
open fracture
osteoarthritis (OA)
osteoblast

osteochondroma
osteoclast
osteocyte
osteomalacia
osteomyelitis
osteonecrosis
osteopenia
osteoporosis
osteosarcoma
Paget's disease
pathologic fracture
periosteum
red marrow
rheumatoid arthritis (RA)
rickets
sarcomere
sciatica
scoliosis
sesamoid bone
short bone
simple fracture
skeletal muscle
skeleton
smooth muscle
spiral fracture
spongy bone
sprain
strain
stress fracture
suture
synarthrosis
synovial fluid
synovial joint
tendon
tophus
transverse fracture
yellow marrow

The musculoskeletal system consists of **bones**, **joints**, muscles, **ligaments**, **tendons**, and other connective tissue that provide support for the body and protection of organs. The musculoskeletal system collaborates with the nervous system to make movement possible. It plays a role in homeostasis by storing calcium and other minerals that can be mobilized when needed. Additionally, hematopoiesis occurs in the bones (see the *Hematopoietic Function* chapter).

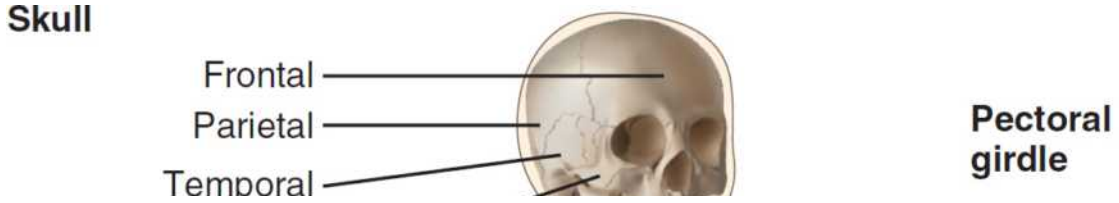
Disorders of the musculoskeletal system may be either acute or chronic. Many of these conditions are easily treatable and leave no lasting effects (e.g., **fractures**). Other conditions (e.g., **fibromyalgia**) can leave the individual with chronic pain or significant disability. These disorders may cause congenital, genetic, autoimmune, trauma, nutritional, and excessive use deficits.

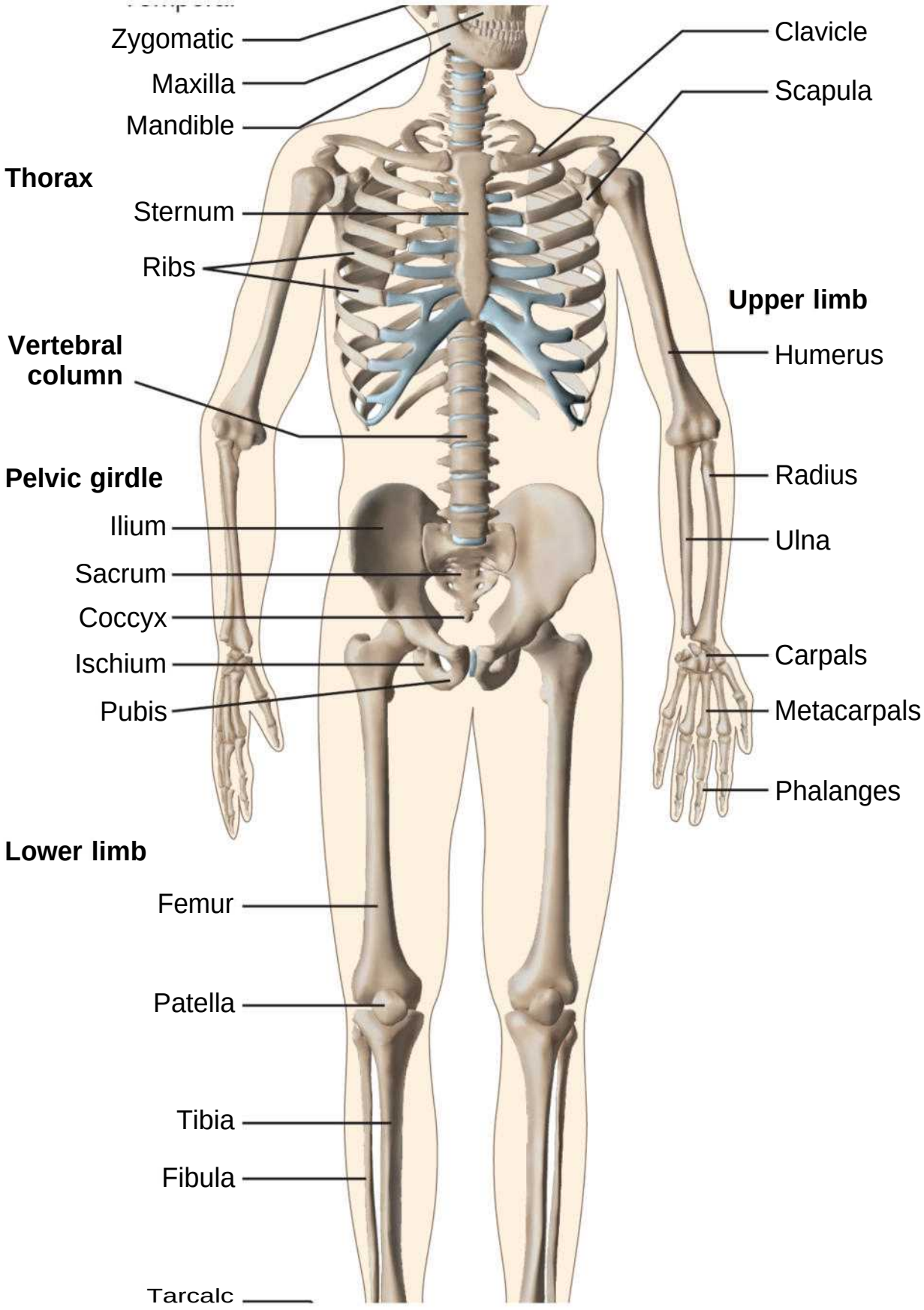
Anatomy and Physiology

The structures of the musculoskeletal system are essential for standing erect and locomotion. This system also gives the human body form and stability while protecting the vital organs. In addition, as noted earlier, it plays a role in homeostasis and is the site for hematopoiesis. The musculoskeletal system consists of bones, joints, muscles, ligaments, tendons, and other connective tissues that work together to accomplish these functions. Connective tissues are the biological material that supports and binds tissues and organs together. The chief components of connective tissue include elastic fibers and collagen (a protein substance).

Bones

Bone is a specialized form of connective tissue. At first glance, bone appears to be a dry, dead material. In fact, the word **skeleton** is derived from a Greek word that means “dried-up body.” Looks can be deceiving, however, because nothing could be further from the truth. Bone is a living, metabolically active tissue. This tissue is the site of fat and mineral storage (especially calcium) as well as hematopoiesis. The human body contains 206 bones of varying shapes and sizes that make up the skeleton (**FIGURE 12-1**). The skeleton provides support and protection for vital organs, such as the heart, lungs, and brain. It is organized into two divisions—axial and appendicular. The **axial skeleton** forms the long axis of the body and includes the skull, vertebral column, and rib cage. The **appendicular skeleton** consists of the bones that form the arms, shoulders, pelvis, and legs.




Zygomatic
Maxilla
Mandible
Thorax
Sternum
Ribs
Vertebral column
Pelvic girdle
Ilium
Sacrum
Coccyx
Ischium
Pubis
Lower limb
Femur
Patella
Tibia
Fibula
Tarcalc
Clavicle
Scapula
Upper limb
Humerus
Radius
Ulna
Carpals
Metacarpals
Phalanges

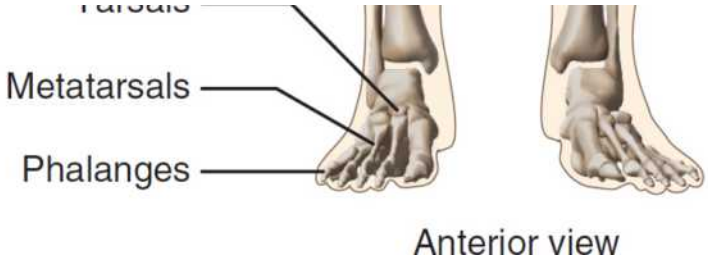
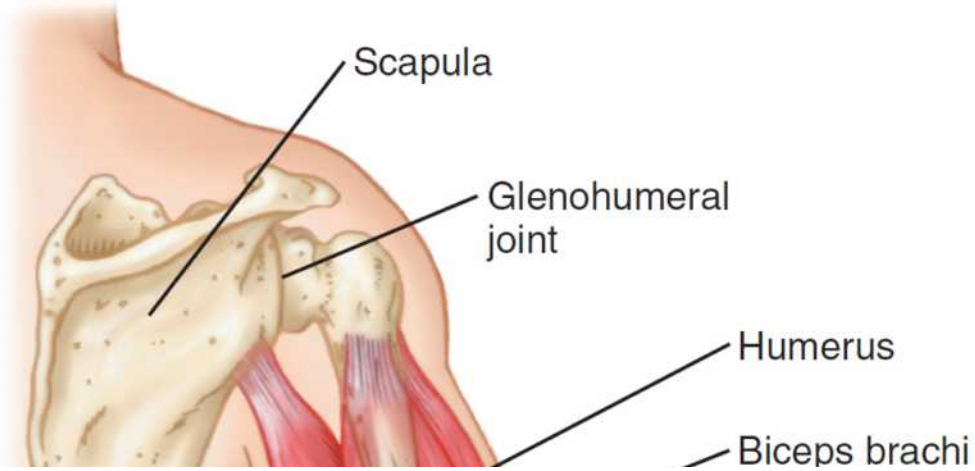
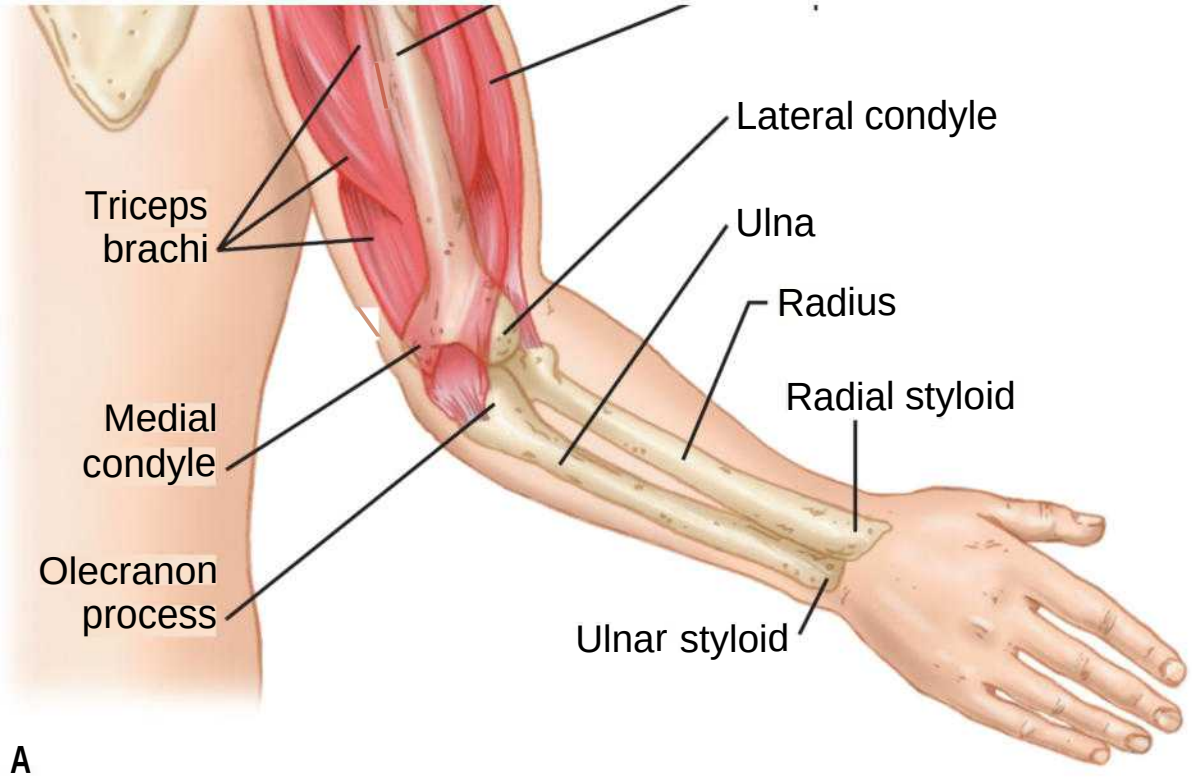


FIGURE 12-1 The human skeleton.

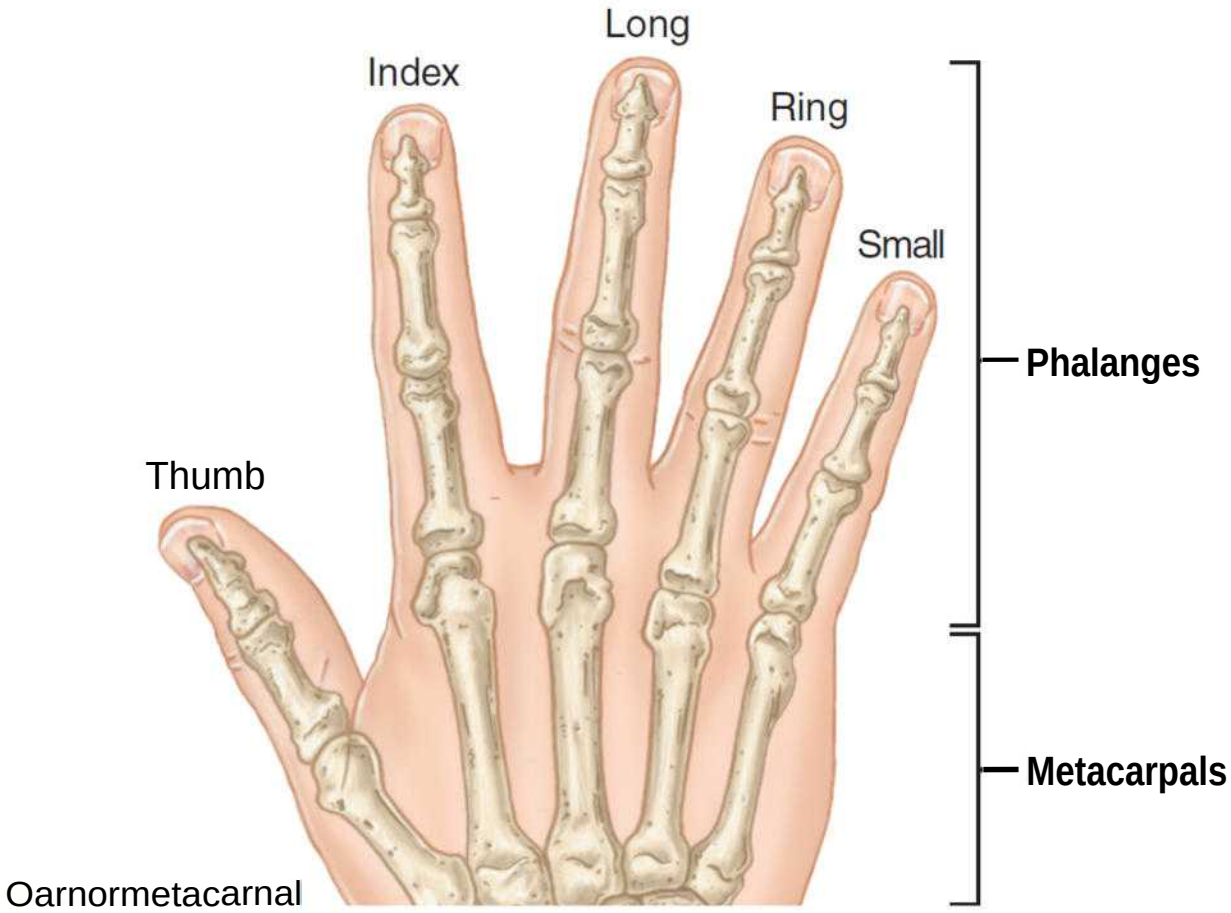
Description

Five types of bones are found within the skeleton—long, short, flat, irregular, and **sesamoid bones** (**FIGURE 12-2**). **Long bones** (**FIGURE 12-3**) have bodies (**diaphyses**) that are longer than they are wide, growth plates (**epiphyses**) at either end, hard outer surfaces (**compact bone**), and inner regions (**spongy bone**) that are less dense than the outer regions and contain **bone marrow**. Both ends of long bones are covered in hyaline **cartilage** to help protect the bone by reducing friction and absorbing shock. Long bones not only include some of the longest bones in the body (e.g., femur, humerus, and tibia) but also some of the smallest (e.g., metacarpals, metatarsals, and phalanges). **Short bones** are approximately as wide as they are long; their primary function is providing support and stability with little movement. Short bones consist of only a thin layer of compact bone along with spongy bone but contain relatively large amounts of bone marrow. Examples of short bones include the carpals and tarsals.





A



Oarnormetacarnal

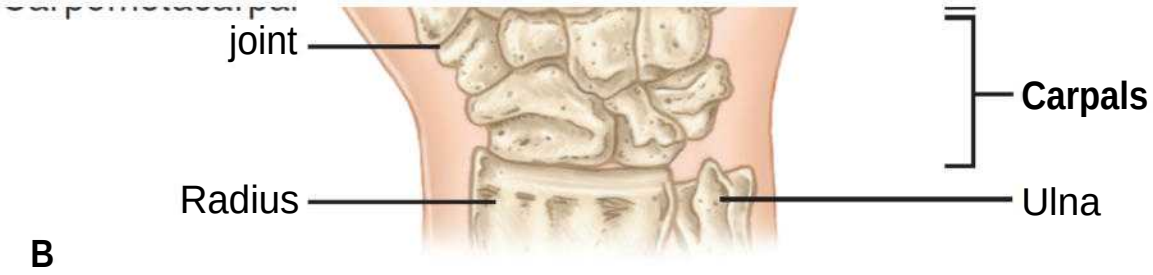


FIGURE 12-2 Classifications of bones. **(A)** The scapula is a flat bone, and the humerus, ulna, and radius are long bones. **(B)** The carpals, or wrist bones, are short bones.

Description

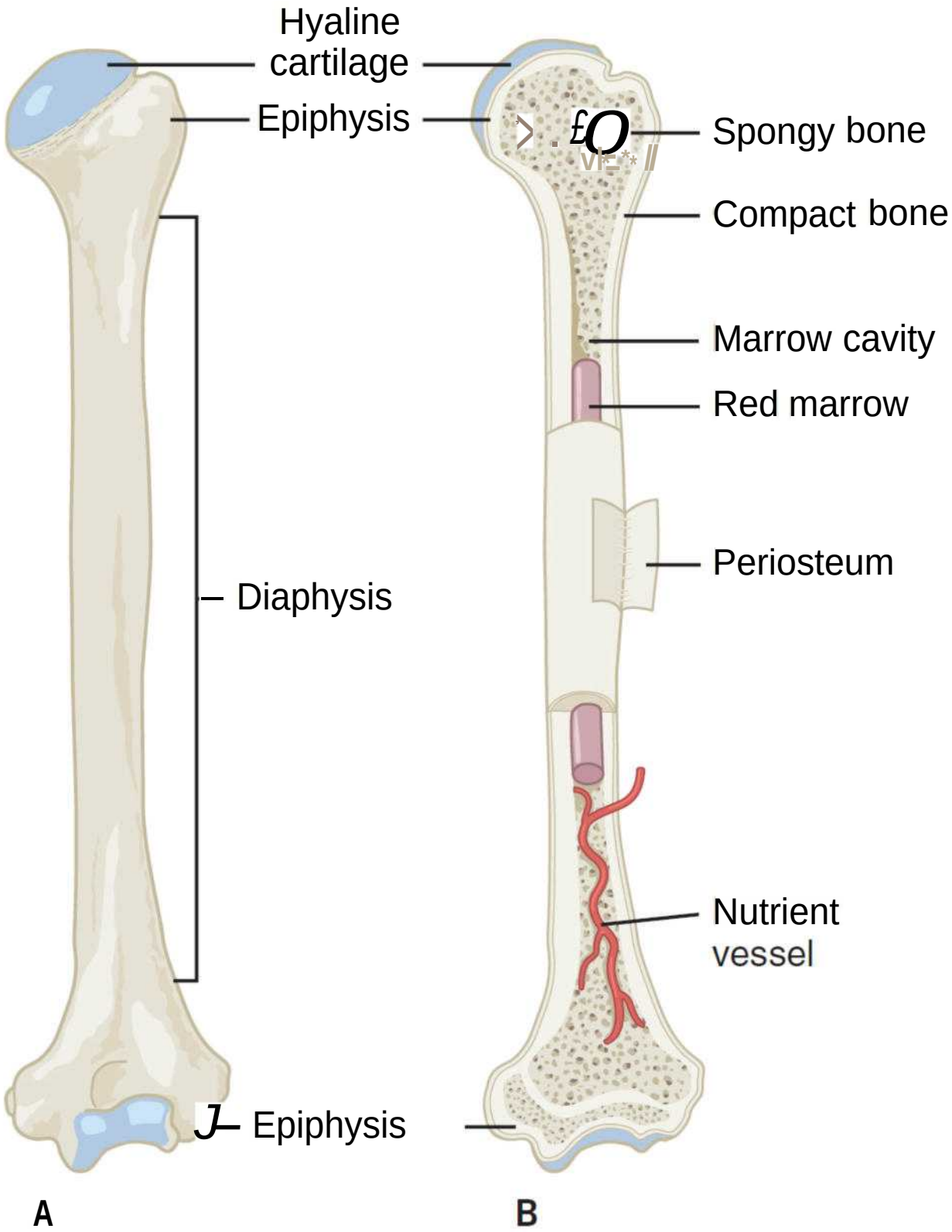


FIGURE 12-3 Long bones. **(A)** The humerus. Notice the long shaft and dilated ends. **(B)** Longitudinal section of the humerus showing compact bone, spongy bone, and marrow.

Description

Flat bones are strong, level plates of bone that provide protection to the body's vital organs and serve as a base for muscular attachment. The anterior and posterior surfaces of flat bones are formed from compact bone to provide strength, and the center consists of spongy bone and varying amounts of bone marrow. In adults, most red blood cells are formed in flat bones. Examples of flat bones include the scapula, sternum, skull, pelvis, and ribs.

Irregular bones include bones that do not fall into any other category, due to their nonuniform shape. They primarily consist of spongy bone, with a thin outer layer of compact bone. Examples of irregular bones include the vertebrae, sacrum, and mandible.

Sesamoid bones are usually short or irregular bones embedded in a tendon. These bones are often present in a tendon where it passes over a joint and serve to protect the tendon. Examples of sesamoid bones include the patella, pisiform (the smallest of the carpals), and the two small bones at the base of the first metatarsal.

A layer of connective tissue called the **periosteum** covers compact bone surfaces. The periosteum serves as the site of muscle attachment (via tendons). The outer surface of the periosteum contains cells that aid in remodeling and repair (**osteoblasts**). The periosteum is richly supplied with blood vessels that enter the bone at numerous sites (**FIGURE 12-4**). These vessels travel through small tubes (Haversian canals) in the compact bone and flow through the spongy bone, providing nutrients and oxygen while removing waste products. The periosteum is also richly supplied with nerve fibers.

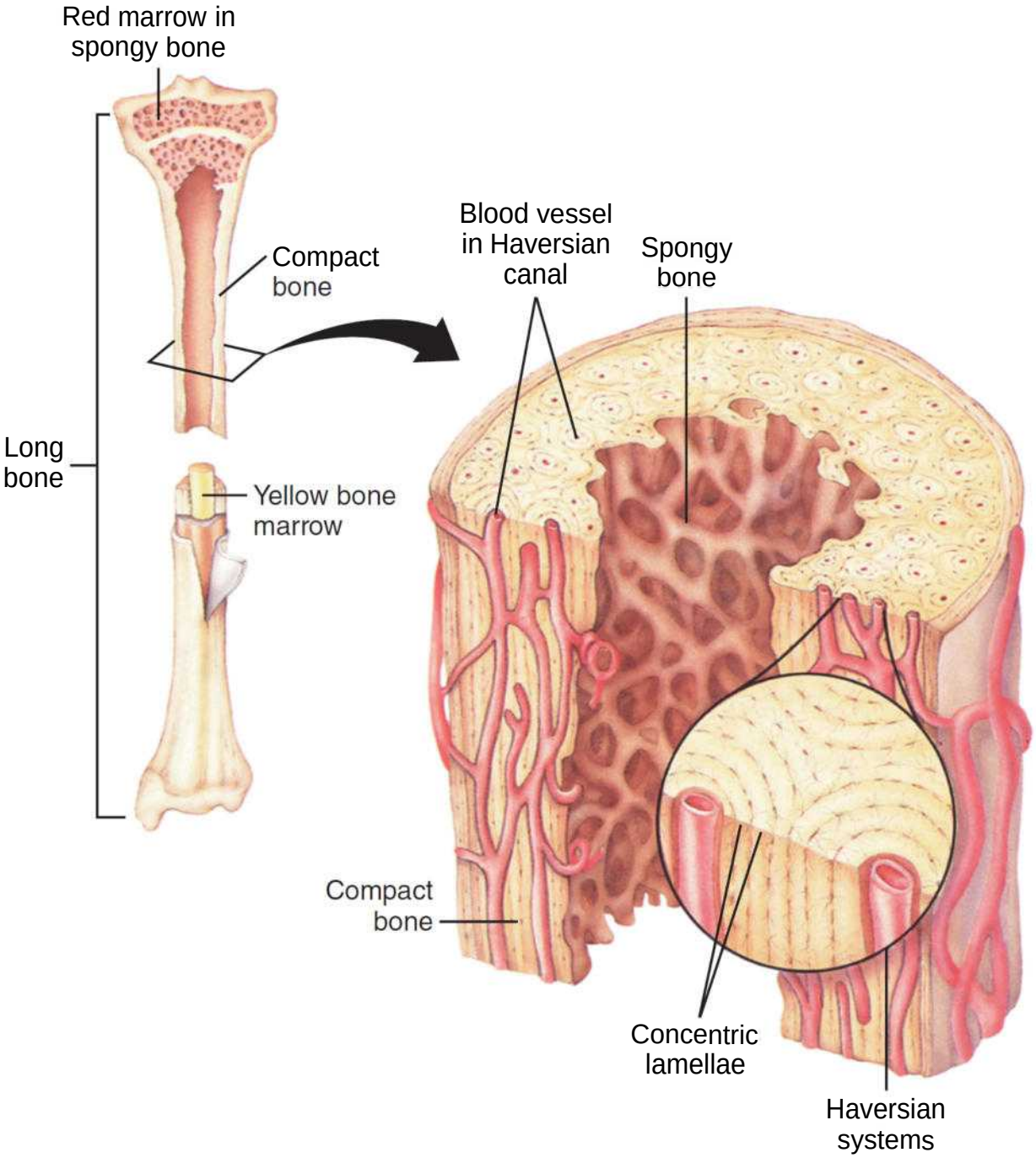


FIGURE 12-4 Shaft of the bone.

Description

Inside the shaft of long bones is a large cavity that holds bone marrow. The marrow cavities in most bones of a fetus or newborn contain **red marrow**. Red marrow, so named because of its color, serves as a blood-cell factory (hematopoiesis). As humans age, this

red marrow is slowly replaced by fat, creating **yellow marrow**. Yellow marrow begins to form during adolescence and is present in most bones by adulthood. At this point, hematopoiesis continues in the vertebrae, pelvis, and a few other sites. The yellow marrow can be reactivated to produce blood cells under certain circumstances (e.g., after an injury).

Bone is a dynamic tissue that is constantly undergoing remodeling to repair aging bone and fractures or to adjust for factors such as changes in activity. For example, spongy bone is remodeled to increase bone strength when a person's activity level increases after periods of inactivity. During remodeling, cells called **osteoclasts** break down some spongy bone, while osteoblasts rebuild new compact bone to increase bone strength (**TABLE 12-1**). Osteoblasts lay down new bone during the remodeling process; when these osteoblasts become surrounded by calcified extracellular material, the complex is referred to as an **osteocyte**. Bone tissue contains many of these osteocytes, which are organized into thin layers called **lamellae** (**FIGURE 12-5**). The osteocytes are embedded in an extracellular material known as the **matrix**. The matrix consists of calcium phosphate crystals (hydroxyapatite) that make the bones hard and strong. It also contains collagen fibers that reinforce the bone, giving it flexible strength. Balance between the mineral components and collagen is necessary for optimal bone function. Bone without adequate mineral quantities is too flexible; bone without adequate collagen amounts is extremely brittle.

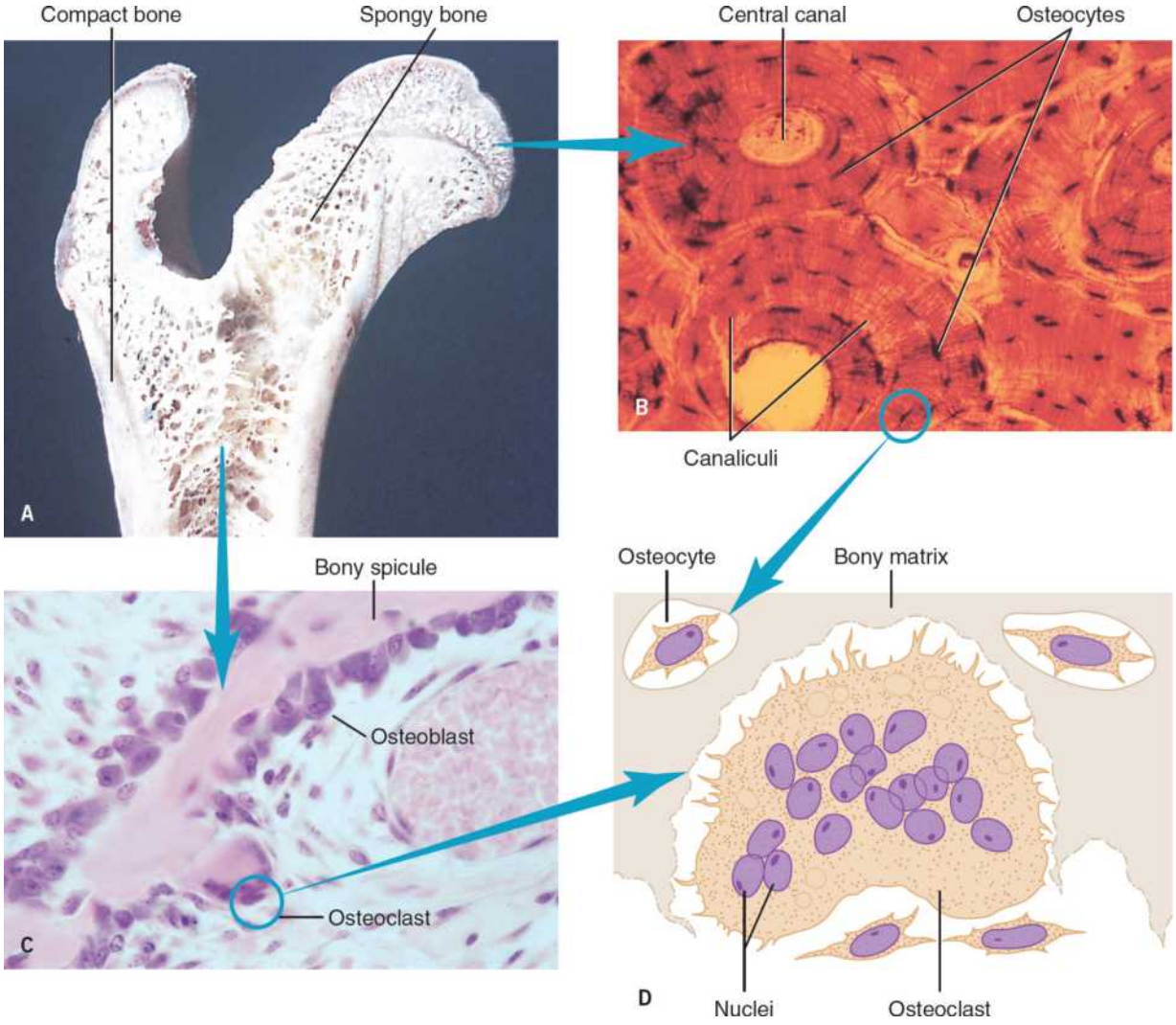


FIGURE 12-5 Bone. **(A)** Compact and spongy bone of the humerus. **(B)** Light micrograph of the lamellae (concentric circles) showing the osteocytes and canaliculi. **(C)** Photomicrograph of spongy bone showing osteoblasts and osteoclasts. **(D)** An osteoclast digesting the surface of a bony spicule (sharp body or spike).

A: © Dr. Robert Calentine/Visuals Unlimited, Inc.; **B:** © Dr. John D. Cunningham/Visuals Unlimited, Inc.; **C:** © R. Kessel/Visuals Unlimited, Inc.

Description

TABLE 12-1	Structural Elements of Bone

Bone Cells	Function
Osteoblasts	Build bone through collagen
Osteoclasts	Enable the matrix to be absorbed; assist with the release of calcium and phosphate
Osteocytes	Mature cells that help maintain the bone matrix; also play a major role in the release of calcium into blood

Several hormones influence bone structure. For example, growth hormone produced by the anterior pituitary gland works with thyroid hormones to control normal bone growth (see the *Endocrine Function* chapter). Growth hormone increases the rate of growth by causing cartilage and bone cells to reproduce and lay down their intercellular matrix as well as by stimulating mineralization within the matrix. Bones grow in two ways—appositional growth and endochondral growth. In appositional growth, new bone forms on the surface of an existing bone. In endochondral growth, bone eventually replaces new cartilage growth in the epiphyseal plate. Calcitonin and parathyroid hormone regulate bone remodeling and mineralization of calcium (see the *Endocrine Function* chapter). Estrogen inhibits the formation of osteoclasts in women, whereas testosterone increases bone length and density in men.

Vitamin D also plays a critical role in bone metabolism. This fat-soluble vitamin controls the absorption of calcium from the intestine as well as increases calcium and phosphate reabsorption in the kidneys. Proper nutrition (including adequate intake of dietary calcium and vitamin D) and physical activity from childhood onward are essential for the development and maintenance of healthy bone.

During fetal development, the skeleton forms from **hyaline cartilage**. Cartilage is a shiny connective tissue that is both tough and flexible. Several types of cartilage can be found throughout the body, in the ears, nose, and joints. Hyaline cartilage is the type most closely associated with bone. This cartilage is often found in joints—

structures that connect the bones of the skeleton. Joints are classified based on their degree of movement as moveable, slightly moveable, or immoveable.

The most common type of joint is the freely moveable, or synovial, joint (**FIGURE 12-6**). Although **synovial joints** are complex and vary significantly, they all share similar features. Specifically, these joints contain cartilage that is lubricated by a transparent viscous fluid (**synovial fluid**) secreted by the synovial membrane—a soft tissue that lines the noncartilaginous surfaces within joints. This lubricated cartilage reduces friction by providing a slippery surface that enables the bones to move freely. In addition to lubrication, synovial fluid contains leukocytes that fight infections in the joints and delivers nutrients to the cartilage. The second commonality among synovial joints is the presence of a **joint capsule**, a structure that joins one bone to another. The outer layer of the synovial joint capsule consists of dense connective tissue attached to the periosteum of adjacent bones. Many of these joints contain parallel bundles of dense connective tissue called "ligaments." Ligaments connect bones to bones in a joint and provide support to the joint.

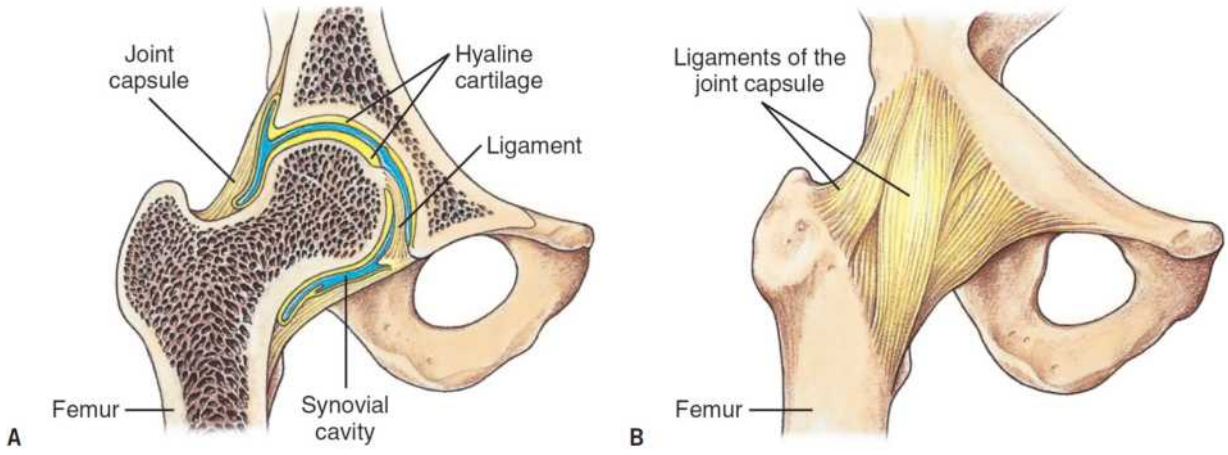


FIGURE 12-6 A synovial joint. **(A)** A cross section through the hip joint (a ball-and-socket joint) showing the structures of the synovial joint. **(B)** Ligaments in the outer portion of the joint capsule help support the joint.

Slightly moveable joints, known as **amphiarthroses**, can be seen in the vertebral column (**FIGURE 12-7**). An intervertebral disk unites the components of each vertebra. The inner portion of this disk serves as a cushion, absorbing the impact of walking and running. The outer, fibrous portion holds the disk in place and joins one vertebra to the next.

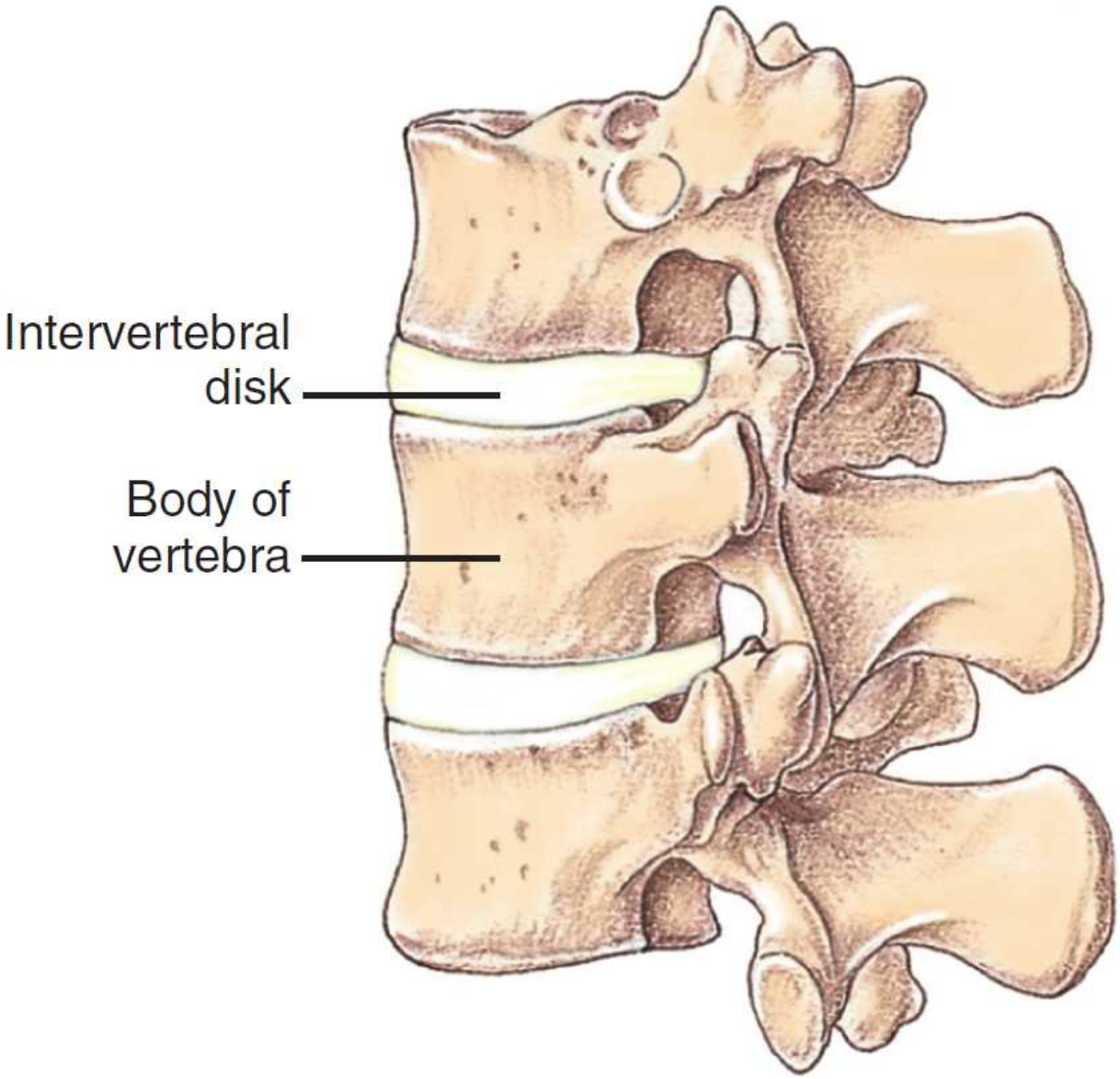


FIGURE 12-7 A slightly moveable joint. The intervertebral disks allow for some movement, giving the vertebral column flexibility.

The skull is an example of an immoveable joint, or **synarthrosis** (**FIGURE 12-8**). In the skull, the bones interlock to form immoveable joints called **sutures**. Fibrous connective tissue extends the space between the interlocking bones, holding them together. Another immoveable joint is the pubic symphysis, where the two pubic bones come together and are held in position by fibrocartilage.

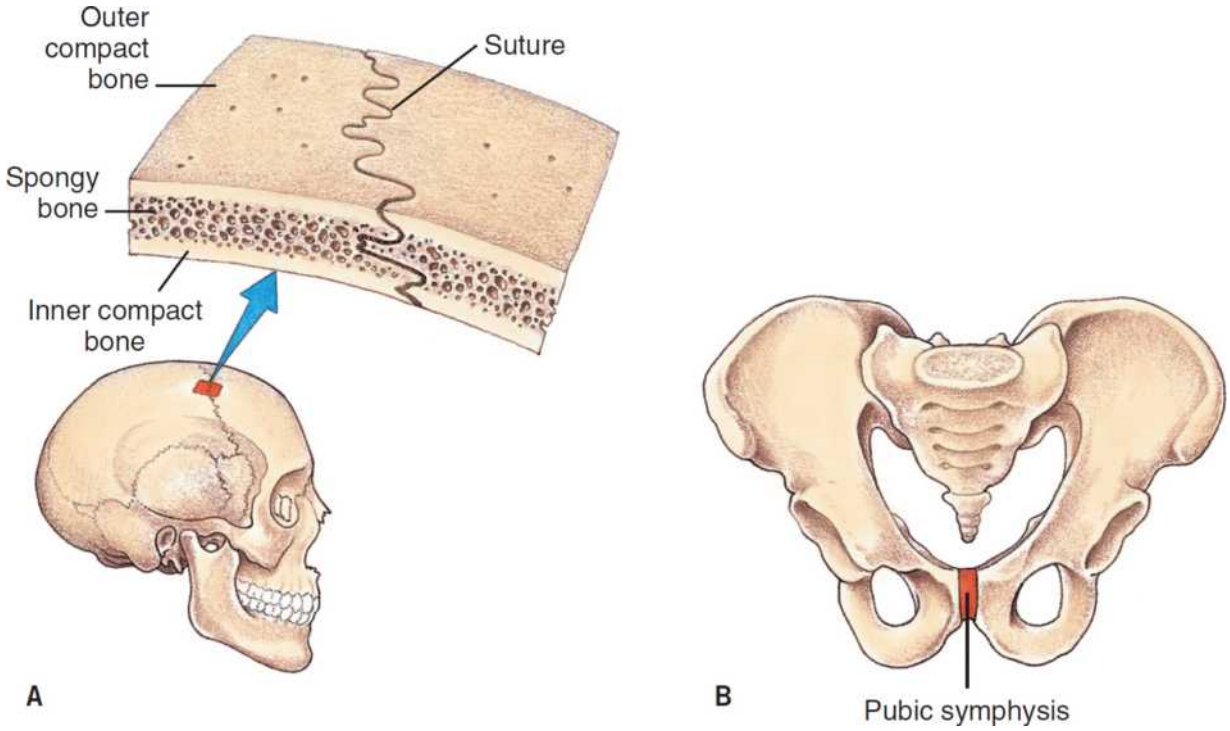


FIGURE 12-8 Immoveable joints. **(A)** Many of the bones of the skull are held in place by joints called sutures. These bones are linked by fibrous tissue, and the joints are immoveable. **(B)** The pubic symphysis is another immoveable joint. During childbirth, it softens and expands to permit delivery.

Muscles

Motion requires a skeleton with moveable joints and muscles acting on the bones. The three types of muscles are skeletal, smooth, and cardiac. **Skeletal muscles** connect to bone, are the most frequently occurring muscle type, and make up approximately 40% of the body's weight. The more than 350 skeletal muscles are under the voluntary control of the brain (**FIGURE 12-9**). **Smooth muscles** line the walls

of hollow organs and tubes; they are also found in the eyes, skin, and glands. Smooth muscles are involuntary, meaning they work without conscious control by the brain. **Cardiac muscle** makes up the heart and is under involuntary control.

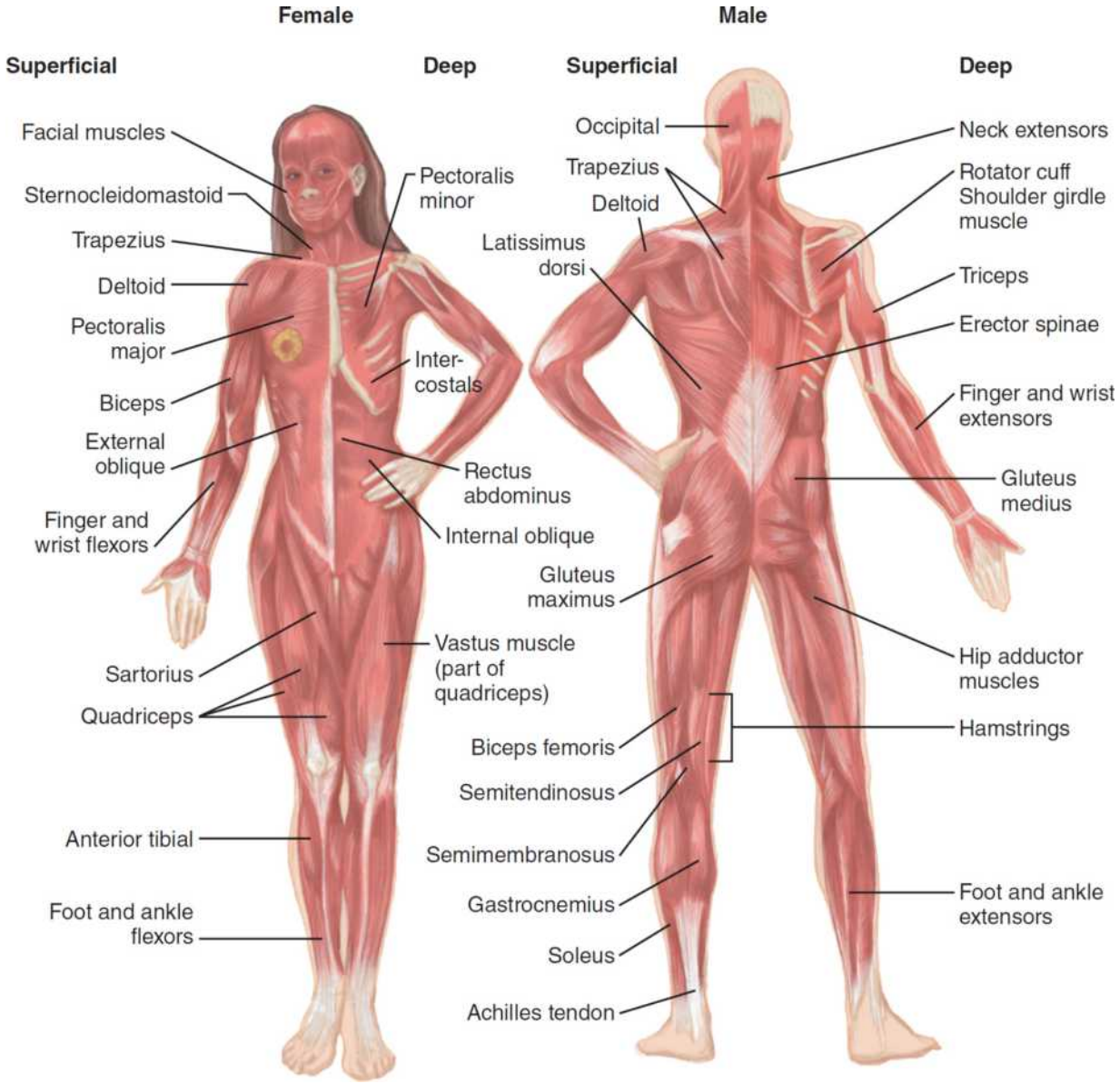


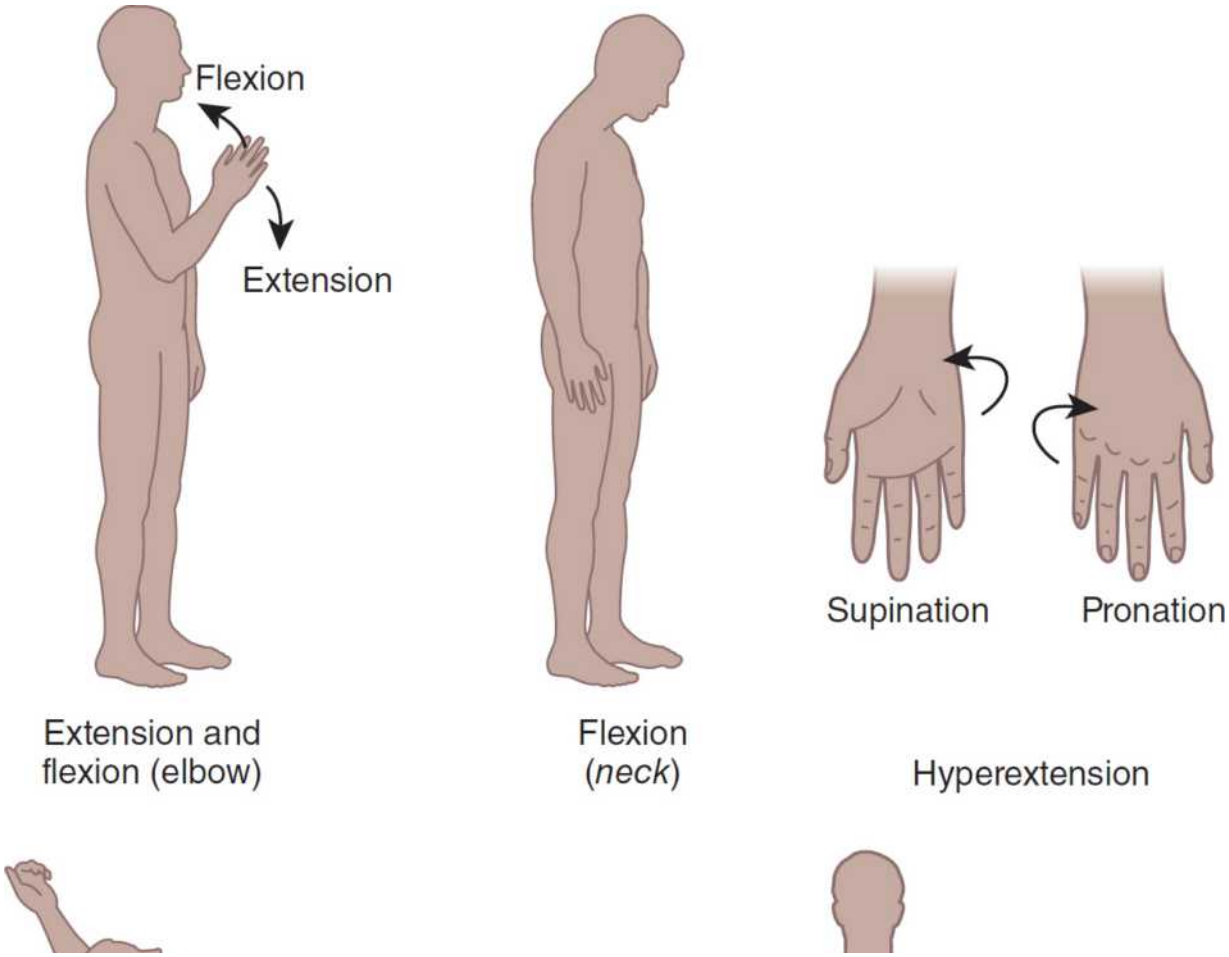
FIGURE 12-9 Skeletal muscles.

Description

Almost every muscle in the body attaches to bones through structures such as tendons. Tendons are specialized tough cords or

bands of dense connective tissue that are continuous extensions of the periosteum.

In addition, most muscles cross one or more joints. Muscles contract to produce movement of the bones at the joints, working in groups to ensure smooth movements (**FIGURE 12-10**). When one muscle contracts to produce a movement, the antagonistic (opposing) muscles relax to allow the movement. Muscles contract in response to nerve stimulation (see the *Neural Function* chapter). Because **muscle fibers** are elastic, the fibers return to their normal length after contracting. Not all skeletal muscles make bones move. Some muscles steady joints, allowing other muscles to act. These muscles assist with posture, permitting the body to sit or stand upright against gravitational pull. Like nerve cells, muscle fibers are excitable cells with high action potentials, allowing them to respond to stimulation rapidly.



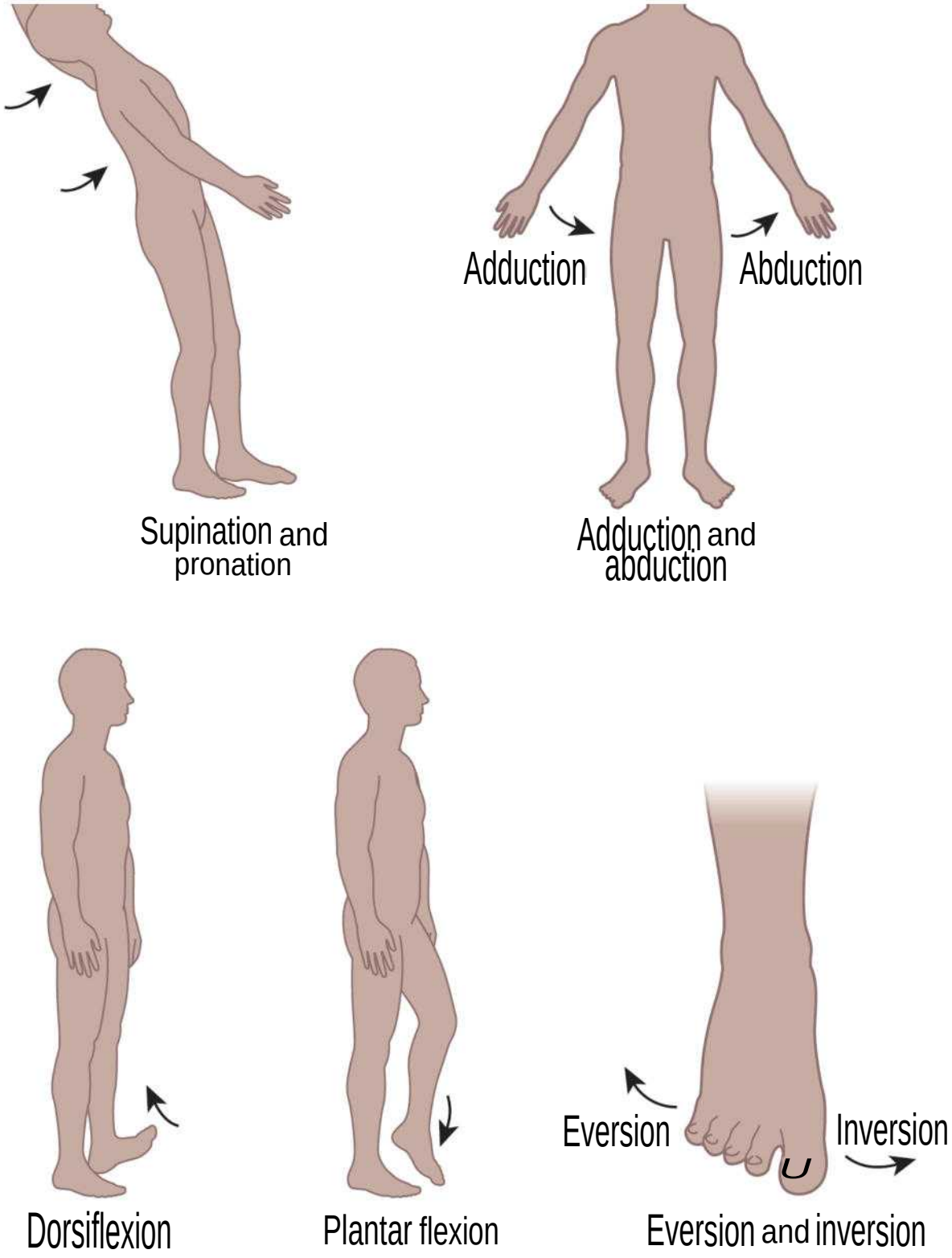
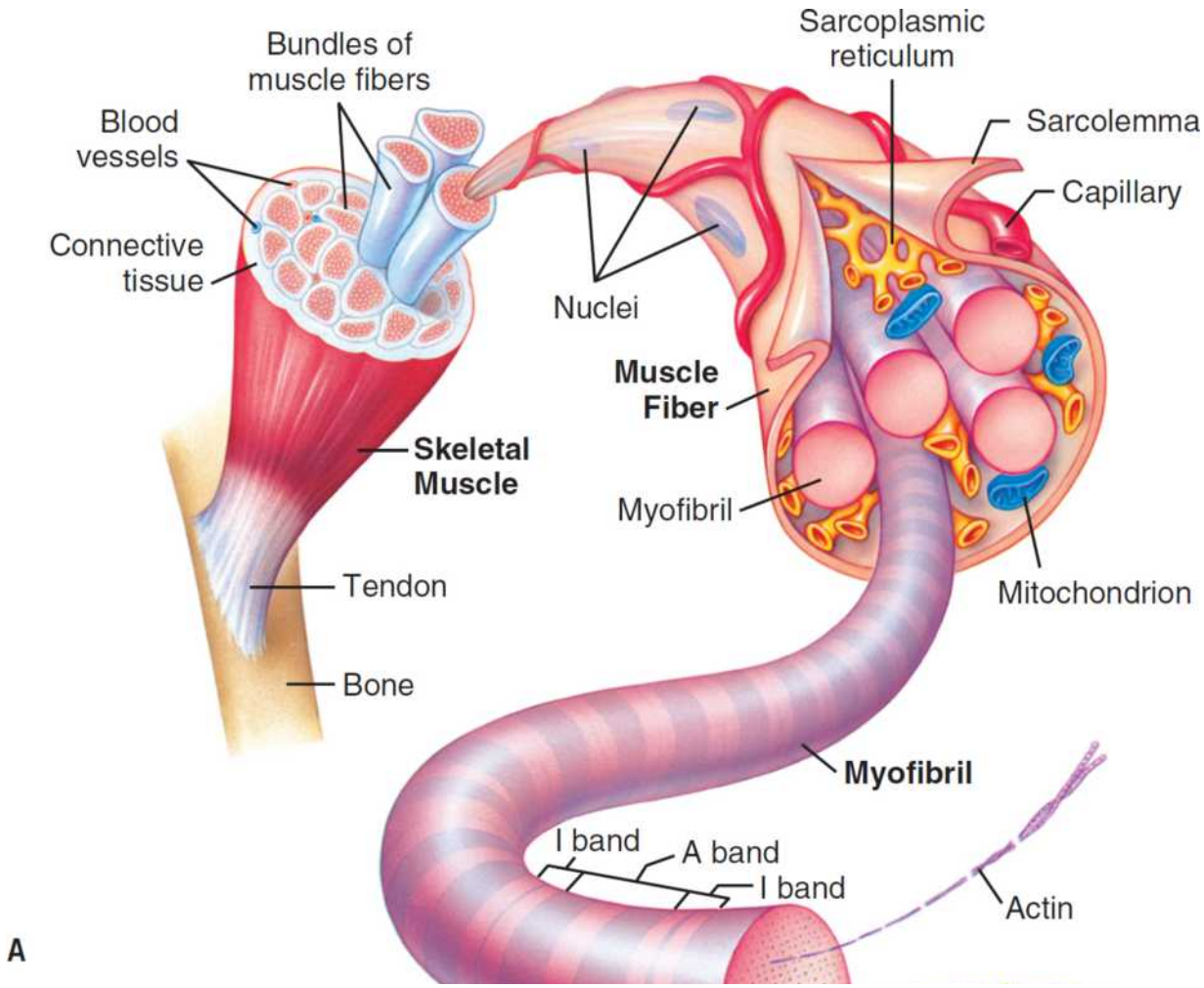
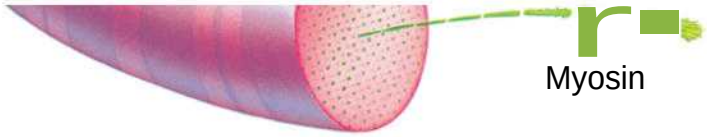


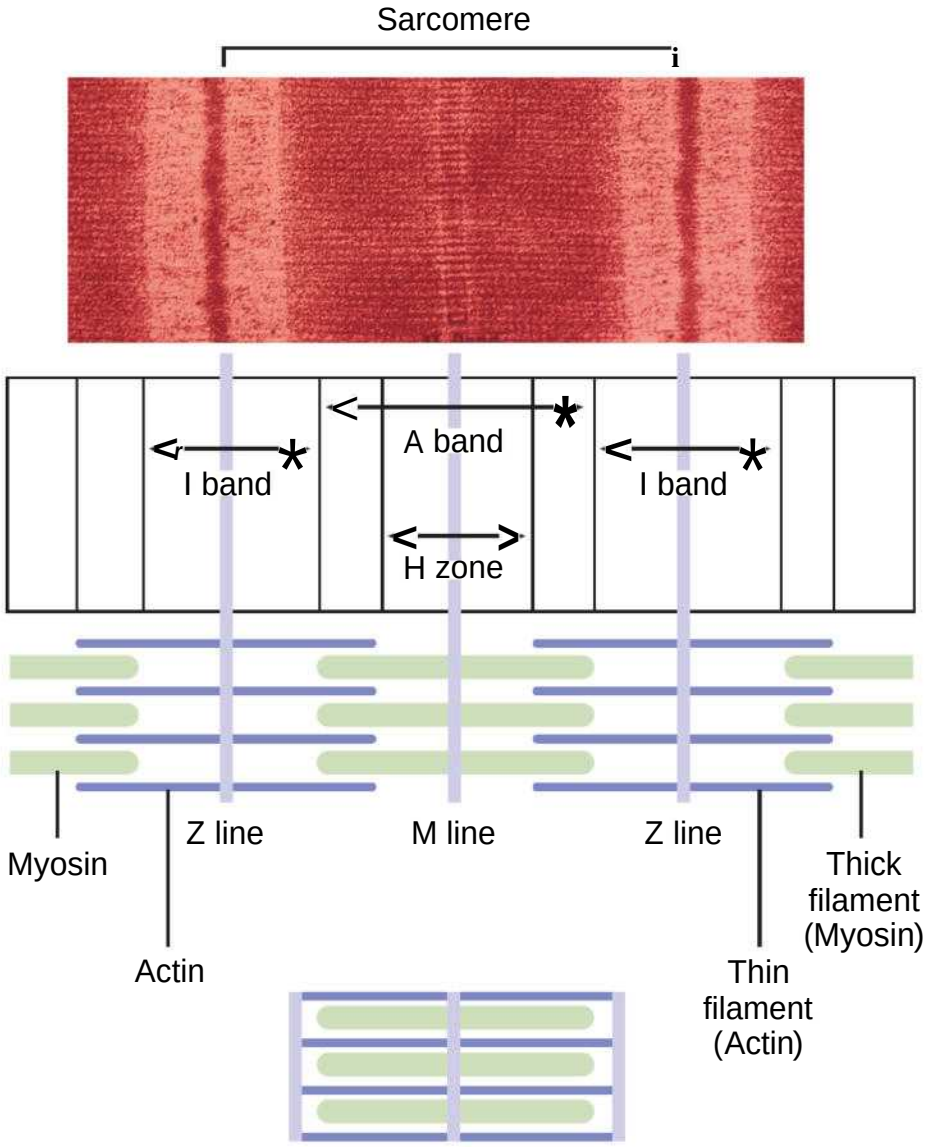
FIGURE 12-10 Common body movements.

Description

Skeletal muscles are composed of muscle fibers, connective tissue, blood vessels, and nerves (**FIGURE 12-11**). Each skeletal muscle fiber or cell is a cylinder with multiple nuclei. Within each fiber are **myofibrils**, threadlike structures extending for the entire length of the muscle fiber. Myofibrils contain two types of **myofilaments** (protein fibers)—**actin** and **myosin**. Actin myofilaments are involved in muscular contractions, cellular movement, and cell shape maintenance. Myosin myofilaments are darker and thicker than their actin counterparts. These fibrous globulins (a type of protein) work with actin to form actomyosin. The alignment of the two kinds of myofilaments gives the skeletal muscle its striated appearance (alternating light and dark bands) (**FIGURE 12-12**). Myofilaments are organized into repeated structural units called **sarcomeres** (Figure 12-11).







B

FIGURE 12-11 **(A)** Structure of a skeletal muscle. **(B)** Structure of a sarcomere.

B: © Don W. Fawcett/Visuals Unlimited, Inc.

Description



FIGURE 12-12 Striated pattern of skeletal muscle.

© Ed Reschke/Photolibrary/Getty Images

Muscle fibers contract when actin filaments slide over myosin filaments. In this process, the myosin filament pulls the actin filament. First, the myosin attaches to the actin when calcium is released from inside the muscle fibers. Calcium is stored in the smooth endoplasmic reticulum (see the *Cellular Function* chapter), which forms an extensive network inside muscle fibers. Impulses from nerve cells—specifically, motor neurons—trigger this release of calcium. Once the calcium causes the head of the myosin to attach to the actin filament, adenosine triphosphate in the muscle provides the energy needed to pull the actin filament inward. To meet the muscle cell's high energy needs, adenosine triphosphate is recycled repeatedly in rapid succession. During vigorous activity, adenosine triphosphate stores become depleted, oxygen levels drop sharply, glucose production ceases, and lactic acid accumulates.

Each muscle fiber is enclosed by a cell membrane (sarcolemma) (**FIGURE 12-13**). In turn, numerous muscle fibers are bundled together and surrounded by connective tissue called "endomysium." Additional connective tissue called "perimysium" surrounds several of these bundles, grouping them together to form a muscle. Yet another layer of connective tissue called "epimysium" and fibrous connective tissue (**fascia**) surround these muscles. This fascia may also surround muscle groups.

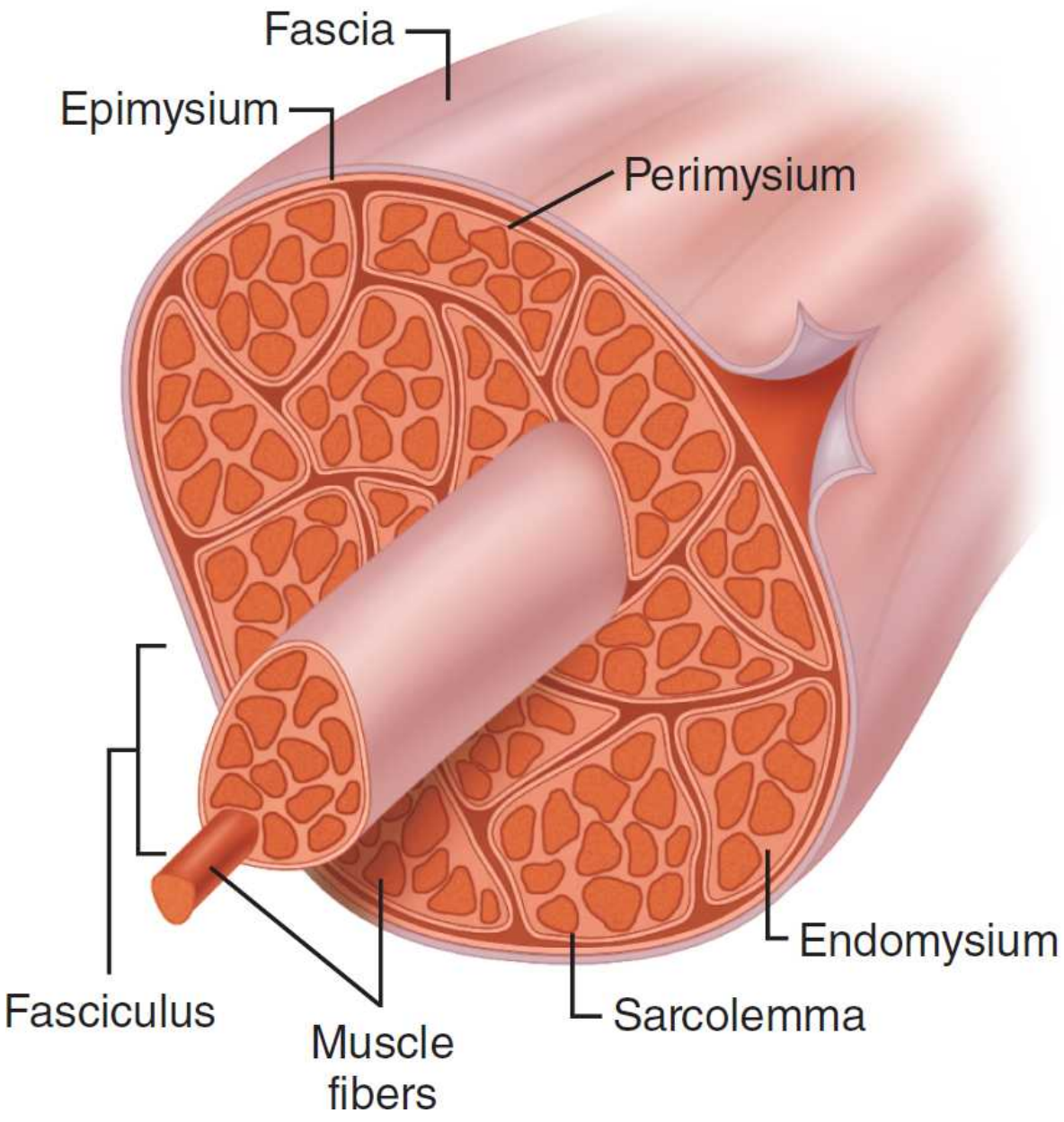


FIGURE 12-13 Muscle group.

In addition to stimulating bone growth, growth hormone causes muscle growth. The number of muscle fibers or cells in a muscle remains relatively constant throughout the life span. Thus, increases in muscle sizes reflect increases in individual muscle fibers rather than greater numbers of fibers. When muscles work harder, they respond by becoming larger and stronger. This increase in size and strength results from an increase in the amount of contractile protein inside the muscle fiber. Unfortunately, muscle protein is produced and destroyed quickly. In fact, approximately half of the muscle gained in a weightlifting program is broken down 2 weeks after ceasing the activity. The only way to maintain the muscle gain is to continue the weightlifting program.

UNDERSTANDING CONDITIONS THAT AFFECT THE MUSCULOSKELETAL SYSTEM

When considering alterations of the musculoskeletal system, organizing them based on their basic underlying pathophysiology can increase understanding. In patients with musculoskeletal system disorders, the primary nursing diagnosis is impaired physical mobility, reflecting the fact that this system's primary function is movement. Interventions are specifically selected to prevent complications of immobility (e.g., **osteoporosis**, renal calculi, thrombus, constipation, and decubiti). Depending on the condition, other nursing diagnoses may include chronic pain, risk for injury, and self-care deficit.

Congenital Musculoskeletal Disorders

Some musculoskeletal disorders are congenital in nature and primarily affect posture. These conditions may be apparent at birth

or, alternatively, may materialize as the child grows. During growth spurts in affected individuals, muscular development lags behind skeletal growth; this lag results in inadequate skeletal support. Additionally, comorbid developmental abnormalities (e.g., Down syndrome and cerebral palsy) may become aggravated during these growth periods. These congenital musculoskeletal disorders require early treatment to prevent progression and complications.

Kyphosis

Kyphosis refers to an increase in the curvature of the thoracic spine outward (**FIGURE 12-14**). Often called "hunchback," kyphosis is rarely present at birth. Instead, it usually appears during the adolescent growth spurts and can appear as poor posture (referred to as "Scheuermann's disease"). In adults, kyphosis usually develops secondary to osteoporosis, degenerative spine disease (e.g., arthritis or disk degeneration), or injury. Severe kyphosis can impair lung expansion and ventilation. Additionally, patients with this disorder are at increased risk for injury because of alterations in their center of gravity. Other manifestations may include fatigue, back pain, and spine stiffness.

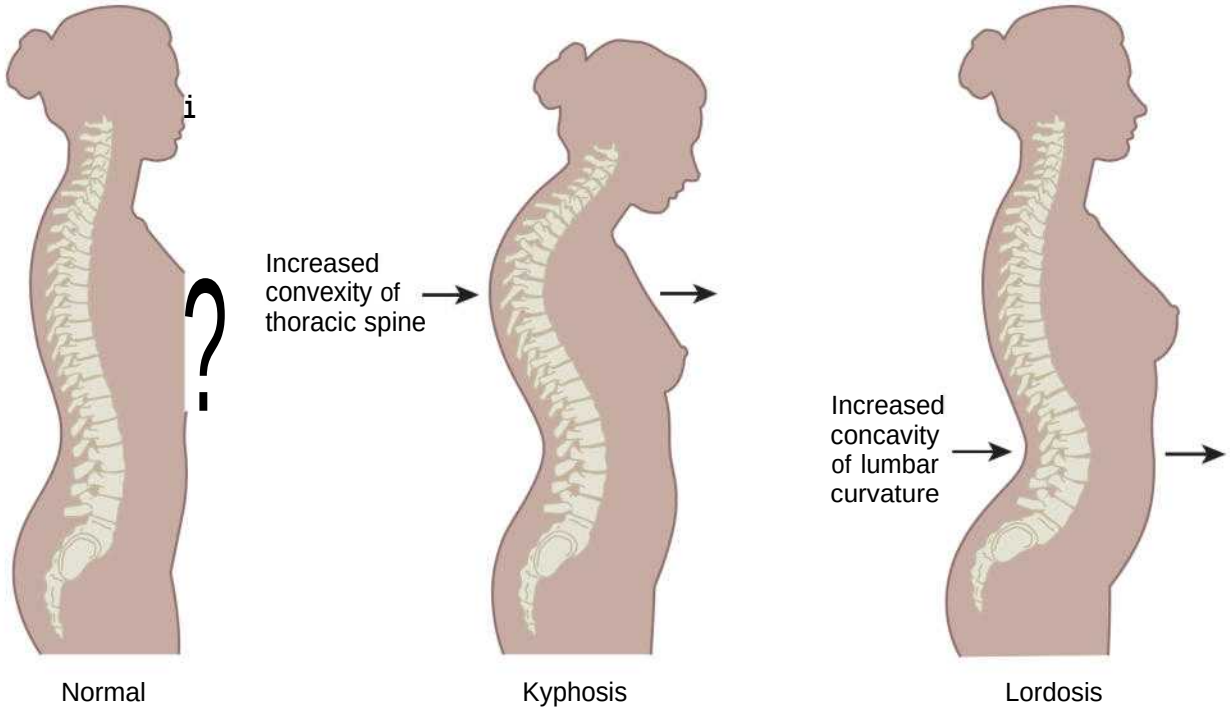


FIGURE 12-14 Kyphosis and lordosis.

Description

Diagnostic procedures for kyphosis include a history, physical examination, spine X-ray, computed tomography (CT), and magnetic resonance imaging (MRI). Exercises (including back strengthening) and proper posture can usually reverse mild deformities. Bracing and surgical correction may be necessary for more severe cases.

Lordosis

Lordosis refers to an exaggerated concave of the lumbar spine (Figure 12-14). Often called “swayback,” lordosis may develop during adolescent growth spurts or because of poor posture. Obesity and pregnancy can increase the tendency toward this posture because of an altered center of gravity and postural compensation. Lordosis is also commonly associated with dwarfism.

Diagnostic procedures for lordosis include a history, physical examination, spine X-ray, CT, and MRI. Much as with kyphosis, treatment for lordosis includes exercises, proper posture, bracing, and surgery.

Scoliosis

Scoliosis refers to a lateral deviation of the spine (**FIGURE 12-15**). This lateral curvature may affect the thoracic area, the lumbar area, or both. Scoliosis may also include a rotation of the vertebrae on their axis. Stress on the vertebrae causes an imbalance in osteoclast activity; therefore, the curvature increases during growth spurts. Scoliosis may also be associated with kyphosis and lordosis.

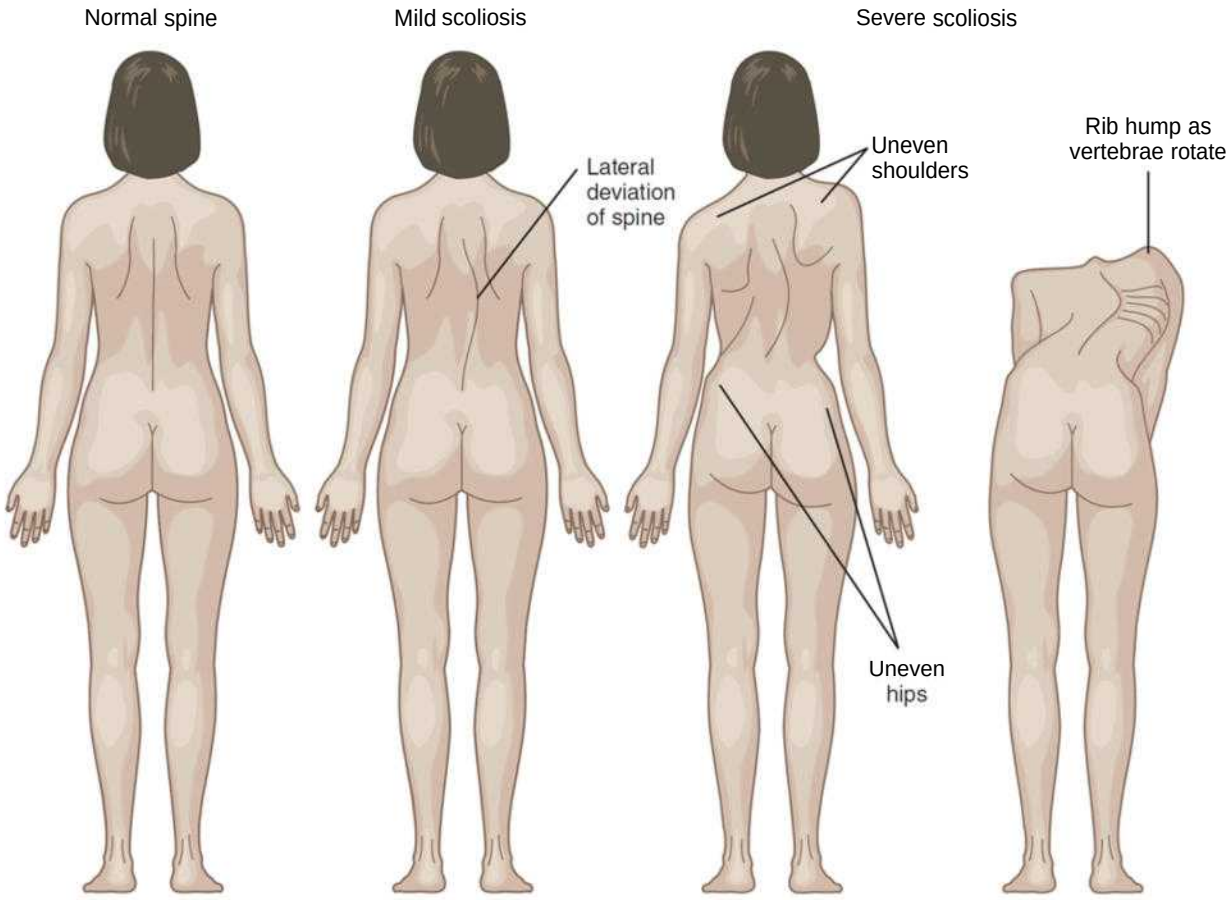


FIGURE 12-15 Scoliosis.

Description

Scoliosis varies in severity and is more common in females. Most cases are idiopathic, but known causes may include genetic influences, embryonic developmental deformities, degenerative

diseases, unequal leg lengths, spinal nerve compression, and asymmetrical muscle support. The genetic influences are autosomal dominant. Embryonic involvement usually affects the hemivertebrae. Degenerative diseases associated with scoliosis include osteoporosis and osteoarthritis. Asymmetrical muscle support disorders that may induce scoliosis include partial paralysis, muscular dystrophy, cerebral palsy, poliomyelitis, trauma, and spinal tumors. Complications of scoliosis include pulmonary compromise, chronic pain, degenerative arthritis of the spine, intervertebral disk disease, and **sciatica**.

Clinical manifestations vary depending on the degree of curvature and are exaggerated when an affected person bends over. These manifestations may include the following symptoms:

- Asymmetrical hip and shoulder alignment
- Asymmetrical thoracic cage
- Asymmetrical gait
- Back pain or discomfort
- Fatigue
- Indications of respiratory compromise (e.g., dyspnea and reduced chest expansion)

Because of the prevalence of scoliosis in adolescent females, schools often conduct periodic scoliosis screening. Diagnostic procedures consist of a history, physical examination (including the Adams forward bend test), spinal X-rays, use of a scoliometer (which measures the angle of trunk rotation), CT, and MRI.

Without treatment, the curvature associated with scoliosis often progresses in adulthood. Patient outcomes improve with early treatment. Treatment strategies may include exercises (including back strengthening), bracing, and surgical correction (with instrumentation or fusion).

Developmental Hip Dysplasia

Developmental dysplasia of the hip (DDH) refers to a continuum of abnormalities in the immature hip that can range from subtle dysplasia (abnormal development) to **dislocation** (**FIGURE 12-16**). These abnormalities can involve the size, shape, orientation, or organization of the femoral head or acetabulum, or both. DDH is thought to result from relaxation of the ligaments around the joint or from in utero positioning. It can be unilateral or bilateral. DDH was formerly referred to as congenital hip dislocation, but it is now recognized that the condition can develop after birth in early infancy or childhood. Additionally, various issues can develop besides dislocation. DDH affects 1% to 7% of all infants (Swarup, Penny, & Dodwell, 2018). Risk factors include breech presentation, presence of other deformities (e.g., torticollis and congenital foot deformity), and positive family history (especially for females).

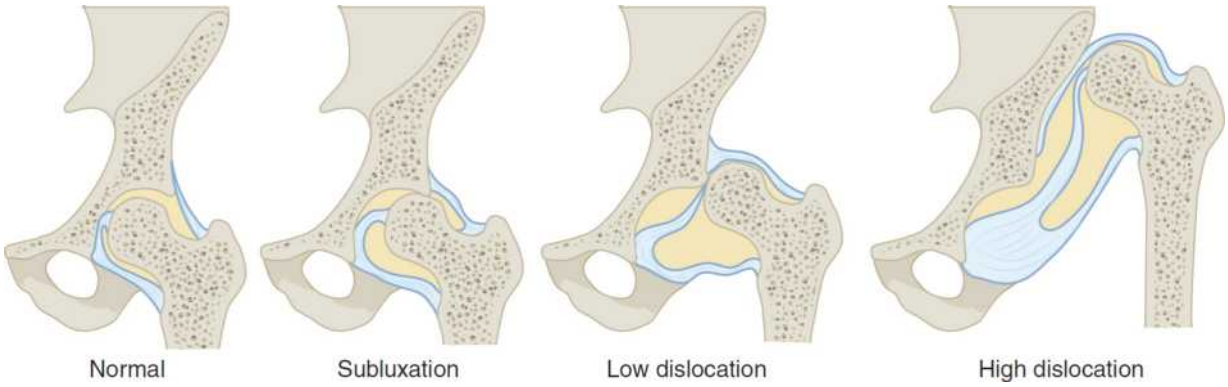


FIGURE 12-16 Developmental hip dysplasia.

Courtesy of International Hip Dysplasia Institute.

Description

With a subluxed hip, the femoral head is displaced from its normal position but still contacts a portion of the acetabulum. The articular surface of the femoral head and the acetabulum have no contact with the dislocated hip. An unstable hip is reduced in the acetabulum but can be subluxed or dislocated. Teratologic hip dysplasia refers to a more severe, fixed dislocation that occurs prenatally, usually in individuals with genetic or neuromuscular disorders.

In newborns, clinical manifestations of DDH include palpable hip instability, unequal leg lengths, and asymmetric thigh skinfolds. Gait abnormalities and limited hip abduction (due to adductor spasm) are more common in older children. Knee height is often unequal, referred to as the “Galeazzi sign.”

All infants should be screened for DDH by physical examination (e.g., Ortolani and Barlow maneuvers). However, physical examination has limited sensitivity, so imaging studies should be performed in high-risk infants. Imaging studies include ultrasonography and X-rays of the hips. If the condition goes undetected and untreated, the affected leg will become shorter, and the hip may become more painful. With any delay in recognition and treatment, the potential for correction without surgery steadily decreases. If DDH is noted in the neonate, the hip is usually reduced immediately after birth, and the acetabulum can form a nearly normal joint with growth. Hip subluxation at birth often corrects spontaneously and may be observed for two weeks without treatment.

If subluxation persists beyond two weeks of age, treatment is indicated, and referrals should be made. Closed reduction and immobilization with bracing (e.g., Pavilik harness) is the first-line treatment for children younger than 6 months. Immobilization with bracing is required for at least 6 weeks on a full-time basis. If a dislocated hip is not reduced within 3 weeks, the brace should be discontinued, and an alternative treatment initiated. Avascular necrosis of the femoral head, likely as a result of hyperabduction, and femoral nerve palsies from hyperflexion may develop with the use of the Pavlik harness.

Closed reduction under anesthesia and hip spica casting is the treatment of choice in children older than 6 months and may be performed if the Pavlik harness is unsuccessful. The hip spica case remains in place for at least 12 weeks. Splints (e.g., Frejka pillow) may also help. Padded diaper and layering diapers are not effective approaches and should not be implemented to correct DDH. Surgery may be required when other treatment fails and in children diagnosed after 6 months of age. Open reduction typically involves lengthening tendons, removing barriers to reduction, and tightening the hip

capsule. Surgical complications may include femoral head **osteonecrosis** and recurrent dislocations.

Osteogenesis Imperfecta

Osteogenesis imperfecta, often referred to as “brittle bone disease,” is a genetic collagen disorder that causes diffuse abnormal bone fragility. Sensorineural hearing loss, blue sclerae (due to a deficiency in connective tissue allowing the underlying vessels to be seen), dentinogenesis imperfecta (abnormal tooth development or deformities), and joint hypermobility may also be seen with this condition. The exact number of people with osteogenesis imperfecta in the United States is unknown, but estimates suggest a minimum of 25,000 people, and perhaps as many as 50,000, are affected (National Institutes of Health [NIH], 2022a).

There are four main types of osteogenesis imperfecta:

- Type I is autosomal dominant and the mildest form.
- Type II (i.e., neonatal lethal type or osteogenesis imperfecta congenita) is autosomal recessive, is the most severe form, and is lethal.
- Type III is autosomal recessive, progressive, and is the most severe nonlethal form.
- Type IV is autosomal dominant, is moderately severe, and has a high survival rate.

Most (90%) people who have one of the four major types have mutations in the genes encoding the pro-alpha chains of Type I procollagen (a structural component of bones, ligaments, and tendons), *COL1A1*, or *COL1A2*. Collagen is the major protein that makes up connective tissue and forms the framework around bones. Other types of osteogenesis imperfecta are rare and are caused by different gene mutations.

Respiratory failure is the most common cause of death in individuals with osteogenesis imperfecta, followed by accidental trauma. Hearing loss is present in most individuals with osteogenesis imperfecta regardless of type. With Type I, clinical manifestations are

usually limited to blue sclerae and musculoskeletal pain due to joint hypermobility. Recurrent fractures in childhood are possible. With Type II, multiple congenital fractures result in shortened extremities, sclerae are blue, and the skull is soft. Because the skull is soft, trauma during delivery can cause intracranial hemorrhage and stillbirth, or newborns may die suddenly in the first weeks after birth. Individuals with Type III have short stature, spinal curvature, and multiple recurrent fractures. Macrocephaly with triangular facies and pectal deformities are common, and scleral coloring varies. With Type IV, fractures are common in childhood, sclera are typically a normal color, and height is moderate to short.

Diagnosis of osteogenesis imperfecta is usually clinical, although no standardized criteria are available. Diagnostic procedures usually include a history, physical examination, and occasionally Type I procollagen (skin biopsy) and genetic testing (*COL1A1* or *COL1A2*). Severe osteogenesis imperfecta can be detected in utero by ultrasonography.

No cure is available, but most individuals with osteogenesis imperfecta live normal lives. Treatment focuses on managing symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength. Treatment strategies include growth hormones and bisphosphonates to increase bone density, decrease bone pain, and minimize fracture risk. Physical therapy and occupational therapy can promote bone density, improve muscle strength, and prevent injury. Use of wheelchairs, braces, and other mobility aids can help with mobility and prevent injury. Orthopedic surgery (e.g., metal rod placement) may also be necessary. Other health promotion strategies include exercise (e.g., swimming and water therapy) and proper diet. Smoking, alcohol, caffeine, and corticosteroids should also be avoided. Cochlear implants may be indicated in some patients with hearing loss.

Traumatic Musculoskeletal Disorders

Traumatic musculoskeletal disorders are usually mild and easily treated; however, occasionally these conditions can result in life-

threatening complications (e.g., **fat embolism** and **osteomyelitis**). Many of these conditions are caused by events like the ones that lead to traumatic neurologic disorders (e.g., falls, motor vehicle accidents, and sports-related injuries). Additionally, neurologic dysfunction may occur in conjunction with the musculoskeletal injury. These traumatic conditions are on the rise because of increasing numbers of children and adults participating in fitness, recreation, and sports activities. Factors contributing to these injuries include inappropriate or inadequate equipment, training, or warm-up techniques; more aggressive approaches to sports; and failure to allow minor injuries to heal.

Fractures

A fracture is a break in the rigid structure of the bone as a result of applied pressure (**FIGURE 12-17**). Fractures are the most common type of traumatic musculoskeletal disorder. They mainly occur as a primary condition because of falls, motor vehicle accidents, and sports-related injuries. Additionally, fractures can occur secondary to conditions that weaken the bone (e.g., osteoporosis, **Paget's disease**, and bone cancer). Fractures are classified based on characteristics such as the direction of the fracture line, the number of fracture lines, or other characteristics (**FIGURE 12-18**). Fracture types include the following:



FIGURE 12-17 **(A)** Compound fracture. **(B)** Greenstick fracture.

A: © Carolina K. Smith, MD/Shutterstock; **B:** © Andres Rodriguez/Shutterstock

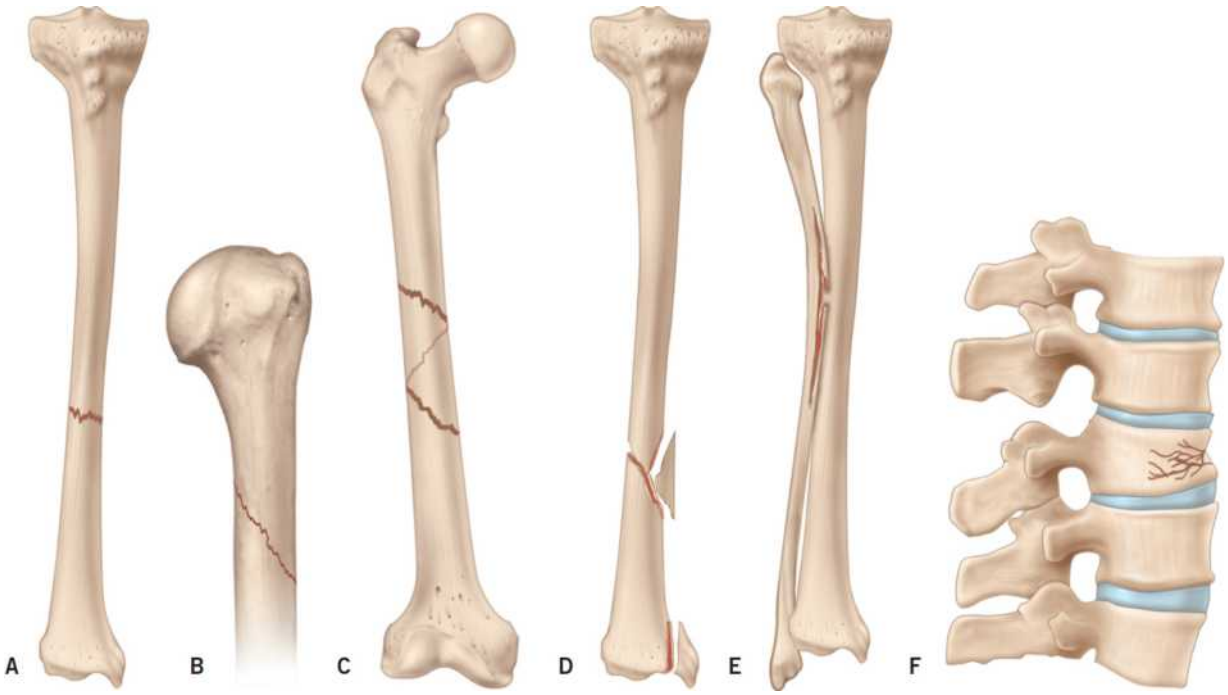


FIGURE 12-18 Classifications of fractures. **(A)** Transverse fracture of the tibia. **(B)** Oblique fracture of the humerus. **(C)** Spiral fracture of the femur. **(D)** Comminuted fracture of the tibia. **(E)** Greenstick fracture of the fibula. **(F)** Compression fracture of a vertebral body.

- **Simple fracture**—a fracture with a single break in the bone and in which bone ends maintain their alignment and position:
  - **Transverse fracture**—a fracture straight across the bone shaft
  - **Oblique fracture**—a fracture at an angle to the bone shaft
  - **Spiral fracture**—a fracture that twists around the bone shaft
- **Comminuted fracture**—a fracture characterized by multiple fracture lines and bone pieces
- **Greenstick fracture**—an **incomplete fracture** in which the bone is bent and only the outer curve of the bend is broken; commonly occurs in children because of minimal calcification and often heals quickly
- **Compression fracture**—a fracture in which the bone is crushed or collapses into small pieces

A variety of other terms may be used to describe a fracture. For example, fractures may be described based on the degree of break. **Complete fractures** occur when the bone is broken into two or more separate pieces; in contrast, in incomplete fractures, the bone is partially broken (e.g., greenstick fracture). Additionally, fractures may be described as open or closed. In **open fractures**, or compound fractures, the skin is broken (**FIGURE 12-19**). The bone fragments or edges may be angled and protrude out of the skin. Open fractures are characterized by more damage to soft tissue and are at risk for infection. In **closed fractures**, the skin is intact. **Impacted fractures** occur when one end of the bone is forced into the adjacent bone. **Pathologic fractures** result from a weakness in the bone structure secondary to conditions, such as bone tumors or osteoporosis. **Stress fractures**, or fatigue fractures, occur from repeated excessive stress. These fractures are common in the tibia, femur, and metatarsals. Finally, **depressed fractures** occur in the skull when the broken piece is forced inward on the brain.



FIGURE 12-19 Open fracture.

Courtesy of Rhonda Hunt.

When a bone breaks, blood from damaged vessels in the periosteum and bone marrow pours into the fracture and forms a hematoma, or blood clot (**FIGURE 12-20**). The break also triggers the inflammatory response. Necrosis of the broken ends of the bone occurs because of the blood vessel damage. Over time, this necrotic tissue is reabsorbed and replaced by new bone. Within a few days of the fracture, fibroblasts (connective tissue from the periosteum) invade the clot. These fibroblasts secrete collagen fibers, which form a mass of cells and fibers called a **callus**. The callus, which takes 2–6 weeks to form, bridges the broken bone ends together inside and outside. At that point, osteoblasts from the periosteum invade the callus, slowly converting the callus to bone. This ossification process can take from 3 weeks to several months (usually 4–6 weeks) to

reach completion. Healing time can vary depending on age, nutritional status, blood supply, and fracture type and location. The callus is initially a large, often palpable structure, but osteoclasts gradually remodel the bone by removing the excess bone. This remodeling process leaves little to no evidence that the fracture occurred and may take as long as a year.

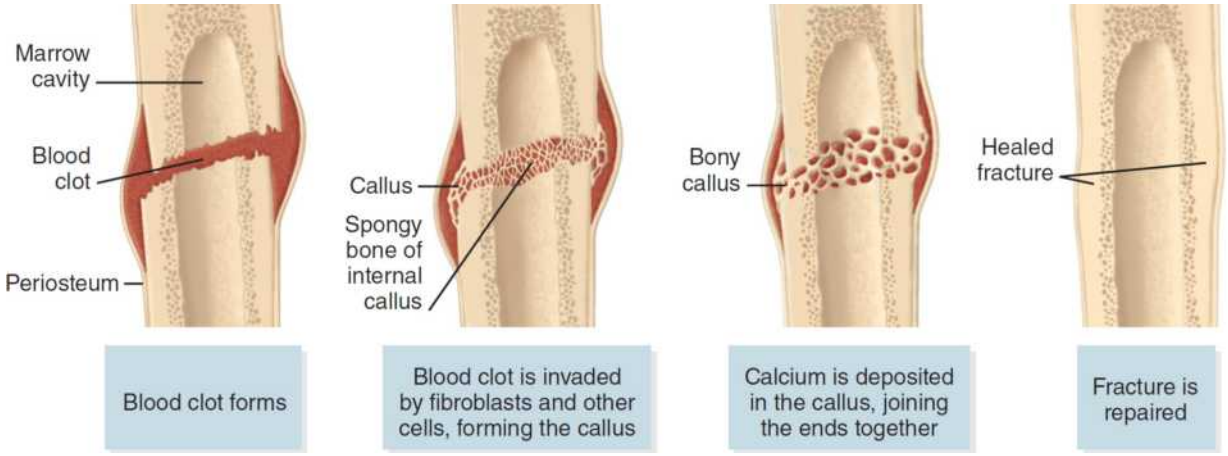


FIGURE 12-20 Stages of fracture repair.

Description

Multiple complications can result from fractures. Delayed union, malunion, or nonunion may occur due to poor nutrition, inadequate blood supply, malalignment, and premature weight bearing. Other fracture complications may include **compartment syndrome**, fat embolism, osteomyelitis, and osteonecrosis:

- Compartment syndrome is a serious condition that results from increased pressure in an internal compartment, usually the muscle fascia in the case of fractures. This pressure impinges on the nerves and blood vessels present within the compartment, potentially compromising the distal extremity. Compartment syndrome requires prompt identification and treatment to prevent permanent tissue damage. Clinical manifestations usually include excruciating pain beyond what would be expected given the injury. Compartment syndrome can be diagnosed by measuring pressures inside the muscle fascia. Treatment usually includes removing the

cast (if present) and performing an immediate fasciotomy to relieve the pressure.

- A fat embolism occurs when fat has an opportunity to enter the bloodstream, such as during surgery. Fatty marrow can also enter the bloodstream after a fracture to one of the long bones or pelvis. The outcome can be fatal if the emboli travel to vital organs, such as the lungs, brain, or heart. Clinical manifestations of fat emboli include hypoxemia, neurologic dysfunction, and petechia on the head or trunk. Treatment consists of mainly hospital-based supportive care (e.g., supplemental oxygen, mechanical ventilator, intravenous fluids), and most patients will fully recover. Fat embolism can be prevented with early immobilization of the fracture.
- Osteomyelitis refers to an infection of the bone tissue. It is a serious complication because it often goes undetected, can take months to resolve, delays healing, and can result in bone or tissue necrosis. Osteomyelitis is treated with potent antibiotic therapy (often delivered on a long-term basis) and surgery (e.g., debridement).
- Osteonecrosis, or avascular necrosis, is death of bone tissue due to a loss of the blood supply to that tissue. It can result from displaced fractures or dislocations. Osteonecrosis often requires surgical replacement of the necrotic bone and/or joint.

The following clinical manifestations of a fracture reflect the tissue trauma caused by the bone fragments as well as the disruption of function:

- Deformity (e.g., angulation, shortening, and rotation)
- Swelling at the site (due to the inflammatory process triggered by the tissue trauma)
- Inability to move the affected limb
- **Crepitus** (grating sound or sensation, usually occurring with movement)

- Pain (results from tissue trauma and muscle spasms triggered by the bone fragments)
- Paresthesia
- Muscle flaccidity progressing to spasms

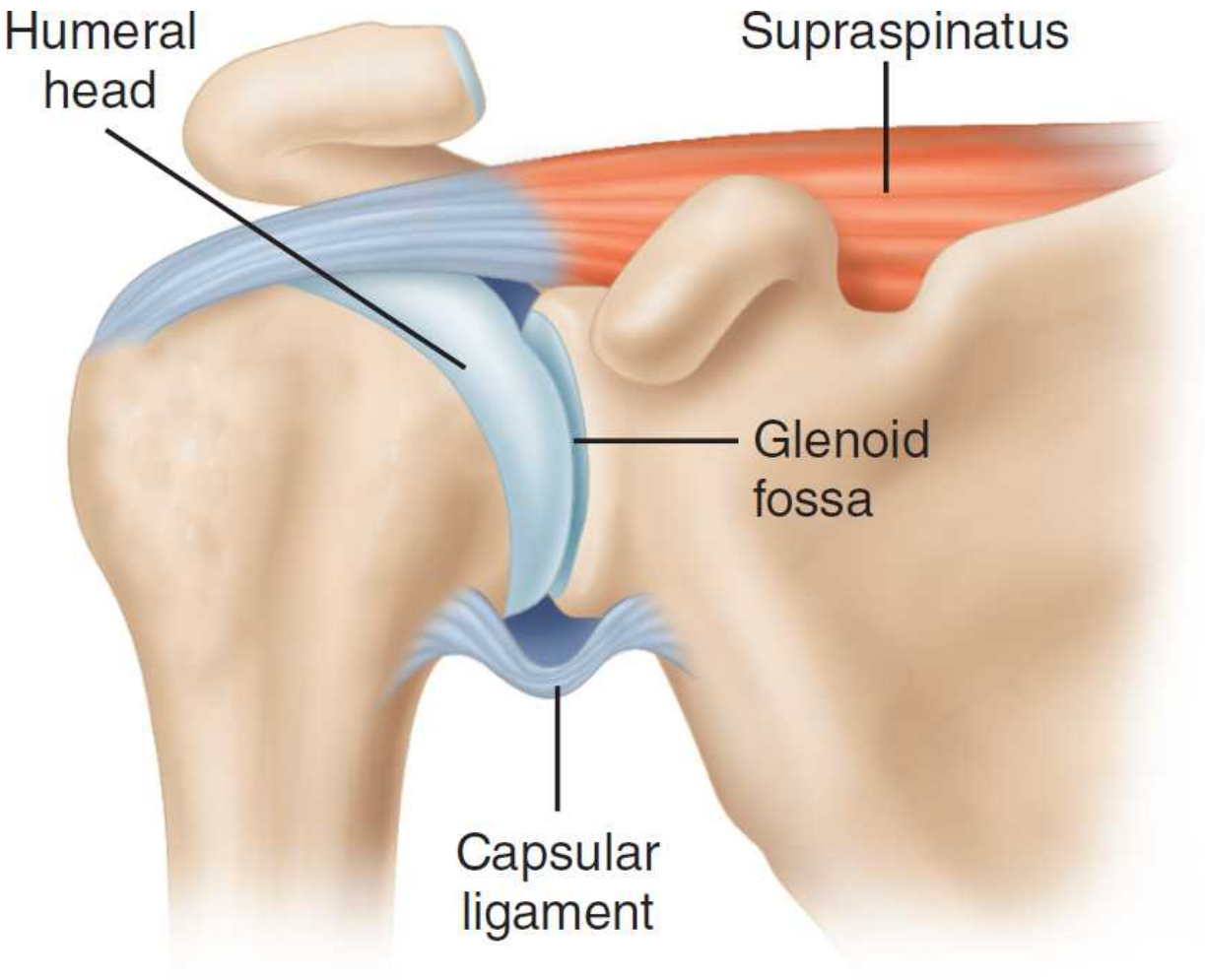
Diagnostic procedures for fractures consist of a history, physical examination (including neurovascular assessment), and X-rays. Treatment strategies include immediate immobilization with devices, such as splints or traction (application of a force or weight pulling a limb). The fracture is reduced to restore the bone to its normal position. Reduction can be accomplished with closed manipulation by applying pressure or traction or with open manipulation through surgery. During surgery, devices such as pins, plates, rods, or screws may be placed to secure the bone fragments in position. These instruments may be either internal and permanent or externally fixed and gradually retracted. Any necrotic tissue or foreign material is also removed in a process called “debridement.” When a fracture is suspected, the individual with the injury should not consume anything by mouth in case surgery is deemed necessary. Surgical repair may be delayed up to a few days after the injury to allow the edema secondary to the inflammatory response to resolve.

Immobilization of the fracture during the healing process is crucial to prevent complications. Long-term immobilization that permits bone healing to occur is accomplished with casts, splints, or traction. Traction maintains bone alignment and prevents muscle spasms. As the fracture is healing, exercise is helpful to limit muscle atrophy, joint stiffness, and contracture formation as well as to maintain adequate circulation.

Dislocation

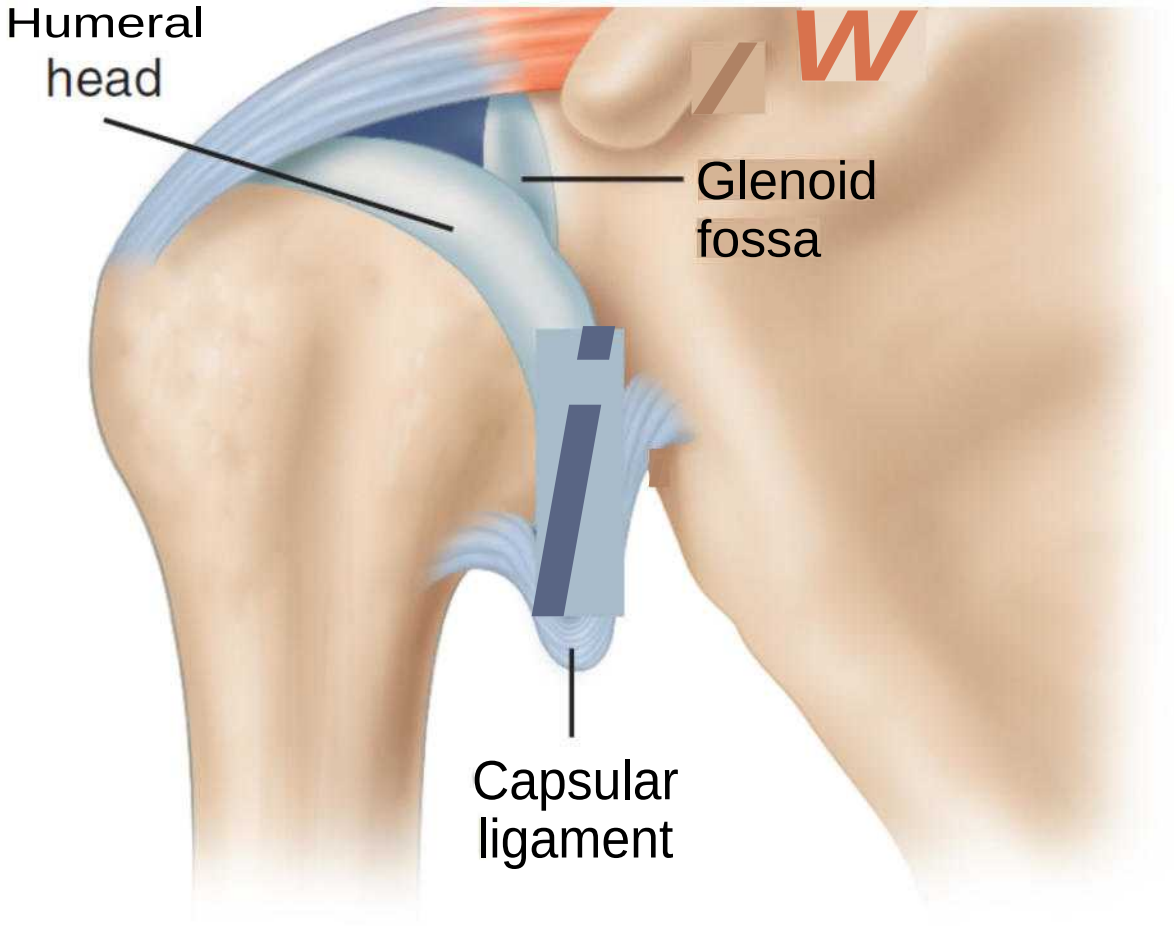
Dislocation refers to the separation of two bones where they meet at a joint (**FIGURE 12-21**). With this type of injury, the two bones are no longer in their normal position. The dislocation may involve a complete or partial (subluxation) loss of contact. Such an injury causes deformity and immobility of the joints and may damage nearby

ligaments and nerves. Dislocations usually result from a sudden impact to the joint (e.g., blow, fall, or other trauma) but may also be congenital (e.g., DDH) or pathologic (e.g., arthritis, ligament injuries, paralysis, or neuromuscular disease). Any joint can be affected, but dislocations are especially common in the shoulder and clavicle joints.



Normal





Anterior dislocation

FIGURE 12-21 Anterior dislocation of the shoulder.

Description

application to practice

Gina Dickerson is a 34-year-old woman who is being admitted to the orthopedic unit following a motor vehicle accident. She was driving her car through an intersection when someone ran a stop sign and hit her vehicle. Ms. Dickerson was diagnosed in the emergency department with a compound fracture of the left femur and a comminuted fracture of the left ankle.

When this patient arrived in the orthopedic unit at 4:00 p.m., her left leg was immobilized with an air cast, and ice bags were applied. She was medicated in the emergency department with morphine sulfate, 2 mg intravenously at noon. The nursing admission assessment data revealed that Ms. Dickerson had no significant medical problems. Her vital signs on admission to the unit were as follows: temperature, 99.2°F; pulse, 90 beats per minute; respirations, 24 breaths per minute; oxygen saturation, 95%

on room air; and blood pressure, 140/80 mm Hg. She was scheduled for surgery in the morning to repair both fractures.

1. Explain the types of fractures this patient has incurred.
2. List the top three priority nursing interventions for this patient on admission.
3. What are some complications that this patient is at high risk for developing?
4. What is the significance of the patient's vital signs?

Clinical manifestations of a dislocated joint may include the following signs and symptoms:

- Visibly out-of-place, discolored, or deformed joint
- Limited movement
- Swelling or bruising
- Intense pain, especially with movement or weight bearing
- Paresthesia near the injury (often distal to the injury)

Diagnostic procedures for dislocations consist of a history, physical examination, X-rays, and MRI. Immediately following the injury, treatment strategies focus on limiting tissue damage:

- Immobilize the area above and below the joint with a splint or sling in the position in which the joint was found.
- Do not attempt to straighten or move the joint.
- Assess for tissue perfusion (e.g., perform a blanch test on skin in the affected area) and report any suspected tissue perfusion impairment immediately.
- Apply ice to ease pain and swelling.
- Do not move the person unless the injury has been completely immobilized.
- Do not move a person with an injury to any weight-bearing joint (e.g., hip, pelvis, or knees) unless it is absolutely necessary.
- Do not give the person anything by mouth in case surgery is needed.

After the injury has been stabilized, treatment depends on the site and severity of the injury. Reduction may occur spontaneously, or gentle manipulation may be used to return the bones to their usual position (closed reduction). Depending on the amount of pain and swelling, a local anesthetic or even a general anesthetic may be administered before a closed reduction is performed. Pain usually subsides after the joint is reduced. Surgical reduction (open reduction) may be necessary if blood vessels or nerves are damaged or if the dislocation is a recurrent injury (common with dislocations of the shoulder).

After the reduction, the joint will need to be immobilized with a splint or sling for several weeks. Analgesics and muscle relaxants may be required during this recovery period. After the splint or sling is removed, a gradual rehabilitation program (primarily physical therapy) designed to restore the joint's range of motion and strength is often needed. Strenuous activity involving the injured joint should be avoided until full movement, normal strength, and stability have been regained.

Some dislocations, such as those involving the hip, may need up to several months to heal. Healing of dislocations is also slowed when ligament or soft-tissue damage is present. Preinjury function is usually restored, but some residual deficits may occur in more severe injuries.

Sprains

A **sprain** is an injury to a ligament that often involves stretching or tearing of the ligament. Sprains occur when a joint is forced to move into an unnatural position (e.g., twisting one's ankle). The severity of the sprain is described using a grading scale (**TABLE 12-2**; **FIGURE 12-22**). Of all sprains, ankle and knee sprains occur most often. Such an injury triggers the inflammatory process, resulting in edema and pain at the site. Additionally, blood vessels may be damaged, resulting in bleeding and bruising. Bleeding into the joint capsule can delay healing. If a tear occurs, granulation tissue develops along with the inflammation. Collagen fibers form to create a link between the torn ligament fragments, and eventually fibrous tissue binds them together. Sprained ligaments swell rapidly and are painful. Generally,

the degree of pain reflects the severity of injury. Other clinical manifestations may include joint stiffness, limited function, disability, and discoloration (usually bruising).

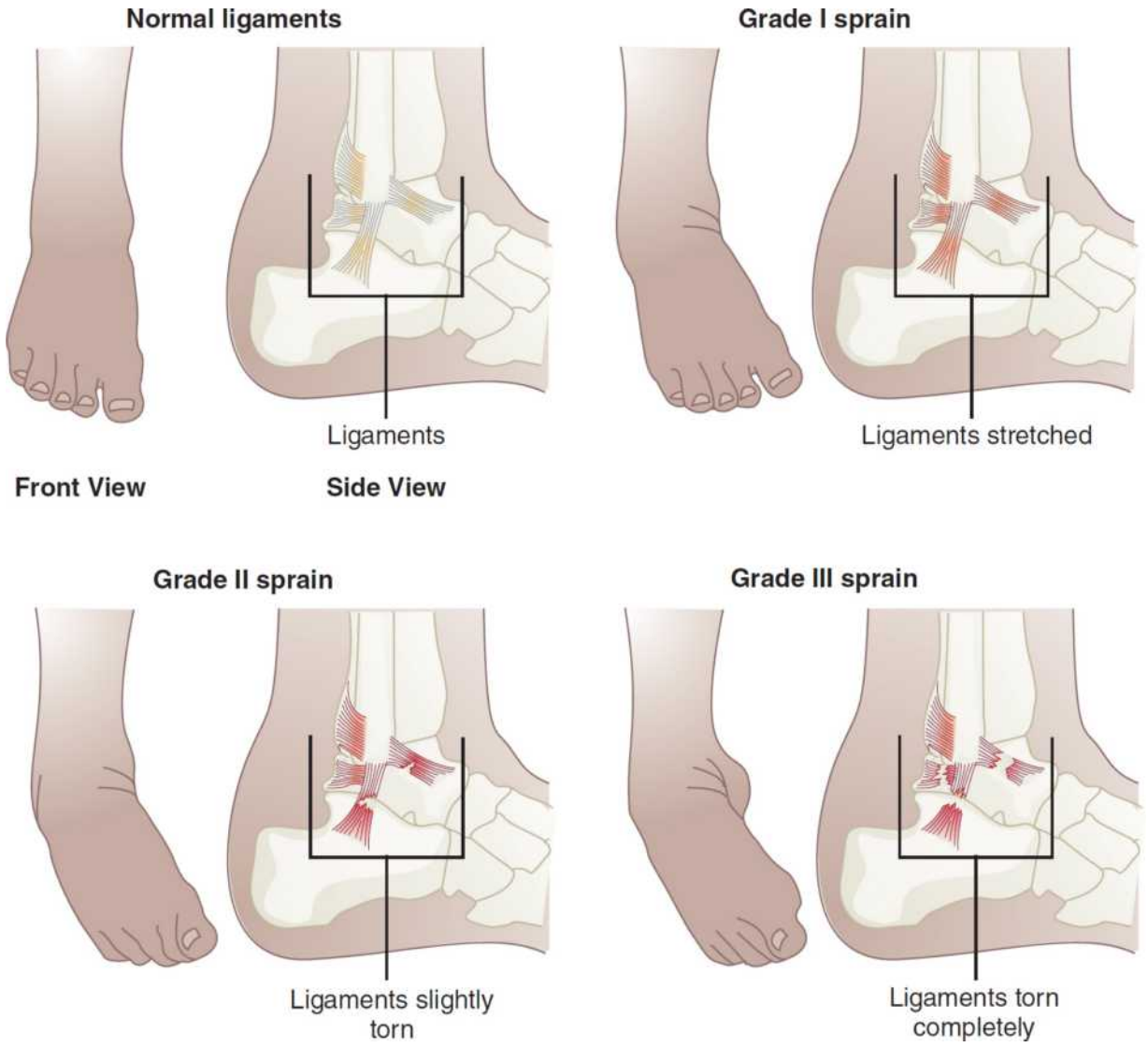


FIGURE 12-22 Sprain grading system.

Description

TABLE 12-2 Sprain Grading System

Grade	Degree of Damage	Pathophysiology	Clinical Findings and Implications
Grade I	Minimal damage or disruption	Microscopic tearing of collagen fibers; joint is stable	Tender without swelling No bruising Active and passive range of motion is painful Prognosis is good, with no expectation of instability or functional loss
Grade II	Moderate damage	Complete tears of some but not all collagen fibers in the ligament	Moderate swelling and bruising Very tender, with more diffuse tenderness than grade I Range of motion is very painful and restricted Joint may be unstable, and functional loss may result
Grade III	Complete disruption of the ligament	Complete tear or rupture of ligament	Prognosis is variable (injury may require surgery) Requires a prolonged healing/rehabilitation period

Description

Diagnostic procedures for sprains usually consist of a history and physical examination. X-rays may be performed if fractures are also suspected, and an MRI may be undertaken with severe injuries.

Although surgical repair may be needed to treat ligament tears, most sprains can be managed at home. Treatment strategies include the following measures:

- Apply ice immediately to reduce pain and swelling. Wrap the ice in a cloth—do not place ice directly on the skin because it can worsen tissue damage.
- Immobilize the joint with a splint or an elastic wrap or bandage (e.g., ACE bandage).
- Elevate the swollen joint above the level of the heart.

Learning Points

Treatment for Soft-Tissue Injuries

Treatment strategies for soft-tissue injuries, such as sprains and strains, can be remembered using the acronym PRICE.

P **P**rotect the injured limb from further injury by not using the joint. The patient may need crutches or splints.

R **R**est the injured limb, but do not avoid all activity; exercise other muscles to minimize deconditioning.

I Ice the affected area (e.g., cold pack, a slush bath, or a compression sleeve filled with cold water) as soon as possible after injury to limit swelling and continue to ice the area for 10–15 minutes (any longer than that may cause tissue damage) 4 times a day for 48 hours.

C Compress the area with an elastic wrap or bandage; compressive wraps or sleeves made from elastic or neoprene are best.

E Elevate the injured limb above the level of the heart whenever possible to help prevent or limit swelling.

- Rest the affected joint for several days and gradually increase activity.
- Provide nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., aspirin and ibuprofen) to relieve pain and inflammation.
- Keep pressure off the injured area until the pain subsides (usually 7–10 days for mild sprains and 3–5 weeks for severe sprains). The injured person may require crutches when walking.
- Repair ligament tears surgically.
- Rehabilitate the injured area (usually including physical therapy) to regain joint motion and strength, beginning within 1 week.

Strains

A **strain** is an injury to a muscle or tendon that often involves stretching or tearing of the muscle or tendon (**FIGURE 12-23**). Strains may occur suddenly or develop over time. Also called a "pulled muscle," a strain results from an awkward muscle movement or excess force that can be caused by an accident, improper use of a muscle, or overuse of a muscle. Excessive physical activity, improper stretching prior to activity, and poor flexibility can contribute to this injury. The lower back is the most common site for strains. The severity of the strain is described using a grading scale similar to that used for sprains (see Table 12-2).

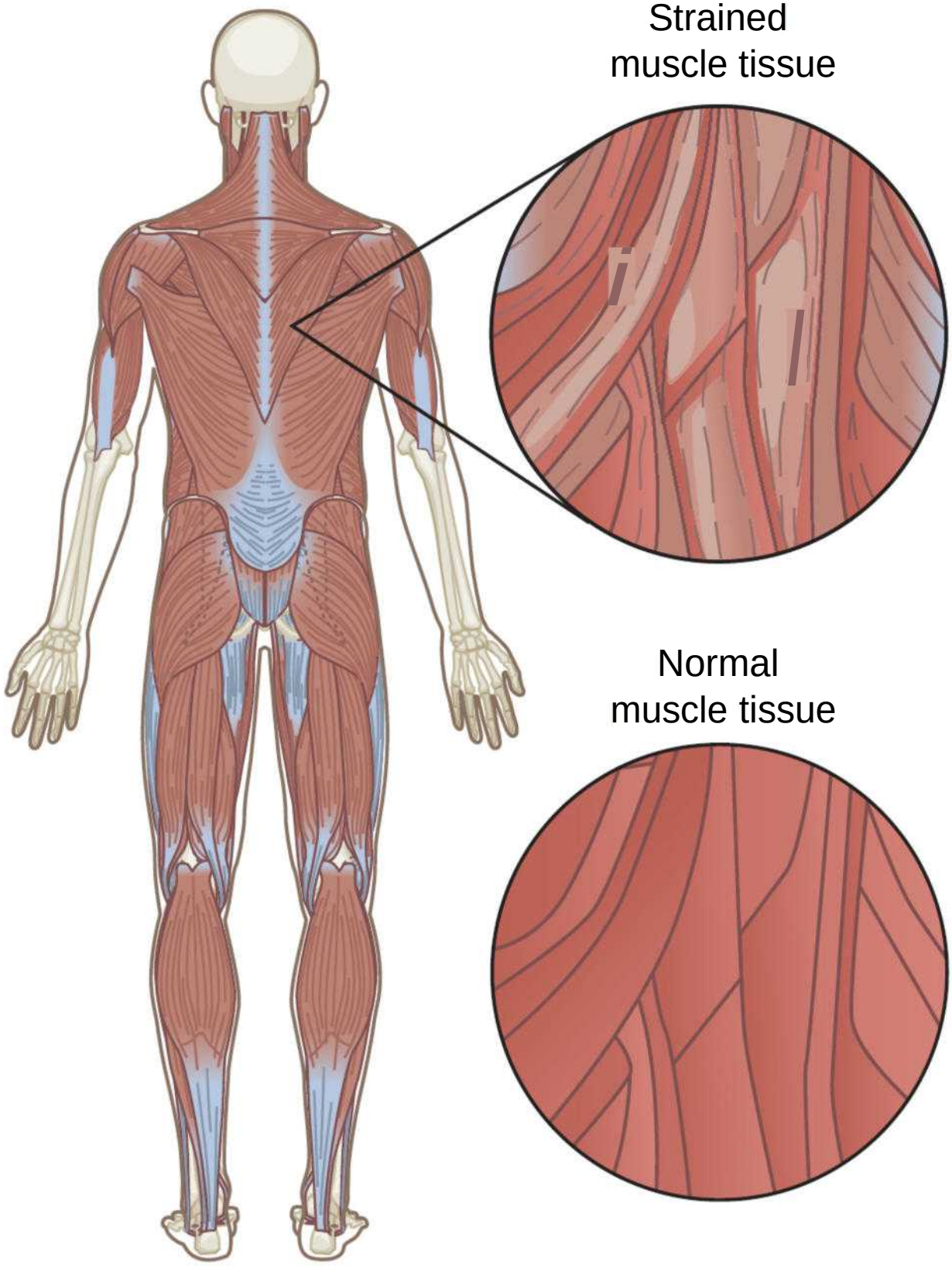


FIGURE 12-23 Strained muscle tissue.

Description

Strains follow the same pathogenesis pathway as sprains (i.e., inflammation, granulation, and bleeding). Scar tissue may form as the tissue heals. Clinical manifestations of a strain include pain, stiffness, difficulty moving the affected muscle, skin discoloration (often bruising), and edema.

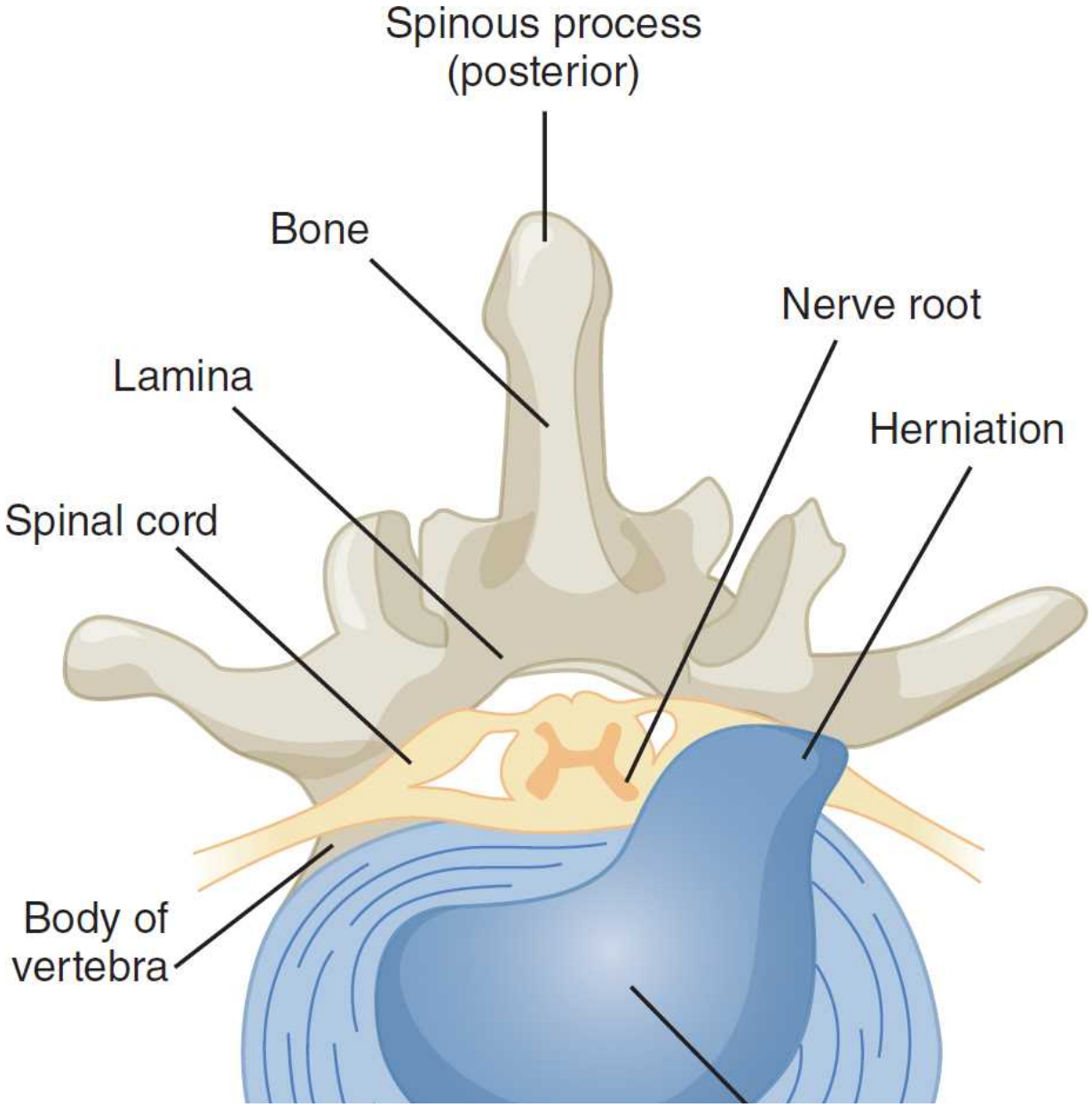
Diagnostic procedures for strains may consist of a history, physical examination, ultrasound, and MRI. X-rays may be performed if fractures are also suspected. Treatment strategies for strains are similar to those for sprains:

- Apply ice immediately to reduce pain and swelling; wrap the ice in cloth, and do not place ice directly on the skin because it can worsen tissue damage.
- Use ice for the first 3 days; after then, either heat or ice may be helpful.
- Rest the affected muscle for at least a day.
- Keep the affected muscle elevated above the level of the heart (if possible).
- Avoid using the affected muscle until pain subsides; then, advance activity slowly and in moderation.
- Use NSAIDs to relieve pain and inflammation.
- Use muscle relaxants to relieve muscle stiffness.
- Repair severe tendon tears surgically.
- Rehabilitate the injured area (usually including physical therapy) to regain muscle movement and strength as necessary.

Herniated Intervertebral Disk

With a **herniated intervertebral disk**, the nucleus pulposus (the inner gelatinous component of the intervertebral disk) protrudes through the annulus fibrosus (the tough outer covering of the disk) (**FIGURE 12-24**). This condition may also be called a “slipped disk” or “ruptured disk.” The tear in the capsule may occur suddenly or gradually. Such

a condition may be considered either an orthopedic or a neurologic problem because protrusions into the extradural space can exert pressure on the spinal cord, interfering with nerve conduction (**FIGURE 12-25**). Sensory, motor, or autonomic function may be impaired depending on the location of injury. The most frequently involved vertebrae are those in the lumbosacral region, but some injuries may involve the cervical disks. If pressure on the nerve tissue or blood supply is prolonged or severe, permanent neurologic damage may result.



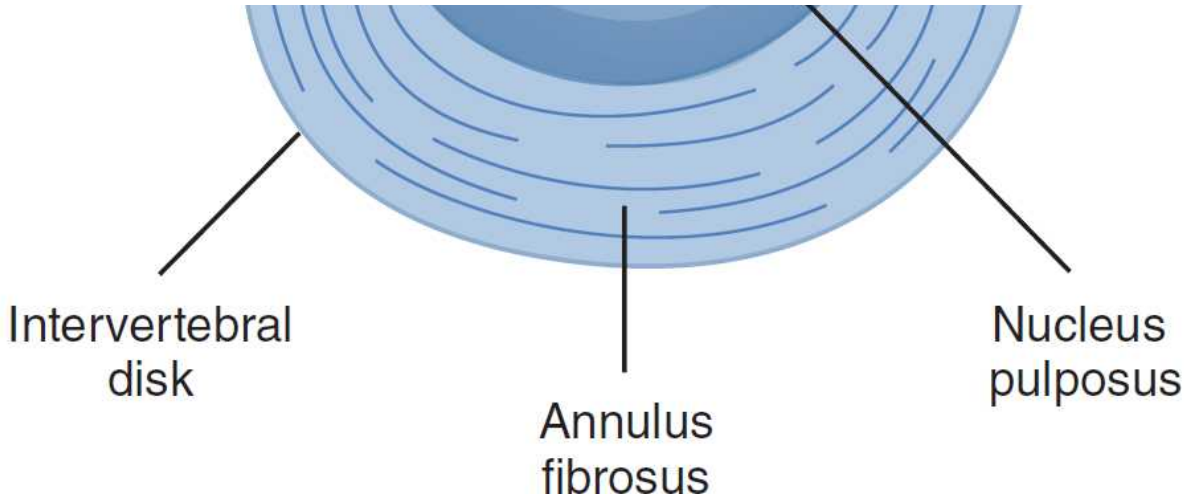
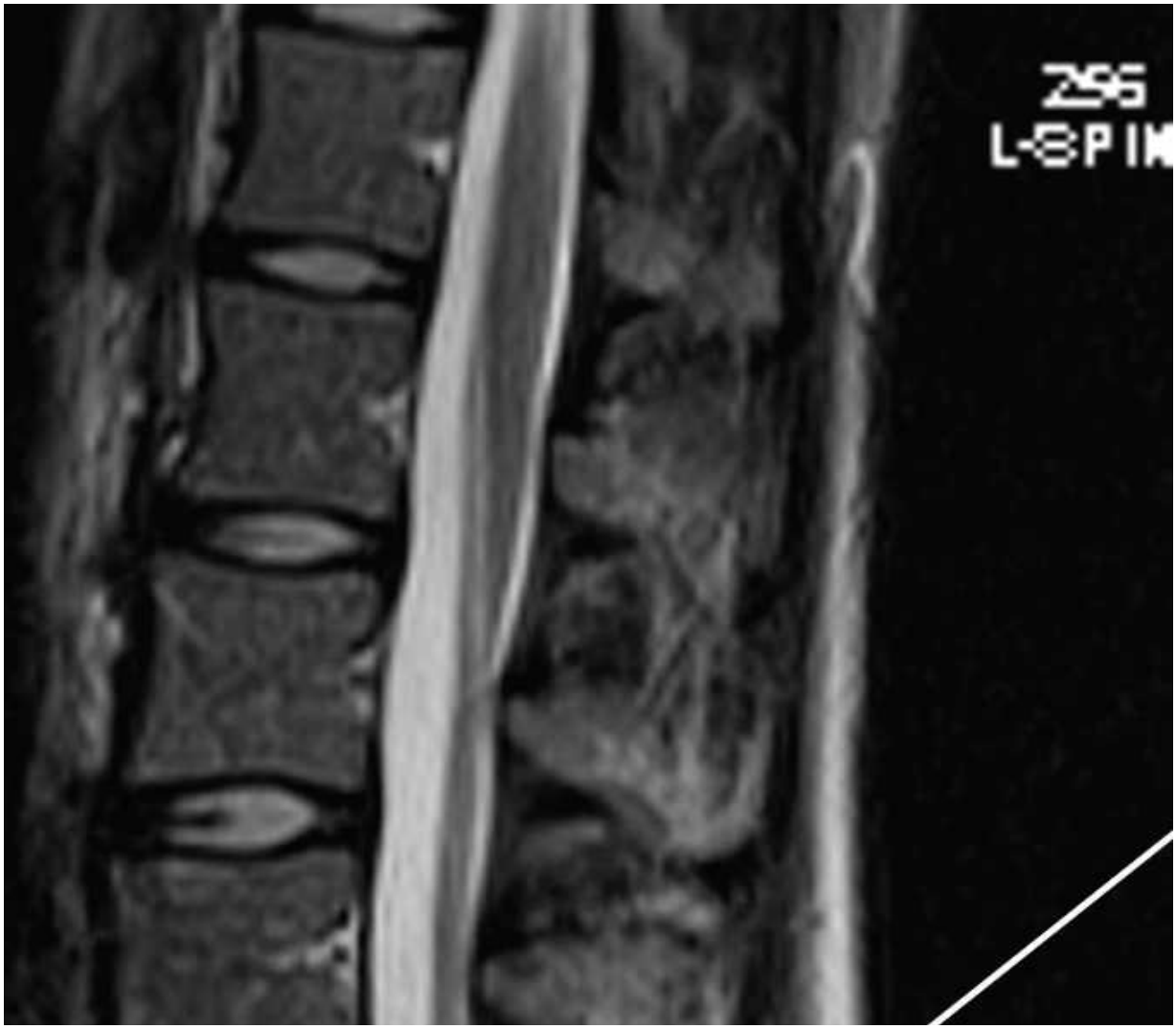


FIGURE 12-24 Herniated vertebral disk.

Description



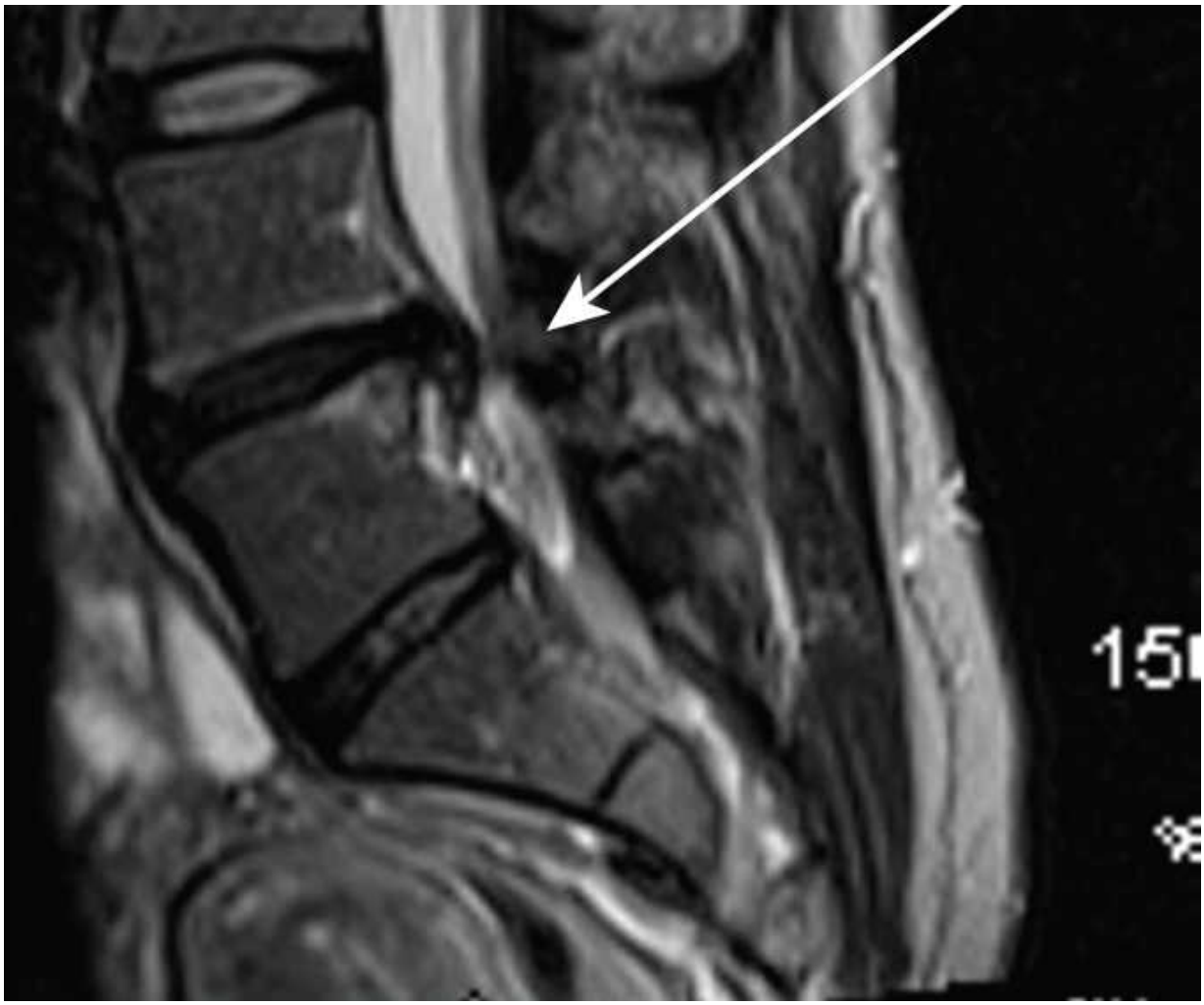


FIGURE 12-25 Spinal cord compression by a herniated disk.

Courtesy of Steven Goldstein, MD.

A herniated intervertebral disk often occurs due to improper body mechanics, lifting heavy objects, repetitive use, or trauma (e.g., a fall or a blow to the back). Additional contributing factors may include vertebral stress secondary to obesity, degenerative changes secondary to aging, and demineralization secondary to metabolic conditions (e.g., osteoporosis).

Herniated intervertebral disks may be asymptomatic. When present, manifestations may include the following symptoms:

- Sciatica (a radiating, aching pain, sometimes with tingling and numbness, that starts in the buttock and extends down the back or

side of one leg)

- Pain, paresthesia, or weakness in the lower back and one leg, or in the neck, shoulder, chest, or arm
- Low back pain or leg pain that is worsened by sitting, coughing, sneezing, laughing, bending, or walking
- Limited mobility

Spinal tumors and herniated intervertebral disks may present similarly, so a differential diagnosis should be made. Diagnostic procedures may consist of a history, physical examination (including neurologic assessment), spinal X-rays, spinal CT, spinal MRI, nerve conduction study, myelogram (injection of contrast medium into the spinal fluid, followed by X-rays), and electromyography.

Immediate treatment for herniated intervertebral disks may include a short period of rest, analgesics, NSAIDs, muscle relaxants, physical therapy (including back-strengthening exercises), heat/cold application, and traction. Most people will recover with such treatment and return to their normal functioning, but a small number of patients will need further treatment, such as injections (e.g., corticosteroid and chemonucleolysis) into the site or surgical repair (e.g., diskectomy, laminectomy, and spinal fusion). Weight loss may be beneficial if the patient is overweight.

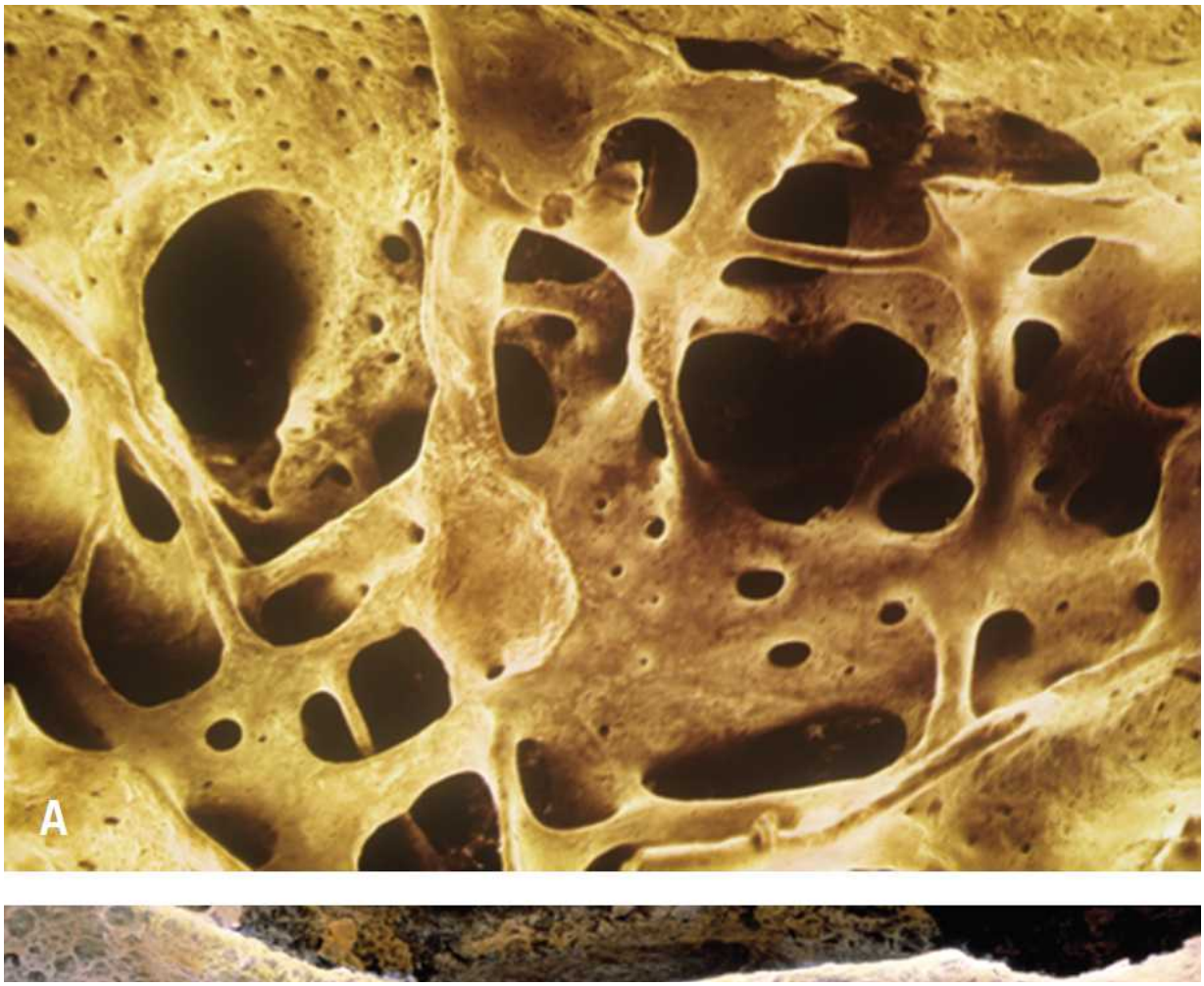
Metabolic Bone Disorders

Metabolic bone disorders encompass a variety of bone conditions associated with mineral abnormalities. These abnormalities may be caused by genetic factors, medications, or dietary deficits. Metabolic bone disorders are usually treated easily once identified, but if left untreated, they can lead to significant complications (e.g., electrolyte disturbances and fractures).

Osteoporosis

Osteoporosis is a condition characterized by a progressive loss of bone calcium that leaves the bones brittle (**FIGURE 12-26**). This loss

can occur due to multiple pathogenetic mechanisms that interact to cause either a decrease in osteoblast activity or an increase in osteoclast activity. The spongy bone becomes porous, particularly in the vertebrae and wrist, and the compact bone becomes thin (**FIGURE 12-27**). Osteoporosis can occur as a primary (nearly all cases) or secondary condition. The major mechanisms of bone loss may involve local changes in cytokine production (e.g., receptor activator of nuclear factor kappa-B ligand [RANKL]) that increase bone resorption by promoting differentiation and maturation of osteoclasts, impaired formation response during bone remodeling, and other factors that affect bone resorption (e.g., parathyroid hormone and vitamin D). Secondary osteoporosis occurs from causes that further accelerate bone loss (e.g., chronic kidney disease, corticosteroid use, nutritional deficits, and immobilization).



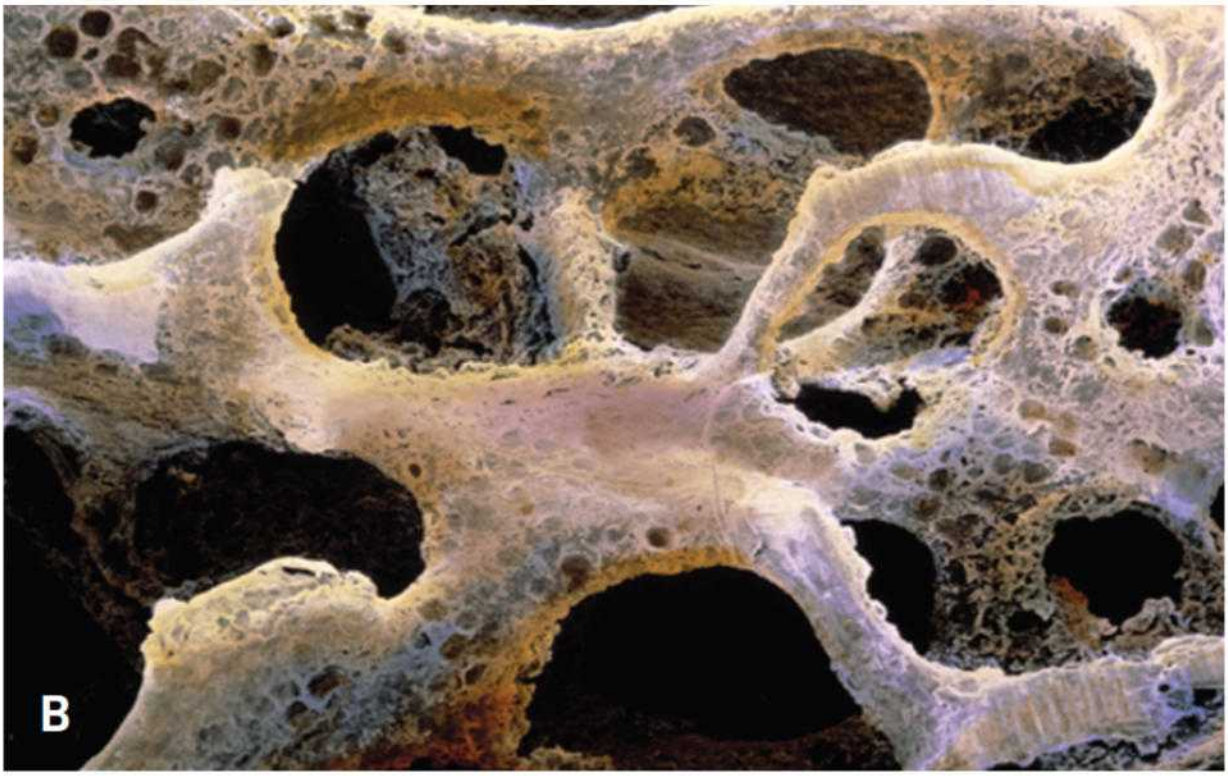


FIGURE 12-26 Osteoporosis. The loss of estrogen or prolonged immobilization weakens bone. In these situations, bone is dissolved and becomes brittle and easily breakable. **(A)** Normal bone. **(B)** Bone weakened by osteoporosis.

A: © Photo Insolite Realite/Science Source; **B:** © Professor Pietro M. Motta/Science Source

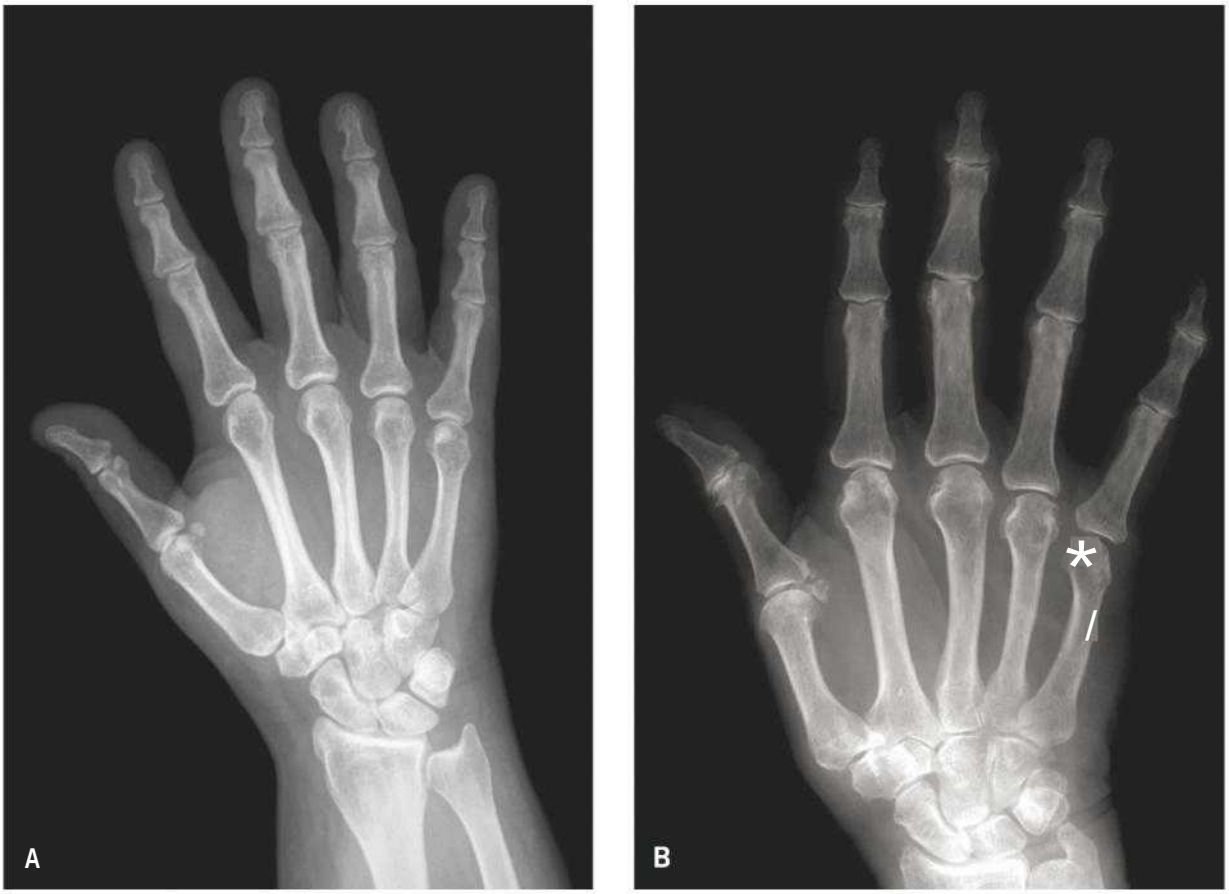


FIGURE 12-27 Bone changes from osteoporosis. **(A)** An X-ray of normal bones. **(B)** An X-ray of bones affected by osteoporosis.

A: © picbyst/Shutterstock; **B:** © Medical Body Scans/Science History Images/Alamy Stock Photo

The incidence of this common disease is affected by factors including genetic, dietary, and hormonal influences. Approximately 54 million Americans have osteoporosis and low bone density, putting them at risk for osteoporosis (Bone Health and Osteoporosis Foundation, 2023).

By age 20, the average woman has acquired most of her skeletal mass. Subsequently, a large decline in bone mass occurs with advanced age, increasing the risk of osteoporosis. For women, this decrease occurs around the time of menopause because of hormonal changes. A person with high bone mass as a young adult is more likely to have a higher bone mass later in life; therefore, achieving

maximum bone mass in young adulthood is important for maintaining bone health throughout the life span. In particular, adequate calcium consumption and physical activity (including weight-bearing exercises) early in life are vital to achieve maximum bone mass in adulthood.

Deficient intake of protein, vitamin C, and vitamin D, as well as excessive intake of phosphorus (which is present in high levels in soda), also increases the risk of osteoporosis. Individuals who have had gastrointestinal procedures, such as a gastrectomy or gastrointestinal bypass, are at particular risk of developing osteoporosis because of the nutritional deficits that often occur as a result of these surgeries. In addition, Caucasians (especially those with fair skin tone) and Asians are at higher risk for developing osteoporosis because of their (genetically determined) smaller bones. Other risk factors include smoking, excessive alcohol or caffeine consumption, use of certain medications (e.g., corticosteroids, chemotherapy, thyroid replacements, heparin, and antacids), specific health conditions (e.g., Cushing disease, thyroid dysfunction, hyperparathyroidism, bone tumors, malabsorption, and anorexia nervosa), being underweight, and family history.

Osteoporosis increases an individual's risk of bone fractures, especially in the wrist, hip, and spine. An estimated one in two women and one in four men aged 50 or older will experience a fracture secondary to osteoporosis. This risk for fractures significantly increases mortality rates in the elderly, particularly in individuals who experience hip fractures (20% of whom will die within a year of the fracture).

Osteoporosis is often asymptomatic in its early stages, and a fracture may be the first indication of its presence. As the disease progresses, clinical manifestations may include the following signs and symptoms:

- **Osteopenia** (bone mass that is less than expected for age, ethnicity, or gender)
- Bone pain or tenderness
- Fractures with little or no trauma

- Low back and neck pain
- Kyphosis (**FIGURE 12-28**)

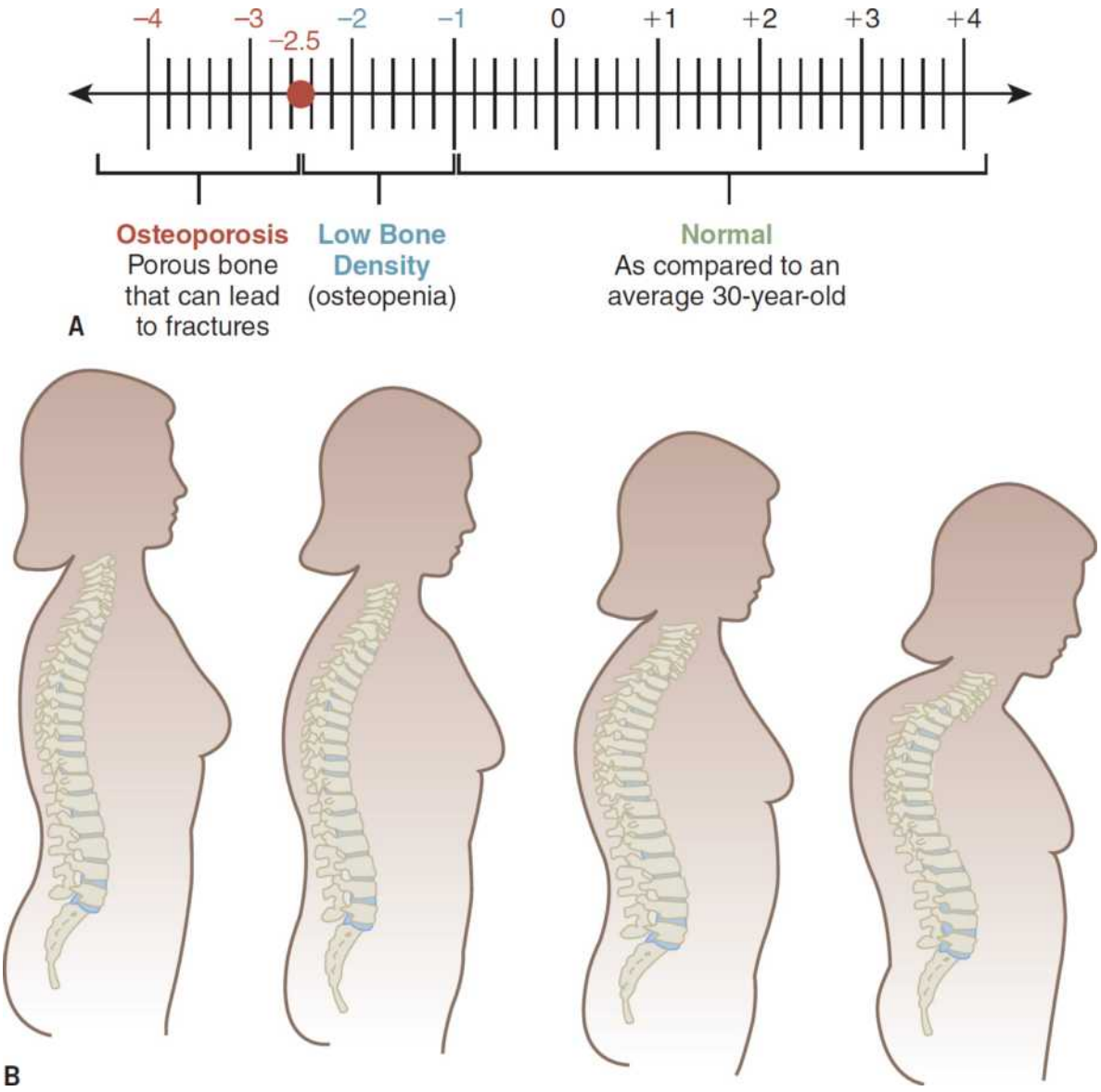


FIGURE 12-28 **(A)** Kyphosis and height changes associated with osteoporosis. **(B)** T-score interpretation.

B: Data from Understanding Bone Density Results, Your T-score and Z-score. Explained by American Bone Health January 13, 2020. Retrieved from https://americanbonehealth.org/bone-density/understanding-the-bone-density-t-score-and-z-score/

Description

* Height reduction (as much as 6 inches) over time

Because of the high prevalence rates of this disease, screening for osteoporosis should be conducted periodically in those persons at risk. Diagnostic procedures include a history, physical examinations, bone mineral density scans (e.g., dual energy X-ray absorptiometry [DEXA]), X-rays, spinal CT, and serum tests (e.g., calcium, thyroid hormones, parathyroid hormone, estrogen, and vitamin D). The DEXA results show bone mineral density reflected with a T-score and a Z-score. A T-score compares the individual's bone mineral density to that of an average healthy 30-year-old adult, reporting the result as a standard deviation from the mean (see Figure 12-28). A Z-score compares the individual's bone mineral density to that of an average person of that age and gender, reporting it as a standard deviation from the mean. A Z-score can be helpful in diagnosing secondary osteoporosis.

Myth Busters

Osteoporosis is a common condition associated with several myths that warrant discussion.

Myth 1: People with osteoporosis can feel their bones getting weaker.

Osteoporosis often has no apparent symptoms. In fact, breaking a bone may be the first clue that someone has osteoporosis. Some people may learn they have osteoporosis after they lose height from one or more vertebral fractures. These fractures can even occur without any noticeable pain. Thus, individuals at risk should be screened for this often "silent" disease.

Myth 2: Children and teens do not need to worry about their bone health.

Although osteoporosis typically appears in older populations, building strong bones and preventing osteoporosis begin in youth. Bone mass peaks around the third decade of life. Being physically active, getting enough calcium and vitamin D early, and maintaining these habits throughout life can build strong bones for later in life.

Myth 3: Osteoporosis isn't serious.

This myth is important to dispel. The fractures that can result from osteoporosis can be very painful and have serious complications. Older individuals are at particular risk for life-altering and life-threatening effects from these fractures. These individuals tend to be immobile for longer periods of time because of their extended healing time, which puts them at risk for problems associated with immobility (e.g., renal calculi, thrombus, constipation, decubiti, and incontinence).

Data from Bone Health. (2023). What is osteoporosis and what causes it? Retrieved from https://www.nof.org/patients/what-is-osteoporosis/

Treatment strategies for osteoporosis focus on minimizing further bone loss and, in some cases, restoring bone density. These strategies may include the following measures:

- Proper nutrition (especially increasing dietary calcium and vitamin D intake)
- Increasing physical activity (including weight-bearing activities)
- Eliminating modifiable risk factors (e.g., smoking cessation and limiting alcohol and caffeine consumption)
- Pharmacologic therapies, including the following:
  - Bisphosphonates (which inhibit bone breakdown, preserve bone mass, and increase bone density)
  - Estrogen receptor modulators (which mimic estrogen)
  - Calcitonin (which increases calcium and phosphate deposits in the bone)
  - Anabolic agents (e.g., parathyroid hormone analogues; raises serum calcium)
  - Romosozumab (a monoclonal antibody against sclerostin, a protein made by osteocytes, with both antiresorptive and anabolic effects)
- Safety measures (e.g., assistive devices, handrails, and removal of clutter)
- Pain management (e.g., analgesics, heat and cold application, and relaxation techniques)
- Surgical repair of fractures or weakened bones

Rickets and Osteomalacia

Rickets is a softening and weakening of bones in children, usually because of an extreme and prolonged vitamin D, calcium, or phosphate deficiency. When this condition occurs in adults, it is called **osteomalacia**. If the blood levels of these minerals become too low, calcium and phosphate are released from the bones to maintain homeostasis. This shift of minerals out of the bone leads to weak and soft bones.

Vitamin D plays an essential role in promoting absorption of calcium and phosphorus from the gastrointestinal tract. This vitamin is absorbed from food or produced by the skin when exposed to sunlight. Insufficient vitamin D production by the skin may occur in people who live in climates with little exposure to sunlight, who must stay indoors (e.g., bedbound or institutionalized persons), who work indoors during the daylight hours, or who have dark skin. Dietary deficiency may occur with persons who are lactose intolerant, do not drink milk products, or follow a vegetarian diet. Infants who are only breastfed may also develop vitamin D deficiency because human milk does not supply the proper amount of vitamin D. Using strong sunscreen and limiting sun exposure to minimize skin cancer risk may also increase the risk for vitamin D deficiency. Conditions that reduce the digestion or absorption of fats (e.g., celiac disease, cystic fibrosis, and undergoing a gastrectomy) will make it more difficult for vitamin D to be absorbed into the body.

Insufficient dietary calcium and phosphorus intake can also lead to rickets, although this condition is rare in developed countries because calcium and phosphorus are found in both milk and green vegetables —which are generally plentiful in the diets of such countries. Rickets may also occur because of genetic influences. Hereditary rickets occurs when the kidneys are unable to reabsorb phosphate. For this reason, rickets may occur in some individuals with renal disease. Occasionally, this metabolic bone disorder may arise in children who have liver disorders or who cannot convert vitamin D to its active form.

Clinical manifestations of rickets and osteomalacia develop slowly, as the bones weaken over time. Rickets may become apparent as the soft bones cannot support the growing child. Manifestations in adults and children usually include the following signs and symptoms:

- Skeletal deformities (e.g., bowed legs, asymmetrical skull, scoliosis, kyphosis, pelvic deformities, sternum projection) (**FIGURE 12-29**)



FIGURE 12-29 Rickets.

© Bunsinth-Nan-Pua/Shutterstock

- Fractures
- Delayed growth in height or limbs
- Dental problems (e.g., defects in tooth structure, dental caries, poor enamel, delayed tooth formation)
- Bone pain (usually a dull, aching pain or tenderness in the spine, pelvis, and legs)

- Muscle cramps or weakness
- Difficulty with ambulation or waddling gait

Diagnostic procedures for rickets and osteomalacia include a history, physical examination, serum mineral levels, serum parathyroid hormone levels, serum alkaline phosphatase, X-rays, and a bone density study. Treatment focuses on correcting or managing the underlying cause. Providing calcium, phosphorus, or vitamin D to remedy a deficiency will eliminate most symptoms. The body's vitamin D levels can be increased through dietary intake (e.g., fish, liver, and processed milk), exposure to moderate amounts of sunlight, or administration of vitamin D supplements. Calcium levels can be increased through dietary intake (e.g., dairy products; dark green, leafy vegetables; and nuts). Positioning or bracing may be used to reduce or prevent deformities associated with rickets and osteomalacia, although some skeletal deformities may require corrective surgery.

Paget's Disease

Paget's disease is a progressive condition characterized by abnormal bone destruction and remodeling, which results in bone deformities (**FIGURE 12-30**). In the usual bone metabolism process, old bone is recycled into new bone throughout the life span. In Paget's disease, the rate at which old bone is broken down and new bone forms is distorted—that is, bone turnover proceeds at 20 times the normal rate. Excessive bone destruction occurs along with the replacement of bone by fibrous tissue and abnormal bone. The new bone is bigger but weakened and filled with new blood vessels (**FIGURE 12-31**). Over time, Paget's disease results in fragile, misshapen bones. This disease may be present in only one or two areas of the skeleton, or it may occur throughout the body. Paget disease often involves the pelvis, long bones, skull, and vertebrae.







FIGURE 12-30 Radiology image of Paget's disease.

© Medical-on-Line/Alamy Stock Photo



FIGURE 12-31 Bone thickening associated with Paget's disease.

© Dr. P. Marazzi/Science Source

The exact cause of Paget's disease is unknown, but it is thought to be caused by a virus capable of increasing osteoclast activity or genetic defects that produce an increase in interferon-6. Approximately 10% of individuals with Paget's disease have

mutations of the *SQSTM1* (sequestosome-1) gene, resulting in increased nuclear factor kappa-B activity that increases osteoclast activity. Several other mutations associated with Paget's disease have also been identified, many of which affect the receptor activator of the nuclear factor kappa-B signaling pathway, which is critical for osteoclast generation and activity.

An estimated 1 to 3 million people are affected by Paget's disease, though the actual numbers may be higher because this condition is often asymptomatic (Alikhan, 2022). Paget's disease is more common in men, persons of central European descent, and persons with a family history.

Paget's disease proceeds through three phases—lytic, mixed lytic, and blastic. At any point in time, multiple stages may be present in different regions of the body. The disease begins with the lytic phase, in which normal bone is resorbed by osteoclasts that are more numerous, are larger, and have more nuclei. These abnormal osteoclasts increase bone turnover. The mixed lytic phase is characterized by rapid increases in bone formation from the numerous osteoblasts present. Although increased in number, these osteoblasts remain morphologically normal. In contrast, the new bone formed by them is abnormal, with collagen fibers being haphazardly deposited throughout the bone structure. In the blastic phase, the bones formed are weak and deformed. The bone marrow becomes infiltrated by excessive fibrous connective tissue and blood vessels, leading to a hypervascular bone state (Alikhan, 2022).

The clinical manifestations of Paget's disease vary depending on the area affected. This condition is often insidious in onset and may be asymptomatic early in its course. When present, clinical manifestations may include the following signs and symptoms:

- Bone pain (may be severe and persistent)
- Skeletal deformities (e.g., bowing of the legs, asymmetrical skull, and enlarged head)
- Fractures
- Headache

- Hearing and vision loss
- Joint pain or stiffness
- Neck pain
- Reduced height
- Warmth over the affected bone
- Paresthesia or radiating pain in the affected region (due to nerve compression)
- Hypercalcemia

Complications of Paget's disease may include pathologic fractures, osteoarthritis, heart failure (related to hypercalcemia and increased cardiac workload, as the body must pump more blood to the affected areas), **osteosarcoma** (bone cancer), and nerve compression.

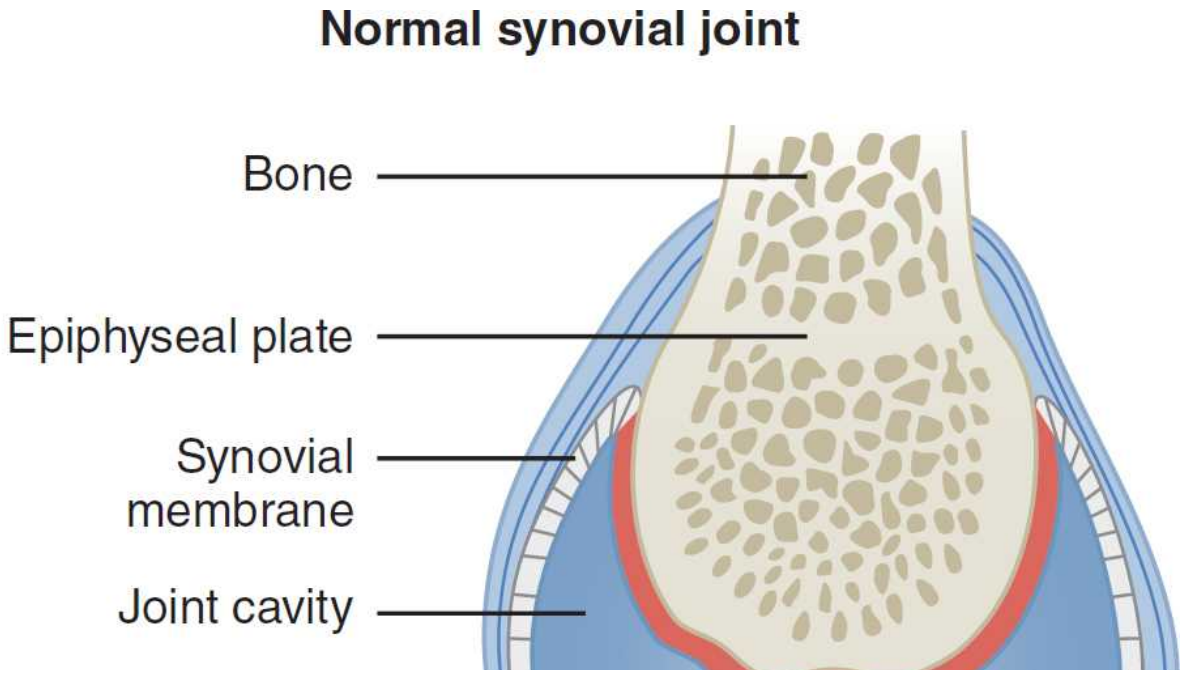
Diagnostic procedures for Paget's disease consist of a history, physical examination, bone scan, X-rays, serum alkaline phosphatase, and serum calcium. Mild cases may require just periodic monitoring—no treatment. Treatment strategies focus on reducing fractures and deformities. Pharmacologic therapies may include bisphosphonates (which increase bone density), calcitonin (which increases bone density), NSAIDs (to alleviate pain and inflammation), and analgesics (to relieve pain). Surgery may be required to correct severe bone deformities.

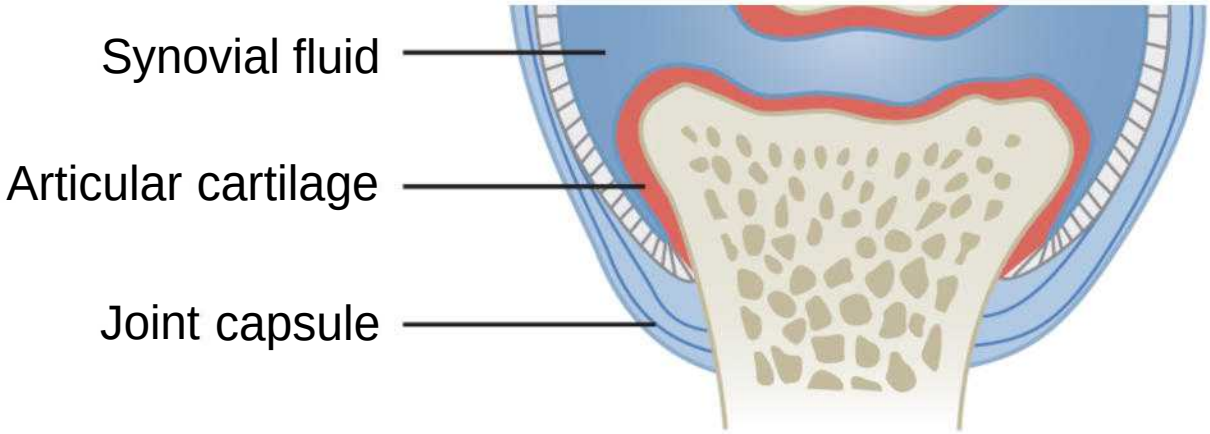
Inflammatory Joint Disorders

Inflammatory joint disorders encompass a group of arthritic conditions that are often degenerative in nature. These conditions are characterized by inflammation, which can be triggered by an autoimmune response, excessive use, increased physical stress, or injury. Complications of these conditions often include chronic pain and disability. Treatment strategies focus on slowing the progression, managing pain, and promoting independence.

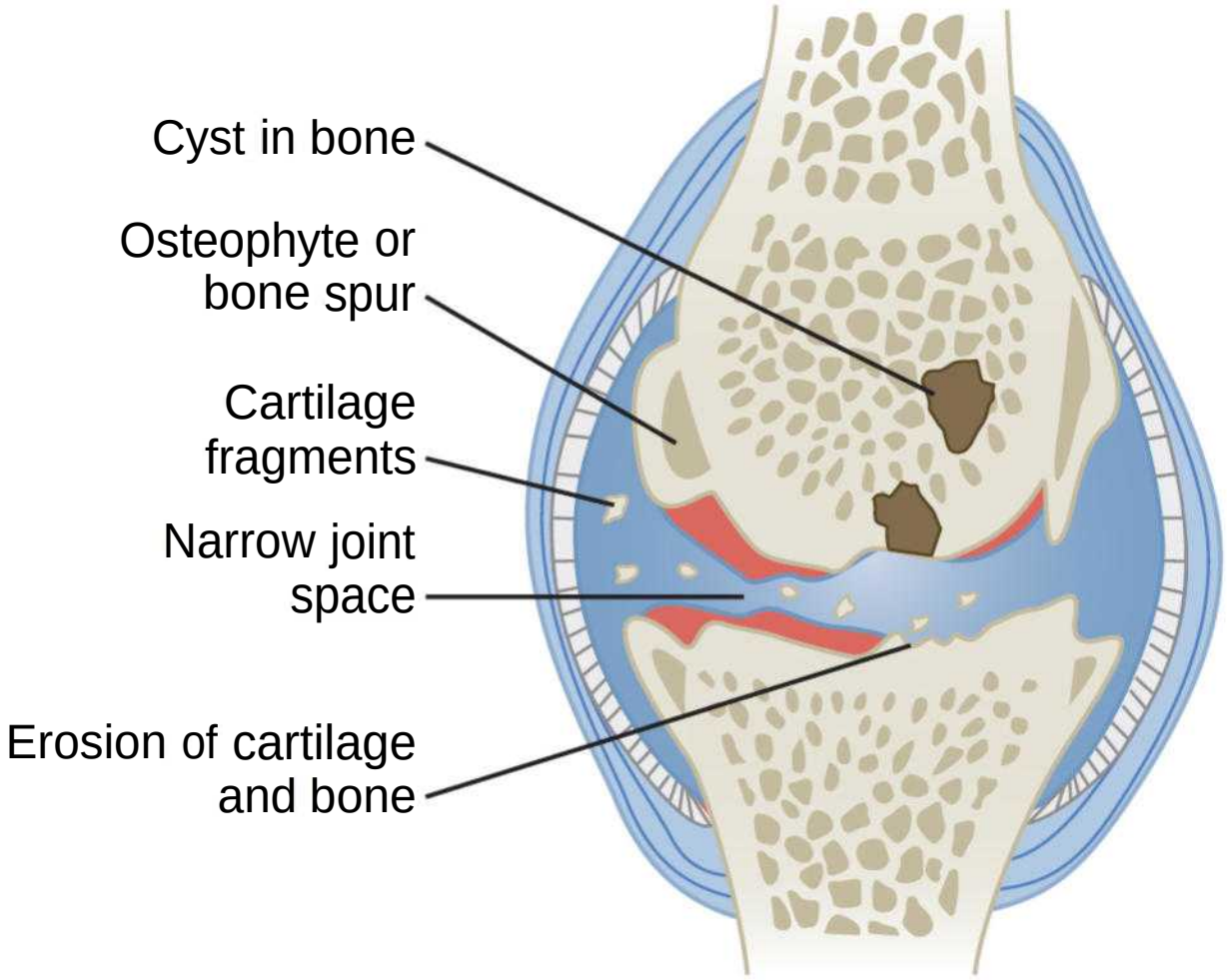
Osteoarthritis

Osteoarthritis (OA), also known as “wear-and-tear arthritis” and “degenerative joint disease,” is a localized joint disease characterized by deterioration of articulating cartilage and its underlying bone as well as bony overgrowth (**FIGURE 12-32**; **TABLE 12-3**). The surface of the cartilage becomes rough and worn, so that it interferes with joint movement. Tissue damage triggers the release of enzymes from local cells that accelerate cartilage disintegration. Eventually, the subchondral bone is exposed and damaged, and cysts and osteophytes (bone spurs) develop as the bone attempts to remold itself. Pieces of the osteophytes and cartilage break off into the synovial cavity, which further increases irritation. Additionally, nearby muscles and ligaments may become weakened and loose. These changes collectively cause narrowing of the joint space, joint instability, stiffness, and pain. The joints most commonly affected by OA are the knees, hips, and joints in the hands and spine. OA is not inflammatory in origin, but inflammation results from the tissue irritation. Erosion of the cartilage usually occurs secondary to excessive mechanical stress on the joint (e.g., from aging, obesity, overuse, injury, and congenital musculoskeletal conditions). Additionally, OA may occur as a primary condition in which the cause is idiopathic.





Pathologic changes in osteoarthritis



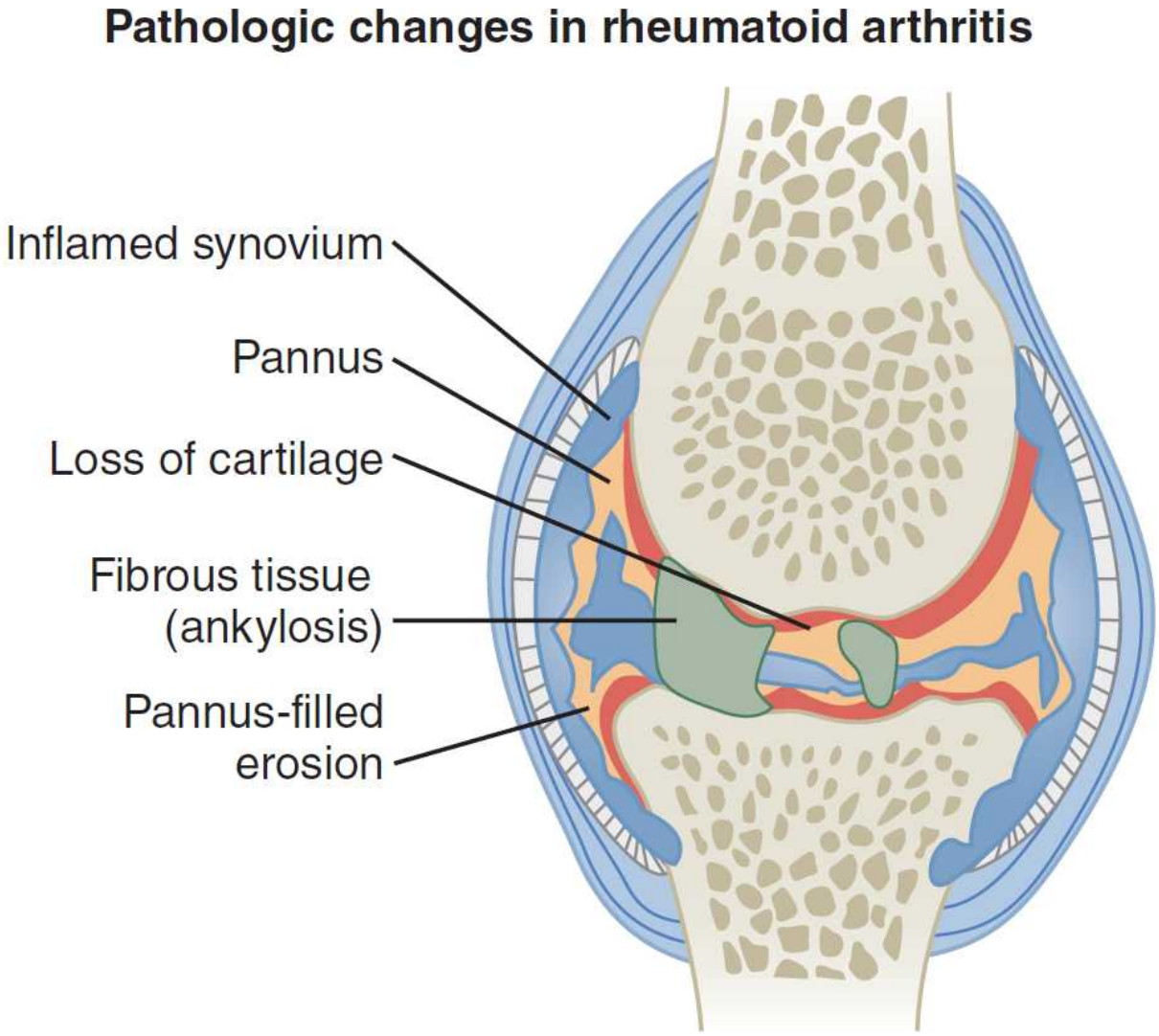


FIGURE 12-32 Pathological changes associated with osteoarthritis and rheumatoid arthritis.

Description

TABLE 12-3 Comparison of Major Features of Common Types of Arthritis

	Osteoarthritis	Rheumatoid Arthritis	Gout
Age and sex of usual patient	Adults, older persons, both sexes (more common in females)	Young and middle-aged, female	Middle-aged, male
Major characteristic	"Wear and tear"; degeneration of articular cartilage	Systemic disease with major effects in joints; causes chronic synovitis	Disturbance of purine metabolism; acute episodes caused by accumulation of uric acid crystals in joints
Secondary effects of disease	Overgrowth of bone; thickening of periarticular soft tissues	Ingrowth of inflammatory tissue over cartilage destroys cartilage, leads to destruction of joint space; deformities are common	Deposits of uric acid in joints with damage to joints (gouty arthritis); soft-tissue tophi
Joints usually affected	Major weight-bearing joints	Small joints of hands and feet	Small joints; joint at base of great toe often affected
Special features	No systemic symptoms or biochemical abnormalities	Autoantibody against gamma globulin (rheumatoid factor)	High blood level of uric acid

Description

The Centers for Disease Control and Prevention (CDC, 2020c) estimates that nearly 32.5 million Americans have OA, with women having higher prevalence rates than men. OA is a significant contributor to disability, healthcare costs, and job loss in the United States.

Disease onset is gradual and usually begins after the age of 40. The following clinical manifestations often develop slowly and worsen over time:

- Joint pain that is exacerbated during or after movement or weight bearing
- Joint tenderness with light pressure
- Joint stiffness, especially upon rising in the morning or after a period of inactivity
- Enlarged, hard joints
- Joint swelling
- Limited joint range of motion
- Crepitus
- Hard nodules around the affected joint (bone spurs)

Diagnostic procedures for OA consist of a history, physical examination, X-rays, and MRI. There is currently no cure for OA. Instead, the goals of treatment are to increase joint strength, maintain joint mobility, reduce disability, and relieve pain. Treatment strategies may include a combination of physical therapy, weight loss/management, ambulatory aids (e.g., walkers and canes), orthopedic devices (e.g., braces and splints), pharmacologic agents, and surgery. Pharmacologic therapies may consist of oral and topical analgesics, NSAIDs (including cyclooxygenase 2 inhibitors), and corticosteroids. Additionally, synthetic synovial fluid and corticosteroids may be injected directly into the joint. Herbal therapies that may be helpful include glucosamine, chondroitin, and ginger, although research evidence is mixed regarding their efficacy. Pain management may focus on adequate rest, heat/cold application, topical agents that create a cool or hot sensation, water therapy (e.g., whirlpool, water aerobics), acupuncture, tai chi, and yoga.

In some cases, surgery may be necessary to repair or replace damaged joints. These procedures may include arthroscopy to trim torn and damaged cartilage, osteotomy to change the alignment of a bone and relieve stress on the bone or joint, surgical fusion, and arthroplasty to completely or partially replace the damaged joint with an artificial joint.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic, autoimmune condition involving multiple joints. RA is mediated by cytokines, chemokines, and metalloproteases. Immune complexes are produced by synovial lining cells and inflamed blood vessels. Plasma cells release antibodies (e.g., rheumatoid factor and anticyclic citrullinated peptide) that contribute to these complexes. In RA, the inflammatory process primarily affects the synovial membrane, but it can also affect other organs (e.g., heart, skin, and eyes). Macrophages travel to the affected synovium early in the disease progression. Helper T cells (i.e., CD4+ cells) also infiltrate the synovial tissue. Macrophages and helper T cells produce pro-inflammatory cytokines and chemokines in the synovium, contributing the systemic and joint manifestations.

Most cases of RA follow a typical autoimmune pattern of remissions and exacerbations. This type of arthritis usually starts with an initial acute inflammatory episode, after which the joint may appear to recover. The process is repeated with each exacerbation and includes synovitis, pannus formation (granulation tissue), cartilage erosion (due to enzymes from the pannus), fibrosis, and **ankylosis** (joint fixation and deformity) (see Figure 12-32; Table 12-3). Over time, the recurring inflammation has a cumulative effect; it thickens the synovium, which can eventually invade and destroy the cartilage and bone within the joint. In addition, the muscles, tendons, and ligaments that hold the joint together weaken and stretch. Gradually, the joint loses its shape and alignment.

The course and the severity of this illness can vary considerably. Nevertheless, RA usually affects joints on both sides of the body equally. Wrists, fingers, knees, feet, and ankles are the most commonly affected.

The exact cause of RA is unknown, but it is thought to be caused by a genetic vulnerability (e.g., human leukocyte antigen) and environmental triggers (e.g., viral infections and cigarette smoking). Risk factors include family history, advancing age (although a juvenile form also exists), and smoking. RA is more common in women, and research is being conducted to explore the potential role that hormones might play in its etiology. RA rates in the United States have declined since 1990. According to the NIH (2022b), an estimated 1.3 million Americans have RA.

The disease onset is usually insidious, with vague manifestations that can mimic other conditions. Occasionally, RA can begin abruptly, mimicking an acute viral syndrome. Virtually any joint, except the distal interphalangeal joints, may be involved. Although most people have arthritic changes in multiple joints (i.e., polyarthritis), some individuals may have only one affected joint (i.e., monoarthritis). Clinical manifestations are progressive and may include the following signs and symptoms:

- Fatigue
- Anorexia

- Low-grade fever
- Lymphadenopathy
- Malaise
- Muscle spasms
- Morning stiffness lasting longer than 1 hour
- Warmth, tenderness, and stiffness in the joints when not used for as little as 1 hour
- Bilateral joint pain
- Swollen and boggy joints
- Limited joint range of motion
- Contractures and joint deformity (e.g., boutonniere deformity and swan neck deformity) (**FIGURE 12-33**)

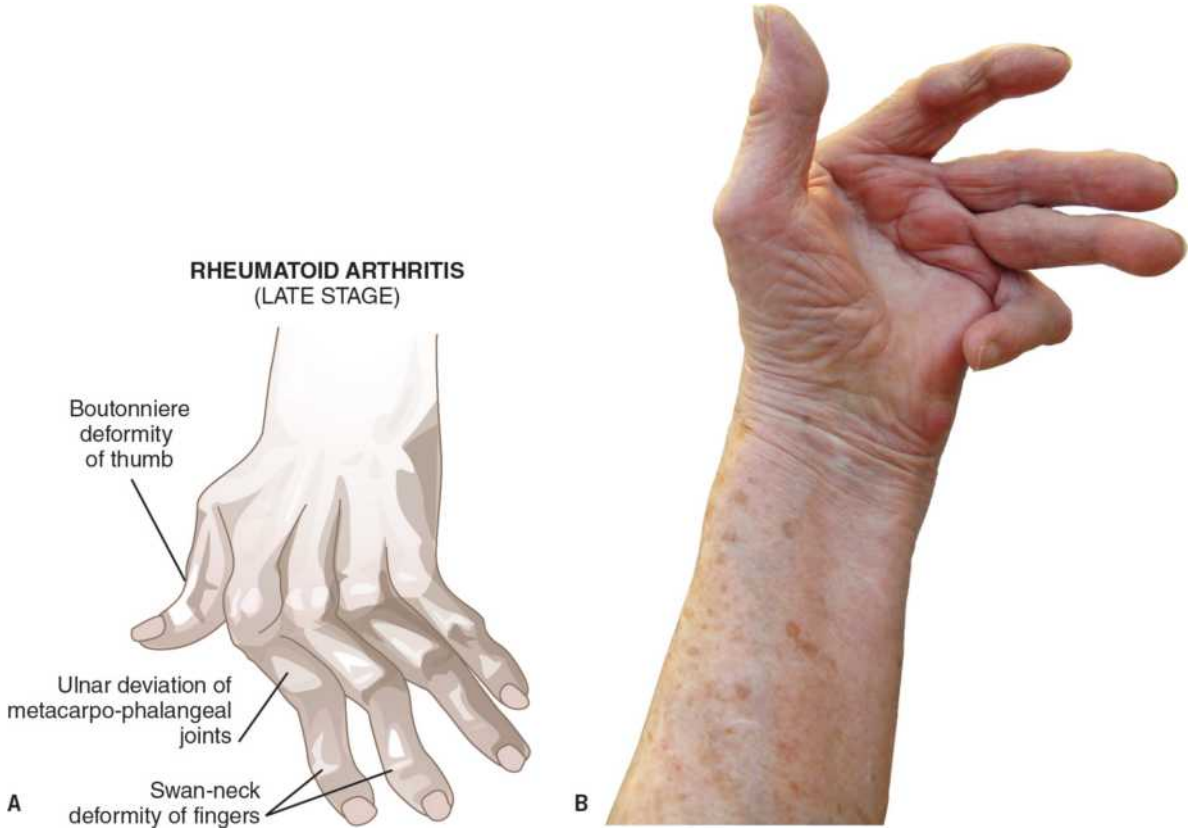


FIGURE 12-33 Joint deformities associated with rheumatoid arthritis.

© Peterfactors/Dreamstime.com

Description

- Unsteady gait
- Depression
- Anemia

RA decreases life expectancy by as much as 7 years. Heart disease, infection, and gastrointestinal bleeding are the most common causes of mortality. The side effects of RA drug therapy account for most of the risk for these conditions. At least 10% of individuals are ultimately severely disabled even with full treatment. Caucasians, women, those with advanced age at onset, and those who smoke have poorer outcomes.

Diagnostic procedures for RA may consist of a history, physical examination, serum rheumatoid factor test, serum anticyclic citrullinated peptide antibody test (more specific to RA than the other serum tests), erythrocyte sedimentation rate test, serum C-reactive protein, serum antinuclear antibody, synovial fluid analysis (rheumatoid factor is usually present), joint X-rays, joint MRIs, and joint ultrasounds. Diagnosis is made based on a set of scoring criteria (Aletaha et al., 2010; **TABLE 12-4**).

TABLE 12-4	Scoring Criteria for Rheumatoid Arthritis

Target population: Patients (1) who have at least one joint with clinical synovitis and (2) in whom the synovitis is not better explained by another disease.			
Score		**Score**	
A. Joint Involvement (Tender/Swollen)		**C. Acute-Phase Reactants**	
1 large joint	0	Normal CRP and ESR	0
2–10 large joints	1	Abnormal CRP and ESR	1
1–3 small joints (± involvements of large joints)	2	**D. Duration of Symptoms**	
4–10 small joints (± involvement of large joints)	3	< 6 weeks	0
> 10 joints (at least 1 small joint)	5	> 6 weeks	1
B. Serology		Add score of categories A–D: ≥ **6/10** = **definite RA**	
Negative RF and ACPA	0		
Low-positive RF/low-positive ACPA	2		
High-positive RF/high-positive ACPA	3		

Description

Abbreviations: ACPA: anti-citrullinated protein antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RA: rheumatoid arthritis; RF: rheumatoid factor.

Data from Aletaha, D., Neogi, T., Silman, A., Funovits, J., Felson, D., & Bingham, C. (2010). 2010 rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis & Rheumatism*, *62*(9), 2569–2581.

There is no cure for RA, so treatment focuses on slowing the progression, managing the pain, and promoting independence. Early aggressive treatment for RA can delay joint destruction. Treatment strategies are complex and often require the support of a multidisciplinary team consisting of a rheumatologist, a nurse, and a wide range of therapists. Strategies may include the following measures:

- Adequate rest and pacing of activities
- Physical and occupational therapy (including therapy directed at maintaining or increasing range of motion)
- Regular exercise
- Pharmacologic therapies, including the following, which may be used in combination with each other:

- Disease-modifying antirheumatic drugs (to decrease inflammatory response), including the following:
  - Immunosuppressant agents (e.g., methotrexate)
  - Antimalarial agents (e.g., hydroxychloroquine [Plaquenil])
  - Gold compounds
- NSAIDs (to relieve pain and inflammation)
- Corticosteroids (either orally or as an intra-articular injection to decrease inflammation)
- Biologic response–modifying agents (e.g., infliximab [Remicade]) (which block tumor necrosis factor, an inflammatory cytokine associated with RA)
- Herbal therapies, including thunder god vine, plant oils, and fish oil

- Nonpharmacologic pain management (e.g., relaxation techniques, tai chi)
- Application of heat and cold
- Splints and braces (to support joints, maintain proper alignment, and prevent deformities)

Emerging Research: Rheumatoid Arthritis Treatment

Research is focused on exploring applications of modulating the immune system to treat cancers and autoimmune diseases. All-trans retinoic acid (ATRA) is showing promise as one such treatment for rheumatoid arthritis that is locally released and harnesses the joint microenvironment for sustained effectiveness. ATRA is a small molecule that is currently approved by the Food and Drug Administration to treat acute promyelocytic leukemia through a systemic administration. In this case, ATRA is injected directly into an affected joint, where it remains in effect for at least several weeks. During that time, ATRA transforms disease-causing cells into disease-stopping cells (i.e., regulatory T cells). These regulatory T cells can treat and prevent the disease elsewhere in the body, making the disease site into a factory of disease fighters (McBride et al., 2023).

- Assistive devices (e.g., walkers and rails)
- Coping strategies and support
- Surgical repair (e.g., synovectomy and arthroplasty)

Gout

Gout is an inflammatory disease resulting from deposits of uric acid crystals (monosodium urate) in tissues and fluids within the body (**FIGURE 12-34**; see Table 12-3). The body produces uric acid when it breaks down purines, a substance naturally found in the body as well as in certain foods (e.g., organ meats, shellfish, anchovies, herring, asparagus, and mushrooms). Normally, uric acid dissolves in the blood and is excreted by the kidneys. Gout results from an overproduction or underexcretion (most common) of uric acid (urate) as well as increased purine intake; however, not all people with hyperuricemia have gout.

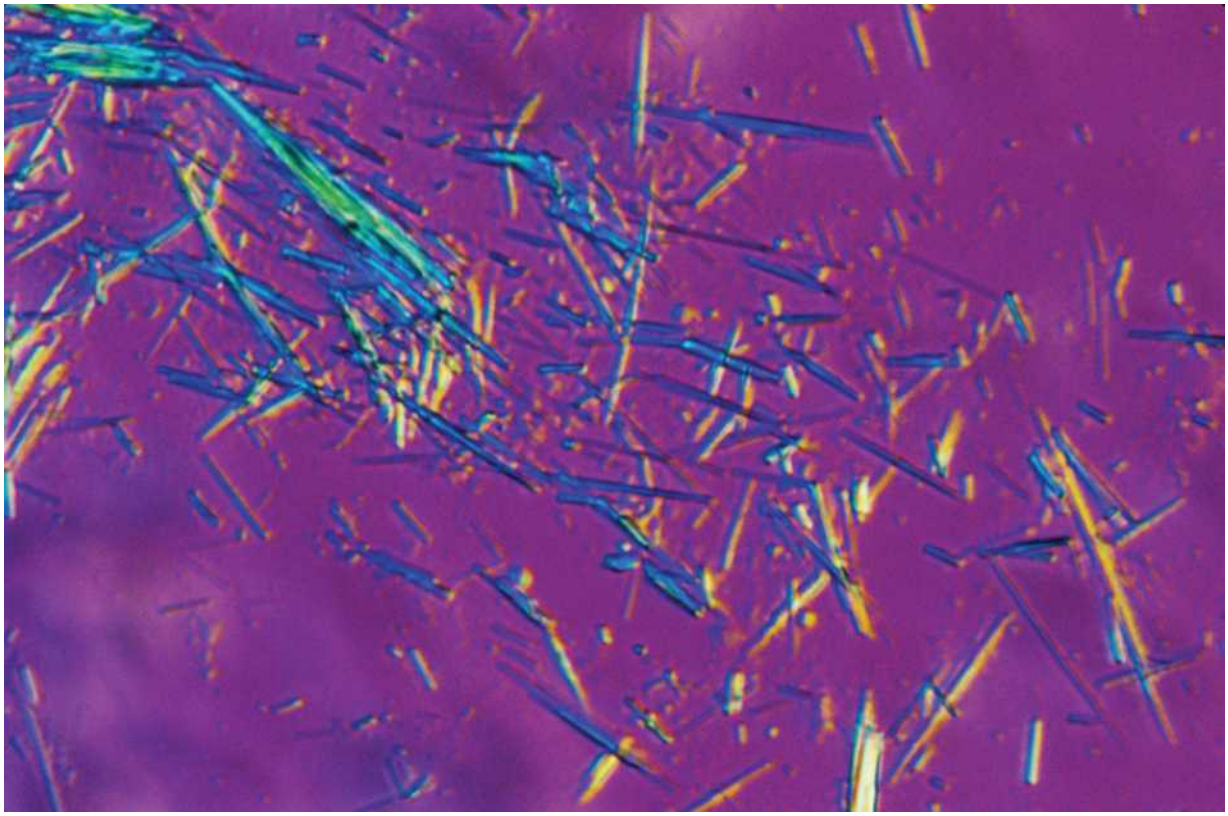


FIGURE 12-34 Uric acid crystals in the synovial fluid.

© Scott Camazine/Science Source

Gout affects approximately 8.3 million people in the United States but is most common in males and African Americans (CDC, 2020a). It may occur as a primary inborn error of metabolism or secondary to some contributing factor. Factors contributing to its development include being overweight or obese, having certain diseases (e.g., hypertension, diabetes mellitus, renal disease, and sickle cell anemia), consuming alcohol (beer and spirits more so than wine), using certain medications (e.g., diuretics), and consuming a diet rich in meat and seafood.

Myth Busters

Arthritis is a common condition associated with several myths that should be dispelled.

Myth 1: Cracking your joints causes arthritis.

As arthritis myths go, this one is a biggie. When you crack a joint, you are actually either snapping the ligament over the joint or pulling on the joint, which causes a negative nitrogen bubble. You are not cracking the bone—just manipulating the joint to make it feel better—so cracking your joints does *not* cause arthritis.

Myth 2: Being double-jointed increases your risk for arthritis.

The term *double-jointed* is actually a misnomer; no one has two joints where there should be one. Some people have hypermobility (or extra flexibility) in their joints, but no evidence suggests this condition causes arthritis. However, hypermobility could cause other injuries, such as sprains, strains, and tears.

Myth 3: Vaccinations can cause arthritis.

This notion is a hot topic, but the Arthritis Foundation's position is that immunizations (particularly rubella vaccinations) do not cause arthritis. No research evidence has supported this myth. Some immunizations can cause some short-term joint aching, but that effect is not the same as arthritis.

Gout typically follows four phases. Initially, the individual with gout is asymptomatic, though uric levels are climbing in the bloodstream and needle-shaped uric acid crystals are being deposited in the

tissues (**FIGURE 12-35**). Over time, these crystals accumulate, damaging tissues. This damage triggers an acute inflammation that characterizes the second phase of gout, referred to as acute flares or attacks. A flare is distinguished by pain, burning, redness, swelling, and warmth at the affected joint lasting days to weeks. Pain may be mild or excruciating. Most initial attacks occur in the lower extremities. The metatarsophalangeal joint of the big toe is the presenting joint for 50% of people with gout. After the acute attack subsides, the person may enter intercritical periods in which the disease remains clinically inactive until the next flare (the third phase). The person with gout continues to have hyperuricemia, which results in continued deposits of uric acid crystals in tissues that cause damage. These intercritical periods become shorter as the disease progresses. Recurrent attacks are often precipitated by sudden increases in serum uric acid. In the final phase, chronic gout is characterized by chronic arthritis, associated with soreness and aching of joints. People with gout may also develop **tophi** (large, hard nodules composed of uric acid crystals deposited in soft tissue), usually in cooler areas of the body (e.g., toes, elbows, ears, and distal finger joints). Because some renal calculi (kidney stones) are made of uric acid, renal calculi may also be associated with gout (see the *Urinary Function* chapter).

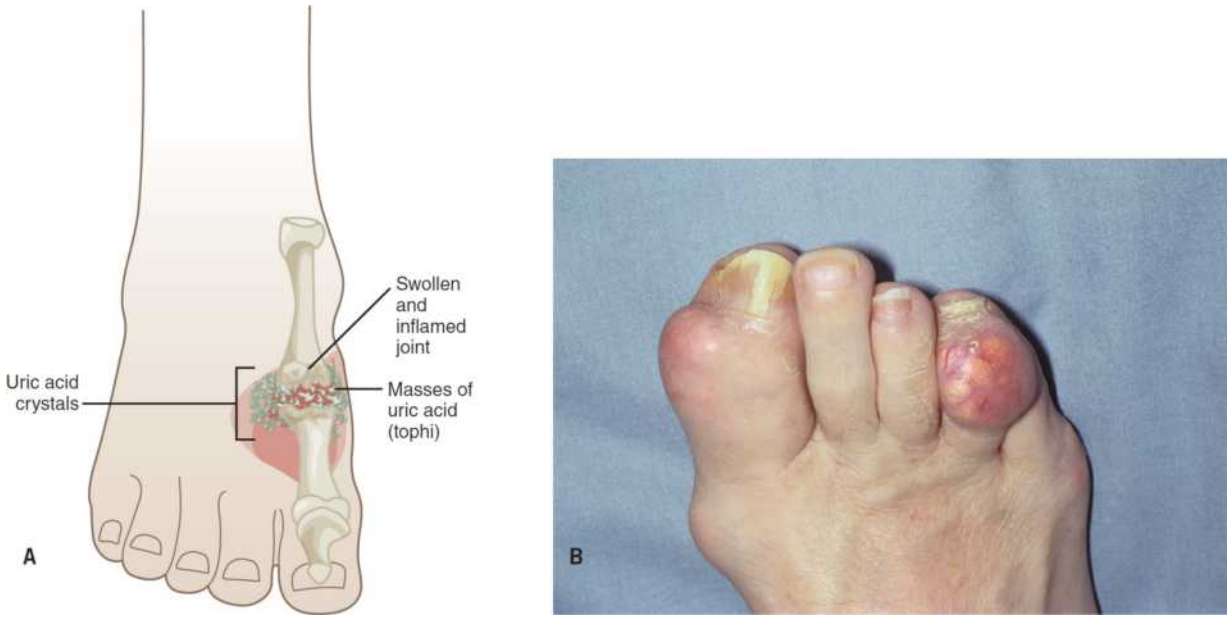


FIGURE 12-35 Gout.

B: © Dr. Ken Greer/Visuals Unlimited, Inc.

Description

Clinical manifestations of gout vary depending on the phase that the individual is experiencing. Manifestations of acute gout attacks include the following symptoms:

- Intense pain at the affected joint (usually the big toe) that frequently starts during the night and is often described as throbbing, crushing, burning, or excruciating
- Joint warmth, redness, swelling, and tenderness (even to light touch)
- Fever

After a first gout attack, patients may have no symptoms for varying lengths of time. Some people may go months or even years between gout attacks. Although some individuals develop chronic gouty arthritis, others have no further attacks. Those patients with chronic arthritis develop joint deformities and limited joint mobility. With chronic gout, joint pain and other symptoms will be present most of the time. Tophi may form below the skin around joints or in other

places with chronic gout. These tophi can cause a local inflammatory response, and draining them may reveal the presence of a chalky material.

Diagnostic procedures for gout include a history, physical examination, serum uric acid levels, urine uric acid levels (will be low in those patients with gout caused by underexcretion), synovial fluid analysis (presence of uric acid crystals), and joint X-rays. Treatment strategies focus on lowering uric acid levels, usually with medications and dietary changes. Medications often vary depending on the current phase of gout the patient is experiencing. Treatment strategies for gout may include the following measures:

- Pharmacologic therapy for acute gout attacks, including the following:
  - NSAIDs to control inflammation and pain; higher doses may be used to stop an acute attack
  - Colchicine, an analgesic that is particularly effective in reducing gout pain
  - Corticosteroids to relieve inflammation and pain
- Pharmacologic therapy to prevent recurrent acute gout attacks, including the following:
  - NSAIDs, daily
  - Colchicine, daily
- Pharmacologic therapies to prevent the complications associated with frequent gout attacks, including the following:
  - Xanthine oxidase inhibitors (e.g., allopurinol [Zyloprim]) to block uric acid production
  - Probenecid (Probalan) to improve renal excretion of uric acid
- Avoiding triggers (e.g., stress, high protein intake, and alcohol intake)

Ankylosing Spondylitis

Ankylosing spondylitis is a progressive inflammatory disorder affecting the sacroiliac joints, intervertebral spaces, and

costovertebral joints. The inflammation associated with this condition starts in the vertebral joints. As the inflammation continues, new bone forms in an attempt to remodel the damage. Fibrosis and calcification, or fusion, of the joints follow. The vertebral joints become fixed, or ankylosed, and lose mobility. Inflammation begins in the lower back at the sacroiliac joints and progresses up the spine. The vertebrae appear square, and the vertebral column becomes rigid and loses curvature (**FIGURE 12-36**).

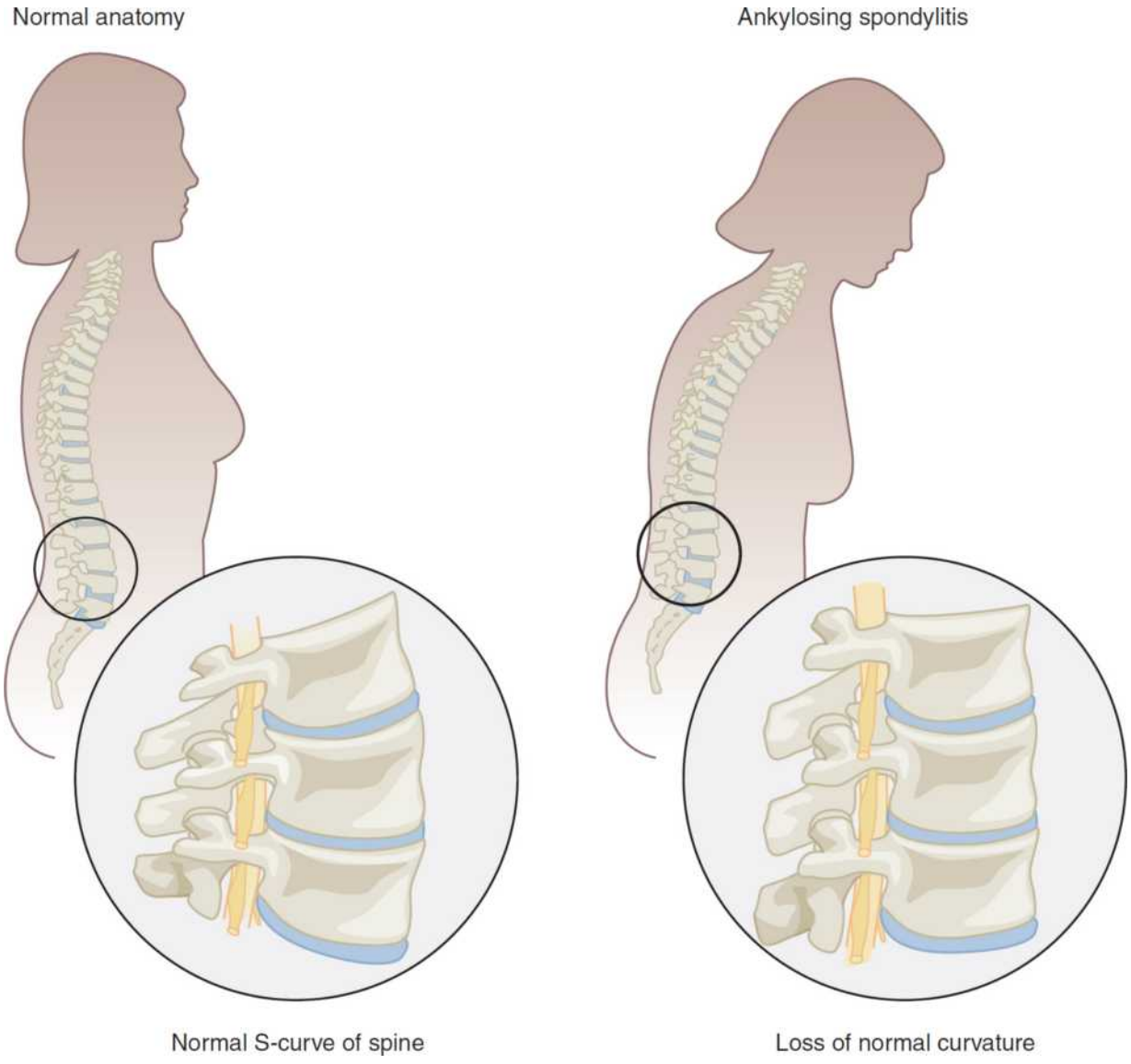


FIGURE 12-36 Ankylosing spondylitis.

Description

The exact cause of ankylosing spondylitis is unknown, although genetic factors seem to be involved. In particular, people who have the *HLA-B27* gene are at significantly increased risk of this condition. Ankylosing spondylitis occurs more frequently in males than in females and typically appears between 20 and 40 years of age. The condition is 10 to 20 times more common among first-degree relatives of patients with ankylosing spondylitis than in the general population. Complications may include kyphosis, osteoporosis, respiratory compromise (due to reduced lung expansion resulting from fusion of the rib cage), endocarditis (inflammation of the internal cardiac structures), and uveitis (inflammation of the eye).

Clinical manifestations of ankylosing spondylitis reflect the decreased joint mobility. The individual may experience periods of remission and exacerbation. The following manifestations may worsen as the disease progresses:

- Intermittent lower back pain (early)
- Pain and stiffness that typically worsen with inactivity (e.g., when sleeping) and improve after activity
- Lower back pain that evolves to include the entire back
- Pain in other joints (especially the shoulders, hips, or lower extremities)
- Muscle spasms
- Fatigue
- Low-grade fever
- Weight loss
- Kyphosis

Diagnostic procedures for ankylosing spondylitis may consist of a history, physical examination, test for serum presence of the *HLA-B27* gene, erythrocyte sedimentation rate, C-reactive protein, spine X-rays, spine CT, and spine MRI. The goal of treatment is to relieve pain and stiffness as well as to prevent or delay complications and spinal deformity. Treatment of ankylosing spondylitis is most successful when it is initiated before the disease causes irreversible

damage (e.g., fusion), especially in positions that limit function. Treatment strategies may include the following measures:

- NSAIDs, disease-modifying antirheumatic drugs, corticosteroids, and tumor necrosis factor blockers to relieve inflammation, pain, and stiffness
- Muscle relaxants to treat muscle spasms
- Physical therapy (including range-of-motion exercises and positioning)
- Surgical repair
- Health-promoting lifestyle behaviors (e.g., proper nutrition, adequate rest, stress management, and smoking cessation)
- Coping strategies and support

Chronic Muscle Disorders

Chronic muscle disorders include conditions that result from a wide range of causes (e.g., genetic predisposition, trauma, and infection). These conditions may lead to chronic pain, weakness, and paralysis. Chronic muscle disorders may be progressive, requiring lifelong treatment. Because most of these conditions have no known cure, treatment is often aimed at managing symptoms.

Muscular Dystrophy

Muscular dystrophy (MD) encompasses a group of inherited noninflammatory disorders characterized by degeneration of skeletal muscle. Muscles become weaker as damage from these disorders worsens. Nine different forms of MD are distinguished (including Becker MD, Duchenne MD, myotonic MD, and limb-girdle MD), each with its own pattern of inheritance (e.g., X-linked recessive, autosomal dominant, and autosomal recessive) and pathogenesis (e.g., age of onset and progression). The commonality across all types is the presence of a muscle protein abnormality (dystrophin). This defect causes muscle dysfunction, weakness, muscle fiber loss, and inflammation, and it may involve other tissues (e.g., cardiac and

smooth muscle tissues). Over time, fat and fibrosis connective tissues eventually replace skeletal muscle fibers in persons with MD.

Some types of MD are rare, whereas others are relatively common. Most types of MD are inherited, but some occur because of a genetic mutation (often spontaneously). Some types cause tremendous disability and rapid decline; in contrast, others are associated with minimal symptoms and hardly noticeable progression. Some types present in childhood, while others present in late adulthood. Duchenne MD is the most common and severe type, affecting only males (X-linked recessive). Complications of MD may include cardiomyopathy, recurrent respiratory infections, respiratory compromise, and death.

Clinical manifestations of MD vary depending on the type. All of the muscles may be affected or just a selected group. In general, manifestations may include the following signs and symptoms:

- Intellectual disability (in some types)
- Muscle weakness that slowly worsens to hypotonia
- Muscle spasms
- Delayed development of muscle motor skills
- Difficulty using one or more muscle groups
- Poor coordination
- Drooling
- Ptosis (eyelid drooping)
- Frequent falls
- Problems walking (e.g., delayed walking)
- Gowers maneuver (an affected child pushes to an erect position by using his or her hands to climb the legs)
- Progressive loss of joint mobility and contractures (e.g., clubfoot and footdrop)
- Unilateral calf hypertrophy
- Scoliosis or lordosis

Diagnostic procedures for MD may consist of a history, physical examination, muscle biopsy, electromyography, electrocardiogram, serum creatine kinase levels, test for serum presence of defective dystrophin, and genetic testing. Additionally, fetal chorionic villus testing can be performed prenatally at 12 weeks' gestation.

There is no cure for MD; however, gene therapy may be feasible. Currently, the goal of treatment is to maintain motor function and prevent deformities as long as possible. Treatment strategies may include physical therapy, proper nutrition, muscle relaxants, immunosuppressant agents, assistive devices (e.g., walker, braces, and splints), and surgical contracture release. Additionally, coping strategies and support for the patient and caregivers may be beneficial.

Fibromyalgia

Fibromyalgia is a syndrome predominantly characterized by widespread muscular pain and fatigue. This disorder affects joints, muscles, tendons, and surrounding tissues. Typically, the occiput, neck, shoulders, thorax, low back, and thighs are involved. No apparent inflammation or degeneration is associated with fibromyalgia. Although its cause remains uncertain, fibromyalgia may be related to an altered pattern of central neurotransmission that results in sensitivity to substance P (a neurotransmitter responsible for pain sensation). Other pain-processing abnormalities that have been identified in patients with fibromyalgia include decreased levels of inhibitory neurotransmitters (e.g., serotonin and norepinephrine), enhanced temporal summation of second pain (delayed, longer-lasting pain), altered endogenous opioid analgesic activity, and dopamine dysregulation. In this condition, the brain's pain receptors seem to develop a sort of pain memory and become more sensitive to pain signals (i.e., lowered pain threshold). Disruption of stage 4 sleep (i.e., rapid eye movement [REM]) may also contribute to fibromyalgia, as may emotional stress. Additional postulated causes include physical or emotional trauma, sleep disturbances, altered skeletal muscle metabolism, infections (e.g., Lyme disease), and genetic predisposition.

Myth Busters

Fibromyalgia remains a mysterious condition, and two myths about fibromyalgia deserve discussion.

Myth 1: Fibromyalgia is an autoimmune disease.

Fibromyalgia is *not* an autoimmune disease. An autoimmune disease occurs when the body mounts an overactive and inappropriate immune response. There is no evidence that fibromyalgia follows this path. However, people with fibromyalgia do commonly have one or more comorbid autoimmune diseases.

Myth 2: Fibromyalgia is a psychological problem.

Fibromyalgia is a physical disorder that manifests with real, measurable, biological abnormalities. This myth probably causes the most frustration for patients with fibromyalgia. After years of being told, "It is all in your head," patients finally have proof that fibromyalgia is a very real physical illness. Research studies have revealed a number of biological abnormalities associated with its development. Nevertheless, despite the scientific evidence, fibromyalgia continues to be dismissed as a psychological problem by many in the medical community, who continue to insist that the symptoms are caused by depression.

The CDC (2020b) estimates that approximately 4 million Americans have fibromyalgia, with the prevalence rates being highest among women. Clinical manifestations may vary depending on the weather, stress, sleep quality, physical activity, and time of day. In general, fibromyalgia is characterized by widespread pain and stiffness, typically described as a constant, dull muscle ache. Fatigue, difficulty concentrating, sleep disturbances, depression, irritable bowel syndrome, headaches, memory problems, and paresthesias (usually bilateral) may also occur with this chronic disorder. Conditions often associated with fibromyalgia include RA, systemic lupus erythematosus, and ankylosing spondylitis.

Diagnostic procedures for fibromyalgia include a history, physical examination, and tests to rule out other conditions. Diagnosis is based on criteria developed by the American College of Rheumatology (Wolfe et al., 2016) and includes the presence of widespread pain (at least 3 months' duration), especially when

cognitive and somatic symptoms (particularly fatigue) are also present and laboratory tests are negative.

Treatment strategies focus on minimizing symptoms and improving overall health. These strategies may include stress reduction, regular exercise, adequate rest, proper nutrition, heat application, massage therapy, acupuncture, physical therapy, analgesics, NSAIDs, antidepressant agents, muscle relaxants, and antiseizure agents (specifically, pregabalin [Lyrica]). Coping strategies, counseling, and support may be helpful as well.

Bone Tumors

Tumors of the musculoskeletal system typically arise from the bone. The majority of bone tumors are malignant and occur as secondary tumors stemming from other cancers (e.g., breast, lung, and prostate). Bone tumors rarely occur as primary tumors. The exact cause of these primary tumors is unknown, but they are more common in men and Caucasians (National Cancer Institute, 2023). Paget disease increases the risk of developing primary bone cancer. The overall 5-year survival rate for bone cancer is approximately 69%.

Bone cancer usually occurs in areas of rapid bone growth and is described based on the type of cell in which the cancer originates. Bone cancer types include the following:

- **Osteochondroma**—a tumor that develops adjacent to growth plates. The most common benign bone tumor, it occurs most often in persons between 10 and 20 years of age.
- Steosarcoma—an aggressive tumor that begins in the bone cells, usually in the femur, tibia, or fibula (**FIGURE 12-37**). It occurs most often in children and young adults.



FIGURE 12-37 Osteosarcoma.

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- **Chondrosarcoma**—a slow-growing tumor that begins in the cartilage cells that are commonly found on the ends of bones. It most frequently affects older adults.
- **Ewing sarcoma**—an aggressive tumor whose origin is unknown. This type of bone tumor may begin in nerve tissue within the bone. Ewing sarcoma occurs most frequently in children and young adults, and it is 10 times more common in Caucasians as compared to other ethnic groups.

Bone tumors are often asymptomatic in their early stages. When present, clinical manifestations usually include pathologic fractures, bone pain, a palpable mass, fatigue, and unintended weight loss.

Diagnostic procedures for bone tumors may consist of a history, physical examination, X-rays, CT, MRI, positron emission

tomography, bone scan, and biopsy. Treatment varies depending on the type and stage of the cancer. Surgical excision or amputation is often the treatment of choice. Radiation and chemotherapy may be used following surgery, if the tumor is inoperable, or in the presence of metastasis.

application to practice

Now that we have discussed conditions of the musculoskeletal system, let's put that knowledge into practice. After receiving the change-of-shift report on the following patients being treated in the orthopedic unit, which patient would you assess first?

- A patient who had an open reduction and internal fixation and casting of a tibia fracture 3 days ago and is complaining of nausea
- A patient who is being discharged with an upper-extremity external fixation device and needs teaching about pin care
- A patient who had an open reduction and internal fixation of a left femoral fracture 6 hours ago and states, "I can't feel my left foot"
- A patient who developed a deep vein thrombosis in the right leg 4 days postoperatively following a hip replacement and has a heparin infusion

Once again, you go through the usual thought process—who would die first, acute versus chronic conditions, Maslow's hierarchy of needs, and patient safety. The patient with the tibia repair is 3 days post-surgery and probably has stabilized. This patient is not exhibiting any signs of distress, and nausea is unpleasant but not life threatening. Next, consider the patient who needs pin care education. Education is important and necessary prior to discharge; however, this need is not life threatening or pressing. Now think about the patient who is 6 hours post femoral fracture repair. With the repair being recent and the patient complaining of numbness, this patient may be experiencing some negative effects from the procedure. The numbness may be merely a residual effect of the anesthesia, but it could also be the result of nerve damage. This patient should stay on the short list. Finally, consider the patient with the deep vein thrombosis. Although the thrombosis is a new development, it is being treated with heparin, and the patient is not exhibiting any clinical manifestations indicating any other issues.

After weighing all the options, the patient 6 hours post femoral repair surgery should be assessed first. This assessment would start by evaluating the neurovascular integrity of the patient's left foot and leg. This neurovascular assessment focuses on the five Ps—pain, pulse, paralysis, paresthesia, and pallor.

SUMMARY

The musculoskeletal system forms the framework for the body, provides support and protection, and allows for movement. Damage to this system is likely to cause issues with mobility. Musculoskeletal disorders vary from short lived and mild to long term and debilitating in nature. Although most of these disorders are not life threatening, many of them can result in life-altering effects. Musculoskeletal damage may be caused by trauma, genetic defects, metabolic imbalances, or daily wear and tear. Supporting musculoskeletal health involves strategies such as weight management, proper nutrition, regular exercise, abstaining from smoking, and observing safety precautions (e.g., wearing safety equipment).

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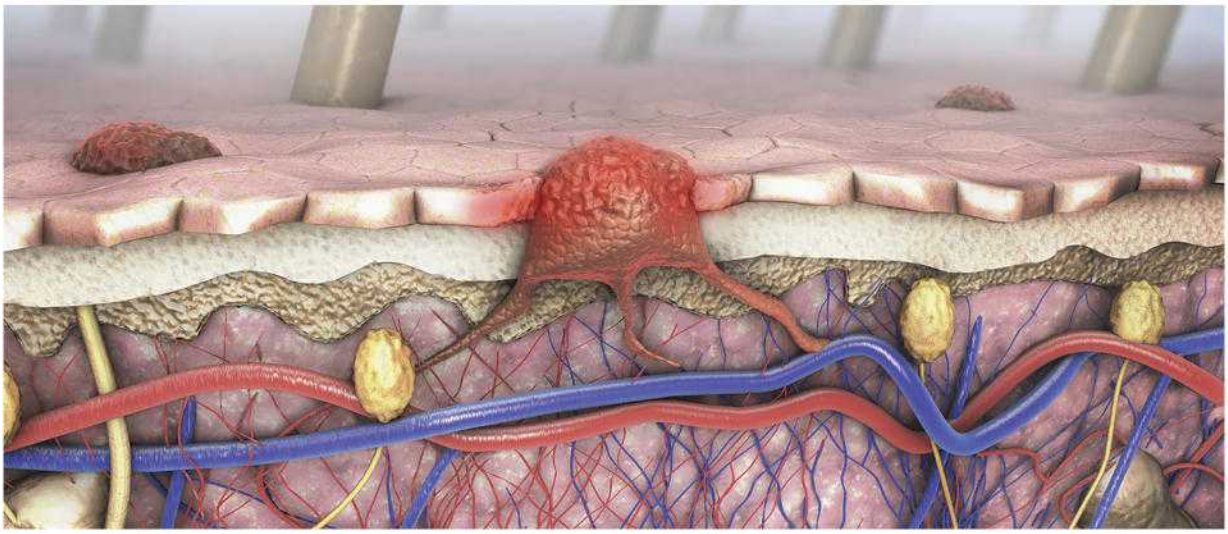
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CHAPTER 13

Integumentary Function

LEARNING OBJECTIVES

- Discuss normal integumentary anatomy and physiology.
- Compare and contrast congenital integumentary disorders.
- Describe and discuss integumentary changes and conditions associated with aging.
- Compare and contrast inflammatory integumentary disorders.
- Compare and contrast infectious integumentary disorders.
- Describe and discuss traumatic integumentary disorders.
- Describe and discuss chronic integumentary disorders.
- Describe and discuss integumentary cancers.

KEY TERMS

acne vulgaris
albinism
apocrine gland
atopic dermatitis
birthmark
burn
café au lait spot
carbuncle
cellulitis
contact dermatitis
dermis
eccrine gland
epidermis
folliculitis

furuncle
hemangioma
herpes simplex type 1
herpes zoster
hypodermis
impetigo
keratin
lentigo
macular stain
melanin
mole
molluscum contagiosum
Mongolian spot
necrotizing fasciitis
papule
pediculosis
pigmented birthmark
port-wine stain
psoriasis
rosacea
scabies
sebaceous gland
sebum
skin
skin cancer
skin tag
tinea
urticaria
vascular birthmark
verruca
vesicle
vitiligo
welt

he integumentary system protects the body from pathogen invasions, regulates temperature, senses environmental changes, and maintains

water balance. This system comprises the **skin**, nails, hair, mucous membranes, and glands. Disorders of the integumentary structures can result in numerous issues because of the extensive functions of this system. Such disorders can stem from a wide range of causes, including congenital defects, advancing age, inflammation, infections, and cancers. Many of these conditions are mild and may not require treatment (e.g., **birthmarks**), whereas others can be life threatening (e.g., **skin cancer**).

Anatomy and Physiology

The skin, along with the nails, hair, mucous membranes, and glands, constitutes the integumentary system. In addition to participating in sensory functions, the integumentary system plays a key role in immunity (see the *Immunity* chapter), temperature regulation, and water balance. Moreover, this system excretes a small amount of waste products. The integumentary system is the body's largest organ system, covering all external surfaces and accounting for approximately 15% of the body's weight.

The skin consists of three layers: the **hypodermis**, the **dermis**, and the **epidermis** (**FIGURE 13-1**). The hypodermis, or subcutaneous tissue, is the innermost layer of the skin, consisting of soft, fatty tissue as well as blood vessels, nerves, and immune cells (e.g., macrophages). The dermis, or middle layer, is composed of dense, irregular connective tissue and little fatty tissue. The dermis includes nerves, hair follicles, smooth muscle, glands, blood vessels, and lymphatic vessels. The epidermis, or outermost layer of the skin, is made up of squamous epithelia, or flat sheets of cells. The epidermis consists of five distinct layers (**FIGURE 13-2**). New cells proliferate from the innermost layer and push upward. The outer layers often contain 25 sheets of dead cells that are continuously shed. Most of these cells produce **keratin**, a protein that strengthens skin, and **melanin**, a pigment that protects the skin from ultraviolet (UV) rays.

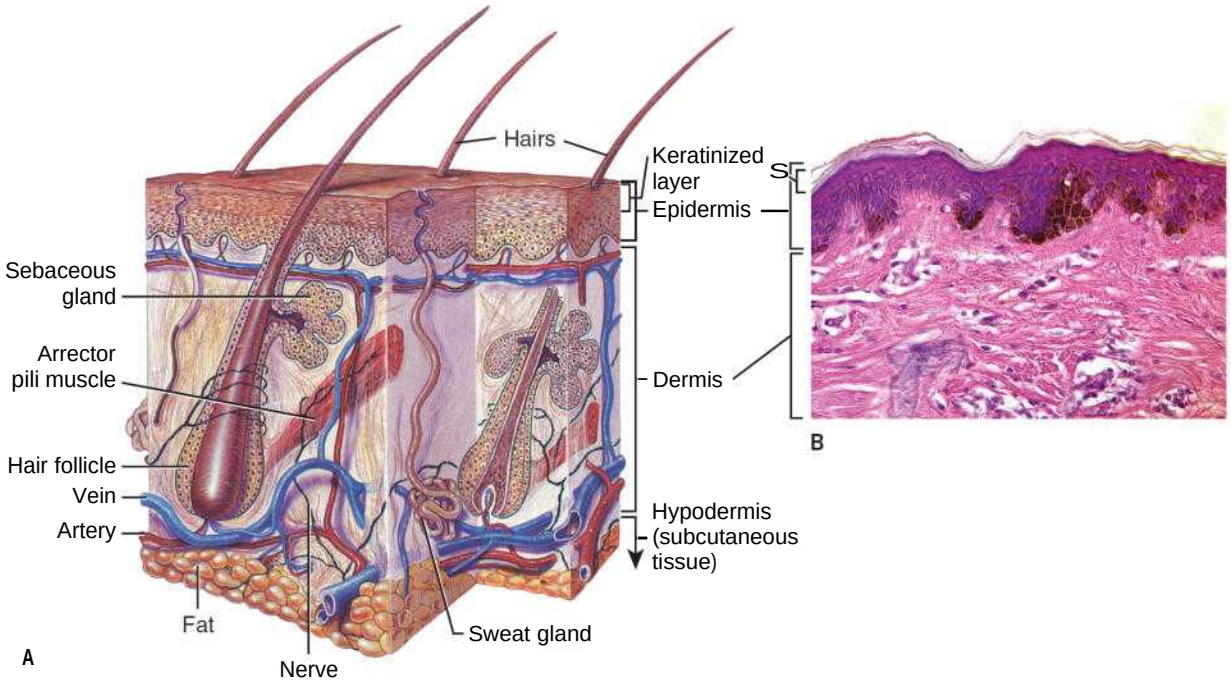


FIGURE 13-1 The layers of the skin.

B: © Donna Beer Stolz, PhD, Center for Biologic Imaging, University of Pittsburgh Medical School.

Description

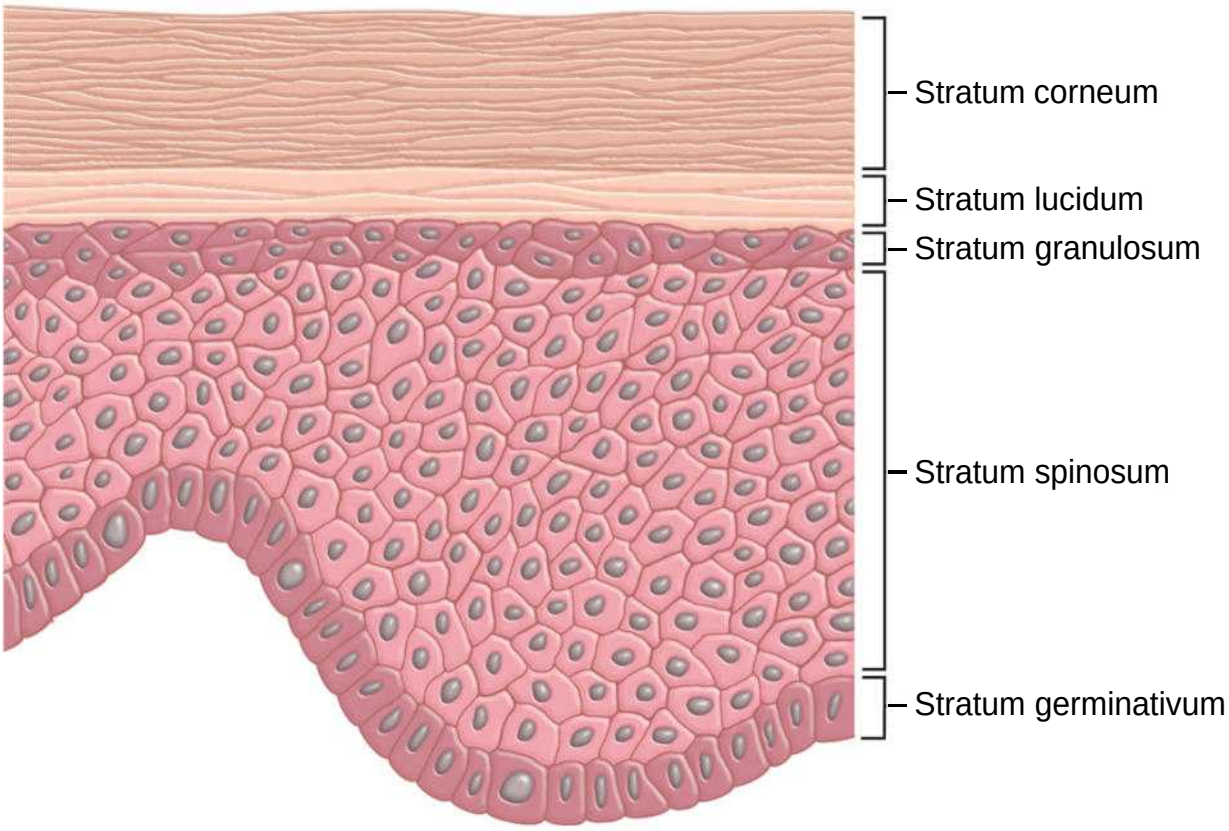


FIGURE 13-2 The layers of the epidermis.

Sebaceous glands produce **sebum**, which moisturizes and protects the skin. Two types of sweat glands are located throughout the skin—eccrine and **apocrine glands**. **Eccrine glands**, also known as “merocrine glands,” secrete sweat through skin pores in response to the sympathetic nervous system. Apocrine glands open into hair follicles in the axillae, scalp, face, and external genitalia.

The skin is home to a complex mixture of normal flora whose composition varies depending on the area of the body. This normal flora consists mostly of bacteria and fungi, which can lead to an opportunistic infection when a skin injury occurs. Such superficial opportunistic infections can develop into severe systemic infections if not managed appropriately.

UNDERSTANDING CONDITIONS THAT AFFECT THE INTEGUMENTARY SYSTEM

When considering alterations of the integumentary system, organizing them based on their basic underlying pathophysiology can increase understanding. With systemic disorders, the primary nursing diagnosis is impaired skin integrity. In such cases, interventions are intended to either prevent such impairment, maintain skin integrity, or improve skin integrity. Because the skin provides a barrier to protect the body from pathogen invasion, an additional nursing diagnosis that is relevant is the risk for infection. Interventions for this diagnosis are directed at minimizing contamination (e.g., hand washing, wound care) and supporting the immune system (e.g., proper nutrition).

Congenital Integumentary Disorders

Congenital disorders of the integumentary system can vary widely in severity. Many conditions occur because of an error during embryonic development. These errors may occur randomly, due to environmental influences, or because of genetic abnormalities. They may cause either minor conditions associated with only aesthetic problems (e.g., birthmarks) or life-altering states (e.g., **albinism**). Occasionally, these seemingly benign conditions may be associated with other, more serious problems that warrant further investigation. Treatment is often unnecessary, but when it is needed, therapeutic options are usually limited.

Birthmarks

Birthmarks are skin anomalies that are present at birth or shortly after. Most are harmless, and some may even shrink or disappear with age. Birthmarks vary from barely noticeable to disfiguring. These abnormalities may be flat or raised, have regular or irregular borders, and have different shades of coloring including brown, tan, black, pale

blue, pink, red, or purple. Birthmarks cannot be prevented and are not the result of anything done or not done during pregnancy. Two types of birthmarks are distinguished—vascular and pigmented.

Vascular Birthmarks

Vascular birthmarks arise from blood vessels that have not formed correctly (e.g., vascular malformations), from vessels that are proliferating (e.g., vascular tumors, such as **hemangiomas**), or due to vessel dilation (e.g., nevus simplex). Due to the vascular involvement, these birthmarks are generally red. The various types of vascular birthmarks include **macular stains**, hemangiomas, and **port-wine stains**.

Macular stains—also called "salmon patches," "angel kisses," and "stork bites"—are the most common type of vascular birthmark (**FIGURE 13-3**). These faint red marks often occur on the forehead, eyelids, posterior neck, nose, upper lip, or posterior head. On a baby, these birthmarks may be more noticeable when crying. Most often, these marks fade on their own by 2 years of age, but they sometimes last into adulthood.



FIGURE 13-3 Macular stain.

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Hemangiomas, also referred to as “strawberries,” are birthmarks that appear as a bright red **papule**, a plaque, or a nodule of extra blood vessels in the skin (**FIGURE 13-4**). They may be either superficial or deep. Deep hemangiomas may have a bluish color because they involve deeper blood vessels. These birthmarks grow during the first year of life and then usually recede over time. Some hemangiomas, particularly larger ones, may leave scars as they recede; these scars can be corrected by minor plastic surgery. Many hemangiomas are found on the head or neck, although they can appear anywhere on the body. Most hemangiomas are benign and not associated with other medical conditions, but they can cause complications if their location interferes with sight, feeding, breathing, or other bodily functions.



FIGURE 13-4 Hemangioma.

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Port-wine stains are discolorations that look like red wine was spilled on an area of the body—hence their name (**FIGURE 13-5**). These birthmarks most often occur on the face, neck, arms, and legs. Port-wine stains can be any size, but they grow only as the child grows. They tend to darken over time and can thicken and have a

cobblestone texture in mid-adulthood unless treated. Port-wine stains will not resolve spontaneously, and those occurring near the eye should be assessed for possible complications.



FIGURE 13-5 Port-wine stain.

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Pigmented Birthmarks

Pigmented birthmarks consist of a cluster of pigment cells that cause color in the skin. These birthmarks can be many different colors, from tan to brown, gray to black, or even blue. The most common pigmented birthmarks are **café au lait spots**, **Mongolian spots**, and **moles**.

Café au lait spots are common birthmarks that are the color of coffee with milk—hence their name (**FIGURE 13-6**). These birthmarks

can appear anywhere on the body and sometimes increase in number as a child gets older. One café au lait spot alone is not usually a concern, but the child should be further evaluated if he or she has several spots larger than a quarter, which can be a sign of neurofibromatosis (see the *Cellular Function* chapter).



FIGURE 13-6 Café au lait spot.

Courtesy of Marnie Pasciuto-Wood.

Mongolian spots are flat bluish-gray patches often found on the lower back or buttocks (**FIGURE 13-7**). These birthmarks are most common on individuals with darker complexions, such as children of Asian, American Indian, African, Hispanic, and southern European descent. They usually fade, often completely, by school age without treatment.



FIGURE 13-7 Mongolian spot.

Courtesy of Wassa Catlow.

Mole (or congenital nevi or hairy nevi) is a general term for “brown nevi” (the singular is *nevus*). Most people get moles at some point in life. When present at birth, the mole is called a “congenital nevus” and will last a lifetime. Large or giant congenital nevi are more likely to develop into skin cancer (melanoma) later in life; however, all moles should be monitored for cancerous changes. Moles can be tan, brown, or black; can be flat or raised; and may have hair growth.

Myth Buster

A persistent myth about birthmarks warrants discussion: *Birthmarks are a result of something the mother did or ate while pregnant*. There is no truth to old wives’ tales about stains being caused by something the mother did or ate. In reality, the cause of most birthmarks is unknown. Birthmarks can be inherited but usually are not, and they typically are unrelated to trauma to the skin during childbirth.

Diagnosis of birthmarks is often made during a physical examination. Treatment strategies vary depending on the type of birthmark, as some birthmarks cannot be treated. Macular stains usually fade away on their own, and the other vascular birthmarks are treatable. Hemangiomas are usually left untreated, as they typically shrink back into themselves by age 9. Larger or more serious hemangiomas often are treated with steroids. Laser therapy is the treatment of choice for port-wine stains. Most port-wine stains lighten significantly after several laser treatments, although some return and need retreatment. Laser treatment is typically started in infancy when the stain and the blood vessels are smaller. Marks on the head and neck are the most responsive to laser treatment.

Pigmented birthmarks are usually left untreated, except for moles and, occasionally, café au lait spots. Moles (particularly large or giant congenital nevi) can be surgically removed. Although café au lait spots can be removed with laser treatment, they often return.

Some birthmarks can be disfiguring and embarrassing for children. Special opaque makeup can be used to conceal or minimize the appearance of some birthmarks. Additionally, support and coping strategies can be helpful.

Disorders of Melanin

Melanin is a pigment that provides color and protection to skin. Disorders involving melanin result in alterations in skin coloring and can leave the skin vulnerable to the harmful effects of UV light. Melanin disorders include albinism and **vitiligo**.

Albinism

Albinism is a condition that results in little or no melanin production. The resulting melanin deficits cause a lack of pigment in the skin, hair, and iris of the eye (**FIGURE 13-8**). In addition to coloring and protection, melanin plays a role in the development of certain optical nerves. Therefore, all forms of albinism cause problems with eye development and function.



FIGURE 13-8 Albinism.

Courtesy of Cassandra Hartley.

Albinism is inherited, with 19 genes having been linked to its different clinical presentations (Marcon & Maia, 2019). This condition affects individuals in all social classes and of all races. The global incidence of albinism is 1 per 20,000 individuals, with a lower rate noted in the United States (1 per 37,000).

Albinism is generally grouped into two categories: oculocutaneous albinism (OCA) and ocular albinism (OA). In OCA, the most severe form, a normal number of melanocytes are present, but melanin production is absent or significantly decreased. OCA occurs in all races. People with this form of albinism appear to have white or pink hair, skin, and iris color; they also have vision problems. Most cases of OCA are autosomal recessive, but autosomal dominant inheritance can occur. There are eight genetic forms of OCA, including:

- Type I—caused by absent (accounts for 40% of all OCA) or reduced levels of tyrosinase (catalyzes several steps in melanin synthesis) activity.
- Type II—caused by mutations in the *P* (pink-eyed) gene and accounts for 50% of all OCA. Although the function of the P protein is unknown, it may involve organelle pH regulation and vacuolar glutathione accumulation. Tyrosinase activity is present with this type of OCA.
- Type III—occurs in individuals with dark skin and is caused by mutations in a *tyrosinase-related protein 1* gene that is important in eumelanin (most common type of melanin) synthesis.
- Type IV—an extremely rare form that is caused by a defect in the *SLC45A2* gene, which codes a membrane transporter protein involved in tyrosinase processing and transferring proteins to melanosomes. This type is the most common form of OCA in Japan.
- Type V—has been linked to chromosome 4q24, an area that may code for lysosomal proteins.
- Type VI—caused by mutations in gene *SLC45A5*, which encodes a membrane transporter protein.
- Type VII—caused by mutations in gene *C10orf11*, which encodes a leucine-rich protein that may play a role in melanocyte differentiation.
- Type VIII—associated with a mutation in the *dopachrome tautomerase* gene on chromosome 13q32, which encodes an enzyme that plays a role in modifying skin pigment color.

OA types, which include Nettles-Falls (OA1) and Forsius-Eriksson (OA2), are extremely rare. These forms are X-linked dominant. The affected person's skin and eye colors are usually normal; however, an eye exam will reveal no coloring of the retina. Individuals with OA1 may also have late-onset sensorineural deafness.

Hermansky-Pudlak syndrome is a form of albinism caused by a single gene; it can occur with a bleeding disorder as well as with lung

and bowel diseases. Other complex diseases may lead to color loss in only a certain area (localized albinism):

- Chédiak-Higashi syndrome—lack of coloring all over the skin, but not complete
- Tuberous sclerosis—small areas without skin coloring
- Waardenburg syndrome—often a lock of hair that grows on the forehead is affected, or no coloring is present in one or both irises

Clinical manifestations of albinism are usually—but not always—apparent in a person's skin, hair, and eye color. Regardless of the effect of albinism on appearance, all people with the disorder experience vision impairments. Manifestations may include the following:

- Skin changes. Although the most recognizable form of albinism results in milky white skin, skin pigmentation can range from white to nearly the same as relatives without albinism. For some people with albinism, skin pigmentation never changes. For others, melanin production may begin or increase during childhood and adolescence, resulting in slight increases in pigmentation. Some people may develop freckles, moles (with or without pigment), or lentigines (large frecklelike spots) with exposure to the sun. Individuals are at high risk for sunburn and skin cancers.
- Hair changes. Hair color can range from very white to brown. People of African or Asian descent who have albinism may have hair color that is yellow, reddish, or brown. Hair color may also change by early adulthood.
- Eye changes. Eye color can range from very light blue to brown and may change with age. The lack of pigment in the irises makes them somewhat translucent, meaning they cannot completely block light from entering the eye. This translucence can cause very light-colored eyes to appear red in some lighting conditions because of light reflecting off the back of the retina and passing back out through the iris again—similar to the "red eye" that occurs in a flash photograph.

- Vision changes. Multiple vision issues can result from the lack of melanin, including the following problems:
  - Nystagmus (rapid, involuntary back-and-forth eye movement)
  - Strabismus (inability of both eyes to stay directed at the same point or to move in unison, or crossed eyes)
  - Extreme nearsightedness or farsightedness
  - Photophobia (sensitivity to light)
  - Astigmatism (abnormally shaped cornea)
  - Functional blindness

Diagnostic procedures for albinism consist of a history, physical examination (including a thorough ophthalmologic exam), and genetic testing (most accurate). Although there is no cure for albinism, people with this disorder can take steps to improve vision and avoid damage from sun exposure:

- Using sunscreen with a high sun protection factor (SPF) against ultraviolet A (UVA) and ultraviolet B (UVB) rays
- Wearing protective clothing (e.g., long-sleeved shirts, long pants, and hats)
- Limiting time outdoors, especially between 10:00 a.m. and 4:00 p.m., when the sun's UV rays are the most intense
- Wearing sunglasses (with UV protection), which may relieve light sensitivity
- Avoiding medications that increase photosensitivity (e.g., fluoroquinolones, tetracyclines, antifungals, antihistamines, HMG-CoA reductase inhibitors, thiazide diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs]) when possible
- Performing routine skin assessments (self-assessments and assessments by a healthcare provider, such as a dermatologist)
- Wearing glasses to correct vision problems and eye position
- Having eye muscle surgery to correct abnormal eye movements (i.e., nystagmus)

Albinism does not impair intellectual development, although people with albinism often feel socially isolated and may experience discrimination. Coping strategies and support may be beneficial in addressing these issues. The visual issues may lead to educational challenges. Educational strategies may include sitting at the front of the classroom, using large-print books and notes, and printing materials with high-contrast colors (e.g., black and white).

Vitiligo

Vitiligo is a rare condition characterized by small patchy areas of hypopigmentation (**FIGURE 13-9**). This disorder occurs when melanocytes die or no longer form melanin, causing slowly enlarging hypopigmented patches of irregular shapes on the skin that are well demarcated. This condition affects people of all races but may be more noticeable and disfiguring in people with dark skin tones. Vitiligo affects an estimated 1% of the population worldwide (National Institutes of Health [NIH], 2023). Its exact cause is unknown, but potential mechanisms include autoimmune melanocyte destruction, reduced melanocyte survival, and primary melanocyte defects. Vitiligo may be inherited (autosomal dominant) or acquired (e.g., sunburn or emotional stress). Variations in more than 30 genes (e.g., *NLRP1* and *PTPN22*), occurring in different combinations, have been associated with increased risk for vitiligo (NIH, 2023). Although vitiligo has also been associated with pernicious anemia, diabetes mellitus, **psoriasis**, and Addison's disease, the strongest association is with thyroid dysfunction (hyper or hypo).

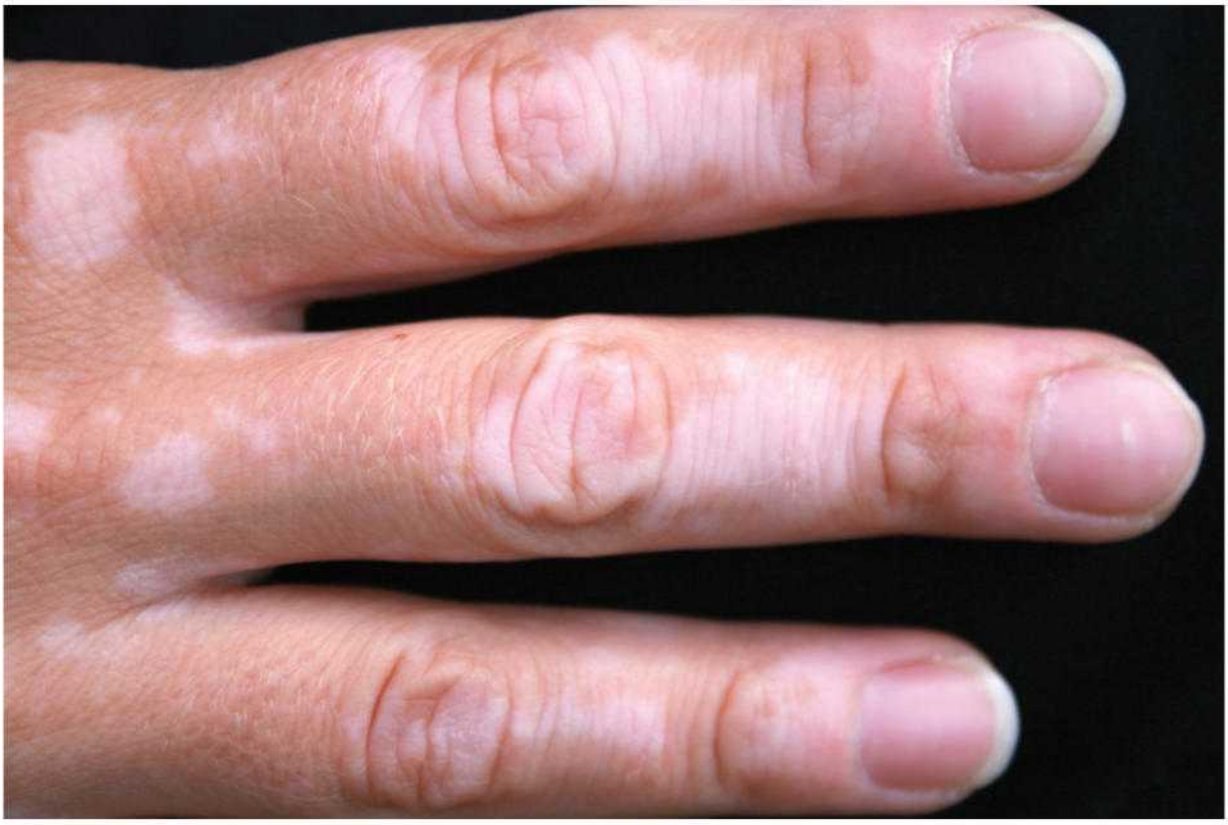


FIGURE 13-9 Vitiligo.

© Nadine Mitchell/Dreamstime.com

Although any area of the body may be affected, depigmentation usually develops first on sun-exposed areas (e.g., hands, feet, arms, face, and lips). While it can start at any age, vitiligo often first appears between 10 and 30 years of age. It generally develops in one of three patterns: focal (depigmentation is limited to one or a few areas of the body), segmental (depigmentation occurs on one side of the body), or generalized (depigmentation is widespread across many parts of the body, often symmetrically).

The natural course of vitiligo is difficult to predict. Sometimes the patches stop forming without treatment. In most cases, pigment loss spreads and can eventually involve most of the skin's surface. In addition to patchy skin depigmentation, clinical manifestations may include depigmentation of the hair, mucous membranes, and retina.

Emerging Research: Vitiligo Treatment

Vitiligo develops in genetically vulnerable individuals when environmental triggers induce stress response in the skin, resulting in an autoimmune reaction in which melanocytes are targeted and destroyed by CD8+ T cells. This process causes the release of IFN-γ^3 which activates the JAK-STAT pathway by binding to JAK1 and 2. This activation triggers the production of the immune mediators, CXCL9/10, by keratinocytes. This cycle continues in a positive feedback loop. Topical janus kinase inhibitors break this cycle and are an emerging treatment modality for vitiligo. One example of this type of medication is ruxolitinib cream (Opzelura), recently approved by the U.S. Food and Drug Administration in 2022. Opzelura has shown promise in patients with nonsegmental vitiligo and depigmentation in at least 10% of their body's surface area with facial involvement (Andrus, 2023).

Diagnosis of vitiligo includes a history, physical examination (including a Wood light exam), skin biopsy, genetic testing, serum autoantibody level measurements, serum thyroid hormone level measurements, and serum vitamin B_{12} level measurements. There is no cure for this disorder. Instead, the goal of treatment is to stop or slow the progression of pigment loss and attempt to return some pigment. Treatment and coping strategies may include the following measures:

- Phototherapy (controlled exposure to intense UV light in a clinic or hospital)
- Pharmacotherapy, including the following medications:
  - Oral synthetic melanizing agents (e.g., trimethylpsoralen [Trisoralen])
  - Topical corticosteroid agents
  - Topical immunosuppressants (e.g., pimecrolimus [Elidel] and tacrolimus [Protopic])
  - Topical repigmenting agents (e.g., methoxsalen [Oxsoralen])
  - Oral or topical photochemotherapy (e.g., psoralen plus UVA radiation)
- Skin graft

- Autologous melanocyte transplant (still experimental)
- Permanent depigmentation of the remaining skin (a last resort reserved for extreme cases)
- Sun safeguards (e.g., sunscreen and protective clothing)
- Coping strategies and support
- Makeup or skin dyes
- Tattooing (most effective around the lips)

Integumentary Changes Associated with Aging

The skin undergoes several changes with aging. Sensations of pain, vibration, cold, heat, pressure, and touch usually decrease over the course of the life span. These changes may be related to decreases in blood flow to touch receptors or the brain as well as fewer receptors that can occur with age. Decreases in these sensations can increase the risk of injury, including falls, decubitus ulcers, **burns**, and hypothermia.

In addition to sensory changes, the skin undergoes other aging-related changes. In particular, it loses elasticity, integrity, and moisture over time. Environmental factors, genetic makeup, and nutrition may all contribute to these changes. The greatest single contributing factor, however, is sun exposure. Natural pigments seem to provide some protection against sun-induced skin damage. Consequently, blue-eyed, fair-skinned people show more of these aging skin changes than people with darker, more heavily pigmented skin. With aging, the epidermis thins, even though the number of cell layers remains unchanged. The number of melanocytes decreases, but the remaining melanocytes increase in size. Aging skin thus appears thin, pale, and translucent. Large pigmented spots (called “age spots,” “liver spots,” or **lentigos**) may appear in sun-exposed areas (**FIGURE 13-10**). Changes in the connective tissue reduce the skin’s strength and elasticity, especially in sun-exposed areas. Dermis blood vessels become fragile, which can lead to bruising, cherry angiomas, and other similar conditions.

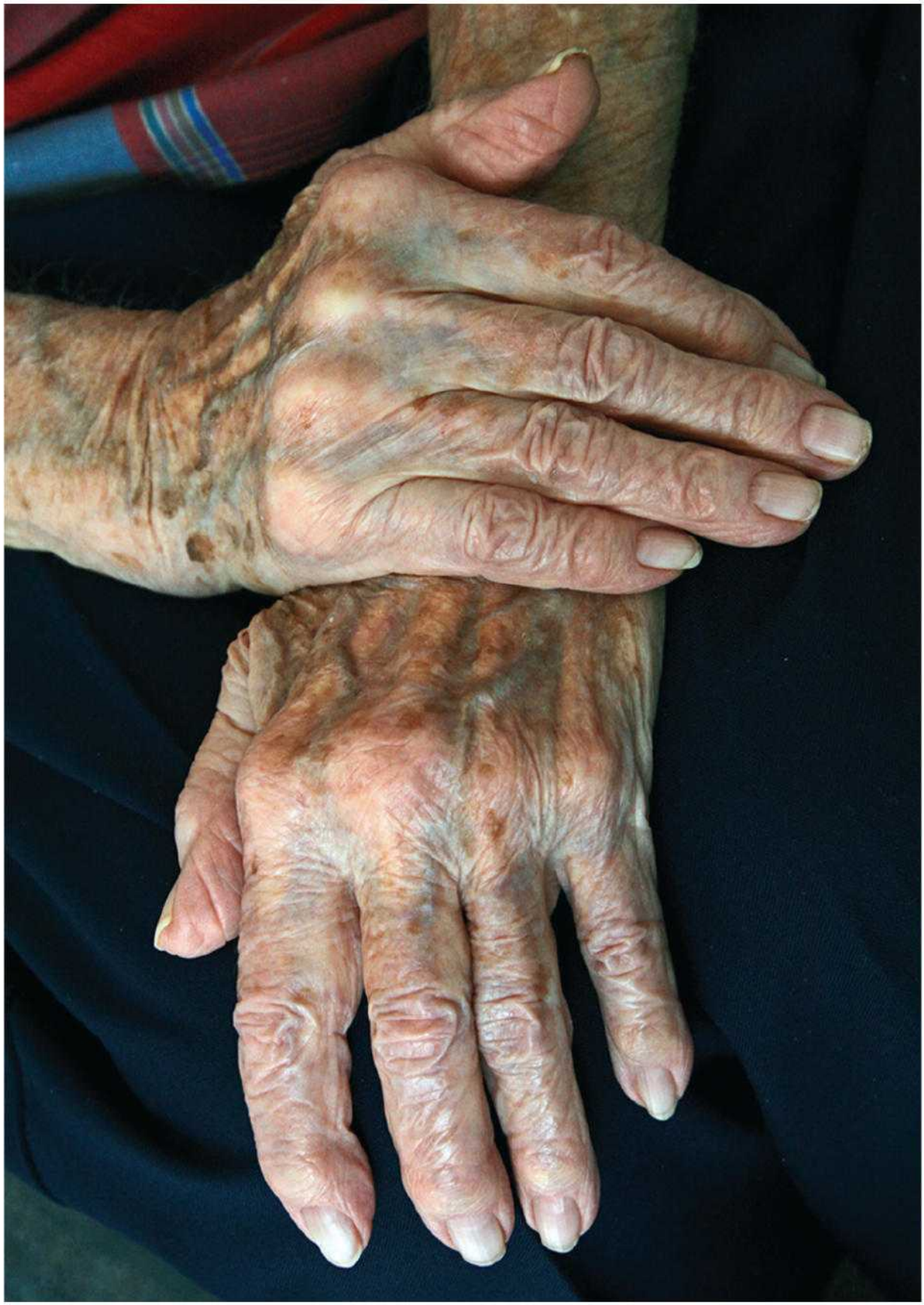


FIGURE 13-10 Lentigo.

Courtesy of Dean Ducas.

Sebaceous glands also produce less sebum over time. Men experience a minimal decrease in sebum production, usually after the age of 80, whereas women gradually produce less sebum beginning after menopause. This decrease in sebum can make it difficult to maintain skin moisture, resulting in dryness and itching. The sweat glands also produce less sweat with aging. The resulting decrease in perspiration contributes to difficulty in controlling body temperature.

The subcutaneous fat layer, which provides insulation and padding, thins with age. This waning layer increases the risk of skin injury and reduces the ability to maintain body temperature. Additionally, its thinning changes the actions of some medications because this fat layer absorbs these medications.

Aging skin repairs itself more slowly than younger skin, such that wound healing may take as much as four times longer to complete. This sluggish repair contributes to decubitus ulcer formation and infections. The presence of chronic diseases (e.g., diabetes mellitus and arteriosclerosis) and other aging-related changes (e.g., impaired immunity and circulatory changes) may further delay healing.

Other skin abnormalities may also develop over time, including the **skin tags** and other blemishes often seen in older people. Skin tags are benign, soft brown or flesh-colored masses that usually occur on the neck (**FIGURE 13-11**). Most skin tags are painless, but they can become inflamed in the presence of constant friction (e.g., from clothing). Skin tags are more common in persons who are obese or have diabetes mellitus. These masses can be removed with surgery, cryotherapy, and cautery.



FIGURE 13-11 Skin tags.

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Inflammatory Integumentary Disorders

Inflammatory skin diseases include a broad group of conditions, ranging in severity from mild itching to serious medical complications. These noncontagious conditions may occur in isolation or in conjunction with other conditions. Most of them can be resolved or managed easily with treatment.

Contact Dermatitis

Contact dermatitis is an acute inflammatory reaction triggered by direct exposure to an irritant or allergen-producing substance (**FIGURE 13-12**). Contact dermatitis is not contagious or life

threatening. It varies in severity depending on the substance, area affected, exposure extent, and individual sensitivity.



FIGURE 13-12 Contact dermatitis.

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Irritant contact dermatitis accounts for 80% of cases. Chemicals (e.g., acids, alkalis, solvents, and metal salts), plants (e.g., poinsettias and peppers), body fluids (e.g., urine and saliva), rubber gloves, and soaps may all cause this condition. This type of contact dermatitis does not involve the immune system but simply triggers the inflammatory response. Irritant contact dermatitis produces a reaction similar to a burn, with its manifestations typically including erythema and edema and sometimes pain, pruritus, and **vesicles** (blisters).

Allergic contact dermatitis results from contact with substances, such as metals, chemicals, adhesives, cosmetics, and plants (e.g., poison ivy and poison sumac). Sensitization occurs on the first

exposure to the substance, and subsequent exposures to the substance produce manifestations owing to a type IV cell-mediated hypersensitivity (see the *Immunity* chapter). The reaction is usually delayed, with manifestations appearing 24–48 hours after exposure. Typically, manifestations of allergic contact dermatitis include pruritus, erythema, and edema at the site, but small vesicles may also be present.

Diagnostic procedures for contact dermatitis include a history, physical examination, and allergy testing. Treatment centers on identifying and removing the causative agent (e.g., rinsing the affected area). If the offending agent can be avoided, the rash usually resolves in 2–4 weeks. Self-care measures, such as wet, cool compresses and anti-inflammatory creams (e.g., corticosteroid agents), can help soothe skin and reduce inflammation. Systemic anti-inflammatory agents may be used in severe cases.

Atopic Dermatitis

Atopic dermatitis, also referred to as "eczema," is a chronic inflammatory condition (**FIGURE 13-13**). It is most common in infants but usually resolves by early adulthood. The prevalence of atopic dermatitis, which primarily affects children in urban areas, has increased over the past 30 years. It tends to be characterized by remissions and exacerbations. The exact cause of atopic dermatitis is unknown, but it may result from an immune system malfunction similar to hypersensitivity (an elevated level of immunoglobulin E is usually present). This condition is thought to be the first of a series of allergic diseases that affect the epithelial surfaces (referred to as the "atopic march" theory)—including food allergies, asthma, and allergic rhinitis (Spergel, 2010). It has an inherited tendency and may be accompanied by asthma and allergic rhinitis. Several genes have been associated with atopic dermatitis (e.g., *CARD11* and *FLG*), but the condition is likely a result of variations in multiple genes.

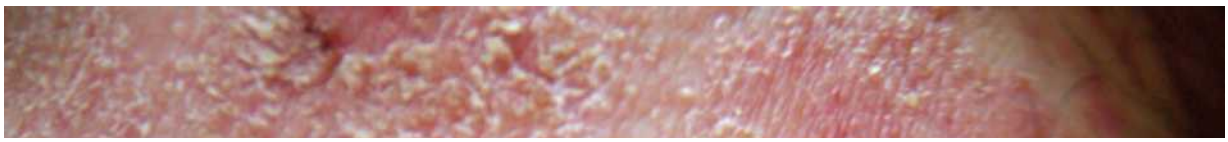




FIGURE 13-13 Atopic dermatitis.

Courtesy of Paul Matthews.

Complications may include secondary bacterial skin infections, neurodermatitis (permanent scarring and discoloration from chronic scratching), and eye problems (e.g., conjunctivitis). Atopic dermatitis may affect any area, but the pattern exhibited tends to be age specific. In young children, the skin lesions primarily affect the face, scalp, hands, or feet. In contrast, the knees and elbows are the most commonly affected sites in older children and adults. Clinical manifestations may be worsened by environmental factors, such as food allergens (e.g., milk, eggs, soy, wheat, and peanuts), airborne allergens (e.g., dust mites, molds, and dander), *Staphylococcus aureus* colonization on the skin, topical products (e.g., cosmetics, fragrances, and harsh soaps), sweating, and rough fabrics. These manifestations include the following signs and symptoms:

- Red to brownish-gray colored skin patches
- Pruritus, which may be severe, especially at night
- Vesicles
- Thickened (lichenified), cracked, or scaly skin
- Irritated, sensitive skin from scratching

Diagnostic procedures for atopic dermatitis include a history, physical examination, allergy testing, and skin biopsy (to rule out other causes). In children, the condition usually improves with age (starting around age 5–6), but flare-ups may occur. Treatment focuses on decreasing the inflammatory process. These strategies may include the following measures:

- Avoiding factors that can worsen manifestations:
  - Long hot baths or showers
  - Dry skin
  - Stress

    - Sweating
    - Rapid changes in temperature
    - Low humidity
    - Solvents, cleaners, soaps, or detergents
    - Wool or synthetic fabrics or clothing
    - Dust or sand
    - Cigarette smoke
    - Certain foods (e.g., eggs, milk, fish, soy, and wheat)
- Avoiding scratching
    - Moisturizing the skin by applying ointments (e.g., petroleum jelly) 2–3 times per day
    - Using a humidifier
- Employing the following strategies when washing or bathing:
    - Keeping water contact brief and using gentle soap
    - Not excessively scrubbing or drying the skin
    - After bathing, applying lubricating creams, lotions, or ointment on the skin while it is damp to trap moisture in the skin
- Using the following pharmacologic agents:
    - Antihistamine agents (topical or oral)
    - Corticosteroid agents (topical or oral)
    - Immunomodulators (topical or oral)
    - Janus kinase inhibitors (topical)
    - Antibiotics (topical or oral if infection is present)
    - Allergen-desensitizing injections
- Receiving phototherapy

Urticaria

Urticaria, or hives, consists of raised erythematous skin lesions (**welts**) (**FIGURE 13-14**). These lesions are a result of a type I hypersensitivity reaction (see the *Immunity* chapter). This reaction is often triggered by food (e.g., shellfish and nuts) or medicine (e.g.,

antibiotics) ingestion. Urticaria may also be a result of emotional stress, excessive perspiration, diseases (e.g., autoimmune conditions and leukemia), and infections (e.g., mononucleosis). It occurs when histamine release is initiated by these substances or conditions. The resulting skin lesions are usually short-lived and harmless, but breathing can be impaired when the swelling occurs around the face (angioedema). Additionally, a type I hypersensitivity reaction can progress to an anaphylactic reaction (see the *Immunity* chapter) and shock (see the *Cardiovascular Function* chapter). The diffuse welts may grow large, spread, and fuse together. These welts turn white when pressure is applied (called “blanching”). In addition to patchy welts, pruritus may be present.





FIGURE 13-14 Urticaria.

© LeventKonuk/iStock/Getty Images Plus/Getty Images

Diagnostic procedures for urticaria include a history, physical examination, allergy testing, and skin biopsy. Treatment focuses on ending the inflammatory reaction and maintaining respiratory status (if appropriate). Mild urticaria may disappear without any treatment. Treatment strategies to reduce itching and swelling include the following measures:

- Avoiding hot baths or showers
- Avoiding irritating the area (e.g., with tight-fitting clothing or rubbing)
- Taking antihistamines (e.g., diphenhydramine [Benadryl])

Severe reactions, especially if angioedema is present, may require epinephrine (adrenaline) or corticosteroid injections. Additionally, airway maintenance may be necessary, including an artificial airway, oxygen therapy, and mechanical ventilation. Epinephrine and other

bronchodilator agents can also be administered directly into the respiratory tract to improve ventilation.

Psoriasis

Psoriasis is a common chronic inflammatory condition that affects the life cycle of the skin cells, specifically keratinocytes (**FIGURE 13-15**). Cellular proliferation is significantly increased in this disorder, such that cells build up too rapidly on the skin's surface (**FIGURE 13-16**). The process of skin cells growing in the innermost layers of the skin and then rising to the surface normally takes weeks, but with psoriasis, this process occurs over 3–4 days. The ensuing buildup leads to thickening of the dermis and epidermis because the dead cells cannot be shed fast enough.





FIGURE 13-15 Psoriasis.

Courtesy of Yale Residents' Slide Collection, Dermatology Department, Yale University School of Medicine.

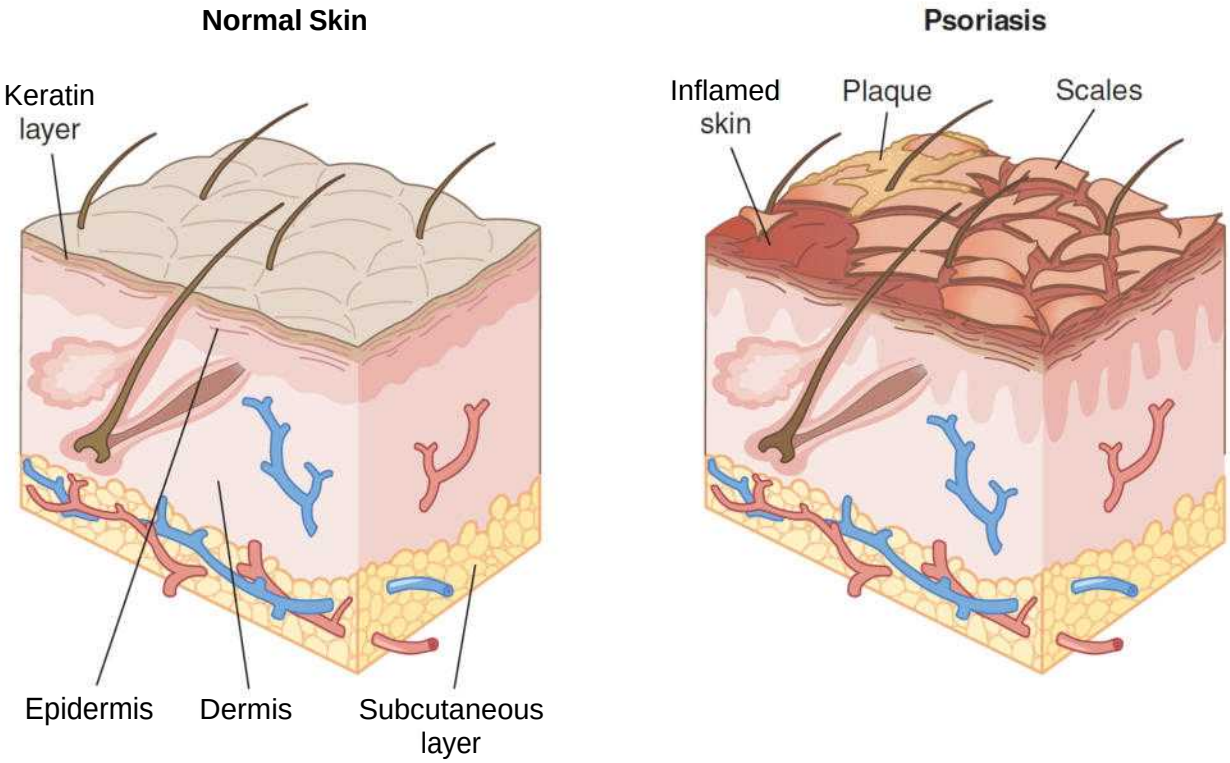


FIGURE 13-16 Cellular changes associated with psoriasis.

Description

The exact cause of psoriasis is unknown, but it does seem to be multifactorial in origin. In particular, environmental factors (e.g., sunburn, infection, stress, cold), trauma, infections (e.g., human immunodeficiency virus [HIV] and beta-hemolytic *Streptococci*), obesity, excessive alcohol consumption, certain medications (e.g., beta blockers, antimalaria agents, lithium, and angiotensin-converting enzyme [ACE] inhibitors), genetic factors (e.g., human leukocyte alleles), and immunologic factors (e.g., high levels of tumor necrosis factor) all seem to play roles in its etiology. This skin condition could be a result of an autoimmune process in which the body—specifically T lymphocytes—mistakes normal skin cells as foreign. Cytokines are then released, which stimulate keratinocyte proliferation.

Psoriasis can affect people of any age, but its onset most frequently occurs between 15 and 35 years of age. The onset may be sudden or gradual, and many patients will experience remissions

and exacerbations. The following factors may trigger a psoriasis exacerbation or make the condition more difficult to treat:

- Bacterial or viral infections in any location
- Dry air or dry skin
- Skin injuries (e.g., cuts, burns, and insect bites)
- Use of certain medicines (e.g., antimalaria agents, beta blockers, and lithium)
- Stress
- Too little or too much sunlight
- Excessive alcohol consumption
- Tobacco smoking
- Obesity

The severity of psoriasis varies widely, from being a mere nuisance to being disabling. As many as 30% of persons with psoriasis also have arthritis, a combination referred to as psoriatic arthritis. In general, psoriasis may be severe in persons who have a weakened immune system (e.g., those with acquired immunodeficiency syndrome [AIDS], those with autoimmune conditions, or those who are receiving chemotherapy).

Psoriatic lesions begin as a small, red papule (a firm and solid elevated area) that then enlarges. These lesions most often occur on the elbows, knees, and trunk but can appear anywhere on the body. The early lesions can progress to one of the following types of more advanced psoriatic lesions:

- Erythrodermic—intense erythema that covers a large area
- Guttate—small pink-red spots
- Inverse—erythema and irritation that occur in the armpits, groin, and skin folds
- Plaque—thick red patches covered by flaky silver-white scales (the most common type)
- Pustular—white blisters surrounded by erythema

Other manifestations may include the following signs and symptoms:

- Pruritus
- Genital lesions in males
- Joint pain or aching (psoriatic arthritis)
- Nail changes, such as thickening, yellow-brown spots, dents (pits) on the nail surface, and separation of the nail from the base
- Severe dandruff on the scalp

Diagnostic procedures for psoriasis include a history, physical examination, X-rays (if joint pain is present), and skin biopsy (to rule out other causes). Other tests may be conducted to rule out conditions that mimic psoriasis (e.g., seborrheic dermatitis and **tinea** corporis).

No cure exists for psoriasis, but treatment can improve symptoms significantly in most cases. The goal of psoriasis treatment is to interrupt the process that leads to cell buildup and improve manifestations. Treatment usually requires a multipronged approach and includes three main approaches—topical treatments, phototherapy, and systemic medications:

- Topical treatments:
  - Corticosteroid agents—to slow cell turnover by suppressing the immune system
  - Vitamin D analogues—to slow down the skin cell growth
  - Anthralin (Dritho-Scalp)—to normalize DNA activity in skin cells, remove scales, and smooth skin
  - Retinoids—to normalize DNA activity in skin cells and possibly decrease inflammation
  - Calcineurin inhibitors—to disrupt the activation of T lymphocytes, thereby reducing inflammation and plaque buildup
  - Salicylic acid—to promote shedding of dead skin cells and reduce scaling

- Coal tar—to reduce scaling, itching, and inflammation, although the mechanism of action remains unknown
- Moisturizers—to reduce dryness, itching, and scaling; ointment-based moisturizers are the most effective
- Dandruff shampoo—to reduce cellular turnover

- Phototherapy:
  - Sunlight—UV light, whether natural or artificial, to cause activated T lymphocytes in the skin to die, which slows cell turnover, reduces scaling, and decreases inflammation
  - Broadband UVB phototherapy—to slow cellular growth
  - Narrowband UVB phototherapy—a newer and more effective treatment than broadband UVB treatment
  - Photochemotherapy, or psoralen plus UVA light—administering psoralen, a light-sensitizing medication, before exposure to UVA light to increase the response to the light
  - Excimer laser—a controlled beam of UVB light of a specific wavelength that is directed to only the involved skin
- Oral or injected pharmacotherapy (primarily reserved for severe or resistant cases and used for brief periods because of the potential serious side effects):
  - Retinoids—related to vitamin A; this group of drugs may reduce the production of skin cells
  - Methotrexate—decreases the production of skin cells and suppresses inflammation
  - Cyclosporine—suppresses the immune system similarly to methotrexate
  - Hydroxyurea—suppresses the immune system but not as effectively as methotrexate and cyclosporine
  - Immunomodulator drugs—block interactions between certain immune system cells

In addition to these main strategies, stress management (e.g., coping strategies and support) and avoiding psoriasis triggers may be

beneficial. Limiting foods that trigger inflammation may also minimize symptoms. Foods that have shown to trigger inflammation include gluten, processed foods high in trans fats and refined starches and sugars, red meat (high in a polyunsaturated fat called “arachidonic acid”), diary products (contains arachidonic acid and the protein casein, which has also been linked to inflammation), “nightshade plants” (i.e., peppers, white potatoes, eggplants, tomatoes; contain solanine that may trigger inflammation in some people), citrus fruits, and condiments (i.e., pimento, cinnamon, curry, vinegar, mayo, paprika, Tabasco sauce, Worcestershire sauce, and ketchup) (National Psoriasis Foundation, 2022).

Infectious Integumentary Disorders

Skin infections are common and may be caused by a number of pathogens (e.g., bacteria, viruses, and parasites). These organisms usually gain access through a breach in the skin or mucous membranes. They often trigger an inflammatory response as well. Such infections can occur in any of the skin layers or structures (e.g., hair follicles); they may be acute or chronic and vary widely in severity. In most cases, infectious integumentary disorders are easily resolved with treatment.

Bacterial Infections

Any number of bacteria that are present in the body as part of the normal flora or encountered externally may cause bacterial skin infections. These infections can vary in severity from mild to life threatening. Bacteria in the *Staphylococcus* and *Streptococcus* genera are common culprits in integumentary infections. These infections can result in numerous conditions:

- **Folliculitis** refers to infections involving the hair follicles. Folliculitis is characterized by tender, swollen pustules that form around hair follicles, often on the neck, breasts, buttocks, and face. Pruritis may also be present.

- **Furuncles**, or boils, are infections that begin in the hair follicles and then spread into the surrounding dermis. Furuncles most commonly occur on the face, neck, axillae, groin, buttocks, and back. A furuncle lesion starts as a firm, red, painful nodule that develops into a large, painful mass, which frequently drains large amounts of purulent exudate. **Carbuncles** refer to clusters of furuncles.
- **Impetigo** is a common and highly contagious skin infection. Although it can occur without an apparent breach, this infection typically arises from a break in the skin (especially from animal bites, human bites, insect bites, and trauma). Impetigo spreads easily to others by direct contact with skin or contaminated objects (e.g., eating utensils, towels, clothing, and toys). Lesions usually begin as small vesicles that enlarge and rupture, forming a characteristic honey-colored crust (**FIGURE 13-17**). These lesions can spread throughout the body through self-transfer of the exudate. Impetigo is typically caused by *Staphylococci*; these bacteria produce a toxin that causes impetigo to spread to nearby skin. The toxin attacks collagen, a protein that helps bind skin cells together. Once this protein is damaged, bacteria can spread quickly. Pruritus is common, and lymphadenopathy (swollen lymph nodes) can occur near the lesions.



FIGURE 13-17 Impetigo.

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- **Cellulitis** refers to an infection deep in the dermis and subcutaneous tissue. It usually results from a direct invasion of the pathogens through a break in the skin, especially those breaches

where contamination is likely (e.g., intravenous drug use and bites), or spreads from an existing skin infection. Cellulitis appears as a swollen, warm, tender area of erythema (**FIGURE 13-18**). Additionally, systemic manifestations of infection are usually present (e.g., fever, leukocytosis, malaise, and arthralgia). If left untreated, cellulitis can lead to **necrotizing fasciitis**, septicemia, and septic shock.



FIGURE 13-18 Cellulitis.

Courtesy of CDC/Allen W. Mathies, MD/California Emergency Preparedness Office (Calif/EPO), Immunizaiton Branch.

- Necrotizing fasciitis is a serious infection that is generally rare, although its incidence rates are rising. One out of four people who develop this infection will die from the disease. Also known as "flesh-eating bacteria," necrotizing fasciitis can aggressively destroy skin, fat, muscle, and other tissue (**FIGURE 13-19**). This infection typically involves a highly virulent strain of gram-positive

group A beta-hemolytic *Streptococcus* that invades through a minor cut or scrape. The bacteria begin to grow and release harmful toxins that directly destroy the tissue, disrupt blood flow, and break down material in the tissue. The first sign of infection may be a small, reddish, painful area on the skin, which quickly evolves into a painful bronze- or purple-colored patch that grows rapidly. The center of the lesion may become black and necrotic. Exudate is often present. The wound may quickly grow, in less than an hour. Systemic manifestations may include fever, tachycardia, hypotension, and confusion. Complications of necrotizing fasciitis include gangrene, multisystem organ failure, and shock.



FIGURE 13-19 Necrotizing fasciitis.

© Dr. Ken Greer/Visuals Unlimited, Inc.

Diagnostic procedures for all bacterial skin infections center on the identification of the causative organism, usually through cultures. Once the organism is identified, treatment focuses on eradicating the

organism with appropriate antibiotic therapy (either systemic or topical). Care should be taken when draining any wounds, as this procedure can spread the infection. Other strategies may include maintaining adequate hydration, wound care, surgical debridement, drainage, hyperbaric oxygen therapy, antipyretic agents, and analgesic agents.

Viral Infections

A number of viruses can cause a multitude of skin issues, each with its own manifestations and treatments. These infections can result in numerous conditions, including those described in this section.

Herpes Simplex Type 1

Herpes simplex type 1 (HSV-1), or a cold sore, is a viral infection typically affecting the lips (i.e., herpes labialis), mouth (i.e., gingivostomatitis), and face. This common infection usually begins in childhood. HSV-1 can also involve the eyes, leading to conjunctivitis and herpes keratitis. Additionally, infection with this pathogen can result in meningoencephalitis. The virus is transmitted by contact with infected saliva, even if a lesion is not apparent.

The primary HSV-1 infection may be asymptomatic. After this primary infection ends, the virus remains dormant in the sensory nerve ganglion to the trigeminal nerve until it is reactivated, similar to the pathogenesis of HSV type 2 (see the *Reproductive Function* chapter). Reactivation may be a result of an infection, stress, sun exposure, or immunosuppression. When reactivated, HSV-1 causes painful blisters or ulcerations, which are preceded by a burning or tingling sensation up to 6 hours prior to the eruption (prodromal period). The lesions resolve spontaneously within 3 weeks, but healing can be accelerated by administration of oral or topical antiviral agents. Generally, recurrent eruptions are less severe and occur less frequently over time.

Herpes Zoster

Herpes zoster, or shingles, is caused by the varicella-zoster virus. This condition usually appears in the adulthood years after a primary

infection with varicella (chickenpox) has occurred in childhood. Herpes zoster can develop even if the individual has not had an active case of varicella. With the widespread use of varicella vaccines, many individuals are exposed to the virus but do not demonstrate clinical manifestations. The exposure to the virus, with or without clinical manifestations, is sufficient to develop herpes zoster later. Approximately one in three people in the United States will develop shingles in their lifetime (Centers for Disease Control and Prevention [CDC], 2023b).

After the initial varicella infection, the virus lies dormant on a cranial nerve or a spinal nerve dermatome until it becomes activated years later. Because the virus affects this nerve only, the condition typically demonstrates unilateral manifestations—for example, pain, paresthesia, and a vesicular rash that develops in a line over the area innervated by the affected nerve (**FIGURE 13-20**). The rash may appear red or silvery, and it occurs on one side of the head or torso depending on the nerve affected. The skin often becomes extremely sensitive, and pruritus may be present. The rash may persist for weeks to months. In some cases, especially in older persons, postherpetic neuralgia or pain may continue long after the rash disappears. Blindness may result if the eye is affected.



FIGURE 13-20 Herpes zoster.

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Antiviral agents can limit the condition's duration and severity when initiated within 72 hours of onset of lesion, and antidepressant and anticonvulsant agents have been beneficial in relieving the neuralgia associated with shingles. Vaccines are available to prevent both varicella and herpes zoster infections. Fewer than 4% of patients with herpes zoster experience another outbreak. The herpes zoster vaccine can be given even if the individual has had the condition previously, with the intention of lowering the risk of developing it again later.

Verrucae

Verrucae, or warts, are caused by a number of human papillomaviruses (HPVs). These skin lesions can develop at any age and often resolve spontaneously. They can be transmitted through direct skin contact between people or within the same person.

Trauma and maceration can facilitate the initial skin inoculation, but the virus can also spread through autoinoculation. Immunocompromised individuals are at higher risk of developing lesions that spread and are difficult to treat. Humoral immunity provides resistance to HPV infections, and cellular immunity facilitates infection regression once contracted.

HPV replicates in the skin cells, causing irregular thickening. The resulting lesions may vary in color, shape, and texture depending on their type (**FIGURE 13-21**). The different types of warts include verrucae vulgaris (common warts), verruca plana (flat warts), verruca plantaris (flattened warts on the palms and soles), verruca filiformis (long and slender warts on the eyelids, face, neck, or lips), mosaic warts (clusters of verruca plantaris), periungual warts (thickened, fissured, cauliflower-like skin around the nails), and condylomata acuminata (genital warts; see the *Reproductive Function* chapter). Treatment includes a wide range of local applications, such as laser treatments, cryotherapy with liquid nitrogen, electrocautery, and topical medications (e.g., keratolytic, cytotoxic, and antiviral agents), but the verrucae may return after treatment.



FIGURE 13-21 Verrucae.

© Dermatology11/Shutterstock

Molluscum Contagiosum

Molluscum contagiosum is a poxvirus infection that is characterized by clusters of pink, cone-shaped, smooth, waxy, or pearly papules 2 to 5 mm in diameter (**FIGURE 13-22**). This virus commonly results in a localized chronic infection. Transmission occurs by direct contact and spread occurs by autoinoculation and through fomites (e.g., towels and bath sponges) and water. The condition is common among children, and immunocompromised individuals may develop a widespread infection. Treatment strategies include curettage, cryosurgery, laser therapy, electrocautery, and topical irritants (e.g., trichloroacetic acid, cantharidin, and tretinoin). Occasionally, intralesional injections or photodynamic therapy are used.



FIGURE 13-22 Molluscum contagiosum.

© JodiJacobson/E+/Getty Images

Parasitic Infections

Several parasitic infections can occur on the skin, including those caused by fungi and other organisms. These conditions are usually diagnosed through microscopic examination of skin scrapings processed with potassium hydroxide. Many of the causative organisms feed off the dead skin cells of the host and may use the host as a breeding ground. A few of the numerous parasitic skin infections are profiled in this section.

Tinea

Tinea, or dermatophytoses, causes several types of superficial fungal infections of the keratin in skin and nails that are described based on the area of the body affected. These fungi typically grow in warm, moist places (e.g., showers). Tinea typically manifests as a circular, erythematous rash (**FIGURE 13-23**), which is usually associated with

pruritus and burning. Tinea capitis is an infection of the scalp commonly encountered in school-aged children. Along with the typical rash associated with tinea, hair loss at the site is common. Tinea corporis, also called “ringworm,” is an infection of the body. Tinea pedis, also called “athlete’s foot,” involves the feet, especially the toes. Tinea unguium is an infection of the nails, typically the toenails. This infection begins at the tip of one or two nails and then usually spreads to other nails. The nail initially turns white and then brown, causing it to thicken and crack. Tinea barbae, also called “Barber’s itch,” is an infection of the beard area.



FIGURE 13-23 Tinea.

Courtesy of CDC.

A variety of topical and systemic antifungal agents are available to treat tinea infections. Several weeks of treatment may be necessary to resolve the infection. Occasionally, corticosteroids may be used to relieve itching and inflammation.

Scabies

Scabies is a result of a mite (i.e., *Sarcoptes scabiei*) infestation. The male mites fertilize the females and then die. The female mites burrow into the epidermis, laying eggs in a series of tracts over a period of several weeks. After laying the eggs, the female mites die. When the larvae subsequently hatch from the eggs, they migrate to the skin's surface. There, they burrow into the skin in search of nutrients and mature to repeat the cycle. This burrowing appears as small light brown streaks on the skin (**FIGURE 13-24**). The burrowing and fecal matter left behind by the mites trigger the inflammatory process, leading to erythema and intense pruritus. The mites can survive for only short periods without a host, so transmission usually results from close contact.



FIGURE 13-24 Scabies.

Courtesy of CDC.

Several topical treatments for scabies are available, but multiple applications are usually needed to successfully eradicate the infestation. Clothing, linens, and other fabrics will likely require treatment as well.

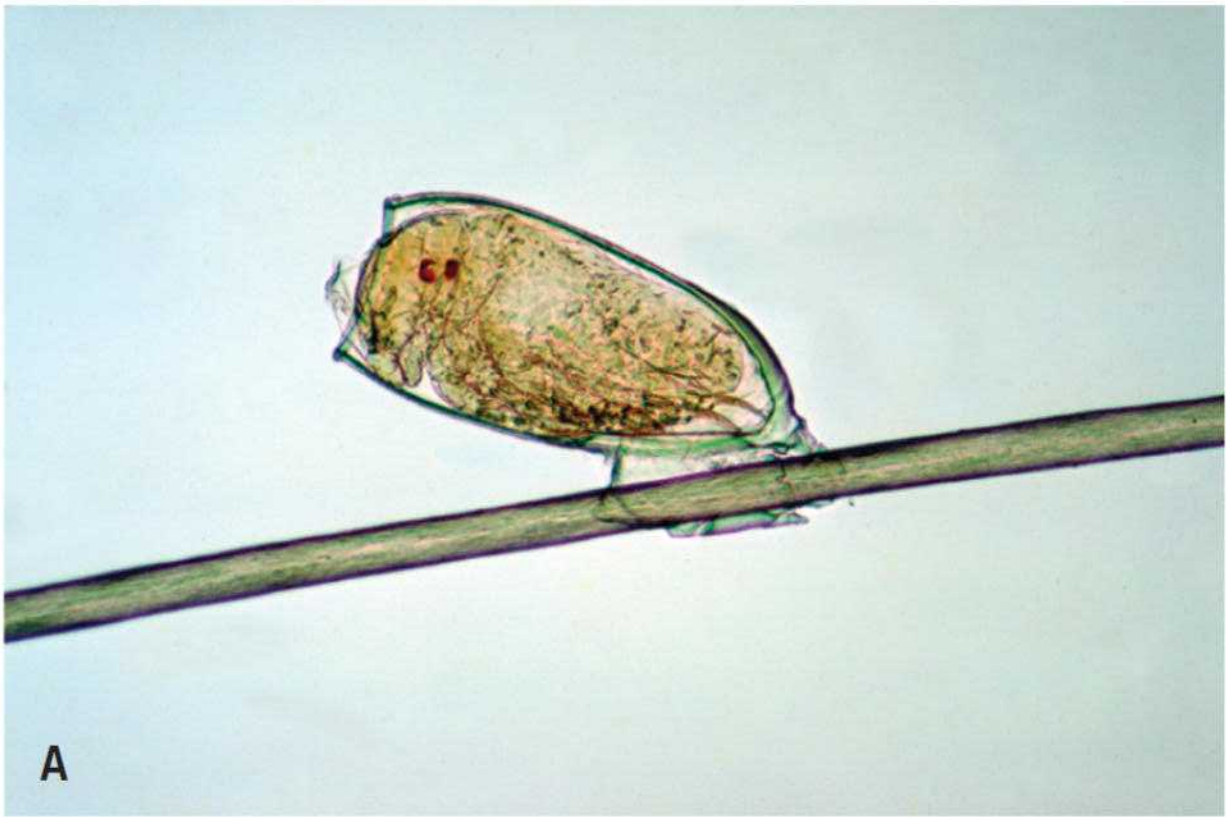
Pediculosis

Pediculosis refers to lice infestation, which can take three forms: *Pediculus humanus corpus* (body louse), *Pediculus pubic* (pubic louse), and *Pediculus humanus capitis* (head louse). Lice are small brown parasitic insects that feed off human blood and cannot survive for long without the human host (**FIGURE 13-25**). The female lice lay eggs (nits) on the hair shaft close to the scalp (**FIGURE 13-26**). The nits appear as small white iridescent shells on the hair. After hatching, the lice bite and suck the host's blood; in turn, the site of the bite develops a highly pruritic macule or papule. Pediculosis is easily transmitted through close contact.



FIGURE 13-25 Louse.

Courtesy of CDC/James Gathany/Frank Collins, PhD.


A


B

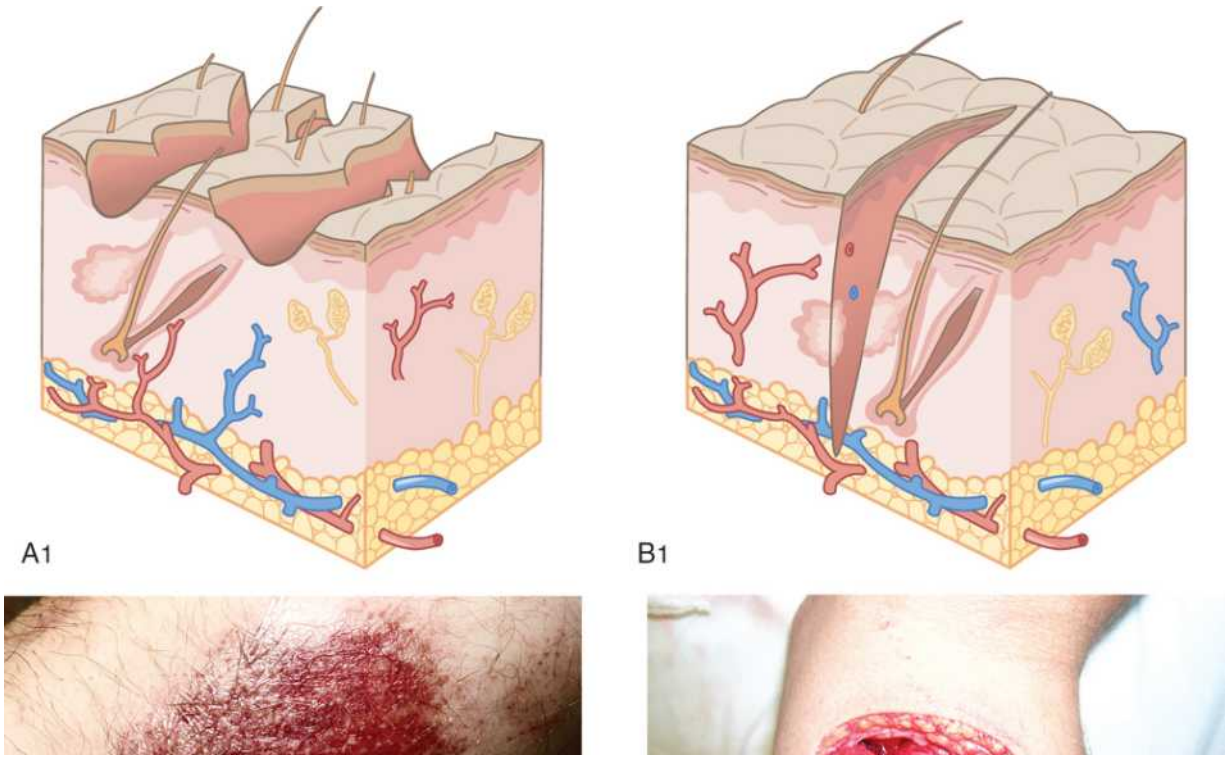
FIGURE 13-26 Nits.

A: Courtesy of CDC/Dr. Dennis D. Juranek; **B:** © hirun/iStock/Getty Images Plus/Getty Images

Several topical treatments for lice are available, but multiple applications are usually needed to successfully eradicate the infestation. Clothing, linens, and other fabrics will likely require treatment as well.

Traumatic Integumentary Disorders

Traumatic integumentary disorders can result from a wide range of injuries. Skin trauma can produce multiple skin conditions, depending on the nature of the injury (FIGURE 13-27). Such injuries may range from mild to life threatening in severity, depending on the location and extent of the injury. Regardless of the nature or extent of the injury, all traumatic skin conditions increase the risk for infection because they create a breach in the body's protective barrier (see the *Immunity* chapter). Although numerous traumatic skin conditions are possible (e.g., lacerations and abrasions), this section focuses on burns.



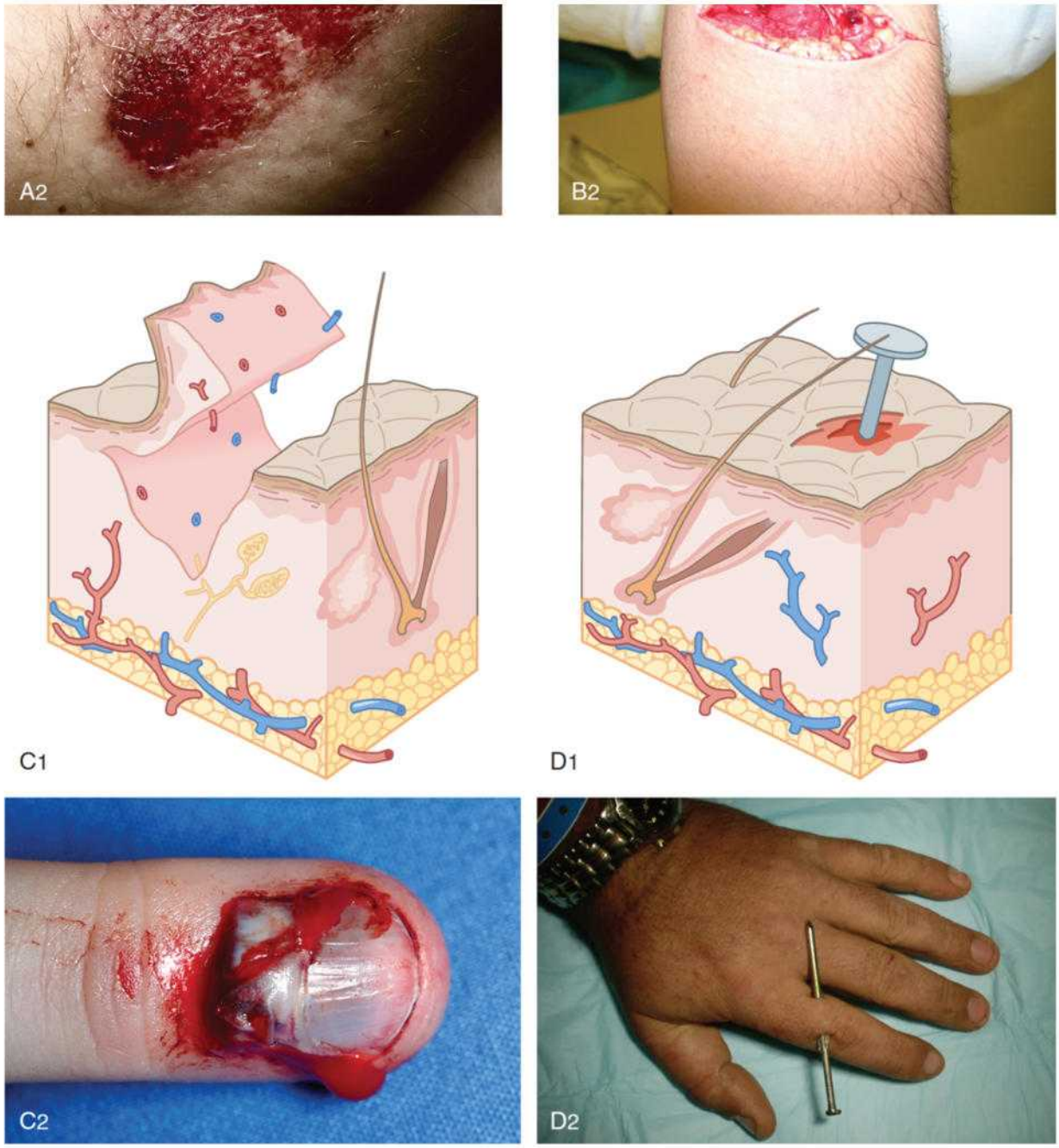


FIGURE 13-27 Types of wounds. **(A)** Abrasion. **(B)** Laceration. **(C)** Avulsion. **(D)** Penetrating wound.

A: © Kondor83/Shutterstock; **B:** © E.M. Singletary, MD. Used with permission; **C:** Scott Camazine/Alamy Stock Photo; **D:** © E.M. Singletary, MD. Used with permission.

Description

Burns

A burn is a skin injury that may result from exposure to either a thermal (heat) or a nonthermal source. Such sources may include dry heat (e.g., fire), wet heat (e.g., steam or hot liquids), radiation, friction, heated objects, natural or artificial UV light, electricity, and chemicals (e.g., acids, alkaline substances, and paint thinner). The burn injury triggers the inflammatory reaction and results in tissue destruction. The severity of the condition varies depending on the location, extent, and nature of the injury. Severity is described, in part, in terms of the levels of the skin that suffer damage (**FIGURE 13-28**):

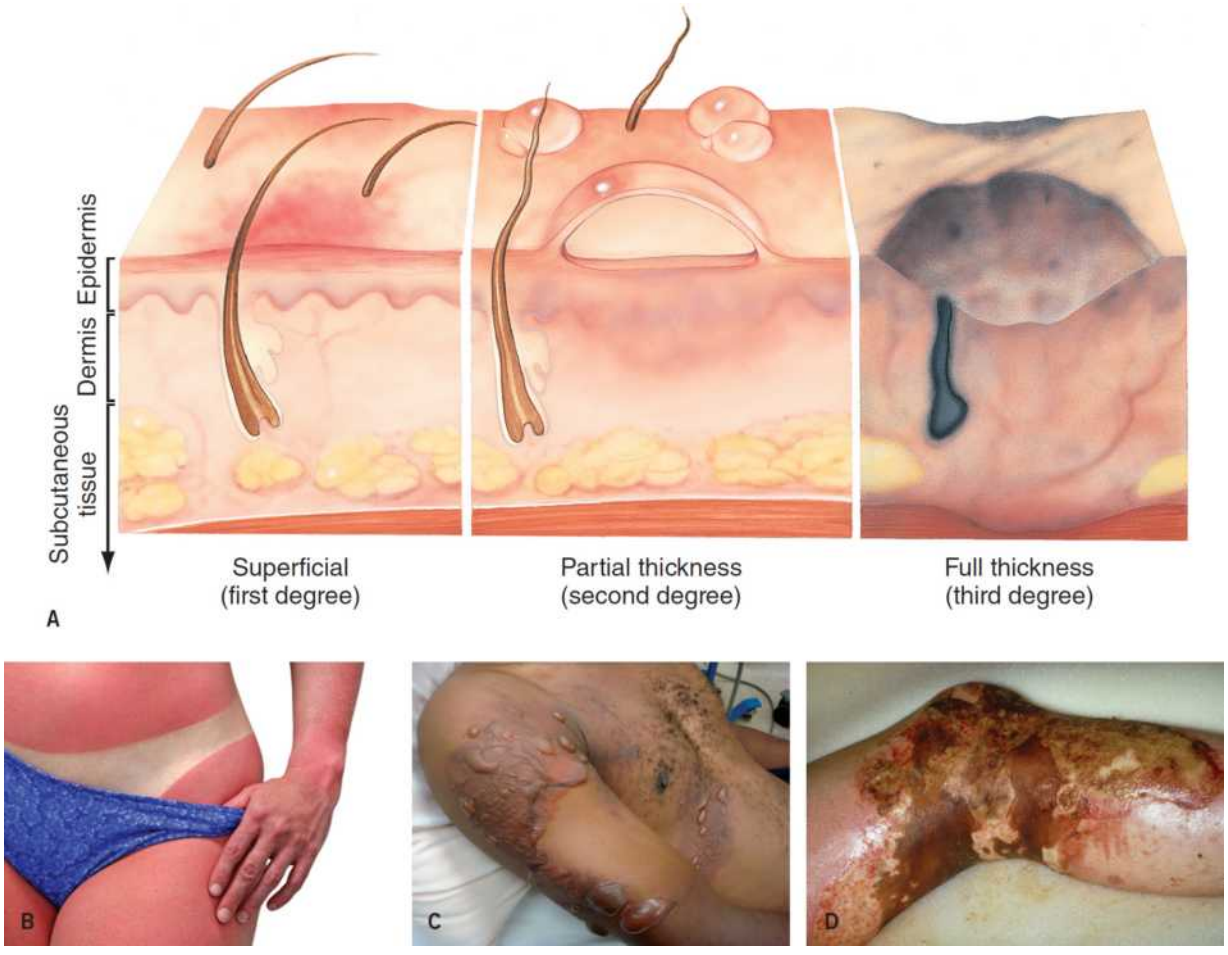


FIGURE 13-28 Burn classification.

B: © Amy Walters/Shutterstock; **C:** Courtesy of Rhonda Hunt; **D:** © John Radcliffe Hospital/Science Source

Description

- First-degree (superficial) burns affect only the epidermis. These burns cause pain, erythema, and edema.
- Second-degree (partial-thickness) burns affect the epidermis and dermis. These burns cause pain, erythema, edema, and blistering. Deep partial-thickness burns involve hair follicles, and scarring is common.
- Third-degree (full-thickness) burns extend into deeper tissues (e.g., fat). These burns cause white or blackened, charred skin that may be numb.

Complication development is usually related to burn severity. Burns may result in any of the following complications:

- Local infection (particularly *Staphylococcus* infection)
- Sepsis
- Hypovolemia (burns can damage blood vessels and plasma proteins, causing fluid shifts; see the *Fluid, Electrolyte, and Acid–Base Homeostasis* chapter)
- Shock (may result from sepsis or hypovolemia)
- Hypothermia (heat is lost through large injuries)
- Respiratory problems (inhaling hot air or smoke can burn the tissues making up the airway, causing inflammation)
- Eschar (stiff, dead tissue)
- Scarring
- Contractures

Diagnostic procedures consist of a history, physical examination (including determining the percentage of the total body surface area [TBSA] affected), chest X-ray, endoscopy (insertion of a flexible tube with a camera into the trachea and upper airway), complete blood count (CBC), and blood chemistry. The TBSA involved is calculated for both partial- and full-thickness burns. It is typically estimated using the rule of nines for adults and the Lund-Browder chart for children. Determining respiratory and cardiovascular status is critical, keeping

in mind that the patient's status may worsen as the pathological changes progress as a result of the burn. The individual should also be monitored for signs of infection (e.g., wound exudate, impaired wound healing, fever, leukocytosis, thrombocytopenia, and hyperglycemia).

Burn treatment is complex and varies depending on the location and severity of the injury. Strategies for minor burns may include the following measures:

- Remove the source of the burn.
- If the skin is unbroken, run cool water over the area or soak it in a cool water bath (not ice water). Keep the damaged area submerged for at least 5 minutes. Applying a clean, cold, wet bandage or towel will also help reduce pain.
- After flushing or soaking the burn, cover it with a dry sterile bandage or clean dressing.
- Protect the burn from pressure and friction.
- Administer analgesics and NSAIDs to relieve pain and swelling.
- Apply moisturizing lotion once the skin has cooled.
- If a second-degree burn covers an area more than 2–3 inches in diameter or if it is located on the hands, feet, face, groin, buttocks, or a major joint, treat the burn as a major burn.

For major burns, the following strategies are used:

- Remove the source of the burn.
- If someone is on fire, have the person stop, drop, and roll. Wrap the person in thick material to smother the flames (e.g., a wool or cotton coat, rug, or blanket). Douse the person with water.
- Do not remove burned clothing that is stuck to the skin. The clothing may be soaked with sterile water or saline and then removed, and surgical removal may be necessary in severe cases.
- Ensure the person is breathing. Initiate rescue breathing and cardiopulmonary resuscitation, if necessary. Continue to monitor

the patient's respiratory status—it can become impaired as edema worsens.

- Maintain respiratory status (e.g., endotracheal intubation with mechanical ventilation and oxygen therapy).
- Cover the burn area with a dry sterile bandage or clean cloth. Do not apply any ointments. Avoid rupturing blisters.
- If fingers or toes are involved, separate them with dry, sterile, nonadhesive dressings.
- Elevate the affected body part above the level of the heart to minimize edema.
- Protect the burn area from pressure and friction.
- Take steps to prevent shock. Place the individual in the Trendelenburg position and cover him or her with a coat or blanket. However, do not place the person in this position if a head, neck, back, or leg injury is suspected or if it makes the person uncomfortable.
- Monitor vital signs for signs of shock (e.g., tachycardia and hypotension).
- Administer intravenous fluids (which may include colloids or crystalloids) using specific formulas (e.g., the Parkland formula).
- Treat hypothermia with warmed intravenous fluids, humidified oxygen, room temperature, and blankets.
- Administer oral, intravenous, or topical analgesics, sedatives, or antibiotics to reduce pain and prevent infection.
- Implement reverse isolation (e.g., gowning and limiting visitors).
- Apply meticulous wound care to limit the risk of infection and to promote healing.
- Apply protective dressings.
- Perform skin grafts to promote tissue regeneration, prevent scarring, and aid the healing process.
- Perform surgery as necessary to close the wound, remove dead tissue, or treat related complications (e.g., scarring and

contractures).

- Provide physical therapy to reduce the effects of scar tissue.
- Increase dietary intake of protein and carbohydrates to promote healing and support the person's increased metabolic needs.

Learning Points

Several actions should be avoided with burns:

- Do *not* apply ointment, butter, ice, medications, cream, oil spray, or any household remedy to a severe burn.
- Do *not* breathe, blow, or cough on the burn.
- Do *not* disturb blistered or necrotic skin.
- Do *not* remove clothing that is stuck to the skin.
- Do *not* give the person anything by mouth if there is a severe burn (surgery may be necessary).
- Do *not* immerse a severe burn in cold water because doing so can cause shock.
- Do *not* place a pillow under the person's head if there is an airway burn because this positioning of the head can close the airway.

Chronic Integumentary Disorders

Pressure Injuries

Pressure injuries are soft-tissue injuries that occur as a result of unrelieved mechanical pressure. These injuries are often referred to as "pressure ulcers" or "decubitus ulcers," although less severe injuries may not necessarily be associated with skin ulcerations. The pressure results in areas of necrosis and ulceration where the tissue is compressed between bony prominences and external hard surfaces. While the most common sites for these injuries are the sacrum, ischial tuberosities, trochanters, malleoli, and heels, these injuries can develop anywhere. The effects of the pressure are worsened by friction, shearing forces (unaligned forces pushing in opposite directions), and moisture. Risk factors for pressure injuries include advancing age (owing to reduced subcutaneous fat and

capillary blood flow), impaired circulation and tissue perfusion (like that associated with diabetes mellitus and arteriosclerosis), immobilization, malnutrition, decreased sensation, and incontinence. With an estimated 2.5 million cases occurring each year, pressure injuries are a significant contributor to hospitalization admissions, healthcare costs, and morbidity in the United States.

Compressing soft tissue (i.e., subjecting it to a pressure greater than 12–32 mm Hg) for prolonged periods between bony prominences and external surfaces occludes microcirculation, resulting in tissue ischemia and hypoxia. An injury can develop in 1–2 hours if pressure is not relieved. Friction can occur when the skin rubs against clothing or bedding, causing local erosion and breaks in the epidermis and superficial dermis. Shearing forces can develop when the skin is wedged against a bed, while gravity forces the body downward when the head of the bed is elevated, causing stress and damage to supporting tissues. Moisture (e.g., perspiration and incontinence) breaks tissue down and causes maceration (softening), resulting in irritation.

Pressure injuries are classified using a staging system, depending on the degree of damage. The National Pressure Injury Advisory Panel (NPIAP, 2016) system is the most widely used staging system (**FIGURE 13-29**). However, such injuries do not follow a linear progression through each stage as the numeric system implies. At the first indication of an injury, it may be an advanced stage, and an injury can progress rapidly, skipping stages. With stage I pressure injuries, the skin remains intact, and nonblanchable erythema, usually over a bony prominence, is present. Stage II pressure injuries involve an erosion or blister with or without true ulcerations (defect beyond the level of the epidermis), but subcutaneous tissue is not exposed. The ulcer is superficial with a pink or red wound bed. No slough (layer of dead tissue) or necrotic tissue is present. With stage-III pressure injuries, full-thickness skin loss with damage to subcutaneous tissue down to the underlying fascia is present. Stage-IV pressure injuries involve full-thickness skin loss with extensive destruction, tissue necrosis, and damage to muscle, tendon, bone, or other exposed supporting structures. With deep-tissue pressure injury, the skin may

or may not be intact, and underlying tissue is damaged. Unstageable pressure injuries are characterized by full-thickness skin and tissue loss in which the extent of damage cannot be determined because it is hidden by slough or eschar.

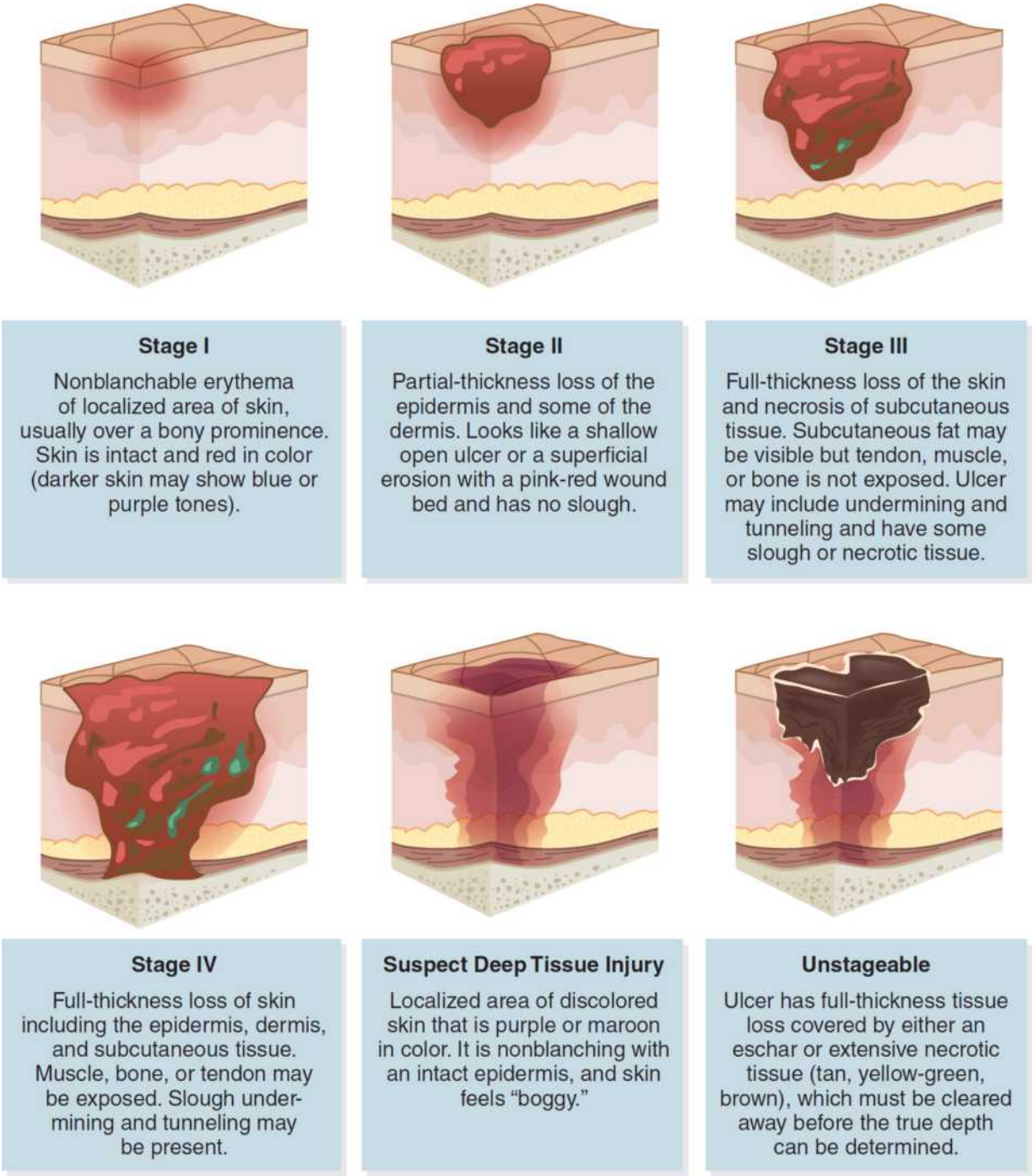


FIGURE 13-29 Pressure ulcer staging.

Description

Pressure injuries may be difficult to heal because the pressure and contributing factors are challenging to mitigate. Additionally, the ulcers can become infected with hospital-acquired, antibiotic-resistant organisms. Other complications may include sinus tracts (tunneling or opening extending from a wound underneath the skin in any direction), osteomyelitis, cellulitis, tissue calcification, bacteremia, meningitis, endocarditis, and squamous cell carcinoma.

Diagnosis is based on physical examination. Depending on the stage, additional tests may include nutritional assessments; CBC; blood cultures; transferrin, prealbumin, albumin, and CD4+ levels; erythrocyte sedimentation rate; C-reactive protein levels; bone biopsy; bone cultures; and magnetic resonance imaging (MRI) with gadolinium. Routine wound cultures are not recommended because all pressure ulcers are heavily colonized by bacteria. Nonhealing ulcers should be assessed for potential complications (e.g., cellulitis, bacteremia, osteomyelitis).

Treatment requires consistent effort to reduce pressure, care for the wound, minimize infection, and support nutritional needs. Pressure reduction includes frequent repositioning, keeping the head of the bed below 30 degrees, protective padding (e.g., pillows, foam wedges, and heel protectors), and dynamic surfaces (e.g., alternating-air mattress, low-air-loss mattress, and air-fluidized mattress).

Wound care will vary depending on the stage and other qualities (e.g., presence of infection). Additionally, strategies may need to change if healing stalls. Wound cleaning (typically with normal saline) should be performed without traumatizing the tissue. Debridement may be necessary to remove necrotic tissue. Debridement may rely on mechanical (e.g., hydrotherapy and wet-to-dry dressings), autolytic (e.g., synthetic occlusive or semi-occlusive dressings), enzymatic (e.g., collagenase, papain, and fibrinolysin), surgical, and biosurgical (e.g., medical maggot therapy) techniques.

Pressure injuries can cause significant pain, so pain management may include oral and topical nonopioid and opioid agents. Topical,

oral, or intravenous antibiotics may also be needed. A diet high in protein is important to support wound healing and may include oral, nasogastric, or parenteral supplementation. Other strategies may include negative-pressure therapy (e.g., wound vacuum-assisted closure), topical recombinant growth factors, electrical stimulation therapy, and therapeutic ultrasonography. Surgical closure or skin grafts may be performed in large and shallow injuries. Scales, such as the NPIAP's Pressure Ulcer Scale for Healing (2016), can be used to monitor progression and response to treatments.

While progress has been made with treatment, healing typically takes weeks. Prevention remains critical to avoid complications. Assessment is an important part of prevention as well. Several scales have been developed to predict the risk of developing pressure injuries, including the Norton Scale (Norton, 1989) and the Braden Scale (Bergstrom et al., 1987). Once at-risk individuals are identified, prevention strategies should be implemented to mitigate the pressure and the contributing factors (e.g., meticulous skin care, mobilization, and proper nutrition).

Chronic Integumentary Disorders

Numerous chronic conditions can affect the integumentary system, some of which have previously been discussed. These conditions vary in severity. Although most are not life threatening, many can have a significant impact on an individual's appearance.

Acne Vulgaris

Acne vulgaris is a skin condition that commonly affects adolescents, although it can occur at any age. With this condition, the skin's pores become clogged with oil, debris, or bacteria. Pores can become inflamed, developing a pustule, nodule, or cyst. Clogged pores may become either raised with a white top (called a "whitehead") or dark (called a "blackhead") (**FIGURE 13-30**). If an infected pore ruptures, the material inside, including oil and bacteria, can spread to the surrounding area and cause an inflammatory reaction. Acne vulgaris commonly appears on the face and shoulders but may also occur on

the trunk, arms, legs, and buttocks. It varies widely in severity, with severe cases sometimes resulting in significant scarring.



FIGURE 13-30 Acne vulgaris.

© sruilk/Shutterstock

Risk factors for acne vulgaris include the following:

- Family history
- Hormonal changes (e.g., changes that occur with menstrual periods, pregnancy, birth control pill use, and stress)
- Use of oily cosmetic and hair products
- Use of certain medications (e.g., corticosteroids, testosterone, estrogen, and phenytoin)

- High levels of humidity and sweating

Diagnostic procedures for acne vulgaris include a history and physical examination. Treatment varies depending on the severity, but these strategies often include the following measures:

- Clean skin gently with mild, nondrying soap to remove all dirt or makeup once or twice a day, including after exercising; however, avoid excessive or repeated skin washing.
- Shampoo hair daily, especially if it is oily.
- Comb or pull hair back to keep it away from the face but avoid tight headbands.
- Avoid squeezing, scratching, picking, or rubbing acne, because doing so can lead to skin infections and scarring.
- Avoid touching affected areas.

Myth Busters

There are a couple of myths regarding acne that warrant clearing up (no pun intended).

Myth 1: Eating greasy foods and chocolate worsens acne.

Contrary to popular belief, greasy foods and chocolate have little effect on acne. Studies are ongoing to determine whether other dietary factors—including consumption of high-starch foods (such as bread, bagels, and chips), which increase blood sugar—may play a role in acne.

Myth 2: Acne is a result of the skin being dirty.

Acne is not caused by dirt. In fact, scrubbing the skin too hard or cleansing with harsh soaps or chemicals irritates the skin and can make acne worse. Simple cleansing of the skin to remove excess oil and dead skin cells is all that is required.

- Avoid oily cosmetics or creams; use water-based or noncomedogenic formulas.
- Use over-the-counter or prescription acne products containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid.

- Administer oral or topical antibiotics (e.g., erythromycin).
- Apply retinoic acid cream or gel (e.g., Retin-A).
- Administer oral isotretinoin (Accutane).
- Administer oral contraceptives to females.
- Use alternative therapies, including tea tree oil, zinc, guggul, and brewer's yeast.
- Apply photodynamic therapy (laser procedure).
- Apply chemical skin peels.
- Use microdermabrasion or dermabrasion.
- Use soft-tissue fillers (e.g., collagen and fat).
- Limit sun exposure.

Rosacea

Rosacea is a chronic inflammatory skin condition that typically affects the face. It is poorly understood but is more prevalent in fair-skinned individuals, persons who bruise easily, and women. There are four subtypes of rosacea: erythematotelangiectatic type, papulopustular (classic presentation), phymatous, and ocular. Rosacea may present as erythema, prominent spiderlike blood vessels (telangiectasia), swelling, or acnelike eruptions (**FIGURE 13-31**). Additional manifestations may include a thickening of the skin on the nose (rhinophyma), a burning or stinging sensation, and red, watery eyes. If left untreated, rosacea is progressive, but most people with this condition experience remissions and exacerbations. Exacerbation triggers are specific to the individual but may include sun or wind exposure, sweating, stress, spicy food, alcohol, hot beverages, hot baths, and cold weather.



FIGURE 13-31 Rosacea.

© sruilk/Shutterstock

Diagnostic procedures for rosacea include a history and physical examination. There is no known cure for rosacea. Instead, treatment strategies center on identifying and avoiding possible triggers, so that affected individuals can reduce exacerbations. These strategies may include the following measures:

- Avoid excessive scrubbing when cleaning.
- Avoid sun exposure (e.g., wear protective hats and clothing, limit exposure time especially between 10:00 a.m. and 4:00 p.m.), and use sunscreen that protects against both UVA and UVB rays every day.
- Avoid prolonged physical exertion in hot weather.
- Manage stress (e.g., through deep breathing and yoga).
- Limit consumption of spicy foods, alcohol, and hot beverages.

- Avoid any other triggers.
- Apply topical or oral antibiotics to control skin eruptions.
- Apply retinoic acid cream or gel (e.g., Retin-A).
- Administer oral isotretinoin (Accutane).
- Perform laser surgery to help reduce the redness.
- Perform surgical reduction of enlarged nose tissue.
- Apply green- or yellow-tinted prefoundation creams and powders to reduce the appearance of redness.

Integumentary Cancers

Skin cancer is an abnormal growth of skin cells. According to the CDC (2023a), skin cancer is the most frequently occurring cancer in the United States, and the number of cases continues to rise. Prevalence rates are highest in Caucasians, persons with a fair complexion, and those with a family history. Cases are slightly higher in women. Almost all cases of skin cancer can be cured. The deadliest of skin cancers, melanoma, has an overall 5-year survival rate is approximately 94% (American Cancer Society, 2023). UV exposure, either natural or artificial, is by far the most significant risk factor for this type of cancer. For this reason, most skin cancers occur on areas that have the most sun exposure (e.g., the arms and neck).

Three major types of skin cancers are distinguished: basal cell carcinoma, squamous cell carcinoma, and melanoma. Basal cell carcinoma, the most common type, develops from abnormal growth of the cells in the lowest layer of the epidermis. Squamous cell carcinoma involves changes in the squamous cells, which are found in the middle layer of the epidermis. Melanoma develops in the melanocytes; it is the least common type but the most serious. Melanoma accounts for the fifth most common new cancer diagnosis in men and women (American Cancer Society, 2023). Basal and squamous cell carcinomas rarely spread, but melanomas often metastasize to other areas.

Skin cancers can vary widely in appearance. They can be small, shiny, waxy, scaly, rough, firm, red, crusty, bleeding, and so on (**FIGURE 13-32**). Given the many possible presentations, any suspicious skin lesion should be examined by a healthcare professional. The following features may be considered “suspicious”:



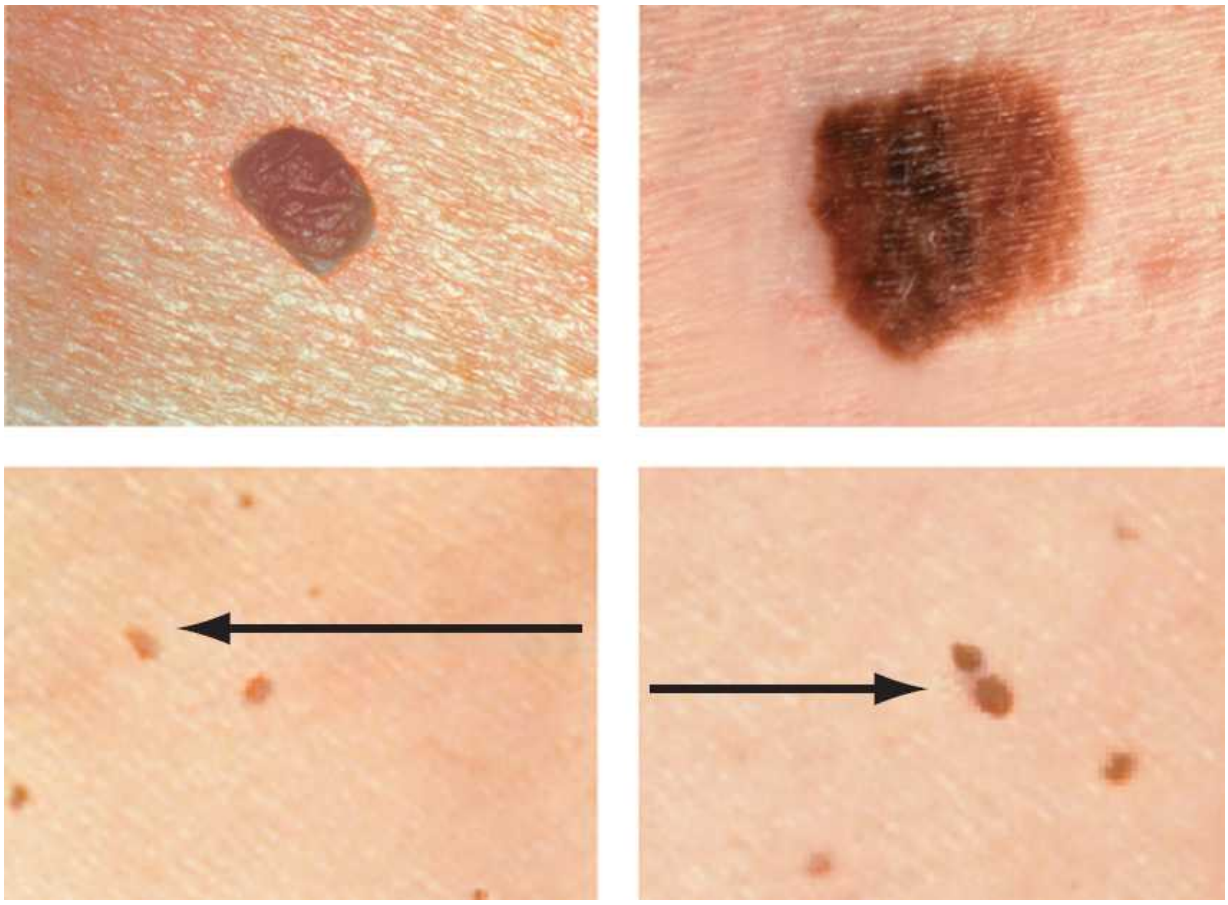


FIGURE 13-32 Skin cancers.

Courtesy of the Skin Cancer Foundation (www.skincancer.org).

Description

- Asymmetry—part of the lesion is different from the other parts
- Borders that are irregular
- Color that varies from one area to another with shades of tan, brown, or black (sometimes white, red, or blue)
- Diameter that is usually (but not always) larger than 6 mm in size
- Any skin growth that bleeds or will not heal
- Any skin growth that changes in appearance over time

Most skin cancers can be prevented by limiting or avoiding exposure to UV light (e.g., by using sunscreen and wearing protective clothing). Early detection is crucial to positive outcomes; with early

detection, even the most aggressive forms can be successfully treated. Diagnostic procedures for skin cancer typically include a history, physical examination, and biopsy.

Removal of the cancerous growths offers the best prognosis. Treatment strategies may include the following measures:

- Cryosurgery
- Excisional surgery
- Laser therapy
- Mohs' surgery (the skin growth is removed layer by layer, examining each layer under the microscope, until no abnormal cells remain)
- Curettage and electrodessication (layers of cancer cells are scraped away using a circular blade [curette], and then an electric needle is used to destroy any remaining cancer cells)
- Radiation therapy
- Chemotherapy

Learning Points

All skin lesions, such as moles, should be monitored for any suspicious changes. These changes can be readily identified—their diagnosis is as easy as A, B, C, and D.

A = Asymmetry—part of the lesion is different from the other
B = Borders—irregular
C = Color—varies from one area to another with shades of tan, brown, or black (sometimes white, red, or blue)
D = Diameter—usually (but not always) larger than 6 mm in size (the diameter of a pencil eraser)

application to practice

Now that we have discussed conditions of the integumentary system, let's put that knowledge into practice. While you are working in a clinic, a patient comes in with multiple lesions. Which lesion should you assess first?

- Raised, tubular, white, snakelike areas on the inner aspects of the wrists

- Irregular blue mole with white specks on the lower leg
- Beige freckles on the backs of both hands
- Large cluster of pustules in the right axilla

Once again, you go through the usual thought process—what would kill the patient first, acute versus chronic conditions, Maslow's hierarchy of needs, and patient safety. First, the lesions on the wrist are likely scars and do not pose any threat. Now, consider the blue mole. Blue is a suspicious color for a mole, and there is color variation in the patient's mole. These findings strongly indicate skin cancer, so keep that lesion on your list. Moving on to the freckles, the color is not suspicious, and there are no other suspicious indications. These lesions are not likely to pose any threat. Finally, consider the pustules under the axilla. These likely indicate a superficial skin infection. A skin infection is acute but not generally life threatening. After considering all the lesions, you should assess the mole first.

SUMMARY

The integumentary system plays a vital role in homeostasis and well-being by protecting the body from invasion by pathogens, maintaining water balance, sensing changes in the environment, and regulating body temperature. Conditions affecting this system can cause issues with any or all of these functions. Some of these conditions can be prevented through measures such as limiting UV light exposure through using sunscreen that protects against UVA and UVB rays, wearing protective clothing, and limiting time outdoors, especially between 10:00 a.m. and 4:00 p.m., when the sun's rays are the most intense. Early diagnosis and treatment of other conditions can improve prognosis.

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CHAPTER 14

Sensory Function

LEARNING OBJECTIVES

- Discuss normal sensory anatomy and physiology.
- Compare and contrast congenital sensory disorders.
- Describe and discuss sensory conditions associated with aging.
- Compare and contrast infectious and inflammatory sensory disorders.
- Describe and discuss traumatic sensory disorders.
- Describe and discuss chronic sensory disorders.
- Describe and discuss sensory cancers.
- Describe and discuss miscellaneous sensory conditions.

KEY TERMS

acute otitis media
amblyopia
anotia
anterior chamber
aqueous humor
atresia
auricle
cataract
choroid
ciliary body
closed-angle glaucoma
cochlea
cone
congenital cataract

congenital glaucoma
congenital hearing loss
conjunctiva
conjunctivitis
cornea
diplopia
ear
Eustachian tube
external ear canal
eye
glaucoma
incus
inner ear
intractable pain
iris
keratitis
lacrimal duct
lacrimal gland
lens
macular degeneration
malleus
Ménière's disease
microtia
middle ear
neuropathic pain
nystagmus
open-angle glaucoma
optic nerve
organ of Corti
ossicle
otitis externa
otosclerosis
outer ear
oval window
pain
pain threshold
pain tolerance
phantom pain

pinna
posterior chamber
presbycusis
presbyopia
pupil
referred pain
retina
retinal detachment
rod
saccule
sclera
semicircular canal
somatic pain
stapes
strabismus
tinnitus
tympanic membrane
utricle
vertigo
vestibular apparatus
vestibule
visceral pain
vitreous humor

The human body has a complex surveillance system that senses changes in the internal and external environments. This vigilant system utilizes numerous receptors throughout the body to detect even subtle alterations; these receptors are located in the skin, internal organs, and other tissue. The stimuli perceived by these receptors give rise to sensations, including those related to the general and special senses (**TABLE 14-1**). The general senses include **pain**, light touch, pressure, temperature, and proprioception (position), while the special senses include taste, smell, sight, hearing, and balance. Disorders of the sensory structures can result in sensory dysfunction. These disorders can result from a wide range

of causes, including congenital defects, advancing age, infections, and cancers.

TABLE 14-1 Summary of the General and Special Senses

Sense	Stimulus	Receptor
General senses	Pain	Naked nerve endings
	Light touch	Merkel disks; naked nerve endings around hair follicles;
	Pressure	Meissner corpuscles; Ruffini corpuscles; end bulbs
	Temperature	Pacinian corpuscles
	Proprioception	Naked nerve endings
		Golgi tendon organs; muscle spindles; receptors similar to Meissner corpuscles in the joints
Special senses	Taste	Taste buds
	Smell	Olfactory epithelium
	Sight	Retina
	Hearing	Organ of Corti
	Balance	Crista ampullaris in the semicircular canals; maculae in utricle and saccule

Anatomy and Physiology

The ability to sense changes in its ever-changing internal and external environments allows the body to respond to those stimuli and to function properly. Sensations are detected by receptors, which then convert the stimuli into nerve impulses. These impulses travel to the brain by cranial or spinal nerves to be processed and appreciated (**FIGURE 14-1**). The human body contains five types of receptors for the general and special senses: (1) mechanoreceptors—activated by mechanical stimuli, such as touch or pressure; (2) chemoreceptors—activated by chemicals in the blood, food, or air; (3) thermoreceptors—activated by heat or cold; (4) photoreceptors—activated by light; and (5) nociceptors—activated by painful stimuli. General sense receptors can take the form of either exposed or encapsulated nerve endings (**FIGURE 14-2**). The exposed nerve endings detect pain, temperature, and light touch; they are located in the skin, bones, and internal organs. One or more layers of cells surround encapsulated nerve endings. A variety of encapsulated nerve endings (e.g., Pacinian corpuscles, Meissner corpuscles, Krause end bulbs, and Ruffini corpuscles) are located throughout the body that serve a variety of senses. Many of these sensory receptors (especially those for pain, temperature, and pressure) will stop generating impulses after an extended exposure to stimuli through adaptation.

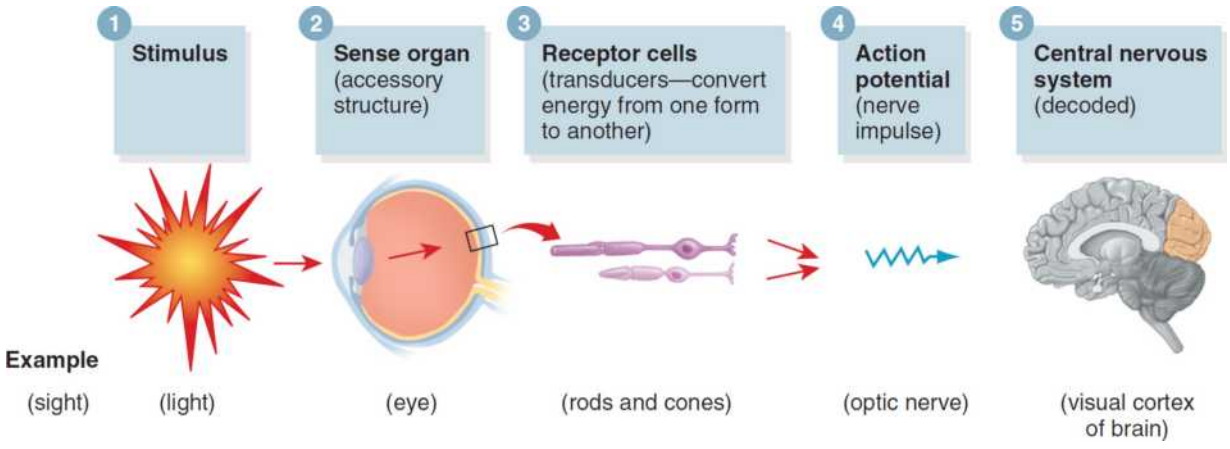


FIGURE 14-1 The general sensory pathway.

Description

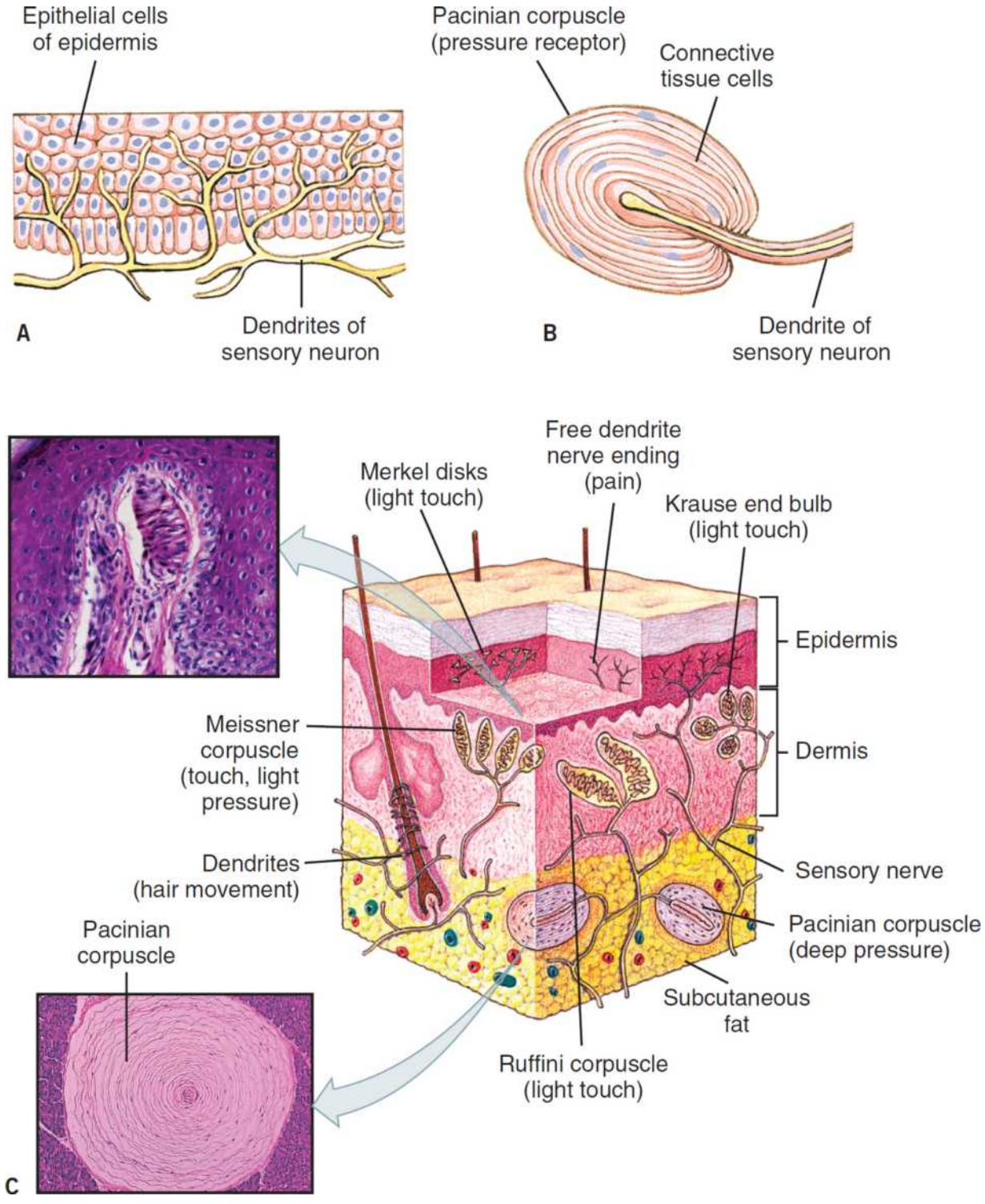


FIGURE 14-2 General sense receptors are either **(A)** exposed nerve endings or **(B)** encapsulated nerve endings. **(C)** The skin houses many of the receptors for the general senses. The Pacinian corpuscle, often located in the dermis of the skin, detects pressure. The Meissner corpuscle, found just beneath the epidermis, detects light touch.

C2: © Astrid & Hans-Friender Michler/Science Source; **C3:** © Carolina Biological Supply Co/Visuals Unlimited, Inc.

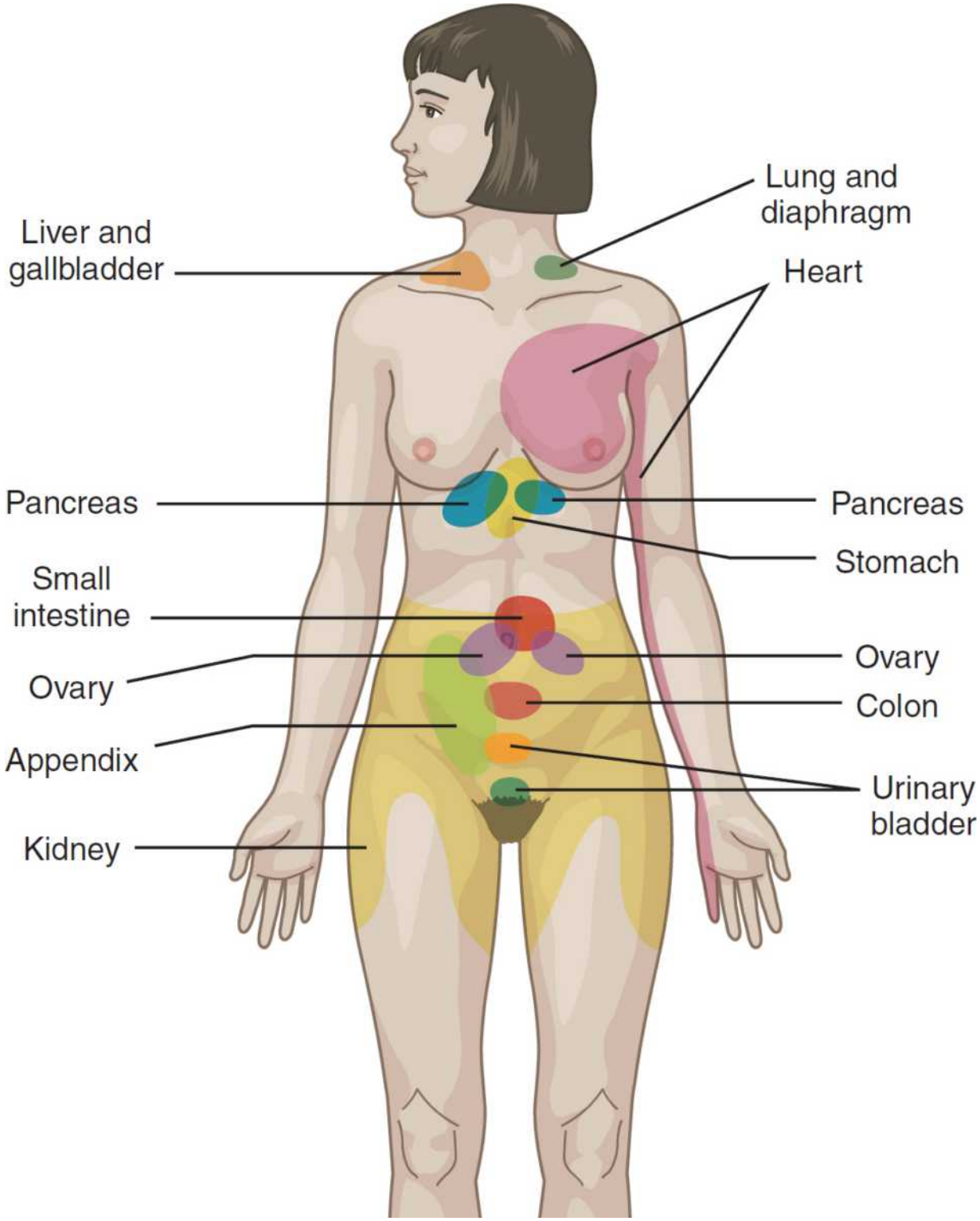
Description

Pain is associated with many conditions and, therefore, warrants further discussion. Pain is a protective mechanism, warning the body that something is wrong. In addition, pain is the most common reason people seek medical attention and can aid in diagnosis. Pain is a subjective feeling, and the perception of pain and the level at which it is sensed (**pain threshold**) can be influenced by affective (emotional), behavioral, cognitive (beliefs and attitudes), sensory (perceptual), and physiologic factors. Unrelieved pain can delay healing, stimulate the stress response (see the *Immunity* chapter), and result in **pain tolerance**.

The body perceives two types of pain, each with its own cause, location, and characteristics. **Somatic pain** results from noxious stimuli to the skin, joints, muscles, and tendons. These stimuli may include cutting, crushing, pinching, extreme temperature, and irritating chemicals. Somatic pain is generally easy to pinpoint. In contrast, **visceral pain** results from noxious stimuli to internal organs. These stimuli may include expansion and hypoxia.

Visceral pain is usually vague and diffuse. Pain may even be sensed on body surfaces at distant locations from the originating organ, a phenomenon called **referred pain** (**FIGURE 14-3**). The exact mechanism by which referred pain arises is unknown, but it is thought to result from the brain's misinterpretation of the visceral impulses as somatic impulses because both types of impulses enter the spinal cord at the same location (see the *Neural Function* chapter). The term **phantom pain** describes pain that exists after the removal of a body part (e.g., amputation), in which the affected person feels the discomfort of the removed part. In such a case, the

severing of neurons may result in spontaneous firing of spinal cord neurons because normal sensory input has been lost. This type of pain can be extremely distressing but usually resolves with time.



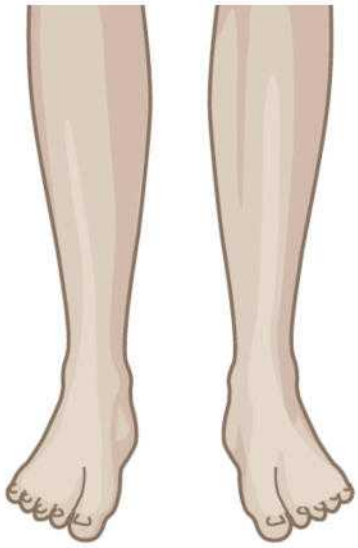


FIGURE 14-3 Referred pain. Visceral pain is often felt on the body surface at the points indicated by the colored areas.

Description

Intractable pain describes chronically progressing pain that is unrelenting and severely debilitating. This type of pain does not usually respond well to typical pharmacologic pain treatments (e.g., analgesics and narcotics). Intractable pain is common with severe injuries, especially those crushing in nature.

Neuropathic pain describes pain that results from damage to peripheral nerves by disease (e.g., diabetes mellitus) or injury; it tends to be both chronic and intractable. Patients with neuropathic pain also experience losses of the senses of touch and pressure. This condition causes an unusual sensation of paresthesia (numbness) and pain at the same time. The resulting pain is often described as a "prickly," "stabbing," or "burning" sensation.

Eyes

The human **eye** is a remarkable organ that allows us to perceive the environment in which we live. Human eyes are globe-shaped organs located in orbits in the anterior skull. Each eye consists of three distinct layers (**FIGURE 14-4**; **TABLE 14-2**).

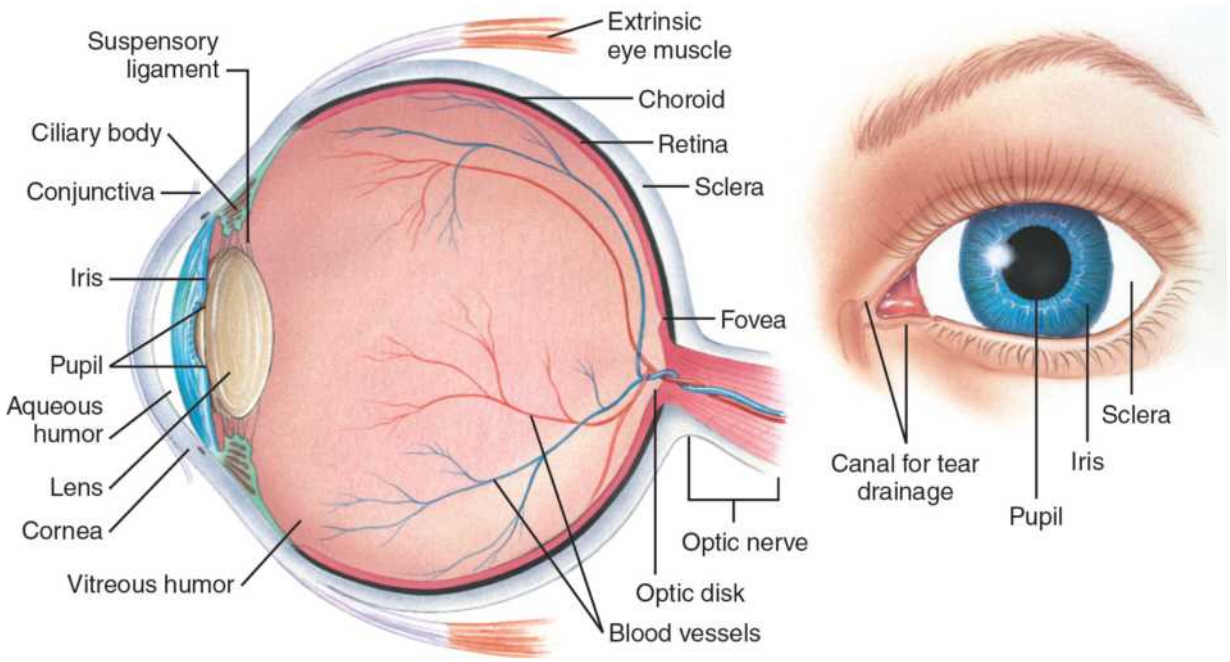


FIGURE 14-4 Anatomy of the eye.

Description

TABLE 14-2 Structures and Functions of the Eye

Structure		Function
Wall		
Outer layer	Sclera	Provides insertion for extrinsic eye muscles
	Cornea	Allows light to enter; bends incoming light
Middle layer	Choroid	Absorbs stray light; provides nutrients to eye structures
	Ciliary body	Regulates the lens, allowing it to focus images
	Iris	Regulates the amount of light entering the eye
Inner layer	Retina	Responds to light, converting light to nerve impulses
Accessory structures and components	Lens	Focuses images on the retina
	Vitreous humor	Holds the retina and lens in place
	Aqueous humor	Supplies nutrients to structures in contact with the anterior cavity of the eye
		Transmits impulses from the retina to the brain



The outermost layer of the eye is composed of a durable fibrous material called the **sclera** (white area) and a clear **lens** on the anterior side called the **cornea**. Tendons and muscles attach to the sclera to control eye movement. The cornea allows light to enter the eye.

The middle layer of the eye consists of the **choroid**, which contains melanin that absorbs any stray light. The anterior portion of the choroid forms the **ciliary body**, whose smooth muscle fibers control the shape of the lens, allowing it to focus on incoming light. The **iris** is the colored portion of the eye, and the **pupil** is the dark opening in the center of the iris. The choroid layer and the pigmented section of the **retina** give the pupil its black appearance. The iris contains smooth muscle fibers that control the diameter of the pupil to regulate light entering the eye. The pupil opens and closes reflexively in response to light intensity.

The innermost layer of the eye is the retina. It contains a pigmented outer layer and an inner layer consisting of photoreceptors and nerve cells (**FIGURE 14-5**). The retina is weakly attached to the choroid, making it vulnerable to damage. The retina contains two types of photoreceptors—**rods** and **cones**. The nearly 150 million rods in each eye are sensitive to low light and function at night. By comparison, each eye contains approximately 6 million cones, which can operate only in bright light and are responsible for visual acuity and color vision.

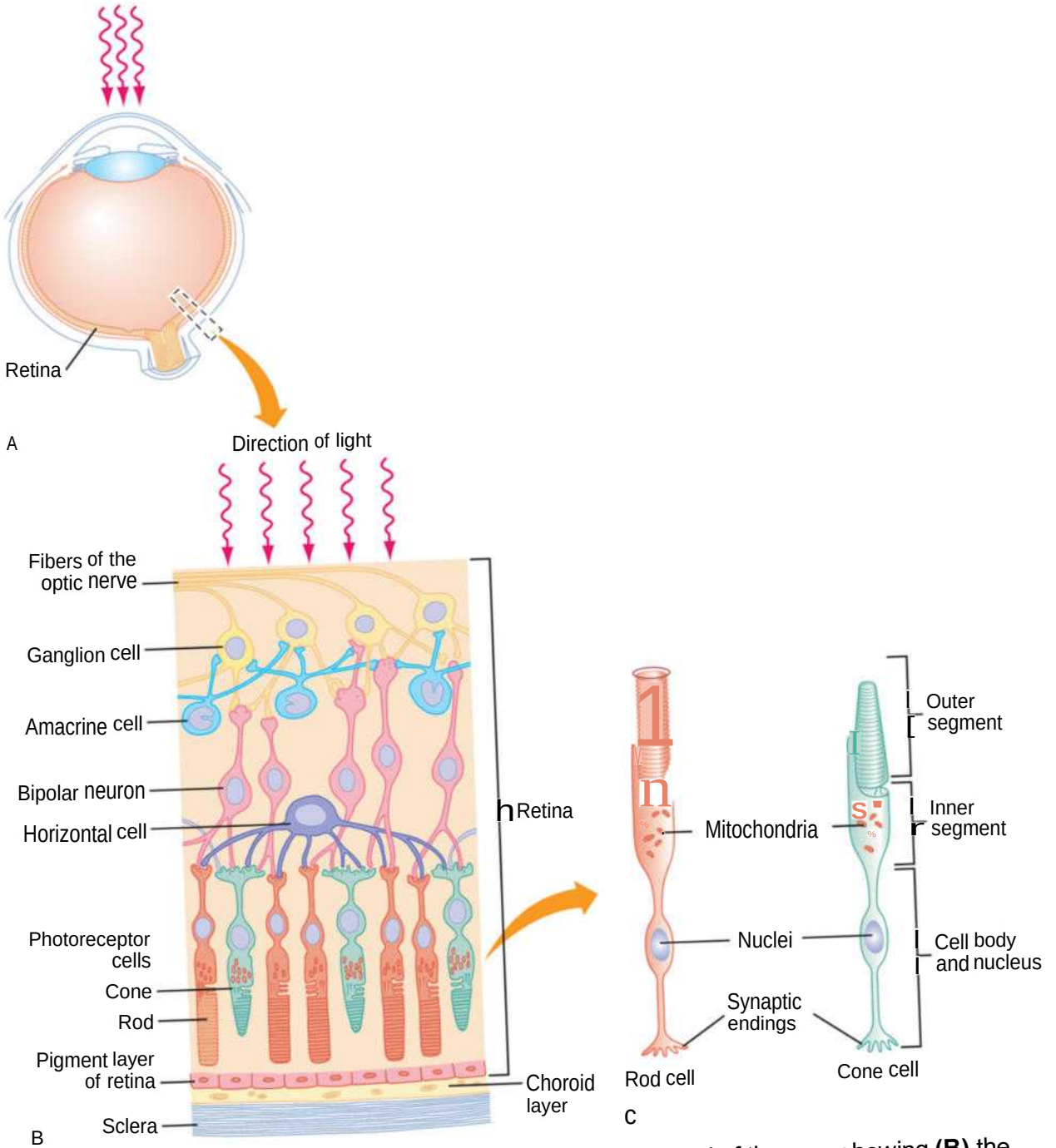


FIGURE 14-5 The retina. **(A)** Cross section through the wall of the eye, showing **(B)** the arrangement of the cellular components of the retina. **(C)** The structure of the rods and cones.

Description

The axons of the ganglion cells come together at the back of the eye to form the **optic nerve**. This area contains no photoreceptors

and is insensitive to light. Visual images are cast upside down onto the retina, and impulses are transmitted to the visual cortex in the brain. The retina processes some of the image, and then the brain processes the rest.

The lens is a flexible transparent structure that lies behind the iris in the eye. Smooth muscles attached to the lens alter its shape, thereby allowing it to focus on various objects. The lens separates the eye's interior into two cavities—the anterior and **posterior chambers**. The **anterior chamber** is in front of the lens, while the posterior chamber is behind the lens. The anterior chamber contains a watery liquid called **aqueous humor** that provides nutrients to the cornea and lens and carries away cellular waste products. A clear, gelatinous material called **vitreous humor** fills the posterior chamber. The pressures exerted by these liquids give the eye its shape.

The inner surface of the eyelid and the exposed surface of the eye are covered by a fragile membrane called the **conjunctiva** and kept moist by the **lacrimal glands**. Blinking cleans the eye by sweeping the fluid across the eye. Tears drain on the inner side of the eye through two **lacrimal ducts**.

Ears

The human **ear** serves to detect and process sound as well as detect body position and maintain balance. The human ear has three separate divisions, designated as the outer, middle, and **inner ear** (**FIGURE 14-6**; **TABLE 14-3**). The **outer ear** consists of the **auricle** (or **pinna**), ear lobe, and **external ear canal**. The **middle ear** includes the **tympanic membrane** and the **ossicles**. The inner ear is comprised of the **cochlea**, **semicircular canals**, **saccule**, and **utricle**.

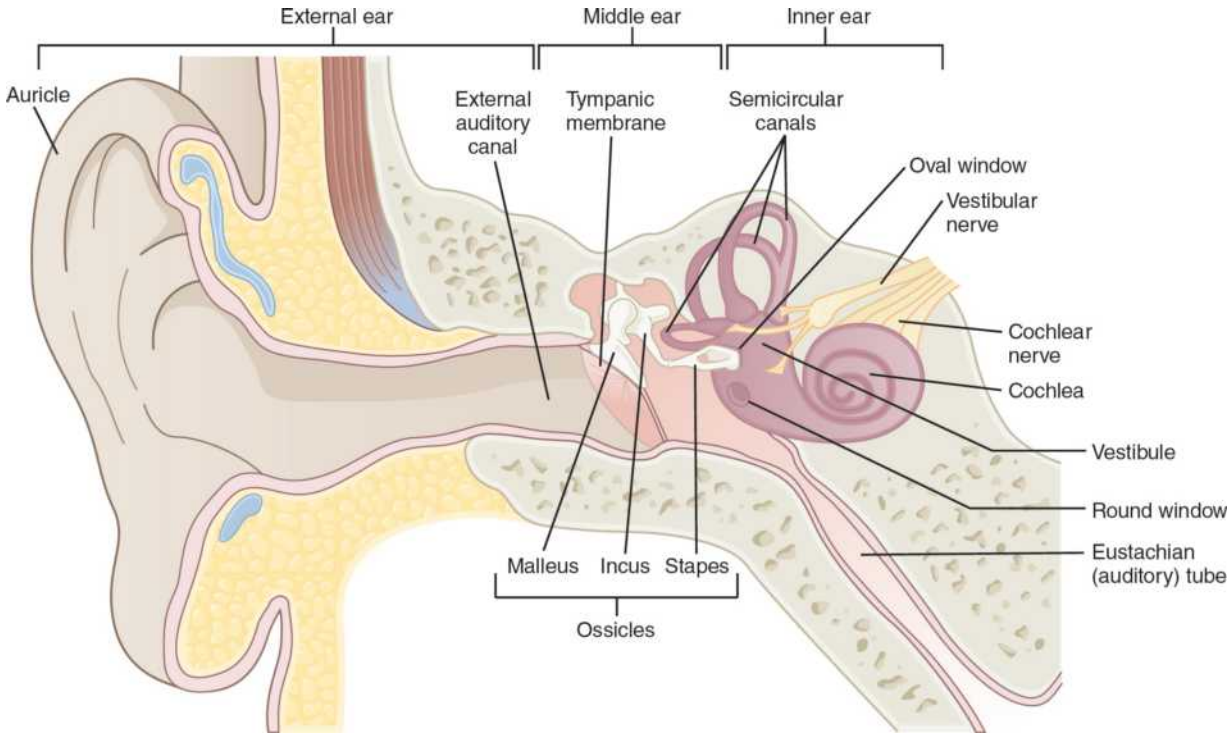


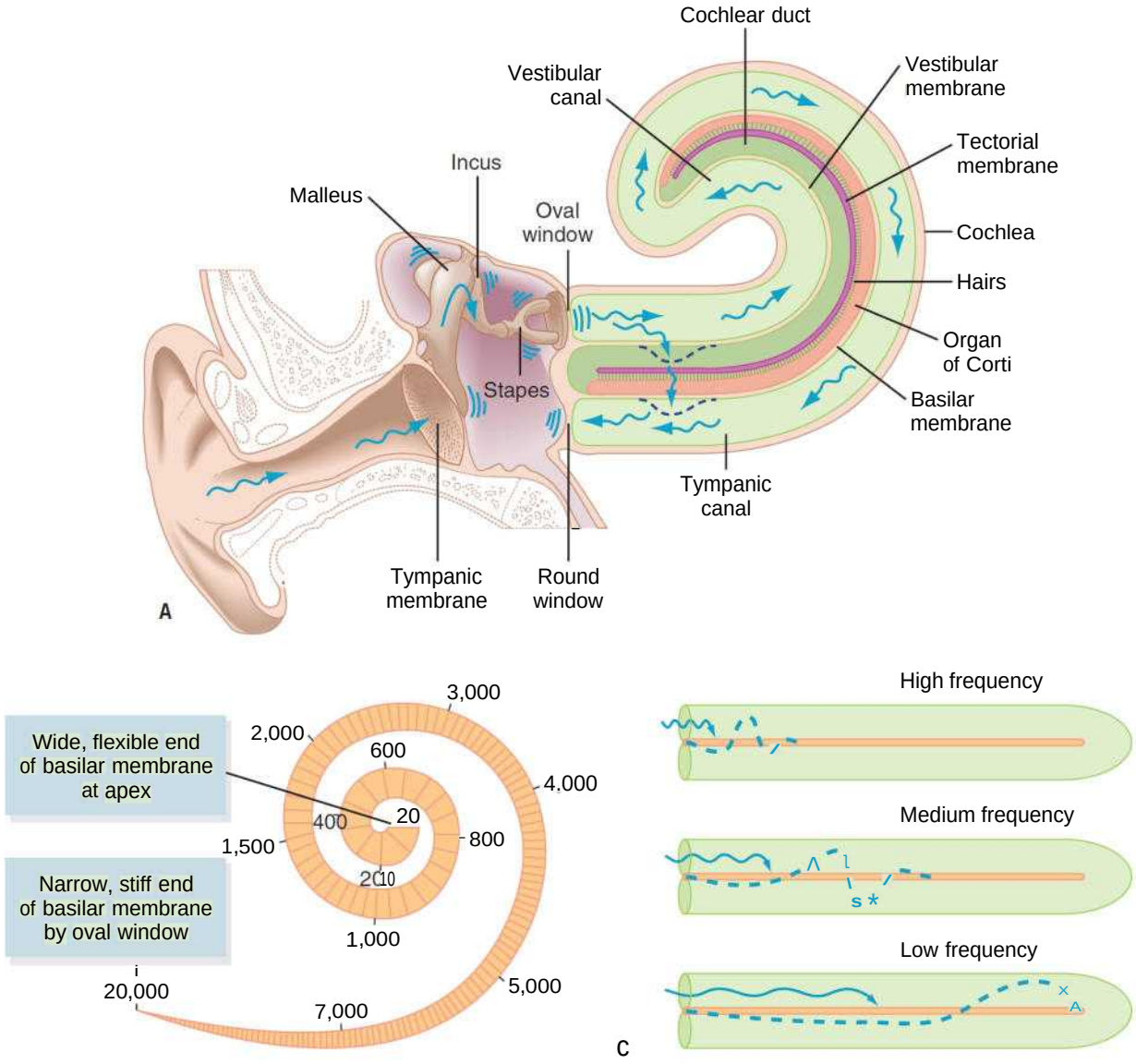
FIGURE 14-6 The structures of the ear.

Description

TABLE 14-3 Structures and Functions of the Ear

Part	Structure	Function
Outer ear	Auricle Ear lobe External auditory canal	Funnels sound waves into the external auditory canal No role Directs sound waves to the eardrum
Middle ear	Tympanic membrane, or eardrum Ossicles	Vibrates when struck by sound waves Transmit sound to the cochlea in the inner ear
Inner ear	Cochlea Semicircular canals Saccule and utricle	Converts fluid waves to nerve impulses Detect head movement Detect head movement and linear acceleration

Sound enters the ear through the auricle (**FIGURE 14-7**). The auricle, an irregularly shaped cartilage, channels sound into the ear. The sound travels through the external ear canal until it reaches the tympanic membrane. The tympanic membrane, or eardrum, separates the outer and middle ear. When sound hits the tympanic membrane, it creates vibrations that are then transmitted to the ossicles. The ossicles consist of three bones—the **malleus** (hammer), the **incus** (anvil), and the **stapes** (stirrup). The malleus lies near the tympanic membrane; vibrations from the membranes cause it to rock back and forth. This rocking causes the incus to vibrate, which in turn causes the stapes to move in and out against the **oval window**. The oval window is the opening to the inner ear, which is covered with a membrane. The vibrations created by the tympanic membrane are amplified as they are transmitted through the structures to the inner ear. Movement of the oval window causes fluid within the cochlea to vibrate, creating waves. The cochlea is a spiral-shaped structure that houses the **organ of Corti** (**FIGURE 14-8**). The organ of Corti contains hearing receptors in the form of hair cells. Vibrations at the organ of Corti stimulate the movement of these hairs, whose bases are wrapped with dendrites. Hair movement causes the dendrites to form nerve impulses that travel to the brain via the vestibulocochlear nerve, also known as cranial nerve VIII (see the *Neural Function* chapter).



The numbers indicate the frequencies with which different regions of the basilar membrane maximally vibrate.

FIGURE 14-7 Transmission of sound through the ear. The cochlea is shown unwound here to simplify the depiction. **(A)** Vibrations are transmitted from the stirrup (stapes) to the oval window. Fluid pressure waves are established in the vestibular canal and pass to the tympanic canal, causing the basilar membrane to vibrate. **(B)** A representation of the basilar membrane, showing the points along its length where the various wavelengths of sound are perceived. Notice that the basilar membrane is narrowest at the base of the cochlea at the oval window end and widest at the apex. **(C)** High-frequency sounds set the basilar membrane near the base of the cochlea into motion. Hair cells send impulses to the brain, which interprets the signals as a high-pitch sound. Low-frequency sounds stimulate the basilar membrane where it is widest and most flexible.

Description

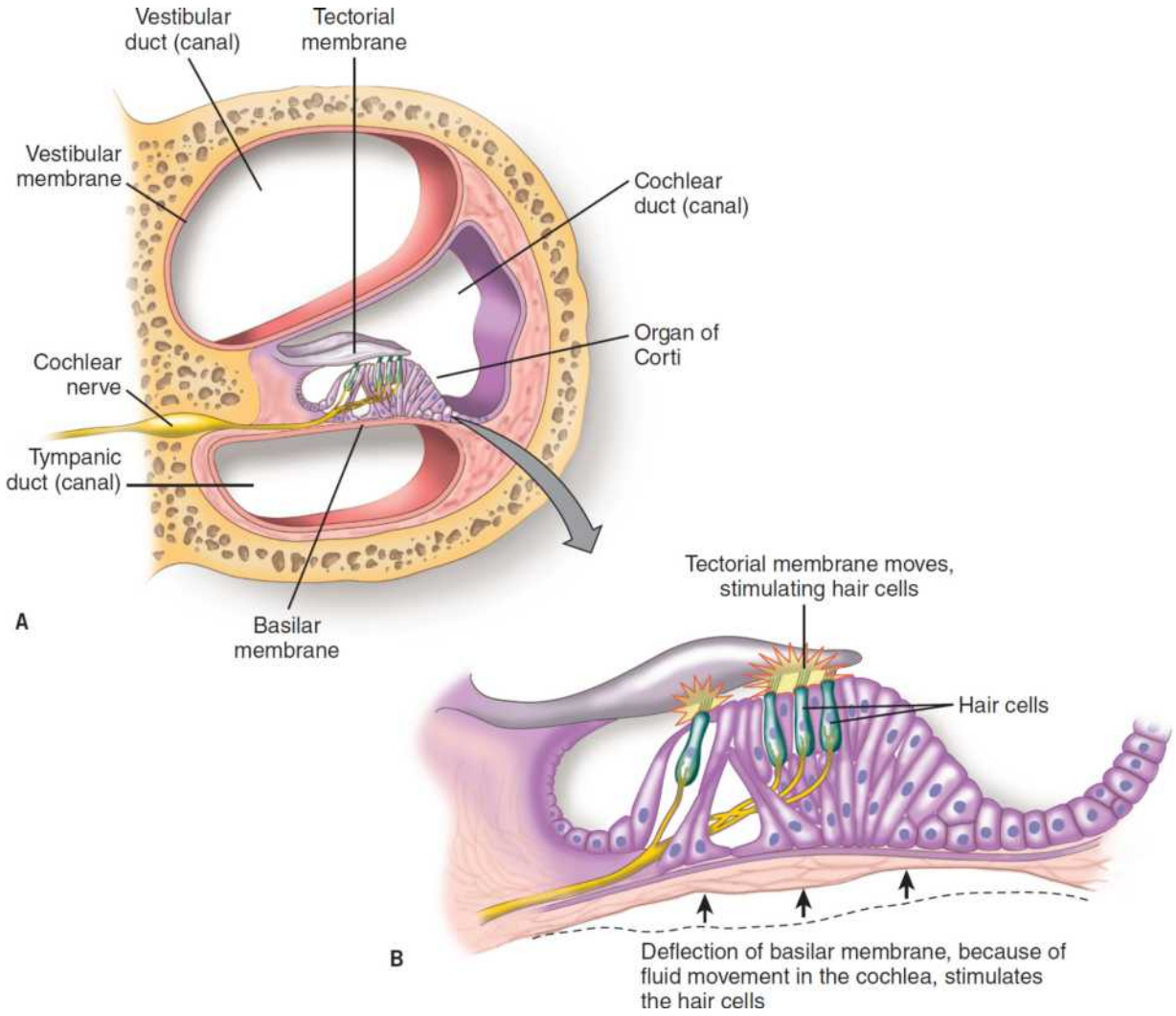


FIGURE 14-8 Cross section of the cochlea. **(A)** Notice the three fluid-filled canals and the central position of the organ of Corti. **(B)** Hair cells of the organ of Corti are embedded in the overlying tectorial membrane. Vibration of the basilar membrane stimulates these hair cells.

Description

The inner ear also holds the **vestibular apparatus** (**FIGURE 14-9**), which consists of two parts—the semicircular canals and the **vestibule**. The semicircular canals are three ringlike, fluid-filled structures that house receptors for body position and movement. The fluid in the semicircular canals works much like a carpenter's level. Movement of the head causes the fluid in the semicircular canal to

move; this movement then stimulates dendrites to send impulses to the brain to report the movement. The vestibule is a bony chamber positioned between the cochlea and the semicircular canals; it houses receptors that respond to body position and movement. The vestibule contains the utricle and the saccule, both of which have receptor organs. Nerve impulses generated in the vestibular apparatus travel to a cluster of nerve cell bodies in the brainstem. At the brainstem, these impulses are combined with input from the eyes, skin, joints, and muscles. This center then directs the information to many areas of the brain (see the *Neural Function* chapter). The majority of the information travels on a pathway to the cerebral cortex, increasing awareness of position and movement. Another pathway leads to the muscles of the limbs and torso; information sent through this pathway enables these muscles to maintain balance and correct body position, if necessary.

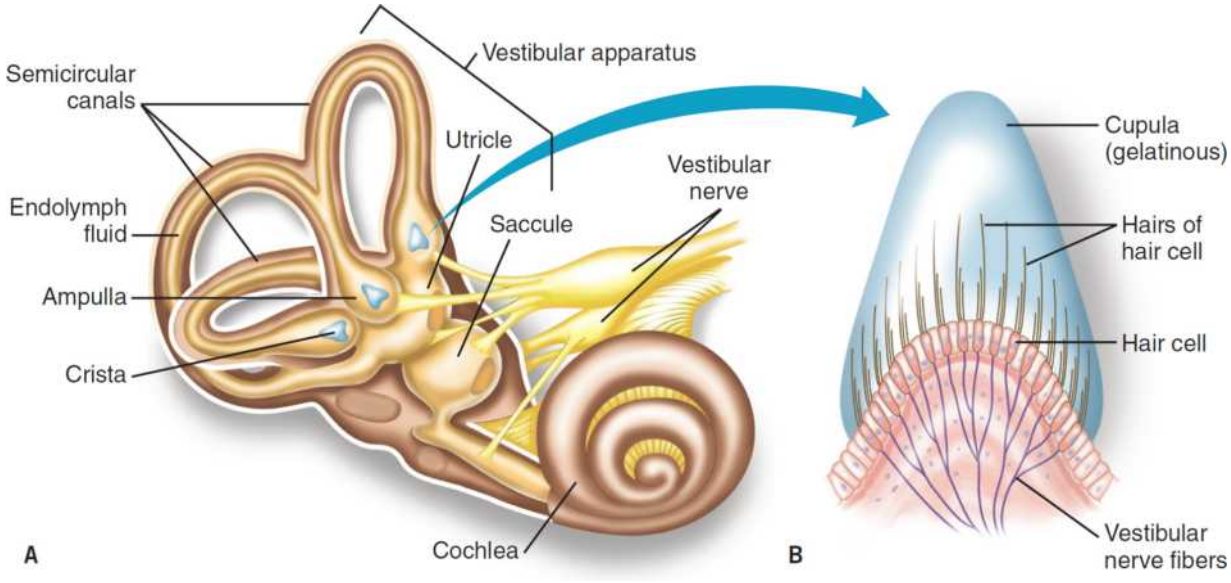


FIGURE 14-9 Vestibular apparatus. **(A)** This illustration shows the location of the cristae in the ampullae of the semicircular canals. The semicircular canals are filled with endolymph. **(B)** When the head spins, the endolymph is set into motion. This action deflects the gelatinous cupula of the crista, thereby stimulating the receptor cells.

Description

The middle ear also opens into the pharynx via the **Eustachian tube**. The Eustachian tube acts as a pressure valve. Normally closed, it may open with activities such as yawning and swallowing. Opening the Eustachian tube allows air to flow in and out of the middle ear, equalizing the internal and external pressures on the tympanic membrane. The function of the Eustachian tube becomes apparent when the ears "pop" while taking off in an airplane. This popping sensation results from pressure being released from the Eustachian tubes.

UNDERSTANDING CONDITIONS THAT AFFECT THE SENSES

When considering sensory conditions, organizing them based on their basic underlying pathophysiology can increase understanding. In sensory disorders, the primary nursing diagnosis is altered sensory perception. Interventions focus on overcoming those deficits. Because the senses receive and process environmental information, an additional nursing diagnosis that is relevant is risk for injury. Interventions directed at minimizing injury are specific to the sensory deficit.

Congenital Sensory Disorders

Congenital sensory disorders vary widely in severity. Many different conditions may arise when an error occurs during embryonic development. These errors may occur randomly, be due to environmental influences, or occur because of genetic abnormalities. They may result in minor conditions with only aesthetic problems (e.g., **microtia**) or life-altering states (e.g., **congenital cataracts**). Treatment is often unnecessary, but when needed, therapeutic options are usually limited.

Eyes

Congenital eye conditions are rare. These conditions vary widely in severity, but vision impairment is present to some degree in most cases. These conditions seldom happen in isolation, but rather are typically associated with other disorders.

Congenital Cataracts

Congenital cataracts involve a clouding of the lens that is present at birth or develops over time (usually during the first 10 years of life). These **cataracts** are typically located in the center of the lens (i.e., nuclear) but can also involve the lens material underneath the anterior and posterior lens capsule. They may be unilateral or bilateral. The clouding of the usually clear lens results in hazy vision. Most cases are sporadic, and no specific cause can be identified. However, congenital cataracts have also been associated with several genetic and chromosomal conditions (e.g., Down syndrome, Turner syndrome, and galactosemia) as well as intrauterine infection exposure (e.g., congenital rubella, syphilis, toxoplasmosis, and herpes simplex). In addition, congenital cataracts may result from an isolated familial anomaly that is usually autosomal dominant.

In addition to clouding of the lens, clinical manifestations usually include a failure of an affected infant to demonstrate visual awareness; the presence of **nystagmus** (rapid, involuntary back-and-forth eye movement), **strabismus** (crossed eyes), and **amblyopia** (lazy eye); and an absence of the red reflex (reddish-orange reflection of light from the back of the eye or fundus). Diagnostic procedures for congenital cataracts consist of a history and physical examination (including a thorough ophthalmologic exam). Additional tests may be necessary to determine other associated conditions.

In some cases, congenital cataracts are mild and do not affect vision; these cases require no treatment. Moderate to severe cataracts that affect vision will require cataract extraction surgery, followed by placement of an artificial intraocular lens. Patching to force the child to use the weaker eye may be required to prevent

amblyopia. Treatment for any underlying disorder may also be needed.

Ears

Congenital conditions affecting the ears usually result from an absence or malformation of the external ear. These conditions may or may not affect hearing. **Anotia** refers to the absence of the auricle, while microtia refers to an underdeveloped, small auricle (**FIGURE 14-10**). Persons with anotia and microtia may also lack an external ear canal (**atresia**). These conditions are more common in males than in females and are often associated with other congenital conditions affecting the head (e.g., hemifacial microsomia, Goldenhar syndrome, and Treacher Collins syndrome). Such congenital ear conditions may be unilateral or bilateral. In addition to these structural abnormalities, **congenital hearing loss** can occur because of damage associated with maternal rubella and syphilis infection during pregnancy.

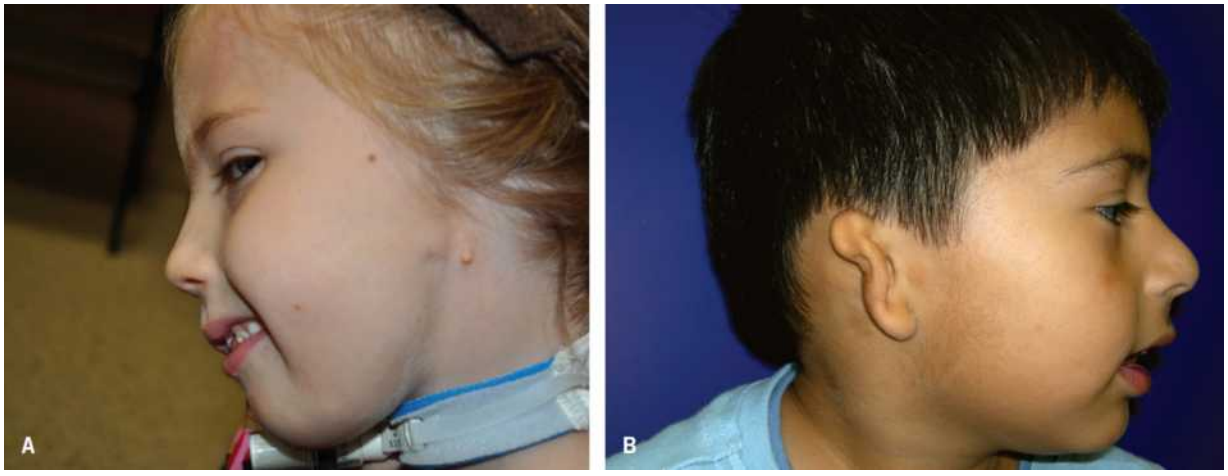


FIGURE 14-10 **(A)** Anotia. **(B)** Microtia.

Courtesy of Dr. Arturo Bonilla, Microtia—Congenital Ear Deformity Institute (http://microtia.org).

Description

Sensory Conditions Associated with Aging

The way in which the body senses and responds to sensory input changes with age. In general, the senses become less acute and less able to distinguish details. These sensory changes vary in severity but can have a tremendous impact on lifestyle and quality of life. Aging increases the threshold needed to perceive sensory input, so the amount of sensory input needed to be aware of the sensation becomes greater. Physical changes in the body part related to the sensation account for most of the other sensation changes. Hearing and vision changes can be the most dramatic, but all senses can be affected by aging. Equipment, such as glasses and hearing aids, or changes in lifestyle can compensate for many of these sensory aging changes.

Eyes

Age-related eye changes may begin as early as 30 years of age. Such changes include less tear production as well as structural deteriorations. All of the eye structures change to some degree with aging. The cornea becomes less sensitive, so injuries may go unnoticed. By age 60, pupils decrease to about one-third of the size they were at age 20. The pupil may also react more slowly in response to darkness or bright light than it did in one's youth. The lens becomes yellowed, less flexible, and slightly cloudy. The fat pads supporting the eye decrease, and the eye sinks back into the skull. The eye muscles weaken, decreasing the ability to rotate the eye fully and limiting the visual field. Visual acuity also may gradually decline.

Glasses or contact lenses may help correct these age-related vision changes. Nearly all persons aged 55 years or older need glasses at least part of the time. However, the severity of changes varies. Only 15% to 20% of elderly persons have vision deficits severe enough to impair driving ability, and only 5% become unable to read.

The most common eye problem associated with aging is difficulty focusing the eyes (accommodation), a condition called **presbyopia**. Additionally, intolerance to glare as well as difficulty adapting to darkness and brightness may be experienced, making driving at night

difficult. Inability to distinguish colors can also become more pronounced with age. Keeping a red light on in darkened rooms (such as the hallway or bathroom) may make it easier to see than using a regular night light because it produces less glare than a white lightbulb.

Ears

All of the ear structures thicken and change with aging, affecting balance and hearing. Hearing may decline slightly, especially regarding high-frequency sounds. This hearing loss is accelerated in people who were exposed to excessive noise or smoking when they were younger. Such age-related hearing loss is called **presbycusis**. Some hearing loss is almost inevitable, but an estimated 30% of all people older than age 65 have significant hearing impairment. Hearing acuity (sharpness) may decline slightly beginning at about 50 years of age, possibly caused by changes in the auditory nerve. In addition, the brain may have a slightly decreased ability to process or translate sounds into meaningful information. Impacted cerumen, another cause of impaired hearing, also becomes more common with increasing age.

Sensorineural hearing loss involves damage to the inner ear, the auditory nerve, or the brain. This type of hearing loss may or may not respond to treatment, but hearing aids can improve function. Conductive hearing loss occurs when an individual has problems transmitting sound through the outer and middle ear to the inner ear. Surgery or a hearing aid may be helpful for this type of hearing loss, depending on the specific cause.

Persistent, abnormal ear noise (**tinnitus**) is another common hearing problem, especially for older adults. Tinnitus—often described as a ringing, buzzing, roaring, or humming sound—is usually a result of mild hearing loss.

Infectious and Inflammatory Sensory Disorders

Infectious sensory disorders are associated with a wide range of causative agents, whose presence often triggers the inflammatory

response. These conditions may be acute or chronic and vary widely in severity. In most cases, infectious sensory disorders usually resolve with treatment.

Eyes

Eye infections can result from a variety of pathogenic organisms, usually bacteria and viruses. Many of these infections are self-limited, and most respond well to treatment. However, severe or untreated infections can lead to visual impairment. These conditions can also be caused by other events that can trigger the inflammatory process (e.g., trauma, allergens, and irritants).

Conjunctivitis

Conjunctivitis, or pink eye, refers to an infection or inflammation of the conjunctiva, the lining of the eyelids and sclera (**FIGURE 14-11**). Conjunctivitis may be caused by viruses (most common), bacteria (e.g., *Staphylococcus*, *Chlamydia* and gonorrhea), allergens (e.g., pollen and dust), chemical irritants, or trauma. Each cause produces slightly different manifestations. Regardless of its cause, conjunctivitis is characterized by edema, blurry vision, photophobia, and pain. Viral infections normally produce a watery or mucuslike exudate. Bacterial infections usually produce a yellow-green exudate. Allergens and irritants typically produce redness, itching, and excessive tearing.

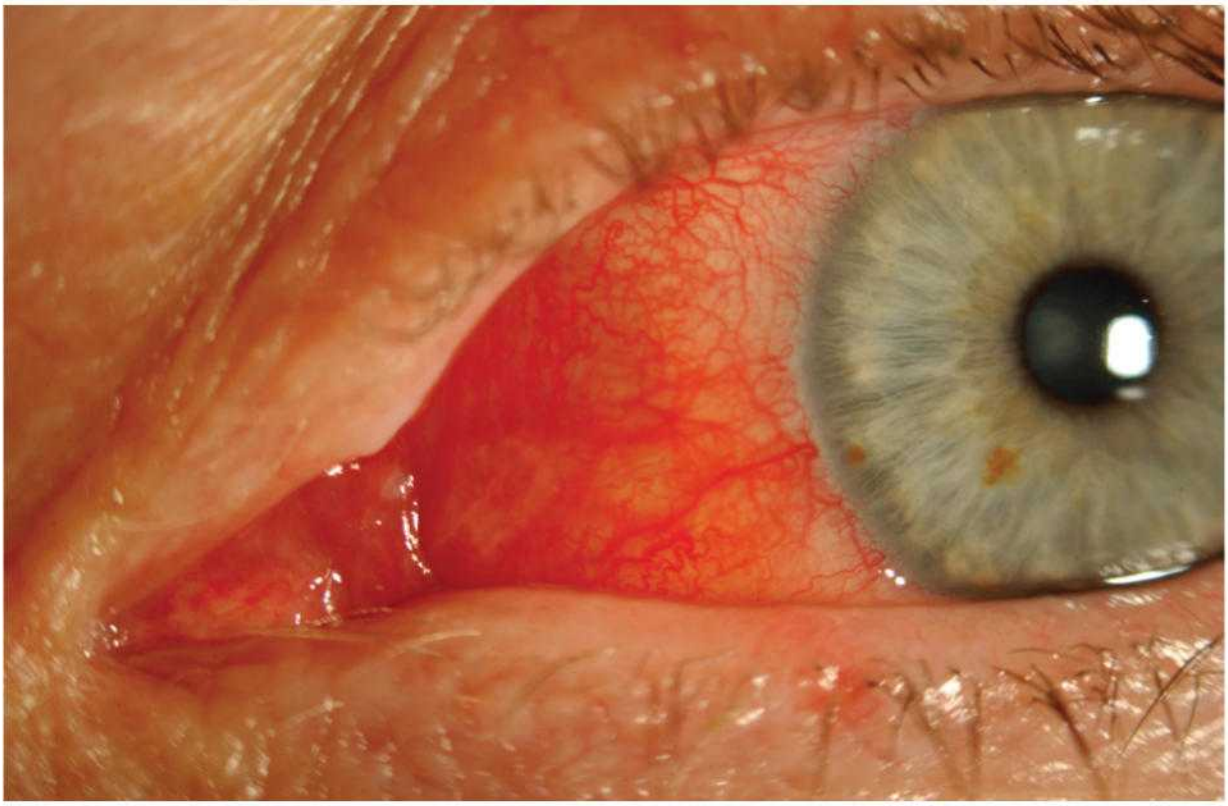


FIGURE 14-11 Conjunctivitis.

Courtesy of John T. Halgren, MD, University of Nebraska Medical Center.

Risk factors for developing conjunctivitis include wearing contact lenses as well as using contaminated makeup or ophthalmic medications. Bacterial and viral conjunctivitis are highly contagious through direct contact, and steps are necessary to prevent transmission of the infection (e.g., hand washing, limiting contact, proper eye hygiene, and discarding contaminated ophthalmic products).

Diagnostic procedures for conjunctivitis focus on identifying the causative agent and include a history, physical examination (including an ophthalmic examination, often conducted by an ophthalmologist), and drainage culture. Many cases of conjunctivitis will resolve without treatment. Treatment may vary depending on the underlying cause, with therapeutic strategies including ophthalmic or oral antibiotics, antihistamines, corticosteroid agents, and artificial tears. Additionally,

warm moist compresses can soothe the discomfort associated with conjunctivitis. Cool compresses can improve edema, if present.

Maternal transmission of sexually transmitted infections to the infant's eyes can occur during vaginal delivery. Because those infections can potentially cause blindness, infants of such mothers are generally treated with ophthalmic antibiotics shortly after birth.

Keratitis

Keratitis refers to an inflammation of the cornea that can be triggered by an infection or trauma (**FIGURE 14-12**). Infections maybe caused by bacteria (e.g., *Staphylococcus, Pseudomonas*, nocardia), viral (e.g., herpes simplex, varicella zoster, Epstein-Barr, and cytomegalovirus), oomycetes (funguslike eukaryotic microorganism; e.g., pythium), and fungi (e.g., microsporidia, filamentous, candida). Herpes simplex type 1 virus can be self-transmitted from the mouth and cause an ulcerated form of keratitis. Common traumatic causes of keratitis include artificial ultraviolet (UV) exposure, welding, contact lens overuse, and abrasions. Occasionally keratitis can be a result of systemic issues, especially connective tissue disorders. Some systemic causes include rheumatoid arthritis, Wegner granulomatosis (granulomatosis with polyangiitis), systemic lupus erythematosus, and polychondritis. Clinical manifestations reflect the inflammatory process and include severe pain, erythema, drainage (clear or mucopurulent), excessive tearing, photophobia, and visual disturbances.

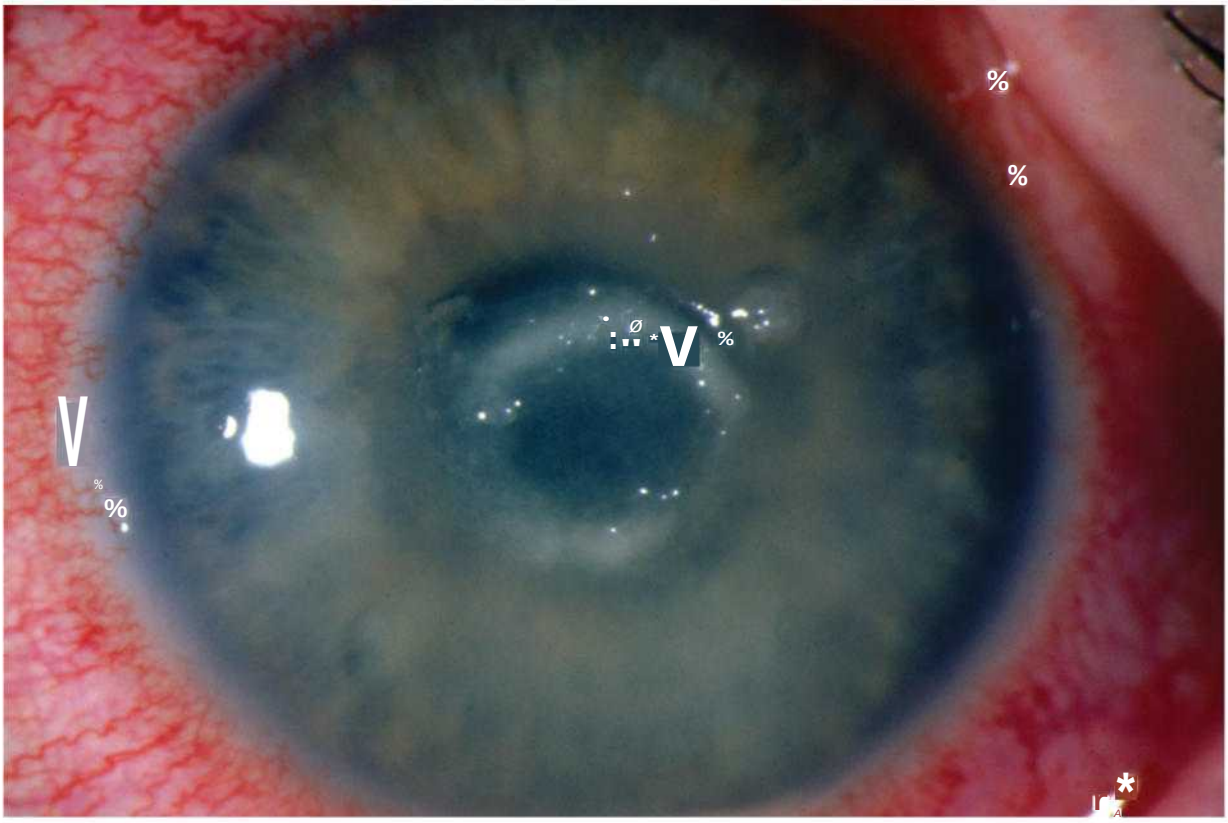


FIGURE 14-12 Keratitis.

Courtesy of Christopher J. Rapuano, MD, Cornea Service, Wills Eye, Professor, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA.

Diagnostic procedures for keratitis focus on identifying the causative agent and include a history, physical examination (including an ophthalmic examination, often conducted by an ophthalmologist), and drainage culture. Treatment varies depending on the underlying etiology, but strategies often include ophthalmic or oral antibiotics and corticosteroid agents.

Ears

Ear infections can result from a variety of pathogens, usually bacterial or viral. These conditions are classified based on the area of the ear infected and typically resolve with treatment.

Acute Otitis Media

Acute Otitis media (AOM) describes an infection or inflammation of the middle ear. AOM is a common condition in young children (typically between the ages of 3 months and 3 years). The Eustachian tubes of young children are narrower, straighter, and shorter than those of adults and older children—a developmental variation in anatomy that decreases the ability of fluid to drain from the young child's middle ear adequately. In addition to these structural differences, a young child's immune system is less equipped to manage infections (see the *Immunity* chapter) than that of an adult or older child. Another cause of fluid accumulation in the middle ear is adenoid enlargement, usually due to inflammation. Because of their close proximity to the Eustachian tubes, enlargement of the adenoids can compress the tubes.

Typically, AOM begins as a viral upper respiratory infection, so it is more common in the winter months than in the rest of the year. The viral infection migrates to the middle ear, causing accumulation of fluid behind the tympanic membrane. This fluid buildup provides a prime medium for secondary bacterial growth. Additional risk factors include childcare in group settings, feeding infants in the supine position, environmental smoke exposure, pacifier use, a history of allergic rhinitis, and presence of orofacial deformities (e.g., cleft lip or palate). *Streptococcus pneumoniae* and *Haemophilus influenzae* are frequent bacterial causes of AOM.

AOM can lead to effusions (fluid accumulation), rupture of the tympanic membrane, scar tissue formation, and conductive hearing loss. Additionally, the infection can spread to nearby structures and cause mastoiditis, cholesteatoma (a benign epithelial cell tumor on the tympanic membrane), meningitis, and osteomyelitis.

Clinical manifestations can vary depending on age; in some cases, the infection may be asymptomatic. When present, manifestations frequently include the following signs and symptoms:

- Ear pain (related to pressure in the middle ear)
- Crying or irritability
- Rubbing or pulling at the ear

- Mild hearing deficits
- Sleep disturbances
- Red, bulging tympanic membrane
- Indications of infection (e.g., fever, malaise, and chills)
- Purulent or clear exudate from the external ear canal (if the tympanic membrane ruptures)
- Nausea, vomiting, and diarrhea
- Headache

Diagnostic procedures for AOM consist of a history, a physical examination (including an otologic examination), drainage culture (if drainage is present), and hearing test (if the individual has recurrent infections). The otologic examination usually includes visualization of the tympanic membrane, tympanometry (which measures tympanic membrane movement), and acoustic reflectometry (reflection of sound).

Treatment focuses on eradicating any infection present, decreasing the amount of fluid in the middle ear, and managing pain. Strategies may include oral or otologic antibiotics and analgesics, although otologic therapy usually is not effective unless the tympanic membrane has ruptured. Antipyretics may be necessary to control fever. Drainage tubes (tympanostomy tubes) can be inserted to facilitate fluid drainage for children with recurrent otitis media (**FIGURE 14-13**). Removal of the adenoids may also be performed with the placement of tympanostomy tubes.

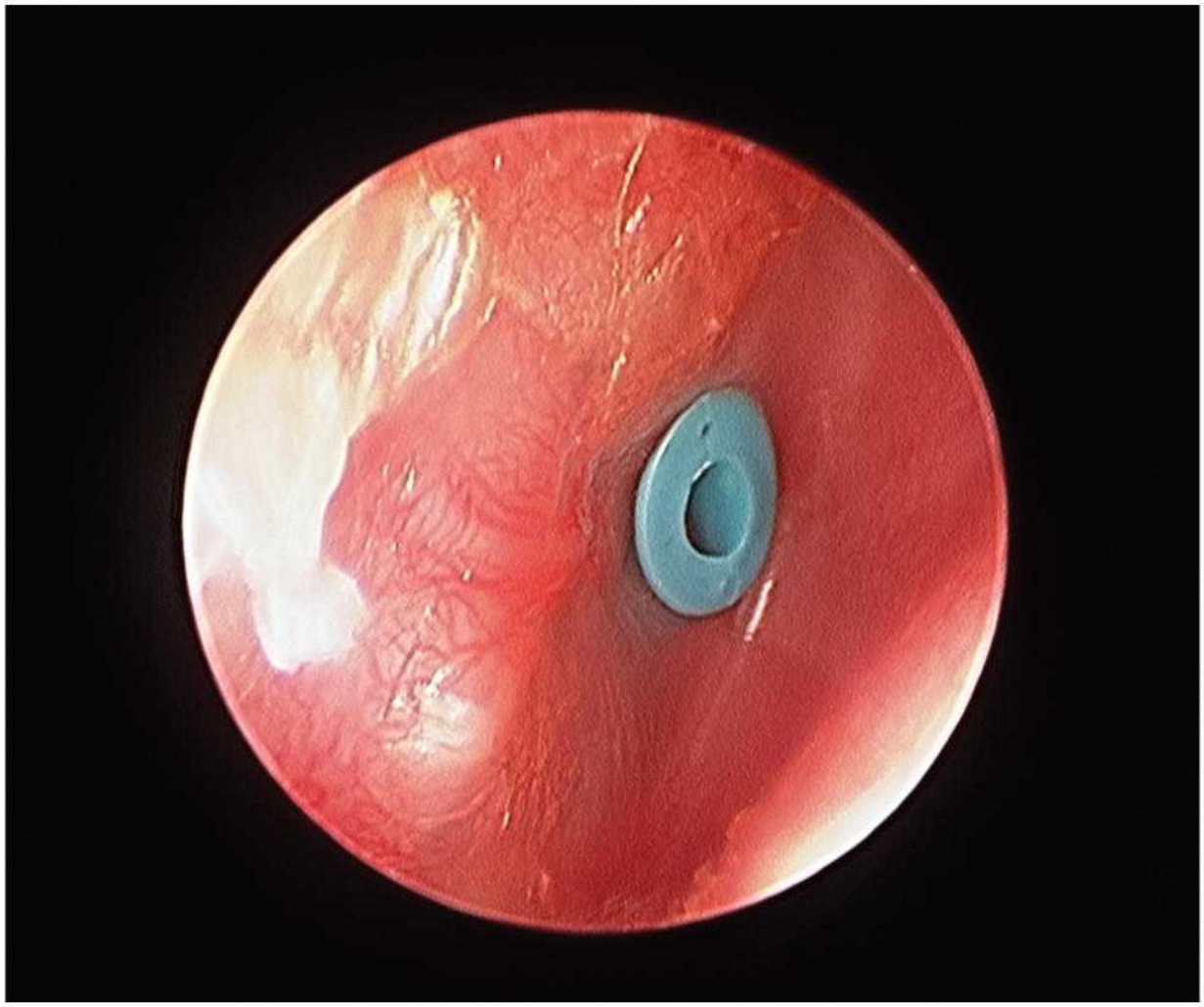


FIGURE 14-13 Tympanostomy tubes.

Courtesy of Andrew Heaford and Richard Smith, University of Iowa.

Otitis Externa

Otitis externa, or "swimmer's ear," refers to an acute infection or inflammation of the external ear canal or auricle. Otitis externa is usually bacterial in origin (often *Pseudomonas aeruginosa*) but may also be fungal. It generally arises from moisture in the ear that creates an environment for bacterial or fungal growth or introduction of the organisms from external sources. Risk factors include swimming in contaminated water, scratching the outside or inside of the ear, irritants, and insertion of foreign objects (e.g., cotton swabs, earphones, and ear plugs) into the ears. The presence of allergies,

psoriasis, eczema, or seborrheic dermatitis can also predispose someone to otitis externa. Most cases of otitis externa are mild and respond well to treatment, but occasionally this condition can lead to hearing loss, cellulitis, necrosis, osteomyelitis, and meningitis. Clinical manifestations of otitis externa include ear pain that worsens with auricle movement, purulent exudate, pruritus, a sensation of fullness in the ear, and hearing deficits.

Diagnostic procedures typically consist of a history, physical examination (including an otologic examination), and exudate analysis (e.g., culture and sensitivity). Because of the easy access to the external ear canal, treatment strategies are typically applied locally. These strategies may include otologic antibiotic, antifungal, corticosteroid, and analgesic agents. Additionally, the external ear canal may be cleaned (e.g., via lavage of warm saline), and a cotton wick may be inserted to increase medication penetration and absorb drainage. Prevention strategies include drying the ears after swimming or bathing with an alcohol-based product (or 1:1 mixture of rubbing alcohol and white vinegar) as long as the tympanic membrane is intact, avoiding insertion of foreign objects into the ear, wearing ear plugs, and treating pools properly.

Traumatic Sensory Disorders

Traumatic sensory disorders can result from a wide range of injuries and can vary widely in severity. Often the patient's prognosis depends on prompt treatment.

Eyes

Eye trauma can result from numerous types of injuries, including direct physical trauma and chemical burns. Any of the eye structures can be involved, including the eyelid, the cornea, or the entire eye globe. These conditions may vary in severity from mild (e.g., a black eye) to sight threatening (e.g., corneal abrasions and **closed-angle glaucoma**). The eye is highly vulnerable to injury, and vision deficits often result from such damage. Clinical manifestations vary depending on the nature of the injury but may include eye pain,

edema, blurry vision, **diplopia** (double vision), dry eyes, photophobia, floaters, pupil dilation, and pupils that are unresponsive to light.

Early diagnosis and treatment can prevent or limit the severity of visual deficits. Diagnostic procedures consist of a history and physical examination (including an ophthalmic examination, often by an ophthalmologist). Treatment strategies may include the following measures:

- Flushing the irritant out of the eye with sterile saline
- Avoiding rubbing the eye (can worsen the damage)
- Leaving an embedded object in the eye
- Covering the eye with a sterile dressing or cloth
- Applying eye patches to protect the eye during the healing process
- Repairing any damage surgically

Ears

Ear trauma can result from a variety of injuries to any of the internal or external ear structures. These injuries may stem from direct physical trauma (e.g., foreign objects and insects) or exposure to excessively loud noises (e.g., explosions and gunshots). Such events can result in permanent hearing deficits. Clinical manifestations of ear trauma may include bloody or clear exudate, tinnitus, dizziness, ear pain, hearing deficits, nausea, vomiting, edema, and a sensation that an object is in the ear.

Treatment strategies vary depending on the nature of the injury. These strategies may include the following measures:

- Removing the object if it is visible and easily removed
- Flushing the ear with sterile water or saline to remove small objects (alcohol or mineral oil may be used for insects to kill them, limiting the trauma during their removal)
- Performing surgery to remove objects or repair the damage
- Limiting exposure to loud sounds as structures heal

Chronic Sensory Disorders

Numerous chronic conditions can affect the sensory organs. These conditions are often mild and easily managed. In some cases, however, they may cause significant sensory deficits.

Eyes

Many chronic conditions affecting the eyes are progressive and can result in visual deficits. Most of these conditions can be prevented. With early treatment, most cases can be managed effectively.

Glaucoma

Glaucoma refers to a group of eye conditions that lead to damage to the optic nerve. This damage is often caused by increased intraocular pressure, but it can also result from decreased blood flow to the optic nerve (**FIGURE 14-14**). Pressures inside the eye can climb when the outflow of aqueous humor becomes blocked or when the production of aqueous humor increases to an abnormal level. These increased pressures cause ischemia and degeneration of the optic nerve.

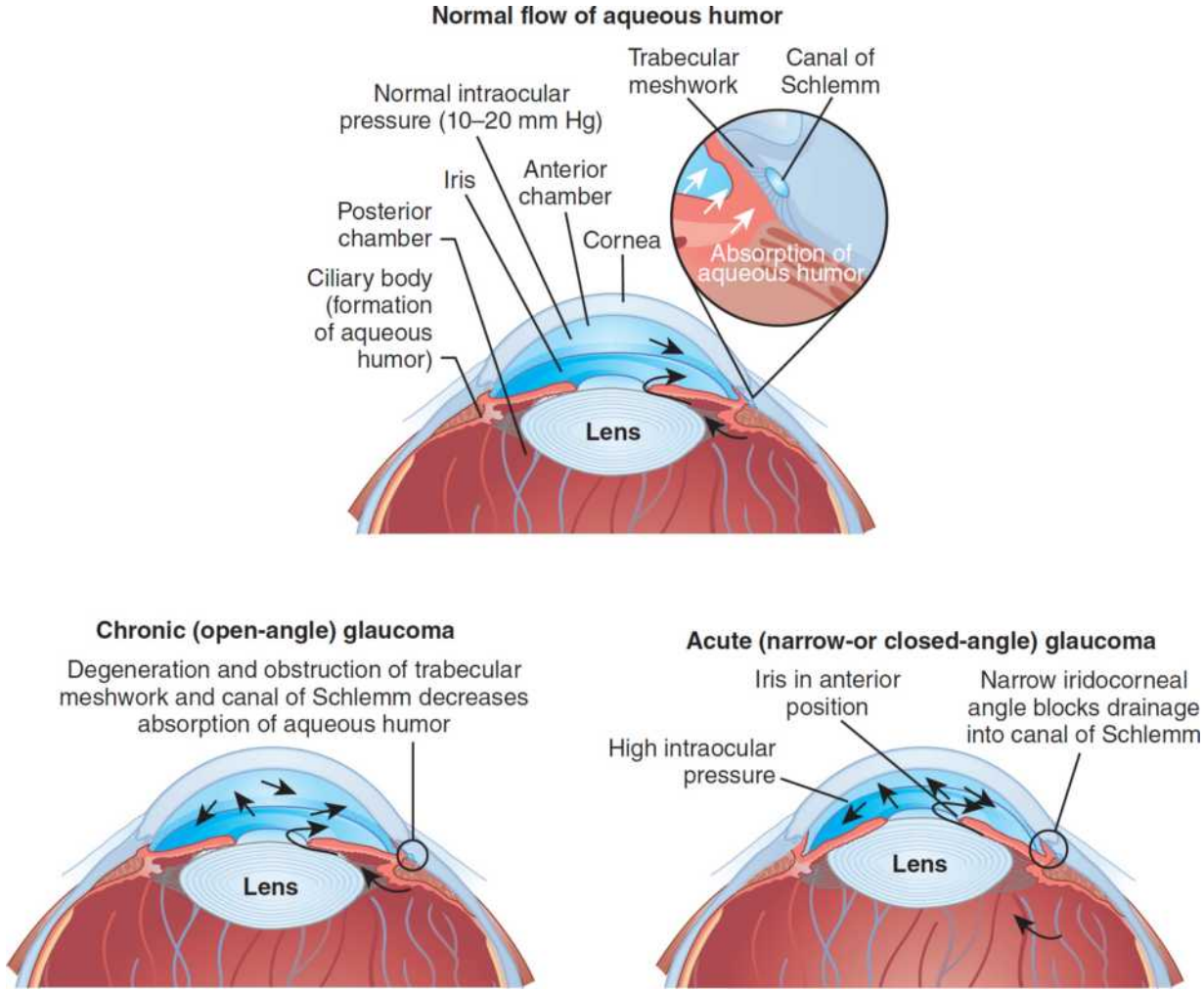


FIGURE 14-14 Types of glaucoma.

Description

Glaucoma is the second leading cause of blindness (after diabetic retinopathy) in the United States, and the vision loss is permanent. There are three types of glaucoma:

- **Open-angle glaucoma**. Open-angle glaucoma is the most common type, and it has several subtypes (e.g., trabecular, idiopathic, obstructive, traumatic). Angle refers to the angle formed by the junction of the iris and cornea at the periphery of the anterior chamber. For reasons that are unclear, intraocular pressure may increase gradually over an extended period. This type of glaucoma is chronic and tends to run in families, and rates are six to eight

times higher among African American individuals than among people of other races. Other risk factors include age, thin cornea, systemic hypertension, diabetes, and myopia. Clinical manifestations typically include painless, insidious, bilateral changes in vision (e.g., tunnel vision, blurred vision, halos around lights, and decreased color discrimination). Because the vision changes are gradual and other manifestations rarely occur, open-angle glaucoma can often be overlooked or misdiagnosed as presbyopia.

application to practice

One night Tammy, a 24-year-old female, was cleaning her ears with a cotton swab as she did every night as a part of her hygiene routine. She was in a hurry to go out on a date. Her hand slipped as she was cleaning her ears with the cotton swab, and the swab went deep into her right ear. Her ear immediately began to bleed. She continued to get dressed for her date, assuming the bleeding would stop, but it did not. Tammy decided to cancel the date and have her ear checked by a healthcare provider at the after-hours clinic.

At the clinic, the healthcare provider told Tammy that she had probably perforated her tympanic membrane, and it would likely heal in a few weeks. The bleeding continued for the next 24 hours, so Tammy called the clinic again. The healthcare provider at the clinic referred her to an ear, nose, and throat specialist the next day. During her visit with the specialist, Tammy explained the incident with the cotton swab, and the specialist reminded her—as she had heard many times before—"Never put anything smaller than your elbow in your ear." Upon examination, the specialist determined that Tammy had a severe perforation of her tympanic membrane that required surgical repair with skin grafting to prevent permanent severe hearing loss.

After the surgical repair, Tammy continues to have significant hearing loss in her right ear. The risk for graft rejection remains. Steps to protect her hearing are vital and include limiting exposure to excessive noise and avoiding ototoxic medications.

- Angle-closure glaucoma. Angle-closure glaucoma results from a sudden blockage of aqueous humor outflow. This blockage can be caused by trauma, sudden pupil dilation (e.g., exposure to bright light after prolonged exposure to darkness), prolonged pupil dilation (e.g., medications for eye examinations), and emotional stress. It can be acute, subacute, and chronic. Angle-closure glaucoma is typically unilateral but may affect both eyes. Clinical manifestations

are usually sudden in onset and worsen quickly. These manifestations may include severe eye pain, headache, nausea, vomiting, a nonreactive pupil, erythema, haziness of the cornea, and vision changes (e.g., halos around lights and cloudy vision).

- **Congenital glaucoma**. This type of glaucoma, which is present at birth, results from abnormal development of outflow channels (trabecular meshwork) of the eye. Congenital glaucoma follows an X-linked recessive hereditary pattern. It may go unnoticed for a few months after birth. Clinical manifestations may include excessive lacrimation, photophobia, corneal edema, a gray-white appearance of the cornea, enlarged eye globe, and vision deficits.

Diagnostic procedures for glaucoma consist of a history and physical examination (including an ophthalmic examination). The ophthalmic examination typically involves a gonioscopy (use of a special lens to see the outflow channels of the angle), tonometry (which measures intraocular pressure), optic nerve imaging, pupillary reflex response, retinal examination, slit lamp examination (using a microscope and light to examine the anterior eye structures), visual acuity testing, and visual field measurement.

Emerging Research: Glaucoma Treatment

Ophthalmic drops have traditionally been the first line of treatment for newly diagnosed glaucoma. However, some patients have difficulty with administering them properly, so healthcare providers often proceed with surgical treatment. In recent years, new medications have become available, the use of selective laser trabeculoplasty as first-line treatment is increasing, and several new, safer micro-invasive surgery options have changed the traditional glaucoma management.

Two new categories of glaucoma medication have shown to significantly decrease eye pressures as compared to long standing treatments. Nitric oxide-donating prostaglandins and Rho kinase inhibitors are challenging traditional regimens. These two categories have demonstrated efficacy in lowering IOP by draining fluid out of the eye with once-daily dosing and few side effects (Glaucoma Research Foundation, 2021).

Treatment focuses on decreasing intraocular pressure. Early detection and treatment are crucial to preserve vision, so persons at increased risk for glaucoma should be routinely screened for this condition (usually once a year). Treatment strategies vary depending on the type.

Strategies for open-angle glaucoma may include the following measures:

- Ophthalmic medications (usually a combination of two or three types), including the following:
  - Prostaglandin-like compounds (preferred; to increase aqueous humor outflow)
  - Beta blockers (to reduce aqueous humor production)
  - $Alpha_2$-adrenergic agonists (to protect the optic nerve)
  - Carbonic anhydrase inhibitors (to reduce aqueous humor production)
  - Alpha agonists (to reduce production and increase drainage of aqueous humor)
  - Rho kinase inhibitors (to decrease the adhesion of leukocytes and by slowing leukocyte-induced damage)
  - Miotic or cholinergic agents (to increase aqueous humor outflow)
  - Epinephrine compounds (to increase aqueous humor outflow)
  - *N*-methyl-d-aspartate receptor antagonists (may protect the optic nerve)
- Oral medications (not generally effective when used alone), including carbonic anhydrase inhibitors
- Laser surgery to open aqueous humor outflow
- Filtering surgery (to remove a small section of the trabecular meshwork)
- Drainage implants
- Chronic disease management

The main strategy for treating angle-closure glaucoma is Timolol, pilocarpine, and brimonidine ophthalmic drops as well as a systemic osmotic agent, followed by iridotomy, a surgical laser procedure that opens a new channel in the iris.

The main strategy for treating congenital glaucoma is surgery to open the aqueous humor outflow channels (e.g., laser, filtering, and drainage implants).

Cataracts

A cataract is opacity or clouding of the lens (**FIGURE 14-15**). Cataracts can occur as a congenital condition (previously discussed), or they can develop later in life. Over time, proteins in the lens break down, making the lens cloudy. Risk factors for adult-onset cataracts include family history, advancing age, smoking, alcohol use, UV light exposure (natural or artificial), exposure to x-rays, heat from infrared exposure, metabolic conditions (e.g., diabetes mellitus), certain medications (e.g., corticosteroids), undernutrition, and eye injury (e.g., trauma and infection). Cataracts are the leading cause of blindness worldwide. In the United States, 20% of people aged 65 to 74 have cataracts, and 50% of people over the age of 75 have cataracts.



FIGURE 14-15 Cataracts.

Courtesy of National Eye Institute/NIH.

Cataracts may affect one or both eyes and do not necessarily affect eyes symmetrically. The opacity can occur anywhere on the lens. In addition to the cloudy appearance of the lens, clinical manifestations may include the following signs and symptoms:

- Cloudy, fuzzy, foggy, or filmy vision (**FIGURE 14-16**)



FIGURE 14-16 Visual changes associated with cataracts.

Modified from photo © Effrosyni Labropoulou/Dreamstime.com

- Color intensity loss
- Diplopia
- Impaired night vision, gradually progressing to impaired day vision
- Halos around lights
- Photosensitivity
- Frequent changes in eyeglasses or contact lens prescription

Diagnostic procedures for cataracts consist of a history and physical examination (including an ophthalmic examination). The ophthalmic examination typically involves visual acuity testing, retinal examination, and slit lamp examination.

Surgery is the only effective treatment for cataracts. Surgical procedures may include removal of the cataract (e.g., phacoemulsification) or a lens transplant. Surgery is typically performed one eye at a time, as an outpatient procedure with a local anesthetic. Recovery time is usually short, and the prognosis is good. Additional strategies may include managing or eliminating contributing factors.

Macular Degeneration

Macular degeneration refers to a deterioration of the macular area of the retina that causes irreversible central vision loss. Macular degeneration is caused by impaired blood supply to the macula, which results in cellular waste accumulation and ischemia. The most significant risk factor for this condition is advancing age. Macular degeneration is more common in persons with a family history and is most prevalent in females and Caucasians. Genetic variants, including abnormal complement factor H, have also been associated with macular degeneration. Additional risk factors include smoking, increased UV light exposure (natural or artificial), high-fat diet,

decreased carotenoid intake, cardiovascular disease, hypertension, and obesity.

Two types of macular generation are distinguished: dry (nonexudative or atrophic) and wet (exudative or neovascular). Dry macular degeneration—the most common form—occurs when the blood vessels under the macula become thin and brittle. Small yellow deposits (drusen) form under the macula. These deposits increase in size and number, blurring vision and creating a dim spot in the central vision. Wet macular degeneration occurs in only approximately 10% of people with macular degeneration. In this type, brittle vessels break down, and new, abnormal, fragile blood vessels grow under the macula (choroidal neovascularization). These vessels leak blood and fluid, leading to macula damage. Although it is not as common as dry macular degeneration, this form causes more vision loss. Dry macular degeneration progresses gradually (over years) in contrast to the wet form, which results in vision loss over weeks or months.

Macular degeneration is often asymptomatic initially. The most common manifestation of the dry form is blurry vision with a loss of central vision. The most frequent manifestations of the wet form are distortion of straight lines, dark spots in central vision, and sudden loss of central vision.

Diagnostic procedures for macular degeneration consist of a history and physical examination (including an ophthalmic examination). The ophthalmic examination usually involves visual acuity using the Amsler grid, retinal examination, fluorescein angiogram (uses dye and a camera to evaluate retinal blood flow), and optical coherence tomography (noninvasive retinal imaging).

No treatment exists for dry macular degeneration. However, a combination of vitamins, antioxidants, and zinc—often called the “Age-Related Eye Disease Study 2 formula” (Chew et al., 2013)—may slow the disease’s progression. Smokers should not use this treatment, but smoking cessation decreases the progression. The recommended supplements contain the following nutrients:

- 500 mg of vitamin C
- 400 IU of vitamin E

- 80 mg of zinc
- 2 mg of copper
- 10 mg of lutein
- 2 mg of zeaxanthin

Although there is no cure for wet macular degeneration, the following treatment strategies may be used:

- Laser surgery—specifically, laser photocoagulation (in which a laser is used to destroy the abnormal blood vessels)
- Photodynamic therapy (in which light activates an injected drug to destroy leaking blood vessels)
- Antiangiogenesis or antivascular endothelial growth factor therapy (medications injected into the eye that slow the formation of new blood vessels in the eye)

Low-vision aids (e.g., magnifying glasses and large print) and occupational therapy can also improve independence and quality of life.

Ears

Many chronic conditions affecting the ears are progressive and can result in hearing deficits. Some of these conditions are preventable. With early treatment, most cases can be managed.

Otosclerosis

Otosclerosis refers to an abnormal bone growth in the middle ear, usually involving an imbalance in bone formation and resorption. The cause of otosclerosis is unknown, but it appears to have a hereditary component. In this condition, an abnormal spongelike bone grows in the middle ear, preventing the ear structures from vibrating in response to sound waves. As the abnormal bone grows, hearing loss progressively worsens. Nerve loss can occur in conjunction with the conductive hearing loss. Otosclerosis is most common in young adults, women, and Caucasians. Pregnancy may also trigger

otosclerosis. Typically, otosclerosis affects both ears, and tinnitus and **vertigo** may be present as well.

Diagnostic procedures consist of a history, physical examination (including a hearing test), and temporal bone computed tomography (CT). Treatment for otosclerosis focuses on minimizing hearing loss or improving hearing. These strategies may include the following measures:

- Bisphosphonates typically used in osteoporosis to inhibit osteoclastic activity (i.e., decrease bone resorption) and possibly help control the bony abnormalities
- Medications, such as oral fluoride, calcium, or vitamin D, which may help to control the hearing loss (although their efficacy remains in question)
- Hearing aids to treat hearing loss
- Surgery to remove the stapes (stapedectomy) and replace it with a prosthesis to cure the condition
- Laser surgery to create an opening in the stapes (stapedotomy) with or without placement of the prosthetic device

Ménière's Disease

Ménière's disease is a disorder of the inner ear that results from endolymph swelling. This swelling stretches the membranes and interferes with the hair receptors in the cochlea and vestibule. The exact cause is unknown, but Ménière's disease may be associated with metabolic disturbances, hormonal imbalances, autoimmune diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis), head injuries, otitis media, and syphilis. Additional risk factors include allergic rhinitis, alcohol abuse, stress, fatigue, certain medications (e.g., aspirin), and respiratory infections. Peak incidence is between ages 20 and 50.

Clinical manifestations of Ménière's disease typically occur in waves of acute episodes that last several months, followed by brief periods of relief. These attacks may be triggered by changes in barometric pressure or any of the risk factors. The main

manifestations include intermittent episodes of vertigo, tinnitus, unilateral sensorineural (low-frequency) hearing loss, and a sensation of ear fullness. Other manifestations include nausea, vomiting, diarrhea, headache, and uncontrollable eye movement. Repeated episodes can lead to permanent hearing loss.

No reliable diagnostic test is available for Ménière's disease, so diagnosis is typically made clinically. Diagnostic procedures for Ménière's disease consist of a history, physical examination (including a neurologic assessment), hearing test, balance test, electrocholeography (which measures fluid accumulation in the ear), electronystagmography (in which balance sensors are placed in the inner ear to assess balance in relation to eye movement), caloric stimulation (instillation of a warm or cold solution into the inner ear to test eye reflexes), head CT, and head magnetic resonance imaging (MRI).

There is no cure for Ménière's disease. Instead, treatment focuses on relieving inner ear pressure and relieving symptoms. Strategies may include the following measures:

- Antihistamine agents (to decrease fluid accumulation)
- Benzodiazepines (to improve vertigo)
- Anticholinergic agents (to decrease fluid accumulation)
- Diuretics (to decrease fluid accumulation)
- Antiemetic agents (to improve nausea and vomiting)
- Limiting dietary sodium intake (to decrease fluid retention)
- Avoiding triggers (e.g., alcohol and stress)
- Middle ear injections of gentamicin (an ototoxic antibiotic that can reduce balance structures) or corticosteroids (to reduce swelling)
- Partial or complete surgical removal of the endolymph or inner ear
- Vestibular nerve resection
- Hearing aids
- Meniett device (for difficult-to-treat vertigo; it improves fluid exchange by applying pulses of pressure to the ear canal through a ventilation tube)

* Physical therapy to improve balance

Sensory Organ Cancers

Any of the sensory organs can develop cancer, but such disease is rare. The severity varies depending on the type of cancer, and treatment often follows the typical cancer management regimens (e.g., chemotherapy, radiation, and surgery) (see the *Hematopoietic Function* chapter). Ear cancer is extremely rare and typically involves skin cancer (see the *Integumentary Function* chapter) of the auricle. For this reason, ear cancer is not covered in this discussion.

Eyes

An uncommon condition, eye cancer can affect any part of the eye, from the eyelid to the intraocular structures. The most common intraocular cancers in adults are melanoma and lymphoma. The most frequent eye cancer in children is retinoblastoma. Cancer can also metastasize to the eye from other parts of the body. According to the American Cancer Society (2023), eye cancer is most common in Caucasians and men and has an overall 5-year survival rate of approximately 80%. Clinical manifestations of eye cancer typically include some sort of visual disturbance (e.g., losing part of the visual field, blurry vision, floaters, and seeing flashing lights). Also, a growing dark spot on the iris, change in the shape or size of the pupil, bulging of the eye, or change in eye movement may be noted. Pain is rare unless the tumor has extended beyond the eye.

Most cases of eye cancer are found during a routine ophthalmic examination (e.g., finding dark spots on the iris). Additional diagnostic procedures may include a history, ultrasound, fluorescein angiography (imaging of blood vessels in the eye using contrast dye), biopsy, and other tests to detect and evaluate metastasis (e.g., CT and MRI).

Treatment varies depending on the cancer type, location, and size. Surgery is the foundation of most eye cancer treatment, and it may entail removal of all (enucleation) or part of the eye (e.g., iridectomy and choroidectomy). Additionally, radiation may be used (e.g., teletherapy and brachytherapy). Less frequently, laser therapy and

chemotherapy maybe used. A prosthetic eye may be used if the entire eye is removed.

Miscellaneous Sensory Organ Conditions

Several sensory organ conditions that do not fall under the previously discussed categories warrant discussion.

Eyes

A few eye conditions that do not fit the previously discussed categories can occur. These conditions may be manifestations of other problems or happen alone. Some of these conditions are minor, causing minimal deficits. Others can cause severe visual deficits.

Strabismus

Strabismus, or crossed eyes, is a gaze deviation of one eye (FIGURE 14-17). With strabismus, the eyes do not coordinate or align properly to focus on the same object together, resulting in diplopia. This condition most often appears at birth or shortly after. In children, the brain will begin to ignore the input from one of the eyes. If the brain continues to ignore one eye, the eye will never function properly, and permanent visual deficits may result (e.g., amblyopia). A weak or hypertonic eye muscle, a short muscle, or a neurologic deficit can cause strabismus. These defects are often associated with chromosomal defects (e.g., Down syndrome), intrauterine infection exposure (e.g., congenital rubella), eye cancers (e.g., retinoblastoma), and traumatic brain injuries.



FIGURE 14-17 Strabismus.

© Justin Paget/Shutterstock

Diagnostic procedures for strabismus consist of a history and physical examination (including an ophthalmic examination and a neurologic examination). Treatment focuses on strengthening the weak eye and realigning the eyes. It often involves resting the normally aligned eye to strengthen the misaligned eye. Strategies usually include prism glasses, eye muscle exercises, eye patching, and surgery.

Amblyopia

Amblyopia, or lazy eye, is the loss of one eye's ability to see details. It is the most common cause of vision problems in children. Amblyopia occurs when the brain and the eyes do not work together properly—that is, the brain favors one eye. The preferred eye has normal vision, but because the brain ignores the other eye, vision does not develop normally. The normal eye attempts to compensate for the affected eye, creating a vicious cycle in which the normal eye becomes stronger and the affected eye becomes weaker. The brain stops growing between 5 and 10 years of age, at which time this condition becomes permanent.

Strabismus is the most frequent cause of amblyopia. Other causes include a family history, bilateral astigmatism, congenital cataracts, farsightedness, and nearsightedness.

Diagnostic procedures for amblyopia consist of a history and physical examination (including an ophthalmic examination). Much like with strabismus, treatment focuses on strengthening the weak eye and realigning the eyes. It often involves resting the normal eye to strengthen the weaker eye. Strategies usually include wearing prism glasses, eye muscle exercises, eye patching, ophthalmic medication (atropine may be used to dilate the pupil of the normal eye to "chemically patch" it), and surgery.

Retinal Detachment

Retinal detachment is an acute condition that occurs when the retina separates from its supporting structures. This separation can happen spontaneously or because of severe nearsightedness (myopia), previous cataract surgery, trauma, diabetes mellitus, inflammation, degenerative aging changes, scar tissue, and family history. Retinal detachment occurs when vitreous humor leaks through a retinal tear and accumulates underneath the retina. Leakage can also occur through tiny holes where the retina has thinned due to aging or other retinal disorders. Less commonly, fluid can leak directly underneath the retina without a tear or break. As vitreous humor collects underneath the retina, it peels away from the underlying choroid. These detached areas may expand over time, like wallpaper that, once torn, slowly peels off a wall. In turn, the retina becomes ischemic and stops functioning, causing vision loss.

Retinal detachment is typically painless. Clinical manifestations often include flashes of light in the peripheral visual field, blurred vision, floaters, and darkening vision (like a curtain drawn across a visual field). Diagnostic procedures consist of a history and physical examination (including an ophthalmic examination, often performed by an ophthalmologist). The ophthalmic examination may involve an electroretinogram (a record of the electrical currents in the retina produced by visual stimuli), fluorescein angiography, intraocular pressure measurements, ophthalmoscopy, a refraction test, retinal photography, color discrimination, visual acuity testing, slit lamp examination, and eye ultrasound.

Retinal detachment is a medical emergency requiring immediate treatment. Surgery is often the best treatment option. Surgical options include a cryopexy (intense cold application to the area with an ice probe to form scar tissue, which holds the retina to the underlying layer), laser surgery (to seal the tears or holes in the retina), pneumatic retinopexy (placing a gas bubble in the eye to help the retina float back into place), scleral buckle (indents the eye wall), and vitrectomy (removes gel or scar tissue pulling on the retina). These procedures may be performed alone or in combination with each other.

Ears

A few ear conditions that do not fit the previously discussed categories can occur. These conditions may be manifestations of other problems or happen alone. Most of these conditions are mild, causing only minor issues.

Tinnitus

Tinnitus describes hearing abnormal noises in the ear—noises that may be described as a ringing, buzzing, humming, whistling, roaring, or blowing. Tinnitus is a common problem, affecting approximately 45 million Americans (American Tinnitus Association, 2022). It is not a condition itself but rather a symptom of an underlying issue. Although tinnitus can be bothersome, it does not usually warrant significant concern. Tinnitus may be associated with presbycusis, exposure to excessive noise, cerumen impaction, otosclerosis, Ménière's disease, stress, head injury, acoustic neuroma (a benign tumor on the acoustic nerve), atherosclerosis, hypertension, carotid stenosis, arteriovenous malformation, caffeine, and ototoxic medications (e.g., many antibiotics, aspirin, chemotherapies, and diuretics).

Diagnostic procedures for tinnitus focus on identifying the underlying cause. These procedures may consist of a history, physical examination (including a complete hearing test and otoscopic examination), and additional tests as necessary to identify the cause. Treating the underlying disorder (e.g., removing cerumen and controlling blood pressure) will resolve tinnitus in most cases. If needed, additional strategies may include the following measures:

- Tricyclic antidepressants to reduce tinnitus symptoms
- Alprazolam (Niravam, Xanax), a benzodiazepine, to reduce tinnitus symptoms
- Acamprosate (Campral), a drug used to treat alcoholism, to relieve tinnitus
- Masking tinnitus symptoms with white-noise machines and hearing aids

- Avoiding factors that can worsen tinnitus (e.g., caffeine, smoking, and ototoxic medications)

Vertigo

Vertigo refers to an illusion of motion. It is not the same as dizziness. Dizziness is feeling "lightheaded," or as though one might faint. In contrast, people experiencing vertigo have a sensation that they or the room is spinning or moving. In addition to the sensation of movement, clinical manifestations may include nausea and vomiting.

application to practice

Now that we have discussed the conditions of the sensory function system, let's put that knowledge into practice. While working in a clinic, you encounter the following patients. Which patient would be at greatest risk for developing significant vision problems?

- A postpartum woman
- A young man who has diabetes mellitus
- A middle-aged adult who takes aspirin daily
- An older man with mild presbyopia

When determining who is at greatest risk, start by counting risk factors. The postpartum woman has no significant risk factors that would damage her vision. Now consider the young man with diabetes. Diabetic retinopathy is the number one cause of blindness. The fact that the patient is young means he could have the condition longer, increasing his likelihood of developing vision problems. Moving on to the middle-aged man taking aspirin, this patient has no significant risk factors for vision issues. Finally, consider the older man with mild presbyopia. Increased age is a risk factor for many eye conditions. Mild presbyopia is part of normal aging, however, and does not increase the risk of other conditions. In contrast, severe presbyopia does increase the risk of vision problems. Considering all of these patients, the young man with diabetes is at the highest risk for vision problems. Knowing that, the patient should have an annual eye exam.

Two types of vertigo are distinguished—peripheral and central. Peripheral vertigo occurs when there is a problem with the vestibular labyrinth, semicircular canals, or vestibular nerve. Certain medications (e.g., aminoglycoside antibiotics), head injury, Ménière's disease, nerve compression, infection, and inflammation may cause this type of vertigo. Central vertigo occurs when there is a problem in the

brain, particularly in the brainstem or cerebellum. Arteriosclerosis, certain medications (e.g., antiseizure agents and aspirin), alcohol, migraines, multiple sclerosis, and seizures may cause this type of vertigo.

Diagnostic strategies for vertigo include a history, physical examination, and other tests to determine the underlying etiology (e.g., head CT and MRI). Pharmacology is the mainstay of treatment. The medications used for this purpose include anticholinergic agents, antihistamines (especially meclizine [Antivert]), benzodiazepines, and antiemetics. Safety precautions should also be taken to prevent injury from falls (e.g., changing positions slowly and mobility assistance).

SUMMARY

The sensory organs work together to sense changes in the body's internal and external environment. This information is then relayed to the nervous system for interpretation and response. Disorders of these organs can significantly affect the body's sensory function and can even be life altering. Some of these conditions can be prevented by restricting noise exposure (e.g., wearing protective ear coverings and minimizing music volume) and shielding the eyes (e.g., by wearing protective eye goggles and UV-protective sunglasses). Early diagnosis and treatment of other conditions can improve prognosis.

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APPENDIX A

Normal Lab Values

Cardiac Packet

CPK-MB/CPK relative index	< 2.5%
CPK—total	WM: 60–320 units/L WF: 50–200 units/L BM: 130–450 units/L BF: 60–270 units/L
Glucose	70–110 mg/dL
LDH—total LDH-1	100–190 units/L 14–26%
Troponin 1	Negative

CBC

RBC count	M: 4.5–6.0 million/cc F: 4.0–5.5 million/cc
Hct	M: 40–50% F: 35–45%
Hgb	M: 14–18 g/dL F: 12–16 g/dL
RBC indices MCV MCH	 80–95 μm^3 27–31 pg 32–36 g/dL

MCHC	11–15%
RDW	
WBC count	5,000–10,000/mm^3
Granulocytes	2,500–8,000/mm^3
Neutrophils	50–500/mm^3
Eosinophils	25–100/mm^3
Basophils	
Agranulocytes	1,000–4,000/mm^3
Lymphocytes	100–700/mm^3
Monocytes	
Platelet count	150,000–400,000/mm^3

Chem 7, Chem 12, Chem 20, Hepatic Function Panel, Renal Function Panel, Abdominal Pain Panel

ALP	30–100 units/L
ALT (SGPT)	5–40 units/L
Amylase	50–190 units/L
AST (SGOT)	5–40 units/L
Bilirubin—total	0.1–1.25 mg/dL
Direct	0.1–0.3 mg/dL
Indirect	0.2–1.0 mg/dL
BUN	8–20 mg/dL
Ca^{++}—total	9–11 mg/dL
Ionized	4.25–5.25 mg/dL

Coagulation Tests

Coagulation factors	200–400 mg/dL
I (fibrinogen)	80–120%
II (prothrombin)	
d-Dimer	< 250 mcg/L

FDPs	< 10 mcg/mL
Platelet count	150,000–400,000/mm^3
PT	11–15 s
PTT aPTT	60–80 s 25–40 s
Thrombin time	10–13 s

CSF

Pressure	70–200 mm H_2O
Color	Clear
Protein	10–45 mg/dL
Glucose	45–78 mg/dL
WBCs—total	< 5 cells/mm^3
Neutrophils	0–4%
Lymphocytes	60–80%
Monocytes	20–50%

Electrolyte Panel

Na^+	135–145 mEq/L
K^+	3.5–5 mEq/L
Cl	91–110 mEq/L
CO_2	20–30 mEq/L

Lipid Profile

HDL	M: > 45 mg/dL F: > 55 mg/dL

LDL	60–180 mg/dL
VLDL	25–50%
Total cholesterol	< 200 mg/dL
Triglycerides	M: 40–60 mg/dL F: > 35–135 mg/dL

Toxicology: Toxic Levels

Drug Serum Screen	
Acetaminophen	> 250 mcg/mL
Alcohol Intoxicated Stuporous Comatose	0.1–0.4% 0.4–0.5% > 0.5%
ASA	> 300 mcg/mL
Barbitals Sedatives Anticonvulsants	> 10 mcg/mL > 40 mcg/mL
Carboxyhemoglobin	> 20%
Dilantin	> 20 mcg/mL
Lead	> 40 mcg/mL
Lithium	> 2.0 mEq/L

Drug Urine Screen	
Amphetamine	> 3 mcg/mL
Diet suppressants	> 15 mcg/mL
Dextroamphetamine phenmetrazine	> 50 mcg/mL
Methamphetamine	> 40 mcg/mL

Mercury	> 100 mcg/day

Urinalysis

Volume	750–1,800 cc/day
pH	4.6–8.0
Appearance	Clear
Color	Amber
Specific gravity	1.003–1.030
Osmolality	250–1,000 mOsm/L
Albumin	10–100 mg/day
Amylase	< 17 units/h
Calcium	< 250 mg/day
Creatinine	0.75–1.5 g/day
Glucose	< 500 mg/day
Potassium	25–125 mEq/day
Protein	0–8 mg/dL
Sodium	40–220 mEq/day
Urea nitrogen	10–20 g/day
Uric acid	250–750 mg/day

APPENDIX B

Root Words and Combining Forms

Root Word	Combining Form	Definition	Example
A			
abdomen	abdomin/o	abdomen	abdominocentesis
acanth		thorn	acanthosis
achilles	achill/o	Achilles' heel	achillobursitis
acid	acid/o	acid (pH)	acidosis
acoust	acoust/o	hearing	acoustics
acr	acr/o	extremity	acroarthritis
actin	actin/o	ray	actinodermatitis
acu	acul/o	needle	acupuncture
aden	aden/o	gland	adenosis
adip	adip/o	fat	adipocyte
adren	adren/o	adrenal gland	adrenomegaly
aer	aer/o	air	aerophore
agglutinat	agglutinat/o	clumping	agglutination
albin	albin/o	white	albinuria
albumin	albumin/o	protein	albuminuria
alkali	alkali/o	basic (pH)	alkalosis
all	all/o	other	allochromasia
alveoli	alveol/o	small hole, air sac	alveoloclasia
ambly	ambly/o	dull	amblyopia
ambul	ambul/o	walk	ambulate
ametr	ametr/o	disproportionate	ametropia
amnion	amni/o	amnion	amniocentesis
amyl	amyl/o	starch	amylorrhea
andr	andr/o	man (male)	androgenous
angi	angi/o	vessel	angioplasty
angina	angin/o	choke	anginose

Description

aniso	anis/o	unequal	anisocytosis
ankyl	ankyl/o	stiffened, crooked	ankylosis
anthrac	anthrac/o	coal	anthracosis
antr	antr/o	cavity	antroscopy
anus	an/o	anus	anoscope
aort	aort/o	aorta	aortography
append	append/o	appendix	appendectomy
arachn	arachn/o	spider	arachnoid
arteri	arteri/o	artery	arterial
arthr	arthr/o	joint	arthroscopy
atel	atel/o	imperfect, incomplete	atelectasis
ather	ather/o	fatty	atherosclerosis
atri	atri/o	atrium, chamber	atriomegaly
audi	audi/o	hear	audiology
aur	aur/o	ear	aural
axill	axill/o	armpit	axillary
B			
bacteri	bacteri/o	bacteria	bacteriuria
balan	balan/o	glans	balanitis
bas	bas/o	base (pH)	basophyl
bil	bil/i	gall, bile	biliary
bilirubin	bilirubin/o	bilirubin	hyperbilirubinism
bio	bi/o	lile	biosphere
blephar	blephar/o	eyelid	blepharitis
bol	bol/o	cast, throw	anabolic
brachy	brachy/o	arm	brachyocephalic
bronch	bronch/o	bronchi	bronchitis
bucc	bucc/o	cheek	buccocclusion
burs	burs/o	pouch	bursitis
C			
cac	cac/o	bad, diseased	cachexia
calc	calc/**i**	calcium	calciuria
calcane	calcane/o	heel bone	calcaneodynia
capn	capn/i	smoke, carbon dioxide	hypercapnia
carcin	carcin/o	cancer	carcinoma
cardi	cardi/o	heart	cardioplagia

Description

carp	carp/o	wrist	carpopedal
cata	cat/a	down, downward	catatonic
caud	caud/o	tail	caudal
caus	caus/o	heat	causalgia
cecum	cec/o	cecum	cecoileostomy
celi	celi/o	abdomen	celioma
centr	centr/i	center	centrilobular
cephal	cephal/o	head	cephalhydrocele
cerebell	cerebell/o	little brain (cerebellum)	cerebellospinal
cerebr	cerebr/o	brain (cerebrum)	cerebromalacia
cerumin	cerumin/o	wax	ceruminolysis
cervic	cervic/o	neck	cervicofacial
cheil	cheil/o	lip	cheilosis
chem	chem/o	chemical	chemotherapy
cholangi	cholangi/o	bile vessel	cholangioma
chole	chole/o	gall, bile	cholecystogram
choledoch	choledoch/o	common bile duct	choledochotomy
cholester	cholester/o	cholesterol, fat	cholesterosis
chondr	chondr/o	cartilage	chondrocarcinoma
chori	chori/o	chorion	chorioadenonia
choroid	choroid/o	choroid	choroiditis
cine	cine/o	motion	cineradiography
cinemato	cinemat/o	motion	cinematoradiograph
cirrho	cirrh/o	yellow, tawny	cirrhosis
cis	cis/o	cut	excision
cistern	cistern/o	reservoir, cavity	cisternography
clavic	clavic/o	clavicle	clavicotomy
clavicul	clavicul/o	clavicle	clavicular
cleid	cleid/o	clavicle	cleidorrhexis
cion	clon/o	turmoil	clonogenic
coagul	coagul/o	clot	coagulopathy
coccidioid	coccidioid/o	fungus	coccidioidomycosis
coccyx	coccyg/o	tail bone	coccygodynia
cochle	cochle/o	snail	cochleotopic
coit	coit/o	coming together	coitus

Description

coll	coll/o	glutinous, jelly-like	colragenitis
colon	colon/o	colon	colonoscopy
colp	colp/o	vagina	colporrhaphy
condyl	condyl/o	knuckle	condyloma
coni	coni/o	dust	coniosis
copr	copr/o	feces, excrement	coprostasis
cord	cord/o	cord	cordotomy
coria	cori/o	pupil (eye)	diplocoria
cortic	cortic/o	cortex	corticosterone
cost	cost/o	rib	costosternal
cox	cox/o	hip	coxalgia
crani	crani/o	skull	craniotomy
cretin	cretin/o	cretin	cretinism
crin	crin/o	secrete	endocrinology
crypt	crypt/o	hidden	cryptorchidism
culd	culd/o	cul-de-sac	culdocentesis
cutane	cutan/o	skin	subcutaneous
eyel	eyel/o	ciliary body	cycloplegia
cyst	cyst/o	bladder	cystistaxia
cyt	cyt/o	cell	cytoplasm

D

dacry	dacry/o	tear	dacryoma
dactyl	dactyl/o	finger, toe	dactylospasm
dem	dem/o	people	endemic
dendr	dendr/o	branched	dendrltis
dent	dent/i	tooth	dentifrice
derm	derm/o	skin	dermomycosis
dermat	dermat/o	skin	dermatitis
didym	didym/o	testis	didymalgia
dilat	dilat/o	widen	dilation
dipl	dipl/o	double	diplopia
dips	dips/o	thirst	dipsomania
disk	disk/o	disk	diskectomy
diverticul	diverticul/o	diverticula	diverticulitis
dont	dont/o	tooth	oligodontia
dos	dos/**i**	giving	dosimeter

duoden	duoden/o	duodenum	duodenostomy
dur	dur/o	hard	duroarachnitis
E			
electr	electr/o	electricity	electrocardiogram
embol	embol/o	throwing in	embolism
emmetr	emmetr/o	ideal	emmetropia
emphys	emphys/o	inflate	emphysema
encephal	encephal/o	brain	encephalogram
enter	enter/o	intestine	enteritis
epidem	epidem/o	upon people	epidemic
epididym	epididym/o	epididymis	epididymectomy
episi	episi/o	vulva, pudenda	episiotomy
erythrocyt	erythrocyt/o	red blood cell	erythrocytosis
esophage	esophag/o	esophagus	esophagocele
esthesi	esthesi/o	feeling	anesthesia
F			
fasci	fasci/o	hand	fasciodis
fibr	fibr/o	fiber	fibroma
fibrin	fibrin/o	fiber	fibrinogen
fibul	fibul/o	fibula	fibular
fluor/o	fluor/o	fluorescence	fluoroscopy
foramin	foraml n/o	foramen, opening	foraminotomy
format	format/o	formation	malformation
G			
galact	galact/o	milk	galactorrhea
gangli	gangli/o	knot	ganglionectomy
gastr	gastr/o	stomach	gastritis
gen	gen/o	beginning, origin	genesis
genet	genet/o	producing	genetics
genit	genit/o	genitals	genitourinary
genital	genital/o	genitals	hypogenitalia
ger	ger/o	old age	geriatric
geront	geront/o	aged	gerontology
gigant	gigant/o	giant	gigantism
gingiv	gingiv/o	gums	gingivitis

Description

glandul	glandul/o	little acorn, gland	glandular
glomerul	glomerul/o	little ball	glomerulitis
gloss	gloss/o	tongue	glossopharyngeal
glue	gluc/o	glucose, sugar	glucocorticoid
glye	glyc/o	sugar	glycogenesis
gonad	gonad/o	ovaries, testes	gonadotropin
goni	goni/o	angle	gonioscope
granul	granul/o	granular	granulocyte
gravid	gravid/o	pregnant	primigravida
gynec	gynec/o	female	gynecology
H			
halat	halat/o	breathe	inhalation
hem	hem/o	blood	hemoglobin
hemat	hemat/o	blood	hematocrit
hepat	hepat/o	liver	hepatoma
herni	herni/o	hernia	herniotomy
hidr	hidr/o	sweat	anhidrosis
hirsut	hirsut/o	hair	hirsutism
hist	hist/o	tissue	histology
hoi	hol/o	whole	holography
humer	humer/o	humerus	humeral
hydr	hydr/o	water	hydrocele
hymen	hymen/o	hymen	hymenectomy
hypn	hypn/o	sleep	hypnosis
hyster	hyster/o	womb, uterus	hysterectomy
I			
ichthy	ichthy/o	fish (scaly)	ichthyosis
icter	icter/o	jaundice	icterogenic
ile	ile/o	ileum	ileostomy
ili	ili/o	ilium	iliosacral
immun	immun/o	safe, protect	immunotherapy
insul	insul/o	pancreatic islets	insuloma
insulin	insulin/o	insulin	insulinogenic
ion	ion/o	ion	ionoradioscope
irid	irid/o	iris	iridomalacia

Description

ischem	ischem/o	hold back	ischemic
ischi	ischi/o	hip	ischiodynia
J			
jejun	jejun/o	jejunum	jejunotomy
K			
kary	kary/o	nucleu (cell)	karyotype
kel	kel/o	tumor	keloid
kerat	kerat/o	cornea	keratitis
ket	ket/o	ketone	ketosis
kinesi	kinesi/o	motion	bradykmesia
kinet	kinet/o	motion	kinetosis
kyph	kyph/o	hump	kyphosis
L			
labyrinth	labyrinth/o	maze	labyrinthitis
lacrim	lacrim/o	tear	lacrimotomy
lamin	lamin/o	shin plate	laminectomy
lapar	lapar/o	flank, abdomen	laparotomy
laryng	laryng/o	larynx	laryngoscope
later	later/o	side	lateroflexion
laxat	laxat/o	loosen	laxative
lei	lei/o	smooth	leiomyosarcoma
letharg	letharg/o	drowsiness	lethargy
lingu	lingu/o	tongue	nigralingua
lip	lip/o	fat	lipoatrophy
lith	lith/o	stone	lithotripsy
lob	lob/o	lobe	lobotomy
log	log/o	word, study	logomania
lord	lord/o	bending, curvature	lordosis
lumb	lumb/o	loin	lumbodynia
lymph	lymph/o	lymph, lymph gland	lymphoma
M			
mamm	mamm/o	breast	mammogram
mandibul	mandibul/o	lower jaw	mandibular
mast	mast/a	breast	mastectomy
maxill	maxill/o	upper jaw	maxillotomy

Description

meat	meat/o	passage	meatotomy
mediastin	mediastin/o	mediastinum	mediastinitis
medull	medull/o	marrow, spinal	medulloepithelioma
melan	melan/o	black	melanoma
men	men/o	month, menstruate	dysmenorrhea
mening	mening/o	membrane	meningitis
menisc	menisc/o	crescent shape	meniscitis
metr	metr/o	uterus	metritis
micturit	micturit/o	urinate	micturition
mitr	mitr/o	mitral valve	mitral
morph	morph/o	form, shape	morphology
muc	muc/o	mucus	mucositis
muscul	muscul/o	muscle	musculoskeletal
my	my/o	muscle	myoblast
myc	myc/o	fungus	mycosis
myel	myel/o	spinal cord	myeloma
myring	myring/o	membrane, mucus	myringoplasty
N			
narc	narc/o	night, sleep	narcosis
nas	nas/o	nose	nasogastric
necr	necr/o	death	necrosis
nephr	nephr/o	kidney	nephrema
neur	neur/o	nerve	neuroma
neutr	neutr/o	neither, neutral (pH)	neutrophil
noct	noct/o	night	nocturia
nude	nucle/o	nucleus, central	nuclear
nyct	nyct/o	night	nyctalgia
nyctal	nyctal/o	blind, night	nyctalopia
0			
ocul	ocul/o	eye	oculopupillary
olecran	olecran/o	elbow	olecranarthopathy
oment	oment/o	omentum	omentectomy
omphal	omphal/o	umbilicus	omphalitis
one	onc/o	tumor	oncology
onych	onych/o	nail	onychitis
oophor	oophor/o	ovary	oophoritis

Description

ophthalm	ophthalm/o	eye	ophthalmopathy
opt	opt/o	eye	optomyometer
orchi	orchi/o	testicle	orchitis
orchid	orchid/o	testicle	orchidopexy
organ	organ/o	organ	organomegaly
oscill	oscill/o	swing	oscillopsia
osm	osm/o	smell	anosmia
oste	oste/o	bone	osteorrhapy
ot	ot/o	ear	otosclerosis
ov	ov/**i**, ov/o	egg	oviduct, ovoplasm
ovul	ovul/o	egg, ovum	ovulate
ox	ox/o	oxygen	anoxia
oxy	oxy/o	oxygen	oxytocin
P			
palat	palat/o	palate	palatitis
pancreat	pancreat/o	pancreas	pancreatitis
papill	papill/o	papilla	papilledema
par	par/o	bear	paroxysm
parathyr	parathyr/o	parathyroid gland	parathyroidism
patell	patell/o	patella, kneecap	patellapexy
path	path/o	disease	pathology
ped	ped/o	foot	pedal
ped	ped/i	child	pediatrics
pedicul	pedicul/o	louse	pediculosis
pen	pen/o	penis	penitis
pept	pept/o	digest	peptogenic
perine	perine/o	perineum	perineocele
phac	phac/o	lens	phacosclerosis
phag	phag/u	eat, engulf	phagocyte
phalange	phalang/o	finger, toe	phalangectomy
pharmac	pharmac/o	drug	pharmacotherapy
pharyng	pharyng/o	pharynx	pharyngitis
phe	phe/o	dusky, muzzle	pheochromocytoma
phim	phlm/o	muscle	phimosis
phleb	phleb/o	vein	phlebitis

Description

phon	phon/o	sound, voice	phonopathy
phragm	phragm/o	partition	diaphragm
phragma	phragmat/o	partition	diaphragmatocele
phren	phren/o	diaphragm	phrenoplegia
physi	physi/o	nature	physiology
physic	physic/o	nature	physician
pin	pin/o	drink, pinlitary gland	pinocytosis
pineal	pineal/o	pineal body	pinealoma
pituitar	pituitar/o	pituitary gland	pituitarism
pleur	pleur/o	pleura	pleuritis
pneum	pneum/o	air	pneumothorax
pneumon	pneumon/o	lung	pneumonitis
poikil	poikil/o	irregular shape, passage	poikilocytosis
por	por/o	passage	poroma
porphyr	porphyr/o	porphyrin, purple	porphyrinuria
presby	presby/o	old	presbycusis
proct	proct/o	rectum, anus	proctatectomy, proctalgia
prostat	prostat/o	prostate	prostatectomy
psych	psych/o	mind	psychology
pteryg	pteryg/o	winglike	pterygomandibular
ptyal	ptyal/o	saliva	ptyalorrhea
pub	pub/o	pubis	pubovesical
pulm	pulm/o	lung	pulmometer
pulmon	pulmon/o	lung	pulmonectomy
pupill	pupill/o	pupil	pupillary
py	py/o	pus	pyorrhea
pyel	pyel/o	renal pelvis	pyelonephritis
pylor	pylor/o	pyloris	pyloroplasty
pyr	pyr/o	fire	pyrogenic
pyret	pyret/o	fever	pyretogenic
R			
rachi	rachi/o	spine	rachiomyelitis
radi	radi/o	ray, radius	radionecrosis
radiat	radiat/o	radiant	radiation
radic	radic/o	root	radicotomy
radicul	radicul/o	root	radiculitis

Description

rect	rect/o	rectum, loosen	rectocele, relaxation
ren	ren/o	kidney	renogastric
reticul	reticul/o	net, network	reticulocyte
retin	retin/o	retina	retinitis
rhabd	rhabd/o	rod	rhabdomyoma
rhin	rhin/o	nose	rhinorrhagia
rhythm	rhythm/o	rhythm	arrhythmia
rhytid	rhytid/o	wrinkle	rhytidectomy
S			
sacr	sacr/o	sacrum	sacrodynia
salping	salping/o	tube	salpingopexy
sanguin	sanguin/o	blood	consanguinity
sarc	sarc/o	flesh	sarcoma
seapul	seapul/o	scapula	scapulopexy
schiz	schiz/o	split	schizophrenia
scler	scler/o	hard, fibrous	scleroderma
scoli	scoli/o	curvature	scoliosis
scot	scot/o	dark	scotoma
seb	seb/o	oil	seborrhea
senil	senil/o	old	senilism
ser	ser/o	serum	serology
sial	sial/o	saliva	sialadenitis
sid	sid/o	iron	sideropenia
sigmoid	sigmoid/o	sigmoid, colon	sigmoidoscope
sin	sin/o	curve	sinoatrial
sit	sit/o	foot	sitotherapy
somat	somat/o	body	somatotropic
somn	somn/o	sleep	somnambulism
son	son/o	sound	sonogram
sperm	sperm/o	seed	spermolysis
spermat	spermat/o	seed	spermatocyst
sphincter	sphincter/o	closure	sphincteroplasty
sphygm	sphygm/o	pulse	sphygmomanometer
spin	spin/o	thorn, spine	spinocerebellar
spir	spir/o	breath	spirometer

Description

spir	spir/o	coil	spiradenoma
splen	spler/o	spleen	splenectomy
spondyl	spondyl/o	vertebra	spondylitis
staped	staped/o	stapes, stirrup	stapedectomy
staphyl	staphyl/o	cluster, uvula	staphyloplasty
steat	steat/o	fat	steatolysis
sten	sten/o	narrowing	stenosis
stern	stern/o	sternum	sternalgia
steth	steth/o	chest	stethoscope
stigmat	stigmat/o	point	stigmatism
stomat	stomat/o	mouth, opening	stomatitis
strept	strept/o	chain	streptococcus
sympath	sympath/o	sympathy	sympathectomy
syphil	syphil/o	syphilis	syphilopsychosis

T

tars	tars/o	ankle bone	tarsectomy
ten	ten/o	tendon	tenorrhagia
tendin	tendin/o	tendon	tendinitis
tendon	tendon/o	tendon	tendonitis
terat	terat/o	monster	teratoma
test	test/o	testis	testalgia
thalass	thalass/o	sea	thalassemia
than	than/o	death	euthanasia
thel	thel/o	nipple	thelorrhagia
therm	therm/o	heat	hydrothermic
thromb	thromb/o	blood clot	thrombosis
thym	thym/o	thymus	thymopexy
thyr	thyr/o	thyroid	thyroptosis
tibi	tibi/a	tibia	tibial
tinnit	tinnit/o	jingling	tinnitus
toe	toc/o	birth	tocology
tom	tom/o	cut	tomography
ton	ton/o	tone, tension	tonography
tonsill	tonsill/o	tonsil	tonsillitis
top	top/o	place	topography
torti	torti/o	twisted	torticollis

Description

toxic	toxic/o	poison	toxicology
trache	trache/o	trachea	tracheostomy
traumat	traumat/o	wound, injure	traumatology
trephinat	trephinat/o	bore	trephination
trich	trich/o	hair	trichomycosis
trigon	trigon/o	trigone	trigonitis
trap	trop/o	turn	neurotropism
tubercul	tubercul/o	swelling	tuberculosis
tympan	tympan/o	drum	tympanitis
U			
ul	ul/o	scar	ulectomy
ulcer	ulcer/o	surface excavation	ulcerogenic
uln	uln/o	elbow	ulnad
ungu	ungu/o	nail	ungula
ur	ur/o	urine	uremia
ureter	ureter/o	ureter	ureterolith
urethr	urethr/o	urethra	urethrocystitis
urin	urin/**i**	urine	uriniparous
urinat	urinat/o	urine	urination
uter	uter/o	uterus	uteralgia
uve	uve/o	uvea	uveitis
V			
vag	vag/o	vagus nerve, wandering	vagotomy
vagin	vagin/o	vagina	vaginectomy
varic	varic/o	twisted vein	varicocele
vas	vas/o	vessel, duct	vasotripsy
vascul	vascul/o	small vessel	vasculopathy
vector	vector/o	carrier	vectorcardiogram
ven	ven/o	vein	venostasis
vener	vener/o	desire, love (sexual intercourse)	venereal
veni	veni/o	vein	venisuture
ventricul	ventricul/o	ventricle	ventriculitis
vertebr	vertebr/o	vertebra	vertebrectomy
vertig	vertig/o	dizziness, vesicle	vertigo
vesic	vesic/o	vesicle	vesicocele

Description

vesicul	vesicul/o	vesicle	vesiculotomy
vir	vir/o	virus	viruria
viril	viril/o	masculine	virilism
viscer	viscer/o	body organs	viscerogenic
vitamin	vitamin/o	vitamin	hypervitaminosis
vitre	vitre/o	vitreous humor	vitreous
vulv	vulv/o	vulva	vulvovaginitis
X			
xanth	xanth/o	yellow	xanthemia
xen	xen/o	alien, foreign	xenophobia
xiph	xiph/o	sword	xiphoid
Z			
zo	zo/o	animal	zooderma
zon	zon/o	encircling area	zonesthesia
zyg	zyg/o	joined	zygodactyly

Description

Glossary

achlorhydria

Decrease in stomach acid production, occasionally because of atrophic gastritis.

acne vulgaris

A skin condition that commonly affects adolescents but can occur at any age. In this condition, the skin's pores become clogged with oil, debris, or bacteria. The pore can become inflamed, developing a pustule, nodule, or cyst.

acquired immunity

Immunity that results from subsequent exposures to an antigen because memory cells recall the antigen as foreign and antibody production occurs rapidly.

acromegaly

Increase in bone size caused by excessive growth hormone levels in adulthood.

actin

One of two types of myofilaments. It is involved in muscular contractions, cellular movement, and cell shape maintenance.

action potential

The creation of neural charges.

active acquired immunity

The immunity gained by actively obtaining an antigen through invasion or vaccination. In active immunity, a person makes his or her own antibodies, and protection is usually long term.

active infection

Phase that occurs when the primary infection can no longer be controlled, and clinical manifestations are generally apparent. It is often used in describing tuberculosis progression. During this phase, tuberculosis can spread throughout the lungs and to other organs.

active transport

The movement of a substance from an area of lower concentration to an area of higher concentration, against a concentration gradient.

acute

Regarding disease, a condition that is short term in nature, occurring and resolving quickly.

acute bronchitis

An inflammation of the tracheobronchial tree or large bronchi, most commonly caused by a wide range of viruses. The airways become inflamed and narrowed due to the results of the inflammatory process.

acute gastritis

Type of gastritis that usually develops suddenly and is likely to be accompanied by nausea and epigastric pain. It can take the form of either a mild, transient irritation or a severe ulceration with hemorrhage.

acute lung injury (ALI)

A slightly less severe form of acute respiratory distress syndrome.

acute renal failure (ARF)

A sudden loss of renal function. This loss is generally reversible and is most common in critically ill, hospitalized patients. Also called acute kidney injury.

acute respiratory distress syndrome (ARDS)

A sudden failure of the respiratory system, often occurring from fluid accumulation in the alveoli. ARDS has many other names, such as “shock lung,” “wet lung,” and “stiff lung.”

acute respiratory failure (ARF)

A serious, life-threatening condition that can result from many pulmonary disorders. Oxygen levels become dangerously low, or carbon dioxide levels become dangerously high. The low oxygen levels are unable to meet the body’s metabolic needs.

acute tissue rejection

The most common and treatable type of tissue rejection. This type of rejection usually occurs between 4 days and 3 months following a transplant. Acute reactions are cell mediated and result in transplant cell destruction (lysis) or necrosis.

adaptation

Method by which cells attempt to prevent their own death from environmental changes. They may modify their size, numbers, or types in an attempt to manage these changes and maintain homeostasis.

adaptive or acquired defenses

Immunity that results in antibody development in response to antigen.

Addison's disease

A condition resulting from a deficiency of adrenal cortex hormones.

adrenal gland

Gland with an inner portion and an outer portion that is located on a kidney.

afferent arteriole

Point at which the blood enters the glomerulus.

afferent nerve

A type of nerve of the peripheral nervous system, which carries impulses from the body to the brain. Also called *sensory nerve.*

afferent tract

Fibers that carry sensory information in the form of action potentials from the periphery back to the brain. Also called *ascending fibers.*

afterload

The pressure the left ventricle must exert to get the blood out of the heart and into the aorta. The higher the afterload, the harder it is for the heart to eject the blood, thus lowering stroke volume and increasing blood pressure.

AIDS dementia complex

Dementia that occurs in the later stages of acquired immunodeficiency syndrome (AIDS). The human immunodeficiency virus (HIV) invades the brain tissue and may be exacerbated by other infections and tumors that are frequently associated with AIDS. Also called *HIV-associated encephalopathy*.

alarm

The first stage of the general adaptation syndrome, which includes the generalized stimulation of the sympathetic nervous system, resulting in the release of catecholamines and cortisol. Also known as the fight-or-flight response.

albinism

A recessive condition that results in little or no melanin production.

aldosterone

A hormone secreted by the adrenal cortex that increases blood volume by increasing the reabsorption of sodium in the kidneys; sodium attracts water. Increasing water reabsorption will increase blood volume. Aldosterone is the principal mineralocorticoid.

allele

One gene may have many variants, which determines a characteristic.

allogeneic

Type of transplant in which tissue is used from the same species and is of similar tissue type but is not identical. Most transplants use allogeneic tissue.

alpha cell

One of five types of cells in the islets of Langerhans; it secretes glucagon.

alveolus (plural: alveoli)

A hollow, saclike structure that is the final branching of the respiratory tree and acts as the primary gas exchange unit of the lung.

Alzheimer's disease (AD)

The most common form of dementia. It causes healthy brain tissue to degenerate and atrophy.

amblyopia

The loss of one eye's ability to see details. Amblyopia is the most common cause of vision problems in children. It occurs when the brain and eyes do not work together properly; the brain favors one eye. Also called "lazy eye."

amenorrhea

The absence of menstruation.

ammonia

A metabolic waste managed by the kidneys. This highly toxic product results from the breakdown of amino acids in the liver.

amphiarthrosis

A slightly moveable joint that can be seen in the vertebral column.

ampulla

A pouch that joins the seminal vesicles to form the ejaculatory duct in the male reproductive system. Stores semen and contributes secretions to it.

amylin

Substance that is released from the beta cells along with insulin. Amylin has a synergistic relationship with insulin to control glucose.

amyotrophic lateral sclerosis (ALS)

A disease that involves damage of the upper motor neurons of the cerebral cortex and lower motor neurons of the brainstem and spinal cord. Also called "Lou Gehrig's disease" after the famous baseball player who died of it.

anaphase

Phase of mitosis in which chromosomes separate and move to opposite poles.

anaphylactic shock

Type of distributive shock that is a consequence of an allergic reaction. The allergic reaction leads to a cascade of events similar to that of septic shock, except the mediators differ. Additionally, bronchospasms and laryngeal edema that can impair the patient's respiratory status occur.

anaplasia

The loss of cell differentiation that occurs with cancer.

anasarca

Edema that is generalized throughout the body.

anemia

A common acquired or inherited disorder of the erythrocytes that impairs the oxygen-carrying capacity of the blood.

aneurysm

Condition of the walls of an artery caused by high pressures, plaque, and infections. The artery walls weaken and balloon outward.

angina

Chest pain with a cardiac origin.

anion

A negatively charged electrolyte.

anion gap

The difference between the sum of cations and anions found in plasma.

ankylosing spondylitis

A progressive inflammatory disorder affecting the sacroiliac joints, intervertebral spaces, and costovertebral joints.

ankylosis

Joint fixation and deformity.

anotia

The absence of the auricle.

anteflexed

Tilted forward. Usually used in reference to the uterus.

anterior chamber

The cavity of the eye interior that is in front of the lens.

antibody-producing cell

Type of B cell that produces millions of antibody molecules during its 24-hour life span.

antidiuretic hormone (ADH)

Hormone secreted by the posterior pituitary gland that increases water reabsorption in the kidney, which in turn increases blood volume and blood pressure. It is also a vasoconstrictor.

antigen

A foreign agent that triggers an immune reaction.

aorta

The largest artery in the body, which originates from the left ventricle.

aortic valve

A three-leaflet valve that guides the passage of blood from the left ventricle to the aorta and prevents the backward flow of blood.

apocrine gland

Gland that opens into hair follicles in the axillae, scalp, face, and external genitalia.

apoptosis

Mechanism of programmed cell death that occurs because of morphologic changes in cells.

appendicitis

An inflammation of the vermiform appendix. The inflammation can be life threatening and is most often caused by an infection.

appendicular skeleton

One of the two divisions of the human skeleton. It consists of bones that form the arms, shoulders, pelvis, and legs.

appendix

A small, wormlike structure attached to the cecum with seemingly no function but plenty of potential to cause harm if it becomes inflamed.

aqueous humor

Watery liquid in the anterior chamber of the eye that provides nutrients to the cornea and lens and carries away cellular waste products.

arachnoid layer

The middle layer of the meninges, named for its spider web–like vascular system.

areola

An area of pigmentation surrounding the nipple of the breast.

areolar gland

Gland that produces secretions that protect and lubricate the nipple and areola of the breast during breastfeeding.

arrhythmia

Deviations from normal electric conduction in the heart. Arrhythmias vary in severity and are classified according to their origins. Also called *dysrhythmia.*

arterial blood gas (ABG)

The long-standing principal diagnostic tool for evaluating acid–base balance. It measures pH and the levels of oxygen and carbon dioxide in arterial blood.

arteriole

Small blood vessel that branches off arteries near the heart.

artery

A blood vessel that carries blood away from the heart.

ascending fibers

Fibers that carry sensory information in the form of action potentials from the periphery back to the brain. The ascending fibers have a variety of tracts that communicate specific sensory input. Also called *afferent tracts*.

ascending testicle

A testicle that has returned to the lower abdomen and cannot easily be guided back into the scrotum. Also called “acquired undescended testicle.”

ascites

Fluid that accumulates in the peritoneal cavity.

aspiration

The entrance of food into the trachea and lungs.

aspiration pneumonia

Type of pneumonia that frequently occurs when the gag reflex is impaired because of a brain injury or anesthesia. It can also occur because of impaired lower esophageal sphincter closure

secondary to nasogastric tube placement or disease (e.g., gastroesophageal reflux disease). The introduction of gastric secretions or other substances into the lungs damages the tissue and triggers the inflammatory reaction.

asthma

A chronic pulmonary disease that produces intermittent, reversible airway obstruction. It is characterized by acute airway inflammation, bronchoconstriction, bronchospasm, bronchiole edema, and mucus production. Asthma is the most common chronic illness in children.

atelectasis

Incomplete alveolar expansion or collapse of the alveoli. It occurs when the walls of the alveoli stick together.

atherosclerosis

A chronic inflammatory disease characterized by thickening and hardening of the arterial wall. Lesions (or plaques) composed of lipids develop on the vessel wall and calcify over time. Development of these lesions causes vessel obstruction, platelet aggregation, and vasoconstriction.

atopic dermatitis

A chronic inflammatory skin condition triggered by an allergen.

atresia

A condition in which a body passage is closed or missing. It includes lack of the valve opening in the heart to allow blood flow (pulmonary atresia) and lack of an external ear canal (aural atresia).

atrial natriuretic peptide

A hormone released when the atria of the myocardium is overstretched, indicating increased fluid volume.

atrioventricular (AV) node

The area of the heart located between the atria and the ventricles that receives impulses from the sinoatrial node. The impulses are delayed or move slowly through the atrioventricular node to allow for complete ventricular filling. This area can initiate impulses if the sinoatrial node begins failing.

atrophic gastritis

Stomach condition caused by shrinkage and inflammation of the stomach lining.

atrophy

State that occurs because of decreased work demands on a cell. When cellular work demands decrease, the cells decrease in size and number.

aura

An unusual sensation (e.g., smells, tastes, or visual hallucinations) that occurs just prior to an impending seizure. Some people with focal seizures, especially complex focal seizures, may experience auras. These auras are actually simple focal seizures in which the person maintains consciousness.

auricle

The irregularly shaped cartilage that channels sound into the ear. Also referred to as the *pinna*.

autoimmune

Type of reaction in which the body's normal defenses become self-destructive—recognizing self as foreign.

autologous

Type of transplant in which the host and the donor are the same person, such as when someone donates his or her own blood prior to a scheduled surgery and then receives it during the surgery.

automaticity

A process whereby cardiac cells generate an impulse to contract even with no external nerve stimulus.

automatism

Strange, repetitious behavior exhibited by a person having a complex focal seizure.

autonomic hyperreflexia

A massive sympathetic response that can cause headaches, hypertension, tachycardia, seizures, stroke, and death; most commonly associated with spinal cord injuries above the sixth thoracic vertebra.

autonomic nervous system

System that controls smooth muscles and is responsible for the fight-or-flight response.

autoregulation

A mechanism to maintain tissue perfusion in which the blood vessels dilate to increase blood flow and constrict if the intracranial pressure is increased.

autosomal dominant

Type of disorder in which a single gene mutation is passed from an affected parent to an offspring regardless of sex. Autosomal dominant disorders occur with homozygous and heterozygous allele pairs.

autosomal recessive

Type of disorder in which single gene mutations are passed from an affected parent to an offspring regardless of sex but occur only in homozygous allele pairs.

autosome

A paired set of chromosomes in deoxyribonucleic acid (DNA).

axial skeleton

One of two divisions of the human skeleton. It forms the long axis of the body and includes the skull, vertebral column, and rib cage.

axon

A projection of a neuron that makes connections with nearby cells. Axons transmit impulses away from the cell body.

azotemia

A buildup of waste products.

B cell

A cell that is a major part of the body's defense. B cells mature in the bone marrow, where they differentiate into memory cells or immunoglobulin-secreting (antibody) cells. B cells eliminate bacteria, neutralize bacterial toxins, prevent viral reinfection, and produce immediate inflammatory response. Each B cell has receptor sites for a specific antigen; when it encounters the antigen, the B cell becomes activated and multiplies into either an antibody-producing cell or a memory cell.

bacterial pneumonia

A form of pneumonia that is more severe than viral pneumonia and can result from viral pneumonia.

baroreceptor

Receptor in the carotid artery that detects the pressure in the heart and arteries.

Bartholin glands

Glands that lie just within the labia minor and provide lubrication during sexual intercourse.

basal ganglion (plural: ganglia)

A key structure deep within the cerebrum, diencephalon, and midbrain. The basal ganglia play a pivotal role in coordination, motor movement, and posture.

base excess/deficit

The concentration of buffer—in particular, bicarbonate. Positive values indicate an excess of base or a deficit of acid. Negative values indicate a deficit of base or an excess of acid.

basilar skull fracture

A fracture located at the base of the skull and usually accompanied by cerebrospinal fluid leakage.

benign

Near-normal differentiated condition of a cell or tumor, which causes fewer problems than an abnormal cell or tumor. Benign cells are usually encapsulated and are unable to metastasize.

benign prostatic hyperplasia (BPH)

A common, nonmalignant enlargement of the prostate gland that occurs as men age.

beta cell

One of five types of cells in the islets of Langerhans; it secretes insulin.

bicarbonate–carbonic acid system

A buffer mechanism that is the largest system in the extracellular fluid. Carbonic acid and bicarbonate (base) are the key players in this system.

bile

A green or yellowish liquid that contains water, bile salts (formed from cholesterol), conjugated bilirubin, cholesterol, and electrolytes (including bicarbonate).

birthmark

A skin anomaly that is present at birth or shortly after.

bladder

A reservoir where urine is held until excretion.

bladder cancer

Any cancer that forms in the tissue of the bladder.

bone

A specialized form of connective tissue. This living, metabolically active tissue is the site of fat and mineral storage (especially calcium) as well as hematopoiesis.

bone marrow

Soft fatty tissue found inside bones.

Bowman capsule

A double-membrane chamber that surrounds the glomerulus.

brain

Organ located within the skull that contains billions of neurons.

brainstem

Part of the central nervous system that includes the pons, cerebellum, and medulla. It connects the brain to the spinal cord. The brainstem is crucial for many basic body functions, and injury to this structure can easily result in death.

breast cancer

Cancer of the breast; the most common malignancy in women, and the second leading cause of cancer death in women.

bronchiole

Part of the lung that controls airflow.

bronchiolitis

A common viral infection of the bronchioles, most frequently caused by the respiratory syncytial virus. The infection most often occurs in children younger than 1 year of age, and incidence increases in the fall and winter months.

bronchopneumonia

The most frequent type of pneumonia. It is generally a patchy pneumonia throughout several lobes.

bronchus (plural: bronchi)

Large tube leading from the trachea to the lungs that carries air to and from the lungs.

bundle branches

Specialized cardiac muscle cells that branch off the bundle of His to conduct electrical impulses through the ventricles.

bundle of His

Collection of specialized cardiac muscle cells that conduct electrical impulses from the atrioventricular node.

burn

A skin injury that can result from a thermal or a nonthermal source. These sources may include dry heat, wet heat, radiation, friction, heated objects, natural or artificial ultraviolet light, electricity, and chemicals.

café au lait spot

Common type of birthmark that is the color of coffee with milk.

calcitonin

Hormone secreted by the thyroid that regulates serum calcium levels. It alters serum calcium levels by inhibiting osteoclast activity and stimulating osteoblast activity.

calcium

The most abundant mineral in the body. It is necessary for bone and teeth formation, muscle contractility, coagulation, and other body processes.

callus

A mass of cells and fibers that bridges broken bone ends together inside and outside.

calyx (plural: calyces)

Tube through which urine drains from the renal pyramid of the medulla to the renal pelvis for excretion through the ureters.

cancer

The disease state associated with uncontrolled cellular growth. Key features include rapid, uncontrolled proliferation and a loss of differentiation.

candidiasis

A yeast infection caused by the common fungus *Candida albicans*.

capillary

Small branching vessels that connect arterioles and venules. Additionally, carbon dioxide and waste products are passed from the cells into the capillaries.

carbuncle

A cluster of boils (or *furuncles*).

carcinogenesis

The process by which cancer develops. It occurs in three phases: initiation, promotion, and progression.

cardiac muscle

Type of muscle that constitutes the heart and is under involuntary control.

cardiac output

The amount of blood the heart pumps in 1 minute. Cardiac output (CO) is determined by stroke volume (SV) and heart rate (HR) (CO = SV × HR).

cardiac tamponade

Condition that results when fluid accumulates in the pericardial cavity to the point that it compresses the heart. This compression prevents the heart from filling during diastole, resulting in decreased cardiac output.

cardiogenic shock

Type of shock in which the left ventricle cannot maintain adequate cardiac output. Compensatory mechanisms of heart failure are triggered; however, these mechanisms increase cardiac workload and oxygen consumption, resulting in decreased contractility. Consequently, tissue and organ perfusion decrease, leading to multisystem organ failure.

cardiomyopathy

A group of conditions affecting the myocardium. Cardiomyopathies are classified into three groups: dilated, hypertrophic, and restrictive.

cartilage

A shiny connective tissue that is tough and flexible. Several types of cartilage can be found throughout the body in the ears, nose, bones, and joints.

caseous necrosis

Type of necrosis that occurs when the necrotic cells disintegrate, but the cellular debris remains present for months or years.

cataract

Opacity or clouding of the lens of the eye.

cation

A positively charged electrolyte.

cauda equina

Individual nerve roots of the spinal cord at the vertebral canal.

cauda equina syndrome

Injury to the nerve roots in the area of the cauda equina.

cecum

A pouch at the end of the small intestine.

celiac disease

An inherited, autoimmune, malabsorption disorder. Also called celiac sprue.

cell membrane

The semipermeable boundary containing the cell and its components.

cellulitis

An infection deep in the dermis and subcutaneous tissue. Cellulitis usually results from a direct invasion through a breach in the skin, especially those breaches where contamination is likely.

central nervous system (CNS)

Body system made up of the brain and spinal cord.

cerebellum

Part of the brainstem that communicates with other regions of the brain to coordinate the synergistic motion of muscle movement and balance as well as cognition.

cerebral aneurysm

A localized outpouching of a cerebral artery. This weakening of the artery may either occur as a congenital defect or develop later in life.

cerebral contusion

A bruising of the brain with rupture of small blood vessels and edema. Most contusions result from a blunt blow to the head that causes the brain to make a sudden impact with the skull.

cerebral palsy (CP)

A group of nonprogressive disorders that appear in infancy or early childhood and permanently affect motor movement and muscle coordination. In addition to motor dysfunction, other cerebral functioning may be affected.

cerebrospinal fluid (CSF)

A plasmalike liquid that fills the space between the arachnoid and pia mater layers of the brain to provide additional cushioning and support to the central nervous system.

cerebrovascular accident (CVA)

An interruption of cerebral blood supply. A CVA is an infarction of the brain, so it is often referred to as a “brain attack.” Also called “stroke.”

cerebrum

The largest region of the brain; it controls the higher thought processes (e.g., those that interpret touch, vision, and hearing,

as well as speech, reasoning, emotion, learning, and fine control of movement).

cervical cancer

Cancer of the cervix. The Pap smear can detect precancerous changes. Procedures can be performed to remove these precancerous cells, limiting the likelihood of these changes progressing to permanent malignant changes.

cervix

The narrow opening from the vagina to the uterus.

chancre

An infected ulcerative lesion often associated with sexually transmitted infections, such as genital herpes.

chemoreceptor

A receptor that detects chemical changes in the blood.

chlamydia

One of the most prevalent sexually transmitted infections; caused by *Chlamydia trachomatis*.

chloride

A mineral electrolyte and the major extracellular anion. Chloride assists in fluid distribution by attaching to sodium or water.

cholecystitis

Inflammation or infection in the biliary system caused by calculi.

cholelithiasis

Gallstones; a common condition that affects both genders and all ethnic groups relatively equally.

chondrosarcoma

A slow-growing tumor that begins in cartilage cells that are commonly found on the ends of bones.

chordee

A downward curvature of the penis.

chorea

Uncontrolled rapid, jerky movements.

choroid

The part of the middle layer of the eye that contains melanin, which absorbs stray light.

chromosome

A threadlike structure of deoxyribonucleic acid (DNA) and protein found in the nucleus of most living cells. Carries genetic information (i.e., genes).

chronic

State that occurs when an acute disease does not resolve in a short period of time. A chronic disease often has fewer notable signs than an acute disease, and it occurs over a longer period of time. Chronic diseases might not ever resolve but may become manageable.

chronic bronchitis

An obstructive respiratory disorder characterized by inflammation of the bronchi, a productive cough, and excessive mucus production. Chronic bronchitis differs from acute bronchitis in that the chronic type is not necessarily caused by an infection, and symptoms persist longer.

chronic gastritis

Type of gastritis that develops gradually and is likely to be accompanied by a dull epigastric pain and a sensation of fullness after minimal intake. It can be asymptomatic.

chronic kidney disease

A gradual loss of renal function that is irreversible.

chronic obstructive pulmonary disease (COPD)

A group of chronic respiratory disorders characterized by irreversible, progressive tissue degeneration and airway obstruction.

chronic overdistention

Condition caused by a perceived inability to interrupt work to void. This chronic avoidance of emptying the bladder results in detrusor muscle areflexia and overflow incontinence. Also called “nurse’s bladder” and “teacher’s bladder.”

chronic tissue rejection

Type of tissue rejection that occurs from about 4 months to years after the transplant. This reaction is most likely due to an antibody-mediated immune response. Antibodies and complement proteins become deposited in the transplanted tissue vessel walls, resulting in decreased blood flow and ischemia.

chronotropic

Affecting the rate of contraction.

Chvostek sign

An indicator of hypocalcemia in which a spasm or brief contraction of the corner of the mouth, nose, eye, and muscles in the cheek results from tapping the facial nerve in front of the ear.

chyme

A mixture of food that has been chemically digested and churned in the stomach.

ciliary body

The part of the middle layer of the eye that contains smooth muscle fibers that control the shape of the lens and enable it to focus on incoming light.

cilium (plural: cilia)

Organelle that moves in a wavelike motion to propel mucus and trapped particles upward to the mouth where they can be expectorated.

cirrhosis

Chronic, progressive, irreversible, diffuse damage to the liver resulting in decreased liver function.

cleft lip

Congenital defect that results from failure of the maxillary processes and nasal elevations or upper lip to fuse during development. It may occur with a cleft palate. A cleft lip and palate can affect the appearance of one's face and may lead to problems with feeding, speech, ear infections, and hearing.

cleft palate

An opening between the oral cavity and the nasal cavity. It may occur with a cleft lip. A cleft lip and palate can affect the appearance of one's face and may lead to problems with feeding, speech, ear infections, and hearing.

clitoris

Part of the vulva formed by the connection of the two labia minor. The clitoris is sensitive to stimulation and becomes filled with blood during sexual arousal. It contains two corpora cavernosa, similar to the penis.

closed-angle glaucoma

Type of glaucoma that results from a sudden blockage of aqueous humor outflow; it is a medical emergency.

closed fracture

Type of fracture in which the skin is intact.

coagulative necrosis

Type of necrosis that usually results from an interruption in blood flow.

cochlea

A spiral-shaped structure in the inner ear that houses the organ of Corti.

colon

Part of the lower gastrointestinal tract that makes up most of the large intestine. The colon has three relatively straight sections (ascending, transverse, and descending). It absorbs 90% of the water and electrolytes that enter this structure.

colorectal cancer

Cancer of the colon and/or rectum.

comminuted fracture

A fracture characterized by multiple fracture lines and bone pieces.

comminuted skull fracture

A skull fracture characterized by several fracture lines.

communicating hydrocephalus

Cerebrospinal fluid accumulation that occurs when the fluid is not properly absorbed by the bloodstream.

community-acquired pneumonia

Pneumonia that is acquired outside the hospital or healthcare setting.

compact bone

The hard outer surface of a bone.

compartment syndrome

A serious condition that results from pressure increases in a body compartment, usually the muscle fascia in the case of fractures. The pressure impinges on the nerves and blood vessels contained within the compartment, potentially compromising the distal extremity.

compensatory mechanism

Physiologic response to homeostatic imbalance in an attempt to maintain normalcy.

complete fracture

Type of fracture in which the bone is broken into two or more separate pieces.

complication

A new problem that arises as a result of a disease.

compound skull fracture

A skull fracture where brain tissue is exposed.

compression fracture

Type of fracture in which the skin is broken. The bone fragments or edges may be angled and protrude out of the skin. Compound fractures are associated with more damage to soft tissue and carry a greater risk for infection. Also called *open fracture*.

concussion

A momentary interruption of brain function. Concussions usually result from a mild blow to the head that causes sudden movement of the brain, disrupting neurologic functioning. Concussions may or may not lead to a loss of consciousness.

Amnesia, confusion, sleep disturbances, and headaches may follow a concussion for a period of weeks or months.

conductivity

The ability of cells to conduct electrical impulses.

condyloma acuminatum (plural: condylomata acuminata)

Benign genital wart caused by the group of viruses called *human papillomaviruses*.

cone

A photoreceptor in the eye that operates in bright light and is responsible for visual acuity and color vision. There are approximately 6 million cones in the human eye.

congenital

Conditions involving defects or damage to a developing fetus.

congenital cataract

A clouding of the usually clear lens of the eye that is present at birth. It results in hazy vision.

congenital glaucoma

Type of glaucoma that is present at birth. It is a result of abnormal development of outflow channels (trabecular meshwork) of the eye.

congenital hearing loss

Loss of hearing that can occur because of damage associated with maternal rubella and syphilis infection during pregnancy.

conjunctiva

A fragile membrane that covers the inner surface of the eyelid and the exposed surface of the eye.

conjunctivitis

An infection or inflammation of the conjunctiva, the lining of the eyelids and sclera.

constipation

A change in bowel pattern characterized by infrequent passage of stool.

constrictive pericarditis

Condition that results from chronic inflammation of the pericardium. The pericardium becomes thick and fibrous and adheres to the heart. The loss of elasticity restricts cardiac filling, which causes systemic congestion and decreases cardiac output.

contact dermatitis

An acute inflammatory reaction triggered by direct exposure to an irritant or allergen-producing substance.

contrecoup

The second area of damage in a traumatic brain injury. Where the brain first impacts the skull is the coup; the brain then rebounds and impacts the opposite side of the skull, which is the contrecoup.

convalescence

The stage of recovery following a disease that may last for days or months.

cornea

A clear lens on the anterior side of the outermost layer of the eye that allows light to enter the eye.

coronary artery disease (CAD)

Disease that occurs when atherosclerosis develops in the arteries supplying the myocardium. Blood flow temporarily

diminishes in the coronary arteries, causing subsequent oxygen reduction to the cardiac muscle.

cortex

The outer portion of an adrenal gland that is regulated by negative feedback involving the hypothalamus and adrenocorticotropic hormones.

cortisol

The principal glucocorticoid, which increases serum glucose levels.

coup

The initial area that the brain impacts in the skull in a traumatic brain injury.

Cowper glands

Two pea-sized glands adjacent to the urethra that secrete an alkaline fluid into the urethra to neutralize acidity caused by urine transportation. Cowper gland secretions can sometimes be seen at the meatus before ejaculation. This secretion aids in lubrication of the penis during sexual intercourse and may contain some sperm left over from a previous ejaculation.

cranial nerves

Set of nerves through which the brain accomplishes a variety of physiologically vital functions and cognitive activities. Twelve pairs branch directly from the base of the brain.

crenation

Shrinkage of a cell as a result of too much water moving out of the cell.

crepitus

A grating sound.

Creutzfeldt-Jakob disease (CJD)

A rare but rapidly progressive form of dementia caused by an infectious prion.

Crohn's disease

An insidious, slow-developing, progressive condition that often develops in adolescence. It is characterized by patchy areas of inflammation involving the full thickness of the intestinal wall and ulcerations.

cryptorchidism

A congenital condition in which one or both testes do not descend from the abdomen to the scrotum prior to birth.

curative

A goal of treatment aimed at eradicating disease.

Curling ulcer

Stress ulcer associated with a burn.

Cushing reflex

A mechanism to maintain tissue perfusion in which a complex cascade of events results in increased blood pressure.

Cushing syndrome

Excessive cortisol levels that result from the increased corticotropin levels.

Cushing triad

Increased blood pressure, bradycardia, and changes in respiratory pattern that result from unresolved vasoconstriction, increased cardiac contractility, and increased cardiac output.

Cushing ulcer

Stress ulcer associated with a head injury.

cystic fibrosis

A common inherited respiratory disorder that presents at birth. This life-threatening condition causes severe lung damage and nutrition deficits.

cystitis

Inflammation of the bladder.

cystocele

Condition that occurs when the bladder protrudes into the anterior wall of the vagina.

cytoplasm

A colorless viscous liquid inside the cell that contains water, nutrients, ions, dissolved gases, and waste products; it is where the cellular work takes place.

cytotoxic cell

Type of T cell that destroys cells infected with viruses by releasing lymphokines that destroy cell walls. Also called *killer cell* and *effector cell*.

deamination

The process of stripping amino groups from molecules.

defecation

The expulsion of the feces from the rectum.

degenerative

Related to conditions that cause parts of the body to deteriorate.

dehydration

Fluid deficit.

delta cell

One of five types of cells in the islets of Langerhans; it secretes somatostatin.

dementia

A group of conditions in which cortical function is decreased, impairing cognitive skills and motor coordination. Issues with memory are common with dementia and include short-term memory losses as well as confusion of historical events.

dendrite

A projection of a neuron that makes connections with nearby cells. Dendrites transmit impulses toward the cell body.

deoxyribonucleic acid (DNA)

A double-stranded chain of nucleotides that is the primary component of chromosomes.

depolarization

An increase in electrical charge through the exchange of ions across the cell membrane caused by the rapid inflow of positively charged sodium ions.

depressed (skull) fracture

Type of fracture that occurs in the skull when the broken piece is forced inward on the brain.

dermatome

The area of the skin innervated by a given pair of spinal sensory nerves. Each spinal nerve, except for the first cervical vertebra, has a specific body surface area from which it obtains sensory information.

dermis

The middle layer of the skin, which is composed of dense, irregular connective tissue and little fat tissue. The dermis includes nerves, hair follicles, smooth muscle, glands, blood vessels, and lymphatic vessels.

descending fibers

Fibers that carry motor impulses in the form of action potentials from the brain to the fibers of the peripheral nervous system. Also called *efferent tracts*.

detrusor hyperreflexia

Increased contractile activity of the detrusor muscle of the bladder, resulting in urinary incontinence.

developmental

Arising during embryonic or fetal development.

diabetes insipidus

Excessive fluid excretion in the kidneys caused by deficient antidiuretic hormone levels.

diabetes mellitus (DM)

A group of conditions characterized by hyperglycemia (high serum glucose levels) resulting from defects in insulin production, insulin action, or both.

diabetic ketoacidosis

A pH imbalance characterized by increased ketones in the urine caused by insufficient insulin; if cells are starved for energy, the body may begin to break down fat-producing toxic acids (ketones).

diagnosis

Identification of disease.

diaphragm

A dome-shaped muscle that separates the thoracic and abdominal cavities and aids in respiration.

diaphysis

The body of a bone.

diarrhea

A change in bowel pattern characterized by an increased frequency, amount, and water content of the stool.

diastole

The bottom number in a blood pressure reading, which indicates rest or relaxation by the ventricles.

diastolic dysfunction

Type of heart failure characterized by decreased ventricular filling resulting from abnormal myocardial relaxation and increased left ventricular pressure. This type of heart failure is caused by conditions that stiffen the myocardium, such as coronary artery disease, hypertrophic and restrictive cardiomyopathy, and pericardial disease.

diencephalon

Part of the brain that includes the thalamus and hypothalamus.

differentiation

A process by which cells become specialized in terms of cell type, function, structure, and cell cycle. This process does not begin until approximately 15–60 days after the sperm and ova unite.

diffusion

The movement of solutes (particles dissolved in a solvent) from an area of higher concentration to lower concentration.

dilated cardiomyopathy

Type of cardiomyopathy that affects systolic function. It is the most common type of cardiomyopathy.

diplopia

Double vision.

disease

The state in which a bodily function is no longer occurring normally. Diseases range in severity from merely causing temporary stress to causing life-changing complications.

dislocation

The separation of two bones where they meet at a joint.

dissecting aneurysm

A false aneurysm in which weakening occurs in the inner layers of a blood vessel.

disseminated intravascular coagulation (DIC)

A life-threatening disorder that occurs as a complication of other diseases and conditions. Clotting factors become abnormally active, often because of an inappropriate immune reaction. Hypercoagulation is followed by hemorrhaging as the clotting factors are completely utilized.

distributive shock

Type of shock in which vasodilation causes hypovolemia.

diverticula

An outwardly bulging pouch of the intestinal wall that occurs when mucosa sections or large intestine submucosa layers herniate through a weakened muscular layer.

diverticular disease

Conditions related to the development of diverticula.

diverticulitis

A state in which diverticula have become inflamed, usually because of retained fecal matter. Diverticulitis can result in potentially fatal obstructions, infection, abscess, perforation, peritonitis, hemorrhage, and shock.

diverticulosis

Asymptomatic diverticular disease. Usually there are multiple diverticula present.

dominant

More powerful. In genetics, the dominant allele is more likely to be expressed in the offspring than the recessive one.

dorsal root

Root formed from about 6–8 dorsal rootlets. The roots combine to form the spinal nerve.

dromotropic

Affecting the rate of electrical conduction.

drug-induced asthma

A type of asthma that is frequently caused by aspirin and can be fatal. Reactions can be delayed up to 12 hours after drug ingestion.

dry gangrene

Type of gangrene that occurs when bacterial presence is minimal, and the skin has a dry dark brown or black appearance.

duodenal ulcer

Type of peptic ulcer that is commonly associated with excessive acid or *Helicobacter pylori* infections. Manifestations typically include epigastric pain that is relieved in the presence of food.

dura mater

The tough outer layer of the central nervous system.

dwarfism

Short stature caused by deficient levels of growth hormone, somatotropin, or somatotropin-releasing hormone.

dyslipidemia

An increased level of lipids in the blood. These lipids include cholesterol and triglycerides, which are necessary for cellular membrane formation. Also called *hyperlipidemia.*

dysmenorrhea

Painful menstruation, to the extent that it impairs usual daily activities.

dysphagia

Difficulty swallowing.

dysplasia

The final cellular adaptation, in which cells mutate into cells of a different size, shape, and appearance.

dysrhythmia

Deviations from normal electric conduction in the heart. Dysrhythmias vary in severity and are classified according to their origins. Also called *arrhythmia*.

ear

Organ that detects and processes sound, detects body position, and maintains balance.

eccrine gland

Gland that secretes sweat through skin pores in response to the sympathetic nervous system. Also called “merocrine gland.”

eclampsia

An acute and life-threatening complication of pregnancy, characterized by tonic–clonic seizures, usually occurring in a patient who has developed preeclampsia.

ectopic pregnancy

Pregnancy in which the zygote does not reach the uterus but rather implants outside the uterus.

ectopic testes

Undescended testes that deviate from the path of descent.

edema

Excess fluid in the interstitial space. Edema is a problem of fluid distribution, not necessarily of fluid overload.

effector cell

One of two major types of T cells that work to destroy antigens. Also called *killer cell*.

efferent arteriole

Point at which blood exits the glomerulus.

efferent nerve

A type of nerve that carries impulses from the brain to the corresponding muscle receptor, resulting in muscle contraction and movement. Also called *motor nerve.*

efferent tracts

Tracts that carry motor impulses in the form of action potentials from the brain to the fibers of the peripheral nervous system. Also called *descending fibers.*

ejaculation

Propulsion of sperm-containing fluid.

ejaculatory duct

Canal in the male reproductive tract formed by union of the vas deferens and the duct from the seminal vesicle.

electrolyte

A chemical that is a charged conductor when it is dissolved in water.

embolus

A portion or all of a thrombus that breaks loose and travels through the circulatory system until it embeds in a smaller vessel. Any other traveling bodies (e.g., air, fat, tissue, bacteria, amniotic fluid, tumor cells, and foreign substances) can become emboli as well.

emesis

The involuntary or voluntary forceful ejection of chyme from the stomach up through the esophagus and out the mouth. It is a common event that can result from a wide range of conditions. Also called *vomiting.*

emphysema

An obstructive respiratory disorder that results in the destruction of the alveolar walls, leading to large, permanently inflated alveoli.

encephalitis

An inflammation of the brain and spinal cord, usually resulting from an infection.

endocardium

The inner epithelial layer of the heart that makes up the valves.

endocytosis

The act of bringing a substance into a cell.

endometrial cancer

Cancer of the inner lining of the uterus; a common malignancy in women.

endometriosis

Condition in which the endometrium begins growing in areas outside the uterus.

endometrium

The inner mucosal lining of the uterine wall that undergoes hormonal changes to facilitate and maintain pregnancy.

enuresis

Involuntary urination by a child after the age of 4–5 years, when bladder control is expected.

enzyme

Protein that facilitates chemical reactions in cells.

epidemic

Increasing cases of a disease in a group.

epidemiology

Tracking patterns of diseases in a group of people. This tracking includes occurrence, incidence, prevalence, transmission, and distribution of the disease.

epidermis

The outermost layer of the skin, which is composed of squamous epithelia.

epididymis

Structure in the male reproductive tract that stores sperm up to 6 weeks until ejaculation.

epididymitis

An inflammation of the epididymis, the duct connecting the testes to the vas deferens.

epidural hematoma

Hematoma that results from bleeding between the dura and skull, usually caused by an arterial tear.

epiglottis

Part of the respiratory system that closes the larynx when food is swallowed.

epiglottitis

A life-threatening inflammation of the epiglottis, the protective cartilage lid covering the tracheal opening.

epilepsy

A disorder that results from spontaneous firing of abnormal neurons; it is characterized by recurrent seizures for which there is no underlying or correctable cause.

epinephrine

Hormone produced by the medulla during times of stress. With norepinephrine, it mediates the fight-or-flight response of the sympathetic nervous system.

epiphysis

The growth plates at either end of a bone.

epispadias

The urethral meatus occurring on the dorsal surface of the penis instead of the end.

epithalamus

Dorsal posterior segment of the diencephalon, which includes the habenula, the stria medullaris, and the pineal body.

epsilon cell

One of five types of cells in the islets of Langerhans; it secretes ghrelin.

erectile dysfunction (ED)

The inability to attain or maintain a penile erection sufficient to complete sexual intercourse. Also called “impotence.”

erythrocyte

Red blood cell.

erythropoietin

Hormone produced by the kidney that promotes the formation of red blood cells in the bone marrow.

esophageal cancer

Cancer of the esophagus; usually a squamous cell carcinoma.

esophagus

Part of the upper gastrointestinal system that has muscular rings to move the food toward the stomach.

essential hypertension

Type of hypertension in which there is no identifiable cause, which occurs in 90% to 95% of hypertension cases in adults. This type of hypertension tends to develop gradually over many years. Also called *primary hypertension*.

etiology

The cause of a disease.

Eustachian tube

A pressure valve for the tympanic membrane.

Ewing sarcoma

An aggressive tumor for which the origin is unknown. It may begin in nerve tissue within the bone.

Exacerbation

Disease state that occurs when the manifestations increase after a period of remission.

Excitability

The ability of the cells to respond to electrical impulses.

Exercise-induced asthma

Common type of asthma in which episodes usually occur 10–15 minutes after activity ends. Symptoms can linger for an hour with exercise-induced asthma.

Exhaustion

The third stage of the general adaptation syndrome, which is initiated if a stressor is prolonged or overwhelms the body. During the exhaustion phase, the body becomes depleted and damage may appear as homeostasis can no longer be maintained. As the body's defenses are utilized, disease or death results.

Exocytosis

The release of materials from a cell, usually with the assistance of a vesicle.

Exophthalmos

Protruding eyes with decreased blinking and movement. It can either be bilateral (as often seen in thyroid disorders) or unilateral (as often seen in an orbital tumor).

Expiration

Exhalation; one of the two phases of breathing.

Expiratory reserve volume

The amount of air beyond the tidal volume that can be exhaled forcefully, which is beyond the normal passive exhalation.

Exsanguination

The spillage of blood out of the circulatory system as the result of a ruptured aneurysm.

External ear canal

Part of the ear through which sound travels until it reaches the tympanic membrane.

Extracellular fluid

Fluid found outside the cells.

Extrinsic asthma

A condition caused by increased immunoglobulin E synthesis and airway inflammation, resulting in mast cell destruction and inflammatory mediator release. Extrinsic triggers include allergens such as food, pollen, dust, and medications. This type of asthma usually presents in childhood or adolescence.

Eye

One of two globe-shaped organs located in orbits in the anterior skull that allow the brain to perceive the environment.

Facilitated diffusion

The movement of substances from an area of lower concentration to an area of higher concentration with the assistance of a carrier molecule.

Fallopian tubes

Two cylinders that extend from the fundus of the uterus to near the ovaries.

Fascia

Fibrous connective tissue that surrounds muscles. It may also surround muscle groups.

Fat embolism

Condition that occurs when fatty marrow enters the bloodstream after a fracture to one of the long bones. The emboli can travel to vital organs, such as the lungs, brain, or heart.

fat necrosis

Type of necrosis that occurs when lipase enzymes break down intracellular triglycerides into free fatty acids.

fatty streaks

Early stages of atherosclerosis. These streaks are made up of macrophages, and cholesterol accumulates within the

macrophages.

feces

Mixture of the undigested or unabsorbed remnants in the colon, along with bacteria (one-third of the feces). Feces also introduce mucus (approximately 300 mL daily) to aid in bowel movements, even in times of decreased dietary intake.

fibrocystic breast mass

The presence of numerous benign nodules in the breast.

fibromyalgia

A syndrome predominantly characterized by widespread muscular pain and fatigue. Fibromyalgia affects muscles, tendons, and surrounding tissue but not the joints.

fibrous plaque

A lesion associated with atherosclerosis; a pearly white area within an artery that causes the intimal surface to bulge into the lumen. It is composed of lipid, cell debris, smooth muscle cells, collagen, and, in older persons, calcium.

flat bone

Strong, flat plate of bone that protects the body's vital organs and provides a base for muscular attachment. The anterior and posterior surfaces of flat bones are formed from compact bone to provide strength, and the center consists of spongy bone and varying amounts of bone marrow.

flexor reflex

A withdrawal reflex in response to touching an unpleasant stimulus. The flexor reflex causes the muscles of a limb to withdraw the limb from the source of the stimulus without any conscious action.

fluid deficit

Condition that occurs when total body fluid levels are not sufficient to meet the body's needs.

fluid excess

Condition that occurs when total body fluid levels are greater than the body's needs.

fluid volume deficit

Fluid deficit of the intravascular compartment. Also called *hypovolemia.*

fluid volume excess

Excess fluid in the intravascular compartment. Also called *hypervolemia.*

focal seizure

One of two categories of seizures; it occurs in just one part of the brain. Also called *partial seizure.*

follicle

One of several functional units of the thyroid gland. These follicles produce thyroxine (T_4), triiodothyronine (T_3), and thyrocalcitonin (calcitonin).

folliculitis

Infections involving the hair follicles. Folliculitis is characterized by tender, swollen areas that form around hair follicles, often on the neck, breasts, buttocks, and face.

foramen magnum

The large and only opening in the skull.

forced expiratory volume in 1 second

The amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.

forced vital capacity

The amount of air that can be forcibly exhaled from the lungs after a forced inspiration.

foreskin

A sheath of loose skin that covers the glans penis at birth. The foreskin is often surgically removed for hygienic, cultural, or religious reasons.

fracture

A break in the rigid structure of the bone.

frank blood

Blood that is bright red.

free radicals

Injurious, unstable agents that can cause cell death.

frontal lobe

Lobe of the brain that facilitates voluntary motor activity and plays a role in personality traits.

fully compensated

A pH level that has returned to normal.

functional incontinence

Type of incontinence that occurs in many older adults, especially people in long-term residential care facilities, in which a physical or mental impairment prevents them from reaching the toilet in time.

furuncle

An infection that begins in the hair follicles and then spreads into the surrounding dermis. The lesion starts as a firm, red, painful nodule that develops into a large painful mass, which frequently drains large amounts of purulent exudate. Also called a “boil.”

fusiform aneurysm

An aneurysm that occurs around the entire circumference of a blood vessel. One of two major types of true aneurysms.

gallbladder

A small saclike organ located on the undersurface of the liver that serves as a reservoir for bile. In addition to storing bile, the gallbladder concentrates the bile by removing water.

gangrene

A form of coagulative necrosis that is characterized by a combination of impaired blood flow and bacterial invasion.

gas gangrene

Type of gangrene that develops because of *Clostridium*, an anaerobic bacterium. This type of gangrene is the most serious and has the greatest potential for being fatal.

gastric cancer

Cancer of the stomach, which occurs in several forms.

gastric ulcer

Type of peptic ulcer that is uncommon but deadly. Gastric ulcers typically are associated with malignancy and nonsteroidal anti-inflammatory drug use. Pain associated with gastric ulcers typically worsens with eating.

gastritis

An inflammation of the mucosal lining of the stomach that can be either acute or chronic.

gastroenteritis

Inflammation of the stomach and intestines, usually because of an infection or allergic reaction.

gastroesophageal reflux disease (GERD)

A condition in which chyme periodically backs up from the stomach into the esophagus. Occasionally, bile can back up into the esophagus. The presence of these gastric secretions irritates the esophageal mucosa.

gene

A segment of deoxyribonucleic acid (DNA) that serves as a template of protein synthesis.

general adaptation syndrome

A cluster of systemic manifestations resulting from body modifications made in an attempt to cope with a stressor.

generalized seizure

A seizure that results from abnormal neuronal activity on both sides of the brain. It may cause loss of consciousness, falls, or massive muscle spasms.

genetic

Related to the passage of physical, biochemical, and physiologic traits from biological parents to their children.

genetics

The study of heredity—the passage of physical, biochemical, and physiologic traits from biological parents to their children.

genital herpes

A sexually transmitted infection that causes blisters on the genitals and in the reproductive tract.

gestation

The support of fetal development from conception to birth by the female reproductive system.

gestational diabetes

A form of glucose intolerance diagnosed for the first-time during pregnancy.

ghrelin

Substance secreted by the epsilon cells; it stimulates hunger.

gigantism

Tall stature caused by excessive growth hormone levels prior to puberty.

glaucoma

A group of eye conditions that lead to damage to the optic nerve. This damage is often caused by increased intraocular pressure but can also be caused by decreased blood flow to the optic nerve.

glomerular filtration rate (GFR)

The best measure of renal functioning; it measures the speed at which blood moves through the glomerulus. GFR can be calculated using a formula that incorporates serum creatinine levels, age, gender, and ethnicity. Usual GFR is approximately 125 mL/min.

glomerulonephritis

A bilateral inflammatory disorder of the glomeruli that typically follows a streptococcal infection.

glomerulus

A cluster of capillaries in the kidneys through which blood passes.

glucagon

Substance secreted by alpha cells that is released when serum glucose levels fall. Glucagon stimulates the breakdown of glycogen to glucose, which raises serum glucose levels.

glucocorticoid

Steroid that is secreted by the middle region of the adrenal cortex.

glucose

A sugar molecule that provides energy.

goiter

A visible enlargement of the thyroid gland.

gonadocorticoid

Sex hormone secreted by the innermost region of the adrenal cortex.

gonorrhea

Sexually transmitted infection caused by *Neisseria gonorrhoeae*. Referred to colloquially as “the clap.”

gout

An inflammatory disease resulting from deposits of uric acid crystals in tissues and fluids within the body.

grading

System used to measure cell appearance in tumors and other neoplasms by classifying the degree of cellular differentiation. The grading score is from G1 to G4, with G4 indicating high differentiation.

graft-versus-host rejection

Type of tissue rejection in which the graft fights the host. This potentially life-threatening type of reaction occurs only with bone marrow transplants. The immunocompetent graft cells recognize the host cells as foreign and organize a cell-mediated attack. The host is usually immunocompromised and unable to fight the graft cells.

Graves' disease

An autoimmune condition that stimulates thyroid hormone production.

greenstick fracture

An incomplete fracture in which the bone is bent and only the outer curve of the bend is broken.

gross total incontinence

A continuous leaking of urine, day and night, or the periodic uncontrollable leaking of large volumes of urine. In these cases, the bladder has no storage capacity.

gyrus (plural: gyri)

A fold that increases the surface area of the cerebrum. At birth, these folds are minimal, but they increase as the brain develops into adulthood.

Hashimoto's thyroiditis

The most common cause of thyroid gland failure. Also called "autoimmune thyroiditis."

HCO_3

Bicarbonate. Part of the body's buffer system, it is secreted by the kidneys.

health

The absence of disease. This definition can be expanded to include wellness of mind, body, and spirit. It is a person's normal state.

heart failure

A condition in which the heart is unable to pump an adequate amount of blood to meet metabolic needs. This pump inadequacy leads to decreased cardiac output, increased preload, and

increased afterload. These three events result in decreased contractility and stroke volume.

helper cell

A type of regulator cell that activates, or calls up, B cells to produce antibodies.

hemangioma

A vascular birthmark that appears as a bright red patch or a nodule of extra blood vessels in the skin. Also called a "strawberry."

hematemesis

Blood in the vomitus. It has a characteristic brown granular appearance like coffee grounds.

hematocrit

A laboratory expression of how much of the blood volume is being occupied by erythrocytes.

hematoma

A collection of blood in the tissue that develops from ruptured blood vessels. Hematomas can develop immediately or slowly and are classified by their location.

hematopoiesis

The process of blood formation; it occurs primarily in the bone marrow.

hemoglobin

Part of an erythrocyte. It binds to oxygen, giving blood its red color.

hemoglobin S

An abnormal type of hemoglobin that distorts the shape of erythrocytes, especially in a setting of low oxygen. These fragile,

sickle-shaped cells deliver less oxygen to the body's tissues. Such cells also can easily clog small blood vessels and break into pieces that disrupt blood flow.

hemoglobin system

Buffer mechanism in the erythrocytes that works by binding to or releasing hydrogen and carbon dioxide.

hemolysis

Excessive destruction of erythrocytes that causes hemolytic anemia.

hemophilia A

An X-linked recessive bleeding disorder that involves a deficit or abnormality of clotting factor VIII. Also called "classic hemophilia."

hemorrhagic stroke

The deadliest kind of stroke (i.e., cerebral vascular accident); it occurs when blood vessels rupture inside the brain.

hepatic artery

Part of the liver's dual blood supply; it carries oxygenated blood from the general circulation to the liver at a rate of approximately 300 mL/min to nourish the liver.

hepatitis

An inflammation of the liver that can be caused by infection (usually viral), alcohol, medications, or autoimmune disease.

hepatobiliary system

The liver, gallbladder, and pancreas, collectively. They are called a system because of their close proximity to one another and their complementary functions.

hereditary

Transmitted before birth.

herniated intervertebral disk

A state in which the nucleus pulposus protrudes through the annulus fibrosus. Also called “slipped disk” and “ruptured disk.”

herniation

The displacement of brain tissue.

herpes simplex type 1

A viral infection typically affecting the lips, mouth, and face. This common infection usually begins in childhood. Also called a “cold sore.”

herpes simplex virus (HSV)

One of a family of more than 70 herpesviruses; the cause of genital herpes.

herpes zoster

A viral infection caused by the varicella-zoster virus. The condition appears in adulthood years after a primary infection of varicella (i.e., chickenpox) in childhood. The virus lies dormant on a cranial nerve or a spinal nerve dermatome until it becomes activated years later; it affects this nerve only. Also called “shingles.”

heterozygous

Allele pair in which one allele is dominant and the other allele is recessive for a particular gene.

hiatal hernia

Condition in which a section of the stomach protrudes upward through an opening in the diaphragm toward the lung.

high-density lipoprotein (HDL)

A type of lipid that assists with removing cholesterol from the body. Also called “good cholesterol.”

homeostasis

Equilibrium, balance, consistency, or stability. In the body, this self-regulating, give-and-take system responds to minor changes in the body’s status through compensation mechanisms. Compensation mechanisms attempt to counteract those changes and return the body to its normal state.

homozygous

Identical allele pair for a particular gene.

host-versus-graft rejection

The most common type of tissue rejection in which the host fights the graft.

human papillomavirus (HPV)

A virus that can cause benign warts, genital warts, as well as reproductive (e.g., cervical and penile) and anal cancers. There are more than 70 different types of HPVs.

Huntington’s disease (HD)

A condition caused by a genetically programmed degeneration of neurons in the brain. It is an autosomal dominant disorder involving a defect on chromosome 4. Also called “Huntington chorea.”

hyaline cartilage

The type of cartilage most associated with bone, often found in joints.

hydrocele

Fluid accumulation between the layers of the tunica vaginalis or along the spermatic cord.

hydrocephalus

A condition in which excess cerebrospinal fluid (CSF) accumulates within the skull, which dilates the ventricles and compresses the brain and blood vessels. The pressure from the excess CSF thins the cortex, causing severe brain damage.

hydronephrosis

An abnormal dilation of the renal pelvis and the calyces of one or both kidneys that occurs secondary to a disease.

hymen

A thin connective tissue that covers the external vaginal opening to some degree.

hyperacute tissue rejection

Type of tissue rejection that occurs immediately to 3 days after a transplant. Hyperacute reactions occur due to a complement response in which the recipient has antibodies against the donor. This complement response triggers a systemic inflammatory reaction. The response is so quick that often the tissue has not had a chance to establish vascularization; as a result, the tissue becomes permanently necrotic.

hypercalcemia

Condition in which ionizing calcium levels climb above 5 mEq/L. Hypercalcemia results from excessive intake of ionizing calcium or release of ionizing calcium from the bone as well as inadequate excretion.

hyperchloremia

An excess amount of chloride in the blood (more than 108 mEq/L). It is usually a result of an underlying condition and without its own clinical manifestations.

hyperglycemia

An excess amount of glucose in the blood (more than 180 mg/dL). It can be a result of an underlying condition (e.g., diabetes mellitus) or use of medications (e.g., corticosteroid agents).

hyperkalemia

Serum potassium level greater than 5 mEq/L. Hyperkalemia is unusual in the healthy individual and may be a medical emergency.

hypermagnesemia

Condition in which magnesium levels increase to more than 2.5 mEq/L. This rare electrolyte imbalance usually results from renal failure or excessive laxative or antacid use.

hypernatremia

Condition that results from high serum sodium levels (more than 145 mEq/L). The excessive sodium levels generally lead to high serum osmolality (more than 295 mOsm/kg) because of the imbalance between sodium and water.

hyperparathyroidism

A condition of excessive parathyroid hormone production by the parathyroid glands.

hyperphosphatemia

Condition in which phosphorus levels climb above 4.5 mg/dL.

hyperpituitarism

A condition in which the pituitary gland secretes excessive amounts of one or all of the pituitary hormones.

hyperplasia

An increase in the number of cells in an organ or tissue. This increase occurs only in cells that can perform mitotic division, such as epithelial cells.

hyperprolactinemia

Excessive prolactin levels that result in menstrual dysfunction and galactorrhea (inappropriate lactation).

hypersensitivity

An inflated or inappropriate response to an antigen. The result is inflammation and destruction of healthy tissue. Hypersensitivity reactions may be immediate, occurring within minutes to hours of reexposure, or delayed, occurring several hours after reexposure.

hypertension

A state of prolonged elevation in blood pressure.

hyperthyroidism

Hypermetabolic state caused by excessive thyroid hormones that result from increased thyrotropin levels.

hypertonic solution

An intravascular solution that has a higher concentration of solutes than those in the intravascular compartment. Hypertonic solutions cause fluid to shift from the intracellular space to the intravascular space.

hypertrophic cardiomyopathy

Type of cardiomyopathy that mainly affects diastolic function.

hypertrophy

Condition in which cells increase in size in an attempt to meet the body's increased work demand. This change may be a result of normal or abnormal changes.

hypervolemia

Excess fluid in the intravascular compartment.

hypocalcemia

Condition in which ionized calcium levels fall below 4 mEq/L. Hypocalcemia occurs from increased losses or decreased intake of ionized calcium.

hypochloremia

Condition in which chloride levels fall below 98 mEq/L. Hypochloremia rarely occurs in the absence of other electrolyte abnormalities and, therefore, does not have its own set of clinical manifestations.

hypodermis

The innermost layer of the skin. It is composed of soft, fatty tissue as well as blood vessels, nerves, and immune cells. Also called “subcutaneous tissue.”

hypoglycemia

A low serum glucose level.

hypokalemia

Condition in which potassium levels drop below 3.5 mEq/L. Usually, hypokalemia results from excessive loss, inadequate intake, or increased cellular uptake of potassium.

hypomagnesemia

Condition in which magnesium levels drop below 1.8 mEq/L.

hyponatremia

Condition that results from low serum sodium levels (less than 135 mEq/L). Serum osmolality levels also fall below 275 mOsm.

hypoparathyroidism

Condition in which the parathyroid gland does not produce enough parathyroid hormone.

hypophosphatemia

Condition in which phosphorus levels drop below 2.5 mg/dL.

hypopituitarism

A rare, complex condition in which the pituitary gland does not produce enough of some or all of its hormones.

hypospadias

Condition in which the urethral meatus is found on the ventral surface of the penis instead of the distal end.

hypothalamic–pituitary axis

Hormones produced by the anterior pituitary gland and regulated by the hypothalamus.

hypothalamus

The basal portion of the diencephalon, which regulates the pituitary gland. The hypothalamus connects the nervous and endocrine systems; it regulates many bodily functions.

hypothyroidism

Condition in which the thyroid does not produce enough thyroid hormones.

hypotonic solution

An intravascular solution that has a lower concentration of solutes than that found in the intravascular compartment. Administration of hypotonic solutions causes fluid to shift from the intravascular space to the intracellular space.

hypovolemia

Fluid deficit of the intravascular compartment.

hypovolemic shock

Type of shock in which venous return declines because of external blood volume losses. Preload drops, decreasing ventricular filling and stroke volume.

iatrogenic

Caused by an unintended effect of a medical treatment.

idiopathic

Unknown, usually in reference to disease causes.

idiopathic thrombocytopenic purpura (ITP)

A hypocoagulopathy state as a result of the immune system destroying its own platelets. It can be either acute or chronic.

immunodeficiency

A diminished or absent immune response that increases susceptibility to infections.

impacted fracture

Type of fracture in which one end of the bone is forced into the adjacent bone.

impetigo

A common and highly contagious skin infection. Although it can occur without an apparent break, impetigo typically arises from a breach in the skin. It spreads easily to others by direct contact with skin or contaminated objects. Lesions usually begin as a small vesicle that enlarges and ruptures, forming a characteristic honey-colored crust.

impregnation

The fertilization of eggs.

incomplete fracture

Type of fracture in which the bone is partially broken.

increased intracranial pressure

Increased volume in the limited space of the cranial cavity. Increased intracranial pressure may occur because of a traumatic brain injury or because of other conditions that would increase the volume in the skull.

incus

Bone in the ear that vibrates as a result of the malleus rocking, which in turn causes the stapes to move in and out against the oval window. Also called the “anvil.”

infantile hypertrophic pyloric stenosis (IHPS)

A narrowing and obstruction of the pyloric sphincter due to enlargement (hypertrophy) of the pyloric muscle that occurs within the first few months of life.

infarction

Permanent damage to tissue due to an obstruction of blood supply.

infectious mononucleosis

A disease caused by the Epstein-Barr virus, a common virus of the herpes family. Most people are exposed to the virus as children, and because of the exposure, they develop immunity to the virus and do not ever develop infectious mononucleosis. Also called “mono” and the “kissing disease.”

infectious rhinitis

The common cold viral upper respiratory infection. The most frequent culprit is a rhinovirus, but it can be caused by many viruses.

infective endocarditis

An infection of the endocardium. Previously called “bacterial endocarditis.”

inferior vena cava

Large vein that carries deoxygenated blood from the lower half of the body to the right atrium.

infertility

A biological inability to contribute to reproduction.

inflammatory

Triggering inflammation.

inflammatory bowel disease (IBD)

Chronic inflammation of the gastrointestinal tract, usually the intestines.

inflammatory response

A series of reactions triggered by damage or trauma to body tissue.

influenza

A viral infection that may affect the upper and lower respiratory tracts. There are three strains: A, B, and C. The virus is highly adaptive and constantly mutates, preventing the development of any long-term immune defense.

initiation

Phase of carcinogenesis in which exposure of the cell to a substance or event causes deoxyribonucleic acid (DNA) damage or mutation.

innate immunity

Nonspecific defense mechanisms that are activated immediately or within a few hours in the presence of an antigen. These mechanisms include physical barriers, chemicals, and the general immune response (e.g., inflammatory response, complement system, phagocytes); they respond to antigens in a generic way

and do not provide long-term protection against specific antigens.

inner ear

Division of the ear that consists of the cochlea, semicircular canals, saccule, and utricle.

inotropic

The strength of contraction.

insidious

Onset of a disease with vague symptoms.

inspiration

Inhalation; one of the two phases of breathing. Inspiration is an active neural process that begins with nerve impulses traveling from the brain to the diaphragm.

inspiratory reserve volume

The amount of air beyond the tidal volume that can be taken in with the deepest inhalation.

insulin

Hormone secreted by beta cells of the pancreas that is released when serum glucose levels increase. Insulin stimulates cellular uptake of glucose, which decreases serum glucose levels.

interferon

A small protein that is released from cells infected by viruses. It prevents the virus from replicating and boosts the immune system.

interneuron

A neuron that connects the sensory and motor neurons in the spinal cord.

interstitial

A fluid compartment between the cells.

interstitial pneumonia

A type of pneumonia that occurs in the areas between the alveoli. Interstitial pneumonia is usually caused by viruses (e.g., influenza type A and B) or by uncommon bacteria (e.g., *Legionella*). Also called “atypical pneumonia.”

intestinal obstruction

Blockage of intestinal contents in the small intestine or large intestine.

intracellular fluid

Fluid found inside the cells.

intracerebral hematoma

A collection of blood in the brain tissue. Intracerebral hematomas are caused by contusion or shearing injuries but can also result from hypertension, cerebral vascular accidents (i.e., strokes), aneurysms, or vascular abnormalities.

intractable pain

Chronically progressing pain that is unrelenting and severely debilitating. This type of pain does not usually respond well to typical pharmacologic pain treatments. Intractable pain is common with severe injuries, especially crushing injuries.

intrarenal condition

Cause of acute renal failure that directly damages the structures of the kidneys.

intravascular

A fluid compartment inside the blood vessels.

intrinsic asthma

Type of asthma that usually presents after age 35 and is not an allergic reaction. Intrinsic triggers include upper respiratory infections, air pollution, emotional stress, smoking, exercise, and cold exposure.

iris

The colored portion of the eye. The iris contains smooth muscle fibers that control changes in the diameter of the pupil to regulate the amount of light entering the eye.

irregular bone

One of the five types of bones found within the skeleton. Irregular bones do not fall into any other category, due to their nonuniform shape. They primarily consist of spongy bone, with a thin outer layer of compact bone.

irritable bowel syndrome (IBS)

A chronic gastrointestinal condition characterized by exacerbations associated with stress. IBS includes alterations in bowel pattern and abdominal pain not explained by structural or biochemical abnormalities.

ischemia

Decreased blood flow to tissue or an organ. It essentially strangles the tissue or organ by limiting the supply of necessary nutrients and oxygen.

ischemic stroke

The most common type of stroke (i.e., cerebral vascular accident). It is caused by an interruption in cerebral blood flow, often resulting from a thrombus or embolus.

islet of Langerhans

Area situated among the many small acini in the pancreas that carries out endocrine functions. The human pancreas contains approximately 1 million islets of Langerhans, and each islet of Langerhans contains five types of cells.

isotonic solution

An intravascular solution that has concentrations of solutes equal to those in the intravascular compartment. Because of these solute concentrations, isotonic solutions allow fluid to move equally between compartments.

isthmus

A thin band of tissue that connects the two lobes of the thyroid gland by extending across the anterior aspect of the trachea.

jaundice

A yellowish discoloration of the skin and sclera caused by an excessive amount of bilirubin in the bloodstream. It can result from bile entering the bloodstream or erythrocyte lysis.

joint

A structure that connects bones of the skeleton. Joints are classified by their degree of movement: moveable, slightly moveable, and immoveable.

joint capsule

The saclike envelope enclosing the cavity of a synovial joint.

karyotype

A representation of a person’s individual set of chromosomes.

keratin

A protein that strengthens skin.

keratitis

An inflammation of the cornea that can be triggered by an infection or trauma.

killer cell

A type of T cell that destroys cells infected with viruses by releasing lymphokines that destroy cell walls. Also called *cytotoxic cell* and *effector cell*.

kyphosis

An increase in the curvature of the thoracic spine outward. Also called “hunchback.”

labia majora

The two large, fatty skin folds of the external female genitalia that protect the perineum and aid in lubrication.

labia minora

Two small, firm skin folds located just inside the labia majora of the external female genitalia.

lacrimal duct

The duct through which tears drain on the inner side of each eye.

lacrimal gland

The gland that keeps the inner surface of the eyelid and the exposed surface of the eye moist.

lactation

The production and secretion of milk for the feeding of offspring.

lamella (plural: lamellae)

A thin layer of osteocytes.

large intestine

Part of the lower gastrointestinal tract. It is 5 feet long in adults and contains the cecum, colon, and rectum.

laryngitis

An inflammation of the larynx that is usually a result of an infection, increased upper respiratory exudate, or overuse. With laryngitis, the vocal cords become irritated and edematous because of the inflammatory process. This inflammation distorts sounds, leading to hoarseness and in some cases making the voice undetectable.

laryngotracheobronchitis

A common viral infection in children 1–2 years of age, although older children and adults may also contract it. It usually begins as an upper respiratory infection with nasal congestion and cough. The larynx and surrounding area swell, leading to airway narrowing and obstruction. This swelling can lead to respiratory failure. Also called “croup.”

larynx

The larynx is made of cartilage and plays a central role in swallowing and talking. Also called the “voice box.”

latent herpes genitalis

The second stage of genital herpes, which begins once the antibodies are formed.

latent syphilis

The final stage of syphilis. The early latency stage begins when the secondary symptoms disappear and lasts 1–4 years. The late latency stage can last for years as the infection spreads to the brain, nervous system, heart, skin, and bones. Also called “tertiary syphilis.”

left atrium

Receiving chamber on the left side of the heart. It receives blood from the pulmonary circulation; after leaving this chamber, blood

travels to the left ventricle.

left-sided heart failure

Type of heart failure that results from ineffective left ventricular contractility. As cardiac output falls, blood that is not being pumped out into the body backs up first in the left atrium and then in the pulmonary circulation.

left ventricle

Pumping chamber on the left side of the heart. This chamber pumps blood to the systemic circulation.

Legionnaires' disease

A specific type of pneumonia that is caused by *Legionella pneumophila*. The bacteria thrive in warm, moist environments, particularly air-conditioning systems and spas. Legionnaires' disease is not contagious. Most people acquire this type of pneumonia from inhaling the bacteria as they are spread by an air-conditioning system or spa.

leiomyoma

A uterine fibroid; a firm, rubbery growth of the myometrium.

lens

A transparent flexible structure that lies behind the iris of the eye. Smooth muscles attached to the lens alter its shape, allowing the lens to focus on objects.

lentigo

A large, pigmented spot that may appear in a sun-exposed area. Also called "age spot" or "liver spot."

leukemia

A cancer of the leukocytes. With leukemia, the bone marrow makes abnormal leukocytes. Leukemia cells do not die when

they should, so they sometimes crowd out normal leukocytes, erythrocytes, and thrombocytes. This crowding makes it difficult for normal blood cells to do their work.

leukocyte

White blood cell.

leukocytopenia

Decreased white blood cell level; it can indicate an immune deficiency state (e.g., bone marrow suppression).

leukocytosis

Increased white blood cell level; it can indicate an active infectious process.

ligament

A bundle of dense connective tissue that connects bones to bones in a joint and provides support to the joint.

linear skull fracture

A simple crack in the skull.

lipid

Any of a broad group of naturally occurring molecules that includes fats, fat-soluble vitamins (such as vitamins A, D, E, and K), monoglycerides, diglycerides, phospholipids, and others. The main biological functions of lipids are as energy storage locations, as structural components of cell membranes, and as important signaling molecules.

lipid bilayer

A fatty double covering that makes up the membrane of a cell. The interior surface of the bilayer is uncharged and primarily consists of lipids. The exterior surface of the bilayer is charged and is less fatty than the interior surface.

liquefaction necrosis

Type of necrosis that occurs when caustic enzymes dissolve and liquefy necrotic cells.

liver

An organ that performs as many as 500 different functions. Some of the liver's primary roles are vital for homeostasis.

liver cancer

Cancer of the liver. It most commonly occurs as a secondary tumor that has metastasized from the breast, lung, or other gastrointestinal structures.

lobar pneumonia

Type of pneumonia confined to a single lobe in the lung and described based on that affected lobe (e.g., right upper lobe).

lobe

Subdivision of a bodily organ or part, delineated by shape or connective tissue. Examples can be seen in the lung and brain.

local adaptation syndrome

The localized version of general adaptation syndrome. In this syndrome, the body attempts to limit the damage associated with a stressor by confining the stressor to one location.

long bone

One of the five types of bones found within the skeleton. A long bone has a body that is longer than it is wide, growth plates at either end, a hard outer surface, and an inner region that is less dense than the outer region and contains bone marrow.

longitudinal fissure

The dividing point of the cerebrum into right and left hemispheres.

lordosis

An exaggerated concave of the lumbar spine. Also called “swayback.”

low-density lipoprotein (LDL)

A lipid that is a major contributor to the plaque formation associated with atherosclerosis. Also called “bad cholesterol.”

lower esophageal sphincter (LES)

Part of the upper gastrointestinal system that relaxes to allow food to enter the stomach and that prevents the stomach contents from refluxing into the esophagus.

lung

Organ responsible for gas exchange.

lung cancer

Cancer of the lung. The third most common neoplasm, which can arise as either a primary or secondary tumor.

lymph

Fluid that drains from the lymph capillaries into larger vessels and ducts that empty into large veins at the base of the neck. The movement of lymph occurs much in the same way that blood moves through veins, with the assistance of valves and movement.

lymphatic system

An extensive network of vessels and glands that returns excess fluid in body tissue to the circulatory system and works with the immune system.

lymphedema

Swelling, usually in the arms and legs, because of lymph obstruction. Lymphedema can occur on its own or as a result of

another disease or condition.

lysis

Bursting of a cell; for example, it can occur when too much water enters the cell membrane, causing excessive swelling.

macular degeneration

A deterioration of the macular area of the retina caused by impaired blood supply to the macula that results in cellular waste accumulation and ischemia.

macular stain

The most common type of vascular birthmark. These faint red marks often occur on the forehead, eyelids, posterior neck, nose, upper lip, or posterior head. Also called “salmon patch,” “angel kiss,” and “stork bite.”

magnesium

An intracellular cation that is mostly stored in the bone and muscle.

malignant

State of a tumor that is usually made up of undifferentiated nonfunctioning cells that are reproducing rapidly. Malignant tumors often penetrate surrounding tissue and spread to secondary sites.

malignant hypertension

An intensified form of hypertension that may not respond well to treatment efforts.

malleus

A bone that lies near the tympanic membrane of the ear. Vibrations from the membrane cause the malleus to rock back and forth. Also called the “hammer.”

mammary glands

Glands located in the breast of the male and female but function only in females. They produce milk when stimulated to do so.

manifestation

The clinical effects or evidence of a disease. Manifestations may include both signs (what can be seen or measured) and symptoms (what the patient describes).

mastication

Chewing.

mastitis

An inflammation of the breast tissue that can be associated with infection and lactation.

matrix

Extracellular material in which osteocytes are embedded. The matrix consists of calcium phosphate crystals that make the bones hard and strong. It also contains collagen fibers that reinforce the bone, giving it flexible strength.

meatus

An opening or passageway.

medulla

1. The part of the brainstem that acts as the conduction pathway for ascending and descending nerve tracts. The medulla coordinates heart rate, peripheral vascular resistance, breathing, swallowing, vomiting, coughing, and sneezing. 2. The inner portion of an adrenal gland. It is regulated by nerve impulses from the hypothalamus and produces epinephrine and norepinephrine during times of stress.

meiosis

A form of cell division that occurs only in mature sperm and ova.

melanin

A pigment that provides color to the skin as well as protection from ultraviolet (UV) rays. Disorders involving melanin result in alterations in skin coloring and can leave the skin vulnerable to the harmful effects of UV light. Melanin disorders include albinism and vitiligo.

melena

Dark, tarry stool associated with a significant amount of bleeding high in the gastrointestinal tract.

memory cell

Type of B cell that aids in the body's quick response to subsequent exposures to an antigen because memory cells recall the antigen as foreign and antibody production occurs rapidly.

Ménière's disease

A disorder of the inner ear that results from endolymph swelling, which stretches the membranes and interferes with the hair receptors in the cochlea and vestibule.

meninges

A set of three tough membranes that encase the central nervous system.

meningitis

An inflammation of the meninges, usually resulting from an infection.

meningocele

A rare form of spina bifida that involves a bony defect in which the meninges protrude through a vertebral opening.

menopause

The complete and permanent cessation of the menstrual cycle.

menstrual cycle

A series of monthly changes in females that begin at puberty and continue through the reproductive years.

menstruation

Shedding of the endometrium. It generally occurs on a regular basis (usually every 28 days) during the reproductive years of women. Also called a “period.”

mesentery

A double-layer peritoneum containing blood vessels and nerves that supply the intestinal wall.

metabolic

Related to the body’s metabolism.

metabolic acidosis

Condition that results from a deficiency of bicarbonate or an excess of hydrogen.

metabolic alkalosis

Condition that results from an excess of bicarbonate or a deficiency of hydrogen.

metabolic syndrome

A cluster of risk factors occurring together—hyperglycemia, high blood pressure, hypercholesterolemia, and increased waist circumference. Metabolic syndrome increases a person’s risk for developing cardiovascular disease, diabetes mellitus, and stroke (i.e., cerebral vascular accident).

metaphase

Phase of mitosis in which the spindle fibers attach to centromeres and chromosomes align.

metaplasia

The process of one adult cell being replaced by another cell type.

metastasize

To spread (e.g., as seen with cancer cells).

microtia

An underdeveloped small auricle.

micturition

Urination.

midbrain

The smallest region of the brain, which acts as a sort of relay station for auditory and visual information. The midbrain controls the visual and auditory systems as well as eye movement.

middle ear

Division of the ear that includes the tympanic membrane and the ossicles.

Middle East respiratory syndrome (MERS)

An emerging illness caused by a coronavirus family. It is currently isolated to four countries in the Arabian Peninsula.

mineralocorticoid

Steroid produced by the outermost region of the adrenal cortex.

minute respiratory volume

The amount of air inhaled and exhaled in 1 minute. It is determined by the tidal volume multiplied by the respirations per minute.

mitosis

The most common form of cell division, in which the cell divides into two separate cells. In mitosis, the division of one cell results

in two genetically identical and equal daughter cells. This process occurs in four phases: prophase, metaphase, anaphase, and telophase.

mitral valve

A bicuspid valve that guides the passage of blood from the left atrium to the left ventricle and prevents the backward flow of blood.

mixed dysfunction

A categorization of heart failure that is a combination of systolic and diastolic dysfunction.

mixed incontinence

Type of incontinence in which the individual experiences symptoms of more than one type of urinary incontinence.

mole

A brown nevus. Moles can be tan, brown, or black; can be flat or raised; and may have hair growth.

Mongolian spot

Type of birthmark that is a flat bluish-gray area often found on the lower back or buttocks. These birthmarks are most common on individuals with darker complexions.

Monro-Kellie hypothesis

A supposition that states the cranial cavity cannot be compressed, and the volume inside the cavity is fixed (normal intracranial pressure is 60–200 mm H_2O or 4–15 mm Hg). The skull and its components create a state of volume equilibrium, such that any increase in volume of one component must be compensated by a decrease in volume of another component.

mons pubis

The pad of fat over the symphysis pubis that becomes covered with hair after puberty.

morbidity

The disease rate within a group.

mortality

The death rate from a particular disease.

motor nerve

A type of nerve that carries impulses from the brain to the corresponding muscle receptor, resulting in muscle contraction and movement. Also called *efferent nerve*.

mucosa

The innermost of the four layers of the walls of the gastrointestinal tract. The mucosa produces mucus.

mucus

A thick, sticky substance produced by the goblet cells in the epithelial lining of the nose, trachea, and bronchi.

multifactorial disorder

A result of an interaction between genes and environmental factors. Such a disorder does not follow a clear-cut pattern of inheritance. Multifactorial disorders may be present at birth, as with cleft lip or palate, or they may be expressed later in life, as with hypertension.

multiple myeloma

A cancer of the plasma cells that most often affects older adults. Multiple myeloma is characterized by excessive numbers of abnormal plasma cells in the bone marrow, which crowd out the blood-forming cells and cause Bence Jones proteins to be excreted in the urine.

multiple sclerosis (MS)

A debilitating autoimmune condition that involves a progressive and irreversible demyelination of brain, spinal cord, and cranial nerve neurons. This damage occurs in diffuse patches throughout the nervous system and slows or stops nerve impulses.

muscle fiber

Muscle cell that is a cylinder with multiple nuclei.

muscle layer

One of the four layers of the walls of the gastrointestinal tract. It includes circular and longitudinal smooth muscle layers. This layer contracts in a wavelike motion to propel food through the gastrointestinal tract.

muscular dystrophy (MD)

A group of inherited disorders characterized by degeneration of skeletal muscle. Muscles become weaker as damage worsens. There are nine different forms of muscular dystrophy.

myasthenia gravis

An autoimmune condition in which acetylcholine receptors are impaired or destroyed by immunoglobulin G autoantibodies, leading to a disruption of normal communication between the nerve and muscle at the neuromuscular junction.

myasthenic crisis

A potentially life-threatening complication of myasthenia gravis that occurs when the muscles become too weak to maintain adequate ventilation.

mycoplasma pneumoniae

A common type of pneumonia that usually affects people younger than 40 years of age.

myelin sheath

Covering that surrounds axons to increase the rate of impulse transmission.

myelomeningocele

The most severe form of spina bifida. In this form, the spinal canal remains open along several vertebrae in the lower or middle back. Also called “open spina bifida.”

myocardial infarction (MI)

Death of the myocardium from sudden blockage of coronary artery blood flow. Other names for a myocardial infarction include heart attack and acute coronary syndrome.

myocarditis

An inflammation of the myocardium. In this uncommon condition, a period of at least several weeks (in some cases a decade) separates exposure to the causative agent and the development of symptoms.

myocardium

The middle layer of the heart; the muscle portion of the organ.

myofibril

A threadlike structure that extends the entire length of the muscle fiber.

myofilament

Protein fibers found in muscle fibers.

myometrium

The middle layer of the uterine wall, made up of smooth muscle and a vascular system. During pregnancy, the vascular system radically increases to support the fetus.

myosin

One of two types of myofilaments—the darker and thicker of the two types. Myosin myofilaments are fibrous globulins that work with actin to form actomyosin.

myxedema

Advanced hypothyroidism. This condition is rare, but when it occurs, it can be life threatening. Clinical manifestations include marked hypotension, respiratory depression, hypothermia, lethargy, and coma.

nausea

A subjective urge to vomit that may precede vomiting.

necrosis

Death of most of all the cells in an organ or tissue due to damage as a result of disease, injury, or lack of blood supply.

necrotizing fasciitis

A rare, serious infection that can aggressively destroy skin, fat, muscle, and other tissue. One out of four people with this infection will die because of it. Also called “flesh-eating bacteria.”

negative feedback system

One of two types of feedback systems that maintain homeostasis (the other is a positive feedback system). The negative feedback system, which is the most common type, works to maintain a deficit in the system. Examples of negative feedback systems include temperature and glucose regulation.

neoplasm

A cellular growth that is no longer responding to normal regulator processes, usually because of a mutation. Also called a *tumor.*

neoplastic

Related to abnormal or uncontrolled cellular growth.

nephritic syndrome

Inflammatory injury to the glomeruli that can occur when antibodies interact with normally occurring antigens in the glomeruli.

nephrolithiasis

The presence of renal calculi (kidney stones).

nephron

One of the 1–2 million microscopic filtering units in the kidney. Each is similar to a long-stemmed funnel and has multiple sections, and each section is responsible for excreting or reabsorbing specific substances.

nephrotic syndrome

Condition that results from antibody–antigen complexes lodging in the glomerular membrane, triggering the complement system.

nerve

Part of the peripheral nervous system that consists of bundles of nerve fibers, where each fiber is part of the neuron.

neurogenic bladder

All types of bladder dysfunctions caused by an interruption of normal bladder nerve innervation.

neurogenic shock

Type of distributive shock in which a loss of sympathetic tone in vascular smooth muscle and autonomic function leads to massive vasodilation. Blood pools in the venous system, leading to decreased venous return, cardiac output, and hypotension.

neuroglia

Type of cell that plays several important supportive roles in the nervous system. Neuroglia cells scaffold neural tissue as well as

isolate and protect neuron cell membranes. Additionally, they regulate interstitial fluid, defend the neuron against pathogens, and assist with neural repair.

neuromelanin

A specialized dark pigment found in the brain.

neuron

The fundamental unit of the nervous system. Neurons generate bioelectric impulses and transmit them from one area of the body to another.

neuropathic pain

Pain that results from damage to peripheral nerves by disease or injury. This type of pain tends to be chronic and intractable.

neurotransmitter

Chemical that is released from the presynaptic terminal and crosses the synaptic cleft in one direction to stimulate an electrical reaction in nearby neurons.

neutropenia

An insufficient number of circulating neutrophils (fewer than 1,500 cells/μL; the normal range is 2,000–7,500 cells/μL). With fewer of these first responders, the body is poorly equipped to fight infections. The degree to which the body can fight infections, especially bacterial infections, is related to the severity of the neutropenia.

neutrophil

An infection-fighting agent. Usually the first cells to arrive on the scene of an infection, neutrophils are attracted by various chemicals released by infected tissue. Neutrophils escape from the capillary wall and migrate to the site of infection. Once they

arrive at the site, neutrophils phagocytize microorganisms, preventing the infection from spreading.

nipple

A pigmented projection of the breast that is surrounded by the areola.

nocturnal asthma

Type of asthma that usually occurs between 3:00 a.m. and 7:00 a.m. and is thought to be related to circadian rhythms. At night, cortisol and epinephrine levels decrease, while histamine levels increase.

nocturnal enuresis

Involuntary urination at night while sleeping. Also called “bed-wetting.”

node of Ranvier

Node that separates Schwann cells.

non-small-cell carcinoma

An aggressive type of lung cancer; the most common type of malignant lung cancer. It has several subgroups—squamous cell carcinoma, adenocarcinoma, and bronchioalveolar carcinoma. Often referred to as “bronchogenic carcinoma.”

noncommunicating hydrocephalus

Type of hydrocephalus that occurs when the cerebrospinal fluid flow is disrupted or not properly absorbed by the bloodstream. Also called “obstructive hydrocephalus.”

nonvolatile acid

An acid produced from sources other than carbon dioxide, which is not excreted by the lungs.

norepinephrine

Hormone produced by the medulla during times of stress. With epinephrine, it mediates the fight-or-flight response of the sympathetic nervous system.

nosocomial pneumonia

Pneumonia that develops more than 48 hours after a hospital admission.

nucleotides

Molecules that join to form ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).

nucleus

The control center of the cell, which contains all the genetic information (i.e., deoxyribonucleic acid [DNA]) for the cell and is surrounded by a double membrane. The nucleus regulates cell growth, metabolism, and reproduction.

nystagmus

Rapid, involuntary back-and-forth eye movement.

oblique fracture

A fracture at an angle to the bone shaft.

obstructive hydrocephalus

A type of hydrocephalus that occurs when cerebrospinal fluid flow is disrupted or not properly absorbed by the bloodstream.

occipital lobe

Lobe of the brain that processes visual information.

occult blood

Blood that occurs in small amounts and is not usually readily apparent.

occupational asthma

A type of asthma that is caused by a reaction to substances encountered at work. Symptoms develop over time, worsening with each exposure and improving when one is away from work.

oncogene

Gene that activates cell division and influences embryonic development.

oogenesis

The generation of eggs.

open-angle glaucoma

Type of glaucoma in which intraocular pressure increases gradually over an extended period. It is the most common type.

open fracture

Type of fracture in which the skin is broken. The bone fragments or edges may be angled and protrude out of the skin. Open fractures are associated with more damage to soft tissue and carry a greater risk for infection. Also called “compound fracture.”

opportunistic infection

An infection caused by pathogens that do not normally cause disease in healthy individuals.

optic nerve

The nerve formed at the back of the eye by axons of the ganglion cells coming together. This area contains no photoreceptors and is insensitive to light.

oral cancer

Cancer anywhere in the mouth. Most are squamous cell carcinomas of the tongue and mouth floor. Approximately 75% of

cases can be attributed to the use of smoked and smokeless tobacco.

organ of Corti

Part of the cochlea that contains hearing receptors, the hair cells. Vibrations at the organ of Corti stimulate hair movement.

organelle

An internal cellular structure. Organelles perform the work that maintains the cell's life.

orgasm

The climax of pleasurable sensations.

osmolarity

Solute concentration.

osmosis

The movement of water or another solvent across the cellular membrane from an area of low solute concentration to an area of high solute concentration.

osmotic pressure

The tendency of water to move by osmosis.

ossicle

Part of the ear consisting of three bones—malleus, incus, and stapes.

osteoarthritis (OA)

A localized joint disease characterized by deterioration of articulating cartilage and its underlying bone as well as bony overgrowth. The surface of the cartilage becomes rough and worn, interfering with joint movement. Also called "wear-and-tear arthritis" and "degenerative joint disease."

osteoblast

Cell on the outer surface of the periosteum that aids in remodeling and repair by rebuilding new compact bone to increase bone strength.

osteochondroma

A type of benign tumor that consists of cartilage and bone.

osteoclast

A cell that breaks down some spongy bone.

osteocyte

Osteoblast that has become surrounded by calcified extracellular material.

osteomalacia

A softening and weakening of bones in adults, usually because of an extreme and prolonged vitamin D, calcium, or phosphate deficiency.

osteomyelitis

An infection of the bone tissue.

osteonecrosis

Death of bone tissue due to a loss of blood supply. Also called “avascular necrosis.”

osteopenia

Bone mass that is less than expected for age, ethnicity, or gender.

osteoporosis

A condition characterized by a progressive loss of bone calcium that leaves the bones brittle.

osteosarcoma

An aggressive tumor that begins in the bone cells, usually in the femur, tibia, or fibula.

otitis externa

An infection or inflammation of the external ear canal or auricle. Also called “swimmer’s ear.”

otitis media

An infection or inflammation of the middle ear. It is a common condition in young children.

otosclerosis

An abnormal bone growth in the middle ear, usually involving an imbalance in bone formation and resorption.

outer ear

Division of the ear that consists of the auricle (or pinna), ear lobe, and external ear canal.

oval window

The opening to the inner ear covered with a membrane. Movement of the oval window causes fluid within the cochlea to vibrate, creating waves.

ovarian cancer

Cancer of the ovaries. There is no reliable screening test, it is difficult to treat, and it often has metastasized at the time of diagnosis. However, advances in treatment are improving the survival rates.

ovarian cyst

A benign fluid-filled sac on the ovary. Often the cyst forms in the ovulation process. Instead of the follicle releasing the egg, the fluid stays in the follicle, creating a cyst.

ovaries

Paired almond-shaped organs located on each side of the uterus.

overactive bladder

Urge incontinence with no known cause.

overflow incontinence

Incontinence as a result of an inability to empty the bladder.

ovulation

The transportation of the eggs.

pacemaker

Cells that create the rhythmic chemical impulses that in turn cause contraction of the heart muscle. The rate at which these impulses fire controls the heart rate.

$PaCO_2$

Partial pressure of carbon dioxide; it indicates the adequacy of pulmonary ventilation.

Paget's disease

A progressive condition characterized by abnormal bone destruction and remodeling, which results in bone deformities.

pain

A subjective feeling that serves as a protective mechanism, warning the body when something is wrong. In addition, pain is the most common reason why people seek medical attention and can be used to aid diagnosis.

pain threshold

The point at which pain is perceived.

pain tolerance

The amount of pain that an individual can physically and emotionally withstand.

palliative

Treatment aimed at increasing comfort.

pancreas

An organ with exocrine digestive functions and endocrine functions. The pancreas lies underneath the stomach and liver and between the two kidneys in the retroperitoneum.

pancreatic cancer

An aggressive malignancy (most commonly adenocarcinoma) of the pancreas that can quickly spread to structures nearby.

pancreatic polypeptide

Substance secreted by cells that is thought to regulate some of the pancreatic activities.

pancreatitis

An inflammation of the pancreas that can be acute or chronic.

pancytopenia

A lack of erythrocytes, leukocytes, and platelets.

pandemic

An epidemic that has spread to a larger population.

panhypopituitarism

A condition consisting of an inadequate or absent production of the anterior pituitary hormones.

papule

A small, red, elevated area of the skin.

paralysis

A lack of voluntary use of the affected limbs.

paralytic ileus

A functional intestinal obstruction.

paraphimosis

A condition in which the foreskin is retracted and cannot be returned over the glans penis.

paraplegia

Loss of lower-extremity function.

parasympathetic nervous system

Subdivision of the autonomic nervous system that is responsible for the rest-and-digest response.

parathyroid gland

A gland located on the posterior surface of the thyroid. There are usually four of these glands, each of which secretes parathyroid hormone.

parathyroid hormone (PTH)

A hormone that works in opposition to calcitonin to regulate serum calcium levels.

parietal lobe

The lobe of the brain that receives and interprets sensory input, except for smell, hearing, and vision.

parietal peritoneum layer

The outer layer of the peritoneum that covers the abdominal wall as well as the top of the bladder and uterus.

Parkinson's disease

A progressive condition involving the destruction of the substantia nigra in the brain. This destruction results in a lack of dopamine, a chemical messenger that allows smooth, coordinated muscle movement.

partial pressure of oxygen

The concentration of oxygen in the blood.

partially compensated

Partially corrected by physiological compensatory mechanisms.

parturition

The birth of the fetus.

passive acquired immunity

The protection gained by receiving antibodies made outside the body by another person, animal, or recombinant deoxyribonucleic acid (DNA). In passive immunity, the person is not actively producing antibodies, and protection is short lived. Examples of passive immunity include mother-to-fetus transfer through placental or breastfeeding transference.

pathogenesis

The development of a disease.

pathologic fracture

A type of fracture that results from a weakness in the bone structure secondary to conditions such as tumors or osteoporosis.

pathophysiology

The study of changes in normal anatomy and physiology associated with disease or injury.

pediculosis

A lice infestation that can take three forms—*Pediculus humanus corpus* (body louse), *Pediculus pubic* (pubic louse), and *Pediculus humanus capitis* (head louse). Lice are small, brown, parasitic insects that feed off human blood and cannot survive for long without the human host.

pelvic inflammatory disease (PID)

An infection of the female reproductive system.

penile cancer

Cancer of the penis. The exact cause is unknown, but risk is thought to be increased by the presence of smegma, being

uncircumcised, poor hygiene, phimosis, and human papillomavirus infection.

penis

Part of the male external genitalia; it contains erectile tissue that fills with blood during sexual arousal.

peptic ulcer disease (PUD)

Erosive lesions affecting the lining of the stomach or duodenum.

perfusion

The process of delivering oxygen and nutrients with arterial blood to tissue.

pericardial effusion

Fluid accumulation between the pericardium and the heart.

pericarditis

An inflammation of the pericardium. The fluid may be serous, purulent, serosanguineous, or hemorrhagic. As the pericardial tissue becomes inflamed, the swollen tissue rubs together, creating friction.

pericardium

Sac that encloses, protects, and supports the heart.

perimetrium

The outer serous layer of the uterine wall that covers all of the fundus and part of the corpus but none of the cervix.

periosteum

A layer of connective tissue that covers compact bone surfaces. It serves as the site of muscle attachment (via tendons).

peripheral nerve

A nerve that branches from a plexus and supplies sensory and motor functions to many areas of the body.

peripheral nervous system (PNS)

A division of the nervous system made up of the nerves.

peripheral vascular disease (PVD)

A narrowing in the peripheral vessels. Most often this condition is caused by atherosclerosis, but it can also be caused by thrombus, inflammation (e.g., thromboangiitis obliterans), or vasospasms (e.g., Raynaud's disease and Raynaud's phenomenon).

peripheral vascular resistance (PVR)

The force opposing the blood in the peripheral circulation. PVR increases as the diameter and elasticity of the blood vessels decrease.

peristalsis

The wavelike contraction of the muscle layer of the gastrointestinal tract that propels food through the gastrointestinal tract.

peritoneal cavity

The space between the parietal peritoneum layer and the visceral peritoneum layer. It contains serous fluid that decreases friction and facilitates movement of the peritoneum.

peritoneum

The large serous membrane that lines the abdominal cavity.

peritonitis

An inflammation of the peritoneum that can be life threatening.

pH

A measure of hydrogen concentration in the plasma. It is a negative logarithm that reflects hydrogen concentrations; the higher the hydrogen concentration, the lower the pH number.

phagocytosis

Endocytosis that involves solid particles. Also called “cell eating.”

phantom pain

Pain that exists after the removal of a body part. The affected person may feel the discomfort of the removed part. The severing of neurons may result in spontaneous firing of spinal cord neurons because normal sensory input has been lost. This type of pain can be very distressing but usually resolves with time.

pharynx

Passageway that connects the oral and nasal cavities to the larynx.

phenotype

The outward physical expression of genes, such as eye color.

pheochromocytoma

A rare tumor of the adrenal medulla. The tumor excretes epinephrine and norepinephrine and can be life threatening because of the effects of those hormones.

phimosis

Condition that occurs when the foreskin cannot be retracted from the glans penis.

phosphate system

Buffer mechanism that acts much like the bicarbonate–carbonic acid system. Buffering in this system primarily takes place in the kidneys by moving hydrogen.

phosphorus

An ion that is a component of phosphate. It is found in the bones and, in smaller quantities, in the bloodstream.

pia mater

The innermost layer of the meninges; it rests directly on the brain and spinal cord.

pigmented birthmark

A birthmark made of a cluster of pigment cells, which cause color in skin. These birthmarks can be many different colors, from tan to brown, gray to black, or even blue.

pinna

The irregularly shaped cartilage that channels sound into the ear. Also referred to as the *auricle*.

pinocytosis

Endocytosis that involves a liquid. Also called “cell drinking.”

pituitary gland

Pea-sized gland located at the base of the brain. It can be divided into two parts—the anterior and posterior pituitary gland. The pituitary gland is often referred to as the “master gland.” Despite its small size, this gland secretes several hormones that influence many different body functions.

placenta

A vascular organ that develops during pregnancy to nourish the fetus through the umbilical cord.

plasma

Liquid portion of the blood, primarily composed of protein.

plasma membrane

The semipermeable boundary of a cell containing the cell and its components. Also called *cell membrane*.

plasmin

An enzyme that dissolves clots once healing has occurred.

pleural effusion

The accumulation of excess fluid in the pleural cavity that can compress the lungs and limit their expansion during inhalation.

pleurisy

Inflammation of the pleural membranes that leads to swollen and irregular tissue. This inflammation is often associated with pneumonia and creates friction in the pleural membranes.

plexus

An organized collaboration of several intersected nerves.

***Pneumocystis jirovecii* pneumonia**

A specific type of pneumonia that is caused by a yeastlike fungus, *P. jirovecii*. It occurs as an opportunistic infection and can be fatal to immunocompromised individuals (e.g., children or those with AIDS or cancer).

pneumonia

An inflammatory process that may be caused by numerous infectious agents (e.g., bacteria, viruses, and fungi) and injurious agents or events (e.g., aspiration and smoke). *Streptococcus pneumoniae* is responsible for 75% of all cases of pneumonia.

pneumothorax

Air in the pleural cavity. The presence of atmospheric air in the pleural cavity and the separation to pleural membranes can lead to atelectasis. The pressure can cause a partial or complete collapse of a lung.

polycystic kidney disease (PKD)

An inherited disorder characterized by numerous grape-like clusters of fluid-filled cysts in both kidneys.

polycystic ovary syndrome

A condition in which the ovary becomes enlarged and contains numerous cysts.

polydipsia

Excessive thirst.

polyphagia

An increase in the hunger sensation.

polyuria

An increase in the amount of water that is excreted.

pons

The part of the brainstem that contains the nerves that regulate sleep and breathing.

port-wine stain

Vascular birthmark that looks like wine was spilled on an area of the body. These birthmarks most often occur on the face, neck, arms, and legs.

portal hypertension

Increase in vessel pressures in the hepatic artery and the portal vein. This increased pressure is often associated with liver disease.

portal vein

Part of the liver's dual blood supply; it carries partially deoxygenated blood from the stomach, pancreas, spleen, and small and large intestines to the liver at a rate of approximately 1,000 mL/min so that the liver can process nutrients and digestion by-products.

positive feedback system

One of two types of feedback systems that maintain homeostasis (the other is a negative feedback system). The

positive feedback system works to increase an output in the system. An example of a positive feedback system is a blood clot.

posterior chamber

The cavity of the eye interior that is behind the lens.

postictal period

The period following a generalized seizure, during which the individual may be confused, be fatigued, and fall into a deep sleep.

postrenal condition

Cause of acute renal failure that interferes with urine excretion.

postsynaptic cell membrane

The membrane that receives and responds to a signal (binds neurotransmitter) from the presynaptic cell.

potassium

The primary intracellular cation. Potassium plays a crucial role in electrical conduction, acid–base balance, and metabolism (carbohydrate, protein, and glucose).

PP cell

One of five types of cells in the islets of Langerhans; it secretes a pancreatic polypeptide.

predisposing factor

Tendency that puts an individual at risk for developing certain diseases.

pregnancy-induced hypertension (PIH)

Hypertension that occurs for the first time during pregnancy. It occurs in 5% to 8% of all pregnancies.

preload

The amount of blood returning to the heart, which the heart has to manage. Both afterload and preload can affect blood pressure. As afterload and preload increase, blood pressure increases.

premenstrual dysphoric syndrome

A severe form of premenstrual syndrome that is characterized by severe depression, tension, and irritability.

premenstrual syndrome (PMS)

A group of physical and emotional symptoms that affect many women prior to menstruation for reasons not fully understood.

prerenal condition

Cause of acute renal failure that disrupts blood flow on its way to the kidneys.

presbycusis

Age-related hearing loss.

presbyopia

Difficulty focusing the eyes resulting from age-related changes.

presynaptic terminal

Terminal bouton or some similar structure. It is a specialized area within the axon of the presynaptic cell that contains neurotransmitters enclosed in small membrane-bound spheres.

prevention

Strategies used to avoid the development of disease in individuals or groups.

priapism

A prolonged, painful erection.

primary herpes genitalis

The first stage of genital herpes. It usually occurs within 2–10 days of exposure and is characterized by blisters or open lesions, fever, headache, muscle aches, swollen lymph nodes in the groin area, painful urination, and vaginal discharge.

primary hypertension

Type of hypertension in which there is no identifiable cause. It occurs in 90% to 95% of hypertension cases in adults and tends to develop gradually over many years. Also called “essential hypertension.”

primary immunodeficiency

Type of immunodeficiency that involves basic developmental failures, many resulting from genetic or congenital abnormalities (e.g., hypogammaglobulinemia).

primary syphilis

The first stage of syphilis. Painless chancres (usually one) form at the site of infection about 2–3 weeks after initial infection.

primary tuberculosis infection

One of two stages of tuberculosis pathogenesis. In this stage, infection occurs when the bacillus first enters the body.

prion

An abnormal protein particle that causes proteins to fold abnormally, especially in nervous tissue.

prodrome

In infection with the herpes simplex virus, a tingling or burning sensation at the site just before a lesion appears.

prognosis

An individual’s likelihood of surviving, making a full recovery, or regaining normal functioning after developing a disease.

programmed cell death

The process of eliminating unwanted cells. Also called *apoptosis.*

progression

Phase of carcinogenesis in which the tumor invades, metastasizes, and becomes drug resistant. The final phase of carcinogenesis, it is irreversible.

progressive stage

State of shock that begins when the compensatory mechanisms fail to maintain cardiac output. Tissues become hypoxic, cells switch to anaerobic metabolism, lactic acid builds up, and metabolic acidosis develops.

prolactin

A hormone from the anterior pituitary gland that stimulates milk production.

proliferation

The regulated process by which cells divide and reproduce.

promotion

Phase of carcinogenesis in which the mutated cells are exposed to factors that promote their growth. It may occur just after initiation or years later, and it can be reversible if the promoting factors are removed.

prophase

Phase of mitosis in which the chromosomes condense, and the nuclear membrane disintegrates.

prophylactic

Treatment aimed at preventing disease.

prostate cancer

Cancer of the prostate. It is the most common cancer among men. The slow-growing tumor is often confined to the prostate, improving the prognosis.

prostate gland

A chestnut-shaped gland at the base of the urethra in men; it produces fluid that mixes with the sperm and secretions of the seminal vesicles. This prostate fluid decreases acidity of the secretions, increases sperm motility, and prolongs sperm life.

prostatitis

Inflammation of the prostate, which can be either acute or chronic.

protein system

The most abundant buffering system. Proteins can act as an acid or a base by binding to or releasing hydrogen. Proteins exist in intracellular and extracellular fluid but are most abundant inside the cell.

protoplasm

A colorless, viscous liquid containing water, nutrients, ions, dissolved gases, and waste products, where the cellular work takes place. Also called *cytoplasm*.

psoriasis

A common chronic inflammatory condition that affects the life cycle of the skin cells.

pulmonary artery

Vessel that carries deoxygenated blood from the right ventricle to the lungs for oxygenation.

pulmonary circulation

The portion of the cardiovascular system that carries oxygen-depleted blood away from the heart and to the lungs and then returns oxygenated blood back to the heart.

pulmonary vein

Vessel that carries oxygenated blood from the lungs to the left atrium.

pulmonic valve

A three-leaflet valve that guides the passage of blood from the right ventricle to the pulmonary artery and prevents the backward flow of blood.

pulse pressure

The difference between the systolic and diastolic blood pressures.

pupil

The dark opening in the center of the iris that opens and closes reflexively in response to light intensity.

Purkinje network of fibers

Area of specialized cells in the heart that receives impulses from the bundle branches and stimulates ventricular contraction.

pus

Yellowish-white wound drainage, usually produced by infected tissue and consisting of dead white cells, bacteria, tissue debris, and serum.

pyelonephritis

An infection that has reached one or both kidneys.

pyloric sphincter

A muscular ring through which chyme passes as it leaves the stomach in small, varying amounts. It prevents reflux of bile from

the small intestines into the stomach.

pyloric stenosis

A narrowing and obstruction of the pyloric sphincter.

pyrogen

A substance released by bacteria or viruses that can produce a fever.

quadriplegia

Loss of all or most function in all four limbs; also known as tetraplegia.

Raynaud's disease

A condition that results from vasospasms of arteries—most often of the hands—which occur because of sympathetic stimulation.

recessive

Less influential. In genetics, the recessive allele is less likely to be expressed in the offspring than the dominant one.

rectocele

Condition that occurs when the rectum protrudes through the posterior wall of the vagina.

rectum

A reservoir to store feces.

recurrent herpes genitalis

The fourth stage of genital herpes; characterized by the reactivation of the virus and clinical manifestations.

red marrow

Bone marrow that serves as the blood-cell factory (hematopoiesis). As humans age, this red marrow is slowly replaced by fat, creating yellow marrow.

reduce

A fracture treatment in which the broken bone fragments are brought together to promote healing. Reduction can be accomplished by manual manipulation or surgery.

referred pain

Pain at distant locations from the originating site.

reflex incontinence

Urinary incontinence caused by trauma or damage to the nervous system.

regulator cell

One of two major types of T cells that work to destroy antigens. Regulator cells include helper T cells and suppressor T cells.

regurgitation

A backward flow. In the heart, it occurs when the valve leaflets do not completely close. Incompetent or insufficient valves allow blood to flow in both directions. In the stomach, it occurs when food is vomited.

remission

Disease state that occurs when the manifestations subside.

renal artery

The artery that supplies each kidney with blood.

renal capsule

Connective tissue that surrounds the kidneys.

renal cell carcinoma

The most frequently occurring kidney cancer in adults. It is most common in individuals 50–70 years of age.

renal cortex

The area immediately beneath the renal capsule that contains the functional units of the kidney.

renal hilum

The opening in the kidney that the renal artery and nerves enter and the renal vein and ureter exit.

renal pelvis

Funnel-like area in the center of the kidney into which urine drains.

renal sinus

A cavity into which the renal hilum opens.

renin–angiotensin–aldosterone system

A vital control and compensatory mechanism that is activated when renal blood flow is decreased, often in hypotensive states. When blood flow is decreased to the kidneys, renin is released from the kidneys, which in turn activates angiotensin I to become converted to angiotensin II (a vasoconstrictor) and stimulates aldosterone secretion. In hypotensive states, this mechanism raises blood pressure and maintains vital organs. In chronic disease states, such as hypertension, it is inappropriately activated because of vasoconstriction to the kidneys, further contributing to the hypertension.

repolarization

1. The recovery of the ventricles, represented by T waves. Repolarization of the atria does not appear on an electrocardiogram because it is hidden by the other more prominent waveforms. 2. Restoration of the resting potential of the cell membrane.

residual volume

Volume of air left in the lungs after maximum exhalation.

resistance

The second stage of the general adaptation syndrome. In this stage, the body chooses the most effective and advantageous defense. Cortisol levels and the sympathetic nervous system return to normal, causing the fight-or-flight symptoms to disappear. The body will either adapt or alter its functioning in an attempt to limit problems or become desensitized to the stressor.

respiratory acidosis

Condition that results from carbon dioxide retention, which leads to increased carbonic acid and, in turn, decreased pH.

respiratory alkalosis

Condition that results from excess exhalation of carbon dioxide, which leads to carbonic acid deficits and pH increases.

resting potential

A slight charge that the plasma side of the neuron membrane has at rest because of the sodium ions concentrated on the outside of the cell.

restrictive cardiomyopathy

Type of cardiomyopathy that is characterized by rigidity of the ventricles leading to diastolic dysfunction.

retching

A strong, unproductive effort to vomit.

retention

An inability to empty the bladder.

reticular activation system

Specialized nerve fibers through which the reticular formation sends impulses to the cerebral cortex. The reticular formation and reticular activation system are responsible for alertness during the day and can prevent sleeping at night.

reticular formation

A region of the brainstem in which most of the branches of the many nerve fibers passing through the brainstem terminate. The reticular formation acts like a gatekeeper, receiving all incoming and outgoing information. It sends impulses to the cerebral cortex through specialized nerve fibers.

retina

The innermost layer of the eye. It contains an outer pigmented layer and an inner layer consisting of photoreceptors and nerve cells. The retina is weakly attached to the choroid, making it vulnerable to damage.

retinal detachment

An acute condition in which the retina separates from its supporting structures.

retractile testicle

A testicle that moves back and forth between the scrotum and the lower abdomen. Such a testicle is easily returned to the scrotum through gentle manipulation.

retroflexed

Tilted backward. Often used in reference to the uterus.

rheumatoid arthritis (RA)

A systemic, autoimmune condition involving multiple joints. In RA, the inflammatory process primarily affects the synovial membrane, but it can also affect other organs.

rhinosinusitis

An inflammation of the sinus cavities, most often caused by a viral infection. Previously referred to as “sinusitis.”

rickets

A softening and weakening of bones in children, usually because of an extreme and prolonged vitamin D, calcium, or phosphate deficiency.

right atrium

Receiving chamber on the right side of the heart. It receives blood from the peripheral circulation, and blood leaves this chamber and travels to the right ventricle.

right-sided heart failure

Type of heart failure that results from an ineffective right ventricular contractility. As a result, blood does not move appropriately out of the right ventricle. Blood backs up first into the right atrium and then into the peripheral circulation, causing increased pressures in the capillary bed.

right ventricle

Pumping chamber of the left side of the heart. It pumps blood to the pulmonary circulation.

rod

A photoreceptor in the eye that is sensitive to low light and that functions at night. There are nearly 150 million rods in the human eye.

rootlet

A small nerve along the dorsal and ventral surfaces of the spinal cord from which spinal nerves arise.

rosacea

A chronic inflammatory skin condition that typically affects the face. Rosacea is poorly understood, but it is prevalent in persons who are fair skinned, persons who bruise easily, and women. It

may present as erythema, prominent spiderlike blood vessels (telangiectasia), swelling, or acnelike eruptions.

rugae

Wrinkles in the stomach that unfold as the stomach fills.

saccular aneurysm

A bulge on the side of a blood vessel. One of two major types of true aneurysms.

saccule

A bed of sensory cells situated in the inner ear. It translates head movements into neural impulses that the brain can interpret.

sarcomere

Repeated structural unit into which myofilaments are organized.

scabies

A result of a mite infestation. The female mites burrow into the epidermis, laying eggs over a period of several weeks. The larvae hatch from the eggs and then migrate to the skin's surface. The larvae burrow into the skin in search of nutrients and mature to repeat the cycle. The burrowing and fecal matter left by the mites trigger the inflammatory process, leading to erythema and pruritus.

Schwann cell

A cell that produces the myelin sheath.

sciatica

A radiating, aching pain, sometimes with tingling and numbness, that starts in the buttock and extends down the back or side of one leg.

sclera

White fibrous material of the outermost layer of the eye.

scoliosis

A lateral deviation of the spine. This lateral curvature may affect the thoracic or lumbar area or both. Scoliosis may also include a rotation of the vertebrae on their axis.

scrotum

A sac of skin just below the penis that contains the testes, epididymis, and lower spermatic cords.

sebaceous gland

A gland that produces sebum.

sebum

Secretion of the sebaceous gland that moisturizes and protects the skin.

secondary glaucoma

Type of glaucoma that is a result of certain medications, eye diseases, and systemic diseases.

secondary hypertension

High blood pressure caused by another medical condition. Examples include kidney disease, artheriosclerosis, adrenal dysfunction, thyroid problems, and obstructive sleep apnea.

secondary immunodeficiency

An acquired immunodeficiency that involves a loss of immune function because of a specific cause (e.g., infection, splenectomy, malnutrition, hepatic disease, drug therapy, or stress).

secondary syphilis

Stage of syphilis that occurs about 2–8 weeks after the first chancres form. Approximately 33% of those individuals who do not have their primary syphilis treated will develop this second

stage. This stage is characterized by a generalized brown-red rash that does not itch.

secondary tuberculosis infection

A condition that occurs when the primary tuberculosis (TB) infection can no longer be controlled, such that the TB spreads throughout the lungs and other organs.

seizure

A transient physical or behavior alteration that results from an abnormal electrical activity in the brain.

selectively permeable

Condition that allows a cell to maintain internal balance or homeostasis.

semen

Fluid made up of ejaculatory fluid and sperm. It flows from the ejaculatory duct to the urethra, where it is released from the penis during sexual intercourse.

semicircular canal

A ringlike, fluid-filled structure that houses receptors for body position and movement. Movement of the head causes the fluid in the semicircular canal to move. Fluid movement stimulates dendrites to send impulses to the brain to report this movement. There are three semicircular canals in each human ear.

seminal vesicles

A pair of pouches that secrete an alkaline ejaculatory fluid containing sugar, protein, and prostaglandins. The seminal vesicles join with the ampulla to form the ejaculatory duct.

sensory nerve

A type of nerve of the peripheral nervous system. It carries impulses from the body to the brain. Also called *afferent nerve.*

septic shock

Type of distributive shock in which a bacterium's endotoxins activate an immune reaction. Inflammatory mediators are triggered, increasing capillary permeability and fluid shifts from the vascular compartment to the tissue. Falling cardiac output leads to multisystem organ failure.

serosa

The outermost of the four layers of the walls of the gastrointestinal tract.

sesamoid bone

One of the five types of bones found within the skeleton. Sesamoid bones are usually short or irregular bones embedded in a tendon. They are typically present in a tendon where it passes over a joint and serve to protect the tendon.

severe acute respiratory syndrome (SARS)

A respiratory illness that presents similarly to atypical pneumonia. Prevalence rates are higher in Asian countries. SARS is caused by a coronavirus, SARS-CoV. Transmission occurs through inhalation of respiratory droplets, close contact, or oral–fecal contact. SARS has high mortality and morbidity rates.

sex-linked

Type of genetic disorder that is caused by genes located on the sex chromosomes.

sexually transmitted infection (STI)

Any of a broad range of infections that can be contracted through sexual contact. Sometimes referred to as “sexually transmitted disease (STD).”

shedding herpes genitalis

The third stage of herpes, wherein the virus is reactivated but produces no symptoms.

shock

A clinical syndrome resulting from inadequate tissue and organ perfusion because of decreased blood volume or circulatory stagnation.

short bone

One of the five types of bones found within the skeleton. Short bones are approximately as wide as they are long, and their primary function is to provide support and stability with little movement. Short bones contain only a thin layer of compact bone, along with spongy bone and relatively large amounts of bone marrow.

signs

Clinical manifestations that can be seen or measured.

simple fracture

A fracture with a single break in the bone and bone ends that maintain their alignment and position.

sinoatrial (SA) node

Area of the heart where the conduction pathway originates. All impulses originating in the SA node travel through the right and left atria, resulting in atrial contraction. The SA node automatically generates impulses ranging from 60 to 100 beats per minute (sinus rhythm).

sinusitis

An inflammation of the sinus cavities, most often caused by a viral infection. More recently referred to as rhinosinusitis.

skeletal muscle

Muscle that connects to bone. The most frequently occurring muscle type, it makes up approximately 40% of the body's weight.

skeleton

The 206 bones of varying shapes and sizes in the human body. The skeleton provides support and protection for vital organs such as the heart, lungs, and brain.

Skene gland

Gland in the mucosal lining of the vagina that secretes a protective lubricating fluid during sexual intercourse.

skin

Outer covering of the body that is composed of three layers—endodermis, dermis, and epidermis.

skin cancer

An abnormal growth of skin cells.

skin tag

A benign soft brown or flesh-colored growth, usually on the neck.

small-cell carcinoma

A type of lung cancer that occurs almost exclusively in heavy smokers and is less frequent than non-small-cell cancers. Also called "oat-cell carcinoma."

small intestine

The longest section of the gastrointestinal tract (approximately 20 feet long in adults). This length allows for adequate nutrient

absorption as the small intestine continues the digestion process. In the small intestine, the enzymes that have been secreted into the gastrointestinal tract break the large food molecules into smaller molecules, which are then absorbed.

smegma

An oily secretion produced by the glans that can combine with dead skin to form a cheesy substance. If the smegma is not regularly removed from under the foreskin, the penis can become irritated and infected.

smooth muscle

Type of muscle that lines the walls of hollow organs and tubes and is found in the eyes, skin, and glands. Smooth muscles are involuntary.

sodium

The most significant cation. Sodium is the most prevalent electrolyte of extracellular fluid, and its primary function is to control serum osmolality and water balance.

somatic pain

One of two types of pain the body perceives. It results from noxious stimuli to the skin, joints, muscles, and tendons. These stimuli may include cutting, crushing, pinching, extreme temperature, and irritating chemicals. Somatic pain is generally easy to pinpoint.

somatostatin

Hormone secreted by delta cells that regulates insulin and glucagon.

spermatic cord

A cordlike structure, consisting of the vas deferens and its accompanying arteries, veins, nerves, and lymphatic vessels, that passes from the abdominal cavity through the inguinal canal down into the scrotum to the back of the testicle.

spermatocele

A sperm-containing cyst that develops between the testes and the epididymis.

spermatogenesis

The generation of sperm.

spina bifida

A neural tube defect that can vary in severity from mild to debilitating. Neural tube development begins early in pregnancy, starting at the cervical area and progressing toward the lumbar area, and the neural tube usually closes by the fourth week of gestation. In spina bifida, the posterior spinous processes on the vertebra fail to fuse. This opening permits the meninges and spinal cord to herniate, resulting in neurologic impairment.

spina bifida occulta

The mildest form of spina bifida. It results in a small gap in one or more of the vertebrae. The spinal nerves and meninges do not usually protrude through the opening, so most children with this form have no clinical manifestations and do not experience any neurologic deficits.

spinal cord

A long, thin, tubular bundle of nervous tissue that exits the skull through the large and only opening in the skull, the foramen magnum.

spinal cord injury (SCI)

Injury that occurs directly to the spinal cord or indirectly to surrounding bones, tissues, or blood vessels.

spinal reflex arc

The process that creates an unconscious response to stimuli.

spinal shock

A temporary suppression of neurologic function because of spinal cord compression. In spinal shock, neurologic function gradually returns.

spiral fracture

A fracture that twists around the bone shaft.

spongy bone

The inner region of a bone, which is less dense than the outer region.

spontaneous pneumothorax

Type of pneumothorax that develops when air enters the pleural cavity from an opening in the internal airways.

sprain

An injury to a ligament that often involves stretching or tearing of the ligament.

stable angina pectoris

Type of cardiac chest pain that is a result of ischemia that is initiated by increased demand (activity) and relieved with the reduction of that demand (rest).

stapes

One of the three ossicles in the middle ear. Also called “stirrup.”

status asthmaticus

A life-threatening, prolonged asthma attack that does not respond to usual treatment.

status epilepticus

Seizures that last longer than 5 minutes or subsequent seizures that occur before the individual has fully regained consciousness from previous seizures.

stenosis

A narrowing of a tubular structure, such as the heart valves or blood vessels. When the heart valves are stenosed, blood moving through the valves is reduced, causing blood to back up in the chamber just before the valve.

stomach

An expandable food and liquid reservoir. When empty, the stomach wall shrinks, forming wrinkles called rugae. As the stomach fills, the rugae unfold and the wall stretches to accommodate a volume of as much as 2–4 L.

strabismus

A gaze deviation of one eye. With strabismus, the eyes do not coordinate to focus on the same object together, resulting in diplopia. Also called “cross-eyes.”

strain

An injury to a muscle or tendon that often involves stretching or tearing of the muscle or tendon.

stress fracture

Type of fracture that occurs from repeated excessive stress. Also called “fatigue fracture.”

stress incontinence

Loss of urine from pressure exerted on the bladder by coughing, sneezing, laughing, exercising, or lifting something heavy. Stress

incontinence occurs when the sphincter muscle of the bladder weakens.

stress ulcer

Type of peptic ulcer disease that develops because of a major physiologic stressor on the body.

stroke volume

The amount of blood ejected from the heart with each contraction. In addition to afterload, stroke volume is affected by preload.

subarachnoid hemorrhage

Bleeding in the space between the arachnoid and the pia mater in the brain. The primary clinical presentation is a severe headache with a sudden onset that is worse near the back of the head.

subdural hematoma

A collection of blood that develops between the dura mater and the arachnoid in the brain, frequently caused by a small venous tear. Because it is a result of a venous tear, a subdural hematoma generally develops slowly.

submucosa layer

One of four layers of the walls of the gastrointestinal tract. It is composed of connective tissue that includes blood vessels, nerves, lymphatics, and secretory glands.

substantia nigra

A brain structure located in the mesencephalon (midbrain) that plays an important role in reward, addiction, and movement. Substantia nigra is Latin for “black substance,” as parts of the substantia nigra appear darker than neighboring areas due to

high levels of neuromelanin. Parkinson's disease is caused by the death of dopaminergic neurons in the substantia nigra pars compacta.

subthalamus

Part of the thalamus that participates in motor activities.

sulcus (plural: sulci)

The grooves in between the gyri of the brain.

superior vena cava

Large vein that carries deoxygenated blood from the upper half of the body to the right atrium.

suppressor cell

A type of regulator cell that turns antibody production off.

surfactant

A substance on the surface of the alveoli. Surfactant is a lipoprotein produced by alveolus cells and has a detergent-like quality. This watery substance produces surface tension on the alveolus, which enhances pulmonary compliance and prevents the alveoli from collapsing.

suture

An immoveable joint in the skull.

sympathetic nervous system (SNS)

Subdivision of the autonomic nervous system that is responsible for the fight-or-flight response.

symptoms

Clinical manifestations that are described by the patient.

synapse

The junction between two neurons. It includes the presynaptic terminal, the synaptic cleft (space between neurons), and a

postsynaptic cell membrane.

synaptic cleft

Space between neurons.

synarthrosis

An immoveable joint.

syndrome

A group of signs and symptoms that occur together.

syndrome of inappropriate antidiuretic hormone (SIADH)

Condition of increased renal water retention caused by excessive antidiuretic levels.

syngeneic

Type of transplant in which tissue from the identical twin of the host is used.

synovial fluid

A transparent viscous fluid secreted by the synovial membrane that lubricates cartilage in the synovial joints.

synovial joint

A freely moveable joint; it is the most common type of joint. Synovial joints contain cartilage that is lubricated by a transparent viscous fluid secreted by the synovial membrane.

syphilis

An ulcerative sexually transmitted infection caused by *Treponema pallidum*, a spiral-shaped (spirochete) bacterium that requires a warm, moist environment to survive.

systemic circulation

The part of the cardiovascular system that carries oxygenated blood away from the heart to the body and returns deoxygenated blood back to the heart.

systemic lupus erythematosus (SLE)

A chronic, autoimmune, inflammatory disorder that can affect any connective tissue. It is thought that B cells are activated for unknown reasons to produce autoantibodies and autoantigens that combine to form immune complexes.

systole

The top number of a blood pressure reading, which indicates work done by the ventricles.

systolic dysfunction

Type of heart failure characterized by decreased cardiac output due to decreased contractility.

T_3

Triiodothyronine; a hormone produced by the follicles of the thyroid gland to regulate cellular metabolism and growth and development.

T_4

Thyroxine; a hormone produced by the follicles of the thyroid gland to regulate cellular metabolism and growth and development.

T cell

A cell that is a major part of the body's defense. It is produced in the bone marrow and matures in the thymus—hence its name. Two major types of T cells work to destroy antigens—regulator cells and effector cells.

telophase

Phase of mitosis in which chromosomes arrive at each pole and new membranes are formed.

temporal lobe

The lobe of the brain that plays an essential role in hearing and memory.

tendon

Specialized tough cord or band of dense connective tissue that is a continuous extension of the periosteum.

tension pneumothorax

The most serious type of pneumothorax; it occurs when the pressure in the pleural space is greater than the atmospheric pressure. This increased pressure is due to trapped air in the pleural space or entering air from a positive-pressure mechanical ventilator.

teratogen

A birth defect–causing agent.

terminal bouton

Minuscule bulge into which several small fibers terminate. These terminal boutons communicate with neurons, muscle fibers, or glands.

tertiary syphilis

The final stage of syphilis. The early latency stage begins when the secondary symptoms disappear and lasts 1–4 years. The late latency stage can last for years as the infection spreads to the brain, nervous system, heart, skin, and bones. Also called *latent syphilis*.

testes

Gonads; organs that produce sperm and the sex hormones.

testicular cancer

Cancer of the testicles. Testicular cancer can occur as a slow-growing or fast-growing tumor. Risk for developing testicular

cancer is thought to be increased by family history, infection, trauma, and cryptorchidism. Testicular cancer usually affects one testicle but can affect both.

testicular torsion

An abnormal rotation of the testis on the spermatic cord.

testosterone

Hormone that gives males their classic secondary sex characteristics and sex drive. Testosterone also regulates metabolism and protein anabolism, inhibits pituitary secretion of the gonadotropins, and promotes potassium excretion and renal sodium reabsorption.

thalamus

Part of the diencephalon that receives and relays most of the sensory input, affects mood, and initiates body movements (especially those associated with fear or anger).

third spacing

Significant fluid increases in compartments where fluid does not normally collect (e.g., peritoneum). Fluid in these compartments is not easily exchanged among the other extracellular fluids.

thromboangiitis obliterans

An inflammatory condition of the arteries. Also known as “Buerger’s disease.”

thrombocyte

A blood platelet.

thrombocytopenia

Decreased platelet levels; a condition that increases the risk of bleeding and infection.

thrombocytosis

Increased platelet levels; a condition that increases the risk of thrombus formation.

thromboplastin

A factor in blood clotting that is stimulated by the release of thromboplastin from damaged cells lining blood vessels.

thrombotic thrombocytopenic purpura (TTP)

A coagulation disorder that is a result of a deficiency of an enzyme necessary for cleaving von Willebrand factor.

thrombus

A blood clot that consists of platelets, fibrin, and red and white blood cells. These clots can form anywhere in the circulatory system.

thyroid gland

A gland located at the base of the neck below the larynx that consists of two lobes, one on either side of the trachea.

thyroid-stimulating hormone (TSH)

Hormone produced by the pituitary gland that stimulates the thyroid to produce T_3 and T_4.

thyrotoxicosis

Thyroid crisis; a sudden worsening of hyperthyroidism symptoms that may occur with infection or stress. Fever, decreased mental alertness, and abdominal pain may occur. Thyrotoxicosis is a medical emergency.

tidal volume

The amount of air involved in one normal inhalation and exhalation.

tinea

A parasite that causes several types of superficial fungal infections, which are described by the area of the body affected. Tinea corporis, or ringworm, is an infection of the body. Tinea pedis, or athlete's foot, involves the feet, especially the toes. Tinea unguium is an infection of the nails, typically the toenails.

tinnitus

A persistent perception of abnormal noises in the ear, which may be described as ringing, buzzing, humming, whistling, roaring, or blowing.

TNM staging

Method of expressing the extent of cancer by evaluating the tumor size, nodal involvement, and metastatic progress.

tonicity

The osmotic pressure of two solutions separated by a semipermeable membrane.

tophus (plural: tophi)

A large hard nodule consisting of uric acid crystals deposited in soft tissues, usually in cooler areas of the body.

trachea

The windpipe; it carries air from the oral and nasal cavities to the lungs.

transcellular

A third compartment of fluid in the body, in addition to the interstitial and intravascular compartments. The transcellular compartment refers to the space between cells.

transient incontinence

Urinary incontinence resulting from a temporary condition.

transient ischemic attack (TIA)

A temporary episode of cerebral ischemia that results in symptoms of neurologic deficits. TIAs are often called ministrokes because these neurologic deficits mimic a cerebral vascular accident or stroke except that these deficits resolve within 24 hours (1–2 hours in most cases).

transverse fracture

A fracture straight across the bone shaft.

traumatic brain injury (TBI)

Injury that is usually caused by a sudden and violent blow or jolt to the head (called a “closed injury”) or a penetrating (known as an “open injury”) head injury that disrupts the normal brain function.

traumatic pneumothorax

Type of pneumothorax that is caused by any blunt or penetrating injury to the chest. These injuries can inadvertently occur during certain medical procedures.

treatment

Strategies used to manage or cure a disease.

trichomoniasis

Infection caused by *Trichomonas vaginalis*, a one-celled anaerobic organism. This extracellular parasite can burrow under the mucosal lining. Colloquially referred to as “trick.”

tricuspid valve

A three-leaflet valve that guides the passage of blood from the right atria to the right ventricle and prevents the backward flow of blood.

Trousseau sign

An indicator of hypocalcemia in which a strategically placed blood pressure cuff elicits a carpal spasm.

tuberculosis (TB)

A potentially serious infectious disease that is increasing globally after declining in previous decades. TB is caused by Mycobacterium tuberculosis.

tumor

A cellular growth that is no longer responding to normal regulator processes. Also called *neoplasm.*

tumor grading system

The degree of differentiation of a malignancy. The grading system determines the degree of differentiation on a scale of 1 to 4 in order of clinical severity, with grade 1 cancers being well differentiated and less likely to cause problems and grade 4 cancers being undifferentiated, meaning they are highly likely to cause problems because they do not resemble any characteristics of the original tissue.

tunica adventitia

The outer layer of the blood vessels, which consists of elastic and fibrous connective tissue.

tunica intima

The smooth, thin inner layer of the blood vessels.

tunica media

The middle layer of the blood vessels, which is composed of elastic tissue and smooth muscle that is responsible for the vessel's ability to constrict and dilate.

tympanic membrane

Part of the ear that separates the outer ear and the middle ear. Sound hits the tympanic membrane, creating vibrations. Also called “eardrum.”

type 1 diabetes

Type of diabetes mellitus that develops when the body’s immune system destroys pancreatic beta cells. To survive, people with type 1 diabetes must have insulin delivered by injection or a pump. This form of diabetes usually strikes children and young adults, although disease onset can occur at any age. Previously called “insulin-dependent diabetes” and “juvenile-onset diabetes.”

type 2 diabetes

Type of diabetes that usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce it. Previously called “non-insulin-dependent diabetes” and “adult-onset diabetes.”

type I hypersensitivity

Immunoglobulin E–mediated type of hypersensitivity in which an allergen activates T cells that then bind to mast cells. Repeated exposure to relatively large doses of the allergen is usually necessary to cause this response.

type II hypersensitivity

Tissue-specific type of hypersensitivity that generally involves the destruction of a target cell by an antibody-directed cell-surface antigen. Immunoglobulin G or M reacts with an antigen on the cell, activating the complement system. The effects of type II reactions include cell lysis and phagocytosis.

type III hypersensitivity

Immune complex–mediated type of hypersensitivity in which circulating antigen–antibody complexes accumulate and are deposited in the tissue. This accumulation triggers the complement system, causing local inflammation and increased vascular permeability, so more complexes accumulate.

type IV hypersensitivity

Cell-mediated type of hypersensitivity that involves a delayed processing of the antigen by the macrophages. Once processed, the antigen is presented to the T cells, resulting in the release of lymphokines that cause inflammation and antigen destruction.

type A influenza

The most common type of influenza virus. It includes several subtypes, including H1N1. Type A influenza is usually responsible for the most serious epidemics and global pandemics.

type B influenza

Type of influenza virus that can cause regional epidemics, although the disease it produces is generally milder than that caused by type A influenza.

type C influenza

Type of influenza virus that causes sporadic cases and minor local outbreaks. Type C has never been connected with a large epidemic.

ulcerative colitis

A progressive condition of the rectum and colon mucosa that usually develops in the second or third decade of life. Inflammation causes epithelium loss, surface erosion, and ulceration.

uncompensated

Not corrected by physiological compensatory mechanisms.

unstable angina

A change in cardiac chest pain; the pain becomes unpredictable, occurs at rest, or increases in frequency or intensity. It is considered a preinfarction state.

urea

One of the three most significant metabolic wastes managed by the kidneys.

uremia

Waste accumulation due to renal impairment.

ureter

Part of the urinary system that transports the urine, using peristaltic actions, to the bladder for storage.

urethra

Tube that transports urine out of the body from the bladder, and, in males, transports semen.

urge incontinence

A sudden, intense urge to urinate, followed by an involuntary loss of urine.

uric acid

A metabolism by-product managed by the kidneys that is a result of the breakdown of nucleotides, the building blocks of deoxyribonucleic acid (DNA).

urinary incontinence

Involuntary loss of urine.

urinary tract infection (UTI)

Infection of the urinary tract that often ascends from the urinary meatus. It is typically caused by *Escherichia coli* and occurs

more frequently in females.

urination

The voluntary contraction of the bladder and relaxation of the external sphincter, forcing urine out through the urethra.

urticaria

Raised erythematous skin lesions that are a result of a type I hypersensitivity reaction. Also called “hives.”

uterine prolapse

The descent of the uterus or cervix into the vagina.

uterus

A hollow pear-shaped organ held in place by the broad, round uterosacral ligaments.

utricle

A division of the inner ear that detects motion and position.

vagina

A hollow tunnel-like structure that extends from the cervix to the external genitalia.

varicocele

A dilated vein in the spermatic cord.

varicose vein

A dilated, tortuous, engorged vein that develops because of improper venous valve function. The most common location in which varicose veins occur is the legs, but they can be found in the esophagus (esophageal varices) and the rectum (hemorrhoids). Also called “varicosity.”

vas deferens

Part of the male duct system that carries sperm out of the testes.

vascular birthmark

Birthmark that consists of blood vessels that have not formed correctly; therefore, these birthmarks are generally red.

vein

A blood vessel that carries blood back to the heart.

ventilation

The transportation of air from the atmosphere to the lungs and out again.

ventilation-to-perfusion ratio (VQ ratio)

A measurement used to assess the efficacy and adequacy of ventilation and perfusion. Also called VQ ratio.

ventral root

A root formed from approximately 6–8 ventral rootlets. The roots then combine to form a spinal nerve.

ventricle

A hollow area. In the brain, ventricles are interconnected, and cerebrospinal fluid fills and flows freely between them. In the heart, ventricles are pumping chambers.

venule

A blood vessel that is larger than a capillary. Venules merge together to form veins.

verruca (plural: verrucae)

A viral infection caused by any of a number of the human papillomaviruses. Verrucae can develop at any age and often resolve spontaneously. They can be transmitted through direct skin contact between people or within the same person. Also called “plantar wart.”

vertebral canal

Part of the central nervous system through which the spinal cord extends to the second lumbar vertebra.

vertigo

An illusion of motion. People experiencing vertigo have a sensation that they or the room is spinning or moving.

vesicle

A blister.

vestibular apparatus

Part of the inner ear that includes the semicircular canals and the vestibule.

vestibule

1. A bony chamber positioned between the cochlea and semicircular canals of the ear. The vestibule houses receptors that respond to body position and movement. 2. The area of the vagina that contains the urethral and vaginal opening.

viral pneumonia

A form of pneumonia that is usually mild and heals without intervention but that can lead to a virulent bacterial pneumonia.

visceral pain

One of the two types of pain the body perceives. It results from noxious stimuli to internal organs and may include expansion and hypoxia. Visceral pain is usually vague and diffuse. It may even be sensed on body surfaces at distant locations from the originating organ.

visceral peritoneum layer

The inner layer of the peritoneum that encases the abdominal organs.

vital capacity

The sum of the tidal volume and reserves in the lungs.

vitiligo

A rare condition characterized by small patchy areas of hypopigmentation. Vitiligo occurs when the cells that produce melanin die or no longer form melanin, leading to slowly enlarging white patches of irregular shapes on the skin.

vitreous humor

A clear, gelatinous material that fills the posterior chamber of the eye.

volatile acid

Acid that can be excreted by the lungs.

volatile gas

Gas that can be excreted by the lungs.

vomiting

The involuntary or voluntary forceful ejection of chyme from the stomach up through the esophagus and out of the mouth. It is a common event that often results from a wide range of conditions. Also called *emesis.*

vomitus

The stomach contents ejected beyond the mouth during vomiting.

von Willebrand disease

A common bleeding disorder caused by a defect or deficiency of a blood clotting protein called von Willebrand factor.

vulva

The structures of external female genitalia. These structures include the mons pubis, the labia majora, the labia minora, the clitoris, and the vestibule.

water intoxication

Fluid excess that occurs in the intracellular space.

welt

A raised erythematous skin lesion.

wet gangrene

Type of gangrene that occurs with liquefaction necrosis. Extensive damage from bacteria and white blood cells combines to produce a liquid wound.

white matter

Bundles of myelinated nerves.

Wilms tumor

A rare kidney cancer that primarily affects children. Also called nephroblastoma.

xenogenic

Type of transplant in which tissue is used from a different species.

yellow marrow

Bone marrow that begins to form during adolescence and is present in most bones by adulthood. Yellow marrow can be reactivated to produce blood cells under certain circumstances.

Zika virus disease

Condition resulting from an infection of the Zika virus, a member of the virus family Flaviviridae. The virus spreads mostly by the bite of an infected *Aedes* species mosquito but can also be transmitted from mother to fetus and through sexual contact.

zygote

A fertilized egg.

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The furnace produces heat in the house with a sensor signal from the thermostat that senses the heat loss from the roof, walls, and windows. The flow is indicated with arrows.

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The data in the format, cell: shape; size, are listed as follows. Mycoplasma: spherical with one cell; 0.2 micrometer. Yeast cell, saccharomyces cerevisiae: elongated cylinder with rounded ends; 6 micrometers. Fibroblast: spindle-shaped cells with an oval flat nucleus; 20 micrometers. Nerve cell: shaped like a tree, there are branches from the circular cell body connected to a trunk; 20 micrometers to 10 centimeters. Plant cell: Appear like small balloons surrounded by a strong cell wall; 50 micrometers.

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The human cell consists of three parts: the cell membrane, the nucleus, and, between the two, the cytoplasm. The nucleus consists of the nucleolus, nuclear pore, and the nuclear envelope. The cytoplasm consists of the following parts: rough endoplasmic reticulum, smooth endoplasmic reticulum, ribosome, Golgi apparatus, peroxisomes, mitochondrion, free ribosomes, microtubules, centrioles, lysosome, and cytoplasm. The cell membrane consists of the following parts: plasma membrane, microfilaments, cilia, basal body of the flagellum, and flagellum.

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Small uncharged polar molecules that can cross the membrane are as follows: H 2 O and N H 3. Lipid-soluble substances that can cross the membrane are as follows: Hydrocarbon. Water-soluble substances or large uncharged polar molecules, such as glucose and other sugars, cannot cross the membrane. Ions, such as N a positive, K positive, H positive, C l negative, and C a positive positive, cannot cross the membrane.

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One side of the plasma membrane is marked outside, an area of high concentration of lipid-soluble molecules. The other side of the membrane is marked inside. Some molecules from the outside area pass through the plasma membrane to the inside area.

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Part A: A plastic bag filled with sugar water, and with holes punched in it to allow only water to pass through it, is immersed in a beaker of pure water. The sucrose molecules are indicated as small circles. Part B: An enlarged plastic bag filled with sugar water is featured. Arrows indicate water movement into the bag to areas with higher concentrations of sugar. The sucrose molecules are indicated as small circles.

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The layer above the plasma membrane is labeled outside of the cell, and that below the membrane is labeled inside of the cell. Within the membrane lies the transport protein to facilitate the movement of molecules, substances, and ions across the membrane. A solute molecule, indicated as a small circle, placed outside of the cell passes across the binding site at the center of the transport protein to the inside of the cell. The solute molecule moves downhill from regions of higher to lower concentration. An iodine ion, indicated as a small circle, placed outside of the cell attaches itself to the recognition site in the transport protein. The A T P on the inside of the cell attaches itself to the A T P binding site. The iodine ion moves from the recognition site down to the inside of the cell, and the A T P molecule splits into A D P and phosphate. The ion moves across a cell membrane from a region of lower concentration to a region of higher concentration.

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Endocytosis: The large molecules to be internalized surrounded by an area of plasma membrane buds off inside the cell through the plasma membrane, to form a vesicle containing the ingested material. Phagocytosis: The organism to be internalized surrounded by an area of plasma membrane buds off inside the cell through the plasma membrane, to form a vesicle containing the ingested material. Pinocytosis: The liquid to be internalized surrounded by an area of plasma membrane buds off inside

the cell through the plasma membrane, to form a vesicle containing the ingested material. Exocytosis: The membrane-bound vesicles containing cellular molecules are transported to the plasma membrane. The vesicles fuse with the cell membrane and expel their contents to the exterior of the cell as a secretory product.

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Food contains carbohydrates, proteins, and fats, which are broken down into their basic units as follows: Carbohydrates into glucose; proteins into amino acids; fats into fatty acids. Glucose and amino acids are converted into pyruvate; fatty acids are broken down into acetyl C o A. Pyruvate leads to acetyl C o A. The oxidation of acetyl C o A, derived from carbohydrates, fats, and proteins, forms the citric acid cycle. A T P is produced in the citric acid cycle.

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Before the active phases of mitosis and meiosis is the interphase period which consists of a pair of homologous chromosomes. During this phase, the conditions are made ideal for cell division or replication. Mitosis, Prophase: The chromosomes inside the cell's nucleus are duplicated, and each of the two identical copies is attached forming tight structures. Metaphase: The replicated chromosomes pair to attach to the spindle and line up one below the other. Anaphase, telophase, and cytokinesis: The sister chromatids

are pulled apart and move toward the opposite poles of the cell and become independent. Diploid: Two daughter cells, each containing one copy of each chromosome. Meiosis, Prophase 1: The chromosomes inside the cell's nucleus are duplicated, and each of the two identical copies is attached forming tight structures. Metaphase 1: The replicated homologous chromosomes pair align at the metaphase plate. Anaphase 1, telophase 1, and cytokinesis: Two chromosomes from each pair are pulled apart and move toward the opposite poles of the cell. Prophase 2: The two pairs separate and form two centrosomes. Anaphase 2, telophase 2, and cytokinesis: Sister chromatids are separate. The chromosomes separate at the centromeres; the spindle fibers pull the separated chromosomes toward each pole of the cell, and the chromosomes are enclosed in nuclear membranes. Cytokinesis follows, dividing the cytoplasm of the two cells. Haploid: Four cells, gametes, each containing a single copy of each chromosome. A diagram of the structure of a chromosome is featured below. The chromosome, which is a spiral structure formed by the two strings of D N A, is divided into three different parts: the centromere, the chromatid, and the telomere. The center of the chromosome is referred to as the centromere; the arms are the chromatids; and the telomere represents the end of the chromosome.

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Left flow diagram: The adult stem cell divisions, with a kind of each division, are listed as follows. Hematopoietic stem cells: blood cells, Epithelial stem cells: epithelial cells, Neuronal stem cells: neuronal cells, and Mesenchymal stem cells. The mesenchymal stem cell divisions, with a kind of each division, are listed as follows. Adipocyte: fat tissue, Chondrocyte: cartilage, Osteocyte: bone, Fibroblast: tendon or ligament, Myocyte: muscle. Right flow diagram: The development of multi-cellular organisms begins from a single-celled zygote, which undergoes rapid cell division to form the blastocyst. The blastocyst has inner cell mass or is pluripotent. The embryonic stem cells are derived from the blastocyst stage. They differentiate into all derivatives of the three primary germ layers: ectoderm, endoderm, and mesoderm. The organs formed by each layer are below. Endoderm: lung, intestines, and liver; Ectoderm: Skin and neurons; Mesoderm: heart, muscle, and kidneys.

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The nervous tissue is found in the brain, spinal cord, and nerves. The types of muscle tissue in the human body are cardiac muscle, smooth muscle, and skeletal muscle. The different types of connective tissue found in the body are fat and other soft padding tissue, bone, and tendon. The epithelial tissue lines the gastrointestinal tract organs and other hollow organs; an example is the skin surface or epidermis.

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The connective tissues are divided into loose connective tissue or areolar, dense connective tissue, blood, bone, cartilage, and adipose tissue. The three components of dense and loose connective tissues are cells, ground substance, and fibers. Ground substances and fibers make up the matrix. The specialized forms of connective tissue, blood, bone, cartilage, and adipose tissue, are made up of cells embedded in the matrix. Blood: It has four main components, plasma or matrix, red blood cells, white blood cells, and platelets. Bone: The osteon unit consists of a central canal, which is surrounded by concentric rings in the matrix. Between the rings, the bone cells are located. Adipose tissue contains fat droplets, nuclei, and cells embedded in the matrix.

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The nervous tissue consists of two basic types of cells, neurons and neuroglia. Neurons: The main part is the cell body which contains the nucleus, cytoplasm, and cell organelles. Branch-like extensions surrounding the cell body are labeled as dendrites. A neuron consists of a long stem-like projection labeled an axon. Neuroglia: The glial cells are smaller in size but greater in number and surround the neuron.

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The specific types of adaptive changes include atrophy, hypertrophy, hyperplasia, metaplasia, dysplasia, and neoplasia or malignancy. Normal cells: Contain small uniformly shaped nuclei; conformity in cell size and shape; cell tissues demarcated. Hypertrophy: The enlargement of individual cells. Atrophy: Decrease in the size of the cells. Hyperplasia: Increase in the number of cells. Metaplasia: The process in which one adult cell is replaced by another cell type. Dysplasia: Abnormal changes in cellular shape, size, or organization. Neoplasia or malignancy: A type of abnormal and excessive growth of tissue, which invades other tissues.

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A normal cell features the nucleus, mitochondria, Golgi apparatus, and the endoplasmic reticulum in the cytoplasm. Necrosis, a kind of cell death following trauma or injury: As a result of trauma, the normal cell swells, and beyond a certain point, the cell bursts on the rupture of the plasma membrane. Some components of the dying cell trigger inflammation and come into contact with healthy cells, and inflammation follows. Apoptosis, a programmed cell death: As a result of any of the four factors, D N A damage, withdrawal of essential growth factors or nutrients, detachment from the substrate, or attack by cytotoxic lymphocyte, the nucleus in the normal cell breaks to form fragments. This results in cell fragments and causes the membrane to bulge outward. These bulges separate from the cell, taking a portion of

cytoplasm with them, to become apoptotic bodies. This is followed by rapid phagocytosis or engulfment of fragments by neighboring cells. No inflammatory response is noted.

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Carcinogenesis occurs in two stages: Conversion or initiation and development or promotion and progression. Initiation: This stage features a normal D N A. The effect of D N A-reactive carcinogen, inherited mutation, epigenetic carcinogen on a normal cell, and the damages of hormonal imbalance, immune system alteration, or tissue injury caused to the tissues, leads to the next phase, mutated or precancerous cell. Development and progression: This phase features a mutated D N A. A promotor applied to the mutated cell results in the abnormal cell dividing and multiplying into malignant or cancer cells. The D N A in this phase features the activation and expression of oncogenes.

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A group of cells, labeled relatively normal cells, is surrounded by an outer surface, labeled capsule. These tumors depict a slower growth rate. The bulging skin above the growing cells is labeled slowly expanding mass. A group of abnormal cells that are irregular in size and shape, with the tissue and blood cells invaded and affected with necrosis. The surface of the skin under this quickly multiplying mass is very uneven and expanding.

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The first step is the enzyme secretion by cancer cells and motility factors. This is followed by the disruption of the basement membrane in blood vessels. The cancer cells escape into circulation, with the movement of undetected cells out of the blood. This leads to the secretion of enzymes, and the cell wall is cut. The new tissue is invaded downstream. With the occurrence of chemical attraction, malignant cells target specific sites. This results in the invasion of the new site, leading to the multiplication of cells. The metastatic tumor appears at this stage.

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The steps of metastasis include separation from the primary tumor in the extracellular matrix, invasion through tissues around the initial lesion and penetration of their basement membranes, entry into the blood vessels, and survival within the blood. Host lymphocytes attach to the tumor cells along with the platelets. This becomes the metastasized tumor, from which a section labeled as metastatic tumor breaks out from the bloodstream into another area.

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Stage 0: When abnormal cells are found in the wall, or mucosa, of the colon, it is considered stage 0 colon cancer. Stage 1: Cancer that has invaded the mucosa and the submucosa is considered stage 1 colon cancer. The

submucosa is the underlining of the large intestine and it lies beneath the mucosa. Stage 2: When cancer has spread past the colon wall, but has not affected the lymph nodes, it is considered stage 2 colon cancer. Stage 3: Cancer that has spread past the lining of the colon and has affected the lymph nodes, but not the other organs in the body, is considered stage 3 colon cancer. In stage 4 colon cancer, the cancer spreads to other organs in the body through the blood and lymph nodes.

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Punnett's square predicts possible genotypes for a single gene locus of offspring from a specific set of parents. Data from the matrix, presented in the format, color of mother's eyes, color of father's eyes: color of child's eyes, are as follows. Brown, brown: brown. Brown, blue: brown. Blue, brown: brown. Blue, blue: blue.

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The hypothalamus in the brain is in charge of the stress response. When a stress response is triggered, it sends signals to two other structures: the pituitary gland and the adrenal medulla. The hypothalamus stimulates the pituitary gland. The pituitary gland secretes adrenocorticotropic hormone. The adrenocorticotropic hormone stimulates the adrenal glands to produce glucocorticoids. The production of glucocorticoids leads to an increase in access to energy

storage, and body metabolism speeds up, resulting in the fight-or-flight response. This is the pituitary-adrenal axis. The sympathoadrenal pathway begins with the nerve signal from the brain that stimulates the production of adrenaline or epinephrine from the medulla of the adrenal gland. This leads to increased heart rate, breathing rate, and blood sugar, further contributing to the fight-or-flight response.

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The horizontal axis is labeled time. The vertical axis is labeled resistance to stress. Stage 1, alarm reaction: This is the somatic response to the first exposure to a localized or general stressor and initially lowers the basal state of resistance. The body mobilizes its resources. Stage 2, resistance: if continued exposure to the stressor is compatible with adaptation, resistance levels off and eventually begins to decline. Stage 3, exhaustion: following long-term exposure to the stressor, adaptation capability is eventually exhausted. Resistance is depleted, leading to exhaustion.

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Diseases and ailments in the different systems of the body, which have been attributed to stress, are listed as follows. Nervous system: anxiety, depression, fatigue, insomnia, loss of motivation, nervous tic, neuropsychological manifestations, and overeating. Integumentary system: acne,

eczema, hair loss, neurodermatitis, psoriasis. Cardiovascular system: coronary artery disease, disturbances of heart rate and rhythm, hypertension, and stroke. Gastrointestinal system: diarrhea, gastritis, irritable bowel syndrome, nausea and vomiting, ulcerative colitis. Genitourinary system: diuresis, frigidity, impotence, irritable bladder, and menstrual irregularity. Respiratory system: asthma, hay fever, increased respiration. Immune system, autoimmune disease, immunodeficiency, immunosuppression. Endocrine system: diabetes mellitus, hyperglycemia. Musculoskeletal system: inflammatory disease of connective tissue, muscle contraction backache, tension headache, and rheumatoid arthritis.

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When tissue is first injured, the blood vessels dilate bringing increased blood flow to the injured area. The walls of the blood vessels, which normally allow only water and salts to pass through easily, become more permeable. Fluid and phagocytic white blood cells pass out of capillaries. Lymphatic drainage removes dissolved poisonous substances. The most important feature of inflammation is the accumulation of white blood cells at the site of injury. Most of these cells are phagocytes that ingest bacteria and other foreign particles and also clean up cellular debris caused by the injury. The injury is illustrated as the piercing of a thorn. Microbes enter into the skin at the site of injury to the skin surface.

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When a virus infects a person, it invades a cell. The cell in which the virus has entered is labeled the host cell. Immune cells release interferone which binds with receptors on uninvaded cells. The uninvaded cells produce inactive enzymes that are capable of breaking down viral messenger R N A and inhibiting protein synthesis. The viruses try to enter cells that have been activated by interferon. Viral-blocking enzymes in the cell are immediately activated. This activation protects the newly invaded cells from the virus being multiplied in these cells.

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Lysis: The outer boundary or cell membrane is broken down or destroyed in order to release a complement to the target cell. Opsonization: A process in which the complement receptor identifies the invading particle, bacteria, to the phagocyte. The phagocyte, an immune cell, engulfs and destructs the bacteria. Activation of inflammatory response: Degranulation is the cellular process that releases and activates molecules. Extravasation is the leakage of white blood cells in the tissue. Clearance of immune complexes: insoluble immune complexes, and antigen-antibody complexes, which are formed are cleared by the phagocytic cells of the immune system.

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A human bone has lymphoblasts or bone marrow stem cells. The primary parts of the immune system include the bone marrow and thymus. Humoral immunity or antibody-mediated immunity: The bone marrow consists of the B cells, which mature in the marrow, and migrate to lymph nodes. The B cells differentiate into plasma B cells that can produce antibodies against a specific antigen and memory B cells. The humoral immune system deals with antigens from pathogens that are freely circulating, or outside the infected cells. Antibodies produced by the B cells will bind to antigens, neutralizing them. Cell-mediated immunity: The T cells travel from the Thymus. This type of immunity occurs inside infected cells and is mediated by the T lymphocytes, which migrate to lymph nodes. The pathogen's antigens are expressed on the cell surface or an antigen-presenting cell. A macrophage engulfs foreign substances, and the processed antigen is featured. The various types of sensitized T cells in circulation listed are helper T cells, memory T cells, suppressor T cells, and cytotoxic T cells in the presence of antibodies. The antibody binds to a specific antigen. The structure of a typical antibody molecule contains four chains; each chain has a variable region at its amino terminus, which contributes to the antigen-binding site, and a constant region in the C-terminus.

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There are two specific types of antigens, labeled allergens. First exposure: Mediators are derived from resident mast

cells basophils activated by I g E, plasma cells, and B cells, and from T H cells that recognize allergen-derived peptides. A P Cs mediate the cellular immune response by processing and presenting antigens for recognition by T H cells. Re-exposure to the same allergen cross-links the bound I g E on sensitized cells, resulting in anaphylactic degranulation, which is the immediate and explosive release of pharmacologically active pre-formed mediators like histamine, leukotriene, and other mediators.

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In this hypersensitivity reaction, specific antibodies bind to cell surface antigen and destroy the cell. The destruction is depicted in three ways: complement-mediated cell lysis; antibody-dependent cell-mediated cytotoxicity; and opsonization. Antibody-dependent cell-mediated cytotoxicity: Specific antibodies, Y-shaped proteins produced by B cells, recognize and attach to antigens on the surface of target cells. Immune cells, like natural killer cells and macrophages, have receptors that bind to the F c region of the attached antibodies. Once bound, the effector cells activate their cytotoxic machinery, releasing various chemicals like perforin and granzymes. These chemicals break down the target cell's membrane, causing it to lyse and die. In complement activation, a cascade of proteins circulating in the blood amplifies and directs the immune response. Antibodies specific to the virus bind to its surface. Virolysis happens when the actual destruction of the virus by the

complement system is done. Opsonization: When an antigen enters into host body, antibodies are produced. The antibody binds to antigen through F a b region, and the F c region is free. The phagocytic cells have receptors that bind to the F c region of antibody. The receptors are labeled as F c gamma R and C 3 b. The antibody molecule directly cross-links antigens with phagocytic cells. This cross-linkage activates phagocytic cells and increases the rate of phagocytosis.

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Step 1: Type A blood donor along with type A antigen enters the bloodstream of the type B recipient. Step 2: Anti-A antibodies in type B recipients bind to donated type A red blood cells. Step 3: The bound anti-A antibodies activate complement cascade, releasing hemoglobin.

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First pregnancy with an R h-positive fetus: The illustration features an R h-negative pregnant mother and an enlarged view of an R h-positive fetus in her womb. R h-red blood cells enter the mother’s circulation. Anti-R h antibodies are produced upon exposure to fetal R h antigens. Second pregnancy with an R h-positive fetus: Anti-R h antibodies remain in the mother’s circulation and cross the placenta. Maternal anti-R h antibodies attack and destroy fetal R h red blood cells. The illustration features an R h-negative pregnant mother and an enlarged view of an R h-positive

fetus in her womb. The mother is injected with R h o, D immune globulin during pregnancy. R h-positive red blood cells enter the mother’s circulation. Anti-R h antibodies bind and inactivate fetal R h antigens before they stimulate the immune response in the mother.

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Initial Sensitization: Exposure to an allergen happens for the first time. B cells specific to the allergen are activated and begin proliferating. C D 4-positive T cells differentiate into T subscript H cells under the influence of the allergen. T H cells produce I L 4, which stimulates B cells to switch antibody production to I g E. B cells differentiate into plasma cells, which begin producing large amounts of allergen-specific I g E antibodies and memory cells. Plasma cells release allergen-specific I g E into the bloodstream. I g E antibodies bind to F c receptors on mast cells and basophils, sensitizing these cells to the allergen. Re-exposure to allergens leads to antigen-antibody complex formation. Allergen-specific I g E antibodies bind to the allergen in the bloodstream, forming large immune complexes. Immune complexes circulate in the bloodstream. I g E is bound to F c receptors on mast cells, and basophils get cross-linked when they encounter the allergen again. Mast cells and basophils degranulate, releasing a cascade of inflammatory mediators that work to activate the small blood vessels, blood platelets, smooth muscle cells, mucous glands, sensory nerve endings, and eosinophils.

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Part A features the effects of first exposure to poison ivy. First exposure results in sensitization of the dendritic cell at an exposed site. This stimulates helper T cells, which leads to the production of memory helper T cells. Part B features the effects of a second exposure to poison ivy. The memory helper T cells inclined to become reactivated on future exposures are reactivated and produce inflammatory cytokines. The cytokines stimulate macrophages and cytotoxic T cells to induce an inflammatory lesion at the exposed site.

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Genetic predisposition in immune-related genes, like human leukocyte antigen, cytokine pathways, and autoimmune regulator protein, may lower the threshold for the activation of autoreactive T cells. Environmental triggers such as infection, the microbiome, and traumatic insults generate a proinflammatory environment that supports the activation of autoreactive T cells. Defective regulation of T regulation cells such as F O X P 3, C T L A 4, I L 2, etcetera function to suppress autoreactive T cells. The autoreactive T cell and antigen-presenting cell contribute to the activation and proliferation of autoreactive T cells, which result in tissue injury.

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Fusion of H I V binds to the host cell surface. H I V infection hinges on a precise choreography between three key players: the viral envelope protein g p120, the T-cell surface protein C D 4 positive, and the co-receptor molecules C C R 5 and C X C R 4. H I V R N A, reverse transcriptase, integrase, and other viral proteins enter the host cell. Viral D N A is formed by reverse transcription as a preintegration complex with viral R N A with reverse transcriptase. Viral D N A is transported across the nucleus and integrated into the host D N A with intergrase, forming new viral R N A. New viral R N A is used as genomic R N A and to make viral proteins. New viral R N A and proteins move to the cell surface, and a new, immature H I V is formed. The virus is released. Viral protease cleaves new polyproteins to create mature virions. The text above reads, Foreign invaders signal nearby neutrophils to squeeze through endothelial cells that line the blood vessel and enter the infected tissue.

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The innermost region of an H I V virion consists of a cone-shaped core that includes two copies of the single-stranded R N A genome and the enzyme reverse transcriptase. This core is enclosed by a capsid, which is enclosed by a viral envelope and an associated matrix. The envelope glycoproteins are embedded in the lipid membrane of the virus, which covers the entire surface of the H I V.

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There are many cellular structures in the composition of blood. The body weight includes 8 percent of whole blood and 92 percent of other fluids and tissues. The different constituents of blood are plasma, which covers 55 percent of the volume, and formed elements, which cover the remaining 45 percent of the total blood volume. Of the total weight of plasma, proteins occupy seven percent, water 91.5 percent, and other solutes 1.5 percent. Proteins are classified into the below solutes with the respective percentages: Albumins: 54 percent; globulins: 38 percent; fibrinogen: 7 percent; all others: 1 percent. Other solutes comprise the following: electrolytes, nutrients, gases, regulatory substances, and waste products. Of the total number per microliter of the formed elements, platelets occupy 150,000 to 400,000, white blood cells occupy 5,000 to 10,000, and red blood cells occupy 4.8 to 5.4 million. White blood cells are classified as follows: neutrophils occupy 60 to 70 percent; lymphocytes occupy 20 to 25 percent; monocytes occupy 3 to 8 percent; eosinophils occupy 2 to 4 percent; and basophils occupy 0.5 to 1.0 percent.

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Damage to a blood vessel causes blood clotting. Red blood cells and platelets are included. Platelets adhere to the cut edges of the vessel, and more platelets are joined, forming a platelet plug and stopping the external bleeding. Smaller molecules, called clotting factors, cause strands of blood-

borne materials, labeled fibrin, to stick together, sealing the inside of the wound.

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The process requires coagulation factors, calcium, and phospholipids. The coagulation factors listed are tissue factor clotting factors 8 a, 9 a, 11 a, and 12 a. An enzyme, Factor X a is synthesized. Protein C and protein S are two proteins in the blood that help regulate blood clot formation. Protein C activation by thrombin in the absence of T M is inhibited by calcium. Prothrombin, a vitamin K-dependent coagulation factor, on activation cleaves to form thrombin and, in turn, acts as a serine protease that converts fibrinogen to fibrin

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A multipotential hematopoietic stem cell, or hemocytoblast, is divided into two daughter cells: the common myeloid progenitor and the common lymphoid progenitor. The myeloid progenitor cells differentiate into megakaryocytes, erythrocytes, mast cells, and myeloblasts. The megakaryocyte cells form thrombocytes. The myeloblast cells form basophils, neutrophils, eosinophils, and monocytes. Monocytes, the largest type of leukocyte, differentiate into macrophages and myeloid-lineage dendritic cells. The natural killer cell, or large granular cell, and the small lymphocytes are derived from the common lymphoid

progenitor cells. The small lymphocytes are divided into T lymphocytes and B lymphocytes. The plasma cell arises from the B lymphocyte.

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Hemoglobins are indicated as molecules in the red blood cells in erythrocytes. The hemoglobin molecule comprises four divisions, which are in the shape of folded polypeptides labeled globin. Within each globin fold of every hemoglobin molecule, there is an iron atom labeled heme. A magnified view of the heme atom is included.

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Erythrocytes, hepcidin, and transferrin, which are responsible for ferric-iron delivery, are present in the bloodstream. Duodenum takes in ferrous iron through D M T 1, and hepcidin downregulates iron absorption by binding to the iron-exporter ferroportin. Transferrin in the bloodstream binds ferric iron and transports it to various tissues, including the bone marrow, for hemoglobin production. Bone marrow or erythrocyte generation: transferrin delivers ferric-iron to the bone marrow; the carrier protein for transferrin is the transferrin receptor and leads to the production of hemoglobin; Spleen, recycling: Erythrocytes and hepcidin move from the bloodstream to the spleen. Inside the spleen, ferric iron from the erythrocyte becomes ferritin. Liver, storage: Transferrin delivers ferric iron to the liver; the

carrier protein for transferrin is the transferrin receptor; within the liver, ferrous iron is stored as ferritin. Ferrous iron, through ferroportin, is transported to the bloodstream as ferric iron. Iron loss: In the body, additional iron requirements and iron losses are mainly through feces, menstruation, pregnancy, and lactation.

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The blood vessel with the endothelial cells is featured. Foreign invaders, like bacteria, signal nearby neutrophils in the bloodstream to squeeze through endothelial cells that line the blood vessels and enter the infected tissue. Through phagocytosis, the neutrophil ingests the bacteria and releases toxic products that kill bacteria.

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The test has the following components: viral capsid antigen, V C A I g A, V C A I g G, V C A I g M, E A I g G, and E D N A I g G. Line graph: The horizontal axis is labeled incubation period symptoms and lists immediate, weeks, months, and years. The vertical axis is labeled antibody level. The curve for V C A I g M features antibodies that appear early and disappear within weeks. The curve for V C A I g G features the appearance of the antibodies in the immediate phase, peaks within weeks after onset, and persists for life. The curve for V C A I g A features the antibodies' early appearance and disappearance within weeks. The curve for

E A I g G features the appearance of the antibodies in the acute phase and usually decreases to undetectable levels within weeks. The curve for E D N A I g G features antibodies that develop six to eight weeks after primary infection and are detectable for life. Table: There are three main columns: interpretation, non-specific tests, and antibodies against. The second column is further divided into heterophylic antibodies and atypical lymphocytes. The third column is further divided into V C A, E A, and E D N A. V C A is further divided into three columns: V C A I g M, V C A I g G, and V C A I g A. E A is further divided into two columns: E A D and E A R. The sub-column for E D N A is E D N A I g G. The row entries in the format, interpretation: heterophylic antibodies; atypical lymphocytes; V C A I g M; V C A I g G; V C A I g A; E A D; E A R; E D N A I g G, are as follows: Row 1. No infection: all negative. Row 2. Infectious mononucleosis: three positive signs; three positive signs; two positives; three positives; positive; positive; positive or negative; negative. Row 3. Past infection: negative; negative; negative; two positives; negative; negative; positive or negative; two positives. Row 4. Reactivation: negative; negative; positive; three positives; two positives; positive; positive.

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Stages 1, 2, 3, and 4 are determined by how much the disease has spread from a single lymph node region to the rest of the body. Stage 1: The lymphoma cells are found in

one lymph node group, the neck. Stage 2: The lymphoma cells are found in four lymph node groups, the neck, underarm, and two above the diaphragm. Stage 3: The lymphoma cells are found in seven lymph node groups, one each in the neck and underarm, two above the diaphragm, and three below the diaphragm. Stage 4: This stage features the spread of the lymphoma cells to the other organs of the body, like the liver and lungs.

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The size of M C V with the respective type of anemia and the causes are listed as follows: With low levels and a smaller than average size, the type of anemia is microcytic, and the causes are listed as follows: iron deficiency, thalassemia, chronic disease, and lead poisoning. With normal levels and normal size, the type of anemia is normocytic, and the causes listed are acute bleeding, aplastic, hemolytic, low erythropoietin, and malignancy. With high levels and a larger-than-normal size, the type of anemia is macrocytic, and the causes are listed as pernicious and low folate.

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Hemoglobin is a large molecule composed of two alpha chains and two beta chains in red blood cells. The subunits are in the shape of folded polypeptides in a helical shape. Within each folded polypeptide is a structure containing an iron atom labeled heme group.

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Deformed R B C results in three major issues affecting the circulatory system: hypercoagulability and platelet dysfunction, ineffective erythropoiesis, and hemolysis. Patients with thalassemia have increased phosphatidylserine expression, decreased coagulation factor expression, and abnormal R O S production. Hemolysis has increased G I absorption of iron and treatment-related iron overload. Hypercoagulability and platelet dysfunction lead to thromboembolism and vascular dysfunction. Ineffective erythropoiesis causes anemia, cortical thinning or bone marrow expansion, and extramedullary erythropoiesis. Cortical thinning or bone marrow expansion causes bone pain and fractures. Extramedullary erythropoiesis causes bone pain and fractures, hepatomegaly, and splenomegaly. Hemolysis results in anemia, gallstones, and iron deposition in visceral organs such as the parathyroid and thyroid glands, pituitary gland, pancreas, testes and ovaries, liver, and heart. Iron deposition in the parathyroid and thyroid glands, pituitary gland, pancreas, and testes and ovaries results in endocrine dysfunction. Iron deposition in the heart results in arrhythmias and heart failure. Iron deposition in the liver results in cirrhosis. Endocrine dysfunction, cirrhosis, arrhythmias, and heart failure come under the effects of secondary hemochromatosis.

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The precipitating mechanism necessitates the need to treat the underlying problem. Treatment is for either damage to tissue or endothelial cells. Tissue damage causes increased tissue thromboplastin, activating the extrinsic pathway of coagulation. The treatment involved at this stage is the use of heparin to prevent micro-clotting, which is controversial. Damage to endothelial cells causes an intrinsic pathway of coagulation. Both pathways of coagulation result in intravascular coagulation, producing microthrombi. In the case of tissue damage, thrombi are produced, resulting in the activation of the fibrinolytic system, the digestion of fibrin clots, and the inhibition of platelet function. The production of thrombi also results in the occlusion of small blood vessels and tissue necrosis. After the production of microthrombi in the case of damage to endothelial cells, the following treatments are done: cryoprecipitate factor V M, fresh frozen plasma given, and platelets supplied. The treatments result in the consumption of clotting factors, leading to thrombocytopenia and decreased clotting factors. Thrombocytopenia and decreased clotting factors cause bleeding. The treatment for bleeding is a supply of blood.

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In the center is the heart and its chambers, the left Atrium and left Ventricle below it with the bicuspid valve in between. The Right Atrium and Right Ventricle below it, are separated by the tricuspid valve. On either side of the heart are the lungs, labeled Pulmonary circulation. The major artery Aorta

moves upward and downward in the body taking oxygenated blood to a network of capillaries labeled Systemic circulation. The capillaries carry blood with carbon dioxide to the Superior vena Cava vein on top and the Inferior Vena Cava vein below toward the Right Atrium. The Pulmonary arteries carry this blood to the lungs and Pulmonary veins carry oxygenated blood from both the lungs to the Aorta.

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At the bottom is the lung alveolus tissue with the artery containing disc-shaped blood platelets running along the tissue. Just above the tissue is a network of Lung alveoli capillaries that carry oxygenated blood to the pulmonary venule to the artery. The Lung alveoli capillaries carry blood with Carbon dioxide to the Pulmonary arteriole away from the lungs.

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The vertical cross-section of the outer wall layers of the heart, the outer pericardium, and the inner myocardium; the heart's four chambers, the two Atria above and ventricles below. The outer walls of the ventricles are thicker than those of the Atria. The inner heart epithelial layer is the endocardium that forms the valves between the chambers.

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The three layers of the heart wall are Pericardium, Myocardium, and the innermost Endocardium which encases the four chambers within. The chambers are Left and Right Atrium on top and Left and Right Ventricle below with the Interventricular septum separating them. The blood enters the heart's Right Atrium through the Superior vena cava from the head, and Inferior vena cava from the body and is pumped into the Right ventricle. The right and left Pulmonary arteries take the oxygen poor blood to the lungs. The right and left pulmonary veins carry oxygenated blood into the left Atrium and it is pumped into the Left ventricle. From here, the Aorta carries the blood to all parts of the body.

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The top illustration features the P wave, P R segment, Q R S complex, S T segment, and the T wave. The P wave is a small, rounded wave at the start. The P R segment is the flat line between the P wave and the Q R S complex. The Q R S complex is the largest and most prominent part of the electrocardiogram waveform. It consists of three deflections: the Q wave, which is downward, the R wave, which is upward, and the S wave, which is downward. The S T segment is the flat line following the Q R S complex. The T wave is the last curve following the S T segment. The distance between the start and end of the Q R S complex is labeled as the Q R S interval. The distance between the start of the Q R S complex and the end of the T wave is labeled as the Q T interval. The line graph is below. The horizontal axis is

labeled milliseconds and lists 0 and 300. The vertical axis is labeled millivolts and ranges from negative 90 to 30. The line in the graph begins at negative 90 and is flat up to o milliseconds. This flat line is labeled phase 4, or resting membrane potential with potassium current I subscript K 1. The line peaks from negative 90 to 30 at 0 milliseconds when there is an influx of N A positive. The top half of the vertical line is labeled phase 0, or depolarization with sodium current I subscript N a. Then, voltage-gated K positive channels rapidly activate, letting K positive out of the cell and repolarizing the membrane. The line depresses slightly from 30 to 10 and is labeled as phase 1 or rapid repolarization with potassium current I subscript t o. The line plateaus up to a few milliseconds, where there is an inflow of C s 2 positive and N a positive. The line after this decreases in a curve to a negative 90 at 300 milliseconds. The initial half of the decrease with an outflow of K positive is labeled phase 2 or plateau with calcium current I subscript C a. The lower half of the decrease is labeled phase 3 or repolarization with potassium currents I subscript K s and I subscript K r. The flat line at negative 90 after 300 milliseconds is labeled phase 4 with outflow of A T Pase and an inflow of N a positive.

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The cross-section depicts the four chambers of the heart. In the right atrium is the Sinoatrial or S A node which is the pacemaker that generates an electrical stimulus to activate

both atria. The impulse travels from the S A node to the Atrioventricular or A V node and continues through the Interatrial and Internodal bundles via the Bundle of His down to the ventricles. The bundle of His divides into the Right and left branches of A V bundle. Along the ventricular walls are branched fibers labeled Purkinje fibers.

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In the center is an illustration of a bean-shaped kidney, the renal artery and vein and the ureter going downward. When the blood pressure falls, the kidneys release renin which activates the secretion of angiotensin I, which is in turn converted to angiotensin II, a vasoconstrictor. This stimulates aldosterone secretion. Aldosterone causes Salt retention and increases blood volume and therefore Blood pressure rises.

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On the right is a venule carrying blood to the heart, and on the left is an arteriole carrying blood away from the heart. These two blood vessels are connected by a thoroughfare channel surrounded by an intricate network of smaller thin-walled vessels called capillaries. At the junction of the capillaries and the thoroughfare channel are Precapillary sphincters.

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The diagram on the left depicts the chambers of the heart and the arteries labeled. The top two chambers are the Right atrium and left Atrium, and the bottom two are the Right Ventricle and Left ventricle. From the top center, the arteries on the right are as follows. Left coronary artery behind the pulmonary trunk, Circumflex artery, and Anterior interventricular artery. The arteries on the left are Superior vena cava, Right coronary artery, and Marginal artery. In the center is the Posterior interventricular artery. The diagram on the right has the veins labeled as follows. On the right are the Great cardiac vein, Anterior cardiac vein, and Middle cardiac vein. The Coronary sinus is at the center of the heart. The veins on the left are Superior vena cava and Small cardiac vein.

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In figure A, the wall layers of an artery from inside to outside are as follows. Endothelium, elastic tissue, Circular smooth muscle, and Connective tissue with elastic fibers. An image alongside depicts the artery wall in a vertical cross-section. An arteriole branches from the artery. Figure B depicts a capillary looking like a twig with branches and the outer layer is labeled Endothelium. A slide image depicts a tubular capillary with disc-shaped platelets in it. Figure C depicts the wall layers of a vein from inside to outside are as follows. A W-shaped valve is innermost, covered by the Endothelium, elastic tissue, Circular smooth muscle, and Connective tissue. An image above depicts the elongated vein with a

horizontal W-shaped valve between the side walls. Another image on the side depicts a horizontal cross-section of the vein. A venule branches from the vein.

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Diagram A is the silhouette of a man with the parts of the Lymphatic system superimposed and labeled on it. The parts and their positions labeled on the right are tonsils, Lymph node in the neck, Thymus, Spleen, Peyer patch in the small intestine, Lymph node in the groin, Bone marrow and Lymphatic vessels in the leg. On the left are the Right lymphatic duct in the neck, Subclavian vein and Superior vena cava from the heart, Thoracic duct, and Appendix. Figure B is an enlarged illustration of the Lymph node. It is round with petal-shaped structures protruding on all sides. It is connected by a valve to a network of capillaries arising from a vein, a venule, and an artery and arteriole on either side, along with lymphatic capillaries. The valve pushes the fluid into tissues, of which 10 percent enters the lymphatic system and 90 percent reenters the cardiovascular system.

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On the left is a normal heart, with a thin outer wall, and the blood vessels emerging from the top. On the right, the heart depicts Cardiac tamponade, wherein there is accumulation of fluid along the inner wall making it appear thick.

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Row 1. World Health Organization 1995: Phenotype: Hypertrophic C M, Dilated C M, Restricted C M, Arrhythmogenic R V, and Unclassified. Row 2. American Heart Association 2006: Primary C M consists of Genetic: Hypertrophic, Arrhythmogenic R V, L V non-compaction, and Mitochondrial myopathies; Mixed: Dilated and Restricted; Acquired: Mycarditis, Peripartum, Stress-provoked or Tako-Tsubo, Tachycardia-induced, Infants of diabetic mothers. Secondary C M consists of Systemic disease with C M: Storage disorders, Neuromuscular and neurological diseases, Cardio-facial syndromes, Infiltrative disease, Endocrine disorders, and Autoimmune or collagen disease. Row 3. European Society of Cardiology 2008: Hypertrophic C M, Dilated C M, Restricted C M, Arrhythmogenic R V, and Unclassified, which are Familial or genetic with Unidentified gene defect or Disease subtype; or Non-familial or genetic which could be Idiopathic or Disease subtype.

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On the top left is a normal heart with the parts labeled as follows. Aorta, Mitral valve, Aortic valve, Left ventricle, and Septum. The top right image is of a heart with Dilated cardiomyopathy. The right ventricle is much enlarged. The bottom left image is of a heart with Hypertrophic cardiomyopathy. There is an Enlarged stiff septum and size of the right ventricle is much smaller. The bottom right image is of a heart with Restrictive cardiomyopathy. The walls of the right ventricle are stiff with an undulating edge.

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The waveforms, features, and causes are illustrated for each dysrhythmia. The supraventricular rhythms are the following: Sinus bradycardia: The features are as follows: The rate is less than 60 beats per minute. The rhythm is regular. P waves occur before each Q R S complex. Look the same in shape and size. P R interval is normal, ranging from 0.12 seconds to 0.20 seconds. The Q R S complexes occur after each P wave. Look the same in shape and size, which is normal and less than 0.12 seconds. The causes are normal in a well-conditioned heart, for example, athletes; increased intracranial pressure; increased vagal tone due to straining during bowel movement, vomiting, intubation, or mechanical ventilation; sick sinus syndrome; inferior-wall M I; and may also occur with anticholinesterase, beta-adrenergic blocker, digoxin, or morphine use. Sinus tachycardia: The features are as follows: The rate is greater than 100 beats per minute. The rhythm is regular. P waves occur before each Q R S complex. Look the same in shape and size. P R interval is normal from 0.12 seconds to 0.20 seconds. The Q R S complexes occur after each P wave. Look the same in shape and size, which is normal and less than 0.12 seconds. The causes are a normal physiologic response to fever, exercise, anxiety, pain, and dehydration; they may also accompany shock, left-sided heart failure, anemia, hypovolemia, and pulmonary embolism; they may also occur with atropine, epinephrine, caffeine, alcohol, and amphetamine or nicotine use. Atrial flutter: The features are

as follows: The rate is greater than 100 beats per minute. The rhythm is regular but may vary depending on the degree of A V block. P waves cannot be found; replaced by flutter or F waves, which may have a sawtooth pattern. The P R interval cannot be determined. The Q R S complexes look the same in shape and size; normal and less than 0.12 seconds. The causes are heart failure, tricuspid or mitral valve disease, pulmonary embolism, cor pulmonale, interior-wall M I, pericarditis, and digoxin toxicity. Atrial fibrillation: The features are as follows: The rate is greater than 100 beats per minute and grossly irregular from 350 to 450 beats per minute. The rhythm is irregular. P waves cannot be found. Look the same in shape and size. The P R interval cannot be determined. The Q R S complexes look the same in shape and size. The causes are heart failure, C O P D, ischemic heart disease, sepsis, pulmonary embolism, rheumatic heart disease, hypertension, and mitral stenosis; complications of coronary bypass or valve replacement surgery; and nifedipine and digoxin use. Paroxysmal supraventricular tachycardia: The features are as follows: The rate is greater than 100 beats per minute. The rhythm is regular. P waves occur before each Q R S complex but may be hidden in the preceding T wave. Look the same in shape and size but differs from a normal sinus P wave. P R interval is normal from 0.12 seconds to 0.20 seconds but may differ from the P R interval associated with a normal sinus beat. The Q R S complexes occur after each P wave. Look the same in shape and size which is normal and less than 0.12 seconds.

The causes are intrinsic abnormality of A V conduction system; physical or psychological stress, hypoxia, hypokalemia, cardiomyopathy, congenital heart disease, M I, valvular disease, Wolff-Parkinson- White syndrome, cor pulmonale, hyperthyroidism; digoxin toxicity, use of caffeine, marijuana, or C N S stimulants. Junctional rhythm: The features are as follows. The rate is greater than 60 beats per minute. The ventricular rate is usually greater than 60 beats per minute. 60 to 100 beats per minute is an accelerated junctional rhythm. The rhythm is regular but irregular if escape beats occur. P waves cannot be found or are nonexistent or hidden; usually inverted if visible. P R interval cannot be determined when present and is less than 0.12 seconds. The Q R S complexes look the same in shape and size, which is normal and less than 0.12 seconds, except in aberrant conditions. The causes are inferior-wall M I or ischemia, hypoxia, vagal stimulation, sick sinus syndrome; acute rheumatic fever; valve surgery; and digoxin toxicity. The ventricular rhythms are the following: Premature ventricular contraction or P V C. The distance between two peaks of the Q R S complex is labeled as a compensatory pause in the waveform reading. The features are as follows: The rate is irregular. Rhythm is atrial rhythm regular, ventricular rhythm irregular. P waves cannot be found. The P R interval cannot be determined. The Q R S complexes are wide and distorted and greater than or equal to 0.12 seconds; premature Q R S complexes occurring alone, in pairs, or in threes, alternating with normal beats; focus from

one or more sites; ominous when clustered, multifocal, with R wave on T pattern. The causes are heart failure; previous or acute M I, ischemia, or contusion; myocardial irritation by ventricular catheter or a pacemaker; hypokalemia; hypocalcemia; hypomagnesemia; drug toxicity of digoxin, aminophylline, tricyclic antidepressant, beta-adrenergic blocker, isoproterenol, and dopamine; caffeine, tobacco, or alcohol use; psychological stress, anxiety, pain, or exercise. Ventricular tachycardia: The features are as follows: The rate is greater than 100 beats per minute. The rhythm is regular. The P waves cannot be found or hidden within Q R S complex. The P R interval cannot be determined. The Q R S complexes look the same in shape and size; wide and bizarre hypercalcemia; hypomagnesemia; pulmonary and greater than or equal to 0.12 seconds. The causes are myocardial ischemia, M I, or aneurysm; coronary artery disease; rheumatic heart disease; mitral valve prolapse; heart failure; cardiomyopathy; ventricular catheters; hypokalemia; hypercalcemia; hypomagnesemia; pulmonary embolism; digoxin; procainamide, epinephrine, or quinidine toxicity; anxiety. Ventricular fibrillation: The features are as follows: The rate is greater than 100 beats per minute. The rhythm is irregular, chaotic, and rapid. The P waves cannot be found. The P R interval cannot be determined. The Q R S complexes are wide and irregular and the ventricle is just quivering. The causes are myocardial ischemia, M I, untreated ventricular tachycardia, R-on-T phenomenon, hypokalemia, hyperkalemia, hypercalcemia, hypoxemia,

alkalosis, electric shock, hypothermia; digoxin, epinephrine, or quinidine toxicity. The heart blocks are the following: First-degree A V block: The missed peak of the Q R S complex is marked in the waveform reading and labeled as dropped beat. The features are as follows: The rate varies. The rhythm is regular. The P waves occur before each Q R S complex; look the same in shape and size. The P R interval is long and greater than 0.20 seconds. The Q R S complexes occur after each P wave; look the same in shape and size and are normal with less than 0,12 seconds. The causes may be seen in healthy people; inferior-wall M I or ischemia, hypothyroidism, hypokalemia, digoxin toxicity; quinidine, procainamide, beta-adrenergic blocker, calcium channel blocker, or amiodarone use. Second-degree A V block: Mobitz 1 or Wenckebach: The features are as follows. The rate is slow to normal. The atrial rhythm is regular, and ventricular rhythm is irregular. The P waves occur before each Q R S complex; look the same in shape and size. The P R interval is normal and from 0.12 to 0.20 seconds; progressively lengthens until there is a missed beat, then the cycle or grouping repeats itself. Q R S complexes: Look the same in shape and size; normal and less than 0.12 seconds. The causes are inferior-wall M I, cardiac surgery, acute rheumatic fever, vagal stimulation; digoxin toxicity; propranolol, quinidine, or procainamide use. Second-degree A V block: Mobitz 2: The missed peak of the Q R S complex is marked in the waveform reading and labeled as dropped beat. The features are as follows. The rate is slow to normal.

The atrial rhythm is regular, and ventricular rhythm is regular or irregular with varying degrees of block. The P waves occur before each Q R S complex; look the same in shape and size. The P R interval is normal and ranges from 0.12 to 0.20 seconds; normal P R interval is key identifier of this rhythm. Q R S complexes: Look the same in shape and size; normal and less than 0.12 seconds if the level of the block is above the bundle of His; wide and greater than or equal to 0.12 seconds if the level of the block is below the bundle of His. The causes are severe coronary artery disease, anterior-wall M I, acute myocarditis; digoxin toxicity. Third-degree heart block or complete heart block. The distance between four peaks of the Q R S complexes is labeled ventricular Rate. Two arrows point next to the Q R S complexes and are labeled P wave is in here. The features are as follows: The rate is less than 60 beats per minute. The rhythm is regular and the ventricular rhythm rate is slower than atrial rate. The P waves look the same in shape and size but are fused into the Q R S complex or T wave. The P R interval cannot be determined. The Q R S complexes look the same in shape and size unless the P wave is fused into the Q R S complex. It is normal with less than 0.12 seconds if the level of the block is above the bundle of His and wide, greater than or equal to 0.12 seconds if the level of the block is below the bundle of His. The causes are inferior or anterior-wall M I, congenital abnormality, rheumatic fever, hypoxia; postoperative complication of mitral valve replacement; postprocedure complications of radiofrequency ablation in or

near A V nodal tissue; Lev's disease, fibrosis and calcification that spreads from cardiac structures to the conductive tissue; digoxin toxicity. Asystole: The features are as follows: The rate and rhythm are none. The P waves, P R interval, and Q R S complexes are not discernible. The causes are myocardial ischemia, M I, aortic valve disease, heart failure, hypoxia, hypokalemia, severe acidosis, electric shock, ventricular arrhythmia, A V block, pulmonary embolism, heart rupture, cardiac tamponade, hyperkalemia; electromechanical dissociation; cocaine overdose. The text at the bottom reads, notes. A V equals atrioventricular. B p m equals beats per minute. C N S equals central nervous system. C O P D equals chronic obstructive pulmonary disease. M I equals myocardial infarction.

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An example of myocardial infarction of the Left ventricle. There will be loss of heart muscle and decreased cardiac output. Treatment to break cycle is Alpha-adrenergic blockers, Vasodilators, Calcium blockers, Beta blockers, and Digoxin, A C E inhibitors and Diuretics. These will help to Activate compensation mechanisms, Stimulates S N S, leading to Vasoconstriction and increased resistance for left ventricle, Increased heart rate and force which is increased work for heart, stimulate renin secretion, leading to Activation of angiotensin, vasoconstriction, Stimulation of aldosterone secretion, Increased Sodium and water retention, Increased blood volume and Increased work for heart. These

compensations maintain cardiac output for a time, Heart muscle of the left ventricle weakens, Left-sided H F: Left ventricle does not fully empty hence Decreased cardiac output, Blood backs up in pulmonary circulation, Pulmonary congestion. This leads to Right-sided H F: Right ventricle weakens and cannot fully empty, Blood backs up in systemic circulation, and Edema in legs and digestive system.

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Diagram A for Left-sided heart failure depicts the heart, its chambers and blood vessels. Two blood vessels are connected to the lungs and the kidney. Text above reads as follows. 1. Left ventricle weakens and cannot empty. 2. Decreased cardiac output to system. 3. Decreased renal blood flow stimulates renin-angiotensin and aldosterone secretion. 4. Backup of blood into pulmonary vein. 5. High pressure in pulmonary capillaries leads to pulmonary congestion or edema. Text below the lung reads, Less blood here. Diagram B for Right-sided heart failure depicts the heart, its chambers and blood vessels. Two blood vessels are connected to the lungs and one to the kidney. Text below the lung reads, Less blood here. Text above reads as follows. 1. Right ventricle weakens and cannot empty. 2. Decreased cardiac output to system. 3. Decreased renal blood flow stimulates renin-angiotensin and aldosterone secretion. 4. Backup of blood into systemic vein or the venae cavae. 5. Increased venous pressure results in edema in

legs and liver and abdominal organs. 6. Very high venous pressure causes distended neck veins and cerebral edema.

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Stage A: At risk for heart failure. Risk for H F but no current or previous H F clinical manifestations, structural or functional heart disease, or abnormal biomarkers. Hypertension, C V D, diabetes, obesity, previous cardiotoxic agent exposure, or family history of cardiomyopathy present. Stage B: Pre-heart failure. No current or previous H F clinical manifestations but one of the following is present: Structural heart disease, or Increased filling pressures, Risk factors and increased natriuretic peptide levels, Consistently elevated cardiac troponin in the absence of other competing diagnoses. Stage C: Symptomatic heart failure. Presence of current or previous H F clinical manifestations. Stage D: Advanced heart failure. Presence of more severe H F clinical manifestations that interfere with daily activities and recurrent hospitalizations despite usual treatments.

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Stage A: At-risk for heart failure. G D M T: S G L T 2 i in patients with D M-1. Additional Medical Therapies once G D M T optimize: Optimal control of B P-1. Optimal Management of C V D -1. Stage B: Pre-heart failure. G D M T: S G L T 2 i in patients with D M-1; A C E i -1; A R B if A C E I intolerant-1; Beta blocker-1. Additional Medical Therapies once G D M

T optimize: Optimal control of B P-1. Optimal Management of C V D-1. Stages C and D: Stage C: Symptomatic heart failure and Stage D: Advanced heart failure. H F r E F and L V E F less than or equal to 40percent: G D M T: A R N 1 in N Y H A 2-3; A C E i or A R B in N Y H A 2-4-1; Beta blocker-1; M R A-1; S G L T 2 i -1; Diuretics, as needed-1; Hydral-nitrates for N Y H A 3-4, in African American patients -1. Additional Medical Therapies once G D M T optimize: Ivabradine -2a; Vericiguat -2b; Digoxin -2b; PUFA -2b; Potassium binders-2b. H F m r E F L V E F 41 to 49percent: G D M T: Diuretics, as needed-1; S G L T 2 i -2a; A C E i, A R B, A R N I -2b; M R A -2b; Beta blocker -2b; H F p E F L V E F more than or equal to 50percent: G D M T: Diuretics, as needed-1; S G L T 2 i -2a; A R N i -2b; M R A -2b; A R B -2b. Note: 1: Strong. 2a: Moderate. 2b: Weak.

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The extreme left image is of a Saccular aneurysm where there is a balloon-shaped bulge on one side of the blood vessel. The image in the center is labeled Fusiform aneurysm where the entire blood vessel has ballooned. The image on the right is a Dissecting aneurysm. A cross-section of the blood vessel depicting the inner lining of the blood torn and separating from the arterial wall.

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Stage 1: Dietary intake of cholesterol and triglycerides. Bile dissolves the cholesterol and triglycerides from the intestines into Chylomicrons. Stage 2: The Chylomicrons are absorbed into blood and lymph. The oval-shaped Chylomicron particles travel through the blood vessel into the liver. Stage 3: Lipid uptake by adipose and skeletal muscle cells. Stage 4: Remnants are sent to the liver. Stage 5: Liver synthesize lipoproteins. Stage 6: L D L transports cholesterol to cells. Stage 7: L D L particles get attached to L D L receptor in smooth muscle and endothelial tissue. Stage 8: H D L particles transport cholesterol from cells to liver.

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The primary prevention includes an assessment of A S C V D risk in each age group and emphasizes adherence to a healthy lifestyle. If L D L-C is greater than or equal to 190 milligrams per deciliter or greater than 4.9 millimoles per liter, there is no risk assessment, and it is high-intensity statin or class 1. If there is diabetes mellitus and the age is between 40 and 75 years, it is moderate-intensity statin or class 1 or needs risk assessment to consider high-intensity statin or class 2 a. If the age is greater than or equal to 75 years, they need clinical assessment and risk discussion. If the age is between 0 and 19 years, a lifestyle to prevent or reduce A S C V D risk is advised. The diagnosis of familial hypercholesterolemia leading to statin is done. If the age is between 20 and 39 years, estimate the lifetime risk to encourage a lifestyle to reduce A S C V D risk. Consider

statin if family history includes premature A S C V D and L D L-C is greater than or equal to 10 milligrams per deciliter or greater than 4.1 millimoles per liter. If the age is between 40 and 75 years and L D L-C is greater than or equal to 70 and less than 190 milligrams per deciliter or greater than or equal to 1.8 and less than 4.9 millimoles per liter without diabetes mellitus, the 10-year A S C V D risk percent begins the risk discussion. The following steps in the age group between 40 and 75 years are as follows: If it is less than 5 percent, or low risk, and between 5 percent and less than 7.5 percent, or borderline risk, then risk discussion should emphasize lifestyle to reduce risk factors, or class 1. If it is 5 percent to less than 7.5 percent or borderline, then risk discussion: if risk enhancers are present, then risk discussion regarding moderate-intensity statin therapy or class 2 b. If it is greater than or equal to 7.5 and less than 20 percent, or intermediate risk, then risk discussion: If the risk estimate plus enhancers favor statin, initiate moderate-intensity statin to reduce L D L-C by 30 percent to 49 percent, or class 1. If the risk decision is uncertain, consider measuring C A C in selected adults. C A C equals 0, lowers risk; consider no statin, unless diabetes, family history of premature C H D, or cigarette smoking are present. C A C equals 1 to 99 favors statin, especially after age 55. C A C equals 100 plus and or greater than or equal to the seventy-fifth percentile, initiate statin therapy. If it is greater than or equal to 20 percent, or high risk, then risk discussion: initiate statin to reduce L D L-C less than or equal to 50 percent, or class 1. The text on

the left reads, A S C V D risk enhancers: family history of premature A S C V D. persistently elevated L D L-C greater than or equal to 160 milligrams per deciliter or greater than or equal to 4.1 millimoles per liter. Chronic kidney disease. Conditions specific to women, for example, preclampsia and premature menopause. Inflammatory diseases, especially rheumatoid arthritis, psoriasis, and H I V. ethnicity, for example, South Asian ancestry, Lipid biomarkers: persistently elevated triglycerides, greater than or equal to 175 milligrams per deciliter or greater than or equal to 2.0 millimoles per liter. In selected individuals, if measured, h s-C R P greater than or equal to 2.0 milligrams per liter. L p, a level greater than 50 milligrams per deciliter or greater than 125 millimoles per liter. A p o B greater than or equal to 130 milligrams per deciliter. The ankle-brachial index, or A B I is less than 0.9. The note at the bottom reads, abbreviations. A C S, acute coronary syndrome. Atherosclerotic cardiovascular disease. H D L-C, high-density lipoprotein cholesterol. L D L-C, low-density lipoprotein cholesterol. Myocardial infarction. P C S K 9 I, P C S K 9 inhibitor. Asterisk: very high risk includes a history of multiple major A S C V D events or one major A S C V D event and multiple high-risk conditions.

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Clinical A S C V D: With healthy lifestyle. Those with A S C V D not at very high-risk: Age: less than or equal to 75 years: If High-intensity statin, Goal: L D L- C more than or equal to 50

percent, Class 1: If high intensity statin not tolerated, use moderate intensity statin Class 1. If on maximal statin therapy and L D L-C is more than or equal to 70 percent, milligrams per d L is more than or equal to 1.8 millimeters mol per Liter, adding ezetimibe may be reasonable, Class 2 b. If Age is more than 75 years, initiation of moderate or high-intensity statin is reasonable, Class 2 a. Continuation of high-intensity statin is reasonable, Class 2 a. Very high-risk-A S C V D and High-intensity or maximal statin Class 1. If on maximal statin and L D L-C is more than or equal to 70 milligrams per d Liter or 1.8 milli moles per Liter, adding ezetimibe is reasonable Class 2 a. If P C S K 9-I is considered, add ezetimibe to maximal statin before adding P C S K 9-I Class 1. Dashed arrow indicates R C T supported efficacy, but is less cost effective. If on clinically judged maximal L D L-C, lowering therapy and L D L-C more than or equal to 70 milligram per d Liter or 1.8 mmol per Liter, or non-H D L-C 100 milligram per d Liter or 2.6 mmol per Liter, adding P C S K 9-I is reasonable Class 2 a. Abbreviations: A C S, acute coronary syndrome; A S C V D, atherosclerotic cardiovascular disease; H D L-C, high-density lipoprotein cholesterol; L D L-C, low-density lipoprotein cholesterol; M I, myocardial infarction; P C S K 9-I, P C S K 9 inhibitor. Very high risk includes a history of multiple major A S C V D events or 1 major A S C V D event and multiple high-risk conditions.

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The illustration on the top is of a small cylinder labeled clear artery, with arrows going through. Below this is an image of a small cylinder labeled Partial obstruction, with a thick coating on its inner wall, and an arrow passing through. The image at the bottom is labeled Total obstruction and the inner space of the cylinder is completely filled with substance. An arrow is depicted bouncing off the cylinder. The flowchart on the right defines Atherosclerosis as the narrowing of large arteries by cholesterol plaque and thrombus in different parts of the body as follows. Heart: Partial occlusion of the Coronary arteries causes Angina pectoris or ischemic heart disease. Total occlusion of the Coronary arteries causes Myocardial infarction or M I. Brain: Partial occlusion of the Carotid or cerebral arteries causes Transient ischemic attack. Total occlusion of the Carotid or cerebral arteries causes Cerebrovascular accident or C V A. Narrowing of peripheral arteries like the Aorta causes Aneurysm, Occlusion, Rupture, and hemorrhage; and in the legs causes Peripheral vascular disease, Gangrene, and amputation.

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The four cross-sections depict the cylindrical artery with the layers of the artery wall. In the first image, the outer wall is made up of normal, smooth muscle cells. A small break in the innermost layer is labeled Damaged endothelium. In the second image, a small fatty streak has formed at the break of the endothelium. In the third image, the streak has enlarged into a patch of Fibrous plaque made of Fibers and

Fats, partially obstructing the artery. Fatty deposits accumulate in the wall of the artery. In the fourth image, a large plaque has spread almost across the artery passage and obstructing the artery.

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The bottom illustration has three diagrams. In the first image, a thin tube covered with a mesh is inserted into the artery blocked by fatty plaque along the wall. In the second image the stent is ballooned to widen the space that is blocked by plaque. In the third image, the stent is further ballooned to ensure the free flow of blood. The illustration on top depicts the heart and the stent placed within the artery permanently.

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The base of the pyramid is labeled Vascular Wall Injury. Explanatory text below reads,' Trauma or surgery, Venipuncture, Chemical irritation, Heart valve disease or replacement, Atherosclerosis, and Indwelling catheters. The right side is labeled Circulatory Stasis. Explanatory text below reads,' Atrial fibrillation, Left ventricular dysfunction, Immobility or paralysis, Venous insufficiency or varicose veins, Venous obstruction from tumor, obesity, or pregnancy. The left side is labeled Hypercoagulable State. Explanatory text below reads,' Malignancy, Pregnancy and peripartum period, Estrogen therapy, Trauma or surgery of lower

extremity, hip, abdomen, or pelvis, Inflammatory bowel disease, Nephrotic syndrome, Sepsis, and Thrombophilia.

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On the left is a silhouette of a man with the heart and blood vessels of the abdomen and lower extremities superimposed on it, labeled as follows. Femoral vein in the thigh, Popliteal vein below the kneecap, Anterior tibial vein at the shin, and Posterior tibial vein at the ankle. An enlargement on the side depicts a cross-section of a normal vein, where the valve in the vein is open and disc-shaped platelets move freely through. Another enlargement on the side depicts a cross-section of a vein with thrombosis where the valve is open but platelets are grouped together at the bottom forming a mass of platelets.

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On the left is a silhouette of a man with the heart, lungs, and blood vessels of the abdomen and lower extremities superimposed on it. The Femoral vein in the thigh has a clot and upward arrows are marked from the clot toward the heart. An enlargement on the side depicts a cross-section of the vein with blood moving up inside the vein. Another diagram on the right depicts the spinal cord, heart, and lungs. A clot labeled Embolus is depicted in the Pulmonary artery in the right lung. The lower part of the lung below the Pulmonary

artery is darkened and labeled Infarcted area. Text above reads, Pulmonary artery obstructed by the embolus.

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The diagram A on the left of the heart depicts the chambers, the coronary artery, a band of heart muscle across the center. The lower part of the heart is dark and labeled Dead heart muscle. A diagram B on the right depicts the coronary artery, which supplies blood and oxygen to the heart muscle, and its branches below, within the heart. The base of the heart is dark and labeled Dead heart muscle. The upper portion of the heart is labeled Healthy heart muscle. A blood clot in the coronary artery just below the healthy heart muscle blocks the blood flow in the artery and Plaque buildup in the artery below the clot.

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A horizontal cross-section depicts two chambers of the heart with a septum wall in the middle. The chamber on the left is open and a few fibrous structures are present here and there. On the right, a thick tissue covers almost the entire posterior left ventricle wall and only a small hole close to the septum is present.

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A. There is the normal pattern of the P wave, P R interval, Q R S complex, S T segment, and T wave. B. The P wave, P R

interval, Q R S complex, and S T segment are normal. The T wave is inverted. C. The P wave, P R interval, and Q R S complex are normal. The S T segment is lowered from the baseline with an inverted T wave. D. The P wave and the P R interval are normal. The S T segment is elevated to a quarter of the Q R S peak height from the baseline with an inverted T wave. E. The P wave and the P R interval are normal. The S T segment is elevated to half of the Q R S peak height from the baseline with an inverted T wave. F. The P wave is normal. The Q wave is depressed. The S T segment is elevated to half of the Q R S peak height with an inverted T wave.

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The horizontal axis lists a normal state; ischemia and micronecrosis develop; permanent necrosis develops. The vertical axis is labeled the level of cardiac troponin. The right vertical axis has a downward-pointing arrow labeled the ninety-ninth percentile value of cardiac troponin. The line for the level of cardiac troponin is at a very low level, with minor fluctuations in the normal state. It begins to increase when ischemia and micronecrosis develop. The beginning point of the increase is pointed out in the text that reads, onset of myocardial infarction. In a comparatively short period, the line reaches a peak in the permanent necrosis stage. The vertical height of the increase is labeled a high-sensitivity cardiac troponin test. The top three-fourths of the vertical height is labeled present cardiac troponin tests. The top

quarter of the vertical height of the increase is labeled previous cardiac troponin

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The condition of the heart and corresponding treatment are as follows. A change in the condition of plaque in the coronary artery, there is activation of platelets. Treatment: Aspirin, Antiplatelet aggregates, and Glycoprotein 2 b or 3 a inhibitors. Formation of thrombus. Treatment: Thrombolytic therapy, Percutaneous transluminal coronary angioplasty. Coronary blood supply less than demand results in Ischemia of tissue in the region supplied by the artery and Myocardial cell death. Treatment: Nitrates, Beta-adrenergic blockers, Oxygen, Bed rest, and Vasodilators. Altered depolarization of the myocardium results in Pathological Q wave appears, and there is Elevated S T segment, and T-wave changes. Release of lysosomal enzymes gives rise to Elevated C K-M B, Elevated lactate dehydrogenase, Elevated troponin, and myoglobin. Anaerobic glycolysis causes Angina and Lactic acid production. Treatment: Nitroglycerin, and Morphine. Myocardial irritability causes Arrhythmias and Decreased contractility. Treatment: Antiarrhythmics, Beta-adrenergic blockers, Transcutaneous pacing, and Defibrillation. Decreased contractility causes Stimulation of the sympathetic nervous system. Treatment: Nitrates and Vasodilators. This will cause Increased heart rate, Increased afterload, and Increased oxygen needs. Increased afterload causes Vasoconstriction. Decreased contractility causes

Decreased left ventricular function giving rise to Increased afterload. Treatment: Fluid restriction, and Diuretics. Decreased cardiac output causes Decreased left ventricular ejection fraction. Treatment: Angiotensin converting enzyme inhibitors.

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Systemic vasoconstriction leads to Decreased blood flow to the kidney and Increased renin secretion. This could also be caused by Nephrosclerosis or Diabetic nephropathy causing Systemic vasoconstriction which causes Increased peripheral resistance; and Aldosterone secretion leading to Increased blood volume and Increased blood pressure. Other consequences are Damage to renal blood vessels, Increased work for the heart causing left-sided C H F, Damage to cerebral arteries causing stroke, Damage to arterial walls leading to atherosclerosis, and Damage to retinal blood vessels causing blindness.

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Decrease in blood pressure causes Compensations to maintain heart and brain functions, resulting in Stimulation of sympathetic nervous system, marked by Thirst, Anxiety, restlessness, Tachycardia, Vasoconstriction, and pallor. Renin–angiotensin–aldosterone causes Vasoconstriction, Retention of Sodium and water, and oliguria. The increased A D H secretion causes Retention of water. Direct effects of

decreased blood pressure are Lethargy, weakness, Anaerobic metabolism leading to Metabolic acidosis, Vasodilation, and decreased cell function. There is Slow blood flow in microcirculation, so Thrombus forms. Ischemia in organs leads to Necrosis for example in the kidney. Vasodilation and decreased cell function causes Decreased venous return which in turn causes further decrease in cardiac output. This will result in Severe acidosis, C N S depression, Organ damage for example acute renal failure, or lung damage, ultimately resulting in Decompensation.

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The parts include the following: Nasal cavity: a large, air-filled space above and behind the nose in the middle of the face; tongue; hard palate: the horizontal bony plate in the mouth; epiglottis: a leaf-shaped flap of cartilage located behind the tongue; tonsils: two oval-shaped glands that sit at the back of the throat; esophagus: a muscular tube connecting the throat with the stomach; vocal cords: two bands of smooth muscle tissue found in the voice box, larynx: an organ termed the voice box, in the top of the neck; trachea: a cartilaginous tube called the windpipe, which connects the larynx to the bronchi of the lungs; and esophagus: a muscular tube connecting the throat with the stomach.

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The system features the following parts: nasal cavity: a large, air-filled space above and behind the nose in the middle of the face; mouth or oral cavity; pharynx: the part of the throat behind the mouth and nasal cavity, and above the esophagus and larynx; larynx: an organ termed the voice box, in the top of the neck; trachea: a cartilaginous tube labeled the windpipe, which connects the larynx to the bronchi of the lungs; bronchi: a passage or airway in the respiratory system that conducts air into the lungs; terminal bronchiole: the branches that form respiratory bronchioles, which contain a small number of alveoli. The right and left networks of bronchioles are labeled the right bronchus and the left bronchus, respectively. A magnified view of the left lung features the following parts: The bronchioles are the branches into which a bronchus divides; the bronchioles end in clusters of thin-walled air sacs, labeled alveoli; the alveoli are surrounded by a tiny blood vessel network, labeled capillary network; capillaries connect to larger blood vessels, labeled veins; and the arteries are the blood vessels that travel from the heart to the tissues of the body. A magnified inset features the alveoli and capillary exchange network.

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Part A: An illustration features the upper respiratory system, with the location of the vocal cords marked. Part B: An illustration features the longitudinal section of the larynx, with the location of the vocal cords marked. The following parts have been marked: Thyroid cartilage: a structure that sits in

front of the larynx and above the thyroid gland; vocal cords: two bands of smooth muscle tissue found in the larynx or voice box. The top muscle is labeled the ventricular fold or false vocal cord. The bottom muscle is labeled the true vocal cord; the epiglottis is a leaf-shaped flap of cartilage located behind the tongue; and the tracheal cartilages are strong and flexible tissue supporting the trachea. Part C: A photo features the view from above into the larynx of a patient, and the vocal cords are marked.

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Part A: An illustration features a trachea lined with a moist mucous-membrane layer labeled cilia. There are mucous cells in the lining that produce mucus, which traps organisms and other particulates in the air. The cilia transport the mucus toward the mouth. A micrograph features a magnified view of the mucous cell and cilia.

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The cells in the alveolar wall are as follows: type 1 alveolar cell, which permits gases to move into and out of the alveoli; type 2 alveolar cell, which produces surfactant; R B Cs, which are essential for oxygen transport; capillary endothelium cells, which form the capillary wall and permit gas exchange; nucleus; connective tissue cell; connective tissue fibers; interstitial fluid; surfactant reduces surface tension created by water and keeps alveoli from collapsing;

pulmonary capillary: oxygen and carbon dioxide are exchanged here between the blood and the air in the lung; alveolar macrophage: a large mobile cell within the connective tissue of the alveolar walls, which ingests by phagocytosis any foreign particles and infectious microorganisms that reach the alveoli. They also transport indigestible materials to the lymph nodes of the lungs for storage.

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The illustration features the bronchiole, arteries, veins, alveoli, the alveolar wall, capillaries covering the alveoli, and the capillary wall. Deoxygenated blood is carried from the heart to the lungs by the pulmonary arteries and arterioles. Gas exchange takes place at the capillaries covering the alveoli. Carbon dioxide and oxygen are exchanged across two layers of epithelial cells. One layer makes up the wall of the capillary, and one layer makes up the wall of the alveolus. Oxygenated blood is carried from the lungs to the heart by the pulmonary veins and venules.

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Oxygen as O 2 from the inhaled air travels from the alveoli first into the blood plasma. O 2 becomes dissolved O 2 in the plasma of the lung capillaries. When the oxygenated blood reaches the lung capillaries, oxygen is released from the plasma into the red blood cells, where much of it binds to

hemoglobin. When the oxygenated blood reaches the tissues, oxygen is released from the red blood cells and diffuses first into the plasma, as dissolved O 2 in the tissue capillaries, then into the interstitial fluid, and then to the body cells as dissolved O 2 to use up for O 2 consumption.

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The horizontal axis is labeled oxygen pressure in millimeters of mercury, and ranges from 0 to 100, in increments of 20. The vertical axis is labeled percent saturation, S O 2, and ranges from 0 to 100, in increments of 20. The curve for increased affinity has a shift to the left from the curve for normal. The curve for decreased affinity has a shift to the right from the curve for normal. The curve for decreased affinity features acute acidosis with decreased p H value; high P C O 2; increased temperature; high levels of 2, 3-D P G; and abnormal hemoglobin. The curve for normal affinity features normal values The curve for increased affinity features acute alkalosis with increased values of p H; decreased P C O 2; decreased temperature; low levels of 2,3-diphosphoglyceric acid, D P G; carboxyhemoglobin; methemoglobin; and abnormal hemoglobin.

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Increased P C O 2 in blood and cerebrospinal fluid stimulates central chemoreceptors in the medulla. This stimulates the inspiratory muscles that remove more C O 2 from the body.

So, there is decreased P C O 2 which leads to decreased chemoreceptor stimulation. that slows respirations and more C O 2 is retained, resulting in increased P C O 2 in the blood and cerebrospinal fluid. The cycle continues. When respirations slow, the medullary chemoreceptors become insensitive to high P C O 2. There is no increase in respiration, and the O 2 levels show a marked decrease. This results in very low P O 2 levels, which stimulate peripheral chemoreceptors that stimulate inspiratory muscles, which increase respirations. This results in the removal of C O 2, the absorption of more O 2, a decrease in P C O 2, and an increase in P O 2. The respiration is slowed, and the cycle continues.

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The process of breathing is divided into two distinct phases: inspiration and exhalation. Part A, exhalation: an illustration features the diaphragm at rest and relaxed. A corresponding radiograph features the base of the diaphragm in the shape of an arc. Part B, inspiration: an illustration features the diaphragm contracting and lowering, while the neck, chest, and intercostal muscles contract and pull upward, and the breastbone moves up and outward. A corresponding radiograph features an elongated diaphragm with a flat base.

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The vertical axis ranges from 0 to 6000 milliliters in increments of 1000. The respiratory curve starts at 2400, peaks at 3000, and declines back to 2400, rises steeply and peaks at 6000, marked deep inhalation, and lowers down, reaching 1200, marked forced exhalation, and rises to reach the peak at 3000, declines to 2400, rises to 3000, and the curve continues. The area between 0 and 1200 is marked residual volume: 1200 milliliters; the area between 1200 and 2400 is marked expiratory reserve volume: 1200 milliliters; the area between 2400 and 3000 is marked tidal volume: 600 milliliters; and that beyond 3000 is marked inspiratory reserve volume: 2000 to 3000 milliliters.

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Top: An illustration features a healthy mucosa with good airflow and another illustration features necrosis. Upon primary viral infection, for example, rhinovirus or adenovirus, the virus attaches firmly to the respiratory mucosa and invades the tissue, causing necrosis, inflammation, and swelling. Congestion obstructs airways, resulting in poor airflow. Bottom left: An illustration of the human anatomy features the virus reaching the lungs. The virus spreads along the mucosa of the nasal and oral cavity, invading ears, causing otitis media, sinuses, sinusitis, and bronchi, and through the trachea, reaching the lungs, causing pneumonia. Bottom right: An illustration features the invasion of the necrotic area by bacteria. Bacteria, sometimes resistant flora, penetrate the damaged mucous membranes, causing

secondary bacterial infection, leading to inflamed tissue and the formation of purulent exudate.

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The risk of being affected by tuberculosis is primarily in the following environments: weak immune systems, malnutrition, overcrowded living conditions, and substance abuse. When an individual is exposed to airborne droplets, the droplet enters the alveoli, and the inflammatory process begins. Bacilli are isolated and phagocytized. This results in some bacilli being killed, with the purified protein derivative of the individual being positive. Some bacilli enter a dormant stage, which either leads to the individual being immediately infected by tuberculosis or begins with the formation of tubercles. These tubercles are calcified, resulting in the weakening of the immune system and the breakdown of tubercles. This leads to the reactivation of the disease, and the person becomes infectious with the development of symptoms. The chest radiograph and sputum culture indicate the presence of tuberculosis. The treatments to be undergone are antimycobacterial therapy with multiple medications to prevent mutation or resistance, prophylactic drug therapy after exposure, and the Bacille Calmette-Guerin vaccine after exposure when medications are not available.

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Part A: An illustration of the human anatomy features the airways from the nasal cavity through the trachea to the lungs of the body, including the bronchioles. Part B features a magnified view of the airways in the lungs of a normal person. The pathway is visible, and the inside space of the tubular structure, the lumen, is wide. The blood vessels, bands of smooth muscle, and the mucous lining are present. Part C features a magnified view of the airways in the lungs of a person affected by asthma. The blood vessels have been infiltrated by immune cells; there is inflammation and contraction in the smooth muscles, which appear contracted; and the pathway is not visible. There is more excess mucus than normal, and the lumen is narrow.

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Once the dendritic cell has engaged the allergen, it receives signals to migrate to local lymphoid collections, where antigen presentation takes place. The naive T lymphocyte, T h 0, determines the balance between T h 1 and T h 2 responses; I L 12 polarizes T cell differentiation in favor of a T h 1 response, while I L 12 can counteract T h 2 sensitization. There are two types of T helper cells, designated T h 1 and T h 2. T h 2 cells promote the production of I g E antibodies by producing I L 4 and I L 3, which are interleukins that activate B cells to promote the production of I g E antibodies to a specific antigen. One portion of the I g E antibody binds to receptors, F c e R I, on mast cells, but another portion of the I g E antibody remains available to bind to the allergen. If the

allergen binds to the I g E on the mast cell, the mast cell becomes activated to release histamine, leukotrienes, and other cytokines. Subsequent exposures to triggers such as allergens, viruses, colds, irritants, and exercise result in the allergen specific I g E being rapidly produced, and mast cells degranulate and release an array of inflammatory mediators, leading to physiologic effects like a hyperactive response such as bronchospasm, edema, and airway obstruction. In addition, asthmatics also have tissue remodeling, thickening, and the chronic presence of increased numbers of inflammatory cells.

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Step 1, preferred: S A B A P R N. Step 2, preferred: low-dose I C S; alternative: cromolyn, L T R A, nedocromil, or theophylline. Step 3, preferred: low-dose I C S plus L A B A or medium-dose I C S; alternative: low-dose I C S either L T R A, theophylline, or zileuton. Step 4, preferred: medium-dose I C S plus LABA; Alternative: medium-dose I C S plus either L T R A, theophylline, or zileuton. Step 5, preferred: high-dose I C S plus L A B A, and consider omalizumab for patients who have allergies. Step 6, preferred: high-dose I C S plus L A B A plus oral corticosteroid, and consider omalizumab for patients who have allergies. The text below reads, Each step: patient education, environmental control, and management of comorbidities. Steps 2 to 4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma. Quick relief: S A B A as needed for

symptoms. The intensity of treatment depends on the severity of symptoms; up to three treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed. Use of S A B A medication for all patients 2 days a week for symptom relief and not prevention of E I B, generally indicates inadequate control and the need to step up treatment. The text to the right of step 6 reads, Step up if needed: First, check adherence, environmental control, and comorbid conditions; assess control; step down if possible; and asthma is well controlled for at least 3 months. Intermittent asthma is treated with Step 1. Treatment with step 2 continues for persistent asthma: daily medication; consult with an asthma specialist if step 4 care or higher is required; consider a consultation at step 3.

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The document features general information, like the patient's name, doctor, date, doctor's phone number, and hospital or emergency phone number. There are three zones as follows: Green zone: The text reads, Doing Well: No cough, wheezing, chest tightness, or shortness of breath during the day or night; can do usual activities. And if a peak flow meter is used: Peak flow, is more than a, blank line, 80 percent or more of my best peak flow. My best peak flow is blank space. There are blank lines on the right for daily medications medicine, how much to take, and when to take it. The text in the next section reads, Before exercise, check boxes for blank line and 2 or 4 puffs. Yellow zone: Asthma is getting

worse. The text reads, cough, wheeze, chest tightness, or shortness of breath, or waking at night due to asthma, or, can do some, but not all, usual activities. Or, peak flow, blank line to blank line, 50 to 79 percent of my best peak flow. First: Add quick-relief medicine, and keep taking your Green Zone medicine. Blank lines for quick-relief medicine, number of puffs or checkbox for nebulizer once, and 2 or 4 puffs, every 20 minutes for up to 1 hour and Nebulizer, once. Text reads, can repeat every blank line for minutes up to a maximum of blank line doses. Second: If your symptoms, and peak flow, if used, return to the Green zone after 1 hour of above treatment. Check box for continued monitoring to be sure you stay in the green zone. Or, if your symptoms, and peak flow, if used, do not return to the Green zone, after 1 hour of the above treatment. Checkboxes for Take, blank line for quick-relief medicine, blank lines for number of puffs, or Nebulizers; add blank line for oral steroid, milligrams per day, for blank line, 3 to 10 days, call the doctor, before or within blank line hours after taking the oral steroid. Red zone: Medical alert. The text reads, very short breath or quick-relief medicines have not helped, or, cannot do unusual activities, or symptoms are same or get worse after 24 hours in yellow zone, Or, peak flow: less than, blank line, 50 percent of my best peak flow. Take this medicine. Check boxes for blank lines for quick-relief medicine, blank line for number of puffs, or nebulizers, blank lines for oral steroids in milligrams. Then call your doctor now. Go to the hospital or call an ambulance if: you are still in the red zone after 15 minutes and you have

not reached your doctor. At the bottom of the form, the text reads: Danger signs: trouble walking and talking due to shortness of breath; lips or fingernails are blue; Take blank line puffs of blank line, quick-relief medicine and go to the hospital or call for an ambulance blank line for phone, now. The text reads, How to control things that make your asthma worse. This guide suggests things you can do to avoid your asthma triggers. Put a check next to the triggers that you know make your asthma worse and ask your doctor to help you find out if you have other triggers as well. Keep in mind that controlling any allergen usually requires a combination of approaches, and reducing allergens is just one part of a comprehensive asthma management plan. Here are some tips to get started. These tips tend to work better when you use several of them together. Your healthcare provider can help you decide which ones may be right for you. Allergens. Dust Mites. These tiny bugs, too small to see, can be found in every home, in dust, mattresses, pillows, carpets, cloth furniture, sheets and blankets, clothes, stuffed toys, and other cloth-covered items. If you are sensitive: Mattress and pillow covers that prevent dust mites from going through them should be used along with high-efficiency particulate air, H E P A, filtration vacuum cleaners. Consider reducing indoor humidity to below 60 percent. Dehumidifiers or central air conditioning systems can do this. Cockroaches and Rodents. Pests like these leave droppings that may trigger your asthma. If you are sensitive: Consider an integrated pest management plan. Keep food and garbage in closed

containers to decrease the chances for attracting roaches and rodents. Use poison baits, powders, gels, or paste, for example, boric acid, or traps to catch and kill the pests. If you use a spray to kill roaches, stay out of the room until the odor goes away. Animal Dander. Some people are allergic to the flakes of skin or dried saliva from animals with fur or hair. If you are sensitive and have a pet: Consider keeping the pet outdoors. Try limiting your pet to commonly used areas indoors. Indoor Mold. If mold is a trigger for you, you may want to: Explore professional mold removal or cleaning to support complete removal. Wear gloves to avoid touching mold with your bare hands if you must remove it yourself. Always ventilate the area if you use a cleaner with bleach or a strong smell. Pollen and Outdoor Mold. When pollen or mold spore counts are high you should try to: Keep your windows closed. If you can, stay indoors with windows closed from late morning to afternoon when pollen and some mold spore counts are at their highest. If you do go outside, change your clothes as soon as you get inside, and put dirty clothes in a covered hamper or container to avoid spreading allergens inside your home. Ask your healthcare provider if you need to take or increase your anti-inflammatory medicine before the allergy season starts. Irritants. Tobacco Smoke. If you smoke, visit smokefree dot g o v or ask your health care provider for ways to help you quit. Ask family members to quit smoking. Do not allow smoking in your home or car. Smoke, Strong Odors, and Sprays. If possible, avoid using a wood-burning stove, kerosene heater, or fireplace.

Vent gas stoves outside the house. Try to stay away from strong odors and sprays, such as perfume, talcum powder, hair spray, and paints. Vacuum Cleaning. Try to get someone else to vacuum for you once or twice a week if you can. Stay out of rooms while they are being vacuumed and for a short while afterward. If you must vacuum yourself, using H E P A filtration vacuum cleaners may be helpful. Other Things That Can Make Asthma Worse. Sulfites in foods and beverages: Do not drink beer or wine or eat dried fruit, processed potatoes, or shrimp if they cause asthma symptoms. Cold air: Cover your nose and mouth with a scarf on cold or windy days. Other medicines: Tell your doctor about all the medicines you take. Include cold medicines, aspirin, vitamins, and other supplements, and nonselective beta-blockers, including those in eye drops. The United States Department of Health and Human Services National Institutes of Health.

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The human anatomy, with the trachea or windpipe, bronchiole, and lung, is featured. The magnified view of the normal bronchiole, with the bronchiole and alveoli, is featured. The magnified view of the bronchiole and the alveoli with the condition of chronic bronchitis is featured. There is excess mucus formation, and the bronchiole is inflamed. The magnified view of the bronchiole and the alveoli with a condition of emphysema is featured. The bronchiole and alveoli are completely out of shape, with a collapsed bronchiole and enlarged alveoli.

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Cystic fibrosis, an autosomal recessive disorder, leads to exocrine gland dysfunction in sweat glands, which results in excess N a positive and C l content negative content, further electrolyte imbalance, and dehydration. Excessive amounts of thick, sticky mucus obstruct the ducts of exocrine glands in the lungs, digestive tract, and reproductive system, resulting in the following: Lungs: obstruction of airways and frequent infections lead to fibrosis and, further, to cor pulmonale. Digestive tract: meconium ileus or intestinal obstruction in newborns Obstruction of pancreatic ducts, which leads to fibrosis, diabetes mellitus, malabsorption, and malnutrition, and obstruction of bile ducts in the liver, which leads to biliary cirrhosis, malabsorption, and malnutrition. Reproductive tract: obstruction of vas deferens blocks sperm flow, and cervical mucus blocks sperm entry, both of which lead to infertility.

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Lung carcinogenesis results in both molecular and cellular alterations in the lung epithelial cells. The three phases are cancer initiation, promotion, and progression phases. Genetically altered epithelial cells are a result of frequent exposure to carcinogens. If exposure is stopped, it is capable of detoxification and excretion of carcinogens, leading to D N A repair. The next stage is apoptosis, cell cycle arrest, anti-inflammation, and further anti-

angiogenesis. If exposure continues, it causes inflammation, R O S or free radical electrophilic metabolites. This results in the formation of D N A adducts and epigenetic alterations leading to irritated cells or gene mutations. The promotion phase begins at this stage. Persistent D N A damage results in the loss of normal cell functions and uncontrolled cell growth and proliferation. Angiogenesis plays a critical role in the growth of cancer, including tumor growth and lung metastasis.

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The illustration features the lungs, heart, and diaphragm. A wound site is present in the lung. The parietal pleura in the lung is marked. An air leak in the pleural space, between the parietal and visceral pleura, pushes on the outside of the lung, collapsing it.

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There are three major phases of A R D S: the exudative, proliferative, and fibroproliferative phases. The healthy alveolar epithelium is comprised of two types of cells that form a natural barrier: type 1 cells and type 2 cells. The type 1 cells are labeled surfactant secretion. The healthy alveolus has a clear alveolar space and has neutrophils and alveolar macrophages. Another barrier between the alveolus and capillaries is the microvascular endothelium. The interaction between the two separate barriers plays a critical role in

controlling fluid accumulation in the alveolar space. After interaction with pathogens or specific pathogen-derived components, antigen-presenting cells present the pathogen-associated molecular patterns to T cells. This signaling activates immune cells to secrete inflammatory mediators, such as tumor necrosis factor, T N F alpha, interleukin, I L 10, I L 6, and I L 8. Severe inflammation also activates infiltrating leukocytes to release potent cytotoxic mediators, such as proteolytic enzymes, granular enzymes, reactive oxygen species R O S, cytokines, chemokines, and neutrophil extracellular traps N E Ts. The severe inflammation causes the loss of endothelial and epithelial cells by inducing apoptosis and necrosis. Acute respiratory distress syndrome A R D S is an inflammatory disease characterized by dysfunction of pulmonary epithelial and capillary endothelial cells, infiltration of alveolar macrophages and neutrophils, cell apoptosis, necroptosis, NETosis, and fibrosis. Alveolar epithelial cells downregulate ion transport machinery and the production of vascular endothelial growth factor V E G F, leading to alveolar edema. A R D S is the result of an initial acute systemic inflammatory response due to direct or indirect lung injury caused by factors such as smoking, near-drowning, aspiration, sepsis, trauma, ischemia, and exposure to a toxin. Dead cell debris and protein-rich fluid accumulate in the alveolar space to form the hyaline membrane, which is a characteristic pathological finding in the proliferative phase of A R D S. To recover from a lung injury, type 2 alveolar cells differentiate into type 1

alveolar cells. The formation of new vascular endothelial cells improves oxygenation via the recovery of microvascular permeability. Corticosteroids aid in reducing the release of cytokines to control systemic inflammatory responses. The T N F alpha and I L 1 beta produced by macrophages activate neutrophils. M 1 macrophages transited to M 2 macrophages due to the expression of I L 4, I L 10, and I L 13. M 2 macrophages abrogate pro-inflammatory mediators, induced to augment T G F beta and I L 10, and promote resolution of the immune response and wound repair. T G F beta regulates cell proliferation, differentiation, apoptosis, and necroptosis. It also plays an important role in the resolution of pulmonary inflammation and fibrosis formation. Several growth factors, such as M I P 2, angiopoietin, V E G F, and P D G F, promote the deposition of fibronectin and collagen. The severe fibrosis in the fibroproliferative phase leads to lung architecture remodeling marked by fibrosis and honeycomb formation. The horizontal axis of the line graph is labeled time following injury in days and ranges from 0 to 7, and lists later, which is from the second week. The vertical axis is labeled fraction of maximum and ranges from 0 to 1.5 in increments of 0.5. The exudative stage is in the first seven days; the next is the proliferative stage; and beyond is listed as the fibroproliferative stage. The curves for edema, hyaline membranes, interstitial inflammation, and interstitial fibrosis are depicted as follows: During the early phase, the lesion is characterized by high-permeability pulmonary edema, followed by the formation of hyaline membranes. After seven

to ten days, a proliferative phase may develop, with marked interstitial inflammation, fibrosis, and disordered healing.

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An illustration features the total body mass of a female contains 45 percent solids and 55 percent fluids, and that of a male contains 40 percent solids and 60 percent fluids. Fluid found inside the cells, the intracellular fluid that is found in the tissues, I C F, constitutes two-thirds of the total body fluid, and fluid found outside the cells, the extracellular fluid, E C F, constitutes one-third of the total body fluid. 80 percent of E C F is interstitial fluid, or I S F, and 20 percent is intravascular, inside the blood vessels. There is 60 percent of H 2 O in the human body. A table features the water percentage in different parts of the body as follows: Lungs: 90; Blood: 82; Skin: 80; Muscle: 75; Brain: 70; Bones: 22. A graph features the fluid distribution based on gender and age. The horizontal axis lists fetus, preterm, neonatal, child, adult, and older adult. The vertical axis is labeled clinical global impressions scale percent of patients responding and ranges from 0 to 100 in increments of 10. From the fetus to the neonatal stage, the body fluid is indicated as I C F: 67 percent. From child to adult, the body fluid comprises 33 percent, of which I C F holds the major part, followed by I S F plasma, or intravascular, lymph, and transcellular fluid, or T S F. The graph indicates that newborns and infants have higher amounts of water compared to adults.

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The horizontal axis lists E C F with one-third of body water and I C F with two-thirds of body water. The vertical axis is labeled m c o per L H 2 O and ranges from 0 to 200 in increments of 50. The capillary wall lies between the plasma and the intestinal fluid. Plasma is rich in sodium, chloride, and bicarbonate, H C O 3 negative. Sodium is greater than 120 milliosmolar concentration per liter H 2 O; chloride is 100 milliosmolar concentration per liter H 2 O; bicarbonate is greater than 15 milliosmolar concentration per liter H 2 O; K positive is 5 milliosmolar concentration per liter H 2 O; and protein negative is 20 milliosmolar concentration per liter H 2 O. The constituents in interstitial fluid are as follows: Sodium is greater than 100 milliosmolar concentration per liter H 2 O; chloride is 100 milliosmolar concentration per liter H 2 O; bicarbonate is greater than 20 milliosmolar concentration per liter H 2 O; and K positive is 5 milliosmolar concentration per liter H 2 O. There is a cell membrane dividing I C F and E C F. The constitutes in I C F are as follows: k positive is 150 milliosmolar concentration per liter H 2 O; protein negative is 50 milliosmolar concentration per liter H 2 O; bicarbonate is 6 milliosmolar concentration per liter H 2 O; chloride is 7 milliosmolar concentration per liter H 2 O; sodium is 2 milliosmolar concentration per liter H 2 O; and miscellaneous phosphates are 125 milliosmolar concentration per liter H 2 O.

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Filtration: The semipermeable membrane is marked. The movement of water and solutes from a high-pressure area labeled capillary arteriole, marked hydrostatic pressure, I V F, for example, 30 millimeters of mercury, to low pressure, marked hydrostatic pressure, I S F, for example, 2 millimeters of mercury, is featured. Diffusion: The movement of solutes, like sodium and glucose, from high-concentration areas like capillaries to low-concentration areas like I S F is featured. The opposite movement of cell waste is indicated. Osmosis: The transfer of solutes to the venule-containing proteins across cell membranes, from an area of lower concentration, I S F, 3 millimeters of mercury, to one of higher concentration, blood, 25 millimeters of mercury, is featured. Active transport: The cell with the intracellular compartment is featured. The movement of solute carriers and energy from low concentration, I S F, to high concentration, cell, is featured. Capillary exchange includes osmosis, diffusion, active transport, diffusion, and filtration.

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The arteriole is featured on one end and the venule on the other end. A band of smooth muscle fiber runs along both structures. Arterial end: blood pressure is higher than osmotic pressure, and net pressure out and is from the heart. Venous end: osmotic pressure is higher than blood pressure, and net pressure in and is toward the heart. The tissue fluids that exit the capillaries at the arterial end are water, amino acids, glucose, and oxygen. Carbon dioxide

enters the capillaries. The tissue fluids that reenter the capillaries at the venous end are waste and water. The blood pressure of the interstitial fluid is higher at the arterial end than it is at the venous end. The osmotic pressure is higher at the venous end than it is at the arterial end.

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Top: The illustration features two compartments, one labeled high osmotic pressure, which contains more solvents and a smaller number of solutes, and the other labeled low osmotic pressure, which contains fewer solutes and a larger number of solvents, with the semipermeable membrane dividing them. Bottom: The illustration features four compartments with a semipermeable membrane dividing them. One compartment is empty. In the second compartment, less than half is filled with solutes and solvents. In the third compartment, more than half is filled with solutes and solvents. The last compartment is full of solutes and solvents.

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Hypertonic: The extracellular fluid has lower osmolarity than the fluid inside the cell, resulting in water leaving the cell and thereby shrinking the cell. Isotonic: The relative concentrations of solute and water are equal on both sides of the membrane, and there will be no net movement of water into or out of the cell. Hypotonic: The extracellular fluid has a

higher osmolarity than the cell's cytoplasm, resulting in water entering the cell and the cell swelling.

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Top: The illustration features normal tracing of the T wave, P R internal, S T segments, and Q R S, with potassium levels between 3.5 and 5.3 milliequivalents per liter. Bottom: The illustration features a tall, peaked T wave, prolonged P R interval, depressed S T segment, and Q R S wider, with potassium levels greater than 7 milliequivalents per liter.

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Top: The illustration features normal tracing of the T wave, P R internal, S T segments, and Q R S, with potassium levels between 3.5 and 5.3 milliequivalents per liter. Bottom: The illustration features a depressed S T segment, inversion of the T wave, U waves, and Q R S wider, with potassium levels less than 3.5 milliequivalents per liter.

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The p H scale runs from zero to 14. A low p H, close to zero, is very acidic, with many free H-positive ions. A high p H, close to 14, is very basic, with many free O H negative ions. A p H value around seven is neutral. Some popular items with their p H values are listed as follows: Battery acid: 1; vinegar: 2.5; grapefruit juice: 3; black coffee: 5; saliva: 6.7; milk: 6.9; blood: 7.4; baking soda: 8.5; milk of magnesia: 10.5; and lye:

13. Acidic is marked 10 to the power of 0 M H positive. Neutral is marked 10 to the power of negative 7 M H positive. Basic is marked 10 to the power of negative 14 M H positive.

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The diagram features a heart at the top, another at the bottom, lungs to the right of the heart, and a kidney to the left of the heart. The flow begins from the left ventricle of the heart at the top. The different steps to maintain acid-base balance are as follows: 1. Cell metabolism produces acids. 2. Blood: C O 2 plus H 2 O yields H 2 C O 3. 3. H positive binds to H C O 3 in a buffer. 4. Kidneys: H 2C O 3 yields H C O 3 negative plus H positive. H positive is expelled with urine. 5. Blood has less H positive and more H C O 3 negative. 6. Buffer action: Acids become H C O 3 negative and vice versa. 7. C o 3 plus H 2 O yields H 2 C O 3. 8. More acids in the blood and less bicarbonate buffer. The blood enters the right ventricle of the lower heart and leaves from the right atrium of the lower heart. 9. Lungs: H C O 3 yields C O 2 plus H 2 O. 10. C O 2 expired. The blood enters the lobes of the lungs and goes to the left atrium of the upper heart. 11. Blood: less H 2 C O 3.

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Acidosis p H less than 7.35; respiratory: increased P C O 2; metabolic: decreased H C O 3 negative; respiratory

compensation in lungs: hyperventilation and decrease in P C O 2; renal compensation in kidney: increase in bicarbonate reabsorption and H C O 3 negative. Alkalosis p H greater than 7.45; respiratory: decreased in P C O 2; metabolic: increased H C O 3 negative; respiratory compensation in lungs: hypoventilation and increase in P C O 2; renal compensation in kidney: decrease in bicarbonate reabsorption and H C O 3 negative.

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The following parts are labeled: aorta, inferior vena cava, renal artery, kidney, renal vein, ureter, urinary bladder, and urethra. In the illustration that features the cross-section of the kidney, the following parts are labeled: renal column, renal pyramid, renal cortex, renal medulla, renal capsule, peeled back, renal pelvis, and ureter.

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Bladder stretch receptors are activated, which in turn stimulates the parasympathetic pelvic nerve. This initiates the contraction of the detrusor muscle. When an appropriate place is available, voiding happens. In an inappropriate place because of urethral sphincter constriction, no voiding happens. This leads to the overriding of voluntary control, also called incontinence. When incontinence happens, there are five outcomes: urge, which results in overactive detrusor muscle; stress, which results in weak urethral sphincter; a

reflex, which results in S 2 to S 4 damage; intrinsic sphincter deficiency, which results in peripheral neuropathy; or paradoxical which results in urinary retention.

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The following parts are labeled in the illustration: afferent arteriole, from systemic circulation, glomerulus, glomerular capsule, efferent arteriole, to systemic circulation, proximal convoluted tubule, descending limb, capillary network, loop of Henle, ascending limb, distal convoluted tubule, collecting duct, vein, and artery. The vein and the artery run almost transversely between the cortex and the medulla. Urine goes from the afferent arteriole into the glomerular capsule, into the proximal convoluted tubule, into the descending limb, into the ascending limb, into the distal convoluted tubule, into the collecting duct, and passes out. The descending limb, Loop of Henle, ascending limb, and the distal part of the collecting duct are in the medulla, while the other parts are in the cortex. The following parts are labeled in the micrograph: afferent arteriole, from systemic circulation, and efferent arteriole, to systemic circulation.

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The following are labeled: afferent arteriole, efferent arteriole, glomerular capillaries, Bowman’s capsule, glomerular filtration, peritubular capillary, tubular reabsorption, tubular secretion, renal tubule, urine, and

filtered blood. Arrows indicate the movement of the different liquids in the system.

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Blood enters the glomerulus, and glomerular filtration takes place. Arrows indicate the outflow of filtrate in the renal tubule through the renal corpuscle, where there is an output of H 2 O and urine. Arrows indicate the flow of blood to peritubular capillaries. The text in the following points on the right of the illustration reads, 1. Glomerular filtration: creates a plasma-like nitrate of the blood. 2. Tubular reabsorption: removes useful solutes from the filtrate and returns them to the blood. 3. Tubular secretion: removes additional wastes from the blood and adds them to the filtrate. 4. Water conservation: removes water from the urine and returns it to the blood. Concentrates waste.

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The column headers of the first table are A D H level and Effect on Kidney. The row entries are as follows. Row 1: Increased A D H levels, Collecting ducts and the distal convoluted tubules become permeable to water; water moves out of ducts and into blood. To the right, an illustration features H 2 O being expelled from the distal convoluted tubule and the collecting duct. Row 2: Decreased A D H levels. Row 2: Collecting ducts become impermeable to water; water is not reabsorbed from the filtrate and is

excreted. To the right, an illustration features H 2 O traveling down the collecting duct. The column headers of the second table are Aldosterone level and its effect on Kidney. The row entries are as follows. Row 1: Increased aldosterone levels, Tubules increase reabsorption of sodium from the filtrate and decrease reabsorption of potassium; water and sodium thus move from filtrate into the blood, and excess potassium is excreted. On the right, an illustration features K positive traveling down the collecting duct and N a positive and H 2 O being expelled from the collecting duct. Row 2: Decreased aldosterone levels, Row 2: Tubular absorption of sodium and potassium is normal; water is not reabsorbed from the filtrate and is excreted. To the right, an illustration features H 2 O traveling down the collecting duct.

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In the first illustration labeled overflow, the bladder is full, pressure is exerted on the bladder walls, and urine drips out. In the second illustration labeled stress, there is pressure from the top of the bladder, and because of stress, urine drips out. In the third illustration labeled urge, because of the urge, urine drips out.

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In the first inset, a portion of the bladder is magnified and features the normal protective bladder lining. In the second inset, a portion of the bladder is magnified and features the

thinning of the protective bladder lining. In the third inset, a portion of the bladder is magnified to pinpoint bleeding, glomerulations, on the bladder wall. In the fourth inset, a portion of the bladder is magnified and features Hunner's ulcer in the bladder wall.

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The first illustration features the urinary tract, and the following parts are labeled: abdominal aorta, inferior vena cava, renal vein, renal artery, kidney, ureter, urethra, and bladder. Within the bladder, the following are labeled: neutrophils, biofilm, and uropathogenic bacteria. In another illustration of the bladder, fibrinogen and a urinary catheter are indicated. The flow diagram, from bottom to top: Contamination of the periurethral area with a uropathogen from the intestines leads to bacterial colonization of the urethra and migration to the bladder. This leads to two outcomes: bacterial colonization and invasion of the bladder, mediated by pili and adhesions, an inflammatory response in the bladder, and fibrinogen accumulation in the catheter. These outcomes lead to neutrophil infiltration, which leads to bacterial multiplication and immune system subversion. This leads to biofilm formation, which in turn leads to epithelial damage by bacterial toxins and proteases. The next stage is the ascension to the kidneys, which leads to the bacterial colonization of the kidneys. This leads to host tissue damage by bacterial toxins that ultimately lead to bacteremia.

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The following are labeled: transitional cell carcinoma of renal pelvis, polycystic kidney disease, hydronephrosis, dysplasia agenesis of the ureter, thrombi, ureteral calculi, ureteropelvic valve, fibrous band, ureteropelvic structure, transitional cell carcinoma of the bladder, ureteral orifice, urogenital diaphragm, ureteral sphincter, and urethral stenosis. In the case of a man, prostate hypertrophy could occur. In the case of a woman, extrinsic compression could be because of pregnancy, carcinoma of the cervix, endometriosis, or posterior vesicoureteral valve reflux.

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In the first illustration, the following parts are labeled: kidneys, uterus in women behind the bladder, prostate in men below the bladder, bladder, and urethra. The cross-section of the bladder is featured in the illustration. In the second illustration, the following layers are labeled, from top to bottom: fatty layer, muscle, connective tissue, and transitional epithelium. A papillary tumor grows from the base between the connective tissue and transitional epithelium and forms a papilla protruding from the transitional epithelium. A flat tumor starts in the connective tissue and spreads over the transitional epithelium.

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In the illustration with the front view, the following parts are labeled: ureter, urinary bladder, ductus deferens, seminal vesicle, prostate gland, bulbourethral gland, corpus cavernosa, urethra, epididymis, testis, penis, and glans penis. On one side of the illustration, the cross-section view is featured. In the illustration with the side view, the following parts are labeled: ductus deferens, seminal vesicle, bulbourethral gland, epididymis, testis, penis, scrotum, corpus cavernosum, urethra, prostate gland, and pubic bone.

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A. An illustration features a normal glomerulus and the following parts are labeled: parietal epithelial cell, endothelial cell, podocyte, G B M, mesangial cell, and Bowman capsule. B. An illustration features a glomerulus where there are gaps and holes in the G B M caused by glomerular disease. The following are labeled: fibrin, plasma proteins, and inflammatory cells. C. An illustration features a glomerulus with proliferating parietal epithelial cells. The following are labeled: infiltrating macrophage and interstitial fibroblast. D. An illustration features a glomerulus with fibrocellular crescents.

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Non-proliferative glomerulonephritis is divided into three categories: minimal-change glomerulonephritis, membranous glomerulonephritis, and focal segmental glomerulosclerosis.

Minimal change glomerulonephritis: abnormal podocytes seen on electron microscopy; treated with supportive care and prednisolone; most respond well. Membranous glomerulonephritis: thickened glomerular basement membrane; usually idiopathic; one-third have chronic M G N, one-third go into remission, and one-third progress to renal failure. Focal segmental glomerulosclerosis: segments of glomeruli develop sclerosis; present with nephrotic syndrome; genetic causes identified; steroids are often ineffective; 50 percent progress to renal failure. Proliferative glomerulonephritis is divided into I g A nephropathy, membranoproliferative glomerulonephritis, post-infectious glomerulonephritis, and rapidly progressive glomerulonephritis. I g A Nephropathy: most common type of G N in adults; macroscopic hematuria; appears 24 to 48 hours; post-U R T I or G I infection; I g A deposits seen in the matrix. Membranoproliferative Glomerulonephritis: primary, immune-mediated; secondary, S L E, hepatitis; usually progresses to end-stage renal failure. Post-infectious glomerulonephritis: occurs weeks after U R T I; usually strep pyogenes; supportive treatment; Resolves over 2 to 4 weeks. Rapidly Progressive Glomerulonephritis, Crescentic, is divided into vasculitic disorders and Goodpasture's syndrome. Vasculitic disorders are further divided into Wegener's granulomatosis and microscopic polyangitis. Wegener's Granulomatosis: Vasculitis; Lungs, kidneys, and other organs; c A N C A type; treated with steroids plus cyclophosphamide. Microscopic Polyangitis: Small vessel

vasculitis; p A N C A type; Treat with long-term steroids plus or minus cytotoxic agents. Goodpastures syndrome: autoimmune anti-G B M antibody; Glomerulus and lung affected; Hematuria and hemoptysis: Treat with steroids with or without steroid-sparing agents.

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Nephrotic syndrome: Causes: Systemic disease Systemic lupus erythematosus, S L E, Hepatitis B; glomerular capillary membrane affected; Glomerular collagen deposits, Glomerular basement membrane thickening; Increased glomerular permeability; Proteinuria, albumin and immunoglobulins, Lipiduria; Loss of protein: Edema and susceptibility to infection, Loss of fat: Liver increases triglycerides and cholesterol production; Treatment: Prompt treatment of infections, Close surveillance of chronic conditions such as S L E. Nephritic Syndrome: Cause: Inflammatory response; Acute infections: Group B hemolytic streptococcus, Viral infections; Circulating immune complexes become trapped in glomerular membrane; Inflammatory response 10 to 14 days post infection; Cells lining the glomeruli proliferate; Capillary membrane edema and increased permeability; Hematuria, hypertension, proteinuria, edema, azotemia, red blood cell breakdown; Treatment: Prompt treatment of infections, Close surveillance of chronic conditions such as S L E.

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The table has six columns and nine rows. A common heading G F R and A C R categories and risk of adverse outcomes are present for columns 1, 2, and 3 and rows 1, 2, and 3. A C R categories milligrams per millimole Description, Ranges are given horizontally in the first row in the last three columns. Below this, in the second row, the column heads are less than 3 normal to mildly increased, 3 to 30 Moderately increased, and greater than 30 Severely increased. In the third row, the column heads are A 1, A 2, and A 3. Starting from the fourth row, G F R categories milliliter per minute per 1.73 m squared, Description, and Range are given vertically across the rows in the first column. Starting from the fourth row, in columns 2 and 3, the following are given row-wise. 90 Normal and high, G 1; 60 to 80 Mild reduction related to normal range for a young adult, G 2; 45 to 59 Mild to moderate reduction, G 3 a; 30 to 44; Moderate to severe reduction, G 3 b; 15 to 29 Severe reduction, G 4; 15 Kidney failure, G 5. In rows 4 and 5 of column 4, the cells are shaded in green with the following text: No chronic kidney disease in the absence of markers of kidney damage. The cells in row 6 of column 4 and rows 4 and 5 of column 5 are in amber. The cells in row 6 of column 5 and row 7 of column 4 and rows 4 and 5 of column 6 are in pink. The rest of the cells are in red. At the bottom of the table a right arrow and the downward arrow on the side indicate increasing risk. The text at the bottom reads, abbreviations. A C R, albumin creatinine ratio. C K D, chronic kidney disease. G F R, glomerular filtration rate.

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A. In the anterior view, one portion features the cross-section. The following parts are labeled in both illustrations: ureter, urinary bladder, ductus deferens, seminal vesicle, prostate gland, bulbourethral gland or Cowper's glands, urethra, epididymis, testis, penis, and glans penis. In the sagittal section, the following parts are labeled: prostrate gland, pubic bone, urethra, and scrotum. An illustration features the cross-section of the testis, and the following parts are labeled: spermatic cord, nerve, blood vessels, epididymal duct, connective tissue, seminiferous tubules, epididymis, and vas deferens. An illustration features an external view of the scrotum with the raphe labeled. Another illustration features the cross-section that features the muscle layer and deep tissues. The following parts are labeled: spermatic cord, ductus deferens, plexus of testicular veins, testicular artery, autonomic nerve, lymphatic vessel, epididymis, testis, Dartos muscle, scrotal septum, and cremaster muscle.

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A horizontal cross-section features the following parts: dorsal veins, artery, corpus spongiosum, urethra, and corpus cavernosa. The shaft or body of the penis is featured from the tip to about two-thirds of the length of the penis, and the rest of the penis is labeled the root of the penis. The following parts are labeled: lower section of urinary bladder, orifice of

ureter, prostate gland, openings of prostate ducts, bulbourethral or Cowper's gland and duct, bulbourethral gland opening, spongy, erectile tissue, corpus cavernosa, glans penis, prepuce or foreskin, and external urethral orifice.

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From the top: Hypothalamus to pituitary, G n R H is released. From the pituitary to testicles to testosterone, F S H and L H are released. Testosterone goes back to the hypothalamus and the pituitary.

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The following parts are labeled: uterine or fallopian tube, ovary, uterus, endometrium, cervical canal, cervix, vagina, bladder, urethra, pubic bone, clitoris, and labia.

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Half of the image is featured as a cross-section. The following parts are labeled: fundus of uterus, fallopian tube or oviduct, fimbria, egg cell, follicle, endometrium, myometrium, perimetrium, cervix, vagina, broad ligament, round ligament, ovary, suspensory ligament, and ovarian ligament. Another illustration at the bottom left features the position of the female reproductive system in the human body.

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The following parts are labeled in the breast: lobe, lobule, secondary tubules, areola, lactiferous duct, ampulla, and mammary duct. The following parts are labeled on the chest: clavicle, rib, adipose tissue, intercostal muscles, pectoralis major, pectoralis minor, deep fascia, and lung. Two illustrations magnify the tip of the lobe, which features the difference between lobes in lactating and non-lactating breasts. In the non-lactating lobe, the myoepithelial cells are constricted. In the lactating lobes, the following are labeled: milk, myoepithelial cells that are distended, and myoepithelial cells contracting to force milk into ducts.

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The following parts are labeled: antral follicle, ovulated oocyte, ovulation, corpus luteum, corpus albicans, germ cell, follicle, oocyte, and early antral follicle.

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The menstrual phase is between days 0 and 3, the postmenstrual or proliferation phase is between days 3 and 14, the ovulation takes place on day 14, the premenstrual or secretory phase takes place between days 14 and 28, and the menstrual phase begins again. The pituitary gland is connected to the hypothalamus, a gonadotropic-releasing hormone in the brain. The illustration features the L H and F S H quantities in the gonadotropic cycle, follicle development in the ovarian cycle, estrogen and progesterone generation

in the sex hormone cycle and a change in the endometrial thickness in the menstrual or endometrial cycle. The changes in each cycle are numbered. 1. Follicles develop during the menstrual and postmenstrual phases. 2. The amount of estrogen increases on day 8. 3. The thickness of the endometrium increases between days 8 and 10. 4. L H from the pituitary gland peaks on day 13. 5. F S H from the pituitary gland peaks on day 13, and its peak is less than that of L H. 6. Ovulation occurs on day 14. 7. The corpus luteum is formed on day 17. 8. The corpus luteum matures on day 18. 9. Estrogen quantity peaks again between days 18 and 21. 10. Progesterone quantity peaks on day 19. 11. Endometrial thickness increases further on day 22. 12. The quantities of F S H and L H reach a minimum on day 21. 13. During the luteal phase, the corpus luteum undergoes regression. 14. The quantity of estrogen reaches a minimum. 15. The quantity of progesterone reaches a minimum. 16. The thickness of the endometrial wall decreases. The illustration is featured in four categories: the gonadotropin cycle, the ovarian cycle, the sex hormone cycle, and the menstrual or endometrial cycle.

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The following are labeled: ovary, corpus luteum, developing follicles, ovulation, oocyte, uterine tube, fertilization, first mitosis of the ovum, cleavage, morula, blastocyst, uterus, implantation, muscle layer, and endometrial wall.

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The following are labeled: villi, intervillous space, umbilical cord, amniotic sac, amniotic fluid, chorion, amnion, placenta, and uterine wall.

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The potential sites include testis retained in the abdomen, partial descent, descended but not to the bottom of the scrotum, and interruption of descent beyond the external inguinal ring.

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A portion is magnified that features the following: pampiniform plexus, internal spermatic artery, and vas deferens. In testicular torsion, the pampiniform plexus, internal spermatic artery, and vas deferens appear twisted.

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Stage 0: No prolapse; Stage 1: The most distal portion of the prolapse is greater than 1 centimeter proximal to the level of the hymen; Stage 2: The most distal portion of the prolapse is less than 1 centimeter proximal or distal to the level of the hymen; Stage 3: The most distal portion of the prolapse is less than 1 centimeter beyond the hymen but protrudes no further than 2 centimeters less than the total length of the vagina; Stage 4: Complete vaginal eversion.

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Mild endometriosis: endometrial implants are small and appear as patches or streaks. They are found on the ovaries and fallopian tubes. There are mild adhesions. Moderate Endometriosis: endometrial implants are deeper and more extensive. They appear as dark nodules and small cysts filled with blood. Adhesions are thicker and more extensive, causing organs to stick together. Severe Endometriosis: endometrial implants are deeply embedded and widespread. They are quite large and cause significant distortion of pelvic anatomy. There are dense adhesions binding organs together.

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There are five types: intramural fibroids, pedunculated submucosal fibroids, subserosal fibroids, submucosal fibroids, and pedunculated subserosal fibroids.

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The horizontal axis is labeled year and ranges from 2012 to 2021 in increments of 3. The vertical axis is labeled rate per 100000 and ranges from 0 to 800 in increments of 200. The line for women is plotted through (2012, 620), (2015, 600), (2018, 630), (2020, 600), and (2021, 605). The line for total is plotted through (2012, 460), (2015, 420), (2018, 510), (2020, 410), and (2021, 420). The line for men is plotted

through (2012, 280), (2015, 290), (2018, 370), (2020, 300), and (2021, 330). The data from the graph are approximate.

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The horizontal axis is labeled year and ranges from 2012 to 2021 in increments of 3. The vertical axis is labeled rate per 100000 and ranges from 0 to 250 in increments of 50. The line for women is plotted through (2012, 110), (2015, 100), (2018, 125), and (2021, 160). The line for the total is plotted through (2012, 110), (2015, 130), (2018, 160), and (2021, 200). The line for men is plotted through (2012, 110), (2015, 140), (2018, 210), and (2021, 250). The increase is from 110 to greater than 150 approximately.

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The horizontal axis is labeled year and ranges from 2012 to 2021 in increments of 3. The vertical axis is labeled rate per 100000 and ranges from 0 to 250 in increments of 50. The line for total syphilis begins at (2012, 15) and ends at (2021, 55). The lines for primary, secondary, early non-primary, and non-secondary begin at (2012, 5) and end at (2012, 13). All the data from the graph are approximate.

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The horizontal axis is labeled year and ranges from 1999 to 2000 to 2015 to 2016 in unit increments. The vertical axis is labeled percent and ranges from 0 to 50 in increments of 10.

The line for non-Hispanic black begins at (1999 to 2000, 42) and ends at (2015 to 2016, 38), with a few minor peaks. The line for total population begins at (1999 to 2000, 18) and ends at (2015 to 2016, 15). The line for non-Hispanic whites begins at (1999 to 2000, 15) and ends at (2015 to 2016, 10). The line for Mexican Americans begins at (1999 to 2000, 13) and ends at (2015 to 2016, 13), with a few dips and peaks.

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The virus enters the mucous membrane, eye, or cut in the skin and reproduces in the skin cells. Via the sensory nerves, the virus travels up the nerve, crossing the bundle of nerve fibers, and hides in a ganglion near the spinal cord, from where it travels to the brain and the lower body through the spinal cord featured in a cross-section.

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The horizontal axis is labeled year and ranges from 2006 to 2014 in increments of 2 The vertical axis is labeled prevalence per 1000 people, and ranges from 0 to 6 in increments of 2. Five lines are marked for the age groups 15 to 19, 20 to 24, 25 to 29, 30 to 34, and 35 to 39. The following are approximate values. Females: The line for the 15 to 19 age group is plotted through (2006, 3), (2008, 2.5), (2010, 2), (2012, 1.5), and (2014, 1). The line for the 20 to 24 age group is plotted through (2006, 5), (2008, 5), (2010, 4.5), (2012, 4), and (2014, 3). The line for the 25 to 29 age

group is plotted through (2006, 3), (2008, 3.5), (2010, 4), (2012, 3.5), and (2014, 3.25). The line for the 30 to 34 age group is plotted through (2006, 1.75), (2008, 2), (2010, 2.25), (2012, 2), and (2014, 2). The line for the 35 to 39 age group is plotted through (2006, 1.75), (2008, 1.80), (2010, 2.25), (2012, 2), and (2014, 2). Males: The line for the 15 to 19 age group is plotted through (2006, 0.5), (2008, 0.65), (2010, 0.75), (2012, 0.75), and (2014, 0.65). The line for the 20 to 24 age group is plotted through (2006, 3.5), (2008, 4), (2010, 4.25), (2012, 3.75), and (2014, 3.5). The line for the 25 to 29 age group is plotted through (2006, 3.75), (2008, 6), (2010, 6), (2012, 5.5), and (2014, 5). The line for the 30 to 34 age group is plotted through (2006, 2.25), (2008, 3.75), (2010, 4), (2012, 4.5), and (2014, 4). The line for the 35 to 39 age group is plotted through (2006, 2), (2008, 2.25), (2010, 2.25), (2012, 2.25), and (2014, 3).

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The horizontal axis is labeled year and ranges from 1966 to 2016 in increments of 10. The vertical axis is labeled visits in thousands and the ranges from 0 to 4500 in increments of 1500. The following are approximate values. The line for Trichomonas vaginalis infections is plotted through (1966, 500), (1976, 350), (1986, 150), (1996, 125), (2006, 100), and (2016, 100). The line for other vaginal infections is plotted through (1966, 1250), (1976, 2000), (1986, 3000), (1996, 4250), (2006, 4000), and (2016, 3500).

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In the first photo, there is discoloration, and the breast is puckered. In the second photo, there is dimpling around the nipple.

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The normal squamous epithelial cells around the cervix have mild dysplasia due to D N A mutations resulting from exposure to irritants or carcinogens. The changes are detectable by the Pap test, and upon removal of the irritant or carcinogen, the D N A is repaired. If not, it becomes severe dysplasia. Continued exposure to irritants or carcinogens worsens mutations, leading to malignant neoplasms. There is proliferation of undifferentiated cells, and it becomes carcinoma in situ. A superficial, small, localized mass persists for years. Later, it becomes an invasive carcinoma with decreased cell adhesion and invasion of local tissues and lymph nodes.

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The following parts are labeled: food enters the mouth cavity, salivary gland, esophagus, stomach, pancreas, gallbladder or bile storage, liver, small intestine, large intestine, cecum, and anus. The functions include storage and digestion in the stomach and digestion and absorption in the small intestine. Digestion ends and water absorption continues in the large

intestine, and undigested materials are released via the anus.

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The following parts are labeled: oral cavity, pharynx, tongue, esophagus, liver, large intestine, and small intestine. The portion around the oral cavity is magnified, which features the cross-section, and the following parts are labeled: parotid duct, parotid gland, masseter muscle, submandibular duct, submandibular gland, and sublingual gland. The stomach is magnified and features a cross-section, and the following parts are labeled: the gastroesophageal sphincter, stomach, pyloric sphincter, and duodenum of the small intestine. A portion below the liver is magnified and features the gallbladder, the pancreas, and the duodenum of the small intestine. The portion at the beginning of the large intestine is magnified and features a cross-section, and the following parts are labeled: appendix, cecum, ascending portion of the large intestine, and ileum of the small intestine. An inset features the large intestine, and the following parts are labeled: appendix, ileum of the small intestine, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anus.

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In the illustration, the following are labeled: esophagus, cardiac sphincter, the cardiac portion of the stomach,

greater curvature, pyloric portion of the stomach, lesser curvature, pyloric sphincter, and duodenum. The cross-section of a portion of the stomach is featured, and the following smooth muscle layers are labeled: longitudinal, circular, and oblique.

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The following parts are labeled in the first illustration: nasal cavity, soft palate, blocked nasal passage, bolus, pharynx, epiglottis, larynx, trachea or windpipe, and esophagus. The first illustration features how the bolus enters the pharynx and the palate closes the nasal cavity. The second illustration features how the larynx rises to meet the epiglottis. The bolus presses on the epiglottis and bends it downward, closing the opening to the windpipe. The third illustration features how the bolus enters the esophagus.

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Illustrations feature the cross-section of the esophagus with food in it. The portion of the esophagus above the food constricts, and the food is pushed down progressively. Arrows indicate where the esophagus constricts and pushes the food down. The text reads, Ring like peristaltic contractions sweeping down the esophagus. Illustrations feature the stomach and the cross-section of the portion where the esophagus and stomach meet. The first illustration features how the sphincter remains closed when the food is

still in the esophagus. The following parts are labeled: relaxed muscles, after the food has passed down; circular muscles contract, constricting the passageway and pushing food down; food in the esophagus; longitudinal muscles contract, shortening the passageway ahead of food. The second illustration features how the sphincter opens to allow food to enter the stomach.

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The illustration features the cross-section of the villi, and the following parts are labeled: nutrients, villi, absorptive cells, lacteal, and blood capillary. The micrograph features villi and microvilli lining the small intestine walls.

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The first illustration features a fully developed esophagus beside the trachea. The second illustration features Type A: isolated esophageal atresia, where the esophagus is cut into two parts beside the trachea. The third illustration features Type B: atresia with proximal fistula, where the esophagus is cut into two with the top portion attached to the trachea. The fourth illustration features Type C: atresia with distal fistula, where the esophagus is cut into two with the bottom portion attached to the trachea. The fifth illustration features Type D: atresia with double fistula, where the esophagus is cut into two and the top and bottom portions are attached to the trachea. The sixth illustration features Type E: isolated

fistula, H type, where the esophagus is fully formed but attached at one point to the trachea.

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Top row left: Costochondritis, Biliary colic, gallstones, Gallbladder infection, Pulled muscles, Hepatitis, Kidney stone, Pneumonia. Top row right: Pneumonia, Costochondritis, Spleen infection, Enlarged spleen, Hepatitis, Kidney stone, Constipation, Trapped wind. Middle row left: Renal calculi, Kidney infection, Trapped air, Constipation, Muscle strain, Appendicitis. Top row middle: Acid reflux, Heartburn, Myocardial infarction, Gastritis, Stomach ulcer, Duodenal ulcer, Pancreatitis, Epigastric hernia. Middle row right: Constipation, Trapped air, Diverticulitis, Irritable bowel syndrome, Kidney stone or infection, Crohn's, Ulcerative colitis. Bottom row left: Appendicitis, Urinary tract infection, Constipation, Ectopic pregnancy, Mid-cycle menstrual pain, Pelvic infection, Endometriosis, Ovarian cyst, Trapped air, Hernia. Bottom row middle: Acid reflux, Heartburn, Myocardial infarction, Gastritis, Stomach ulcer, Duodenal ulcer, Pancreatitis, Epigastric hernia. Bottom row right: Irritable Bowel Syndrome, Crohn's, Ulcerative colitis, Diverticulitis, Constipation, Trapped air, Mid-cycle menstrual pain, Endometriosis, Pelvic infection, Ovarian cyst, Ectopic pregnancy, Hernia.

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The following are labeled: food, trachea, esophagus, and stomach. The causes are congenital tracheoesophageal fistula, where the food may enter the trachea because of a developmental defect where there is a connection between the esophagus and trachea; fibrosis, which may be caused by scar tissue contracts; compression, where a tumor causes this condition; diverticulum, where undigested food in a pouch obstructs the esophagus; congenital atresia, which is a developmental defect where the tube has blind ends; achalasia, where because of a loss of peristalsis in the lower esophagus, food gets collected; and neurologic damage to cranial nerves five, seven, nine, ten, and twelve.

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There are eight causes, and they are 1. stimulus to the vomiting center. This is featured in the brain region. 2. Vomiting or emetic center coordinates reflex through cranial nerves 5, 7, 9, 10, and 12. This is featured in the medulla at the base of the brain. 3. hypersalivation, pallor, sweat, and tachycardia. This is featured near the oral cavity. 4. The glottis closes; the soft palate rises to close off the airway. This is featured near the trachea and epiglottis. 5. Deep inspiration; diaphragm contracts. This is featured on the diaphragm. 6. The gastroesophageal sphincter and fundus of the stomach relax. This is featured on the stomach. 7. Abdominal muscles contract forcefully. This is featured on the lower abdomen. 8. Antiperistaltic waves. This is featured near the sphincter. The stimuli to the vomiting center in the

brain, from front to back, are unpleasant sights or smells; distention or irritation of the digestive tract; pain, fear; chemicals and drugs that stimulate the chemoreceptor trigger zone; increased intracranial pressure; and motion that stimulates the vestibule in the inner ear. When causes 5, 6, 7, and 8 occur, there is pressure on the stomach, which instigates vomiting.

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The first illustration features a normal esophagus and stomach with the diaphragm behind. The second illustration features Type 1 hiatal hernia or sliding hernia. Here, the gastroesophageal junction and a portion of the stomach are above the diaphragm. The third illustration features Type 2 hiatal hernia or rolling hernia. Here, a portion of the stomach is next to the esophagus. The fourth illustration features Type 3 hiatal hernia or mixed hiatal hernia.

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Person-to-person transmission, specifically gastro oral, is postulated as a mode of infection. The bacteria consist of virulence factors, Helicobacter pylori, and urease. Helicobacter urease buffers the acid environment, where it releases factors that promote tissue damage via inflammatory and immunologic mediators. Helicobacter undergoes adhesion with the motile bacteria attached to the receptors in the mucous layer. The bacteria release toxic

substances into the mucosa. Activated T cells release I F N and I L 2 to the mucosa and induce an immune-mediated response in B cells, which results in immunoglobin release. Immunoglobins form immune complexes, which cause tissue damage. Inflammatory mediator release from the mucosa produces chemokines, resulting in free oxygen radical release. A local or superficial inflammatory response induces free oxygen radical release and causes neutral recruitment and activation. The associated conditions are acute and chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and lymphoma.

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The following are labeled: Liver, left hepatic duct, common hepatic duct, common bile duct, pancreas, pancreatic ducts, duodenum, ampulla of Vater, gallbladder, Kupffer cell, bile ducts, blood sinusoids, right hepatic duct, cystic duct, and liver cells.

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The parts and the effects on them are Brain: hepatic encephalopathy. Eyes: jaundice. Mouth: fetor hepaticus. Shoulder: spider nevi. Esophagus: esophageal varices. Bones: bone marrow changes. Spleen: splenomegaly. Abdomen: ascites, dilated abdominal veins, or caput medusae. Rectum: rectal varices or hemorrhoids. Thigh: bleeding tendency or decreased prothrombin. Groin: altered

hair distribution. Scrotum: testicular atrophy. Hand: liver flap or course hand tremor. Ankle: edema.

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The diagram is categorized into pathophysiology, mechanisms, and complications. Pathophysiology: Row 1: Infections: hepatitis; Autoimmune: auto-immune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis; Toxin: Ethanol; Metabolic D X: non-alcoholic fatty liver disease; Genetic: hereditary hemochromatosis, Wilson, Alpha-1 anti-trypsin. Row 2: Death of hepatocytes, inflammatory destruction of normal hepatic architecture leading to scarring and fibrosis. Row 3: The liver is highly regenerative, but here it must regenerate within extensively scarred or fibrotic tissue, forming nodules of poorly functioning cells that disrupt hepatic vasculature, biliary production or excretion, and other liver functions. Row 4: Cirrhosis. Mechanisms and complications: Cirrhosis may lead to increased resistance to blood flow through the fibrotic liver. This leads to portal hypertension, which is increased blood pressure in the hepatic circulation, which leads to either blood backing up into the collateral venous system or increased hydrostatic pressure in the abdominal capillaries. Complications of blood backing into the collateral venous system are when blood backs into the esophageal varices, hemorrhage could cause an upper G I bleed; when blood backs into the rectal varices, hemorrhage could cause a lower G I bleed; when blood backs into the spleen, it causes

splenomegaly, which in turn is a congested, enlarged spleen that could lead to increased trapping of blood cells within, which could cause pancytopenia. Increased hydrostatic pressure in abdominal capillaries leads to increased vasodilators, which are N O and C O, and fluid exudes from plasma in the capillaries. Fluid exudes from plasma in the capillaries, which may lead to complications such as ascites, fluid exudation into the peritoneal cavity, or edema. Vasodilators cause a decrease in the effective blood volume felt by the kidneys, which in turn leads to the kidneys retaining more water and N a positive increase in blood volume. This leads back to increased hydrostatic pressure in abdominal capillaries. Another complication of cirrhosis is hepatocellular carcinoma, or H C C, 85 percent of H C Cs occur in the background of cirrhosis. Cirrhosis may also lead to decreased liver function, also known as liver insufficiency, which can lead to: low albumin synthesis; liver unable to synthesize clotting factors or anticoagulant proteins; liver unable to remove toxins from the body; or decreased conjugation of bilirubin; decreased secretion of conjugated bilirubin into bile duct canaliculi; and decreased drainage of conjugated bilirubin out of the ducts. Low albumin synthesis leads to decreased oncotic pressure in systemic capillaries. This leads to fluid exuding from plasma in the capillaries into interstitial tissues, which in turn leads to a complication such as edema. The liver is unable to synthesize clotting factors or anticoagulant proteins, leading to low measured clotting factors 10, 5, 2, etcetera, and low Protein C, Protein S,

antithrombin, etcetera. This leads to a pathophysiological state where, usually, the decrease in pro- and anticoagulants is in balance, with no coagulopathy resulting. The liver is unable to remove toxins from the body, leading to toxins, for example, N H 3 build-up, and cross-blood-brain barriers. This leads to complications of encephalopathy and degeneration of neurological function: confusion, anxieties, etcetera. Decreased conjugation of bilirubin, decreased secretion of conjugated bilirubin into bile duct canaliculi, and decreased drainage of conjugated bilirubin out of the ducts lead to the complications of jaundice and sclera icterus when the bilirubin is greater than 40 to 50.

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The following are labeled: esophagus; inside the esophagus: bulging esophageal varices; short gastric veins; spleen: backup of blood into the spleen or splenomegaly; stomach; splenic vein; anastomosis in the splenic vein; high pressure in the inferior mesenteric vein; high pressure in the superior mesenteric vein; coronary or gastric vein; high pressure in the portal vein; liver: scar tissue obstructs blood flow through the liver; very little blood returns through the hepatic vein; inferior vena cava.

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Precipitating factors include alcohol consumption, biliary tract obstruction, cancer, and the mumps virus. This leads to the

activation of pancreatic enzymes inside the pancreatic ducts, for example, trypsin, peptidase, elastase, amylase, and lipase. This leads to the autodigestion of pancreatic tissue. This leads to tissue necrosis and severe inflammation of the pancreas. This leads to two outcomes. Outcome 1: Enzymes and cell contents leak into the general circulation and may cause the following: shock, disseminated intravascular coagulation, and acute respiratory distress syndrome. Outcome 2: Active enzymes leak into the peritoneal cavity and continue to destroy tissue with massive inflammation, which may cause the following: severe pain, hemorrhage and shock, peritonitis, and hypovolemic shock.

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Type 1: Separate hard lumps, like nuts, which are hard to pass. Type 2: sausage-shaped but lumpy. Type 3: Like a sausage but with cracks on its surface. Type 4: Like a sausage or snake, smooth and soft. Type 5: Soft blobs with clear-cut edges that are passed easily. Type 6: Fluffy pieces with ragged edges; a mushy stool. Type 7: Watery, no solid pieces; entirely liquid.

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A diagram of the colon and an inguinal hernia are featured. Portions of the colon are in the cross-section view. The following are the causes of intestinal obstruction and are featured in the illustration: Beside the groin: inguinal hernia.

Near the junction of the ascending and transverse colon: volvulus, where the telescoping of the ileum inside the adjacent section of the colon is marked. Ascending colon: intussusception, where blood vessels are drawn in between layers and compressed. Transverse colon: tumor. Descending colon: diverticulitis, where it is inflamed and the diverticulum is filled with feces. Above this, the colon is narrowed by scar tissue.

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The effects have the following sequence: 1. Site of obstruction in the abdomen. 2. Increased fluid and gas lead to distention. 3. Distention causes increased peristalsis to force contents past obstruction, leading to colicky pain. 4. Severe vomiting from distention and pain leads to dehydration and electrolyte imbalance. 5. Increased pressure on the wall causes more fluid to enter the intestine. 6. Decreased blood pressure and hypovolemic shock as fluid shift into the intestine continues, third spacing. 7. Continued pressure on the intestinal wall causes edema, ischemia of the wall, and decreased peristalsis. 8. Prolonged ischemia causes increased permeability and necrosis of the wall; intestinal bacteria and toxins leak into the blood and peritoneal cavity, causing peritonitis. The intestines are marked as empty with no absorption. The bacteria in the obstruction and the related vein are labeled.

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Some direct causes of bacterial peritonitis are perforated appendix, intestinal obstruction, mesenteric thrombosis, pelvic inflammatory disease, and septic abortion. Some causes of chemical peritonitis are perforated ulcers, ruptured gallbladder, pancreatitis, ruptured spleen, hemorrhage into the peritoneal cavity, and ruptured bladder. These lead to the following stages of development: Inflammation of the intestinal wall, increased permeability, intestinal bacteria leaking out into the peritoneal cavity, bacterial peritonitis, infection and inflammation of the peritoneal membranes, fluid shifting from the peritoneal and intestinal blood vessels, or third spacing, and hypovolemic shock. Bacterial peritonitis is localized temporarily by the omentum and leads to abscess. The parietal peritoneum leads to constant, severe pain and reflex contractions of the abdominal muscle. The contraction leads to a rigid, board like abdomen. Impaired nerve transmission leads to the following stages: decreased peristalsis, paralytic ileus or obstruction, and decreased or absent bowel sounds. Fibrous scar tissue produces adhesions, leading to obstruction at a later time.

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The illustration features the gluten breaks into gliadin and glutenin. Gliadin enters the lamina propria of intestinal villi through the intestinal lumen, combines with tissue transglutaminase, and forms negatively charged gliadin peptide, which gets attached to the antigen-presenting cell. C D 4 plus T cell is attached to the antigen-presenting cell and

B cell. Anti-gliadin antibodies are released by B cell, which releases cytokine I L 15 and causes strong inflammation of the lumen. T cell releases cytokines which cause mild inflammation of lumen.

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The four phases of the disease are Phase 1: pre-disease stage; Phase 2: acute intestinal inflammation; Phase 3: chronicity or resolution; and Phase 4: tissue destruction and complications. In Phase 1, genetic factors and environmental factors initiate triggers that cause impaired barrier function. In Phase 2, translocation of microbial products occurs, which leads to immune cell activation, which is part of Phase 3. At this stage, failure of regulatory mechanisms, activation of effector cells, and production of pro-inflammatory mediators occur. This leads to chronic inflammation. Chronic inflammation leads to fibrosis, stenosis, abscess, fistula, cancer, and extra-intestinal manifestations, and these occur in Phase 4. Genetic factors include antimicrobial peptides, autophagy, the handling of bacteria, chemokines, and cytokines. Environmental factors include microorganisms, diet, infections, stress, N S A I Ds or nonsteroidal anti-inflammatory drugs, appendectomy, smoking, and antibiotics.

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In the normal colon, the goblet cell line is uniform and well-defined. The top layer of the normal colon is marked as an

affected mucosal layer only. In ulcerative colitis, the crypts are distorted and are with abscesses.

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Low-FODMAP diet food choices Fruits: banana, blueberry, cantaloupe, clementine, cranberry, grapes, grapefruit, honeydew, kiwi, lemon, lime, orange, pineapple, papaya, raspberry, rhubarb, strawberry, and tangelo. A note at the bottom reads, If fruit is dried, eat in small quantities. An illustration of a half-eaten banana is depicted above the note. Vegetables: Alfalfa, bamboo, shoots, bok choy, carrot, celery, chives, cucumber, eggplant, green beans, lettuce, leeks, parsnip, potato, red or orange bell peppers, pickles, radish, scallions, seaweed, spinach, yellow squash, tomato, and zucchini. Herbs: basil, coriander, marjoram, mint, oregano, parsley, rosemary, and thyme. An illustration of broccoli florets and cut carrots is included. Grains: Cereals: gluten-free bread or cereal products. Rice: white, brown, or wild; oats, corn chips, and corn tortillas; other: amaranth, millet, quinoa, tapioca, cornmeal, or polenta. An illustration of some grains is included. Dairy: Milk: lactose-free milk, rice, or coconut milk; lactose-free ice cream; butter; yogurt: lactose-free; cheese: cheddar, swiss, parmesan, feta, lactose-free cottage cheese. An illustration features a tub of yogurt. Meat and Seafood: An illustration of ham is present; Sweeteners: sugar asterisk, Splenda, aspartame, 100 percent maple syrup asterisk; fats: oil, nuts or seeds, asterisk, no pistachios or cashews, mayo; Drinks: water, coffee asterisk,

black or green tea; avoid chamomile, fennel, and oolong. A note with an asterisk reads, Small amounts. Avoid or reduce these foods containing FODMAPS. Fructose. Fruits: apple, mango, pear, watermelon, juice, and large amounts of dried fruit. An illustration of a few slices of cut fruit is present. Sweeteners: honey, high-fructose corn syrup, and molasses. Lactose. Milk: milk from cows, goats, or sheep; custard; ice cream. Cheese: soft, unripened cheese, for example, cottage, cream, mascarpone, ricotta, or American gouda. A note at the bottom reads small amounts of sour cream are okay. Fructan. Vegetables: asparagus, beets, broccoli, Brussels sprouts, cabbage, fennel, garlic, onion, and chicory root. An illustration of broccoli is present. Other: wheat, rye, barley, couscous, regular bread, pasta, and inulin. Polyols. Fruit: apricot, avocado, blackberry, cherry, nectarine, peach, plum, prune, and fig. Vegetables: cauliflower, corn, mushrooms, and sweet potatoes. Sweeteners: ending in ol, for example, xylitol, sorbitol, and isomalt. Galactans. Legumes: beans, chickpeas, lentils. Other: soy and almond milk, soybeans, and pistachios. A note at the bottom reads, However, tofu is low FODMAP.

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A. A photo features several diverticula seen from outside the colon. B. A photo features a close-up view of a diverticulum. C. A photo features several diverticula inside the colon. D. A radiograph of the diverticula in the colon.

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The following parts are illustrated and labeled on the body: The thyroid gland is at the throat, the thymus gland is present in children only in the middle of the chest, the adrenal gland is on top of the kidneys, which is in the upper abdomen area, and the pancreas is indicated in between the kidneys. The testes are also labeled. A portion of the brain is magnified, and the following parts are labeled: Pineal gland, hypothalamus, and pituitary gland. A portion of the thyroid gland that features the parathyroid glands on the back of the thyroid gland. From the testes, an illustration of the gonads is depicted, and beside it is an illustration of the uterus and the ovaries to indicate the female version.

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A portion of the anterior pituitary is magnified with the endocrine cells releasing hormones into the blood vessel. A portion of the neurosecretory cell and the posterior pituitary is magnified that features the neurosecretory cells releasing hormones into the blood vessel.

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A. An illustration features the cross-section of the brain. The following parts are labeled: Bone, the hypothalamus, and the pituitary gland. B An illustration features a magnified view of the structure of the pituitary gland and the hypothalamus and the portal system. The following parts are labeled:

Neurosecretory neurons of the hypothalamus, arterial inflow, anterior pituitary, venous outflow, and the posterior pituitary. The following are parts of the portal system: capillaries, vein, and capillaries in anterior pituitary. Hypothalamic hormones: Oxytocin affects the mammary glands. An illustration of a baby drinking milk from the breast is present. Smooth muscle of uterus. An illustration of the uterus along with the fallopian tubes and ovaries is present. Antidiuretic hormone or A D H affects kidney tubules. An illustration of a kidney is included. Anterior pituitary hormones: Thyroid-stimulating hormone or T S H affects the thyroid. An illustration of the thyroid is present. Adrenocorticotropin or A C T H affects the adrenal cortex. An illustration of the adrenal gland above the kidney is present. Prolactin, P R L affects the mammary glands. An illustration of a baby drinking milk from the breast is present. Growth hormone or G H affects the bone and tissues. An illustration of a bone is included. Gonadotropins, F S H and L H, affect the ovaries and the testes. An illustration of an ovary and testes are present.

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A. An illustration features the pancreas in between the kidneys. The following parts are labeled: adrenal gland, aorta, left kidney, duodenum, and right kidney. The head of the pancreas is situated near the base of the right kidney and the duodenum, the body of the pancreas is in the middle, and the tail of the pancreas ends near the middle of the left kidney. B. An illustration features a magnified portion of the islets of

Langerhans in the pancreas. The following are labeled: capillaries, alpha cells, and beta cells. C. A micrograph features an islet of Langerhans surrounded by acini.

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The following parts are labeled: hypothalamus, anterior pituitary, blood vessel, and the thyroid gland. A label that reads, Internal and external environmental conditions that increase the body's need for thyroid hormones is on the hypothalamus. A label that reads, Hypothalamus secretes a releasing factor to the anterior pituitary is near the blood vessel that is in between the hypothalamus and the anterior pituitary. A label that reads, Anterior pituitary releases more thyroid-stimulating hormone or T S H into the body's circulatory system is near the arrow that points from the anterior pituitary to the thyroid gland. A label on the thyroid gland reads, Thyroid produces more thyroid hormones is on the thyroid gland. A label that reads, Sufficient blood levels of thyroid hormones inhibit T S H secretion is near the arrow that points from the hormones produced by the thyroid gland to the pituitary gland. The hypothalamus secretion of the releasing factor is labeled as long-term regulation. The working of the T S H and the thyroid gland is labeled as daily regulation.

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A. A man with a very short stature stands on a measuring device with a vertical scale. B. A photo features a woman with gigantism standing in a room. She is very tall with broad shoulders. Her head is very close to the roof of the room.

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A. A photo features a girl standing straight and smiling. B. A photo features a young woman standing between two young men. C. A photo features the woman standing with two other women, a man, and two children. The woman is big in size when compared to others in the photo.

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In the illustration, the portion with the goiter is magnified and a normal thyroid on one side, and a goiter that is an enlarged thyroid gland on the other side.

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A. A photo of the side view of one eye that is protruding. B. A photo of the protruding eyes of a person.

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The following parts are illustrated on the person: cross-section of the brain, the spinal cord, the heart, the kidney, the uterus, and the femur. The signs and symptoms are given against each body part. From the brain: emotional

disturbance and enlarged sella turcica. From the face: moon face. From the back shoulder: buffalo hump. From the spinal cord: osteoporosis. From the heart: cardiac hypertrophy or hypertension. From the adrenal glands at the top of the kidney: adrenal tumor or hyperplasia. From the abdomen: obesity and abdominal striae. From the uterus: amenorrhea. From the thighs: muscle weakness. From the knees: thin, wrinkled skin. From the shin: purpura. From near the ankle: skin ulcers because of poor wound healing.

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A. A photo features a woman with a round, moon facial appearance. B. A photo features a woman with a normal facial appearance.

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A. Two photos feature the front view and side view of a woman who has a big abdomen. B. A photo features the front view of the woman with a reduced abdomen.

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The following are labeled: vertebra, dura mater, arachnoid, pia mater, and spinal cord. A spinal cord section is enlarged and features layers and parts. The following are labeled: central canal, gray matter, white matter, spinal cord, pia mater, subarachnoid space, arachnoid, ventral root, dorsal root ganglion, subdural space, dura mater, and spinal nerve.

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The following are parts of the central nervous system: ependymal cells, oligodendrocytes, astrocytes, and microglia. The following are parts of the peripheral nervous system: satellite cells and Schwann cells. Ependymal cells: These cells are columnar with tentacle-like extensions on top, and they are loosely joined. Each cell has a nucleus in the middle. Oligodendrocyte: This cell has a nucleus in the middle, and its extensions are wrapped around other structures. Astrocyte: This cell has a nucleus in the middle, and it branches itself out to attach itself to other structures. Microglia: This cell has a nucleus in the middle and is shaped like an oval with uneven borders. Satellite cells: These are small cells that surround neurons. Schwann cells: These cells are wrapped around axons, and they have a nucleus.

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An illustration features a stretched-out neuron that is attached to muscle fibers. The following are labeled: cell body, nucleus, dendrites, axon, axon collateral, and muscle fibers. The neuron is presented from left to right, and arrows indicate the direction of conduction.

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A. An illustration features the myelin sheath covering the axon of a neuron. The myelinated axon resembles a string of sausages. The following are labeled: cell body, myelin sheath,

node of Ranvier, and axon. At the nodes, the side toward the cell body is negative, and the side facing outward is positive. Arrows indicate the impulses from node to node. Another illustration features a myelinated axon. The length of the myelin sheath from node to node is 1 millimeter, and the following parts are labeled: axon, myelin, and nodes of Ranvier. B. A micrograph features the cross-section of an axon. The myelin sheath surrounds the axon as a thick band.

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An illustration features the synaptic cleft. The following parts are labeled: postsynaptic neuron, receptors on the postsynaptic membrane-bound to the neurotransmitter, mitochondrion, vesicles containing neurotransmitters, synaptic cleft, and presynaptic neuron. An arrow toward the synaptic cleft in the presynaptic neuron indicates the direction of the conduction of nerve impulses.

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A line graph features the sodium and potassium permeability against action potential. The horizontal axis is labeled time in milliseconds and the values range from 1 to 8 in unit increments. The left vertical axis is labeled membrane potential in millivolts and ranges from negative 70 to positive 30. The right vertical axis is labeled membrane permeability and ranges from 1 to 600. The lines in the graph denote N as a positive permeability, K positive permeability, and action

potential. The following are approximate values. N a positive permeability: (0, negative 90), (1, 20), (2, negative 90), (3, negative 90), (4, negative 90), (5, negative 90), (6, negative 90), (7, negative 90), (8, negative 90). The line ends at 1 in the right vertical axis. K positive permeability: (1, negative 80), (2, negative 40), (3, negative 50), (4, negative 80), (5, negative 80), (6, negative 80), (7, negative 80), (8, negative 80). The line ends at 75 in the right vertical axis. Action potential: (1, negative 70), (2, 30), (3, negative 78), (4, negative 75), (5, negative 75), (6, negative 75), (7, negative 75), (8, negative 75). The line ends at 100 in the right vertical axis. An illustration features how the end of the axon away from the neuron's body becomes depolarized in response to a signal. A tube is divided into two: the left end, approximately one-fourth of the tube, is positive and labeled depolarized with four curved arrows pointing from the middle to the sides, two toward the left and two toward the right. The right end, approximately three-fourths of the tube, is negative. An illustration features how depolarization extends through the axon as the initial part of the membrane repolarizes. A tube is divided into three: the left end, approximately one-fourth of the tube, is negative and labeled repolarizing. The middle part, approximately one-fourth of the tube, is positive and labeled depolarized with four curved arrows pointing from the middle to the sides, two toward the left and two toward the right. The right end, approximately half of the tube, is negative and labeled resting. An illustration features how action potential spreads across the axon. A tube is divided

into four parts; from the left, the first part is negative and labeled resting. The second part is negative and labeled as repolarizing. The third part is positive and labeled depolarized with four curved arrows pointing from the middle to the sides, two toward the left and two toward the right. The fourth part is negative.

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The following are labeled: Medulla, Pons, midbrain, cerebrum, Diencephalon: hypothalamus and thalamus, meninges, skull, brain stem, cerebellum, and spinal cord.

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The front of the brain is on the left, and the back is on the right. The parts labeled are the frontal lobe, parietal lobe, occipital lobe, temporal lobe, occipital lobe, and central sulcus. The cerebral cortex is divided into three: motor cortex, association cortex, and sensory cortex. The areas that are parts of the motor cortex are Supplementary motor area that is involved in the programming of complex movements. This is on the inner surface and not visible. Premotor cortex is involved in the coordination of complex movements. Broca's areas are involved in speech formation. Primary motor cortex that is involved in voluntary movement. The areas that are parts of the association cortex are the prefrontal association cortex, which is involved in planning for voluntary activity, decision-making, and personality traits.

Limbic association cortex is involved in motivation, emotion, and memory. This is mostly on the inner and bottom surfaces of the temporal lobe. The posterior parietal cortex is involved in the integration of somatosensory and visual input and is important for complex movements. Wernicke's area is involved in speech understanding. Parietal-temporal-occipital association cortex is involved in the integration of all sensory input and is important in language. The areas that are parts of the sensory cortex are The primary auditory cortex is surrounded by a higher-order auditory cortex, and it is involved in hearing. Primary sensory cortex that is involved in sensation. Primary visual cortex is surrounded by higher-order visual cortex, and it is involved in sight.

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The vertical cross-section of the brain along the center is featured. The labeled parts are cerebral cortex, hypothalamus, thalamus which is medial, brain stem which is divided into midbrain, pons, medulla, cerebellum, and spinal cord. The basal nuclei which are lateral to thalamus are featured as a separate illustration with their location indicated by dotted lines in the center of the brain. The text on the right in separate sections reads, Cerebral cortex: Receives sensory information from skin, muscles, glands, and organs. Sends messages to move skeletal muscles. Integrates incoming and outgoing nerve impulses. Performs associative activities such as thinking, learning, and remembering. Basal nuclei: Play a role in the coordination of slow, sustained

movements. Suppress useless patterns of movement. Thalamus: Relays most sensory information from the spinal cord and certain parts of the brain to the cerebral cortex. Interprets certain sensory messages such as those of pain, temperature, and pressure. Hypothalamus: Controls various homeostatic functions such as body temperature, respiration, and heart rate. Directs hormone secretions of the pituitary. Cerebellum: Coordinates subconscious movements of skeletal muscles. Contributes to muscle tone, posture, balance, and equilibrium. Brainstem: Origin of many cranial nerves. Reflex center for movements of eyeballs, head, and trunk. Regulates heart rate and breathing. Plays a role in consciousness. Transmits impulses between brain and spinal cord.

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The following parts are labeled: pons, hypothalamus, prefrontal cortex, thalamus, cerebellum, and spinal cord. Arrows indicate ascending sensory tracts and descending motor tracts in the spinal cord. Auditory impulses via the pons and visual impulses move to the hypothalamus, and radiation is sent to the entire cerebral cortex. Reticular formation happens in a region in the pons.

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The spinal cord is divided into three parts: the cervical cord with eight pairs of cervical nerves; the thoracic cord with

twelve pairs of thoracic nerves; the cauda equina with five pairs of lumbar nerves, five pairs of sacral nerves, and the coccygeal nerve.

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An illustration features a bent leg with a reflex hammer positioned below the knee and the quadriceps muscles surrounding the femur. A label that reads stretch receptor in muscle sends message along afferent neuron when ligament below patella is struck points to an afferent neuron in the quadriceps muscle. The afferent neuron is connected to the illustration of a portion of the spinal cord, and the label that points to the illustration reads, Impulse sent to spinal cord, passed to motor neuron. A label that reads impulse reaches quadriceps muscle, which is stimulated to contract points to the motor neuron in the quadriceps muscle.

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The illustration features the index finger of a hand touching a vessel with boiling contents. Sensor: The thermal pain receptor in the finger runs along the afferent pathway into the integrating center, which is the spinal cord, and the efferent pathway from the spinal cord that triggers the effector: arm muscles, biceps or flexors, and triceps or extensors, causes them to pull away as a response. Excitory interneurons, inhibitory interneurons, and the ascending pathway to the brain are labeled. The components of a reflex arc are the

receptor and sensor, afferent pathway, integrating center, efferent pathway, and effector organs.

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The illustration of a human body is divided into two, one half features the front view and the other half features the back view. The nerves in the front view, from top to bottom are C 3, C 4, C 5, T 1, T 2, C 5, C 6, C 7, C 8, L 1, S 2, S 3, L 2, L 3, L 4, L 5, and S 1. The nerves in the back view, from top to bottom are C 3, C 4, C 5, C 6, C 7, C 8, T 1, T2, L 1, L 2, L 3, L 4, L 5, S 1, S 2, S 3, L 1, L 2, L 3, L 4, and L 5.

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The following parts are labeled: sensory neuron axon, dorsal root, dorsal root ganglion, sensory neuron cell body, sensory neuron axon, spinal nerve, motor neuron axon, ventral root, motor neuron cell body, interneuron, and motor neuron dendrites. Arrow indicates the path of a message to the brain and from the brain.

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The first cranial nerve is the olfactory nerve and conveys sensory information related to smell. The second is the optic nerve and conveys information related to vision. The third is the common oculomotor nerve which is related to eye movement and pupil constriction. The fourth is the trochlear nerve and it is related to eye movement. The fifth is the

trigeminal nerve which is related to somatosensory information from the face and head and muscles for chewing. The sixth is the external oculomotor nerve and it is related to eye movement. The seventh is the facial nerve and which is related to taste, somatosensory information from ear, and controls muscles used in facial expression. The eighth is the auditory nerve and it is related to hearing and balance. The ninth is the glossopharyngeal nerve which is related to taste; somatosensory information from tongue, tonsil, pharynx; controls some muscles used in swallowing. The tenth is the Vagus nerve and it is related to sensory, motor and autonomic functions of viscera, glands, digestion, and heart rate. The eleventh is the accessory nerve and it is related to muscles that control head movement. The twelfth nerve is hypoglossal and it controls the muscles of the tongue.

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The sympathetic division has the fight or flight function. The sympathetic functions performed by various locations for the spinal cord, from top to bottom, are as follows: Dilate pupil, nasal mucosa, activate sublingual and submandibular glands, stop secretion by the salivary glands, dilate bronchioles, speed up heartbeat, secrete adrenaline by the adrenal glands on the kidney, decrease motility of the intestine, retain colon contents, retain colon contents, and delay bladder emptying. The parasympathetic division has the rest and digest function. The parasympathetic functions performed by the medulla are to constrict pupil, activate lacrimal glad,

secrete saliva, construct bronchioles, slow down heartbeat, increase secretion in liver, activate stomach, spleen, and pancreas, and increase motility of the intestines. The parasympathetic actions performed by the pelvic nerve are empty colon and empty bladder.

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The first illustration features the side view of the brain in the skull. In the brain, arrows from the middle pointing outward indicate compressed brain because of which the ventricles are enlarged and the aqueduct of the Sylvius is blocked. The second illustration features the cross-section of the brain that features the cerebrum where there is ischemia and necrosis of brain tissue, dilated lateral and third ventricles, and blocked flow of C S F.

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The first illustration features a portion of the spinal cord where there is a gap between the two vertebrae. The structure of the spinal cord is normal. The second illustration features a portion of the spinal cord where a sac is formed between two vertebrae, and the sac protrudes outside. The structure of the spinal cord is normal. The third illustration features a portion of the spinal cord where a sac is formed between two vertebrae, and the sac protrudes with the spinal cord and nerves involved in the structure.

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The first set of illustrations features a side view of the head with the skull and the brain and is labeled forward and backward closed head injury. The natural position of the brain is present. The second illustration features an injury to the front or anterior aspect of the brain, which impacts the back cranial wall, and the head is in a backward-leaning position. The third illustration features an injury to the rear or posterior aspect of the brain, which impacts the front cranial wall, and the head is in a forward-leaning position. The fourth illustration features the front and rear of the brain are damaged. The second set of illustrations features the front view of the head and the brain and is labeled side-to-side closed head injury. The first illustration is labeled natural position. The second illustration features the right side of the brain impacting the cranial wall. The third illustration features the left side of the brain impacting the cranial wall. The fourth illustration features damage to both sides of the brain.

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The first two illustrations, labeled closed injury and direct and contrecoup injury, feature closed brain injuries, and the third and fourth illustrations, labeled open injury, feature open brain injuries. The first illustration features a side view of the head with the skull and the brain. The head is in a forward-bending position, and the front part of the brain is labeled direct injury and marked 1. An arrow from the back to the front on top of the skull is labeled impact. The second illustration features a side view of the head with the skull and the brain. Rebound of

the skull happens when the head is thrown backward, and a contrecoup injury takes place at the base of the brain, which hits the skull and is marked 2. The third illustration features a side view of the head with the skull and the brain. An object like a brick hits the top of the head, and bleeding and edema take place in the brain. This type of injury is labeled a depressed fracture. The fourth illustration features the front view of the head, where there is damage to the skull and bone fragments penetrating the brain.

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The title of the form reads, Glasgow Coma scale: Do it this way. G C S at 40. Eyes. Verbal. Motor. Institute of Neurological Sciences N H S Greater Glasgow and Clyde. There are four stages as icons below the title. One of a question mark, one of an eye, one of three concentric circles, and one with a tick mark, and they are labeled check, observe, stimulate, and rate, respectively. The text below check reads, for factors interfering with communication, ability to respond, and other injuries. The text below observes reads, eye-opening, content of speech, and movements of right and left sides. The text below stimulates reads, sounds, spoken, or shouted requests. Physical. Pressure on fingertip, trapezius, or supraorbital notch. The text below rate reads, assign according to the highest response observed. A four-column table is below. The column headers are criterion, observed, rating, and score. Under the heading Eye-opening, the items in the criterion column are open before stimulus;

after spoken or shouted request; after fingertip stimulus; no opening at any time; no interfering factor; closed by local factor. A tick mark is against each item in the observed column. In the rating column, the entries are spontaneous, to sound, to pressure, none, and nontestable. The score against each entry is 4, 3, 2, 1, and N T, respectively. Under the heading verbal response, the entries in the criterion column correctly give name, place, and date. Not oriented, but communication coherent; Intelligible single words; only moans or groans; no audible response, no interfering factor; Factor interfering with communication. A tick mark is against each entry in the observed column. In the rating column, the entries are oriented, confused, words, sounds, none, and nontestable. The score against each entry is 5, 4, 3, 2, 1, and N T, respectively. Under the best motor response, the items in the criterion column are obeys two-part request; brings hand above clavicle to stimulus on head and neck; bends arm at elbow rapidly but features not predominantly abnormal; bends arm at elbow, features clearly predominantly abnormal; Extends arm at elbow; No movement in arms and legs, no interfering factor; Paralyzed or other limiting factor. A tick mark is against each entry in the observed column. In the rating column, the items are obeying commands, localizing, normal flexion, extension, none, and non-testable. The score against each entry is 6, 5, 4, 3, 2, 1, and N T, respectively. Below the table are two sets of illustrations labeled sites for physical stimulation and features of flexion responses. Under the heading Sites for Physical Stimulation,

there are three illustrations titled: fingertip pressure below, which is an illustration of a person's thumb and fingers holding another person's finger; trapezius inch below, which is an illustration of a hand holding the portion between the neck and the shoulder; supraorbital notch below, which is an illustration of a thumb pressing a person's right eyebrow. The text under the heading Features of flexion responses reads, modified with permission from Van Der Naalt 2004 Ned Tijdschr Geneeskd. Below this is an illustration of a person with two sets of arrows pointing toward the forearm from either side. The right forearm is held against the body, and the other is held away from the body. On the side of the illustration with the forearm against the body, the text reads, Abnormal flexion. Slow Stereotyped, Arm across chest, Forearm rotates, Thumb clenched, Leg extends. On the other side of the illustration, with an extended forearm, the text reads, Normal flexion. Rapid, variable, Arm away from body. Below the illustrations, the text reads, Visit w w w dot Glasgow coma scale dot o r g. Available in more than 25 languages. Graphic design by Margaret Frej based on layout and illustrations from Medical Illustration M I, 268093 c Sir Graham Teasdale 2015.

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Space-occupying lesions put pressure on all sides of the brain. The brain comprises 300 to 400 milliliters of tissue and 900 to 1200 milliliters of intracellular fluid. Extracellular fluid

made of C S F from the lumbar cistern, 100 to 150 milliliters, and blood from the jugular vein, 100 to 150 milliliters.

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The horizontal axis is labeled time with the following stages: compensation, ischemia, and irreversible damage. The vertical axis is labeled as increasing intracranial pressure in an upward direction. Four lines feature systolic blood pressure, diastolic blood pressure, pulse, and respiration. Both the pulse and respiration lines are stable during compensation and then go downward gradually during ischemia and irreversible damage. The diastolic blood pressure very gradually rises over time, and the systolic blood pressure, after some stability, gradually rises, and the gap between the systolic blood pressure and diastolic blood pressure, indicating increasing pulse pressure, widens.

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The brain inside the skull is illustrated. A V-shaped depression at the top is labeled falx cerebri. The folds on the bottom right side of the brain are labeled tentorium cerebelli. The space on the outside of the brainstem is labeled the foramen magnum. An arrow that curves from the tentorium cerebelli toward the brain stem and outward is labeled 1. A downward arrow in the center is labeled 2. A curved arrow from the base of the falx cerebri and upward is labeled 3. An arrow that points from the inside to a projection on the left

side is labeled 4. A curved arrow from the left of the brain stem and inward is labeled 5. A downward arrow on the brain stem is labeled 6.

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An illustration features a man lying down in the supine position with his legs stretched out, his toes pointing forward, and his wrists flexed over his chest. An illustration features a man lying down in the supine position with his legs stretched out and toes pointing forward; his arms are stretched out to his sides, and the wrists are flexed out. An illustration features a man lying down in the supine position with his legs stretched out and toes pointing forward; one of his arms is stretched out to his side and the wrist is flexed out; the other arm is bent and placed over his chest with his wrist flexed out.

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The man is wearing a seat belt, and an arrow depicts the forward movement of his head caused by the impact. The head is magnified, and the cross-section of the neck features anterior dislocation at C 5, a torn posterior longitudinal ligament, and distortion of the cord.

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The first illustration features mechanical damage where an impact in the shape of lightning hits the spinal cord. The

second illustration features inflammation and angiogenesis in the area. Blood vessels, microglia, and macrophages are labeled. The third illustration features glial scar formation, where neurons and astrocytes form a web under the surface of the damaged area. The fourth illustration features structural tissue regeneration. Oligodendrocytes are labeled. The horizontal axis features the following timeline after S C I: Hours, days, weeks, and months. The first graph features the detrimental and beneficial immune system responses to S C I as follows: The detrimental response of M 1-like microglia and macrophages peaks after a few days and then decreases. The beneficial response of M 2-like microglia and macrophages remains constant at a small value. The detrimental response of neutrophils peaks slightly after a few hours, and the beneficial response remains constant for some days at a small value. The detrimental response of T cell infiltration is constant at a low value for days, and the beneficial response is constant at a low value between hours and months. The detrimental response of the cytokine or chemokine storm peaks after hours and decreases; the beneficial response remains constant at a low value between hours and months. The detrimental response of glial scarring, the beneficial response of regeneration, and the detrimental response of degeneration increase gradually over months. The second graph features the cellular events that follow the initial S C I. The B B B leakage peaks sharply after hours, decreases to a minimum, and remains constant for months. Microglia peaks after hours decreases gradually

to a moderate value over weeks, and remains constant for months. Infiltration of immune cells starts after hours and peaks. C D 2 0 0 L has a flat, moderate peak for days and weeks. Angiogenesis peaks near the end of the day. Axonal sprouting increases gradually from days to a moderate value and remains constant over months. Gliosis peaks after a few weeks and decreases gradually to a moderate value over time. Neurogenesis increases slightly after a few weeks, reaches a peak, and then decreases.

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An adult presents with a headache. If meningitis is suspected, follow meningitis protocols. Otherwise, does the patient have any of the following red-flag features? Thunderclap headache: see the Thunderclap headache pathway below. New headache in the older population. New onset headache with a history of cancer or immunodeficiency. Headache with mental state changes. Headache with fever, neck stiffness, and meningeal signs. Headache with focal neurologic deficit, if not previously documented as a migraine with aura. Substance abuse with amphetamine or cocaine. The patient is pregnant or postpartum. Headache causing wakening from sleep or worsened by the Valsalva maneuver. Progressively worsening headache. Significant trauma: see the head trauma pathway below. Anti-coagulation, including aspirin and clopidogrel. History of seizures in non-epileptics Headache is different from a usual migraine. If the answer is yes, C T

head is generally indicated. If the answer to the question, are any of the following suspected? is no, and if the headache is ongoing, consult neurology. If the answer is yes, then for head trauma, follow head trauma protocols; for temporal arteritis, diagnosis is based on a combination of clinical suspicion, elevated E S R, and temporal artery biopsy. Imaging may not usually be required, but an ultrasound may be considered; for trigeminal neuralgia, do an M R I; for thunderclap headache, follow thunderclap headache protocols; for carotid or vertebral artery dissection, do a C T angiography or M R I and an M R angiography, M R A; for cerebral venous thrombosis, do a C T venography or M R I and an M R venography, M R V. If the answer is no to the above red flag indications, significant pathology is unlikely but not excluded. And if there is an ongoing headache, consult neurology.

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The front of the brain is on the left, and the back is on the right. The parts labeled are the frontal lobe, parietal lobe, occipital lobe, and temporal lobe. Frontal Lobe: Jacksonian seizure, tingling feeling in hand or arm. Adversive seizures, eyes or head both turn to one side. Parietal Lobe: Tingling in or jerking of the leg, arm, or face. Temporal Lobe: Strange smell or taste; altered behavior; feeling as if I have been there before or I have seen that before; deja vu; lip-smacking or chewing movements. Occipital Lobe: flashing lights or spots, vomiting.

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The first illustration features the tonic phase, where the person is lying in the supine position with generalized stiffening of body and limbs, and the back is arched. There is urinary incontinence and cyanosis in the head, with epileptic cries. The second illustration features the clonic phase, where the person is lying in the supine position with clonic jerks of limbs, body, and head; salivary frothing; eyes blinking; and cyanosis in the head. The third illustration features postictal confusional fatigue, where the person is lying in the supine position with the limbs and body limp.

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In the neuron of a person with multiple sclerosis, myelination on the axon is damaged or there is demyelination.

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They are head tremors, masklike face, stooped posture, rigidity in the back, arms flexed at elbows and wrists, hips and knees slightly flexed, tremors in the legs, short, and shuffling steps.

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The nerve cell is small in size and appears underdeveloped in the atrophied muscle cell due to A L S.

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The following parts are labeled. Skull: Frontal, Parietal, Temporal, Zygomatic, Maxilla, Mandible; Pectoral girdle: Clavicle, Scapula; Thorax: Sternum, ribs; Upper limb: Humerus, Radius, Ulna, Carpals, Metacarpals, Phalanges; Vertebral column; Pelvic girdle: ilium, sacrum, coccyx, ischium, pubis; Lower limb: Femur, Patella, Tibia, Fibula, Tarsals, Metatarsals, Phalanges.

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An illustration features the bones of the upper limb and the following bones are labeled: Scapula, Glenohumeral joint, Triceps brachi, Humerus, Biceps brachi, Lateral condyle, Medial condyle, Olecranon process, Ulna, Radius, Radial styloid, and Ulnar styloid. An illustration features the bones in the hand. From the base of the hand, they are classified as carpals, metacarpals, and phalanges. The radius, ulna, carpometacarpal joint, thumb, index finger, long finger, ring finger, and small finger are labeled.

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A. An illustration features a long bone and the following parts are labeled: Hyaline cartilage, epiphysis at the top, diaphysis, and epiphysis at the bottom. B. An illustration features the cross-section of a long bone on both ends of the bone. The following parts are labeled: spongy bone, compact bone, red

marrow, periosteum, a layer below the surface of the bone, and nutrient vessel.

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The following parts are labeled: red marrow on spongy bone, compact bone, and yellow bone marrow. A portion of the cross-section is magnified and features the following: blood vessels in the Haversian canal, spongy bone, and compact bone. An inset magnifies a section of the bone and features concentric lamellae and Haversian systems.

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A. A photo of the head of a humerus where compact bone and spongy bone are labeled. B. A micrograph of the lamella and the following are labeled: central canal, osteocytes, and canaliculi. C. A micrograph of the osteoblast, osteoclast, and bony spicule in a spongy bone. D. An illustration of the osteocytes around an osteoclast with several nuclei within in bony matrix.

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The superficial muscles in the illustration of a female include the facial muscles, Sternocleidomastoid, Trapezius, Deltoid, Pectoralis major, Biceps, External oblique, Finger and wrist flexors, Sartorius, Quadriceps, Anterior tibial, Foot and ankle flexors. The deep muscles include Pectoralis minor, Intercostals, Rectus abdominus, Internal oblique, Vastus

muscle which is part of quadriceps. The superficial muscles in the illustration of the male include: Occipital, Trapezius, Deltoid, Latissimus dorsi, Gluteus maximus, Biceps femoris, Semitendinosus, Semimembranosus, Gastrocnemius, Soleus, Achilles tendon. The deep muscles include: Neck extensors, Rotator cuff Shoulder girdle muscle, Triceps, Erector spinae, Finger and wrist extensors, Gluteus medius, Hip adductor muscles, Hamstrings, Foot and ankle extensors.

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The first illustration features a man standing with one arm bent at the elbow. If the forearm is moved toward the self, then the movement is labeled flexion. If the forearm is stretched forward, then the movement is labeled extension. The second illustration features a man bending his head forward and looking down. This is flexion of the neck. The third illustration features a pair of hands in hyperextension. One hand is supinated and the other is pronated. The fourth illustration features a man leaning backward with one arm lifted over his head and the other stretched in front. Two arrows behind the man indicate supination and pronation. The fifth illustration features a man standing with his arms stretched to the sides. If he moves the hand toward him, the movement is labeled adduction. If he moves the hand away from him, the movement is labeled abduction. Arrows indicate adduction and abduction. The sixth illustration features a man standing and raising the toes of one leg upward, this

movement is labeled dorsiflexion. The seventh illustration features a man standing and pointing the toes of one leg downward, this movement is labeled plantar flexion. The eighth illustration features a foot. If the foot is moved pointing away from the body, the movement is labeled eversion. If the foot is moved toward the body, the movement is labeled inversion.

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A. The skeletal muscle consists of bundles of muscle fibers surrounded by connective tissue and blood vessels. The muscle is attached to a tendon, which in turn is attached to a bone. A fiber consists of a layer of sarcolemma, surrounded by capillaries. Sarcolemma consists of nuclei. A layer of sarcoplasmic reticulum is under sarcolemma. The muscle fiber consists of myofibrils and mitochondrion. The myofibrils consist of actin and myosin, two bands on its surface: alternating I band and A band. B. An accompanying illustration features the structure of a sarcomere, with I bands and A bands. The center of I band is Z line, and the center of A band is M line. H zone is at the center of A band. The bands consist of parallel, horizontal, alternating thick filament myosin and thin filament actin. Actin and myosin are not aligned. In a contracting sarcomere, the filaments are aligned one below the other.

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The first illustration features a woman with a normal spine. The second illustration features a woman with kyphosis where there is increased convexity of the thoracic spine. The third illustration features a woman with lordosis where there is increased concavity of the lumbar curvature.

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In the first part, illustrations feature the back view of a person with a normal spine, mild scoliosis, severe scoliosis, and very severe scoliosis. The woman with a normal spine has a straight spine. In the woman with mild scoliosis, there is a lateral deviation of the spine. In the woman with severe scoliosis, the shoulders and hips are uneven. In the woman, with very severe scoliosis, she is stooped in front with a rib hump as the vertebrae rotate. In the second part, illustrations are labeled rotation of vertebra and rib deformity. The first diagram features a portion of wedge vertebra, the second diagram features a portion of fused vertebra, and the third diagram features a portion of fused ribs.

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The first illustration features a normal hip joint. The second illustration features subluxation where the head of the femur moves away from its initial position but is still within the socket. The third illustration features low dislocation where the head of the femur is out of the socket. The fourth

illustration features high dislocation where the head of the femur is completely away from the socket.

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The first illustration features blood clots at the site of the fracture. The marrow cavity and periosteum are labeled. The second illustration features a callus forming in the place of the blood clot. The spongy bone of the internal callus is labeled. At this stage, the blood clot is invaded by fibroblasts and other cells, forming the callus. The third illustration features a bony callus forming in the place of the callus. At this stage, calcium is deposited in the callus, joining the ends together. The fourth illustration features a healed fracture where the fracture is repaired.

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In both illustrations, the following are labeled: humeral head, supraspinatus, glenoid fossa, and capsular ligament. The first illustration features a normal shoulder joint. In the second illustration, the capsular ligament is stretched and hanging.

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The illustration features the front view of the foot and the side view of the ankle with the bones and ligaments within. The first illustration features normal ligaments. The second illustration features a Grade 1 sprain where the foot is slightly

twisted because of which the ligaments are stretched. The third illustration features a Grade 2 sprain where the foot is twisted a little more and the ligaments are slightly torn. The fourth illustration features a Grade 3 sprain where there is a twisted foot and the ligaments are torn completely.

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A small portion is magnified that features the strained muscle tissue and another inset features normal muscle tissue. The difference between the two is the strained muscle has a loss of color and is not as plump as the normal muscle tissue.

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The following are labeled: intervertebral disk, annulus fibrosus, nucleus pulposus, the body of the vertebra, herniation, nerve root, spinous process which is posterior, bone, lamina, and spinal cord.

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The first illustration features a woman with a normal spine. The second illustration features a woman with a slightly curved spine because of which she is shorter. The third illustration features a woman with a curved spine and shorter than before. The fourth illustration features a woman with advanced kyphosis because of which the spine is fully curved and she is shorter than before. The values on the scale from left to right are negative 4, negative 3. negative 2.

negative 1, 0, positive 1, positive 2, positive 3, positive 4. If the score is between negative 4 and negative 2.5, it indicates osteoporosis where porous bone can lead to fractures. If the score is between negative 2.5 and negative 1, it indicates low bone density or osteopenia. If this is from negative 1 to positive 4, it is normal as compared to an average 30-year-old.

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In the illustration with normal synovial joint, the following are labeled: bone, epiphyseal plate, synovial membrane, joint cavity, synovial fluid, articular cartilage, and joint capsule. In the illustration that features pathologic changes in osteoarthritis, the following are labeled: cyst in bone, osteophyte or bone spur, cartilage fragments, narrow joint space, erosion of cartilage and bone. In the illustration that features pathologic changes in rheumatoid arthritis, the following are labeled: inflamed synovium, pannus, loss of cartilage, fibrous tissue or ankylosis, and pannus-filled erosion.

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A. An illustration features the hand of a person with late-stage rheumatoid arthritis. The following are labeled: Boutonniere deformity of thumb, ulnar deviation of metacarpophalangeal joints, and Swan-neck deformity of

fingers. B. A photo features the hand of a person with late-stage rheumatoid arthritis.

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A. In the front view of the foot, the bones of the big toe are illustrated. One of the joints is swollen and inflamed, and masses of uric acid, or tophi, and uric acid crystals are labeled. B. There are inflamed lumps in the big toe and the little toe in the feet of a patient in a photo.

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In the first illustration, the spine has a normal S-curve, and that section of the spine is illustrated under magnification. In the second illustration, there is a loss of normal curvature in the spine, and that section of the spine is illustrated under magnification.

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The following layers from top to bottom are labeled: Keratinized layer, epidermis, dermis, hypodermis or subcutaneous tissue. The following parts are labeled in the illustration: hair, sebaceous gland, arrector pili muscle, hair follicle, vein, artery, fat, nerve, and sweat gland.

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In the illustration of normal skin, the following parts are labeled: keratin layer, epidermis, dermis, subcutaneous layer. The keratin layer appears normal. In the illustration of skin with psoriasis, the following are labeled in the keratin layer: inflamed skin, plaque and scales. The layer appears cracked.

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A 1. The illustration features the layers of skin, with the top layer cracked and grooved extensively. A 2. A photo of a grazed wound with slight bleeding, surface-level tissue loss, and inflamed. B 1. The illustration features layers of skin with a deep cut through the layers. The cut reaches the hypodermis. B 2. A photo of a deep cut in the skin with a gaping opening. C 1. The illustration features the layers of the skin with a section of the epidermis and the dermis peeled off. C 2. A photo of a bleeding and peeled-off nail at the base. D 1. The illustration features a nail punctured into the layers of the skin. D 2. A photo of the forefinger of a person with a nail passed right through its middle.

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The illustration features the three layers of the skin, from the top to the bottom, which are the epidermis, dermis, and subcutaneous tissue. The first illustration is labeled. superficial or first-degree. The epidermis is inflamed and dark at the burn site. The second illustration is labeled partial

thickness, or second degree. The epidermis is lifted into fluid-filled bumps at the burn site. The third illustration is labeled full thickness, or third degree. The burn site is burned right through the layers up to the subcutaneous tissue. A. A photo of the skin of the torso, hands, and thigh of a person is burned and appears red. B. A photo of the torso and hands of a person with burn wounds. There are several fluid-filled bumps on the skin with blackened areas. C. A photo of the leg of a person with a severe burn wound. The skin has patches of white and dark brown.

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Stage 1: An illustration features a portion of skin with non-blanchable erythema of a localized area of skin over a bony prominence. The skin is intact and red color. Stage 2: An illustration features a portion of skin with partial-thickness loss of the epidermis and some of the dermis. Looks like a shallow open ulcer or a superficial erosion with a pink-red wound bed and has no slough. Stage 3: An illustration features full-thickness loss of the skin and necrosis of subcutaneous tissue. Subcutaneous fat is visible but tendon, muscle, or bone is not exposed. Ulcer includes undermining and tunneling and has some slough or necrotic tissue. Stage 4: An illustration features full-thickness loss of skin including the epidermis, dermis, and subcutaneous tissue. Muscle, bone, or tendon is exposed. Slough undermining and tunneling are present. Suspect deep tissue injury: Localized area of discolored skin that is purple or maroon. It is non-

blanching with an intact epidermis and the skin feels boggy. Unstageable: An illustration features a portion of skin with ulcer that has full-thickness tissue loss covered by an eschar or extensive necrotic tissue, tan, yellow-green, or brown, which must be cleared away before the true depth can be determined.

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The first photo features a raised bump on the skin. The second photo features a small black area with uneven edges on one side. The third photo features a dark brown, raised bump on the skin. The fourth photo features a black area on the skin with irregular shapes and edges. The fifth photo features a round, dark brown nodule on the skin. The sixth photo features an irregularly edged brown and red patchy area on the skin. The seventh photo features a dark brown patch on the skin with rounded edges. The eighth photo features an asymmetric area on the skin, which is dark and patchy with uneven coloring. The ninth photo features tiny red spots on the skin. The tenth photo features dark-colored spots that are tiny on the skin.

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The sensory pathway is presented as a horizontal flow diagram. The stages of the pathway are stimulus, sense organ or accessory structure, receptor cells or transducers, convert energy from one form to another, action potential or

nerve impulse, and the central nervous system that is decoded. Illustrations are included as examples below each stage. Stimulus: An illustration of a bright light is present. Sense organ: An illustration of an eye is present. Receptor cells: An illustration of rods and cones is present. Action potential: An illustration features a zigzag arrow denoting the optic nerve. Central nervous system: An illustration features the cross-section of the brain with the visual cortex of the brain highlighted.

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A. An illustration features exposed nerve endings where dendrites of sensory neurons grow into the epithelial cells of the epidermis. B. An illustration features encapsulated nerve endings where a dendrite of a sensory neuron is encapsulated in a Pacinian corpuscle or pressure receptor with connective tissue cells. C. An illustration features the cross-section of a block of skin. The following parts are labeled: epidermis, dermis, sensory nerve, Pacinian corpuscle for deep pressure, subcutaneous fat, Ruffini corpuscle for light touch, dendrites for hair movement, Meissner corpuscle for touch and light pressure, Merkel disks for light touch, free dendrite nerve ending for pain, and Krause end bulb for light touch. Micrographs of the Meissner corpuscle and Pacinian corpuscle are included.

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Liver and gallbladder: right side of the neck. Lung and diaphragm: left side of the neck. Heart: left side of the chest and medial side of the left arm. Stomach: center of the upper trunk. Pancreas: either side of the stomach. Appendix: Right side of the lower trunk. Small intestine, ovary, colon, and urinary bladder: one below the other in the middle of the lower trunk. Kidney: lower trunk and upper thighs.

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The first illustration features a side view of the cross-section of the human eye. The following parts are labeled: Extrinsic eye muscle, choroid, retina, sclera, fovea, optic nerve, optic disk, blood vessels, vitreous humor, cornea, lens, aqueous humor, pupil, iris, conjunctiva, ciliary body, and suspensory ligament. The second illustration features the human eye. The following are labeled: Canal for tear drainage, pupil, iris, and sclera.

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A. An illustration features the side view of the cross-section of the eye. The eye is looking up, and the retina is labeled. A portion of the retina is magnified and features the arrangement of cellular components. B. An illustration features the arrangement of cellular components of the retina. From bottom to top, the three layers are the sclera, choroid layer, and retina. The layers of the retina from bottom to top are the pigment layer of the retina, rod, cone,

photoreceptor cells, horizontal cells, bipolar neurons, amacrine cells, ganglion cells, and fibers of the optic nerve. Light falls on the layer with the fibers of the optic nerve. C. Illustrations feature the structure and parts of the rod cell and cone cell. The cells are divided into an outer segment, an inner segment, a cell body, and a nucleus. The synaptic endings, nuclei, and mitochondria in them are labeled.

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The following parts are labeled: External ear: auricle, external auditory canal. Middle ear: tympanic membrane and the ossicles: malleus, incus, and stapes. Inner ear: semicircular canals, oval window, vestibular nerve, cochlear nerve, cochlea, vestibule, round window, eustachian or auditory tube.

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The illustration features the structures of the ear. The following parts are labeled: tympanic membrane, malleus, incus, stapes, oval window, vestibular canal, cochlear duct, vestibular membrane, tectorial membrane, cochlea, hairs, organ of corti, basilar membrane, tympanic canal, round window. Zigzag arrows indicate the path sound travels through the ear. B. Basilar membrane is represented as a spiral. The center is labeled, wide, flexible end of basilar membrane at apex. The end is labeled, narrow, stiff end of basilar membrane by oval window. The numbers, from the

center of the membrane to the end, are 20, 200, 400, 600, 800, 1,000, 1,500, 2,000, 3,000, 4,000, 5,000, 7,000, and 20,000. The numbers indicate the frequencies with which different regions of the basilar membrane maximally vibrate. C. High-frequency sounds stimulate the narrow end of the basilar membrane, medium-frequency sounds stimulate a broader portion of the basilar membrane, and low-frequency sounds stimulate the broadest portion of the basilar membrane.

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A. An illustration features the cross-section of the cochlea. The following parts are labeled: cochlear duct or canal, organ of Corti, basilar membrane, tympanic duct or canal, cochlear nerve, vestibular membrane, vestibular duct or canal, and tectorial membrane. B. An illustration features a magnified view of the middle of the cochlea, which is the organ of Corti. Deflection of the basilar membrane, because of fluid movement in the cochlea, stimulates the hair cells. The hair cells of the organ of Corti are labeled, and movement of the tectorial membrane, stimulating hair cells, is included.

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A. An illustration features the vestibular apparatus. The following are labeled: cochlea, crista, ampulla, endolymph fluid, semicircular canals, utricle, saccule, and vestibular nerve. B. An illustration features the structure of a crista. The

following are labeled: cupula, which is gelatinous; hairs of hair cells; hair cells; vestibular nerve fibers.

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A. A photo of a child with anotia, which is the absence of the auricle. B. A photo of a child with microtia, which is an underdeveloped and malformed auricle.

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An illustration features the cross-section of an eye that is looking upward with a normal flow of aqueous humor. The following are labeled: ciliary body with the formation of aqueous humor, posterior chamber, iris, lens, anterior chamber, normal intraocular pressure of 10 to 20 millimeters of mercury, and cornea. An inset features the magnification of a section of the eye where the absorption of aqueous humor happens. The trabecular meshwork and the canal of Schlemm are labeled. Arrows indicate intraocular pressure. An illustration features the cross-section of an eye that is looking upward with chronic or open-angle glaucoma. Degeneration and obstruction of the trabecular meshwork and canal of Schlemm that decrease the absorption of aqueous humor are indicated. An illustration features the cross-section of an eye that is looking upward with acute, narrow, or closed-angle glaucoma. High intraocular pressure, an iris in the anterior position, and a narrow iridocorneal

angle block drainage into the canal of Schlemm are indicated.

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The table consists of seven columns: Hypersensitivity type, origin of hypersensitivity, antibody involved, cells involved, mediators involved, evidence of hypersensitivity, and examples. Row entries are as follows. Type 1: I g E mediated; B lymphocytes; I g E; mast cells, basophils; histamine, serotonin, leukotrienes, prostaglandins; immediate, 30 minutes or less, or delayed, hours; allergic rhinitis, systemic anaphylaxis, asthma. Type 2: Cytotoxic; B lymphocytes; I g G, I g M; R B Cs, W B Cs; complement; 5 to 8 hours; transfusion reactions; hemolytic disease of newborns. Type 3: Immune complex; B lymphocytes; I g G; host tissue cells; complement; 2 to 8 hours; serum sickness, Arthus phenomenon, S L E, rheumatic fever, rheumatoid arthritis. Type 4: Cellular; T lymphocytes; none; host tissue cells; cytokines; 1 to 3 days; contact dermatitis, infection, allergy, Crohn’s disease.

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The table consists of five columns: Type, onset, mechanism and vessel history, type of hypersensitivity, and other. Under Host-versus-graft rejection, row entries are as follows. Row 1. Type: Hyperacute. Onset: Up to 3 days. Mechanism and vessel history: Preformed antibodies directed against the

donor tissue. Caused by accidental A B O blood type incompatibility. Presents while still in surgery with thrombosis and occlusion of graft vessels. Type of hypersensitivity: 2. Other: Very rare. Row 2. Type: Acute. Onset: 4 days to 3 months. Mechanism and vessel history: T-cell-mediated immune response directed against the foreign M H C. Inflammation and leukocyte infiltration of graft vessels results. Type of hypersensitivity: 4. Other: Most common type. Row 3. Type: Chronic. Onset: 4 Months to years. Mechanism and vessel history: T-cell-mediated process resulting from the foreign M H C, looking like, a self M H C carrying an antigen. Results in intimal thickening and fibrosis of graft vessels as well as graft atrophy. Type of hypersensitivity: 3 and 4. Other: No data. Under Graft-versus-host rejection, row entries are as follows. Row 4. Type: No data. Onset: Varies. Mechanism and vessel history: Donor T cells in the graft proliferate and attack the recipient's tissue. Type of hypersensitivity: 4. Other: Associated with bone marrow transplants. Presents with diarrhea, rash and jaundice.

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The table consists of the following text. All patients classified as having systemic lupus erythematosus. S L E, must have a serum titer of antinuclear antibody of at least 1:80 on human epithelial-2–positive cells or an equivalent positive test. In addition, a patient must tally at least 10 points from these criteria. A criterion is not counted if it has a more likely

explanation than S L E. Occurrence of the criterion only once is sufficient to tally the relevant points, and the time when a patient is positive for one criterion need not overlap with the time when the patient is positive for other criteria. S L E classification requires points from at least one clinical domain, and if a patient is positive for more than one criterion in a domain, only the criterion with the highest point value counts: The table has two heads: Clinical domains and immunologic domains. The first head has two columns: Clinical domains and points. Under constitutional domain, row entries are as follows. Row 1. Fever; 2. Under cutaneous domain, row entries are as follows. Row 2. Nonscarring alopecia; 2. Row 3. Oral ulcers; 2. Row 4. Subacute cutaneous or discoid lupus; 4. Row 5. Acute cutaneous lupus; 6. Under arthritis domain, row entries are as follows. Row 6. Synovitis in at least two joints or tenderness in at least two joints, and at least 30 minutes of morning stiffness; 6. Under Neurologic domain, row entries are as follows. Row 7. Delirium; 2. Row 8. Psychosis; 3. Row 9. Seizure; 5. Under serositis domain, row entries are as follows. Row 10. Pleural or pericardial effusion; 5. Row 11. Acute pericarditis; 6. Under hematologic domain, row entries are as follows. Row 12. Leukopenia; 3. Row 13. Thrombocytopenia; 4. Row 14. Autoimmune hemolysis; 4. Under renal domain, row entries are as follows. Row 15. Proteinuria greater than 0.5 grams per 24 hours; 4. Row 16: Class 2 or 5 lupus nephritis; 8. Row 17: Class 3 or 4 lupus nephritis; 10. The second head has two columns: Immunologic domains and points.

Under antiphospholipid antibody domain, row entries are as follows. Row 1. Anticardiolipin l g C greater than 40 G P L or anti-beta 2 G P 1 l g C greater than 40 units or lupus anticoagulant; 2. Under complement proteins domain, row entries are as follows. Row 2. Low C 3 or low C 4; 3. Row 3. Low C 4 and low C 4; 4. Under highly specific antibody domain, row entries are as follows. Row 4. Anti-d s D N A antibody; 6. Row 5. Anti-Smith antibody; 7. Source line reads, Data from Aringer, M., Costenbader, K., Daikh, D., Brinks, R., Mosca, M., Ramsey-Goldman, R., Johnson, S. 2019. 2019 European League Against Rheumatism or American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatology, 71, 9, 1400 to 1412.

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The table consists of four columns: Parameter, I T P, T T P, and D I C. Row entries are as follows. Row 1. Pathogenesis. Antiplatelet antibodies. Endothelial defect. Thrombin excess. Row 2. Clinical condition. Not ill. Ill-appearing. Ill-appearing. Row 3. Red blood cells. Normal. Schistocytes. Schistocytes. Row 4. Prothrombin time, P T; international normalized ratio, I N R. Normal. Normal, slight increase. Increased. Row 5. Partial thromboplastin time, P T T. Normal. Normal, slight increase. Increased. Row 6. Fibrinogen. Normal. Normal. Decreased. Row 7. Fibrinogen degradation. Normal. Normal, slight increase. Increased. Row 8. Delta-Dimer. Normal. Normal, slight increase. Increased. Row 9. Management.

Supportive, steroids, intravenous immunoglobulin, I V G, splenectomy. Supportive. Plasma exchange, steroids. Supportive.

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The table consists of four columns: Nonmodifiable Risk Factors, Modifiable Risk Factors, Negative Risk Factors, and Emerging Risk Factors. Row entries are as follows. Row 1. Nonmodifiable Risk Factors: Age: men greater than 45 years; women greater than 55 years or premature menopause. Family history: history of premature coronary artery disease in first-degree male relatives greater than 55 years or first-degree female relatives greater than 65 years. Modifiable Risk Factors: Tobacco use. Obesity. Physical inactivity. Stress. Diabetes mellitus. Hyperlipidemia, specifically L D L and lipoprotein, a. Hypertension. Diet high in fat and calories and low in phytochemicals, found in fruits and vegetables; fiber; omega-3 fatty acids; and vitamins C, D, and E. Negative Risk Factors: High H D L cholesterol. Emerging Risk Factors: Elevated C-reactive protein, homocysteine levels, and apoprotein B.

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“The table consists of five columns: Symptoms, Infectious Rhinitis, Influenza, COVID-19, and Respiratory Syncytial Virus. Row entries are as follows. Row 1. Onset. Gradual. Sudden. Gradual. Gradual. Row 2. Fever. Rare. Usual; high,

100 degrees Fahrenheit to 102 degrees Fahrenheit, but occasionally higher, especially in young children; lasts 3 to 4 days. Common. Common. Row 3. Headache. Rare. Common. Common. Common. Row 4. Myalgia. Slight. Usual; often severe. Sometimes. Rare. Row 5. Malaise. Sometimes. Usual; can last up to 2 to 3 weeks. Common. Sometimes. Row 6. Exhaustion. Never. Usual; at the beginning of the illness. Common. Sometimes. Row 7. Stuffy nose. Common. Sometimes. Common. Common. Row 8. Loss of taste and smell. Rare. Rare. Common. Rare. Row 9. Sneezing. Usual. Sometimes. Common. Common. Row 10. Sore throat. Common. Sometimes. Common. Common. Row 11. Chest discomfort, cough. Mild to moderate, nonproductive cough. Common; can be severe. Common; can be severe. Common; can be severe. Row 12. Shortness of breath or dyspnea. Rare. Rare. Common. Sometimes. Row 13. Wheezing. Rare. Rare. Sometimes. Sometimes. Row 14. Diarrhea. Never. Sometimes. Sometimes. Rare. Row 15. Vomiting. Never. Sometimes. Sometimes. Rare.”

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The table consists of three columns: Lobar pneumonia, bronchopneumonia, and interstitial pneumonia. Row entries are as follows. Row 1. Distribution: All of one or two lobes. Scattered small patches. Scattered small patches. Row 2. Cause: Streptococcus pneumonia. Multiple bacteria. Influenza virus; Mycoplasma. Row 3. Pathophysiology: Inflammation of the alveolar wall and leakage of cells, fibrin,

and fluid into alveoli, causing consolidation. Inflammation and purulent exudates in alveoli, often developing from pooled secretions or irritation. Interstitial inflammation around alveoli, necrosis of bronchial epithelium. Row 4. Onset: Sudden and acute. Insidious. Variable. Row 5. Signs: High fever, Chills, Productive cough of rusty sputum, Rales progressing to absent breath sounds in affected lobes. Mild fever, Productive cough of yellow-green sputum, Dyspnea. Variable fever, Nonproductive hacking cough, Headache, Myalgia.

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The table consists of five columns: Step and classification asterisk, daytime symptoms, nighttime symptoms, P E F or F E V 1 superscript dagger, and P E F variability. Row 1. Step 1: Mild intermittent. lesser than or equal to 2 per week. lesser than or equal to 2 per week. greater than or equal to 80 percent. less than 20 percent. Row 2. Step 2: Mild persistent. Greater than 2 per week, but less than daily. Greater than 2 nights per month. Greater than 80 percent. 20 to 30 percent. Row 3. Step 3: Moderate persistent; daily. greater than 1 night per week. 60 to 80 percent. greater than 30 percent. Row 4. Step 4: Severe persistent. continual. frequent. lesser than or equal to 60 percent. Greater than 30 percent. Text below the table reads, Abbreviations: F E V 1: forced expiratory volume in 1 second; P E F: peak expiratory flow, rate. Asterisk reads, Classification is based on symptoms and lung function before treatment. Patients should be

assigned to the most severe step in which any feature occurs. Dragger reads, Percentage of predicted function. Source line reads, Data from National Heart, Lung, and Blood Institute. 2020. National Asthma Education and Prevention Program, Focused Update Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. N I H Publication Number 08-5846. Retrieved from h t t p s colon forward slash forward slash w w w dot n h l b i dot n i h dot g o v forward slash resources forward slash 2020 hyphen focused hyphen updates hyphen asthma hyphen management hyphen guidelines.

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“The table consists of seven columns: Electrolyte, normal serum levels asterisk, imbalance, causes, consequences, manifestations, and treatments. Row entries are as follows. Row 1. Electrolyte: Sodium, N a plus. Normal serum levels, asterisk: 135 to 145 mill equivalent per liter. Imbalance: Hypernatremia, greater than 145 mill equivalent per liter. Causes: Excessive N a plus, for example, seawater ingestion, hypertonic I V F, cushing syndrome, corticosteroids. Deficient water, H 2 O, for example, decreased water intake, vomiting, diarrhea, excessive sweating, diuretics, diabetes insipidus, hyperventilation, and burns. Consequences: Cellular dehydration. Hyperchloremia. Manifestations: Neuromuscular dysfunction, for example, lethargy, confusion, headache, muscle cramps, weakness, restlessness, seizures, coma. Hypovolemia, for example,

thirst, dry mucous membranes, tachycardia, hypotension, and decreased urine output. Treatments: Treat underlying cause. Replace fluid, for example, glucose-electrolyte oral solutions, and hypotonic I V F. Diuretics if hypervolemic. Row 2. Electrolyte: Sodium, N a plus. Normal serum levels, asterisk: 135 to 145 mill equivalent per liter. Imbalance: Hyponatremia, less than 135 mill equivalent per liter. Causes: Deficient N a plus, for example, diuretics, vomiting, diarrhea, excessive sweating, Addison's disease, adrenal insufficiency, restricted N a plus intake. Excessive H 2 O, for example, hypotonic I V F, hyperglycemia, excessive water intake, renal failure, S I A D H, and heart failure. Consequences: Hypochloremia. Manifestations: Neuromuscular dysfunction, for example., lethargy, confusion, headache, muscle cramps, weakness, restlessness, diminished deep tendon reflexes, seizures, coma. Gastrointestinal disturbances, for example, anorexia, abdominal cramps, nausea, vomiting, and diarrhea. Hypovolemia, for example, thirst, dry mucous membranes, poor skin turgor, tachycardia, hypotension, and decreased urine output. Hypervolemia, for example, hypertension, edema, weight gain, increased urine output. Treatments: Treat underlying cause. Limit fluids if hypervolemic. Increase oral N a plus. Row 3. Electrolyte: Chloride, C l minus. Normal serum levels asterisk: 98 to 108 mill equivalent per liter. Imbalance: Hyperchloremia, greater than 108 mill equivalent per liter. Causes: Increased C l minus intake or exchange, for example, hypernatremia, hypertonic I V F, metabolic

acidosis, and hyperkalemia. Decreased C l minus excretion, for example, hyperparathyroidism, hyperaldosteronism, and renal failure. Consequences: Metabolic acidosis. Hyperkalemia. Manifestations: No direct clinical symptoms. Symptoms generally associated with underlying cause, metabolic acidosis, or hyperkalemia. Treatments: Treat underlying cause. Hypotonic I V F and diuretics to correct hypernatremia H C O 3 to correct acidosis. Row 4. Electrolyte: Chloride, C l minus. Normal serum levels asterisk: 98 to 108 mill equivalent per liter. Imbalance: Hypochloremia, less than 98 mill equivalent per liter. Causes: Decreased C l minus intake or exchange, for example, hyponatremia, excessive water intake, and hypokalemia. Decreased C l minus excretion, for example, diuretics, vomiting, diarrhea, and metabolic alkalosis. Consequences: Metabolic alkalosis. Manifestations: No direct clinical symptoms. Symptoms generally associated with underlying cause, metabolic alkalosis, or hypokalemia. Treatments: Treat underlying cause. Increase oral N a plus and hypertonic I V F to correct hyponatremia. Ammonium chloride. Gastric lavage." "The table consists of seven columns: Electrolyte, normal serum levels asterisk, Imbalance, causes, consequences, manifestations, and treatments. Row entries are as follows. Row 7. Electrolyte: Calcium, C a plus plus. Normal serum levels, asterisk: 4 to 5 mill equivalent per liter or 8.6 to 10.2 milligrams per deciliter. Imbalance: Hypercalcemia, greater than 5 mill equivalent per liter or 10.2 milligrams per deciliter. Causes: Inadequate C a

plus plus intake or release, for example, calcium antacids, supplemental calcium, cancer, immobilization, corticosteroids, vitamin D deficiency, hypophosphatemia, and hypermagnesemia. Deficient C a plus plus excretion, for example, renal failure, thiazide diuretics, and hyperparathyroidism. Consequences: Hyperchloremia. Hypomagnesemia. Hyperphosphatemia. Manifestations: Neuromuscular dysfunction, for example, personality changes, confusion, decreased memory, headache, lethargy, stupor, coma, muscle weakness, and decreased deep tendon reflexes. Cardiovascular dysfunction, for example, short Q T interval, dysrhythmias, and hypertension. Gastrointestinal disturbances, for example, anorexia, nausea, vomiting, abdominal pain, constipation, and pancreatitis. Renal issues, for example, renal calculi, polyuria, renal insufficiency, and dehydration. Treatments: Treat underlying cause. Manage dysrhythmias. Oral phosphate. Increase mobility. Calcitonin. I V F. Diuretics. Row 8. Electrolyte: Calcium, C a plus plus. Normal serum levels asterisk: 4 to 5 mill equivalent per liter or 8.6 to 10.2 milligrams per deciliter. Imbalance: Hypercalcemia, less than 5 mill equivalent per liter or 10.2 milligrams per deciliter. Causes: Excessive C a plus plus losses, for example, hypoparathyroidism, renal failure, hyperphosphatemia, hypomagnesemia, alkalosis, pancreatitis, diarrhea, diuretics, calcitonin, and gentamicin. Deficient C a plus plus intake, for example, malnutrition. Consequences: Hypermagnesemia. Hypophosphatemia. Manifestations: Neuromuscular

dysfunction, for example, anxiety, confusion, depression, irritability, fatigue, lethargy, paresthesia, increased deep tendon reflexes, tremors, muscle spasms, seizures, laryngeal spasms. Cardiovascular dysfunction, for example, prolonged Q T interval, dysrhythmias, and hypotension. Gastrointestinal disturbances, for example, increased bowel sounds, abdominal cramps, and diarrhea. Hematologic dysfunctions, for example, increased bleeding tendency. Skeletal issues, for example, osteomalacia, osteoporosis, and fractures. Treatments: Treat underlying cause. Oral C a plus plus supplements I V calcium gluconate. Vitamin D supplements. Limit phosphorus intake. ” “The table consists of seven columns: Electrolyte, normal serum levels asterisk, Imbalance, causes, consequences, manifestations, and treatments. Row entries are as follows. Row 9. Electrolyte: Phosphorus, P minus. Normal serum levels asterisk: 2.5 to 4.5 milligrams per deciliter. Imbalance: Hyperphosphatemia, greater than 4.5 milligrams per deciliter. Causes: Deficient P minus excretion, for example, renal failure, hypoparathyroidism, adrenal insufficiency, hypothyroidism, and laxatives. Excessive P minus intake or cellular exchange, for example, burns, trauma, hypocalcemia, and acidosis. Consequences: Hypocalcemia. Hypermagnesemia. Manifestations: Similar to manifestations associated with hypocalcemia. Treatments: Treat underlying cause. Limit P minus intake. Aluminum hydroxide or aluminum carbonate. Treat hypocalcemia. Row 10. Electrolyte: Phosphorus, P minus. Normal serum levels

asterisk: 2.5 to 4.5 milligrams per deciliter. Imbalance: Hypophosphatemia, less than milligrams per deciliter. Causes: Excessive P minus excretion or cellular exchange, for example, renal failure, hyperparathyroidism, and alkalosis. Deficient P minus intake, for example, malnutrition, vitamin D deficiency, and hypermagnesemia. Consequences: Hypercalcemia. Hypomagnesemia. Manifestations: Similar to manifestations associated with hypercalcemia. Treatments: Treat underlying cause. Oral P minus supplements I V potassium phosphate. Treat hypercalcemia. Row 11. Electrolyte: Magnesium, M g plus plus. Normal serum levels asterisk: 1.8 to 2.4 mill equivalent per liter. Imbalance: Hypermagnesemia, greater than 2.4 mill equivalent per liter. Causes: Excessive M g plus plus intake, for example, magnesium-containing laxatives or antacids. Deficient M g plus plus excretion, for example, renal failure. Consequences: Hypocalcemia. Hyperphosphatemia. Manifestations: Similar to manifestations associated with hypocalcemia. Treatments: Treat underlying cause. Diuretics. Hypotonic I V F. Dialysis. I V calcium. Row 12. Electrolyte: Magnesium, M g plus plus. Normal serum levels asterisk: 1.8 to 2.4 mill equivalent per liter. Imbalance: Hypomagnesemia, less than 1.8 mill equivalent per liter. Causes: Deficient M g plus plus intake, for example, malnutrition. Excessive M g plus plus excretion, for example, diarrhea and diuretics. Consequences: Hypercalcemia. Hypophosphatemia. Manifestations: Similar to manifestations associated with hypercalcemia. Treatments:

Treat underlying cause. Oral M g plus plus supplements I V M g plus plus. Row 13. Electrolyte: Bicarbonate, H C O 3. Normal serum levels asterisk: 22 to 26 mill equivalent per liter. Imbalance: Metabolic acidosis, less than 22 mill equivalent per liter. Causes: H C O 3 deficits, for example, diarrhea and renal failure. Acid excess, for example, tissue hypoxia, ketoacidosis, and poisonings. Consequences: Hyperchloremia. Hyperkalemia. Hyperphosphatemia. Manifestations: Neuromuscular dysfunction, for example, headache, malaise, weakness, fatigue, lethargy, and coma. Cardiovascular dysfunction, for example, dysrhythmias, hypotension, and shock. Gastrointestinal disturbances, for example, anorexia, nausea, and vomiting. Respiratory dysfunction, for example, Kussmaul respirations. Treatments: Treat underlying cause I V H C O 3. Correct electrolyte disturbances. Improve oxygenation, for example, supplemental oxygen and mechanical ventilation. Row 14. Electrolyte: Bicarbonate, H C O 3. Normal serum levels, asterisk: 22 to 26 mill equivalent per liter. Imbalance: Metabolic alkalosis, greater than 26 mill equivalent per liter. Causes: H C O 3 excess, for example, antacids and hypochloremia. Acid deficits, for example, vomiting, hypokalemia, renal failure, diuretics, hyperaldosteronism. Consequences: Hypochloremia. Hypokalemia. Hypocalcemia. Hypophosphatemia. Manifestations: Neuromuscular dysfunction, for example, confusion, hyperactive reflexes, paresthesia, tetany, seizures, and coma. Cardiovascular dysfunction, for example,

dysrhythmias. Respiratory dysfunction, for example, respiratory depression. Treatments: Treat underlying cause. I V F. Correct electrolyte disturbances. Diamox. Arginine hydrochloride. Weak hydrochloric acid solution. Asterisk reads, Values may vary slightly." The table consists of seven columns: Electrolyte, normal serum levels asterisk, imbalance, causes, consequences, manifestations, and treatments. Row entries are as follows. Row 5. Electrolyte: Potassium, K plus. Normal serum levels asterisk: 3.5 to 5 mill equivalent per liter. Imbalance: Hyperkalemia, greater than 5 mill equivalent per liter. Causes: Deficient K plus excretion, for example, renal failure, Addison's disease, potassium-sparing diuretics, N S A I Ds, A C E inhibitors, and Gordon syndrome. Excessive K plus intake, for example, supplemental potassium and salt substitutes. Increased K plus release from cells, for example, acidosis, blood transfusions, and burns. Consequences: Hyperchloremia. Hyponatremia. Metabolic acidosis. Manifestations: Cardiovascular dysfunction, for example, peaked T wave, depressed S T segment, bradycardia, and cardiac arrest. Neuromuscular dysfunction, for example, weakness, paresthesia, muscle cramps, flaccid paralysis, and anxiety. Respiratory dysfunction, for example, respiratory depression. Gastrointestinal disturbances, for example, abdominal cramping, nausea, and diarrhea. Treatments: Treat underlying cause prior to correcting the hyperkalemia. Calcium gluconate to minimize dysrhythmias. Decrease K plus intake. Kayexalate. I V F. Potassium-losing diuretics.

Dialysis. Insulin infusion with glucose-containing I V F. Row 6. Electrolyte: Potassium, K plus. Normal serum levels asterisk: 3.5 to 5 mill equivalent per liter. Imbalance: Hypokalemia, less than 3.5 mill equivalent per liter. Causes: Excessive K plus loss, for example, vomiting, diarrhea, potassium-losing diuretics, corticosteroids, and Cushing syndrome. Deficient K plus intake, for example, malnutrition. Increased K plus shift into cells, for example, alkalosis and insulin excess. Consequences: Hypochloremia. Hypernatremia. Metabolic alkalosis. Manifestations: Cardiovascular dysfunction, for example, flattened T wave, depressed S T segment, presence of a U wave, hypotension, irregular pulse, and cardiac arrest). Neuromuscular dysfunction, for example, weakness, paresthesia, muscle cramps, hyporeflexia, and confusion. Gastrointestinal disturbances, for example, anorexia, abdominal distention, nausea, constipation, and decreased bowel sounds. Treatments: Treat underlying cause. Oral K plus supplements. I V F with K plus.

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The table consists of five columns: Acid-base disorder, p H, P a C O 2, H C O 3, and compensation. Row entries are as follows. Row 1. Respiratory acidosis. Less than 7.4, A. Greater than 45 millimeters of mercury, A. Normal. H C O 3 greater than 26 milliequivalents per liter, B. Row 2. Respiratory alkalosis. Greater than 7.4, B. Less than 35 millimeters of mercury, B. Normal. H C O 3 less than 22 milli equivalents per liter, A. Row 3. Metabolic acidosis. Less than

7.4, A. Normal. Less than 22 mill equivalents per liter, A. P a C O 2 less than 35 millimeters of mercury, B. Row 4. Metabolic alkalosis. Greater than 7.4, B. Normal. Greater than 26 milliequivalents per liter, B. P a C O 2 greater than 45 millimeters of mercury, A.

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The table consists of seven columns: Causes, onset, location, characteristics, description, radiation, and intensity. Row entries are as follows. Row 1. Appendicitis. Usually gradual but can be sudden. Periumbilical early; R L Q late. Diffuse early, localized late. Ache. None. plus plus to plus plus plus. Row 2. Cholecystitis. Sudden. R U Q or M U Q. Localized. Cramping. Back or right shoulder. plus plus. Row 3. Acute Pancreatitis. Sudden. Epigastric, upper abdominal. Localized. Blunt. Back. plus plus to plus plus plus. Row 4. Diverticulitis. Gradual. L L Q. Localized. Ache. None. plus to plus plus. Row 5. Perforated peptic ulcer. Sudden. Epigastric. Localized early, diffuse late. Burning sensation. None. plus plus plus. Row 6. Small bowel obstruction. Gradual. Periumbilical. Diffuse. Cramping. None. plus plus. Row 7. Ruptured abdominal aortic aneurysm. Sudden. Abdominal back, flank. Diffuse. Tearing. None. plus plus plus. Row 8. Gastroenteritis. Gradual. Periumbilical, epigastric. Diffuse. Cramping. None. plus to plus plus. Row 9. Pelvic inflammation disease. Gradual. L Q, pelvic. Localized. Blunt. Upper thigh. plus plus to plus plus plus. Row 10. Ruptured

ectopic pregnancy. Gradual. L Q, pelvic. Localized. Sharp. None. plus plus.

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The table consists of six columns: Characteristic, type A, type B, type C, type D, and type E. Row entries are as follows. Row 1. Mode of transmission. Waterborne. Perinatal. Venereal. Venereal. Waterborne. Row 2. Mode of transmission. Fecal–oral. Blood or skin. Blood or skin. Blood. Fecal–oral. Row 3. Mode of transmission. Venereal. Venereal. No data. No data. Perinatal. Row 4. Incubation period, ranges in days. 15 to 42. 42 to 160. 14 to 160. 28 to 180. 14 to 56. Row 5. Onset. Abrupt. Insidious. Insidious. Insidious. Abrupt. Under head symptoms, row entries are as follows. Row 6. Fever. Common. Uncommon. Uncommon. Common. Common. Row 7. Nausea or vomiting. Common. Common. Common. Common. Common. Row 8. Jaundice. More common in adults than in children. Occasionally. Uncommon. Common. Common. Under head outcome, row entries are as follows. Row 9. Severity. Mild. Moderate. Mild. Moderate to severe. Severe. Row 10. Fulminating hepatitis. less than 0.5 percent. Greater than 1 percent. Rare. 3 to 4 percent with coinfection with hepatitis B. 0.3 to 3 percent, 20 percent in pregnant women. Row 11. Mortality rate. Low, less than 1 percent. Low, 1 to 3 percent. Low, 2 percent. High, 5 percent. Moderate; high with pregnancy. Row 12. Chronic hepatitis. No. Yes, 5 to 10 percent. Yes, 80 percent. Less than 5 percent with coinfection, 80 percent with

superinfection. Rare, usually associated with immunodeficiency. Row 13. Carrier state. No. Yes, 1 million in the United States. Yes. Yes. No. Row 14. Relapse. Yes. Yes. Persistent. Unknown. Unknown. Row 15. Carcinoma. No. Yes, 25 to 40 percent. Yes, 25 to 30 percent. No increase above that for hepatitis B. Unknown but not likely. Row 16. Develop cirrhosis. No. 40 percent. 30 percent. Yes, with superinfection. Rare. Row 17. Source of virus. Feces. Blood or blood-derived body fluids. Blood or blood-derived body fluids. Blood or blood-derived body fluids. Feces. Row 18. Chronic infection. No. Yes. Yes. Yes. Yes. Row 19. Prevention. Pre- or post-exposure immunization. Pre- or post-exposure immunization. Blood donor screening; risk behavior modification. Pre- or post-exposure immunization; risk behavior modification. Ensure safe drinking water.

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The table consists of two main columns: Inflammatory bowel disease and irritable bowel syndrome. Inflammatory bowel disease is further divided into two columns: Ulcerative colitis and Crohn’s disease. Row entries are as follows. Row 1. Epidemiology: Gradual, progressive onset. Insidious onset. Late teens and early adulthood. Row 2. Epidemiology: Peak ages 15 to 30. Ages 15 to 40. No data. Row 3. Epidemiology: Caucasian greater than African American. Female is greater than male. Female is greater than male. Row 4. Epidemiology: Female greater than male. No data. No data. Row 5. Pathology: Possible autoimmune infection

may precipitate familial tendency. Possible autoimmune infection may precipitate genetic predisposition. Cause unknown. Row 6. Pathology: Continuous, irregular superficial inflammation of mucosal layer of colon and rectum. Skipping ulcerations involving mucosal and submucosal layers along the entire G I tract; 50 percent involve small intestine or colon. Increased bowel response to stimuli and visceral hypersensitivity. Row 7. Pathology: Strictures and fistulas uncommon. Strictures and fistulas common. Altered perception of central nervous system. Under head signs and symptoms, row entries are as follows. Row 8. Abdominal pain: Intermittent, mild crampy tenderness. Crampy or steady, periumbilical or right lower quadrant. Sharp, burning; may be diffuse or affect only left lower quadrant. Row 9. Mass present: No. Common. No. Row 10. Bleeding: Common. Occasionally. No. Row 11. Diarrhea: Frequent watery stools with blood and mucus. Chronic, recurrent; may have some blood. Intermittent, predominant, Symptom varies with individual. Row 12. Perianal lesions: No. One-third develop perianal abscesses or fistulas. No. Row 13. Weight loss: With severe diarrhea. Common. No. Row 14. Fever or malaise: During severe exacerbation. With exacerbation and abscess formation. No. Row 15. Psychological: As a result of long-standing disease. As a result of long-standing disease. Exacerbation with stressful situations. Row 16. Course and prognosis: 75 to 80 percent relapse after first attack, most have mild to moderate disease, routine colonoscopy with biopsy after having the disease for 7 to 8

years because of increased colon cancer risk. Recurrent, progressive, typically need surgery after 7 years to treat or repair fistulas or abscesses, shortened life span. Chronic, intermittent, rare functional limitations.

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The table consists of four columns: Neurotransmitter, receptor, primary locations, and responses. Row entries are as follows. Row 1. Acetylcholine, cholinergic. Nicotinic. Postganglionic neurons. Stimulation of smooth muscle and gland secretions. Row 2. Acetylcholine, cholinergic. Muscarinic. Parasympathetic target: organs other than the heart. Stimulation of smooth muscle and gland secretions. Row 3. Acetylcholine, cholinergic. Muscarinic. Heart. Decreased heart rate and force of contraction. Row 4. Norepinephrine, adrenergic. Alpha subscript 1. All sympathetic target organs except the heart. Constriction of blood vessels, dilation of pupils. Row 5. Norepinephrine, adrenergic. Alpha subscript 2. Presynaptic adrenergic nerve terminals. Inhibition of release of norepinephrine. Row 6. Norepinephrine, adrenergic. Beta subscript 1. Heart and kidneys. Increased heart rate and force of contraction; release of rennin. Row 7. Norepinephrine, adrenergic. Beta subscript 2. All other sympathetic target organs. Dilation of bronchial passages; vasodilation in muscles and liver; relaxation of uterine muscle; release of insulin.

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The table consists of four columns: Type of dementia, history, clinical manifestations, and pathophysiology. Row entries are as follows. Row 1. Type of dementia: Alzheimer's disease, 50 to 80 percent of all dementia cases. History: Gradual, progressive onset. Clinical manifestations: Memory loss, especially for names and recent events, language deficits, rapid forgetting, impaired visuospatial skills, normal gait and neurologic exam early, later affective disturbances; behavioral symptoms such as aggression. Pathophysiology: Generalized atrophy, for example, medial temporal, beta-amyloid plaques, neurofibrillary tangles. Row 2. Type of dementia: Vascular, 20 to 30 percent. History: Abrupt or gradual onset. Clinical manifestations: Focal neurologic signs, signs of vascular disease. Pathophysiology: Strokes, lacunar infarcts, white matter lesions, vulnerable to cerebrovascular events. Row 3. Type of dementia: Lewy body, 10 to 25 percent. History: Insidious onset; progressive without fluctuations. Clinical manifestations: Fluctuating cognition, visual hallucinations, neuroleptic sensitivity, shuffling gait, increased tone, tremors, falls. Pathophysiology: Generalized atrophy, lewy bodies in cortex and midbrain. Row 4. Type of dementia: Frontotemporal, 10 to 15 percent. History: Insidious onset; typically in 50s to 60s; rapid progression. Clinical manifestations: Disinhibition, socially inappropriate behavior, poor judgment, apathy, decreased motivation, poor executive function. Pathophysiology: Frontal and temporal atrophy, pick cells and Pick bodies in cortex.

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The table consists of four columns: Grade, degree of damage, pathophysiology, and clinical findings and implications. Row entries are as follows. Row 1. Grade 1. Minimal damage or disruption. Microscopic tearing of collagen fibers; joint is stable. Tender without swelling; no bruising; active and passive range of motion are painful prognosis is good, with no expectation of instability or functional loss. Row 2. Grade 2. Moderate damage. Complete tears of some but not all collagen fibers in the ligament. Moderate swelling and bruising; very tender, with more diffuse tenderness than grade 1; range of motion is very painful and restricted; joint may be unstable, and functional loss may result. Row 3. Grade 3. Complete disruption of the ligament. Complete tear or rupture of ligament. Prognosis is variable, injury may require surgery; requires a prolonged healing or rehabilitation period.

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The table consists of three columns: Osteoarthritis, Rheumatoid arthritis, and gout. Row entries are as follows. Row 1. Age and sex of usual patient: Adults, older persons, both sexes, more common in females. Young and middle-aged, female. Middle-aged, male. Row 2. Major characteristic: Wear and tear; degeneration of articular cartilage. Systemic disease with major effects in joints; causes chronic synovitis. Disturbance of purine metabolism;

acute episodes caused by accumulation of uric acid crystals in joints. Row 3. Secondary effects of disease: Overgrowth of bone; thickening of periarticular soft tissues. Ingrowth of inflammatory tissue over cartilage destroys cartilage, leads to destruction of joint space; deformities are common. Deposits of uric acid in joints with damage to joints, gouty arthritis; soft-tissue tophi. Row 4. Joints usually affected: Major weight-bearing joints. Small joints of hands and feet. Small joints; joint at base of great toe often affected. Row 5. Special features: No systemic symptoms or biochemical abnormalities. Autoantibody against gamma globulin, rheumatoid factor. High blood level of uric acid.

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The table consists of the following text. Target population: Patients, 1, who have at least one joint with clinical synovitis and, 2, in whom the synovitis not better explained by another disease. The table consists of one column: Score. Under head A. Joint involvement, tender or swollen, row entries are as follows. Row 1. 1 large joint. 0. Row 2. 2 to 10 large joints. 1. Row 3. 1 to 3 small joints, plus or minus involvements of large joints. 2. Row 4. 4 to 10 small joints, plus or minus involvements of large joints. 3. Row 5. Greater than 10 joints, at least 1 small joint. 5. Under head B. Serology, row entries are as follows. Row 6. Negative R F and A C P A. 0. Row 7. Low-positive R F or low-positive A C P A. 2. Row 8. High-positive R F or high-positive A C P A. 3. Under head C. Acute-phase reactants, row entries are as follows. Row 9.

Normal C R P and E S R. 0. Row 10. Abnormal C R P and E S R. 1. Under head D. Duration of symptoms, row entries are as follows. Row 11. less than 6 weeks. 0. Row 12. Greater than 6 weeks. 1. Row 13. Add score of categories A to D: Greater than or equal to 6 over 10 equals definite R A.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 1. Abdomen. Abdomen forward slash o. Abdomen. Abdominocentesis. Row 2. Acanth. No data. Thorn. acanthosis. Row 3. Achilles. Achill forward slash o. Achilles' heel. Achillobursitis. Row 4. Acid. Acid forward slash o. Acid, p H. Acidosis. Row 5. Acoust. Acoust forward slash o. hearing. acoustics. Row 6. Acr. Acr forward slash o. extremity. acroarthritis. Row 7. Actin. Actin forward slash o. ray. actinodermatitis. Row 8. Acu. Acul forward slash o. needle. acupuncture. Row 9. Aden. aden forward slash o. gland. adenosis. Row 10. Adip. Adip forward slash o. fat. adipocyte. Row 11. Adren. adren forward slash o. adrenal gland. adrenomegaly. Row 12. Aer. aer forward slash o. air. aerophore. Row 13. Agglutinat. agglutinat forward slash o. clumping. agglutination. Row 14. Albin. albin forward slash o. white. albinuria. Row 15. Albumin. albumin forward slash o. protein. albuminuria. Row 16. Alkali. alkali forward slash o. basic, p H. alkalosis. Row 17. All. all forward slash o. other. allochromasia. Row 18. Alveoli. alveol forward slash o. small hole, air sac. alveoloclasia. Row 19. Ambly. ambly forward slash o. dull. amblyopia. Row 20. Ambul. ambul

forward slash o. walk. ambulate. Row 21. Ametr. ametr forward slash o. disproportionate. ametropia. Row 22. Amnion. amni forward slash o. amnion. amniocentesis. Row 23. Amyl. amyl forward slash o. starch. amylorrhea. Row 24. Andr. andr forward slash o. man, male. androgenus. Row 25. Angi. angi forward slash o. vessel. angioplasty. Row 26: Angina. angin forward slash o. choke. anginose. The table consists of four columns: root word, combining form, definition, and example. Under A, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 27: Aniso. anis forward slash o. unequal. anisocytosis. Row 28: Ankyl. ankyl forward slash o. stiffened, crooked. ankylosis. Row 29: Anthrac. anthrac forward slash o. coal. anthracosis. Row 30: Antr. antr forward slash o. cavity. antroscopy. Row 31: Anus. an forward slash o. anus. anoscope. Row 32: Aort. aort forward slash o. aorta. aortography. Row 33. Append. append forward slash o. appendix. appendectomy. Row 34: Arachn. arachn forward slash o. spider. arachnoid. Row 35: Arteri. arteri forward slash o. artery. arterial. Row 36: Arthr. arthr forward slash o. joint. arthroscopy. Row 37: Atel. atel forward slash o. imperfect, incomplete. atelectasis. Row 37: Ather. ather forward slash o. fatty. atherosclerosis. Row 39: Atri. atri forward slash o. atrium, chamber. atriomegaly. Row 40: Audi. audi forward slash o. hear. audiology. Row 41: Aur. aur forward slash o. ear. aural. Row 42: Axill. axill forward slash

o. armpit. axillary. Under B, row entries are as follows. Row 43: Bacteri. Bacteri forward slash o. bacteria. bacteriuria. Row 44: Balan. balan forward slash o. glans. balanitis. Row 45: Bas. bas forward slash o. base, p H. basophyl. Row 46: Bil. bil forward slash i. gall, bile. biliary. Row 47: Bilirubin. bilirubin forward slash o. bilirubin. hyperbilirubinism. Row 48: Bio. bi forward slash o. life. biosphere. Row 49: Blephar. blephar forward slash o. eyelid. blepharitis. Row 50: Bol. bol forward slash o. cast, throw. anabolic. Row 51: Brachy. brachy forward slash o. arm. brachyocephalic. Row 52: Bronch. bronch forward slash . bronchi. bronchitis. Row 53: Bucc. bucc forward slash o. cheek. buccocclusion. Row 54: Burs. burs forward slash o. pouch. bursitis. Under C, row entries are as follows. Row 55: Cac. cac forward slash o. bad, diseased. cachexia. Row 56: Calc. calc forward slash i. calcium. calciuria. Row 57: Calcane. calcane forward slash o. heel bone. calcaneodynia. Row 58: Capn. capn forward slash i. smoke, carbon dioxide. hypercapnia. Row 59: Carcin. carcin forward slash o. cancer. carcinoma. Row 60: Cardi. cardi forward slash o. heart. cardioplagia. The table consists of four columns: root word, combining form, definition, and example. Under C, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 61: Carp. carp forward slash o. wrist. carpopedal. Row 62: Cata. cat forward slash a. down, downward. catatonic. Row 63: Caud. caud forward

slash o. tail. caudal. Row 64: Caus. caus forward slash o. heat. causalgia. Row 65: Cecum. cec forward slash o. cecum. cecoileostomy. Row 66: celi. celi forward slash o. abdomen. celioma. Row 67: Centr. centr forward slash i. center. centrilobular. Row 68: Cephal. cephal forward slash o. head. cephalhydrocele. Row 69: Cerebell. cerebell forward slash o. little brain, cerebellum. cerebellospinal. Row 70: Cerebr. cerebr forward slash o. brain, cerebrum. cerebromalacia. Row 71: Cerumin. cerumin forward slash o. wax. ceruminolysis. Row 72: Cervic. cervic forward slash o. neck. cervicofacial. Row 73: Cheil. cheil forward slash o. lip. cheilosis. Row 74: Chem. chem forward slash o. chemical. chemotherapy. Row 75: Cholangi. cholangi forward slash o. bile vessel. cholangioma. Row 76: Chole. chole forward slash o. gall, bile. cholecystogram. Row 77: Choledoch. choledoch forward slash o. common bile duct. choledochotomy. Row 78: Cholester. cholester forward slash o. cholesterol, fat. cholesterosis. Row 79: chondr. chondr forward slash o. cartilage. chondrocarcinoma. Row 80: Chori. chori forward slash o. chorion. chorioadenonia. Row 81: Choroid. choroid forward slash o. choroid. choroiditis. Row 82: Cine. cine forward slash o. motion. cineradiography. Row 83: Cinemato. cinemat forward slash o. motion. cinematoradiograph. Row 84: Cirrho. cirrh forward slash o. yellow, tawny. cirrhosis. Row 85: Cis. cis forward slash o. cut. excision. Row 86: Cistern. cistern forward slash o. reservoir, cavity. cisternography. Row 87: Clavic. clavic forward slash o. clavicle. clavicotomy. Row 88: Clavicul. clavicul forward

slash o. clavicle. clavicular. Row 89: Cleid. cleid forward slash o. clavicle. cleidorrhexis. Row 90: clon. clon forward slash o. turmoil. clonogenic. Row 91: Coagul. coagul forward slash o. clot. coagulopathy. Row 92: Coccidioid. coccidioid forward slash o. fungus. coccidioidmycosis. Row 93: Coccyx. coccyg forward slash o. tail bone. coccygodynia. Row 94: Cochle. cochle forward slash o. snail. cochleotopic. Row 95: Coit. coit forward slash o. coming together. coitis. The table consists of four columns: root word, combining form, definition, and example. Under C, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 96: Coll. coll forward slash o. glutinous, jelly-like. colragenitis. Row 97: Colon. colon forward slash o. colon. colonoscopy. Row 98: Colp. colp forward slash o. vagina. colporrhapy. Row 99: Condyl. condyl forward slash o. knuckle. condyloma. Row 100: Coni. coni forward slash o. dust. coniosis. Row 101: Copr. copr forward slash o. feces, excrement. coprostasis. Row 102: Cord. cord forward slash o. cord. cordotomy. Row 103: Coria. cori forward slash o. pupil, eye. diplocoria. Row 104: Cortic. cortic forward slash o. cortex. corticosterone. Row 105: Cost. cost forward slash o. rib. costosternal. Row 106: Cox. cox forward slash o. hip. coxalgia. Row 107: Crani. crani forward slash o. skull. craniotomy. Row 108: Cretin. cretin forward slash o. cretin. cretinism. Row 109: Crin. crin

forward slash o. secrete. endocrinology. Row 110: Crypt. crypt forward slash o. hidden. cryptorchism. Row 111: Culd. culd forward slash o. cul-de-sac. culdocentesis. Row 112: Cutane. cutan forward slash o. skin. subcutaneous. Row 113: cycl. cycl forward slash o. ciliary body. cycloplegia. Row 114: Cyst. cyst forward slash o. bladder. cystistaxia. Row 115: Cyt. cyt forward slash o. cell. cytoplasm. Under D, row entries are as follows. Row 116: Dacry. dacry forward slash o. tear. dacryoma. Row 117: Dactyl. dactyl forward slash o. finger, toe. dactylospasm. Row 118: Dem. dem forward slash o. people. endemic. Row 119: Dendr. dendr forward slash o. branched. dendritis. Row 120: Dent. dent forward slash i. tooth. dentifrice. Row 121: Derm. derm forward slash o. skin. dermomycosis. Row 122: Dermat. dermat forward slash o. skin. dermatitis. Row 123: Didym. didym forward slash o. testis. didymalgia. Row 124: Dilat. dilat forward slash o. widen. dilation. Row 125: Dipl. dipl forward slash o. double. diplopia. Row 126: Dips. dips forward slash o. thirst. dipsomania. Row 127: Disk. disk forward slash o. disk. diskectomy. Row 128: Diverticul. diverticul forward slash o. diverticula. diverticulitis. Row 129: Dont. dont forward slash o. tooth. oligodontia. Row 130: Dos. dos forward slash i. giving. dosimeter. The table consists of four columns: root word, combining form, definition, and example. Under D, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 131: Duoden. Duoden forward slash o. duodenum. duodenostomy. Row 132: Dur. Dur forward slash o. hard. duroarachnitis. Under E, row entries are as follows. Row 133: electr. electr forward slash o. electricity. electrocardiogram. Row 134: Embol. embol forward slash o. throwing in. embolism. Row 135: Emmetr. emmetr forward slash o. ideal. emmetropia. Row 136: Emphys. emphys forward slash o. inflate. emphysema. Row 137: Encephal. encephal forward slash o. brain. encephalogram. Row 138: Enter. enter forward slash o. intestine. enteritis. Row 139: Epidem. epidem forward slash o. upon people. epidemic. Row 140: Epididym. epididym forward slash o. epididymis. epididymectomy. Row 141: Episi. episi forward slash o. vulva, pudenda. episiotomy. Row 142: Erythrocyt. erythrocyt forward slash o. red blood cell. erythrocytosis. Row 143: Esophage. esophag forward slash o. esophagus. esophagocele. Row 144: Esthesi. esthesi forward slash o. feeling. anesthesia. Under F, row entries are as follows. Row 145: Fasci. fasci forward slash o. hand. fasciodis. Row 146: Fibr. fibr forward slash o. fiber. fibroma. Row 147: Fibrin. fibrin forward slash o. fiber. fibrinogen. Row 148: Fibul. fibul forward slash o. fibula. fibular. Row 149: Fluor forward slash o. fluor forward slash o. fluorescence. fluoroscopy. Row 150: Foramin. foramin forward slash o. foramen, opening. foraminoctomy. Row 151: Format. format forward slash o. formation. malformation. Under G, row entries are as follows. Row 152: Galact. galact forward slash

o. milk. galactorrhea. Row 153: Gangli. gangli forward slash o. knot. ganglionectomy. Row 154: Gastr. gastr forward slash o. stomach. gastritis. Row 155: Gen. gen forward slash o. beginning, origin. genesis. Row 156: Genet. genet forward slash o. producing. genetics. Row 157: Genit. genit forward slash o. genitals. genitourinary. Row 158: Genital. genital forward slash o. genitals. hypogenitalia. Row 159: Ger. ger forward slash o. old age. geriatric. Row 160: Geront. geront forward slash o. aged. gerontology. Row 161: Gigant. gigant forward slash o. giant. gigantism. Row 162: Gingiv. gingiv forward slash o. gums. gingivitis. The table consists of four columns: root word, combining form, definition, and example. Under G, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 163: Glandul. glandul forward slash o. little acorn, gland. glandular. Row 164: Glomerul. glomerul forward slash o. little ball. glomerulitis. Row 165: Gloss. gloss forward slash o. tongue. glossopharyngeal. Row 166: Gluc. gluc forward slash o. glucose, sugar. glucocorticoid. Row 167: Glyc. glyc forward slash o. sugar. glycogenesis. Row 168: Gonad. gonad forward slash o. ovaries, testes. gonadotropin. Row 169: Goni. goni forward slash o. angle. gonioscope. Row 170: Granul. granul forward slash o. granular. granulocyte. Row 171: Gravid. gravid forward slash o. pregnant. primigravida. Row 172: Gynec. gynec forward slash o. female. gynecology. Under H, row

entries are as follows. Row 173: Halat. halat forward slash o. breathe. inhalation. Row 174: Hem. hem forward slash o. blood. hemoglobin. Row 175: Hemat. hemat forward slash o. blood. hematocrit. Row 176: Hepat. hepat forward slash o. liver. hepatoma. Row 177: Herni. herni forward slash o. hernia. herniotomy. Row 178: Hidr. hidr forward slash o. sweat. anhidrosis. Row 179: Hirsut. hirsut forward slash o. hair. hirsutism. Row 180: Hist. hist forward slash o. tissue. histology. Row 181: Hol. hol forward slash o. whole. holography. Row 182: Humer. humer forward slash o. humerus. humeral. Row 183: Hydr. hydr forward slash o. water. hydrocele. Row 184: Hymen. hymen forward slash o. hymen. hymenectomy. Row 185: Hypn. hypn forward slash o. sleep. hypnosis. Row 186: Hyster. hyster forward slash o. womb, uterus. hysterectomy. Under I, row entries are as follows. Row 187: Ichthy. ichthy forward slash o. fish, scaly. ichthyosos. Row 188: Icter. icter forward slash o. jaundice. icterogenic. Row 189: Ile. ile forward slash o. ileum. ileostomy. Row 190: Ili. ili forward slash o. ilium. iliosacral. Row 191: Immun. immun forward slash o. safe, protect. immunotherapy. Row 192: Insul. insul forward slash o. pancreatic islets. insuloma. Row 193: Insulin. insulin forward slash o. insulin. insulinogenic. Row 194: Ion. ion forward slash o. ion. ionoradioscope. Row 195: Irid. irid forward slash o. iris. iridomalacia. The table consists of four columns: root word, combining form, definition, and example. Under I, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 196: Ischem. Ischem forward slash o. hold back. ischemic. Row 197: Ischi. ischi forward slash o. hip. ischiodynia. Under J, row entries are as follows. Row 198: Jejun. jejun forward slash o. jejunum. jejunotomy. Under K, row entries are as follows. Row 199: Kary. kary forward slash o. nucleu, cell. karyotype. Row 200: Kel. kel forward slash o. tumor. keloid. Row 201: Kerat. kerat forward slash o. cornea. keratitis. Row 202: Ket. ket forward slash o. ketone. ketosis. Row 203: Kinesi. kinesi forward slash o. motion. bradykinesia. Row 204: Kinet. kinet forward slash o. motion. kinetosis. Row 205: Kyph. kyph forward slash o. hump. kyphosis. Under L, row entries are as follows. Row 206: Labyrinth. labyrinth forward slash o. maze. labyrinthitis. Row 207: Lacrim. lacrim forward slash o. tear. lacrimotomy. Row 208: Lamin. lamin forward slash o. shin plate. laminectomy. Row 209: Lapar. lapar forward slash o. flank, abdomen. laparotomy. Row 210: Laryng. laryng forward slash o. larynx. laryngoscope. Row 211: Later. later forward slash o. side. lateroflexion. Row 212: Laxat. laxat forward slash o. loosen. laxative. Row 213: Lei. lei forward slash o. smooth. leiomyosarcoma. Row 214: letharg. letharg forward slash o. drowsiness. lethargy. Row 215: lingu. lingu forward slash o. tongue. nigralingua. Row 216: Lip. lip forward slash o. fat. lipoatrophy. Row 217: Lith. lith forward slash o. stone. lithotripsy. Row 218: Lob. lob forward slash o. lobe. lobotomy. Row 219: log. log forward slash o. word, study. logomania. Row 220: Lord. lord forward slash o. bending, curvature.

lordosis. Row 221: Lumb. lumb forward slash o. loin. lumbodynia. Row 222: Lymph. lymph forward slash o. lymph, lymph gland. lymphoma. Under M, row entries are as follows. Row 223: Mamm. mamm forward slash o. breast. mammogram. Row 224: Mandibul. mandibul forward slash o. lower jaw. mandibular. Row 225: Mast. mast forward slash a. breast. mastectomy. Row 226: Maxill. maxill forward slash o. upper jaw. maxillotomy. The table consists of four columns: root word, combining form, definition, and example. Under M, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 227: Meat. Meat forward slash o. passage. meatotomy. Row 228: Mediastin. mediastin forward slash o. mediastinum. mediastinits. Row 229: Medull. medull forward slash o. marrow, spinal. medulloepithelioma. Row 230: Melan. melan forward slash o. black. melanoma. Row 231: Men. men forward slash o. month, menstruate. dysmenorrheal. Row 232: Mening. mening forward slash o. membrane. meningitis. Row 233: Menisc. menisc forward slash o. crescent shape. meniscitis. Row 234: Metr. metr forward slash o. uterus. metritis. Row 235: Micturit. micturit forward slash o. urinate. micturition. Row 236: Mitr. mitr forward slash o. mitral valve. mitral. Row 237: Morph. morph forward slash o. form, shape. morphology. Row 238: Muc. muc forward slash o. mucus. mucositis. Row 239: Muscul. muscul forward slash o.

muscle. musculoskelectal. Row 240: My. my forward slash o. muscle. myoblast. Row 241: Myc. myc forward slash o. fungus. mycosis. Row 242: Myel. myel forward slash o. spinal cord. myeloma. Row 243: Myring. myring forward slash o. membrane, mucus. myringoplasty. Under N, row entries are as follows. Row 244: Narc. narc forward slash o. night, sleep. narcosis. Row 245: Nas. nas forward slash o. nose. nasogastric. Row 246: Necr. necr forward slash o. death. necrosis. Row 247: Nephr. nephr forward slash o. kidney. nephrema. Row 248: Neur. neur forward slash o. nerve. neuroma. Row 249: Neutr. neutr forward slash o. neither, neutral, p H. neutrophyl. Row 250: Noct. noct forward slash o. night. nocturia. Row 251: Nucle. nucle forward slash o. nucleus, central. nuclear. Row 252: Nyct. nyct forward slash o. night. nyctalgia. Row 253: Nyctal. nyctal forward slash o. blind, night. nyctalopia. Under O, row entries are as follows. Row 254: Ocul. ocul forward slash o. eye. oculopupillary. Row 255: Olecran. olecran forward slash o. elbow. olecranarthopathy. Row 256: Oment. oment forward slash o. omentun. omentectomy. Row 257: Omphal. omphal forward slash o. umbilicus. omphalitis. Row 258: Onc. onc forward slash o. tumor. oncology. Row 259: Onych. onych forward slash o. nail. onychitis. Row 260: Oophor. oophor forward slash o. ovary. oophoritis. The table consists of four columns: root word, combining form, definition, and example. Under O, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 261: Ophthalm. Ophthalm forward slash o. eye. ophthalmopathy. Row 262: Opt. opt forward slash o. eye. optomyometer. Row 263: Orchi. orchi forward slash o. testicle. orchitis. Row 264: Orchid. orchid forward slash o. testicle. orchidopexy. Row 265: Organ. organ forward slash o. organ. organomegaly. Row 266: Oscill. oscill forward slash o. swing. oscillopsia. Row 267: Osm. osm forward slash o. smell. anosmia. Row 268: Oste. oste forward slash o. bone. osteorrhapy. Row 269: Ot. ot forward slash o, ov forward slash i, ov forward slash o. ear, egg. otosclerosis, oviduct, ovoplasm. Row 270: Ovul. ovul forward slash o. egg, ovum. ovulate. Row 271: Ox. ox forward slash o. oxygen. anoxia. Row 272: Oxy. oxy forward slash o. oxygen. oxytoxin. Under P, row entries are as follows. Row 273: Palat. palat forward slash o. palate. palatitis. Row 274: Pancreat. pancreat forward slash o. pancreas. pancreatitis. Row 275: Papill. papill forward slash o. papilla. papilledema. Row 276: Par. par forward slash o. bear. paroxysm. Row 277: Parathyr. parathyr forward slash o. parathyroid gland. parathyroidism. Row 278: Patell. patell forward slash o. patella, kneecap. patellapexy. Row 279: Path. path forward slash o. disease. pathology. Row 280: Ped. ped forward slash o. foot. pedal. Row 281: Ped. ped forward slash i. child. pediatrics. Row 282: Pedicul. pedicul forward slash o. louse. pediculosis. Row 283: Pen. pen forward slash o. penis. penitis. Row 284: Pept. pept forward slash o. digest. peptogenic. Row 285: Perine. perine forward

slash o. perineum. perineocele. Row 286: Phac. phac forward slash o. lens. phacosclerosis. Row 287: Phag. phag forward slash u. eat, engulf. phagocyte. Row 288: Phalange. phalang forward slash o. finger, toe. phalangectomy. Row 289: Pharmac. pharmac forward slash o. drug. pharmacotherapy. Row 290: Pharyng. pharyng forward slash o. pharynx. pharyngitis. Row 291: Phe. phe forward slash o. dusky, muzzle. pheochromocytoma. Row 292: Phim. phim forward slash o. muscle. phimosis. Row 293: phleb. phleb forward slash o. vein. phlebitis. The table consists of four columns: root word, combining form, definition, and example. Under P, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 294: Phon. phon forward slash o. sound, voice. phonopathy. Row 295: phragm. phragm forward slash o. partition. diaphragm. Row 296: Phragma. phragmat forward slash o. partition. diaphragmatocele. Row 297: Phren. phren forward slash o. diaphragm. phrenoplegia. Row 298: Physi. physi forward slash o. nature. physiology. Row 299: Physic. physic forward slash o. nature. physician. Row 300: Pin. pin forward slash o. drink, pinlitary gland. pinocytosis. Row 301: Pineal. pineal forward slash o. pineal body. pinealoma. Row 302: Pituitar. pituitar forward slash o. pituitary gland. pituitarism. Row 303: Pleur. pleur forward slash o. pleura. pleuritis. Row 304: Pneum. pneum forward slash o. air. pneumothorax. Row 305:

Pneumon. pneumon forward slash o. lung. pneumonitis. Row 306: Poikil. poikil forward slash o. irregular shape, passage. poikilocytosis. Row 307: Por. por forward slash o. passage. poroma. Row 308: Porphyr. porphyr forward slash o. porphyrin, purple. porphyrinuria. Row 309: Presby. presby forward slash o. old. presbycusis. Row 310: Proct. proct forward slash o. rectum, anus. proctatestomy, proctalgia. Row 311: Prostat. prostat forward slash o. prostate. prostatectomy. Row 312: Psych. psych forward slash o. mind. psychology. Row 313: Pteryg. pteryg forward slash o. winglike. pterygomandibular. Row 314: Ptyal. ptyal forward slash o. salvia. ptyalorrhea. Row 315: Pub. pub forward slash o. pubis. pubovesical. Row 316: Pulm. pulm forward slash o. lung. pulmometer. Row 317: Pulmon. pulmon forward slash o. lung. pulmonectomy. Row 318: Pupill. pupill forward slash o. pupil. papillary. Row 319: Py. py forward slash o. pus. pyorrhea. Row 320: Pyel. pyel forward slash o. renal pelvis. pyelonephritis. Row 321: Pylor. pylor forward slash o. pyloris. pyloroplasty. Row 322: Pyr. pyr forward slash o. fire. pyrogenic. Row 323: Pyret. pyret forward slash o. fever. pyretogenic. Under R, row entries are as follows. Row 334: Rachi. rachi forward slash o. spine. rachiomyelitis. Row 335: Radi. radi forward slash o. ray, radius. radionecrosis. Row 336: Radiat. radiat forward slash o. radiant. radiation. Row 337: Rradic. radic forward slash o. root. radicotomy. Row 338: Radicul. radicul forward slash o. root. radiculitis. The table consists of four columns: root word, combining form, definition, and example. Under R, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 339: Rect. rect forward slash o. rectum, loosen. rectocele, relaxation. Row 340: Ren. ren forward slash o. kidney. renogastric. Row 341: Reticul. reticul forward slash o. net, network. reticulocyte. Row 342: Retin. retin forward slash o. retina. retinitis. Row 343: Rhabd. rhabd forward slash o. rod. rhabdomyoma. Row 344: Rhin. rhin forward slash o. nose. rhinorrhagia. Row 345: Rhythm. rhythm forward slash o. rhythm. arrhythmia. Row 346: Rhytid. rhytid forward slash o. wrinkle. rhytidectomy. Under S, row entries are as follows. Row 347: Sacr. sacr forward slash o. sacrum. sacrodynia. Row 348: Salping. salping forward slash o. tube. salpingopexy. Row 349: Sanguin. sanguin forward slash o. blood. consanguinity. Row 350: Sarc. sarc forward slash o. flesh. sarcoma. Row 351: Scapul. scapul forward slash o. scapula. scapulopexy. Row 352: Schiz. schiz forward slash o. split. schizophrenia. Row 353: Scler. scler forward slash o. hard, fibrous. scleroderma. Row 354: Scoli. scoli forward slash o. curvature. scoliosis. Row 355: Scot. scot forward slash o. dark. scotoma. Row 356: Seb. seb forward slash o. oil. seborrhea. Row 357: Senil. senil forward slash o. old. senilism. Row 358: Ser. ser forward slash o. serum. serology. Row 359: Sial. sial forward slash o. saliva. sialadenitis. Row 360: Sid. sid forward slash o. iron. sideropenia. Row 361: Sigmoid. sigmoid forward slash o. sigmoid, colon. sigmoidoscope. Row 362: Sin. sin forward slash o. curve. sinoatrial. Row 363: Sit. sit forward slash o.

foot. sitotherapy. Row 364: Somat. somat forward slash o. body. somatotrophic. Row 365: Somn. somn forward slash o. sleep. somnambulism. Row 366: Son. son forward slash o. sound. sonogram. Row 367: Sperm. sperm forward slash o. seed. spermolysis. Row 368: Spermat. spermat forward slash o. seed. spermatocyst. Row 369: Sphincter. sphincter forward slash o. closure. sphincteroplasty. Row 370: Sphygm. sphygm forward slash o. pulse. sphygmomanometer. Row 371: Spin. spin forward slash o. thorn, spine. spinocerebellar. Row 372: Spir. spir forward slash o. breath. spirometer. The table consists of four columns: root word, combining form, definition, and example. Under S, row entries are as follows.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 373: Spir. spir forward slash o. coil. spiradenoma. Row 374: splen. splen forward slash o. spleen. splenectomy. Row 375: Spondyl. spondyl forward slash o. vertebra. spondylitis. Row 376: Staped. staped forward slash o. stapes, stirrup. stapedectomy. Row 377: Staphyl. staphyl forward slash o. cluster, uvula. staphyloplasty. Row 378: Steat. steat forward slash o. fat. steatolysis. Row 379: Sten. sten forward slash o. narrowing. stenosis. Row 380: Stern. stern forward slash o. sternum. sternalgia. Row 381: Steth. steth forward slash o. cheststethoscope. Row 382: Stigmat. stigmat forward slash o. point. stigmatism. Row 383: Stomat. stomat forward slash

o. mouth, opening. stomatitis. Row 384: Strept. strept forward slash o. chain. streptococcus. Row 385: Sympath. sympath forward slash o. sympathy. sympathectomy. Row 386: Syphil. syphil forward slash o. syphilis. syphilopsychosis. Under T, row entries are as follows. Row 387: Tars. tars forward slash o. ankle bone. tarsectomy. Row 388: Ten. ten forward slash o. tendon. tenorrhagia. Row 389: Tendin. tendin forward slash o. tendon. tendinitis. Row 390: Tendon. tendon forward slash o. tendon. tendonitis. Row 391: Terat. terat forward slash o. monster. teratoma. Row 392: Test. test forward slash o. testis. testalgia. Row 393: Thalass. thalass forward slash o. sea. thalassemia. Row 394: Than. than forward slash o. death. euthanasia. Row 395: Thel. thel forward slash o. nipple. thelorrhagia. Row 396: Therm. therm forward slash o. heat. hydrothermic. Row 397: Thromb. thromb forward slash o. blood clot. thrombosis. Row 398: Thym. thym forward slash o. thymus. thymopexy. Row 399: Thyr. thyr forward slash o. thyroid. thyroptoss. Row 400: Tibi. tibi forward slash o. tibia. tibial. Row 401: Tinnit. tinnit forward slash o. jingling. tinnitus. Row 402: Toc. toc forward slash o. birth. tocology. Row 403: Tom. tom forward slash o. cut. tomography. Row 404: Ton. ton forward slash o. tone, tension. tonography. Row 405: Tonsill. tonsill forward slash o. tonsil. tonsillitis. Row 406: Top. top forward slash o. place. topography. Row 407: Torti. torti forward slash o. twisted. torticollis.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 408: Toxic. toxic forward slash o. poison. toxicology. Row 409: Trache. trache forward slash o. trachea. tracheostomy. Row 140: Traumat. traumat forward slash o. wound, injure. traumatology. Row 411: Trephinat. trephinat forward slash o. bore. trephination. Row 412: Trich. trich forward slash o. hair. trichomycosis. Row 413: Trigon. trigon forward slash o. trigone. trigonitis. Row 414: Trop. trop forward slash o. turn. neurotropism. Row 415: Tubercul. tubercul forward slash o. swelling. tuberculosis. Row 416: Tympan. tympan forward slash o. drum. tympanitis. Under U, row entries are as follows. Row 417: Ul. ul forward slash o. scar. ulectomy. Row 418: Ulcer. ulcer forward slash o. surface excavation. ulcerogenic. Row 419: Uln. uln forward slash o. elbow. ulnad. Row 420: Ungu. ungu forward slash o. nail. ungula. Row 421: Ur. ur forward slash o. urine. uremia. Row 422: Ureter. ureter forward slash o. ureter. ureterolith. Row 423: Urethr. urethr forward slash o. urethra. urethrocystitis. Row 424: Urin. urin forward slash i. urine. uriniparous. Row 425: Urinat. urinat forward slash o. urine. urination. Row 426: Uter. uter forward slash o. uterus. uteralgia. Row 427: Uve. uve forward slash o. uvea. uveitis. Under V, row entries are as follows. Row 428: Vag. vag forward slash o. vagus nerve, wandering. vagotomy. Row 429: Vagin. vagin forward slash o. vagina. vaginectomy. Row 430: Varic. varic forward slash o. twisted vein. varicocele. Row 431: Vas. vas forward slash o. vessel, duct. vasotripsy. Row 432: Vascul. vascul forward slash o. small vessel.

vasculopathy. Row 433: Vector. vector forward slash o. carrier. vectorcardiogram. Row 434: Ven. ven forward slash o. vein. venostasis. Row 435: Vener. vener forward slash o. desire, love, sexual intercourse. venereal. Row 436: Veni. veni forward slash o. vein. venisuture. Row 437: Ventricul. ventricul forward slash o. ventricle. ventriculitis. Row 438: Vertebr. vertebr forward slash o. vertebra. vertebrectomy. Row 439: Vertig. vertig forward slash o. dizziness, vesicle. vertigo. Row 440: Vesic. vesic forward slash o. vesicle. vesicocele.

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The table consists of two columns. Under head lipid profile, row entries are as follows. Row 441: Vesicul. vesicul forward slash o. vesicle. vesiculotomy. Row 442: Vir. vir forward slash o. virus. viruria. Row 443: Viril. viril forward slash o. masculine. virilism. Row 444: Viscer. viscer forward slash o. body organs. visceroenic. Row 445: Vitamin. vitamin forward slash o. vitamin. hypervitaminosis. Row 446: Vitre. vitre forward slash o. vitreous humor. vitreous. Row 447: Vulv. vulv forward slash o. vulva. vulvovaginitis. Under X, row entries are as follows. Row 448: Xanth. xanth forward slash o. yellow. xanthemia. Row 449: Xen. xen forward slash o. alien, foreign. xenophobia. Row 450: Xiph. xiph forward slash o. sword. xiphoid. Under Z, row entries are as follows. Row 451: Zo. zo forward slash o. animal. zooderma. Row 452: Zon. zon forward slash o. encircling area. zonesthesia. Row 453: Zyg. zyg forward slash o. joined. zygodactyly.

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