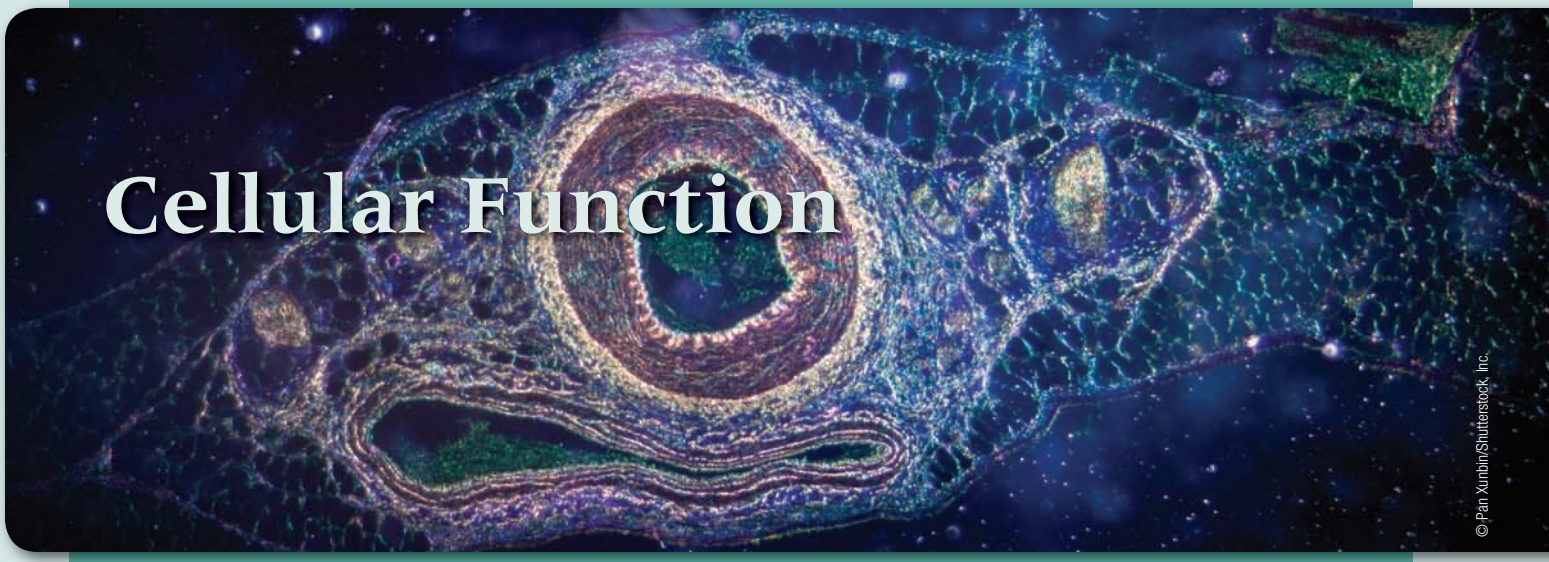
CHAPTER 1

Cellular Function



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LEARNING OBJECTIVES

- Describe basic cellular structures and function.
- 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
genes
genetics
glucose
grading
heterozygous
homozygous
hyperplasia
hypertrophy
initiation
ischemia
karyotype
lipid bilayer
liquefaction necrosis
lysis
malignant
meiosis
metaphase
metaplasia
metastasize
mitosis
multifactorial disorders
necrosis
neoplasm
nucleotide
nucleus
oncogene
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

Pathophysiology inquiry 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 with bacteria or viruses, or billions of cells, such as with 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, these diseases can be reduced to their cellular level. Diseases are likely to occur because of 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 miniorganisms that are the result of millions of years of evolution. Cells can arise only from a preexisting cell. 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.

The basic components of cells include the cytoplasm, the nucleus, and the 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**, or the control center of the cell, contains all the genetic information (DNA) and is surrounded by a double membrane (FIGURE 1-3). The nucleus regulates cell growth, metabolism, and reproduction. The **cell membrane**, or **plasma membrane**, is the semipermeable boundary containing the cell and its components (FIGURE 1-4). 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. The exterior surface of the bilayer is charged and is less fatty than the interior surface. 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).

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 process, 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 dissolved in water. Passage across the cell membrane is accomplished through several mechanisms, including diffusion, osmosis, facilitated diffusion, active transport, endocytosis, and exocytosis.

Diffusion is the movement of solutes—that is, particles dissolved in a solvent—from an area of higher concentration to an area of lower concentration (FIGURE 1-5). The degree of diffusion depends on the permeability of the membrane and the concentration gradient, which is the difference in concentrations of substances on either side of the membrane. Smaller particles diffuse more easily than larger ones, and less viscous solutions diffuse more rapidly than thicker solutions. Many substances, such as oxygen, enter the cell through diffusion.

LEARNING POINTS

To illustrate 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 with no 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 it 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

To understand osmosis, envision a plastic bag filled with sugar water and with holes punched in it that allow only water to pass through them. If this bag is submerged in distilled water (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 1-6). In our bodies, osmosis allows the cells to remain hydrated.

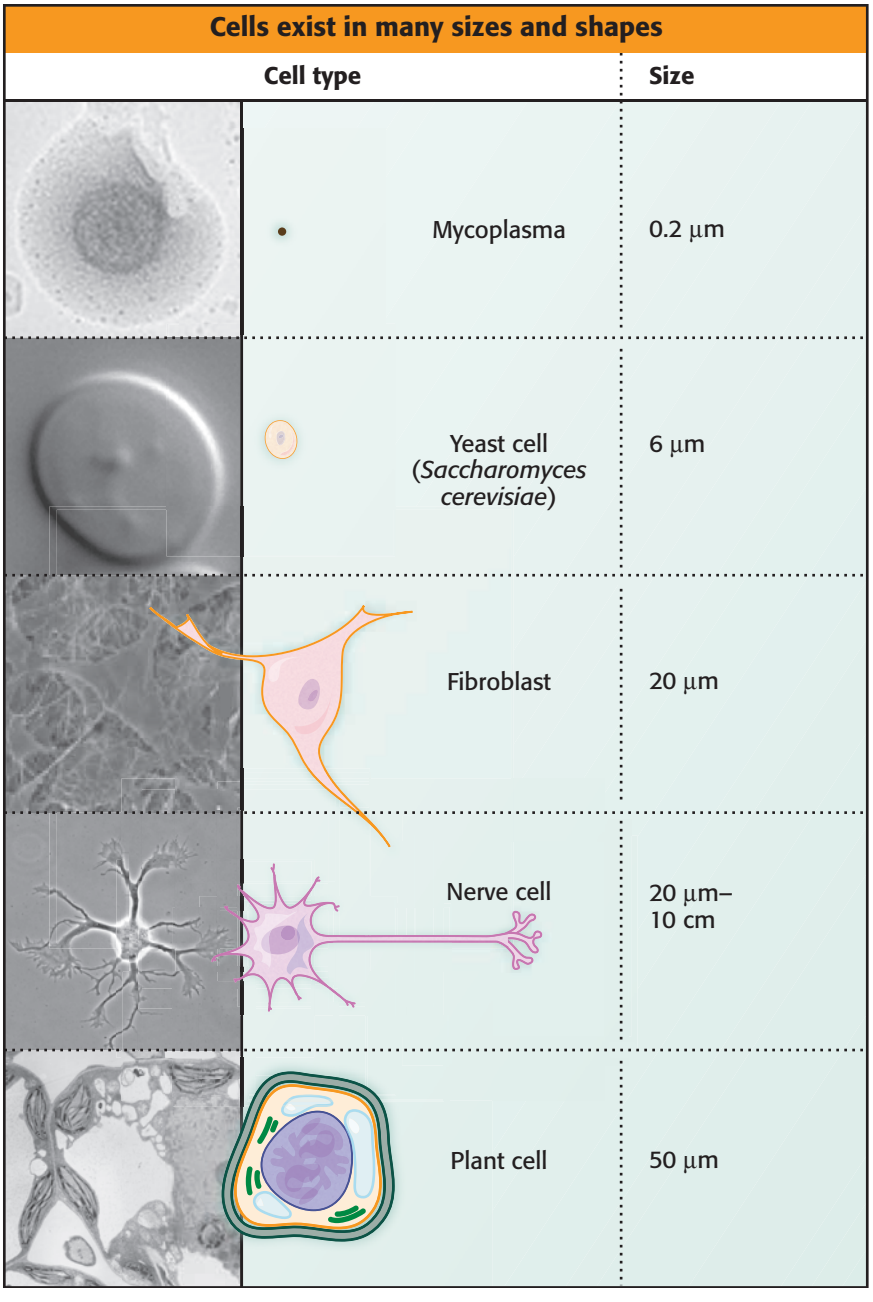

FIGURE 1-1 Cells vary greatly in size and shape. Some cells are spherical, while others are long extensions.

Courtesy of Tim Pietzcker, Universitat Ulm

Courtesy of Fred Winston, Harvard Medical School

Courtesty of Junzo Desaki, Ehime University School of Medicine

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

Courtesy of Ming H. Chen, University of Alberta

Osmosis is 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. 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. 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, and examples can be found in the functioning of the kidneys.

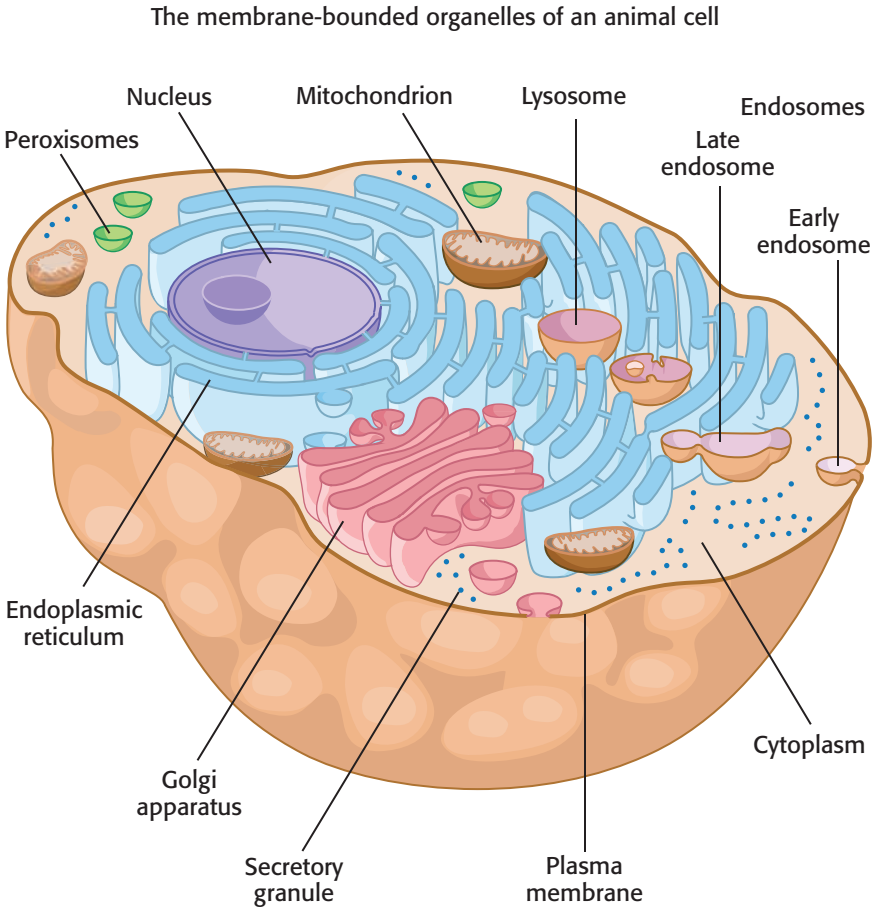

FIGURE 1-2 The cytoplasm contains several organelles.

Lewin, B., Cassimeris, L., Lingapa, V., & Plopper, G. (Eds.). (2007). *Cells*. Sudbury, MA: Jones & Bartlett.

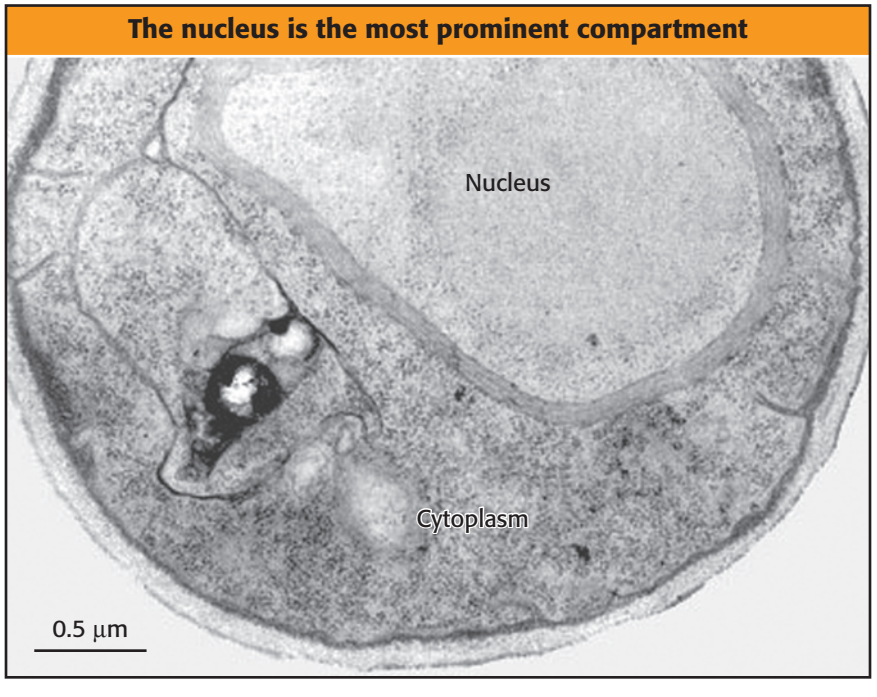

FIGURE 1-3 Although the proportion of the cell that is taken up by the nucleus varies according to cell type, the nucleus is usually the largest and most prominent cellular compartment.

TABLE 1-1 Overview of Cell Organelles

Organelle	Structure	Function
Nucleus	Round or oval body; surrounded by nuclear envelope.	Contains the genetic information necessary for control of cell structure and function; DNA contains hereditary information.
Nucleolus	Round or oval body in the nucleus consisting of DNA and RNA.	Produces ribosomal RNA.
Endoplasmic reticulum (ER)	Network of membranous tubules in the cytoplasm of the cell. Smooth endoplasmic reticulum (SER) contains no ribosomes. Rough endoplasmic reticulum (RER) is studded with ribosomes.	SER is involved in the production of phospholipids and has many different functions in different cells; RER is the site of the synthesis of lysosomal enzymes and proteins for extracellular use.
Ribosomes	Small particles found in the cytoplasm; made of RNA and protein.	Aid in the production of proteins on the RER and polysomes.
Golgi complex	Series of flattened sacs usually located near the nucleus.	Sorts, chemically modifies, and packages proteins produced on 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 for release.
Food vacuole	Membrane-bound vesicle containing material engulfed by the cell.	Stores ingested material and combines with lysosomes.
Lysosome	Round, membrane-bound structure containing digestive enzymes.	Combines with food vacuoles and digests materials engulfed by cells.
Peroximomes	Small structures containing enzymes.	Break down various potentially toxic intracellular molecules.
Mitochondria	Round, oval, or elongated structures with a double membrane. The inner membrane is thrown into folds.	Complete the breakdown of glucose, producing nicotine adenine dinucleotide (NADH) and adenosine triphosphate (ATP).
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.
Centrioles	Small cylindrical bodies composed of microtubules arranged in nine sets of triplets; found in animal cells, not plants.	Help organize spindle apparatus necessary for cell division.

Chiras, D. (2011). *Human biology* (7th ed.). Burlington, MA: Jones & Bartlett Learning.

Facilitated diffusion is the movement of substances from an area of lower concentration to an area of higher concentration with the assistance of a carrier molecule (FIGURE 1-7). 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. **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 1-7). This movement will require a carrier molecule and energy because of the effort required to go against the gradient. This energy is usually in the form of adenosine triphosphate (ATP).

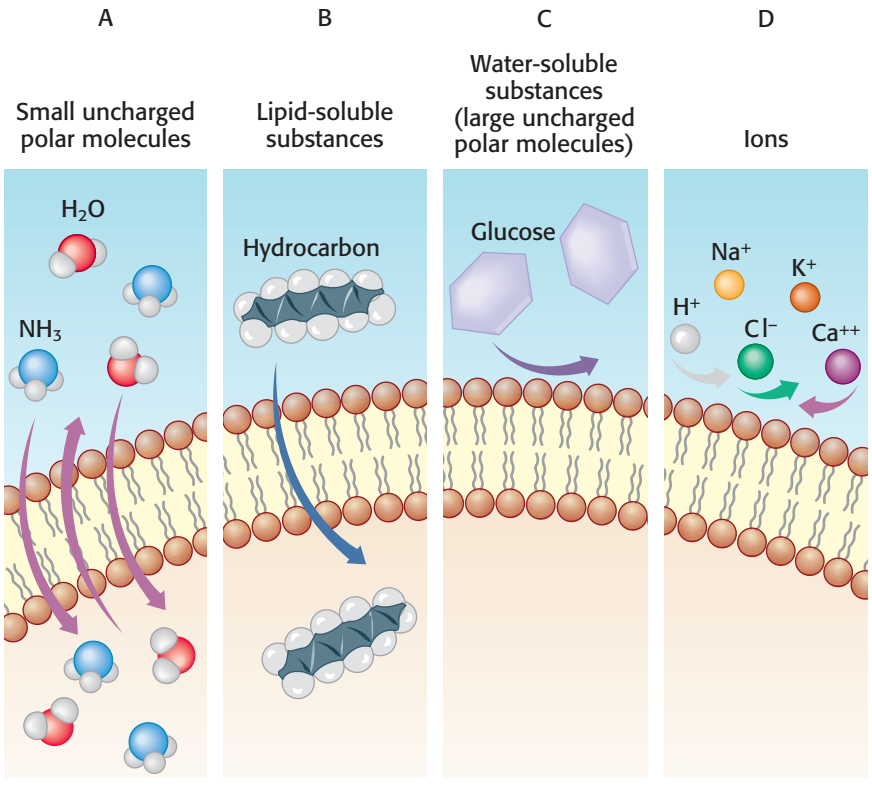

FIGURE 1-4 A selectively permeable membrane maintains homeostasis by allowing some molecules to pass through while others may not.

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Endocytosis is the process of bringing a substance into the cell (FIGURE 1-8). The cell membrane surrounds the particles, engulfing them. **Phagocytosis**, or cell eating, occurs when the process involves solid particles. **Pinocytosis**, or cell drinking, takes place when the process involves a liquid. Components of the immune system use endocytosis, 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 1-8). Often glands secrete hormones using exocytosis.

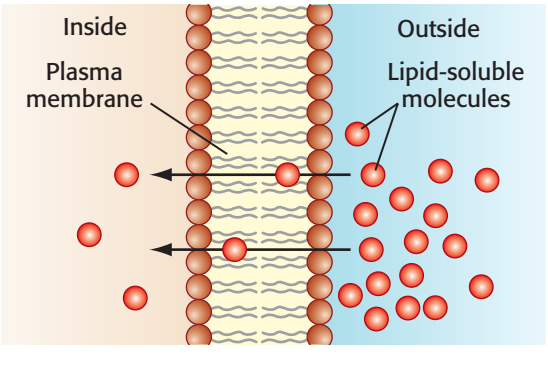

FIGURE 1-5 Lipid-soluble substances pass through the membrane directly via simple diffusion.

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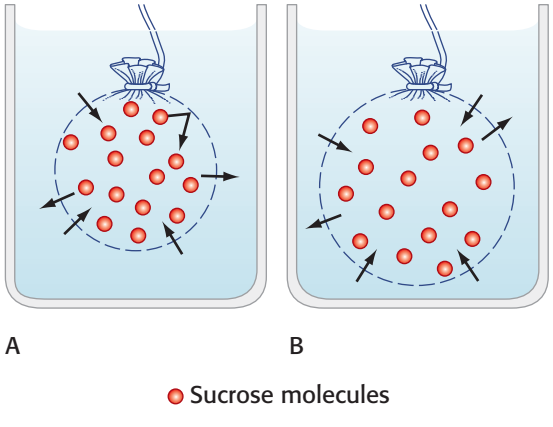


FIGURE 1-6 (a) When a bag of sugar water is immersed in a solution of pure water, (b) water will diffuse into the bag toward the lower concentrations of water, causing the bag to swell.

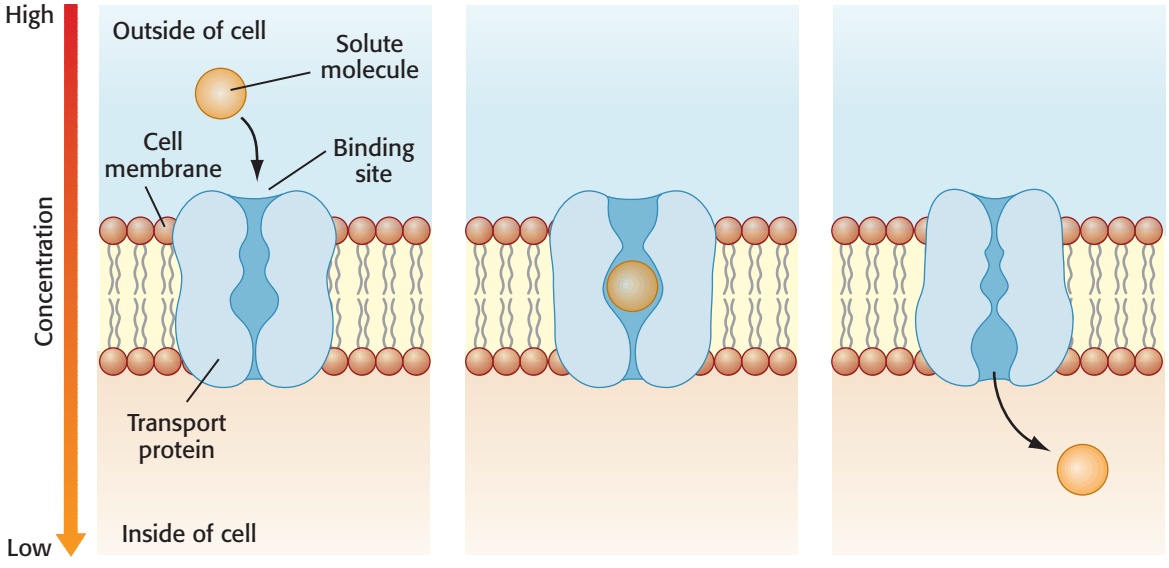
Chiras, D. (2011). *Human biology* (7th ed.). Burlington, MA: Jones & Bartlett Learning.

LEARNING POINTS

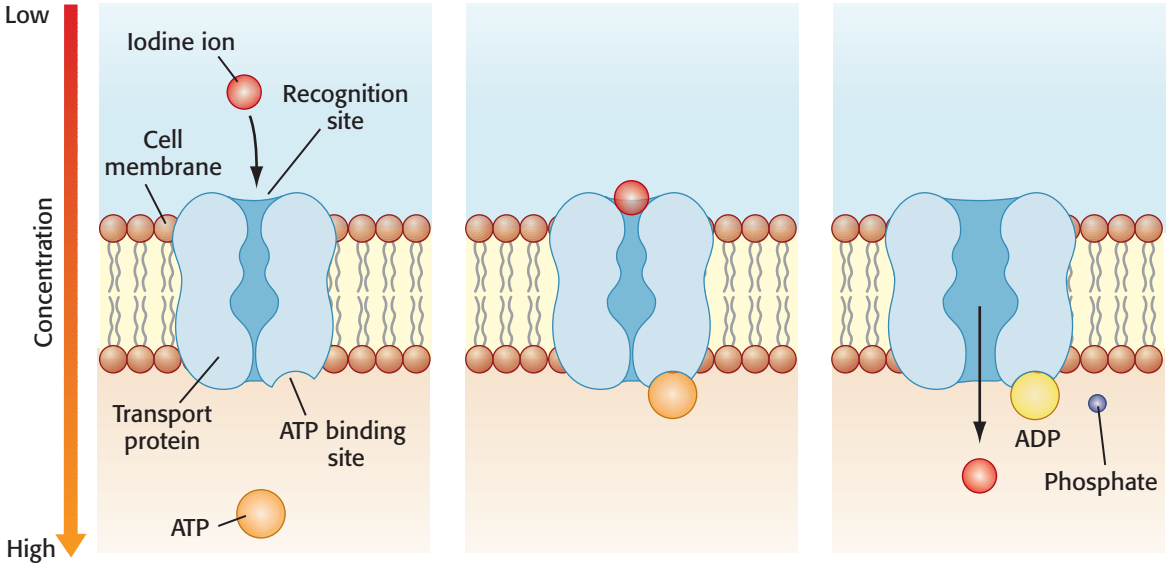
To understand active transport, consider the overfilled elevator again. If the door opens and someone from outside the elevator attempts to get in, it will require much effort (energy) to enter the full elevator. The sodium–potassium pump is an example of active transport in the body. Energy is required to move sodium out of the cell where the concentrations are high and move potassium into the cell where the concentrations are high.

Energy Production

Energy can be a mystery to many of us. To understand energy, first we must understand that it comes in many forms. 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). Food enters the gastrointestinal tract, where it is broken down into sugars, amino acids, and



(a) Facilitated diffusion



(b) Active transport

FIGURE 1-7 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.

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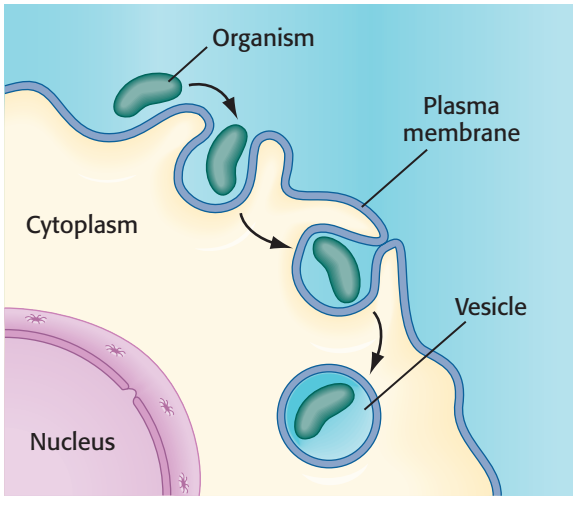
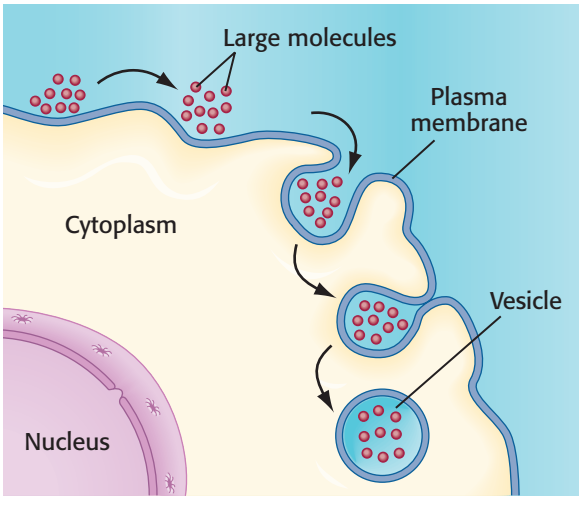
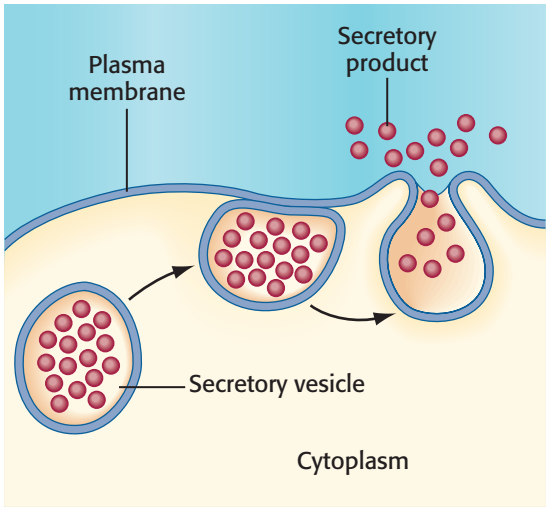


A Endocytosis



Pinocytosis



B Exocytosis

FIGURE 1-8 (a) Cells can engulf large particles, cell fragments, and even entire cells. (b) Cells can also get rid of large particles.
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fatty acids. These substances then are 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). Acetyl CoA enters the Krebs cycle, a high-electron-producing process, of the mitochondria. During the Krebs cycle, these molecules go through a complex series of reactions that result in the production of large amounts of ATP.

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. 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. This process occurs in four steps—prophase, metaphase, anaphase, and

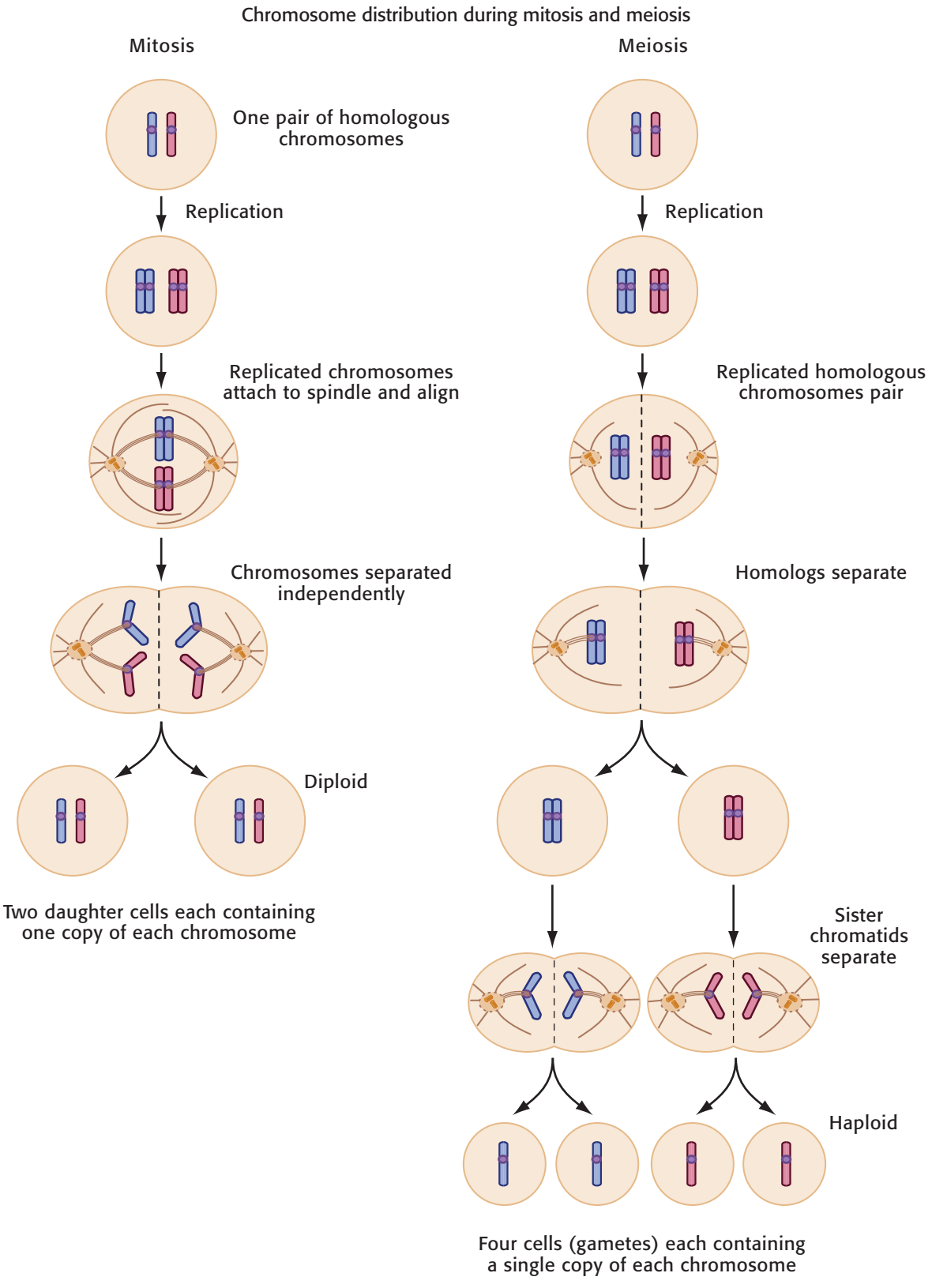

FIGURE 1-9 Mitosis and meiosis.

Lewin, B., et al. (2007). *Cells*. Sudbury, MA: Jones & Bartlett.

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**. **Meiosis** is a form of cell division that occurs only in mature sperm and ova (Figure 1-9). Normally, human cells contain 46 chromosomes, but sperm and ova contain 23 chromosomes each. When the sperm and ova join, the resulting organism has 46 chromosomes.

Differentiation is 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. During this time, the embryo is the most susceptible to damage because of environmental influences. Differentiation is the process by which the primitive stem cells of the embryo develop into the highly specialized cells of the human (e.g., cardiac cells and nerve cells).

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**. 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 normal or abnormal depending on whether they were mediated through standard pathways. They may also be permanent or reversible. Nevertheless, once the stimulus is removed, adaptation ceases. Specific types of adaptive changes include atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia (FIGURE 1-10).

Atrophy occurs because of decreased work demands on the cell. The body attempts to work as efficiently as possible to conserve energy and resources. When cellular work demands decrease, the cells decrease in size and number.

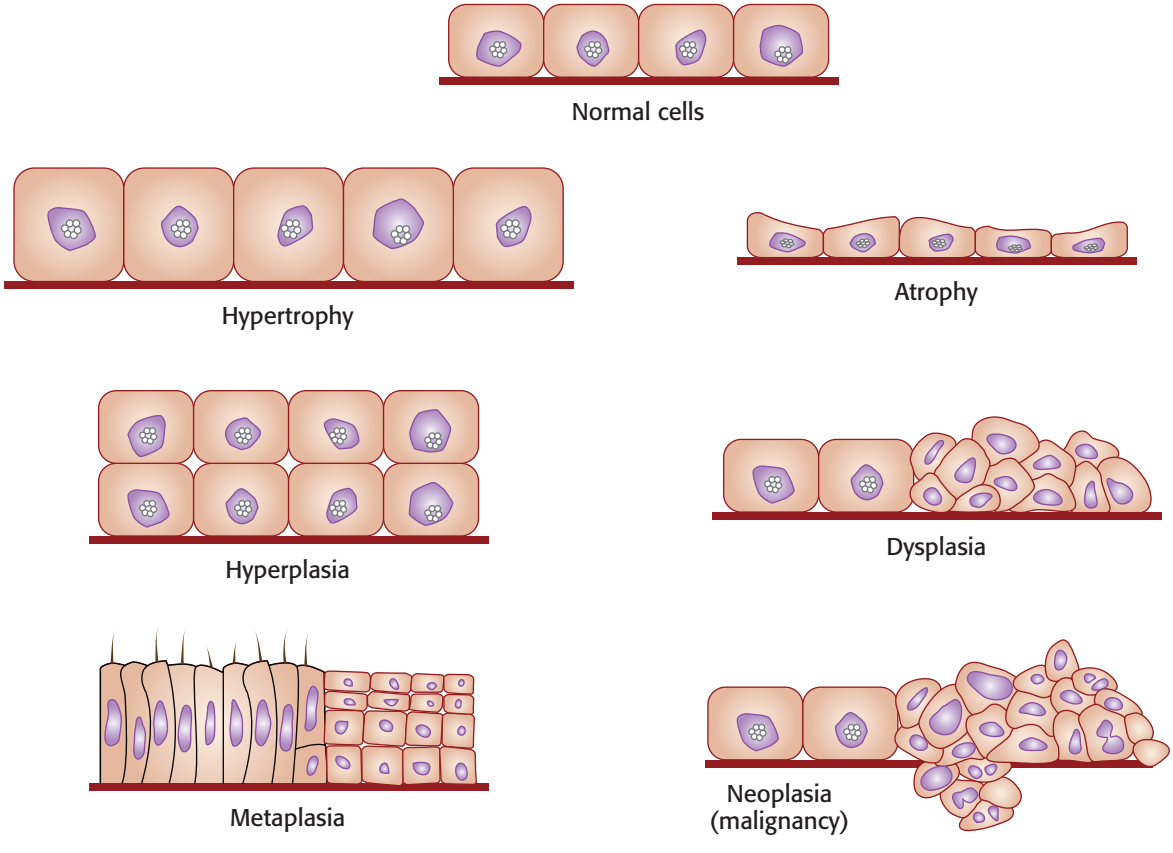

FIGURE 1-10 Cellular adaptation: abnormal cellular growth patterns.

These atrophied cells utilize less oxygen, and their organelles decrease in size and number. Causes of atrophy include disuse, denervation, endocrine hypofunction, inadequate nutrition, and ischemia. An example of disuse atrophy can be seen when a muscle shrinks in an extremity that has been in a cast for an extended period. Denervation atrophy is closely associated to disuse; it can be seen in when a muscle shrinks in a paralyzed extremity. Atrophy because of a loss of endocrine function can be seen 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 demand. 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 body builder diligently performs biceps curls with weights—the biceps gets larger. This type of hypertrophy is a normal change. An abnormal hypertrophic change can be seen with hypertension. Just as the biceps muscle grows larger from increased work, the cardiac muscle will thicken and enlarge when increased workload is placed on it because of the hypertension. The biceps muscle increases in strength and function when its workload is increased; however, 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. The hyperplasia process is usually a result of normal stimuli. Examples of hyperplasia include menstruation, liver regeneration, wound healing, and skin warts. Hyperplasia is different from hypertrophy, but they often occur together because of similar triggers.

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 to another type of epithelial cell, but they will not be replaced with nerve cells. Some examples of metaplastic changes can be seen in ciliary changes that occur in the respiratory tract because of chronic smoking or vitamin A deficiency. Metaplasia does not necessarily lead to cancerous changes; however, if the stimulus is not removed, cancerous changes will likely occur.

The final cellular adaption is dysplasia. In **dysplasia**, cells mutate into cells of a different size, shape, and appearance. 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., cigarette smoke, human papillomavirus).

Cellular Death and Injury

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) biologic agents (e.g., viruses, bacteria, and parasites), and (5) nutritional imbalances.

Death is a part of the human existence, and it is 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 (FIGURE 1-11). 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 rather may be a result of environmental triggers. Apoptosis is important in tissue development, immune defense, and cancer prevention. However, this mechanism can result in inappropriate destruction of cells if it is unregulated. 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 1-11). **Ischemia** refers to decreased blood flow to tissue or an organ. This

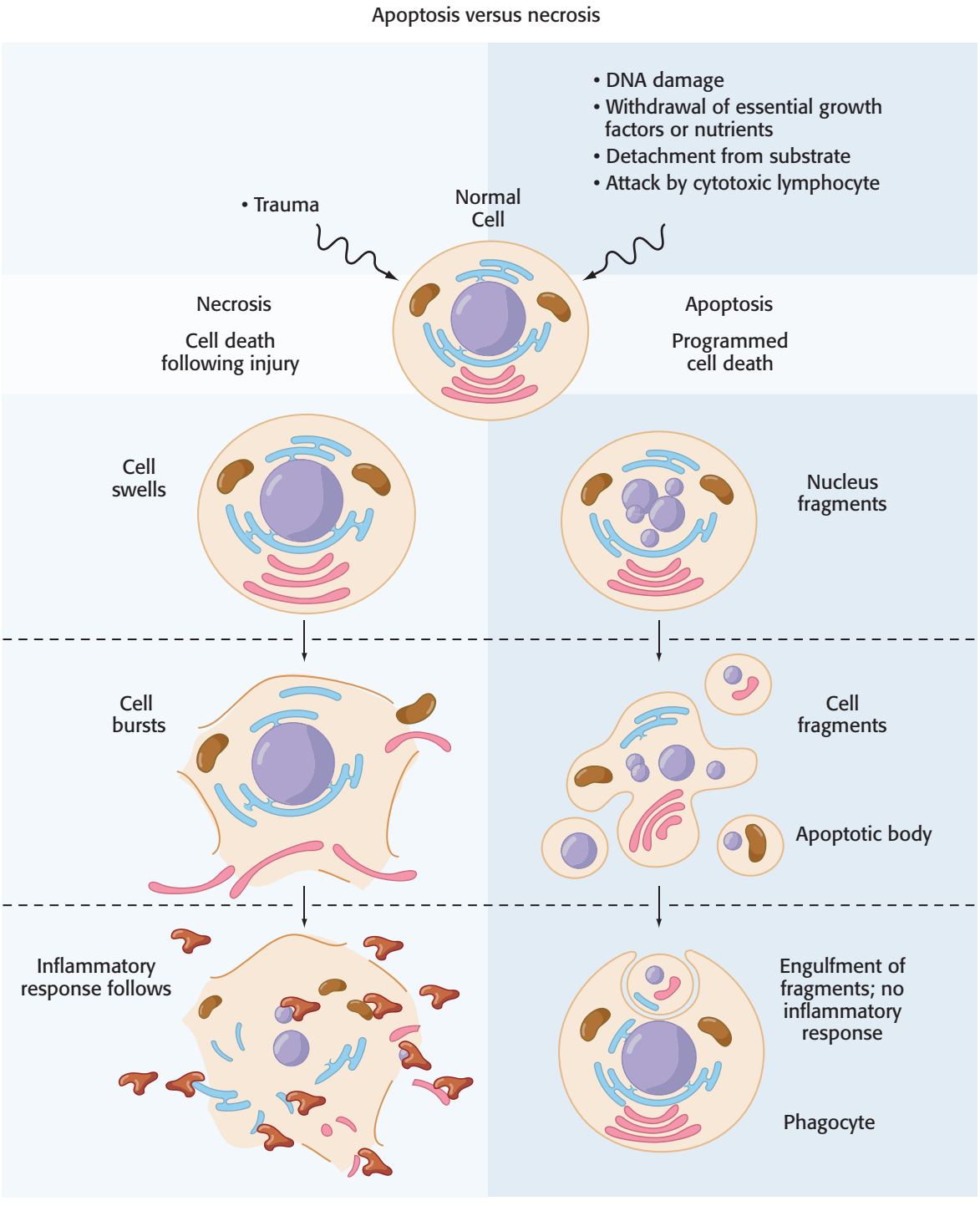

FIGURE 1-11 Cellular damage can result in necrosis, which has a different appearance than apoptosis, as organelles swell and the plasma membrane ruptures.

Lewin, B., et al. (2007). *Cells.* Sudbury, MA: Jones & Bartlett.

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 **necrosis**. 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.

Necrosis can take one of several pathways. **Liquefaction necrosis** (FIGURE 1-12) occurs when caustic enzymes dissolve and liquefy necrotic cells. The most common site of this type of necrosis is the brain, because it contains a

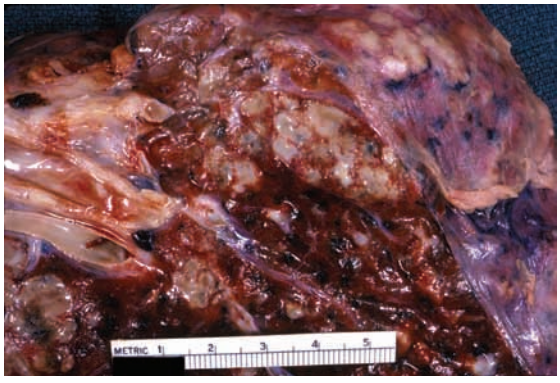

FIGURE 1-12 Liquefaction necrosis.

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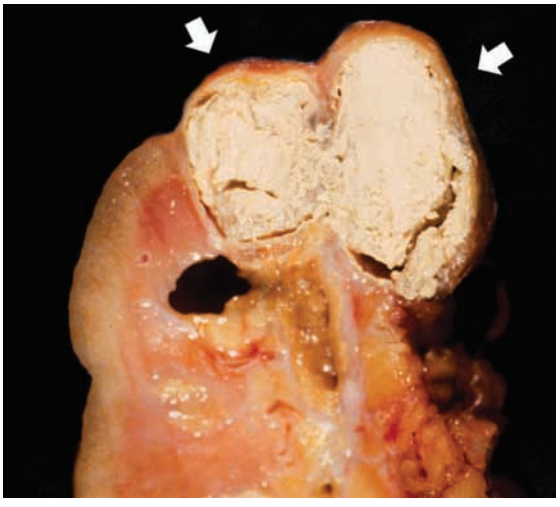


FIGURE 1-13 Caseous necrosis.

Gibson, M. S., Pucket, M. L., & Shelly, M. E. (2004). Renal tuberculosis. *Radiographics, 24*(1), 251–256.

plentiful supply of these enzymes. **Caseous necrosis** (FIGURE 1-13) occurs when the necrotic cells disintegrate but the cellular debris remains in the area for months or years. This type of necrosis has a cottage cheese–like appearance, and it is most commonly noted with pulmonary tuberculosis. **Fat necrosis** (FIGURE 1-14) occurs when lipase enzymes break down intracellular triglycerides into free fatty acids. These fatty acids then combine with magnesium, sodium, and calcium, forming soaps. These soaps give fat necrosis an opaque, chalky appearance. **Coagulative necrosis** (FIGURE 1-15) 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.

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. Gangrene can occur in three forms—dry, wet, and gas. **Dry gangrene** (FIGURE 1-16) occurs when bacterial presence is minimal, and the skin has a dry, dark brown, or black appearance. **Wet gangrene** (FIGURE 1-17) occurs with liquefaction necrosis. Extensive damage from bacteria and white blood cells produces a liquid wound. Wet gangrene can occur in extremities and internal organs. **Gas gangrene** (FIGURE 1-18) develops because of the presence of *Clostridium*, an anaerobic bacterium. This type of gangrene is the most serious and has the most potential for being fatal. The bacterium releases toxins that destroy surrounding cells, so that the infection spreads rapidly. The gas released from this process bubbles from the tissue, often underneath the skin.

Another important mechanism of cellular injury is free radicals. **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

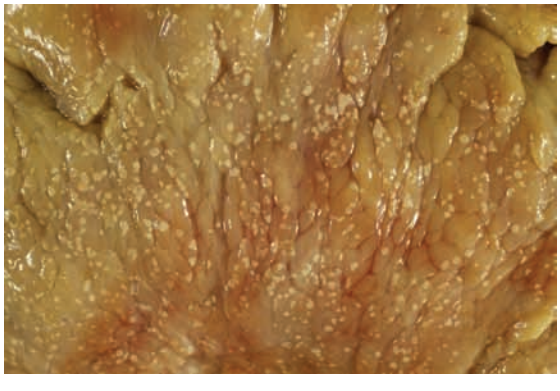


FIGURE 1-14 Fat necrosis.

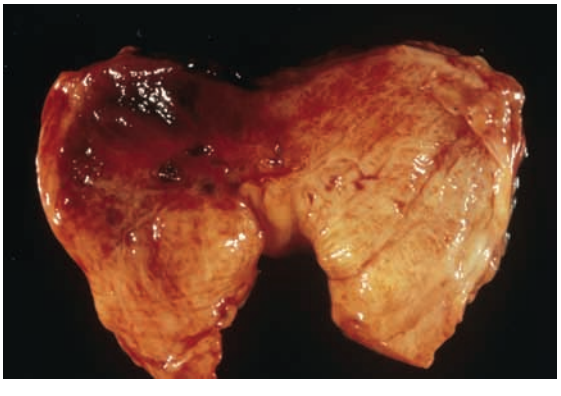


FIGURE 1-15 Coagulative necrosis.

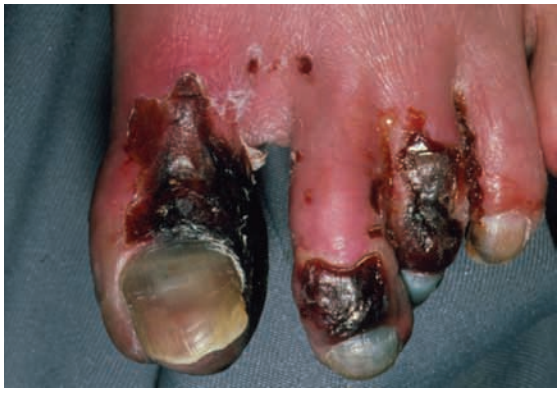


FIGURE 1-16 Dry gangrene.

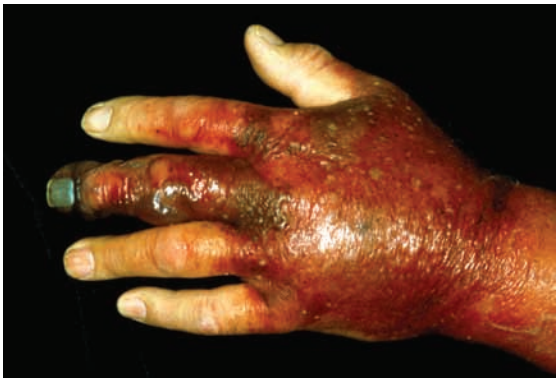


FIGURE 1-17 Wet gangrene.

damage. Such an atom has an unpaired electron, making it unstable. In an attempt to stabilize itself, the atom borrows an electron from a surrounding 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 *Body Defenses* chapter) that might occur because of this process, and certain dietary components can aid in this fight (e.g., vitamins C and E, and beta-carotene). Free radicals have been linked to cancer, aging, and a variety of other conditions.

Neoplasm

When the process of cellular proliferation or differentiation goes wrong, neoplasms can develop. A **neoplasm**, or **tumor**, is a cellular growth that is no longer responding to normal regulator 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. Thus cancer cells differ from normal cells in size, shape, number, differentiation, purpose, and function.

Carcinogenesis, the process by which cancer develops, occurs in three phases: initiation, promotion, and progression (FIGURE 1-19). **Initiation** involves the exposure of the cell to a substance or event (e.g., chemicals, viruses, or radiation) that causes DNA damage or mutation. Usually the body has enzymes that detect these events and repair the damage. If the event is overlooked, then the mutation can become permanent and is passed on to future cellular generations. **Promotion** involves the mutated cells' exposure to factors (e.g., hormones, nitrates, or nicotine) that promote growth. This phase may occur just after initiation or years later, and it can be reversible if the promoting factors are removed. In **progression**, the tumor invades, metastasizes (spreads), and becomes drug resistant. This final phase is permanent or irreversible.

A healthy body is equipped with the necessary defenses to shield it against cancer (see the *Body Defenses* chapter). When those defenses fail, however, cancer prevails. Evidence suggests that these defenses may fail because of a combination of complex interactions between carcinogen exposure and genetic mutations. Numerous genes have been identified as causing cancers. **Oncogenes** activate cell division and influence embryonic development. Some of these cancer-producing genes may remain harmless until altered by a genetic or acquired mutation. Common causes of acquired mutations include viruses, radiation, environmental and dietary carcinogens, and hormones. Other factors that can increase a person's likelihood of developing cancer include age, nutritional status, hormonal balance, and stress response. As we age, statistically there is a higher likelihood of a DNA transcription error occurring; we are also more likely to have more carcinogen exposure. Examples of how changes in nutritional status increase the likelihood of cancer can be seen in free radical damage. Some cancers almost feed off of hormones, meaning they grow faster in the presence of particular hormones. Finally, the immune system is impaired during stress states, which can affect its ability to find and respond to carcinogenesis.

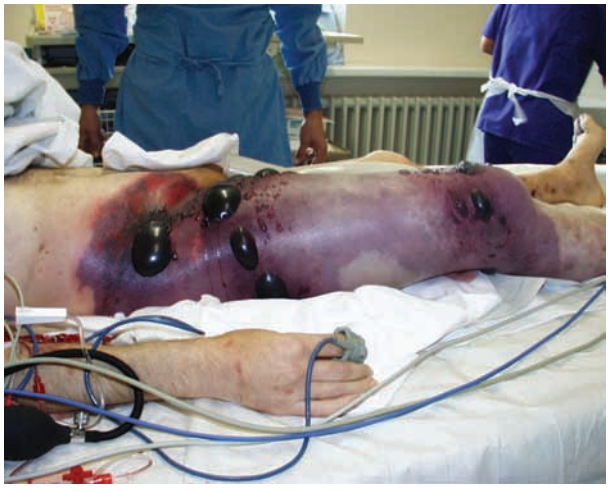


FIGURE 1-18 Gas gangrene.

Schropfer, E., et al. (2008). Diagnosis and misdiagnosis of necrotizing soft tissue infections: Three case reports. *Cases Journal, 1*, 252.

The loss of differentiation that occurs with cancer is referred to as **anaplasia**. Anaplasia occurs in varying degrees. The less the cell resembles the original cell, the more anaplastic the cell. Anaplastic cells may begin functioning as completely different cells, often producing hormones or hormone-like substances.

Benign and Malignant Tumors

Two major types of neoplasms are benign and malignant (**TABLE 1-2**; FIGURE 1-20). **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 are unable to **metastasize**, or spread. 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.

Malignant tumors usually are undifferentiated (more anaplastic), nonfunctioning cells that are reproducing rapidly. Malignant tumors often penetrate surrounding tissue and spread to secondary sites. The tumor's ability to metastasize (FIGURE 1-21; FIGURE 1-22) depends on its ability to access and survive in the circulatory or the 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 1-3**).

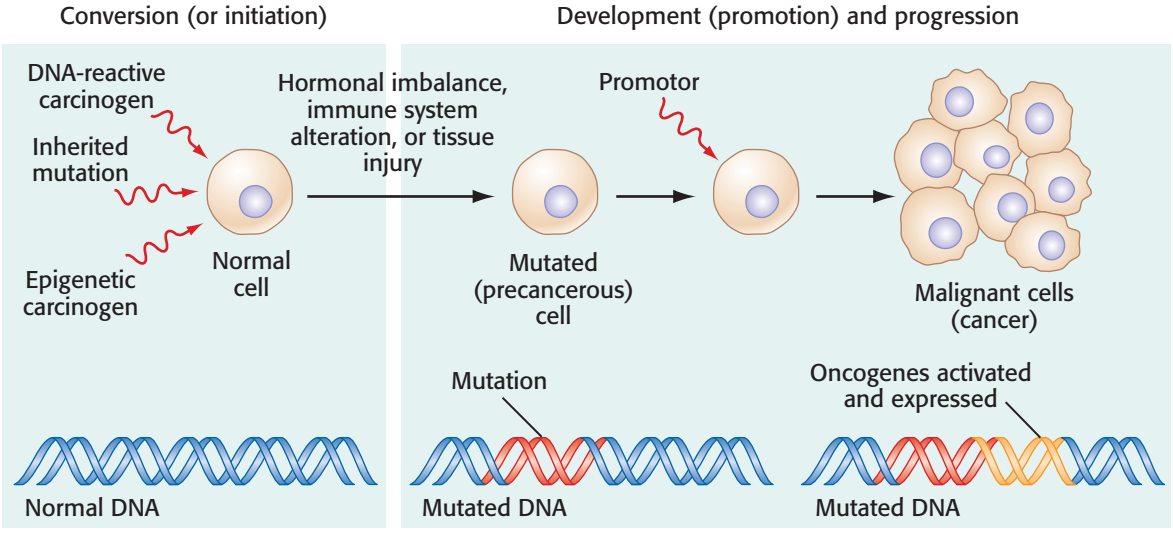


FIGURE 1-19 Carcinogenesis: the stages leading to cancer.

MYTH BUSTERS

MYTH 1: STANDING IN FRONT OF A MICROWAVE OVEN WHILE IT IS COOKING FOOD CAN INCREASE YOUR RISK FOR CANCER.

This is a common myth that 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 non-ionizing 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 non-ionizing radiation. Currently, Food and Drug Administration guidelines limit the amount of the non-ionizing radiation microwave ovens can emit, further decreasing the cancer risk.

MYTH 2: USING CELL PHONES CAN INCREASE YOUR RISK OF CANCER.

This is another common myth. Cell phones use the same non-ionizing microwave radiation as microwave ovens to emit a signal. Even though these devices may be in close proximity to your head while in use, evidence does not support that they promote an increased 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.

Regardless of the type of tumor, several factors are imperative 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

TABLE 1-2 Characteristics of Benign and Malignant Tumors

	Benign Tumors	Malignant Tumors
Cells	Similar to normal cells Differentiated Mitosis fairly normal	Varied in size and shape Many undifferentiated Mitosis increased and atypical
Growth	Relatively slow Expanding mass Frequently encapsulated	Rapid growth Cells 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
Life threatening	Only in certain locations (e.g., brain)	Yes, by tissue destruction and spread

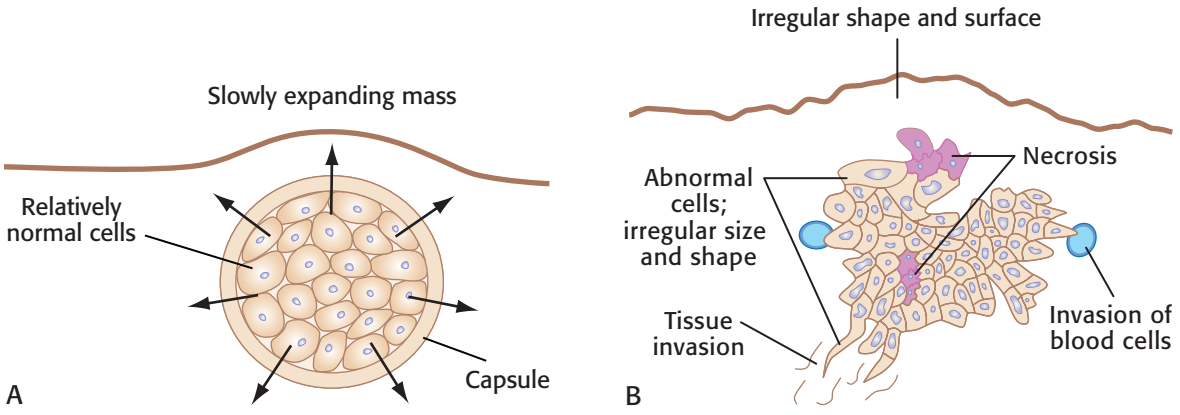


FIGURE 1-20 Characteristics of (a) benign and (b) malignant tumors.

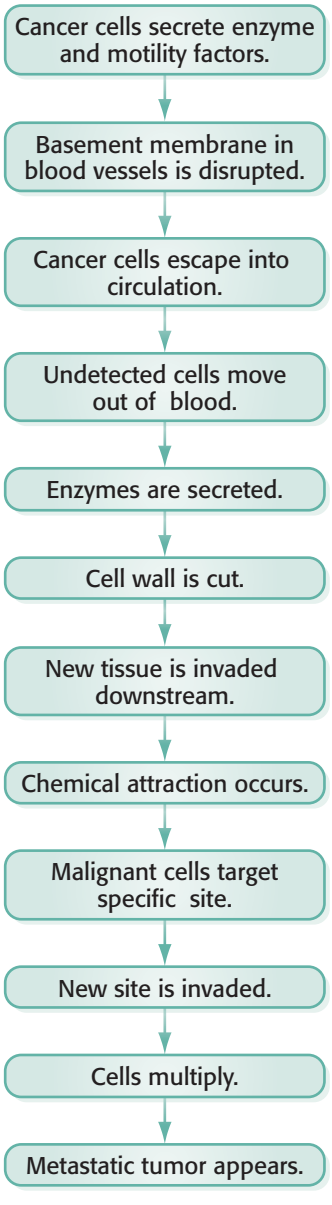


FIGURE 1-21 How cancer metastasizes.

be a result of the 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, is a result of 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

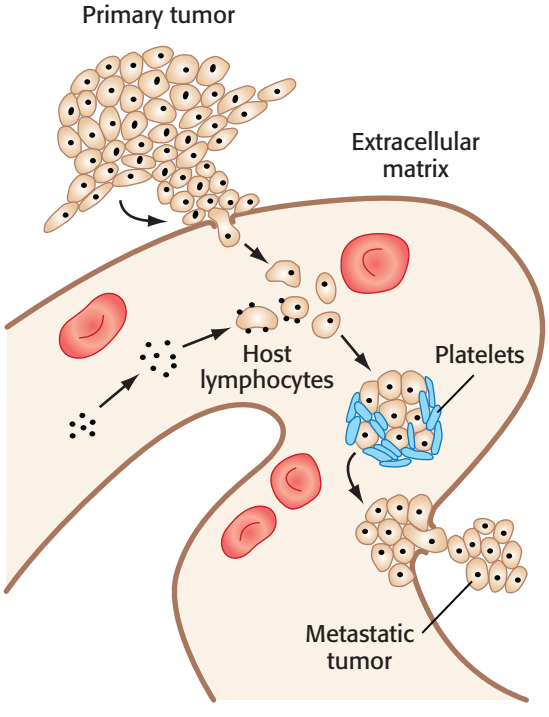


FIGURE 1-22 Pathogenesis of metastasis.

TABLE 1-3 Common Sites of Metastasis

Cancer Type	Sites for Metastasis
Breast	Axillary lymph nodes, lung, liver, bone, brain
Colorectal	Liver, lung, peritoneum
Lung	Liver, brain, bone
Ovarian	Peritoneum, diaphragm, liver, lung
Prostate	Bone
Testicular	Lungs, liver

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.

Diagnosis

Diagnosis of cancer is complex and is specific to the type of cancer suspected. This chapter provides a basic overview of cancer diagnostic procedures; more specifics are presented in future chapters as specific cancers are discussed. A set of diagnostic procedures usually follows a thorough history and physical examination. These diagnostic procedures may vary depending on the type of cancer suspected. The intention of these 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 most clear and 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 staging the cancer (**TABLE 1-4**). 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 1-5**). These tumor markers not only aid in cancer detection, but they also assist in tracking disease progression and treatment response.

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 problems because they are more like the original tissue. By comparison, grade 4 cancers are undifferentiated, meaning they are highly likely to cause 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 1-23).

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 either **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 surrounding tissue. Chemotherapy involves the administration of a wide range of medications that destroy replicating tumor cells. Radiation includes the use of ionizing radiation 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 treatment that uses

TABLE 1-4 Cancer Screening Guidelines

Screening Area	Recommendations
Breast	
Mammogram	Every year age 40 and older
Clinical breast examination	Every year age 40 and older; every 3 years for ages 20 to 39
Breast self-examination	Suggested monthly for age 20 and older
Cervix	
Papanicolaou (Pap) test	Every 3 years between the ages of 21 to 29 Every 5 years between the ages of 30 to 65 Not necessary after age 65 unless serious cervical precancer or cancer present in the last 20 years
Endometrium	
Endometrial biopsy	Yearly beginning at age 35 for those women at risk for colon cancer
Prostate	
Prostate-specific antigen (PSA)	Yearly beginning at age 50, unless at high risk, then beginning at age 40
Digital rectal examination	Yearly beginning at age 50, unless at high risk, then beginning at age 40
Colon and Rectum	
Fecal occult blood test	Yearly age 50 and older
Fecal immunochemical test	Yearly age 50 and older
Stool DNA test	Interval uncertain for age 50 and older
Flexible sigmoidoscopy	Every 5 years age 50 and older
Barium enema	Every 5 years age 50 and older
Colonoscopy	Every 10 years age 50 and older
Virtual colonography	Every 5 years age 50 and older

Data from American Cancer Society (www.cancer.org) and National Cancer Institute (www.cancer.gov).

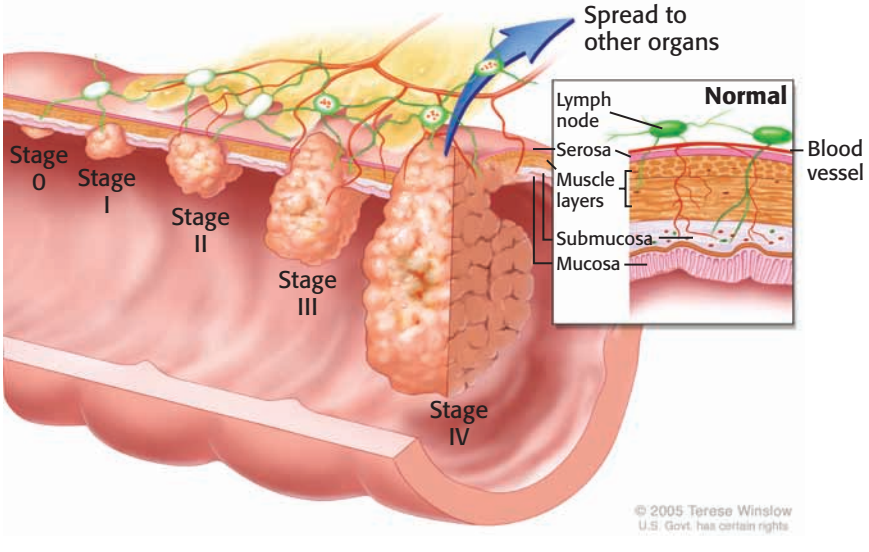


FIGURE 1-23 TNM staging system. The example shown is staging of colorectal cancer.

TABLE 1-5 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
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
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)

TABLE 1-5 Common Tumor Cell Markers (*continued*)

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

drugs to identify and attack cancer cells; this drug therapy differs from the traditional chemotherapy. Hormone therapy involves administering specific hormones that inhibit the growth of certain cancers. Immunotherapy involves administering 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 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 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 for 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 circulation or lymph system, the worse the patient's prognosis. 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, it is noteworthy that 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 these disorders. These 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 mutations that can result in serious disability or death can be transmitted through genetic material. 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.

Genetics

The cellular instructions and information are carried with our **genes**. A gene is a segment of **deoxyribonucleic acid (DNA)** that serves as a template of protein synthesis. DNA is a long double-stranded chain of nucleotides called **chromosomes**. The **nucleotides** consist of a five-carbon sugar (deoxyribose), a phosphate group, and one of four nitrogen bases (cytosine, thymine, guanine, or adenine). An estimated three billion nucleotides make up the human genome. Each gene can contain hundreds to thousands of these nucleotides. Of the 46 chromosomes, the 22 sets of paired chromosomes are called **autosomes**, and the remaining two make up the sex chromosomes (paired X chromosomes for females and an X and a Y for males). A representation of a person's individual set of chromosomes is referred to as **karyotype**, and the physical expression of those genes is referred to as **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 one gene that may have many variants (**alleles**) (**TABLE 1-6**). 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 to each offspring, male or female. An example of an X-linked disorder is Klinefelter's syndrome. Some traits require a combination of two or more genes and environmental factors, or multifactorial inheritance. Some examples of this type of inheritance include height, diabetes mellitus, and obesity.

Autosomal Dominant Disorders

Autosomal dominant disorders are single gene mutations that are passed from an affected parent to an offspring regardless of sex.

application to practice

History

Mrs. Turner is a 47-year-old Caucasian 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. Turner neither smokes nor drinks, and she follows a daily exercise regimen. Approximately 2 months ago, Mrs. Turner's husband 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. Turner became concerned when it seemed to grow bigger.

Mrs. Turner is the mother of two children, 8 and 6 years old. Mrs. Turner 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. Turner is an only child, born to her parents late in their life. 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. Turner's family.

Current Status

On exam, a 2- to 3-cm mass was palpated in the upper quadrant of Mrs. Turner'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. Turner said that she noticed these lumps in her left breast 2 weeks ago but stated that the lumps in her left breast became palpable and bothersome about 12 days from the start of menses. A reproductive history disclosed that the onset of menses occurred at the age of 10. There is no history of dysmenorrhea associated with her periods, although Mrs. Turner states that 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 result of a bone scan and other diagnostic procedures were negative.

1. Mrs. Turner is considered to be at increased risk for developing breast cancer. Which of the following factors is most positively related to this high-risk profile?
   - A. History of breast cancer in family members
   - B. History of cystic breast disease
   - C. Early onset of menarche
   - D. Trauma related to birth of her children
2. Which of the following best explains the existence of an enlarged right axillary lymph node in Mrs. Turner?
   - 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.

Mrs. Turner was taken to surgery 3 days later, and a modified radical mastectomy was performed. 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. Turner's tumor was estrogen dependent. She returned to her room with a drain in place. Her 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.

3. Mrs. Turner's tumor was staged at stage III using the TNM staging system. Pathological exam of the surgically removed tissue sample placed Mrs. Turner'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 catalogue individuals with breast tumors for statistical analysis.
   - D. All of the above.
4. Which activities by Mrs. Turner increase her likelihood for a good prognosis?
5. What was the rationale for hormone therapy with Mrs. Turner?

TABLE 1-6 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's syndrome)
Huntington's disease	Congenital heart disease	Polysomy X (Klinefelter's syndrome)
Marfan's syndrome	Myelomeningocele	Trisomy 18 (Edwards' syndrome)
Autosomal Recessive	Schizophrenia	
Albinism		
Color blindness		
Cystic fibrosis		
Phenylketonuria		
Sickle cell anemia		
Tay-Sachs disease		
X-linked Recessive		
Duchenne muscular dystrophy		
Hemophilia A		

Moini, J. (2013). *Introduction to pathology for the physical therapist assistant*. Burlington, MA: Jones & Bartlett Learning.

Autosomal dominant disorders occur with both homozygous and heterozygous 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 they have a "double dose" of the gene. These 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 1-24). The condition results from a single gene mutation on chromosome 15, fibrillin-1, that leads to elastin and collagen defects. These defects produce a variety of ocular, skeletal, and cardiovascular disorders. Some clinical manifestations of Marfan syndrome include the following:

- 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
- Nearsightedness and lens displacement (ocular hallmark)
- Valvular defects (e.g., redundancy of leaflets, stretching of the chordae tendineae, mitral valve regurgitation, and aortic regurgitation)
- Coarctation of the aorta (most life threatening)

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

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

A thorough history and physical examination are vital in diagnosing Marfan syndrome. In most cases, the family history is positive for the disease or the symptoms, but as many as 30% of patients have no family history of this condition. A physical examination would reveal the presence of the hallmark lens displacement and other symptoms of the disease. Diagnostic procedures include a skin biopsy that would be positive for fibrillin, X-rays that would confirm


Courtesy of Rick Guidotti/Positive Exposure/National Marfan Foundation

FIGURE 1-24 Marfan syndrome.

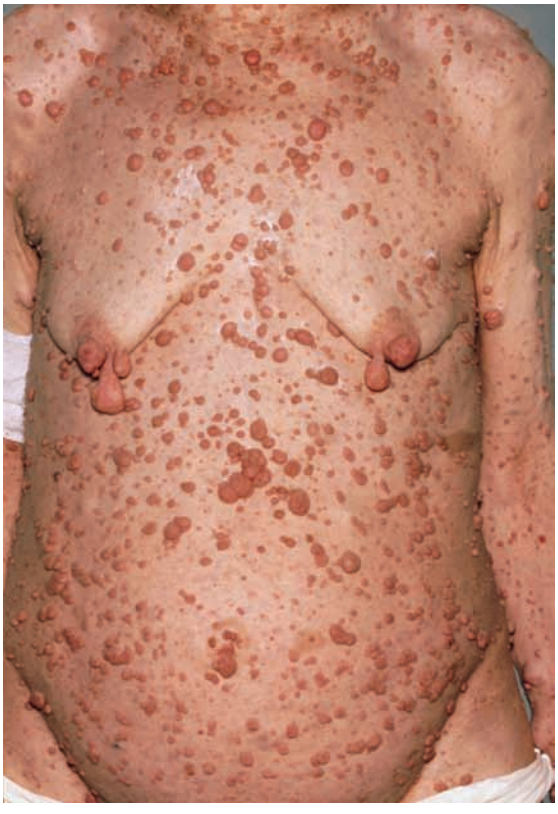

© SPL/Science Source

FIGURE 1-25 Neurofibromatosis type 1.

the skeletal abnormalities, an echocardiogram that would reveal the cardiac abnormality, and a DNA analysis for the gene. 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 closure of long bones, thereby limiting height
- Beta-adrenergic blockers 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 two main types. Type 1 (FIGURE 1-25) involves cutaneous lesions that may include raised lumps, café au lait spots (brown pigmented birthmarks), and freckling; this type is caused by a mutation on chromosome 17. Type 2 involves bilateral acoustic (eighth cranial nerve) tumors that cause hearing loss; it is caused by a mutation on chromosome 22.

People with neurofibromatosis can be affected in many ways. For example, an increased incidence of learning disabilities and seizure disorders is associated with neurofibromatosis. The appearance of the lesions may vary between individuals, but the lesions can be disfiguring in some cases. There is no cure for neurofibromatosis, but surgeries may be necessary to remove the lesions for palliative or safety reasons. A small risk that the type 1 lesions may develop into cancer exists. Other issues that may develop with type 1 include ocular problems, scoliosis, and bone defects.

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 allele pairs. Those persons with heterozygous pairs 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, the enzyme necessary for the conversion of phenylalanine to tyrosine, due to a mutation on chromosome 12. This deficiency leads to toxic levels of phenylalinine in the blood, causing central nervous system damage. If untreated, PKU leads to severe intellectual disability. Symptoms develop slowly and can go undetected. Because untreated cases almost always lead to intellectual disability, newborns are routinely screened for PKU shortly after birth by testing for high serum phenylalanine levels. If untreated, newborns can develop the following clinical manifestations:

- Failure to meet milestones
- Microcephaly
- Progressive neurological decline
- Seizures
- Hyperactivity
- Electrocardiograph (EKG) abnormalities
- Learning disability
- Mousy-smelling urine, skin, hair, and sweat
- Eczema

Treatment for PKU involves consumption of a diet low in phenylalanine. Newborns may be breastfed, but the quantity of breastmilk taken in has to be monitored. Special infant formulas are available for supplementation. Dietary restrictions include avoiding proteins and minimizing starches. Oral medications are available to lower phenylalanine (e.g., sapropterin [Kuvan]), and gene therapy has also demonstrated promise in treating PKU.

Tay-Sachs Disease

Tay-Sachs disease is a deficiency or absence of hexosaminidase A, which is a lysosomal enzyme necessary to metabolize certain lipids called gangliosides. These lipids accumulate in the lysosomes of nerve cells and progressively destroy and demyelinate nerve cells. This destruction of nerve cells leads to a progressive mental and motor deterioration, often causing death by 5 years of age. Tay-Sachs disease is caused by a defective gene on chromosome 15 and almost exclusively affects individuals of Jewish descent, of whom about 1 in every 27 is a carrier. Clinical manifestations of Tay-Sachs usually appear between 3 to 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
- Progressive vision loss
- Deafness and blindness
- Seizure activity
- Paralysis
- Spasticity
- Pneumonia

Tay-Sachs disease 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 this disease, genetic counseling is important for persons of Jewish ancestry and individuals with a positive family history. No cure for Tay-Sachs disease exists; most treatments are supportive. Those supportive approaches include parenteral nutrition (tube feedings), pulmonary hygiene (e.g., suctioning and postural drainage), skin care, 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 1-26) is an X-linked dominant disorder associated with a single trinucleotide gene sequence (FMR1) on the X chromosome, which leads to failure to express a protein necessary for neural tube development. 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
- Seizures
- Speech and language delays
- Tendency to avoid eye contact

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.

© Courtesy of Nikki Deal

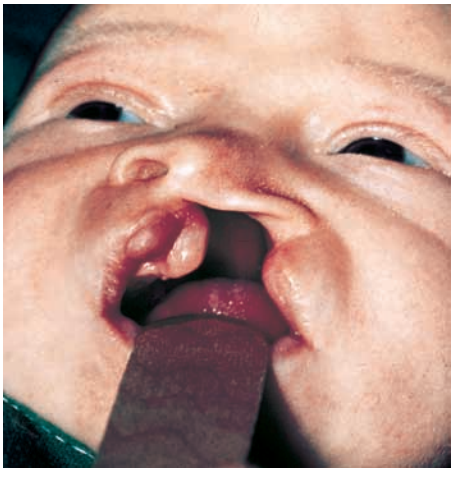
FIGURE 1-26 Fragile X syndrome.

Multifactorial Disorders

Most **multifactorial disorders** are the result of an interaction between genes and environmental factors. These disorders do 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. Environmental factors that play roles in these disorders may include any of a number of **teratogens** (birth defect–causing agents) such as infections, chemicals, or radiation.

Cleft Lip and Cleft Palate

Cleft lip and palate may occur either together or separately. These conditions develop in the second month of pregnancy, when the facial structures do not fuse properly. Maternal smoking and diabetes are significant risk factors for their development. Additionally, these defects are more prevalent in Native Americans and Asian Americans, with African Americans having the lowest prevalence. The deformities may be unilateral or bilateral. The severity of the deformity ranges from a mild notch to involvement of the lip, palate, and tongue (FIGURE 1-27). Feeding and nutritional issues may occur because of these structural problems, which affect the ability to nurse/eat. Clinical manifestations are obvious at birth and can be detected 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.



Courtesy of Leonard V. Crowley, MD, Century College

FIGURE 1-27 Cleft lip and palate.

Chromosomal Disorders

Chromosomal disorders are a major category of genetic disorders that result most often from 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 15–60 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 result in 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 results in three

FIGURE 1-28 Down syndrome.

copies of chromosome 21 (FIGURE 1-28). Risk of this mutation increases with greater parental age and environmental teratogen exposure. 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)
- Single crease on the palm (simian crease)
- White spots on the iris
- Intellectual disability
- Congenital heart defects
- 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. Clinical manifestations 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's syndrome, is the result of a deletion of part or all of an X chromosome (FIGURE 1-29). This condition occurs in about 1 of every 2,000 live births. Turner's 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
- Visual disturbances (e.g., glaucoma)
- Ear infections
- Hearing loss
- Reduced bone mass, which increases the risk for fractures

Turner's syndrome is treated by administering female sex hormones to promote 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.

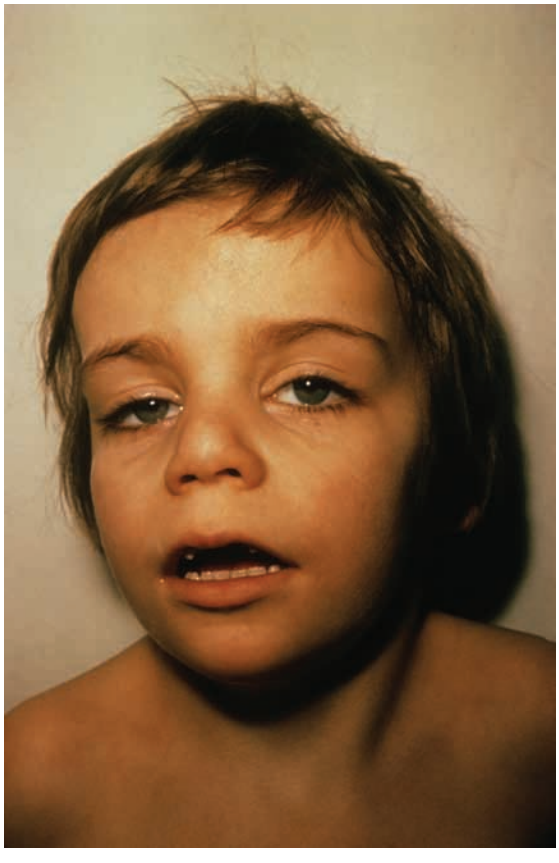


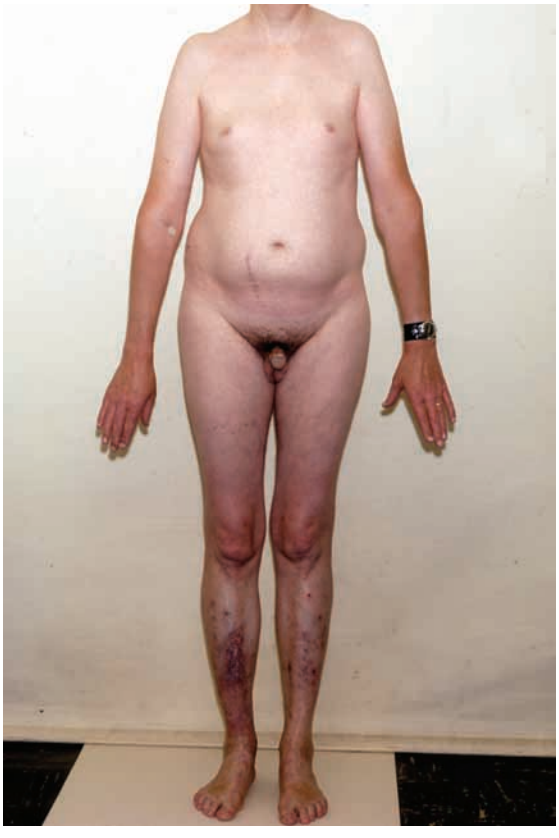
FIGURE 1-29 Turner's syndrome.

Polysomy X

Polysomy X, or Klinefelter's 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 (FIGURE 1-30). The syndrome usually becomes apparent at puberty when testicles fail to mature, rendering affected boys infertile. Clinical manifestations of Klinefelter's syndrome include the following:

- 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
- Increased incidence of pulmonary disease and varicose veins

Other problems that can develop include osteoporosis and breast cancer. Diagnostic procedures consist of 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.



Courtesy of www.dermnet.com

FIGURE 1-30 Klinefelter's syndrome.

CHAPTER 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. These neoplasms can be 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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