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Contents in Brief

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The *Curiosity* rover on Mars.

1

Basic Chemistry

Chapter Outline

AP On August 6, 2012, NASA's *Curiosity* rover successfully landed on the surface of Mars. Previous missions, including the long-lived *Spirit* and *Opportunity* rovers, focused on exploring the planet and detecting whether water once existed on Mars. *Curiosity* was designed to explore whether Mars at one time may have had the conditions to support life by looking for elements that we know are associated with life on Earth.

Curiosity possesses a collection of highly sophisticated instruments that can detect trace levels of specific elements and minerals in the Martian soil and rocks. For example, ChemCam uses a small laser to blast away portions of rocks. As the rocks are vaporized, another instrument records the types of elements and molecules that are released. ChemCam can determine whether the rocks were formed in the presence of water, a molecule that is essential for life as we know it. Another set of experiments is called SAM (Sample Analysis at Mars), which contains an instrument, called a spectrometer, that can be used to detect the presence of carbon, hydrogen, nitrogen, and oxygen in the Martian soil. Other spectrometers on *Curiosity* are also able to detect the presence of elements and chemical compounds that are associated with life. In its first year of operation, *Curiosity* detected water in the soil of Mars, and it is providing insights into whether the conditions on Mars may have supported life in the past. In the process, we may better understand how life evolved on our planet.

As you read through the chapter, think about these Essential Questions:

1. Why do living organisms require matter and free energy, and from where do they get it? 2.A.1.a.3
2. How do subatomic particles determine the chemical properties of an atom and its bonding tendencies? 2.A.2.d.3 2.A.2.g.3
3. How are water's unique properties important to life on Earth? 2.A.2.d.3 4.A.1

Following *the* BIG IDEAS

BIG IDEA 2 — Knowledge of the properties of atoms, the bonds they make, and the unique properties they possess help explain the structure and functions of life systems.

BIG IDEA 4 — The chemistry of life, its atomic and molecular structure, will explain how life works at all levels of organization.

1.1 Chemical Elements

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe how protons, neutrons, and electrons relate to atomic structure.
2. Use the periodic table to evaluate relationships between atomic number and mass number.
3. Describe how variations in an atomic nucleus account for its physical properties.
4. Determine how electrons are configured around a nucleus.

Throw a ball, pat your cat, rake leaves, turn a page; everything we touch—from the water we drink to the air we breathe—is composed of matter. **Matter** refers to anything that takes up space and has mass. Although matter has many diverse forms—anything from molten lava to kidney stones—it exists in only four distinct states: solid, liquid, gas, or plasma.

Elements

All matter, both nonliving and living, is composed of basic substances called **elements.** An element is a substance that cannot be broken down to simpler substances by ordinary chemical means. Each element has its own unique properties, such as density, solubility, melting point, and reactivity. It is quite remarkable that, in the known universe, there are only 92 naturally occurring elements (see Appendix C) that serve as the building blocks of matter. Other elements have been artificially constructed by physicists and are not biologically important.

Both the Earth's crust and all organisms are composed of elements, but they differ as to which ones are common. Only six elements—carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulfur—are basic to life and make up about 95% of the body weight of organisms. The properties of these elements are essential to the uniqueness of cells and organisms, such as both the human and the tree in Figure 1.1. Other elements, such as potassium, calcium, iron, magnesium, and zinc, are also important to life.

Atoms

In the early 1800s, the English scientist John Dalton (1776–1844) developed the *atomic theory,* which says that elements consist of tiny particles called **atoms** (Gk. *atomos,* "uncut, indivisible"). An atom is the smallest part of an element that displays the properties of the element. An element and its atoms share the same name. One or two letters create the **atomic symbol** that stands for this name. For example, the symbol H means a hydrogen atom, the symbol Rn stands for radon, and the symbol Na (L. *natrium*) is used for a sodium atom.

Physicists have identified a number of subatomic particles that make up atoms. The three best-known subatomic particles are positively charged **protons,** uncharged **neutrons,** and negatively charged **electrons.** Protons and neutrons are located within

Figure 1.1 A comparison of the elements that make up the Earth's crust and living organisms. The graph inset shows that the Earth's crust primarily contains the elements silicon (Si), aluminum (Al), and oxygen (O). Living organisms, such as the tree and human, primarily contain the elements oxygen (O), nitrogen (N), carbon (C), and hydrogen (H). Biological molecules also often contain the elements sulfur (S) and phosphorus (P).

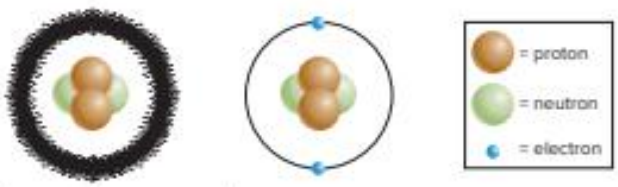
the nucleus of an atom, and electrons move about the nucleus. Figure 1.2 shows the arrangement of the subatomic particles in a helium atom, which has only two electrons. Since the precise location of the electrons is difficult to establish, we often indicate their probable positions using shading (Fig. 1.2*a*). When we are using a model of an atom—for example, to predict a chemical reaction—we indicate the average location of the electrons using **electron shells** (Fig. 1.2*b*).

The concept of an atom has changed greatly since Dalton's day. Today's physicists are using high-energy supercolliders, such as the Large Hadron Collider in Europe, to explore the intricate structure of the atom.

It is also important to note that the majority of an atom is empty space. If an atom could be drawn the size of a football field, the nucleus would be like a gumball in the center of the field, and the electrons would be tiny specks whirling about in the upper stands. We should also realize that both of the models in Figure 1.2 indicate only where the electrons are expected to be most of the time. In our analogy, the electrons might very well stray outside the stadium at times.

Atomic Number and Mass Number

Atoms have not only an atomic symbol but also an atomic number and a mass number. All the atoms of an element have the same number of protons housed in the nucleus. This is called the **atomic number,** which accounts for the unique properties of this type of atom. Generally, atoms are assumed to be electrically neutral, meaning that the number of electrons is the same as the number of protons in the atom. The atomic number tells you not only the number of protons but also the number of electrons.



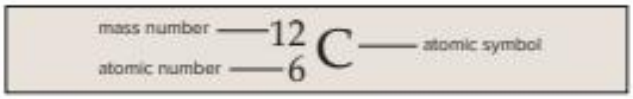
a. b.

Subatomic Particles			
Particle	Electric Charge	Atomic Mass Unit (AMU)	Location
Proton	+1	1	Nucleus
Neutron	0	1	Nucleus
Electron	−1	0	Electron shell

c.

Figure 1.2 Model of helium (He). Atoms contain subatomic particles, which are located as shown. Protons and neutrons are found within the nucleus, and electrons are outside the nucleus. **a.** The shading shows the probable location of the electrons in the helium atom. **b.** The average location of an electron is sometimes represented by an electron shell. **c.** The electric charge and the atomic mass units (AMU) of the subatomic particles vary as shown.

Each atom also has its own **mass number,** which is the sum of the protons and neutrons in the nucleus. Protons and neutrons are assigned one atomic mass unit (AMU) each. Electrons are so small that their AMU is considered zero in most calculations (Fig. 1.2*c*). By convention, when an atom stands alone (and not in the periodic table, discussed next), the atomic number is written as a subscript to the lower left of the atomic symbol. The mass number is written as a superscript to the upper left of the atomic symbol:

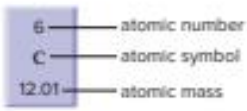


Whereas each atom of an element has the same atomic number, the number of neutrons may vary slightly. **Isotopes** (Gk. *isos,* "equal") are atoms of the same element that differ in the number of neutrons. For example, the element carbon has three naturally occurring isotopes:

$$^{12}_{6}C \qquad ^{13}_{6}C \qquad ^{14}_{6}C$$

It is important to note that the term *mass* is used, not *weight,* because mass is constant, while weight changes according to the gravitational force of a body. The gravitational force of the Earth is greater than that of the moon; therefore, substances weigh less on the moon, even though their mass has not changed.

The term **atomic mass** refers to the average mass for all the isotopes of that atom. Since the majority of carbon is carbon 12, the atomic mass of carbon is closer to 12 than to 13 or 14. To determine the number of neutrons from the atomic mass, subtract the number of protons from the atomic mass and take the closest whole number.



The Periodic Table

Once chemists discovered a number of the elements, they began to realize that even though each element consists of a different atom, certain chemical and physical characteristics recur. The periodic table, developed by the Russian chemist Dmitri Mendeleev (1834–1907), was constructed as a way to group the elements, and therefore atoms, according to these characteristics.

Figure 1.3 is a portion of the periodic table, which is shown in total in Appendix C. In the periodic table, the horizontal rows are called periods, and the vertical columns are called groups. The atomic number of every atom in a period increases by one if you read from left to right. All the atoms in a group share similar chemical characteristics, namely in the type of chemical bonds that they form. For example, the atoms in group VIII are called the noble gases, because they are inert and rarely react with another atom. Helium, neon, argon, and krypton are all examples of noble gases.

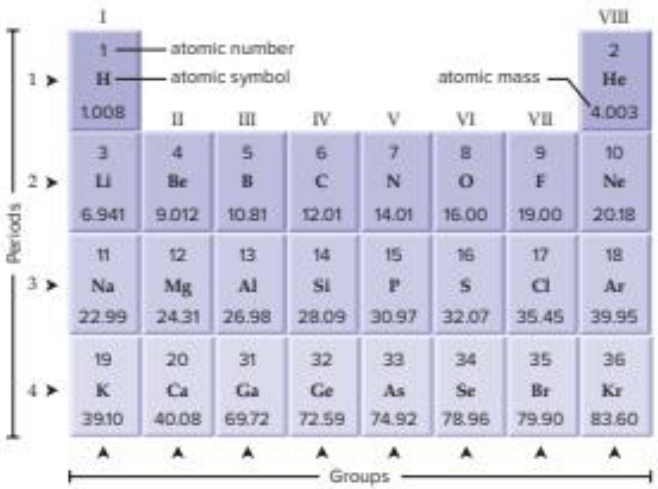


Figure 1.3 A portion of the periodic table. In the periodic table, elements are listed in the order of their atomic numbers but are arranged so that each element is placed in a group (vertical column) and period (horizontal row). All the atoms in a particular group have the same number of valence electrons and therefore share common chemical characteristics. Each period shows the number of electron shells for an element. This abbreviated periodic table contains the elements most important in biology; the complete periodic table is in Appendix C.

Radioactive Isotopes

Some isotopes of an element are unstable, or radioactive. For example, unlike the other two isotopes of carbon, carbon 14 changes over time into nitrogen 14, which is a stable isotope of the element nitrogen. As carbon 14 decays, it releases various types of energy in the form of rays and subatomic particles. The radiation given off by radioactive isotopes can be detected in various ways. The Geiger counter is an instrument that is commonly used to detect radiation. In 1896, the French physicist Antoine-Henri Becquerel (1852–1908) discovered that a sample of uranium would produce a bright image on a photographic plate even in the dark, and a similar method of detecting radiation is still in use today. Marie Curie (1867–1934), who worked with Becquerel, coined the term *radioactivity* and contributed much to its study. Today, biologists use radiation to date objects from our distant past, to create images, and to trace the movement of substances in the body.

Low Levels of Radiation

The chemical behavior of a radioactive isotope is essentially the same as that of the stable isotopes of an element. This means that you can put a small amount of radioactive isotope in a sample and it becomes a *tracer* by which to detect molecular changes. Melvin Calvin and his co-workers used carbon 14 to detect all the various reactions that occur during the process of photosynthesis.

The importance of chemistry to medicine is nowhere more evident than in the many medical uses of radioactive isotopes. Specific tracers are used in imaging the body's organs and tissues. For example, after a patient drinks a solution containing a minute amount of iodine 131, it becomes concentrated in the thyroid—the only organ to take it up. A subsequent image of the thyroid indicates whether it is healthy in structure and function (Fig. 1.4*a*).

Positron-emission tomography (PET) is a way to determine the comparative activity of tissues. Radioactively labeled glucose, which emits a subatomic particle known as a positron, is injected into the body. The radiation given off is detected by sensors and analyzed by a computer. The result is a color image that shows which tissues have taken up the glucose and are therefore metabolically active. The red areas surrounded by green in Figure 1.4*b* indicate which areas of the brain are most active. PET scans of the brain are used to evaluate patients who have memory disorders of an undetermined cause or suspected brain tumors or seizure disorders that might benefit from surgery. PET scans, utilizing radioactive thallium, can detect signs of coronary artery disease and low blood flow to the heart.

High Levels of Radiation

Radioactive substances in the environment can harm cells, damage DNA, and cause cancer. When Marie Curie was studying radiation, its harmful effects were not known, and she and many of her co-workers developed cancer. The release of radioactive particles following a nuclear power plant accident, as occurred in Japan in 2011 following a tsunami, can have far-reaching and long-lasting effects on human health. The harmful effects of radiation can be put to good use, however (Fig. 1.5). Radiation from radioactive isotopes has been used for many years to sterilize medical and dental products. Radiation is now used to sterilize the U.S. mail and other packages to free them of possible pathogens, such as anthrax spores. High radiation is often used to kill cancer cells. Targeted radioisotopes can be introduced into the body, so that the subatomic particles emitted destroy only cancer cells, with little risk to the rest of the body.

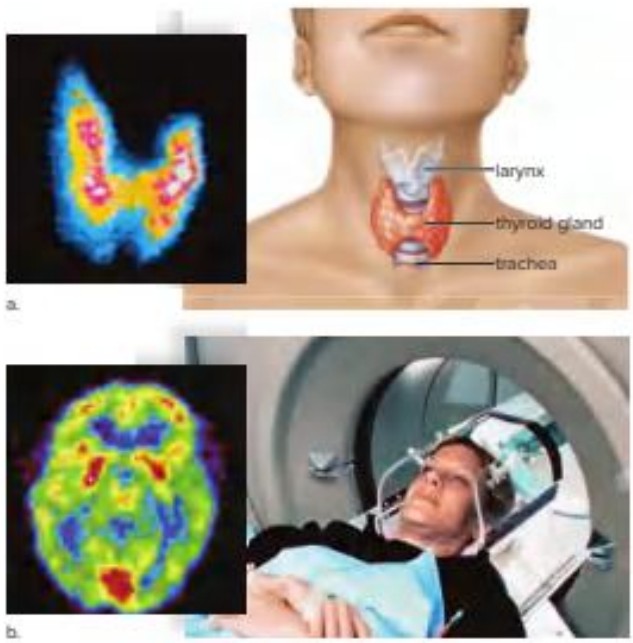


Figure 1.4 Low levels of radiation. **a.** Medical scan of the thyroid gland (colored image) indicates the presence of a tumor that does not take up radioactive iodine. **b.** A positron-emission tomography (PET) scan reveals which portions of the brain are most active (green and red colors).

a. b.

Figure 1.5 High levels of radiation. **a.** Radiation used to kill bacteria and fungi on peaches reduces spoilage and allows them to stay fresh for a longer period of time. **b.** Physicians use targeted radiation therapy to kill cancer cells.

Electrons and Energy

Various models may be used to illustrate the structure of a single atom. While the number of neutrons and protons may easily be depicted, since they are located in the nucleus, it is not possible to determine the precise location of any individual electron at any given moment. One of the more common models is the Bohr model (Fig. 1.6), developed by the physicist Niels Bohr (1885–1962).

In the Bohr model, the electron shells (also called electron orbitals) about the nucleus are used to represent the average energy levels of an electron. Because the negatively charged electrons are attracted to the positively charged nucleus, it takes energy to push them away and keep them in their own shell. The more distant the shell, the more energy it takes. Therefore, it is more accurate to speak of electrons as being at particular energy levels in relation to the nucleus. Electrons may move between energy levels. For example, when we explore the processes of photosynthesis, you will learn that when atoms absorb the energy of the sun, electrons are boosted to a higher energy level. Later, as the electrons return to their original energy level, energy is released and transformed into chemical energy. This chemical energy supports all life on Earth; therefore, our very existence is dependent on the energy of electrons.

Let's take a more detailed look at the Bohr models depicted in Figure 1.6. The first shell is closest to the nucleus and can contain two electrons; the second shell can contain eight electrons. In all atoms, the lower shells are filled with electrons before the next higher level contains any electrons.

The sulfur atom, with an atomic number of 16, has two electrons in the first shell, eight electrons in the second shell, and six electrons in the outer, third shell. Revisit the periodic table (see Fig. 1.3), and note that sulfur is in the third period. In other words, the period tells you how many shells an atom has. Also note that sulfur is in group VI. The group tells you how many electrons an atom has in its outer shell.

Regardless of how many shells an atom has, the outermost shell is called the **valence shell.** The valence shell is important, because it determines many of an atom's chemical properties. If an atom has only one shell, the valence shell is complete when it has two electrons. In atoms with more than one shell, the valence shell is most stable when it has eight electrons. This is called the **octet rule.** Each atom in a group within the periodic table has the same number of electrons in its valence shell. As mentioned previously, all the atoms in group VIII of the periodic table have eight electrons in their valence shell. These elements are also called the noble gases, because they do not ordinarily react.

The electrons in the valence shells play an important role in determining how an element undergoes chemical reactions. Atoms with fewer than eight electrons in the outer shell react with other atoms in such a way that after the reaction each has a stable outer shell. As we will see, the number of electrons in an atom's valence shell determines whether the atom gives up, accepts, or shares electrons to acquire eight electrons in the outer shell.

Check Your Progress 1.1

1. Contrast atomic number and mass number.
2. Examine the periods and groups from the periodic table to determine the electron configuration of chlorine.
3. Explain how two isotopes of an element vary with regard to their atomic structure.

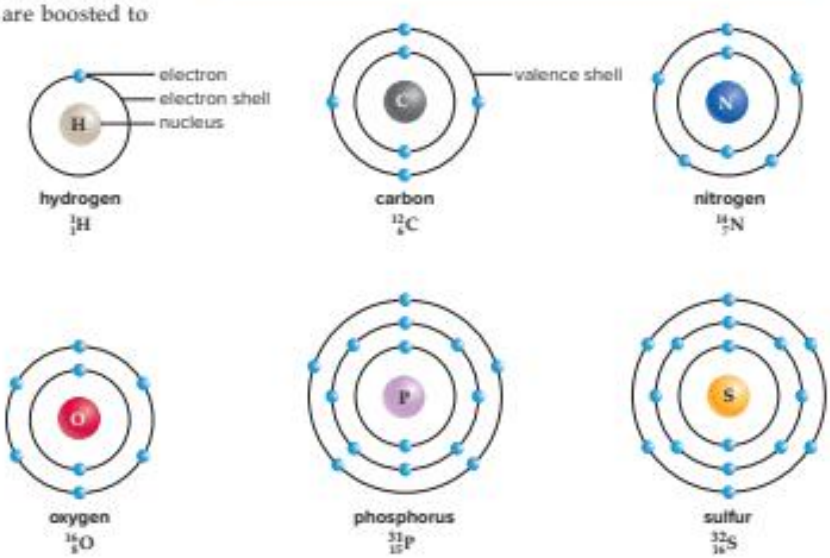


Figure 1.6 Bohr models of atoms. Electrons orbit the nucleus at particular energy levels (electron shells). The first shell contains up to two electrons, and thereafter each shell is most stable when it contains 8 electrons. Atoms with an atomic number above 20 may have more electrons in their outer shells. The outermost, or valence, shell helps determine the atom's chemical properties and how many other elements it can interact with.

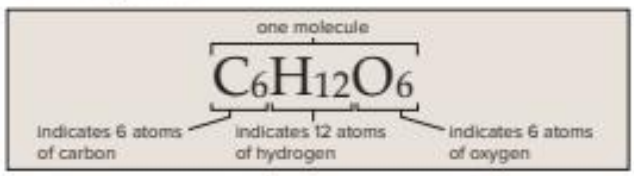
1.2 Molecules and Compounds

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe how elements are combined into molecules and compounds.
2. List the different types of bonds that occur between elements.
3. Explain the difference between a polar and a nonpolar covalent bond.

A **molecule** exists when two or more elements bond together; it is the smallest part of a compound that retains its chemical properties. A **compound** is a molecule containing at least two different elements. In practice, these two terms are used interchangeably, but in biology we usually speak of molecules. Water (H_2O) is a molecule that contains atoms of hydrogen and oxygen. A **formula** tells you the number of each kind of atom in a molecule. For example, the formula for glucose is:



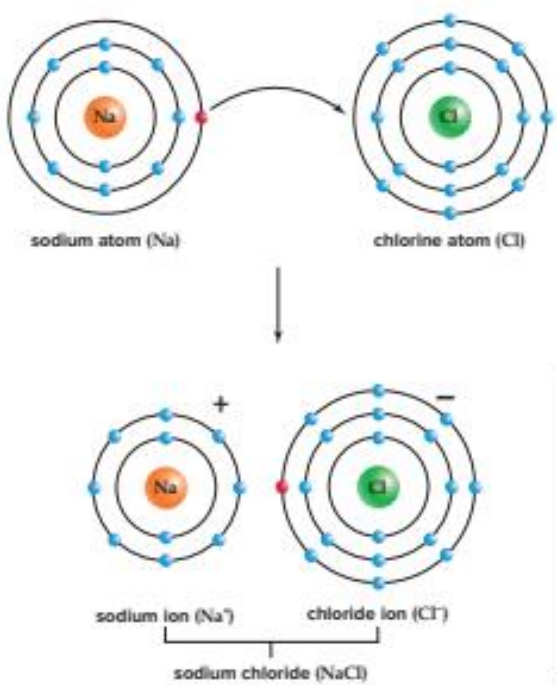
Electrons possess energy, as do the bonds between atoms. Organisms are directly dependent on chemical-bond energy to maintain their organization. As you may know, organisms routinely break down glucose, the sugar shown above, to obtain energy. When a chemical reaction occurs, as when glucose is broken down, electrons shift in their relationship to one another, and energy is released. Spontaneous reactions, which occur freely, always release energy.

Ionic Bonding

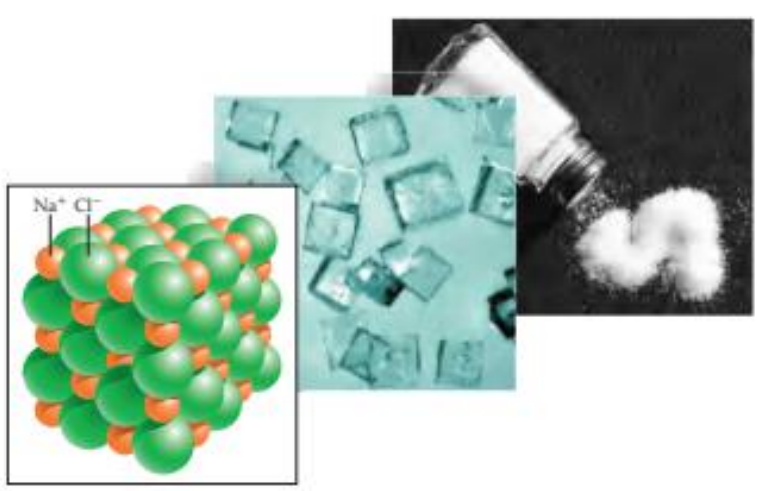
Sodium (Na), with only one electron in its valence shell, tends to be an electron donor (Fig. 1.7*a*). Once it gives up this electron, the second shell, with its stable configuration of eight electrons, becomes its outer shell. Chlorine (Cl), on the other hand, tends to be an electron acceptor. Its valence shell has seven electrons, so if it acquires only one more electron it has a stable outer shell. When a sodium atom and a chlorine atom come together, an electron is transferred from the sodium atom to the chlorine atom. Now both atoms have eight electrons in their outer shells.

This electron transfer, however, causes a charge imbalance in each atom. After giving up an electron, the sodium atom has one more proton than it has electrons; therefore, it has a net charge of +1 (symbolized by Na^+). After accepting an electron, the chlorine atom has one more electron than it has protons; therefore, it has a net charge of −1 (symbolized by Cl^-). These charged particles are called **ions.** Sodium (Na^+) and chloride (Cl^-) are not the only biologically important ions. Some, such as potassium (K^+), are formed by the transfer of a single electron to another atom; others, such as calcium (Ca^{2+}) and magnesium (Mg^{2+}), are formed by the transfer of two electrons.

Ionic compounds are held together by an attraction between negatively and positively charged ions, called an **ionic bond.** When sodium reacts with chlorine, an ionic compound called sodium chloride (NaCl) results. Sodium chloride is an example of a salt. It is commonly called table salt, because it is used to season food (Fig. 1.7*b*). Salts are solid substances that usually separate and exist as individual ions in water.



a.



b.

Figure 1.7 Formation of sodium chloride (table salt). **a.** During the formation of sodium chloride, an electron is transferred from the sodium atom to the chlorine atom. At the completion of the reaction, each atom has eight electrons in the outer shell, but each also carries a charge as shown. **b.** In a sodium chloride crystal, ionic bonding between Na^+ and Cl^- causes the atoms to assume a three-dimensional lattice in which each sodium ion is surrounded by six chloride ions, and each chloride ion is surrounded by six sodium ions. The result is crystals of salt as in table salt.

Covalent Bonding

A **covalent bond** results when two atoms share electrons in such a way that each atom has an octet of electrons in the outer shell (or two electrons, in the case of hydrogen). In a hydrogen atom, the outer shell is complete when it contains two electrons. If hydrogen is in the presence of a strong electron acceptor, it gives up its electron to become a hydrogen ion (H^+). But if this is not possible, hydrogen can share with another atom and thereby have a completed outer shell. For example, one hydrogen atom will share with another hydrogen atom. Their two electron shells overlap, and the electrons are shared between them (Fig. 1.8*a*). Because they share the electron pair, each atom has a completed outer shell.

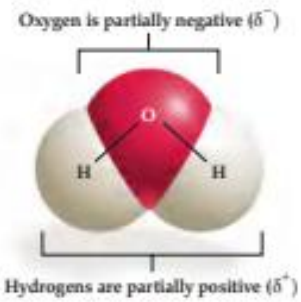
A more common way to symbolize that atoms are sharing electrons is to draw a line between the two atoms, as in the structural formula H—H. Just as a handshake requires two hands, one from each person, a covalent bond between two atoms requires two electrons, one from each atom. In a molecular formula, the line is omitted and the molecule is simply written as H_2.

Sometimes, atoms share more than one pair of electrons to complete their octets. A double covalent bond occurs when two atoms share two pairs of electrons (Fig. 1.8*b*). To show that oxygen gas (O_2) contains a double bond, the molecule can be written as O = O. It is also possible for atoms to form triple covalent bonds, as in nitrogen gas (N_2), which can be written as N≡N. Single covalent bonds between atoms are quite strong, but double and triple bonds are even stronger.

Nonpolar and Polar Covalent Bonds

When the sharing of electrons between two atoms is equal, the covalent bond is said to be a **nonpolar covalent bond.** However, in some cases one atom is able to attract electrons to a greater degree than the other atom. In this case, we say that the atom that has a greater attraction for a shared pair of electrons has a greater **electronegativity.** When electrons are not shared equally, the covalent bond is a **polar covalent bond.**

The shape of a molecule may also influence whether it is polar or nonpolar. While carbon is larger and has more protons than a hydrogen atom, the symmetrical nature of a methane molecule cancels out any polarities; thus, methane is a nonpolar molecule. Not so in water, which has this shape:



In water, the oxygen atom is more electronegative than the hydrogen atoms; as a result, water molecules are polar. Moreover, because of its nonsymmetrical shape, the polar bonds cannot cancel each other, and water is a polar molecule. The more electronegative end of the molecule is designated slightly negative (δ^-), and the hydrogens are designated slightly positive (δ^+).

Water is not the only polar molecule in living organisms. For example, the amine group (—NH_2) is polar, and this causes amino acids and nucleic acids to exhibit polarity, as we will see in the next chapter. The polarity of molecules affects how they interact with other molecules.

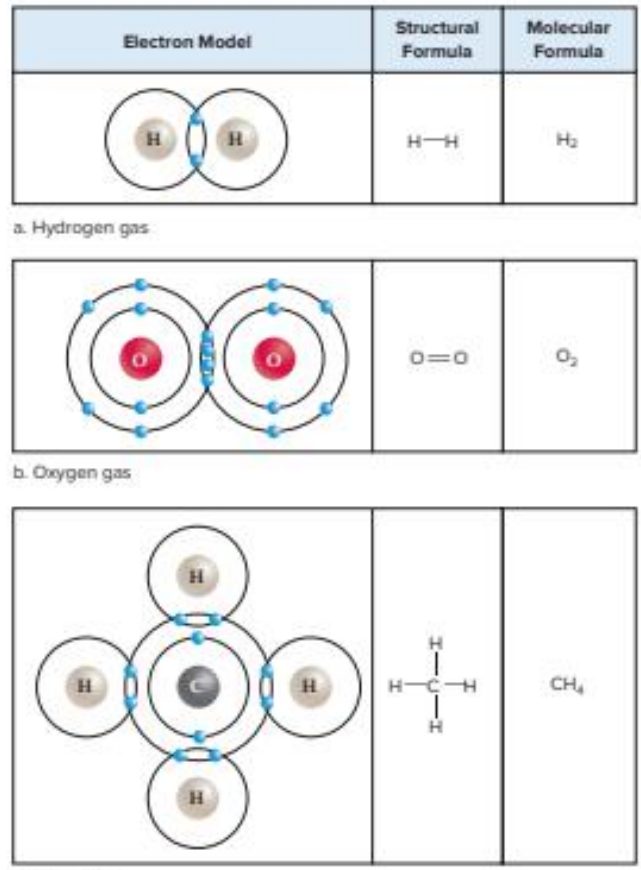


Figure 1.8 Covalently bonded molecules. In a covalent bond, atoms share electrons, allowing each atom to have a completed outer shell. **a.** A molecule of hydrogen (H_2) contains two hydrogen atoms sharing a pair of electrons. This single covalent bond can be represented in any of the three ways shown. **b.** A molecule of oxygen (O_2) contains two oxygen atoms sharing two pairs of electrons. This results in a double covalent bond. **c.** A molecule of methane (CH_4) contains one carbon atom bonded to four hydrogen atoms.

Check Your Progress 1.2

1. Compare and contrast an ionic bond with a covalent bond.
2. Describe the process by which ions are formed.
3. Explain why methane is nonpolar but water is polar.

1.3 Chemistry of Water

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe how water associates with other molecules in solution.
2. Describe why the properties of water are important to life.
3. Analyze how water's solid, liquid, and vapor states allow life to exist on Earth.

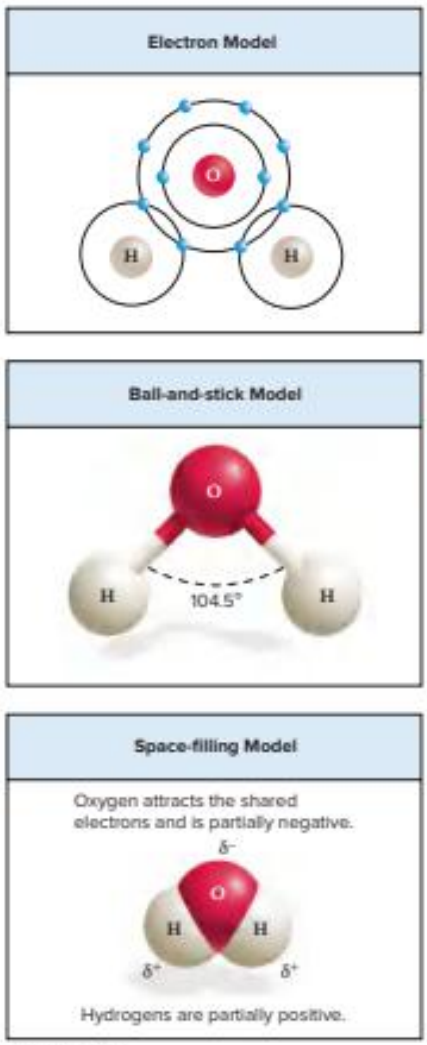
Figure 1.9*a* recaps what we know about the water molecule. The structural formula at the top shows that when water forms, an oxygen atom is sharing electrons with two hydrogen atoms. The ball-and-stick model in the center shows that the covalent bonds between oxygen and each of the hydrogens are at an angle of 104.5°. Finally, the space-filling model gives us the three-dimensional shape of the molecule and indicates its polarity.

In biology, we often state that structure relates to function. This is true at a variety of organizational levels, including molecules such as water. For example, hormones have specific shapes that allow them to be recognized by the cells in the body. We can stay well only when antibodies recognize the shapes of disease-causing agents, the way a key fits a lock, and are able to remove them.

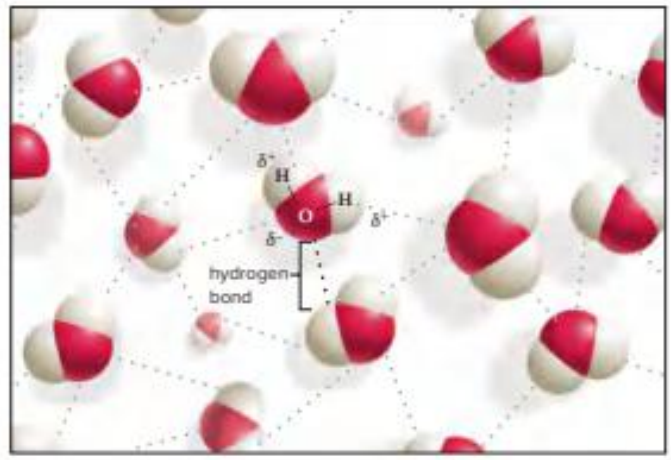
The shape of a water molecule and its polarity result in the formation of hydrogen bonds. A **hydrogen bond** is caused by the attraction of a slightly positive hydrogen to a slightly negative atom in the vicinity. In carbon dioxide, O = C = O, a slight difference in polarity between carbon and the oxygens is present, but because carbon dioxide is symmetrical, the opposing charges cancel one another and hydrogen bonding does not occur.

Hydrogen Bonding

The dotted lines in Figure 1.9*b* indicate that the hydrogen atoms in one water molecule are attracted to the oxygen



a. Water (H_2O)



b. Hydrogen bonding between water molecules

Figure 1.9 Water molecule. **a.** Three models for the structure of water. The electron model does not indicate the shape of the molecule. The ball-and-stick model shows that the two bonds in a water molecule are angled at 104.5°. The space-filling model also shows the V shape of a water molecule. **b.** Hydrogen bonding between water molecules. Each water molecule can hydrogen bond with up to four other molecules, in three dimensions. When in a liquid state, water is constantly forming and breaking hydrogen bonds.

atoms in other water molecules. Each of these hydrogen bonds is weaker than an ionic or covalent bond. The dotted lines indicate that hydrogen bonds are more easily broken than the other bonds.

Hydrogen bonding is not unique to water. Other biological molecules, such as DNA, have polar covalent bonds involving an electropositive hydrogen and usually an electronegative oxygen or nitrogen. In these instances, a hydrogen bond can occur within the same molecule or between nearby molecules.

Although a single hydrogen bond is more easily broken than a single covalent bond, multiple hydrogen bonds are collectively quite strong. Hydrogen bonds between cellular molecules help maintain their proper structure and function. For example, hydrogen bonds hold the two strands of DNA together. When DNA makes a copy of itself, hydrogen bonds easily break, allowing DNA to unzip. But normally, the hydrogen bonds add stability to the DNA molecule. Similarly, the shape of protein molecules is often maintained by hydrogen bonding between different parts of the same molecule. As we will see, many of the important properties of water are the result of hydrogen bonding.

Properties of Water

The first cell(s) evolved in water, and all living organisms are 70–90% water. Because of hydrogen bonding, water molecules cling together, and this association gives water its unique chemical properties. Without hydrogen bonding between molecules, water would freeze at –100°C and boil at –91°C, making most of the water on Earth steam, and life unlikely. Hydrogen bonding is responsible for water being a liquid at temperatures typically found on the Earth's surface. It freezes at 0°C and boils at 100°C. These and other unique properties of water make it essential to the existence of life as we know it. As noted in the chapter opener, the search for life on other planets often begins with the search for water.

Water Has a High Heat Capacity

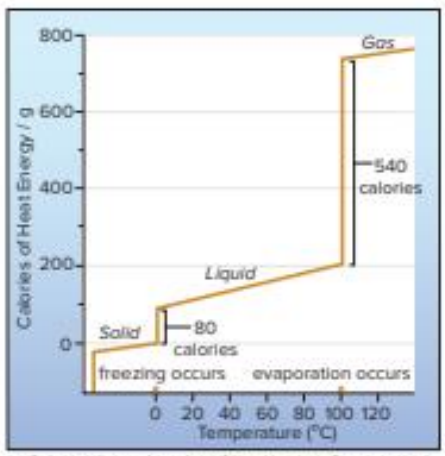
A **calorie** is the amount of heat energy needed to raise the temperature of 1 g of water 1°C. In comparison, other covalently bonded liquids require input of only about half this amount of energy to rise in temperature 1°C. The many hydrogen bonds that link water molecules together help water absorb heat without a great change in temperature. Converting 1 g of the coldest liquid water to ice requires the loss of 80 calories of heat energy (Fig. 1.10*a*). Water holds on to its heat, and its temperature falls more slowly than that of other liquids. This property of water is important not only for aquatic organisms but for all life.

Because the temperature of water rises and falls slowly, organisms are better able to maintain their normal internal temperatures and are protected from rapid temperature changes.

Water Has a High Heat of Evaporation

When water boils, it evaporates, meaning that it vaporizes into the environment. Converting 1 g of the hottest water to a gas requires an input of 540 calories of energy. Water has a high heat of evaporation because hydrogen bonds must be broken before water boils.

Water's high heat of vaporization gives animals in a hot environment an efficient way to release excess body heat. When an animal sweats, or gets splashed, body heat is used to vaporize water, thus cooling the animal (Fig. 1.10*b*). Because of water's high heat of vaporization and ability to hold on to its heat, temperatures along the coasts are moderate. During the summer, the ocean absorbs and stores solar heat, and during the winter, the ocean releases it slowly. In contrast, the interior regions of continents experience abrupt changes in temperatures.



a. Calories lost when 1 g of liquid water freezes and calories required when 1 g of liquid water evaporates.

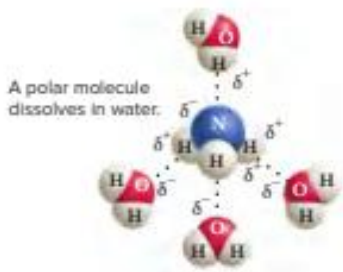
b. Bodies of organisms cool when their heat is used to evaporate water.

Figure 1.10 Temperature and water. **a.** Water can be a solid, a liquid, or a gas at naturally occurring environmental temperatures. At room temperature and pressure, water is a liquid. When water freezes and becomes a solid (ice), it gives off heat, and this heat can help keep the environmental temperature higher than expected. On the other hand, when water evaporates, it takes up a large amount of heat as it changes from a liquid to a gas. **b.** This means that splashing water on the body will help keep body temperature within a normal range.

Water Is a Solvent

Due to its polarity, water facilitates chemical reactions, both outside and within living systems. As a solvent, it dissolves a great number of substances, especially those that are also polar. A **solution** contains dissolved substances, which are then called **solutes.** When ionic salts—for example, sodium chloride (NaCl)—are put into water, the negative ends of the water molecules are attracted to the sodium ions, and the positive ends of the water molecules are attracted to the chloride ions. This attraction causes the sodium ions and the chloride ions to separate, or dissociate, in water.

Water is also a solvent for larger polar molecules, such as ammonia (NH_3).



Molecules that can attract water are said to be **hydrophilic** (Gk. *hydrias,* "of water"; *phileo,* "love"). When ions and molecules disperse in water, they move about and collide, allowing reactions to occur. Nonionized and nonpolar molecules that cannot attract water are said to be **hydrophobic** (Gk. *phobos,* "fear"). Hydrophilic molecules tend to attract other polar molecules; similarly, hydrophobic substances usually associate with other nonpolar molecules. Gasoline contains nonpolar molecules; therefore, it does not mix with water and is hydrophobic.

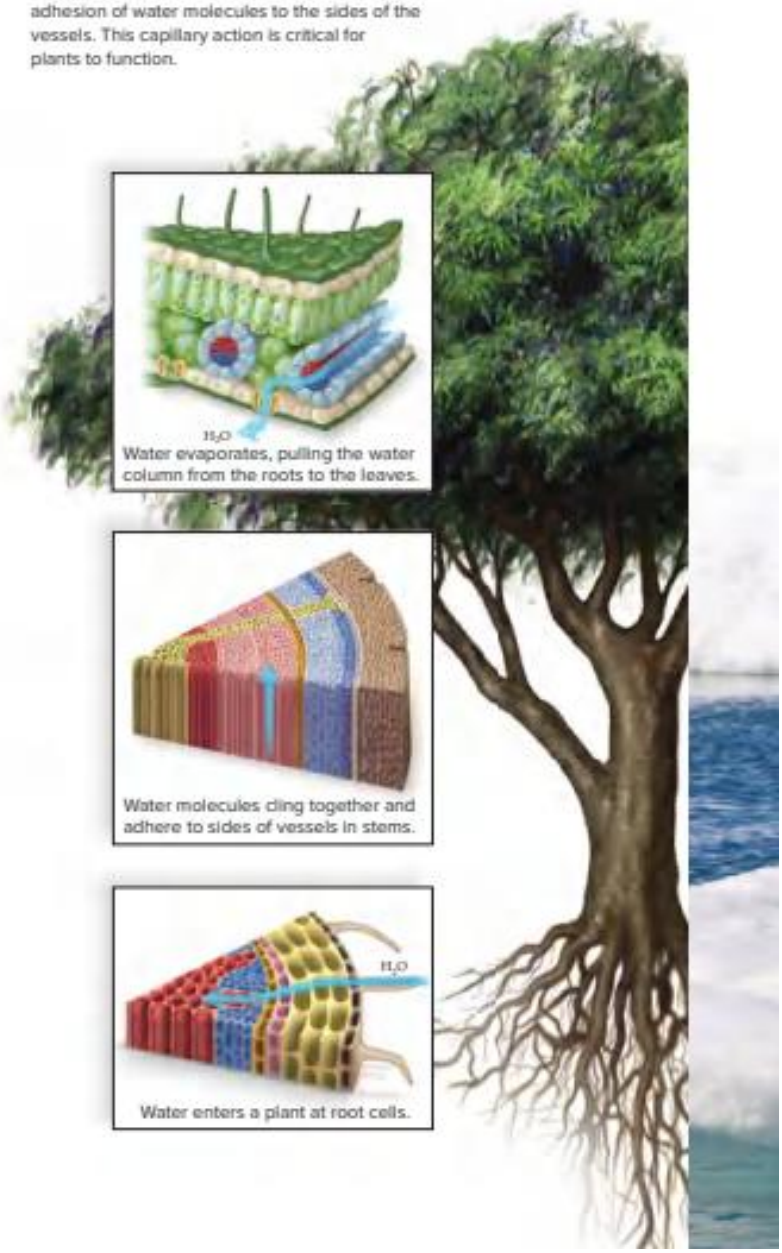
Water Molecules Are Cohesive and Adhesive

Cohesion refers to the ability of water molecules to cling to each other due to hydrogen bonding. At any moment in time, a water molecule can form hydrogen bonds with at most four other water molecules. Because of cohesion, water exists as a liquid under the conditions of temperature and pressure present at the Earth's surface. The strong cohesion of water molecules is apparent because water flows freely, yet water molecules do not separate from each other.

Adhesion refers to the ability of water molecules to cling to other polar surfaces. This is a result of water's polarity. Multicellular animals often contain internal vessels in which water assists the transport of nutrients and wastes, because the cohesion and adhesion of water allow blood to fill the tubular vessels of the cardiovascular system. For example, the liquid portion of our blood, which transports dissolved and suspended substances about the body, is 90% water.

Cohesion and adhesion also contribute to the transport of water in plants. Plants have their roots anchored in the soil, where they absorb water, but the leaves are uplifted and exposed to solar energy. Water evaporating from the leaves is immediately replaced with water molecules from transport vessels that extend from the roots to the leaves (Fig. 1.11). Because water molecules are

Figure 1.11 Water molecules are cohesive and adhesive.
Cohesion and adhesion play an important role in the movement of water in a plant. When water evaporates from the leaves, the water column is pulled upward due to the cohesion of water molecules to one another and the adhesion of water molecules to the sides of the vessels. This capillary action is critical for plants to function.



cohesive, a tension is created that pulls the water column up from the roots. Adhesion of water to the walls of the transport vessels also helps prevent the water column from breaking apart. This capillary action is essential to plant life.

Because water molecules are attracted to each other, they cling together where the liquid surface is exposed to air. The stronger the force between molecules in a liquid, the greater the **surface tension.** Water's high surface tension makes it possible for humans to skip rocks on water. Water striders, a common insect, can even walk on the surface of a pond without breaking the surface.

Frozen Water (Ice) Is Less Dense Than Liquid Water

As liquid water cools, the molecules come closer together. Water is most dense at 4°C, but the water molecules are still moving about (Fig. 1.12). At temperatures below 4°C, only vibrational movement occurs, and hydrogen bonding becomes more rigid but also more open. This means that water expands as it reaches 0°C and freezes, which is why cans of soda burst when placed in a freezer, or why frost heaves make northern roads bumpy in the winter. It also means that ice is less dense than liquid water, and therefore ice floats on liquid water.

If ice did not float on water, it would sink to the bottom, and ponds, lakes, and perhaps even the ocean would freeze solid, making life impossible in the water and on land. Instead, bodies of water always freeze from the top down. When a body of water freezes on the surface, the ice acts as an insulator to prevent the water below it from freezing. This allows aquatic organisms to survive the winter. As ice melts in the spring, it draws heat from the environment, helping prevent a sudden change in temperature, which might be harmful to life.

Check Your Progress 1.3

1. Explain how water's structure relates to the formation of hydrogen bonds.
2. Explain how hydrogen bonds relate to the properties of water.
3. Explain how spraying water on your body helps cool it off.

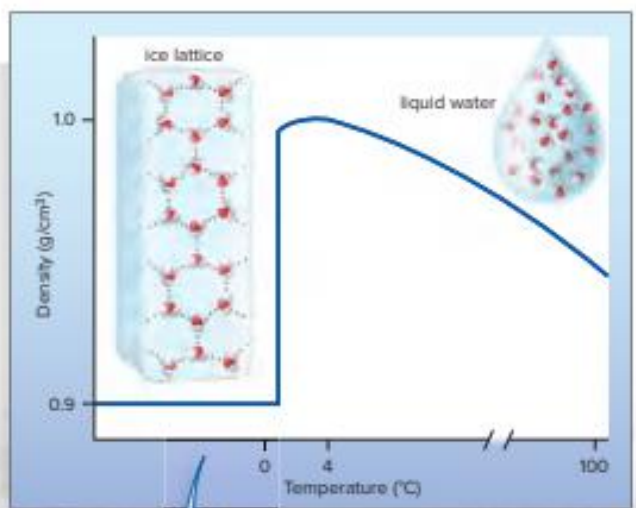


Figure 1.12 Ice is less dense than water. **a.** Water is more dense at 4°C than at 0°C. Most substances contract when they solidify, but water expands when it freezes, because in ice, water molecules form a lattice in which the hydrogen bonds are farther apart than in liquid water. **b.** This property of water allows ice to flow, providing habitats for some aquatic species and protecting other species that live beneath the ice.

1.4 Acids and Bases

Learning Outcomes

Upon completion of this section, you should be able to

1. Distinguish between an acid and a base.
2. Explain the relationship betwteen H^+ or OH^- concentration and pH.
3. Analyze how buffers prevent large pH changes in solutions.

When water ionizes, it releases an equal number of **hydrogen ions** (H^+) (sometimes just called protons[1]) and **hydroxide ions** (OH^-):

$$\underset{\text{water}}{H{-}O{-}H} \rightleftharpoons \underset{\text{hydrogen ion}}{H^+} + \underset{\text{hydroxide ion}}{OH^-}$$

Only a few water molecules at a time dissociate, and the actual number of H^+ and OH^- is very small (1×10^{-7} moles/liter).[2]

Acidic Solutions (High H^+ Concentrations)

Lemon juice, vinegar, tomatoes, and coffee are all acidic solutions. What do they have in common? **Acids** are substances that dissociate in water, releasing hydrogen ions (H^+). The acidity of a substance depends on how fully it dissociates in water. For example, hydrochloric acid (HCl) is a strong acid that dissociates almost completely in this manner:

$$HCl \longrightarrow H^+ + Cl^-$$

If hydrochloric acid is added to a beaker of water, the number of hydrogen ions (H^+) increases greatly.

Basic Solutions (Low H^+ Concentration)

Milk of magnesia and ammonia are common basic solutions familiar to most people. **Bases** are substances that either take up hydrogen ions (H^+) or release hydroxide ions (OH^-). For example, sodium hydroxide (NaOH) is a strong base that dissociates almost completely in this manner:

$$NaOH \longrightarrow Na^+ + OH^-$$

If sodium hydroxide is added to a beaker of water, the number of hydroxide ions increases.

pH Scale

The **pH scale** is used to indicate the acidity or basicity (alkalinity) of a solution.[3] The pH scale (Fig. 1.13) ranges from 0 to 14. A pH of 7 represents a neutral state in which the hydrogen ion and hydroxide ion concentrations are equal. A pH below 7 is an acidic solution, because the hydrogen ion concentration is greater than the hydroxide concentration. A pH above 7 is basic, because the $[OH^-]$ is greater than the $[H^+]$. Further, as we move down the pH scale from pH 14 to pH 0, each unit is 10 times more acidic than the previous unit. As we move up the scale from 0 to 14, each unit is 10 times more basic than the previous unit. Therefore, pH 5 is 100 times more acidic than pH 7 and 100 times more basic than pH 3.

The pH scale was devised to eliminate the use of cumbersome numbers. For example, the possible hydrogen ion concentrations of a solution are on the left of this listing and the pH is on the right:

$[H^+]$ (moles per liter)		pH
0.000001	$= 1 \times 10^{-6}$	6
0.0000001	$= 1 \times 10^{-7}$	7
0.00000001	$= 1 \times 10^{-8}$	8

To further illustrate the relationship between hydrogen ion concentration and pH, consider the following question. Which of the pH values listed indicates a higher hydrogen ion concentration $[H^+]$ than pH 7, and therefore would be an acidic solution? A number with a smaller negative exponent indicates a greater quantity of hydrogen ions than one with a larger negative exponent. Therefore, pH 6 is an acidic solution.

The Big Idea 4 feature "The Impact of Acid Deposition" describes detrimental environmental consequences of low pH rain and snow. In humans, pH needs to be maintained within a narrow range, or there are health consequences. The pH of blood is around 7.4, and blood is buffered in the manner described next to keep the pH within a normal range.

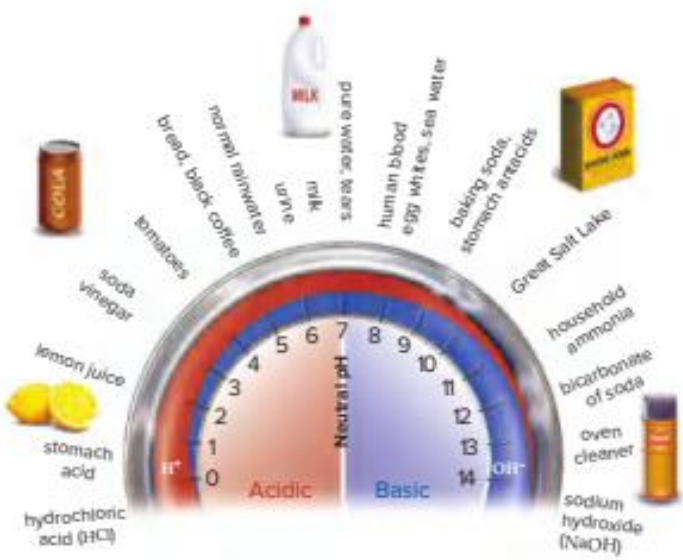


Figure 1.13 The pH scale. The pH scale ranges from 0 to 14, with 0 being the most acidic and 14 being the most basic. pH 7 (neutral pH) has equal amounts of hydrogen ions (H^+) and hydroxide ions (OH^-). An acidic pH has more H^+ than OH^- and a basic pH has more OH^- than H^+.

1 A hydrogen atom contains one electron and one proton. A hydrogen ion has only one proton, so it is often simply called a proton.
2 In chemistry, a mole is defined as 6.02×10^{23} of any atom, molecule, or ion. For example, 6.02×10^{23} atoms of 12C would have a mass of exactly 12 g. The same number of glucose molecules (1 mole) would have a mass of 180 g.
3 pH is defined as the negative log of the hydrogen ion concentration $[H^+]$. A log is the power to which 10 must be raised to produce a given number.

BIG IDEA 4: Interdependent Relationships

The Impact of Acid Deposition

Acid Deposition

Normally, rainwater has a pH of about 5.6 because the carbon dioxide in the air combines with water to give a weak solution of carbonic acid. Acid deposition includes rain or snow that has a pH of less than 5, as well as dry acidic particles that fall to Earth from the atmosphere.

When fossil fuels such as coal, oil, and gasoline are burned, sulfur dioxide and nitrogen oxides combine with water to produce sulfuric and nitric acids. These pollutants are generally found eastward of where they originated because of wind patterns. The use of very tall smokestacks causes them to be carried even hundreds of miles away. For example, acid rain in southeastern Canada results from the burning of fossil fuels in factories and power plants in the midwestern United States.

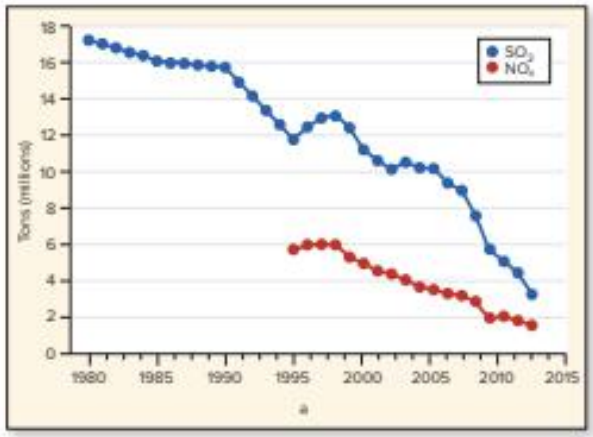


Figure 1A Trends in U.S. acid rain emissions. The burning of fossil fuels in factories, automobiles, and other industrial processes produces chemicals like SO_2 and NO_x that lead to acid deposition and destruction of the environment. Clean air legislation and stricter emission standards over the past several decades have resulted in steady decreases in SO_2 and NO_x, chemicals that lead to acid rain. Source: EPA.gov

Impact on Lakes

Acid rain adversely affects many aspects of biological systems. Aluminum may leach from the soil of lakes, particularly in areas where the soil is thin and lacks limestone (calcium carbonate, or $CaCO_3$) as a buffer. Acid rain may convert mercury in lake bottom sediments to toxic methyl mercury. Methyl mercury accumulates in fish, which wildlife and people eat. Over time, methyl mercury can accumulate in body tissues and cause serious sensory and muscular health problems. Acid rain in Canada and New England has caused hundreds of lakes to be devoid of fish, and in some cases, any life at all.

Impact on Forests

The leaves of plants damaged by acid rain can no longer carry on photosynthesis as before. When plants are under stress, they become susceptible to diseases and pests of all types. Forests on mountaintops receive more rain than those at lower levels; therefore, they are more affected by acid rain. Forests are also damaged when toxic chemicals such as aluminum are leached from the soil. These kill soil fungi that assist roots in acquiring the nutrients trees need. In New England and the southern Appalachians, millions of acres of high-elevation forests have been devastated. Sulfur dioxide and nitrogen oxides, the main precursors of acid rain, have been steadily decreasing in the United States due to clean air legislation and strict emission limits (see Fig. 1A).

Impact on Humans and Structures

Humans may be affected by acid rain. Inhaling dry sulfate and nitrate particles appears to increase the occurrence of respiratory illnesses, such as asthma. Buildings and monuments made of limestone and marble break down when exposed to acid rain. The paint on homes and automobiles is likewise degraded. However, damage to natural systems and human structures due to acid rain is likely to decrease if we continue efforts to reduce chemicals that contribute to acid rain.

Questions to Consider

1. What acid rain trends are evident from the EPA data?
2. How might manufacturers modify industrial processing to reduce sulfur dioxide and nitrogen oxide contamination?
3. How might we prevent methyl mercury from entering biological systems and reduce the amount already present?

Buffers and pH

A **buffer** is a chemical or a combination of chemicals that keeps pH within normal limits. Many commercial products, such as shampoos or deodorants, are buffered as an added incentive for us to buy them.

In living organisms, the pH of body fluids is maintained within a narrow range, or else molecules don't function correctly and our health suffers. The pH of our blood when we are healthy is always about 7.4—that is, just slightly basic (alkaline). If the blood pH drops to about 7, acidosis results. If the blood pH rises to about 7.8, alkalosis results. Both conditions can be life threatening, so the blood pH must be kept around 7.4. Normally, pH stability is possible because the body has built-in mechanisms to prevent pH changes. Buffers are one of these important mechanisms.

Buffers help keep the pH within normal limits because they are chemicals or combinations of chemicals that take up excess hydrogen ions (H^+) or hydroxide ions (OH^-). For example, carbonic acid (H_2CO_3) is a weak acid that minimally dissociates and then re-forms in the following manner:

$$\underset{\text{carbonic acid}}{H_2CO_3} \underset{\text{re-forms}}{\overset{\text{dissociates}}{\rightleftharpoons}} H^+ + \underset{\text{bicarbonate ion}}{HCO_3^-}$$

Blood always contains a combination of some carbonic acid and some bicarbonate ions. When hydrogen ions (H^+) are added to blood, the following reaction reduces acidity:

$$H^+ + HCO_3^- \longrightarrow H_2CO_3$$

When hydroxide ions (OH^-) are added to blood, this reaction reduces basicity:

$$OH^- + H_2CO_3 \longrightarrow HCO_3^- + H_2O$$

These reactions prevent any significant change in blood pH.

Check Your Progress 1.4

1. Explain the difference in H^+ concentration between an acid and a base.
2. Determine how much more acidic a pH of 2.0 is than a pH of 4.0.
3. Summarize how buffers play an important role in the physiology of living organisms.

Reviewing *the* BIG IDEAS

BIG IDEA 2

As in all systems, chemistry involves inputs and outputs, with resulting changes in free energy; biological systems must increase inputs of free energy to maintain order. 2.A.1.a.3

The movement of electrons between molecules allows energy transfer in living organisms. 2.A.2.d.3; 2.A.2.g.3

Water is a polar molecule that forms hydrogen bonds with other water molecules and with other polar molecules; the ability to form hydrogen bonds is the basis for water's unique properties that are essential to life, including performance as a universal solvent, high specific heat capacity, cohesion, adhesion, thermal conductivity, and heats of vaporization and fusion. 2.A.2.d.3; *IE*

BIG IDEA 4

All biological systems, including molecular ones, are composed of interacting parts that result in emergent properties not only at the atomic and molecular level, but at the organismal, population, community, and ecosystem levels. 4.A.1 *commentary*

SUMMARIZE

AP Answering the Essential Questions

Living organisms need matter and free energy to maintain homeostasis, grow, and reproduce. Energy deficiencies are disruptive to individuals, populations, and ecosystems. To offset entropy, available energy (input) must exceed the energy that an organism uses (output). Sources of free energy include radiant energy from the sun and chemical energy stored in the bonds of molecules.

Composition of matter Living organisms are composed of **matter** which, in turn, is composed of pure substances called **elements.** Of the 92 naturally occurring elements, only six—carbon, hydrogen, oxygen, nitrogen, phosphorus, and sulfur—make up about 95% of the body weight of organisms. However, traces of other elements also are needed for life processes. For example, without sodium and potassium, the nervous system could not conduct impulses along neurons; without iron, hemoglobin in red blood cells could not carry oxygen.

Each element consists of tiny particles called **atoms** comprised of even smaller subatomic particles that include positively charged **protons,** uncharged **neutrons,** and negatively charged **electrons.** Protons and neutrons are located within the nucleus of an atom, and electrons orbit the nucleus. These subatomic particles, especially the position and arrangement of electrons, determine an atom's unique properties and, consequently, an element's physical and chemical properties. Because the negatively charged electrons are attracted to the atom's positively charged nucleus, the potential energy of electrons increases as the distance from the nucleus increases. In one model of the atom (Bohr model), electrons are located in shells representing energy levels, and each shell can hold a specific number of electrons. The first shell closest to the nucleus can hold two electrons, and each additional shell can hold eight electrons. Electrons occupying the outermost shell are called valence electrons. The valence shell determines many of an atom's chemical

properties. An atom is most stable when its valence shell contains the maximum number of electrons, either two or eight, and will combine with other atoms to fill the valence shell by transferring or sharing electrons. When an atom donates an electron, it loses energy; when an atom gains an electron, it gains energy. Remember, it's all about the electrons.

Molecules and bonds The transferring or sharing of electrons between atoms results in **molecules** consisting of two or more atoms of the same element such as O_2 or different elements such as $C_6H_{12}O_6$ (glucose). Because electrons possess energy, the **bonds** between atoms also contain energy, and organisms tap into chemical bond energy to carry out life processes such as growth and reproduction. For example, when glucose is broken down, electrons shift in their relationship to one another, and free energy is released, thus becoming available for use by the organism. Types of bonds include ionic, covalent, and polar covalent.

Recall that the purpose of bonding is to fill outermost valence shells with the maximum number of electrons. In **ionic bonding,** atoms transfer valence electrons to each other, with one atom acting as the electron donor, and the second atom acting as the electron acceptor. This complete transfer of electrons generates two oppositely charged atoms called ions. An example of ionic bonding is the formation of sodium chloride (NaCl) or common table salt in which an electron is transferred from the sodium atom to the chlorine atom. This electron transfer results in a charge imbalance in each atom (Na^+ and Cl^-) which are then held together by electrostatic attraction. When it comes to ions, opposites attract!

Covalent bonds form when two atoms share electrons in their outer shells. For example, because the valence shell of hydrogen contains only one electron, the atom either combines with another hydrogen atom to form H_2, a diatomic gas, or gives up its lone electron to become a hydrogen ion (H^+) (we will get back to the importance of having hydrogen ions available when we study photosynthesis and cellular respiration). When the sharing of electrons between two atoms is equal (e.g., O_2 or CH_4), the covalent bond is said to be nonpolar. However, if one atom attracts electrons to a greater degree (is more electronegative) than the other atom, the bond is called a **polar covalent bond.** An example of a polar covalent bond is water (H_2O) in which the oxygen atom is more electronegative than the hydrogen atoms; consequently, the oxygen atom acquires a slightly positive charge, and each hydrogen atom acquires a slightly positive charge as electrons are drawn toward oxygen. The electrons are still shared, but they are shared unequally because of the differences in electronegativity. The polarity of molecules often results in unique properties and affects how they interact with other molecules.

Hydrogen bonding At all levels of biological organization, from molecules and cells to populations and ecosystems, there is a relationship between structure and function. The shape of the water molecule and its polarity make **hydrogen bonding** possible when the slightly positive hydrogen of one water molecule is attracted to the slightly negative oxygen of another water molecule in the vicinity. Hydrogen bonding occurs in other biological molecules, including DNA. In fact, without hydrogen bonds, DNA would not be able to copy itself. Although hydrogen bonds are weaker than either ionic or covalent bonds, they help molecules maintain their structure and function. With respect to water, hydrogen bond formation contributes to unique properties that are vital to sustain life on Earth, including high heat capacity, high heat of evaporation, cohesion, adhesion, surface tension and the ability to dissolve other molecules. Without water's ability to stick to itself (cohesion) and to other polar substances (adhesion), water would not be able to travel up a large tree to the leaves where photosynthesis occurs.

ASSESS

Choose the best answer for each question.

1.1 Chemical Elements

1. The atomic number tells you the
   a. number of neutrons in the nucleus.
   b. number of protons in the atom.
   c. number of its electrons if the atom is neutral.
   d. Both b and c are correct.
2. Isotopes differ in their
   a. number of protons.
   b. atomic number.
   c. number of neutrons.
   d. number of electrons.
3. The periodic table provides us with what information?
   a. the atomic number, symbol, and mass
   b. how many shells an atom has
   c. how many electrons are in the outer shell
   d. All of these are correct.
4. Which of the subatomic particles contributes almost no weight to an atom?
   a. protons in the electron shells
   b. electrons in the nucleus
   c. neutrons in the nucleus
   d. electrons at various energy levels

1.2 Molecules and Compounds

5. An atom that has two electrons in the valence shell, such as magnesium, would most likely
   a. share to acquire a completed outer shell.
   b. lose these two electrons and become a negatively charged ion.
   c. lose these two electrons and become a positively charged ion.
   d. bind with carbon by way of hydrogen bonds.
6. When an atom gains electrons, it
   a. forms a negatively charged ion.
   b. forms a positively charged ion.
   c. forms covalent bonds.
   d. forms ionic bonds.
7. An unequal sharing of electrons is a characteristic of a/an
   a. ionic bond.
   b. polar covalent bond.
   c. nonpolar covalent bond.
   d. All of these are correct.

1.3 Chemistry of Water

8. Hydrogen bonds are formed as a result of which of the following?
   a. ionic bonds
   b. nonpolar covalent bonds
   c. polar covalent bonds
   d. None of these are correct.
9. Which of these properties of water can be attributed to hydrogen bonding between water molecules?
   a. Water stabilizes temperature inside and outside the cell.
   b. Water molecules are cohesive.
   c. Water is a solvent for many molecules.
   d. All of the above are correct.

For questions 10–13, match the statements with a property of water in the key.

KEY:

a. Water flows because it is cohesive.
b. Water holds its heat.
c. Water has neutral pH.
d. Water has a high heat of vaporization.

10. Sweating helps cool us off.
11. Our blood is composed mostly of water and cells.
12. Our blood is just about pH 7.
13. We usually maintain a normal body temperature.

1.4 Acids and Bases

14. $H_2CO_3/NaHCO_3$ is a buffer system in the body. What effect will the addition of an acid have on the pH of a solution that is buffered?
    a. The pH will rise.
    b. The pH will lower.
    c. The pH will not change.
    d. All of these are correct.
15. Which of these best describes the changes that occur when a solution goes from pH 5 to pH 7?
    a. The solution is now 100 times more acidic.
    b. The solution is now 100 times more basic.
    c. The hydrogen ion concentration decreases by only a factor of 20, as the solution goes from basic to acidic.
    d. The hydrogen ion concentration changes by only a factor of 20, as the solution goes from acidic to basic.

ENGAGE

AP Applying the Big Ideas

1. BIG IDEA 2 Scientists have been searching outer space for signs of water because it is the current understanding of life is that it requires water to sustain. They have detected conclusively that the dwarf planet Ceres, found in the asteroid belt between Mars and Jupiter, not only contains a thick mantle of ice that, if melted, would amount to more fresh water than is present on Earth, but also emits plumes of water vapor when it is located close to the sun.
    a. **Describe** TWO kinds of data that could be collected by scientists to provide a direct answer to the question, how can scientists determine that a substance they sample on Earth or elsewhere is water and not another substance?
    b. **Explain** how the data you suggested in part (a) would provide a direct answer to the question.

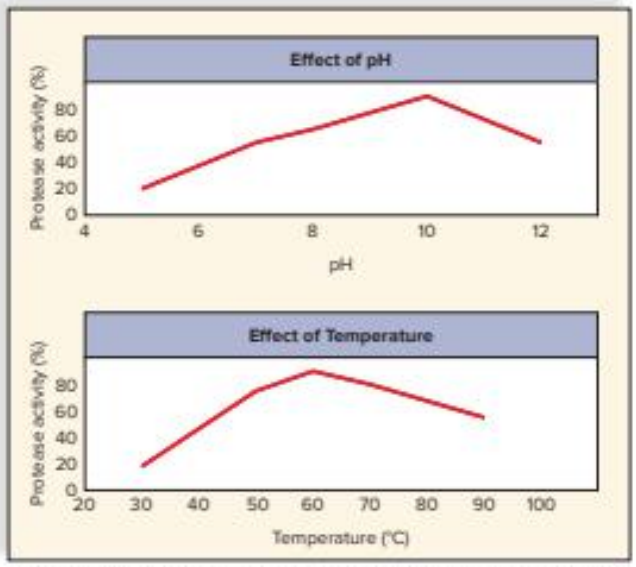
2. BIG IDEA 4 Explain how the structure of molecules contributes to their properties and/or function, citing specific examples.

AP Applying the Science Practices

How do pH and temperature affect protease activity? Proteases are enzymes that break down protein. Bacterial proteases often are used in detergents to help remove stains such as egg, grass, blood, and sweat from clothes.

Data and Observations

A protease from a newly isolated strain of bacteria was studied over a range of pH values and temperatures.



* Data obtained from: Adinarayana, et al. 2003. Purification and partial characterization of thermostable serine alkaline protease from a newly isolated *Bacillus subtilis* PE-11. *AAPS PharmSciTech 4: article 56.*

Think Critically SP 5 SP 6 SP 7

1. **Identify** the range of pH values and temperatures used in the experiment.
2. **Summarize** the results of the two graphs.
3. **Infer** if a laundry detergent is basic and requires hot water to be most effective, would this protease be useful? Explain.

Trans fats are an organic molecule found in processed foods.

2

The Chemistry of Organic Molecules

AP All life is interconnected, because it uses a common set of chemicals to build larger, more complex molecules. These macromolecules—namely, carbohydrates, lipids, proteins, and nucleic acids—are combined to produce different structures, which lead them to have different functions. However, at times, some of these macromolecules can produce health issues in humans. For example, historically we have associated cardiovascular health problems with high levels of cholesterol and fat in the diet. However, we now know that trans fats are worse offenders than saturated fats when it comes to cardiovascular health. While trans fats are found naturally in small quantities in milk and meat products, the majority of trans fats are obtained from processed foods. Historically, the food industry added trans fats not only to increase the shelf life of processed food but also to enhance the flavor and texture.The Food and Drug Administration (FDA) now directs that trans fat content must be disclosed on Nutrition Facts panels of food products.

An understanding of the structure and function of carbohydrates, lipids, proteins, and nucleic acids is important not only for knowing the main building blocks of cells but also for understanding how to establish a healthy diet.

As you read through the chapter, think about these Essential Questions:

1. What elements comprise each of the four groups of macromolecules? 2.A.3.a.1
2. How are complex polymers synthesized from simpler monomers? 1.D.1.a.3 1.D.2.b.1
3. How does the molecular structure of the four groups of macromolecules determine the function(s) of each group? 4.A.1.b.1-3 4.A.1.a.1-3
4. How can changes in environmental conditions change the function of a macromolecule? 3.A.1.a-b 3.C.1.a 3.C.1.d

Chapter Outline

Following *the* BIG IDEAS

BIG IDEA 1 — The diversity of biological life is the result of changes in DNA sequences and the biomolecules for which they code.

BIG IDEA 2 — Carbon's stable and versatile covalent bonding leads to tremendous variety in the carbohydrates, lipids, proteins, and nucleic acids observed in living organisms.

BIG IDEA 3 — Nucleic acids are unique among the biomolecules in their ability to store and transmit genetic information.

BIG IDEA 4 — Macromolecules form the functional basis for all cellular systems.

2.1 Organic Molecules

Learning Outcomes

Upon completion of this section, you should be able to

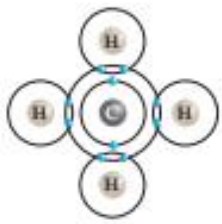
1. Explain how the properties of carbon enable it to produce diverse organic molecules.
2. Explain the relationship between a functional group and the chemical reactivity of an organic molecule.
3. Compare the role of dehydration synthesis and hydrolytic reactions in organic chemistry.

Chemists of the nineteenth century thought that the molecules of cells must contain a vital force, so they divided chemistry into **organic chemistry,** the chemistry of living organisms, and **inorganic chemistry,** the chemistry of nonliving matter. We still use this terminology, even though many types of organic molecules can now be synthesized in the laboratory. Today, we simply use the term **organic** to identify those molecules and compounds that contain both carbon and hydrogen atoms.

There are only four classes of organic molecules in any living organism: carbohydrates, lipids, proteins, and nucleic acids. Collectively, these are called the **biomolecules;** despite the limited number of types, their functions in a cell are quite diverse. A bacterial cell contains some 5,000 different organic molecules, and a plant or an animal cell has twice that number. The diversity of life (Fig. 2.1) is possible because of the diversity of organic molecules. Despite their functional differences, the variety of organic molecules is based on the unique chemical properties of the carbon atom.

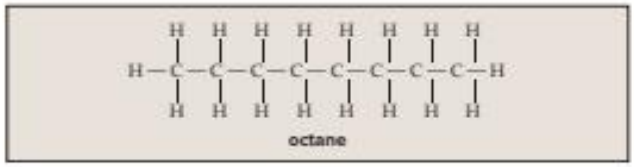
The Carbon Atom

What is there about carbon that makes organic molecules the same but also different? Carbon is quite small, with only a total of six electrons: two electrons in the first shell and four electrons in the outer shell. To acquire four electrons to complete its outer shell, a carbon atom almost always forms covalent bonds. Carbon can form covalent bonds with as many as four other elements.



Methane

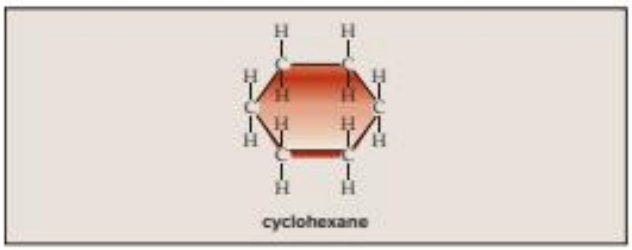
Generally, carbon forms those bonds with other atoms of carbon, plus hydrogen, nitrogen, oxygen, phosphorus, and sulfur—the same elements that make up most of the weight of living organisms. The ability of carbon to share electrons with other carbon atoms plays an important role in establishing the shape, and therefore the function, of the biomolecules. This is because the C–C bond is very stable and allows the formation of long carbon chains. The molecules termed hydrocarbons, such as the octane molecule below, are chains of carbon atoms that have additional bonds exclusively with hydrogen atoms.



octane

Figure 2.1 Carbon and life. Carbon is the basis of life as we know it. The structure of carbon allows for the formation of (**a**) the lipids that store energy in this canola plant; (**b**) carbohydrates that provide structure for this tree; (**c**) the proteins that form the hemoglobin of red blood cells; and (**d**) the genetic material that allows this lioness to pass on information to her offspring.

In addition to long, linear molecules, hydrocarbons may also form a ring structure when placed in a water environment:



In addition to forming single bonds, carbon can form double bonds with itself and other atoms. Double bonds aren't as flexible as single bonds, and they restrict the movement of bonded atoms. Double bonds affect a molecule's shape and therefore influence its function. The presence of double bonds is one way to distinguish between saturated and unsaturated fats, which are important to heart health. Carbon is also capable of forming triple bonds with itself, as in acetylene, H−C≡C−H, a gas used in industrial welding. Branches may also form at any carbon atom, allowing the formation of long, complex carbon chains. This flexibility makes carbon the ideal building block for biomolecules, and it plays an important role in establishing the diversity of organic molecules that we observe in nature.

The Carbon Skeleton and Functional Groups

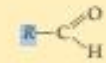
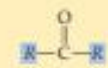
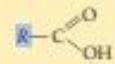
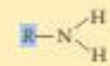
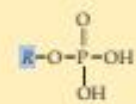
The carbon chain of an organic molecule is called its skeleton, or backbone. Just as a skeleton accounts for your body's shape, so does the carbon skeleton of an organic molecule account for its shape. The diversity of vertebrates, species with a backbone, results from the overall shapes of the organisms and the types of appendages (fins, wings, limbs) they have developed. Likewise, the diversity of organic molecules comes from the attachment of different functional groups to the carbon skeleton.

A **functional group** is a specific combination of bonded atoms that always has the same chemical properties and therefore always reacts in the same way, regardless of the carbon skeleton to which it is attached. The majority of the chemical reactivity of a biomolecule can be attributed to its functional groups, rather than to the carbon skeleton to which it is attached.

Typically, the carbon skeleton acts as a framework for the positioning of the functional groups. Table 2.1 lists some of the more common funtional groups. The *R* indicates the "remainder" of the molecule. This is the place on the functional group that attaches to the carbon skeleton.

The configuration of the functional groups determines the properties of the biomolecule. For example, the addition of an −OH (hydroxyl group) to a carbon skeleton turns that molecule into an alcohol. When an −OH replaces one of the hydrogens in ethane, a 2-carbon hydrocarbon, it becomes ethanol, a type of alcohol that is familiar. Whereas ethane, like other hydrocarbons, is hydrophobic (not soluble in water), ethanol is hydrophilic (soluble in water), because the −OH functional group makes the otherwise nonpolar carbon skeleton polar. Because cells are 70–90% water, the ability to interact with and be soluble in water profoundly affects the function of organic molecules in cells.

Table 2.1 Functional Groups

Group	Structure	Compound	Significance
Hydroxyl	R—OH	Alcohol as in ethanol	Polar, forms hydrogen bond Present in sugars, some amino acids
Carbonyl		Aldehyde as in formaldehyde	Polar Present in sugars
		Ketone as in acetone	Polar Present in sugars
Carboxyl (acidic)		Carboxylic acid as in acetic acid	Polar, acidic Present in fatty acids, amino acids
Amino		Amine as in tryptophan	Polar, basic, forms hydrogen bonds Present in amino acids
Sulfhydryl	R—SH	Thiol as in ethanethiol	Forms disulfide bonds Present in some amino acids
Phosphate		Organic phosphate as in phosphorylated molecules	Polar, acidic Present in nucleotides, phospholipids

R = remainder of molecule

Another example is organic molecules that contain carboxyl groups (−COOH). Carboxyl groups are highly polar. In a water environment, they tend to ionize and release hydrogen ions in solution, therfore acting as an acid:

$$-COOH \longrightarrow -COO^- + H^+$$

The attached functional groups determine not only the polarity of an organic molecule but also the types of reactions it will undergo. You will see that alcohols react with carboxyl groups when a fat forms, and that carboxyl groups react with amino groups during protein formation.

Figure 2.2 Isomers. Isomers have the same molecular formula but different atomic configurations. Both of these compounds have the formula $C_3H_6O_3$. In glyceraldehyde, a colorless crystalline solid, oxygen is double-bonded to an end carbon. In dihydroxyacetone, a white crystalline solid, oxygen is double-bonded to the middle carbon.

Isomers

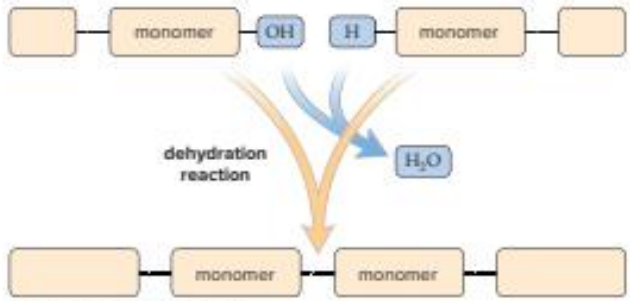
Isomers (Gk. *isos,* "equal") are organic molecules that have identical molecular formulas but different arrangements of atoms. The two molecules in Figure 2.2 are isomers of one another; they have the same molecular formula but different functional groups. Therefore, we would expect them to have different properties and react differently in chemical reactions. In essence, isomers are variations in the molecular structure of a molecule. Isomers are another example of how the chemistry of carbon leads to variations in the structure of organic molecules.

The Biomolecules of Cells

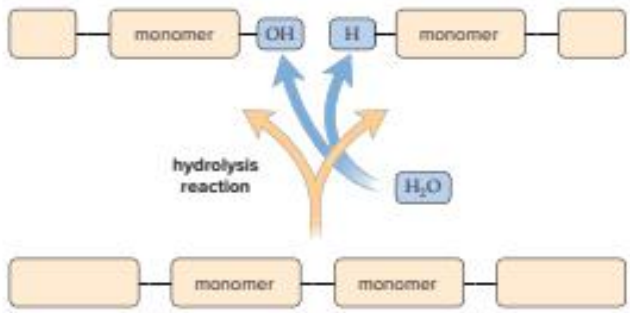
Many of the biomolecules you are familiar with, such as carbohydrates, lipids, proteins, and nucleic acids, are macromolecules, meaning that they contain smaller subunits joined together (Table 2.2). The carbohydrates, proteins, and nucleic acids are referred to as **polymers,** since they are constructed by linking together a large number of the same type of subunit, called a **monomer.** Lipids are not polymers, because they contain two different types of subunits (glycerol and fatty acids). Polymers may vary considerably in length. Just as a train increases in length when boxcars are hitched together one by one, so a polymer gets longer as monomers bond to one another.

Synthesis and Degradation

To build, or synthesize, a macromolecule, the cell uses a condensation reaction. This is commonly called a **dehydration reaction,** because the equivalent of a water molecule—that is, an −OH (hydroxyl group) and an −H (hydrogen atom)—is removed as



a. Synthesis of a biomolecule



b. Degradation of a biomolecule

Figure 2.3 Synthesis and degradation of biomolecules. **a.** In cells, synthesis often occurs when subunits bond during a dehydration reaction (removal of H_2O). **b.** Degradation occurs when the subunits separate during a hydrolysis reaction (the addition of H_2O).

subunits are joined. Therefore, water molecules are formed as biomolecules are synthesized (Fig. 2.3*a*).

To break down biomolecules, a cell uses an opposite type of reaction. During a **hydrolysis reaction** (Gk. *hydro,* "water"; *lyse,* "break"), an −OH group from water attaches to one subunit, and an −H from water attaches to the other subunit. In other words, hydrolytic reactions break down biomolecules by adding water to them (Fig. 2.3*b*).

These reactions rarely occur spontaneously. Usually, special molecules called *enzymes* act as catalysts that allow the reaction to occur or speed up the rate of the reaction. We will take a closer look at enzymes.

Table 2.2 Biomolecules

Category	Subunits (monomers)	Polymer
Carbohydrates*	Monosaccharide	Polysaccharide
Lipids	Glycerol and fatty acids	Fat
Proteins*	Amino acids	Polypeptide
Nucleic acids*	Nucleotide	DNA, RNA

*form polymers

Check Your Progress 2.1

1. Describe the properties of a carbon atom that make it ideally suited to produce varied carbon skeletons.
2. Explain why the substitution of a carboxyl group for a hydroxyl group in a biomolecule would change the molecule's function.
3. Explain why water is needed for the breakdown of a biomolecule.

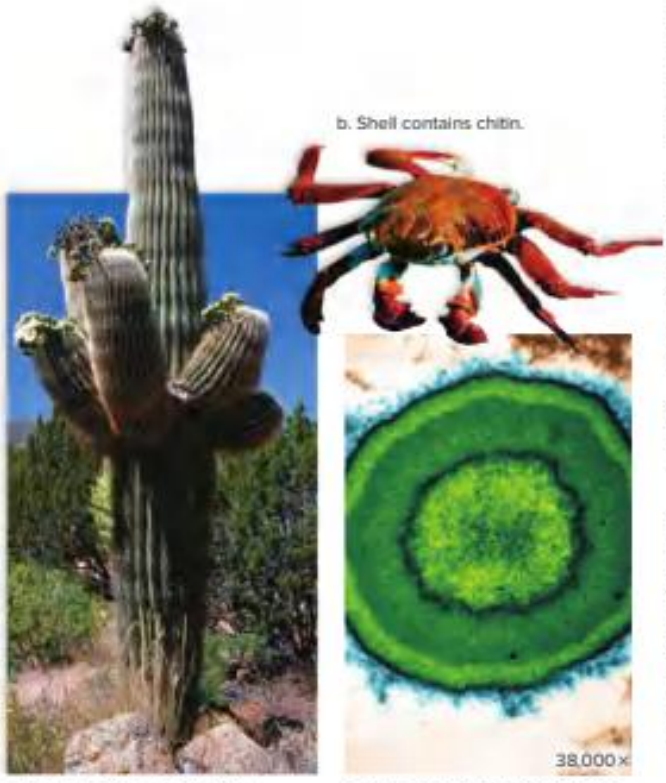
2.2 Carbohydrates

Learning Outcomes

Upon completion of this section, you should be able to

1. Summarize the role of carbohydrates in a cell.
2. Distinguish among the forms of carbohydrates.
3. Compare the energy and structural uses of starch, glycogen, and cellulose.

Carbohydrates are almost universally used as an immediate energy source in living organisms, but in some organisms they also have a structural function (Fig. 2.4). The majority of carbohydrates have a carbon to hydrogen to oxygen ratio of 1:2:1 (CH_2O). The term *carbohydrate* (literally, carbon-water) includes single sugar molecules and chains of sugars. Chain length varies from a few sugars to hundreds of sugars. The monomer subunits, called monosaccharides, are assembled into long polymer chains called polysaccharides.



a. Cell walls contain cellulose. c. Cell walls contain peptidoglycan.

Figure 2.4 Carbohydrates as structural materials. **a.** Plants, such as the cactus shown here, have the carbohydrate cellulose in their cell walls. **b.** The shell of a crab contains a carbohydrate called chitin. **c.** The cell walls of bacteria contain a carbohydrate known as peptidoglycan.

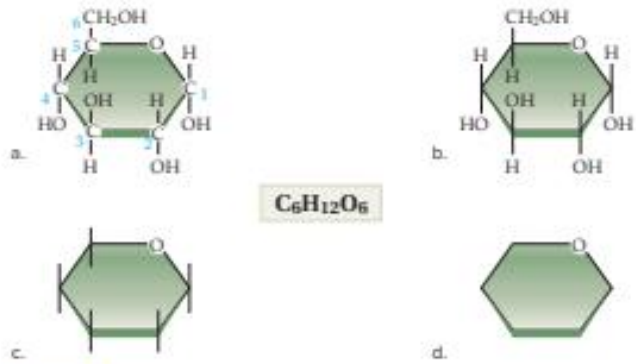


Figure 2.5 Glucose. Glucose is the common form of monosaccharide that provides energy for cells. Each of these structural formulas is glucose. **a.** The carbon skeleton and all attached groups are shown. **b.** The carbon skeleton is omitted. **c.** The carbon skeleton and attached groups are omitted. **d.** Only the ring shape, which includes one oxygen atom, remains.

Monosaccharides

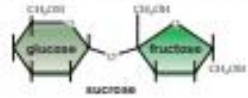
Monosaccharides (Gk. *monos,* "single"; *sacchar,* "sugar") consist of only a single sugar molecule and are commonly called simple sugars. A monosaccharide can have a carbon backbone of three to seven carbons. For example, **pentoses** (Gk. *pent,* "five") are monosacharides with five carbons, and **hexoses** (Gk. *hex,* "six") are monosaccharides with six carbons. Monosaccharides have a large number of hydroxyl groups, and the presence of this polar functional group makes them soluble in water.

An example of a hexose is **glucose** (Fig. 2.5). Glucose has a molecular formula of $C_6H_{12}O_6$. Despite the fact that glucose has several isomers, such as fructose and galactose, we usually think of $C_6H_{12}O_6$ as glucose. Glucose is critical to biological function and is the major source of cellular fuel for all living organisms. Glucose is the molecule that is broken down and converted into stored chemical energy (ATP) during cellular respiration in nearly all types of organisms.

Ribose and **deoxyribose,** with five carbon atoms, are pentose sugars that are significant because they are found, respectively, in the nucleic acids RNA and DNA. RNA and DNA will be discussed in more detail when we examine nucleic acids later in the chapter.

Disaccharides

A **disaccharide** contains two monosaccharides that have joined during a dehydration reaction. Figure 2.6 shows how the disaccharide maltose (an ingredient used in brewing) is formed when two glucose molecules bond together. Note the position of the bond that results when the −OH groups participating in the reaction project below the ring. When the enzymes in our digestive system break this bond, the result is two glucose molecules.



Sucrose (the structure shown above) is another disaccharide of special interest, because it is sugar we use at home to sweeten

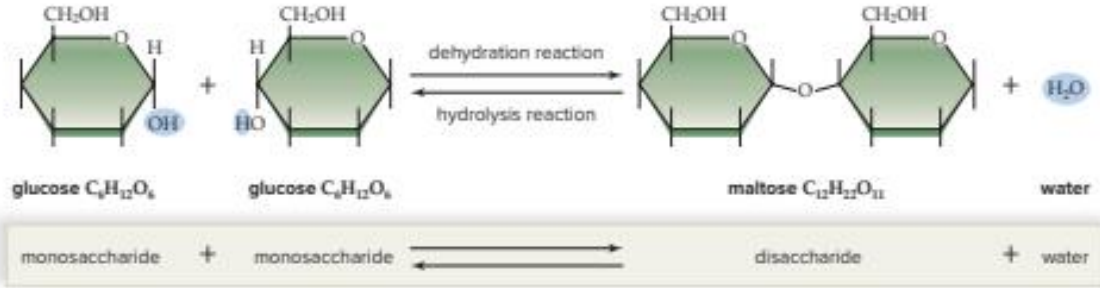
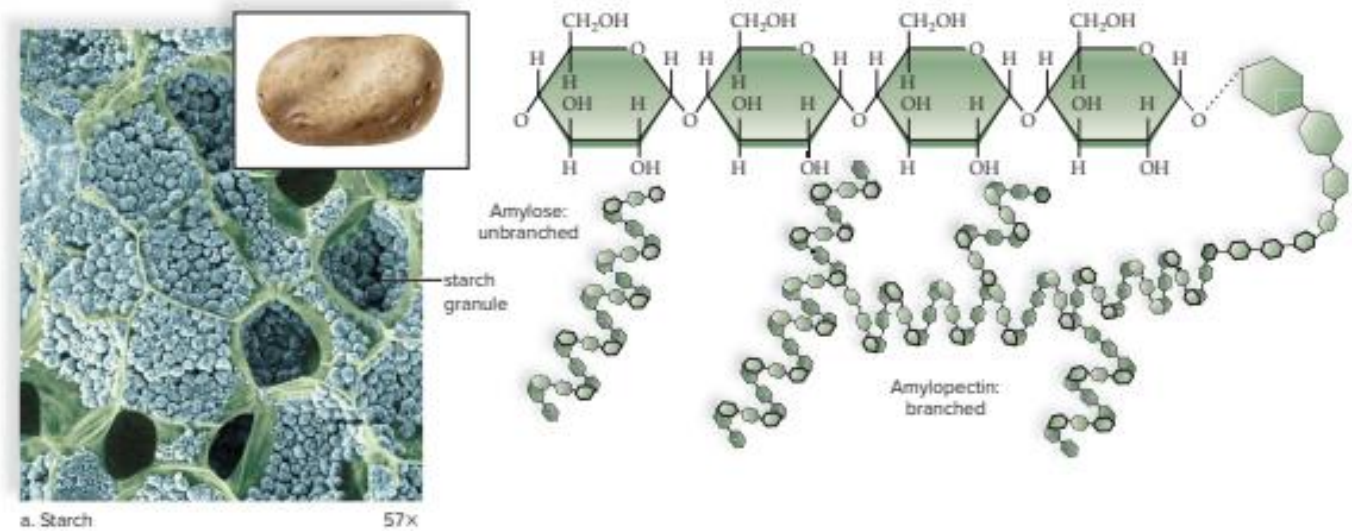


Figure 2.6 Synthesis and degradation of maltose, a disaccharide. Synthesis of maltose occurs following a dehydration reaction when a bond forms between two glucose molecules, and water is removed. Degradation of maltose occurs following a hydrolysis reaction when this bond is broken by the addition of water.



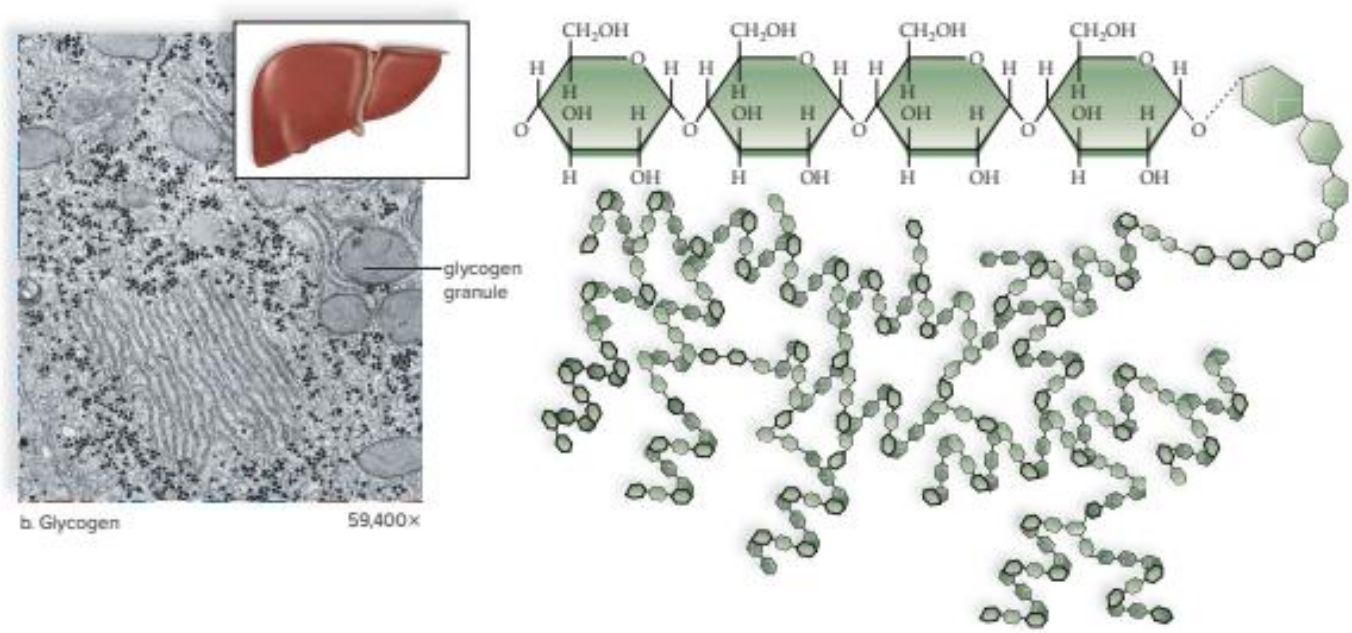


Figure 2.7 Starch and glycogen structure and function. **a.** The electron micrograph shows the location of starch in plant cells. Starch is a chain of glucose molecules that can be branched or unbranched. **b.** The electron micrograph shows glycogen deposits in a portion of a liver cell. Glycogen is a highly branched polymer of glucose molecules.

our food. Sucrose is also the form in which sugar is transported in plants. We acquire sucrose from plants such as sugarcane and sugar beets. You may also have heard of lactose, a disaccharide found in milk. Lactose is glucose combined with galactose. Individuals who are *lactose intolerant* lack the enzyme (called lactase) that breaks down lactose. To prevent gastrointestinal discomfort, they can either avoid foods that contain lactose (e.g., dairy products) or take nutritional supplements that contain the enzyme.

Polysaccharides: Energy-Storage Molecules

Polysaccharides are long polymers of monosaccharides. Due to their length, they are sometimes referred to as complex carbohydrates. Some types of polysaccharides function as short-term energy-storage molecules. When an organism requires energy, the polysaccharide is broken down to release sugar molecules. The helical shape of the polysaccharides in Figure 2.7 exposes the sugar linkages to the hydrolytic enzymes that can break them down.

Plants store glucose as **starch.** The cells of a potato contain granules, where starch resides during winter until energy is needed for growth in the spring. Notice in Figure 2.7*a* that starch exists in two forms: One form (amylose) is unbranched and the other (amylopectin) is branched. When a polysaccharide is branched, there is no main carbon chain, because new chains occur at regular intervals, always at the sixth carbon of the monomer.

Animals store glucose as **glycogen.** In our bodies and those of other vertebrates, liver cells contain granules, where glycogen is stored until needed. The storage and release of glucose from liver cells are controlled by hormones. After we eat, the release of the hormone insulin from the pancreas promotes the storage of glucose as glycogen. Notice in Figure 2.7*b* that glycogen is even more branched than starch.

Polysaccharides serve as storage molecules because they are not as soluble in water and are much larger than a simple sugar. Therefore, polysaccharides cannot easily pass through the plasma membrane, a sheetlike structure that encloses cells.

Polysaccharides: Structural Molecules

Structural polysaccharides include **cellulose** in plants, **chitin** in animals and fungi, and **peptidoglycan** in bacteria (see Fig. 2.4). In all three, monomers are joined by the type of bond shown for cellulose in Figure 2.8. The cellulose monomer is simply glucose, but

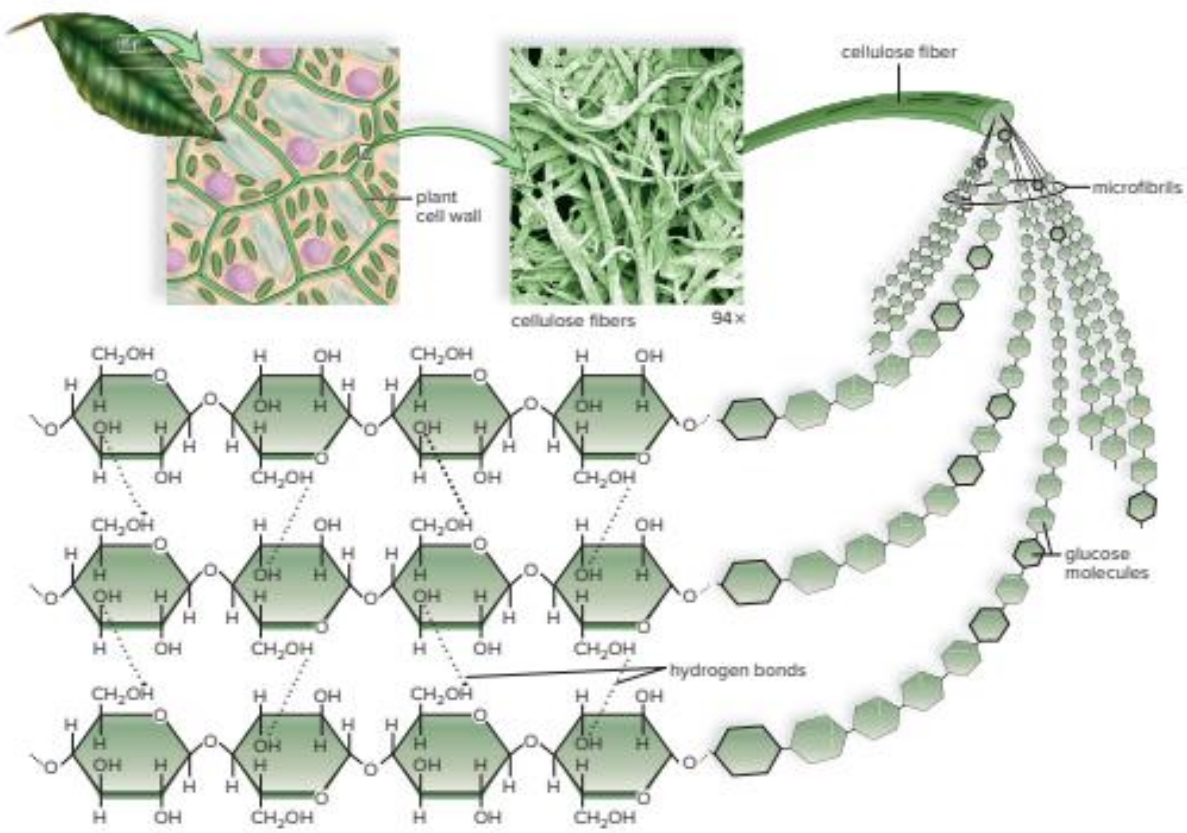


Figure 2.8 Cellulose fibrils. Cellulose fibers criss-cross in plant cell walls for added strength. A cellulose fiber contains several microfibrils, each a polymer of glucose molecules—notice that the linkage bonds differ from those of starch. Every other glucose is flipped, permitting hydrogen bonding and greater strength between the microfibrils.

in chitin, the monomer has an attached amino group. The structure of peptidoglycan is even more complex, because each monomer also has an amino acid chain. In both cases, the addition of a functional group to the glucose monomer changes its chemical properties.

Cellulose is the most abundant carbohydrate and, in fact, the most abundant organic molecule on Earth—over 100 billion tons of cellulose are produced by plants each year. Wood, a cellulose plant product, is used for construction, and cotton is used for cloth. Because of the structure of the bonds between the glucose molecules, animals are not able to digest cellulose. However, some microorganisms can. The protozoans in the gut of termites enable these insects to digest wood. In cows and other ruminants, microorganisms break down cellulose in a special digestive-tract pouch before the "cud" is returned to the mouth for more chewing and reswallowing. In rabbits, microorganisms digest cellulose in a pouch, where it is packaged into pellets. In order to make use of these nutrient pellets, rabbits have to reswallow them as soon as they pass out at the anus. For other animals that have no means of digesting cellulose, cellulose serves as dietary fiber, which maintains regularity of fecal elimination.

Chitin is found in fungal cell walls and in the exoskeletons of crabs and related animals, such as lobsters, scorpions, and insects. Chitin, like cellulose, cannot be digested by animals; however, humans have found many other good uses for chitin. Seeds are coated with chitin, and this protects them from attack by soil fungi. Because chitin also has antibacterial and antiviral properties, it is processed and used in medicine as a wound dressing and suture material. Chitin is even useful in the production of cosmetics and various foods.

Check Your Progress 2.2

1. Summarize the general characteristics of carbohydrates and their roles in living organisms.
2. Describe how monosaccharides are combined to form disaccharides.
3. Explain why humans cannot utilize the glucose in cellulose as a nutrient source.

Table 2.3 Lipids

Type	Functions	Human Uses
Fats	Long-term energy storage and insulation in animals	Butter, lard
Oils	Long-term energy storage in plants and their seeds	Cooking oils
Phospholipids	Component of plasma membrane	Food additive
Steroids	Component of plasma membrane (cholesterol), sex hormones	Medicines
Waxes	Protection, prevention of water loss (cuticle of plant surfaces), beeswax, earwax	Candles, polishes

2.3 Lipids

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe why lipids are essential to living organisms.
2. Distinguish between saturated and unsaturated fatty acids.
3. Contrast the structures of fats, phospholipids, and steroids.
4. Compare the functions of phospholipids and steroids in cells.

A variety of organic compounds are classified as **lipids** (Gk. *lipos*, "fat") (Table 2.3). These compounds are insoluble in water due to their hydrocarbon chains. Hydrogens bonded only to carbon are nonpolar and have no tendency to form hydrogen bonds with water molecules. **Fats,** more fomally called the triglycerides, are the primary lipid used by animals for both insulation and long-term energy storage. Fat is distrubuted throughout the body, but the majority is found just beneath the skin of most animals, where it helps retain body heat. Triglycerides in plants are commonly referred to as **oils.** We are familiar with fats and oils, because we use them as foods and for cooking. However, increasingly they are also being used as a form of alternative fuel source, such as biodiesel, for our industrialized societies.

In addition to the triglycerides, phospholipids, steroids, and waxes are important lipids found in living organisms. The next sections will explore the structure and function of these classes of lipids.

Triglycerides: Long-Term Energy Storage

Triglycerides contain two types of subunit molecules: fatty acids and glycerol. Each **fatty acid** consists of a long hydrocarbon chain with an even number of carbons and a −COOH (carboxyl) group at one end. Most of the fatty acids in cells contain 16 or 18 carbon atoms per molecule, although smaller ones are also found. The fatty acid chains may be either saturated or unsaturated (Fig. 2.9). **Saturated fatty acids** (Fig. 2.9*a*) have no double bonds between the carbon atoms and contain as many hydrogens as they can hold. **Unsaturated fatty acids** (Fig. 2.9*b*) have double bonds in the carbon chain, which reduces the number of bonded hydrogen atoms. In addition, double bonds in unsaturated fatty acids may have chemical groups arranged on the same side (termed *cis configuration*) or on opposite sides (termed *trans configuration*) of the double bond. A **trans fat** is a triglyceride that has at least one bond in a trans configuration. The cis or trans configuration of an unsaturated fatty acid affects its biological activity.

Glycerol is a 3-carbon compound with three −OH groups. The −OH groups are polar, making glycerol soluble in water. When a fat or an oil forms, the −COOH functional groups of three fatty acids react with the −OH groups of glycerol during a dehydration reaction (Fig. 2.10), resulting in a fat molecule and three molecules of water. Fats and oils are degraded during a hydrolysis reaction. Notice that triglycerides have many nonpolar C−H bonds; therefore, they do not mix with water. Even though cooking oils and water are both liquid, they do not mix, even after

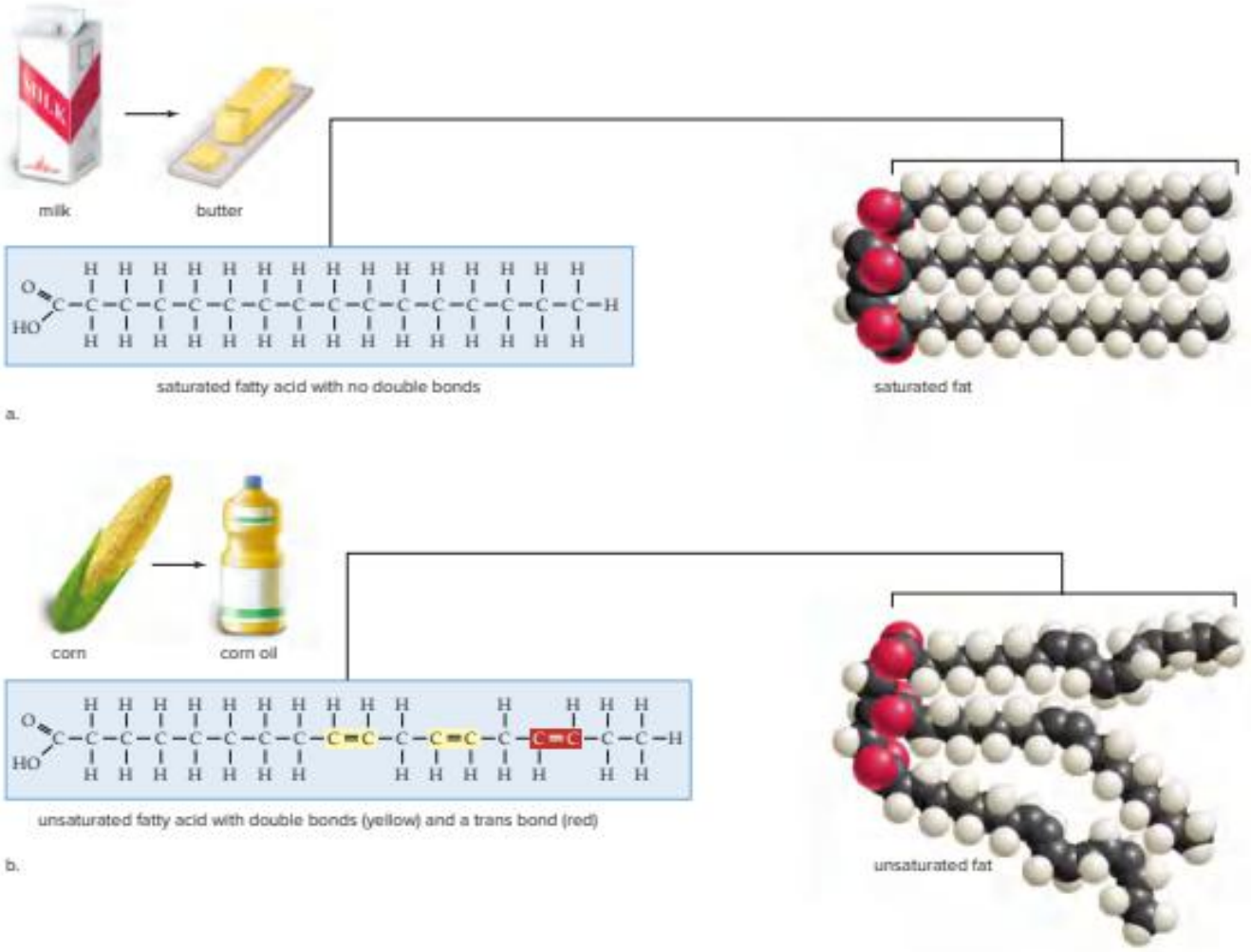


Figure 2.9 Saturated and unsaturated fatty acids. A fatty acid has a carboxyl group attached to a long hydrocarbon chain. **a.** If there are no double bonds between the carbons in the chain, the fatty acid is saturated. **b.** If there are double bonds between some of the carbons, the fatty acid is unsaturated and a kink occurs in the chain.

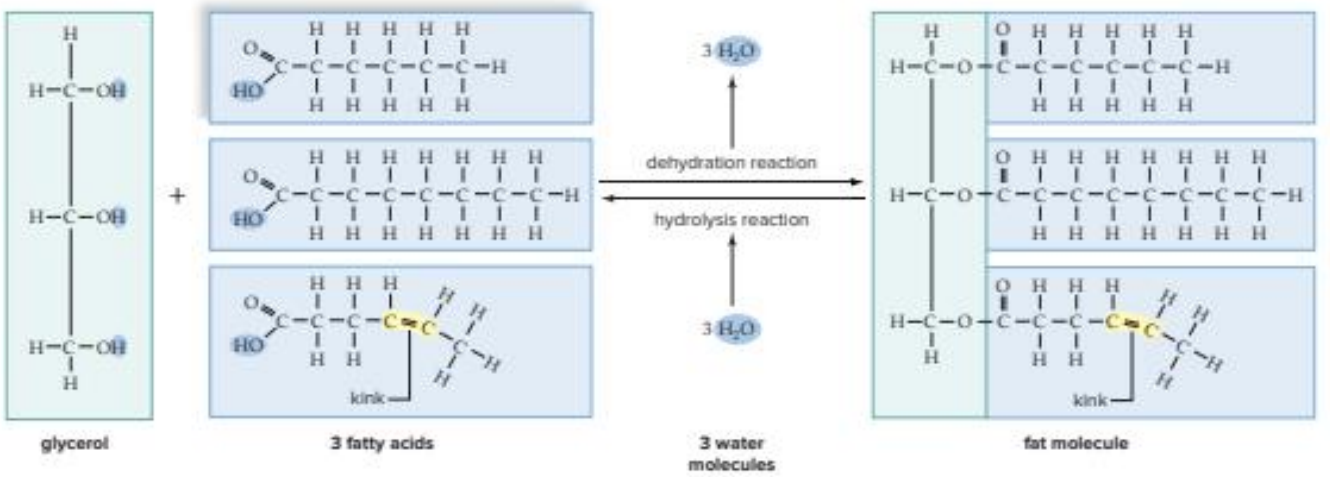


Figure 2.10 Synthesis and degradation of a triglyceride. Following a dehydration reaction, glycerol is bonded to three fatty acid molecules as fat forms and water is given off. Following a hydrolysis reaction, the bonds are broken due to the addition of water.

BIG IDEA 2: Energy and Molecular Building Blocks

Saturated and Trans Fats in Foods

You have probably heard that you should limit the amount of saturated fats and trans fats in your diet. But why? We know that saturated fats, which come from animals and are solid at room temperature, have effects in the body that are different from those of unsaturated fats, which come from plants and are liquid at room temperature. Saturated fats are flat molecules that easily stick together in the blood, and too much saturated fat has been shown by scientists to negatively affect heart health, contributing to clogging of arteries and cardiovascular disease (CVD). By comparison, unsaturated fats seem to help prevent CVD, because they don't stick together in the blood and therefore don't clog arteries.

Unsaturated fats might be healthier for you, but plant oils can easily go rancid and aren't solid at room temperature, which makes them more difficult to cook with and to use in solid food products. To get around this problem, food manufacturers hydrogenated unsaturated fatty acids by heating the oil and exposing it to hydrogen gas. This treatment made the otherwise liquid plant oils semisolid at room temperature and gave foods containing partially hydrogenated oils better shelf life.

An unintended consequence of hydrogenation, however, was the formation of trans fats. Many commercially packaged foods contain trans fats, which recently have been shown to increase LDL (sometimes called bad cholesterol) and lower HDL (sometimes called good cholesterol) levels in the blood. Trans fat consumption also appears to increase risk of CVD and heart attack.

At one point, investigators thought that the total amount of lipid in the diet caused coronary and other heart-related diseases. As scientific evidence accumulated showing a distinction between the effects of saturated and unsaturated fats, public perception changed. Until recently, trans fats were of little concern to the general public, and people readily consumed them without much thought. As science has brought the negative effects of trans fats to light, perception has changed once again. Public outcry has prompted changes in the food services industry, with clear labeling of trans fats on all food products and with more restaurants using trans fat–free oils during cooking. This is a good example of how our perceptions change over time based on scientific evidence, and it illustrates the essential role that science plays in the common good. Science constantly refines what we know as new evidence provides greater insights into how we function and live.

Questions to Consider

1. What is the chemical structure of a trans fat compared to that of a non-trans fat?
2. How much trans fat do you consume daily?
3. How would you balance the needs of the food industry with the health risks associated with changing the chemical composition of a food?

shaking, because the nonpolar oil and polar water are chemically incompatible.

Triglycerides containing fatty acids with unsaturated bonds melt at a lower temperature than those containing only saturated fatty acids. The reason is that a double bond creates a kink in the fatty acid chain that prevents close packing between the hydrocarbon chains (Fig. 2.10). We can infer that butter, a fat that is solid at room temperature, must contain primarily saturated fatty acids, whereas corn oil, which is a liquid even when placed in the refrigerator, must contain primarily unsaturated fatty acids. This difference has applications useful to living organisms. For example, the feet of reindeer and penguins contain unsaturated triglycerides, and this helps protect those exposed parts from freezing.

In general, fats, which most often come from animals, are solid at room temperature, whereas oils, which come from plants, are liquid at room temperature. Diets high in animal fat have been associated with circulatory disorders, because saturated fats and other molecules can accumulate inside the lining of blood vessels and block blood flow. Health organizations have recommended replacing fat with oils such as olive oil and canola oil in our diet whenever possible.

Nearly all animals use fat rather than glycogen for long-term energy storage. Gram for gram, fat stores more energy than glycogen. The C−H bonds of fatty acids make them a richer source of chemical energy than glycogen, because more bonds with stored energy are present in fatty acids; in contrast, glycogen has many C−OH bonds, which are less energetic bonds. Also, fat droplets do not contain water, because they are nonpolar. Small birds, such as the broad-tailed hummingbird, store a great deal of fat before they start their long spring and fall migratory flights. About 0.15 g of fat per gram of body weight is accumulated each day. If the same amount of energy were stored as glycogen, a bird would be so heavy it would not be able to fly.

Phospholipids: Membrane Components

Phospholipids are basically triglycerides, except that in place of the third fatty acid attached to glycerol, there is a polar phosphate group (Fig. 2.11*a*). This portion of the molecule becomes the polar head, while the hydrocarbon chains of the fatty acids become the nonpolar tails. Notice in Figure 2.11*a* that a double bond causes a tail to kink.

Phospholipids have hydrophilic heads and hydrophobic tails. When exposed to water, phospholipids tend to arrange themselves so that the polar heads are oriented toward water and the nonpolar fatty acid tails are oriented away from water. In living organisms, which are made mostly of water, phospholipids tend to become a bilayer (double layer), because the polar heads

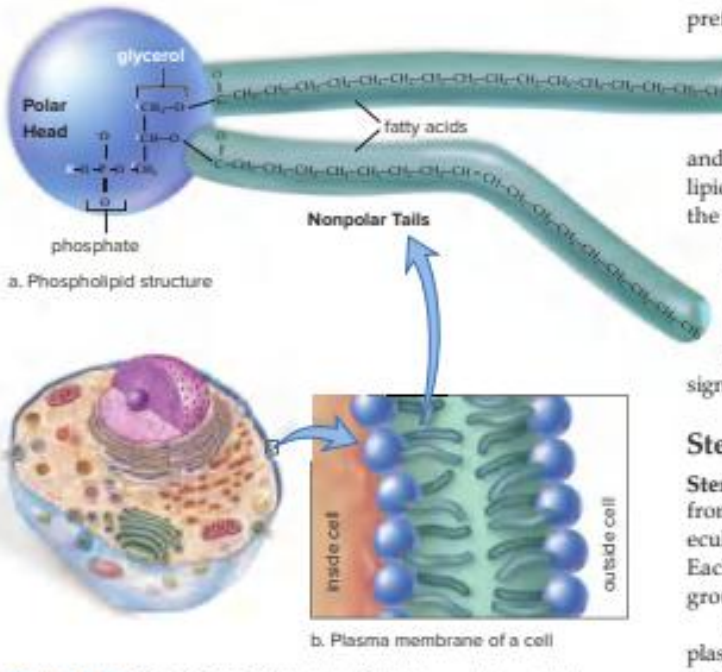


Figure 2.11 Phospholipids form membranes. **a.** Phospholipids are constructed like fats, except that in place of the third fatty acid, they have a polar phosphate group. The hydrophilic (polar) head is soluble in water, whereas the two hydrophobic (nonpolar) tails are not. A tail has a kink wherever there is an unsaturated bond. **b.** Because of their structure, phospholipids form a bilayer that serves as the major component of a cell's plasma membrane. The fluidity of the plasma membrane is affected by kinks in the phospholipids' tails.

prefer to interact with other polar molecules, such as water. Conversely, the nonpolar tails associate together and stay away from polar water molecules. Thus, phospholipids arrange themselves like a "sandwich," with the polar heads facing the outside (the bread slices) and the fatty acid tails on the inside (the filling). This phospholipid bilayer is a key component used to keep cells separate from the biological compartments within cells.

The plasma membrane that surrounds cells consists primarily of a phospholipid bilayer (Fig. 2.11*b*). The presence of kinks in the tails causes the plasma membrane to be fluid across a range of temperatures found in nature. A plasma membrane is essential to the structure and function of a cell, and this signifies the importance of phospholipids to living organisms.

Steroids: Four Fused Rings

Steroids are lipids with structures that are entirely different from those of triglycerides and phospholipids. Steroid molecules have skeletons of four fused carbon rings (Fig. 2.12*a*). Each type of steroid differs primarily by the types of functional groups attached to the carbon skeleton.

Cholesterol is an essential component of an animal cell's plasma membrane, where it provides physical stability. Cholesterol is the precursor of several other steroids, such as the sex hormones testosterone and estrogen (Fig. 2.12*b, c*). The male sex hormone, testosterone, is formed primarily in the testes, and the female sex hormone, estrogen, is formed primarily in the ovaries. Testosterone and estrogen differ only by the functional groups attached to the same carbon skeleton, yet each has its own profound effect on the body and sexuality of an animal. Human and plant estrogens

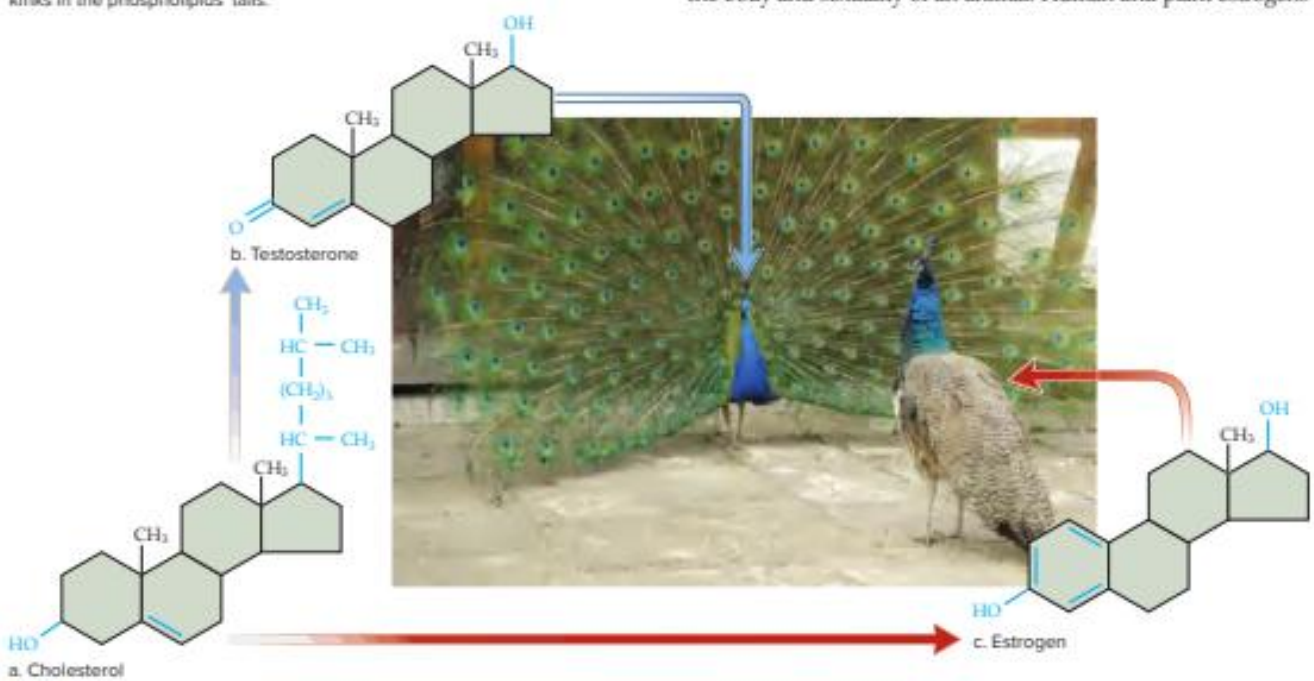


Figure 2.12 Steroid diversity. **a.** Built like cholesterol, (**b**) testosterone and (**c**) estrogen have different effects on the body due to different functional groups attached to the same carbon skeleton. Testosterone is the male sex hormone active in peacocks (*left*), and estrogen is the female sex hormone active in pealhens (*right*). These hormones are present in many living creatures.

a.

b.

Figure 2.13 Waxes. Waxes are a type of lipid. **a.** Fruits are protected by a waxy coating, which is visible on these plums. **b.** Bees secrete the wax that allows them to build a comb, where they store honey.

are similar in structure, and if estrogen therapy is recommended, some women prefer taking soy products in preference to estrogen from animals.

Cholesterol can also contribute to circulatory disorders. The presence of cholesterol encourages the accumulation of fatty material inside the lining of blood vessels, which decreases the size of the opening and thereby can result in high blood pressure. Cholesterol-lowering medications are available.

Waxes

In **waxes,** long-chain fatty acids are connected to carbon chains containing alcohol functional groups. Waxes are solid at normal temperatures, because they have a high melting point. Being hydrophobic, they are also waterproof and resistant to degradation. In many plants, waxes, along with other molecules, form a protective cuticle (covering) that prevents the loss of water from all exposed parts (Fig. 2.13*a*). In many animals, waxes are involved in skin and fur maintenance. In humans, wax is produced by glands in the outer ear canal. Earwax contains cerumin, an organic compound that, at the very least, repels insects and in some cases even kills them. It also traps dust and dirt, preventing these contaminants from reaching the eardrum. A honeybee produces beeswax in glands on the underside of its abdomen. Beeswax is used to make the six-sided cells of the comb, where honey is stored (Fig. 2.13*b*). Honey contains the sugars fructose and glucose, breakdown products of the sugar sucrose. In humans, waxes are produced by glands in the ear. These waxes waterproof the ear canal and prevent the growth of bacteria.

Check Your Progress 2.3

1. List the functions of triglycerides, phospholipids, steroids, and waxes.
2. Contrast the structure of a saturated fatty acid with that of an unsaturated fatty acid.
3. Explain why phospholipids form a bilayer in water.

2.4 Proteins

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the functions of proteins in cells.
2. Explain how a polypeptide is constructed from amino acids.
3. Compare the four levels of protein structure.
4. Understand the factors that affect protein structure and function.

Proteins (Gk. *proteios,* "first place") are of primary importance to the structure and function of cells. As much as 50% of the dry weight of most cells consists of proteins. Several hundred thousand proteins have been identified. The following are some of their many functions in animals:

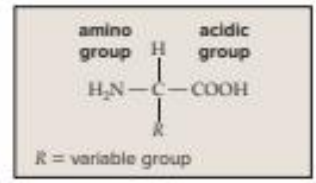
- *Metabolism* Enzyme proteins bring reactants together and thereby speed chemical reactions in cells. They are specific for one particular type of reaction and function best at specific body temperatures and pH.
- *Support* Some proteins have a structural function. For example, keratin makes up hair and nails, while collagen gives strength to ligaments, tendons, and skin.
- *Transport* Channel and carrier proteins in the plasma membrane regulate what substances enter and exit cells. Other proteins transport molecules in the blood of animals; hemoglobin is a complex protein that transports oxygen to tissues and cells.
- *Defense* Antibodies are proteins of our immune system that combine with foreign substances, called antigens. Antibodies bind and prevent antigens from destroying cells and upsetting homeostasis.
- *Regulation* Some hormones are proteins that regulate how cells behave. They serve as intercellular messengers that influence cell metabolism. The hormone insulin regulates how much glucose is in the blood and in cells; the presence of growth hormone during childhood and adolescence determines the height of an individual.
- *Motion* The contractile proteins actin and myosin allow parts of cells to move and cause muscles to contract. Muscle

contraction allows animals to travel from place to place. All cells contain proteins that move cell components to different internal locations. Without such proteins, cells would not be able to function.

Proteins are such a major part of living organisms that tissues and cells of the body can sometimes be characterized by the proteins they contain or produce. For example, muscle cells contain large amounts of actin and myosin for contraction; red blood cells are filled with hemoglobin for oxygen transport; and support tissues, such as ligaments and tendons, contain the protein collagen, which is composed of tough fibers.

Amino Acids: Protein Monomers

Proteins are polymers constructed from amino acid monomers. The name **amino acid** is used because one of the functional groups in the amino acid is $-NH_2$ (an amino group) and another is $-COOH$ (an acid group). The third group is called an *R* (variable) group. The structure of an amino acid is as follows:



Note that the central carbon atom in an amino acid bonds to a hydrogen atom and to three other groups of atoms, one of which is the *R* group. Amino acids differ according to their particular *R* group (Fig. 2.14). The *R* groups range in complexity from a single

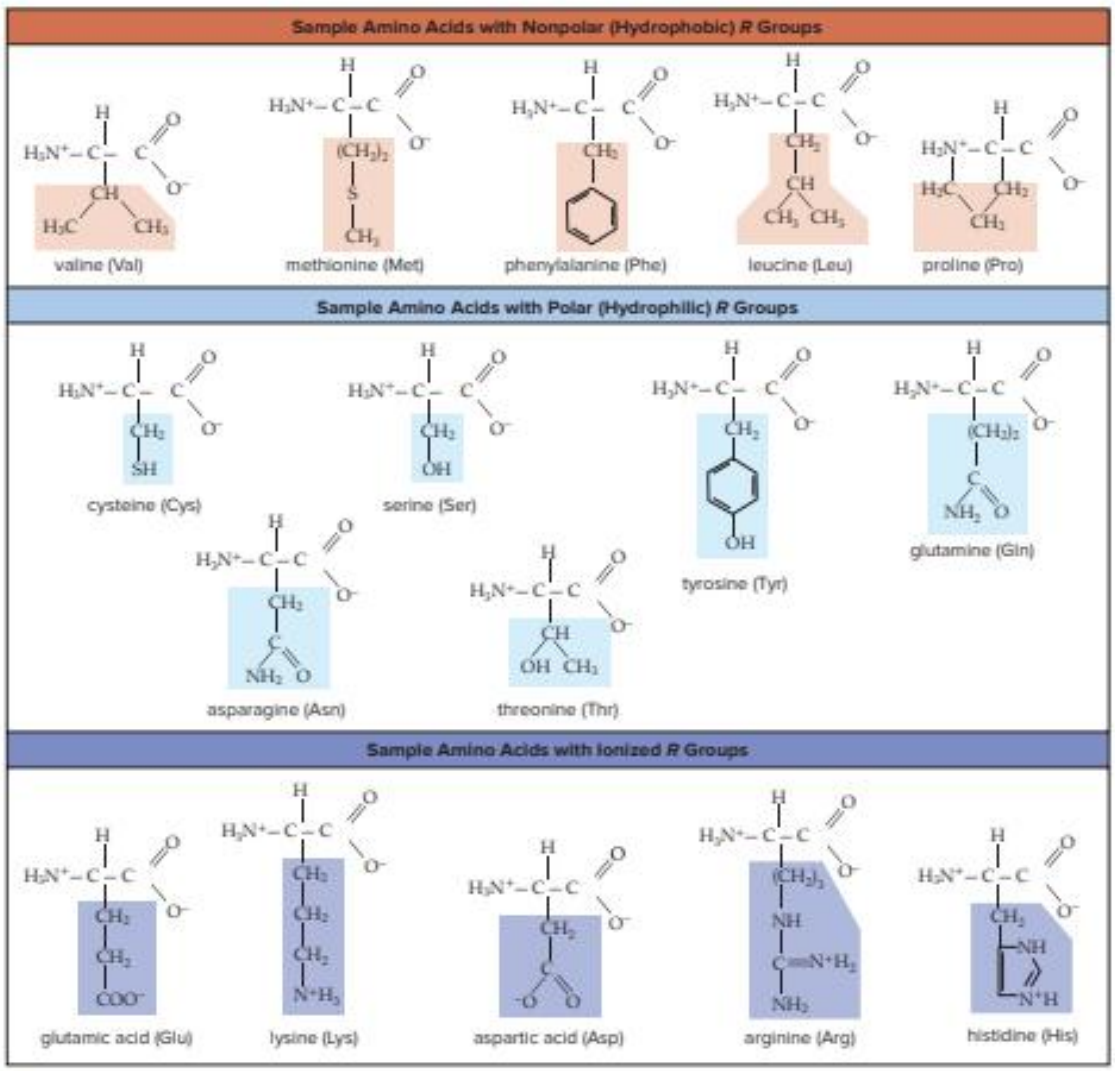
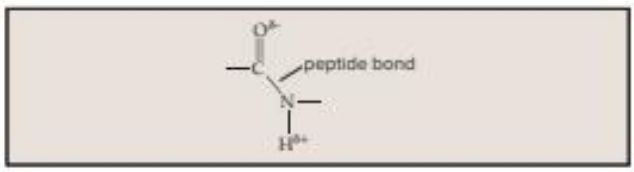


Figure 2.14 Amino acids. Polypeptides contain 20 different kinds of amino acids, some of which are shown here. Amino acids differ by the particular *R* group (shaded area of the molecule) attached to the central carbon. Some *R* groups are nonpolar and hydrophobic (top), some are polar and hydrophilic (center), and some are ionized and hydrophilic (bottom). The amino acids are shown in ionized form.

hydrogen atom to complicated ring compounds. Some *R* groups are polar and associate with water, whereas others are nonpolar and do not. Also, the amino acid cysteine has an *R* group that ends with a −SH (sulfide) group, which often covalently connects one chain of amino acids to another by a disulfide bond, −S−S−. Several other amino acids commonly found in cells are shown in Figure 2.14.

Amino acids are linked by dehydration reactions that link the carboxyl group of one amino acid to the amino group of another amino acid (Fig. 2.15). The resulting covalent bond between two amino acids is called a **peptide bond.** The atoms associated with the peptide bond share the electrons unevenly, because oxygen is more electronegative than nitrogen. Therefore, the hydrogen attached to the nitrogen has a slightly positive charge, while the oxygen has a slightly negative charge:



The polarity of the peptide bond means that hydrogen bonding is possible between the −CO of one amino acid and the −NH of another amino acid in a polypeptide. This hydrogen bonding influences the structure, or shape, of a protein.

A **peptide** is two or more amino acids bonded together, and a **polypeptide** is a chain of many amino acids joined by peptide bonds. A protein is a polypeptide that has been folded into a particular shape and has function. Some proteins may consist of more than one polypeptide chain, making it possible for some proteins to have a very large number of amino acids.

The amino acid sequence greatly influences the final three-dimensional shape and function of a protein. Each protein has a sequence of amino acids that is defined by information contained within a gene. This amino acid sequence forms the basis for all levels of protein structure, which directly affect protein function. Proteins that have an abnormal sequence often have a three-dimensional shape that causes them to function improperly. From an evolutionary perspective, we also know that, for a particular protein, the sequences of amino acids are highly similar within a species and are different across species.

Shape of Proteins

Proteins may have up to four levels of structural organization: primary, secondary, tertiary, and quaternary (Fig. 2.16).

Primary Structure

The *primary structure* of a protein is the linear sequence of amino acids. Hundreds of thousands of different polypeptides can be built from just 20 amino acids. Changing the sequence of 20 amino acids in a polypeptide can produce a huge array of different proteins. The sequence of the amino acids in the primary structure is determined by the information contained within genes, which are part of the DNA of the cell.

Secondary Structure

The *secondary structure* of a protein occurs when the polypeptide coils or folds in a particular way (Fig. 2.16).

Linus Pauling and Robert Corey, who began studying the structure of amino acids in the late 1930s, concluded that a coiling they called an α (alpha) helix and a pleated sheet they called a β (beta) sheet were two basic patterns of structure that amino acids assumed within a polypeptide. The names came from the fact that the α helix was the first, and the β sheet the second, pattern they discovered. Each polypeptide can have multiple α helices and β pleated sheets.

The spiral shape of α helices is formed by hydrogen bonding between every fourth amino acid within the polypeptide chain, whereas β sheets are formed when the polypeptide turns back upon itself, allowing hydrogen bonding to occur between extended lengths of the polypeptide. *Fibrous proteins,* which are structural proteins, exist only as helices or pleated sheets that hydrogen bond to each other. Examples are keratin, a protein in hair, and silk, a protein that forms spider webs. Both of these proteins have only a secondary structure (Fig. 2.17).

Tertiary Structure

A *tertiary structure* is the folding that results in the final three-dimensional shape of a polypeptide. *Globular proteins,* which tend to ball up into rounded shapes, have tertiary structure.

The interaction of hydrophobic amino acids in the polypeptide chain with the surrounding water is a major factor in how proteins fold into, and maintain, their final shape. These nonpolar amino acids tend to group together in the interior of a protein, to be as far away from water as possible. In contrast, the polar hydrophilic and ionic amino acids interact well with water and tend to orient themselves on the protein's surface. These chemical interactions, along with hydrogen bonds, ionic bonds, and covalent bonds between *R* groups, all contribute to the tertiary structure of a protein. Strong disulfide linkages (−S−S−) in particular help maintain the tertiary shape.

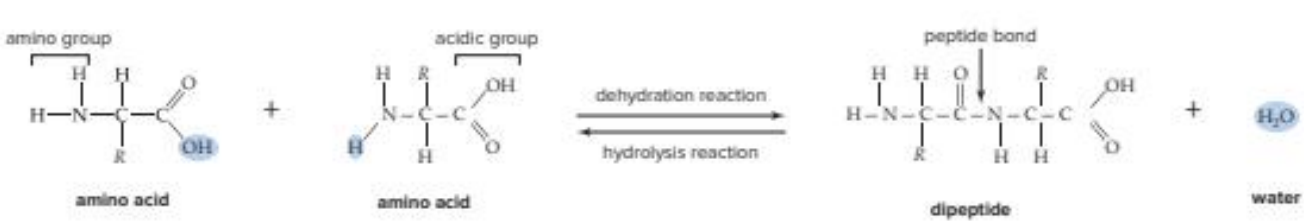


Figure 2.15 Synthesis and degradation of a peptide. Following a dehydration reaction, a peptide bond joins two amino acids and a water molecule is released. Following a hydrolysis reaction, the bond is broken due to the addition of water.

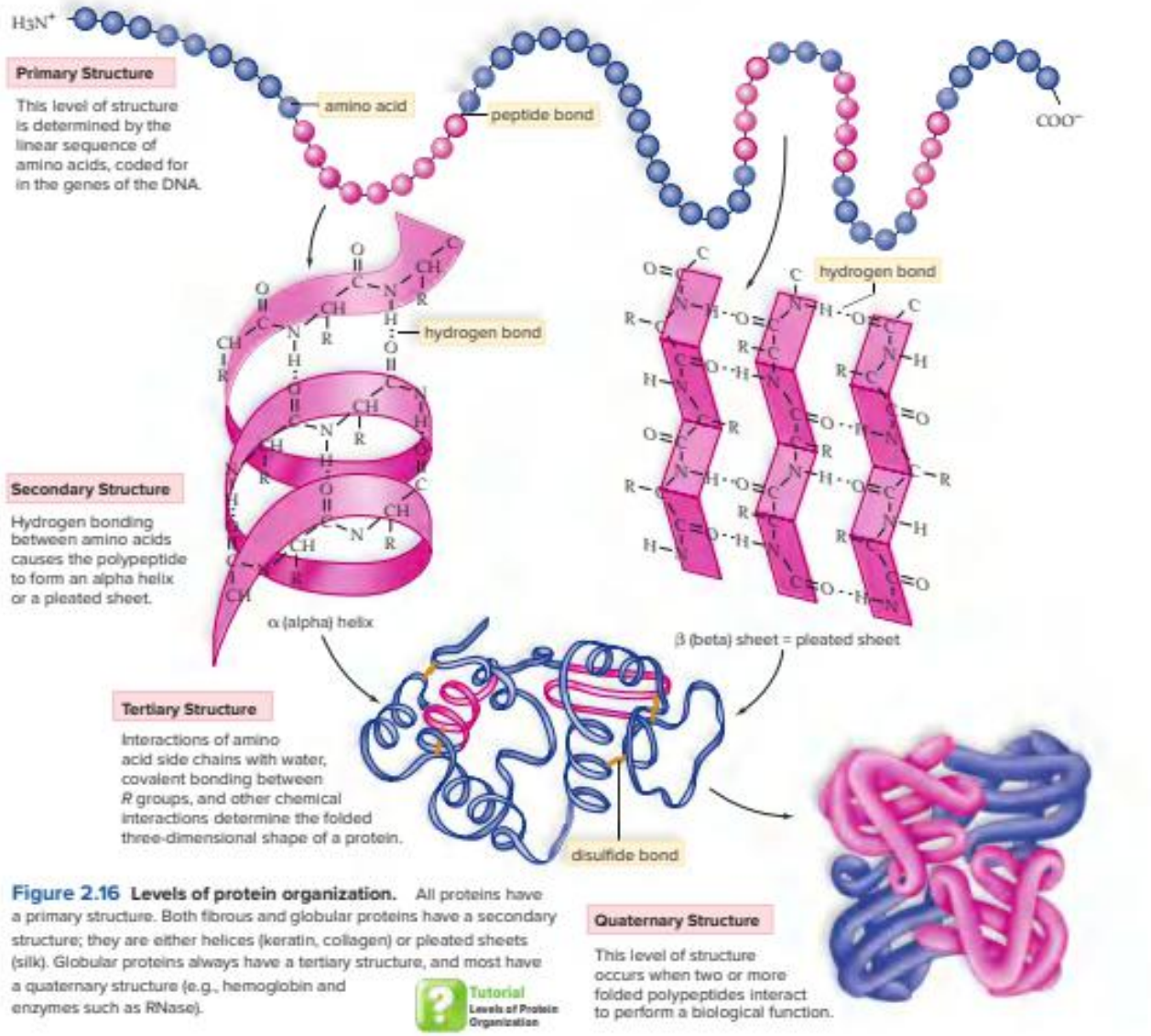


Figure 2.16 Levels of protein organization. All proteins have a primary structure. Both fibrous and globular proteins have a secondary structure; they are either helices (keratin, collagen) or pleated sheets (silk). Globular proteins always have a tertiary structure, and most have a quaternary structure (e.g., hemoglobin and enzymes such as RNase).

Figure 2.17 Fibrous proteins. Fibrous proteins are structural proteins. **a.** Keratin—found, for example, in hair, horns, and hooves—exemplifies fibrous proteins that are helical for most of their length. **b.** A chemical treatment, called a perm, may be used to alter the secondary structure of the keratin proteins. **c.** Silk made by spiders is fibrous proteins that are pleated sheets for most of their length. Hydrogen bonding between parts of the molecule causes the pleated sheet to double back on itself.

Most enzymes are globular proteins. Enzymes work best at a specific temperature, and each one has an optimal pH, at which the rate of the reaction is highest. At this temperature and pH, the enzyme can maintain its normal shape. A high temperature and change in pH can disrupt the interactions that maintain the shape of the enzyme. When a protein loses its natural shape, it is said to be **denatured.** An organism can die if too many proteins become denatured, because it can no longer maintain the metabolic processes necessary for life.

Quaternary Structure

Some proteins have a *quaternary structure,* because they consist of more than one polypeptide. Hemoglobin, the protein that transports oxygen in the blood, is a globular protein that consists of four polypeptides. Each polypeptide in hemoglobin has a primary, secondary, and tertiary structure. However, a protein can have only two polypeptides and still have quaternary structure.

The Importance of Protein Folding

The function of a protein is directly associated with its three-dimensional structure. Therefore, the correct folding of a protein is important. Changes in the instructions in the genes encoding a protein may result in changes in either the structure of the protein or the way it folds. At times, this may be deterimental, as is the case for diseases such as cystic fibrosis. However, sometimes these changes are less damaging. Minor changes in the proteins associated with hair or eye color are examples of variation in protein structure that are not detrimental to an organism.

Cells contain *chaperone proteins,* which help new proteins fold into their normal shape. Initially, researchers thought that chaperone proteins only ensured that proteins folded properly, but now it appears that they might correct any misfolding of a new protein. In any case, without fully functioning chaperone proteins, a cell's proteins may not be functional, because they have misfolded. Several diseases in humans, such as Alzheimer disease, are associated with misshapen proteins.

Other diseases in humans are due to misfolded proteins, but the cause may be different. For years, investigators have been studying fatal brain diseases, known as TSEs,[1] that have no cure because no infective agent could be found. Mad cow disease is a well-known example of a TSE disease. Now it appears that TSE diseases might be due to misfolded proteins, called **prions,** that cause other proteins of the same type to fold the wrong way, too.

Check Your Progress **2.4**

1. List the roles of proteins in living organisms.
2. Describe how two amino acids are combined to form a polypeptide.
3. Summarize the differences among primary, secondary, teriary, and quaternary structure.
4. Describe the consequences of incorrect protein folding.

1 TSEs: transmissible spongiform encephalopathies.

2.5 Nucleic Acids

Learning Outcomes

Upon completion of this section, you should be able to

1. Distinguish between a nucleotide and nucleic acid.
2. Compare the structure and function of DNA and RNA nucleic acids.
3. Explain how ATP is able to store energy.

Each cell has a storehouse of information that specifies how a cell should behave, respond to the environment, and divide to make new cells. **Nucleic acids,** which are polymers of nucleotides, store information, include instructions for life, and conduct chemical reactions. **DNA** (**deoxyribonucleic acid**) is one type of nucleic acid that not only stores information about how to copy, or replicate, itself but also specifies the order in which amino acids are to be joined to make a protein.

RNA (**ribonucleic acid**) is another diverse type of nucleic acid that has multiple uses. Messenger RNA (mRNA) is a temporary copy of a gene in the DNA that specifies what the amino acid sequence will be during the process of protein synthesis. Transfer RNA (tRNA) is also necessary in synthesizing proteins, and it helps translate the sequence of nucleic acids in a gene into the correct sequence of amino acids during protein synthesis. Ribosomal RNA (rRNA) works as an enzyme to form the peptide bonds between amino acids in a polypeptide. A wide range of other RNA molecules also perform important functions within the cell.

Not all nucleotides are made into DNA or RNA polymers. Some nucleotides are directly involved in metabolic functions in cells. For example, some are components of **coenzymes,** nonprotein organic molecules that help regulate enzymatic reactions. **ATP** (**adenosine triphosphate**) is a nucleotide that stores large amounts of energy needed for synthetic reactions and for various other energy-requiring processes in cells.

Structure of DNA and RNA

Every **nucleotide** is comprised of three types of molecules: a pentose sugar, a phosphate (phosphoric acid), and a nitrogen-containing base (Fig. 2.18*a*). In DNA, the pentose sugar is deoxyribose, and in RNA the pentose sugar is ribose. A difference in the structure of these 5-carbon sugars accounts for their respective names, because, as you might guess, deoxyribose lacks an oxygen atom found in ribose (Fig. 2.18*b*).

Both DNA and RNA contain combinations of four nucleotides (Fig. 2.18*c*), but these differ somewhat between the two nucleic acids (Table 2.4). Nucleotides that have a base with a single ring are called pyrimidines, and nucleotides with a double ring are called purines. In DNA, the pyrimidine bases are cytosine and thymine; in RNA, the pyrimidine bases are cytosine and uracil. Both DNA and RNA contain the purine bases adenine and guanine. These molecules are called bases because their presence raises the pH of a solution. Table 2.4 summarizes the differences between DNA and RNA.

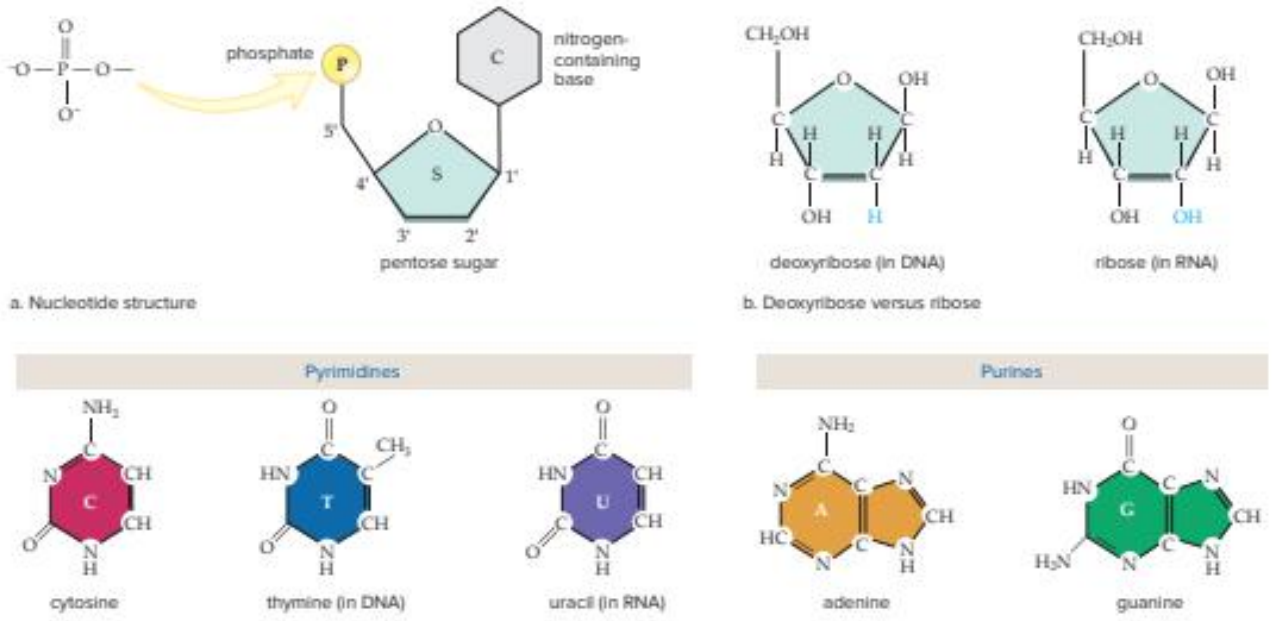


Figure 2.18 Nucleotides. **a.** A nucleotide consists of a pentose sugar, a phosphate molecule, and a nitrogen-containing base. **b.** DNA contains the sugar deoxyribose, and RNA contains the sugar ribose. **c.** DNA contains the pyrimidines C and T and the purines A and G. RNA contains the pyrimidines C and U and the purines A and G.

Table 2.4 DNA Structure Compared to RNA Structure

	DNA	RNA
Sugar	Deoxyribose	Ribose
Bases	Adenine, guanine, thymine, cytosine	Adenine, guanine, uracil, cytosine
Strands	Double-stranded with base pairing	Usually single-stranded
Helix	Yes	No

Nucleotides are joined into a DNA or an RNA polymer by a series of dehydration reactions. The resulting polymer is a linear molecule called a strand, in which the backbone is made up of an alternating series of sugar-phosphate-sugar-phosphate molecules. The bases project to one side of the backbone. Nucleotides are joined in an order specified by the strand they are copied from. DNA is double-stranded, and RNA is single-stranded (Fig. 2.19).

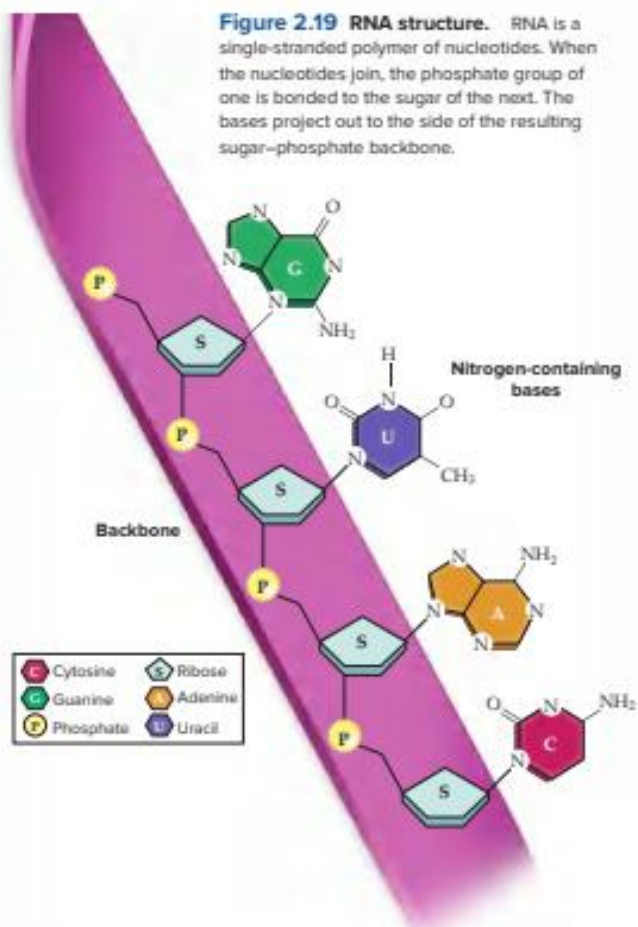


Figure 2.19 RNA structure. RNA is a single-stranded polymer of nucleotides. When the nucleotides join, the phosphate group of one is bonded to the sugar of the next. The bases project out to the side of the resulting sugar–phosphate backbone.

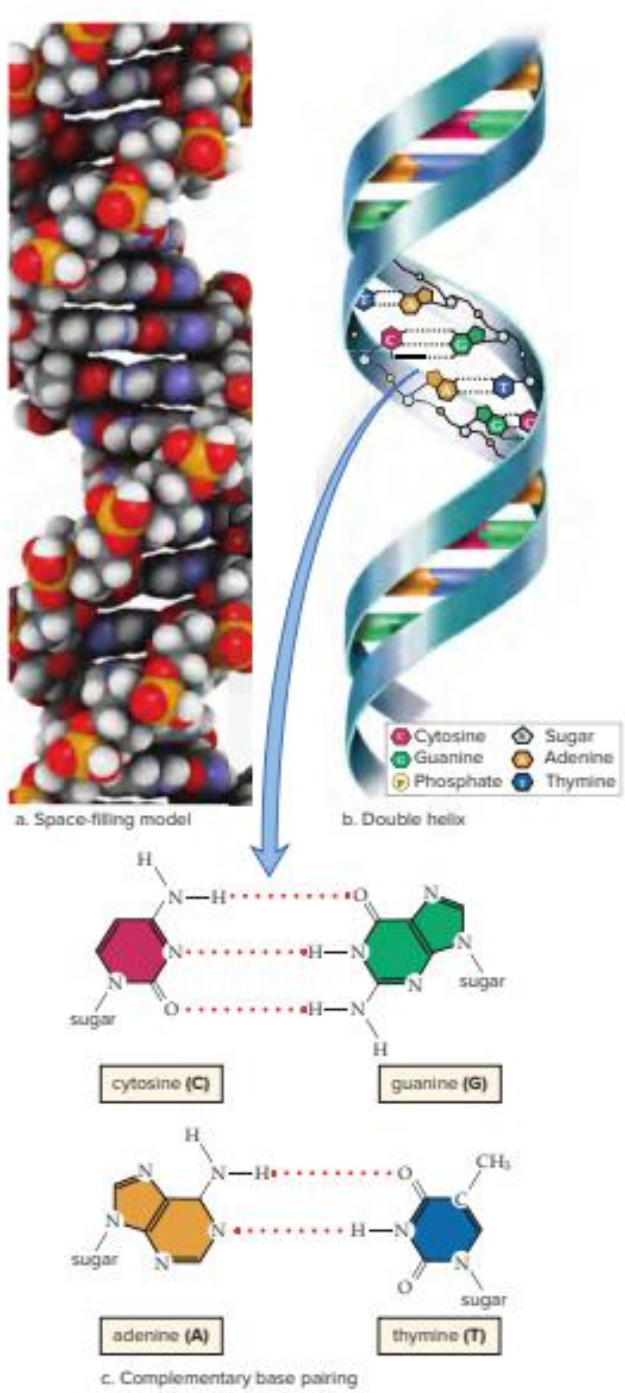


Figure 2.20 DNA structure. **a.** Space-filling model of DNA. **b.** DNA is a double helix in which the two polynucleotide strands twist about each other. **c.** Hydrogen bonds (dotted lines) occur between the complementarily paired bases: C is always paired with G, and A is always paired with T.

The two strands in double-stranded DNA usually twist around each other to form a double helix (Fig. 2.20*a, b*). The two strands are held together by hydrogen bonds between pyrimidine and purine base pairs. The bases can be in any order within a strand, but between strands, thymine (T) is always paired with adenine (A), and guanine (G) is always paired with cytosine (C). This is called **complementary base pairing.** Therefore, regardless of the order or the quantity of any particular base pair, the number of purine bases (A + G) always equals the number of pyrimidine bases (T + C) (Fig. 2.20*c*). We will take a closer look at the structure of DNA and RNA.

ATP (Adenosine Triphosphate)

ATP is a nucleotide comprised of adenine and ribose (adenosine) and three phosphates (triphosphate). The three phosphate groups are attached together and to ribose, the pentose sugar (Fig. 2.21).

ATP is a high-energy molecule, because the last two phosphate bonds are unstable and are easily broken. In cells, hydrolysis of the terminal phosphate bond produces the molecule **ADP** (**adenosine diphosphate**), a phosphate molecule Ⓟ, and lots of energy to do cellular work.

The energy that is released by ATP hydrolysis is used to power many cellular processes, including enzyme reactions, cell communication, and cell division. ATP hydrolysis is chemically favored, because ADP and Ⓟ are more stable than the original ATP molecule. Even though the third phosphate bond is broken, it is the whole molecule that releases energy.

In many cases, the hydrolysis of the ATP nucleotide is coupled to chemically unfavorable reactions in cells to allow these reactions to proceed. For example, key steps in the synthesis of macromolecules, such as carbohydrates and proteins, are able to proceed because the energy from ATP breakdown is used to pay the energy costs of the chemical reaction. ATP also supplies the energy for muscle contraction and nerve impulse conduction. Just as you spend money when you pay for a product or service, cells "spend" ATP when they need something. That's why ATP is called the energy currency of cells.

Check Your Progress 2.5

1. Examine how a nucleic acid stores information.
2. Describe the three components of a nucleotide.
3. Evaluate the properties of ATP that make it an ideal carrier of energy.

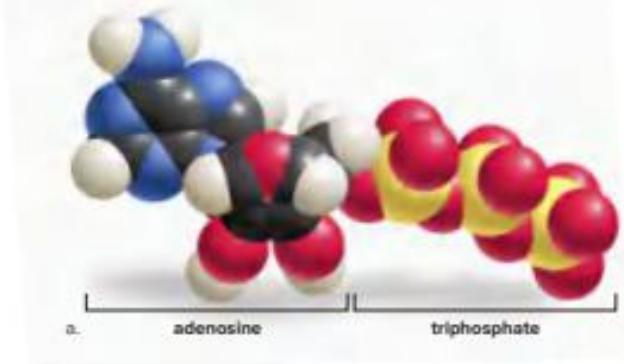
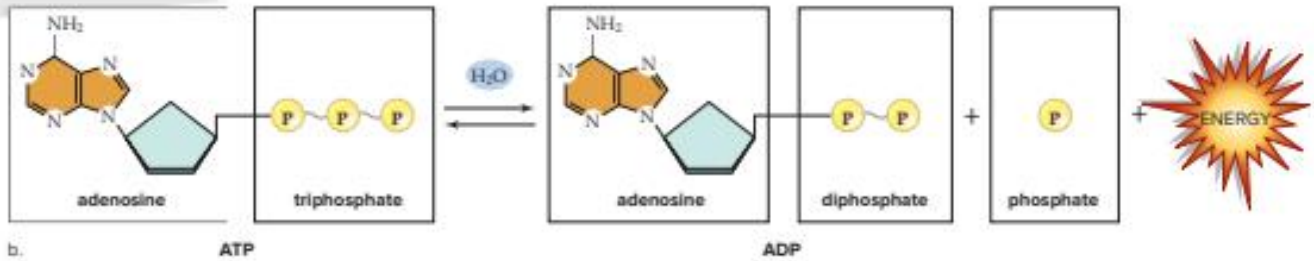


Figure 2.21 ATP. ATP, the universal energy currency of cells, is composed of adenosine and three phosphate groups. **a.** Space-filling model of ATP. **b.** When cells require energy, ATP becomes ADP + Ⓟ, and energy is released.



REVIEWING *the* BIG IDEAS

BIG IDEA 1

Molecules evolve from simple to complex, with building block monomers often joining to form polymers with the ability to replicate, store, and transfer information. Specific molecular building blocks seem to be universally used in all organisms on Earth. 1.D.1.a.3; 1.D.2.b.1

A change in nucleic acid sequence often alters amino acid sequence, which may alter the structure and function of the protein produced, leading to a change within a species that is subject to natural selection. 1.A.1.c; *3.C.1.a.; 3.C.1.d*

BIG IDEA 2

Carbon, nitrogen, phosphorus, and other molecules and atoms from the environment are used to build the carbohydrates, lipids, proteins, and nucleic acids that make up living organisms. 2.A.3.a.1

Organisms may capture free energy stored in carbon compounds to power cellular processes. 2.A.2.a-b

BIG IDEA 3

Genetic information is stored and transmitted in the form of specific sequences of DNA and RNA nucleotides. 3.A.1.a.1

BIG IDEA 4

The orientation of biomolecules influences their structure, replication, and bond formation. 4.A.1.b. 1-3

Lipids and carbohydrates serve in structure and energy store roles. 4.A.1 a.3-4

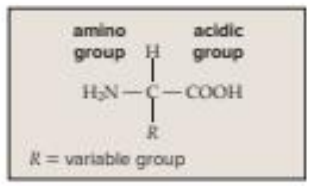
Nucleotide sequences encode biological information, while amino acid sequences dictate the structure and function of proteins. 4.A.1.a.1-3

SUMMARIZE

AP Answering the Essential Questions

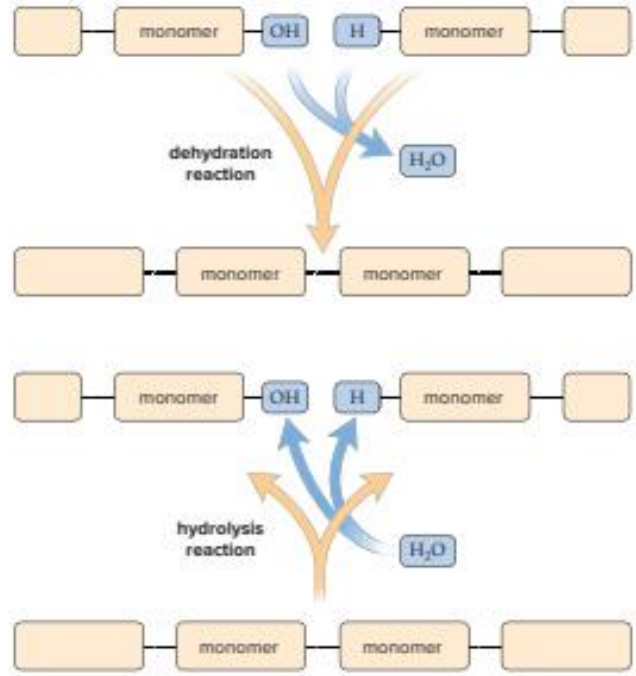
Living organisms are composed of large carbon-based molecules that can be grouped into four categories, each with particular structures and functions. These molecules of life are **carbohydrates, lipids, proteins,** and **nucleic acids.** We learned that in addition to carbon, biomolecules are comprised of five other elements—sulfur, phosphorus, oxygen, nitrogen, and hydrogen—in different quantities and arrangements. Collectively, these key elements can be remembered by the acronym SPONCH. Molecules containing carbon (C) can covalently bond to SPONCH atoms. Because the additional atoms have different electronegativities, molecules containing them have different properties. Two of these functional groups are NH_2 and COOH; amino groups (NH_2) make a molecule more basic, whereas carboxyl groups (COOH) make a molecule more acidic. Adding a phosphate group (OPO_3^{2-}) to a lipid makes a lipid with both hydrophobic (nonpolar) and hydrophilic (polar) regions, a concept that will be studied in detail in Chapter 5 when we explore the structure and function of cell membranes.

The molecules of life As a group, carbohydrates are composed of C, H, and O in the ratio CH_2O or carbon hydrated with, you guessed it, H_2O or water. Different carbohydrates have different functions; some store energy while others strengthen the cell walls of plants. Lipids also are sources of energy and are composed of C, H, and O, but these atoms are arranged quiet differently than they are in carbohydrates. Special types of lipids—the amphipathic phospholipids—are components of cell membranes that help regulate the passage of materials across them. Proteins are long chains of different sequences of amino acids that all contain an amino group (NH_2), a carboxyl group (COOH), and a variable group, with two amino acids containing sulfur (S).



With different arrangements of 20 amino acid "letters," think how many "words" in the form of proteins can be made. The functions of proteins are many and diverse, including catalyzing chemical reactions (enzymes), providing structural support, protecting against disease, and coordinating cellular responses to outside signals. Nucleic acids, more familiarly known as DNA and RNA, contain phosphorus (P) in addition to C, H, O, and N and store and transmit hereditary information.

In many cases, the molecules comprising living material are very large aggregates of smaller molecules. Thus, biomolecules are commonly referred to as **macromolecules** or **polymers.** Polymers are built by linking together a large number of building blocks called monomers. In a strand of beads, if each bead represents a monomer, the entire strand is the polymer. The properties of the monomers determine the nature of the polymer built from them. For example, complex carbohydrates such as starch are composed of simple ring-shaped sugars such as glucose. Long chains of polymers are assembled by chemical reactions known as **dehydration synthesis** in which a molecule of water is removed between two linking monomers. Conversely, polymers can be broken down by **hydrolysis** or the addition of water.



Protein structure We have already described how macromolecules can be broken down by the addition of water, but other environmental conditions also can affect their structure and, consequently, their function. As you recall, proteins are composed of amino acid monomers linked together to form a polypeptide via dehydration synthesis and peptide bond formation. When a protein is synthesized, the primary chain of amino acids may fold due to the formation of various bonds and other molecular interactions between parts of the chain, creating a unique three-dimensional shape. Proteins have four levels of structure: primary, secondary, tertiary, and quarternary, each with different functions. For example, most biological catalysts or enzymes are tertiary or globular proteins with many variations and pockets that can act as active or recognition sites for substrates (we will learn more about enzyme structure and function in a later chapter). Quaternary proteins consist of two or more polypeptide chains aggregated into one functional molecule; examples of quaternary proteins are hemoglobin that carries oxygen in our red blood cells and collagen that makes our skin and ligaments flexible. Because many of the forces holding together the tertiary structure of a protein are weak forces, they are subject to disruption by environmental conditions, including changes in pH and temperature. Once the structure of the protein changes, it is difficult for it to function in its original capacity. Similarly, changes in nucleotide sequences in DNA or RNA can result in a change in amino acid sequence coded and, consequently, the polypeptide produced. Such a change is called a **mutation** and often results in a new trait that can be beneficial or detrimental to the organism.

ASSESS

Choose the best answer for each question.

2.1 Organic Molecules

1. A hydrophilic group is
   a. attracted to water.
   b. a polar and/or an ionized group.
   c. found at the end of fatty acids.
   d. All of these are correct.
2. Which of these is not a characteristic of carbon?
   a. forms four covalent bonds
   b. bonds with other carbon atoms
   c. is sometimes ionic
   d. can form long chains
3. Which of the following reactions combines two monomers to produce a polymer?
   a. dehydration
   b. hydrolysis
   c. phosphorylation
   d. None of the above are correct.

2.2 Carbohydrates

4. The monomers of the carbohydrates are the
   a. polysaccharides.
   b. disaccharides.
   c. monosaccharides.
   d. waxes.
5. Which of the following polysaccharides is used as an energy-storage molecule in plants?
   a. glycogen
   b. chitin
   c. starch
   d. cellulose
6. Fructose and galactose are both isomers of
   a. glycogen.
   b. glucose.
   c. starch.
   d. maltose.

2.3 Lipids

7. A fatty acid is unsaturated if it
   a. contains hydrogen.
   b. contains carbon–carbon double bonds.
   c. contains a carboxyl (acidic) group.
   d. is bound to a glycerol.
8. Which of the following is incorrect regarding phospholipids?
   a. The heads are polar.
   b. The tails are nonpolar.
   c. They contain a phosphate group in place of one fatty acid.
   d. They are energy-storage molecules in the cell.
9. A lipid that contains four fused carbon rings is a
   a. triglyceride.
   b. wax.
   c. phospholipid.
   d. steroid.

2.4 Proteins

10. The chemical differences between one amino acid and another is due to which of the following?
    a. amino group
    b. carboxyl group
    c. *R* group
    d. peptide bondv
11. Which of the following levels of protein structure is determined by interactions of more than one polypeptide chain?
    a. primary
    b. secondary
    c. tertiary
    d. quaternary
12. Which of the following is formed by the linking of two amino acids?
    a. a peptide bond
    b. a functional group
    c. quaternary structure
    d. an ionic bond

2.5 Nucleic Acids

13. Which of the following is incorrect regarding nucleotides?
    a. They contain a sugar, a nitrogen-containing base, and a phosphate group.
    b. They are the monomers of fats and polysaccharides.
    c. They join together by alternating covalent bonds between the sugars and phosphate groups.
    d. They are present in both DNA and RNA.
14. Which of the following is correct regarding ATP?
    a. It is an amino acid.
    b. It has a helical structure.
    c. It is a high-energy molecule that can break down to ADP and phosphate.
    d. It is a nucleotide component of DNA and RNA.
15. Which of the following is correct concerning an RNA molecule?
    a. It contains the sugar ribose.
    b. It may contain uracil as a nitrogen-containing base.
    c. It contains a phosphate molecule.
    d. All of the above are correct.

ENGAGE

AP Applying the Big Ideas

1. BIG IDEA 1 Molecules evolve from simple to complex, with building block monomers often joining to form polymers with the ability to replicate, store, and transfer information.
   a. **Describe** TWO specific subcomponents that define nucleic acids.
   b. **Explain** how each of the subcomponents you described in part (a) contributes to the functionality of the polymer to replicate, store, and transfer information.

2. BIG IDEA 2 Free energy from the sun and carbon from the environment contribute to the production of carbohydrates, essential polymers for fueling cells, as well as providing storage and structure.
   a. **Describe** TWO specific subcomponents that define carbohydrates.
   b. **Explain** how each of the subcomponents you described in part (a) contributes to the functionality of the polymer.

3. BIG IDEA 3 One particular inherited blood disorder is caused by the substitution of valine (an amino acid with a nonpolar, hydrophobic side chain) for glutamic acid (an amino acid with a negatively-charged, hydrophilic side chain).
   a. **Predict** how this substitution impacts the structure and function of the globular proteins found in the blood of patients with this disorder.
   b. **Explain** why your predictions for part (a) are justified.

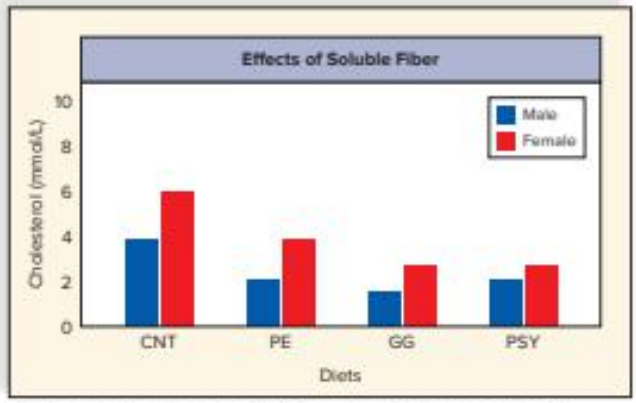
4. BIG IDEA 4 The subcomponents of biological molecules and their sequence determine the properties of that molecule. Proteins, of primary importance to cells, carry out many diverse functions in cells. Their sequence is dictated by amino acids.
   a. **Describe** TWO specific subcomponents that define amino acids.
   b. **Explain** how each of the subcomponents you described in part (a) contributes to the properties of the amino acids and proteins.

AP Applying the Science Practices

Does soluble fiber affect cholesterol levels? High amounts of a steroid called cholesterol in the blood are associated with the development of heart disease. Researchers study the effects of soluble fiber in the diet on cholesterol.

Data and Observations

This experiment evaluated the effects of three soluble fibers on cholesterol levels in the blood: pectin (PE), guar gum (GG), and psyllium (PSY). Cellulose was the control (CNT).



* Data obtained from: Shen, et al. 1998. Dietary soluble fiber lowers plasma LDL cholesterol concentrations by altering lipoprotein metabolism in female Guinea pigs. Journal of Nutrition 128: 1434–1441.

Think Critically SP 2 SP 5

1. **Calculate** the percentage of change in cholesterol levels as compared to the control.
2. **Describe** the effects that soluble fiber appears to have on cholesterol levels in the blood.

Electron micrograph of *Giardia lamblia*, a cause of diarrhea.

3

Cell Structure and Function

AP The Dutch shopkeeper Antonie van Leeuwenhoek (1632–1723) may have been the first person to see living cells. Using a microscope he built himself, he looked at everything possible, from the plaque between his teeth to his own feces. During one of these observations, he discovered "animalcules a moving prettily. Their bodies were somewhat longer than broad, and the belly, which was flat-lie, furnished with sundry little paws. . . ." In this way, Antonie van Leeuwenhoek reported seeing the parasite *Giardia lamblia* (also known as *Giardia intestinalis*). We now know that *Giardia* is a cause of some forms of diarrhea, especially in water supplies that have been contaminated by fecal material. And it is very common; up to 20% of the world's population may be infected with *Giardia*. While *Giardia* are single-celled parasites, and humans consist of trillions of cells, the cells of both of these organisms share may similar characteristics.

In this chapter, you will see that cells are the fundamental building blocks of organisms, organized to carry out basic metabolic functions and adapt to changing environmental conditions. The presentation concentrates on the generalized bacterial, animal, or plant cell; however, all cells are specialized in particular ways.

As you read through the chapter, think about these Essential Questions:

1. Why are most cells so small? 2.A.3.b.1 2.A.3.b.2
2. What structures do all cells share? What evidence supports the theory that eukaryotes evolved from prokaryotic cells? 1.B.1 2.B.3.c 4.B.2.a.1
3. What are structural differences between the genetic material of prokaryotes and eukaryotes? 2.B.3.c 3.A.1.a.2 4.A.2
4. What features allow eukaryotic cells to function? 4.A.2. a-g

Chapter Outline

Following *the* BIG IDEAS

BIG IDEA 1	All cells are produced from existing cells, creating an unbroken lineage back to the first cells almost four billion years ago.
BIG IDEA 2	Eukaryotic cells contain multiple cooperating and specialized organelles which produce the structure and accomplish the functions necessary for life.
BIG IDEA 3	Every cell contains DNA (with or without a nuclear cover) which encrypts the information for all of its structures and functional molecules.
BIG IDEA 4	Cellular systems metabolize and adapt to changing environmental conditions.

3.1 Cellular Level of Organization

Learning Outcomes

Upon completion of this section, you should be able to

1. Understand that cells are the basic unit of life.
2. List the basic principles of the cell theory.
3. Recognize how the surface-area-to-volume ratio limits the size of a cell.

Cells are the basic units of life. All of the chemistry and biomolecules we have discussed to this point are necessary but insufficient on their own to support life. It is only when these components are brought together and organized into a cell that life is possible.

All organisms are made up of cells. When we observe plants, animals, and other organisms, it is important to realize that what we are seeing is a collection of cells that work together in a highly organized, regulated manner and thus conduct the business of life. Figure 3.1 shows the connection between whole organisms and their component cells. Although the cellular basis of life is clear to us now, scientists were unaware of this fact as recently as 200 years ago. The link between cells and life became clear to microscopists during the 1830s.

The **cell** is the smallest unit of living matter. The collective work of the nineteenth-century scientists Robert Brown (1773–1858), Matthias Schleiden (1804–1881), and Theodor Schwann (1810–1882) helped determine that plants and animals are composed of cells. Further work by the German physician Rudolph Virchow (1821–1902) showed that cells self-reproduce and that "every cell comes from a preexisting cell." Today, we know that various illnesses of the body, such as diabetes and prostate cancer, are due to cellular malfunction. Countless scientific investigations since that time verify these initial findings. From these results, we can infer that all life on Earth today came from cells in ancient times, and that all cells are related in some way. In reality, a continuity of cells has been present from generation to generation, even back to the very first cell (or cells) in the history of life.

Today, some life-forms exist as single cells, whereas others are complex, interconnected systems of cells. When single-celled organisms reproduce, a single cell divides and becomes two new organisms. When multicellular organisms grow, many cells divide. The presence of many cells allows some to specialize to do particular jobs within the multicellular organism, including the cells that create genetic variation through sexual reproduction.

The work of Schleiden, Schwann, and Virchow helped created the **cell theory.** It states that

1. All organisms are composed of cells.
2. Cells are the basic units of structure and function in organisms.
3. Cells come only from preexisting cells because cells are self-reproducing.

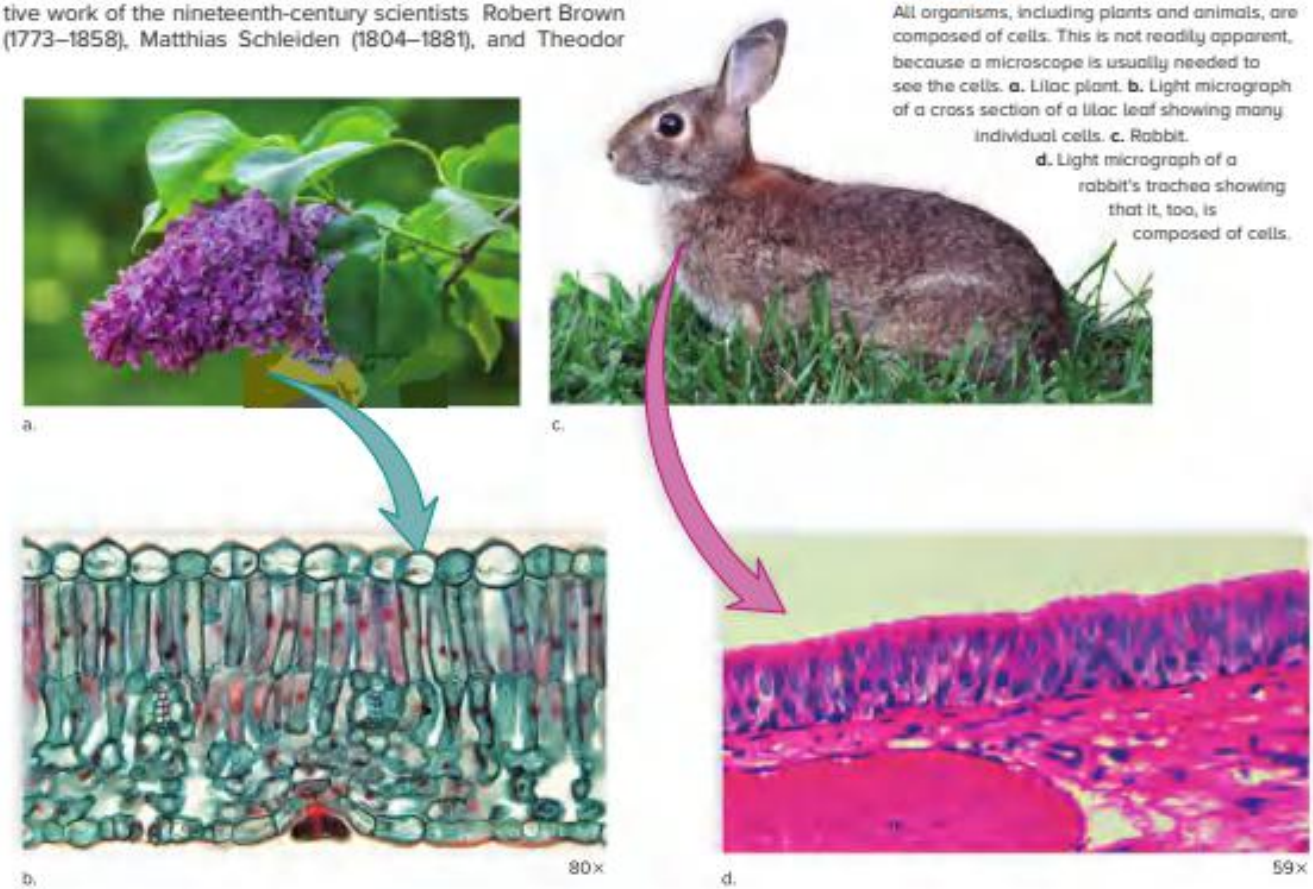


Figure 3.1 Organisms and cells. All organisms, including plants and animals, are composed of cells. This is not readily apparent, because a microscope is usually needed to see the cells. **a.** Lilac plant. **b.** Light micrograph of a cross section of a lilac leaf showing many individual cells. **c.** Rabbit. **d.** Light micrograph of a rabbit's trachea showing that it, too, is composed of cells.

Cell Size

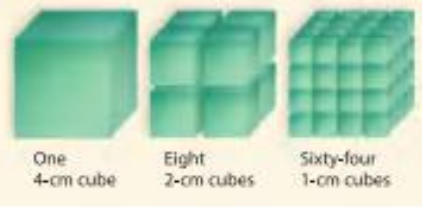
Although they range in size, cells are generally quite small. A frog's egg, at about 1 millimeter (mm) in diameter, is large enough to be seen by the human eye. But most cells are far smaller than 1 mm; some are even as small as 1 micrometer (μm)—one-thousandth of a millimeter. Cell inclusions and macromolecules are smaller than a micrometer and are measured in terms of nanometers (nm).

Because of their size, very small biological structures can only be viewed with microscopes, which magnify a visual image. Figure 3.2 shows the visual range of the eye, light microscope, and electron microscope; the discussion of microscopy in the Nature of Science feature, "Microscopy Today," on page 60 explains why the electron microscope allows us to see so much more detail than the light microscope does.

Why are cells so small? To answer this question, consider that a cell is a system by itself; as such, it needs a surface area large enough to allow adequate nutrients to enter and for wastes to be eliminated. Small cells, not large cells, are likely to have an adequate surface area for exchanging wastes for nutrients. As cells increase in size, the surface area becomes inadequate to exchange the materials that the volume of the cell requires.

Figure 3.3 illustrates that dividing a large cube into smaller cubes provides a lot more surface area per volume. This relationship is called the **surface-area-to-volume ratio.** Calculations show that a 1-cm cube has a surface-area-to-volume ratio of 6:1, whereas a 4-cm cube has a surface-area-to-volume ratio of 1.5:1. In general, a higher surface-area-to-volume ratio increases the efficiency of transporting materials into and out of the cell.

A mental image might help you visualize the importance of surface-area-to-volume ratios and why this relationship favors smaller cells. Imagine a small room and a large room filled with people. The small room, which holds 20 people, has only two doors, and the large room, which holds 80 people, has four doors. If a fire occurred in both rooms, it would be faster to get the people out of the smaller room, because it has the more favorable ratio of doors to people. Similarly, a small cell size is more advantageous for exchanging molecules because of its greater surface-area-to-volume ratio.



Total surface area (height × width × number of sides × number of cubes)	96 cm^2	192 cm^2	384 cm^2
Total volume (height × width × length × number of cubes)	64 cm^3	64 cm^3	64 cm^3
Surface area/Volume of each cube (surface area ÷ volume)	1.5:1	3:1	6:1

Figure 3.3 Surface-area-to-volume relationships. As cell size decreases from 4 cm^2 to 1 cm^2, the surface-area-to-volume ratio increases.

Check Your Progress 3.1

1. Explain why cells are alive but macromolecules are not.
2. State the components of the cell theory.
3. Explain why a large surface-area-to-volume ratio is needed for the proper functioning of cells.

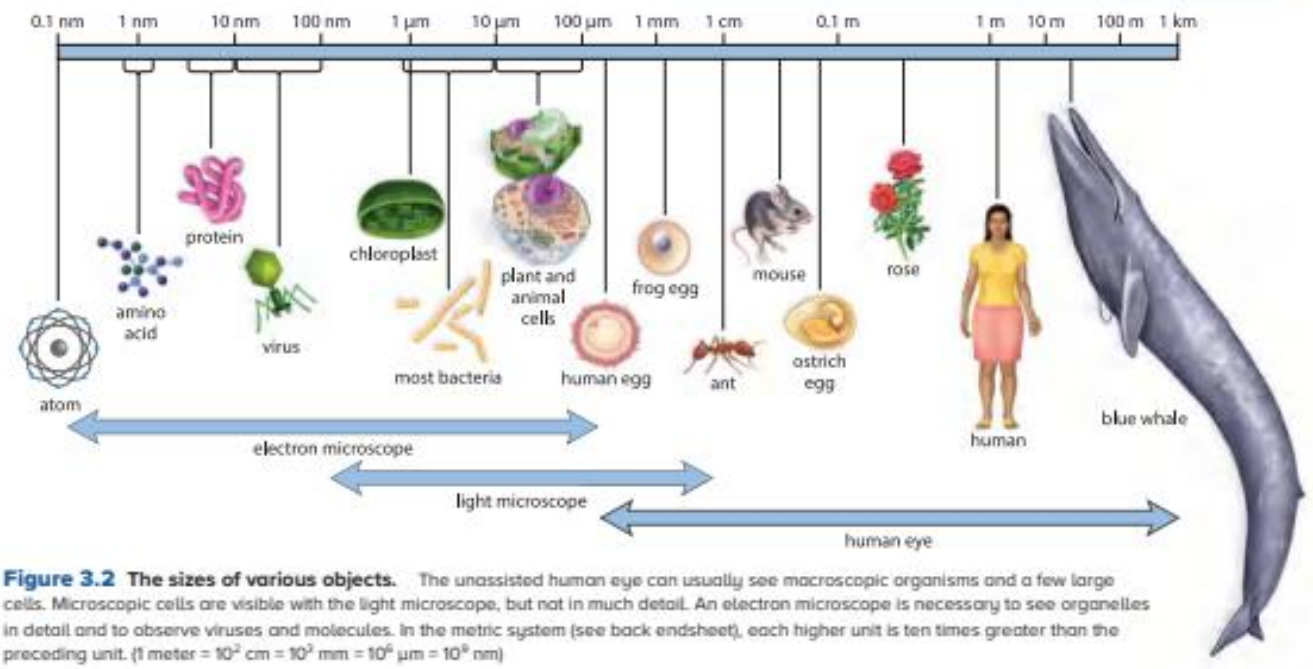


Figure 3.2 The sizes of various objects. The unassisted human eye can usually see macroscopic organisms and a few large cells. Microscopic cells are visible with the light microscope, but not in much detail. An electron microscope is necessary to see organelles in detail and to observe viruses and molecules. In the metric system (see back endsheet), each higher unit is ten times greater than the preceding unit. (1 meter = 10^2 cm = 10^3 mm = 10^6 μm = 10^9 nm)

Nature of Science

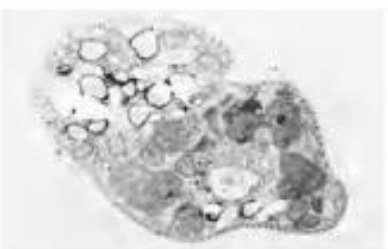
Microscopy Today

Because cells are the basic unit of life, the more we learn about cells, the more we understand life. Cells were not discovered until the seventeenth century, when the microscope was invented. Since that time, various types of microscopes have been developed for studying cells and their components.

Many times when scientists don't have suitable tools to investigate natural phenomena, they invent them. Microscopes have given scientists a deeper look into how life works than is possible with the naked eye. Today, there are many types of microscopes. A *compound light microscope* uses a set of glass lenses to focus light rays passing through a specimen to produce an image that is viewed by the human eye. A *transmission electron microscope* (*TEM*) uses a set of electromagnetic lenses to focus electrons passing through a specimen to produce an image, which is projected onto a fluorescent screen or photographic film. A *scanning electron microscope* (*SEM*) uses a narrow beam of electrons to scan over the surface of a specimen that is coated with a thin metal layer. Secondary electrons given off by the metal are detected and used to produce a three-dimensional image on a television screen. Figure 3A shows these three types of microscopic images.

200×

Euglena, light micrograph

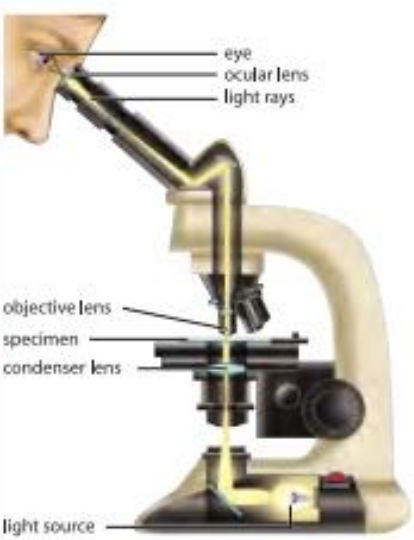


12,500×

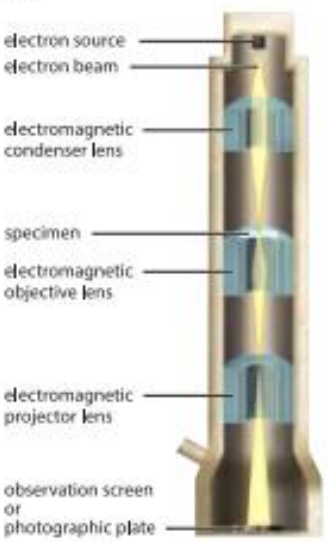
Euglena, transmission electron micrograph

1,520×

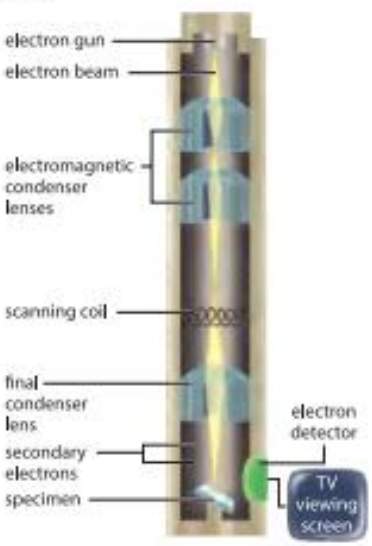
Euglena, scanning electron micrograph



a. Compound light microscope



b. Transmission electron microscope



c. Scanning electron microscope

Figure 3A Diagram of microscopes with accompanying micrographs of *Euglena gracilis*. **a.** The compound light microscope and **(b)** the transmission electron microscope provide an internal view of an organism. **c.** The scanning electron microscope provides an external view of an organism.

Magnification, Resolution, and Contrast

Magnification is the ratio between the size of an image and its actual size. Electron microscopes magnify to a greater extent than do compound light microscopes. A light microscope can magnify objects about a thousand times, but an electron microscope can magnify them hundreds of thousands of times. The difference lies in the means of illumination. The path of light rays and electrons moving through space is wavelike, but the wavelength of electrons is much shorter than the wavelength of light. This difference in wavelength accounts for the electron microscope's greater magnifying capability and its greater ability to distinguish between two points (resolving power).

Resolution is the minimum distance between two objects that allows them to be seen as two separate objects. A microscope with poor resolution might enable a student to see only one cellular granule, while the microscope with the better resolution would show two granules next to each other. The greater the resolving power, the greater the detail seen.

If oil is placed between the sample and the objective lens of the compound light microscope, the resolving power is increased, and if ultraviolet light is used instead of visible light, it is also increased. But typically, a light microscope can resolve down to 0.2 µm, while the transmission electron microscope can resolve down to 0.0002 µm. If the resolving power of the average human eye is set at 1.0, then the typical compound light microscope is about 500, and the transmission electron microscope is 100,000 (Fig. 3Ab).

The ability to make out, or resolve, a particular object can depend on *contrast*, a difference in the shading of an object compared to its background. Higher contrast is often achieved by staining cells with colored dyes (light microscopy) or with electron-dense metals (electron microscopy), which make them easier to see. Optical methods such as phase contrast and differential interference contrast (Fig. 1B) can also be used to improve contrast. Using fluorescently tagged antibodies can also help us visualize subcellular components such as specific proteins (see Fig. 3.19).

Illumination, Viewing, and Recording

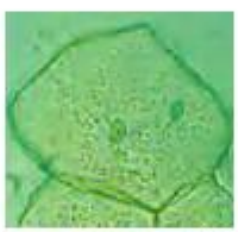
Light rays can be bent (refracted) and brought to focus as they pass through glass lenses, but electrons do not pass through glass. Electrons have a charge that allows them to be brought into focus by electromagnetic lenses. The human eye uses light to see an object but cannot use electrons for the same purpose. Therefore, electrons leaving the specimen in the electron microscope are directed toward a screen or a photographic plate that is sensitive to their presence. Humans can view the image on the screen or photograph.

A major advancement in illumination has been the introduction of *confocal microscopy*, which uses a laser beam scanned across the specimen to focus on a single shallow plane within the cell. The microscopist can "optically section" the specimen by focusing up and down, and a series of optical sections can be combined in a computer to create a three-dimensional image, which can be displayed and rotated on the computer screen.

An image from a microscope may be recorded by placing a television camera where the eye would view the image. The television camera converts the light image into an electronic image, which can be entered into a computer. In *video-enhanced contrast microscopy*, the computer makes the darkest areas of the original image much darker and the lightest areas of the original much lighter. The result is a high-contrast image with deep blacks and bright whites. Even more contrast can be introduced by the computer if shades of gray are replaced by colors.

250×

Bright-field. Light passing through the specimen is brought directly into focus. Usually, the low level of contrast within the specimen interferes with viewing all but its largest components.



225×

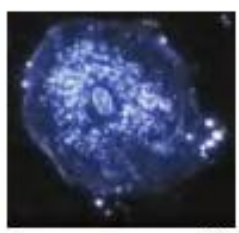
Bright-field (stained). Dyes are used to stain the specimen. Certain components take up the dye more than other components, and therefore contrast is enhanced.

160×

Differential interference contrast. Optical methods are used to enhance density differences within the specimen so that certain regions appear brighter than others. This technique is used to view living cells, chromosomes, and organelle masses.

600×

Phase contrast. Density differences in the specimen cause light rays to come out of "phase." The microscope enhances these phase differences so that some regions of the specimen appear brighter or darker than others. The technique is widely used to observe living cells and organelles.



600×

Dark-field. Light is passed through the specimen at an oblique angle so that the objective lens receives only light diffracted and scattered by the object. This technique is used to view organelles, which appear quite bright against a dark field.

Figure 3B Photomicrographs of cheek cells. Bright-field microscopy is the most common form used with a compound light microscope. Other types of microscopy include differential interference contrast, phase contrast, and dark-field.

3.2 Prokaryotic Cells

Learning Outcomes

Upon completion of this section, you should be able to

1. Examine the evolutionary relatedness of prokaryotes, eukaryotes, and archaeans.
2. Describe the fundamental components of a bacterial cell.

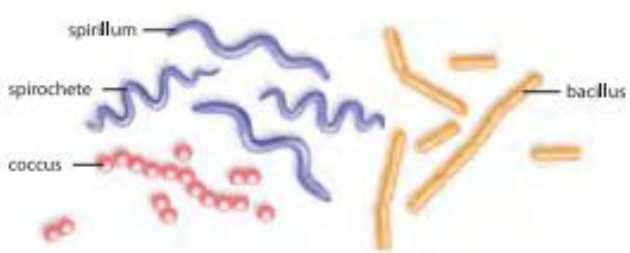
Fundamentally, two different types of cells exist in nature. **Prokaryotic cells** (Gk. *pro,* "before"; *karyon,* "kernel, nucleus") lack a membrane-bound nucleus. **Eukaryotic cells** (Gk. *eu,* "true") possess a nucleus. The bacteria and archaeans were once thought to be closely related because of their similar size and shape. Comparisons of DNA and RNA sequences now show archaeans to be biochemically distinct from either the bacteria or the eukaryotes. These comparisons also suggest that the archaeans are more closely related to the eukaryotes than the bacteria. Two of the three domains, the Eubacteria and Archaea, are prokaryotic cells, while all eukaryotic cells are assigned to domain Eukarya.

Prokaryotes as a group are one of the most abundant and diverse life-forms on Earth, and they are present in great numbers in the air, water, and soil, as well as living in and on other organisms. Although they are structurally less complicated than eukaryotes, their metabolic capabilities as a group far exceed those of eukaryotes. Prokaryotes are an extremely successful group of organisms whose evolutionary history dates back to the first cells on Earth.

Bacteria are well known because they cause some serious diseases, such as tuberculosis, anthrax, tetanus, throat infections, and gonorrhea. But many species of bacteria are important to the environment, because they decompose the remains of dead organisms and contribute to ecological cycles. Bacteria also assist humans in still another way—we use them to manufacture all sorts of products, from industrial chemicals to foodstuffs and drugs. For example, today we know how to place human genes in certain cultured bacteria so that they can produce human insulin, a necessary hormone for the treatment of diabetes.

The Structure of Prokaryotes

Prokaryotes are quite small; an average size is 1.1–1.5 µm wide and 2.0–6.0 µm long. The majority of the prokaryotes have one of these basic shapes:

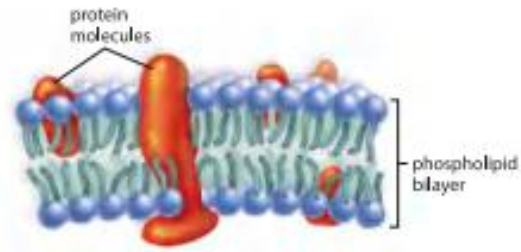


A rod-shaped bacterium is called a **bacillus,** while a spherical-shaped bacterium is a **coccus.** Both of these can occur as pairs or chains, and in addition, cocci can occur as clusters. Some long rods are twisted into spirals, in which case they are **spirilla** if they are rigid or **spirochetes** if they are flexible.

Figure 3.4 shows the generalized structure of a bacterium. "Generalized" means that not all bacteria have all the structures depicted, and some have more than one of each. Also, for the sake of discussion, we divide the organization of bacteria into the cell envelope, the cytoplasm, and the external structures.

Cell Envelope

In bacteria, the **cell envelope** includes the plasma membrane, the cell wall, and the glycocalyx. The **plasma membrane** is a phospholipid bilayer with embedded proteins:



The plasma membrane has the important function of regulating the entrance and exit of substances into and out of the cytoplasm. Regulating the flow of materials into and out of the cytoplasm is necessary in order to maintain its normal composition.

In prokaryotes, the plasma membrane can form internal pouches called *mesosomes*. Mesosomes most likely increase the internal surface area for the attachment of enzymes that are carrying on metabolic activities.

The **cell wall** maintains the shape of the cell, even if the cytoplasm should happen to take up an abundance of water. The cell wall of a bacterium contains peptidoglycan, a complex molecule containing a unique amino disaccharide and peptide fragments.

The **glycocalyx** is a layer of polysaccharides that lies outside the cell wall in some bacteria. When the layer is well organized and not easily washed off, it is called a **capsule.** A slime layer, on the other hand, is not well organized and is easily removed. The glycocalyx aids against drying out and helps bacteria resist a host's immune system. It also helps bacteria attach to almost any surface.

Cytoplasm

The **cytoplasm** is a semifluid solution composed of water and inorganic and organic molecules encased by a plasma membrane. Among the organic molecules are a variety of enzymes, which speed the many types of chemical reactions involved in metabolism.

While prokaryotes lack a membrane-bound nucleus, their DNA is located in a region of the cytoplasm called the **nucleoid.** Furthermore, eukaryotic cells typically have multiple chromosomes, but prokaryotes have a single, coiled chromosome. Many prokaryotes also have extrachromosomal pieces of circular DNA called **plasmids.** Plasmids are routinely used in biotechnology

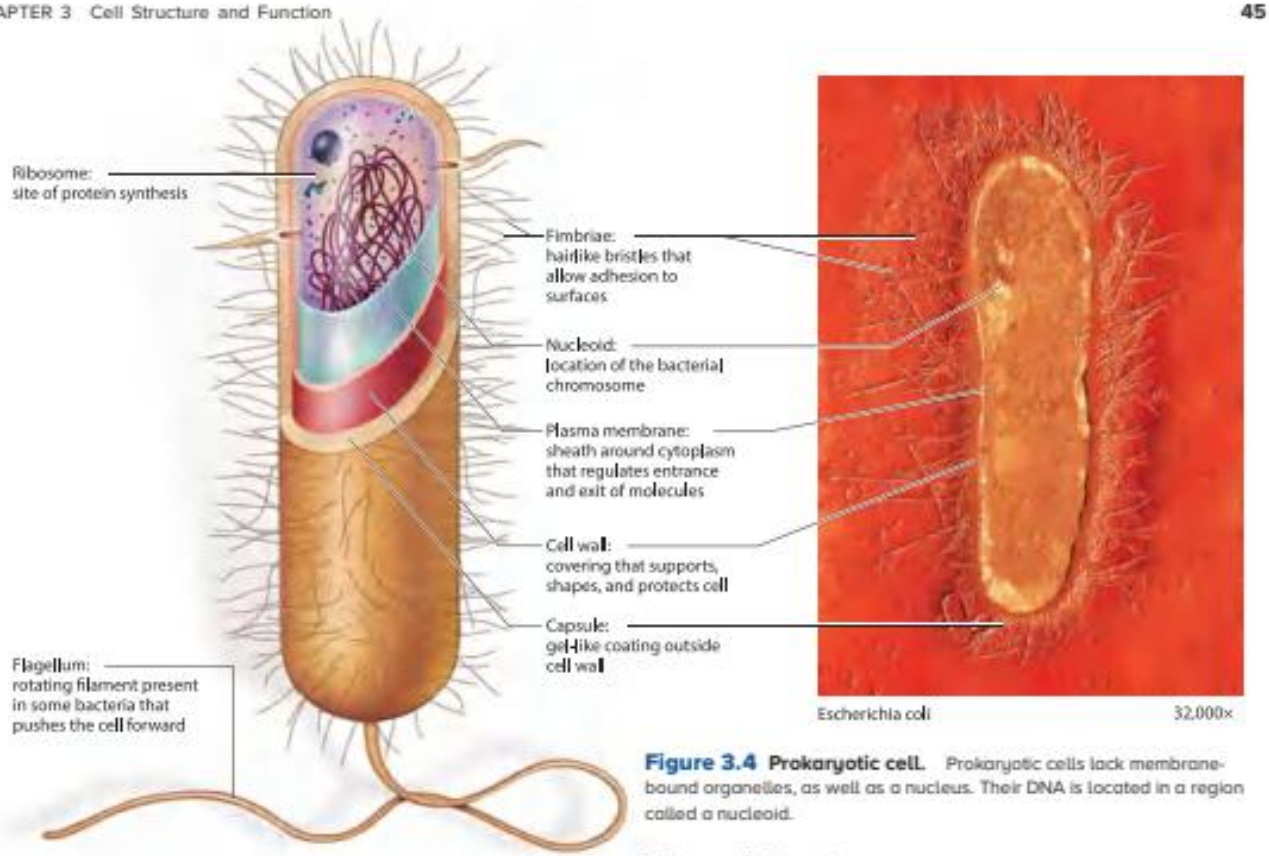


Figure 3.4 Prokaryotic cell. Prokaryotic cells lack membrane-bound organelles, as well as a nucleus. Their DNA is located in a region called a nucleoid.

laboratories as a vector to transport DNA into a bacterium. Procedures such as this are possible because all life on Earth is constructed from the same four DNA nucleotides: A, G, C, and T. Biotechnology plays an important role in the production of new medicines and many of the commerical products we use every day.

The many proteins encoded by the prokaryotic DNA are synthesized on tiny structures in the cytoplasm called **ribosomes.** A prokaryotic cell contains thousands of ribosomes that are similar in shape and function but are smaller than eukaryotic ribosomes. Like their eukaryotic counterparts, prokaryotic ribosomes still contain RNA and protein in two subunits.

There is a tremendous amount of metabolic diversity in the prokaryotes. Some prokaryotes carry out metabolism in the same manner as animals (by ingesting other organisms), but the **cyanobacteria** are a form of bacteria that are capable of photosynthesis in the same manner as plants. These organisms live in water, in ditches, on buildings, and on the bark of trees. Their cytoplasm contains extensive internal membranes called **thylakoids** (Gk. *thylakon*, "small sac"), where chlorophyll and other pigments absorb solar energy for the production of carbohydrates. Cyanobacteria are called the blue-green bacteria, because some have a pigment that adds a shade of blue to the cell, in addition to the green color of chlorophyll. The cyanobacteria release oxygen as a by-product of photosynthesis, and ancestral cyanobacteria were some of the earliest photosynthesizers on Earth. Many sources of evidence show that the composition of the early Earth's atmosphere was changed by the addition of oxygen.

External Structures

The external structures of a prokaryote, namely the flagella, fimbriae, and conjugation pili, are made of protein. Motile prokaryotes can propel themselves in water by the means of appendages called **flagella** (usually 20 nm in diameter and 1–70 nm long). The prokaryotic flagellum is one of the great wonders of nature, and it consists of a filament, a hook, and a basal body. The basal body is a series of rings anchored in the cell wall and membrane. Unlike the flagellum of the eukaryotes, which has a whiplike motion, the flagellum of a prokaryote rotates 360 degrees. Sometimes flagella occur only at the two ends of a cell, and sometimes they are dispersed randomly over the surface. The number and location of flagella can be used to help distinguish different types of prokaryotes.

Fimbriae are small, bristlelike fibers that sprout from the cell surface. They are not involved in locomotion; instead, fimbriae are involved in attaching prokaryotes to a surface. **Conjugation pili** are rigid, tubular structures used by prokaryotes to pass DNA from cell to cell. Prokaryotes reproduce asexually by binary fission, but they can exchange DNA by way of the conjugation pili. They can also take up DNA from the external medium or by way of viruses.

Check Your Progress 3.2

1. Explain the major differences between a prokaryotic and eukaryotic cell.
2. Describe the functions of the bacterial cell envelope, cytoplasm, and external structures.

3.3 Introduction to Eukaryotic Cells

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe how the endosymbiotic theory explains eukaryotic cell structure.
2. Summarize the functions of the organelles in a eukaryotic cell.
3. Compare and contrast the structure of animal and plant cells.

Eukaryotic cells, like prokaryotic cells, have a plasma membrane that separates the contents of the cell from the environment and that regulates the passage of molecules into and out of the cytoplasm. The plasma membrane is a phospholipid bilayer with embedded proteins. What distinguishes eukaryotic cells from prokaryotic cells is the presence of a nucleus and internal membrane-bound compartments, called **organelles.** Nearly all organelles are surrounded by a membrane with embedded proteins, many of which are enzymes. These enzymes make products specific to that organelle, but their action benefits the whole cell system. Each organelle carries out specialized functions, which together allow the cell to be more efficient and successful. These features would have given the new cell a selective advantage over other cells.

Origin of the Eukaryotic Cell

The fossil record, which is based on the remains of ancient life, suggests that the first cells were prokaryotes. Therefore, scientists believe that eukaryotic cells evolved from prokaryotic cells. Biochemical data suggest that eukaryotes are more closely related to the archaea than the bacteria. The eukaryotic cell probably evolved from a prokaryotic cell in stages. The distinguishing characteristic of the eukaryotic cell, the nucleus, is believed to have evolved due to the invagination of the plasma membrane (Fig. 3.5). The same process also explains the origin of organelles such as the endoplasmic reticulum and the Golgi apparatus.

There is strong evidence that the origin of the energy organelles occurred when a larger eukaryotic cell engulfed smaller prokaryotic cells. Observations in the laboratory indicate that an amoeba infected with bacteria can become dependent upon them. Some investigators believe mitochondria and chloroplasts are derived from prokaryotes that were taken up by larger cells (Fig. 3.5). Perhaps mitochondria were originally aerobic heterotrophic bacteria and chloroplasts were originally cyanobacteria. The eukaryotic host cell would have benefited from an ability to utilize oxygen or synthesize organic food when, by chance, the prokaryote was taken up and not destroyed. After the prokaryote entered the host cell, the two would have begun living together cooperatively. This proposal is known as the **endosymbiotic theory** (*endo-*, "in"; *symbiosis*, "living together"). Some of the evidence supporting this hypothesis is as follows:

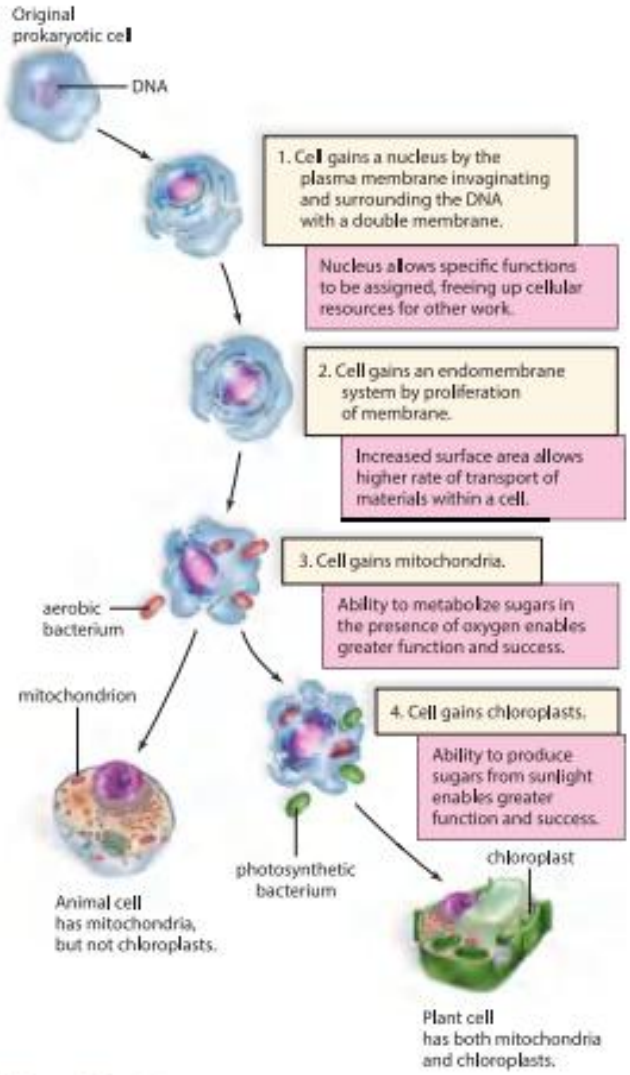
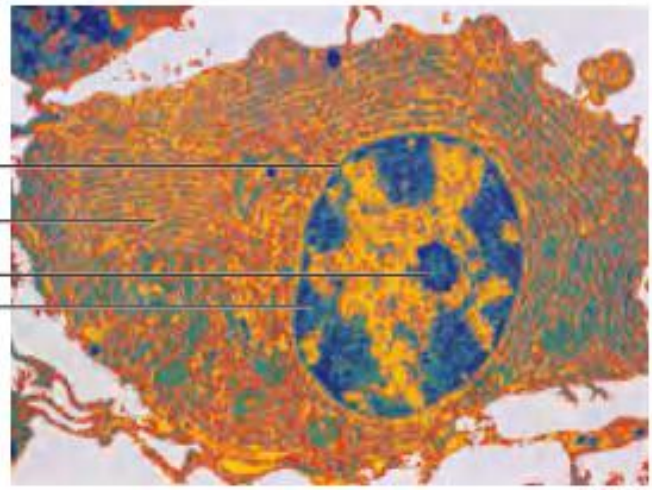
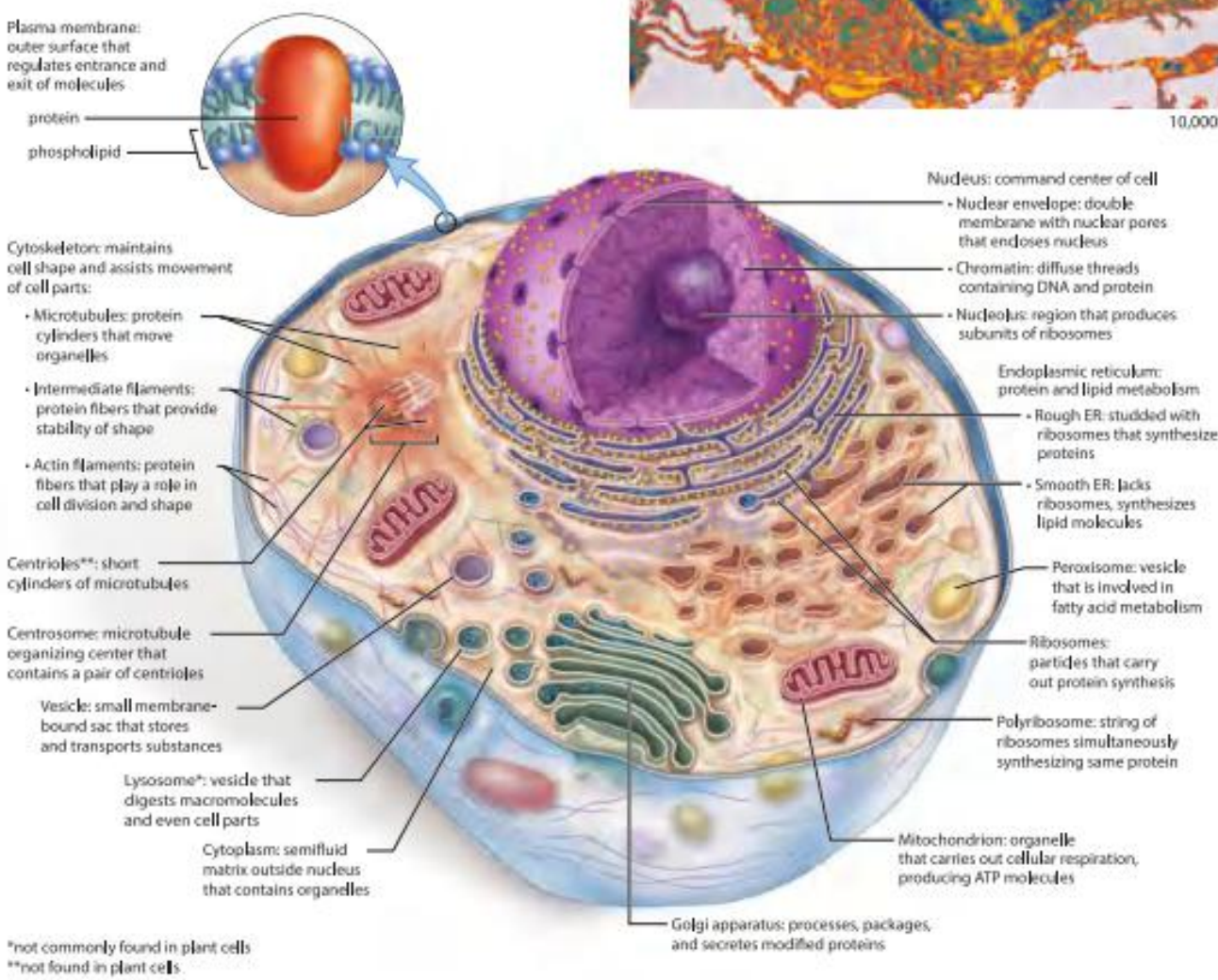


Figure 3.5 Origin of organelles. Invagination of the plasma membrane could have created the nuclear envelope and an endomembrane system that involves several organelles. The endosymbiotic theory states that mitochondria and chloroplasts were independent prokaryotes that took up residence in a eukaryotic cell. Endosymbiosis was a first step toward the origin of the eukaryotic cell during the evolutionary history of life.

- Mitochondria and chloroplasts are similar to bacteria in size and in structure.
- Both organelles are surrounded by a double membrane—the outer membrane may be derived from the engulfing vesicle, and the inner one may be derived from the plasma membrane of the original prokaryote.
- Mitochondria and chloroplasts contain a limited amount of genetic material and divide by splitting. Their DNA (deoxyribonucleic acid) is a circular loop like that of prokaryotes.
- Although most of the proteins within mitochondria and chloroplasts are now produced by the eukaryotic host, they do have their own ribosomes and they do produce some proteins. Their ribosomes resemble those of prokaryotes.

Figure 3.6 Typical animal cell. Micrograph of a human cell (right) and drawing of a generalized animal cell (below).





- The RNA (ribonucleic acid) base sequence of the ribosomes in chloroplasts and mitochondria also suggests a prokaryotic origin of these organelles.

Structure of a Eukaryotic Cell

Figures 3.6 and 3.7 show general features of fully evolved, present-day animal and plant cells. Specialized cells, as opposed to generalized cells, do not necessarily contain all the structures depicted and may have more or fewer copies of any particular organelle, depending on their particular function. These generalized depictions of plant and animal cells are useful for study purposes. A baseline understanding of cell structure and function will be helpful when you study the function of specialized cells later in this text. Overall, the cell can be seen as a system of interconnected organelles that work together to metabolize, regulate, and conduct life processes. For example, the nucleus is a compartment that houses the genetic material within eukaryotic chromosomes and contains hereditary information. The nucleus communicates with ribosomes

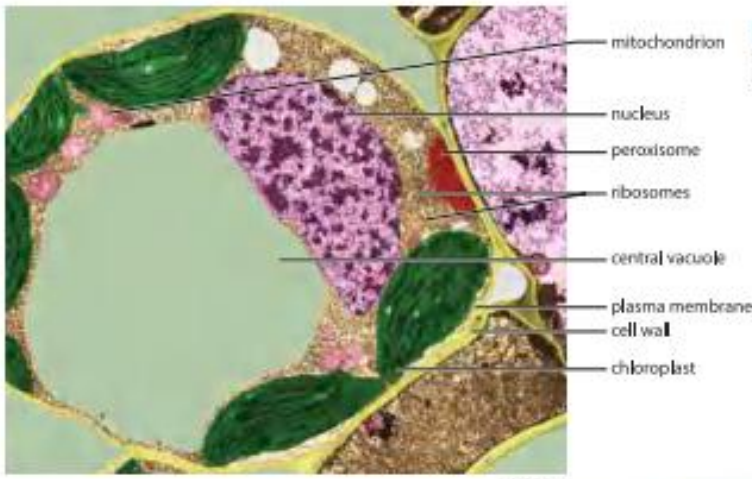
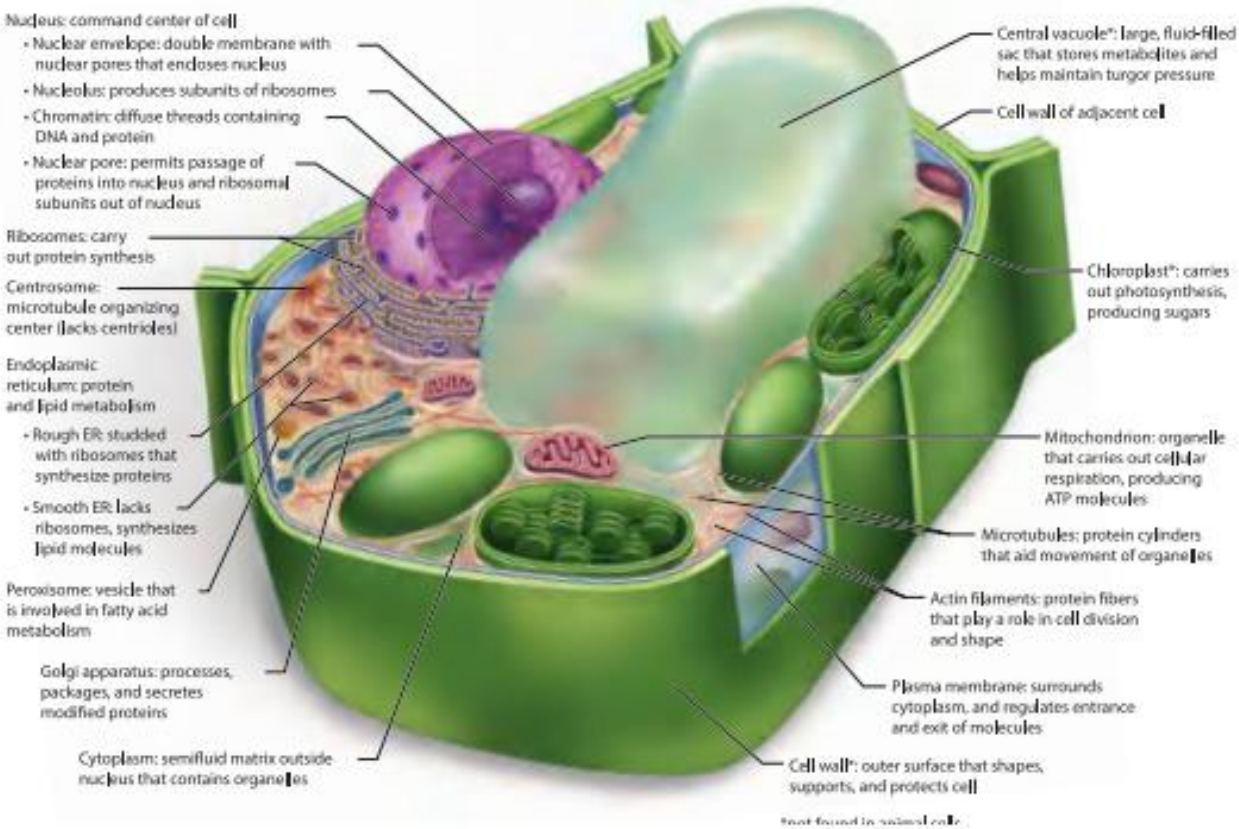


Figure 3.7 Typical plant cell. False-colored micrograph of a young plant cell (*left*) and drawing of a generalized plant cell (*below*).



in the cytoplasm, and the organelles of the endomembrane system—notably the endoplasmic reticulum and the Golgi apparatus—communicate with one another.

Production of specific molecules takes place inside or on the surface of organelles. As mentioned, enzymes embedded in the organelles' membranes make these molecules. These products are then transported around the cell by transport **vesicles,** membranous sacs that enclose the molecules and keep them separate from the cytoplasm. For example, the endoplasmic reticulum communicates with the Golgi apparatus by means of transport vesicles. Communication with the energy-related organelles—mitochondria and chloroplasts—is less obvious, but it does occur, because they import particular molecules from the cytoplasm.

Vesicles move around by means of an extensive network or lattice of protein fibers called the **cytoskeleton,** which also maintains cell shape and assists with cell movement. The protein fibers serve as tracks for the transport vesicles that are taking molecules from one organelle to another. Organelles are also moved from place to place using this transport system. Think of the cytoskeleton as a three-dimensional road system inside cells used to transport important cargo from place to place. The cytoskeleton is discussed in detail later in this chapter.

In addition to the plasma membrane, some eukaryotic cells, notably plant cells and those of fungi and many protists, have a cell wall. A plant cell wall contains cellulose and, therefore, has a different composition from the bacterial cell wall.

Cells can vary the proportion of organelles they have, depending on the specialized function of the cell. For example, a liver cell whose function is partly to detoxify drugs and other ingested compounds contains a greater proportion of smooth endoplasmic reticulum, the organelle that accomplishes that task. A nerve cell, whose job is to conduct electrical signals across long distances, contains more plasma membrane relative to other cells. Other cells may specialize so extensively that they completely lose an organelle, like a red blood cell that ejects its nucleus to increase the surface area needed to carry oxygen in the blood.

Check Your Progress 3.3

1. Summarize the benefits of compartmentalization found in cells.
2. Examine why organelles increase cell efficiency and function.
3. Explain the origins of the nucleus, chloroplast, and mitochondria of eukaryotic cells.

3.4 The Nucleus and Ribosomes

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the structure and function of the nucleus.
2. Describe the flow of information from DNA to a protein.
3. Explain the role of ribosomes in protein synthesis.

The **nucleus** is essential to the life of a eukaryotic cell. It contains the genetic information that is passed on from cell to cell and from generation to generation. It specifies the information that ribosomes use to carry out protein synthesis. It also contains instructions for copying itself.

The Nucleus

The nucleus, which has a diameter of about 5 μm, is a prominent structure in the eukaryotic cell (Fig. 3.8). It generally appears as an oval structure located near the center of most cells. Some cells, such as skeletal muscle cells, can have more than one nucleus. The interior of the nucleus contains a semifluid matrix called the **nucleoplasm.** The nucleus is the command center of the cell. It contains **chromatin** (Gk. *chroma,* "color"), which is a

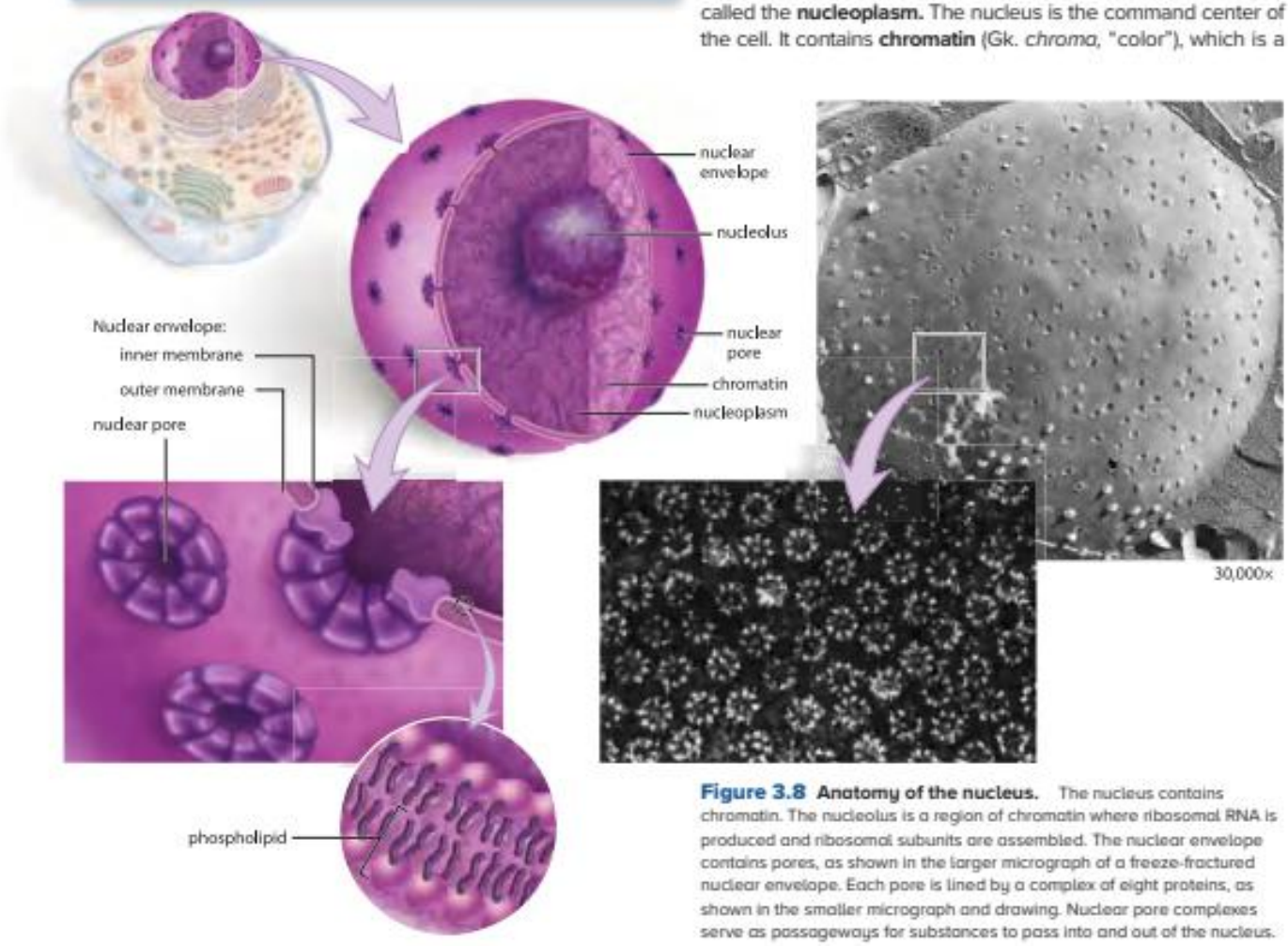


Figure 3.8 Anatomy of the nucleus. The nucleus contains chromatin. The nucleolus is a region of chromatin where ribosomal RNA is produced and ribosomal subunits are assembled. The nuclear envelope contains pores, as shown in the larger micrograph of a freeze-fractured nuclear envelope. Each pore is lined by a complex of eight proteins, as shown in the smaller micrograph and drawing. Nuclear pore complexes serve as passageways for substances to pass into and out of the nucleus.

combination of proteins and nucleic acids. Chromatin looks grainy, but actually it is a network of strands that condenses and undergoes coiling into rodlike structures called **chromosomes,** just before the cell divides. The chromosomes are the carriers of genetic information. This information is organized on the chromosome as **genes,** the basic units of heredity. All the cells of an individual contain the same number of chromosomes, and the mechanics of nuclear division ensure that each daughter cell receives the normal number of chromosomes, except for the egg and sperm, which usually have half this number.

Three types of ribonucleic acid (RNA) are produced in the nucleus: *ribosomal RNA* (*rRNA*), *messenger RNA* (*mRNA*), and *transfer RNA* (*tRNA*). Ribosomal RNA is produced in the **nucleolus,** a dark region of chromatin where rRNA joins with proteins to form the subunits of ribosomes. Ribosomes are small bodies in the cytoplasm that facilitate protein synthesis. Messenger RNA, a mobile molecule, acts as an intermediary for DNA, a sedentary molecule, which specifies the sequence of amino acids in a protein. Transfer RNA participates in the assembly of amino acids into a polypeptide by recognizing both mRNA and amino acids during protein synthesis.

The nucleus is important to cell structure and function, because it specifies the code to make proteins. Although the nucleus is physically separated from the cytoplasm by a double membrane known as the **nuclear envelope,** it is still able to communicate with the cytoplasm through nuclear pores. **Nuclear pores** are of sufficient size (100 nm) to permit the passage of ribosomal subunits and mRNA out of the nucleus into the cytoplasm, as well as the passage of proteins from the cytoplasm into the nucleus. High-resolution electron micrographs show that nonmembrane components associated with the pores form a nuclear pore complex. Nuclear pore complexes act as gatekeepers to regulate what goes into and out of a nucleus.

Ribosomes

Ribosomes are particles where protein synthesis occurs. A large and small ribosomal subunit, each comprised of a mix of proteins and rRNA, are necessary components of a functional ribosome. In eukaryotes, ribosomes are 20 nm by 30 nm, and in prokaryotes they are slightly smaller. The number of ribosomes in a cell varies depending on its functions; for example, pancreatic cells and those of other glands have many ribosomes because they produce secretions that contain proteins.

In eukaryotic cells, some ribosomes occur freely within the cytoplasm, either singly or in groups called **polyribosomes,** whereas others are attached to the endoplasmic reticulum (ER), a membranous system of flattened saccules (small sacs) and tubules (see section 1.5). In the nucleus, the information within a gene is copied into mRNA, which is exported through a nuclear pore complex into the cytoplasm. Ribosomes receive the mRNA, which carries a coded message from DNA indicating the correct sequence of amino acids in a particular protein. Proteins synthesized by cytoplasmic ribosomes are used in the cytoplasm, and those synthesized by attached ribosomes end up in the ER.

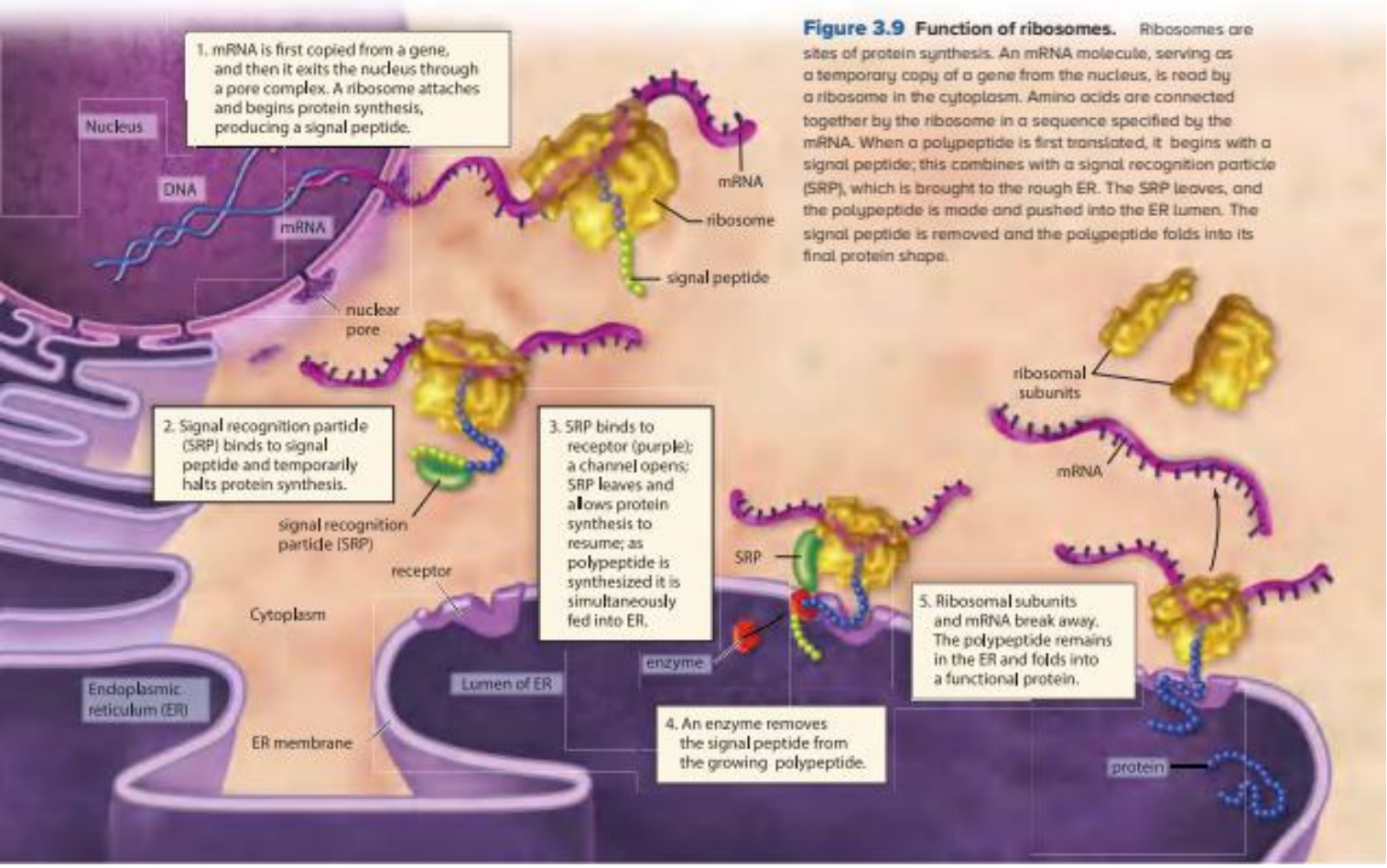


Figure 3.9 Function of ribosomes. Ribosomes are sites of protein synthesis. An mRNA molecule, serving as a temporary copy of a gene from the nucleus, is read by a ribosome in the cytoplasm. Amino acids are connected together by the ribosome in a sequence specified by the mRNA. When a polypeptide is first translated, it begins with a signal peptide; this combines with a signal recognition particle (SRP), which is brought to the rough ER. The SRP leaves, and the polypeptide is made and pushed into the ER lumen. The signal peptide is removed and the polypeptide folds into its final protein shape.

What causes a ribosome to bind to the endoplasmic reticulum? Binding occurs only if the protein being synthesized by a ribosome begins with a sequence of amino acids called a *signal peptide*. The signal peptide binds a particle (signal recognition particle, SRP), which then binds to a receptor on the ER. Once the protein enters the ER, an enzyme cleaves off the signal peptide, and the protein ends up within the lumen (interior) of the ER, where it folds into its final shape (Fig. 3.9).

The sequence of DNA being transcribed into mRNA, and this in turn being translated into a protein, occurs in all living cells, at least during some point in their lifespan. Because of its universality, the DNA–mRNA–protein sequence of events is termed the *central dogma of molecular biology*.

Check Your Progress 3.4

1. Distinguish between the chromatin and chromosomes within the nucleus.
2. Explain the importance of the nuclear pores.
3. Describe the sequence of events that transfers information from a gene to a functional protein.

3.5 The Endomembrane System

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain the importance of the endomembrane system in cellular function.
2. Examine how the ER, Golgi apparatus, and lysosomes differ from one another.
3. Describe how endomembrane vesicles are able to fuse with organelles.

The **endomembrane system** consists of the nuclear envelope, the membranes of the endoplasmic reticulum, the Golgi apparatus, and several types of vesicles. This system compartmentalizes the cell so that particular enzymatic reactions are restricted to specific regions and overall cell efficiency is increased. The vesicles transport molecules from one part of the system to another.

Endoplasmic Reticulum

The **endoplasmic reticulum** (**ER**) (Gk. *endon*, "within"; *plasma*, "something molded"; L. *reticulum*, "net"), consisting of a complicated system of membranous channels and saccules (flattened vesicles), is physically continuous with the nuclear envelope (Fig. 3.10). The ER consists of rough ER and smooth ER, which have different structures and functions.

Rough ER is studded with ribosomes on the side of the membrane that faces the cytoplasm, giving it the capacity to produce proteins. Inside its lumen, the rough ER allows proteins to fold and take on their final three-dimensional shape. The rough ER also contains enzymes that can add carbohydrate (sugar) chains to proteins, forming glycoproteins that are important in many cell functions.

Smooth ER, which is continuous with the nuclear envelope and the rough ER, does not have attached ribosomes. Certain organs contain cells with an abundance of smooth ER, depending on the organ's function. In some organs, increased smooth ER helps produce more lipids. For example, in the liver, smooth ER helps detoxify drugs. Regardless of functional differences, both rough and smooth ER form vesicles that transport molecules to other parts of the cell, notably the Golgi apparatus.

The Golgi Apparatus

The **Golgi apparatus** is named for Camillo Golgi (1843–1926), who discovered its presence in cells in 1898. The Golgi apparatus typically consists of a stack of 3 to 20 slightly curved, flattened saccules whose appearance can be compared to a stack of pancakes (Fig. 3.11). In animal cells, one side of the stack (the

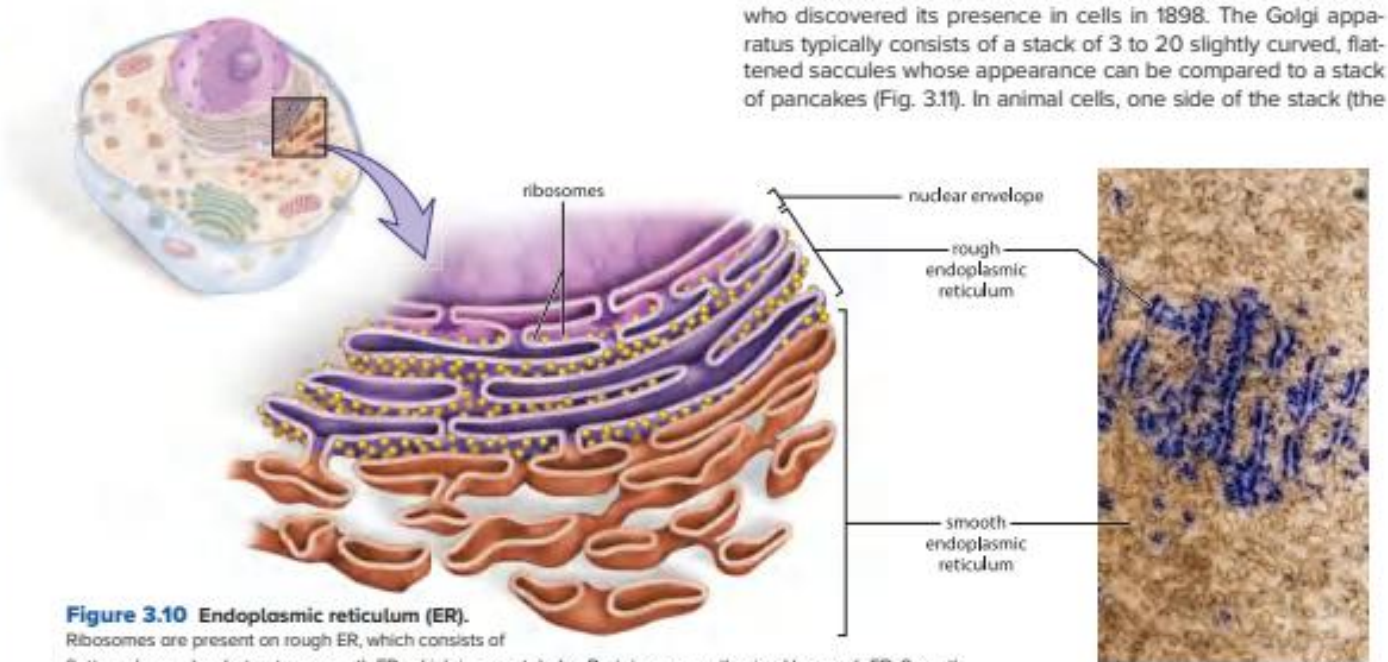


Figure 3.10 Endoplasmic reticulum (ER).
Ribosomes are present on rough ER, which consists of flattened saccules, but not on smooth ER, which is more tubular. Proteins are synthesized by rough ER. Smooth ER is involved in lipid synthesis, detoxification reactions, and several other possible functions.

cis, or inner, face) is directed toward the ER, and the other side of the stack (the trans, or outer, face) is directed toward the plasma membrane. Vesicles can frequently be seen at the edges of the saccules.

Protein-filled vesicles that bud from the rough ER and lipid-filled vesicles that bud from the smooth ER are received by the Golgi apparatus at its inner face. These substances are altered as they move through the saccules. For example, the Golgi apparatus contains enzymes that modify the carbohydrate chains first attached to proteins in the rough ER. It can modify one sugar into another sugar on glycoproteins. In some cases, the modified carbohydrate chain serves as a signal molecule or molecular address label that determines the protein's final destination in the cell.

The Golgi apparatus sorts the modified molecules and packages them into vesicles that depart from the outer face. These vesicles may be transported to various locations within the cell, depending on their molecular address labels. In animal cells, some of these vesicles are lysosomes, which are discussed next. Other vesicles may return to the ER or proceed to the plasma membrane, where they merge and discharge their contents to the outside of the cell by exocytosis.

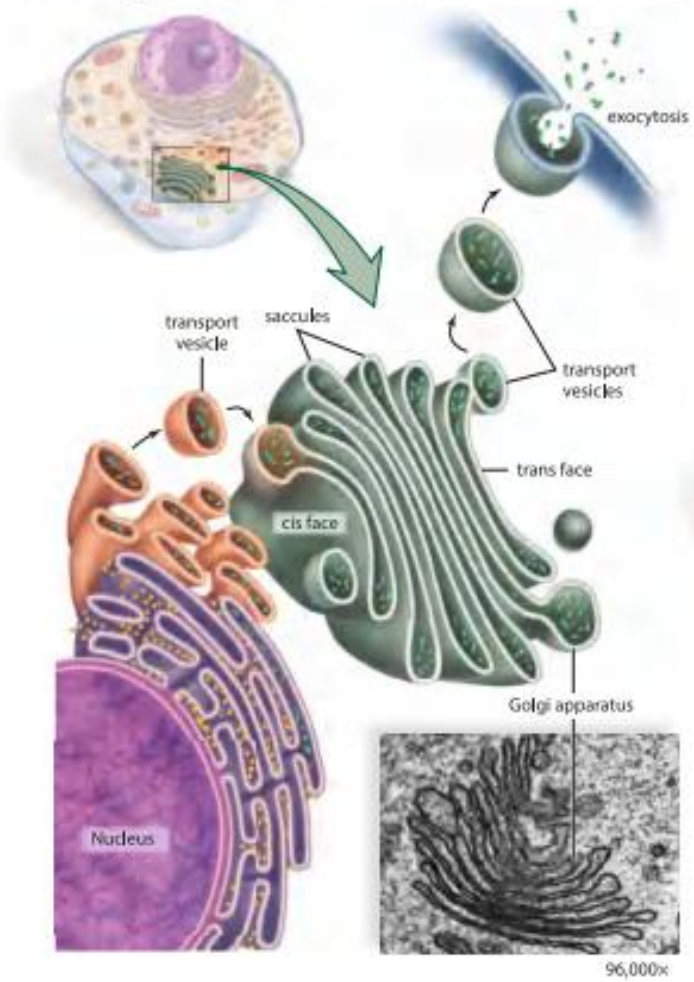


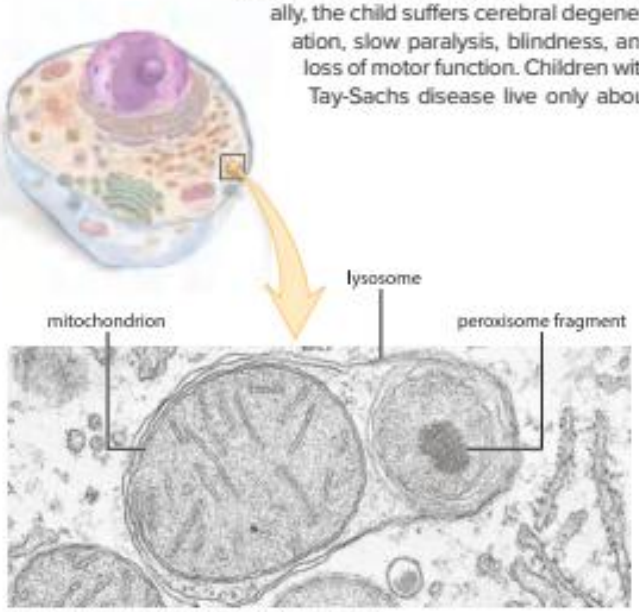
Figure 3.11 Golgi apparatus. The Golgi apparatus is a stack of flattened, curved saccules. It processes proteins and lipids and packages them in transport vesicles that either distribute these molecules to various locations within the cell or secrete them externally.

Lysosomes

Lysosomes (Gk. *lyo*, "loose"; *soma*, "body") are membrane-bound vesicles produced by the Golgi apparatus. They have a very low pH and store powerful hydrolytic-digestive enzymes in an inactive state. Lysosomes act much like your stomach in that they assist in digesting material taken into the cell. They also destroy nonfunctional organelles and portions of cytoplasm (Fig. 3.12).

Materials can be taken into a cell by vesicle or vacuole formation at the plasma membrane. When a lysosome fuses with either, the lysosomal enzymes are activated and digest the material into simpler subunits that are exported into the cytoplasm and recycled by other cell processes. White blood cells, specialized to protect the body from foreign entities, are well known for engulfing pathogens (e.g., disease-causing viruses and bacteria), which are then broken down in lysosomes. White blood cells have a greater proportion of lysosomes than other cells, because their specialized function is the digestion of foreign bodies.

A number of human lysosomal storage diseases are due to a missing lysosomal enzyme. In Tay-Sachs disease, the missing enzyme digests a fatty substance that helps insulate nerve cells and increases their efficiency. The fatty substance accumulates in so many storage bodies that nerve cells die off. Affected individuals appear normal at birth but begin to develop neurological problems at 4 to 6 months of age. Eventually, the child suffers cerebral degeneration, slow paralysis, blindness, and loss of motor function. Children with Tay-Sachs disease live only about



Mitochondrion and a peroxisome in a lysosome

Figure 3.12 Lysosomes. Lysosomes, which bud off the Golgi apparatus in cells, are filled with hydrolytic enzymes that digest molecules and parts of the cell. Here a lysosome digests a worn mitochondrion and a peroxisome.

3 to 4 years. The use of gene therapy to provide the enzyme to the cells may be able to treat Tay-Sachs disease.

Endomembrane System Summary

You have seen that the endomembrane system is a series of membranous organelles that work together and communicate by means of transport vesicles. The endoplasmic reticulum (ER) and the Golgi apparatus are essentially flattened saccules, and lysosomes are specialized vesicles.

Organelles within the endomembrane system can interact because their membranes readily fuse together, and because membrane-associated proteins enable communication and specialized functions. Figure 3.13 shows how the components of the endomembrane system work together. Products of both rough ER and smooth ER are carried in transport vesicles to the Golgi apparatus, where they are further modified. Using signaling sequences and molecular address labels, the Golgi apparatus sorts these products and packages them into vesicles that transport them to various cellular destinations. Secretory vesicles take the proteins to the plasma membrane, where they exit the cell by exocytosis. For example, the pancreas produces digestive enzymes.

In animal cells, the Golgi apparatus also produces lysosomes that contain stored hydrolytic enzymes. Lysosomes fuse with incoming vesicles from the plasma membrane and digest macromolecules taken into a cell.

Check Your Progress 3.5

1. Contrast the structure and functions of rough and smooth endoplasmic reticulum.
2. Describe the relationship between the components of the endomembrane system.
3. Examine how cellular function would be affected if the Golgi apparatus ceased to function.

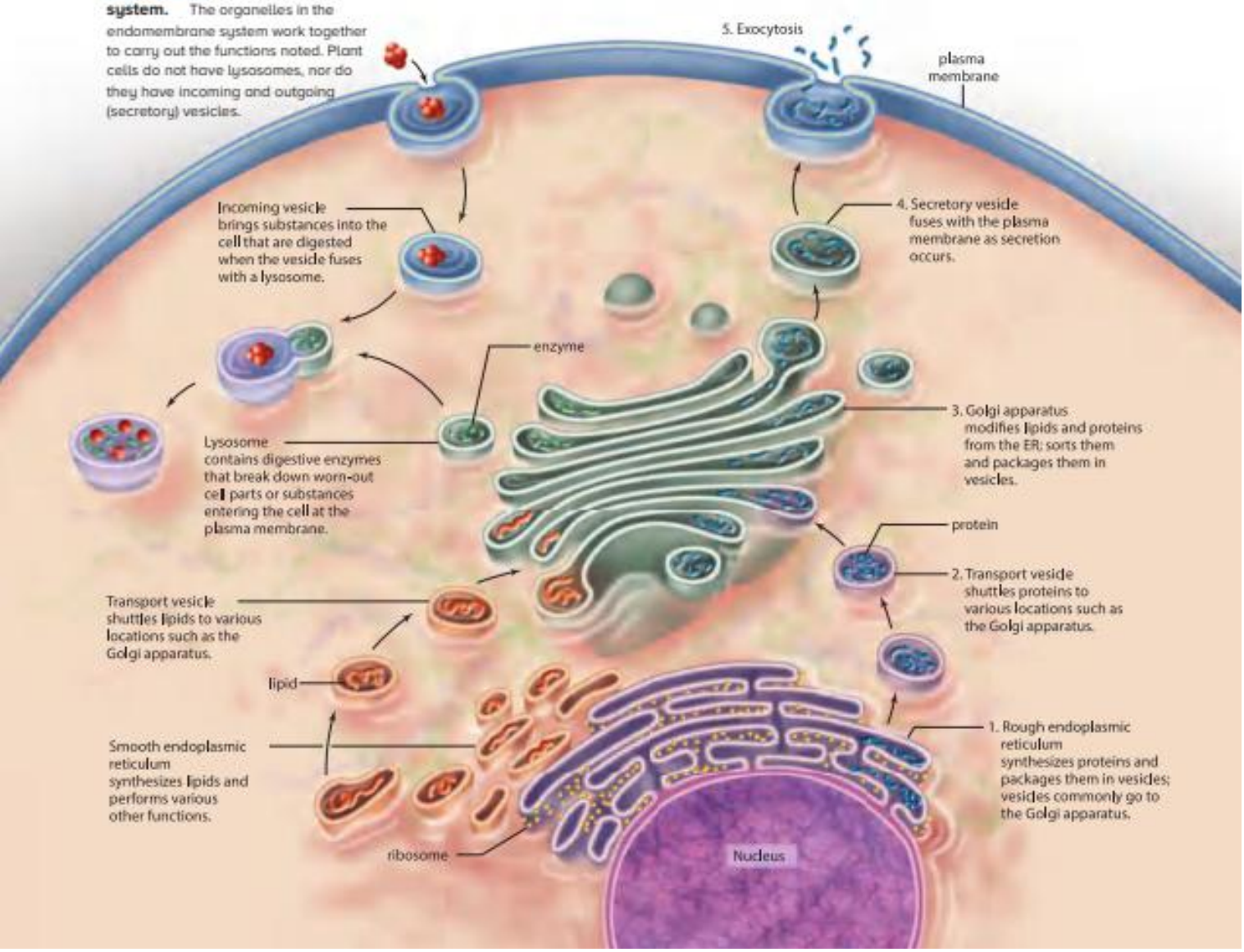


Figure 3.13 Endomembrane system. The organelles in the endomembrane system work together to carry out the functions noted. Plant cells do not have lysosomes, nor do they have incoming and outgoing (secretory) vesicles.

3.6 Microbodies and Vacuoles

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the role of peroxisomes and vacuoles in cell function.
2. Contrast peroxisomes and vacuoles with endomembrane organelles.

Eukaryotic cells contain a variety of membrane-bound vesicles, called **microbodies,** that contain specialized enzymes to perform specific metabolic functions. One example is the peroxisome. In addition, cells may contain large storage areas called vacoules.

Peroxisomes

Peroxisomes are membrane-bound vesicles that enclose enzymes that are involved in the breakdown of fatty acids. Unlike the enzymes of lysosomes, which are loaded into the vesicle by the Golgi apparatus, the enzymes in peroxisomes are synthesized by free ribosomes and transported into a peroxisome from the cytoplasm. As the enzymes within the peroxisome oxidize fatty acids, they produce hydrogen peroxide (H_2O_2), a toxic molecule. However, peroxisomes also contain an enzyme called catalase that immediately breaks down H_2O_2 to water and oxygen. You can see this reaction when you apply hydrogen peroxide to a wound; the resulting bubbles occur as catalase breaks down the H_2O_2.

Peroxisomes are metabolic assistants to the other organelles. They have varied functions but are especially prevalent in cells that synthesize and break down lipids. In the liver, some peroxisomes produce bile salts from cholesterol, and others break down fats. The disease adrenoleukodystrophy (ALD) is caused when peroxisomes lack a membrane protein needed to import a specific enzyme and/or long-chain fatty acids from the cytoplasm. As a result, long-chain fatty acids accumulate in the brain, causing neurological damage.

Plant cells also have peroxisomes (Fig. 3.14). In germinating seeds, they oxidize fatty acids into molecules that can be converted to sugars needed by the growing plant. In leaves, peroxisomes can carry out a reaction that is opposite to photosynthesis—the reaction uses up oxygen and releases carbon dioxide.

Vacuoles

Like vesicles, **vacuoles** are membranous sacs, but vacuoles are larger than vesicles. The vacuoles of some protists are quite specialized, including contractile vacuoles for ridding the cell of excess water and digestive vacuoles for breaking down nutrients. Vacuoles usually store substances. In general, few animal cells contain vacuoles; however, fat cells contain a very large, lipid-engorged vacuole that takes up nearly two-thirds of the volume of the cell!

Vacuoles are essential to plant function. Plant vacuoles contain not only water, sugars, and salts but also water-soluble pigments and toxic molecules. The pigments are responsible for many of the red, blue, or purple color of flowers and some leaves. The toxic substances help protect a land plant from herbivorous animals.

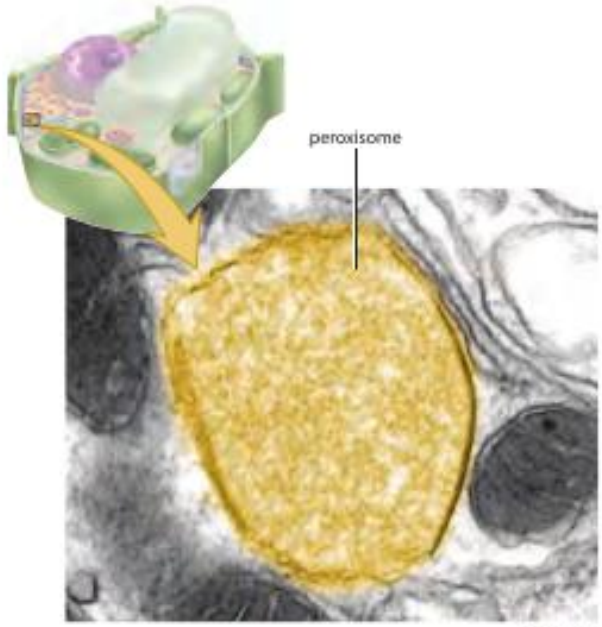


Figure 3.14 Peroxisomes. Peroxisomes contain one or more enzymes that can oxidize various organic substances.

Plant Cell Central Vacuole

Typically, plant cells have a large **central vacuole** that may take up to 90% of the volume of the cell. The vacuole is filled with a watery fluid called cell sap that gives added support to the cell (Fig. 3.15). The central vacuole maintains hydrostatic pressure or turgor pressure in plant cells, which provides structural support. A plant cell can rapidly increase in size by enlarging its vacuole. Eventually, a plant cell also produces more cytoplasm.

The central vacuole functions in storage of both nutrients and waste products. Metabolic waste

Figure 3.15 Plant cell central vacuole. The large central vacuole of plant cells has numerous functions, from storing molecules to helping the cell increase in size.

products are pumped across the vacuole membrane and stored permanently in the central vacuole. As organelles age and become nonfunctional, they fuse with the vacuole, where digestive enzymes break them down. This is a function analogous to that carried out by lysosomes in animal cells.

Check Your Progress 3.6

1. Compare the structure and functions of a peroxisome with those of a lysosome.
2. Distinguish between where peroxisome and lysosome proteins are produced.

3.7 The Energy-Related Organelles

Learning Outcomes

Upon completion of this section, you should be able to

1. Distinguish between the functions of chloroplasts and mitochondria in a cell.
2. Describe the internal structure of mitochondria and chloroplasts.

Life is possible only because a constant input of energy maintains the structure of cells. Chloroplasts and mitochondria are the two eukaryotic membranous organelles that specialize in converting energy to a form that can be used by the cell. Although animal cells contain only mitochondria, plant cells contain both mitochondria and chloroplasts.

During *photosynthesis*, **chloroplasts** (Gk. *chloros*, "green"; *plastos*, "formed, molded") use solar energy to synthesize carbohydrates, which serve as organic nutrient molecules for plants and all life on Earth. Photosynthesis can be represented by this equation:

$$\text{solar energy} + \text{carbon dioxide} + \text{water} \rightarrow \text{carbohydrate} + \text{oxygen}$$

Plants, algae, and cyanobacteria are capable of conducting photosynthesis in this manner, but only plants and algae have chloroplasts, because they are eukaryotes.

In *cellular respiration*, **mitochondria** (sing., mitochondrion) break down carbohydrate-derived products to produce ATP (adenosine triphosphate). Cellular respiration can be represented by this equation:

$$\text{carbohydrate} + \text{oxygen} \rightarrow \text{carbon dioxide} + \text{water} + \text{energy}$$

Here the word *energy* stands for ATP molecules. When a cell needs energy, ATP supplies it. The energy of ATP is used to drive synthetic reactions, active transport, and all energy-requiring processes in cells. Figure 3.16 provides a summary of the interactions between these two energy-producing organelles.

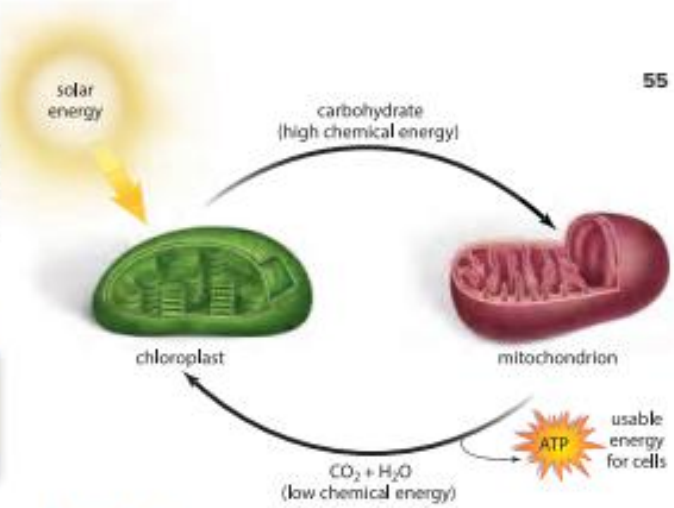


Figure 3.16 Energy-producing organelles. Chloroplasts use sunlight to produce carbohydrates, which in turn are used by the mitochondria. The mitochondria then produce carbon dioxide and water, which is in turn used by the chloroplasts.

Chloroplasts

Some algal cells have only one chloroplast, while some plant cells have as many as a hundred. Chloroplasts can be quite large, being twice as wide and as much as five times the length of a mitochondrion.

Chloroplasts have a three-membrane system (Fig. 3.17). They are surrounded by a double membrane, which includes an outer membrane and an inner membrane. The double membrane encloses the semifluid **stroma,** which contains enzymes and **thylakoids,** disklike sacs formed from a third chloroplast membrane. A stack of thylakoids is a **granum.** The lumens of the thylakoids are believed to form a large, internal compartment called the thylakoid space. Chlorophyll and the other pigments that capture solar energy are located in the thylakoid membrane, and the enzymes that synthesize carbohydrates are located outside the thylakoid in the fluid of the stroma.

The endosymbiotic theory holds that chloroplasts are derived from a photosynthetic bacterium that was engulfed by a eukaryotic cell (see Fig. 3.5). This certainly explains why a chloroplast is surrounded by a double membrane—one membrane is derived from the vesicle that brought the prokaryote into the cell, while the inner membrane is derived from the prokaryote. The endosymbiotic theory is also supported by the finding that chloroplasts have their own prokaryotic-type chromosome and ribosomes, and they produce some of their own enzymes even today.

Other Types of Plastids

A chloroplast is a type of plastid. **Plastids** are plant organelles that are surrounded by a double membrane and have varied functions. *Chromoplasts* contain pigments that result in a yellow, orange, or red color. Chromoplasts are responsible for the color of autumn leaves, fruits, carrots, and some flowers. *Leucoplasts* are generally colorless plastids that synthesize and store starches and oils. A microscopic examination of potato tissue reveals a number of leucoplasts.

Mitochondria

Nearly all eukaryotic cells, and certainly all plant and algal cells in addition to animal cells, contain mitochondria. Even

though mitochondria are smaller than chloroplasts, they can usually be seen using a light microscope. The number of mitochondria can vary depending on the metabolic activities and energy needed within a cell. Some cells, such as liver cells, may have as many as 1,000 mitochondria.

We think of mitochondria as having a shape like that shown in Figure 1.18, but actually they often change shape to be longer and thinner or shorter and broader. Mitochondria can form long, moving chains, or they can remain fixed in one location—typically where energy is most needed. For example, they are packed between the contractile elements of cardiac cells and wrapped around the interior of a sperm's flagellum. In contrast, fat cells contain few mitochondria—they function in fat storage, which does not require energy.

Mitochondria have two membranes, the outer membrane and the inner membrane. The inner membrane is highly convoluted into folds called **cristae** that project into the matrix. These cristae increase the surface area of the inner membrane so much that in a liver cell they account for about one-third the total membrane in the cell. The inner membrane encloses a semifluid **matrix,** which contains mitochondrial DNA and ribosomes. Again, the presence of a double membrane and mitochondrial genes is consistent with the endosymbiotic theory regarding the origin of mitochondria, which was illustrated in Figure 3.5.

Mitochondria are often called the powerhouses of the cell because they produce most of the ATP utilized by the cell. Within the matrix of the mitochondria is a highly concentrated mixture of enzymes that break down carbohydrates and other nutrient molecules. These reactions supply the chemical energy needed for a chain of proteins on the inner membrane to create the conditions that allow ATP synthesis to take place. The entire

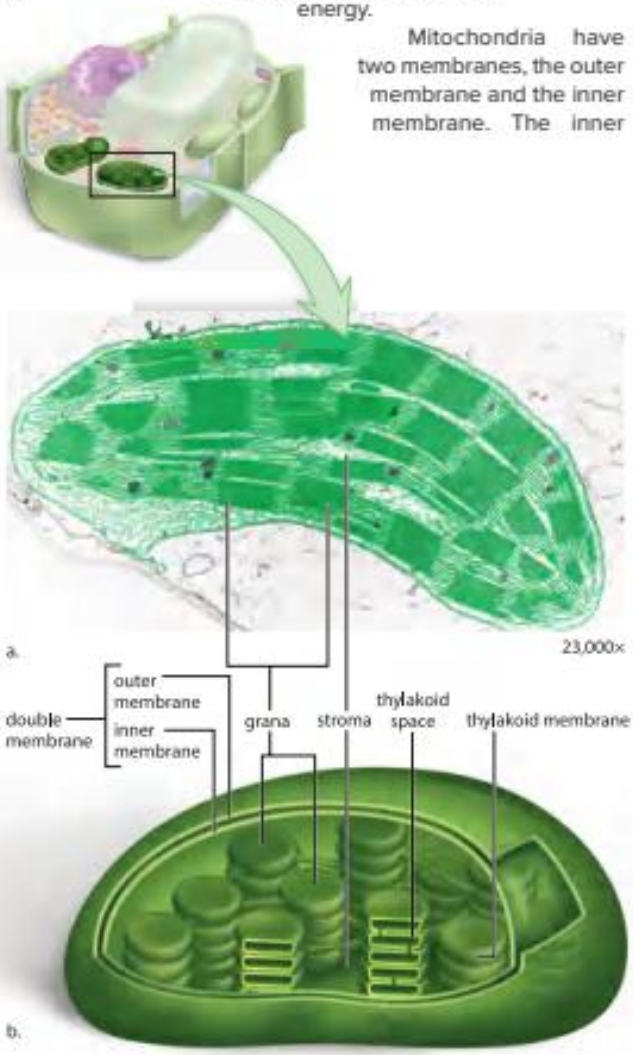


Figure 3.17 Chloroplast structure. Chloroplasts carry out photosynthesis. **a.** Electron micrograph of a longitudinal section of a chloroplast. **b.** Generalized drawing of a chloroplast in which the outer and inner membranes have been cut away to reveal the grana, each of which is a stack of membranous sacs called thylakoids. In some grana, but not all, thylakoid spaces are interconnected.

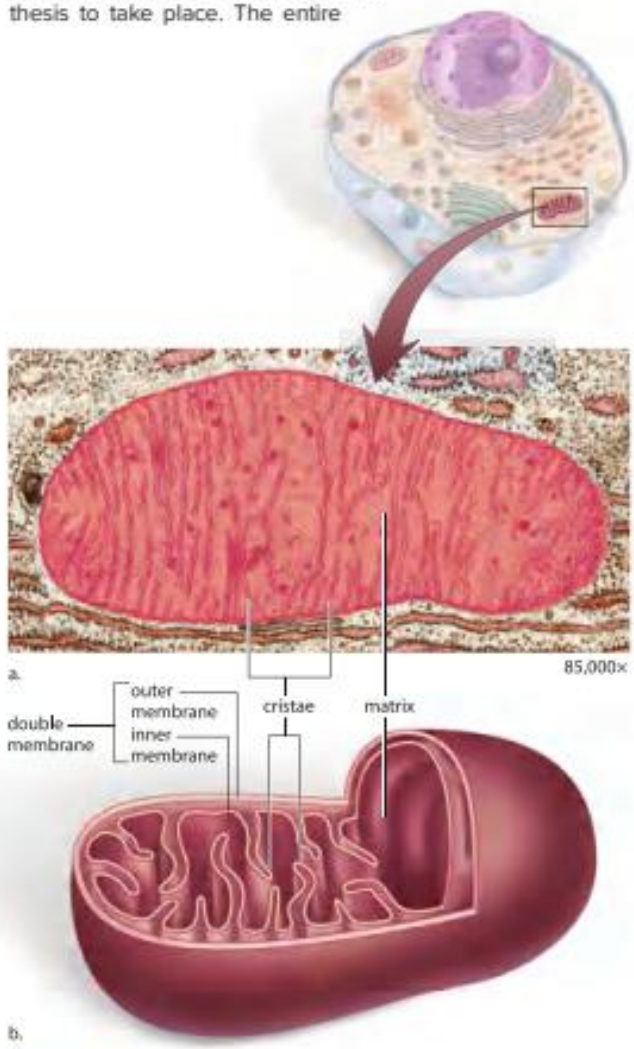


Figure 3.18 Mitochondrion structure. Mitochondria are involved in cellular respiration. **a.** Electron micrograph of a longitudinal section of a mitochondrion. **b.** Generalized drawing in which the outer membrane and portions of the inner membrane have been cut away to reveal the cristae.

process, which also involves the cytoplasm, is called *cellular respiration*, because oxygen is used and carbon dioxide is given off, as shown at the beginning of this section.

Mitochondrial Diseases

So far, dozens of different mitochondrial diseases that affect the brain, muscles, kidneys, heart, liver, eyes, ears, or pancreas have been identified. The common factor among these genetic diseases is that the patient's mitochondria are unable to completely metabolize organic molecules to produce ATP. As a result, toxins accumulate inside the mitochondria and the body. The toxins can be free radicals (substances that readily form harmful compounds when they react with other molecules), and these compounds damage mitochondria over time. In the United States, between 1,000 and 4,000 children per year are born with a mitochondrial disease. In addition, it is possible that many diseases of aging are due to malfunctioning mitochondria.

Check Your Progress **3.7**

1. Summarize the roles of mitochondria and chloroplasts in the cell.
2. Discuss the evidence that chloroplasts and mitochondria are derived from ancient bacteria.
3. Explain why chloroplasts and mitochondria contain complex internal membrane structures.

3.8 The Cytoskeleton

Learning Outcomes

Upon completion of this section, you should be able to

1. Compare the structure and function of actin filaments, intermediate filaments, and microtubules.
2. Describe how motor molecules interact with cytoskeletal elements to produce movement.
3. Explain the diverse roles of microtubules within the cell.

Cells are exposed to many physical forces. Cell shape, movement, and internal transport all require structural support, provided by the cytoskeleton. The protein components of the cytoskeleton (Gk. *kytos*, "cell") interconnect and extend from the nucleus to the plasma membrane in eukaryotic cells. Prior to the 1970s, it was believed that the cytoplasm was an unorganized mixture of organic molecules. Then, high-voltage electron microscopes, which can penetrate thicker specimens, showed instead that the cytoplasm is highly organized. The technique of immunofluorescence microscopy identified the makeup of the protein components within the cytoskeletal network (Fig. 3.19).

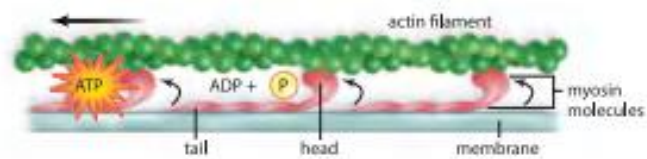
The cytoskeleton contains actin filaments, intermediate filaments, and microtubules, which maintain cell shape and allow the cell and its organelles to move. Therefore, the cytoskeleton is often compared to the bones and muscles of an animal. However, the cytoskeleton is dynamic; it can rearrange its protein components as necessary in response to changes in internal and external environments. A number of different mechanisms appear to regulate this process, including protein phosphatases, which remove phosphates from proteins and bring about assembly, and protein kinases, which phosphorylate proteins and lead to disassembly.

Actin Filaments

Actin filaments (formerly called microfilaments) are long, extremely thin, flexible fibers (about 7 nm in diameter) that occur in bundles or meshlike networks. Each actin filament contains two chains of globular actin monomers twisted about one another in a helical manner.

Actin filaments provide structural support as a dense, complex web just under the plasma membrane, to which they are anchored by special proteins. Sometimes, actin filaments can dynamically rearrange themselves and facilitate cellular movement, such as when an amoeba moves over a surface with pseudopods (L. *pseudo*, "false"; *pod*, "feet"), or when intestinal cell microvilli lengthen and shorten into the gut lumen (the space where ingested food is processed). In plant cells, actin filaments form the tracks along which chloroplasts circulate in a particular direction in a process called cytoplasmic streaming.

Actin filaments move the cell and its organelles by interacting with *motor molecules*, which are proteins that can attach, detach, and reattach farther along an actin filament. The motor molecule myosin uses ATP to pull actin filaments along in this way. Myosin has both a head and a tail. In muscle cells, the tails of several myosin molecules are joined to form a thick filament. In nonmuscle cells, cytoplasmic myosin tails are bound to membranes, but the heads still interact with actin:



During animal cell division, the two new cells form when actin, in conjunction with myosin, pinches off the cells from one another.

Intermediate Filaments

Intermediate filaments (8–11 nm in diameter) are so named because they are intermediate in size between actin filaments and microtubules. They form a ropelike assembly of fibrous polypeptides, but the specific filament type varies according to the tissue. Some intermediate filaments support the nuclear envelope, whereas others support the plasma membrane and take part in the formation of cell-to-cell junctions. In the skin, intermediate filaments made of the protein keratin give great mechanical strength to skin cells. Like other cytoskeletal components, intermediate filaments are highly dynamic and disassemble when phosphate is added to them by a kinase.

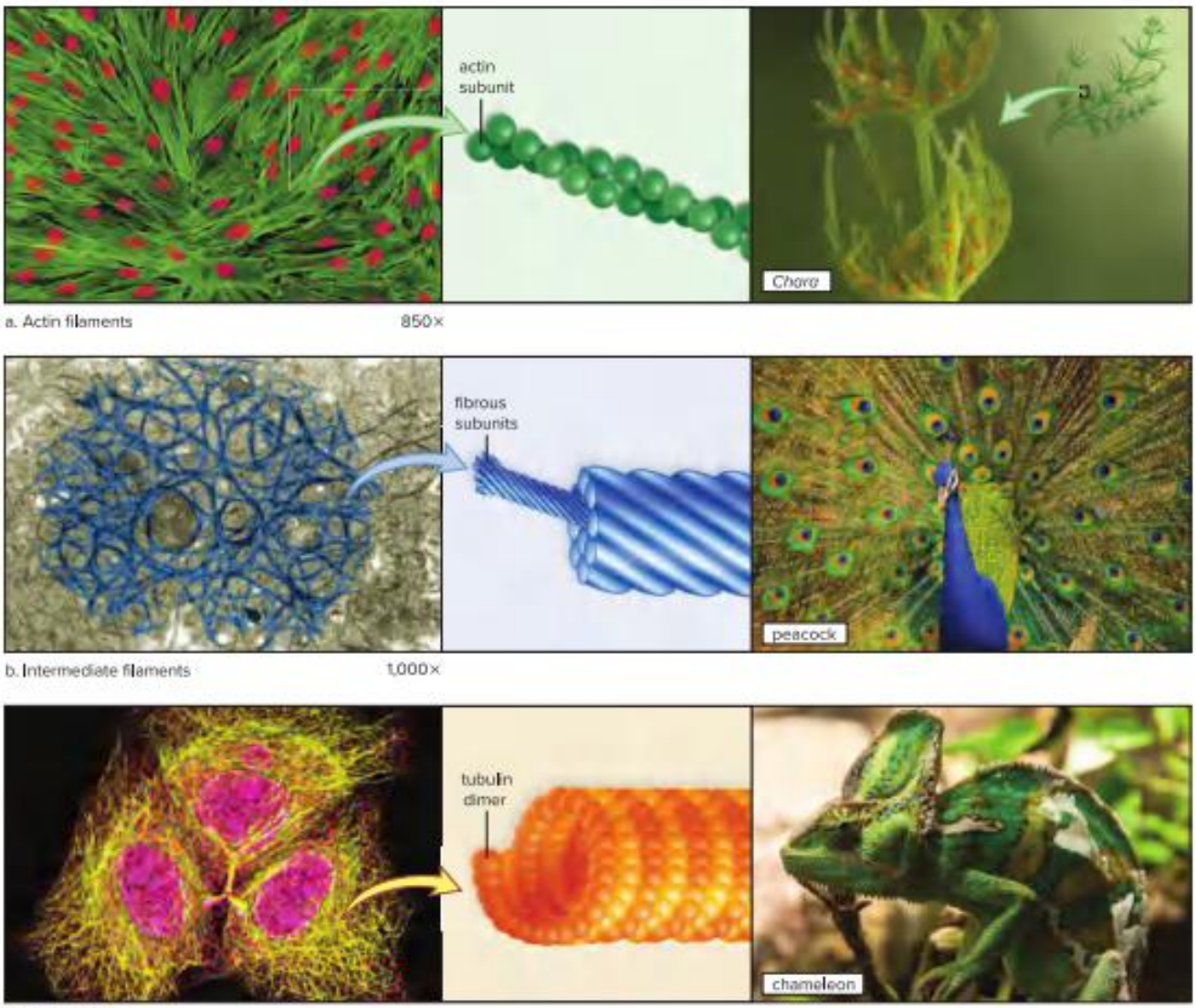
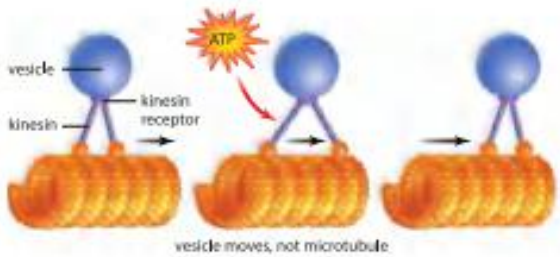


Figure 3.19 The cytoskeleton. The cytoskeleton maintains a cell's shape and allows its parts to move. Three types of protein components make up the cytoskeleton. They can be detected in cells by using labeling and fluorescence microscopy. **a.** *Left to right:* Cells showing a twisted double chain of actin filaments (green fibers). The giant cells of the green alga *Chara* use actin filaments to move organelles within the cell. **b.** *Left to right:* Animal cells showing fibrous, ropelike intermediate filaments (blue fibers). A peacock's colorful feathers are strengthened by intermediate filaments. **c.** *Left to right:* Animal cells showing hollow microtubules made of tubulin dimers (orange fibers). A chameleon's skin cells use microtubules to move pigment granules around so that they take on the color of their environment.

Microtubules

Microtubules (Gk. *mikros*, "small") are small, hollow cylinders about 25 nm in diameter and from 0.2 to 25 μm in length. They are made of a globular protein called tubulin, which is of two types called α and β. Alpha tubulin has a slightly different amino acid sequence than β tubulin. When assembly occurs, α and β tubulin molecules come together as dimers, and the dimers arrange themselves in rows. Microtubules have 13 rows of tubulin dimers, surrounding what appears in electron micrographs to be an empty central core.

Microtubule assembly is under the regulatory control of a microtubule-organizing center (MTOC). In most eukaryotic cells, the main MTOC is in the **centrosome** (Gk. *centrum*, "center"), which lies near the nucleus. Microtubules radiate from the centrosome, helping to maintain the shape of the cell and acting as tracks along which organelles can be moved. Whereas the motor molecule myosin is associated with actin filaments, the motor molecules kinesin and dynein are associated with microtubules:



There are different types of kinesin proteins, each specialized to move one kind of vesicle or cellular organelle. Kinesin moves vesicles or organelles in an opposite direction from dynein. Cytoplasmic dynein is closely related to the molecule dynein found in flagella.

Before a cell divides, microtubules disassemble and then reassemble into a structure called a spindle, which distributes chromosomes in an orderly manner. At the end of cell division, the spindle disassembles, and microtubules reassemble once again into their former array. Plants have evolved various types of poisons that prevent them from being eaten by herbivores. One of these, colchicine, is a plant poison that binds tubulin and blocks the assembly of microtubules.

Centrioles

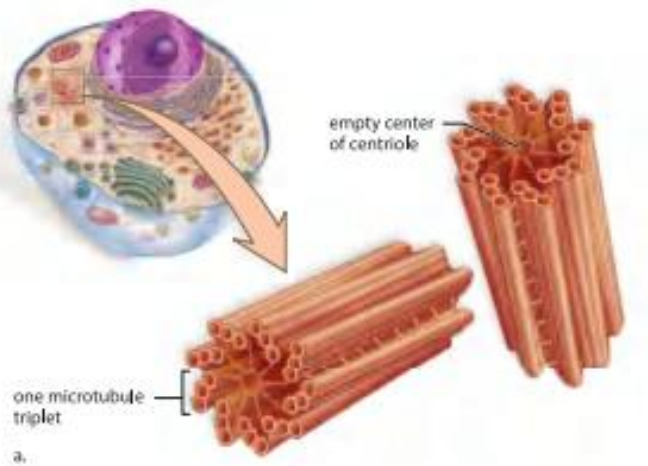
Centrioles are short cylinders with a 9 + 0 pattern of microtubule triplets—nine sets of triplets are arranged in an outer ring, but the center of a centriole does not contain a microtubule. In animal cells and most protists, a centrosome contains two centrioles lying at right angles to each other. A centrosome, as mentioned previously, is the major microtubule-organizing center for the cell. Therefore, it is possible that centrioles are also involved in the process by which microtubules assemble and disassemble.

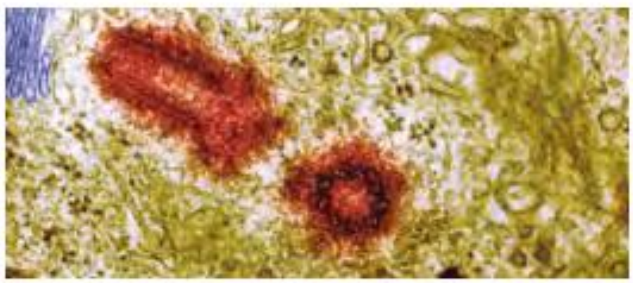
Before an animal cell divides, the centrioles replicate, and the members of each pair are at right angles to one another (Fig. 3.20). Then each pair becomes part of a separate centrosome. During cell division, the centrosomes move apart and most likely function to organize the mitotic spindle. In any case, each new cell has its own centrosome and pair of centrioles. Plant and fungal cells have the equivalent of a centrosome, but this structure does not contain centrioles, suggesting that centrioles are not necessary to the assembly of cytoplasmic microtubules.

A *basal body* is a structure that lies at the base of cilia and flagella and may direct the organization of microtubules within these structures. In other words, a basal body may do for a cilium or flagellum what the centrosome does for the cell. In cells with cilia and flagella, centrioles are believed to give rise to basal bodies.

Cilia and Flagella

Cilia (L. *cilium*, "eyelash, hair") and **flagella** (L. *flagello*, "whip") are hairlike projections that can move either in an undulating fashion, like a whip, or stiffly, like an oar. In free cells, cilia (or flagella) move the cell through liquid. For example, single-celled paramecia are organisms that move by means of cilia, whereas sperm cells move by means of flagella. If the cell is attached to other cells, cilia (or flagella) are capable of moving liquid over the cell. The cells that line our upper respiratory tract have cilia





b. one centrosome: one pair of centrioles

Figure 3.20 Centrioles. **a.** The centrosome of an animal cell contains two centrioles positioned at right angles to each other. **b.** A micrograph of one centrosome containing two centrioles.

that sweep debris trapped within mucus back up into the throat, where it can be swallowed or expelled. This action helps keep the lungs clean.

In eukaryotic cells, cilia are much shorter than flagella, but they have a similar construction. Both are membrane-bound cylinders enclosing a matrix area. In the matrix are nine microtubule doublets arranged in a circle around two central microtubules; this is called the 9 + 2 pattern of microtubules (Fig. 3.21). Cilia and flagella move when the microtubule doublets slide past one another using motor molecules.

As mentioned, each cilium and flagellum has a basal body lying in the cytoplasm at its base. Basal bodies have the same circular arrangement of microtubule triplets as centrioles and are believed to be derived from them. It is possible that basal bodies organize the microtubules within cilia and flagella, but this idea is not supported by the observation that cilia and flagella grow by the addition of tubulin dimers to their tips.

Check Your Progress 3.8

1. Differentiate between the components of the cytoskeleton and how they provide support to the cell.
2. Explain how ATP is used to produce movement in a cell.
3. Describe the role of motor molecules and microtubules in cilia and flagella.

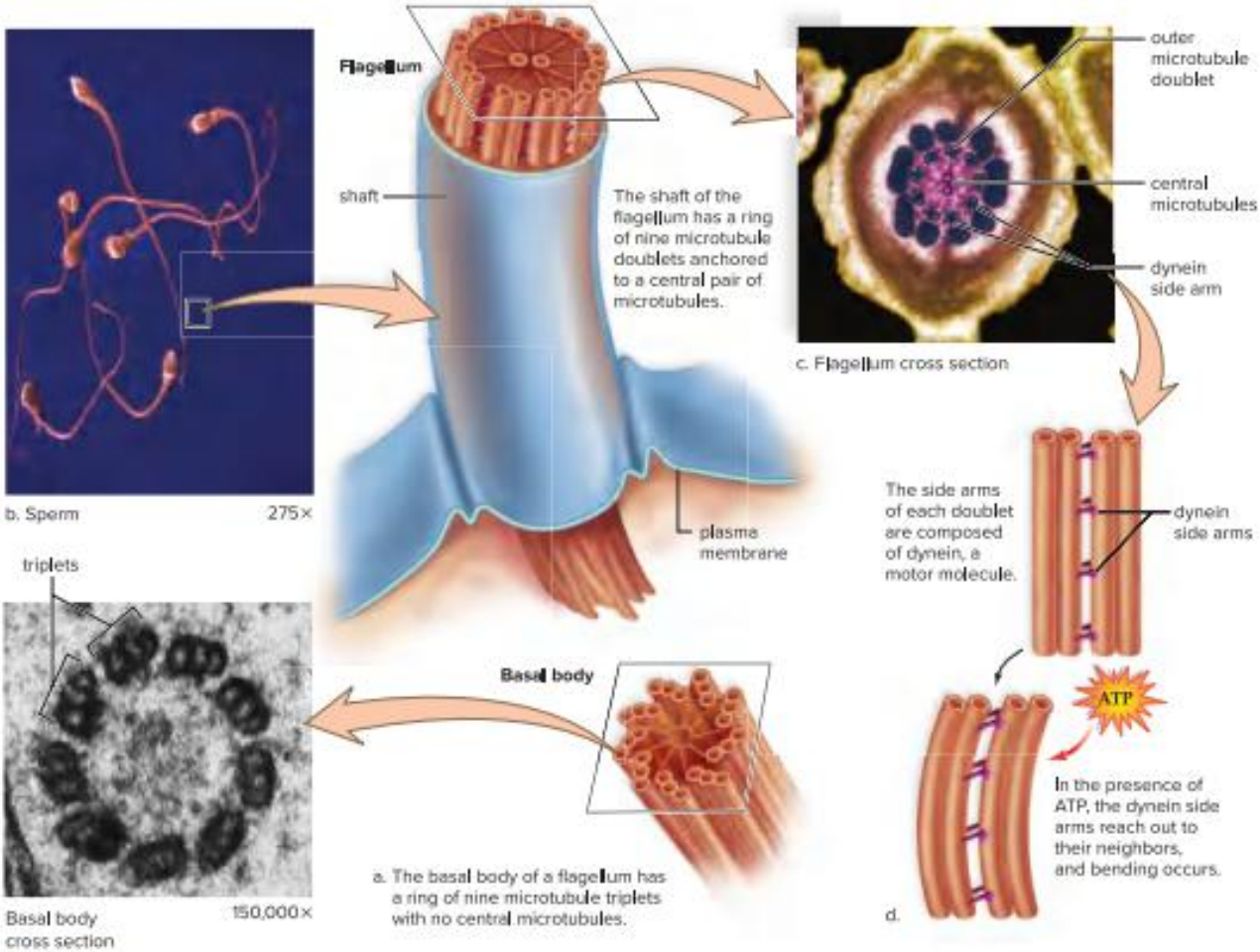


Figure 3.21 Structure of a flagellum. **a.** The basal body of a flagellum has a 9 + 0 pattern of microtubule triplets. Notice the ring of nine triplets, with no central microtubules. **b.** In sperm, the shaft of the flagellum has a 9 + 2 pattern (a ring of nine microtubule doublets surrounds a central pair of microtubules). **c.** In place of the triplets seen in a basal body, a flagellum's outer doublets have side arms of dynein, a motor molecule. **d.** In the presence of ATP, the dynein side arms reach out and attempt to move along their neighboring doublet. Because of the radial spokes connecting the doublets to the central microtubules and motor molecules, bending occurs.

REVIEWING *the* BIG IDEAS

BIG IDEA 1

Fossil records provide evidence that the first cells on Earth were primitive prokaryotes. 1.D.2.a.1

BIG IDEA 2

All cells, from simple to complex, have membranes, ribosomes, and DNA. 2.B.3.c; *4.B.2.a.1*

Large surface area to volume ratios promotes cells' favorable exchange of material. 2.A.3.b.1; 2.A.3.b.2

BIG IDEA 3

The genetic material of the cell is stored in chromosomes composed of DNA. 3.A.1.a.2

BIG IDEA 4

Specialized organelles allow eukaryotic cells to accomplish vital functions, often by compartmentalizing enzymes and metabolic pathways. 4.A.2.a-g; *2.B.3.b.IE*

Cells specialize by modifying surfaces, architecture, and organelle assortment, compartmentalizing chemical reactions, and storage. 4.A.2.g; 4.B.2.a.1

The endomembrane system of eukaryotic cells connects membrane-bound organelles for more efficient delivery and processing of materials. 4.A.2.b,c,e,f

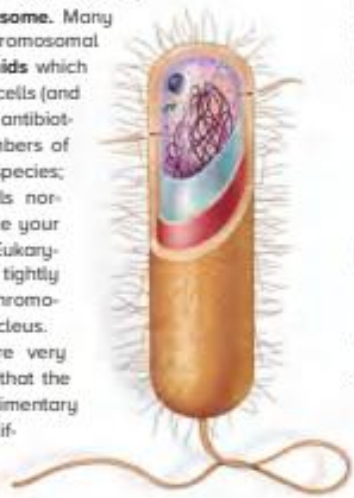
SUMMARIZE

AP Answering the Essential Questions

All living organisms are composed of **cells,** the smallest units of living matter. Most cells are too small to see with the naked eye and require a microscope. Their small size allows them to maintain a large surface-area-to-volume ratio, which facilitates the transport of nutrients and wastes into and out of the cell.

There are three basic types of cells: archaea, prokaryotes, and eukaryotes. Archaea are a unique type, and our main focus will be on prokaryotic and eukaryotic cells (archaea will be discussed in detail in Chapter 20). All cells share common features including a **plasma membrane** that separates the cell from its environment, and organelles called ribosomes which are important for the production of RNA and proteins. In addition, both kinds of cells have DNA to store and transmit hereditary information. However, a major distinction between prokaryotic cells and eukaryotic cells is how they organize their genetic information.

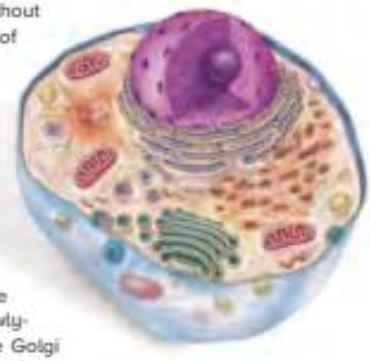
Prokaryotes In prokaryotes, most DNA is stored in a single, coiled **chromosome.** Many bacterial cells also have extrachromosomal DNA in the form of circular **plasmids** which easily can be transferred between cells (and often carry genes for resistance to antibiotics). Eukaryotes have varying numbers of chromosomes depending on the species; for example, human somatic cells normally have 46 chromosomes, while your Labrador retriever puppy has 78. Eukaryotic chromosomes also have DNA tightly wrapped around protein, and chromosomes are confined to the cell's nucleus.



Prokaryotes like bacteria are very small and simple; scientists think that the earliest life forms on Earth were rudimentary prokaryotic cells. Eukaryotic cells differ from prokaryotic cells in that they are much larger and possess a variety of membrane-bound organelles that perform specific functions. They evolved later than prokaryotic cells, and likely evolved from prokaryotic ancestors. Evidence for this can be seen in the **endosymbiotic theory,** which proposes that double membrane-bound organelles, such as mitochondria and chloroplasts, were once independently-living prokaryotes which were engulfed by a larger cell.

Eukaryotes Eukaryotic cells possess numerous organelles that perform specific functions. In addition to the plasma membrane that separates the cell from its environment many organelles also have **membrane systems.** These membrane systems compartmentalize functions such as the storage of enzymes and the synthesis of proteins. We will explore the structure and function of the cell membrane in Chapter 5. **Ribosomes** are small, universal structures comprised of ribosomal RNA and protein and are the site of protein synthesis. The **endoplasmic reticulum** (ER) is a network of membrane-bound tubules and sacs and has two types; smooth ER is the site for lipid synthesis, and rough ER with attached ribosomes is the sites for protein synthesis. The **Golgi apparatus** consists of a series of flattened membrane sacs. Functions of the Golgi include the synthesis and packing of materials for transport and the production of lysosomes. In animal cells, **lysosomes** contain hydrolytic enzymes necessary to break down ingested substances and damaged organelles for recycling of molecules. Large membrane-bound vesicles called **vacuoles** store material, dispose of wastes, and, especially in plants, maintain water balance. **Mitochondria** and **chloroplasts** capture and transform energy from one form to another.

Just like your body contains many different organs and organ systems that work together (try moving your bones without muscles!), the cell organelles of eukaryotes interact to perform a specific task. For example, let's say a cell needs to synthesize Protein X. The instructions for making this protein are programmed in the DNA stored in the nucleus, and the message travels via RNA to the ribosomes attached to the rough endoplasmic reticulum where the protein is synthesized. The newly-made polypeptide travels to the Golgi apparatus where it is modified and packaged for either storage or export. Mitochondria produce energy needed for these processes. Just like the human body, a cell is greater than the sum of its parts!



ASSESS

Choose the best answer for each question.

3.1 Cellular Level of Organization

1. The surface-area-to-volume ratio defines what aspect of a cell?
   a. whether it is eukaryotic or prokaryotic
   b. whether it is plant or animal
   c. its size
   d. its ability to move
2. The cell theory states that
   a. cells are the basic units of life.
   b. all organisms are composed of cells.
   c. all cells come from preexisting cells.
   d. All of these are correct.

3.2 Prokaryotic Cells

3. Which of the following best distinguishes a prokaryotic cell from a eukaryotic cell?
   a. Prokaryotic cells have a cell wall, but eukaryotic cells never do.
   b. Prokaryotic cells are much larger than eukaryotic cells.
   c. Prokaryotic cells have flagella, but eukaryotic cells do not.
   d. Prokaryotic cells do not have a membrane-bound nucleus, but eukaryotic cells do have such a nucleus.
4. Which structures are found in a prokaryotic cell?
   a. cell wall, ribosomes, thylakoids, chromosome
   b. cell wall, plasma membrane, nucleus, flagellum

c. nucleoid, ribosomes, chloroplasts, capsule
d. plasmid, ribosomes, enzymes, DNA, mitochondria

5. A spherical-shaped prokaryotic cell is called a
a. coccus.
b. spirochete.
c. bacillus.
d. None of these are correct.

3.3 Introduction to Eukaryotic Cells

6. Which organelle most likely originated by invagination of the plasma membrane?
a. mitochondria
b. flagella
c. nucleus
d. chloroplasts

7. Which of the following organelles contains its (their) own DNA, suggesting they were once independent prokaryotes?
a. Golgi apparatus
b. mitochondria
c. chloroplasts
d. Both b and c are correct.

3.4 The Nucleus and Ribosomes

8. Which of these is not found in the nucleus?
a. functioning ribosomes
b. chromatin that condenses to chromosomes
c. nucleolus that produces rRNA
d. nucleoplasm instead of cytoplasm

9. The _____ is(are) responsible for protein synthesis in a cell.
a. chromatin
b. chromosomes
c. ribosomes
d. nucleoplasm

10. Which of the following terms indicates the basic unit of hereditary information?
a. gene
b. chromosome
c. chromatin
d. nucleoplasm

3.5 The Endomembrane System

11. Vesicles from the rough ER most likely are on their way to
a. the peroxisomes.
b. the lysosomes.
c. the Golgi apparatus.
d. the plant cell vacuole only.

12. Lysosomes function in
a. protein synthesis.
b. processing and packaging.
c. intracellular digestion.
d. lipid synthesis.

13. Which of the following is reponsible for the synthesis of proteins that are being exported from the cell?
a. smooth ER
b. rough ER
c. lysosome
d. peroxisome

3.6 Microbodies and Vacuoles

14. Vesicles with specific metabolic functions in a cell are called
a. the cytoskeleton.
b. centrioles.
c. ribosomes.
d. microbodies.

15. These microbodies break down fatty acids and contain catalase to break down hydrogen peroxide.
a. lysosome
b. central vacuole
c. peroxisome
d. chromatin

3.7 The Energy-Related Organelles

16. Mitochondria
a. are involved in cellular respiration.
b. break down ATP to release energy for cells.
c. are present in animal cells but not plant cells.
d. All of these are correct.

17. Which organelle releases oxygen?
a. ribosome
b. Golgi apparatus
c. chloroplast
d. smooth ER

18. Which of the following would not be found in a chloroplast?
a. grana
b. thylakoids
c. cristae
d. stroma

3.8 The Cytoskeleton

19. Which of these is not true?
a. Actin filaments are located under the plasma membrane.
b. Microtubules are organized by centrosomes.
c. Intermediate filaments are associated with the nuclear envelope.
d. Motor molecules move materials along intermediate filaments.

20. Cilia and flagella
a. have a 9 + 0 pattern of microtubules, the same as basal bodies.
b. contain myosin that pulls on actin filaments.
c. are organized by basal bodies derived from centrioles.
d. Both a and c are correct.

ENGAGE

AP Applying the Big Ideas

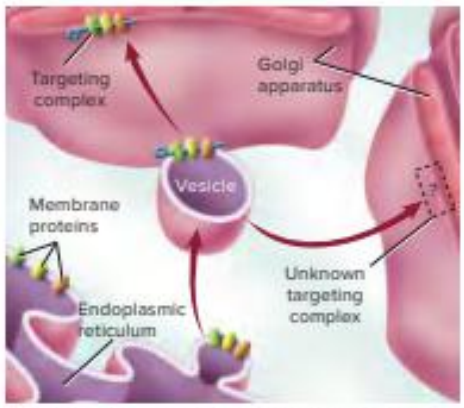
1. BIG IDEA 1 BIG IDEA 3 Organisms share many conserved features that evolved and are widely distributed among organisms today. **Describe** THREE specific examples of evidence from cells and their structures that support the concept of common ancestry for all organisms.

2. BIG IDEA 2 Cells, the smallest units of living matter, make life possible.
   a. **Draw** one generalized prokaryotic cell AND one generalized eukaryotic cell.
   b. **Label** the cellular components.
   c. **Answer** the question: What are two major differences a between prokaryotic and eukaryotic cells? Make sure that these differences are evident in your drawings.

3. BIG IDEA 4 The subcellular components of eukaryotic cells increase cell efficiency.
   a. **Describe** two scenarios where scientists have found subcellular structures interact.
   b. **Explain** how these interactions provide essential functions for the cell.

AP Applying the Science Practices

How is vesicle traffic from the ER to the Golgi apparatus regulated?
Some proteins are synthesized by ribosomes on the endoplasmic reticulum (ER). The proteins are processed in the ER, and vesicles containing these proteins pinch off and migrate to the Golgi apparatus. Scientists currently are studying the molecules that are involved in fusing these vesicles to the Golgi apparatus.



*Data obtained from: Brittle, E. E., and Waters, M. G. 2000. ER-to-golgi traffic—this bud's for you. Science 289: 403–404.

Think Critically SP 1 SP 6

1. **Interpret the diagram** by naming two complexes on the Golgi apparatus that might be involved in vesicle fusion.
2. **Hypothesize** an explanation for vesicle transport based on what you have read about cytoplasm and the cytoskeleton.

4

Membrane Structure and Function

The burning sensation of a chili pepper is caused by interactions of chemicals with the membranes of cells.

Chapter Outline

AP Have you ever bitten into a hot pepper and had the sensation that your mouth was on fire? This is because the chili pepper plant produces a chemical, called capsaicin, that binds to a protein in the plasma membrane of pain receptors in your mouth. In the membrane are channel proteins that allow the movement of calcium ions across the membrane. When these channels are open, movement of the calcium ions into the cell causes the pain receptor to send a signal to the brain. The brain then interprets this signal as a burning sensation. These channels may also be triggered by temperature, an acidic pH, and heat. As long as the capsaicin is present, the pathway will remain active and signals will be sent to the brain. So the quickest way to alleviate the pain is to remove the capsaicin and close the channel protein. Unfortunately, since capsaicin is lipid-soluble, drinking cool water does very little to alleviate the pain. However, drinking milk, or eating bread or rice, often helps remove the capsaicin. Often the first bite is the worst, since the capsaicin causes an initial opening of all the channels simultaneously. The receptors can become desensitized to capsaicin, which is why later bites of the same pepper don't produce the same results.

In this chapter, we will explore not only how cells move materials in and out but also the basic properties of energy and how cells use metabolic pathways and enzymes to conduct the complex reactions needed to sustain life.

As you read through the chapter, think about these Essential Questions:

1. How does the fluid mosaic model of the cell membrane allow for selective permeability? 2.B.1.b.1,4 2.B.3.a-c 2.D.3.a
2. How do signaling pathways detect and respond to changes in a cell's environment? 3.D.3.a-b 3.D.4.a
3. How do membrane-bound organelles in eukaryotic cells confer greater efficiency to cell processes? 4.A.2.a-g 4.B.2.a.1

Following *the* BIG IDEAS

BIG IDEA 2 — The plasma membrane, a feature of all cells, is appropriately called the gatekeeper of the cell because it maintains the identity and integrity of the cells as it "stands guard" over what enters and leaves.

BIG IDEA 3 — Membrane receptor proteins act as intercellular signal receivers.

BIG IDEA 4 — Membranes are an integral part of an interconnected cellular system of communication and response to environment.

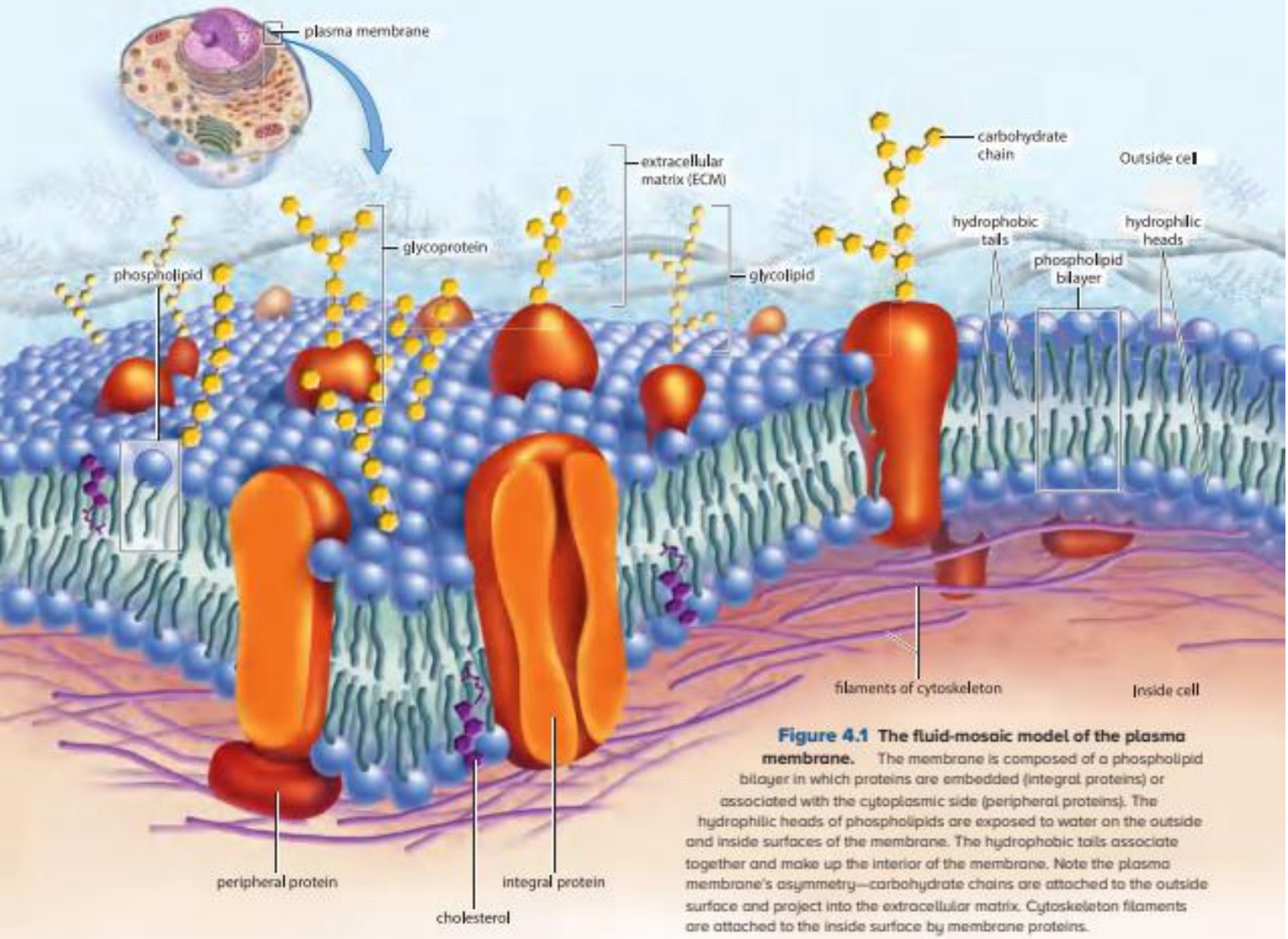


Figure 4.1 The fluid-mosaic model of the plasma membrane. The membrane is composed of a phospholipid bilayer in which proteins are embedded (integral proteins) or associated with the cytoplasmic side (peripheral proteins). The hydrophilic heads of phospholipids are exposed to water on the outside and inside surfaces of the membrane. The hydrophobic tails associate together and make up the interior of the membrane. Note the plasma membrane's asymmetry—carbohydrate chains are attached to the outside surface and project into the extracellular matrix. Cytoskeleton filaments are attached to the inside surface by membrane proteins.

4.1 Plasma Membrane Structure and Function

Learning Outcomes

Upon completion of this section, you should be able to

1. Distinguish between the different structural components of membranes.
2. Describe the nature of the fluid-mosaic model as it relates to membrane structure.
3. Describe the diverse role of proteins in membranes.
4. Explain why the plasma membrane exhibits selective permeability.

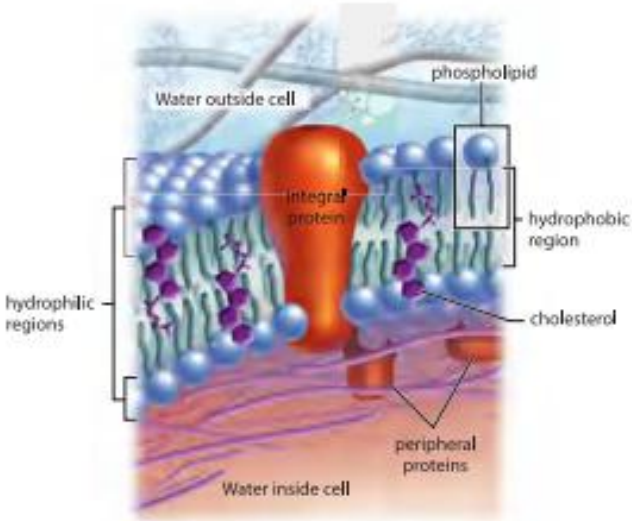
The ability to create compartments is a key feature of cells. Membranes, made of a phospholipid bilayer, create separation between the cell and the external environment as well as compartments within the cell itself. Having separate spaces allows multiple, sometimes incompatible, chemical processes to occur simultaneously. This "division of labor" allows cells to operate more efficiently and respond to changing environmental conditions.

Components of the Plasma Membrane

The structure of a typical animal cell's plasma membrane is depicted in Figure 4.1. In addition to the phospholipid bilayer, membrane components include protein molecules that are either partially or wholly embedded in the bilayer. Cholesterol is another lipid found in the animal plasma membrane; related steroids are found in the plasma membrane of plants. As we will see, cholesterol helps modify the fluidity of the membrane over a range of temperatures.

Recall that a phospholipid is an *amphipathic molecule*, meaning that it has both a hydrophilic (water-loving) region and a hydrophobic (water-fearing) region. The amphipathic nature of phospholipids largely explains why they form a bilayer in water.

Because similar substances associate with one another, the hydrophilic polar heads of the phospholipid molecules naturally associate with the polar water molecules found on the outside and inside of the cell. Likewise, the hydrophobic nonpolar tails associate with each other because they want to "get away" from the polar water.



Cell membranes are highly similar in the types of molecules they contain, which makes them interchangeable and allows them to fuse together fairly easily. What makes one membrane different from another are the types of proteins integrated into the membrane. As shown in Figure 4.1, proteins are scattered throughout the membrane in an irregular pattern, and this pattern can vary from membrane to membrane.

Electron micrographs can be used to study the nature of many membrane proteins. A research method called freeze-fracture freezes, and then splits, the membrane so that the upper and lower layers separate. The proteins remain intact and go with one of the layers. The embedded proteins are called *integral proteins*, whereas the proteins that occur only on the cytoplasmic side of the membrane are called *peripheral proteins*.

Some integral proteins protrude from only one surface of the bilayer, but most span the membrane, with a hydrophobic core region that associates with the nonpolar core of the membrane. Hydrophilic ends of integral proteins protrude from both surfaces of the bilayer, interacting with polar water molecules. Integral proteins can be held in place by attachments to protein fibers of the cytoskeleton (inside) and fibers of the extracellular matrix (outside). Only animal cells have an extracellular matrix (ECM), which contains various protein fibers and very large, complex carbohydrate molecules. The ECM, which is discussed in greater detail in section 4.4, has a number of functions, from lending external support to the plasma membrane to assisting in communication between cells.

Fluid-Mosaic Model

Membranes are not rigid but rather are flexible structures. They consist of a variety of molecules, including phospholipids, cholesterol, and proteins. The **fluid-mosaic model** is used to describe the interactions of these membrane components.

The lipid content of the membrane is responsible for its fluidity. Cells are flexible because the phospholipid bilayer is fluid. At body temperature, the phospholipid bilayer of the plasma membrane has the consistency of olive oil. The greater the concentration of unsaturated fatty acid residues, the more fluid the bilayer. In each monolayer, the fatty acid tails jostle around, and an entire phospholipid molecule can move sideways at a rate averaging about 2 µm—the length of a prokaryotic cell—per second. Although it is possible for phospholipid molecules to flip-flop from one monolayer to the other, they rarely do so, because this would require the hydrophilic head to move through the hydrophobic center of the membrane. However, at times special proteins help the phospholipids flip.

The presence of cholesterol molecules prevents the plasma membrane from becoming too fluid at higher temperatures and too solid at lower temperatures. At higher temperatures, cholesterol stiffens the membrane and makes it less fluid than it would otherwise be. At lower temperatures, cholesterol helps prevent the membrane from freezing by not allowing contact between certain phospholipid tails.

A plasma membrane is considered a mosaic because of the presence of many proteins. The number and kinds of proteins can vary in the plasma membrane and in the membranes of the various organelles. The position of these proteins can shift over time, unless they are anchored to another structure, such as the cytoskeleton. Experiments have been conducted in which the proteins were tagged prior to allowing mouse and human cells to fuse. An hour after fusion, the proteins from each cell type were completely mixed, suggesting that at least some proteins are able to move sideways in the membrane.

Scientists once thought that all membrane proteins could freely move sideways within the fluid bilayer. Today, however, we know that membrane proteins are often associated with the ECM, the cytoskeleton, or both. These connections hold a protein in place and partially anchor the otherwise fluid phospholipid bilayer.

It should be noted that the two sides of the membrane are not identical. Carbohydrate chains (see below) are attached only to molecules on the outside surface, and peripheral proteins occur on one surface or the other. Thus, the membrane is said to be asymmetrical.

Glycoproteins and Glycolipids

Phospholipids and proteins that have attached carbohydrate (sugar) chains are called **glycolipids** and **glycoproteins,** respectively. The carbohydrate (sugar) chains on a cell's exterior can be highly diverse. The chains can vary in the number and sequence of sugars, and in whether the chain is branched. Each cell within an individual has its own "fingerprint" because of these chains. For this reason, glycolipids and glycoproteins play an important role in cellular identification. As you probably know, transplanted tissues are often rejected by the recipient. Rejection occurs because the immune system is

able to detect that the foreign tissue's cells do not have the appropriate carbohydrate chains to be recognized as self. In humans, carbohydrate chains are also the basis for the A, B, and O blood groups.

In animal cells, the carbohydrate chains attached to proteins give the cell a "sugar coat," more properly called a *glycocalyx*. The glycocalyx protects the cell and has various other functions, including cell-to-cell adhesion, reception of signaling molecules, and cell-to-cell recognition.

The Functions of the Proteins

Although the protein components of plasma membranes differ depending on the type of cell and the processes it is undergoing, several types of proteins are likely to be routinely present:

Channel proteins Channel proteins are involved in passing molecules through the membrane. They form a channel that allows a substance to simply move from one side to the other (Fig. 4.2*a*). For example, a channel protein allows hydrogen ions to flow across the inner mitochondrial membrane. Without this movement of hydrogen ions, ATP would never be produced.

Carrier proteins Carrier proteins are also involved in passing molecules through the membrane. They receive a substance and change their shape, and this change moves the substance across the membrane (Fig. 4.2*b*). A carrier protein transports sodium and potassium ions across the plasma membrane of a nerve cell. Without this carrier protein, nerve impulse conduction would be impossible.

Cell recognition proteins Cell recognition proteins are glycoproteins (Fig. 4.2*c*). Among other functions, these proteins help the body recognize when it is being invaded by pathogens, so that an immune response can occur. Without this recognition, pathogens would be able to freely invade the body and hinder its function.

Receptor proteins Receptor proteins have a shape that allows only a specific molecule to bind to it (Fig. 4.2*d*). The binding of this molecule causes the protein to change its shape and thereby bring about a cellular response. The coordination of the body's organs is totally dependent on such signaling molecules. For example, the liver stores glucose after it is signaled to do so by insulin.

Enzymatic proteins Some plasma membrane proteins are enzymes that carry out metabolic reactions directly (Fig. 4.2*e*). Without these enzymes, some of which are attached to the various membranes of the cell, a cell would never be able to perform the chemical reactions needed to maintain its metabolism.

Junction proteins Proteins are involved in forming various types of junctions between animal cells (Fig. 4.2*f*). Signaling molecules that pass through gap junctions allow the cilia of cells that line the respiratory tract to beat in unison.

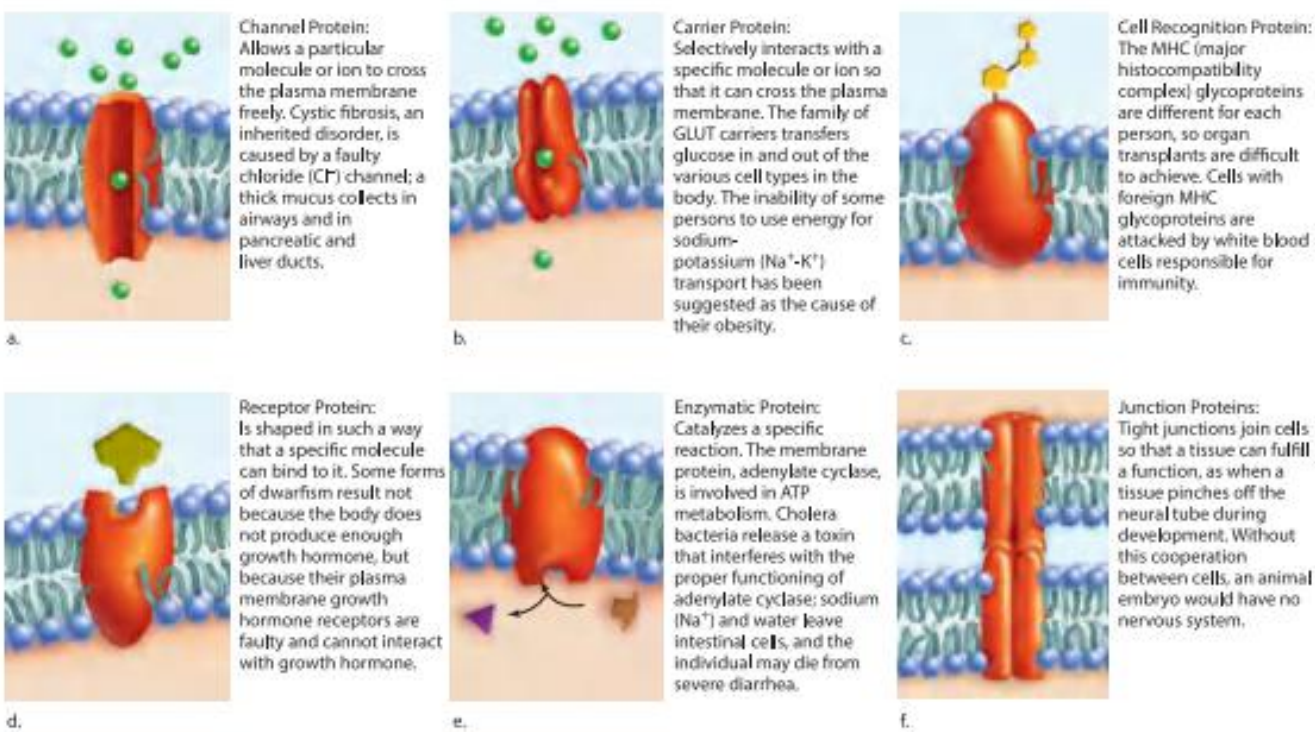


Figure 40.2 Membrane protein diversity. These are some of the functions performed by proteins found in the plasma membrane.

Table 4.1 Passage of Molecules into and out of the Cell

Name	Direction	Requirement	Examples
Diffusion	Toward lower concentration	Concentration gradient	Lipid-soluble molecules, gases
Facilitated transport	Toward lower concentration	Channels or carrier and concentration gradient	Some sugars, amino acids
Active transport	Toward higher concentration	Carrier plus energy	Sugars, amino acids, ions
Bulk transport	Toward outside or inside	Vesicle utilization	Macromolecules

Permeability of the Plasma Membrane

The plasma membrane regulates the passage of molecules into and out of the cell. This function is critical because the cell must maintain its normal composition under changing environmental conditions. The plasma membrane is essential because it is **selectively permeable,** allowing only certain substances into the cell while keeping others out.

Molecules that can freely cross a membrane generally require no energy to do so. Substances that are hydrophobic and therefore similar to the phospholipid center of the membrane are able to diffuse across membranes at no energy cost. Polar molecules, however, are chemically incompatible with the center of the membrane and so require an expenditure of energy to drive their transport.

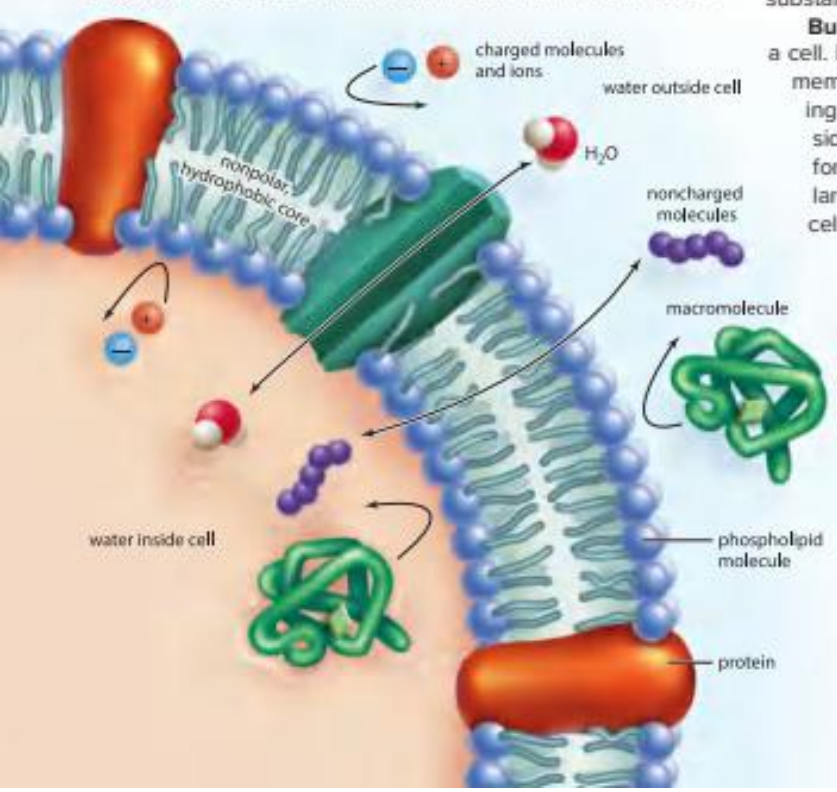
Table 4.1 and Figure 4.3 examine which types of molecules can passively cross a membrane (no energy required) and which may require transport by a carrier protein and/or an expenditure of energy. In general, small, noncharged molecules, such as carbon dioxide, oxygen, glycerol, and alcohol, can freely cross the membrane. They are able to slip between the hydrophilic heads of the phospholipids and pass through the hydrophobic tails of the membrane because they are similarly nonpolar.

These molecules follow their **concentration gradient** as they move from an area where their concentration is high to an area where their concentration is low. Consider that a cell is always using oxygen when it carries on cellular respiration. The internal consumption of oxygen results in a low cellular concentration. Because oxygen concentration is higher outside than inside the cell, oxygen tends to move across the membrane into the cell. The concentration of carbon dioxide, on the other hand, is highest inside the cell, because it is produced during cellular respiration. Therefore, carbon dioxide tends to move with its concentration gradient from inside to outside the cell.

Water, a polar molecule, would not be expected to readily cross the primarily nonpolar membrane. However, scientists have discovered that the majority of cells have channel proteins, called **aquaporins,** that allow water to cross a membrane more quickly than expected. Aquaporins also allow cells to equalize water pressure differences between their interior and exterior environments, so that their membranes don't burst from environmental pressure changes.

Ions and polar molecules, such as glucose and amino acids, can slowly cross a membrane. To move as quickly as is necessary, they are often assisted across the plasma membrane by carrier proteins. Each carrier protein recognizes particular shapes of molecules and must combine with an ion, such as sodium (Na^+), or a molecule, such as glucose, before changing its shape and transporting the molecule across the membrane. Therefore, carrier proteins are specific for the substances they transport across the plasma membrane.

Bulk transport is a way that large particles can exit or enter a cell. During exocytosis, fusion of a vesicle with the plasma membrane moves a particle to outside the membrane. During endocytosis, vesicle formation moves a particle to inside the plasma membrane. Vesicle formation is reserved for movement of macromolecules or even for something larger, such as a virus. As with many other processes, a cell is selective about what enters by endocytosis.



Check Your Progress 4.1

1. Explain why phospholipids play such an important role in the structure of the cell membrane.
2. Describe the role of proteins in the fluid-mosaic model.
3. Compare how cells transport polar and nonpolar molecules across a membrane.

Figure 4.3 How molecules cross the plasma membrane. The curved arrows indicate that these substances cannot passively cross the plasma membrane, and the long, back-and-forth arrows indicate that these substances can diffuse across the plasma membrane.

BIG IDEA 3: Information Storage, Transmission, and Response

How Cells Talk to One Another

All organisms are comprised of cells that are able to sense and respond to specific signals in their environment. A bacterium that lives in your body responds to signaling molecules when it finds food and escapes immune cells in order to stay alive. Signaling helps the bread mold that grows on stale bread detect an opposite mating strain to begin its sexual life cycle. Similarly, the cells of a developing embryo respond to signaling molecules as they move to specific locations and become specific tissues (Fig. 4Aa).

In newborn animals, internal signals such as hormones are essential to ensure that specific tissues develop when and how they should. In plants, external signals, such as a change in the amount of light, tell them when it is time to resume growth or to flower. Internal signaling molecules enable animals and plants to coordinate their cellular activities, to metabolize, and to better respond in a changing environment. The ability of cells to communicate with one another is an essential part of all biological systems.

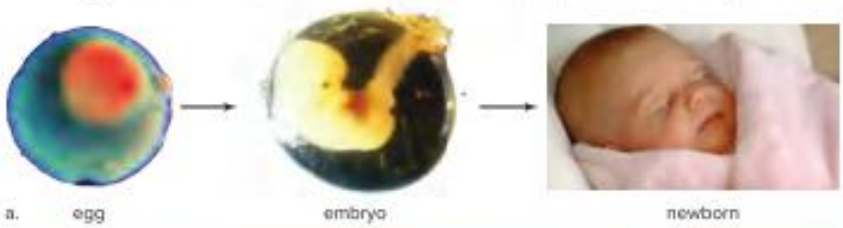
Cell Signaling

The cells of a multicellular organism "talk" to one another by using signaling molecules, sometimes called chemical messengers. Some messengers are produced in one location and, in animals, are carried by the circulatory system to various target sites around the body. For example, the pancreas releases a hormone called insulin, which is transported in blood vessels to the liver, and this signal causes the liver to store glucose as glycogen. Failure of the liver to respond appropriately results in a medical condition called diabetes.

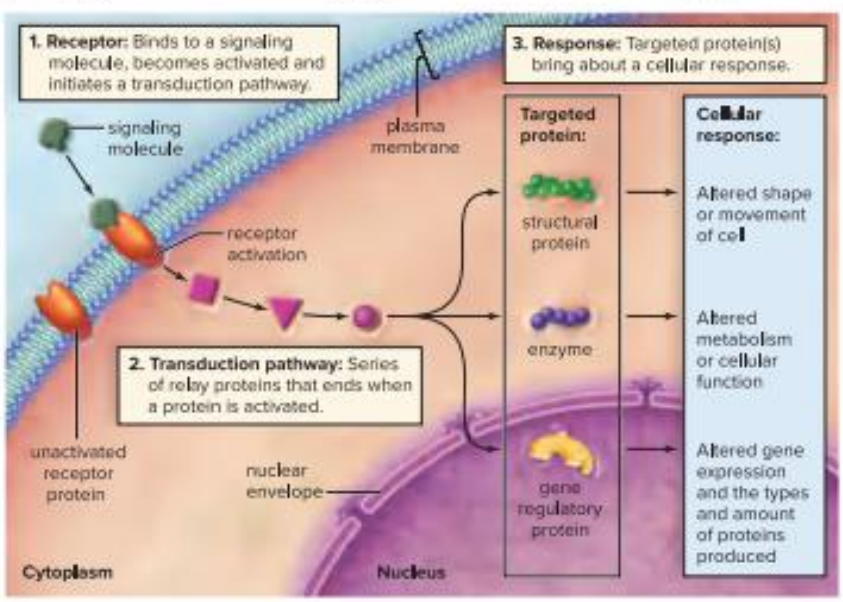
We are particularly interested in growth factors, which act locally as signaling molecules and cause cells to divide. Overproduction of growth factors can disrupt the balance in cellular systems. If left uncorrected, uncontrolled cell growth and formation of a tumor can result. The importance of cell signaling in regulating cell systems is the focus of much research in cell biology.

Cells respond to only certain signaling molecules. Why? Because they must bind to a receptor protein, and only cells that possess matching receptors can respond to certain signaling molecules. Each cell has a mix of receptors, which gives them the ability to respond differently to a variety of external and internal stimuli. Each cell is also able to balance the relative strength of incoming signals in order to change cellular structure or function. If a minimum level of signaling is not met, the cell dies.

Signaling molecules interacting with their receptor is only the beginning of a complex process of communication that tells the cell how to respond. Once a signaling molecule and receptor interact, a cascade of events occurs that increase, decrease, or otherwise change the signal to elicit a cellular response. This process is called a signal transduction pathway. This pathway is analogous to television transmission: A TV camera (the receptor) views a scene and converts it into electrical signals (transduction pathway) that are understood by the TV receiver in your house, which converts these signals to a picture on your screen (the response). The process in cells is more complicated, because each member of the pathway can activate a number of other proteins. As shown in Figure 4Ab, the cell response to a transduction pathway can be a change in the shape or movement of a cell, the activation of a particular enzyme, or the activation of a specific gene.



a. egg embryo newborn



b.

Questions to Consider

1. If your cells needed to respond rapidly to a changing environment, would you want their effect to be short- or long-lived?
2. Given the essential role of signaling in cellular and organismal health, how might diseases arise from signaling errors?

Figure 4A Cell signaling. **a.** The process of signaling helps account for the transformation of an egg into an embryo and then an embryo into a newborn. **b.** The process of signaling involves three steps: binding of the signaling molecule, transduction of the signal, and response of the cell depending on what type of protein is targeted.

4.2 Passive Transport Across a Membrane

Learning Outcomes

Upon completion of this section, you should be able to

1. Compare diffusion and osmosis across a membrane.
2. Describe the role of proteins in the movement of molecules across a membrane.
3. Differentiate among the effects of hypotonic, isotonic, and hypertonic solutions on animal and plant cells.

Diffusion is the movement of molecules from a higher to a lower concentration—that is, down their concentration gradient—until equilibrium is achieved and the molecules are distributed equally. Diffusion is a physical process that results from the random molecular motion that can be observed with any type of molecule. For example, when a crystal of dye is placed in water (Fig. 4.4), the dye and water molecules move in various directions, but their net movement, which is the sum of their motion, is toward the region of lower concentration. Eventually, the dye is dissolved evenly in the water, resulting in equilibrium and a uniformly colored solution.

A **solution** contains both a **solute,** usually a solid, and a **solvent,** usually a liquid. In this case, the solute is the dye and the solvent is the water molecules. Once the solute and solvent are evenly distributed, they continue to move about, but there is no net movement of either one in any direction.

The chemical and physical properties of the plasma membrane allow only a few types of molecules to enter and exit a cell simply by diffusion. Gases can freely diffuse through the lipid bilayer because they are small and nonpolar; this is the mechanism by which oxygen enters cells and carbon dioxide exits cells. This is also how oxygen diffuses from the alveoli (air sacs) of the lungs into the blood in the lung capillaries (Fig. 4.5). After inhalation (breathing in), the concentration of oxygen in the alveoli is higher than that in the blood; therefore, oxygen diffuses into the blood along its concentration gradient.

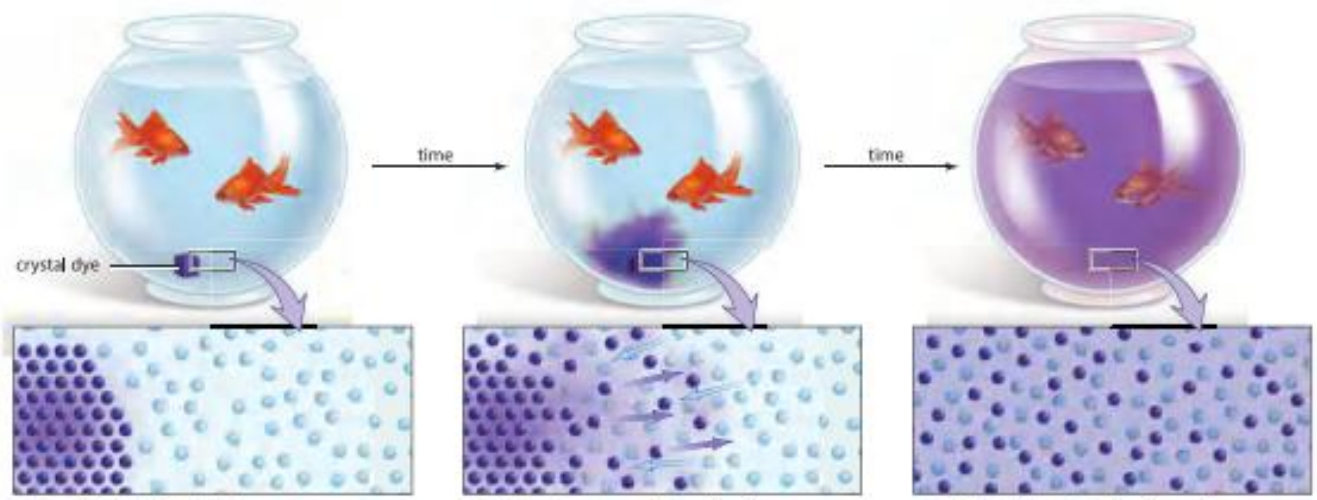
Several factors influence the rate of diffusion, including temperature, pressure, electrical currents, and molecular size. For example, as temperature increases, the rate of diffusion increases. The movement of fishes in the tank would also speed the rate of diffusion (see Fig. 4.4).

Osmosis

The diffusion of water across a selectively permeable membrane from high to low concentration is called **osmosis.** To illustrate osmosis, a thistle tube containing a 10% solute solution[1] is covered at one end by a selectively permeable membrane and then placed in a beaker containing a 5% solute solution (Fig. 4.6*a*). The beaker has a higher concentration of water molecules (lower percentage of solute), and the thistle tube has a lower concentration of water molecules (higher percentage of solute). Diffusion always occurs from higher to lower concentration. Therefore, a net movement of water takes place, moving across the membrane from the beaker to the inside of the thistle tube (Fig. 4.6*b*).

The solute does not diffuse out of the thistle tube. Why not? Because the membrane is not permeable to the solute. As water enters and the solute does not exit, the level of the solution within the thistle tube rises (Fig. 4.6*c*). In the end, the concentration of solute in the thistle tube is less than 10%. Why? Because there is now less solute per unit volume. And the concentration

1 Percent solutions are grams of solute per 100 ml of solvent. Therefore, a 10% solution is 10 g of sugar with water added to make 100 ml of solution.



a. Crystal of dye is placed in the water

b. Diffusion of water and dye molecules

c. Equal distribution of molecules results

Figure 4.4 Process of diffusion. Diffusion is spontaneous, and no chemical energy is required to bring it about. **a.** When a dye crystal is placed in water, it is concentrated in one area. **b.** The dye dissolves in the water, and over time a net movement of dye molecules from a higher to a lower concentration occurs. There is also a net movement of water molecules from a higher to a lower concentration. **c.** Eventually, the water and the dye molecules are equally distributed throughout the container.

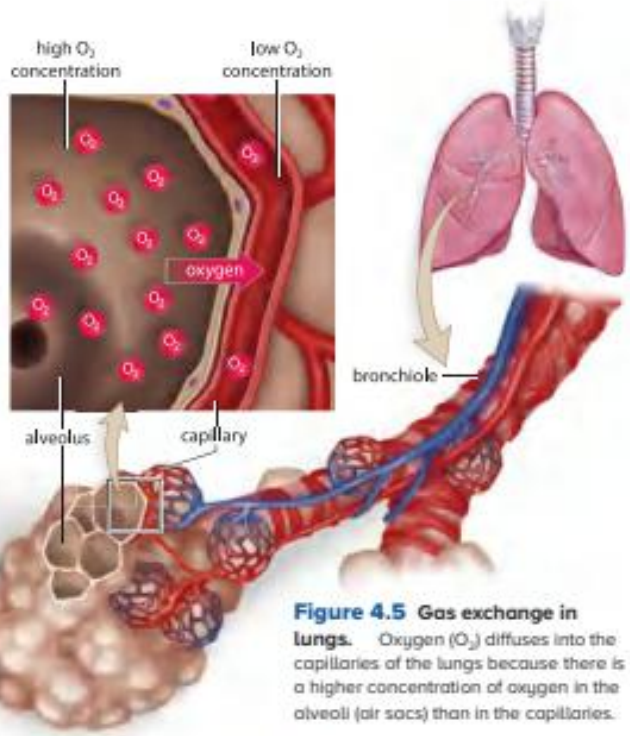


Figure 4.5 Gas exchange in lungs. Oxygen (O_2) diffuses into the capillaries of the lungs because there is a higher concentration of oxygen in the alveoli (air sacs) than in the capillaries.

of solute in the beaker is greater than 5%, because there is now more solute per unit volume.

Water enters the thistle tube due to the osmotic pressure of the solution within the thistle tube until it reaches equilibrium (Fig 4.6*d*). **Osmotic pressure** is the pressure that develops in a system due to osmosis.[2] In other words, the greater the possible osmotic pressure, the more likely it is that water will diffuse in that direction. Due to osmotic pressure, water is absorbed by the kidneys and taken up by capillaries in the tissues. Osmosis also occurs across the plasma membrane, as we'll see next.

Isotonic Solution

In the laboratory, cells are normally placed in **isotonic solutions.** The prefix *iso* means "the same as," and the term **tonicity** refers to the strength of the solution. In an isotonic solution, the solute concentration and the water concentration both inside

2 Osmotic pressure is measured by placing a solution in an osmometer and then immersing the osmometer in pure water. The pressure that develops is the osmotic pressure of a solution.

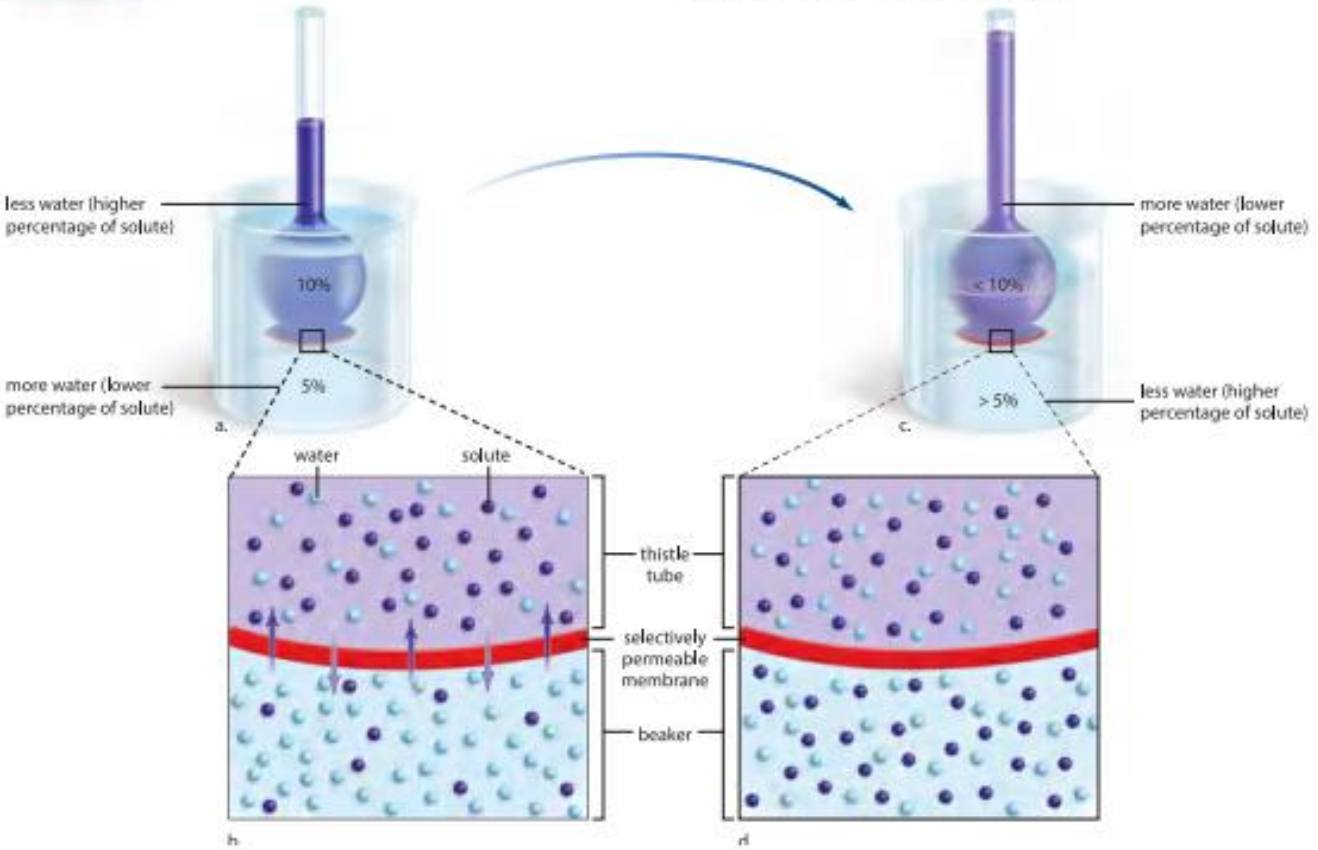


Figure 4.6 Osmosis demonstration. **a.** A thistle tube, covered at the broad end by a selectively permeable membrane, contains a 10% solute solution. The beaker contains a 5% solute solution. **b.** The solute (purple circles) is unable to pass through the membrane, but the water (blue circles) passes through in both directions. There is a net movement of water toward the inside of the thistle tube, where there is a lower percentage of water molecules. **c.** Due to the incoming water molecules, the level of the solution rises in the thistle tube. **d.** Eventually, the concentration of water across the membrane equalizes.

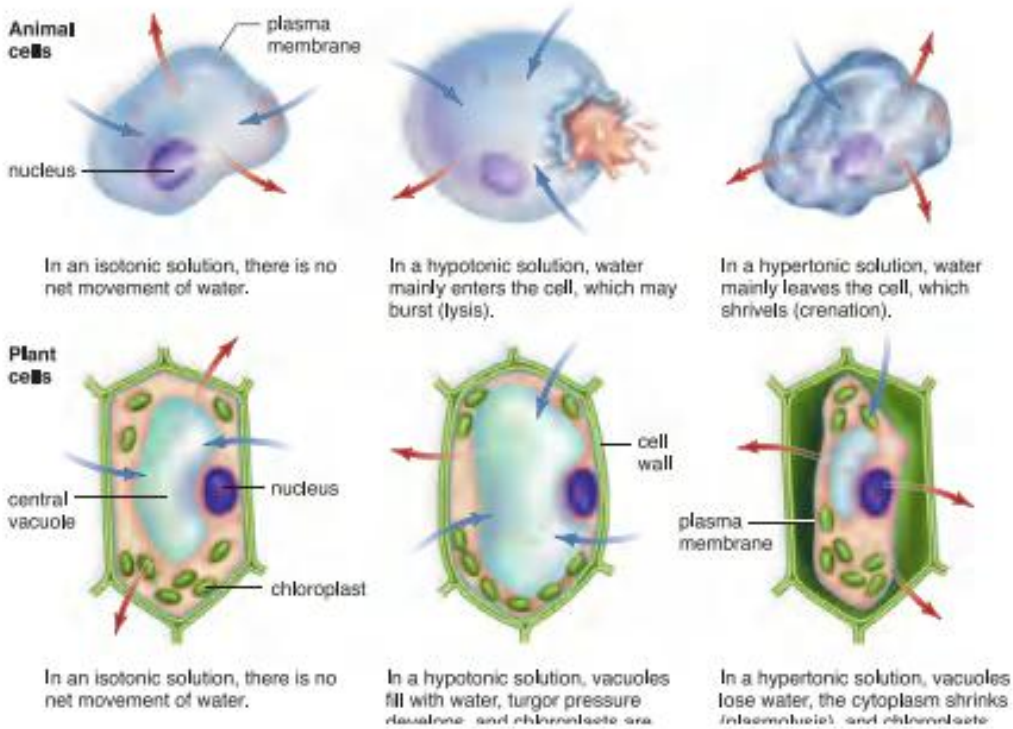


Figure 4.7 Osmosis in animal and plant cells. The arrows indicate the net movement of water molecules. To determine the net movement of water, compare the number of blue arrows (which are taking water molecules into the cell) versus the number of red arrows (which are taking water out of the cell). In an isotonic solution, a cell neither gains nor loses water; in a hypotonic solution, a cell gains water; and in a hypertonic solution, a cell loses water. Tutorial: Osmosis and Tonicity

and outside the cell are equal (Fig. 4.7), and therefore there is no net gain or loss of water. A 0.9% solution of the salt sodium chloride (NaCl) is known to be isotonic to red blood cells. Therefore, intravenous solutions medically administered usually have this tonicity. Terrestrial animals can usually take in either water or salt as needed to maintain the tonicity of their internal environment. Many animals living in an estuary, such as oysters, blue crabs, and some fishes, are able to cope with changes in the salinity (salt concentrations) of their environment using specialized kidneys, gills, and other structures.

Hypotonic Solution

Solutions that cause cells to swell, or even to burst, due to an intake of water are said to be **hypotonic solutions.** The prefix *hypo* means "less than" and refers to a solution with a lower concentration of solute (higher concentration of water) than inside the cell. If a cell is placed in a hypotonic solution, water enters the cell, because the lower cellular concentration of water prompts a net movement of water from the outside to the inside of the cell.

Any concentration of a salt solution lower than 0.9% is hypotonic to red blood cells. Animal cells placed in such a solution expand and sometimes burst because of the buildup of pressure. The term *cytolysis* is used to refer to disrupted cells. **Hemolysis** is the term used to describe cytolysis in red blood cells.

The swelling of a plant cell in a hypotonic solution creates **turgor pressure.** When a plant cell is placed in a hypotonic solution, the cytoplasm expands, because the large central vacuole gains water and the plasma membrane pushes against the rigid cell wall. Unlike animal cells that have no cell wall, the plant cell does not burst, because the cell wall does not give way. Turgor pressure in plant cells is extremely important to the maintenance of the plant's erect position. If you forget to water your plants, they wilt due to decreased turgor pressure.

Organisms that live in fresh water have to avoid taking in too much water. Many protozoans, such as paramecia, have contractile vacuoles that rid the body of excess water. Freshwater fishes have well-developed kidneys that excrete a large volume of dilute urine. These fish still have to take in salts through their gills. Even though freshwater fishes are good osmoregulators, they would not be able to survive in either distilled water or a salty marine environment.

Hypertonic Solution

Solutions that cause cells to shrink or shrivel due to loss of water are said to be **hypertonic solutions.** The prefix *hyper* means "more than" and refers to a solution with a higher percentage of solute (lower concentration of water) outside the cell. If a cell is placed in a hypertonic solution, water leaves the cell; the net movement of water is from the inside to the outside of the cell.

Any concentration of a salt solution higher than 0.9% is hypertonic to red blood cells. If animal cells are placed in this solution, they shrink. The term **crenation** refers to red blood cells in this condition. Meats are sometimes preserved by salting them. The bacteria are not killed by the salt but by the lack of water in the meat.

When a plant cell is placed in a hypertonic solution, the plasma membrane pulls away from the cell wall as the large central vacuole loses water. This is an example of **plasmolysis,** a shrinking of the cytoplasm due to osmosis. The dead plants you may see along a salted roadside died because they were

exposed to a hypertonic solution during the winter. Also, when salt water invades coastal marshes due to storms and human activities, coastal plants die. Without roots to hold the soil, it washes into the sea, doing away with many acres of valuable wetlands.

Marine animals cope with their hypertonic environment in various ways that prevent them from losing excess water to the environment. Sharks increase or decrease urea in their blood until their blood is isotonic with the environment and, in this way, do not lose too much water. Marine fishes and other types of animals drink no water but excrete salts across their gills. Have you ever seen a marine turtle cry? It is ridding its body of salt by means of glands near the eye.

Facilitated Transport

The plasma membrane impedes the passage of all but a few substances. Yet biologically useful molecules are able to rapidly enter and exit the cell either by way of a channel protein or because of carrier proteins in the membrane. These transport proteins are specific; each can transport only a certain type of molecule or ion across the membrane. How carrier proteins function is not completely understood, but after a carrier combines with a molecule, the carrier is believed to undergo a conformational change in shape that moves the molecule across the membrane. Carrier proteins are utilized for both facilitated transport (movement with concentration gradient; requires no energy) and active transport (movement against concentration gradient; requires energy)(see Table 4.1).

Facilitated transport explains how molecules such as glucose and amino acids are rapidly transported across the plasma membrane. Whereas water moves through a channel protein, the passage of glucose and amino acids is facilitated by their reversible combination with carrier proteins, which transport them through the plasma membrane. These carrier proteins are specific. For example, various sugar molecules of identical size might be present inside or outside the cell, but glucose can cross the membrane hundreds of times faster than the other sugars. As stated earlier, this is the reason the membrane can be called selectively permeable.

A model for facilitated transport (Fig. 4.8) shows that after a carrier has assisted the movement of a molecule to the other side of the membrane, it is free to assist the passage of other solute molecules. Neither diffusion nor facilitated transport requires an expenditure of energy, because the molecules are moving down their concentration gradient.

Check Your Progress 4.2

1. Explain why both osmosis and diffusion are passive processes.
2. Describe how a cell would react to a hypertonic or hypotonic solution.
3. Contrast diffusion with facilitated transport.

4.3 Active Transport Across a Membrane

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain how active transport moves substances across a membrane.
2. Compare the energy requirements of passive and active transport.
3. Contrast the bulk transport of large and small substances into a cell.

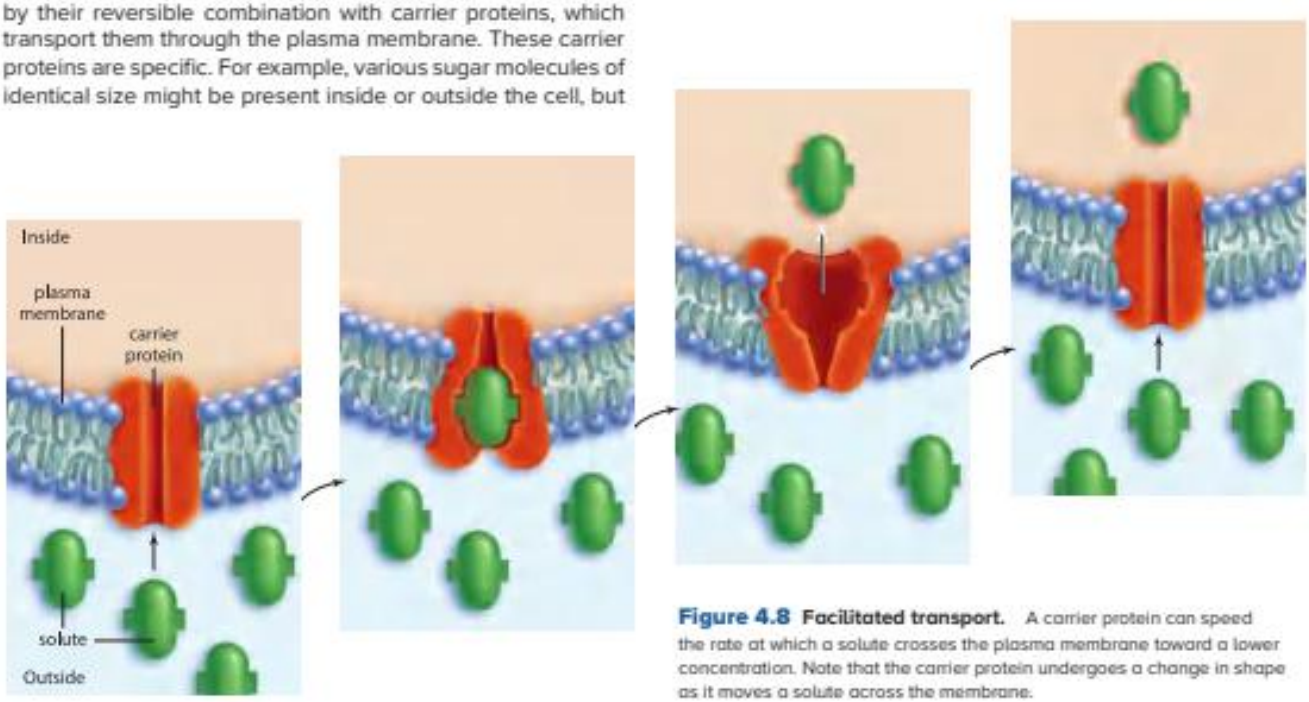


Figure 4.8 Facilitated transport. A carrier protein can speed the rate at which a solute crosses the plasma membrane toward a lower concentration. Note that the carrier protein undergoes a change in shape as it moves a solute across the membrane.

At times, a cell may need to further increase a concentration gradient across a membrane in order to do more work. The process of **active transport** moves molecules against their concentration gradient. Active transport requires energy, usually in the form of ATP. For example, iodine collects in the cells of the thyroid gland; glucose is completely absorbed from the gut by the cells lining the digestive tract; and sodium can be almost completely withdrawn from urine by cells lining the kidney tubules. In each of these instances, molecules move from a lower to a higher concentration, exactly opposite the process of diffusion.

Carrier proteins and an expenditure of energy (ATP) are both needed to transport molecules against their concentration gradient. In this case, the ATP is needed for the carrier to combine with the substance to be transported. Therefore, it is not surprising that cells involved primarily in active transport, such as kidney cells, have a large number of mitochondria near membranes where active transport is occurring.

Proteins involved in active transport often are called pumps because, just as a water pump uses energy to move water against the force of gravity, proteins use energy to move a substance against its concentration gradient. One type of pump that is active in all animal cells, but is especially

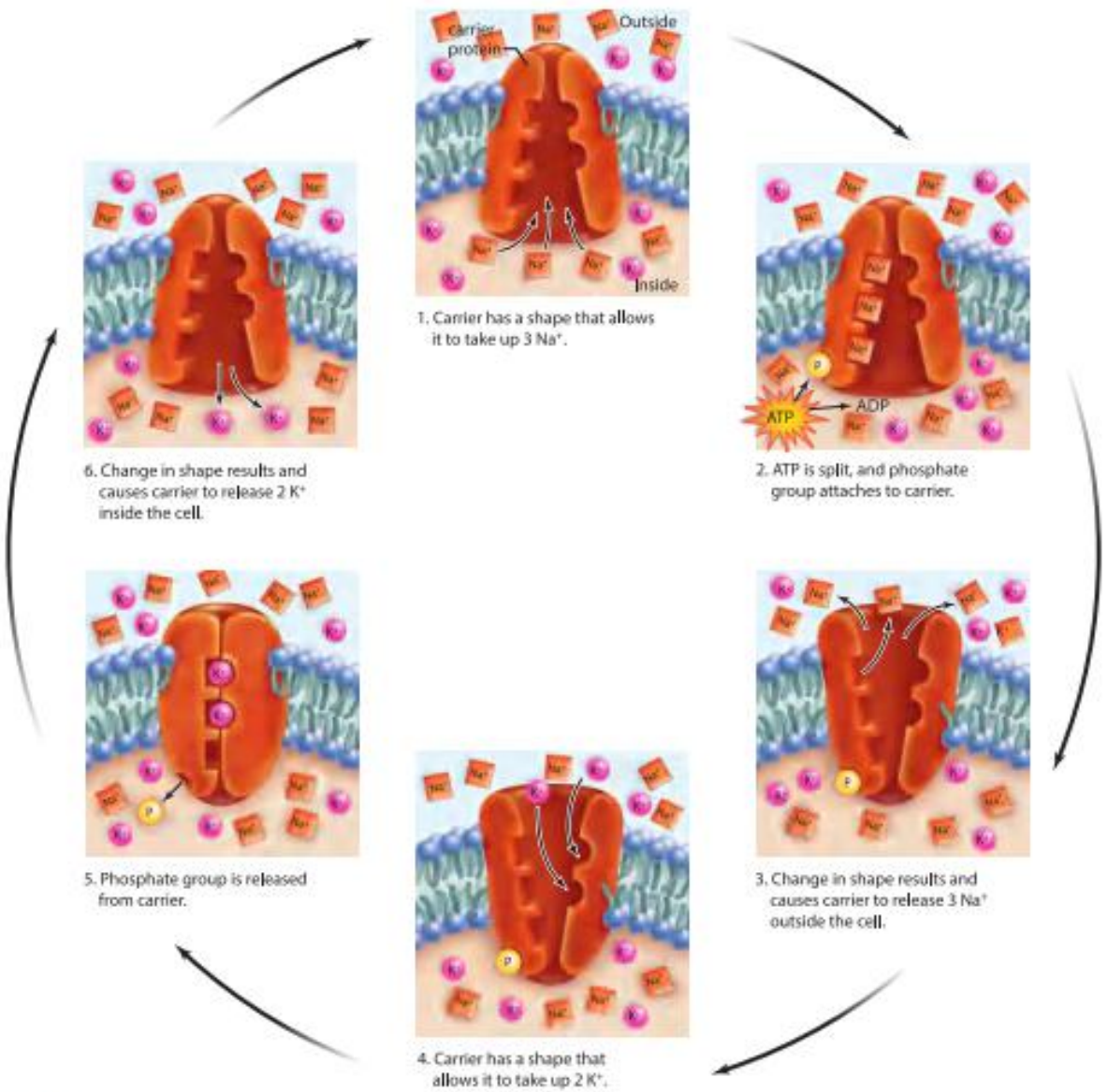


Figure 4.9 The sodium-potassium pump. The same carrier protein transports sodium ions (Na^+) to the outside of the cell and potassium ions (K^+) to the inside of the cell, because it undergoes an ATP-dependent change in shape. Three sodium ions are carried outward for every two potassium ions carried inward; therefore, the inside of the cell is less positively charged compared to the outside.

associated with nerve and muscle cells, moves sodium ions (Na^+) to the outside of the cell and potassium ions (K^+) to the inside of the cell. The transport of sodium and potassium are linked together through the same carrier protein, called a **sodium-potassium pump.**

The sodium-potassium carrier protein has an initial shape that allows it to bind three sodium ions. Phosphate from an ATP molecule is added to the carrier protein, and it changes shape; this shape change moves sodium across the membrane. The new shape is no longer compatible with binding to the sodium, which falls away.

The new shape, however, is compatible with picking up two potassium ions, which bind to their sites. As the phosphate that was added from ATP in an earlier step leaves, the carrier protein assumes its original shape, and the two potassium ions are released inside the cell (Fig. 4.9). The cotransport of three sodium and two potassium creates not only a solute gradient but also an electrical gradient across the plasma membrane.

The passage of salt (NaCl) across a plasma membrane is of primary importance to most cells. The chloride ion (Cl^-) usually crosses the plasma membrane because it is attracted by positively charged sodium ions (Na^+). First sodium ions are pumped across a membrane, and then chloride ions simply diffuse through channels that allow their passage.

As noted in Figure 4.2*a*, the genetic disorder cystic fibrosis results from a faulty chloride channel protein. When chloride is unable to exit a cell, water stays behind. The lack of water outside the cells causes abnormally thick mucus in the bronchial tubes and pancreatic ducts, thus interfering with the function of the lungs and pancreas.

Bulk Transport

How do large molecules such as proteins, polysaccharides, or nucleic acids enter and exit a cell? These molecules are too large to be transported by carrier proteins, so they are instead transported into and out of the cell by vesicles. Membrane vesicles formed around macromolecules require an expenditure of cellular energy, but the cost is worth it, because each vesicle keeps its cargo from mixing with molecules within the cytoplasm that could alter the cell's function. Generally, substances can exit a cell through exocytosis, and enter a cell through endocytosis.

Exocytosis

During **exocytosis,** an intracellular vesicle fuses with the plasma membrane as secretion occurs (Fig. 4.10). Hormones, neurotransmitters, and digestive enzymes are secreted from cells in this manner. The Golgi body often produces the vesicles that carry these cell products to the membrane. During exocytosis, the membrane of the vesicle becomes a part of the plasma membrane, because both are nonpolar. Adding additional vesicle membrane to the plasma membrane can enlarge the cell and is a part of growth in some cells. The proteins released from the vesicle may adhere to the cell surface or become incorporated into an extracellular matrix.

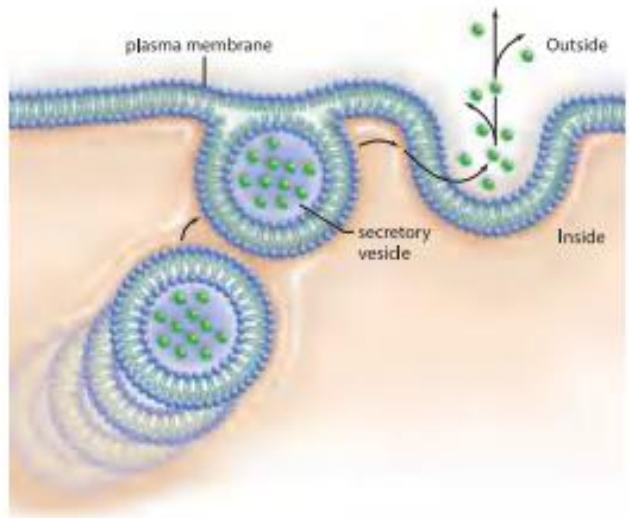


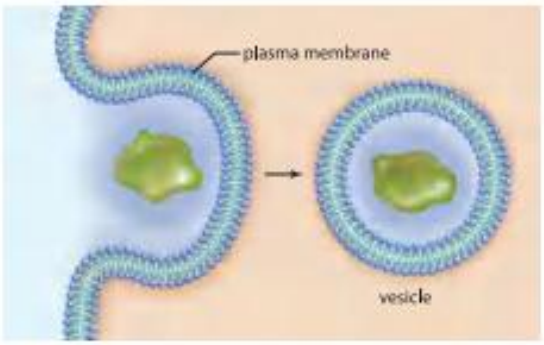
Figure 4.10 Exocytosis. Exocytosis secretes or deposits substances on the outside of the cell.

Cells of particular organs are specialized to produce and export molecules. For example, pancreatic cells produce digestive enzymes or insulin, and anterior pituitary cells produce growth hormone, among other hormones. In these cells, secretory vesicles accumulate near the plasma membrane, and the vesicles release their contents only when the cell is stimulated by a signal received at the plasma membrane. A rise in blood sugar, for example, signals pancreatic cells to release the hormone insulin. This is called regulated secretion, because vesicles fuse with the plasma membrane only when the needs of the body trigger it to do so.

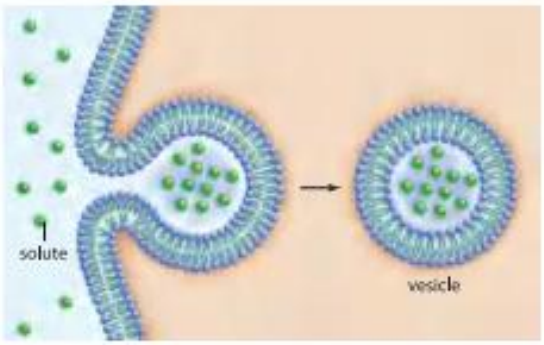
Endocytosis

During **endocytosis,** cells take in substances by forming vesicles around the material. A portion of the plasma membrane invaginates to envelop the substance, and then the membrane pinches off to form an intracellular vesicle. Endocytosis occurs in one of three ways, as illustrated in Figure 4.11. Phagocytosis transports large substances, such as a virus, and pinocytosis transports small substances, such as a macromolecule, into a cell. Receptor-mediated endocytosis is a special form of pinocytosis.

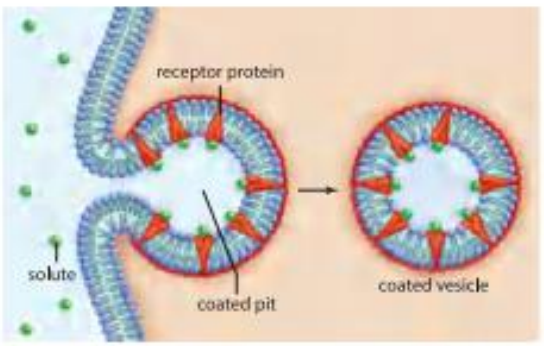
Phagocytosis. When the material taken in by endocytosis is large, such as a food particle or another cell, the process is called **phagocytosis (**Gk. *phagein*, "to eat"). Phagocytosis is common in single-celled organisms, such as amoebas (Fig. 4.11*a*). It also occurs in humans. Certain types of human white blood cells are amoeboid—that is, they are mobile like an amoeba, and they can engulf debris such as worn-out red blood cells or viruses. When an endocytic vesicle fuses with a lysosome, digestion occurs. Later in this text you will see that this process is a necessary and preliminary step toward the development of our immunity to bacterial diseases.



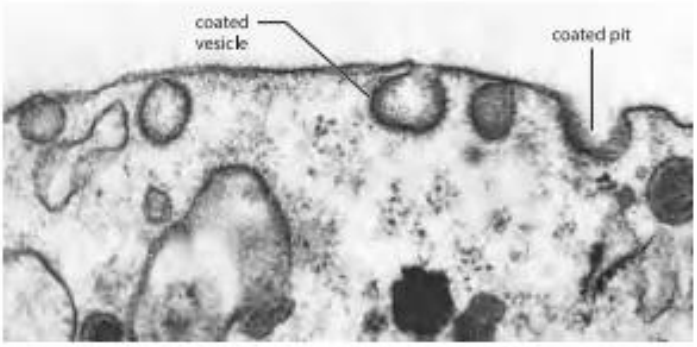
a. Phagocytosis



b. Pinocytosis



c. Receptor-mediated endocytosis



d. Micrograph of receptor-mediated endocytosis in a cell

Figure 4.11 Three methods of endocytosis. **a.** Phagocytosis occurs when the substance to be transported into the cell is large. Digestion occurs when the resulting vacuole fuses with a lysosome. **b.** Pinocytosis occurs when a macromolecule, such as a polypeptide, is transported into the cell. **c,d.** Receptor-mediated endocytosis is a form of pinocytosis. Molecules first bind to specific receptor proteins, which migrate to or are already in a coated pit. The coated vesicle that forms contains the molecules and their receptors.

Pinocytosis. **Pinocytosis** (Gk. *pinein*, "to drink") occurs when vesicles form around a liquid or around very small particles (Fig. 5.11*b*). Blood cells, cells that line the kidney tubules or the intestinal wall, and plant root cells all use pinocytosis to ingest substances.

Whereas phagocytosis can be seen with the light microscope, the electron microscope must be used to observe pinocytic vesicles, which are no larger than 0.1–0.2 µm. Still, pinocytosis involves a significant amount of the plasma membrane, because it occurs continuously. Cells do not shrink in size, because the loss of plasma membrane due to pinocytosis is balanced by the occurrence of exocytosis.

Receptor-Mediated Endocytosis. **Receptor-mediated endocytosis** is a form of pinocytosis that is quite specific, because it uses a receptor protein to recognize compatible molecules and take them into the cell. Molecules such as vitamins, peptide hormones, or lipoproteins can bind to specific receptors, found in special locations in the plasma membrane (Fig. 4.11c). This location is called a coated pit, because there is a layer of protein on the cytoplasmic side of the pit. Once formed, the vesicle is uncoated and may fuse with a lysosome. When empty, a used vesicle fuses with the plasma membrane, and the receptors return to their former location.

Receptor-mediated endocytosis is selective and much more efficient than ordinary pinocytosis. It is involved in uptake and in the transfer and exchange of substances between cells. Such as the uptake of iron from the outside of the cell, for example.

The importance of receptor-mediated endocytosis is demonstrated by a genetic disorder called familial hypercholesterolemia. Cholesterol is transported in blood by a complex of lipids and proteins called low-density lipoprotein (LDL). Ordinarily, body cells take up LDL when LDL receptors gather in a coated pit. But in some individuals, the LDL receptor is unable to bind properly to the coated pit, and the cells are unable to take up cholesterol. Instead, cholesterol accumulates in the walls of arterial blood vessels, leading to high blood pressure, occluded (blocked) arteries, and heart attacks.

Check Your Progress 4.3

1. Compare facilitated transport with active transport.
2. Explain why active transport requires energy.
3. Summarize why a cell would use bulk transport rather than active transport.

4.4 Modification of Cell Surfaces

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain the role of the extracellular matrix in an animal cell.
2. Compare the structure and function of adhesion, tight, and gap junctions in animals.
3. Explain the role of plasmodesmata in plants.

Most cells do not live isolated from other cells. Rather, they live and interact within an external environment that can dramatically affect cell structure and function. This extracellular environment is made up of large molecules produced by nearby cells and secreted from their membranes. In plants, prokaryotes, fungi, and most algae, the extracellular environment is a fairly rigid cell wall, which is consistent with a somewhat sedentary lifestyle. Animals, which tend to be more active, have a more varied extracellular environment, which can change depending on the tissue type.

Cell Surfaces in Animals

Here we examine two types of animal cell surface features: (1) the extracellular matrix outside cells and (2) the junctions between some types of cells. Both of these can connect to the cytoskeleton and contribute to communication between cells, and therefore tissue formation.

Extracellular Matrix

A protective **extracellular matrix (ECM)** is a meshwork of proteins and polysaccharides in close association with the cell that produced them (Fig. 4.12). Collagen and elastin fibers are two well-known structural proteins in the ECM; collagen resists stretching, and elastin gives the ECM resilience. Fibronectin is an adhesive protein (colored green in Figure 4.12) that binds to a protein, called integrin, in the plasma membrane. Integrins are integral membrane proteins that connect to fibronectin externally and to the actin cytoskeleton internally. Through its connections with both the ECM and the cytoskeleton, integrin plays a role in cell signaling, permitting the ECM to influence the activities of the cytoskeleton and, therefore, the shape and activities of the cell.

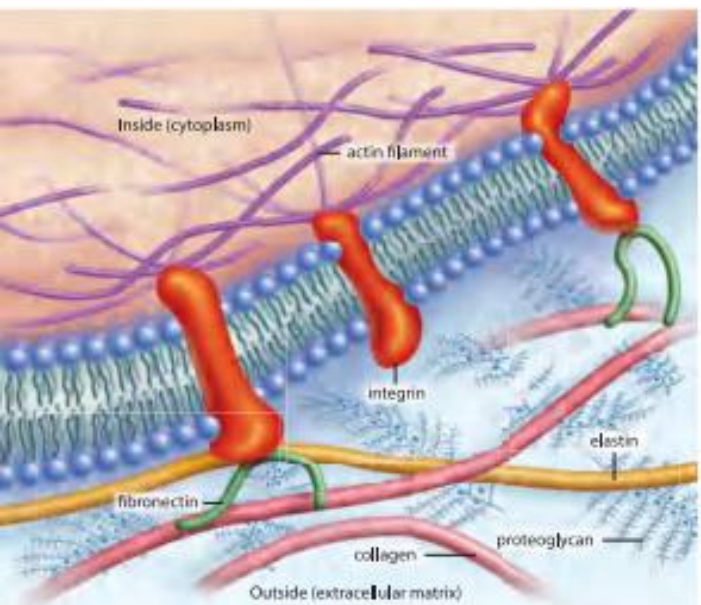


Figure 4.12 Animal cell extracellular matrix. In the extracellular matrix, collagen and elastin have a support function, while fibronectins bind to integrin, and in this way assist communication between the ECM and the cytoskeleton.

Amino sugars in the ECM form multiple polysaccharides that attach to a protein and are, therefore, called proteoglycans. Proteoglycans, in turn, attach to a very long, centrally placed polysaccharide. The entire structure, which looks like an enormous bottle brush, resists compression of the extracellular matrix. Proteoglycans assist cell signaling when they regulate the passage of molecules through the ECM to the plasma membrane, where receptors are located. During development, they help bring about differentiation by guiding cell migration along collagen fibers to specific locations. Thus, the ECM has a dynamic role in all aspects of a cell's behavior.

Later on, in the discussion of tissues, you'll see that the extracellular matrix varies in quantity and consistency. It can be quite flexible, as in loose connective tissue; semiflexible, as in cartilage; or rock solid, as in bone. The extracellular matrix of bone is hard because, in addition to the components mentioned, mineral salts (notably, calcium salts) are deposited outside the cell.

The proportion of cells to ECM also varies. In the small intestine, for example, epithelial cells constitute the majority of the tissue, and the ECM is a thin sheet beneath the cells. In bone, the ECM makes up most of the tissue, with comparatively fewer cells.

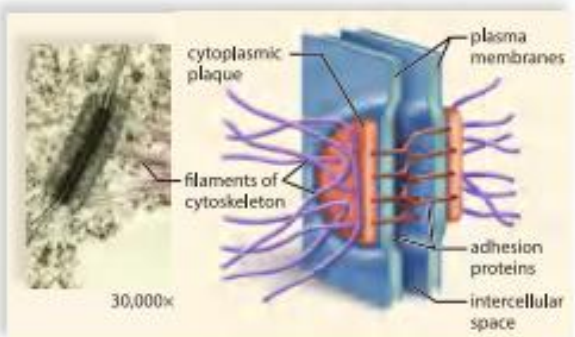
Junctions Between Cells

Certain tissues of vertebrate animals are known to have junctions between their cells that allow them to behave in a coordinated manner. Three types of junctions are shown in Figure 4.13.

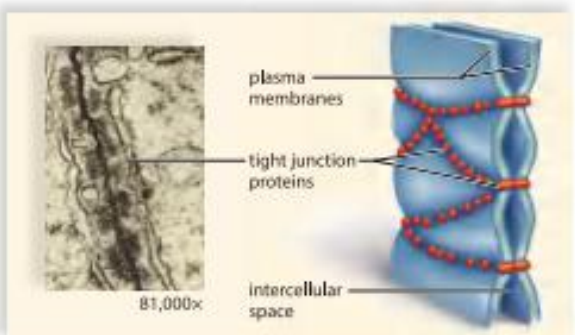
Adhesion junctions mechanically attach adjacent cells. One example of an adhesion junction is the *desmosome*. In desmosomes, internal cytoplasmic plaques firmly attach to the intermediate filament cytoskeleton within each cell and are joined between cells by integral membrane proteins called cadherins. The result is a sturdy but flexible sheet of cells. In some organs—such as the heart, stomach, and bladder, where tissues get stretched—desmosomes hold the cells together. At a *hemidesmosome*, the intermediate filaments of the cytoskeleton are attached to the ECM through integrin proteins. Adhesion junctions are the most common type of intercellular junction between skin cells.

Another type of adhesion junction between adjacent cells is the **tight junction,** which brings cells even closer than desmosomes. Tight junction proteins actually connect plasma membranes between adjacent cells together, producing a zipperlike fastening. Tissues that serve as barriers are held together by tight junctions; in the intestine, the digestive juices stay out of the rest of the body, and in the kidneys the urine stays within kidney tubules, because the cells are joined by tight junctions.

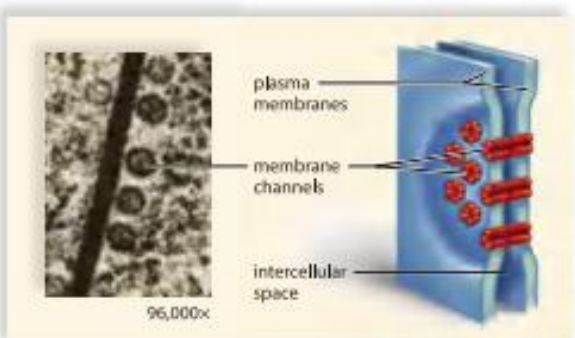
A **gap junction** allows cells to communicate. A gap junction is formed when two identical plasma membrane channels join. The channel of each cell is lined by six plasma membrane proteins. A gap junction lends strength to the cells, but it also allows small molecules and ions to pass between them. Gap junctions are important in heart muscle and smooth muscle, because they permit



a. Adhesion junction



b. Tight junction



c. Gap junction

Figure 4.13 Junctions between cells of the intestinal wall. **a.** In adhesion junctions such as a desmosome, adhesive proteins connect two cells. **b.** Tight junctions between cells form an impermeable barrier because their adjacent plasma membranes are joined and don't allow molecules to pass. **c.** Gap junctions allow communication between two cells because adjacent plasma membrane channels are joined.

the flow of ions that is required for the cells to contract as a unit.

Plant Cell Walls

In addition to a plasma membrane, plant cells are surrounded by a porous **cell wall** that varies in thickness, depending on the function of the cell.

All plant cells have a primary cell wall. The primary cell wall contains cellulose fibrils, in which microfibrils are held together by noncellulose substances. Pectins allow the wall to stretch when the cell is growing, and noncellulose polysaccharides harden the

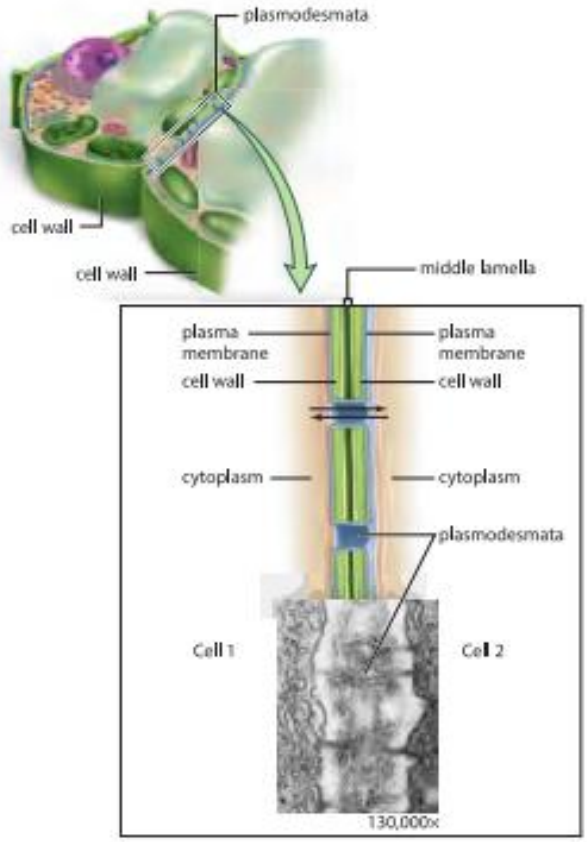


Figure 4.14 Plasmodesmata. Plant cells are joined by membrane-lined channels that contain cytoplasm. Water and small molecules can pass from cell to cell.

wall when the cell is mature. Pectins are especially abundant in the middle lamella, which is a layer of adhesive substances that holds the cells together.

Some cells in woody plants have a secondary wall that forms inside the primary cell wall. The secondary wall has a greater quantity of cellulose fibrils than the primary wall, and layers of cellulose fibrils are laid down at right angles to one another. Lignin, a substance that adds strength, is a common ingredient of secondary cell walls in woody plants.

In a plant, the cytoplasm of living cells is connected by **plasmodesmata** (sing., plasmodesma), numerous narrow, membrane-lined channels that pass through the cell wall (Fig. 4.14). Cytoplasmic strands within these channels allow direct exchange of some materials between adjacent plant cells and eventually connect all the cells within a plant. The plasmodesmata allow only water and small solutes to pass freely from cell to cell. This limitation means that plant cells can maintain their own concentrations of larger substances and differentiate into particular cell types.

Check Your Progress 4.4

1. Describe the composition of the extracellular matrix of an animal cell.
2. Explain why a cell would be connected by a tight junction, rather than a gap junction or an adhesion junction.
3. Explain the role of the plasmodesmata in plant cells.

REVIEWING *the* BIG IDEAS

BIG IDEA 2

The fluid mosaic model combines phospholipids and proteins to form a flexible, asymmetric, amphipathic, responsive, and selectively permeable membrane that often expands surface area to facilitate the movement of molecules across it. 2.B.1.b.1; 2.B.3.a-b

Molecules cross cell membranes based on their size, charge, and polarity; the diffusion of water (osmosis) across membranes is essential for cellular processes. 2.B.1.b.4; 2.B.2.a.3; 2.D.3.a

Diffusion, facilitated diffusion, active transport and endocytosis/exocytosis differ in their direction of molecular movement, assistance by specific membrane proteins, and need for free energy input. 2.B.2.a-c

BIG IDEA 3

Embedded membrane proteins provide structural, enzymatic, passage, recognition, and receptor functions for the cell. 3.B.2.b; 3.D.3.a.2

Cells are able to detect and respond to changes in their environmental using signal transduction pathways; certain diseases are caused by errors in signaling pathways. 3.D.3.a-b; 3.D.4.a

BIG IDEA 4

Membranes that surround various organelles in the cell often interconnect, allowing sequential transport and storage and bringing greater efficiency to the entire cell system. 4.A.2. a-g; 4.B.2.a.1

SUMMARIZE

AP Answering the Essential Questions

Organisms must exchange matter with the environment to carry out physiological processes such as growth and reproduction. For example, carbon moves from the environment to cells where it is incorporated into the carbohydrates, lipids, proteins, and nucleic acids we studied in Chapter 3. Like skin protects your body, membranes provide a barrier for cells, separating their internal and external environments. The molecular structure of the **cell membrane** allows it to act as a gatekeeper for the cell as it "stands guard" over what substances can enter or leave—another great example of the relationship between structure and function.

Plasma membrane structure The molecular structure of the cell membrane described by the **fluid mosaic model** explains how the membrane exhibits **selective permeability;** that is, some substances are able to move across it more easily than others. The ability of cells to regulate chemical exchanges with the environment is essential to life. We know what happens when plants—or people—don't get enough water. The major "ingredients" of cell membranes are proteins and phospholipids, with a dash of cholesterol, glycoproteins, and glycolipids. In Chapter 4 we explored how adding phosphate groups changes the properties of lipids, making them amphipathic or consisting of both polar and nonpolar regions. Consequently, **phospholipids** give membranes overall amphipathic properties, too, with hydrophilic and hydrophobic regions of the **lipid bilayer.** The fatty acid "tails" can be saturated or unsaturated hydrocarbons and, along with cholesterol embedded in the membrane, contribute to the fluidity of the membrane. To throw in a bit of evolution here, variations in the lipid composition of cell membranes reflects adaptations to specific environments; for example, some bacteria that thrive at hot temperatures have phospholipids with reduced fluidity, protecting protein activity under harsh conditions. The hydrophobic interior of the lipid bilayer acts as "quicksand" for some molecules trying to travel across the membrane.

A variety of **proteins** comprise the *mosaic* portion of cell membranes. Embedded proteins can be either hydrophobic or hydrophilic, depending on their amino acid groups. Some proteins span across the bilayer of phospholipids, whereas peripheral proteins are not embedded in the membrane but are bound to the surface of the membrane. Proteins associated with cell membranes provide six major functions: 1) transport of polar or large molecules; 2) enzymatic activity; 3) signal transduction; 4) cell-cell recognition; 5) intercellular joining; and 6) attachment of the cytoskeleton to the extracellular matrix. We will explore the functions of membrane proteins in more depth as we progress through our study of cell processes.

The cell membrane is another example of "the whole is greater than the sum of its parts" because its structure results in **emergent properties** beyond those of the individual components. One of these properties is the ability of the membrane to regulate transport of substances across it, thus maintaining dynamic homeostasis between the internal and external environments of the cell. Nonpolar molecules such as CO_2 and O_2 readily dissolve in the lipid bilayer of the membrane. However, the hydrophobic interior hinders direct passage of ions and other hydrophilic molecules such as glucose across the membrane. But transmembrane proteins serving as transport channels come to the rescue and help move these substances. The movement of vital water across membranes is facilitated by specific channel proteins cleverly called **aquaporins.**

Passive and active transport Moving substances across membranes occurs by passive or active means. **Passive transport** does not require the input of energy because spontaneous movement of molecules occurs from high to low concentrations across membranes. Means of passive transport include **diffusion, facilitated diffusion,** and **osmosis.** An example of diffusion is the movement of O_2 between the air sacs and blood capillaries in the lungs. In facilitated diffusion, molecules still move from high to low concentrations but require transport proteins; examples of facilitated diffusion are the passage of glucose through glucose transporter proteins and the Na^+ and K^+ gated channels we will learn about when we study the nervous system. Osmosis is a special type of diffusion specific to the movement of water molecules across cell membranes through aquaporins. (So, when we say that students learn from their teacher by osmosis, we really mean diffusion!) The movement of water depends on solute concentration—water will move from the area with less solute (and more water molecules) to an area with more solute (and less water). In other words, water moves from an area of higher **water potential** to an area of lower water potential. Animal and plant cells respond a little differently to the movement of water in and out of them

because of the presence of cell walls that allow plant cells to take in more water without bursting. When the concentrations of solute are equal on both sides of the membrane, no *net* movement of water occurs, but it is important to remember that water is always diffusing across a membrane in both directions. Solute concentration, however, will influence the *rate* of osmosis. Sometimes molecules must move across membranes *against* their gradients. This process, called **active transport,** requires an input of energy and the help of **transport proteins.** An example of active transport is the sodium-potassium pump which maintains electrochemical gradients across the membranes of neurons in animals for impulse transmission.

Cell signaling The multiple roles of proteins embedded in a cell membrane cannot be overemphasized. In addition to assisting the passage of molecules across the membrane, proteins also serve as **receptors** for incoming molecular signals that can change cellular behavior. All cells—and all organisms—must be able to detect and respond to stimuli, and **signaling pathways** enable organisms to coordinate their cellular activities, metabolize, and better respond to environmental change. For example, a bacterium that lives in your body responds to signaling molecules when it finds food and escapes immune cells in order to stay alive. In animals, including humans, internal signals like hormones help ensure that specific tissues develop when and how they should; in plants, external signals, such as a change in the amount of light, activate internal pathways that result in flowering. How do cells communicate with each other? How does a hormone released into the blood from the pituitary gland sitting in the middle of your brain "know" when it has reached its **target organ** to initiate a change? The answer begins with a protein embedded in a membrane.

Cells communicate with each other using **signaling molecules,** sometimes called chemical messengers. Some messengers are produced in one location and, in animals, are carried by the circulatory system to various target sites around the body. For example, the pancreas releases insulin which is transported to the liver, causing glucose to be stored as glycogen. Failure of the liver to respond appropriately results in a medical condition called diabetes. How cells respond to signaling molecules involves three steps: binding of the signaling molecule (**reception**), **transduction** of the signal, and **response** of the cell depending on what type of membrane protein is targeted. The pathway begins when the signaling molecule binds to a matching membrane receptor protein. Each cell has a mix of receptors, which gives them the ability to respond different to a variety of stimuli, and each cell is able to balance the strength of the incoming signal in order to change cellular structure or function. Once a signaling molecule and receptor interact, a cascade of events—called transduction—occurs that usually amplifies the signal; during transduction, a series of relay proteins inside the cytoplasm of the cell activate a target protein(s), resulting in a cellular response. The cellular response can change the shape of movement of the cell, alter cellular metabolism or function, or activate a specific gene. We will explore cell signaling in more depth when we study concepts in Chapter 9 (mitosis and the cell cycle) and Chapter 13 (gene expression).

In Chapter 4 we learned about the various **organelles** in eukaryotic cells that carry out specific functions. A major characteristic that distinguishes eukaryotes from prokaryotes is the presence of membrane-bound organelles in addition to DNA housed within a nucleus. We have already seen how the plasma membrane separates the whole cell from its environment and acts as a gatekeeper for the passage of substances in and out of the cell. In addition to the membrane at its outer surface, the eukaryotic cell uses internal membranes to divide the cell into compartments to provide for different local environments and, consequently, to support specific metabolic functions such as photosynthesis and cellular respiration. These internal membranes are composed of the same molecules as the outer plasma membrane; however, each type of membrane has a unique composition of phospholipids and proteins to support the specific function of the organelle. For example, enzymes embedded in the membranes of mitochondria play a vital role in the synthesis of ATP.

AP FOCUS REVIEW GUIDE

Complete the activities in Chapter 2 of your AP Focus Review Guide to review content essential for your AP exam.

ASSESS

Choose the best answer for each question.

4.1 Plasma Membrane Structure and Function

1. In the fluid-mosaic model, the fluid properties are associated with the nature of the _____ and the mosaic pattern is established by the _____.
   a. nucleic acids; phospholipids
   b. phospholipids; embedded proteins
   c. embedded proteins; cholesterol
   d. phospholipids; nucleic acids
2. Which of the following is not a function of proteins present in the plasma membrane?
   a. Proteins assist the passage of materials into the cell.
   b. Proteins interact with and recognize other cells.
   c. Proteins bind with specific hormones.
   d. Proteins produce lipid molecules.
3. The carbohydrate chains projecting from the plasma membrane are involved in
   a. adhesion between cells.
   b. reception of molecules.
   c. cell-to-cell recognition.
   d. All of these are correct.

4.2 Passive Transport Across a Membrane

4. When a cell is placed in a hypotonic solution,
   a. solute exits the cell to equalize the concentration on both sides of the membrane.
   b. water exits the cell toward the area of lower solute concentration.
   c. water enters the cell toward the area of higher solute concentration.
   d. there is no net movement of water or solutes.
5. When a cell is placed in a hypertonic solution,
   a. solute exits the cell to equalize the concentration on both sides of the membrane.
   b. water exits the cell toward the area of lower solute concentration.
   c. water exits the cell toward the area of higher solute concentration.
   d. there is no net movement of water or solute.
6. A plant cell that is placed in a hypertonic solution would experience
   a. crenation.
   b. an increase in turgor pressure.
   c. plasmolysis.
   d. no net changes.
7. Which of the following is incorrect regarding facilitated diffusion?
   a. It is a passive process.
   b. It allows the movement of molecules from areas of low concentration to areas of high concentration.
   c. It may use either channel or carrier proteins.

d. It allows the rapid transport of glucose across the membrane.

4.3 Active Transport Across a Membrane

8. The sodium-potassium pump
   a. helps establish an electrochemical gradient across the membrane.
   b. concentrates sodium on the outside of the membrane.
   c. uses a carrier protein and chemical energy.
   d. All of these are correct.
9. Which of the following processes is involved in the bulk transport of molecules out of the cell?
   a. phagocytosis
   b. pinocytosis
   c. receptor-mediated endocytosis
   d. exocytosis
10. Which process uses special proteins on the surface of the membrane to identify specific molecules for transport into the cell?
    a. phagocytosis
    b. pinocytosis
    c. receptor-mediated endocytosis
    d. exocytosis

4.4 Modification of Cell Surfaces

11. The extracellular matrix
    a. assists in the movement of substances across the plasma membrane.
    b. prevents the loss of water when cells are placed in a hypertonic solution.
    c. has numerous functions that affect the shape and activities of the cell that produced it.
    d. All of these are correct.
12. Which of the following junctions allows for cytoplasm-to-cytoplasm communication between cells?
    a. adhesion junctions
    b. tight junctions
    c. gap junctions
    d. None of these are correct.

ENGAGE

AP Applying the Big Ideas

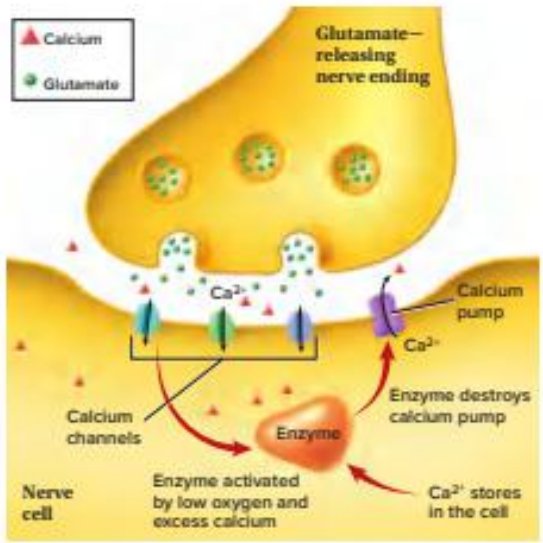
1. BIG IDEA 2 Flexible plasma membranes consist of a variety of molecules whose interactions allow for cells to operate more efficiently and effectively.
   a. **Describe** the structure of the plasma membrane of cells.
   b. **Explain** how structures of the components of the plasma membrane connect to its function as a selectively permeable barrier between the cell and its exterior and within the cell itself.

2. BIG IDEA 3 Cells communicate with each other through direct contact with other cells from a distance or via chemical signaling. In a paragraph, explain this phenomena based on the evidence found in plant cells.
   a. **Describe** what plasmodesmata are and how they function.
   b. **Explain** how plasmodesmata offer evidence of cell communication.

3. BIG IDEA 4 **Propose an explanation** of how variation in molecular units provides cells with a wider range of functions by choosing TWO of the following examples as evidence.
   - A sample of bone tissue was thick with abundant extracellular matrix, while a sample of small intestine epithelial cells contained a thin, flexible sheet of ECM.
   - Two different types of tissue samples were collected and the proteins integrated in their membranes were analyzed and found to vary in both quantity and variety.
   - The pH inside lysosomes of animal cells is significantly lower than that of cytoplasm. Lysosomal enzymes are found to only work inside the lysosome and not on the cytoplasm-side of the plasma membrane.

AP Applying the Science Practices

How are protein channels involved in the death of nerve cells after a stroke? A stroke occurs when a blood clot blocks the flow of oxygen-containing blood in a portion of the brain. Nerve cells in the brain that release glutamate are sensitive to the lack of oxygen and release a flood of glutamate when oxygen is low. During the glutamate flood, the calcium pump is destroyed. This affects the movement of calcium ions into and out of nerve cells. When cells contain excess calcium, homeostasis is disrupted.



*Data obtained from: Choi, D.W. 2005. Neurodegeneration: cellular defenses destroyed. *Nature* 433:696-698.

Think Critically ▶3 ▶6

1. **Interpret** how the glutamate flood destroys the calcium pump.
2. **Predict** what would happen if Ca^{2+} levels were lowered in the nerve cell during a stroke.

1

Metabolism: Energy and Enzymes

Both the impala and the cheetah depend on metabolic reactions to convert the solar energy captured by photosynthesizers.

Chapter Outline

AP All life on Earth ultimately depends on the flow of energy coming from the sun. Photosynthesizing grasses on an African plain provide impalas with organic building blocks and the energy they need to avoid being caught by a cheetah. Eating impalas provides cheetahs with food and the energy they need to be quick enough to catch impalas.

You, like the cheetah, consume plants and animals that get their energy either directly or indirectly from the sun. Solar energy is concentrated enough to allow plants to photosynthesize and make biological molecules, which in turn provide a continual supply of food for you and other creatures within the biosphere.

Living organisms are bound by the laws of thermodynamics. For example, during digestion, energy from chemical bonds in food is transformed into energy used for metabolic processes and work, as well as heat that is lost to the environment.

Many of these metabolic reactions would either not occur or occur too slowly without the help of metabolic assistants called enzymes. Without enzymes, living organisms would not be able to carry out many of the general characteristics of life. As we will see, enzymes play an important role in how our cells, and ultimately our bodies, function.

As you read through the chapter, think about these Essential Questions:

1. How does the structure of ATP enable the molecule to power cellular work? 1.B.1.a.3
2. How do the first and second laws of thermodynamics relate to cell metabolism? 1.A.1.a-h
3. How do enzymes facilitate the chemical reactions that constitute metabolism? 4.A.1.b,c,d
4. How can changes in environmental conditions and other factors affect the rate of an enzyme-catalyzed reaction? 4.A.1.b,c,d

Following *the* BIG IDEAS

BIG IDEA 1	Cells have evolved to metabolize energy in order to support cellular processes important to life.
BIG IDEA 2	Understanding the principles of metabolism and energy transformation and transfer helps us understand how cells and organisms function.
BIG IDEA 4	Energy flows through biological systems, resulting in the ability to do work, even though with each transfer energy is lost as heat.

1.1 Cells and the Flow of Energy

Learning Outcomes

Upon completion of this section, you should be able to

1. Compare potential and kinetic energy.
2. Describe the first and second laws of thermodynamics.
3. Examine how the organization and structure of living organisms are related to heat and entropy.

To maintain their structural organization and carry out metabolic activities, cells—and organisms comprised of cells—need a constant supply of energy. **Energy** is defined as the ability to do work or bring about a change. The general characteristics of life, including growth, development, metabolism, and reproduction, all require energy.

Organic nutrients, made by photosynthesizing producers (algae, plants, and some bacteria), directly provide organisms with energy by capturing energy from sunlight. Considering that producers use light energy to produce organic nutrients, the majority of life on Earth is ultimately dependent on solar energy.

Forms of Energy

Energy occurs in two forms: kinetic and potential energy. **Kinetic energy** is the energy of motion, as when water flows over a waterfall, a ball rolls down a hill, or a moose walks through grass. **Potential energy** is stored energy whose capacity to accomplish work is not being used at the moment. The food we eat has potential energy, because the energy stored in chemical bonds can be converted into various types of kinetic energy. Food is a form of potential energy called **chemical energy,** because it is composed of organic molecules, such as carbohydrates, proteins, and fat. When a moose walks, it converts chemical energy into a type of kinetic energy called **mechanical energy** (Fig. 1.1).

Two Laws of Thermodynamics

In nature, energy flows in biological systems. Figure 6.1 illustrates the flow of energy in a terrestrial ecosystem. Plants capture only a small portion of solar energy, and much of it dissipates as **heat.** When plants photosynthesize and then make use of the food they produce, more heat results. Even with this considerable heat loss, there is enough remaining to sustain a moose and the other organisms in an ecosystem. As organisms metabolize nutrient molecules, all the captured solar energy eventually dissipates as heat. Therefore, we can see that energy flows through the ecosystem and does not cycle within it.

Two **laws of thermodynamics,** formulated by early energy researchers, explain why energy flows through ecosystems and through cells:

> The first law of thermodynamics—the law of conservation of energy—states that energy cannot be created or destroyed, but it can be changed from one form to another.

When leaf cells photosynthesize, they use solar energy to form carbohydrate molecules from carbon dioxide gas and water. Carbohydrates are energy-rich molecules, because they have many bonds that store energy; carbon dioxide and water are energy-poor molecules, because of the relative lack of bonds.

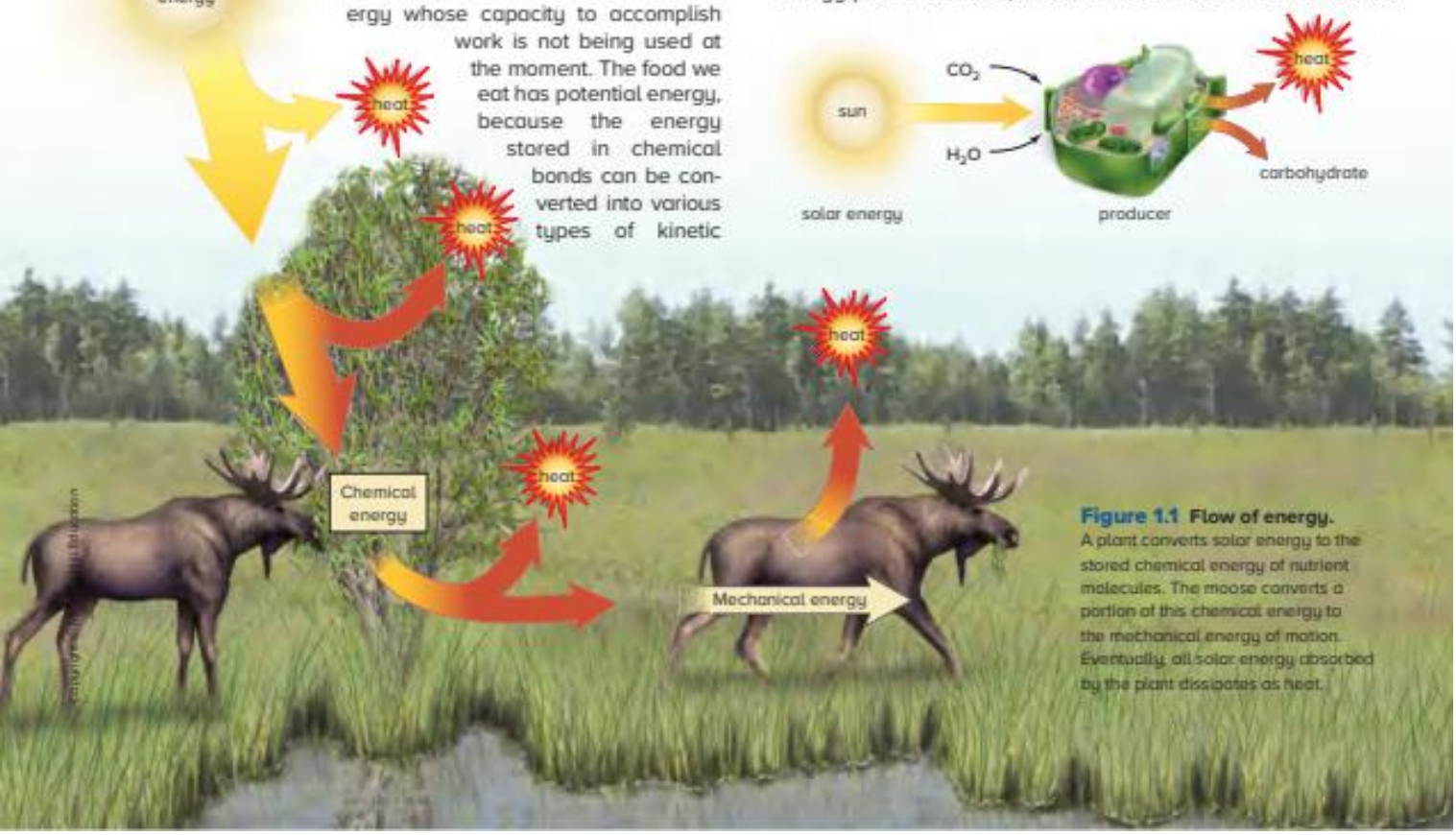
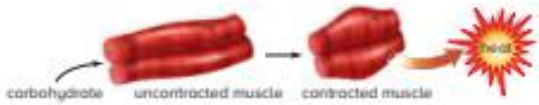


Figure 1.1 Flow of energy.
A plant converts solar energy to the stored chemical energy of nutrient molecules. The moose converts a portion of this chemical energy to the mechanical energy of motion. Eventually, all solar energy absorbed by the plant dissipates as heat.

Not all of the captured solar energy becomes carbohydrates; some becomes heat.

Obviously, plant cells do not create the energy they use to produce carbohydrate molecules; that energy comes from the sun. Is any energy destroyed? No, because the heat the plant cells give off is also a form of energy. Similarly, as a moose walks, it uses the potential energy stored in carbohydrates to kinetically power its muscles. As its cells use this energy, none is destroyed, but each energy exchange produces some heat, which dissipates into the environment.



The second law of thermodynamics therefore applies to living systems:

> The second law of thermodynamics states that energy cannot be changed from one form to another without a loss of usable energy.

In our example, this law is upheld because some of the solar energy taken in by the plant and some of the chemical energy within the nutrient molecules taken in by the moose becomes heat. When heat dissipates into the environment, it is no longer usable—that is, it is not available to do work. Each energy transformation moves us closer to a condition where all usable forms of energy become heat that is lost to the environment. Heat that dissipates into the environment cannot be captured and converted to one of the other forms of energy.

As a result of the second law of thermodynamics, no process requiring a conversion of energy is ever 100% efficient. Much of the energy is lost in the form of heat. In automobiles, the internal combustion engine is between 20% and 30% efficient in converting chemical energy stored in gasoline into mechanical energy used to drive the wheels. The majority of energy is lost as dissipated heat. Cells are capable of about 40% efficiency, with the remaining energy being given off to the surrounding environment as heat.

Cells and Entropy

The second law of thermodynamics can be stated another way: Every energy transformation makes the universe less organized, or structured, and more disordered, or chaotic. The term **entropy** (Gk. *entrope*, "a turning inward") is used to indicate the relative amount of disorganization. Because the processes that occur in cells are energy transformations, the second law means that every process that occurs in cells always does so in a way that increases the total entropy of the universe. The second law means that each cellular process makes less energy available to do useful work in the future.

Figure 1.2 shows two processes that occur in cells. The second law of thermodynamics tells us that glucose tends to break apart into carbon dioxide and water over time. Why? Because glucose is more organized and structured, and therefore less stable, than its breakdown products. Also, hydrogen ions on one side of a membrane tend to move to the other side unless they are prevented from doing so, because when they are distributed randomly, entropy has increased. As an analogy, you know from experience that a neat room is more organized but less stable than a messy room, which

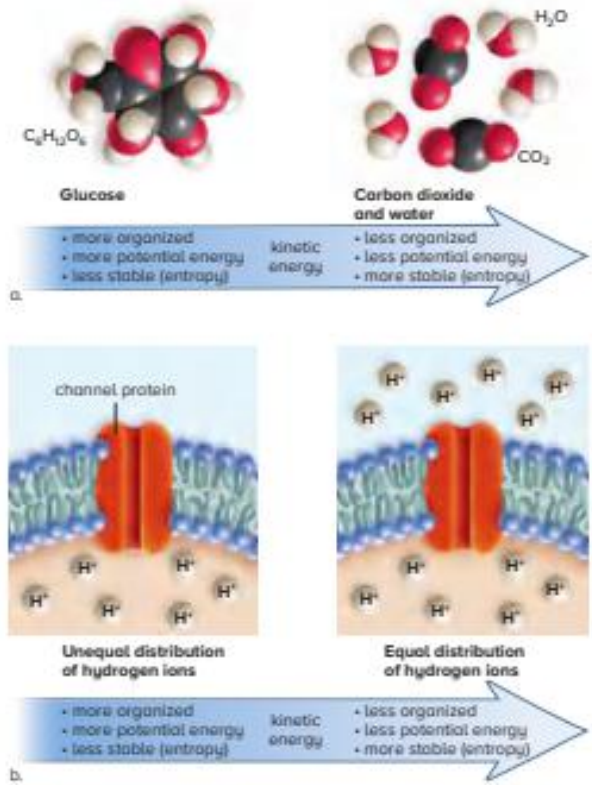


Figure 1.2 Cells and entropy. The second law of thermodynamics tells us that (**a**) glucose, which is more organized, tends to break down to carbon dioxide and water, which are less organized. **b.** Similarly, hydrogen ions (H^+) on one side of a membrane tend to move to the other side, so that the ions are randomly distributed. Both processes result in an increase in entropy.

is disorganized but more stable. Energy is required to return a messy room to a more organized, or neat, state.

On the other hand, you know that some cells can make glucose out of carbon dioxide and water, and all cells can actively move ions to one side of the membrane. How do they do it? By the input of energy from an outside source. Photosynthesizing producers use energy from sunlight to create organized structure in biological molecules. Organisms that consume producers are then able to use this potential energy to kinetically drive their own metabolic processes. Thus, living organisms depend on a constant supply of energy ultimately provided by the sun. The ultimate fate of all solar energy in the biosphere is to become randomized in the universe as heat. A living cell can function because it serves as a temporary repository of order, purchased at the cost of a constant flow of energy.

Check Your Progress 1.1

1. Provide an example of a conversion from potential to kinetic energy.
2. Summarize how the first and second laws of thermodynamics relate to cells.
3. Explain the importance of entropy to a living system.

1.2 Metabolic Reactions and Energy Transformations

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain how the ATP cycle involves both endergonic and exergonic reactions.
2. Describe how energy is stored in a molecule of ATP.
3. Examine how cells use ATP to drive energetically unfavorable reactions.

All living organisms maintain their structure and function through chemical reactions. **Metabolism** is the sum of all the chemical reactions that occur in a cell. **Reactants** are substances that participate in a reaction, while **products** are substances that form as a result of a reaction. In the reaction A + B → C + D, A and B are the reactants, while C and D are the products. Whether a reaction occurs spontaneously—that is, without an input of energy—depends on how much energy is left after the reaction. Using the concept of entropy, or disorder, a reaction occurs spontaneously if it increases the entropy of the universe.

In cell biology, which occurs on a small scale, we are less concerned about the entire universe, which is vast. In such specific instances, cell biologists use the concept of free energy instead of entropy. **Free energy** (also called "delta G," or ΔG) is the amount of energy left to do work after a chemical reaction has occurred. The change in free energy after a reaction occurs is determined by subtracting the free energy content of the reactants from that of the products. A negative result ($-\Delta G$) means that the products have less free energy than the reactants, and the reaction will occur spontaneously. In our reaction, if C and D have less free energy than A and B, then the reaction occurs without additional input of energy.

Metabolism includes both spontaneous reactions and energy-requiring reactions. **Exergonic reactions** are spontaneous and release energy, while **endergonic reactions** require an input of energy to occur. In the body, many reactions, such as protein and carbohydrate synthesis, are endergonic. For these nonspontaneous reactions to occur during metabolism, they must be coupled with exergonic reactions, such that a net spontaneous reaction results. Many biological processes use ATP as an energy carrier between exergonic and endergonic reactions.

ATP: Energy for Cells

ATP (**adenosine triphosphate**) is the common energy currency of cells; when cells require energy, they use ATP. A sedentary oak tree, a flying bat, and a human require vast amounts of ATP. The more active the organism, the greater the demand for ATP. However, cells do not keep a large store of ATP molecules on hand. Instead, they constantly regenerate ATP using **ADP** (**adenosine diphosphate**) and inorganic phosphate, Ⓟ. This is called the ATP cycle (Fig. 1.3). This cycle is powered by the breakdown of glucose and other biomolecules during cellular respiration. However, according to the second law of thermodynamics, this process is not very efficient. Only 39% of the free energy stored in the chemical bonds of a glucose molecule is transformed to ATP; the rest is lost as heat.

There are many biological advantages to the use of ATP as an energy carrier in living systems. ATP provides a common and universal energy currency because it can be used in many different types of reactions. Also, when ATP is converted to energy, ADP, and Ⓟ, the amount of energy released is sufficient to efficiently power most biological functions. In addition, ATP breakdown can be coupled to endergonic reactions in such a way that it minimizes energy loss.

Structure of ATP

ATP is a nucleotide composed of the nitrogen-containing base adenine and the 5-carbon sugar ribose (together called adenosine) and three phosphate groups. The three phosphates of ATP repel each other, creating instability and potential energy (Fig. 1.3). ATP is called a "high-energy" molecule, because a phosphate group can be easily removed. Under cellular conditions, the amount of energy released when ATP is hydrolyzed to ADP + Ⓟ is about 7.3 kcal per **mole.** A mole is a unit of measurement in chemistry that is equal to the molecular weight of a molecule expressed in grams.

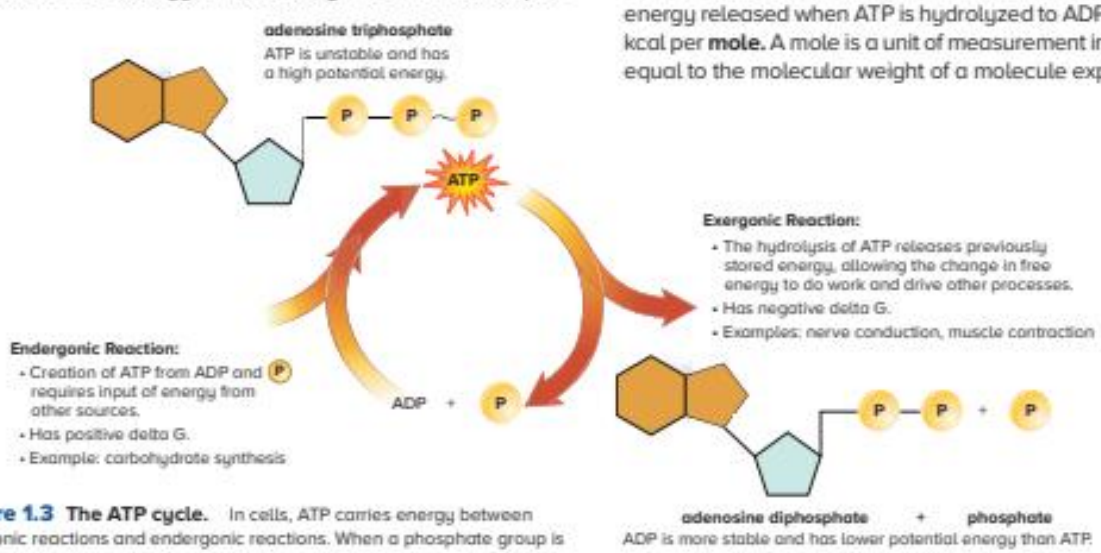


Figure 1.3 The ATP cycle. In cells, ATP carries energy between exergonic reactions and endergonic reactions. When a phosphate group is removed by hydrolysis, ATP releases the appropriate amount of energy for most metabolic reactions.

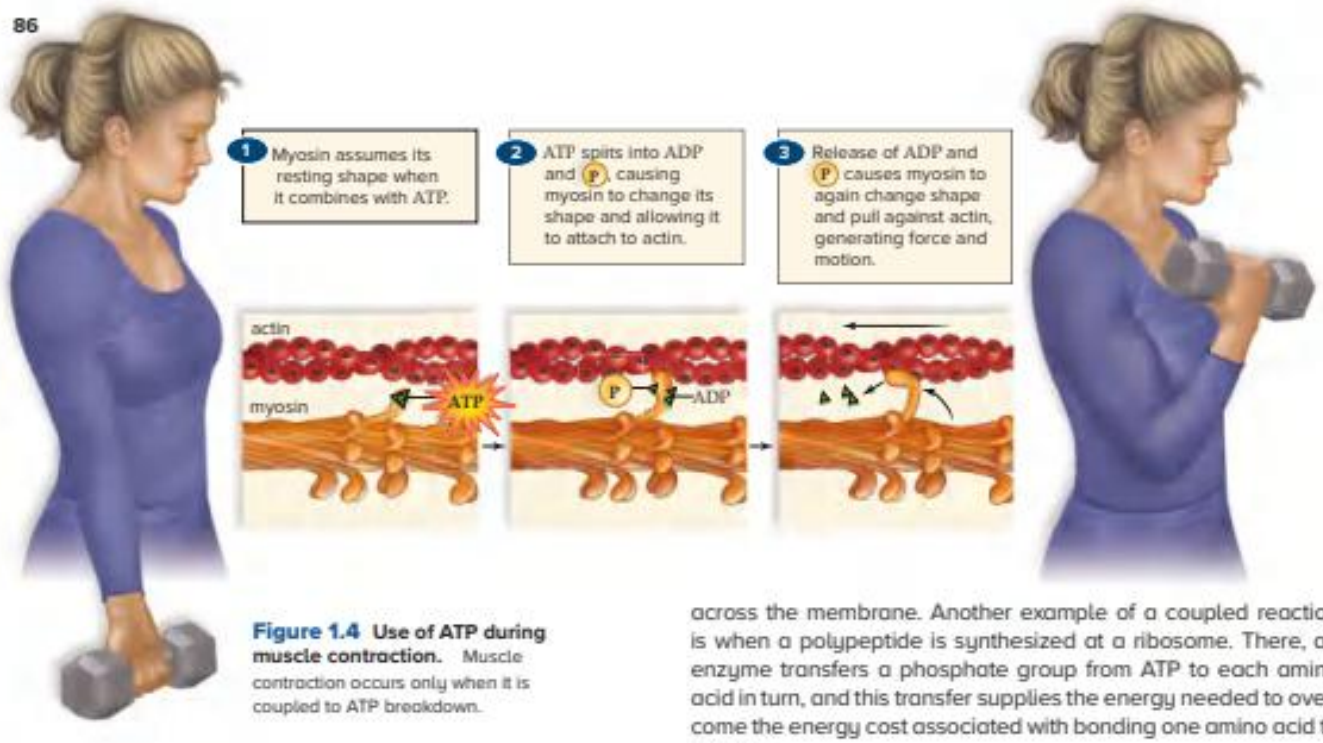
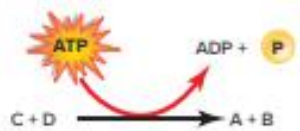


Figure 1.4 Use of ATP during muscle contraction. Muscle contraction occurs only when it is coupled to ATP breakdown.

Coupled Reactions

How can the energy released by ATP hydrolysis be transferred to an endergonic reaction that requires energy and therefore would not ordinarily occur? In other words, how does ATP act as a carrier of chemical energy? How can that energy be transferred efficiently to an energetically unfavorable reaction?

The answer is that ATP breakdown is *coupled* to the energy-requiring reaction, such that both the energetically favorable and unfavorable reactions occur in the same place, at the same time. Usually, the energy-releasing reaction is the hydrolysis of ATP. Because the cleavage of ATP's phosphate groups releases more energy than the amount consumed by the energy-requiring reaction, the net reaction is exergonic, entropy increases, and both reactions proceed. The simplest way to represent a coupled reaction is like this:



This reaction tells you that coupling occurs, but it does not show how coupling is achieved. A cell has two main ways to couple ATP hydrolysis to an energy-requiring reaction: ATP is used to energize a reactant, or ATP is used to change the shape of a reactant. Both can be achieved by transferring a phosphate group to the reactant, so that the product is *phosphorylated*.

For example, when a polar ion moves across the nonpolar plasma membrane of a cell, it requires a carrier protein. In order to make the carrier protein assume a shape conducive to the ion, ATP is hydrolyzed; then, instead of the last phosphate group floating away, an enzyme attaches it to a carrier protein. The negatively charged phosphate causes the protein to undergo a change in shape that allows it to interact with and move the ion across the membrane. Another example of a coupled reaction is when a polypeptide is synthesized at a ribosome. There, an enzyme transfers a phosphate group from ATP to each amino acid in turn, and this transfer supplies the energy needed to overcome the energy cost associated with bonding one amino acid to another.

Through coupled reactions, ATP drives forward the energetically unfavorable processes that must occur to create the high degree of order and structure essential for life. Macromolecules must be made and organized to form cells and tissues; the internal composition of the cell and the organism must be maintained; and movement of cellular organelles and the organism must occur if life is to continue.

Functions of ATP in Cells

In living systems, ATP can be used for the following:

Chemical work. ATP supplies the energy needed to synthesize macromolecules (anabolism) that make up the cell, and therefore the organism.

Transport work. ATP supplies the energy needed to pump substances across the plasma membrane.

Mechanical work. ATP supplies the energy needed to permit muscles to contract, cilia and flagella to beat, chromosomes to move, and so forth. In most cases, ATP is the immediate source of energy for these processes.

Figure 1.4 shows an example of how ATP hydrolysis provides the necessary energy for muscle contraction. During muscle contraction, myosin filaments pull actin filaments to the center of the cell, and the muscle shortens. First, the myosin head combines with ATP (three connected green triangles) and takes on its resting shape. Next, ATP breaks down to ADP (two connected green triangles) plus Ⓟ (one green triangle). The resulting change in shape allows myosin to attach to actin. Finally, the release of ADP and Ⓟ from the myosin head causes it to change its shape again and pull on the actin filament. The cycle then repeats. During this cycle, chemical energy has been transformed to mechanical energy, and entropy has increased.

Check Your Progress 1.2

1. Explain why ATP is an effective short-term energy storage molecule.
2. Summarize the ATP cycle.
3. Examine how transferring a phosphate from ATP changes a molecule's structure and function.

1.3 Metabolic Pathways and Enzymes

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain the purpose of a metabolic pathway and how enzymes help regulate it.
2. Recognize how enzymes influence the activation energy rates of a chemical reaction.
3. Distinguish between conditions and factors that affect an enzyme's rate of reaction.

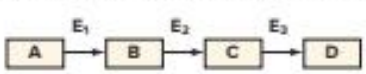
The chemical reactions that constitute metabolism would not easily occur without the use of organic catalysts called enzymes. An **enzyme** is a protein molecule that speeds a chemical reaction without itself being affected by the reaction. Enzymes allow reactions to occur under mild conditions, and they regulate metabolism, partly by eliminating nonspecific side reactions.

Not all enzymes are proteins. **Ribozymes,** which are made of RNA instead of proteins, can also serve as biological catalysts. Ribozymes are involved in the synthesis of RNA and the synthesis of proteins at ribosomes.

Chemical reactions do not occur haphazardly in healthy cells; they are usually part of a **metabolic pathway,** a series of linked reactions. Metabolic pathways begin with a particular reactant and end with a final product. Many specific steps can be involved in a metabolic pathway, and each step is a chemical reaction catalyzed by an enzyme.The reactants in an enzymatic reaction are called the **substrates** for that enzyme. The substrates for the first reaction are converted into products, and those products then serve as the substrates for the next enzyme-catalyzed reaction. One reaction leads to the next reaction in an organized, highly regulated manner.

This arrangement makes it possible for one pathway to interact with several others, because different pathways may have several molecules in common. Also, metabolic pathways are useful for releasing and capturing small increments of molecular energy rather than releasing it all at once. Ultimately, enzymes in metabolic pathways enable cells to regulate and respond to changing environmental conditions.

The diagram below illustrates a simple metabolic pathway:



In this diagram, A is the substrate for E_1, and B is the product. Now B becomes the substrate for E_2, and C is the product. This process continues until the final product, D, forms. Any one of the molecules (A–D) in this metabolic pathway could also be a reactant in another pathway. Many of the metabolic pathways in living organisms are highly branched, and interactions between metabolic pathways are very common. It is important to note that each step in the metabolic pathway can be regulated because each step requires an enzyme. The specificity of enzymes allows the regulation of metabolism. The presence of particular enzymes helps determine which metabolic pathways are operative. In addition, some substrates can produce more than one type of product, depending on which pathway is open to them. Therefore, which enzyme is present determines which product is produced, as well as determining the direction of metabolism, without several alternative pathways being activated. As we will see, the ability to regulate these pathways gives our cells fine control over how they respond in a changing environment and helps maximize cell efficiency.

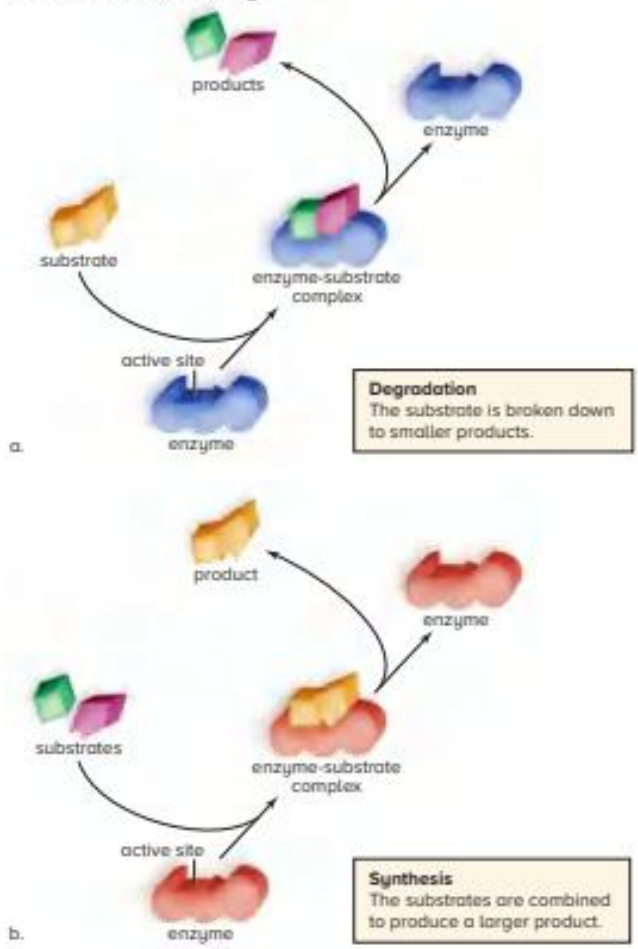


Figure 1.5 Enzymatic actions. Enzymes have an active site where the substrate(s) specifically fit together, so that the reaction will occur. Following the reaction, the product or products are released, and the enzyme is free to act again. Certain enzymes carry out (**a**) degradation, and others carry out (**b**) synthesis.

Enzyme-Substrate Complex

In most instances, only one small part of the enzyme, called the **active site,** associates directly with the substrate (Fig. 1.5). In the active site, the enzyme and substrate are positioned in such a way that they more easily fit together, seemingly as a key fits a lock. However, an active site differs from a lock and key because it undergoes a slight change in shape to accommodate the substrate(s). This is called the **induced fit model,** because the enzyme is induced to undergo a slight alteration to achieve optimum fit for the substrates.

The change in shape of the active site facilitates the reaction that now occurs. After the reaction has been completed, the product or products are released, and the active site returns to its original state, ready to bind to another substrate molecule. Only a small amount of enzyme is actually needed in a cell, because enzymes are not used up by the reaction; they merely enable it to happen more quickly.

Some enzymes do more than simply form a complex with their substrate(s); they participate in the reaction. Trypsin digests protein by breaking peptide bonds. The active site of trypsin contains three amino acids with *R* groups that actually interact with members of the peptide bond—first to break the bond and then to introduce the components of water. This illustrates that the formation of the enzyme-substrate complex is very important in speeding the reaction. Because enzymes bind only with their substrates, they are sometimes named for their substrates and usually end in *-ase*. For example, lipase is involved in hydrolyzing lipids.

Energy of Activation

Molecules frequently do not react with one another unless they are activated in some way. In the lab, for example, in the absence of an enzyme, molecules may be heated in order to increase the number of effective collisions. The energy that must be added to cause molecules to react with one another is called the **energy of activation** (E_a). Activation energy is essential to keep molecules from spontaneously degrading within the cell. Figure 1.6 shows that an enzyme effectively lowers E_a, thus reducing the energy needed for a chemical reaction to begin. It is important to note that the enzyme has no effect on the energy content of the product; rather, it only influences the rate of the reaction. Reducing the energy of activation increases the rate at which the reaction may occur. For this reason, enzymes are often referred to as catalysts of chemical reactions.

Factors Affecting Enzymatic Speed

Generally, enzymes work quickly, and in some instances they can increase the reaction rate more than 10 million times. The rate of a reaction is the amount of product produced per unit time. This rate depends on how much substrate is available to associate at the active sites of enzymes. Therefore, increasing the amount of substrate and the amount of enzyme can increase the rate of the reaction. Any factor that alters the shape of the active site—such as pH, temperature, or an inhibitor—can cause a change in the shape of the enzyme, called **denaturation.** Denaturation prevents an enzyme from binding to its substrate efficiently and thus can decrease the rate of a reaction. Thus, enzymes require specific conditions to be met in order to be fully operational. In fact, some enzymes require additional molecules called cofactors, which help speed the rate of the reaction, because they help bind the substrate to the active site, or they participate in the reaction at the active site.

Substrate Concentration

Molecules must collide to react. Generally, enzyme activity increases as substrate concentration increases, because there are more collisions between substrate molecules and the enzyme. As more substrate molecules fill active sites, more product results per unit of time. But when the active sites are filled almost continuously with substrate, the rate of the reaction can no longer increase. Maximum rate has been reached.

Just as the amount of substrate can increase or limit the rate of an enzymatic reaction, so the amount of active enzyme can also increase or limit the rate of an enzymatic reaction. Therefore, sufficient concentrations of substrate and enzymes are necessary to achieve maximum reaction rate.

Optimal pH

Each enzyme also has an optimal pH at which the reaction rate is highest. Figure 1.7 shows the optimal pH for the enzymes pepsin and trypsin. At their respective pH values, each enzyme can maintain its normal structural configuration, which enables optimum function. The globular structure of an enzyme is dependent on interactions, such as

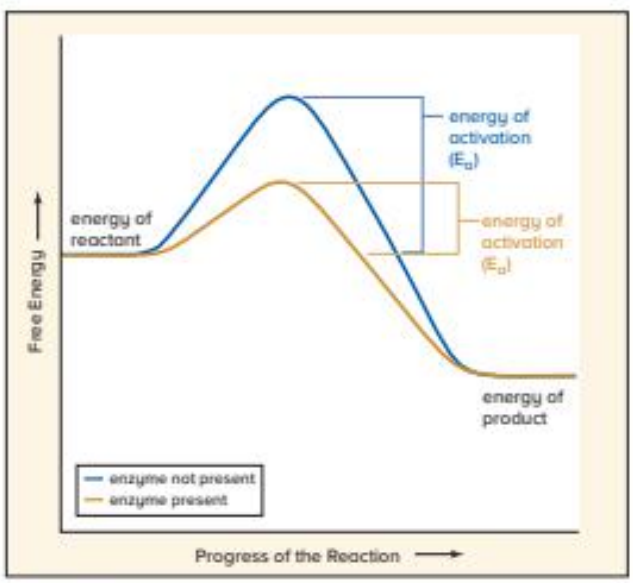


Figure 1.6 Energy of activation (E_a). Enzymes speed the rate of reactions, because they lower the amount of energy required for the reactants to activate. Even spontaneous reactions like this one, in which the energy of the product is less than the energy of the reactant, speed up when an enzyme is present.

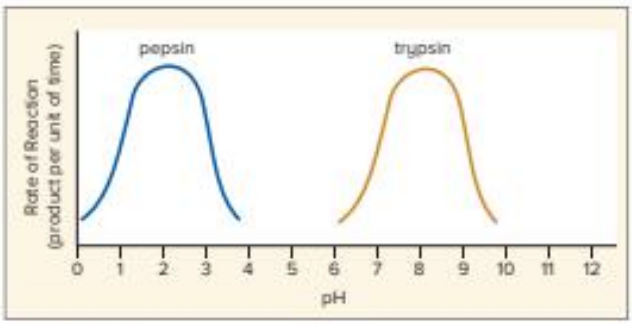


Figure 1.7 The effect of pH on rate of reaction. The optimal pH for pepsin, an enzyme that acts in the stomach, is about 2, while the optimal pH for trypsin, an enzyme that acts in the small intestine, is about 8. Enzyme shape is best maintained at the optimal pH, which allows it to function best and bind with its substrates.

hydrogen bonding, between *R* groups. A change in pH can alter the ionization of these side chains, causing the enzyme to denature. Under extreme conditions of pH, the enzyme loses its structure and becomes inactive.

Temperature

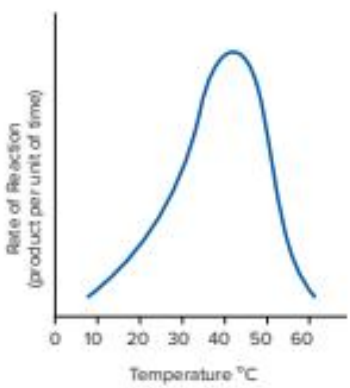
Typically, as temperature rises, enzyme activity increases (Fig. 1.8*a*). This occurs because warmer temperatures cause more effective collisions between enzyme and substrate. The body temperature of an animal seems to affect whether it is normally active or inactive (Fig. 1.8*b*, *c*). It has been suggested that mammals are more prevalent today than reptiles because they maintain a warm internal temperature that allows their enzymes to work at a rapid rate.

In the laboratory and in your body, if the temperature rises beyond a certain point, enzyme activity eventually levels out and then declines rapidly, because the enzyme is denatured. Exceptions to this generalization do occur. For example, some prokaryotes can live in hot springs because their enzymes do not denature. These organisms are responsible for the brilliant colors of the hot springs. Another exception involves the coat color of animals. Siamese cats have inherited a mutation that causes an enzyme to be active only at cooler body temperatures. The enzyme's activity causes the cooler regions of the body—the face, ears, legs, and tail—to be dark in color (Fig. 1.9). The coat color pattern in several other animals can be explained similarly.

Enzyme Cofactors and Coenzymes

Many enzymes require the presence of an inorganic ion or a nonprotein organic molecule at the active site in order to work properly; these necessary ions or molecules are called **cofactors** (Fig. 1.10). The inorganic ions include metals such as copper, zinc, or iron. The nonprotein organic molecules are called **coenzymes.** These cofactors participate in the reaction and may even accept or contribute atoms to the reactions. Examples of these are **NAD$^+$** (**nicotinamide adenine dinucleotide**), **FAD** (**flavin adenine dinucleotide**), and **NADP$^+$** (**nicotinamide adenine dinucleotide phosphate**), each of which plays a significant role in either cellular respiration or photosynthesis.

Vitamins are often components of coenzymes. **Vitamins** are relatively small, organic molecules that are required in trace amounts in our diet and in the diets of other animals for synthesis of coenzymes. The vitamin becomes part of a coenzyme's molecular structure. For example, the vitamin niacin is part of the coenzyme NAD$^+$ and riboflavin (B_2) is a component of the coenzyme FAD. If a vitamin is not



a. Rate of reaction as a function of temperature

b. Body temperature of ectothermic animals often limits rates of reactions.

c. Body temperature of endothermic animals promotes rates of reactions.

Figure 1.8 The effect of temperature on rate of reaction. **a.** Usually, the rate of an enzymatic reaction doubles with every 10°C rise in temperature. This enzymatic reaction is maximum at about 40°C; then it decreases until the reaction stops altogether, because the enzyme has become denatured. **b.** The body temperature of ectothermic animals, such as iguanas, which take on the temperature of their environment, often limits rates of reactions. **c.** The body temperature of endothermic animals, such as polar bears, promotes rates of reaction.

STUDENT NOTES

Figure 1.9 The effect of temperature on enzymes. Siamese cats have inherited a mutation that causes an enzyme to be active only at cooler body temperatures. Therefore, only certain regions of the body are dark in color.

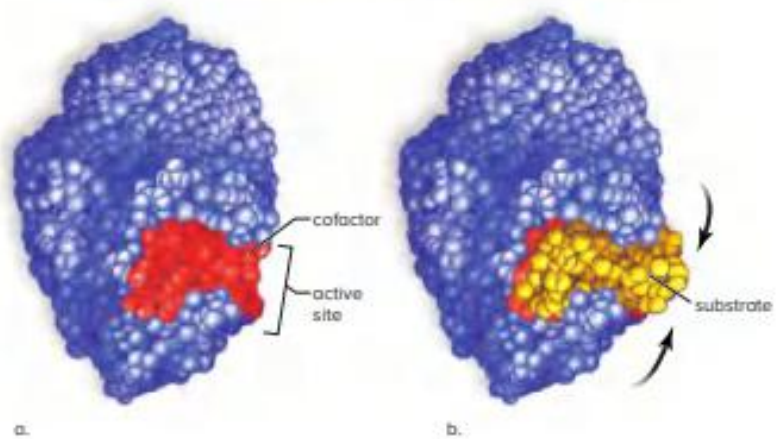


Figure 1.10 Cofactors at active site. **a.** Cofactors, including inorganic ions and organic coenzymes, may participate in the reaction at (**b**) the active site.

available, enzymatic activity will decrease, and the result will be a vitamin-deficiency disorder. In humans, a niacin deficiency results in a skin disease called pellagra, and riboflavin deficiency results in cracks at the corners of the mouth.

Enzyme Inhibition

Sometimes it is necessary to limit the activity of an enzyme. **Enzyme inhibition** occurs when a molecule (the inhibitor) binds to an en-zyme and decreases its activity. In Figure 1.11, F is the end product of a metabolic pathway that can act as an inhibitor. This type of inhibition is beneficial, because once sufficient end product is present, inhibiting further production can conserve raw materials and energy.

Figure 1.11 also illustrates **noncompetitive inhibition,** because the inhibitor (F, the end product) binds to the en-zyme E_1 at a location other than the active site. The site is called an **allosteric site.** When an inhibitor is at the allosteric

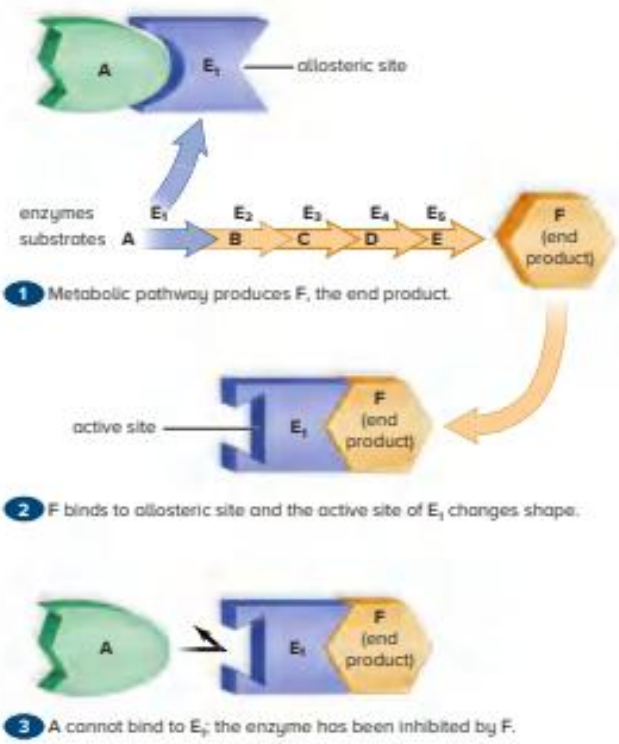


Figure 1.11 Noncompetitive inhibition of an enzyme.
In the pathway, A–E are substrates, E_1–E_5 are enzymes, and F is the end product of the pathway that inhibits enzyme E_1. This negative feedback is useful, because it prevents wasteful production of product F when it is not needed.

site, the active site of the enzyme changes shape, which in turn changes its function.

In Figure 1.11, the enzyme E_1 is inhibited, because it is unable to bind to A, its substrate. The inhibition of E_1 means that the metabolic pathway is inhibited and no more end product is produced, until conditions change and more end product is needed.

In contrast to noncompetitive inhibition, **competitive inhibition** occurs when an inhibitor and the substrate compete for the active site of an enzyme. Product forms only when the substrate, not the inhibitor, is at the active site. In this way, the amount of product is regulated.

Normally, enzyme inhibition is reversible, and the enzyme is not damaged by being inhibited. When enzyme inhibition is irreversible, the inhibitor permanently inactivates or destroys an enzyme.

Check Your Progress 1.3

1. Explain how enzymes are involved in metabolic pathways.
2. Describe how an enzyme interacts with a substrate to reduce the energy of activation.
3. List the environmental conditions that may influence enzyme activity.

1.4 Oxidation-Reduction Reactions and Metabolism

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain how the reactions for photosynthesis and cellular respiration represent oxidation-reduction reactions.
2. Summarize the relationship between the metabolic reactions of photosynthesis and cellular respiration.

In the next two chapters, you will explore two important metabolic pathways: cellular respiration and photosynthesis . Both of these pathways are based on the use of special enzymes to facilitate the movement of electrons. The movement of these electrons plays a major role in the energy-related reactions associated with these pathways.

Oxidation-Reduction Reactions

When oxygen (O) combines with a metal such as iron or magnesium (Mg), oxygen receives electrons and becomes an ion that is negatively charged. The metal loses electrons and becomes an ion that is positively charged. When magnesium oxide (MgO) forms, it is appropriate to say that magnesium has been oxidized. On the other hand, oxygen has been reduced, because it has gained negative charges (i.e., electrons). Reactions that involve the gain and loss of electrons are called oxidation-reduction reactions. Sometimes, the terms *oxidation* and *reduction* are applied to other reactions, whether or not oxygen is involved. In a discussion of metabolic reactions, oxidation represents the loss of electrons, and reduction is the gain of electrons. In the reaction $Na + Cl \rightarrow NaCl$, sodium has been oxidized (loss of electron), and chlorine has been reduced (gain of electrons). Because oxidation and reduction go hand-in-hand, the entire reaction is called a **redox reaction.** One easy way to remember what is happening in redox reactions is to remember the term OIL RIG:

OIL RIG

Oxidation Is Loss Reduction Is Gain

The terms *oxidation* and *reduction* also apply to covalent reactions in cells. In this case, however, oxidation is the loss of hydrogen atoms ($e^- + H^+$), and reduction is the gain of hydrogen atoms. Notice that when a molecule loses a hydrogen atom it has lost an electron, and when a molecule gains a hydrogen atom it has gained an electron. This form of oxidation-reduction is exemplified in the overall equations for photosynthesis and cellular respiration.

Chloroplasts and Photosynthesis

The chloroplasts in plants capture solar energy and use it to convert water and carbon dioxide into a carbohydrate. Oxygen

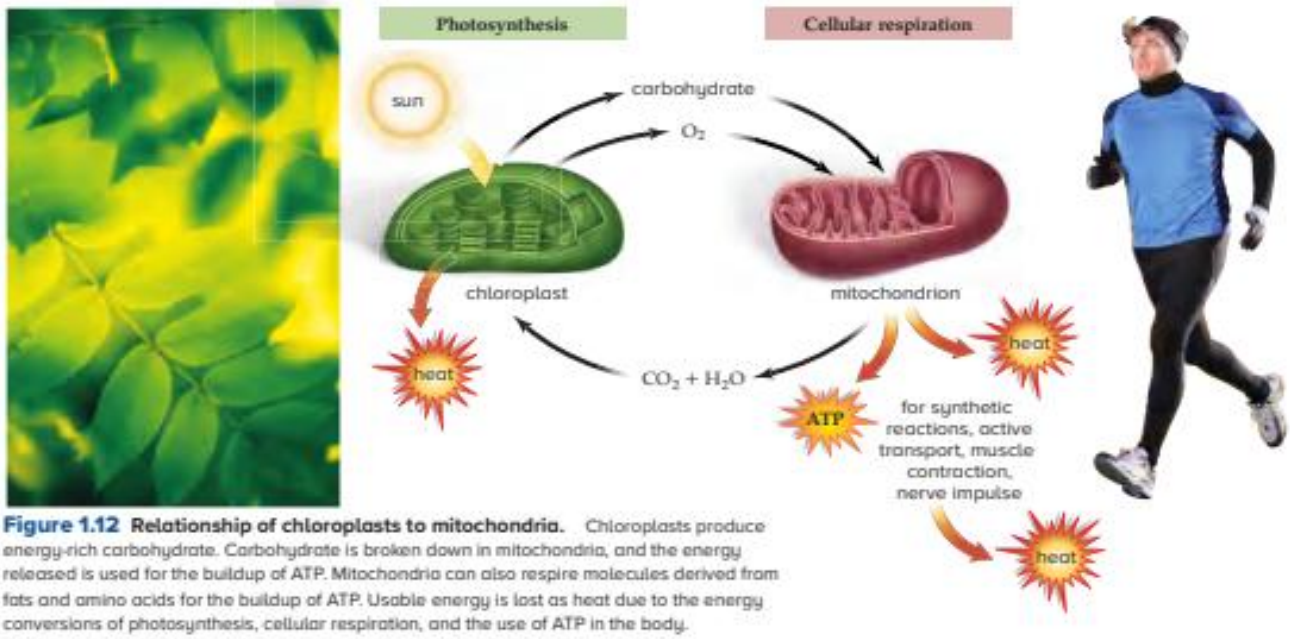


Figure 1.12 Relationship of chloroplasts to mitochondria. Chloroplasts produce energy-rich carbohydrate. Carbohydrate is broken down in mitochondria, and the energy released is used for the buildup of ATP. Mitochondria can also respire molecules derived from fats and amino acids for the buildup of ATP. Usable energy is lost as heat due to the energy conversions of photosynthesis, cellular respiration, and the use of ATP in the body.

is a by-product that is released (Fig. 1.12, *left*). The overall equation for photosynthesis can be written like this:

$$\text{energy} + \underset{\text{carbon dioxide}}{6\ CO_2} + \underset{\text{water}}{6\ H_2O} \longrightarrow \underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{oxygen}}{6\ O_2}$$

This equation shows that during photosynthesis hydrogen atoms are transferred from water to carbon dioxide as glucose forms. In this reaction, therefore, carbon dioxide has been reduced and water has been oxidized. It takes energy to reduce carbon dioxide to glucose, and this energy is supplied by solar energy. Chloroplasts are able to capture solar energy and convert it to the chemical energy of ATP, which is used along with hydrogen atoms to reduce carbon dioxide.

The reduction of carbon dioxide to form a mole of glucose stores 686 kcal in the chemical bonds of glucose. This is the energy that living organisms utilize to support themselves only because carbohydrates (and other nutrients) can be oxidized in mitochondria.

Mitochondria and Cellular Respiration

Mitochondria, present in both plants and animals, oxidize carbohydrates and use the released energy to build ATP molecules (Fig. 1.12, *right*). Cellular respiration therefore consumes oxygen and produces carbon dioxide and water, the very molecules taken up by chloroplasts. The overall equation for cellular respiration is the opposite of the one we used to represent photosynthesis:

$$\underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{oxygen}}{6\ O_2} \longrightarrow \underset{\text{carbon dioxide}}{6\ CO_2} + \underset{\text{water}}{6\ H_2O} + \text{energy}$$

In this reaction, glucose has lost hydrogen atoms (been oxidized), and oxygen has gained hydrogen atoms (been reduced). When oxygen gains electrons, it becomes water. The complete oxidation of a mole of glucose releases 686 kcal of energy, and some of this energy is used to synthesize ATP molecules. If the energy within glucose were released all at once, most of it would dissipate as heat instead of some of it being used to produce ATP. Instead, cells oxidize glucose step by step. The energy is gradually stored and then converted to that of ATP molecules, which is used in animals in the many ways listed in Figure 1.12.

Figure 1.12 shows us very well that chloroplasts and mitochondria are involved in a cycle. Carbohydrate produced within chloroplasts becomes a fuel for cellular respiration in mitochondria, while carbon dioxide released by mitochondria becomes a substrate during photosynthesis in chloroplasts. These organelles are involved in a redox cycle, because carbon dioxide is reduced during photosynthesis and carbohydrate is oxidized during cellular respiration. Note that energy does not cycle between the two organelles; instead, it flows from the sun through each step of photosynthesis and cellular respiration until it eventually becomes unusable heat as ATP is used by the cell.

Check Your Progress 1.4

1. Compare the role of carbon dioxide in photosynthesis and cellular respiration.
2. Distinguish how energy from electrons is used to establish an electrochemical gradient in chloroplasts and mitochondria.

REVIEWING *the* BIG IDEAS

BIG IDEA 1

Many metabolic pathways, and the use of ATP as an energy source to drive these pathways, are conserved features that evolved millions of years ago and are widely distributed among organisms today. 1.B.1.a.3

BIG IDEA 2

All living systems require free energy to maintain order, grow, and reproduce and employ different strategies to capture, store, and use free energy; the loss of free energy can be disruptive to biological systems, from cells and individual organisms to populations and ecosystems. 1.A.1.a,d,e,f

The first and second laws of thermodynamics apply to living systems; energy and matter cannot be created or destroyed, and to power cellular processes energy input must exceed free energy lost to entropy. 1.A.1. b.

Organisms use various strategies such as photosynthesis and cellular respiration to capture, transform, store, and transfer free energy for use in biological processes. 1.A.2. a-h

BIG IDEA 4

Interactions among organisms and with their environment result in the transfer of free energy. 4.A.6.a,d,g

Cells undergo chemical reactions on a constant basis, and enzymes facilitate metabolic pathways by catalyzing these reactions. 4.A.1.b,c,d

SUMMARIZE

AP Answering the Essential Questions

Living systems, from cells to ecosystems, require free energy to maintain order and grow, and they use various strategies to capture, transform, store, and transfer energy. Examples of these strategies include photosynthesis and cellular respiration. In **photosynthesis,** plants capture solar energy and store it in sugars, whereas in **cellular respiration,** cells tap into this stored energy to perform various types of work, such as the movement of solutes across cell. An organism's **metabolism**—the sum of its chemical reactions—is an emergent property resulting from interactions between molecules that often occur in a stepwise flow. Metabolic pathways either release energy by breaking down complex molecules or consume energy. For an organism to survive, the input of energy must exceed the amount of energy used.

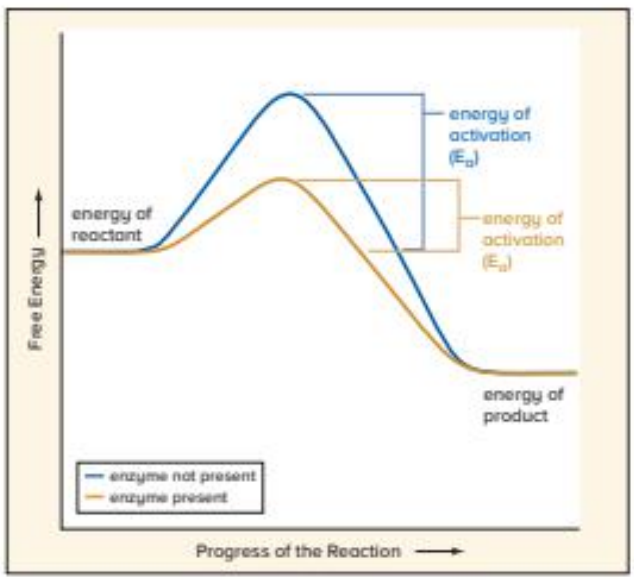
Thermodynamics and living systems Cells cannot create energy, but according to the first law of thermodynamics, it can be transferred and transformed. By converting solar energy to chemical energy in photosynthesis, plants act as an energy transformer, not an energy producer, because the original source of energy is sunlight, not the sugar that is made. During every energy transfer or transformation, some energy becomes unavailable to do work. As we will see when we study energy flow through an ecosystem, when energy is transferred among organisms in a food chain, little energy is available to the organisms at the top of the chain because great amount of energy is "lost" from the system as heat as it is transferred from organism to organism. In a previous chemistry or physics course, you likely studied how the loss of usable energy as heat makes the universe as a whole more disorganized, a phenomenon known as **entropy.** According to the second law of thermodynamics, every cellular process increases the total entropy of the universe, and cells need to be efficient in how they capture and use energy. For example, glucose, which is more organized, tends to break down to carbon dioxide and water, which are less organized; the movement molecules move across membranes from an area of high concentration to low concentration also increases entropy.

ATP is the common energy "currency" of all cells and can be used in many types of chemical reactions. When cells require energy, they use ATP. Because cells do not store a surplus of ATP molecules, they need to regenerate this energy-carrying molecule. ATP is a nucleotide consisting of the five-carbon sugar ribose, the nitrogen-containing base adenine, and three phosphate groups that repel each other, creating instability and potential energy. When ATP is hydrolyzed (Chapter 4), energy is released, and cells use the change in free energy to do work such as contract a muscle or pump solute across a membrane in active transport. The breakdown of ATP is *coupled* to an energy-requiring reaction, and, thus, energy is transferred. A cell has two main ways to couple ATP hydrolysis to an energy-requiring reaction: ATP is used to energize a reaction, or ATP is used to change the shape of a reactant. Both can be achieved by transferring a phosphate group to the reactant, phosphorylating the product. We will explore phosphorylation in more depth when we study photosynthesis, cellular respiration, and cell signaling.

The role of enzymes Many chemical reactions in cells occur spontaneously without requiring outside energy, but may occur too slowly. For example, the disaccharide sucrose (table sugar) will break down into two monosaccharides, glucose and fructose, with a release of free energy. However, a solution of sucrose dissolved in sterile water will sit for a long time without hydrolyzing. If we add a small amount of the enzyme sucrase to the solution, the sucrose will dissolve almost immediately. (Most of us don't have a bottle of sucrase in the pantry, so that's why when we add sugar to sweeten iced tea, we stir.) An **enzyme** like sucrase is a macromolecule—most often a protein—that acts as a **catalyst** to speed up a chemical reaction by lowering the activation energy barrier.

Chemical reactions between molecules involve both bond breaking and bond forming. When the bonds of the product molecules form, energy is released as heat. To start the reaction, the substrates or reactants must absorb energy to reach an unstable state where bonds can break. This initial investment of energy is known as the **energy of activation.** Adding an enzyme lowers the amount of activation energy necessary to start the reaction. Enzymes are very specific for the reactions they catalyze; this specificity results from—again—the relationship between structure and function. As was previously described,

most enzymes are proteins, and as we studied in Chapter 4, proteins can have a variety of three-dimensional shapes because of various intermolecular bonds. Enzymes are no exception. Only one part of the enzyme, the active site, directly interacts with the substrate via **induced fit,** altering the shape of the enzyme to facilitate the reaction. After the reaction has been completed, the product(s) is released, and the active site returns to its original shape, ready to bind to another substrate molecule. Like most catalysts, only a small amount of enzyme is needed, and they work quickly.



The rate of an enzyme-catalyzed reaction depends on several factors, including the amount of substrate and enzyme, the presences of coenzymes or cofactors, and other factors that can change the shape of the active site—a phenomenon called **denaturation**—such as pH, temperature, or the presence of a competitive or noncompetitive inhibitor. Enzymes work most efficiently under optimal conditions; for example, pepsin, an enzyme that helps break down proteins in the stomach, works best at pH 2, whereas trypsin, an enzyme in the small intestine, works best at pH 8. Most human enzymes also work best at optimal temperatures of about 35-40°C (close to human body temperature).

ASSESS

Choose the best answer for each question.

1.1 Cells and the Flow of Energy

1. The fact that energy transformations increase the amount of entropy is the basis of which of the following?
   a. cell theory
   b. first law of thermodynamics
   c. second law of thermodynamics
   d. oxidation-reduction reactions
2. The energy stored in the carbon-carbon bonds of glucose is an example of _____ energy.
   a. kinetic
   b. potential
   c. chemical
   d. Both b and c are correct.
3. During energy transformations, the majority of energy is converted to
   a. chemical bonds.
   b. heat.
   c. ATP.
   d. glucose molecules.

1.2 Metabolic Reactions and Energy Transformations

4. Exergonic reactions
   a. are spontaneous.
   b. have a negative delta G value.
   c. release energy.
   d. All of these are correct.
5. Which of the following is incorrect regarding ATP?
   a. It is the energy currency of the cell.
   b. It is stable.
   c. It is recycled using ADP and inorganic phosphate.
   d. Cells keep only small amounts of ATP on hand.
6. The sum of all the chemical reactions in a cell is called
   a. free energy.
   b. entropy.
   c. metabolism.
   d. oxidation-reduction reactions.

1.3 Metabolic Pathways and Enzymes

7. Which of the following is incorrect regarding the active site of an enzyme?
   a. is unique to that enzyme
   b. is the part of the enzyme where its substrate can fit
   c. can be used over and over again
   d. is not affected by environmental factors, such as pH and temperature
8. Which of the following environmental conditions may have an influence on enzyme activity?
   a. substrate concentration
   b. temperature
   c. pH
   d. All of these are correct.
9. In which of the following does an inhibitor bind to an allosteric site on an enzyme?
   a. competitive inhibition
   b. noncompetitive inhibition
   c. redox reactions
   d. None of the above are correct.
10. Enzymes catalyze chemical reactions by which of the following?
    a. lowering the energy of activation in the reaction
    b. raising the energy of activation in the reaction
    c. increasing entropy
    d. increasing the free energy of the products

1.4 Oxidation-Reduction Reactions and Metabolism

11. The gain of electrons by a molecule is called
    a. inhibition.
    b. entropy.
    c. oxidation.
    d. reduction.

12. In which of the following processes is carbon dioxide reduced to form carbohydrate?
    a. cellular respiration
    b. noncompetitive inhibition
    c. photosynthesis
    d. induced fit model

ENGAGE

AP Applying the Big Ideas

1. BIG IDEA 1 In targeted therapy used to treat cancer, drugs target certain parts of the cell and the signals that are needed for cancer to develop and grow. Some targeted therapies make use of enzyme inhibitors that target enzymes such as DNA polymerase, an enzyme required for DNA replication.

   In a paragraph, **describe** how enzyme inhibitors function and explain why this method of cancer treatment is a viable option.

2. BIG IDEA 2 Free energy is the amount of energy left to do work after a reaction occurs and is determined by subtracting the free energy content of the reactants from that of the products. Scientists claim that free energy is required for living systems to maintain organization, to grow, or to reproduce, but multiple strategies for capturing, storing and using it exist in different living systems.

   In a paragraph, **being as specific and detailed as possible,** justify this claim using at least THREE examples.

3. BIG IDEA 4 Nicotinamide adenine dinucleotide (NAD^+) is involved with many types of oxidation reactions where alcohols are converted to ketones or aldehydes. It is noted in the lab that in the absence of niacin, the rate of hydrogen transfer as seen in cellular respiration by NAD^+ is greatly reduced and cells do not thrive.
   a. Based on the lab observations described above, **analyze** the role niacin and NAD^+ play in metabolic reactions?
   b. **Explain** how this relates to how molecular interactions affect structure and function.

AP Applying the Science Practices

Analyze the Data

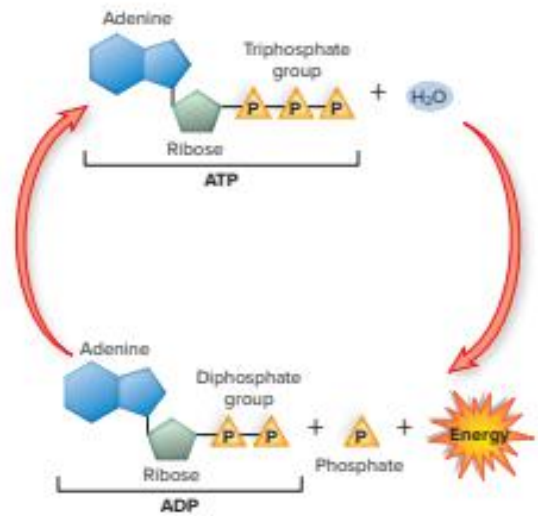
Does ATP concentration impact cell motility? Understanding that ATP is a unit of energy for the cell, researchers studied the effect of increased concentration of ATP on the beat frequency of cellular flagella.

Data and Observations

No movement was observed at concentrations of 0 to 4 µM ATP. When the ATP concentration was raised to 8 µM, about 20-30% of the flagella beat at a frequency of about one beat every two seconds. In 12 µM ATP, they were 95-100% motile, with a beat frequency of about one per second.

Think Critically SP 1 SP 4 SP 5

1. **Construct a graph** to illustrate the findings of these researchers.
2. **Explain** what is happening to the cell as ATP concentration increases.
3. What would happen if other nucleotides, such as ITP, CTP, UTP or GTP were substituted for ATP? **Design** a follow-up investigation that would test this question.



2

Photosynthesis

Chapter Outline

Biofuels may one day come from modifying the process of photosynthesis.

AP Photosynthesis is a powerful process. Plants, algae, and some bacteria carry out a series of chemical reactions during photosynthesis that harness CO_2 from the air, and they combine water from the soil with sunlight to create the molecules that living organisms rely on—oxygen, carbohydrates, oils, and amino acids.

Photosynthesis can also be the key to solving our world's fuel crisis. Plant researchers are tweaking the basic chemistry of photosynthesis to create commercially important oils and fuels. One example is work being done with *Camelina*, a drought-resistant, oilseed crop. Scientists are modifying how *Camelina* captures sunlight by genetically engineering the plant so that the leaves at the top are lighter, allowing sunlight to pass through to the lower leaves, improving the efficiency of photosynthesis. Another goal improves the absorption of CO_2, providing the raw materials for oil production, which are precursors for potential biofuels.

Other researchers are focusing on terpene—another end result of photosynthesis. Terpene is a high-energy organic molecule, produced by pine trees, that makes turpentine. Ongoing research aims to increase terpene production and process this to make a domestic source of diesel and aviation biofuels. In the future, you may be on a commercial flight where the meal providing fuel for your body and the diesel fueling the airplane can both trace their origins to a photosynthesizing plant.

As you read through the chapter, think about these Essential Questions:

1. What types of organisms use photosynthesis to obtain the free energy necessary for life processes? 1.B.1.a.3
2. How do plants capture solar energy and convert it to chemical energy of food? 2.A.2.a.1
3. What is the relationship between photosynthesis and cellular respiration in terms of reactants and products? How are these processes interdependent? 4.A.6.a,c,d

Following *the* BIG IDEAS

BIG IDEA 1 — Plants have evolved the ability to capture solar energy and store it in carbon-based organic nutrients.

BIG IDEA 2 — All life on Earth depends on the energy stored in carbohydrates produced through photosynthesis.

BIG IDEA 4 — Organic nutrients produced by plants through photosynthesis are passed on to other organisms in a food web that have evolved to feed on plants, thus transferring free energy among members of the web.

2.1 Photosynthetic Organisms

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain how autotrophs are able to produce their own food.
2. Describe the components of a chloroplast.
3. Compare the roles of oxygen and carbon dioxide in autotrophs and heterotrophs.

Photosynthesis converts solar energy into the chemical energy of a carbohydrate. Photosynthetic organisms, including plants, algae, and cyanobacteria, are called **autotrophs,** because they produce their own food (Fig. 2.1*a*). It has been estimated that all of the world's green organisms together produce between 100 billion and 200 billion metric tons of sugar each year. Imagine enough sugar cubes to re-create the volume of 2 million Empire State Buildings!

No wonder photosynthetic organisms are able to sustain themselves and all other living organisms on Earth. With few exceptions, it is possible to trace any food chain back to plants and algae. In other words, producers, which have the ability to synthesize carbohydrates, feed not only themselves but also consumers, which must take in preformed organic molecules. Collectively, consumers are called **heterotrophs.** Both autotrophs and heterotrophs use organic molecules produced by photosynthesis as a source of building blocks for growth and repair and as a source of chemical energy for cellular work.

Photosynthesizers also produce copious amounts of oxygen gas (O_2) as a by-product. Oxygen, required by organisms for cellular respiration, rises high into the atmosphere, where it forms an ozone shield that filters out ultraviolet radiation and makes terrestrial life possible.

Oil and coal provide about 90% of the energy needed to power vehicles, factories, computers, and a multitude of electrically energized appliances. The energy within that oil and coal was originally captured from the sun by plants and algae growing millions of years ago—thus the name "fossil fuels." Today's trees are also commonly used as fuel. Fermentation of plant materials produces ethanol, which can be used to fuel automobiles directly or as a gasoline additive.

The products of photosynthesis are critical to humankind in a number of other ways. They serve as a source of building materials, fabrics, paper, and pharmaceuticals. Of course, we also appreciate green plants for the simple beauty of an orchid blossom, the scent of a rose, or the majesty of the forests.

Figure 2.1 Autotrophs and the relationship to heterotrophs. **a.** Photosynthetic organisms (autotrophs) include cyanobacteria (*left*); algae, such as kelp (*middle*); and plants (*right*). **b.** Photosynthetic organisms harness the energy from the sun and provide gases and nutrients for heterotrophs. Heterotrophs generate chemical energy and produce carbon dioxide and water.

Photosynthesis in Flowering Plants

Photosynthesis takes place in the green portions of plants. The leaves of a flowering plant contain mesophyll tissue, in which cells are specialized for photosynthesis (Fig. 2.2). The raw materials for photosynthesis are water and carbon dioxide. The roots of a plant absorb water, which then moves in vascular tissue up the stem to a leaf by way of the leaf veins. Carbon dioxide in the air enters a leaf through small openings called **stomata** (sing., stoma). After entering a leaf, carbon dioxide and water diffuse into **chloroplasts** (Gk. *chloros,* "green"; *plastos,* "formed, molded"), the organelles that carry on photosynthesis.

A double membrane surrounds a chloroplast, and its semifluid interior is called the **stroma** (Gk. *stroma,* "bed, mattress"). A different membrane system within the stroma forms flattened sacs called **thylakoids** (Gk. *thylakos,* "sack"), which in some places are stacked to form **grana** (sing., granum). The space of each thylakoid is thought to be connected to the space of every other thylakoid within a chloroplast, thereby forming an inner compartment within chloroplasts, called the thylakoid space. Overall, chloroplast membranes provide a tremendous surface area for photosynthesis to occur.

The thylakoid membrane contains **chlorophyll** and other pigments that are capable of absorbing the solar energy that drives photosynthesis. The stroma contains an enzyme-rich solution, where carbon dioxide is first attached to an organic compound and then reduced to a carbohydrate.

Humans and other respiring organisms release carbon dioxide into the air. Some of the same carbon dioxide molecules enter a leaf through the stoma and are converted to carbohydrate. Carbohydrate, in the form of glucose, is the chief source of chemical energy for most organisms. Thus, an interdependent relationship exists between organisms that make their own food (autotrophs) and those that consume their food (heterotrophs) (see Fig. 2.1*b*).

Check Your Progress 2.1

1. Describe three major groups of photosynthetic organisms.
2. Distinguish the part of a chloroplast that absorbs solar energy from the part that forms a carbohydrate.

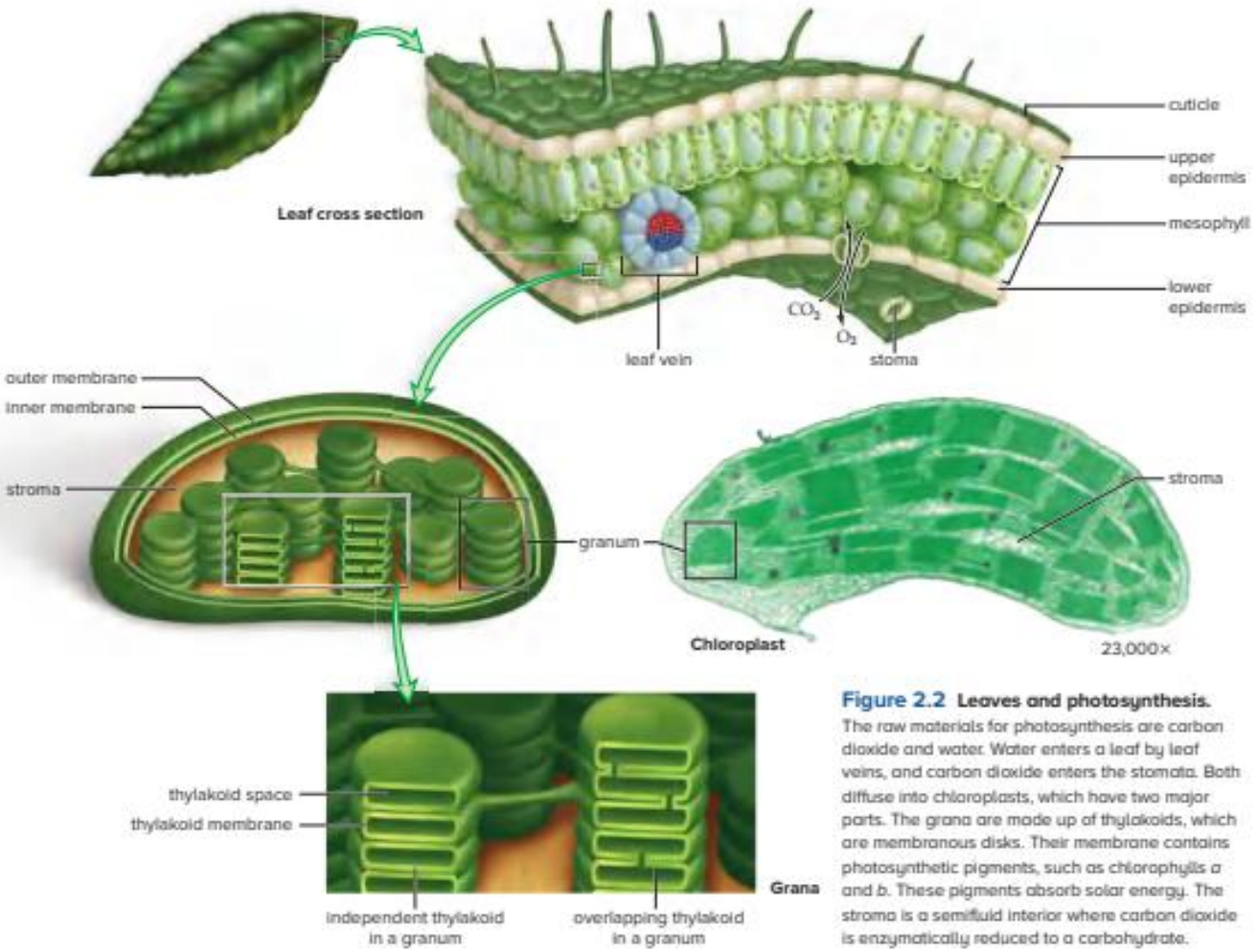


Figure 2.2 Leaves and photosynthesis. The raw materials for photosynthesis are carbon dioxide and water. Water enters a leaf by leaf veins, and carbon dioxide enters the stomata. Both diffuse into chloroplasts, which have two major parts. The grana are made up of thylakoids, which are membranous disks. Their membrane contains photosynthetic pigments, such as chlorophylls *a* and *b*. These pigments absorb solar energy. The stroma is a semifluid interior where carbon dioxide is enzymatically reduced to a carbohydrate.

2.2 The Process of Photosynthesis

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the overall process of photosynthesis.
2. Compare energy input and output of the light reaction.
3. Compare carbon input and output of the Calvin cycle reaction.

The overall process of photosynthesis can be represented by an equation:

$$6\,CO_2 + 12\,H_2O \xrightarrow{\text{solar energy}} 6\,(CH_2O) + 6\,H_2O + 6\,O_2$$

In this equation, (CH_2O) represents carbohydrate. If the equation were multiplied by 6, the carbohydrate would be $C_6H_{12}O_6$, or glucose.

The overall equation implies that photosynthesis involves oxidation-reduction (redox) and the movement of electrons from one molecule to another. Recall that oxidation is the loss of electrons, and reduction is the gain of electrons. In living organisms, the electrons are very often accompanied by hydrogen ions, so that oxidation is the loss of hydrogen atoms ($H^+ + e^-$) and reduction is the gain of hydrogen atoms. This simplified rewrite of the equation makes it clear that carbon dioxide has been reduced and water has been oxidized:

$$CO_2 + H_2O \xrightarrow{\text{solar energy}} (CH_2O) + O_2$$

(Reduction: $CO_2 \rightarrow (CH_2O)$; Oxidation: $H_2O \rightarrow O_2$)

It takes hydrogen atoms and a lot of energy to reduce carbon dioxide. From your study of energy and enzymes, you might expect that solar energy is not used directly during photosynthesis; rather, it is converted to ATP molecules. ATP is the energy currency of cells and, when cells need something, they spend ATP. In this case, solar energy is used to generate the ATP needed to reduce carbon dioxide to a carbohydrate. Of course, this carbohydrate represents the food produced by plants, algae, and cyanobacteria that feeds the biosphere.

The Role of NADP⁺/NADPH

As you have learned previously, the electrons needed to reduce carbon dioxide are carried by a coenzyme. $NADP^+$ is the coenzyme of oxidation-reduction (redox coenzyme) active during photosynthesis. When $NADP^+$ is reduced, it has accepted two electrons and one hydrogen atom, and when NADPH is oxidized, it gives up its electrons:

$$NADP^+ + 2\,e^- + H^+ \longrightarrow NADPH$$

What molecule supplies the electrons that reduce $NADP^+$ during photosynthesis? Put a sprig of *Elodea* in a beaker and supply it with light, and you will observe a bubbling (Fig. 2.3). The bubbling occurs because the plant is releasing oxygen as it photosynthesizes.

Figure 2.3 Photosynthesis releases oxygen. Bubbling indicates that the aquatic plant *Elodea* releases O_2 gas when it photosynthesizes.

A famous experiment performed by C. B. van Niel of Stanford University found that the oxygen given off by photosynthesizers comes from water. Van Niel performed two separate experiments. When an isotope of oxygen, ^{18}O, was a part of water, the O_2 given off by the plant contained ^{18}O. When ^{18}O was a part of carbon dioxide supplied to a plant, the O_2 given off by a plant did not contain the ^{18}O. Why not? Because the oxygen in carbon dioxide doesn't come from water; it comes from the air. This was the first step toward discovering that water splits during photosynthesis. When water splits, oxygen is released and the hydrogen atoms ($H^+ + e^-$) are taken up by $NADP^+$. Later, NADPH reduces carbon dioxide to a carbohydrate.

Two Sets of Reactions

How does photosynthesis occur? The process can be divided into two stages, the light reactions and the Calvin cycle reactions. The term *photosynthesis* comes from the associations between these two stages: The prefix *photo* refers to the light reactions that capture the waves of sunlight needed for the *synthesis* of carbohydrates occurring in the Calvin cycle. The light reactions take place on thylakoids, and the Calvin cycle takes place in the stroma.

Light Reactions

The **light reactions** are so named because they occur only when the sun is out. The green pigment chlorophyll, present in thylakoid membranes, is largely responsible for absorbing the solar energy that drives photosynthesis.

During the light reactions, solar energy energizes electrons, which move down an electron transport chain. As the electrons move down the chain, energy is released and captured to produce ATP molecules. Energized electrons are also taken up by $NADP^+$, which is reduced and becomes NADPH. This equation can be used to summarize the light reactions, because during the light reactions solar energy is converted to chemical energy:

$$\text{solar energy} \longrightarrow \text{chemical energy (ATP, NADPH)}$$

Calvin Cycle Reactions

The **Calvin cycle reactions** are named for Melvin Calvin, who in 1961 received a Nobel Prize in Chemistry for discovering the enzymatic reactions that reduce carbon dioxide to a carbohydrate in the stroma of chloroplasts (Fig. 2.4). The enzymes that speed the reduction of carbon dioxide during both day and night are located in the semifluid substance of the chloroplast stroma.

During the Calvin cycle reactions, CO_2 is taken up and then reduced to a carbohydrate that can later be converted to glucose. This equation can be used to summarize the Calvin cycle reactions, because during these reactions, the ATP and NADPH formed during the light reactions are used to reduce carbon dioxide:

chemical energy (ATP, NADPH) ⟶ chemical energy (carbohydrate)

Summary

Figure 2.5 summarizes our discussion so far and shows that during the light reactions, (1) solar energy is absorbed, (2) water is split so that oxygen is released, and (3) ATP and NADPH are produced.

During the Calvin cycle reactions, (1) CO_2 is absorbed and (2) reduced to a carbohydrate (CH_2O) by utilizing ATP and NADPH from the light reactions (bottom set of red arrows). The top set of red arrows takes ADP + Ⓟ and $NADP^+$ back to light reactions, where they become ATP and NADPH once more, so that carbohydrate production can continue.

Figure 2.4 Melvin Calvin. Melvin Calvin, a chemist, is most noted for his work using a carbon 14 isotope to follow the route that carbon travels through a plant during photosynthesis.

Check Your Progress 2.2

1. Explain how redox reactions are used in photosynthesis.
2. Describe the role of enzymes during photosynthesis.

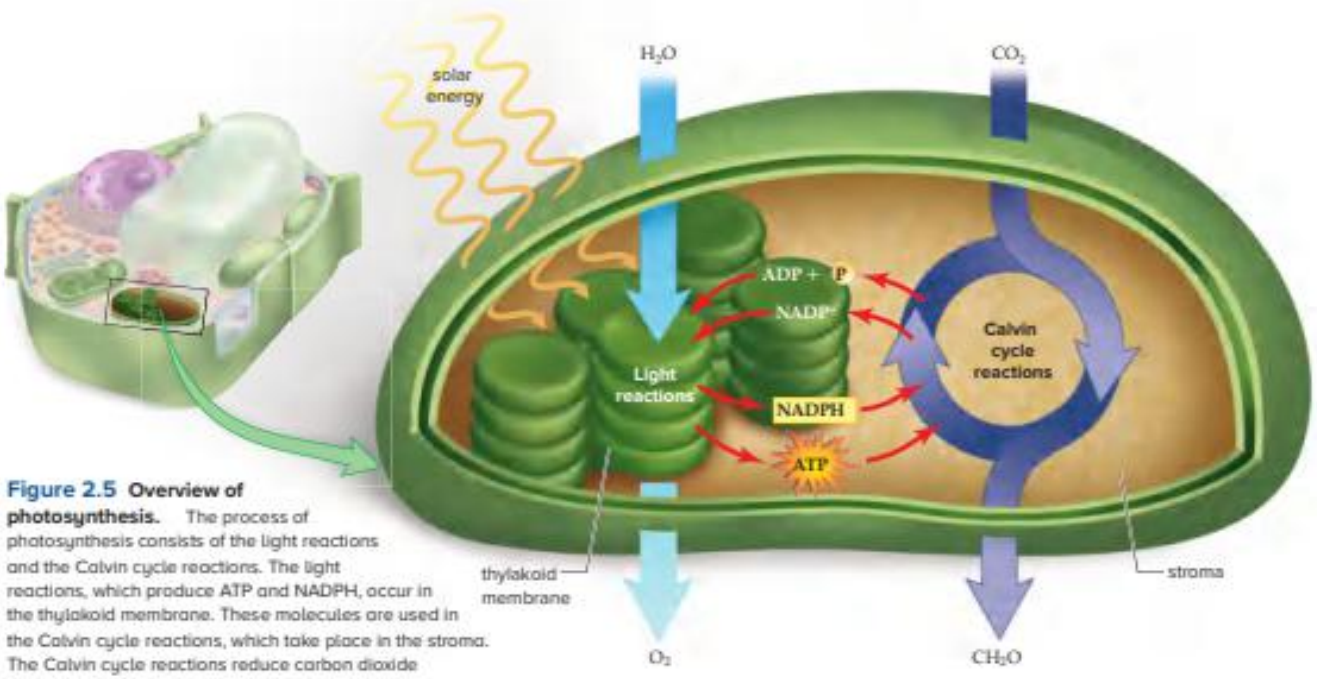


Figure 2.5 Overview of photosynthesis. The process of photosynthesis consists of the light reactions and the Calvin cycle reactions. The light reactions, which produce ATP and NADPH, occur in the thylakoid membrane. These molecules are used in the Calvin cycle reactions, which take place in the stroma. The Calvin cycle reactions reduce carbon dioxide to a carbohydrate.

2.3 Plants Convert Solar Energy

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the relationship between wavelength and energy in the electromagnetic spectrum.
2. Explain the role of photosynthetic pigments in harnessing solar energy.
3. Examine how ATP and NADPH are produced from redox reactions and membrane gradients.

Solar energy can be described in terms of its wavelength and its energy content. Figure 2.6*a* shows the types of radiant energy from the shortest wavelength, gamma rays, to the longest, radio waves. Most of the radiation reaching the Earth is within the visible-light range. Higher-energy wavelengths are screened out by the ozone layer in the atmosphere before they reach the Earth's surface, and lower-energy wavelengths are screened out by water vapor and carbon dioxide. Because visible light is the most prevalent in the environment, organisms have evolved to use these wavelengths. For example, human eyes have cone cells that respond to color wavelengths, and plants have pigments that are energized by most of the same wavelengths (Fig. 2.6).

Pigments and Photosystems

Pigment molecules absorb wavelengths of light. Most pigments absorb only some wavelengths; they reflect or transmit the other wavelengths. The pigments in chloroplasts are capable of absorbing various portions of visible light. This is called their **absorption spectrum.**

Photosynthetic organisms differ in the type of chlorophyll they contain. In plants, chlorophyll *a* and chlorophyll *b* play prominent roles in photosynthesis. **Carotenoids** play an accessory role. Both chlorophylls *a* and *b* absorb violet, blue, and red light better than the light of other colors. Because green light is transmitted and reflected by chlorophyll, plant leaves appear green to us. In short, plants are green because they do *not* use the green wavelength! The carotenoids, which are shades of yellow and orange, are able to absorb light in the violet-blue-green range. These pigments become noticeable in the fall when chlorophyll breaks down.

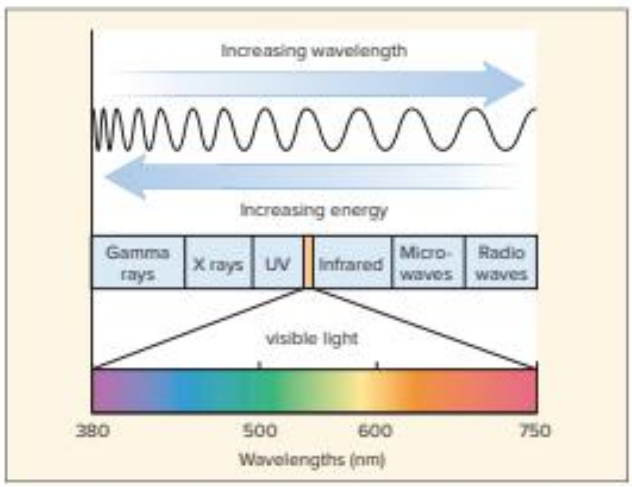
How do you determine the absorption spectrum of pigments? To identify the absorption spectrum of a particular pigment, a purified sample is exposed to different wavelengths of light inside an instrument called a spectrophotometer. A spectrophotometer measures the amount of light that passes through the sample, and from this it is possible to calculate how much was absorbed. The amount of light absorbed at each wavelength is plotted on a graph, and the result is a record of the pigment's absorption spectrum (Fig. 2.6*b*). Notice the low absorbance reading for the green and yellow wavelengths and recall why plants are green.

A **photosystem** consists of a pigment complex (molecules of chlorophyll *a*, chlorophyll *b*, and the carotenoids) and electron acceptor molecules within the thylakoid membrane. The pigment complex serves as an "antenna" for gathering solar energy.

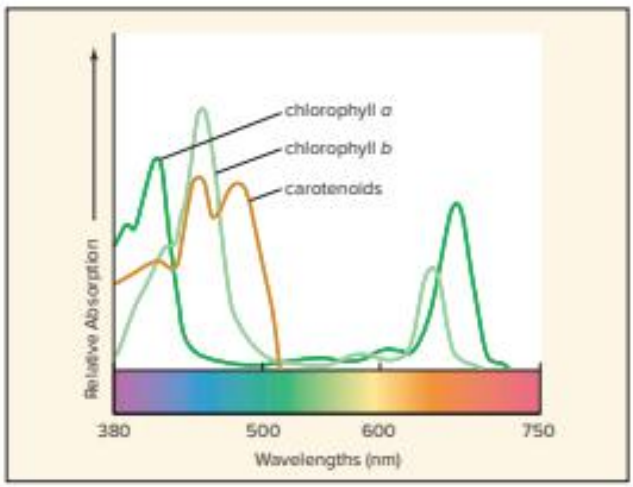
Electron Flow in the Light Reactions

The light reactions utilize two photosystems, called photosystem I (PS I) and photosystem II (PS II). The photosystems are named for the order in which they were discovered, not for the order in which they occur in the thylakoid membrane or participate in the photosynthetic process.

During the light reactions, electrons usually, but not always, follow a **noncyclic pathway** that begins with photosystem II (Fig. 2.7). The pigment complex absorbs solar energy, which is then passed from one pigment to the other until it is concentrated in a particular pair of chlorophyll *a* molecules, called the *reaction center*. Electrons (e^-) in the reaction center become so energized that they escape from the reaction center and move to nearby electron acceptor molecules.



a. The electromagnetic spectrum includes visible light.



b. Absorption spectrum of photosynthetic pigments.

Figure 2.6 Photosynthetic pigments and photosynthesis. **a.** The wavelengths in visible light differ according to energy content and color. **b.** The photosynthetic pigments in chlorophylls *a* and *b* and the carotenoids absorb certain wavelengths within visible light. This is their absorption spectrum.

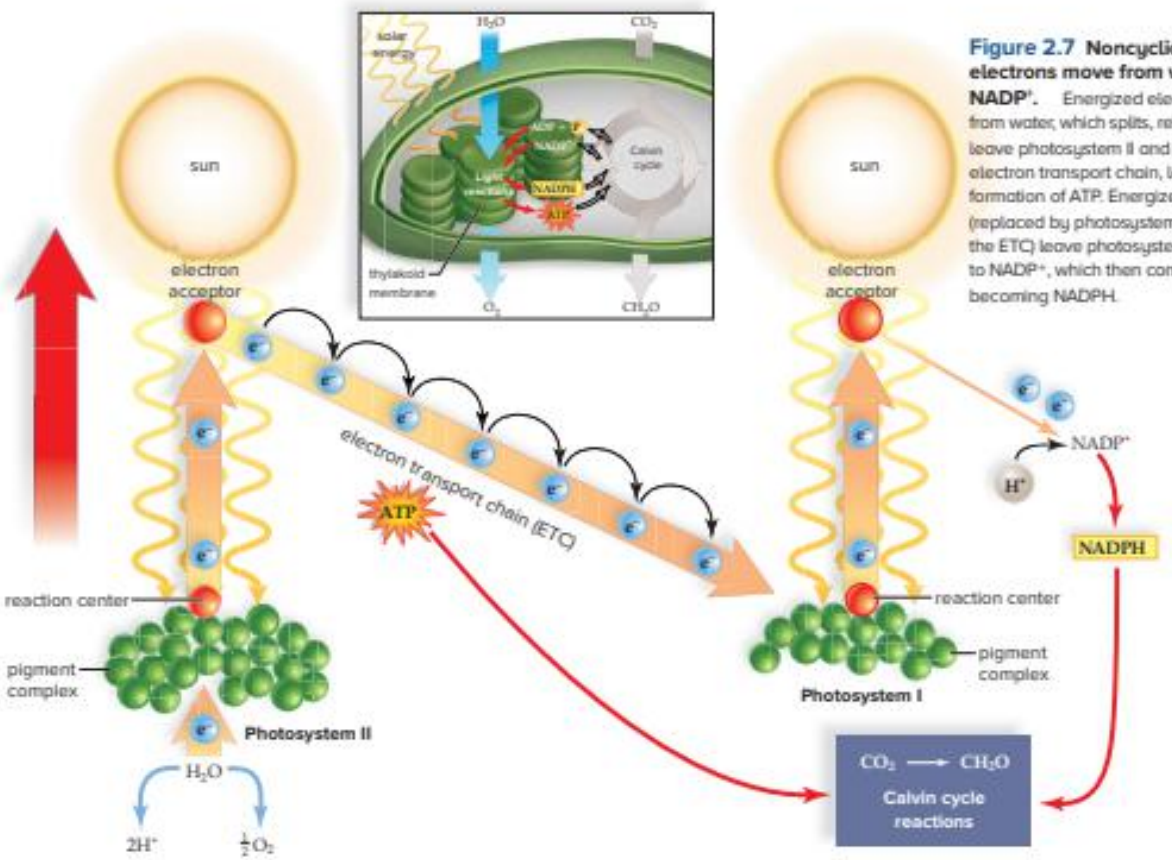


Figure 2.7 Noncyclic pathway: electrons move from water to NADP⁺. Energized electrons (replaced from water, which splits, releasing oxygen) leave photosystem II and pass down an electron transport chain, leading to the formation of ATP. Energized electrons (replaced by photosystem II by way of the ETC) leave photosystem I and pass to $NADP^+$, which then combines with H^+, becoming NADPH.

PS II would disintegrate without replacement electrons, and these are removed from water, which splits, releasing oxygen to the atmosphere. Notice that with the loss of electrons, water has been oxidized and that the oxygen released during photosynthesis does come from water. Many organisms, including plants themselves and humans, use this oxygen within their mitochondria to make ATP. The hydrogen ions (H^+) stay in the thylakoid space and contribute to the formation of a hydrogen ion gradient.

An electron acceptor sends energized electrons, received from the reaction center, down an **electron transport chain (ETC)**, a series of carriers that pass electrons from one to the other. As the electrons pass from one carrier to the next, energy is captured and stored in the form of a hydrogen ion (H^+) gradient. When these hydrogen ions flow down their electrochemical gradient through ATP synthase complexes, ATP production occurs (see Fig. 2.9). Notice that this ATP is then used by the Calvin cycle reactions in the stroma to reduce carbon dioxide to a carbohydrate.

When the PS I pigment complex absorbs solar energy, energized electrons leave its reaction center and are captured by electron acceptors. (Low-energy electrons from the *electron transport chain* adjacent to PS II replace those lost by PS I.) The electron acceptors in PS I pass their electrons to $NADP^+$ molecules. Each $NADP^+$ accepts two electrons and an H^+ to become reduced and forms NADPH. This NADPH is then used by the Calvin cycle reactions in the stroma along with ATP in the reduction of carbon dioxide to a carbohydrate.

ATP and NADPH are not made in equal amounts during the light reactions, and more ATP than NADPH is required during the Calvin cycle. Where does this extra ATP come from? Every so often, an electron moving down the noncyclic pathway is rerouted back to an earlier point in the electron transport chain. The **cyclic pathway,** which occurs in many prokaryotes, and at high oxygen levels in eukaryotes, enables electrons to participate in additional redox reactions, moving more H^+ across the thylakoid membrane and through ATP synthase, ultimately producing more ATP (Fig. 2.8).

Organization of the Thylakoid Membrane

As we have discussed, the following molecular complexes are present in the thylakoid membrane (Fig. 2.9):

PS II, which consists of a pigment complex and electron acceptor molecules, receives electrons from water as water splits, releasing oxygen.

The electron transport chain (ETC), consisting of Pq (plastoquinone) and cytochrome complexes, carries electrons from PS II to PS I via redox reactions. Pq also pumps H^+ from the stroma into the thylakoid space.

PS I, which also consists of a pigment complex and electron acceptor molecules, is adjacent to NADP reductase, which reduces $NADP^+$ to NADPH.

The **ATP synthase** complex, which has a channel and a protruding ATP synthase, is an enzyme that joins ADP + Ⓟ.

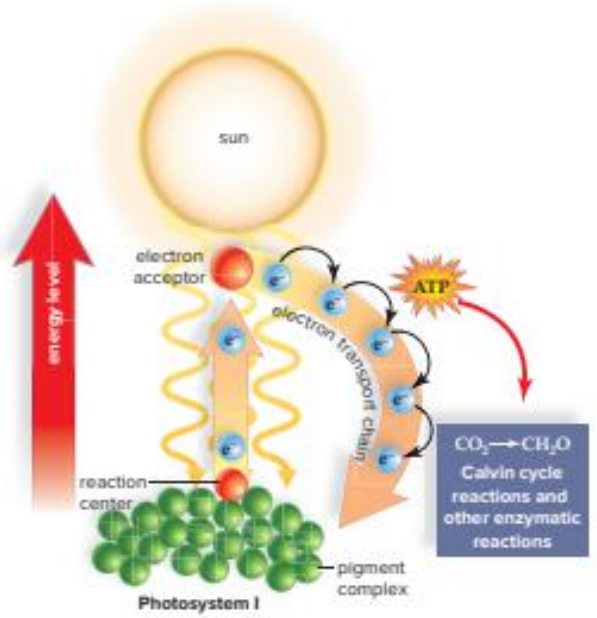


Figure 2.8 Cyclic electron pathway. Electrons leave and return to photosystem I. Energized electrons leave the photosystem I reaction center and are taken up by an electron acceptor, which passes them down an electron transport chain before they return to photosystem I. Only ATP production occurs as a result of this pathway.

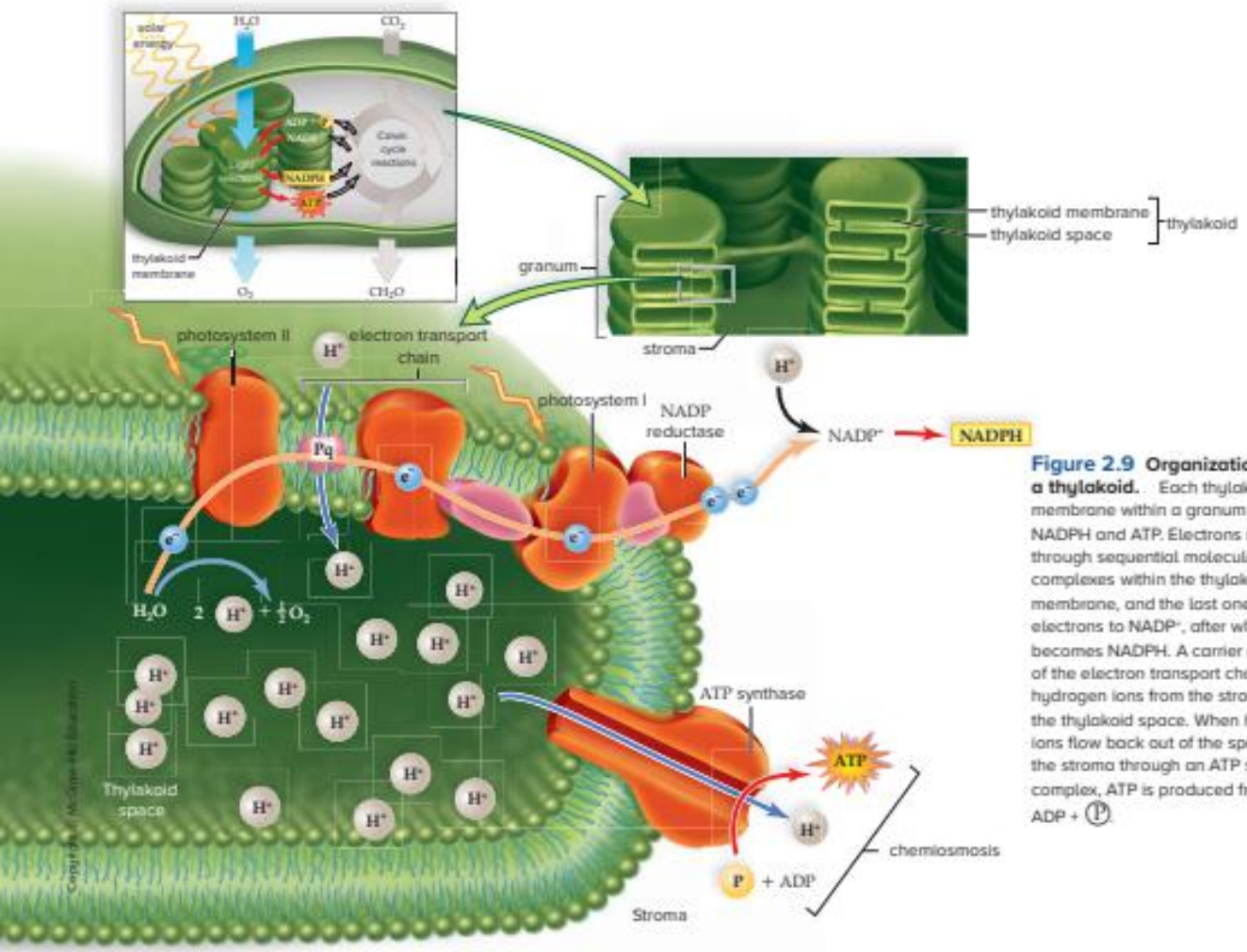


Figure 2.9 Organization of a thylakoid. Each thylakoid membrane within a granum produces NADPH and ATP. Electrons move through sequential molecular complexes within the thylakoid membrane, and the last one passes electrons to $NADP^+$, after which it becomes NADPH. A carrier at the start of the electron transport chain pumps hydrogen ions from the stroma into the thylakoid space. When hydrogen ions flow back out of the space into the stroma through an ATP synthase complex, ATP is produced from ADP + Ⓟ.

Tropical Rain Forest Destruction and Climate Change

Leonardo DiCaprio not only is a famous actor but also strives to make global changes through his foundation. One aspect of the Leonardo DiCaprio Foundation is the protection of tropical rain forests. Most people think about saving the fragile species of plants and animals that live in the rain forest, but globally there is a larger issue at hand.

Climate change is a suite of global symptoms largely due to the introduction of certain gases into the atmosphere. For at least a thousand years prior to 1850, atmospheric carbon dioxide (CO_2) levels remained fairly constant at 0.028%. Since the 1850s, when industrialization began, the amount of CO_2 in the atmosphere has increased to 0.038% (Fig. 2A).

Role of Carbon Dioxide

In much the same way as the panes of a greenhouse, CO_2 and other gases in our atmosphere trap radiant heat from the sun. Therefore, these gases are called greenhouse gases. Without any greenhouse gases, the Earth's temperature would be about 33°C cooler than it is now. Likewise, increasing the concentration of greenhouse gases makes the Earth warmer and water more acidic.

Certainly, the burning of fossil fuels adds CO_2 to the atmosphere. But another factor that contributes to an increase in atmospheric CO_2 is tropical rain forest destruction.

Role of Tropical Rain Forests

Many scientists consider tropical rain forests to be the "lungs" of the Earth. Between 10 and 30 million hectares of rain forests are lost every year to ranching, logging, mining, and otherwise developing areas of the forest for human needs.

Each year, deforestation in tropical rain forests accounts for 10–20% of all CO_2 in the atmosphere. With your body, if you lose lung capacity, you lose body function. Similarly, the consequence of losing forests is greater trouble for climate change, because burning a forest adds CO_2 to the atmosphere and removes the trees that would ordinarily absorb CO_2.

The Earth Is a System

Carbon dioxide is removed from the air via photosynthesis, which takes place in forests, oceans, and other terrestrial and marine ecosystems. In fact, photosynthesis produces organic matter, which is estimated to be several hundred times the mass of the people living on Earth. Thus, these environments act as a sink for CO_2, preventing too much from accumulating in the atmosphere, where CO_2 can affect global temperatures and bring about climate change.

Despite their reduction in size from an original 15% to less than 5% of land surface today, tropical rain forests make a substantial contribution to global CO_2 removal. They are a critical element of the Earth's systems and, like any biological system, are essential for normal, healthy function. Tropical rain forests contribute greatly to the uptake of CO_2 and the productivity of photosynthesis, because they are the most efficient of all terrestrial ecosystems.

Tropical rain forests occur near the equator. They can exist wherever temperatures are above 26°C and rainfall is heavy (100–200 cm per year) and regular. Huge trees with buttressed trunks and broad, undivided, dark-green leaves predominate. Nearly all land plants in a tropical rain forest are woody, and woody vines are abundant.

It might be hypothesized that an increased amount of CO_2 in the atmosphere would cause photosynthesis to increase in the remaining portion of the forest. Recent studies, however, are showing that the opposite is true. Too much CO_2 can decrease photosynthesis, because increased temperatures can reduce water and mineral availability. Scientists working with wheat showed a decrease in the production of nitrogen-containing compounds; another study showed increased herbivory as plants were unable to produce their defense toxins at higher temperatures.

These and other studies show that, for the Earth, as for any biological system, equilibrium is necessary for health. As a biological system, the Earth is sensitive to environmental change. Our ability to properly balance human activity with the needs of the biosphere requires that we become educated about how the Earth functions.

Questions to Consider

1. How can a rise in temperature affect the production of food crops?
2. How can increased CO_2 levels affect the organisms that live in water?

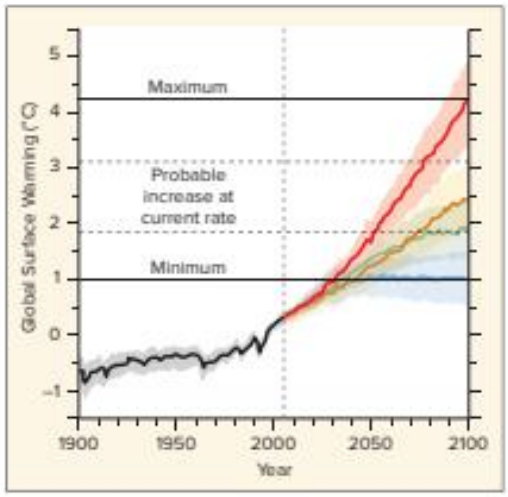


Figure 2A Climate change. Mean global temperature change is expected to rise due to the introduction of greenhouse gases into the atmosphere. (Source: nature.com: "Nature Climate Change," 3 [October 2012]: 369–73, doi:10.1038/nclimate1716.)

ATP Production

The thylakoid space acts as a reservoir for many hydrogen ions (H^+). First, each time water is oxidized, two H^+ remain in the thylakoid space. Second, as the electrons move from carrier to carrier via redox reactions along the electron transport chain, the electrons give up energy, which is used to pump H^+ from the stroma into the thylakoid space. Therefore, there are more H^+ in the thylakoid space than in the stroma. This difference and the resulting flow of H^+ (often referred to as protons in this context) from high to low concentration provide kinetic energy that allows an ATP synthase complex enzyme to enzymatically produce ATP from ADP + Ⓟ. This method of producing ATP is called **chemiosmosis,** because ATP production is tied to the establishment of an H^+ gradient.

Check Your Progress 2.3

1. Distinguish visible light from the electromagnetic spectrum.
2. Describe the movement of electrons from water to $NADP^+$ in the light reactions.

2.4 Plants Fix Carbon Dioxide

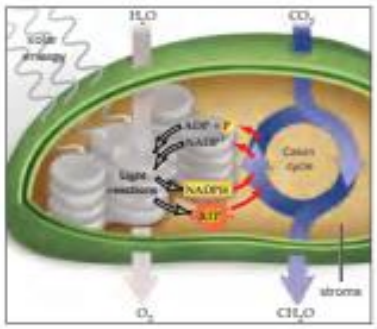
Learning Outcomes

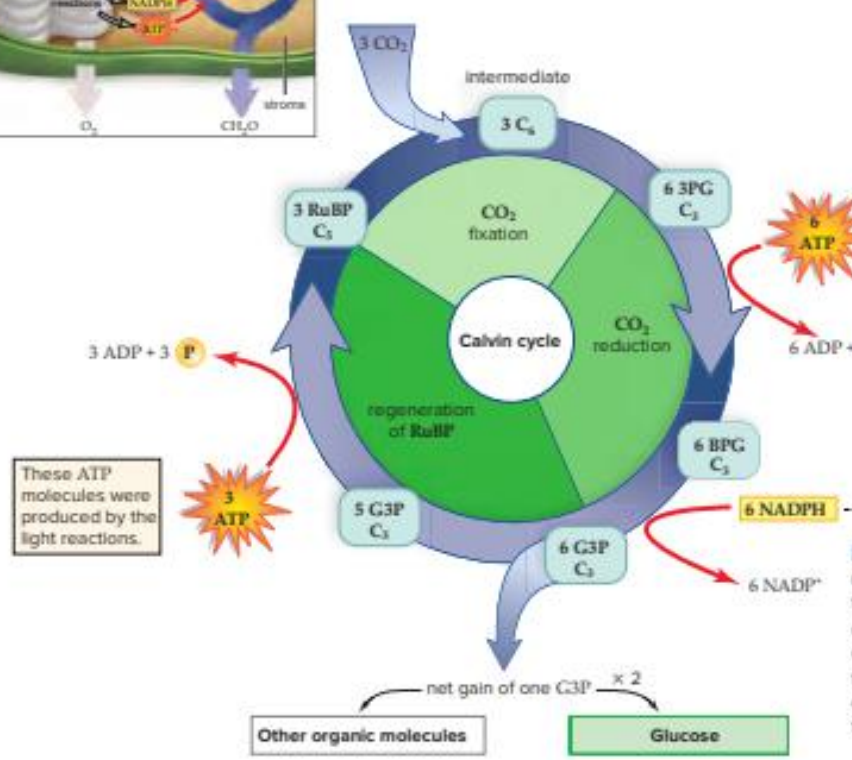
Upon completion of this section, you should be able to

1. Describe the three steps of the Calvin cycle and when ATP and/or NADPH is needed.
2. Evaluate the significance of RuBP carboxylase enzyme to photosynthesis.
3. Explain how glyceraldehyde-3-phosphate (G3P) is used to produce other necessary plant molecules.

During the light reactions, the high-energy molecules ATP and NADPH were produced. The Calvin cycle, another series of chemical reactions, will use these high-energy molecules for an amazing process—carbon dioxide fixation. Carbon dioxide in its gas form is all around us in our atmosphere. We and other respiring organisms release it as waste during cellular respiration. Unfortunately, CO_2 is unattainable by heterotrophs—we cannot harness or extract CO_2 from the air and then use those carbon atoms to make sugar. Plants, and other autotrophs, can take the carbon from CO_2 gas and convert, or "fix," it in the bonds of a carbohydrate. The word *fixation* is not limited to photosynthesis. As you will learn in later chapters, some bacteria can undergo fixation by removing nitrogen from the air and fixing it into organic molecules.

The Calvin cycle is a series of reactions that can occur in the dark, but it uses the products of the light reactions to reduce carbon dioxide captured from the atmosphere to a carbohydrate. The Calvin cycle has three steps: (1) carbon dioxide fixation, (2) carbon dioxide reduction, and (3) regeneration of RuBP (Fig. 2.10).





Metabolites of the Calvin Cycle	
RuBP	ribulose-1,5-bisphosphate
3PG	3-phosphoglycerate
BPG	1,3-bisphosphoglycerate
G3P	glyceraldehyde-3-phosphate

Figure 2.10 The Calvin cycle reactions. The Calvin cycle is divided into three portions: CO_2 fixation, CO_2 reduction, and regeneration of RuBP. Because five G3P are needed to re-form three RuBP, it takes three turns of the cycle to have a net gain of one G3P. Two G3P molecules are needed to form glucose.

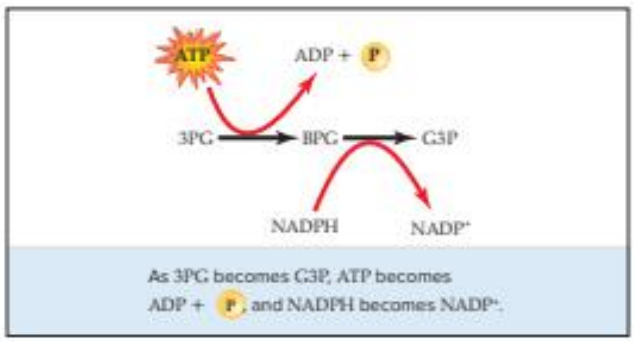
Step 1: Fixation of Carbon Dioxide

Carbon dioxide fixation is the first step of the Calvin cycle. During this reaction, a molecule of carbon dioxide from the atmosphere is attached to RuBP (ribulose-1,5-bisphosphate), a 5-carbon molecule. The result is one 6-carbon molecule, which splits into two 3-carbon molecules.

The enzyme that speeds this reaction, called **RuBP carboxylase,** is a protein that makes up about 20–50% of the protein content of chloroplasts. The reason for its abundance may be that it is unusually slow—it processes only a few molecules of substrate per second compared to thousands per second for a typical enzyme—so there has to be a lot of it to keep the Calvin cycle going.

Step 2: Reduction of Carbon Dioxide

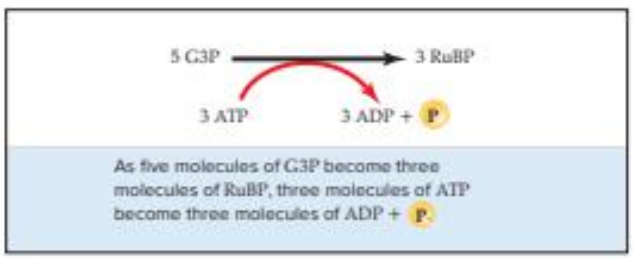
The first 3-carbon molecule in the Calvin cycle is called 3PG (3-phosphoglycerate). Each of two 3PG molecules undergoes reduction to G3P (glyceraldehyde-3-phosphate) in two steps:



Energy and electrons are needed for this reduction reaction, and they are supplied by the ATP and NADPH that were made during the light reactions. The difference between 3PG, BPG, and G3P (all with 3 carbons) is that G3P is reduced, has more electrons, and is now more chemically able to store energy and form larger organic molecules, such as glucose.

Step 3: Regeneration of RuBP

Notice that the Calvin cycle reactions in Figure 2.10 are multiplied by 3 because it takes three turns of the Calvin cycle to allow one G3P to exit. Why? For every three turns of the Calvin cycle, five molecules of G3P are used to re-form three molecules of RuBP, and the cycle continues. Notice that 5 × 3 (carbons in G3P) = 3 × 5 (carbons in RuBP):



This reaction also uses some of the ATP produced by the light reactions.

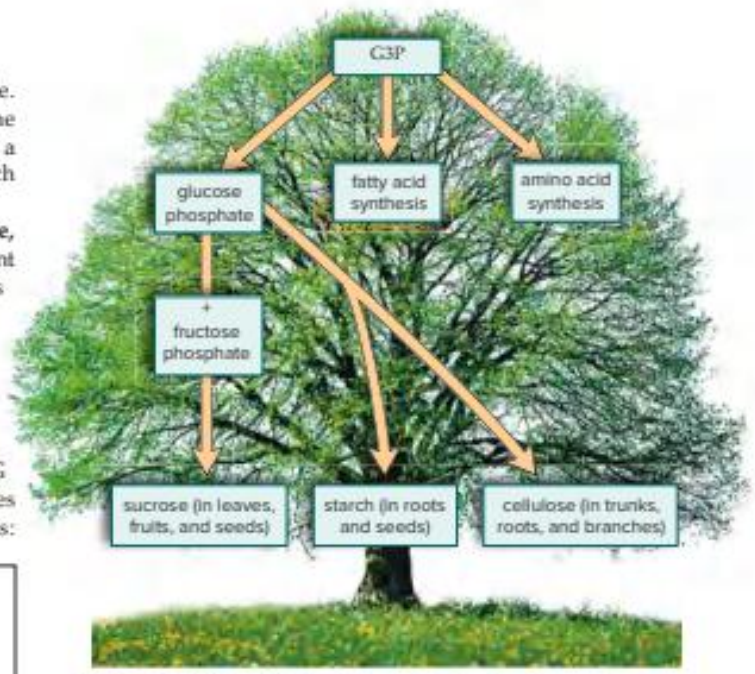


Figure 2.11 Fate of G3P. G3P is the first reactant in a number of plant cell metabolic pathways. From this starting point, different carbohydrates can be produced, such as sucrose, starch, and cellulose. Fatty acid synthesis leads to triglycerides making up plant oils, and production of amino acids allows the plant to make proteins.

The Importance of the Calvin Cycle

G3P is the product of the Calvin cycle that can be converted to other molecules a plant needs. Notice that glucose phosphate is among the organic molecules that result from G3P metabolism (Fig. 2.11). This is of interest to us because glucose is the molecule that plants and animals most often metabolize to produce the ATP molecules they require for their energy needs.

Glucose phosphate can be combined with fructose (and the phosphate removed) to form sucrose, the molecule that plants use to transport carbohydrates from one part of the plant to the other. Glucose phosphate is also the starting point for the synthesis of starch and cellulose. Starch is the storage form of glucose. Some starch is stored in chloroplasts, but most starch is stored in amyloplasts in roots. Cellulose is a structural component of plant cell walls and becomes fiber in our diet, because we are unable to digest it.

A plant can use the hydrocarbon skeleton of G3P to form fatty acids and glycerol, which are combined in plant oils. We are all familiar with corn oil, sunflower oil, and olive oil, used in cooking. As mentioned in the beginning of the chapter, researchers are modifying photosynthesis to produce oils that could also be used as fuel. When nitrogen is added to the hydrocarbon skeleton derived from G3P, amino acids are formed, allowing the plant to produce protein.

Check Your Progress 2.4

1. Describe the three major steps of the Calvin cycle.
2. Illustrate why it takes three turns of the Calvin cycle to produce one G3P.

2.5 Other Types of Photosynthesis

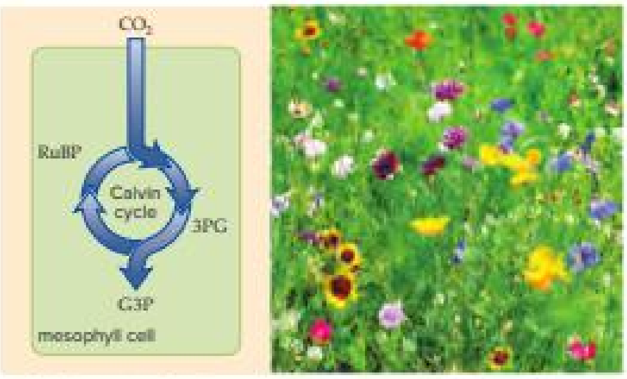
Learning Outcomes

Upon completion of this section, you should be able to

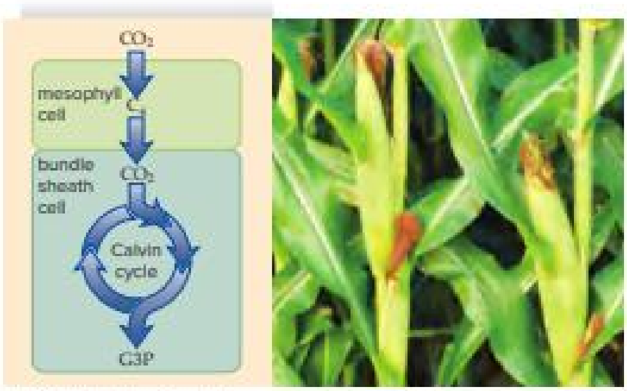
1. Compare the internal location of photosynthesis in C_3 and C_4 plants.
2. Contrast C_3/C_4 modes of photosynthesis with CAM photosynthesis.
3. Explain how different ways of achieving photosynthesis allow plants to adapt to particular environments.

The majority of plants, such as azaleas, maples, and tulips, carry on photosynthesis as previously described and are called **C_3 plants** (Fig. 2.12*a*). C_3 plants use the enzyme RuBP carboxylase to fix CO_2 to RuBP in mesophyll (photosynthetic) cells. The first detected molecule following fixation is the 3-carbon molecule 3PG:

$$\text{RuBP} + CO_2 \xrightarrow{\text{RuBP carboxylase}} 2\ \text{3PG}$$



a. CO_2 fixation in a C_3 plant, wildflowers



b. CO_2 fixation in a C_4 plant, corn, *Zea mays*

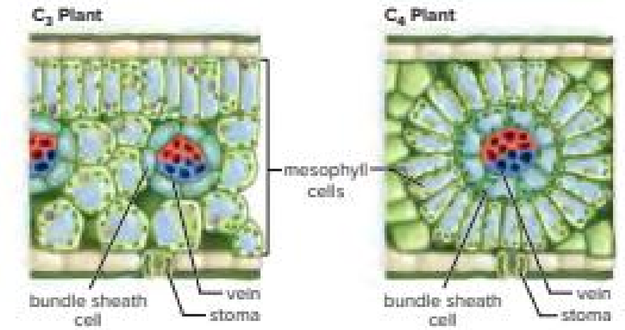
Figure 2.12 Carbon dioxide fixation in C_3 and C_4 plants. **a.** In C_3 plants, CO_2 is taken up by the Calvin cycle directly in mesophyll cells. **b.** C_4 plants form a C_4 molecule in mesophyll cells prior to releasing CO_2 to the Calvin cycle in bundle sheath cells.

As shown in Figure 2.2, leaves have small openings called stomata, through which water can leave and carbon dioxide (CO_2) can enter. If the weather is hot and dry, the stomata close, conserving water. (Water loss might cause the plant to wilt and die.) Now the concentration of CO_2 decreases in leaves, while O_2, a by-product of photosynthesis, increases. When O_2 rises in C_3 plants, RuBP carboxylase combines it with RuBP instead of CO_2. The result is one molecule of 3PG and the eventual release of CO_2. This is called **photorespiration,** because in the presence of light (*photo*), oxygen is taken up and CO_2 is released (*respiration*).

An adaptation called C_4 photosynthesis enables some plants to avoid photorespiration.

C_4 Photosynthesis

In a C_3 plant, the mesophyll cells contain well-formed chloroplasts and are arranged in parallel layers. In a C_4 leaf, the bundle sheath cells, as well as the mesophyll cells, contain chloroplasts. Further, the mesophyll cells are arranged concentrically around the bundle sheath cells:



C_4 plants fix CO_2 to PEP (phosphoenolpyruvate, a C_3 molecule) using the enzyme PEP carboxylase (PEPCase). The result is oxaloacetate, a C_4 molecule:

$$\text{PEP} + CO_2 \xrightarrow{\text{PEPCase}} \text{oxaloacetate}$$

In a C_4 plant, CO_2 is taken up in mesophyll cells, and then malate, a reduced form of oxaloacetate, is pumped into the bundle sheath cells (Fig. 2.12*b*). Only here does CO_2 enter the Calvin cycle.

Because it takes energy to pump molecules, you would think that the C_4 pathway would be disadvantageous. Yet in hot, dry climates, the net photosynthetic rate of C_4 plants, such as sugarcane, corn, and Bermuda grass, is about two to three times that of C_3 plants (e.g., wheat, rice, and oats). Why do C_4 plants enjoy such an advantage? The answer is that they can avoid photorespiration, discussed previously. Photorespiration is wasteful, because it is not part of the Calvin cycle. Photorespiration does not occur in C_4 leaves because PEPCase, unlike RuBP carboxylase, does not combine with O_2. Even when stomata are closed, CO_2 is delivered to the Calvin cycle in the bundle sheath cells.

When the weather is moderate, C_3 plants ordinarily have the advantage, but when the weather becomes hot and dry, C_4 plants have the advantage, and we can expect them to predominate. In the early summer, C_3 plants such as Kentucky bluegrass and creeping

bent grass predominate in lawns in the cooler parts of the United States, but by midsummer, crabgrass, a C_4 plant, begins to take over.

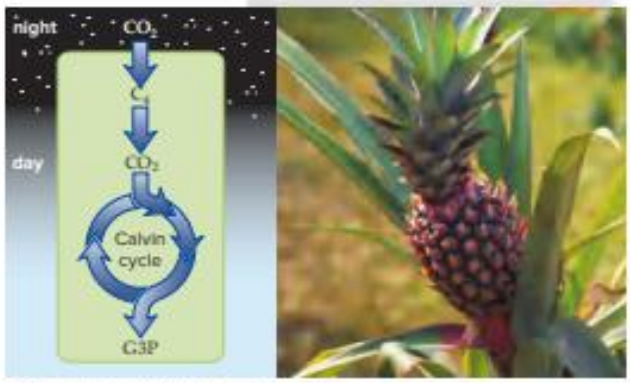
CAM Photosynthesis

CAM stands for crassulacean-acid metabolism; the Crassulaceae is a family of flowering succulent (water-containing) plants, such as a jade plant, that live in warm, dry regions of the world. CAM was first discovered in these plants, but now it is known to be prevalent among other groups of plants as well, such as pineapples.

Whereas a C_4 plant represents partitioning in space—carbon dioxide fixation occurs in mesophyll cells, while the Calvin cycle occurs in bundle sheath cells—CAM is partitioning by the use of time. During the night, CAM plants use PEPCase to fix some CO_2, forming C_4 molecules, which are stored in large vacuoles in mesophyll cells. During the day, C_4 molecules (malate) release CO_2 to the Calvin cycle when NADPH and ATP are available from the light reactions (Fig. 2.13). The primary advantage for this partitioning again has to do with the conservation of water. CAM plants open their stomata only at night; therefore, only at that time does atmospheric CO_2 enter the plant. During the day, the stomata close; this conserves water, but CO_2 cannot enter the plant. Photosynthesis in a CAM plant is minimal, because a limited amount of CO_2 is fixed at night, but it does allow CAM plants to live under stressful conditions.

Photosynthesis and Adaptation to the Environment

The different types of photosynthesis give us an opportunity to consider that organisms are metabolically adapted to their environment. Each method of photosynthesis has its advantages and disadvantages, depending on the climate.



CO_2 fixation in a CAM plant, pineapple, *Ananas comosus*

Figure 2.13 Carbon dioxide fixation in a CAM plant. CAM plants, such as pineapple, fix CO_2 at night, forming a C_4 molecule that is released to the Calvin cycle during the day.

C_4 plants most likely evolved in, and are adapted to, areas of high light intensities, high temperatures, and limited rainfall. C_4 plants, however, are more sensitive to cold, and C_3 plants do better than C_4 plants below 25°C. CAM plants, on the other hand, compete well with either type of plant when the environment is extremely arid. Surprisingly, CAM is quite widespread and has evolved into 23 families of flowering plants, including some lilies and orchids! And it is found among nonflowering plants, including some ferns and cone-bearing trees.

Check Your Progress 2.5

1. Describe some plants that use a method of photosynthesis other than C_3 photosynthesis.
2. Explain why C_4 photosynthesis is advantageous in hot, dry conditions.

Reviewing *the* BIG IDEAS

BIG IDEA 1

Autotrophs that evolved early in Earth's history likely used reducing agents such as hydrogen sulfide as a source of electrons. 1.B.1.a.3; *2.A.2.a.1*

Photoautotrophs capture free energy from sunlight; the ability to use water as a source of electrons, followed by the release of oxygen into the atmosphere, likely evolved in a common ancestor of cyanobacteria, plants, algae, and certain other unicellular eukaryotes. 1.B.1.a.3; *2.A.2.a.1*; *2.A.2.e*

BIG IDEA 2

Autotrophs make their own food, whereas heterotrophs take in food made by other organisms. 2.A.2.a,b

Through a series of coordinated metabolic pathways, photosynthesis captures free energy in sunlight that, in turn, is used to produce carbohydrates and other organic molecules from carbon dioxide and water, providing free energy to drive cellular processes in all organisms. 2.A.2.c,d

BIG IDEA 4

The double-membraned structure of chloroplasts allows cells to capture solar energy and convert it to chemical energy in photosynthesis. 4.A.2.g

Autotrophs take in carbon dioxide from the environment when they photosynthesize; in turn, carbon dioxide is returned to the atmosphere when autotrophs and heterotrophs carry on cellular respiration, thus cycling carbon atoms through living organisms. 4.A.6.a,c,d

Interactions among organisms and with their environment result in the transfer of free energy, with food chains and food webs dependent upon the carbohydrates produced by photosynthesis. 4.A.6.a,d

SUMMARIZE

AP Answering the Essential Questions

Living vorganisms require free energy to maintain order, grow, and reproduce, and they use various strategies to capture, transform, store, and transfer energy. Two of these strategies are **photosynthesis** and **cellular respiration.** Plants, algae, some unicellular eukaryotes, and cyanobacteria are **autotrophs** and make their own food by photosynthesis, transforming solar energy into the chemical energy of sugars. In turn, **heterotrophs** consume the products of photosynthesis to meet their energy demands. This concept carries through the various levels in a food chain or food web: plants use sunlight to produce chemical energy (food) for themselves and other organisms (consumers). If plants disappeared, Earth would not be able to support life—a good argument to protect ecosystems.

Early autotrophs The earliest autotrophs that evolved on Earth—the chemoautotrophs—captured free energy from small inorganic molecules like H_2S from their environment in the absence of oxygen. Today photoautotrophs capture free energy present in sunlight. The wavelengths of light captured possess enough energy to split water, providing a source of hydrogen ions, electrons, and oxygen gas. (You'll soon see why autotrophs need hydrogen ions and electrons.) Several million years ago this resulted in an increasingly oxidizing atmosphere. Aerobic cellular respiration taps into the oxidizing ability of oxygen, allowing organic compounds to be used as fuel to power cellular processes. Thus, photosynthesis and cellular respiration are interdependent processes. Photosynthesis generates oxygen and organic molecules that are used by the mitochondria of eukaryotes as fuel for cellular respiration. Both processes produce **ATP,** the energy currency of the cell. The waste products of cellular respiration, carbon dioxide and water, cycle back as the raw materials for photosynthesis. The overall equation for photosynthesis shows that it is a redox reaction in which carbon dioxide is reduced, and water is oxidized:

$$\text{Energy} + 6\,CO_2 + 6\,H_2O \longrightarrow C_6H_{12}O_6 + 6\,O_2$$

The photosynthetic process Photosynthesis consists of two stages: the light-dependent or light-capturing reactions (nicknamed the light reactions) and the Calvin cycle. The light reactions take place in the thylakoid membranes of the chloroplasts, and the Calvin cycle occurs in the stroma of the chloroplasts. The light reactions begin with the capture of solar energy in the visible light range. Light-capturing pigments are embedded in the thylakoid membranes. Chlorophylls *a* and *b* absorb violet, blue, and red wavelengths best and reflect green. The carotenoids absorb violet-blue-green light and reflect yellow-to-orange light. What chlorophylls predominant are influenced by environmental factors, including temperature (that's why the leaves of many trees turn different colors in the fall). Also embedded in the internal membranes of chloroplasts are two **photosystems** (PS I and PS II), which are pigment complexes that capture solar energy and excite electrons to higher energy levels. In the noncyclic pathway, PS II captures ph otons of light at a slightly higher energy level than PS I, energizing chlorophyll *a* electrons. The oxidation (splitting) of water replaces these electrons in the reaction-center chlorophyll *a* molecules. Oxygen is released to the atmosphere, and hydrogen ions (H^+) remain in the thylakoid space. PS I and PS II are connected by the transfer of higher free energy electrons through an electron transport chain (ETC), which pumps H^+ across the thylakoid membrane by chemiosmosis—a gradient used to make ATP via ATP synthase. In PS I light-energized electrons are captured by $NADP^+$, which combines with H^+ from the stroma to become NADPH. In the cyclic pathway carried on by some bacteria, ATP is generated but not NADPH.

The free energy yield of the light reactions stored in ATP and NADPH will be used to power the reactions of the Calvin cycle for **carbon fixation.** In carbon fixation, CO_2 from the atmosphere is reduced to carbohydrate, namely a three-carbon molecule called G3P (glyceraldehyde-3-phosphate, in case you are curious). Molecules of G3P can be used to synthesize all the organic materials a plant needs. (You don't need to memorize all the substrates, products, and enzymes in the Calvin cycle, but if provided with a diagram of the cycle, you should be able to follow it.) During the first stage of the Calvin cycle, the enzyme RuBP carboxylase "fixes" carbon from CO_2 to RuBP, producing an unstable six-carbon molecule that immediately splits into two 3-carbon molecules. As the cycle progresses, carbohydrate is produced using NADPH and ATP from the light reactions. Each "turn" of the Calvin cycle produces one G3P molecule; five other G3P molecules are used to regenerate RUBP. It takes two G3P molecules to produce one molecule of glucose ($C_6H_{12}O_6$).

ASSESS

Choose the best answer for each question.

2.1 Photosynthetic Organisms

1. All of the following are examples of organisms that can photosynthesize EXCEPT
   a. cyanobacteria.
   b. pine trees.
   c. cacti.
   d. mushrooms.
2. Carbon dioxide enters leaves through a small opening called the
   a. stoma.
   b. stroma.
   c. thylakoid.
   d. granum.

2.2 The Process of Photosynthesis

3. The function of light reactions is to
   a. obtain CO_2.
   b. make carbohydrate.
   c. convert light energy into a usable form of chemical energy.
   d. regenerate RuBP.
4. The Calvin cycle reactions
   a. produce carbohydrate.
   b. convert one form of chemical energy into a different form of chemical energy.
   c. regenerate more RuBP.
   d. All of these are correct.

2.3 Plants Convert Solar Energy

5. The final acceptor of electrons during the light reactions of the noncyclic electron pathway is
   a. PS I.
   b. PS II.
   c. ATP.
   d. $NADP^+$.
   e. water.
6. The oxygen given off by photosynthesis comes from
   a. H_2O.
   b. CO_2.
   c. glucose.
   d. RuBP.
7. Chemiosmosis
   a. depends on complexes in the thylakoid membrane.
   b. depends on an electrochemical gradient.
   c. depends on a difference in H^+ concentration between the thylakoid space and the stroma.
   d. All of these are correct.

2.4 Plants Fix Carbon Dioxide

For questions 8–10, indicate whether the statement is true (T) or false (F).

8. RuBP carboxylase is the enzyme that fixes carbon dioxide to RuBP in the Calvin cycle. _____
9. When 3PG becomes G3P during the light reactions, carbon dioxide is reduced to carbohydrate. _____
10. NADPH and ATP cycle between the Calvin cycle and the light reactions constantly. _____

11. The ATP and NADPH from the light reactions are used to
    a. split water.
    b. cause RuBP carboxylase to fix CO_2.
    c. re-form the photosystems.
    d. convert 3PG to G3P.

2.5 Other Types of Photosynthesis

12. CAM photosynthesis
    a. is the same as C_4 photosynthesis.
    b. is an adaptation to cold environments in the Southern Hemisphere.
    c. is prevalent in desert plants that close their stomata during the day.
    d. occurs in plants that live in marshy areas.
13. C_4 photosynthesis
    a. is the same as C_3 photosynthesis, because it takes place in chloroplasts.
    b. occurs in plants whose bundle sheath cells contain chloroplasts.
    c. is an advantage when the weather is hot and dry.
    d. Both b and c are correct.

ENGAGE

AP Applying the Big Ideas

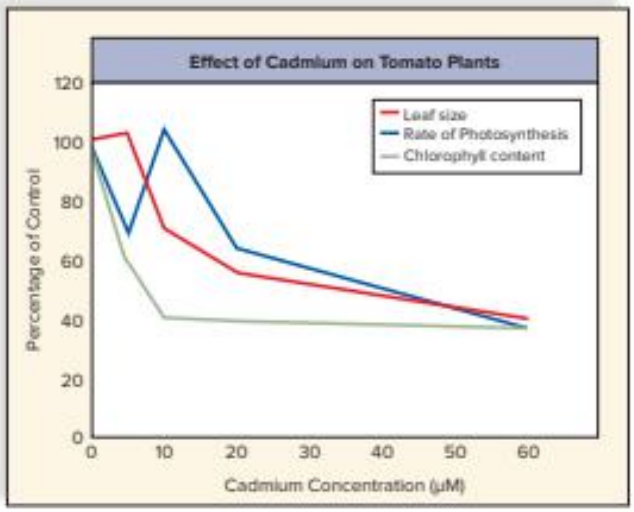
1. BIG IDEA 1 Scientists claim that organisms share many conserved core processes and features that evolved and are widely distributed among organisms today. **Defend this claim** using TWO pieces of evidence from metabolic pathways.

2. BIG IDEA 2 Construct an explanation of the mechanism and structural features of CELLS that allow organisms to capture, store or use free energy.
   a. **Describe** TWO mechanisms or structural features of cells employed for use in photosynthesis.
   b. **Explain** how the two features you described in part (a) function to allow organisms to capture, store or use free energy.

3. BIG IDEA 4 **Construct an explanation** for how variation in pigment molecules and the absorption of light by chloroplasts provides cells with a wider range of functions. Feel free to refer to evidence produced through scientific practices.

AP Applying the Science Practices

Cadmium is a heavy metal that is toxic to humans, plants, and animals. It is often found as a contaminant in soil. Use the data below to answer questions about the effect of cadmium on photosynthesis in tomato plants.



Data obtained from: Chaffei, C., et al. 2004. Cadmium toxicity induced changes in nitrogen management in *Lycopersicon esculentum* leading to a metabolic safeguard through an amino acid storage strategy. *Plant and Cell Physiology* 45(11): 1681–1693.

Think Critically SP 1 SP 5 SP 7

1. What was the effect of cadmium on leaf size, chlorophyll content, and photosynthesis rate?
2. At what concentration of cadmium was the largest effect on leaf size observed? On chlorophyll content? On photosynthesis rate?
3. Predict the effects on cellular respiration if an animal eats contaminated tomatoes.

My Notes

Every cell of this rock climber is manufacturing and using ATP.

3

Cellular Respiration

AP A rock climber, a bacterium moving through a solution, an ocelot climbing a tree, or a snail moving slowly to hide under a rock—each, including the tree, is making and using ATP. ATP is an ancient "molecular fossil." Its molecular structure, plus its presence in the first cell or cells that arose on Earth, accounts for its being the universal energy currency of cells.

ATP is unique among the cell's storehouse of chemicals; amino acids join to make a protein, and nucleotides join to make DNA or RNA, but ATP is singular and works alone. Whether you go swimming, take a tennis class, or just hang out, ATP molecules provide the energy needed for nerve conduction, muscle contraction, and any other cellular process that requires energy. Cellular respiration, by which cells harvest the energy of organic compounds and convert it to ATP molecules, is the topic of this chapter. It's a process that requires many steps and involves the cytoplasm and the mitochondria, the powerhouses of the cell.

As you read through the chapter, think about these Essential Questions:

1. How are the processes of photosynthesis and cellular respiration interdependent? 1.B.1.a.3
2. What is the role of the electron transport system in producing ATP? 2.A.2.b.2
3. What is the role of enzymes in regulating cellular respiration? 4.A.2.d.1-3

Chapter Outline

Following *the* BIG IDEAS

BIG IDEA 1 — The majority of organisms on Earth use cellular respiration, indicating an ancient biological lineage.

BIG IDEA 2 — Chemical energy in the bonds of food molecules can be released in small, regulated steps through cellular respiration, transferring free energy to create ATP molecules.

BIG IDEA 4 — The energy for life typically originates with sunlight; this solar energy passes to the chloroplast where some of it is stored in the chemical energy of carbohydrates, which are passed to mitochondria where some is stored in the chemical energy of ATP molecules.

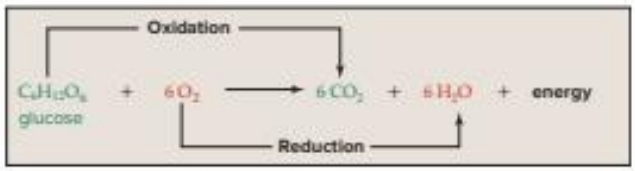
3.1 Overview of Cellular Respiration

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the overall reaction for glucose breakdown and show that it is a redox reaction.
2. Examine the role of the NADH and $FADH_2$ redox reactions in cellular respiration.
3. Summarize the phases of cellular respiration.

Cellular respiration is the process by which cells acquire energy by breaking down nutrient molecules produced by photosynthesizers. Cellular respiration requires oxygen (O_2) and gives off carbon dioxide (CO_2), which, in effect, is the opposite of photosynthesis. In fact, it is the reason any animal or human breathes (Fig. 3.1) and why plants require a supply of oxygen. This chemical interaction between animals and plants is important, because animals, like humans, breathe the oxygen made by photosynthesizers. Most often, cellular respiration involves the complete breakdown of glucose to carbon dioxide and water (H_2O):



This equation shows that cellular respiration is an oxidation-reduction reaction. Recall that oxidation is the loss of electrons and reduction is the gain of electrons therefore, glucose has been oxidized and O_2 has been reduced. Also remember that a hydrogen atom consists of a hydrogen ion plus an electron ($H^+ + e^-$). Therefore, when hydrogen atoms are removed from glucose, so are electrons; similarly, when hydrogen atoms are added to oxygen, so are electrons.

Glucose is a high-energy molecule, but its breakdown products, CO_2 and H_2O, are low-energy molecules. Therefore, as the equation shows, energy is released. This is the energy that will be used to produce ATP molecules. The cell carries out cellular respiration in order to build up ATP molecules.

The pathways of cellular respiration allow the energy within a glucose molecule to be released slowly, so that ATP can be produced gradually. Cells would lose a tremendous amount of energy if glucose breakdown occurred all at once—most of the energy would become nonusable heat. The step-by-step breakdown of glucose to CO_2 and H_2O usually produces a maximum yield of 36 to 38 ATP molecules, dependent on the conditions to be discussed later. The energy in these ATP molecules is equivalent to about 39% of the energy that was available in glucose. Even though it might seem less efficient, this conversion is more efficient than many others; for example, only between 20% and 30% of the energy within gasoline is converted to the motion of a car.

NAD^+ and FAD

Cellular respiration involves many individual metabolic reactions, each one catalyzed by its own enzyme. Enzymes of particular significance are those that use **NAD^+**, a coenzyme of oxidation-reduction (sometimes called a redox coenzyme). When a metabolite is oxidized, NAD^+ accepts two electrons plus a hydrogen ion (H^+), and NADH results. The electrons received by NAD^+ are high-energy electrons that are usually carried to the electron transport chain (see Fig. 6.12):

$$NAD^+ + 2e^- + H^+ \longrightarrow NADH$$

NAD^+ can oxidize a metabolite by accepting electrons and can reduce a metabolite by giving up electrons. Only a small amount of NAD^+ needs to be present in a cell, because each NAD^+ molecule is used over and over again. **FAD,** another coenzyme of

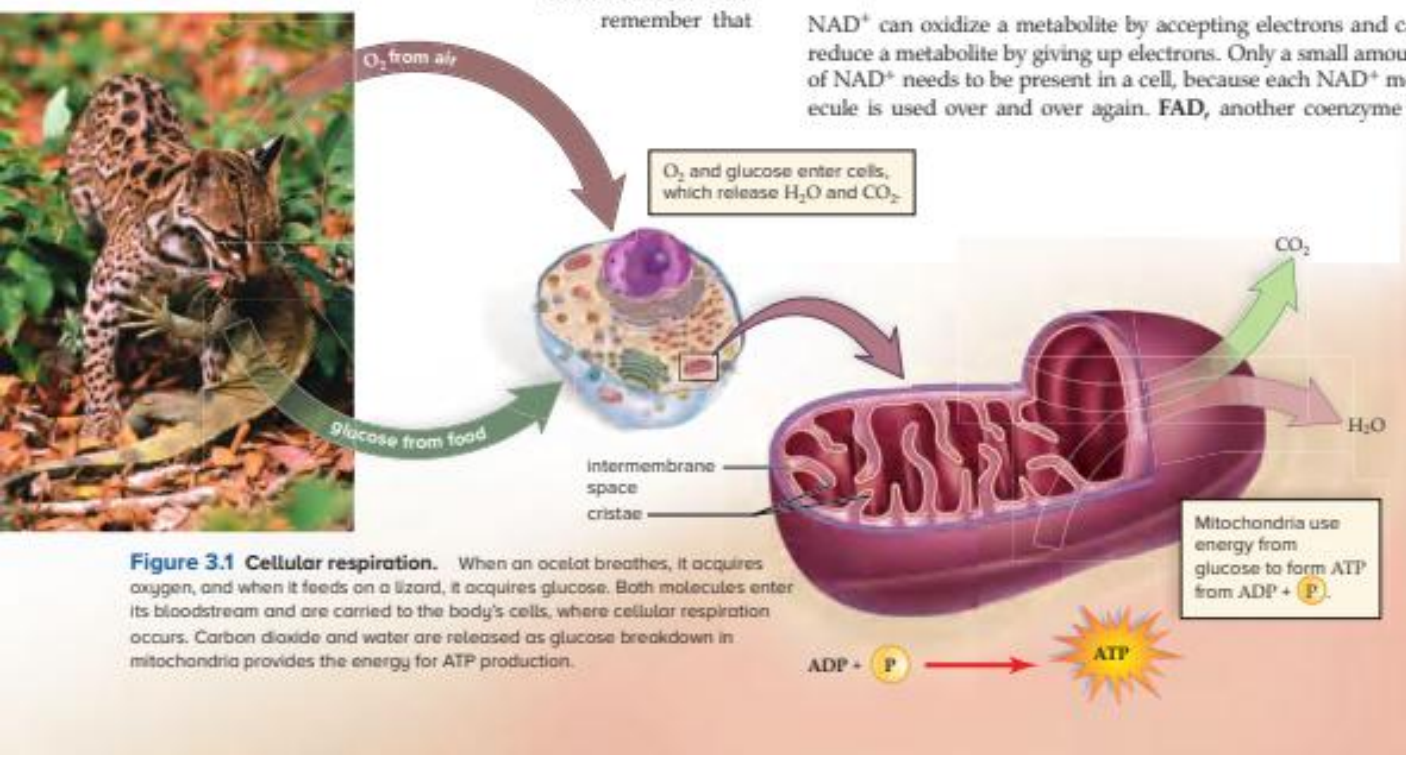


Figure 3.1 Cellular respiration. When an ocelot breathes, it acquires oxygen, and when it feeds on a lizard, it acquires glucose. Both molecules enter its bloodstream and are carried to the body's cells, where cellular respiration occurs. Carbon dioxide and water are released as glucose breakdown in mitochondria provides the energy for ATP production.

oxidation-reduction, is sometimes used instead of NAD^+. FAD accepts two electrons and two hydrogen ions (H^+) to become $FADH_2$.

Phases of Cellular Respiration

Cellular respiration involves four phases: glycolysis, the preparatory reaction, the citric acid cycle, and the electron transport chain (Fig. 3.2). Glycolysis takes place outside the mitochondria and does not require the presence of oxygen. Therefore, glycolysis is **anaerobic.** The other phases of cellular respiration take place inside the mitochondria, where oxygen is the final acceptor of electrons. Because they require oxygen, these phases are called **aerobic.**

During these phases, notice where CO_2 and H_2O, the end products of cellular respiration, and ATP, the main outcome of respiration, are produced.

- *Glycolysis* (Gk. *glycos,* "sugar"; *lysis,* "splitting") is the breakdown of glucose (a 6-carbon molecule) to two molecules of pyruvate (two 3-carbon molecules). Oxidation results in NADH and provides enough energy for the net gain of two ATP molecules.
- The *preparatory (prep) reaction* takes place in the matrix of the mitochondrion. Pyruvate is broken down from a 3-carbon (C_3) to a 2-carbon (C_2) acetyl group, and a 1-carbon CO_2 molecule is released. Since glycolysis ends with two molecules of pyruvate, the prep reaction occurs twice per glucose molecule.
- The *citric acid cycle* also takes place in the matrix of the mitochondrion. Each 2-carbon acetyl group matches up with a 4-carbon molecule, forming two 6-carbon citrate molecules. As citrate bonds are broken and oxidation occurs, NADH and $FADH_2$ are formed, and two CO_2 per citrate are released. The citric acid cycle is able to produce one ATP per turn. Because two acetyl groups enter the cycle per glucose molecule, the cycle turns twice.
- The *electron transport chain* (*ETC*) is a series of carriers on the cristae of the mitochondria. NADH and $FADH_2$ give up their high-energy electrons to the chain. Energy is released and captured as the electrons move from a higher-energy to a lower-energy state during each redox reaction. Later, this energy is used for the production of between 32 and 34 ATP by chemiosmosis. After oxygen receives electrons at the end of the chain, it combines with hydrogen ions (H^+) and becomes water (H_2O).

Pyruvate, the end product of glycolysis, is a pivotal metabolite; its further treatment depends on whether oxygen is available. If oxygen is available, pyruvate enters a mitochondrion and is broken down completely to CO_2 and H_2O, as shown in the cellular respiration equation (page 130). If oxygen is not available, pyruvate is further metabolized in the cytoplasm by an anaerobic process called **fermentation.** Fermentation results in a net gain of only two ATP per glucose molecule.

Check Your Progress 3.1

1. Describe how the formula for cellular respiration includes both oxidation and reduction reactions.
2. Explain why NAD^+ and FAD are needed during cellular respiration.
3. Describe the four phases of complete glucose breakdown, including which release CO_2 and which produce H_2O.

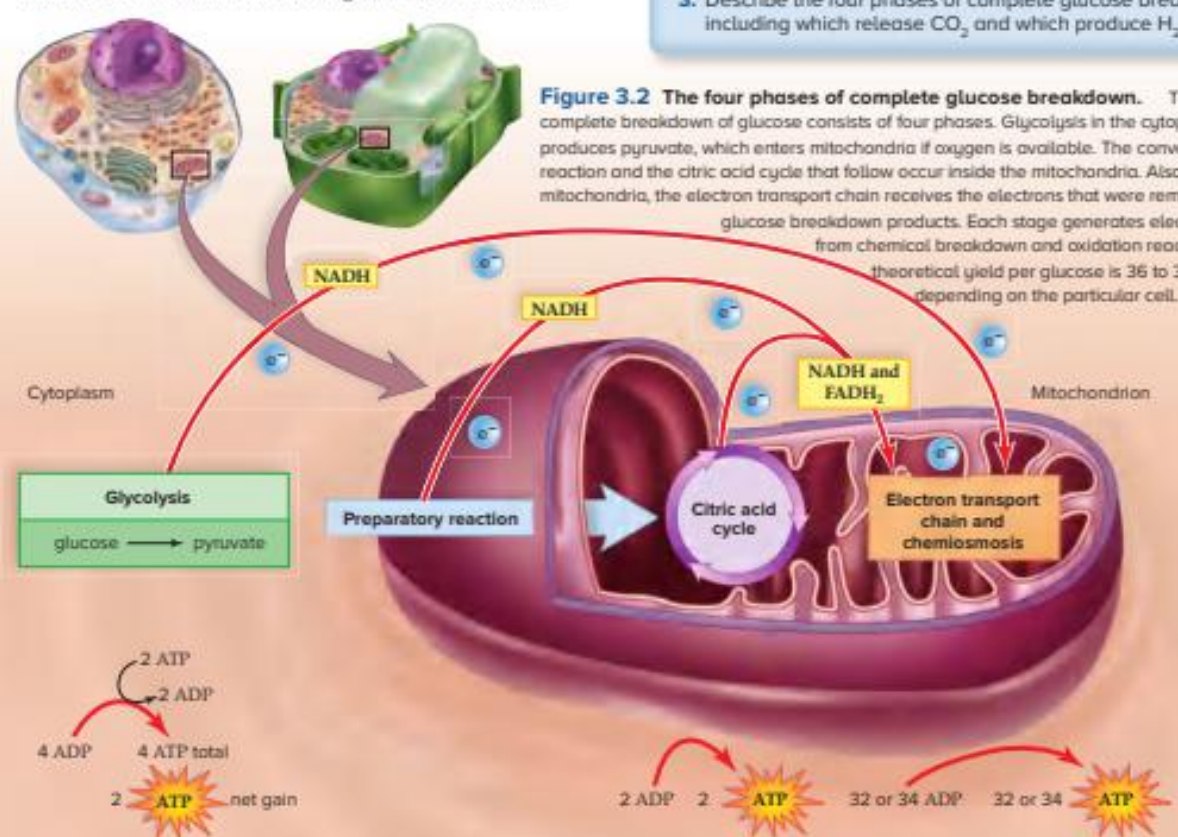


Figure 3.2 The four phases of complete glucose breakdown. The complete breakdown of glucose consists of four phases. Glycolysis in the cytoplasm produces pyruvate, which enters mitochondria if oxygen is available. The conversion reaction and the citric acid cycle that follow occur inside the mitochondria. Also, inside mitochondria, the electron transport chain receives the electrons that were removed from glucose breakdown products. Each stage generates electrons (e^-) from chemical breakdown and oxidation reactions. The theoretical yield per glucose is 36 to 38 ATP, depending on the particular cell.

3.2 Outside the Mitochondria: Glycolysis

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the role of glycolysis in cellular respiration.
2. List the inputs and outputs of glycolysis.
3. Explain how energy-investment and energy-harvesting steps of glycolysis result in two net ATP.

Glycolysis, which takes place within the cytoplasm outside the mitochondria, is the breakdown of C_6 (6-carbon) glucose to two C_3 (3-carbon) pyruvate molecules. Since glycolysis occurs universally in organisms, it most likely evolved before the citric acid cycle and the electron transport chain. This may be why glycolysis occurs in the cytoplasm and does not require oxygen. There was no free oxygen in Earth's early atmosphere.

Glycolysis is a series of ten reactions, and just as you would expect for a metabolic pathway, each step has its own enzyme. The pathway can be conveniently divided into the energy-investment step and the energy-harvesting steps. During the energy-investment step, ATP is used to "jump-start" glycolysis. During the energy-harvesting steps, four total ATP are made, producing two net ATP overall.

Energy-Investment Step

As glycolysis begins, two ATP are used to activate glucose by adding phosphate. Glucose eventually splits into two C_3 molecules known as G3P, the same molecule produced during photosynthesis. Each G3P has a phosphate group, each of which is acquired from an ATP molecule. From this point on, each C_3 molecule undergoes the same series of reactions.

Energy-Harvesting Steps

Oxidation of G3P now occurs by the removal of electrons accompanied by hydrogen ions. In duplicate reactions, electrons are picked up by coenzyme NAD^+, which becomes

$$2\,NAD^+ + 4\,e^- + 2\,H^+ \longrightarrow 2\,NADH$$

When O_2 is available, each NADH molecule carries two high-energy electrons to the electron transport chain and becomes NAD^+ again. In this way, NAD^+ is recycled and used again.

The addition of inorganic phosphate results in a high-energy phosphate group on each C_3 molecule. These phosphate groups are used to directly synthesize two ATP in the later steps of glycolysis. This is called **substrate-level ATP synthesis,** also called *substrate-level phosphorylation,* because an enzyme passes a high-energy phosphate to ADP, and ATP results (Fig. 3.3). Notice that this is an example of a coupled reaction: An energy-releasing reaction is driving forward an energy-requiring reaction on the surface of the enzyme.

Oxidation occurs again, but by the removal of H_2O. Substrate-level ATP synthesis occurs again per each C_3, and two molecules of pyruvate result. Subtracting the two ATP that were used to get started, and the four ATP produced overall, there is a net gain of two ATP from glycolysis (Fig. 3.4).

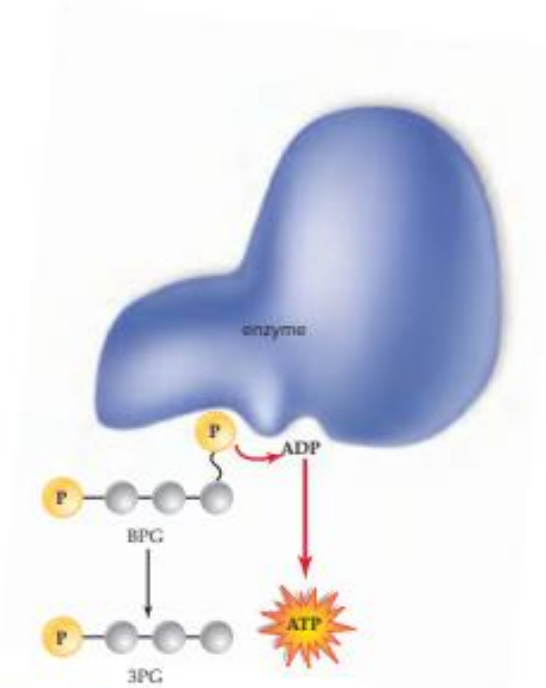
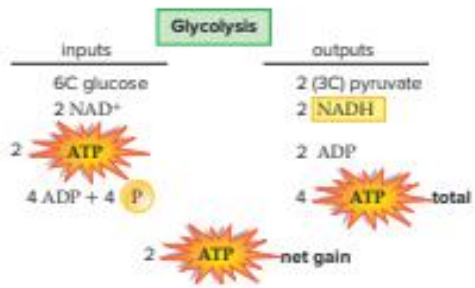


Figure 3.3 Substrate-level ATP synthesis. Substrates participating in the reaction are oriented on the enzyme. A phosphate group is transferred to ADP, producing one ATP molecule. During glycolysis (see Fig. 3.4), BPG is a C_3 substrate (each gray ball is a carbon atom) that gives up a phosphate group to ADP. This reaction occurs twice per glucose molecule.

Inputs and Outputs of Glycolysis

All together, the inputs and outputs of glycolysis are as follows:



Notice that, so far, we have accounted for only 2 of the 36 to 38 ATP molecules that are theoretically possible when glucose is completely broken down to CO_2 and H_2O. When O_2 is available, the end product of glycolysis, pyruvate, enters the mitochondria, where it is metabolized. If O_2 is not available, fermentation, which is discussed next, occurs.

Check Your Progress 3.2

1. Examine where ATP is used and produced in glycolysis.
2. Explain how ATP is produced from ADP and phosphate during glycolysis.
3. Summarize the location, inputs, and outputs of glycolysis.

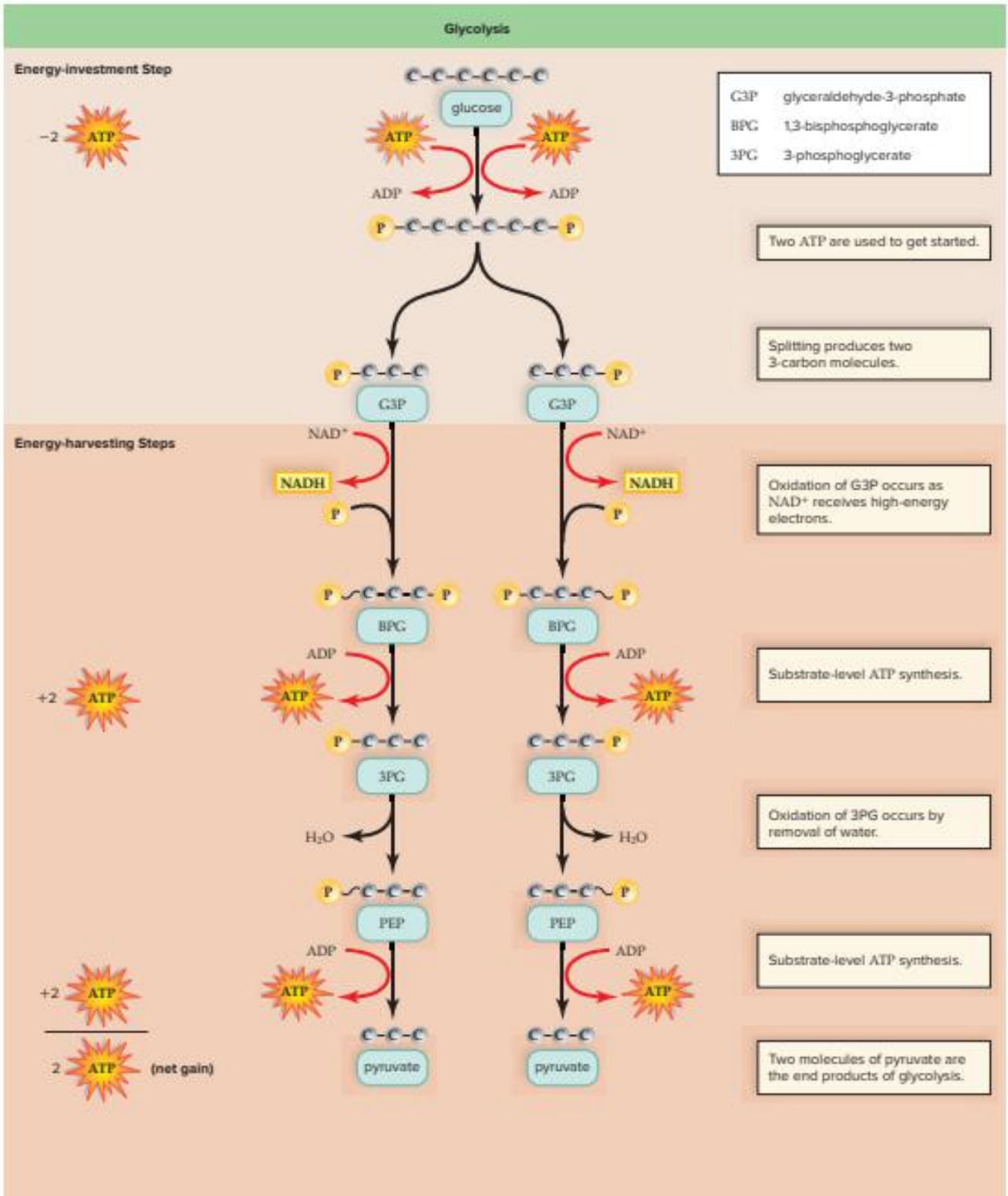


Figure 3.4 Glycolysis. This metabolic pathway begins with C_6 glucose (each gray ball is a carbon atom) and ends with two C_3 pyruvate molecules. Net gain of two ATP molecules can be calculated by subtracting those expended during the energy-investment step from those produced during the energy-harvesting steps. Each of the ten steps is catalyzed by a specialized enzyme.

3.3 Outside the Mitochondria: Fermentation

Learning Outcomes

Upon completion of this section, you should be able to

1. Summarize the two fermentation pathways.
2. Discuss the conditions under which organisms may switch between cellular respiration and fermentation.
3. Compare the benefits and drawbacks of fermentation.

Complete glucose breakdown requires an input of oxygen to keep the electron transport chain working. So how does the cell produce energy if oxygen is limited? **Fermentation** is an anaerobic process that produces a limited amount of ATP in the absence of oxygen. In animal cells, including human cells, pyruvate, the end product of glycolysis, is reduced by NADH to lactate (Fig. 3.5). Depending on their particular enzymes, bacteria vary as to whether they produce an organic acid, such as lactate, or an alcohol and CO_2. Yeasts are good examples of organisms that generate ethyl alcohol and CO_2 as a result of fermentation.

Why is it beneficial for pyruvate to be reduced when oxygen is not available? Because the cell still needs energy when oxygen is absent. The fermentation reaction regenerates NAD^+, which is required for the first step in the energy-harvesting phase of glycolysis. This NAD^+ is now "free" to return to the earlier reaction (see return arrow in Fig. 3.5) and become reduced once more. Although this process generates much less ATP than when oxygen is present and glucose is fully metabolized into CO_2 and H_2O in the ETC, glycolysis and substrate-level ATP synthesis produce enough energy for the cell to continue working.

Advantages and Disadvantages of Fermentation

As discussed in the Big Idea 2 feature, "Fermentation and Food Production," people have long used anaerobic bacteria that produce lactate to create cheese, yogurt, and sauerkraut—even before we knew that bacteria were responsible! Other bacteria produce chemicals of industrial importance, including isopropanol, butyric acid, proprionic acid, and acetic acid when they ferment. Yeasts, of course, are used to make breads rise.

Despite its low yield of only two ATP made by substrate-level ATP synthesis, lactic acid fermentation is essential to certain animals and tissues. Typically, animals use lactic acid fermentation for a rapid burst of energy, such as a cheetah chasing a gazelle. Also, when muscles are working vigorously over a short period of time, lactic acid fermentation provides them with ATP, even though oxygen is temporarily in limited supply.

Efficiency of Fermentation

The two ATP produced per glucose during alcoholic fermentation and lactic acid fermentation are equivalent to 14.6 kcal. Complete glucose breakdown to CO_2 and H_2O represents a possible energy yield of 686 kcal per molecule. Therefore, the efficiency of fermentation is only 14.6 kcal/686 kcal × 100, or 2.1% of the total possible for the complete breakdown of glucose. The inputs and outputs of fermentation are shown here:

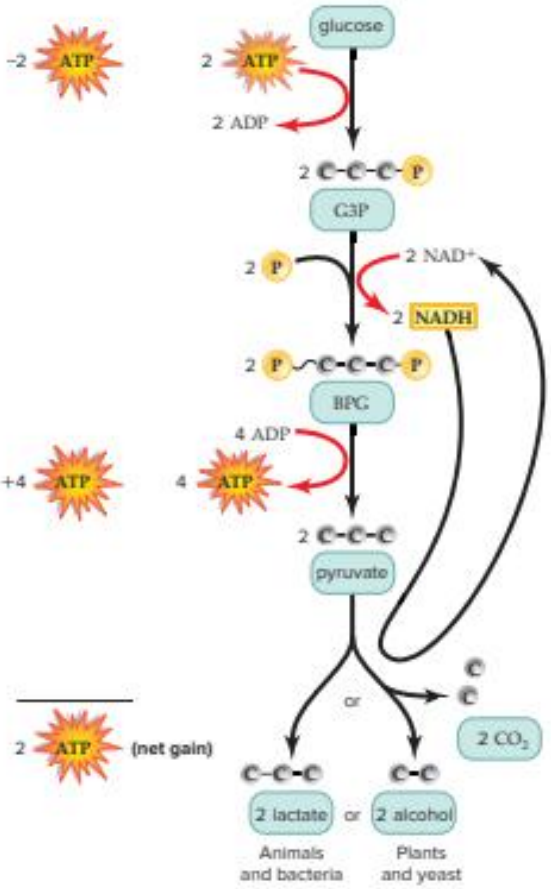
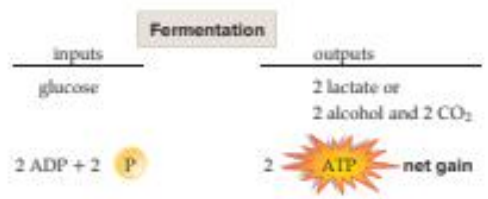


Figure 3.5 Fermentation. Fermentation consists of glycolysis followed by a reduction of pyruvate. This recycles NAD^+ and it returns to the glycolytic pathway to pick up more electrons. As with glycolysis, each step is catalyzed by a specialized enzyme.



The two ATP produced by fermentation fall far short of the theoretical 36 to 38 ATP molecules that may be produced by cellular respiration. To achieve this number of ATP per glucose molecule, it is necessary to move on to the reactions and pathways that occur with oxygen in the mitochondria.

Check Your Progress 3.3

1. Explain fermentation's role in NAD^+ regeneration.
2. Summarize the two forms of fermentation.
3. List the advantages and disadvantages of fermentation.

BIG IDEA 2: Energy and Molecular Building Blocks

Fermentation and Food Production

At the grocery store, you will find such items as bread, yogurt, soy sauce and pickles (Fig. 3A). These are just a few of the many foods that are produced when microorganisms ferment (break down sugar in the absence of oxygen). Foods produced by fermentation last longer, because the fermenting organisms have removed many of the nutrients that would attract other organisms. The products of fermentation can even be dangerous to the very organisms that produced them, as when yeasts are killed by the alcohol they produce.

Yeast Fermentation

Baker's yeast, *Saccharomyces cerevisiae*, is added to bread for the purpose of leavening—the dough rises when the yeasts give off CO_2. The ethyl alcohol produced by the fermenting yeast evaporates during baking. The many varieties of sourdough breads obtain their leavening from a starter composed of fermenting yeasts along with bacteria from the environment. Depending on the community of microorganisms in the starter, the flavor of the bread may range from sour and tangy, as in San Francisco–style sourdough, to a milder taste, such as that produced by most Amish friendship bread recipes.

Bacterial Fermentation

Yogurt, sour cream, and cheese are produced through the action of various lactic acid bacteria that cause milk to sour. Milk contains lactose, which these bacteria use as a carbohydrate source for fermentation. Yogurt, for example, is made by adding lactic acid bacteria, such as *Streptococcus thermophilus* and *Lactobacillus bulgaricus*, to milk and then incubating it to encourage the bacteria to convert the lactose. During the production of cheese, an enzyme called rennin must also be added to the milk to cause it to coagulate and become solid.

Old-fashioned brine cucumber pickles, sauerkraut, and kimchi are pickled vegetables produced by the action of acid-producing, fermenting bacteria that can survive in high-salt environments. Salt is used to draw liquid out of the vegetables and to aid in their preservation. The bacteria need not be added to the vegetables, because they are already present on the surfaces of the plants.

Soy Sauce Production

Soy sauce is traditionally made by adding a mold, *Aspergillus*, and a combination of yeasts and fermenting bacteria to soybeans and wheat. The mold breaks down starch, supplying the fermenting microorganisms with sugar they can use to produce organic acids.

As you can see from each of these examples, fermentation is a biologically and economically important process that scientists use for the betterment of our lives.

Questions to Consider

1. How would the production of fermentation products differ from that of other food products?
2. What products of fermentation do you use on a daily basis?

Figure 3A Products from fermentation. Fermentation of different carbohydrates by microorganisms like bacteria and yeast helps produce the products shown.

3.4 Inside the Mitochondria

Learning Outcomes

Upon completion of this section, you should be able to

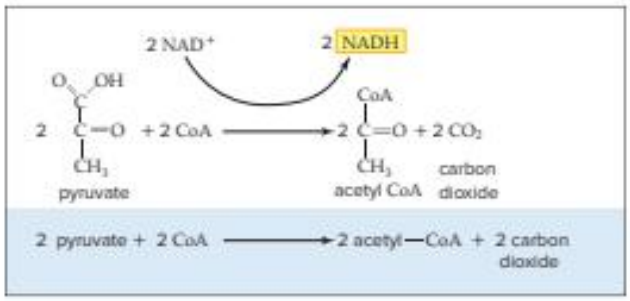
1. Explain the fate of each carbon during the complete aerobic metabolism of glucose.
2. Contrast substrate-level phosphorylation and chemiosmosis as methods of ATP synthesis.
3. Describe how electron energy from redox reactions is used to create a proton gradient.

The preparatory (prep) reaction, the citric acid cycle, and the electron transport chain, which are needed for the complete breakdown of glucose, take place within the mitochondria. A **mitochondrion** has a double membrane with an intermembrane space (between the outer and inner membrane). Cristae are folds of inner membrane that jut out into the matrix, the innermost compartment, which is filled with a gel-like fluid (Fig. 3.6). Like a chloroplast, a mitochondrion is highly structured, so we would expect reactions to be located in particular parts of this organelle.

The enzymes that speed the prep reaction and the citric acid cycle are arranged in the matrix, and the electron transport chain is located in the cristae in a very organized manner. Most of the ATP from cellular respiration is produced in mitochondria; therefore, mitochondria are often called the powerhouses of the cell.

The Preparatory Reaction

The **preparatory (prep) reaction** is so called because it converts products from glycolysis into products that enter the citric acid cycle. In this reaction, the C_3 pyruvate is converted to a C_2 acetyl group and CO_2 is given off. This is an oxidation reaction in which electrons are removed from pyruvate by NAD^+ and NADH is formed. One prep reaction occurs per pyruvate, so the prep reaction occurs twice per glucose molecule:



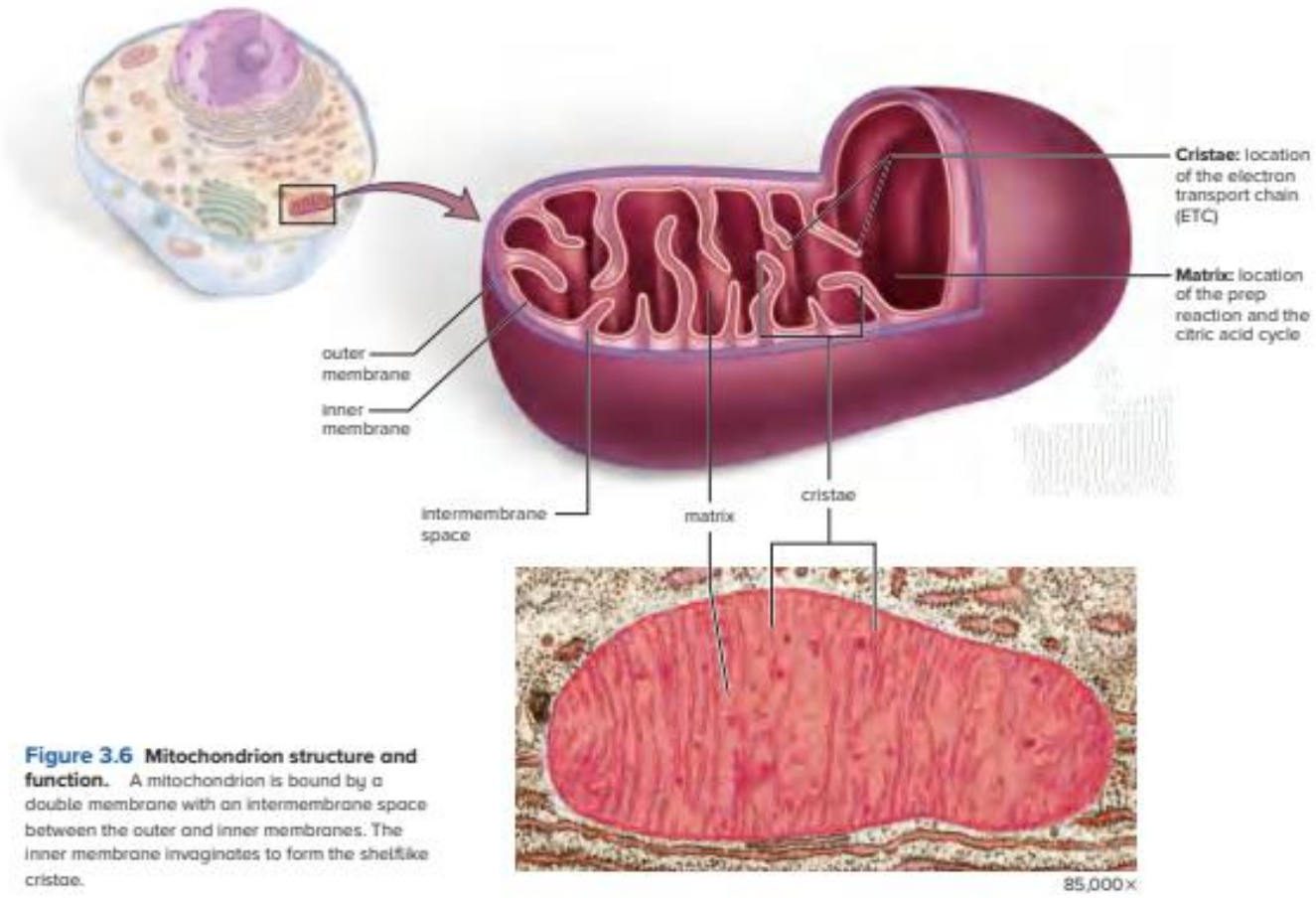


Figure 3.6 Mitochondrion structure and function. A mitochondrion is bound by a double membrane with an intermembrane space between the outer and inner membranes. The inner membrane invaginates to form the shelflike cristae.

The C_2 acetyl group is combined with a molecule known as CoA. CoA will carry the acetyl group to the citric acid cycle in the mitochondrial matrix. The two NADH carry electrons to the electron transport chain. What about the CO_2? In vertebrates, such as ourselves, CO_2 freely diffuses out of cells into the blood, which transports it to the lungs, where it is exhaled.

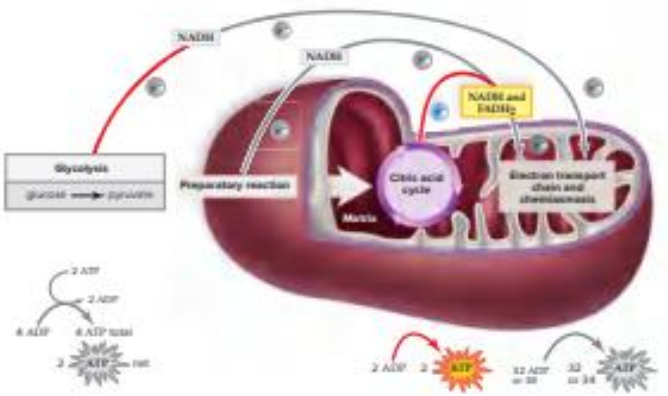
The Citric Acid Cycle

The **citric acid cycle,** also called the Krebs cycle, is a cyclical metabolic pathway located in the matrix of mitochondria (Fig. 3.7). At the start of the citric acid cycle, the (C_2) acetyl group carried by CoA joins with a C_4 molecule, and a C_6 citrate molecule results. During the cycle, oxidation occurs when electrons are accepted by NAD^+ in three instances and by FAD in one instance. Therefore, three NADH and one $FADH_2$ are formed as a result of one turn of the citric acid cycle. Also, the acetyl group received from the prep reaction is oxidized to two CO_2 molecules. Substrate-level ATP synthesis is also an important event of the citric acid cycle. In substrate-level ATP synthesis, you will recall, an enzyme passes a high-energy phosphate to ADP, and ATP results.

Because the citric acid cycle turns twice for each original glucose molecule, the inputs and outputs of the citric acid cycle per glucose molecule are as follows:

Citric acid cycle

inputs	outputs
2 (2C) acetyl groups	4 CO_2
6 NAD^+	6 NADH
2 FAD	2 $FADH_2$
2 ADP + 2 P	2 ATP



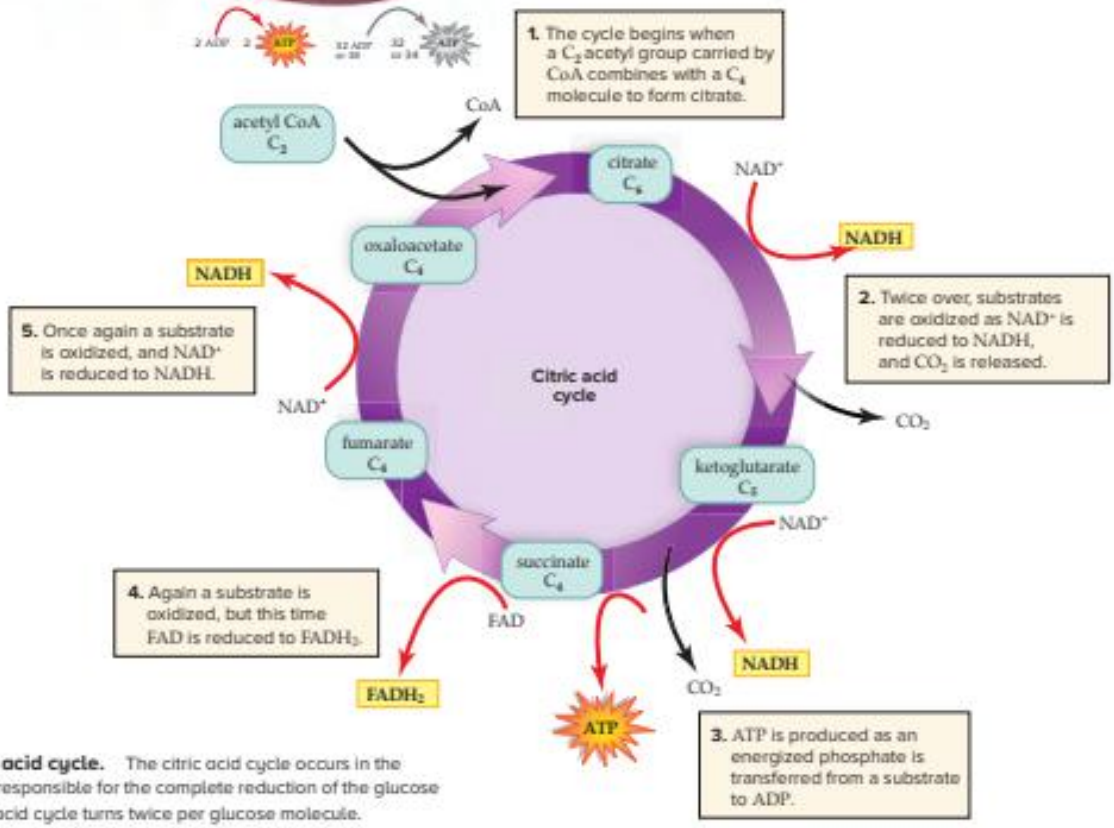


Figure 3.7 Citric acid cycle. The citric acid cycle occurs in the mitochondria and is responsible for the complete reduction of the glucose molecule. The citric acid cycle turns twice per glucose molecule.

Production of CO_2

The six carbon atoms originally located in a glucose molecule have now become CO_2. The prep reaction produces the first two CO_2, and the citric acid cycle produces the last four CO_2 per glucose molecule. We have already mentioned that this is the CO_2 humans and animals breathe out.

Thus far, we have broken down glucose to CO_2 and hydrogen atoms. Recall that, as bonds are broken and glucose gets converted to CO_2, energy in the form of high-energy electrons is released. NADH and $FADH_2$ capture those high-energy electrons and carry them to the electron transport chain, as discussed next.

Electron Transport Chain

The **electron transport chain** (**ETC**), located in the cristae of the mitochondria and the plasma membrane of aerobic prokaryotes, is a series of carriers that pass electrons from one to the other. The high-energy electrons that enter the electron transport chain are carried by NADH and $FADH_2$. Figure 3.8 is arranged to show that high-energy electrons enter the chain and low-energy electrons leave the chain.

Members of the Chain

When NADH gives up its electrons, it becomes oxidized to NAD^+, and when $FADH_2$ gives up its electrons, it becomes oxidized to FAD. The next carrier gains the electrons and is reduced. This oxidation-reduction reaction starts the process, and each of the carriers, in turn, becomes reduced and then oxidized as the electrons move down the chain.

Many of the redox carriers are cytochrome molecules. A **cytochrome** is a protein that has a tightly bound heme group with a central atom of iron, the same as hemoglobin does. When the iron accepts electrons, it becomes reduced, and when iron gives them up, it becomes oxidized. As the pair of electrons is passed from carrier to carrier, energy is captured and eventually used to form ATP molecules. A number of poisons, such as cyanide, cause death by binding to and blocking the function of cytochromes.

What is the role of oxygen in cellular respiration and the reason we breathe to take in oxygen? Oxygen is the final acceptor of electrons from the electron transport chain. Oxygen receives the energy-spent electrons from the last of the carriers (i.e., cytochrome oxidase). After receiving electrons, oxygen combines with hydrogen ions, and water forms:

$$\tfrac{1}{2}O_2 + 2e^- + 2H^+ \longrightarrow H_2O$$

The critical role of oxygen as the final acceptor of electrons during cellular respiration is exemplified by noting that if oxygen is not present, the chain does not function, and no ATP is produced by mitochondria. The limited capacity of the body to form ATP in a way that does not involve the electron transport chain means that death eventually results if oxygen is not available.

Cycling of Carriers

When NADH delivers high-energy electrons to the first carrier of the electron transport chain, enough energy has been captured by the time the electrons are received by O_2 to permit the production of three ATP molecules. When $FADH_2$ delivers high-energy electrons to the electron transport chain, two ATP are produced.

Once NADH has delivered electrons to the electron transport chain and has become NAD^+, it is able to return and pick up more hydrogen atoms. The reuse of coenzymes increases cellular efficiency, because the cell does not have to constantly make new NAD^+; it simply recycles what is already there.

The ETC Pumps Hydrogen Ions. Essentially, the electron transport chain consists of three protein complexes and two carriers. The three protein complexes are the NADH-Q reductase complex, the cytochrome reductase complex, and the cytochrome oxidase complex. The two other carriers that transport electrons between the complexes are coenzyme Q and cytochrome *c* (Fig. 3.8).

We have already seen that the members of the electron transport chain accept electrons, which they pass from one to the other via redox reactions. So what happens to the hydrogen ions (H^+) carried by NADH and $FADH_2$? The complexes of the electron transport chain use the energy released during redox reactions to pump these hydrogen ions from the matrix into the intermembrane space of a mitochondrion.

The vertical arrows in Figure 3.8 show that the protein complexes of the electron transport chain all pump H^+ into the intermembrane space. Energy obtained from electron passage is needed, because H^+ ions are pumped and actively transported against their gradient. This means the few H^+ ions in the matrix will be moved to the intermembrane space, where there are already many H^+ ions. Just as the walls of a dam hold back water, allowing it to collect, so do cristae hold back hydrogen ions. Eventually, a strong electrochemical gradient develops; about ten times as many H^+ are found in the intermembrane space as are present in the matrix.

The ATP Synthase Complex Produces ATP. The ATP synthase complex can be likened to the gates of a dam. When the gates of a hydroelectric dam are opened, water rushes through, and electricity (energy) is produced. Similarly, when H^+ flows down a gradient from the intermembrane space into the matrix, the enzyme ATP synthase synthesizes ATP from ADP + Ⓟ. This process is called **chemiosmosis,** because ATP production is tied to the establishment of an H^+ gradient.

Once formed, ATP moves out of mitochondria and is used to perform cellular work, during which it breaks down to ADP and Ⓟ. These molecules are then returned to mitochondria for recycling. At any given time, the amount of ATP in a human would sustain life for only about a minute; therefore, ATP synthase must constantly produce ATP. It is estimated that mitochondria produce our body weight in ATP every day.

Active Tissues Contain More Mitochondria. Active tissues, such as muscles, require greater amounts of ATP and have more mitochondria than less active cells. When a burst of energy is required, however, muscles still utilize fermentation.

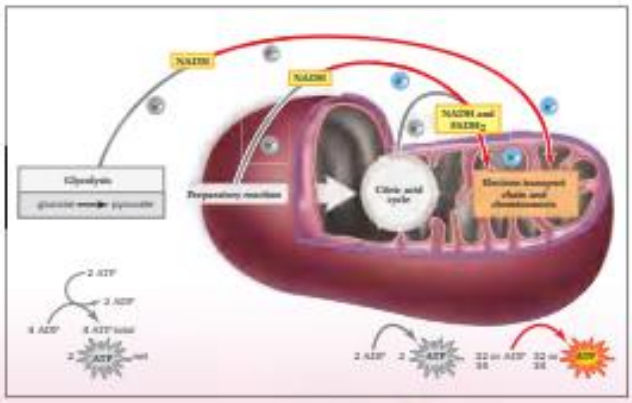
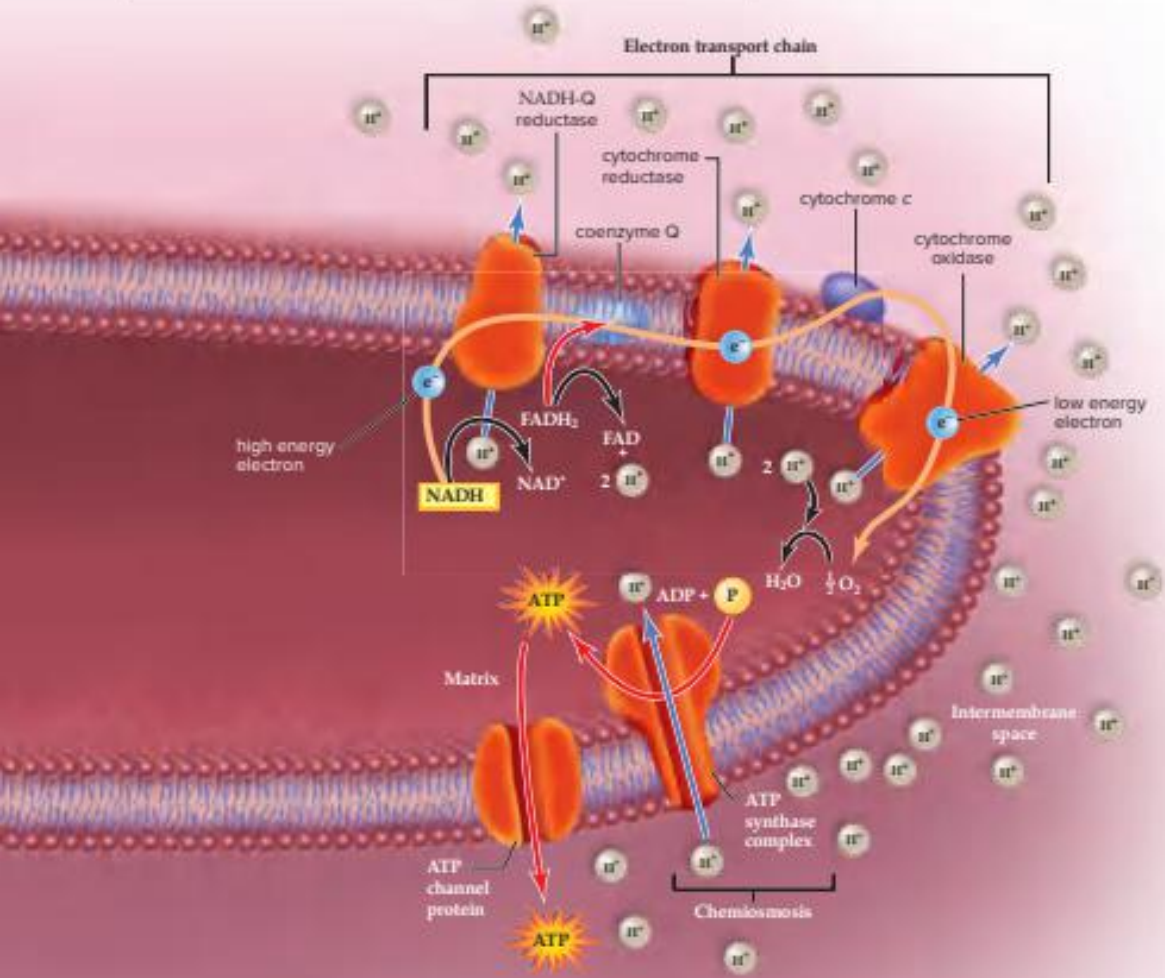


Figure 3.8 Organization and function of the electron transport chain. The electron transport chain is located in the mitochondrial cristae. NADH and $FADH_2$ take electrons to the electron transport chain. As electrons move from one protein complex to the other via redox reactions, energy is used to pump hydrogen ions (H^+) from the matrix into the intermembrane space. As hydrogen ions flow down a concentration gradient from the intermembrane space into the mitochondrial matrix, ATP is synthesized by the enzyme ATP synthase. For every pair of electrons that enters by way of NADH, three ATP result. For every pair of electrons that enters by way of $FADH_2$, two ATP result. Oxygen, the final acceptor of the electrons, becomes a part of water. ATP leaves the matrix by way of a channel protein.



As an example of the relative amounts of ATP, consider that the dark meat of chickens, namely the thigh meat, contains more mitochondria than the white meat of the breast. This suggests that chickens mainly walk or run, rather than fly, about the barnyard.

Energy Yield from Glucose Metabolism

Figure 3.9 calculates the theoretical ATP yield for the complete breakdown of glucose to CO_2 and H_2O during cellular respiration. Notice that the diagram includes the number of ATP produced directly by glycolysis and the citric acid cycle (to the *left*), as well as the number produced as a result of electrons passing down the electron transport chain (to the *right*). A maximum of 32 to 34 ATP molecules may be produced by the electron transport chain.

Substrate-Level ATP Synthesis

Per glucose molecule, there is a net gain of two ATP from glycolysis, which takes place in the cytoplasm. The citric acid cycle, which occurs in the matrix of mitochondria, accounts for two ATP per

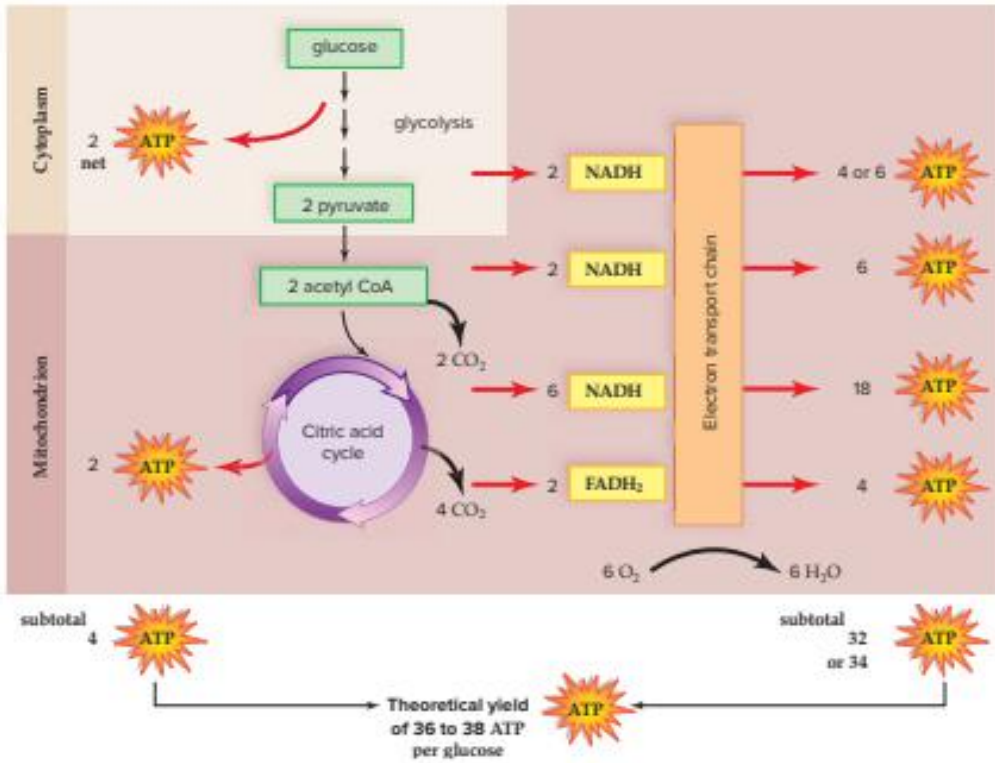


Figure 3.9 Accounting of energy yield per glucose molecule breakdown. Substrate-level ATP synthesis during glycolysis and the citric acid cycle accounts for 4 ATP. The electron transport chain accounts for 32 or 34 ATP, making the theoretical grand total of ATP between 36 and 38 ATP. Other factors may reduce the efficiency of cellular respiration. For example, cells differ as to the delivery of the electrons from NADH generated outside the mitochondria. If they are delivered by a shuttle mechanism to the start of the electron transport chain, 6 ATP result; otherwise, 4 ATP result.

glucose molecule. This means that a total of four ATP are formed by substrate-level ATP synthesis outside the electron transport chain.

ETC and Chemiosmosis

Most ATP is produced by the electron transport chain and chemiosmosis. Per glucose molecule, ten NADH and two $FADH_2$ take electrons to the electron transport chain. For each NADH formed *inside* the mitochondria by the citric acid cycle, three ATP result, but for each $FADH_2$, only two ATP are produced. Figure 3.8 explains the reason for this difference: $FADH_2$ delivers its electrons to the transport chain after NADH, and therefore these electrons do not participate in as many redox reactions and don't pump as many H^+ as NADH. Therefore, $FADH_2$ cannot account for as much ATP production.

Efficiency of Cellular Respiration

Figure 3.9 provides the theoretical ATP for each stage of cellular respiration. However, we know now that cells rarely ever achieve these theoretical values. Several factors can lower the ATP yield for each molecule of glucose entering the pathway:

- In some cells, NADH cannot cross mitochondrial membranes, but a "shuttle" mechanism allows its electrons to be delivered to the electron transport chain inside the mitochondria. The cost to the cell is one ATP for each NADH that is shuttled to the ETC. This reduces the overall count of ATP produced as a result of glycolysis, in some cells, to four instead of six ATP.
- At times, cells need to expend energy to move ADP molecules and pyruvate into the cell and to establish protein gradients in the mitochondria.

There is still considerable research into the precise ATP yield per glucose molecule. However, most estimates place the actual yield at around 30 ATP per glucose. Using this number we can calculate that only between 32 and 39 percent of the available energy is usually transferred from glucose to ATP. The rest of the energy is lost in the form of heat.

In the next section, we consider how cellular respiration fits into metabolism as a whole.

Check Your Progress **3.4**

1. Explain when carbon is converted from glucose into carbon dioxide during cellular respiration.
2. Examine which processes during glucose breakdown produce the most ATP.
3. Compare the function of the mitochondrial inner membrane to a hydroelectric dam.

3.5 Metabolism

Learning Outcomes

Upon completion of this section, you should be able to

1. Compare the pathways of carbohydrate, fat, and protein catabolism.
2. Explain how the structure of mitochondria and chloroplasts enables a flow of energy through living organisms.

Key metabolic pathways routinely draw from pools of particular substrates needed to synthesize or degrade larger molecules. Substrates like the end product of glycolysis, pyruvate, exist as a pool that is continuously affected by changes in cellular and environmental conditions (Fig. 3.10). Degradative reactions, termed **catabolism,** that break down molecules must be dynamically balanced with constructive reactions, or **anabolism.** For example, catabolic breakdown of fats will occur when insufficient carbodydrate is present; this breakdown adds to the **metabolic pool** of pyruvate. When energy needs to be stored as fat, pyruvate is taken from the pool. This dynamic balance of catabolism and anabolism is essential to optimal cellular function.

Catabolism

We already know that glucose is broken down during cellular respiration. However, other molecules like fats and proteins can also be broken down as necessary. When a fat is used as an energy source, it breaks down to glycerol and three fatty acids. As Figure 3.10 indicates, glycerol can be converted to pyruvate and enter glycolysis. The fatty acids are converted to 2-carbon acetyl CoA that enters the citric acid cycle. An 18-carbon fatty acid results in nine acetyl CoA molecules. Calculation shows that respiration of these can produce a total of 108 ATP molecules. This is why fats are an efficient form of stored energy—the three long fatty acid chains per fat molecule can produce considerable ATP when needed.

Proteins are less frequently used as an energy source, but they are available as necessary. The carbon skeleton of amino acids can enter glycolysis, be converted to acetyl groups, or enter the citric acid cycle at some other juncture. The carbon skeleton is produced in the liver when an amino acid undergoes **deamination,** or the removal of the amino group. The amino group becomes ammonia (NH_3), which enters the urea cycle and becomes part of urea, the primary excretory product of humans. Just where the carbon skeleton begins degradation depends on the length of the *R* group, since this determines the number of carbons left after deamination.

Anabolism

We have already seen that the building of new molecules requires ATP produced during breakdown of molecules. These catabolic reactions also provide the basic components used to build new molecules. For example, excessive carbohydrate intake can result in the formation of fat. Extra G3P from glycolysis can be converted to glycerol, and acetyl groups from glycolysis can be joined to form fatty acids, which in turn are used to synthesize fat. This explains why you gain weight from eating too much candy, ice cream, or cake.

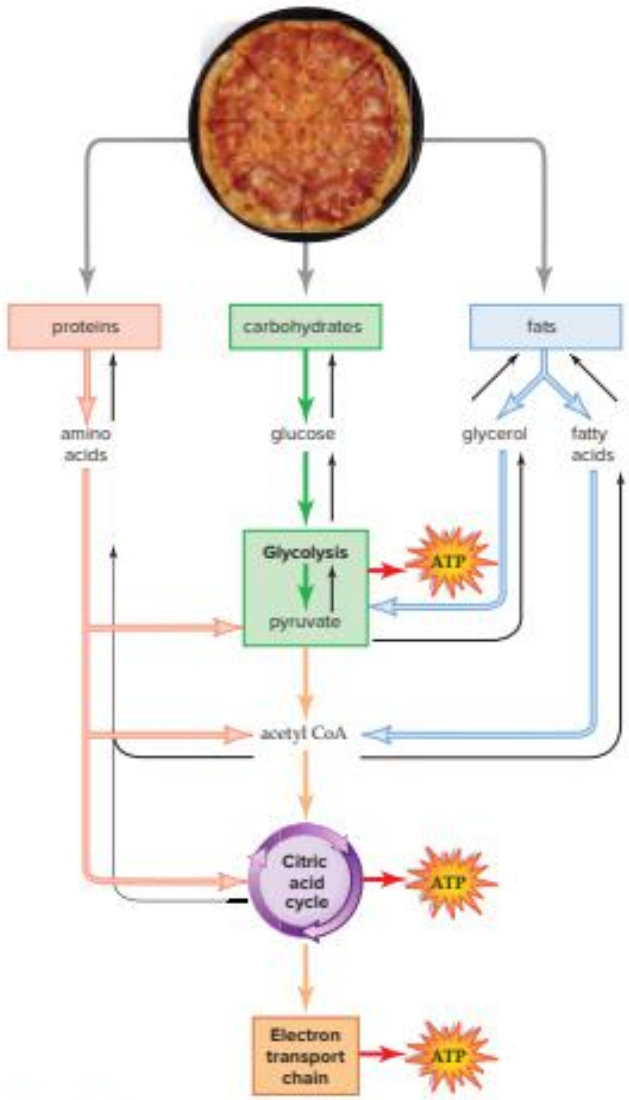


Figure 3.10 The metabolic pool concept. Carbohydrates, fats, and proteins can be used as energy sources, and their monomers (carbohydrates and proteins) or subunits (fats) enter degradative pathways at specific points. Catabolism produces molecules that can also be used for anabolism of other compounds.

Some substrates of the citric acid cycle can be converted to amino acids through transamination—the transfer of an amino group to an organic acid, forming a different amino acid. Plants are able to synthesize all of the amino acids they need. Animals, however, lack some of the enzymes necessary for synthesis of all amino acids. Adult humans, for example, can synthesize 11 of the common amino acids, but they cannot synthesize the other 9. The amino acids that cannot be synthesized must be supplied by

the diet; they are called the essential amino acids. The amino acids that can be synthesized are called nonessential. It is quite possible for animals to suffer from protein deficiency if their diets do not contain adequate quantities of all the essential amino acids.

The Energy Organelles Revisited

The equation for photosynthesis in a chloroplast is opposite that of cellular respiration in a mitochondrion (Fig. 3.11):

$$\text{energy} + 6\,CO_2 + 6\,H_2O \underset{\text{cellular respiration}}{\overset{\text{photosynthesis}}{\rightleftharpoons}} C_6H_{12}O_6 + 6\,O_2$$

While you were studying photosynthesis and cellular respiration, you may have noticed a remarkable similarity in the structural organization of chloroplasts and mitochondria. Through evolution, all organisms are related, and the similar organization of these organelles suggests that they may be related also. The two organelles carry out related but opposite processes:

1. *Use of membrane.* In a chloroplast, an inner membrane forms the thylakoids of the grana. In a mitochondrion, an inner membrane forms the convoluted cristae.
2. *Electron transport chain (ETC).* An ETC is located on the thylakoid membrane of chloroplasts and the cristae of mitochondria. In chloroplasts, the electrons passed down the ETC have been energized by the sun; in mitochondria, energized electrons have been removed from glucose and glucose products. In both, the ETC establishes an electrochemical gradient of H^+ with subsequent ATP production by chemiosmosis.
3. *Enzymes.* In a chloroplast the stroma contains the enzymes of the Calvin cycle, and in mitochondria the matrix contains the enzymes of the citric acid cycle. In the Calvin cycle, NADPH and ATP are used to reduce carbon dioxide to a carbohydrate. In the citric acid cycle, the oxidation of glucose products produces NADH and ATP.

Flow of Energy

The ultimate source of energy for producing a carbohydrate in chloroplasts is the sun; the ultimate goal of cellular respiration in a mitochondrion is the conversion of carbohydrate energy into that of ATP molecules. Therefore, energy flows from the sun, through chloroplasts to carbohydrates, and then through mitochondria to ATP molecules.

This flow of energy maintains biological organization at all levels from molecules to organisms to ultimately the biosphere. In keeping with the energy laws, some energy is lost with each chemical transformation, and eventually the solar energy captured by plants is lost in the form of heat. Therefore, all life depends on a continual input of solar energy.

Although energy flows through organisms, chemicals cycle within natural systems. Aerobic organisms utilize the carbohydrate and oxygen produced by chloroplasts to generate energy within the mitochondria to sustain life. Likewise, the carbon dioxide produced by mitochondria returns to chloroplasts to be used in the manufacture of carbohydrates, producing oxygen as a by-product. Therefore, chloroplasts and mitochondria are instrumental in not only allowing a flow of energy through living organisms but also permitting a cycling of chemicals.

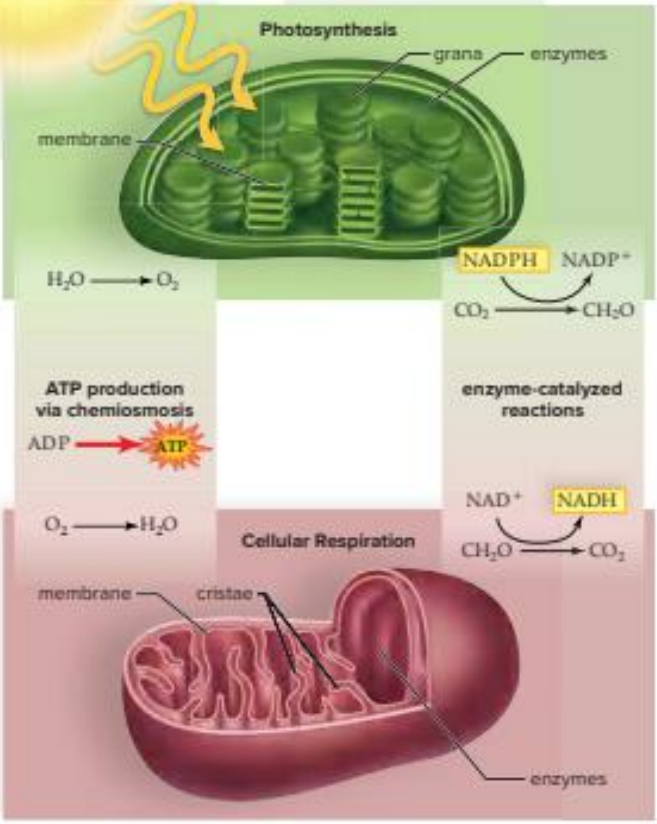


Figure 3.11 Photosynthesis versus cellular respiration.
In photosynthesis (*top*), water is oxidized and oxygen is released; in cellular respiration (*bottom*), oxygen is reduced to water. Both processes have an electron transport chain located within membranes (the grana of chloroplasts and the cristae of mitochondria), where ATP is produced by chemiosmosis. Both have enzyme-catalyzed reactions within the semifluid interior. In photosynthesis, CO_2 is reduced to a carbohydrate; in cellular respiration, a carbohydrate is oxidized to CO_2.

Check Your Progress 3.5

1. Evaluate how catabolism and anabolism are balanced within a cell.
2. Compare the structure and function of chloroplasts and mitochondria.

REVIEWING *the* BIG IDEAS

BIG IDEA 1

All organisms—archaea, bacteria, and eukaryotes—use either anaerobic or aerobic cellular respiration to transfer free energy to the bonds of ATP, the energy currency of the cell; this energy can be used to power cell processes. 1.B.1.a.3

BIG IDEA 2

While the first steps of cellular respiration require no oxygen, aerobic conditions are essential for the function of the electron transport chain. In the absence of O_2, fermentation occurs to eke out small amounts of ATP but creates toxic by-products like alcohol or lactic acid. 2.A.2.b.2

The slow, step-by-step enzymatic processes of glycolysis and the Krebs cycle metabolize carbohydrates to water and CO_2, allowing slow release of free energy that is captured in the creation of ATP by the electron transport chain; the remaining energy is lost as heat. 2.A.2.f.1-5; 2.A.2.g.1-4; *4.B.1.b,c*

NAD and FAD ferry electrons and H^+ ions to the electron transport chain where they power ATP production by chemiosmosis. 2.A.2.f.4.; 2.A.2.g.2-4

The final electron acceptor in aerobic cellular respiration is oxygen. 2.A.2.c. *IE*

BIG IDEA 4

The double-membrane structure of the mitochondrion provides increased surface area and enables compartmentalization of Krebs cycle enzymes and electron transport chain functions. 4.A.2.d.1-3

In cellular respiration, carbohydrates or other groups of organic molecules are oxidized while oxygen is reduced, producing water; the "waste products" of respiration are the raw materials of photosynthesis. Energy flows, but molecules recycle. 4.A.6.a

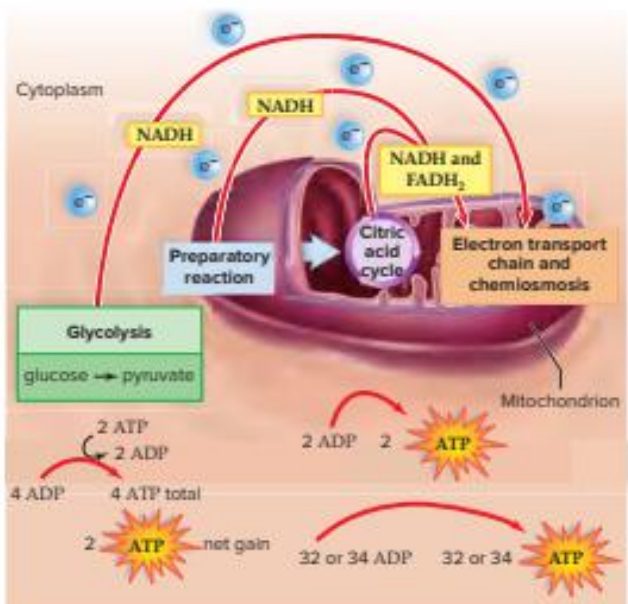
SUMMARIZE

AP Answering the Essential Questions

Living organisms require free energy for life processes such as growth and reproduction. All organisms carry out some form of **cellular respiration** as an energy-procuring strategy, whether or not oxygen is present. Although cellular respiration and photosynthesis evolved independently, today they are interdependent processes. In photosynthesis, water is oxidized and oxygen is released; in respiration, oxygen is reduced to water. Both have an electron transport chain embedded within membranes, where ATP is produced by chemiosmosis, and both have enzyme-catalyzed reactions within the semi-fluid interior of chloroplasts and mitochondria. In photosynthesis, CO_2 is reduced to a carbohydrate, whereas in respiration, a carbohydrate is oxidized to CO_2 through oxidation-reduction (redox) reactions. Do you see similarities between the chemical equation for cellular respiration below and the equation for photosynthesis?

$$C_6H_{12}O_6 + 6\,O_2 \longrightarrow 6\,CO_2 + 6\,H_2O + \text{energy}$$

The complete breakdown of glucose occurs in four phases: glycolysis, an intermediate reaction, the citric acid or Krebs cycle, and the electron transport chain. **Glycolysis** occurs in the cytoplasm of cells and produces pyruvate, which enters the mitochondrion if oxygen is available. The mitochondrion is the site of the citric acid or **Krebs cycle;** each stage of the cycle generates electrons (e^-) from oxidation reactions. Also, inside the mitochondrion, the **electron transport chain** (ETC) receives the electrons that were removed from glucose breakdown products. If oxygen is present, the theoretical energy yield per glucose molecule is 36 to 38 ATP, depending on the particular cell.



Glycolysis Let's explore the stages of cellular respiration in more detail, beginning with glycolysis. Scientists think that glycolysis evolved in ancient prokaryotes to make ATP before oxygen was present in Earth's atmosphere (remember from our study of photosynthesis that appreciable quantities of O_2 did not accumulate in the atmosphere until cyanobacteria began photosynthesizing). Glycolysis begins with one C_6 glucose molecule and ends with two C_3 **pyruvate** molecules.

Destabilizing glucose requires an initial investment of energy in the form of ATP (don't worry; the cell will get it back!). As glucose is metabolized, the bonds are rearranged through a series of enzyme-mediate steps, releasing free energy to form ATP from ADP and inorganic phosphate, resulting in the production of pyruvate (remember, we studied enzymes and the molecular structure of ATP, a nucleotide, The net gain of two ATP molecules can be calculated by subtracting the two invested to start the process from those produced during the energy-harvesting steps (you don't have to memorize all the substrates, enzymes, and products in glycolysis or the citric acid cycle, but if provided with diagrams, you should be able to understand the underlying concepts).

The type of ATP synthesis that occurs in glycolysis is referred to as **substrate-level phosphorylation** because it does not require an electron transport system and chemiosmosis. Substrates participating in the reaction are oriented on an enzyme that facilitates the transfer of a phosphate group to ADP, producing one ATP molecule. If oxygen is present (aerobic cellular respiration), the end-product of glycolysis—pyruvate—is transported from the cytoplasm to the mitochondrion, where further oxidation occurs. If oxygen is not present (fermentation and anaerobic respiration), ATP is only produced by substrate-level phosphorylation. In alcohol fermentation, pyruvate is converted to ethanol during lactic acid fermentation, pyruvate is reduced to form lactate as an end-product. Many microorganisms carry out fermentation and anaerobic respiration; without these processes, bread would not rise, and we wouldn't have yogurt, cheese, or soy sauce. Human muscle cells make ATP by lactic acid fermentation when oxygen is scarce, perhaps leading to muscle cramps.

The Krebs cycle The next stage of aerobic respiration, known as the citric acid cycle or the Krebs cycle, occurs in the mitochondrion. The structure of the mitochondrion is similar to the structure of the chloroplast; a mitochondrion is bounded by a double membrane with an intermembrane space located between the outer and inner membrane. The inner membrane folds to increase surface area, forming the shelf-like **cristae.** Electron transport chains are embedded in cristae. In the citric acid cycle, CO_2 is released from intermediate organic molecules, and ATP is synthesized from ADP and inorganic phosphate by substrate-level phosphorylation. Electrons extracted from the intermediate organic molecules are carried by NADH and $FADH_2$ to the electron transport chain.

The electron transport chain The electron transport chain is located in the mitochondrial cristae. Electrons delivered by NADH and $FADH_2$ are passed to a series of electron acceptors embedded in the membrane as they move toward the final electron acceptor, oxygen. As electrons are passed from one protein complex to another via redox reactions, hydrogen ions (H^+) from the matrix (cytoplasm of mitochondrion) are transported into the intermembrane space, creating a proton gradient. The flow of protons back through membrane-bound ATP synthase by chemiosmosis generates ATP from ADP and inorganic phosphate. For every pair of electrons that enters by way of NADH, three ATP result; for every pair of electrons that enters by way of $FADH_2$, two ATP result. Oxygen, the final electron acceptor, becomes part of water. ATP leaves the matrix by way of a channel protein, where it can be used to power cellular processes.

As was previously stated, the stages of aerobic cellular respiration can yield 36–38 ATP, depending on cell type. Other factors may reduce the efficiency of respiration. For example, cells differ in their ability to deliver electrons carried by NADH generated outside the mitochondria. We've focused on the metabolism of glucose, but other carbohydrates, fats, and proteins can be used as energy sources, and their monomers or subunits enter degradative pathways at specific points. The pathways of cellular respiration are regulated by allosteric enzymes at key points in glycolysis and the citric acid cycle, usually by feedback inhibition to conserve resources when too many intermediate or end-products accumulate in the cell.

ASSESS

Choose the best answer for each question.

3.1 Overview of Cellular Respiration

1. The metabolic process that produces the most ATP molecules is
   a. glycolysis.
   b. the citric acid cycle.
   c. the electron transport chain.
   d. fermentation.
2. Which one of these pathways would not be active in an aerobic condition?
   a. glycolysis
   b. electron transport chain
   c. citric acid cycle
   d. fermentation
3. The reduction of NAD^+ produces
   a. acetyl CoA.
   b. pyruvate.
   c. NADH.
   d. oxygen gas.

3.2 Outside the Mitochondria: Glycolysis

4. During glycolysis, what is the net production of ATP per glucose molecule?
   a. 0 c. 8
   b. 2 d. 32
5. The process of glycolysis occurs where in the cell?
   a. chloroplasts
   b. mitocondrion
   c. nucleus
   d. cytoplasm
6. Which of the following is not produced by glycolysis?
   a. NADH
   b. pyruvate
   c. ATP
   d. $FADH_2$

3.3 Outside the Mitochondria: Fermentation

7. Which of these is not true of fermentation?
   a. There is a net gain of only two ATP per glucose.
   b. It occurs in cytoplasm.
   c. NADH donates electrons to the electron transport chain.
   d. It begins with glucose.
8. Fermentation is primarily involved in the recycling of
   a. ADP.
   b. NAD^+.
   c. oxygen.
   d. glucose.

3.4 Inside the Mitochondria

9. The greatest contributor of electrons to the electron transport chain is
   a. oxygen.
   b. glycolysis.
   c. the citric acid cycle.
   d. the prep reaction.
10. Which of these is not true of the citric acid cycle?
   a. The citric acid cycle includes the prep reaction.
   b. The citric acid cycle produces ATP by substrate-level ATP synthesis.
   c. The citric acid cycle occurs in the mitochondria.
   d. The citric acid cycle produces two ATP per glucose molecule.
11. Which of these is not true of the electron transport chain?
   a. The electron transport chain is located on the cristae of the mitochindria.
   b. The electron transport chain produces more NADH than any metabolic pathway.
   c. The electron transport chain contains cytochrome molecules.
   d. The electron transport chain ends when oxygen accepts electrons.
12. The oxygen required by cellular respiration is reduced and becomes part of which molecule?
   a. ATP
   b. H_2O
   c. pyruvate
   d. CO_2

3.5 Metabolism

13. Fatty acids are broken down to
   a. pyruvate molecules, which take electrons to the electron transport chain.
   b. acetyl groups, which enter the citric acid cycle.
   c. glycerol, which is found in fats.
   d. All of these are correct.
14. Which of the following is not common to the chloroplast and mitochondria?
   a. Both use membranes to establish gradients.
   b. Both have an ETC.
   c. Both use sunlight as a source of energy.
   d. Both use a variety of enzymes.

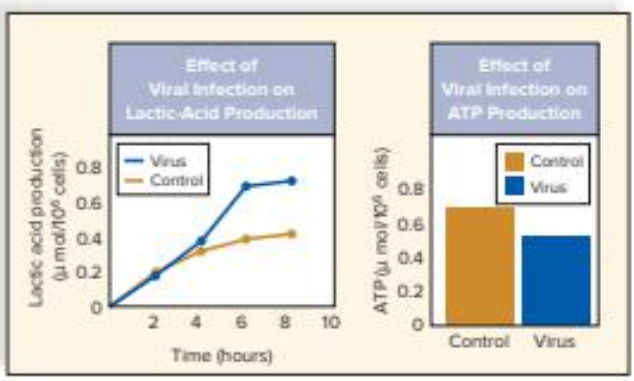
ENGAGE

AP Applying the Big Ideas

1. BIG IDEA 1 Scientists claim that organisms share many conserved core processes and features that evolved and are widely distributed among organisms today. Defend this claim using TWO pieces of evidence from metabolic pathways.
2. BIG IDEA 2 Construct an explanation of the mechanism and structural features of CELLS that allow organisms to capture, store or use free energy.
   a. **Describe** TWO mechanisms or structural features of cells employed for use in photosynthesis.
   b. **Explain** how the two features you described in part (a) function to allow organisms to capture, store or use free energy.
3. BIG IDEA 4 During cellular respiration, nutrient molecules produced by autotrophs are broken down to acquire energy for cells.
   a. **Draw** a model of a mitochondrion and label at least TWO important features.
   b. **Explain** how TWO of the features you labeled in part (a) provide essential functions for the cell.

AP Applying the Science Practices

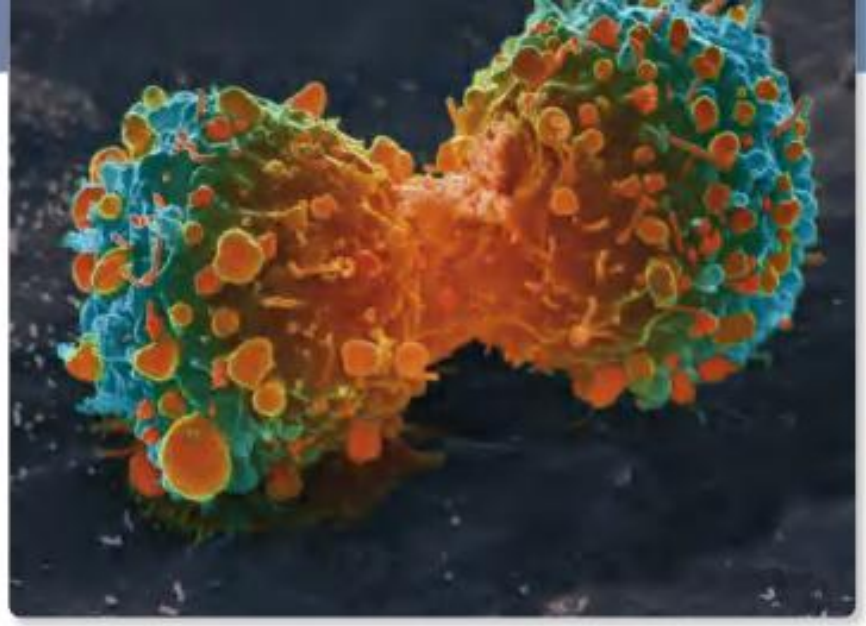
How does viral infection affect cellular respiration? Infection by viruses can significantly affect cellular respiration and the ability of cells to produce ATP. To test the effect of viral infection on the stages of cellular respiration, cells were infected with a virus, and the amount of lactic acid and ATP produced were measured.



Data obtained from: El-Bacha, T., et al. 2004. Mayaro virus infection alters glucose metabolism in cultured cells through activation of the enzyme 6-phosphofructo 1-kinase. *Molecular and Cellular Biochemistry* 266: 191–198.

Think Critically SP 2 SP 5 SP 6

1. **Analyze** how the virus affected lactic acid production in the cells.
2. **Calculate** After 8 hours, by what percentage was the lactic acid higher in the virus group than in the control group? By what percentage was ATP production decreased?
3. **Infer** why having a virus such as the flu might make a person feel tired.



A cell may become cancerous when the regulation of cell division fails.

4

The Cell Cycle and Cellular Reproduction

AP The process of cell division is highly regulated. In humans, life begins as a single cell, yet in a very short period of time the process of cell division produces trillions of cells, each specialized for a particular function. Over 200 different types of cells are found in the human body; although each is specialized, they all work together in harmony.

But what happens when the regulation of cell division fails? In the United States this year, over 76,000 individuals will be diagnosed with melanoma, a form of skin cancer, and around 9,500 people will die from this disease. In many instances of melanoma, exposure to ultraviolet radiation (UV) from the sun has caused a mutation in the regulatory mechanisms of the cell cycle. Without proper regulation, cell division occurs continuously, a characteristic of cancer. For melanoma, this loss of cell cycle control results from a mutation in a gene known as *CDKN2A*. This gene is an example of a tumor suppressor gene, one of the key regulatory mechanisms of the cell cycle. In this chapter we describe the process of cell division, how it is regulated, and how cancer may develop when regulatory mechanisms malfunction.

As you read through the chapter, think about these Essential Questions:

1. Why do all cells—archaea, bacteria, and eukaryotes—have to divide? What does this suggest about the evolution of the process of cell reproduction? 3.A.2.a
2. What is the normal sequence of events in the process of cellular reproduction in a eukaryotic cell? 3.A.2.b.3
3. How do internal and external signals regulate the cell cycle? What is the relationship between cancer and this regulation? 3.A.2.a.2, *IE*

Chapter Outline

Following *the* BIG IDEAS

BIG IDEA 3 For unicellular organisms, cell division results in the formation of two new organisms, while in multicellular organisms it is the basis of growth and repair.

4.1 The Cell Cycle

Learning Outcomes

Upon completion of this section, you should be able to

1. List the stages of interphase, and describe the major events that occur during each stage in preparation for cell division.
2. List the checkpoints that regulate the progression of cells through the cell cycle.
3. Explain the mechanisms within the G_1 cell cycle checkpoint that evaluate growth signals, determine nutrient availability, and assess DNA integrity.

The **cell cycle** is an orderly set of stages that takes place between the time a eukaryotic cell divides and the time the resulting daughter cells also divide. When a cell is going to divide, it grows larger, the number of organelles doubles, and the amount of DNA doubles as DNA replication occurs. The two portions of the cell cycle are interphase, which includes a number of stages, and the mitotic stage, when mitosis and cytokinesis occur.

Interphase

As Figure 4.1 shows, most of the cell cycle is spent in **interphase.** This is the time when a cell performs its usual functions, depending on its location in the body. The amount of time the cell takes for interphase varies widely. Embryonic cells complete the entire cell cycle in just a few hours. For adult mammalian cells, interphase lasts for about 20 hours, which is 90% of the cell cycle. In the past, interphase was known as the resting stage. However, today it is known that interphase is very busy, and that preparations are being made for mitosis. Interphase consists of three stages, referred to as G_1, S, and G_2.

G_1 Stage

Cell biologists named the stage before DNA replication G_1, and they named the stage after DNA replication G_2. G stood for "gap," but now that we know how metabolically active the cell is, it is better to think of G as standing for "growth." During G_1, the cell recovers from the previous division. The cell grows in size, increases the number of organelles (such as mitochondria and ribosomes), and accumulates materials that will be used for DNA synthesis. Otherwise, cells are constantly performing their normal daily functions during G_1, including communicating with other cells, secreting substances, and carrying out cellular respiration.

Some cells, such as nerve and muscle cells, typically do not complete the cell cycle and are permanently arrested. These cells exit interphase and enter a stage called G_0. While in the G_0 stage, the cells continue to perform normal, everyday processes, but no preparations are being made for cell division. Cells may not leave the G_0 stage without proper signals from other cells and other parts of the body. Thus, completion of the cell cycle is very tightly controlled.

S Stage

Following G_1, the cell enters the S stage, when DNA synthesis, or replication, occurs. At the beginning of the S stage, each chromosome is composed of one DNA double helix. Following DNA replication, each chromosome is composed of two identical DNA double helix molecules. Each double helix is called a **chromatid,** and the two identical chromatids are referred to as **sister chromatids.** The sister chromatids remain attached until they are separated during mitosis.

G_2 Stage

Following the S stage, G_2 is the stage from the completion of DNA replication to the onset of mitosis. During this stage, the cell synthesizes the proteins that will assist cell division. For example, it makes the proteins that form microtubules. Microtubules are used during the mitotic stage to form the mitotic spindle that is critical during M stage.

M (Mitotic) Stage

Following interphase, the cell enters the M (for *mitotic*) stage. This cell division stage includes **mitosis** (nuclear division) and **cytokinesis** (division of the cytoplasm). During mitosis,

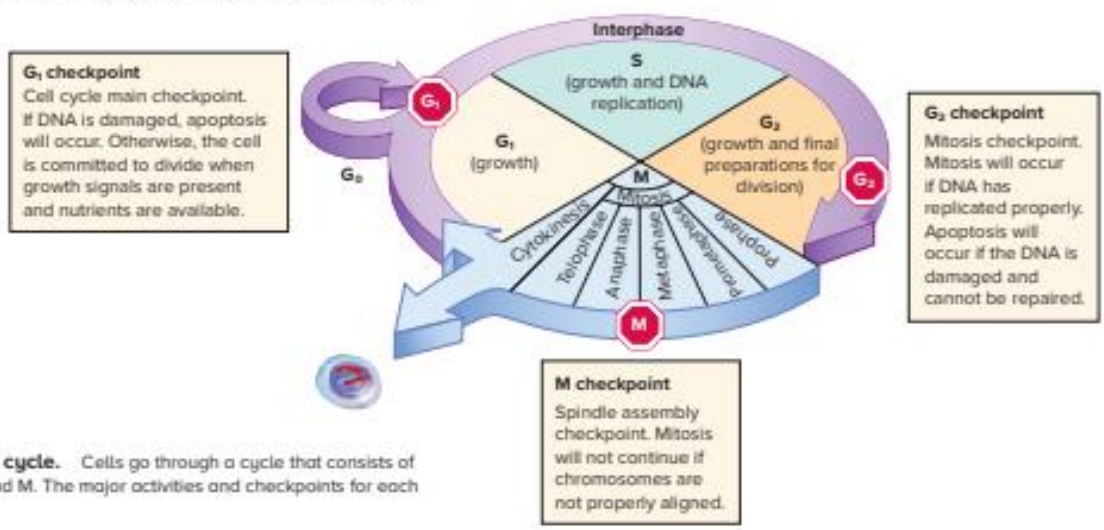


Figure 4.1 The cell cycle. Cells go through a cycle that consists of four stages: G_1, S, G_2, and M. The major activities and checkpoints for each stage are given.

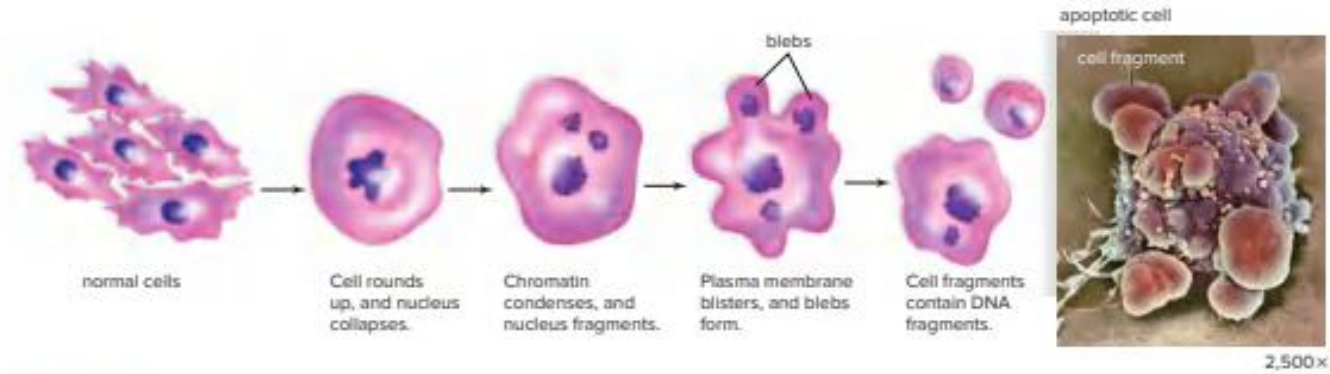


Figure 4.2 Apoptosis. Apoptosis is a sequence of events that results in a fragmented cell. The fragments are phagocytized (engulfed) by white blood cells and neighboring tissue cells.

daughter chromosomes are distributed by the **mitotic spindle** to two daughter nuclei. When division of the cytoplasm is complete, two daughter cells are present.

Control of the Cell Cycle

A **signal** is an agent that influences the activities of a cell. **Growth factors** are signaling proteins received at the plasma membrane. Even cells arrested in G_0 will finish the cell cycle if stimulated to do so by growth factors. In general, signals ensure that the cell cycle stages follow one another in the normal sequence.

Cell Cycle Checkpoints

The red stop signs in Figure 4.1 represent three checkpoints at which the cell cycle either stops or continues on, depending on the internal signals received. Researchers have identified a family of internal signaling proteins, called **cyclins,** that increase and decrease as the cell cycle continues. Specific cyclins must be present for the cell to proceed from the G_1 stage to the S stage and from the G_2 stage to the M stage.

As discussed in the Big Idea 3 feature, "The G_1 Checkpoint," on page 150, the primary checkpoint of the cell cycle is the G_1 checkpoint. In mammalian cells, the signaling protein p53 stops the cycle at the G_1 checkpoint when DNA is damaged. In the name p53, p stands for *p*rotein and 53 represents its molecular weight in kilodaltons. First, p53 attempts to initiate DNA repair, but rising levels of p53 can bring about **apoptosis,** which is programmed cell death (Fig. 4.2). Another protein, called RB, is responsible for interpreting growth signals and nutrient availability signals. RB stands for *r*etino*b*lastoma, a cancer of the retina that occurs when the *RB* gene undergoes a mutation.

The cell cycle may also stop at the G_2 checkpoint if DNA has not finished replicating. This checkpoint prevents the initiation of the M stage before completion of the S stage. If DNA is physically damaged, such as from exposure to solar radiation or X-rays, the G_2 checkpoint also offers the opportunity for DNA to be repaired.

Another cell cycle checkpoint occurs during the mitotic stage. The cycle stops if the chromosomes are not properly attached to the mitotic spindle. Normally, the mitotic spindle ensures that the chromosomes are distributed accurately to the daughter cells.

Apoptosis

Apoptosis is often defined as programmed cell death, because the cell progresses through a typical series of events that bring about its destruction (Fig. 4.2). The cell rounds up, causing it to lose contact with its neighbors. The nucleus fragments, and the plasma membrane develops blisters. Finally, the cell fragments are engulfed by white blood cells and/or neighboring cells.

A remarkable finding of the past few years is that the enzymes that bring about apoptosis, called *caspases*, are always present in the cell. The enzymes are ordinarily held in check by inhibitors, but they can be unleashed by either internal or external signals.

Apoptosis and Cell Division. In living systems, opposing events keep the body in balance and maintain homeostasis. Cell division and apoptosis are two opposing processes that keep the number of cells in the body at an appropriate level. Cell division increases and apoptosis decreases the number of **somatic** (body) **cells.** Both are normal parts of growth and development. An organism begins as a single cell that repeatedly divides to produce many cells, but eventually some cells must die for the organism to take shape. For example, when a tadpole becomes a frog, the tail disappears as apoptosis occurs. In a human embryo, the fingers and toes are at first webbed, but then they are usually freed from one another as a result of apoptosis.

Cell division occurs during your entire life. Even now, your body is producing thousands of new red blood cells, skin cells, and cells that line your respiratory and digestive tracts. Also, if you suffer a cut, cell division repairs the injury. Apoptosis occurs all the time, too, particularly if an abnormal cell that could become cancerous appears or a cell becomes infected with a virus. Death through apoptosis prevents a tumor from developing and helps limit the spread of viruses.

Check Your Progress 4.1

1. List, in order, the stages of the cell cycle and briefly summarize what is happening at each stage.
2. Explain what conditions might cause a cell to halt the cell cycle and state briefly where in the cycle this would occur.
3. Discuss how apoptosis represents a regulatory event of the cell cycle.

The G_1 Checkpoint

Cell division is very tightly regulated, so that only certain cells in an adult body are actively dividing. After cell division occurs, cells enter the G_1 stage. Upon completing G_1, they will divide again, but before this happens they have to pass through the G_1 checkpoint.

The G_1 checkpoint ensures that conditions are right for making the commitment to divide by evaluating the meaning of growth signals, determining the availability of nutrients, and assessing the integrity of DNA. Failure to meet any one of these criteria results in a cell's halting the cell cycle and entering G_0 stage, or undergoing apoptosis if the problems are severe.

Evaluating Growth Signals

Multicellular organisms tightly control cell division, so that it occurs only when needed. Signaling molecules, such as hormones, may be sent from nearby cells or distant tissues to encourage or discourage cells from entering the cell cycle. Such signals may cause a cell to enter a G_0 stage, or complete G_1 and enter the S stage. Growth signals that promote cell division cause a cyclin-dependent-kinase (CDK) to add a phosphate group to the RB protein, a major regulator of the G_1 checkpoint.

Ordinarily, a protein called E2F is bound to RB, but when RB is phosphorylated, its shape changes and it releases E2F. Now, E2F binds to DNA, activating certain genes whose products are needed to complete the cell cycle (Fig. 4Aa). Likewise, growth signals prompt cells that are in G_0 stage to reenter the G_1 stage, complete it, and enter the S stage. If growth signals are sufficient, a cell passes through the G_1 checkpoint and cell division occurs.

Determining Nutrient Availability

Just as experienced hikers ensure that they have sufficient food for their journey, a cell ensures that nutrient levels are adequate before committing to cell division. For example, scientists know that starving cells in culture enter G_0. At that time, phosphate groups are removed from RB (see reverse arrows in Fig. 4Aa); RB does not release E2F; and the proteins needed to complete the cell cycle are not produced. When nutrients become available, CDKs bring about the phosphorylation of RB, which then releases E2F (see forward arrows in Fig. 4Aa). After E2F binds to DNA, the proteins needed to complete the cell cycle are produced. Therefore, you can see that cells do not commit to divide until conditions are conducive for them to do so.

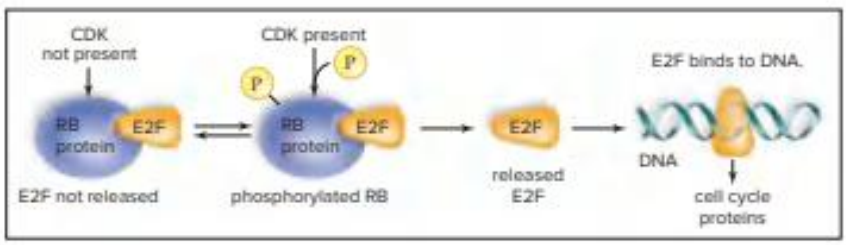
Assessing DNA Integrity

For cell division to occur, DNA must be free of errors and damage. The p53 protein is involved in this quality control function. Ordinarily, p53 is broken down because it has no job to do. In response to DNA damage, CDK phosphorylates p53 (Fig. 4Ab). Now, the molecule is not broken down as usual, and instead its level in the nucleus begins to rise. Phosphorylated p53 binds to DNA; certain genes are activated; and DNA repair proteins are produced. If the DNA damage cannot be repaired, p53 levels continue to rise, and apoptosis is triggered. If the damage is successfully repaired, p53 levels fall, and the cell is allowed to complete G_1 stage—as long as growth signals and nutrients are present, for example.

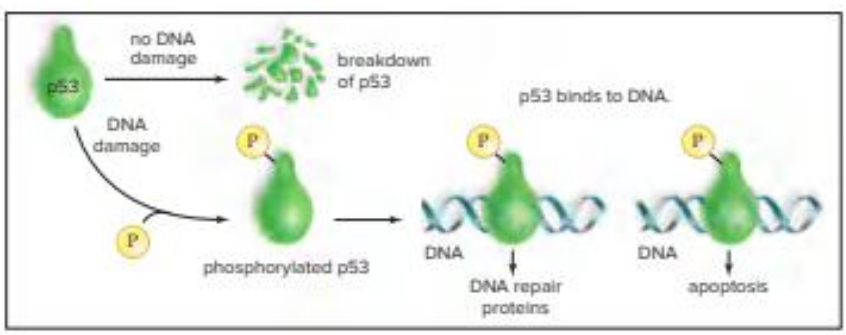
Actually, many criteria must be met for a cell to commit to cell division, and the failure to meet any one of them may cause the cell cycle to be halted and/or apoptosis to be initiated. The G_1 checkpoint is currently an area of intense research, because understanding it holds the key to possibly curing cancer and to unleashing the power of normal, healthy cells to regenerate tissues, which could be used to cure many other human conditions.

Questions to Consider

1. What is the potential effect of an abnormally high level of a growth hormone on the regulation of the cell cycle?
2. Why might some cancers be associated with a mutation in the gene encoding the p53 protein?



a.



b.

Figure 4A Regulation of the G_1 checkpoint. **a.** When CDK (cyclin-dependent-kinase) is not present, RB retains E2F. When CDK is present, a phosphorylated RB releases E2F, and after it binds to DNA, the proteins necessary for completing cell division are produced. **b.** If DNA is damaged, p53 is not broken down; instead, it is involved in producing DNA repair enzymes and in triggering apoptosis when repair is impossible.

4.2 The Eukaryotic Chromosome

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain how DNA becomes sufficiently compacted to fit inside a nucleus.
2. Distinguish between euchromatin and heterochromatin.

Cell biologists and geneticists have been able to construct detailed models of how chromosomes are organized. A eukaryotic chromosome contains a single double helix DNA molecule, but it is composed of more than 50% protein. Some of these proteins are concerned with DNA and RNA synthesis, but a large majority, termed histones, play primarily a structural role.

The five primary types of histone molecules are designated H1, H2A, H2B, H3, and H4. Remarkably, the amino acid sequences of H3 and H4 vary little between organisms. For example, the H4 of peas is only two amino acids different from the H4 of cattle. This similarity suggests that few mutations in the histone proteins have occurred during the course of evolution and that the histones, therefore, have essential functions for survival.

A human cell contains at least 2 m of DNA, yet all of this DNA is packed into a nucleus that is about 6 μm in diameter. The histones are responsible for packaging the DNA so that it can fit into such a small space. First, the DNA double helix is wound at intervals around a core of eight histone molecules (two copies each of H2A, H2B, H3, and H4), giving the appearance of a string of beads (Fig. 4.3*a*). Each bead is called a nucleosome, and the nucleosomes are said to be joined by "linker" DNA.

a. Nucleosomes ("beads on a string")

b. 30-nm fiber

c. Radial loop domains

d. Heterochromatin

e. Metaphase chromosome

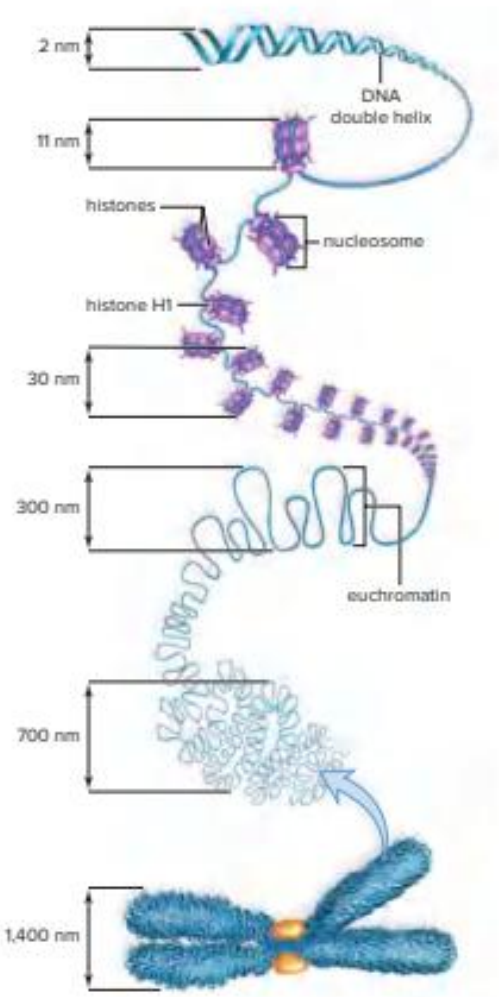


Figure 4.3 Structure of the eukaryotic chromosome. Eukaryotic cells contain nearly 2 m of DNA, yet they must pack it all into a nucleus that is around 6 μm in diameter. Thus, the DNA is compacted by winding it around DNA-binding proteins, called histones, to make nucleosomes. The nucleosomes are further compacted into a zigzag structure, which is then folded upon itself many times to form radial loops, which is the usual compaction state of euchromatin. Heterochromatin is further compacted by scaffold proteins, and further compaction can be achieved prior to mitosis and meiosis.

This string is compacted by folding into a zigzag structure, further shortening the DNA strand (Fig. 4.3*b*). Histone H1 appears to mediate this coiling process. The fiber then loops back and forth into radial loops (Fig. 4.3*c*). This loosely coiled **euchromatin** represents the active chromatin containing genes that are being transcribed. The DNA of euchromatin may be accessed by RNA polymerase and other factors that are needed to promote transcription. In fact, recent research seems to indicate that regulating the level of compaction of the DNA is an important method of controlling gene expression in the cell.

Under a microscope, one often observes dark-stained fibers within the nucleus of the cell. These areas within the nucleus represent a more highly compacted form of the chromosome called **heterochromatin** (Fig. 4.3*d*). Most chromosomes exhibit both levels of compaction in a living cell, depending on which portions of the chromosome are being used more frequently. Heterochromatin is considered inactive chromatin, because the genes contained on it are infrequently transcribed, if at all.

Prior to cell division, a protein scaffold helps further condense the chromosome into a form that is characteristic of metaphase chromosomes (Fig. 4.3*e*). No doubt, compact chromosomes are easier to move about than extended chromatin.

Check Your Progress 4.2

1. Summarize the differences between euchromatin and heterochromatin.
2. List the stages of chromosome compacting, starting with a single DNA strand.

4.3 Mitosis and Cytokinesis

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain how the cell prepares the chromosomes and centrosomes prior to nuclear division.
2. Summarize the major events that occur during mitosis and cytokinesis.
3. Discuss why human stem cells continuously conduct mitosis.

As mentioned, cell division in eukaryotes involves mitosis, which is nuclear division, and cytokinesis, which is division of the cytoplasm. During mitosis, the sister chromatids are separated and distributed to two daughter cells.

Chromosome Number

As we observed in the previous section, the DNA in the chromosomes of eukaryotes is associated with various proteins. When a eukaryotic cell is not undergoing division, the DNA and associated proteins are located within **chromatin,** which has the appearance of a tangled mass of thin threads. Before mitosis begins, chromatin becomes highly coiled and condensed, and it is easy to see the individual chromosomes.

Table 4.1 Diploid Chromosome Numbers of Some Eukaryotes

Type of Organism	Name of Chromosome	Chromosome Number
Fungi	*Saccharomyces cerevisiae* (yeast)	32
Plants	*Pisum sativum* (garden pea)	14
	Solanum tuberosum (potato)	48
	Ophioglossum vulgatum (southern adder's tongue fern)	1,320
Animals	*Drosophila melanogaster* (fruit fly)	8
	Homo sapiens (human)	46
	Carassius auratus (goldfish)	94

When the chromosomes are visible, it is possible to photograph and count them. Each species has a characteristic chromosome number (Table 4.1). This is the full, or **diploid** (**2n**), number (Gk. *diplos,* "twofold"; *-eides,* "like") of chromosomes that is found in all cells of the individual. The diploid number includes two chromosomes of each kind. Most somatic cells of animals are diploid. Half the diploid number, called the **haploid** (**n**) number (Gk. *haplos,* "simple, single"), contains only one chromosome of each kind. The gametes of animals (egg and sperm) are examples of haploid cells.

Preparations for Mitosis

During interphase, a cell must make preparations for cell division. These arrangements include replicating the chromosomes and duplicating most cellular organelles, including the centrosome, which will organize the spindle apparatus necessary for the movement of chromosomes.

Chromosome Duplication

During mitosis, a 2n nucleus divides to produce daughter nuclei that are also 2n. The dividing cell is called the *parent cell,* and the resulting cells are called the *daughter cells.* Before nuclear division takes place, DNA replicates, duplicating the chromosomes in the parent cell. This occurs during the S stage of interphase. Now each chromosome has two identical double helical molecules. Each double helix is a *chromatid,* and the two identical chromatids are called *sister chromatids* (Fig. 4.4). Sister chromatids are constricted and attached to each other at a region called the **centromere.** Protein complexes called **kinetochores** develop on either side of the centromere during cell division.

During nuclear division, the two sister chromatids separate at the centromere, and in this way each duplicated chromosome gives rise to two daughter chromosomes. Each daughter chromosome has only one double helix molecule. The daughter chromosomes are distributed equally to the daughter cells. In this way, each daughter nucleus gets a copy of each chromosome that was in the parent cell.

Division of the Centrosome

The **centrosome** (Gk. *centrum,* "center"; *soma,* "body"), the main microtubule-organizing center of the cell, also divides before mitosis begins. Each centrosome in an animal cell contains a

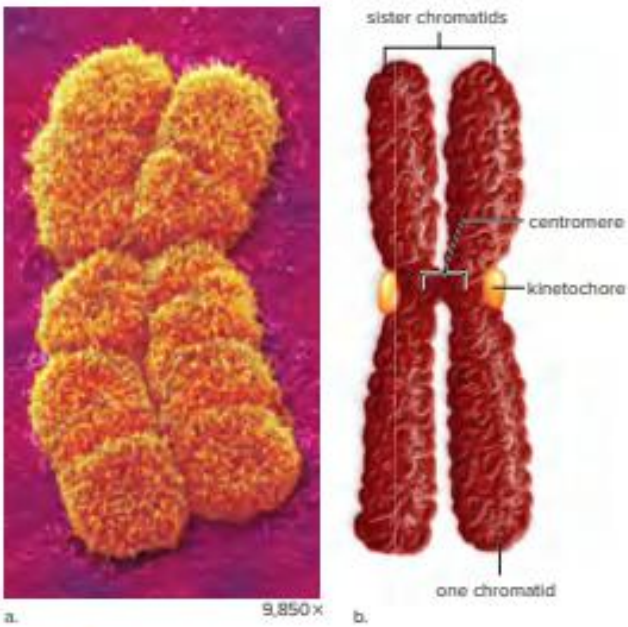


Figure 4.4 Duplicated chromosomes. A duplicated chromosome contains two sister chromatids, each with a copy of the same genes. **a.** Electron micrograph of a highly coiled and condensed chromosome, typical of a nucleus about to divide. **b.** Diagrammatic drawing of a condensed chromosome. The chromatids are held together at a region called the centromere.

pair of barrel-shaped organelles called **centrioles.** Centrioles are not found in plant cells.

The centrosomes organize the mitotic spindle, which contains many fibers, each of which is composed of a bundle of microtubules. Microtubules are hollow cylinders made up of the protein tubulin. They assemble when tubulin subunits join, and when they disassemble, tubulin subunits become free once more. The microtubules of the cytoskeleton disassemble when spindle fibers begin forming. Most likely, this provides tubulin for the formation of the spindle fibers, or it may allow the cell to change shape as needed for cell division.

Phases of Mitosis

Mitosis is a continuous process that is arbitrarily divided into five phases for convenience of description: prophase, prometaphase, metaphase, anaphase, and telophase (Fig. 4.5).

Prophase

It is apparent during **prophase** that nuclear division is about to occur, because chromatin has condensed and the chromosomes are visible. Recall that DNA replication occurred during interphase, and therefore the *parental chromosomes are already duplicated and composed of two sister chromatids held together at a centromere.* Counting the number of centromeres in diagrammatic drawings gives the number of chromosomes for the cell depicted.

During prophase, the nucleolus disappears and the nuclear envelope fragments. The spindle begins to assemble as the two centrosomes migrate away from one another. In animal cells, an array of microtubules radiates toward the plasma membrane from the centrosomes. These structures are called *asters.* It is thought that asters brace the centrioles during later stages of cell division. Notice that the chromosomes have no particular orientation, because the spindle has not yet formed.

Prometaphase (Late Prophase)

During **prometaphase,** preparations for sister chromatid separation are evident. Kinetochores appear on each side of the centromere, and these attach sister chromatids to the *kinetochore spindle fibers.* These fibers extend from the poles to the chromosomes, which will soon be located at the center of the spindle.

The kinetochore fibers attach the sister chromatids to opposite poles of the spindle, and the chromosomes are pulled first toward one pole and then toward the other before the chromosomes come into alignment. Notice that even though the chromosomes are attached to the spindle fibers in prometaphase, they are still not in alignment.

Metaphase

During **metaphase,** the centromeres of chromosomes are now in alignment on a single plane at the center of the cell. The chromosomes usually appear as a straight line across the middle of the cell when viewed under a light microscope. An imaginary plane that is perpendicular and passes through this circle is called the *metaphase plate.* It indicates the future axis of cell division.

Several nonattached spindle fibers, called *polar spindle fibers,* reach beyond the metaphase plate and overlap. A cell cycle checkpoint, the M checkpoint, delays the start of anaphase until the kinetochores of each chromosome are attached properly to spindle fibers and the chromosomes are properly aligned along the metaphase plate.

Anaphase

At the start of **anaphase,** the two sister chromatids of each duplicated chromosome separate at the centromere, giving rise to two daughter chromosomes. Daughter chromosomes, each with a centromere and single chromatid composed of a single double helix, appear to move toward opposite poles. Actually, the daughter chromosomes are being pulled to the opposite poles as the kinetochore spindle fibers disassemble at the region of the kinetochores.

Even as the daughter chromosomes move toward the spindle poles, the poles themselves are moving farther apart, because the polar spindle fibers are sliding past one another. Microtubule-associated proteins, such as the motor molecules kinesin and dynein, are involved in the sliding process. Anaphase is the shortest phase of mitosis.

Telophase

During **telophase,** the spindle disappears as new nuclear envelopes form around the daughter chromosomes. Each daughter nucleus contains the same number and kinds of chromosomes as the original parent cell. Remnants of the polar spindle fibers are still visible between the two nuclei.

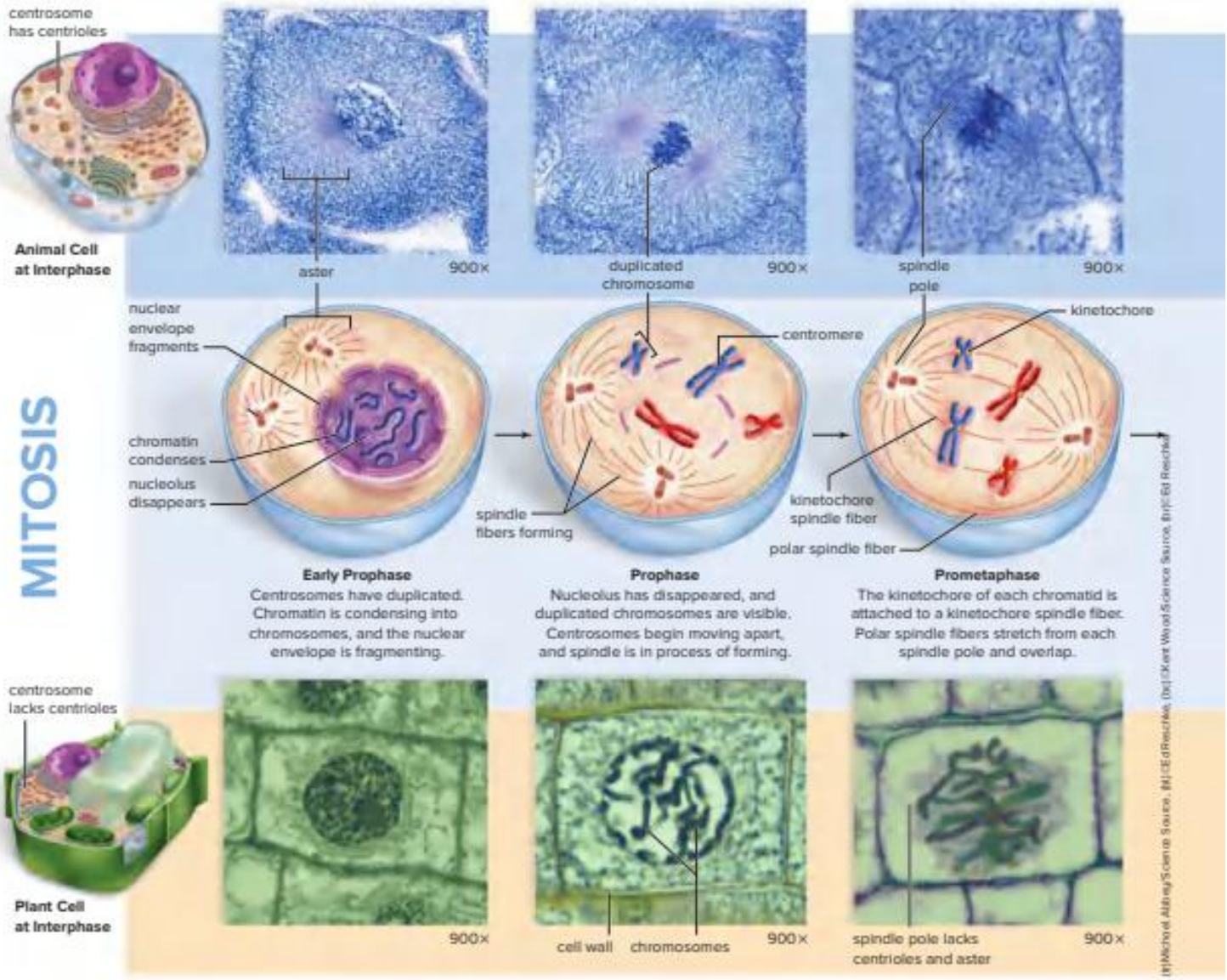


Figure 4.5 Phases of mitosis in animal and plant cells. The blue chromosomes were inherited from one parent, the red from the other parent.

The chromosomes become more diffuse chromatin once again, and a nucleolus appears in each daughter nucleus. Division of the cytoplasm requires cytokinesis, which is discussed in the next section.

Cytokinesis in Animal and Plant Cells

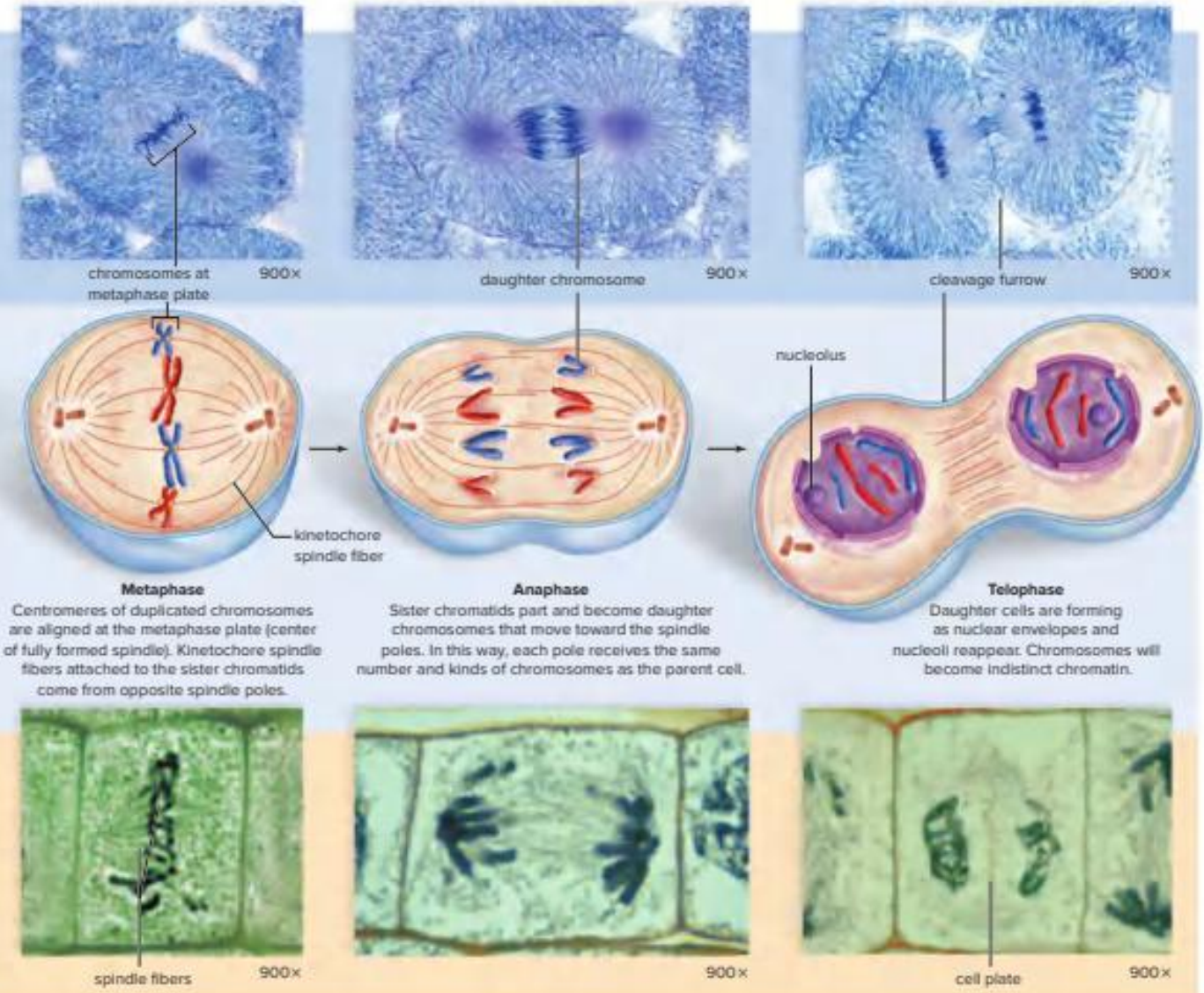
As mentioned previously, cytokinesis is division of the cytoplasm. Cytokinesis accompanies mitosis in most cells, but not all. When mitosis occurs but cytokinesis doesn't occur, the result is a multinucleated cell.

Division of the cytoplasm begins in anaphase, continues in telophase, but does not reach completion until the following interphase begins. By the end of mitosis, each newly forming cell has received a share of the cytoplasmic organelles that duplicated during interphase. Cytokinesis proceeds differently in plant and animal cells because of differences in cell structure.

Cytokinesis in Animal Cells

In animal cells a **cleavage furrow,** which is an indentation of the membrane between the two daughter nuclei, forms just as anaphase draws to a close. By that time, the newly forming cells have received a share of the cytoplasmic organelles that duplicated during the previous interphase.

The cleavage furrow deepens when a band of actin filaments, called the contractile ring, slowly forms a circular constriction between the two daughter cells. The action of the contractile ring can be likened to pulling a drawstring



ever tighter about the middle of a balloon. As the drawstring is pulled tight, the balloon constricts in the middle as the material on either side of the constriction gathers in folds. These folds are represented by the longitudinal lines in Figure 4.6.

A narrow bridge between the two cells can be seen during telophase, and then the contractile ring continues to separate the cytoplasm until there are two independent daughter cells (Fig. 4.6).

Cytokinesis in Plant Cells

Cytokinesis in plant cells occurs by a process different from that seen in animal cells (Fig. 4.7). The rigid cell wall that surrounds plant cells does not permit cytokinesis by furrowing. Instead, cytokinesis in plant cells involves the building of new cell walls between the daughter cells.

Cytokinesis is apparent when a small, flattened disk appears between the two daughter plant cells near the site where the metaphase plate once was. In electron micrographs, it is possible to see that the disk is at right angles to a set of microtubules that radiate outward from the forming nuclei. The Golgi apparatus produces vesicles, which move along the microtubules to the region of the disk. As more vesicles arrive and fuse, a cell plate can be seen. The **cell plate** is simply a newly formed plasma membrane that expands outward until it reaches the old plasma membrane and fuses with this membrane.

The new membrane releases molecules that form the new plant cell walls. These cell walls, known as primary cell walls, are later strengthened by the addition of cellulose fibrils. The space between the daughter cells becomes filled with middle lamella, which cements the primary cell walls together.

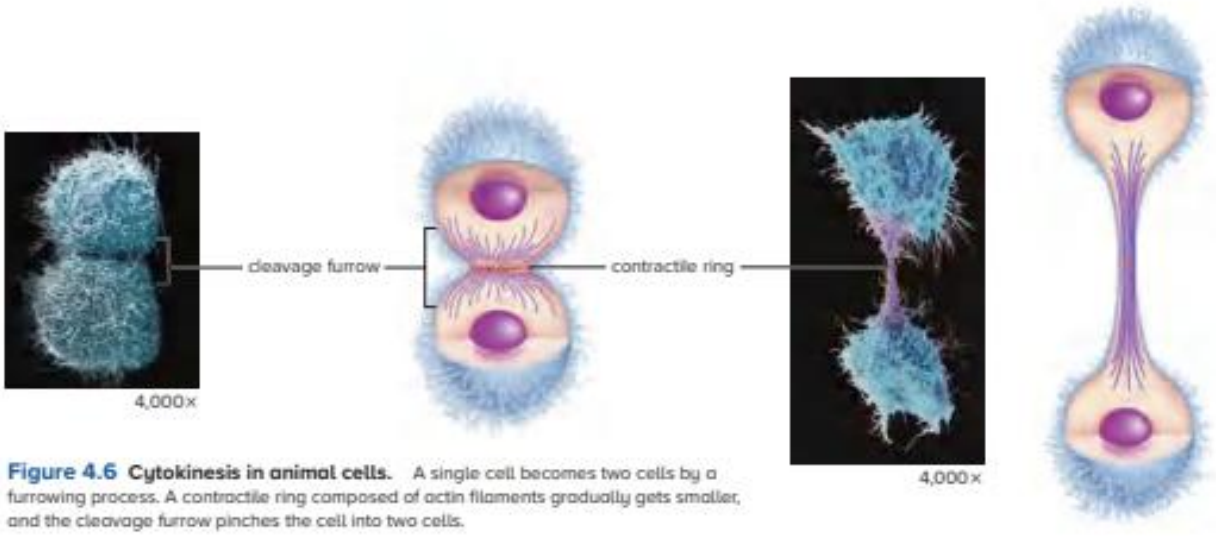


Figure 4.6 Cytokinesis in animal cells. A single cell becomes two cells by a furrowing process. A contractile ring composed of actin filaments gradually gets smaller, and the cleavage furrow pinches the cell into two cells.

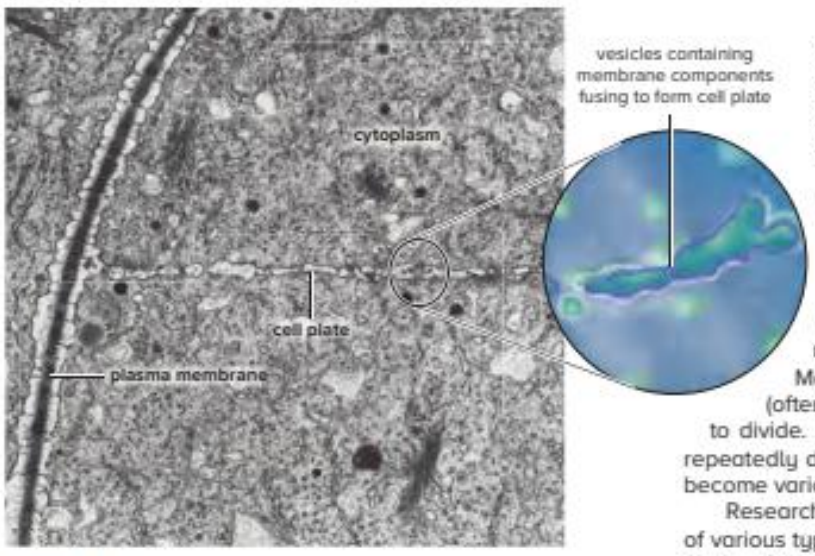


Figure 4.7 Cytokinesis in plant cells. During cytokinesis in a plant cell, a cell plate forms midway between two daughter nuclei and extends to the plasma membrane.

The Functions of Mitosis

Mitosis permits growth and repair. In both plants and animals, mitosis is required during development as a single cell develops into an individual. In plants, the individual could be a fern or daisy, while in animals, the individual could be a grasshopper or a human.

In flowering plants, meristematic tissue retains the ability to divide throughout the life of a plant. Meristematic tissue at the shoot tip accounts for an increase in the height of a plant for as long as it lives. Then, too, lateral meristem accounts for the ability of trees to increase their girth each growing season.

In humans and other mammals, mitosis is necessary as a fertilized egg becomes an embryo and as the embryo becomes a fetus. Mitosis also occurs after birth as a child becomes an adult. Throughout life, mitosis allows a cut to heal or a broken bone to mend.

Stem Cells

Earlier, you learned that the cell cycle is tightly controlled, and that most cells of the body at adulthood are permanently arrested in the G_0 stage. However, mitosis is needed to repair injuries, such as a cut or a broken bone. Many mammalian organs contain stem cells (often called adult stem cells) that retain the ability to divide. As one example, red bone marrow stem cells repeatedly divide to produce millions of cells that go on to become various types of blood cells.

Researchers are learning to manipulate the production of various types of tissues from adult stem cells in the laboratory. If successful, these tissues could be used to cure illnesses. As discussed in the Nature of Science feature, "Reproductive and Therapeutic Cloning," **therapeutic cloning,** which is used to produce human tissues, can begin with either adult stem cells or embryonic stem cells. Embryonic stem cells can also be used for **reproductive cloning,** the production of a new individual.

Check Your Progress 4.3

1. Describe the major events that occur during each phase of mitosis.
2. Summarize the differences between cytokinesis in animal and plant cells and explain why the differences are necessary.
3. Discuss the importance of stem cells in the human body.

Nature of Science

Reproductive and Therapeutic Cloning

Our knowledge of how the cell cycle is controlled has yielded major technological breakthroughs, including reproductive cloning—the ability to clone an adult animal from a normal body cell—and therapeutic cloning, which allows the rapid production of mature cells of a specific type. Both types of cloning are a direct result of recent discoveries about how the cell cycle is controlled.

Reproductive cloning, or the cloning of adult animals, was once thought to be impossible, because investigators found it difficult to have the nucleus of an adult cell "start over" with the cell cycle, even when it was placed in an egg cell that had had its own nucleus removed.

In 1997, Dolly the sheep demonstrated that reproductive cloning is indeed possible. The donor cells were starved before the cell's nucleus was placed in an enucleated egg. This caused them to stop dividing and go into a G_0 (resting) stage, and this made the nuclei amenable to cytoplasmic signals for initiation of development (Fig. 4B*a*). This advance has made it possible to clone all sorts of farm animals that have desirable traits and even to clone rare animals that might otherwise become extinct. Despite the encouraging results, however, there are still obstacles to be overcome, and a ban on the use of federal funds in experiments to clone humans remains firmly in place.

In therapeutic cloning, however, the objective is to produce mature cells of various cell types rather than an individual organism. The purpose of therapeutic cloning is (1) to learn more about how specialization of cells occurs and (2) to provide cells and tissues that could be used to treat human illnesses, such as diabetes, or major injuries like strokes or spinal cord injuries.

There are two possible ways to carry out *therapeutic cloning*. The first way is to use exactly the same procedure as reproductive cloning, except that *embryonic stem cells* (*ESCs*) are separated and each is subjected to a treatment that causes it to develop into a particular type of cell, such as red blood cells, muscle cells, or nerve cells (Fig. 4B*b*). Some have ethical concerns about this type of therapeutic cloning, which is still experimental, because if the embryo were allowed to continue development, it would become an individual.

The second way to carry out therapeutic cloning is to use *adult stem cells*. Stem cells are found in many organs of the adult's body; for example, the bone marrow has stem cells that produce new blood cells. However, adult stem cells are limited in the number of cell types they may become. Nevertheless, scientists are beginning to overcome this obstacle. In 2006, by adding just four genes to adult skin stem cells, Japanese scientists were able to coax the cells, called fibroblasts, into becoming induced pluripotent stem cells (iPS), a type of stem cell that is similar to an ESC. The researchers were then able to create heart and brain cells from the adult stem cells. Other researchers have used this technique to reverse Parkinson-like symptoms in rats.

Although questions exist on the benefits of iPS cells, these advances demonstrate that scientists are actively investigating methods of overcoming the current limitations and ethical concerns of using embryonic stem cells.

Questions to Consider

1. How might the study of therapeutic cloning benefit scientific studies of reproductive cloning?
2. What types of diseases might not be treatable using therapeutic cloning?

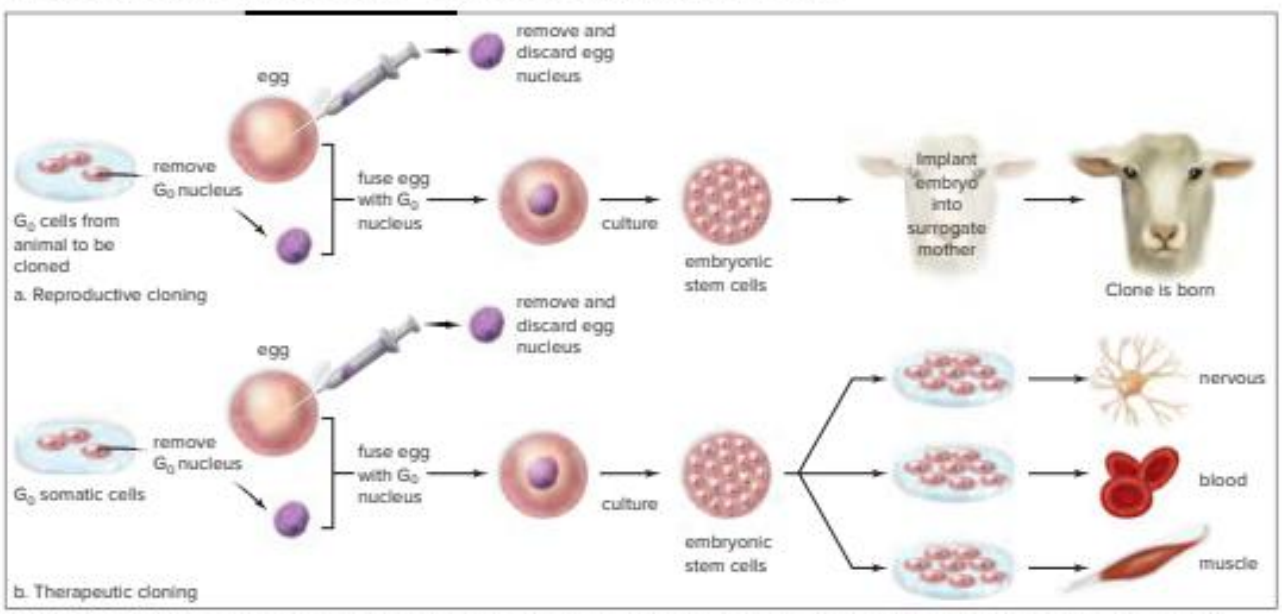


Figure 4B Two types of cloning. **a.** The purpose of reproductive cloning is to produce an individual that is genetically identical to the one that donated a nucleus. The nucleus is placed in an enucleated egg, and, after several mitotic divisions, the embryo is implanted into a surrogate mother for further development. **b.** The purpose of therapeutic cloning is to produce specialized tissue cells. A nucleus is placed in an enucleated egg, and after several mitotic divisions, the embryonic cells (called embryonic stem cells) are separated and treated to become specialized cells.

4.4 The Cell Cycle and Cancer

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the basic characteristics of cancer cells.
2. Explain the difference between a benign and malignant tumor.
3. Distinguish between the roles of the tumor suppressor genes and proto-oncogenes in the regulation of the cell cycle.

Cancer is a cellular growth disorder that occurs when cells divide uncontrollably. Although causes widely differ, most cancers are the result of accumulating mutations that ultimately cause a loss of control of the cell cycle.

Although cancers vary greatly, they usually follow a common multistep progression (Fig. 4.8). Most cancers begin as an abnormal cell growth that is **benign,** or not cancerous, and usually does not grow larger. However, additional mutations may occur, causing the abnormal cells to fail to respond to inhibiting signals that control the cell cycle. When this occurs, the growth becomes **malignant,** meaning that it is cancerous and possesses the ability to spread.

Characteristics of Cancer Cells

The development of cancer is gradual. A mutation in a cell may cause it to become precancerous, but many other regulatory processes within the body prevent it from becoming cancerous. In fact, it may be decades before a cell possesses most or all of the characteristics of a cancer cell (Table 4.2 and Fig. 4.8). Although cancers vary greatly, cells that possess the following characteristics are generally recognized as cancerous:

Cancer cells lack differentiation. Cancer cells are not specialized and do not contribute to the functioning of a tissue. Although cancer cells may still possess many of the characteristics of surrounding normal cells, they usually look distinctly abnormal. Normal cells can enter the cell cycle about 50 times before they are incapable of dividing again. Cancer cells can enter the cell cycle an indefinite number of times and, in this way, seem immortal.

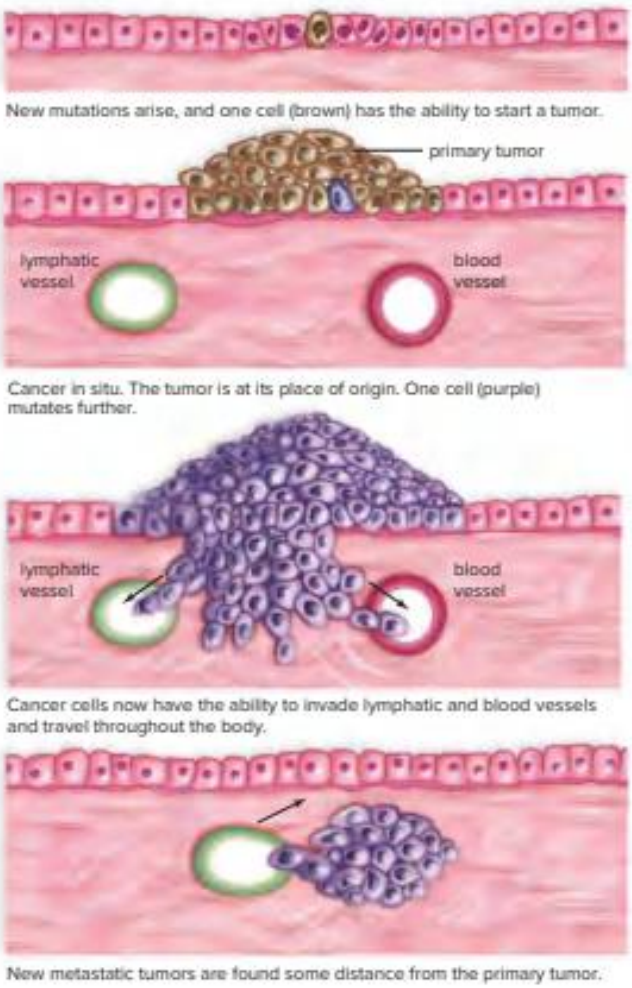
Cancer cells have abnormal nuclei. The nuclei of cancer cells are enlarged and may contain an abnormal number of chromosomes. Extra copies of one or more chromosomes may be present. Often, there are also duplicated portions of some chromosomes present, which causes gene amplification, or extra copies of specific genes. Some chromosomes may also possess deleted portions.

Cancer cells do not undergo apoptosis. Ordinarily, cells with damaged DNA undergo apoptosis, or programmed cell death. The immune system can also recognize abnormal cells and trigger apoptosis, which normally prevents tumors from developing. Cancer cells fail to undergo apoptosis even though they are abnormal cells.

Cancer cells form tumors. Normal cells anchor themselves to a substratum and/or adhere to their neighbors. They exhibit contact inhibition—in other words, when they come in contact with a neighbor, they stop dividing.

Table 4.2 Cancer Cells Versus Normal Cells

Cancer Cells	Normal Cells
Nondifferentiated cells	Differentiated cells
Abnormal nuclei	Normal nuclei
Do not undergo apoptosis	Undergo apoptosis
No contact inhibition	Contact inhibition
Disorganized, multilayered	One organized layer
Undergo metastasis	Remain in original tissue



New mutations arise, and one cell (brown) has the ability to start a tumor.

Cancer in situ. The tumor is at its place of origin. One cell (purple) mutates further.

Cancer cells now have the ability to invade lymphatic and blood vessels and travel throughout the body.

New metastatic tumors are found some distance from the primary tumor.

Figure 4.8 Progression of cancer. The development of cancer requires a series of mutations, leading first to a localized tumor and then to metastatic tumors. With each successive step toward cancer, the most genetically altered and aggressive cell becomes the dominant type of tumor. The cells take on characteristics of embryonic cells; they are not differentiated; they can divide uncontrollably; and they are able to metastasize and spread to other tissues.

Cancer cells have lost all restraint and do not exhibit contact inhibition. The abnormal cancer cells pile on top of one another and grow in multiple layers, forming a **tumor.** During carcinogenesis, the most aggressive cell becomes the dominant cell of the tumor.

Cancer cells undergo metastasis and angiogenesis. Additional mutations may cause a benign tumor, which is usually contained within a capsule and cannot invade adjacent tissue, to become malignant, and spread throughout the body, forming new tumors distant from the primary tumor. These cells now produce enzymes that they normally do not express, allowing tumor cells to invade underlying tissues. Then, they travel through the blood and lymph, to start tumors elsewhere in the body. This process is known as **metastasis.**

Tumors that are actively growing soon encounter another obstacle—the blood vessels supplying nutrients to the tumor cells become insufficient to support the rapid growth of the tumor. In order to grow further, the cells of the tumor must receive additional nutrition. Thus, the formation of new blood vessels is required to bring nutrients and oxygen to support further growth. Additional mutations occurring in tumor cells allow them to direct the growth of new blood vessels into the tumor in a process called **angiogenesis.** Some modes of cancer treatment are aimed at preventing angiogenesis from occurring.

Origin of Cancer

Normal growth and maintenance of body tissues depend on a balance between signals that promote and inhibit cell division. When this balance is upset, conditions such as cancer may occur. Thus, cancer is usually caused by mutations affecting genes that directly or indirectly affect this balance, such as those shown in Figure 4.9. The following two types of genes are usually affected:

1. **Proto-oncogenes** code for proteins that promote the cell cycle and prevent apoptosis. They are often likened to the gas pedal of a car, because they cause the cell cycle to speed up.
2. **Tumor suppressor genes** code for proteins that inhibit the cell cycle and promote apoptosis. They are often likened to the brakes of a car, because they cause the cell cycle to go more slowly or even stop.

Proto-oncogenes Become Oncogenes

Proto-oncogenes are normal genes that promote progression through the cell cycle. They are often at the end of a *stimulatory pathway* extending from the plasma membrane to the nucleus. A stimulus, such as an injury, results in the release of a growth factor that binds to a receptor protein in the plasma membrane. This sets in motion a whole series of enzymatic reactions leading to the activation of genes that promote the cell cycle, both directly and indirectly. Proto-oncogenes include the receptors and signal molecules that make up these pathways.

When mutations occur in proto-oncogenes, they become **oncogenes,** or cancer-causing genes. Oncogenes are under constant stimulation and keep on promoting the cell cycle regardless of circumstances. For example, an oncogene may code for a faulty receptor in the stimulatory pathway such that the cell cycle is stimulated, even when no growth factor is present! Or an oncogene may either specify an abnormal protein product or produce abnormally high levels of a normal product that stimulate the cell cycle to begin or to go to completion. As a result, uncontrolled cell division may occur.

Researchers have identified perhaps 100 oncogenes that can cause increased growth and lead to tumors. The oncogenes most frequently involved in human cancers belong to the *ras* gene family. Mutant forms of the *BRCA1* (*breast cancer predisposition gene 1*) oncogene are associated with certain hereditary forms of breast and ovarian cancer.

Tumor Suppressor Genes Become Inactive

Tumor suppressor genes, on the other hand, directly or indirectly inhibit the cell cycle and prevent cells from dividing uncontrollably. Some tumor suppressor genes prevent progression of the cell cycle when DNA is damaged. Other tumor suppressor genes may promote apoptosis as a last resort.

A mutation in a tumor suppressor gene is much like brake failure in a car; when the mechanism that slows down and stops cell division does not function, the cell cycle accelerates and does not halt. Researchers have identified about a half-dozen tumor suppressor genes. Among these are the *RB* and *p53* genes that code for the RB and p53 proteins. The Big Idea 3 feature, "The G_1 Checkpoint," on page 150 discusses the function of these proteins in controlling the cell cycle. The *RB* tumor suppressor gene was discovered when the inherited condition retinoblastoma was being studied, but malfunctions of this gene have now been identified in many other cancers as well, including breast, prostate, and bladder cancers. The *p53* gene turns on the expression of other genes that inhibit the cell cycle. The p53 protein can also stimulate apoptosis. It is estimated that over half of human cancers involve an abnormal or deleted *p53* gene.

Other Causes of Cancer

As mentioned previously, cancer develops when the delicate balance between promotion and inhibition of cell division is tilted toward uncontrolled cell division. Other mutations may occur within a cell that affect this balance. For example, while a mutation affecting the cell's DNA repair system will not immediately cause cancer, it leads to a much greater chance of a mutation occurring within a proto-oncogene or tumor suppressor gene. And in some cancer cells, mutation of the telomerase enzyme that regulates the length of **telomeres,** or the ends of chromosomes, causes the telomeres to remain at a constant length. Because cells with shortened telomeres normally stop dividing, keeping the telomeres at a constant length allows the cancer cells to continue dividing over and over again.

Check Your Progress 4.4

1. List the major characteristics of cancer cells that distinguish them from normal cells.
2. Distinguish between a malignant and benign tumor.
3. Compare and contrast the effect on the cell cycle of (a) a mutation in a proto-oncogene and (b) a mutation in a tumor suppressor gene.

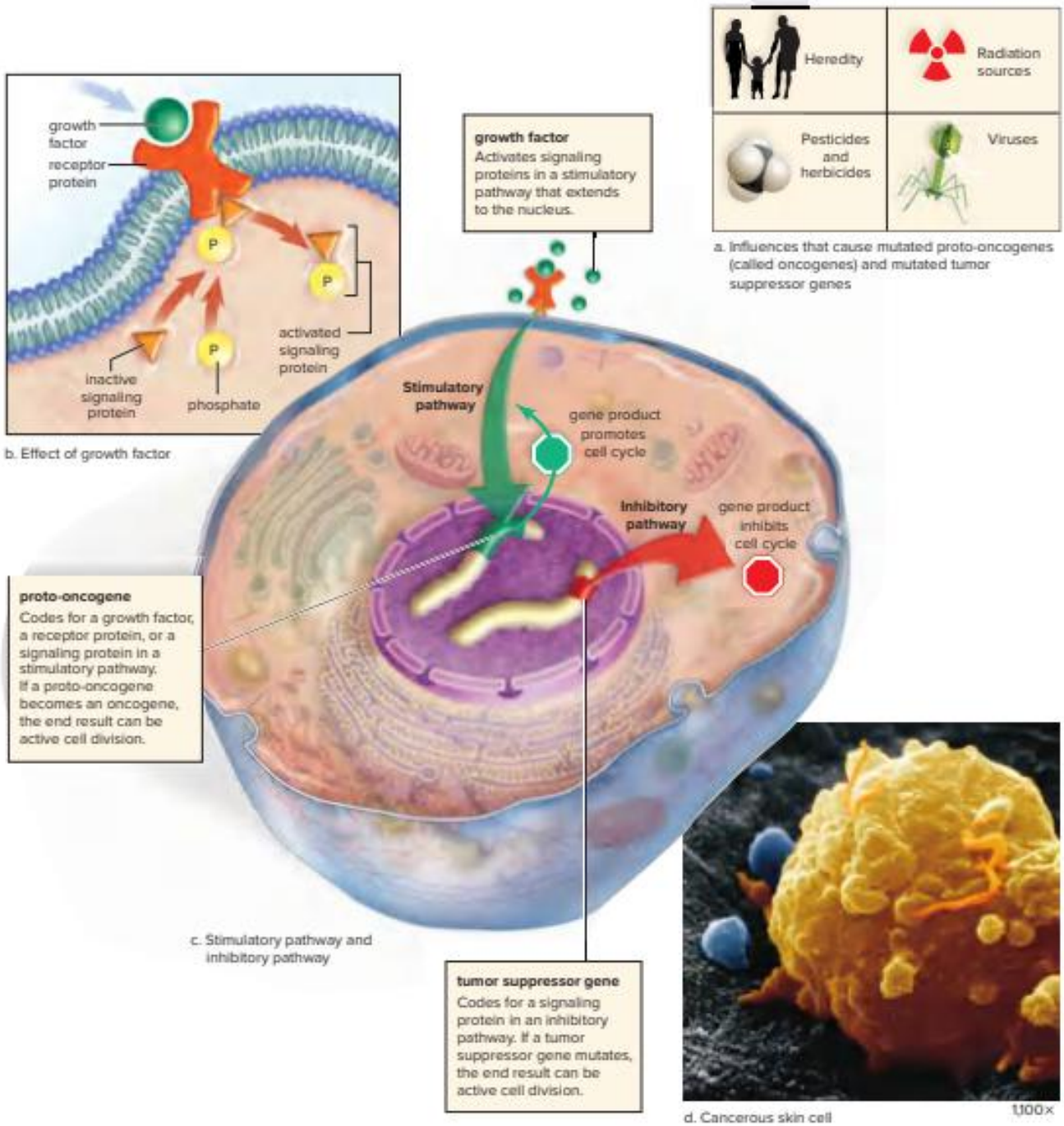


Figure 4.9 Causes of cancer. **a.** Mutated genes that cause cancer can be due to the influences noted. **b.** A growth factor that binds to a receptor protein initiates a reaction that triggers a stimulatory pathway. **c.** A stimulatory pathway that begins at the plasma membrane turns on proto-oncogenes. The products of these genes promote the cell cycle and double back to become part of the stimulatory pathway. When proto-oncogenes become oncogenes, they are turned on all the time. An inhibitory pathway begins with tumor suppressor genes, whose products inhibit the cell cycle. When tumor suppressor genes mutate, the cell cycle is no longer inhibited. **d.** Cancerous skin cell.

4.5 Prokaryotic Cell Division

Learning Outcomes

Upon completion of this section, you should be able to

1. Distinguish between the structures of a prokaryotic and eukaryotic chromosome.
2. Describe the events that occur during binary fission.

Cell division in single-celled organisms, such as prokaryotes, produces two new individuals. This is **asexual reproduction** in which the offspring are genetically identical to the parent. In prokaryotes, reproduction consists of duplicating the single chromosome and distributing a copy to each of the daughter cells. Unless a mutation has occurred, the daughter cells are genetically identical to the parent cell.

The Prokaryotic Chromosome

Prokaryotes (bacteria and archaea) lack a nucleus and other membranous organelles found in eukaryotic cells. Still, they do have a chromosome, which is composed of DNA and a limited number of associated proteins. The single chromosome of prokaryotes contains just a few proteins and is organized differently than eukaryotic chromosomes. A eukaryotic chromosome has many more associated proteins than does a prokaryotic chromosome.

In electron micrographs, the bacterial chromosome appears as an electron-dense, irregularly shaped region called the **nucleoid** (L. *nucleus*, "nucleus, kernel"; Gk. *-eides*, "like"), which is not enclosed by a membrane. When stretched out, the chromosome is seen to be a circular loop with a length that is up to about a thousand times the length of the cell. Special enzymes and proteins help coil the chromosome so that it will fit within the prokaryotic cell.

Binary Fission

Prokaryotes reproduce asexually by binary fission. The process is termed **binary fission** because division (fission) produces two (binary) daughter cells that are identical to the original parent cell. Before division takes place, the cell enlarges, and after DNA replication occurs, there are two chromosomes. These chromosomes attach to a special plasma membrane site and separate by an elongation of the cell that pulls them apart. During this period, a new plasma membrane and cell wall develop and grow inward to divide the cell. When the cell is approximately twice its original length, the new cell wall and plasma membrane for each cell are complete (Fig. 4.10).

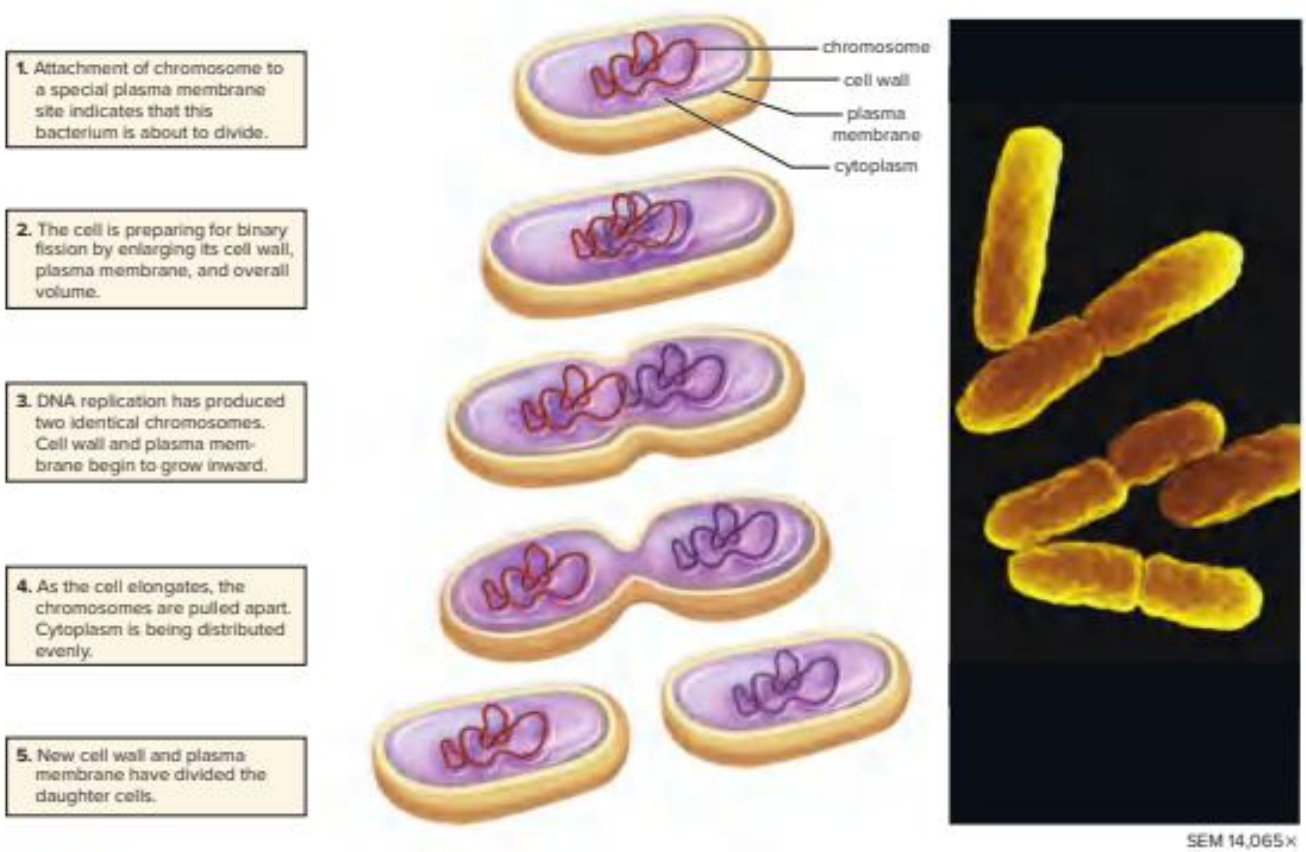


Figure 4.10 Binary fission. First, DNA replicates, and as the cell lengthens, the two chromosomes separate and the cells become divided. The two resulting bacteria are identical.

Escherichia coli, which lives in our intestines, has a generation time (the time it takes the cell to divide) of about 20 minutes under favorable conditions. In about 7 hours, a single cell can increase to over 1 million cells! The division rate of other bacteria varies depending on the species and conditions.

Comparing Prokaryotes and Eukaryotes

Both binary fission and mitosis ensure that each daughter cell is genetically identical to the parent cell. The genes are portions of DNA found in the chromosomes.

Prokaryotes (bacteria and archaea), protists (many algae and protozoans), and some fungi (yeasts) are single-celled. Cell division in single-celled organisms produces two new individuals:

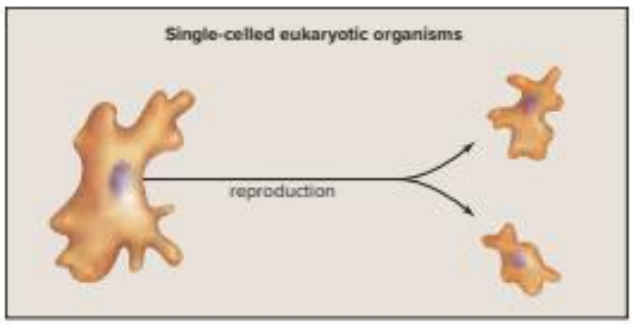
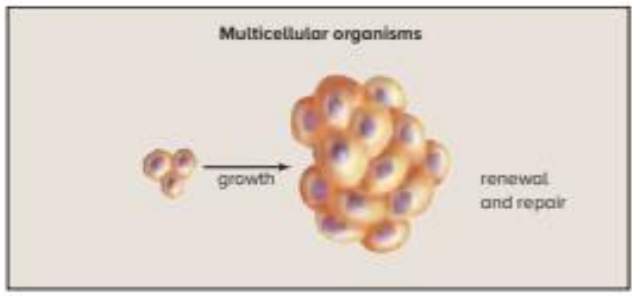


Table 4.3 Functions of Cell Division

Type of Organism	Cell Division	Function
Prokaryotes		
Bacteria and archaea	Binary fission	Asexual reproduction
Eukaryotes		
Protists and some fungi (yeast)	Mitosis and cytokinesis	Asexual reproduction
Other fungi, plants, and animals	Mitosis and cytokinesis	Development, growth, and repair

This is a form of asexual reproduction because one parent has produced identical offspring (Table 4.3).

In multicellular fungi (molds and mushrooms), plants, and animals, cell division is part of the growth process. It produces the multicellular form we recognize as the mature organism. Cell division is also important in multicellular forms for renewal and repair:



The chromosomes of eukaryotic cells are composed of DNA and many associated proteins. The histone proteins organize a chromosome, allowing it to extend as chromatin during interphase and to coil and condense just prior to mitosis. Each species of multicellular eukaryotes has a characteristic number of chromosomes in the nuclei. As a result of mitosis, each daughter cell receives the same number and kinds of chromosomes as the parent cell. The spindle, which appears during mitosis, is involved in distributing the daughter chromosomes to the daughter nuclei. Cytokinesis, either by the formation of a cell plate (plant cells) or by furrowing (animal cells), is division of the cytoplasm.

In prokaryotes, the single chromosome consists largely of DNA with a few associated proteins. During binary fission, this chromosome duplicates, and each daughter cell receives one copy as the parent cell elongates, and a new cell wall and plasma membrane form between the daughter cells. No spindle is involved in binary fission.

Check Your Progress 4.5

1. Explain how binary fission in prokaryotes differs from mitosis and cytokinesis in eukaryotes.
2. Describe the structure of a prokaryotic and a eukaryotic chromosome.

REVIEWING *the* BIG IDEAS

BIG IDEA 3

The omnipresence of mitosis suggests a common cellular evolutionary lineage. 3.A.2.a; *1.B.1.a*

In eukaryotic organisms, mitosis provides for growth of tissues and the repair of damage. In prokaryotes, mitosis provides a means of asexual reproduction. 3.A.2.b.3

Mitosis is preceded by interphase during which cells grow, replicate DNA, and prepare for division. 3.A.2.a.2.*IE*

Chromatid connection and alignment following DNA replication assures equal partitioning of genetic material into new nuclei during mitotic separation. 3.A.2.b.4

The cell cycle includes growth and cell division relying on checkpoints and chemical signals such as growth factors and cyclins to regulate its rate or stopping point. 3.A.2.a.2.*IE*

Programmed cell death (apoptosis) plays a role in normal development and differentiation. 3.A.2.a.2.*IE*; *2.E.1.c*

Mitosis and cytokinesis produce genetically identical cells for repair, growth, and asexual reproduction. 3.A.2.b.2-3

Abnormal cell cycle regulatory mechanisms may explain cancer. 3.A.2.a.2.*IE*

Prokaryotes duplicate a single circular chromosome before binary fission and may transmit extra-chromosomal plasmids to new cells. 3.A.1.a.2-3

SUMMARIZE

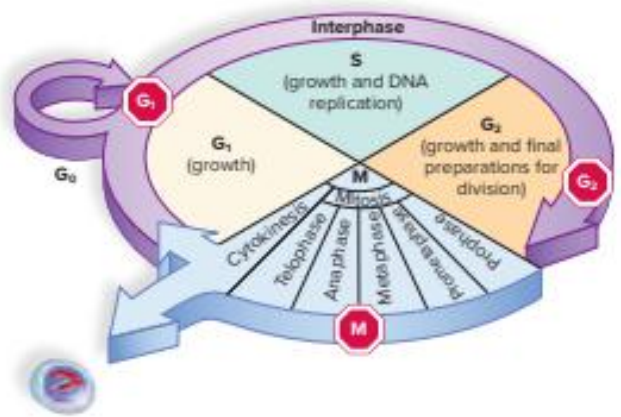
AP Answering the Essential Questions

To continue life, organisms must be able to store, retrieve and transmit genetic information. The double-stranded structure of DNA allows for information to be replicated and passed to the next generation through cell reproduction. In prokaryotes (archaea and bacteria), **binary fission** provides for the formation of new individuals; in eukaryotic organisms, mitosis provides for growth of tissues and the repair of damage. Among eukaryotes, cell division involves both **mitosis** (nuclear division) and division of the cytoplasm **(cytokinesis).** Genetic material is packaged into **chromosomes**—DNA associated with proteins—and prior to mitosis, each chromosome is duplicated to ensure that daughter cells receive the full complement of hereditary information. Each species has a specific number of chromosomes; for example, human somatic cells such as cells comprising skin and muscle tissue contain 46 chromosomes, whereas somatic cells of your family dog have 78. This total number of chromosomes is called the **diploid number** or 2N.

The cell cycle The cell cycle of eukaryotes consists of a set of stages that are highly regulated and includes (1) **interphase,** the preparatory stage, and (2) mitosis followed by (3) cytokinesis. Interphase, in turn, is composed of three sub-stages: G_1 (growth as certain organelles double), S (the synthesis stage, during which DNA is replicated), and G_2 (more growth as the cell prepares to divide). Cells of the body that are no longer dividing are said to be arrested in a G_0 state. During mitosis, the chromosomes are sorted into two daughter cells which normally have the same number of chromosomes as the parent cell (sometimes the daughter cells do not receive the full complement of chromosomes, and we'll talk about this phenomenon when we explore meiosis in Chapter 10).

Interphase represents the portion of the cell cycle between nuclear divisions and, during this time, preparations are made for cell division. These preparations include duplication of most cellular contents, including the centrosome, which organized the mitosis spindle, and mitochondria (think what would happen in terms of energy required for growth and development if a new daughter cell did not receive mitochondria from its parent cell). The cell's DNA is replicated during the S state, at which time the chromosomes, which consists of a single chromatid each, are duplicated and now contain two chromatids attached by a structure called the centromere (can you predict the fate of these two chromatids during division?). During interphase, individual chromosomes are not distinct and are collectively called chromatin.

Following the G_2 stage of interphase, the cell begins mitosis—the process of active division. Mitosis occurs after DNA replication and is a continuous process by which the duplicate chromosomes (chromatids)



attached to spindle fibers align themselves along the equator of the cell and then separate from each other (you do not need to memorize the names of the phases of mitosis, but you need to understand the processes of replication, alignment, and separation, and the order in which they occur). Following mitosis, the cell undergoes cytokinesis, the splitting of the cell into two cells, each with a complete set of chromosomes and a supply of organelles. In animal cells, a furrowing process divides the cytoplasm, while cytokinesis in plant cells involves the formation of a cell plate from which the plasma membrane and the cell wall are completed. Following cell division, cells likely differentiate into specialized types of cell.

Cell cycle regulation To help ensure that the stages of cell division follow each other in the normal sequence, the cell cycle is regulated by external signals and internal controls that act like stop-and-go signs at checkpoints (sort of like TSA at airports). **Growth factors** are signaling proteins received at the dividing cell's plasma membrane and trigger the cell to begin the process of division. **Cyclins** and **cyclin-dependent kinases** are internal signals that increase and decrease as the cell cycle continues. The G_1 checkpoint ensures that conditions for division are favorable and that the proper signals are present, and also checks DNA for damage. If the DNA is damaged, **apoptosis**—programmed cell death—may occur. Apoptosis also plays a role in normal development and differentiation; for example, without apoptosis, our fingers and toes will retain the embryonic webbing between them. Passage through the G_2 checkpoint represents the cell's commitment to mitosis: DNA has replicated, some organelles have duplicated, and the cell is ready to enter mitosis. A final checkpoint, M, ensures that all of the chromosomes are attached to the spindle in preparation for separation. Errors in the regulation of the cell cycle can have detrimental consequences, including the development of cancer.

Cancer results primarily due to the mutation of genes involved in the control of the cell cycle. Cancer cells lack differentiation, have abnormal nuclei, do not undergo apoptosis, form tumors, and metastasize to other organs. Cancer often follows a progression in which DNA mutations accumulate, gradually causing uncontrolled growth and tumor development. Several culprits contributing to the development of cancer have been identified. One offender is *p53* protein (coded for by the *p53* gene) which plays a key role in the G1 checkpoint of cell division. Normal *p53* proteins monitor DNA and destroy cells with irreparable damage to DNA. Thus, the *p53* gene is considered a tumor suppressor gene. Mutations in *p53* can result in the production of abnormal *p53* proteins that fail to stop cell division even if the DNA is damaged, leading to an accumulation of cancer cells. Proto-oncogenes stimulate the cell cycle after they are turned on by environmental signals such as growth factors; oncogenes are mutated proto-oncogenes that stimulate the cell cycle without the need of environmental signals, resulting in unchecked cell division.

The prokaryote cell cycle So far, our discussion has focused on cell division in eukaryotic cells in which mitosis is primarily for the purpose of development, growth, and repair of tissues. However, binary fission in prokaryotes—a process in which the cell simply splits in half after replicating DNA—and mitosis in unicellular eukaryotic protists and fungi allow organisms to reproduce asexually. It should be noted that the structure of the prokaryotic chromosome differs from chromosomes found in eukaryotes. The prokaryotic chromosome has few associated proteins and a single, long loop of DNA. When binary fission occurs, the chromosome attaches to the inside of the plasma membrane and replicates. As the cell elongates, the chromosome duplicates are pulled apart, and the cell divides, resulting in bacteria that, barring mutation, are identical.

ASSESS

Choose the best answer for each question.

4.1 The Cell Cycle

For questions 1–4, match each stage of the cell cycle to its correct description.

Key:

a. G_1 stage
c. G_2 stage
b. S stage
d. M (mitotic) stage

1. At the end of this stage, each chromosome consists of two attached chromatids.
2. During this stage, daughter chromosomes are distributed to two daughter nuclei.
3. The cell doubles its organelles and accumulates the materials needed for DNA synthesis.
4. The cell synthesizes the proteins needed for cell division.
5. Which is not true of the cell cycle?
   a. The cell cycle is controlled by internal/external signals.
   b. Cyclin is a signaling molcule that increases and decreases as the cycle continues.
   c. DNA damage can stop the cell cycle at the G_1 checkpoint.
   d. Apoptosis occurs frequently during the cell cycle.

4.2 The Eukaryotic Chromosome

6. The diploid number of chromosomes
   a. is the 2n number.
   b. is in a parent cell and therefore in the two daughter cells following mitosis.
   c. varies according to the particular organism.
   d. All of these are correct.
7. The form of DNA that contains genes that are actively being transcribed is called
   a. histones.
   b. telomeres.
   c. heterochromatin.
   d. euchromatin.
8. Histones are involved in
   a. regulating the checkpoints of the cell cycle.
   b. lengthening the ends of the telomeres.
   c. compacting the DNA molecule.
   d. cytokinesis.

4.3 Mitosis and Cytokinesis

9. At the metaphase plate during metaphase of mitosis, there are
   a. single chromosomes.
   b. duplicated chromosomes.
   c. G_1 stage chromosomes.
   d. always 23 chromosomes.
10. During which mitotic phases are duplicated chromosomes present?
    a. all but telophase
    b. prophase and anaphase
    c. all but anaphase and telophase
    d. only during metaphase at the metaphase plate

11. Which of these is paired incorrectly?
    a. prometaphase—the kinetochores become attached to spindle fibers
    b. anaphase—daughter chromosomes migrate toward spindle poles
    c. prophase—the nucleolus disappears and the nuclear envelope disintegrates
    d. telophase—a resting phase between cell division cycles

4.4 The Cell Cycle and Cancer

12. Which of the following is not characteristic of cancer cells?
    a. Cancer cells often undergo angiogenesis.
    b. Cancer cells tend to be nonspecialized.
    c. Cancer cells undergo apoptosis.
    d. Cancer cells often have abnormal nuclei.
13. Which of the following statements is true?
    a. Proto-oncogenes cause a loss of control of the cell cycle.
    b. The products of oncogenes may inhibit the cell cycle.
    c. Tumor suppressor gene products inhibit the cell cycle.
    d. A mutation in a tumor suppressor gene may inhibit the cell cycle.

4.5 Prokaryotic Cell Division

14. In contrast to a eukaryotic chromosome, a prokaryotic chromosome
    a. is shorter and fatter.
    b. has a single loop of DNA.
    c. never replicates.
    d. contains many histones.
15. Which of the following is the term used to describe asexual reproduction in a single-celled organism?
    a. cytokinesis
    b. mitosis
    c. binary fission
    d. interphase

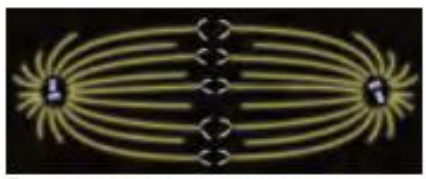
ENGAGE

AP Applying the Big Ideas

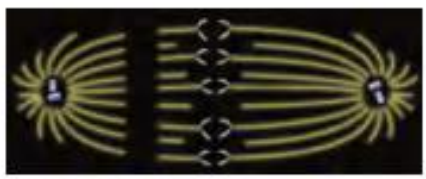
1. BIG IDEA 3 The cell cycle is a complex set of stages that is highly regulated with checkpoints. **Describe** the events that occur in the cell cycle, including at least one checkpoint.

AP Applying the Science Practices

What happens to the microtubules? Scientists performed experiments tracking chromosomes along microtubules during mitosis. They hypothesized that the microtubules are broken down, releasing microtubule subunits as the chromosomes are moved toward the poles of the cell. The microtubules were labeled with a yellow fluorescent dye, and using a laser, the microtubules were marked midway between the poles and the chromosomes by eliminating the fluorescence in the targeting region as shown in the diagram.



Fluorescent-labeled microtubules



Laser-marked microtubules

*Data obtained from: Maddox, P., et al. 2003. Direct observation of microtubule dynamics at kinetochores in *Xenopus* extract spindles: implications for spindle mechanics. *The Journal of Cell Biology* 162: 377–382. Maddox, et al. 2004. Controlled ablations of microtubules using picosecond laser. *Biophysics Journal* 87: 4203–4212.

Think Critically SP 1 SP 6

1. **Explain** the purpose of the fluorescent dye.
2. **Predict** how the cell might appear later in anaphase by drawing a diagram.

1

Meiosis and Sexual Reproduction

Chapter Outline

Meiosis is the process that produces the majority of genetic variation between individuals.

AP What are the chances that there will ever be another human like you on this planet? Because of meiosis, reproduction produces offspring that are genetically different from the parents. Meiosis introduces an enormous amount of diversity; in humans, more than 70 trillion different genetic combinations are possible from the mating of two individuals! In other words, meiosis ensures that, statistically, it is unlikely that anyone will ever be genetically the same as you.

In animals, meiosis begins the process that produces cells called gametes, which play an important role in sexual reproduction. In humans, sperm are the male gametes, and eggs are the female gametes. While meiosis in the two sexes is very similar, there are some important differences in how they occur. One major difference pertains to the age at which the process begins and ends. In males, sperm production does not begin until puberty but then continues throughout a male's lifetime. In females, the process of producing eggs has started before the female is born and ends around menopause. Another difference concerns the number of gametes that can be produced. In males, sperm production is unlimited, whereas females produce only one egg a month.

In this chapter, you will see how meiosis is involved in providing the variation so important in the production of gametes.

As you read through the chapter, think about these Essential Questions:

1. What are the similarities and differences between meiosis and mitosis? 1.A.1.c 1.A.2.b
2. How does the process of meiosis reduce the chromosomes number from diploid to haploid? 3.A.2.c.1-3,5
3. How does meiosis followed by fertilization increase genetic diversity? 4.C.1.b 4.C.2.b

Following *the* BIG IDEAS

BIG IDEA 1 — The variation introduced during meiosis followed by fertilization plays an important role in evolutionary change.

BIG IDEA 3 — In sexually reproducing organisms, meiosis followed by fertilization recombines genetic information from both parents; changes in chromosome structure and number can have consequences for an individual's physiology.

BIG IDEA 4 — The variation produced by meiosis at the cellular levels affects all levels of an organism's physiology.

1.1 Overview of Meiosis

Learning Outcomes

Upon completion of this section, you should be able to

1. Contrast haploid and diploid chromosome numbers.
2. Explain what is meant by *homologous chromosomes*.
3. Summarize the process by which meiosis reduces the chromosome number.

In sexually reproducing organisms, **meiosis** (Gk. *mio,* "less"; *-sis,* "act or process of") is the type of nuclear division that reduces the chromosome number from the diploid (2n) number (Gk. *diplos,* "twofold") to the haploid (n) number (Gk. *haplos,* "single"). The **diploid (2n)** number refers to the total number of chromosomes, which exists in two sets. The **haploid (n)** number of chromosomes is half the diploid number, or a single set of chromosomes. In humans, meiosis reduces the diploid number of 46 chromosomes to the haploid number of 23 chromosomes.

Gametes, or reproductive cells (in animals, these are the sperm and egg), usually have the haploid number of chromosomes. In **sexual reproduction,** haploid gametes, which are produced during meiosis, subsequently merge into a diploid cell called a **zygote.** In plants and animals, the zygote undergoes development to become an adult organism.

Meiosis is necessary in sexually reproducing organisms, because the diploid number of chromosomes has to be reduced by half in each of the parents in order to produce diploid offspring. Otherwise, the number of chromosomes would double with each new generation. Within a few generations, the cells of an animal would be nothing but chromosomes! For example, in humans with a diploid number of 46 chromosomes, in five generations the chromosome number would increase to 1,472 chromosomes (46×2^5). In ten generations, this number would increase to a staggering 47,104 chromosomes (46×2^{10}). The Belgian cytologist (a biologist that studies cells) P.-J. van Beneden (1809–1894), was one of the first to observe that gametes have a reduced chromosome number. When studying the roundworm *Ascaris,* he noticed that the sperm and egg each contain only two chromosomes, while the zygote and subsequent embryonic cells always have four chromosomes.

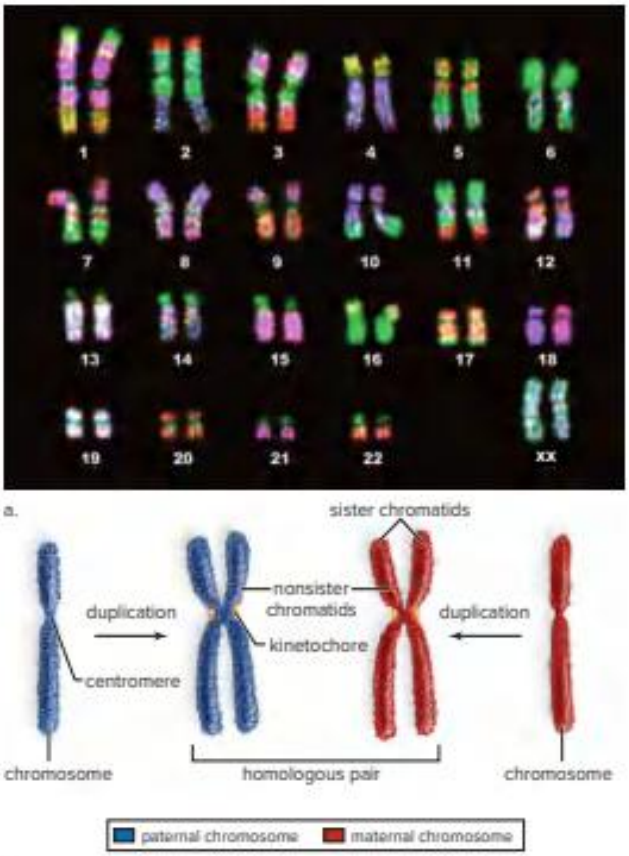


Figure 1.1 Homologous chromosomes. In diploid body cells, the chromosomes occur in pairs called homologous chromosomes. **a.** In this micrograph of stained chromosomes from a human cell, the pairs have been numbered 1–22 and XX. Note that chromosome pairs 1–22 are autosomes, coding for nonsex traits, whereas the XX pair includes the sex chromosomes and helps determine human gender. **b.** These chromosomes are duplicated, and each chromosome in the homologous pair is composed of two chromatids. The sister chromatids contain exactly the same genes; the nonsister chromatids contain genes for the same traits (e.g., type of hair, color of eyes), but one may have DNA that codes for trait variations, such as dark hair versus light hair.

Homologous Pairs of Chromosomes

In diploid body cells, the chromosomes occur in pairs. Figure 1.1*a,* a pictorial display of human chromosomes, called a karyotype, shows the chromosomes arranged according to pairs. The members of each pair are called homologous chromosomes. **Homologous chromosomes,** or **homologues** (Gk. *homologos,* "agreeing, corresponding"), look alike; they have the same length and centromere position. When stained, homologues have a similar banding pattern, because they contain genes for the same traits in the same order in the same locations on both chromosomes in the homologous pair. But while homologous chromosomes have genes for the same traits, such as finger length, the DNA (deoxyribonucleic acid) sequence for the gene on one homologue may code for short fingers and the gene at the same location on the other homologue may code for long fingers. Alternate forms of a gene (as for long fingers and short fingers) are called **alleles.** The DNA sequences of alleles are highly similar, but they are different enough to produce alternative physical traits, such as long or short fingers.

To properly produce a haploid number of chromosomes in gametes, you first have to double the amount of DNA. The chromosomes in Figure 1.1*a* are duplicated as they would be just before nuclear division. Recall that during the S stage of the cell cycle, DNA replicates and the chromosomes become duplicated. The results of the duplication process are depicted in Figure 1.1*b.* When duplicated, a chromosome is composed of two identical parts called sister chromatids, each containing one DNA double helix molecule. The *sister chromatids* are held together at a common region called the centromere.

Why does the zygote have paired chromosomes? One member of a homologous pair was inherited from the male parent, and the other was inherited from the female parent when the haploid sperm and egg fused together. In Figure 1.1*b* and throughout this chapter, the paternal chromosome is colored blue, and the maternal chromosome is colored red. *However, this is simply a method of tracking chromosomes in diagrams. Since chromosomes do not have color, geneticists generally use chromosome length and centromere location to identify homologues.* You will see shortly how meiosis reduces the chromosome number. Whereas the zygote and body cells have homologous pairs of chromosomes, the gametes have only one chromosome of each kind—derived from either the paternal or the maternal homologue.

Meiosis Is Reduction Division

The central purpose of meiosis is to reduce the chromosome number from 2n to n. Meiosis requires two nuclear divisions and produces four haploid daughter cells, each having one of each kind of chromosome. The process begins by replicating the chromosomes, then splitting the matched homologous pairs to go from 2n to n chromosomes during the first division. The second division reduces the amount of DNA in n chromosomes to an amount appropriate for each gamete. Once the DNA has been replicated and chromosomes become a pair, they may exchange genes, creating a genetic mixture different from the parent. The first nuclear division separates each homologous pair, reducing the chromosome number from 2n to n. Even though each daughter cell now has n chromosomes, each chromosome still has a sister chromatid, making a second nuclear division necessary. The end result of meiosis is four gametes with n chromosomes.

Figure 1.2 presents an overview of meiosis, indicating the two nuclear divisions, meiosis I and meiosis II. Prior to meiosis I, DNA replication has occurred; therefore, each chromosome has two sister chromatids. During meiosis I, something new happens that does not occur in mitosis. The homologous chromosomes come together and line up side by side, forming a **synaptonemal complex.** This process is called **synapsis** (Gk. *synaptos,* "united, joined together") and results in a **bivalent** (L. *bis,* "two"; *valens,* "strength")—that is, two homologous chromosomes that stay in close association during the first two phases of meiosis I. Sometimes the term *tetrad* (Gk. *tetra,* "four") is used instead of *bivalent,* because, as you can see, a bivalent contains four chromatids. Chromosomes may recombine or exchange genetic information during this association (see section 1.2).

Following synapsis, homologous pairs align at the metaphase plate, and then the members of each pair separate. This separation means that only one duplicated chromosome from each homologous pair reaches a daughter nucleus, reducing the chromosome number from 2n to n. It is important for each daughter nucleus to have a member from each pair of homologous chromosomes, because only in that way can there be a copy of each kind of chromosome in the daughter nuclei. Notice in Figure 1.2 that two possible combinations of chromosomes in the daughter

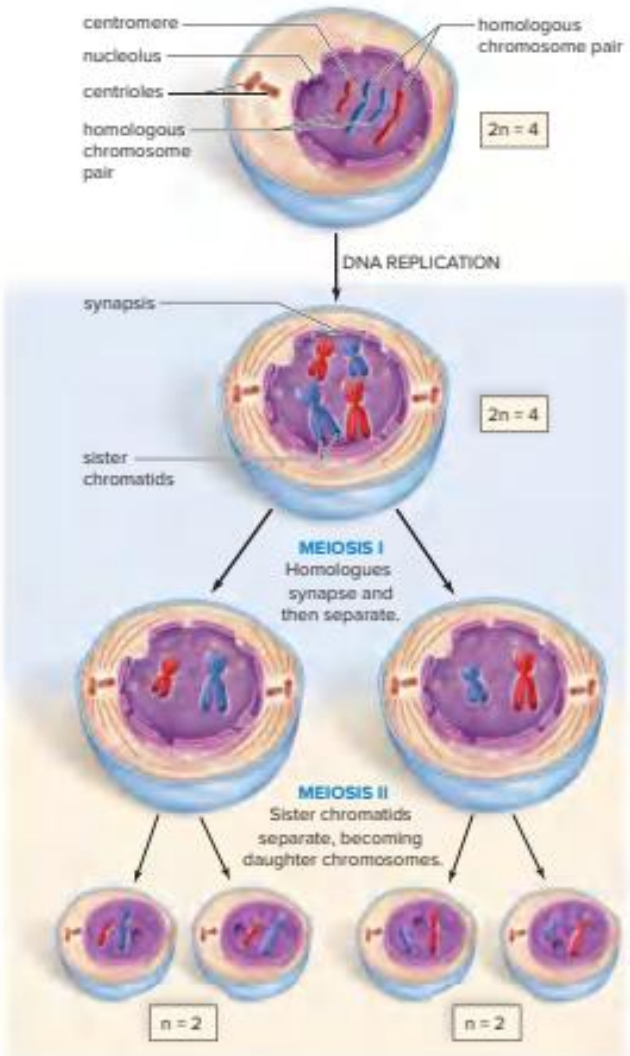


Figure 1.2 Overview of meiosis. Following DNA replication, each chromosome is duplicated and consists of two chromatids. During meiosis I, homologous chromosomes pair and separate. During meiosis II, the sister chromatids of each duplicated chromosome separate. At the completion of meiosis, there are four haploid daughter cells. Each daughter cell has one of each kind of chromosome.

cells are shown: short red with long blue and short blue with long red. Knowing that all daughter cells have to have one short chromosome and one long chromosome, what are the other two possible combinations of chromosomes for these cells?

Notice that DNA replication occurs only once during meiosis; no replication is needed between meiosis I and meiosis II, because the chromosomes are already duplicated; they already have two

sister chromatids. During meiosis II, the sister chromatids separate, becoming daughter chromosomes that move to opposite poles. The chromosomes in each of the four daughter cells now contain only one DNA double helix molecule in the form of a haploid chromosome.

The number of centromeres can be counted to verify that the parent cell has the diploid number of chromosomes. At the end of meiosis I, the chromosome number has been reduced, because there are half as many centromeres present, even though each chromosome still consists of two chromatids each. Each daughter cell that forms has the haploid number of chromosomes. At the end of meiosis II, sister chromatids separate, and each daughter cell that forms still contains the haploid number of chromosomes, each consisting of a single chromatid.

Fate of Daughter Cells

In the plant life cycle, the daughter cells become haploid spores that germinate to become a haploid generation. This generation then produces the gametes by mitosis. In the animal life cycle, the daughter cells become the gametes, either sperm or eggs. The body cells of an animal normally contain the diploid number of chromosomes due to the fusion of sperm and egg during fertilization. If meiotic events go wrong, the gametes can contain the wrong number of chromosomes or altered chromosomes. This possibility and its consequences are discussed in section 1.6.

Check Your Progress 1.1

1. Describe what is meant by *a homologous pair of chromosomes.*
2. Examine how chromosome number changes during meiosis I and meiosis II.
3. Explain the purpose of a bivalent in chromosome pairing.

1.2 Genetic Variation

Learning Outcomes

Upon completion of this section, you should be able to

1. Understand the importance of genetic variation to evolutionary change.
2. Explain how crossing-over contributes to genetic variation.
3. Examine how independent assortment contributes to genetic variation.

We have seen that meiosis provides a way to keep the chromosome number constant generation after generation. Without meiosis, the chromosome number of the next generation would continually increase. The events of meiosis also help ensure that genetic variation occurs with each generation.

Genetic variation is essential for a species to be able to evolve and adapt in a changing environment. Asexually reproducing organisms, such as the prokaryotes, depend primarily on mutations to generate variation among offspring. This is sufficient for their survival, because they produce great numbers of offspring very quickly. Although mutations also occur among sexually reproducing organisms, the reshuffling of genetic material during sexual reproduction ensures that offspring will have a different combination of genes than their parents. Meiosis brings about genetic variation in two key ways: crossing-over and independent assortment of homologous chromosomes.

Genetic Recombination

Crossing-over is an exchange of genetic material between nonsister chromatids of a bivalent during meiosis I. In humans, it is estimated that an average of two to three crossovers occur between the nonsister chromatids during meiosis. At synapsis, homologues line up side by side, and a nucleoprotein lattice appears between them (Fig. 1.3). This lattice holds the bivalent

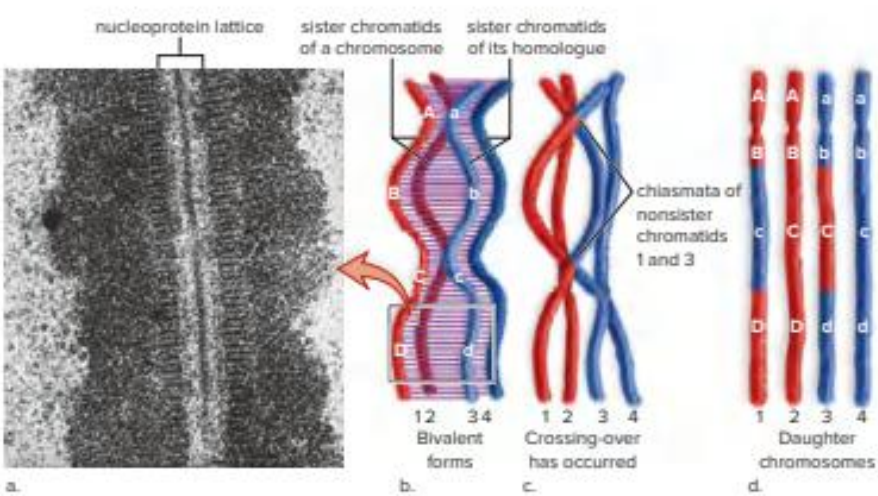


Figure 1.3 Crossing-over during meiosis I. **a.** The homologous chromosomes pair up, and a nucleoprotein lattice develops between them. This is an electron micrograph of the lattice. It "zippers" the members of the bivalent together, so that corresponding genes on paired chromosomes are in alignment. **b.** This visual representation shows only two places where nonsister chromatids 1 and 3 have come in contact. **c.** Chiasmata indicate where crossing-over has occurred. The exchange of color represents the exchange of genetic material. **d.** Following meiosis II, daughter chromosomes have a new combination of genetic material due to crossing-over, which occurred between nonsister chromatids during meiosis I.

together in such a way that the DNA of the duplicated chromosomes of each homologue pair is aligned. This ensures that the genes contained on the nonsister chromatids are directly aligned. Now crossing-over may occur. As the lattice breaks down, homologues are temporarily held together by *chiasmata* (sing., chiasma), regions where the nonsister chromatids are attached due to DNA strand exchange and crossing-over. After exchange of genetic information between the nonsister chromatids, the homologues separate and are distributed to different daughter cells.

To appreciate the significance of crossing-over, keep in mind that the members of a homologous pair can carry slightly different instructions, or alleles, for the same genetic traits. In the end, due to a swapping of genetic material during crossing-over, the chromatids held together by a centromere are no longer identical. Therefore, when the chromatids separate during meiosis II, some of the daughter cells receive daughter chromosomes with recombined alleles. Due to **genetic recombination,** the offspring have a different set of alleles, and therefore genes, than their parents. This increases the genetic variation of the offspring.

Independent Assortment of Homologous Chromosomes

During **independent assortment,** the homologous chromosome pairs separate independently, or randomly. When homologues align at the metaphase plate, the maternal or paternal homologue may be oriented toward either pole. Figure 1.4 shows the possible chromosome orientations for a cell that contains only three pairs of homologous chromosomes. Once all possible alignments of independent assortment are considered for these three pairs, the result will be 2^3, or 8, combinations of maternal and paternal chromosomes in the resulting gametes from this cell, simply due to independent assortment of homologues.

Significance of Genetic Variation

In humans, who have 23 pairs of chromosomes, the possible chromosomal combinations in the gametes is a staggering 2^{23}, or 8,388,608. The variation that results from meiosis is enhanced by **fertilization,** the union of the male and female gametes. The chromosomes donated by the parents are combined, and in humans, this means that there are potentially $(2^{23})^2$, or 70,368,744,000,000, different chromosome combinations in the zygote. This number assumes that there was no crossing-over between the nonsister chromatids prior to independent assortment. If a single crossing-over event occurs, then $(4^{23})^2$, or 4,951,760,200,000,000,000,000,000,000, genetically different zygotes are possible for every couple. Keep in mind that crossing-over can occur several times in each chromosome!

The staggering amount of genetic variation achieved through meiosis is particularly important to the long-term survival of a species, because it increases genetic variation within a population. The process of sexual reproduction brings about genetic recombinations among members of a population.

Asexual reproduction passes on exactly the same combination of chromosomes and genes. Asexual reproduction may be advantageous if the environment remains unchanged. However, if the environment changes, genetic variability among offspring introduced by sexual reproduction may be advantageous. Under the new conditions, some offspring may have a better chance of survival and reproductive success than others in a population. For example, suppose the ambient temperature were to rise due to climate change. This change in the environment could place demands on the physiology of an organism. For example, an animal with less fur, or reduced body fat, could have an advantage over other individuals of its generation.

In a changing environment, sexual reproduction, with its reshuffling of genes due to meiosis and fertilization, might give a few offspring a better chance to survive and reproduce, thereby increasing the possibility of passing on their genes to the next generation.

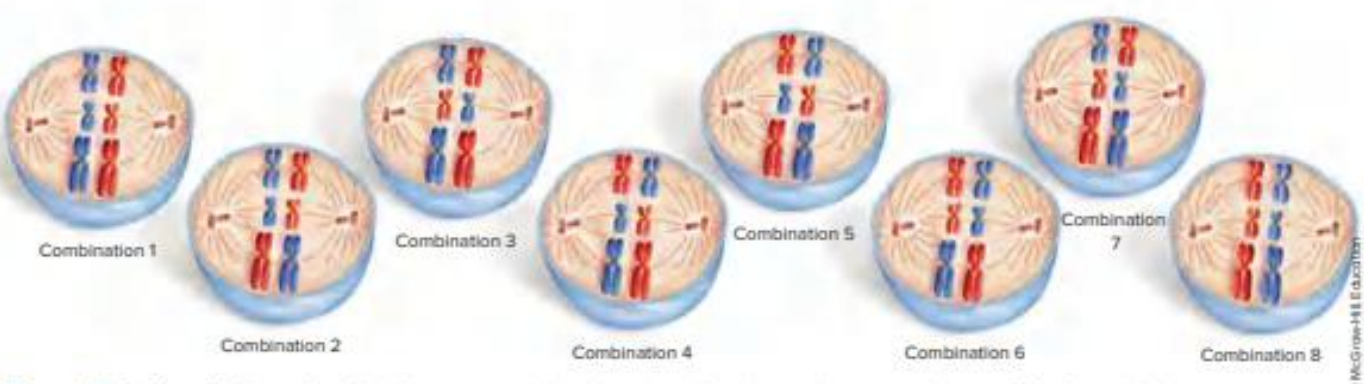


Figure 1.4 Independent assortment. When a parent cell has three pairs of homologous chromosomes, there are 2^3, or 8, possible chromosome alignments at the metaphase plate due to independent assortment. Each possible combination is shown, one in each cell.

BIG IDEA 1: Evolution

Meiosis and the Parthenogenic Lizards

The process of crossing-over plays an important role in the generation of genetic variation for sexually reproducing species. For most species that undergo asexual reproduction, fast generation times and mutation allow for the species to introduce enough variation to respond to environmental changes. But what about species, such as the whiptail lizard shown in Figure 1A, that undergo parthenogenesis? Parthenogenesis is the production of new individuals from unfertilized eggs. It is not uncommon in the animal kingdom; many arthropods, lizards, fish, and salamanders are known to be parthenogenic.

Parthenogenesis is a form of asexual reproduction; only one parent, the female, contributes genetic information to the next generation. But typically, these species do not have the short generation times of other asexual organisms, such as bacteria. At least on the surface, parthenogenesis would seem to limit the amount of genetic variation in the species, and thus reduce the ability of the species to respond to changes in its environment. While some species, such as honeybees, avoid this problem by switching between parthenogenesis and sexual reproduction, truly parthenogenic species appear to be at an evolutionary disadvantage.

Researchers from a team at the Howard Hughes Medical Institute discovered that in a parthenogenic species of lizards (whiptail lizards, genus *Aspidoscelis*) there is a variation in the normal process of meiosis. In most cases, crossing-over during meiosis occurs between the nonsister chromatids of homologous chromosomes. However, in the whiptail lizard, crossing-over occurs between the sister chromatids.

Figure 1A In parthenogenic species, such as the whiptail lizard, variations in the process of meiosis allow the species to increase genetic variation with each generation.

How does this happen? To make this possible, the species doubles the number of chromosomes prior to meiosis—effectively making an additional copy of the genome and forming a pair of homologous chromosomes from a single parent. This doubling allows the reduction division in meiosis to produce diploid (2n) gametes, a requirement for many species that undergo parthenogenesis. Then, the species allows for crossing-over to occur between the sister chromatids themselves. Since there are always slight differences in the sister chromatids (they are never truly identical), small amounts of variation are maintained in the genome, and this is passed on to the next generation. The amount of genetic variation may be small, but this variation in meiosis allows for some level of genetic recombination, thus providing genetic variation to the species.

Questions to Consider

1. Does this process produce the same amount of genetic variation as would occur in normal sexual reproduction?
2. How would you test to determine the amount of genetic variation produced by parthenogenic species?

Check Your Progress 1.2

1. Describe the two main ways in which meiosis contributes to genetic variation.
2. Examine how many combinations of chromosomes are possible in the gametes in a cell with four pairs of homologous chromosomes.
3. Evaluate why meiosis and sexual reproduction are important in responding to the changing environment.

1.3 The Phases of Meiosis

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the phases of meiosis and the major events that occur during each phase.
2. Understand how meiosis reduces the chromosome number from diploid to haploid.

Meiosis consists of two unique, consecutive cell divisions, meiosis I and meiosis II. DNA is replicated in S phase of the cell cycle prior to meiosis I but not meiosis II. Both meiosis I and meiosis II contain a prophase, metaphase, anaphase, and telophase.

Prophase I

It is apparent during prophase I that nuclear division is about to occur, because a spindle forms as the centrosomes migrate away from one another. The nuclear envelope fragments, and the nucleolus disappears.

The homologous chromosomes, each having replicated during S phase of the cell cycle, consist of two sister chromatids. The homologous chromosomes undergo synapsis to form bivalents. At this time, crossing-over may occur between the nonsister chromatids (see Fig. 1.3). As described earlier, crossing-over increases the genetic diversity of the daughter cells, because after crossing-over, the sister chromatids are no longer identical.

Throughout prophase I, the homologous chromosomes have been condensing, so that by now they have the appearance of compacted metaphase chromosomes.

Metaphase I

During metaphase I, the bivalents held together by chiasmata (see Fig. 1.3) have moved toward the metaphase plate (equator of the spindle). Metaphase I is characterized by a fully formed spindle and alignment of the bivalents at the metaphase plate. As in mitosis, kinetochores are seen, but the two kinetochores of a duplicated chromosome are attached to the same kinetochore spindle fiber.

Bivalents independently align themselves at the metaphase plate of the spindle. Either the maternal or paternal homologue of each bivalent may be oriented toward either pole of the cell. The orientation of one bivalent is not dependent on the orientation of the other bivalents. This independent assortment of chromosomes contributes to the genetic variability of the daughter cells, because all possible combinations of chromosomes can occur in the daughter cells.

Anaphase I

During anaphase I, the homologues of each bivalent separate and move to opposite poles, but sister chromatids do not separate. This splitting of the homologous pair reduces the chromosome number from 2n to n. However, each chromosome still has two chromatids (Fig. 1.5).

Telophase I

Completion of telophase I is not necessary during meiosis. That is, the spindle disappears, but new nuclear envelopes need not form before the daughter cells proceed to meiosis II. Also, this phase may or may not be accompanied by cytokinesis, which is separation of the cytoplasm. Notice in Figure 1.5 that the cells have different chromosome combinations than the original parent cell (not all of the combinations are shown in Fig. 1.5). The cells exiting telophase I are also haploid compared to the diploid parent cell.

Interkinesis

Following telophase, the cells enter interkinesis, a short rest period prior to beginning the second nuclear division, meiosis II. The process of **interkinesis** is similar to interphase between mitotic divisions, except that DNA replication does not occur, because the chromosomes are already duplicated.

Meiosis II and Gamete Formation

At the beginning of meiosis II, the two daughter cells contain the haploid number of chromosomes, or one chromosome from each homologous pair. Note that these chromosomes still consist of duplicated sister chromatids at this point. During metaphase II, the chromosomes align at the metaphase plate, but they do not align in homologous pairs, as in meiosis I, because only one chromosome of each homologous pair is present (Fig. 1.5). Thus, the alignment of the chromosomes at the metaphase plate is similar to what is observed during mitosis.

During anaphase II, the sister chromatids separate, becoming daughter chromosomes that are not duplicated. These daughter chromosomes move toward the poles. At the end of telophase II and cytokinesis, there are four haploid cells. Because of crossing-over of chromatids during meiosis I, each gamete most likely contains chromosomes with a mixture of maternal and paternal genes.

As mentioned, following meiosis II, the haploid cells become gametes in animals (see section 1.5). In plants, they become *spores*, reproductive cells that develop into new multicellular structures without the need to fuse with another reproductive cell. The multicellular structure is the haploid generation, which produces gametes. The resulting zygote develops into a diploid generation. Therefore, plants have both haploid and diploid phases in their life cycle, and plants are said to exhibit an *alternation of generations*. In most fungi and algae, the zygote undergoes meiosis, and the daughter cells develop into new individuals. Therefore, the organism is always haploid.

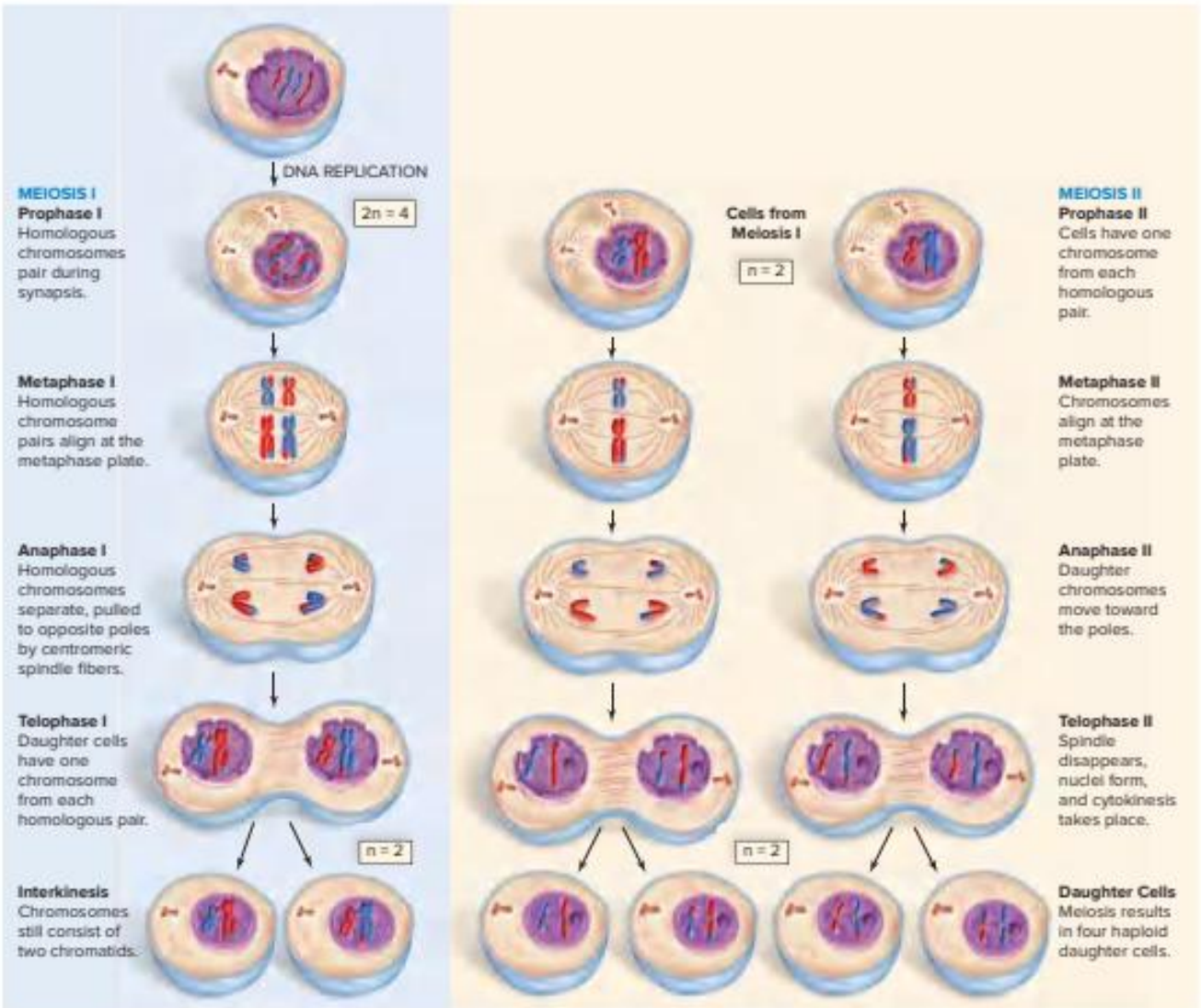


Figure 1.5 Stages of Meiosis. When diploid homologous chromosomes pair during meiosis I, crossing-over occurs, as represented by the exchange of color. Pairs of homologous chromosomes separate during meiosis I, and chromatids separate, becoming haploid daughter chromosomes, with two copies of each during meiosis II. Following meiosis II and the separation of sister chromatids, four haploid daughter cells are produced.

Check Your Progress 1.3

1. Describe the differences between the chromosomal combinations of a cell at metaphase I and metaphase II of meiosis.
2. Explain what would cause daughter cells following meiosis II to contain identical chromosomes or nonidentical chromosomes.
3. Examine what could happen if homologous chromosomes lined up top to bottom instead of side by side during meiosis I.

1.4 Meiosis Compared to Mitosis

Learning Outcomes

Upon completion of this section, you should be able to

1. Contrast changes in chromosome number, genetic variability, and number of daughter cells between meiosis and mitosis.
2. Distinguish the events that occur during prophase I of meiosis that do not occur during prophase of mitosis.
3. Compare chromosome alignment during meiosis I to mitosis.

There are many similarities between the processes of mitosis. In both processes:

- An orderly series of stages, including prophase, prometaphase, metaphase, and telophase are involved in the sorting and divison of the chromosomes.
- The spindle fibers are active in sorting the chromosomes.
- Cytokinesis follows the end of the process to divide the cytoplasm between the daughter cells.

However, the function of mitosis and meiosis in an organism is very different. Mitosis maintains the chromosome number

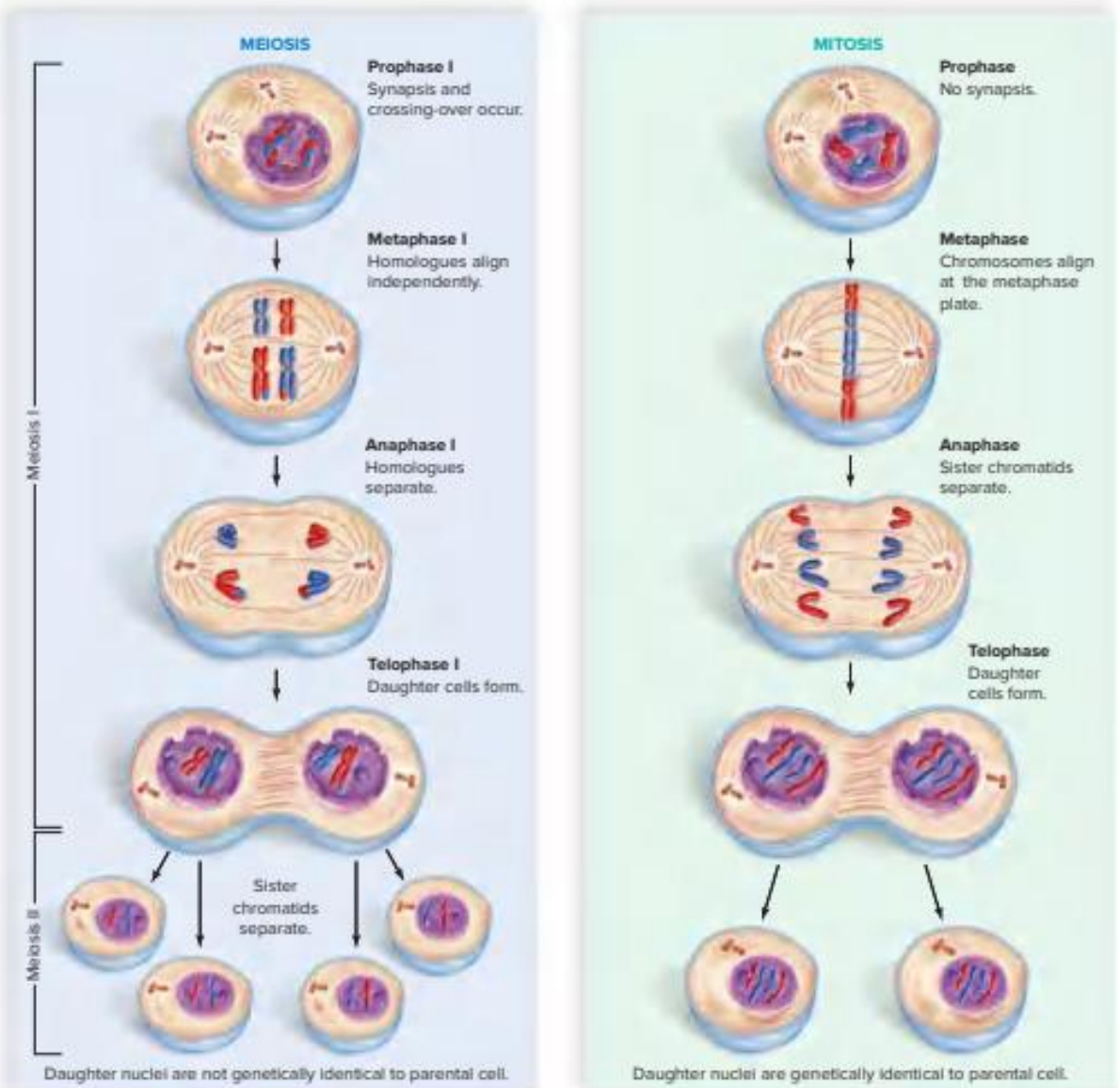


Figure 1.6 Meiosis I compared to mitosis. Why does meiosis produce daughter cells with half the number of chromosomes, whereas mitosis produces daughter cells with the same number of chromosomes as the parent cell? Compare metaphase I of meiosis to metaphase of mitosis. Only in metaphase I of meiosis are the homologous chromosomes paired at the metaphase plate. Members of homologous chromosome pairs separate during anaphase I, and therefore the daughter cells are haploid. The exchange of color between nonsister chromatids represents the crossing-over that occurred during meiosis I. The blue chromosomes were inherited from the paternal parent, and the red chromosomes were inherited from the maternal parent.

between the cells, whereas meiosis is often referred to as reduction division.

Figure 1.6 compares meiosis and mitosis. Several of the fundamental differences between the two processes include:

- Meiosis requires two nuclear divisions, but mitosis requires only one nuclear division.
- Meiosis produces four daughter nuclei. Following cytokinesis, there are four daughter cells. Mitosis followed by cytokinesis results in two daughter cells.
- Following meiosis, the four daughter cells are haploid and have half the chromosome number as the diploid parent cell. Following mitosis, the daughter cells have the same chromosome number as the parent cell.
- Following meiosis, the daughter cells are genetically identical neither to each other nor to the parent cell. Following mitosis, the daughter cells are genetically identical to each other and to the parent cell.

In addition to the fundamental differences between meiosis and mitosis, two specific differences between the two types of nuclear divisions can be categorized. These differences involve occurrence and process.

Occurrence

Meiosis occurs only at certain times in the life cycle of sexually reproducing organisms. In humans, meiosis occurs only in the reproductive organs and produces the gametes. Mitosis is more common, because it occurs in all tissues during growth and repair.

Process

We now compare the processes of both meiosis I and meiosis II to mitosis.

Meiosis I Compared to Mitosis

Notice that these events distinguish meiosis I from mitosis:

- During prophase I, bivalents form and crossing-over occurs. These events do not occur during mitosis.
- During metaphase I of meiosis, bivalents independently align at the metaphase plate. The paired chromosomes have a total of four chromatids each. During metaphase in mitosis, individual chromosomes align at the metaphase plate. They each have two chromatids.
- During anaphase I of meiosis, homologues of each bivalent separate, and duplicated chromosomes (with centromeres intact) move to opposite poles. During anaphase of mitosis, sister chromatids separate, becoming daughter chromosomes that move to opposite poles.

Meiosis II Compared to Mitosis

The events of meiosis II are similar to those of mitosis, except that in meiosis II the nuclei contain the haploid number of chromosomes. In mitosis, the original number of chromosomes is maintained. Meiosis II produces two daughter cells from each parent cell that completes meiosis I, for a total of four daughter cells. These daughter cells contain the same number of chromosomes as they did at the end of meiosis I. Tables 1.1 and 1.2 compare meiosis I and II to mitosis.

Table 1.1 Meiosis I Compared to Mitosis

Meiosis I	Mitosis
Prophase I	**Prophase**
Pairing of homologous chromosomes	No pairing of chromosomes
Metaphase I	**Metaphase**
Bivalents at metaphase plate	Duplicated chromosomes at metaphase plate
Anaphase I	**Anaphase**
Homologues of each bivalent separate, and duplicated chromosomes move to poles	Sister chromatids separate, becoming daughter chromosomes that move to the poles
Telophase I	**Telophase**
Two haploid daughter cells, not identical to the parent cell	Two diploid daughter cells, identical to the parent cell

Table 1.2 Meiosis II Compared to Mitosis

Meiosis II	Mitosis
Prophase II	**Prophase**
No pairing of chromosomes	No pairing of chromosomes
Metaphase II	**Metaphase**
Haploid number of duplicated chromosomes at metaphase plate	Diploid number of duplicated chromosomes at metaphase plate
Anaphase II	**Anaphase**
Sister chromatids separate, becoming daughter chromosomes that move to the poles	Sister chromatids separate, becoming daughter chromosomes that move to the poles
Telophase II	**Telophase**
Four haploid daughter cells, not genetically identical	Two diploid daughter cells, identical to the parent cell

Check Your Progress 1.4

1. Compare chromosome alignment between metaphase I of meiosis and metaphase of mitosis.
2. Explain how meiosis II is more similar to mitosis than to meiosis I.

1.5 The Cycle of Life

Learning Outcomes

Upon completion of this section, you should be able to

1. Contrast the life cycle of plants with the life cycle of animals.
2. Describe spermatogenesis and oogenesis in humans.

The term **life cycle** refers to all the reproductive events that occur from one generation to the next similar generation. In animals and humans the individual is always diploid, and meiosis produces the gametes, the only haploid phase of the life cycle (Fig. 1.7). In contrast, plants have a haploid phase that alternates with a diploid phase. The haploid generation, known as the **gametophyte,** may be larger or smaller than the diploid generation, called the **sporophyte.**

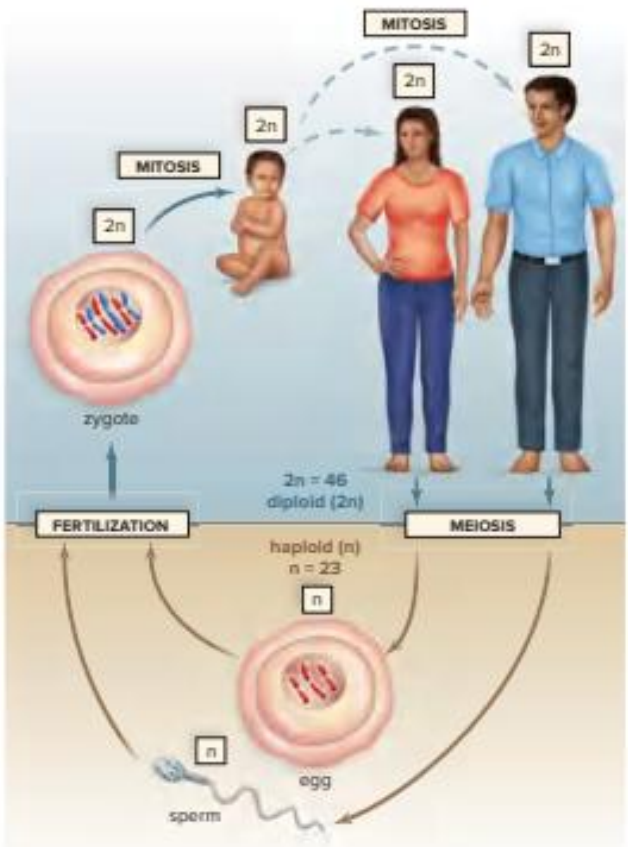


Figure 1.7 Life cycle of humans. Meiosis in males is a part of sperm production, and meiosis in females is a part of egg production. When a haploid sperm fertilizes a haploid egg, the zygote is diploid. The zygote undergoes mitosis as it develops into a newborn child. Mitosis continues throughout life during growth and repair.

Mosses growing on bare rocks and forest floors are the haploid generation, and the diploid generation is short-lived. In most fungi and algae, the zygote is the only diploid portion of the life cycle, and it undergoes meiosis. Therefore, the black mold that grows on bread and the green scum that floats on a pond are haploid.

The majority of plant species, including pine, corn, and sycamore, are usually diploid, and the haploid generation is short-lived. In plants, algae, and fungi, the haploid phase of the life cycle produces gamete nuclei without the need for meiosis, because it has occurred earlier.

Animals are diploid, and meiosis occurs during the production of gametes, called **gametogenesis.** In males, meiosis is a part of **spermatogenesis** (Gk. *sperma,* "seed"), which occurs in the testes and produces sperm. In females, meiosis is a part of **oogenesis** (Gk. *oon,* "egg"), which occurs in the ovaries and produces eggs. A sperm and an egg join at fertilization, restoring the diploid chromosome number. The resulting zygote undergoes mitosis during development of the fetus. After birth, mitosis is involved in the continued growth of the child and the repair of tissues at any time.

Spermatogenesis and Oogenesis in Humans

In human males, spermatogenesis occurs within the testes; in females, oogenesis occurs within the ovaries.

Spermatogenesis

The testes contain stem cells called spermatogonia. These cells keep the testes supplied with primary spermatocytes that undergo spermatogenesis, as described in Figure 1.8, *top.* Primary spermatocytes with 46 chromosomes undergo meiosis I to form two secondary spermatocytes, each with 23 duplicated chromosomes. Secondary spermatocytes undergo meiosis II to produce four spermatids with 23 daughter chromosomes. Spermatids then differentiate into viable sperm (spermatozoa). The spermatozoa will exit the penis via ducts.

Oogenesis

The ovaries contain stem cells, called oogonia, that produce many primary oocytes with 46 chromosomes during fetal development. They even begin oogenesis, but only a few continue when a female has become sexually mature. The result of meiosis I is two haploid cells with 23 chromosomes each (Fig. 1.8, *bottom*). One of these cells, termed the secondary **oocyte,** receives almost all the cytoplasm. The other is a **polar body** that may either disintegrate or divide again.

The secondary oocyte begins meiosis II but stops at metaphase II. Then the secondary oocyte leaves the ovary and enters the uterine tube, where sperm may be present. If no sperm are in the uterine tube, or if a sperm does not enter the secondary oocyte, it eventually disintegrates without completing meiosis. If a sperm does enter the oocyte, some of its contents trigger the completion of meiosis II in the secondary oocyte, and another polar body forms.

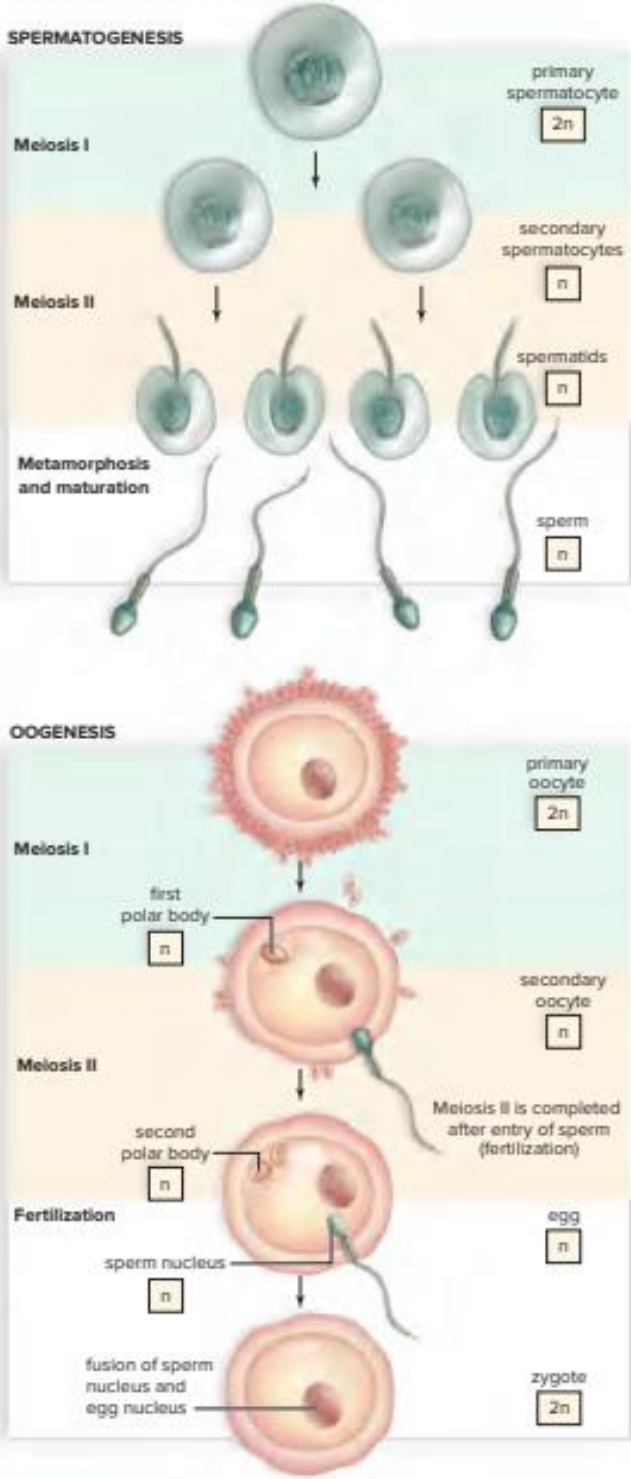


Figure 1.8 Spermatogenesis and oogenesis in mammals. Spermatogenesis produces four viable sperm, whereas oogenesis produces one egg and at least two polar bodies. In humans, both sperm and egg have 23 chromosomes each; therefore, following fertilization, the zygote has 46 chromosomes.

At the completion of oogenesis, following entrance of a sperm, there is one egg and two or three polar bodies. The polar bodies are a way to "dispose of" chromosomes while retaining much of the cytoplasm in the egg. Cytoplasmic molecules and organelles are needed by a developing embryo following fertilization. Some zygote components, such as the centrosome, are contributed by the sperm.

The mature egg has 23 chromosomes, but the zygote formed when the sperm and egg nuclei fuse has 46 chromosomes. Therefore, fertilization restores the diploid number of chromosomes. The production of haploid gametes and subsequent fusion of those gametes into a diploid zygote complete a human life cycle.

Check Your Progress 1.5

1. Describe where cells that undergo meiosis are located in humans.
2. Compare the number of gametes produced during oogenesis and spermatogenesis in humans.

1.6 Changes in Chromosome Number and Structure

Learning Outcomes

Upon completion of this section, you should be able to

1. Distinguish between euploidy and aneuploidy.
2. Explain how nondisjunction can cause monosomy and trisomy aneuploidy.
3. Describe human diseases caused by changes in the number of sex chromosomes.
4. Characterize how changes in chromosome structure can lead to human diseases.

We have seen that crossing-over creates variation within a population and is essential for the normal separation of chromosomes during meiosis. Furthermore, the proper separation of homologous chromosomes during meiosis I and the separation of sister chromatids during meiosis II are essential for the maintenance of normal chromosome numbers in living organisms. Although meiosis almost always proceeds normally, a failure of chromosomes to separate, or **nondisjunction,** may occur, resulting in a gain or loss of chromosomes. Errors in crossing-over may result in extra or missing parts of chromosomes.

Aneuploidy

The correct number of chromosomes in a species is known as **euploidy.** A change in the chromosome number resulting from nondisjunction during meiosis is called **aneuploidy.** Aneuploidy is seen in both plants and animals. Monosomy and trisomy are two aneuploid states.

Monosomy (2n − 1) occurs when an individual has only one of a particular type of chromosome when he or she should have two. **Trisomy** (2n + 1) occurs when an individual has three of a particular type of chromosome when he or she should have two. Both monosomy and trisomy are the result of nondisjunction during mitosis or meiosis. *Primary nondisjunction* occurs during meiosis I when both members of a homologous pair go into the same daughter cell (Fig. 1.9*a*). *Secondary nondisjunction* occurs during meiosis II when the sister chromatids fail to separate and both daughter chromosomes go into the same gamete (Fig. 1.9*b*).

Notice that when secondary nondisjunction occurs, there are two normal gametes and two aneuploid gametes. In contrast, when primary nondisjunction occurs, no normal gametes are produced. Therefore, primary nondisjunction tends to have more deleterious effects than secondary nondisjunction.

In animals, monosomies and trisomies of nonsex, or autosomal, chromosomes are generally lethal, but a trisomic individual is more likely to survive than a monosomic one. In humans, only three autosomal trisomic conditions are known to be viable beyond birth: trisomy 13, 18, and 21. Only trisomy 21 is viable beyond early childhood and is characterized by a distinctive set of physical abnormalities and intellectual disabilities. In comparison, sex chromosome aneuploids are better tolerated in animals and have a better chance of producing survivors.

Trisomy 21

The most common autosomal trisomy seen among humans is trisomy 21, also called Down syndrome. This syndrome is easily recognized by these characteristics: short stature; an eyelid fold; a flat face; stubby fingers; a wide gap between the first and second toes; a large, fissured tongue; a round head; a distinctive palm crease; heart problems; and some degree of intellectual disability, which can sometimes be severe. Individuals with Down syndrome also have a greatly increased risk of developing leukemia and tend to age rapidly, resulting in a shortened life expectancy. In addition, these individuals have an increased chance of developing Alzheimer disease later in life.

The chances of a woman having a child with Down syndrome increase rapidly with age. In women ages 20 to 30, the incidence of trisomy 21 is 1 in 1,400 births; in women 30 to 35, the incidence is about 1 in 750 births. It is thought that the longer the oocytes are stored in the female, the greater the chances of nondisjunction occurring. However, even though an older woman

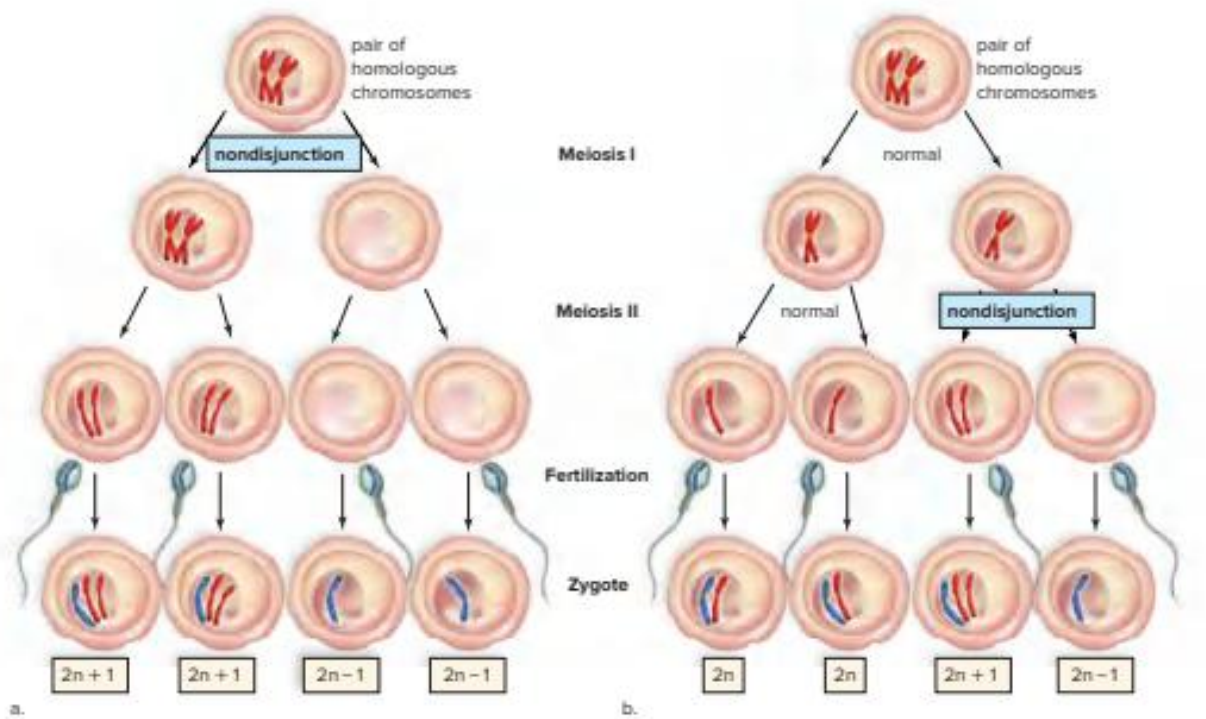


Figure 1.9 Nondisjunction of chromosomes during oogenesis, followed by fertilization with normal sperm. **a.** Nondisjunction can occur during meiosis I (primary nondisjunction) and results in abnormal eggs that also have one more or one less than the normal number of chromosomes. Fertilization of these abnormal eggs with normal sperm results in a zygote with abnormal chromosome numbers. 2n = diploid number of chromosomes. **b.** Nondisjunction can also occur during meiosis II (secondary nondisjunction) if the sister chromatids separate but the resulting daughter chromosomes go into the same daughter cell. Then the egg will have one more or one less than the usual number of chromosomes. Fertilization of these abnormal eggs with normal sperm produces a zygote with abnormal chromosome numbers.

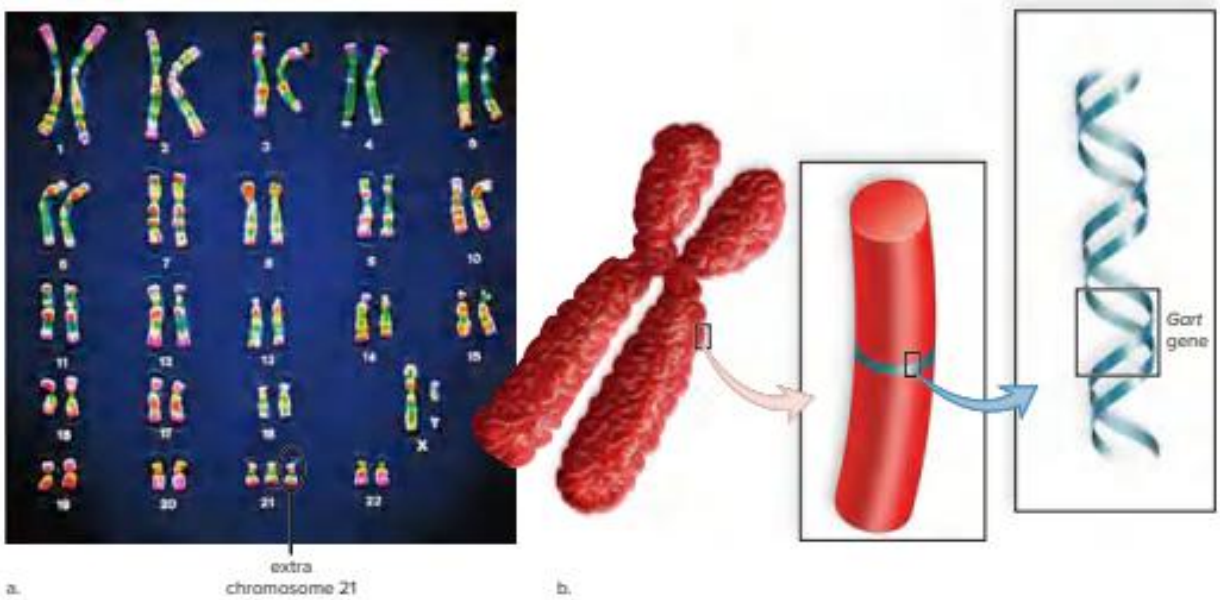


Figure 1.10 Trisomy 21. Persons with Down syndrome, or trisomy 21, have an extra chromosome 21. **b.** The karyotype of an individual with Down syndrome shows three copies of chromosome 21. Therefore, the individual has three copies instead of two copies of each gene on chromosome 21. An extra copy of the *Gart* gene, which leads to high levels of purine in the blood, accounts for many of the characteristics of Down syndrome.

is more likely to have a Down syndrome child, most babies with Down syndrome are born to women younger than age 40, because this is the age group having the most babies. Furthermore, research indicates that in 23% of the cases studied, the sperm contributed the extra chromosome. A **karyotype,** a visual display of the chromosomes arranged by size, shape, and banding pattern, may be performed to identify babies with Down syndrome and other aneuploid conditions (Fig. 1.10).

The genes that cause Down syndrome are located on the long arm of chromosome 21 (Fig. 1.10), and extensive investigative work has been directed toward discovering the specific genes responsible for the characteristics of the syndrome. Thus far, investigators have discovered several genes that may account for various conditions seen in persons with Down syndrome. For example, they have located the genes most likely responsible for the increased tendency toward leukemia, cataracts, and an accelerated rate of aging. Researchers have also discovered that an extra copy of the *Gart* gene causes an increased level of purines in the blood, a finding associated with intellectual disability. One day, it may be possible to control the expression of the *Gart* gene even before birth, so that at least this symptom of Down syndrome does not appear.

Changes in Sex Chromosome Number

An abnormal sex chromosome number is the result of inheriting too many or too few X or Y chromosomes. Nondisjunction during oogenesis or spermatogenesis can result in gametes with an abnormal number of sex chromosomes. However, extra copies of the sex chromosomes are much more easily tolerated in humans than are extra copies of autosomes.

A person with Turner syndrome (XO) is a female, and a person with Klinefelter syndrome (XXY) is a male. However, deletion of the *SRY* gene on the short arm of the Y chromosome results in Swyer syndrome, or an "XY female." Individuals with Swyer syndrome lack a hormone called testis-determining factor, which plays a critical role in the development of male genitals. Furthermore, movement of this gene onto the X chromosome may result in de la Chapelle syndrome, or an "XX male." Men with de la Chapelle syndrome exhibit undersized testes, sterility, and rudimentary breast development. Together, these observations suggest that in humans the presence of the *SRY* gene, not the number of X chromosomes, determines maleness. In its absence, a person develops as a female.

Why are newborns with an abnormal sex chromosome number more likely to survive than those with an abnormal autosome number? Because females have two X chromosomes and males have only one, we might expect females to produce twice the amount of each gene from this chromosome, but both males and females produce roughly the same amount. In reality, both males and females only have one functioning X chromosome. In females, and in males with extra X chromosomes, any additional X chromosomes become an inactive mass called a **Barr body,** named after Murray Barr, the person who discovered it. This inactivation provides a natural method for gene dosage compensation of the sex chromosomes and explains why extra sex chromosomes are more easily tolerated than extra autosomes.

Turner Syndrome. From birth, an XO individual with Turner syndrome has only one sex chromosome, an X; the O signifies the

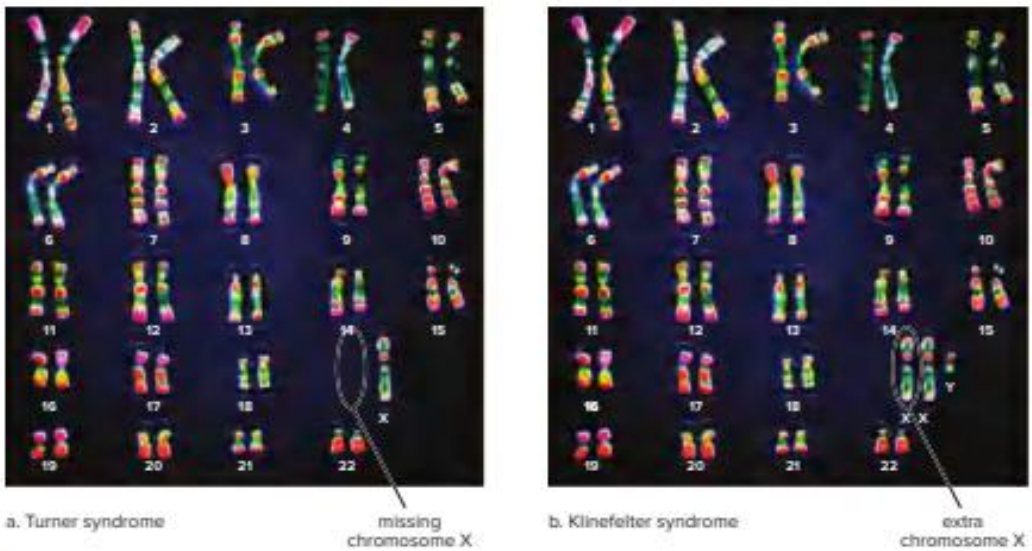


Figure 1.11 Abnormal sex chromosome number. Nondisjunction of sex chromosomes is tolerated better than with autosomes. People with (**a**) Turner syndrome, who have only one X chromosome, as shown, and (**b**) Klinefelter syndrome, who have more than one X chromosome plus a Y chromosome.

absence of a second sex chromosome (Fig. 1.11*a*). Therefore, the nucleus does not contain a Barr body. The approximate incidence is 1 in 10,000 females.

Turner females are short, with a broad chest and widely spaced nipples. These individuals also have a low posterior hairline and neck webbing. The ovaries, oviducts, and uterus are very small and underdeveloped. Turner females do not undergo puberty or menstruate, and their breasts do not develop. However, some have given birth following in vitro fertilization using donor eggs. They usually are of normal intelligence and can lead fairly normal lives if they receive hormone supplements.

Klinefelter Syndrome. A male with Klinefelter syndrome has two or more X chromosomes in addition to a Y chromosome (Fig. 1.11*b*). The extra X chromosomes become Barr bodies. The approximate incidence for Klinefelter syndrome is 1 in 500 to 1,000 males.

In Klinefelter males, the testes and prostate gland are underdeveloped and facial hair is lacking. They may exhibit some breast development. Affected individuals have large hands and feet and very long arms and legs. They are usually slow to learn but do not have an intellectual disability unless they inherit more than two X chromosomes. No matter how many X chromosomes there are, an individual with a Y chromosome is a male.

While males with Klinefelter syndrome exhibit no other major health abnormalities, they have an increased risk of some disorders, including breast cancer, osteoporosis, and lupus, which disproportionately affect females. Although men with Klinefelter syndrome typically do not need medical treatment, some have found that testosterone therapy helps increase muscle strength and concentration ability. Testosterone treatment, however, does not reverse the sterility associated with Klinefelter syndrome due to incomplete testicle development.

Poly-X Females. A poly-X female, sometimes called a superfemale, has more than two X chromosomes and, therefore, extra Barr bodies in the nucleus. Females with three X chromosomes have no distinctive phenotype aside from a tendency to be tall and thin. Although some have delayed motor and language development, as well as learning problems, most poly-X females do not have an intellectual disability. Some may have menstrual difficulties, but many menstruate regularly and are fertile. Children usually have a normal karyotype. The incidence for poly-X females is about 1 in 1,500 females.

Females with more than three X chromosomes occur rarely. Unlike XXX females, XXXX females are usually tall and have a severe intellectual disability. Various physical abnormalities are seen, but they may menstruate normally.

Jacobs Syndrome. XYY males, termed Jacobs syndrome, can result only from nondisjunction during spermatogenesis. Among all live male births, the frequency of the XYY karyotype is about 1 in 1,000. Affected males are usually taller than average, suffer from persistent acne, and tend to have speech and reading problems, but they are fertile and may have children. Despite the extra Y chromosome, there is no difference in behavior between XYY and XY males.

Changes in Chromosome Structure

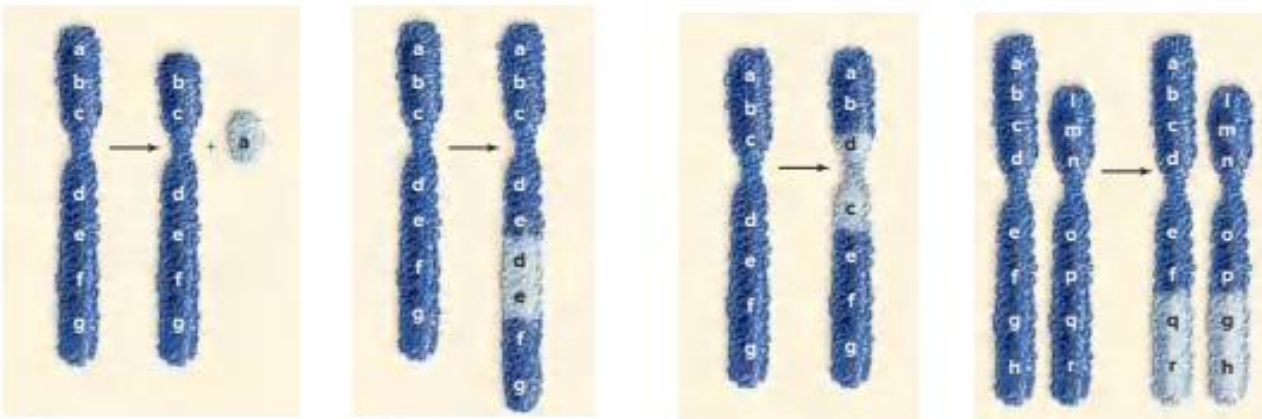
Changes in chromosome structure are another type of chromosomal mutation. Some, but not all, changes in chromosome structure can be detected microscopically. Various agents in the environment, such as radiation, certain organic chemicals, or even viruses, can cause chromosomes to break. Ordinarily, when breaks occur in chromosomes, the two broken ends reunite to give the same sequence of genes. Sometimes, however, the

broken ends of one or more chromosomes do not rejoin in the same pattern as before, and the results are various types of chromosomal mutations.

Changes in chromosome structure include deletions, duplications, translocations, and inversions of chromosome segments. A **deletion** occurs when an end of a chromosome breaks off or when two simultaneous breaks lead to the loss of an internal segment (Fig. 1.12*a*). Even when only one member of a pair of chromosomes is affected, a deletion often causes abnormalities.

A **duplication** is the presence of a chromosomal segment more than once in the same chromosome (Fig. 1.12*b*). Duplications may or may not cause visible abnormalities, depending on the size of the duplicated region. An **inversion** has occurred when a segment of a chromosome has been turned around 180° (Fig. 1.12*c*). Most individuals with inversions exhibit no abnormalities, but this reversed sequence of genes can result in duplications or deletions being passed on to their children, as shown in Figure 1.13.

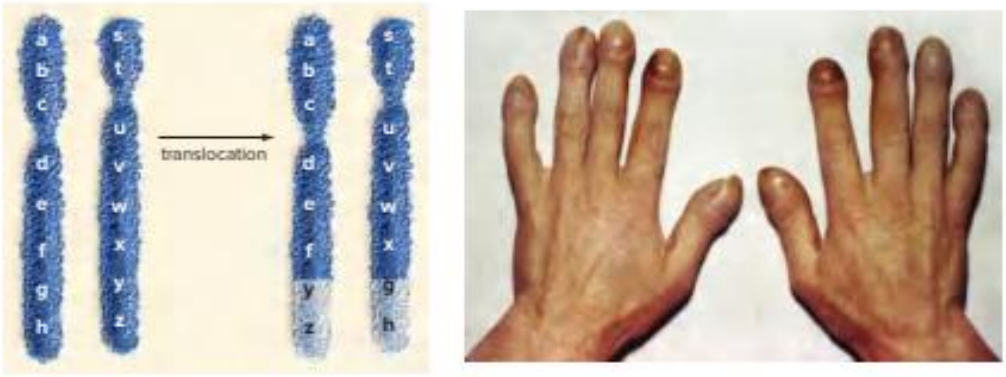
A **translocation** is the movement of a chromosome segment from one chromosome to another, nonhomologous chromosome. The translocation shown in Figure 1.12*d* is *balanced*, meaning that there is a reciprocal swap of one piece of the chromosome for the other. Often, there are no visible effects of the swap, but if the individual has children, they receive one normal copy of the chromosome from the normal parent and one of the abnormal



a. Deletion b. Duplication c. Inversion d. Translocation

Figure 1.12 Types of chromosomal mutations. **a.** Deletion is the loss of a chromosome piece. **b.** Duplication occurs when the same piece is repeated within the chromosome. **c.** Inversion occurs when a piece of chromosome breaks loose and then rejoins in the reversed direction. **d.** Translocation is the exchange of chromosome pieces between nonhomologous pairs.

Figure 1.13 Deletion. When chromosome 7 loses an end piece, the result is Williams syndrome.



a. b.

Figure 1.14 Translocation. **a.** When chromosomes 2 and 20 exchange segments, (**b**) Alagille syndrome, with distinctive body features, sometimes results because of organ malfunction caused by the chromosome 20 translocation.

chromosomes. The translocation is now *unbalanced*, with extra material from one chromosome and missing material from another chromosome. Embryos with unbalanced translocations usually result in miscarriage, but those individuals who are born often have severe symptoms.

Some Down syndrome cases are caused by an unbalanced translocation between chromosomes 21 and 14. In other words, because a portion of chromosome 21 is now attached to a portion of chromosome 14, the individual has three copies of the genes that bring about Down syndrome when they are present in triplet copy. In these cases, Down syndrome is not caused by nondisjunction during meiosis but is passed on normally, as is any other genetic trait.

Human Syndromes

Changes in chromosome structure occur in humans and lead to various syndromes, many of which are just now being discovered. Sometimes changes in chromosome structure can be detected in humans by doing a karyotype. They may also be discovered by studying the inheritance pattern of a disorder in a particular family.

Deletion Syndromes. Williams syndrome occurs when chromosome 7 loses a tiny end piece (see Fig. 1.13). Children who have this syndrome look like pixies, with turned-up noses, wide mouths, a small chin, and large ears. Although their academic skills are poor, they exhibit excellent verbal and musical abilities. The gene that governs the production of the protein elastin is missing, and this affects the health of the cardiovascular system and causes their skin to age prematurely. Such individuals are very friendly but need an ordered life, perhaps because of the loss of a gene for a protein that is normally active in the brain.

Cri du chat ("cat's cry") syndrome is seen when chromosome 5 is missing an end piece. The affected individual has a small head, an intellectual disability, and facial abnormalities. Abnormal development of the glottis and larynx results in the most characteristic symptom—the infant's cry resembles that of a cat.

Translocation Syndromes. A person who has both of the chromosomes involved in a translocation has the normal amount of genetic material and is healthy, unless the chromosome exchange breaks an allele into two pieces. The person who inherits only one of the translocated chromosomes no doubt has only one copy of certain alleles and three copies of certain other alleles. A genetic counselor begins to suspect a translocation has occurred when spontaneous abortions are commonplace and family members suffer from various syndromes. A microscopic technique allows a technician to determine if a translocation has occurred.

Figure 1.14 shows the phenotype of individuals who have a translocation between chromosomes 2 and 20. Although they have the normal amount of genetic material, the rearrangment of the genetic material also commonly causes phenotypic and physiological problems, collectively called Alagille syndrome. People with this syndrome ordinarily have a deletion on chromosome 20 (Fig. 1.14*a*), which can lead to a congenital heart condition called tetralogy of fallot, which produces digital clubbing of the fingers (Fig. 1.14*b*). Liver problems are also common in Alagille syndrome. The symptoms of Alagille syndrome range from mild to severe, so some people may not be aware they have the syndrome until after they've had children.

Translocations can also be responsible for a variety of other disorders, including certain types of cancer. In the 1970s, new staining techniques identified that a translocation from a portion of chromosome 22 to chromosome 9 was responsible for many cases of chronic myelogenous leukemia. This translocated chromosome was called Philadelphia chromosome. In Burkitt lymphoma, a cancer common in children in equatorial Africa, a large tumor develops from lymph glands in the region of the jaw. This disorder involves a translocation from a portion of chromosome 8 to chromosome 14.

Check Your Progress **1.6**

1. Explain the kinds of changes in chromosome number that can be caused by nondisjunction in meiosis.
2. Examine why sex chromosome aneuploidy is more common than autosome aneuploidy.
3. Compare structural changes between an inversion and a translocation.

REVIEWING *the* BIG IDEAS

BIG IDEA 1

Genetic variation and mutation play roles in natural selection, and a diverse gene pool is important for the survival of a species in a changing environment. 1.A.1.c; 1.A.2.b; *3.C.1.d*

Meiosis is a key process in sexual reproduction, with both evolutionary costs and benefits. 1.A.1.c; 1A.2.b; 1.A.3.b.; *3.A.1.c*

BIG IDEA 3

Meiosis and mitosis use similar mechanisms to store, retrieve, and transmit genetic information; however, these two types of cell division occur in different types of cells with different outcomes with respect to chromosome number. 3.A.2.c.1-3,5

Understanding chromosomal behavior during meiosis is critical to understanding how genes segregate during gamete formation and how this contributes to inheritance of traits from one generation to another. 3.A.2.c.1-3,5

Understanding how chromosomes introduce variation by exchanging genetic information during meiosis can help us understand a foundation of genetic diversity. 3.A.2.c.4

Like the cell cycle and mitosis, meiosis is tightly regulated to ensure that homologous chromosomes first pair and then separate during the first division, and that sister chromatids do not separate until the second division. 3.A.1.a.2; 3.A.2.c. 1-3

Certain human genetic disorders can be attributed to changes in chromosome structure and number. 3.A.3.c. *IE*; 3.C.1., a, c

BIG IDEA 4

Variation produced by mutations in DNA and recombination of genetic material through meiosis and fertilization provides an organism with a wider range of functions that may help the organism better respond to environmental change. 4.C.1.b; 4.C.2.b

SUMMARIZE

AP Answering the Essential Questions

In mitosis cells divide: to grow, replace cells, and reproduce asexually. Barring mutation, the daughter cells produced by mitosis receive an identical and complete set of chromosomes and genetic instructions. However, changes in the genetic makeup of a population over time drive both the unity and diversity of life, and organisms have evolved ways to increase variation. Sources of variation include mutations in DNA, recombination of genes during meiosis, and fertilization in sexually reproducing organisms. A genetically diverse gene pool is vital for the survival of species when environmental conditions change.

Meiosis vs. mitosis Unlike mitosis in which daughter cells receive a complete set of chromosomes, **meiosis** reduces the chromosome number of a cell from its diploid (2n) number to its **haploid** (1n) number. In many species, including animals, meiosis is associated with the production of **gametes** (eggs and sperm) for sexual reproduction. Gametes are haploid; on fertilization, the union of egg and sperm restores the diploid chromosome number in the zygote. In turn, the zygote undergoes mitosis as it develops, and cell division continues throughout life during growth and repair. In the mature sexually reproducing organism, meiosis will again be involved in the production of gametes. Before we explore how meiosis reduces the diploid number of chromosomes to haploid, let's talk a little bit more about chromosomes.

Eukaryotic chromosomes consist of DNA tightly coiled around proteins. In diploid somatic body cells like skin or muscle cells, the chromosomes occur in pairs called **homologous chromosomes** or homologues. Homologues contain similar genes, but these genes may have different variations, called alleles (we will study much more about genes in alleles in Chapter 3). In humans, a somatic cell contains 46 chromosomes, or 23 pairs; pairs 1–22 are autosomes, coding for non-sex traits like hair color or dimples, whereas pair 23 includes the sex chromosomes (X and Y) and helps determine gender. At fertilization, the male parent contributes one member of the homologous pair, and the female parent contributes the other member. A simple equation can help us remember this about humans: 23 chromosomes from dad + 23 chromosomes from mom = 46 chromosomes for the zygote. Similar to mitosis, when chromosomes are duplicated, each chromosome in the homologous pair is composed of two sister chromatids. The sister chromatids contain exactly the same genes, but although the nonsister chromatids contain genes for the same traits (e.g., type of hair, color of eyes), one may have DNA that codes for brown hair, while the other chromatid has DNA that codes for blonde hair.

In mitosis, chromosomes replicate once, and the cell divides once. However, meiosis requires two cell divisions—**meiosis I** and **meiosis II**— and results in four daughter cells. Like mitosis, replication of DNA takes place before cell division occurs. During meiosis I, an important event occurs that does not occur in mitosis: the homologous chromosomes pair before they separate, a phenomenon called **synapsis.** The bivalent (two homologues) chromosomes align independently along the equator of the cell, and each daughter cell receives one member of each pair of homologous chromosomes. During meiosis II, the sister chromatids of each duplicated chromosome separate. However, in the interkinesis phase between meiosis I and meiosis II, *DNA does not replicate again.* Remember, the goal of meiosis is to produce four haploid (1n) daughter cells, each with

one member of each kind of chromosome. To accomplish this, DNA replicates once but divides twice (you do not need to memorize the names of the phases of meiosis, but you need to understand the processes of replication, alignment, and separation in meiosis I and meiosis II and the order in which they occur). Like mitosis, the meiotic cell cycle is regulated by external factors and internal signals.

Meiosis and genetic variation Sexual reproduction ensures that offspring have a different genetic makeup than parents, and genetic variation increases the ability of a population to survive. Meiosis contributes to genetic variation in two ways: **crossing-over** and **independent assortment** of homologous chromosomes. When homologous chromosomes pair or synapse in meiosis I, genetic recombination by crossing-over occurs if nonsister chromatids exchange genetic material. Due to crossing-over, the chromatids that separate at the end of meiosis II have a different combination of genes. In addition, when the homologous chromosomes align at the equator of the cell during meiosis I, either the maternal or paternal chromosomes can be facing either pole; in other words, they independently assort themselves. Crossing-over and independent assortment result in all possible combinations of chromosomes in the gametes and many different combinations of genes. Random fertilization of an egg by a sperm further increases genetic variation that may increase an organism's fitness, enabling a greater chance of survival in its environment.

Although meiosis is a controlled process, sometimes it does not go according to plan. **Nondisjunction** during meiosis I or meiosis II may result in gametes having extra or missing copies of chromosomes. If these gametes are used in fertilization, the consequences to the zygote can be deleterious. Down syndrome is a well-known genetic disorder in humans that usually occurs when an individual has trisomy 21 or an extra copy of chromosome 21. Abnormalities in crossing-over may result in deletions, duplications, inversions, and translocations within chromosomes. Many human syndromes with distinct physical and physiological characteristics result from these changes in chromosome structure.

You should be able to compare and contrast the processes of mitosis and meiosis, recognizing their similarities and differences:

- Meiosis requires two nuclear divisions, but mitosis requires only one nuclear division.
- In mitosis and meiosis, DNA replicates and divides. However, in meiosis, DNA replicates once but divides twice due to separation of homologous chromosomes in meiosis I and separation of chromatids in meiosis II.
- Meiosis produces four daughter nuclei, and, following cytokinesis, four daughter cells, whereas mitosis produced two.
- Following meiosis, the four daughter cells are haploid (1n) with half the chromosome number as the diploid (2n) parent cell. Following mitosis, the daughter cells have the same chromosome number as the parent cell.
- Following meiosis, the daughter cells are *not* genetically identical to themselves nor to either parent cell. Following mitosis, the daughter cells are genetically identical to each other and to the parent cell.

ASSESS

Choose the best answer for each question.

1.1 Overview of Meiosis

1. If a parent cell has 16 chromosomes, then each of the daughter cells following meiosis will have
   a. 48 chromosomes.
   b. 32 chromosomes.
   c. 16 chromosomes.
   d. 8 chromosomes.
2. A bivalent is
   a. a homologous chromosome.
   b. the paired homologous chromosomes.
   c. a duplicated chromosome composed of sister chromatids.
   d. the two daughter cells after meiosis I.
3. The synaptonemal complex
   a. forms during prophase I of meiosis.
   b. allows synapsis to occur.
   c. forms between homologous chromosomes.
   d. All of these are correct.

1.2 Genetic Variation

4. Crossing-over occurs between
   a. sister chromatids of the same chromosome.
   b. two different kinds of bivalents.
   c. two different kinds of chromosomes.
   d. nonsister chromatids of a bivalent.
5. Which of the following occurs at metaphase I of meiosis?
   a. independent assortment
   b. crossing-over
   c. interkinesis
   d. formation of new alleles

1.3 The Phases of Meiosis

6. At the metaphase plate during metaphase I of meiosis, there are
   a. unpaired duplicated chromosomes.
   b. bivalents.
   c. homologous pairs of chromosomes.
   d. Both b and c are correct.
7. At the metaphase plate during metaphase II of meiosis, there are
   a. chromosomes consisting of one chromatid.
   b. unpaired duplicated chromosomes.
   c. bivalents.
   d. homologous pairs of chromosomes.
8. During which phase of meiosis do homologous chromosomes separate?
   a. prophase I
   b. telophase I
   c. anaphase I
   d. anaphase II

1.4 Meiosis Compared to Mitosis

9. Mitosis _____ chromosome number, whereas meiosis _____ the chromosome number of the daughter cells.
   a. maintains; increases
   b. increases; maintains
   c. increases; decreases
   d. maintains; decreases

For questions 10–13, match the statements that follow to the items in the key. Answers may be used more than once, and more than one answer may be used.

Key:

a. mitosis
b. meiosis I
c. meiosis II
d. Both meiosis I and meiosis II are correct.
e. All of these are correct.

10. Involves pairing of duplicated homologous chromosomes
11. A parent cell with five duplicated chromosomes will produce daughter cells with five chromosomes consisting of one chromatid each.
12. Nondisjunction may occur, causing abnormal gametes to form.
13. Involved in growth and repair of tissues

1.5 The Cycle of Life

14. Polar bodies are formed during the process of
    a. spermatogenesis.
    b. gametophyte formation.
    c. sporophyte formation.
    d. oogenesis.
15. In humans, gametogenesis results in the formation of
    a. diploid egg and sperm cells.
    b. gametophytes.
    c. haploid egg and sperm cells.
    d. a zygote.

1.6 Changes in Chromosome Number and Structure

16. Nondisjunction during meiosis I of oogenesis will result in eggs that have
    a. the normal number of chromosomes.
    b. one too many chromosomes.
    c. one less than the normal number of chromosomes.
    d. Both b and c are correct.
17. In which of the following is genetic material moved between nonhomologous chromosomes?
    a. insertion
    b. nondisjunction
    c. deletion
    d. translocation
18. Which of the following is not an aneuploid condition?
    a. Turner syndrome
    b. Down syndrome
    c. Alagille syndrome
    d. Klinefelter syndrome

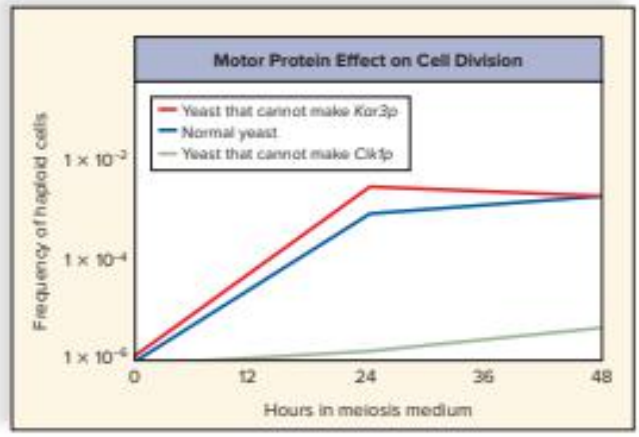
ENGAGE

AP Applying the Big Ideas

1. BIG IDEA 1 Some outwardly visible variations (phenotypes) in species are not directed by the environment but occur through random changes in DNA and through new gene combinations. Some phenotypic variations significantly increase or decrease the fitness of the organism and the population.
    a. **Describe** TWO kinds of data that could be collected by scientists to provide a direct answer to the question, how can scientists determine that a change in chromosome number or structure will decrease the fitness of an organism?
    b. **Explain** how the data you suggested in part (a) would provide a direct answer to the question.
2. BIG IDEA 3 Meiosis, a reduction division, followed by fertilization ensures genetic diversity in sexually reproducing organisms. In a paragraph, **explain** the connection between meiosis and increased genetic diversity necessary for evolution.
3. BIG IDEA 4 The variation produced by meiosis at the cellular level affects all levels of an organism's physiology.
    a. **Describe** TWO kinds of data that could be collected by scientists to provide a direct answer to the question, how does variation in molecular units provide cells with a wider range of functions?
    b. **Explain** how the data you suggested in part (a) would provide a direct answer to the question.

AP Applying the Science Practices

How do motor proteins affect cell division? Many scientists think that motor proteins play an important role in the movement of chromosomes in both mitosis and meiosis. To test this hypothesis, researchers have produced yeast that cannot make the motor protein called Kar3p. They also have produced yeast that cannot make the motor protein called Cik1p, which many think moderates the function of Kar3p. The results of their experiment are shown in the graph to the right.



*Data obtained from: Shanks, et al. 2001. The Kar3-interacting protein Cik1p plays a critical role in passage through meiosis I in *Saccharomyces cerevisiae*. *Genetics* 159: 939–951.

Think Critically SP 5 SP 6

1. **Evaluate** whether Cik1p seems to be important for yeast meiosis. Explain.
2. **Assess** whether Kar3p seems to be necessary for yeast meiosis. Explain.
3. **Conclude** whether all motor proteins seem to play a vital role in meiosis. Explain.

2

Mendelian Patterns of Inheritance

The inability to process phenylalanine is an example of a genetic disorder.

Chapter Outline

AP Have you ever looked at the back of a can of diet soda and wondered what the warning "Phenylketonurics: Contains Phenylalanine" means? Phenylalanine is an amino acid that is found in many foods and the artificial sweetener aspartame. For most people, phenylalanine does not present any problems, since any excess is broken down by enzymes in the body. However, some people, called phenylketonurics, lack a functional copy of this enzyme and thus are unable to break down the phenylalanine. The excess may accumulate in the body, causing a variety of nervous system disorders. An estimated 1 in 10,000 people in the United States are phenylketonurics.

Like the rest of us, you are the product of your family tree. The DNA you inherit from your parents directly affects the proteins that enable your body to function properly. Rare genetic disorders, such as phenylketonuria, pique our curiosity about how traits are inherited from one generation to the next. The process of meiosis can be used to predict the inheritance of a trait, and the genetic diversity produced through meiosis can sometimes lead to phenylketonuria.

Through the patterns of inheritance first described by Mendel, you will learn that certain traits, such as phenylketonuria, are recessive and that it takes two nonfunctional copies of that gene before you are affected. This chapter will introduce you to observable patterns of inheritance, including some human genetic disorders, such as phenylketonuria.

As you read through the chapter, think about these Essential Questions:

1. What is the relationship between genes and their passage from parent to offspring to natural selection and evolution? 1.A.1.c,e 3.A.3.a,b 3.A.2.c
2. How does the behavior of chromosomes during meiosis explain Mendel's laws of segregation and independent assortment? 3.A.4.a-c 3.A.3.a,d
3. How does an understanding of Mendelian genetics help us understand the link between genes and human genetic diseases? 3.A.3.a,d 3.A.4.a-c

Following *the* BIG IDEAS

BIG IDEA 1 — Inheritance of genes within a population is a cornerstone of species' ability to change over time.

BIG IDEA 3 — Gregor Mendel's scientific approach allowed him to establish the basic principles of heredity.

2.1 Gregor Mendel

Learning Outcomes

Upon completion of this section you should be able to

1. Describe how Mendel's scientific approach enabled his genetic experiments to be successful.
2. Contrast blending and the particulate concept of inheritance.

The science of genetics explains the stability of inheritance (why you are human, as are your parents) as well as variations between offspring from one generation to the next (why you have a different combination of traits than your parents). Virtually every culture in history has attempted to explain observed inheritance patterns. An understanding of these patterns has always been important to agriculture, animal husbandry (the science of breeding animals), and medicine.

The Blending Concept of Inheritance

When Gregor Mendel began his work, most plant and animal breeders acknowledged that both sexes contribute equally to a new individual. They thought that parents of contrasting appearance always produced offspring of intermediate appearance. This concept, called the *blending concept of inheritance*, meant that a cross between plants with red flowers and plants with white flowers would yield only plants with pink flowers. When red and white flowers reappeared in future generations, the breeders mistakenly attributed this to instability in the genetic material.

The blending concept of inheritance offered little help to Charles Darwin, the father of evolution. Darwin's theory of natural selection was based on the fact that populations possessed variation that allowed for certain individuals to have a selective advantage. According to the blending concept, over time variation would decrease as individuals became more alike in their traits.

Mendel's Particulate Theory of Inheritance

Gregor Mendel was an Austrian who developed a *particulate theory of inheritance* after performing a series of ingenious experiments in the 1860s (Fig. 2.1*a*). Mendel studied science and mathematics at the University of Vienna, and at the time of his research in genetics, he was a substitute natural science teacher at a local high school.

Mendel was a successful scientist for several reasons. First, he was one of the first scientists to apply mathematics to biology. Most likely his background in mathematics prompted him to apply statistical methods and the laws of probability to his breeding experiments. He was also a careful, deliberate scientist who followed the scientific method very closely and kept very detailed, accurate records. He prepared for his experiments carefully and conducted many preliminary studies with various animals and plants.

Mendel's theory of inheritance is called a particulate theory because it is based on the existence of minute particles, or hereditary units, we now call genes. Inheritance involves the reshuffling of the same genes from generation to generation. The two laws he proposed, the law of segregation and the law of independent assortment, which we will discuss shortly, describe the behavior of these particulate units of heredity as they are passed from one generation to the next. While Mendel did not know of DNA or genetic material, his theories have been well supported by countless experiments of geneticists and molecular biologists.

a. b.

Figure 2.1 Gregor Mendel, 1822–1884. **a.** Mendel grew and tended the pea plants (**b**) he used for his experiments. His experimental approach allowed him to develop several laws of inheritance.

Mendel Worked with the Garden Pea

Mendel's preliminary experiments prompted him to choose the garden pea, *Pisum sativum* (Fig. 2.1*b*), as his experimental organism. The garden pea was a good choice for many reasons. The plants were easy to cultivate and had a short generation time. Although peas normally self-pollinate (pollen only goes to the same flower), they could be cross-pollinated by hand by transferring pollen from the anther (male part of a flower) to the stigma (female part of a flower).

Many varieties of peas were available, and Mendel chose 22 for his experiments. When these varieties self-pollinated, over generations they became *true-breeding*–meaning that all the offspring were the same and exactly like the parent plants. Unlike his predecessors, Mendel studied the inheritance of relatively simple and discrete traits that were not subjective and were easy to observe, such as seed shape, seed color, and flower color. In his crosses, Mendel observed that the offspring did not possess intermediate charactersitics but, rather, were similar in appearance to one of the parents. As we will see, this disproved the blending concept and supported the particulate theory of inheritance.

Check Your Progress 2.1

1. Explain the difference between the particulate theory of inheritance and the blending concept.
2. Explain why the garden pea was a good choice for Mendel's experiments.

2.2 Mendel's Laws

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain Mendel's law of segregation and law of independent assortment.
2. Compare and contrast dominant alleles with recessive alleles and their relation to genotype and phenotype.
3. Use a Punnett square and the law of probability to predict the chances of producing gametes and offspring.

After ensuring that his pea plants were true-breeding—for example, that his tall plants always had tall offspring and his short plants always had short offspring—Mendel was ready to perform cross-pollination experiments (Fig. 2.2). These crosses allowed Mendel to formulate his law of segregation.

Law of Segregation

For these initial experiments, Mendel chose varieties that differed in only one trait (e.g., plant height). If the blending theory of inheritance were correct, the cross should yield plants with an intermediate appearance of medium height compared to the parents, which were all tall or all short.

Mendel's Experimental Design and Results

Mendel called the original, true-breeding all tall or all short parents the *P generation*. The first generation of offspring were called the F_1, or *filial generation* (L. *filius*, "sons and daughters") (Fig. 2.3). He performed reciprocal crosses: First he dusted the pollen of tall plants onto the stigmas of short plants, and then he dusted the pollen of short plants onto the stigmas of tall plants. In both cases, all F_1 offspring resembled the tall parent.

Certainly, these results were contrary to those predicted by the blending theory of inheritance. Rather than being intermediate, all the F_1 plants were tall and resembled only one parent. Did these results mean that the other characteristic (shortness) had disappeared permanently? Apparently not, because when Mendel

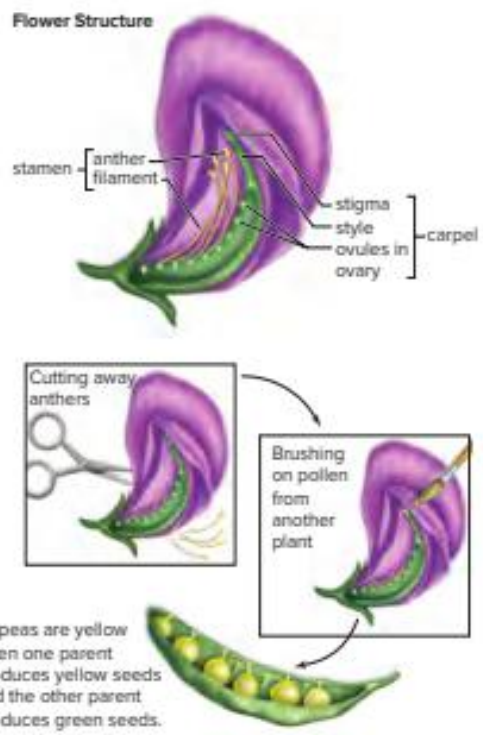


Figure 2.2 Garden pea anatomy. In the garden pea, *Pisum sativum*, pollen grains produced in the anther contain sperm, and ovules in the ovary contain eggs. When Mendel performed crosses, he brushed pollen from one plant onto the stigma of another plant. This cross-pollination allowed sperm to fertilize eggs and ovules to develop into seeds (peas). The open pod shows the seed color trait that resulted from a cross between plants with yellow seeds and plants with green seeds.

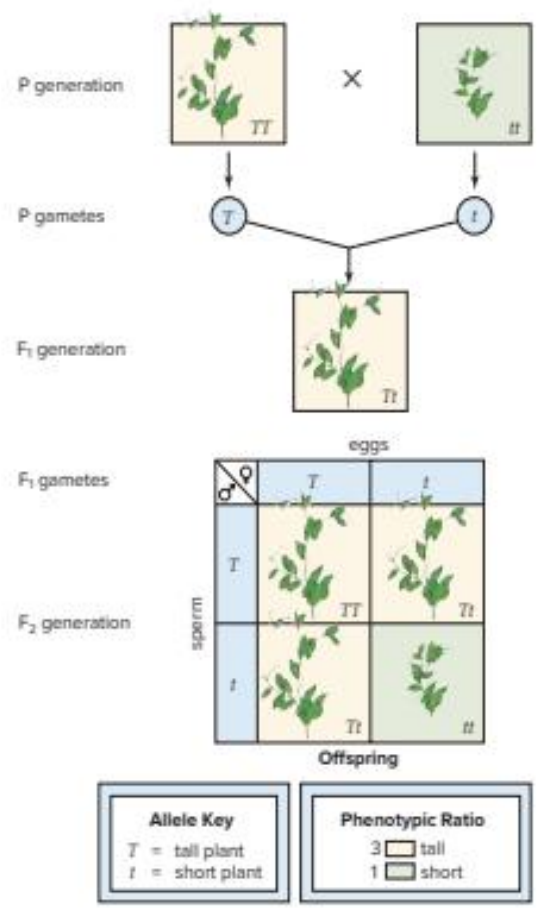


Figure 2.3 Monohybrid cross done by Mendel. The P generation pea plants differ in only one trait—length of the stem. The F_1 generation plants are all tall, but the factor for short has not disappeared, because 14 of the F_2 generation plants are short. The 3:1 ratio allowed Mendel to deduce that individuals have two discrete and separate genetic factors for each trait.

allowed the F_1 plants to self-pollinate, three-fourths of the next generation of offspring, or *F_2 generation*, were tall and one-fourth were short, a 3:1 ratio (Fig. 2.3).

Mendel inferred that the F_1 plants were able to pass on a factor for shortness—it didn't disappear; it just skipped a generation. Because the F_1 plants were tall but clearly still contained the shortness characteristic, Mendel deduced that tallness was dominant to shortness (Fig. 2.3).

Mendel counted many plants in his plant height and other experiments. When he allowed the F_1 pea plants (which were all tall but carried the characteristic for shortness) to self-fertilize and produce offspring, he counted a total of 1,064 plants, of which 787 were tall and 277 were short. This type of experiment is called a **monohybrid cross** (L. *mono*, "single"; *hybrida*, "mixture"), because it is a cross of a single trait (plant height) with organisms that are a hybrid (tall and short characteristics). In fact, in all monohybrid crosses that he performed for the traits shown in Figure 2.4, he found a 3:1 ratio in the F_2 generation. The characteristic for shortness that had disappeared in the F_1 generation reappeared in one-fourth of the F_2 offspring. In a monohybrid cross of two heterozygotes, assuming a simple dominant/recessive relationship, the expected phenotypic ratio is 3:1.

Mendel's Conclusion

Mendel's mathematical approach led him to interpret his results differently than previous breeders. He knew that the same ratio was obtained among the F_2 generation time and time again when he did a monohybrid cross involving one of the seven traits he was studying (Fig. 2.4). Eventually, Mendel arrived at this explanation: A 3:1 ratio among the F_2 offspring was possible if (1) the F_1 parents contained two separate copies of each hereditary factor, one of these being dominant and the other recessive; (2) the factors separated when the gametes were formed, and each gamete carried only one copy of each factor; and (3) random fusion of all possible gametes occurred upon fertilization. Only in this way could shortness reoccur in the F_2 generation. Thinking this,

Trait	Characteristics		F_2 Results		
	Dominant	Recessive	Dominant	Recessive	Ratio
Stem length	Tall	Short	787	277	2.84:1
Pod shape	Inflated	Constricted	882	299	2.95:1
Seed shape	Round	Wrinkled	5,474	1,850	2.96:1
Seed color	Yellow	Green	6,022	2,001	3.01:1
Flower position	Axial	Terminal	651	207	3.14:1
Flower color	Purple	White	705	224	3.15:1
Pod color	Green	Yellow	428	152	2.82:1
		Totals:	14,949	5,010	2.98:1

Figure 2.4 Relationship between observed phenotype and F_2 offspring. Mendel was fortunate in choosing the pea plant, because the traits he observed were quite distinct and easily classified. After crossing F_1 hybrids and counting hundreds of F_2 pea plants for each trait, Mendel discovered that each showed a 3:1 ratio.

Mendel arrived at the first of his laws of inheritance—the law of segregation—which is a cornerstone of his particulate theory of inheritance:

The **law of segregation** states the following:
- Each individual has two factors for each trait.
- The factors segregate (separate) during the formation of the gametes.
- Each gamete contains only one factor from each pair of factors.
- Fertilization gives each new individual two factors for each trait.

Mendel's Cross as Viewed by Modern Genetics

We now know that the traits Mendel studied are controlled by single genes. These genes occur on a homologous pair of chromosomes at a particular location, called the gene **locus** (Fig. 2.5). Alternative versions of a gene are called **alleles** (Gk. *allelon*, "reciprocal, parallel"). A **dominant allele** will mask the expression of a **recessive allele** when they are together in the same organism. The word *dominant* is not meant to imply that the dominant allele is better or stronger than the recessive allele. In both cases, these alleles represent DNA sequences that code for proteins. Often, the dominant allele codes for the protein associated with the normal function of the trait within the cell (such as the production of pigment), while the recessive allele represents a "loss of function," meaning that it codes for a protein that has an altered function or no function within the cell (such as a loss of pigment).

In many cases, the dominant allele is identified by a capital letter, the recessive allele by the same letter but lowercase. Usually, the first letter designating a trait is chosen to identify the allele. Using the plant height example, there is an allele for tallness (*T*) and an allele for shortness (*t*).

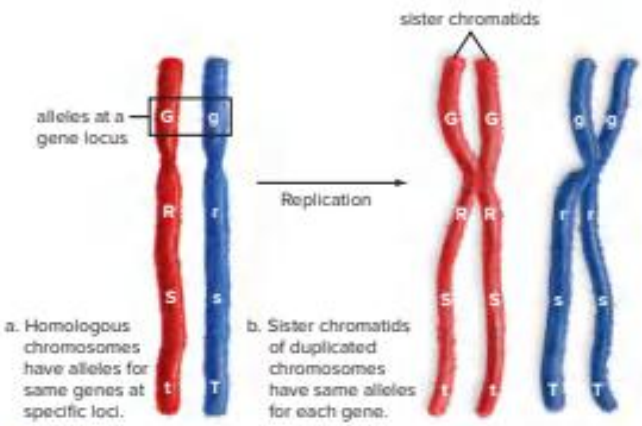


Figure 2.5 Homologous chromosomes. **a.** The letters represent alleles—that is, alternative forms of a gene. Each allelic pair, such as Gg or *Tt*, is located on homologous chromosomes at a particular physical location called a gene locus. **b.** Sister chromatids carry the same alleles in the same order. Proteins made from each allele determine the observable traits.

One way to view the outcome of a genetic cross is to use a Punnett square (see Fig. 2.3), in which all possible types of sperm are lined up vertically and all possible types of eggs are lined up horizontally (or vice versa), and every possible combination of gametes occurs within the squares. In Mendel's cross, the original parents (P generation) were true-breeding; therefore, the tall plants had two alleles for tallness (*TT*), and the short plants had two alleles for shortness (*tt*). When an organism has two identical alleles, as these had, we say it is **homozygous** (Gk. *homo*, "same"). Because the parents were homozygous, all gametes produced by the tall plant contained the allele for tallness (*T*), and all gametes produced by the short plant contained an allele for shortness (*t*).

After cross-pollination between different pea plants, all the individuals of the resulting F_1 generation had one allele for tallness and one for shortness (*Tt*). When an organism has two different alleles at a gene locus, we say that it is **heterozygous** (Gk. *hetero*, "different"). Although the plants of the F_1 generation had one of each type of allele, they were all tall. The allele that is expressed in a heterozygous individual is the dominant allele. The allele that is not expressed in a heterozygote is the recessive allele. This explains why shortness, the recessive trait, skipped a generation in Mendel's experiment.

Previously,, we observed that meiosis is the type of cell division that reduces the chromosome number from diploid (2n) to haploid (n). During meiosis I, the members of bivalents (homologous chromosomes, each having sister chromatids) separate. This means that the two alleles for each gene separate from each other during meiosis (see Fig. 2.7). Therefore, the process of meiosis gives an explanation for Mendel's law of segregation, as well as why only one allele for each trait is in a gamete.

Continuing with the discussion of Mendel's cross (see Fig. 2.3), the F_1 plants produce gametes in which 50% have the dominant allele *T* and 50% have the recessive allele *t*. During the process of fertilization, we assume that all types of sperm (*T* or *t*) have an equal chance to fertilize all types of eggs (*T* or *t*). When this occurs, such a monohybrid cross always produces a 3:1 (dominant-to-recessive) ratio among the offspring. Figure 2.4 gives Mendel's results for several monohybrid crosses, and you can see that the results were always close to 3:1.

Genotype Versus Phenotype

It is obvious from our discussion that two organisms with different allelic combinations for a trait can have the same outward appearance. For example, pea plants with both the *TT* and *Tt* combinations of alleles are tall. For this reason, it is necessary to distinguish between the alleles present in an organism and the appearance of that organism.

The word **genotype** (Gk. *genos*, "birth, origin") refers to the alleles an individual receives at fertilization. Genotype may be indicated by letters or by short, descriptive phrases and represents the DNA sequence for a particular gene. Genotype *TT* is called homozygous dominant, and genotype *tt* is called homozygous recessive. Genotype *Tt* is called heterozygous. These refer to the different ways that alleles can be combined in a cell.

The word **phenotype** (Gk. *phaino*, "appear") refers to the physical appearance of an individual, which is determined by the

proteins produced by the corresponding alleles. A homozygous dominant (*TT*) individual and a heterozygous (*Tt*) individual both show the dominant phenotype and are tall, because they make fully functional proteins that build the tall trait, while a homozygous recessive individual that shows the recessive phenotype and makes less or nonfunctional protein for that trait is short. Thus, the DNA that makes up the genotype produces the proteins that make up the phenotype.

Mendel's Law of Independent Assortment

Mendel performed a second series of crosses in which true-breeding pea plants differed in two traits. For example, he crossed tall plants having green pods with short plants having yellow pods (Fig. 2.6). The F_1 plants showed both dominant characteristics. As before, Mendel then allowed the F_1 plants to self-pollinate. This F_1 cross is known as a **dihybrid cross** (L. *di*, "two"), because the plants are hybrid in two ways. Two possible results could occur in Mendel's F_2 generation:

1. If the dominant factors (*TG*) always segregated into the F_1 gametes together, and the recessive factors (*tg*) always stayed together, then there would be two phenotypes among the F_2 plants—tall plants with green pods and short plants with yellow pods.
2. If the four factors segregated into the F_1 gametes independently, then there would be four phenotypes among the F_2 plants—tall plants with green pods, tall plants with yellow pods, short plants with green pods, and short plants with yellow pods.

Figure 2.6 shows that Mendel observed four phenotypes among the F_2 plants, supporting the second hypothesis. This is how Mendel formulated his second law of heredity—the law of independent assortment:

> The **law of independent assortment** states the following:
> - Each pair of factors segregates (assorts) independently of the other pairs.
> - All possible combinations of factors can occur in the gametes.

Each chromosome carries a large number of alleles; however, the law of independent assortment applies only to alleles on different chromosomes.

We know that the process of meiosis explains why the F_1 plants produced every possible type of gamete and, therefore, four phenotypes appeared among the F_2 generation of Mendel's plants. Figure 2.7 shows a parent cell with two homologous pairs of chromosomes, with alleles *Aa* on one pair and *Bb* on the other pair. Following duplication of the chromosomes during interphase, the parent cell undergoes meiosis I. At metaphase I, the homologous pairs line up independently of one another, such that the chromosomes with *A* alleles have an equal chance of lining up with the *B* alleles or the *b* alleles.

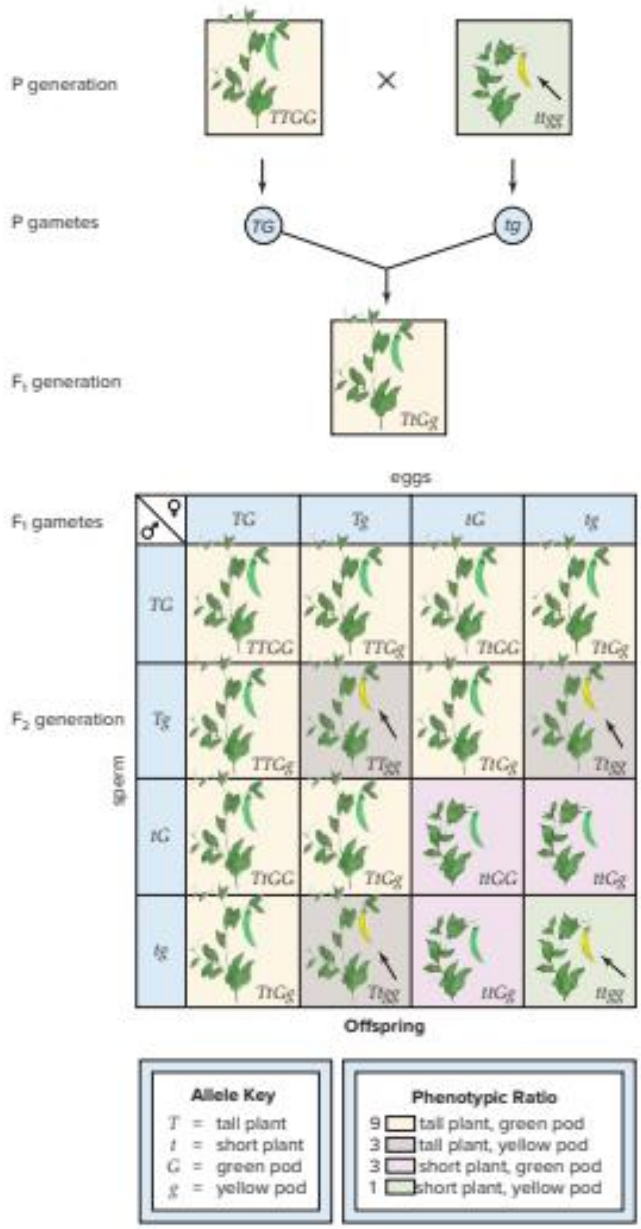


Figure 2.6 Dihybrid cross done by Mendel. P generation plants differ in two traits: length of the stem and color of the pod. The F_1 generation shows only the dominant traits, but all possible phenotypes appear among the F_2 generation, because the F_1 parents are hybrids. The 9:3:3:1 ratio allowed Mendel to deduce that factors segregate into gametes independently of other factors.

The subsequent segregation of the homologous pairs during anaphase I reduces the chromosome number from 2n to n. Because *A* alleles can be sorted with *B* or *b*, and so can the *a* allele, it is possible to create gametes with *AB*, *Ab*, *aB*, and *ab* allele combinations with equal probability.

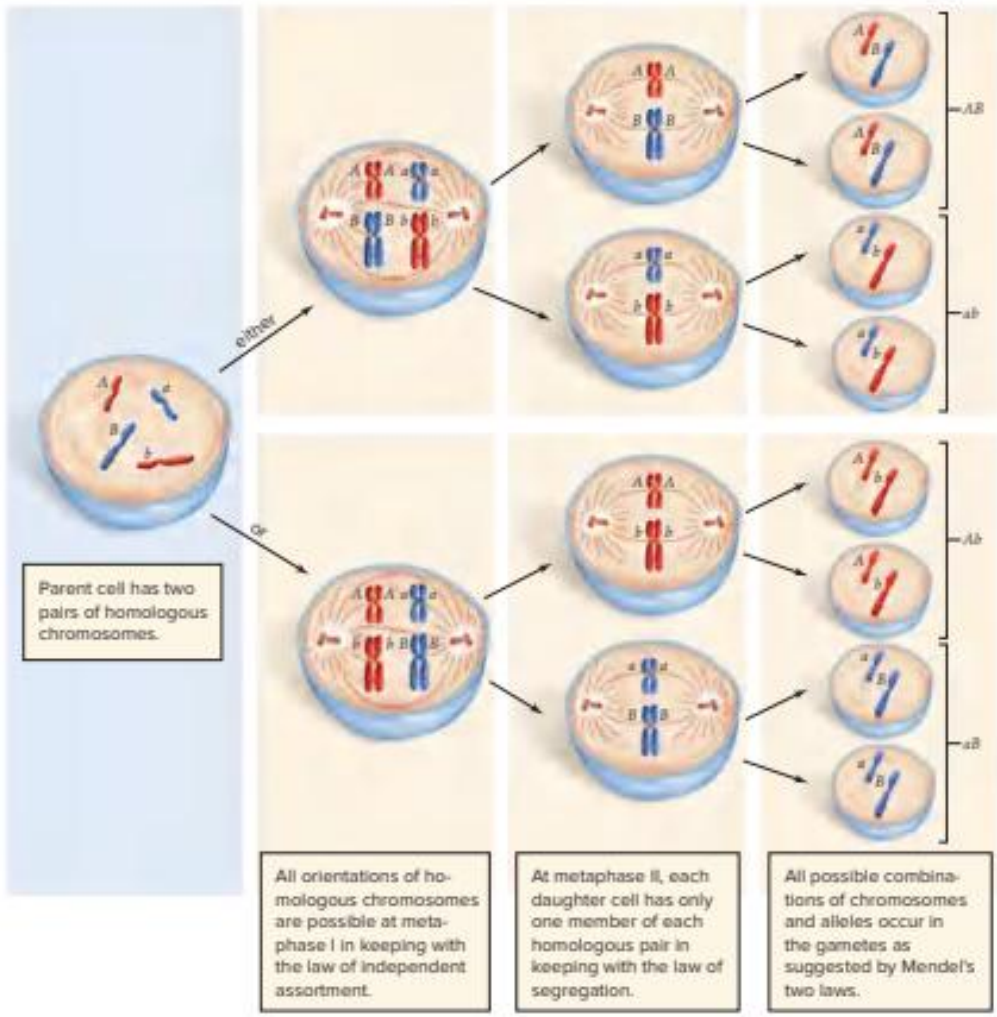


Figure 2.7 Independent assortment and segregation during meiosis. Mendel's laws hold because of the events of meiosis. The homologous pairs of chromosomes line up randomly at the metaphase plate during meiosis I. It doesn't matter which member of a homologous pair faces which spindle pole. In this example, *A* alleles can segregate *B* or *b* alleles. Likewise, *a* alleles can segregate with *B* or *b* alleles. Therefore, the homologous chromosomes, and alleles they carry, segregate independently during gamete formation. All possible combinations of chromosomes and alleles—that is, *AB*, *Ab*, *aB*, and *ab*—occur in the gametes.

The same rule of independent assortment applies for the pea plant example in Figure 2.6. In that case, the possible gametes are the two dominants (such as *TG*), the two recessives (such as *tg*), and the ones that have a dominant and a recessive (such as *Tg* and *tG*). Regardless of whether we are using the A and B chromosome or the T and G chromosome examples, when all possible sperm have an opportunity to fertilize all possible eggs, *the expected phenotypic ratio of a dihybrid cross is always 9:3:3:1.*

Mendel and the Laws of Probability

The diagram we have been using to calculate the results of a cross is called a **Punnett square** (see Figs. 2.3 and 2.6). In a Punnett square, all possible types of sperm are lined up vertically and all possible types of eggs are lined up horizontally (or vice versa), and every possible combination of gametes occurs within the squares. This gives us the ability to easily calculate the chances, or the probability, of genotypes and phenotypes among the offspring. An offspring of the cross illustrated in the Punnett square in Figure 2.8 has a 50% (or ½) chance of receiving an *E* for unattached earlobe or an *e* for attached earlobe from each parent:

The chance of $E = ½$
The chance of $e = ½$

How likely is it that an offspring will inherit a specific set of two alleles, one from each parent? The *product rule* of probability tells

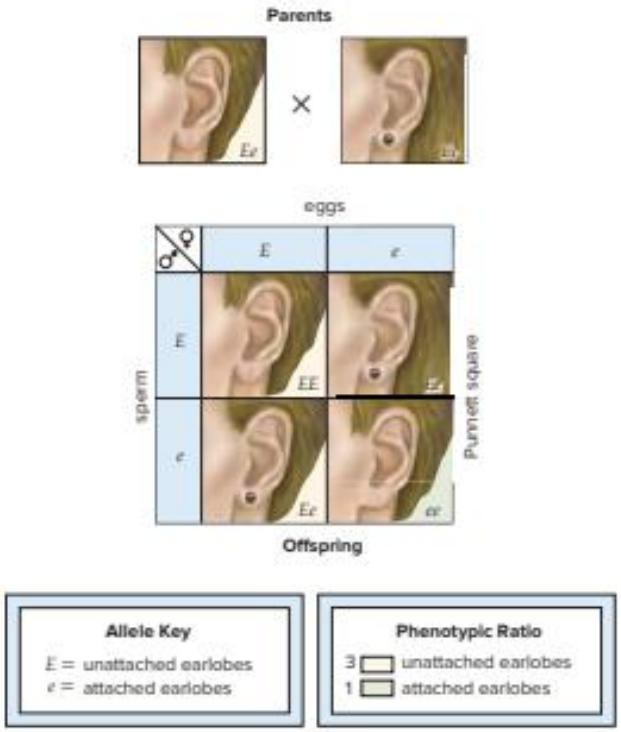


Figure 2.8 Punnett square. A Punnett square can be used to calculate probable results—in this case, a 3:1 phenotypic ratio.

us that we have to multiply the chances of independent events to get the answer:

1. The chance of *EE* = ½ × ½ = ¼
2. The chance of *Ee* = ½ × ½ = ¼
3. The chance of *eE* = ½ × ½ = ¼
4. The chance of *ee* = ½ × ½ = ¼

The Punnett square does this for us, because we can easily see that each of these is ¼ of the total number of squares.

How do we get the phenotypic results? The *sum rule* of probability tells us that when the same event can occur in more than one way, we can add the results. Because 1, 2, and 3 all result in unattached earlobes, we add them up to know that the chance of unattached earlobes is ¾, or 75%. The chance of attached earlobes is ¼, or 25%. The Punnett square doesn't do this for us—we have to add the results ourselves.

The statement "Chance has no memory" is important when considering inheritance across offspring. Every time a couple produces an offspring, the child has the same chances of inheriting the different allele combinations. Thus, for a heterozygous (*Ee*) couple, each child has a 25% chance of having attached (*ee*) earlobes. Inheriting a recessive trait may not seem significant if we are considering earlobes. However, it becomes important when we consider a recessive genetic disorder such as cystic fibrosis, a debilitating respiratory illness. For a heterozygous couple, there is a 25% chance that their child will inherit two recessive alleles and exhibit the disease. And because each child is an independent event, it is possible that all their children—or none of them—will exhibit cystic fibrosis.

We can use the product rule and the sum rule of probability to predict the results of a dihybrid cross, such as the one shown in Figure 2.6. The Punnett square carries out the multiplication, and we add the results to find that the phenotypic ratio is 9:3:3:1. We expect the same results for every dihybrid cross. Therefore, it is not necessary to do a Punnett square over and over again for either a monohybrid or a dihybrid cross. Instead, we can simply remember the probable results of 3:1 and 9:3:3:1. But we have to remember that the 9 represents the two dominant phenotypes together, the 3s are a dominant phenotype with a hidden recessive, and the 1 stands for the double recessive phenotype.

This tells us the probable phenotypic ratio among the offspring, but not the chances for each possible phenotype. Because the dihybrid Punnett square has 16 squares, the chances are $^{9}/_{16}$ for the two dominants together, $^{3}/_{16}$ for the dominants with each recessive, and $^{1}/_{16}$ for the two recessives together.

Mendel counted the results of many similar crosses to get the probable results, and in the laboratory we, too, have to count the results of many individual crosses to get the probable results for a monohybrid or a dihybrid cross. Why? Consider that each time you toss a coin, you have a 50% chance of getting heads or tails. If you toss the coin only a couple of times, you might very well have heads or tails both times. However, if you toss the coin many times, your results are more likely to approach 50% heads and 50% tails.

Testcrosses

To confirm that the F_1 plants of Mendel's one-trait crosses were, in fact, heterozygous, he crossed his F_1 generation tall pea plants with true-breeding short (homozygous recessive) plants; such a mating is termed a **testcross.** These crosses provided Mendel with further support for his law of segregation.

For the cross in Figure 2.9, Mendel reasoned that half the offspring should be tall and half should be short, producing a 1:1 phenotypic ratio. His results supported the hypothesis that alleles segregate when gametes are formed. In Figure 2.9*a*, the homozygous recessive parent can produce only one type of gamete—*t*—and so the Punnett square has only one column. The use of one column signifies that all the gametes carry a *t*. *The expected phenotypic ratio for this type of one-trait cross (heterozygous × recessive) is always 1:1.*

One-Trait Testcross

Today, a one-trait testcross is used to determine if an individual with the dominant phenotype is homozygous dominant (e.g., *TT*) or heterozygous (e.g., *Tt*). Because both of these genotypes produce the dominant phenotype, it is not possible to determine the genotype by observation. Figure 2.9*b* shows that if the individual is homozygous dominant, all the offspring will be tall. Each parent has only one type of gamete and, therefore, a Punnett square is not required to determine the results.

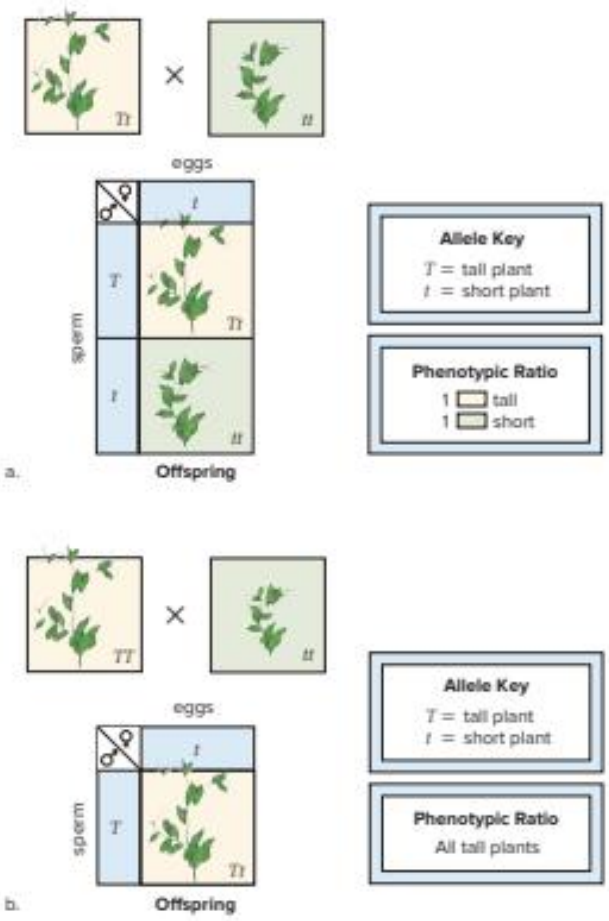


Figure 2.9 One-trait testcrosses. **a.** One-trait testcross when the individual with the dominant phenotype is heterozygous. **b.** One-trait testcross when the individual with the dominant phenotype is homozygous.

Two-Trait Testcross

When doing a two-trait testcross, an individual with the dominant phenotype is crossed with one having the recessive phenotype. Suppose you are working with fruit flies in which

L = long wings	G = gray bodies
l = vestigial (short) wings	g = black bodies

You wouldn't know by examination whether the fly on the left was homozygous or heterozygous for wing and body color. To find out the genotype of the test fly, you cross it with the one on the right. You know by examination that this vestigial-winged and black-bodied fly is homozygous recessive for both traits.

If the test fly is homozygous dominant for both traits with the genotype *LLGG*, it will form only one gamete: *LG*. Therefore, all the offspring from the proposed cross will have long wings and a gray body.

However, if the test fly is heterozygous for both traits with the genotype *LlGg*, it will form four different types of gametes:

Gametes: *LG* *Lg* *lG* *lg*

and can have four different offspring:

The presence of the offspring with vestigial wings and a black body shows that the test fly is heterozygous for both traits and has the genotype *LlGg*. Otherwise, it could not produce this offspring. In general, *the expected phenotypic ratio for this type of two-trait cross (heterozygous for two traits × recessive for both traits) is always 1:1:1:1.*

Check Your Progress 2.2

1. Summarize how Mendel's laws of independent assortment relate to the process of meiosis.
2. Explain why the *Tt* and *TT* genotypes both have the same phenotype.
3. Calculate the probability of producing an *Aabb* individual from an *AaBb* × *AaBb* cross.

2.3 Mendelian Patterns of Inheritance and Human Disease

Learning Outcomes

Upon completion of this section, you should be able to

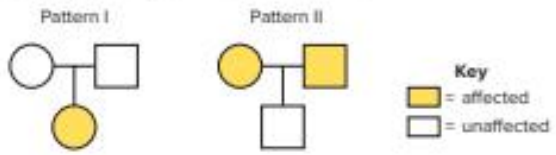
1. Distinguish between an autosomal dominant and an autosomal recessive pattern of inheritance.
2. Identify the pattern of inheritance for selected single-gene human disorders.

Many traits and disorders in humans, as well as other organisms, are genetic in origin and follow Mendel's laws. These traits are often controlled by a single pair of alleles on the autosomal chromosomes. An **autosome** is any chromosome other than a sex (X or Y) chromosome. In section 2.4, we will explore patterns of inheritance associated with the sex chromosomes.

Autosomal Patterns of Inheritance

When a genetic disorder is autosomal dominant, the normal allele (*a*) is recessive, and an individual with the alleles *AA* or *Aa* has the disorder. When a genetic disorder is autosomal recessive, the normal allele (*A*) is dominant, and only individuals with the alleles *aa* have the disorder. A pedigree shows the pattern of inheritance for a particular condition; genetic counselors can use a pedigree to

determine whether a condition is dominant or recessive. Consider these two possible patterns of inheritance:



In a pedigree, males are designated by squares and females by circles. Shaded circles and squares are the affected individuals. The shaded boxes do not indicate whether the condition is dominant or recessive, only that the individual exhibits the trait. A line between a square and a circle represents a union. In the patterns above, a vertical line leads to a single child. If there are more children, they are lined up horizontally. In pattern I, the child is affected, but neither parent is; this can happen if the condition is recessive and both parents are *Aa*. Notice that the parents are **carriers,** because they appear normal (do not express the trait) but are capable of having a child with the genetic disorder. In pattern II, the child is unaffected, but the parents are affected. This can happen if the condition is dominant and the parents are *Aa*.

Figure 2.10 shows other ways to recognize an autosomal recessive pattern of inheritance, and Figure 2.11 identifies the characteristics of an autosomal dominant pattern of inheritance. In these pedigrees, generations are indicated by Roman numerals on the left side. Notice in the third generation of Figure 2.10 that two closely related individuals have produced three children, two of which have the affected phenotype. In this case, a double line denotes consanguineous reproduction, or inbreeding, which is reproduction between two closely related individuals. This illustrates that inbreeding significantly increases the chances of children inheriting two copies of a potentially harmful recessive allele.

Autosomal Recessive Disorders

In humans, a number of autosomal recessive disorders have been identified. In this section, we discuss methemoglobinemia, cystic fibrosis, and phenylketonuria.

Methemoglobinemia

Methemoglobinemia is a relatively harmless disorder that results from an accumulation of methemoglobin in the blood. Hemoglobin, the main oxygen-carrying protein in the blood, is usually converted at a slow rate to an alternate form called methemoglobin. Unlike hemoglobin, which is bright red when carrying oxygen, methemoglobin has a bluish color, similar to that of oxygen-poor blood. Although this process is harmless, individuals with methemoglobinemia are unable to clear the abnormal blue protein from their blood, causing their skin to appear bluish-purple (Fig. 2.12).

Methemoglobinemia was documented for centuries, but its exact cause and genetic link remained mysterious until a persistent and determined physician solved the age-old mystery by doing blood tests and pedigree analysis involving a family known as the "blue Fugates" of Troublesome Creek, Kentucky. Enzyme tests indicated that the blue Fugates lacked the enzyme diaphorase, coded for by a gene on chromosome 22. The enzyme normally converts methemoglobin back to hemoglobin.

The physician treated the disorder in a simple but rather unconventional manner. He injected the Fugates with a dye called

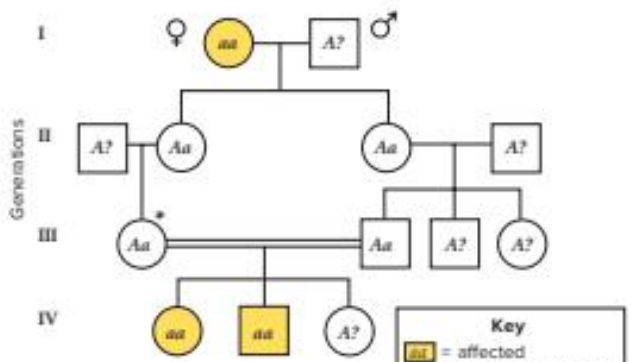


Figure 2.10 Autosomal recessive pedigree. The list gives ways to recognize an autosomal recessive disorder. How would you know the individual at the asterisk is heterozygous? (See Appendix A for the answer.)

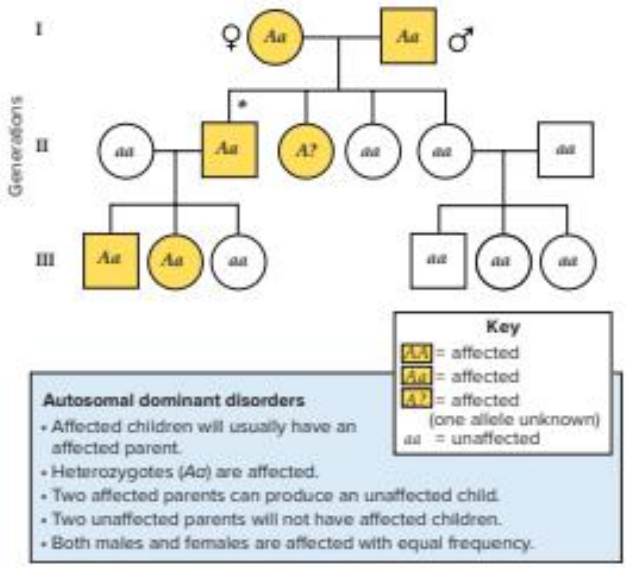


Figure 2.11 Autosomal dominant pedigree. The list gives ways to recognize an autosomal dominant disorder. How would you know the individual at the asterisk is heterozygous? (See Appendix A for the answer.)

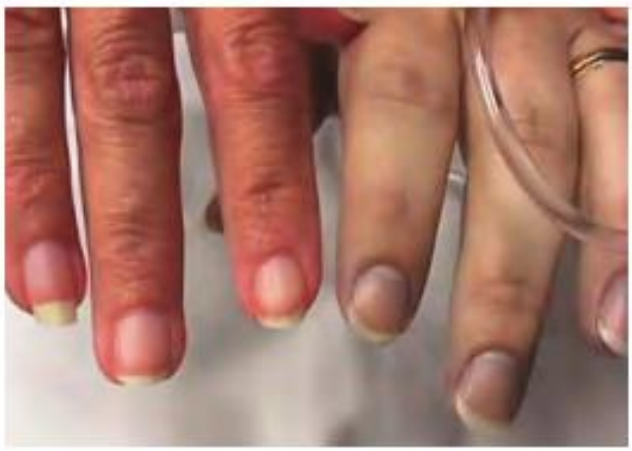


Figure 2.12 Methemoglobinemia. The hands of the woman on the right appear blue due to chemically induced methemoglobinemia.

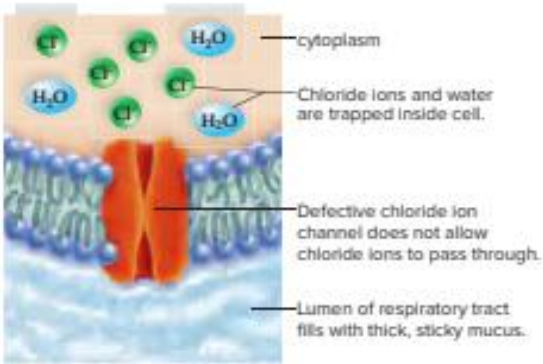


Figure 2.13 Cystic fibrosis. Cystic fibrosis is due to a faulty protein that is supposed to regulate the flow of chloride ions into and out of cells through a channel protein.

methylene blue. This unusual dye can donate electrons to other compounds, successfully converting the excess methemoglobin back into normal hemoglobin. The results were striking but immediate—the patients' skin quickly turned pink after treatment. A pedigree analysis of the Fugates indicated that the trait was common in the family because so many members carried the recessive allele.

Cystic Fibrosis

Cystic fibrosis (CF) is the most common lethal genetic disease among Caucasians in the United States (Fig. 2.13). About 1 in 20 Caucasians is a carrier, and about 1 in 2,000 newborns has the disorder. CF patients exhibit a number of characteristic symptoms, the most obvious being extremely salty sweat. In children with CF, the mucus in the bronchial tubes and pancreatic ducts is particularly thick and viscous, interfering with the function of the lungs and pancreas. To ease breathing, the thick mucus in the lungs has to be loosened periodically, but still the lungs frequently become infected. The clogged pancreatic ducts prevent digestive enzymes from reaching the small intestine, and to improve digestion, patients take digestive enzymes mixed with applesauce before every meal.

Cystic fibrosis is caused by a defective chloride ion channel that is encoded by the *CFTR* allele on chromosome 7. Research has demonstrated that chloride ions (Cl^-) fail to pass through the defective version of the *CFTR* chloride ion channel, which is located on the plasma membrane. Ordinarily, after chloride ions have passed through the channel to the other side of the membrane, sodium ions (Na^+) and water follow. It is believed that lack of water is the cause of the abnormally thick mucus in the bronchial tubes and pancreatic ducts.

In the past few years, a better understanding of the genetic basis of CF, coupled with new treatments, has raised the average life expectancy for CF patients to around 35 years, depending on the severity of the disease. Advances in gene therapy, or the replacement of the faulty allele with a good copy, is showing considerable promise as a method of treating CF.

Interestingly, the mutated *CFTR* allele is believed to have persisted in the human population as a means of surviving potentially fatal diseases. Individuals who are heterozygous have an increased level of protection against diseases such as cholera. This is called a heterozygote advantage.

Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive metabolic disorder that affects nervous system development. Affected individuals lack the enzyme needed for normal metabolism of the amino acid phenylalanine; therefore, it appears in the urine and the blood. Newborns are routinely tested in the hospital for elevated levels of phenylalanine in the blood. If an elevated level is detected, the newborn will develop normally if placed on a diet low in phenylalanine, which must be continued until the brain is fully developed, around the age of 7, or severe intellectual disabilities will develop. Some doctors recommend that the diet continue for life, but in any case, a pregnant woman with phenylketonuria must be on the diet to protect her unborn child.

Autosomal Dominant Disorders

A number of autosomal dominant disorders have been identified in humans. Three relatively well-known autosomal dominant disorders are osteogenesis imperfecta, Huntington disease, and hereditary spherocytosis.

Osteogenesis Imperfecta

Osteogenesis (L. *os,* "bone"; *genesis,* "origin") imperfecta is an autosomal dominant genetic disorder that results in weakened, brittle bones. Although at least nine types of the disorder are known, most are linked to mutations in two genes necessary for the synthesis of type I collagen, one of the most abundant proteins in the human body. Collagen has many roles, including providing strength and rigidity to bone and forming the framework for most of the body's tissues. Osteogenesis imperfecta leads to a defective collagen I that causes the bones to be brittle and weak. Because the mutant collagen can cause structural defects even when combined

with normal collagen I, osteogenesis imperfecta is generally considered to be dominant.

Osteogenesis imperfecta, which has an incidence of approximately 1 in 5,000 live births, affects all racial groups similarly and has been documented since as long as 300 years ago. Some historians think that the Viking chieftain Ivar Ragnarsson, who was known as Ivar the Boneless and was often carried into battle on a shield, had this condition. In most cases, the diagnosis is made in young children who visit the emergency room frequently due to broken bones. Some children with the disorder have an unusual blue tint in the sclera, the white portion of the eye; reduced skin elasticity; weakened teeth; and occasionally heart valve abnormalities. Currently, the disorder is treatable with a number of drugs that help increase bone mass, but these drugs must be taken long-term.

Huntington Disease

Huntington disease is a neurological disorder that leads to progressive degeneration of brain cells. The disease is caused by a mutated copy of the gene for a protein called huntingtin. Most patients appear normal until they are of middle age and have already had children, who may later also be stricken. Occasionally, the first sign of the disease appears during the teen years or even earlier. There is no effective treatment, and death comes 10 to 15 years after the onset of symptoms.

Several years ago, researchers found that the gene for Huntington disease is located on chromosome 4. They developed a test to detect the presence of the gene. However, few people want to know they have inherited the gene, because there is no cure. At least now we know that the disease stems from a mutation that causes the huntingtin protein to have too many copies of the amino acid glutamine. The normal version of huntingtin has stretches of between 10 and 25 glutamines. If huntingtin has more than 36 glutamines, it changes shape and forms large clumps inside neurons. Even worse, it attracts and causes other proteins to clump with it. One of these proteins, called CBP, which helps nerve cells survive, is inactivated when it clumps with huntingtin. Researchers hope to combat the disease by boosting CBP levels.

Hereditary Spherocytosis

Hereditary spherocytosis is an autosomal dominant genetic blood disorder that results from a defective copy of the *ankyrin-1* gene, found on chromosome 8. The protein encoded by this gene serves as a structural component of red blood cells and is responsible for maintaining their disklike shape. The abnormal spherocytosis protein is unable to perform its usual function, causing the affected person's red blood cells to adopt a spherical rather than disklike shape. As a result, the abnormal cells are fragile and burst easily, especially under osmotic stress. Enlargement of the spleen is also commonly seen in people with the disorder.

With an incidence of approximately 1 in 5,000, hereditary spherocytosis is one of the most common hereditary blood disorders. Roughly one-fourth of these cases result from new mutations and are not inherited from either parent. Hereditary spherocytosis exhibits incomplete penetrance, so not all individuals who inherit the mutant allele will actually show the trait. The cause of incomplete penetrance in these cases and others remains poorly understood.

Check Your Progress 2.3

1. Summarize how to distinguish an autosomal recessive disorder from an autosomal dominant disorder using a pedigree.
2. Construct a pedigree of Ivar Ragnarsson's family tree, assuming that his mother, and both her parents, were normal and that Ivar's father's father had osteogenesis imperfecta (mother was normal).

2.4 Beyond Mendelian Inheritance

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain the inheritance pattern of traits when more than two alleles for the trait exist.
2. Contrast incomplete dominance and incomplete penetrance.
3. Describe the effects of pleiotropy on phenotypic traits.
4. Explain the concept of polygenic and multifactorial traits.
5. Understand how X-linked inheritance differs from autosomal inheritance.

Mendelian genetics can be applied to complex patterns of inheritance, such as multiple alleles, incomplete dominance, pleiotropy, and polygenic inheritance.

Multiple Allelic Traits

When a trait is controlled by **multiple alleles,** the gene exists in several allelic forms within a population. For example, although a person's ABO blood type is controlled by a single gene pair, three possible alleles within the human population determine blood type. Each person receives two of these alleles (one from each parent) to determine the presence or absence of antigens on his or her red blood cells.

I^A = A antigen on red blood cells
I^B = B antigen on red blood cells
i = Neither A nor B antigen on red blood cells

The possible phenotypes and genotypes for blood type are as follows:

Phenotype	*Genotype*
A	I^AI^A, I^Ai
B	I^BI^B, I^Bi
AB	I^AI^B
O	ii

The inheritance of the ABO blood group in humans is also an example of **codominance,** because both I^A and I^B are fully expressed in the presence of the other. A person who inherits chromosomes with I^A and I^B alleles will make fully functional A and B protein, and because these alleles are codominant, the resulting mixture of AB protein will give the red blood cell an AB phenotype. On the other

hand, both I^A and I^B are dominant over *i*. Therefore, two genotypes are possible for type A blood, and two genotypes are possible for type B blood.

We can use a Punnett square to confirm that reproduction between a heterozygote with type A blood and a heterozygote with type B blood can result in any one of the four blood types. Such a cross makes it clear that an offspring can have a different blood type than either parent. For this reason, rather than blood type, DNA fingerprinting, also called DNA profiling is used to identify the parents of an individual.

Incomplete Dominance and Incomplete Penetrance

Incomplete dominance is exhibited when a heterozygote has an intermediate phenotype between that of either homozygote. In a cross between a true-breeding, red-flowered four-o'clock plant strain and a true-breeding, white-flowered strain, the offspring have pink flowers. Although this outcome might appear to be an example of the blending theory of inheritance, it is not. Although the phenotypes have blended, the individual alleles are not altered. How do we know? When the pink plants self-pollinate, the offspring plants have a phenotypic ratio of 1 red-flowered : 2 pink-flowered : 1 white-flowered. The reappearance of the three phenotypes in this generation makes it clear that we are still dealing with a single pair of alleles (Fig. 2.14).

Incomplete dominance in four-o'clocks actually has more to do with the amount of pigment protein produced in the plant cells: A double dose of pigment results in red flowers; a single dose of pigment results in pink flowers; and a lack of any pigment produces white flowers.

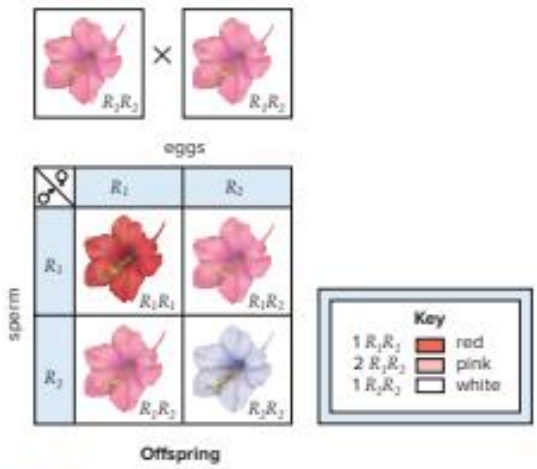


Figure 2.14 Incomplete dominance. When pink four-o'clocks self-pollinate, the results show three phenotypes. This is possible only if the pink parents had an allele for red pigment (R_1) and an allele for no pigment (R_2). Note that alleles involved in incomplete dominance are both given a capital letter.

Human Examples of Incomplete Dominance

In humans, familial hypercholesterolemia (FH) is an example of incomplete dominance. An individual with two alleles for this disorder develops fatty deposits in the skin and tendons and may have a heart attack as a child. An individual with one normal allele and one *FH* allele may suffer a heart attack as a young adult, and an individual with two normal alleles does not have the disorder.

Perhaps the inheritance pattern of other human disorders should be considered one of incomplete dominance. To detect the carriers of cystic fibrosis, for example, it is customary to determine the amount of cellular activity of the gene. When the activity is one-half that of the dominant homozygote, the individual is a carrier, even though the individual does not exhibit the genetic disease. In other words, at the level of gene expression, the homozygotes and heterozygotes differ in the same manner as four-o'clock plants.

A dominant allele may not always lead to the dominant phenotype in a heterozygote, even when the alleles show a true dominant/recessive relationship. The dominant allele in this case does not always determine the phenotype of the individual, so we describe these traits as showing **incomplete penetrance.** In other words, just because a person inherits a dominant allele doesn't mean he or she will fully express the gene or show the dominant phenotype. Many dominant alleles exhibit varying degrees of penetrance.

The best-known example of incomplete penetrance is polydactyly, the presence of one or more extra digits on the hands, the feet, or both. Polydactyly is inherited in an autosomal dominant manner; however, not all individuals who inherit the dominant allele exhibit the trait. The reasons for this are not clear, but expression of polydactyly may require additional environmental factors or be influenced by other genes, as discussed later.

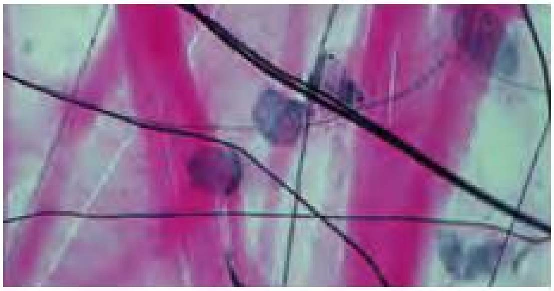
Pleiotropic Effects

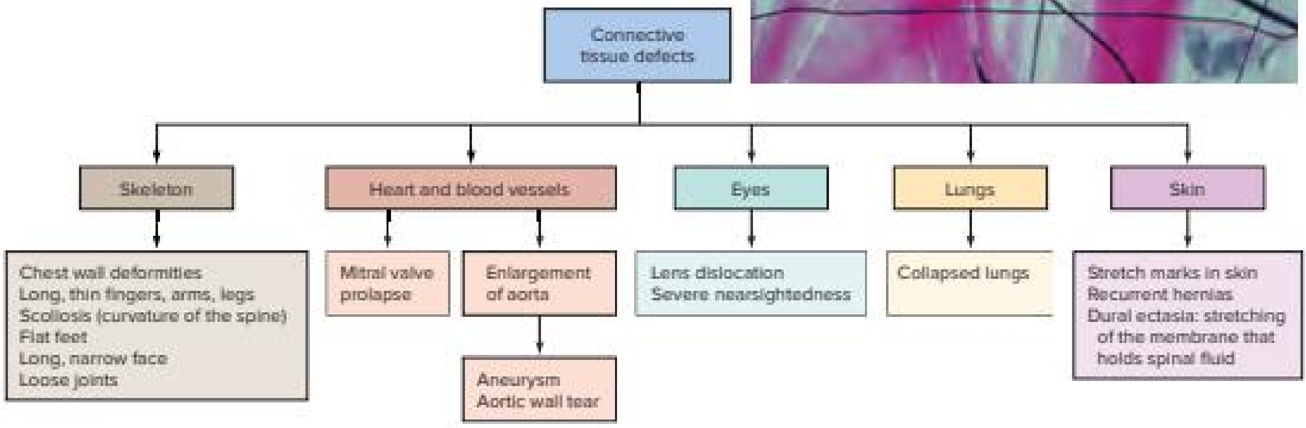
Pleiotropy occurs when a single mutant gene affects two or more distinct and seemingly unrelated traits. For example, persons with Marfan syndrome have disproportionately long arms, legs, hands, and feet; a weakened aorta; poor eyesight; and other characteristics (Fig. 2.15). All of these characteristics are due to the production of abnormal connective tissue.

Marfan syndrome has been linked to a mutated gene (*FBN1*) on chromosome 15 that ordinarily specifies a functional protein called fibrillin. Fibrillin is essential for the formation of elastic fibers in connective tissue. Without the structural support of normal connective tissue, the aorta can burst, particularly if the person is engaged in a strenuous sport, such as volleyball or basketball. Flo Hyman may have been the best American woman volleyball player ever, but she fell to the floor and died at the age of 31, because her aorta gave way during a game. Now that coaches are aware of Marfan syndrome, they are on the lookout for it among very tall basketball players.

Many other disorders, including porphyria and sickle-cell disease, are examples of pleiotropic traits. Porphyria is caused by a chemical insufficiency in the production of hemoglobin, the pigment that makes red blood cells red. The symptoms of porphyria

Figure 2.15 Marfan syndrome. Marfan syndrome illustrates the multiple effects a single gene can have. Marfan syndrome is due to any number of defective connective tissue defects.





are photosensitivity, strong abdominal pain, port-wine-colored urine, and paralysis in the arms and legs. Many members of the British royal family in the late 1700s and early 1800s suffered from this disorder, which can lead to epileptic convulsions, bizarre behavior, and coma.

In a person suffering from sickle-cell disease (Hb^SHb^S), the cells are sickle-shaped. The underlying mutation is in a gene that codes for a type of polypeptide chain in hemoglobin. Of 146 amino acids, the gene mutation changes only one amino acid, but the result is a less-soluble polypeptide chain that stacks up and causes red blood cells to be sickle-shaped. The abnormally shaped sickle cells slow down blood flow and clog small blood vessels. In addition, sickled red blood cells have a shorter life span than normal red blood cells. Affected individuals may exhibit a number of symptoms, including severe anemia, physical weakness, poor circulation, impaired mental function, pain and high fever, rheumatism, paralysis, spleen damage, low resistance to disease, and kidney and heart failure. All of these effects are due to both the tendency of sickled red blood cells to break down and the resulting decreased oxygen-carrying capacity of the blood, which damage the body.

1,600×, colorized SEM

Sickled red blood cell

Although sickle-cell disease is a devastating disorder, from an evolutionary perspective it provides heterozygous individuals with a survival advantage. People who have sickle-cell trait are resistant to the protozoan parasite that causes malaria. The parasite spends part of its life cycle in red blood cells, feeding on hemoglobin, but it cannot complete its life cycle when sickle-shaped cells form and break down earlier than usual. Because of this survival benefit, the sickle-cell allele has been maintained in the human population over evolutionary time.

Polygenic Inheritance

Polygenic inheritance (Gk. *poly*, "many"; L. *genitus*, "producing") occurs when a trait is governed by two or more sets of alleles. Examples include human height, skin color, and the prevalence of diabetes. The individual has a copy of all allelic pairs, possibly located on many different pairs of chromosomes. Each dominant allele has a quantitative effect on the phenotype, and these effects are additive. Therefore, a population is expected to exhibit continuous phenotypic variations, such as a wide variation in human height and weight. In Figure 2.16, a cross between genotypes *AABBCC* and *aabbcc* yields F_1 hybrids with the genotype *AaBbCc*. A range of genotypes and phenotypes results in the F_2 generation that can be depicted as a bell-shaped curve (Fig. 2.16).

Skin Color

Skin color is the result of pigmentation produced by skin cells called melanocytes, and over 100 different genes influence skin color. It is an example of a polygenic trait that is likely controlled by many pairs of alleles, which results in a range of phenotypes. The vast majority of people have skin colors in the middle range, whereas fewer people have skin colors in the extreme range.

Even so, we will use the simplest model and we will assume that skin has only three pairs of alleles (*Aa*, *Bb*, and *Cc*) and that each capital letter contributes pigment to the skin. When a very dark person reproduces with a very light person, the children have medium-brown skin. When two people with the genotype *AaBbCc* reproduce with one another, individuals may range in skin color

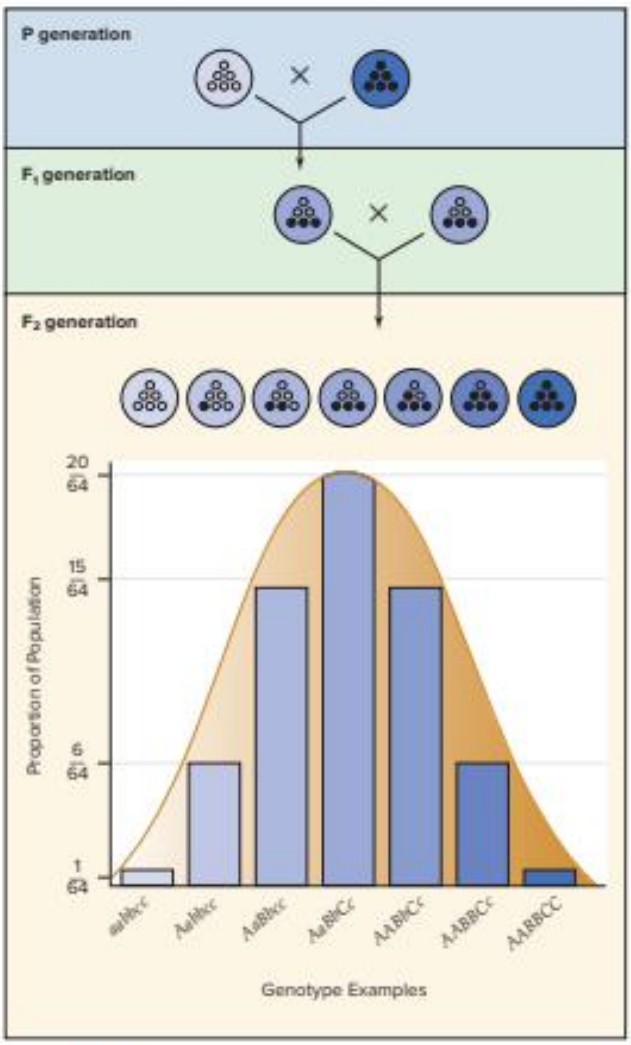


Figure 2.16 Polygenic inheritance. In polygenic inheritance, a number of pairs of genes control the trait. *Above:* Black dots and intensity of blue shading stand for the number of dominant alleles. *Below:* Orange shading shows the degree of environmental influences.

from very dark to very light. The distribution of these phenotypes typically follows a bell-shaped curve, meaning that few people have the extreme phenotypes and most people have the phenotype that lies in the middle. A bell-shaped curve is a common identifying characteristic of a polygenic trait (Fig. 2.17).

However, skin color is also influenced by the sunlight in the environment. Notice again that a range of phenotypes exists for each genotype. For example, individuals who are *AaBbCc* may vary in their skin color, even though they possess the same genotype, and several possible phenotypes fall between the two extremes. The interaction of the environment with polygenic traits is discussed next.

Environmental Influences: Multifactorial Traits

Multifactorial traits are those controlled by polygenes subject to environmental influences. Many genetic disorders, such as cleft lip and/or palate, clubfoot, congenital dislocations of the hip, hypertension, diabetes, schizophrenia, and even allergies and cancers, are probably multifactorial, because they are likely due to the combined action of many genes plus environmental influences. The relative importance of genetic and environmental influences on the phenotype can vary, and often it is a challenge to determine how much of the variation in the phenotype may be attributed to each factor. This is especially true in complex polygenic traits for which there may be an additive effect of multiple genes on the phenotype. If each gene has several alleles, and each allele responds slightly differently to environmental factors, then the phenotype can vary considerably.

Multifactorial traits are a challenge for drug manufacturers, since they must determine the response to a new drug based on genetic factors (for example, the ethnic background of the patient) and environmental factors (such as diet). Temperature is an environmental factor that can influence the phenotypes of plants and animals. Primroses have white flowers when grown above 32°C but red flowers when grown at 24°C.

The coats of Himalayan rabbits are darker in color at the ears, nose, paws, and tail. Himalayan rabbits are known to be homozygous for the allele *ch*, which is involved in the production of melanin. Experimental evidence suggests that the enzyme encoded by this gene is active only at a low temperature and that, therefore, black fur occurs only at the extremities, where body heat is lost to

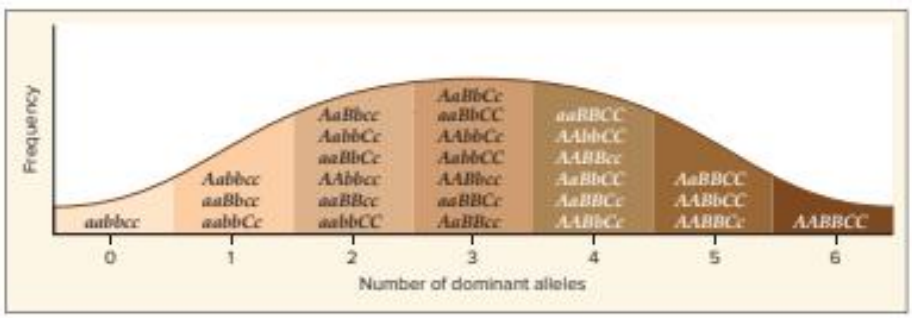


Figure 2.17 Skin color, a polygenic trait. Skin color is controlled by many pairs of alleles, which result in a range of phenotypes. The vast majority of people have skin colors in the middle range, whereas fewer people have skin colors in the extreme range.

the environment. When the animal is placed in a warmer environment, new fur on these body parts is light in color.

Many investigators are trying to determine what percentage of various traits is due to nature (inheritance) and what percentage is due to nurture (the environment). Some studies use twins separated since birth, because if identical twins in different environments share the same trait, the trait is most likely inherited. Identical twins are more similar in their intellectual talents, personality traits, and levels of lifelong happiness than are fraternal twins separated at birth. Biologists conclude that all behavioral traits are partly heritable, and that genes exert their effects by acting together in complex combinations susceptible to environmental influences.

X-linked Inheritance

The X and Y chromosomes in mammals determine the gender of the individual. Females are XX, and males are XY. These chromosomes carry genes that control development; in particular, if the Y chromosome contains an *SRY* gene, the embryo becomes a male. The term **X-linked** is used for genes that have nothing to do with gender yet are carried on the X chromosome. The Y chromosome does not carry these genes and indeed carries very few genes.

This type of inheritance was discovered in the early 1900s by a group at Columbia University headed by Thomas Hunt Morgan. Morgan performed experiments with fruit flies, *Drosophila melanogaster*. Fruit flies are even better subjects for genetic studies than garden peas. They can be easily and inexpensively raised in simple laboratory glassware; after mating, females lay hundreds of eggs during their lifetimes; and the generation time is short, taking only about 10 days from egg to adult. Fruit flies have a sex chromosome pattern similar to that of humans, and therefore Morgan's experiments with X-linked genes apply directly to humans.

Morgan's Experiment

Morgan took a newly discovered mutant male with white eyes and crossed it with a red-eyed female:

	♀		♂
P	red-eyed	×	white-eyed
F_1	red-eyed		red-eyed

From these results, he knew that red eyes are the dominant characteristic and white eyes are the recessive characteristic. He then crossed the F_1 flies. In the F_2 generation, there was the expected 3 red-eyed : 1 white-eyed ratio, but it struck him as odd that all the white-eyed flies were males:

	♀		♂
$F_1 \times F_1$	red-eyed	×	red-eyed
F_2	red-eyed		1 red-eyed : 1 white-eyed

Obviously, a major difference between the male flies and the female flies was their sex chromosomes. Could it be possible that an allele for eye color was on the Y chromosome but not on the X? This idea could be quickly discarded, because usually females have red eyes, and they have no Y chromosome. Perhaps an allele for eye color was on the X, but not on the Y, chromosome. Figure 2.18 indicates that this explanation would match the results obtained in the experiment. These results support the chromosome theory of inheritance by showing that the behavior of a specific allele corresponds exactly with that of a specific chromosome—the X chromosome in *Drosophila*.

Notice that X-linked alleles have a different pattern of inheritance than alleles that are on the autosomes, because the Y chromosome is lacking for these alleles, and the inheritance of a Y chromosome cannot offset the inheritance of an X-linked recessive allele. For the same reason, males always receive an X-linked recessive mutant allele from the female parent—they receive only the Y chromosome from the male parent, and therefore sex-linked recessive traits appear much more frequently in males than in females.

Solving X-linked Genetics Problems

Recall that when solving autosomal genetics problems, the allele key and genotypes can be represented as follows:

Allele key	*Genotypes*
L = long wings	*LL*, *Ll*
l = short wings	*ll*

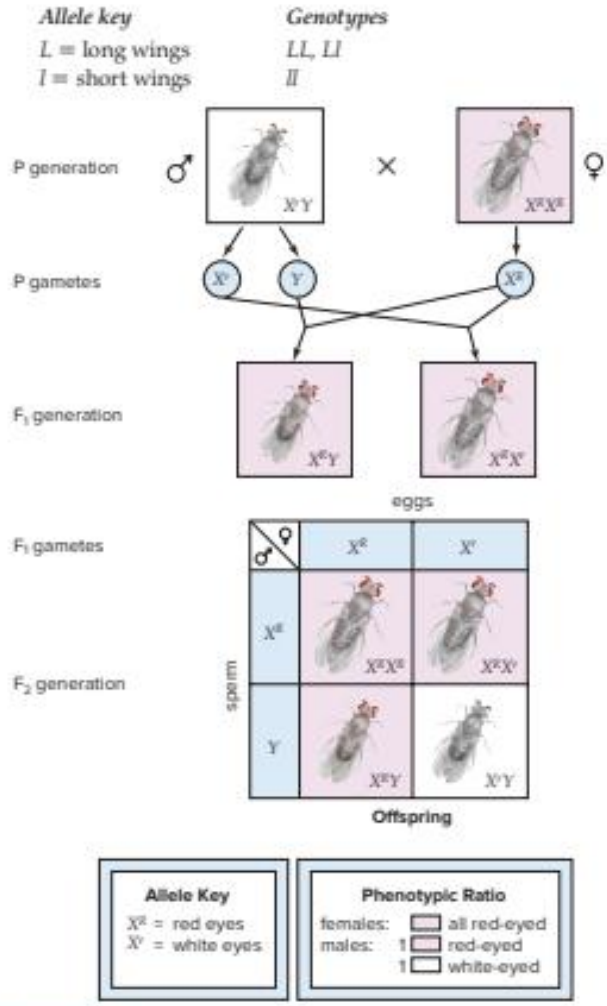


Figure 2.18 X-linked inheritance. Once researchers deduced that the alleles for red/white eye color are on the X chromosome in *Drosophila*, they were able to explain their experimental results. Males with white eyes in the F_2 generation inherit the recessive allele only from the female parent; they receive a Y chromosome lacking the allele for eye color from the male parent.

When predicting inheritance of sex-linked traits, however, it is necessary to indicate the sex chromosomes of each individual. As noted in Figure 2.18, however, the allele key for an X-linked gene shows an allele attached to the X:

Allele key
X^R = red eyes
X^r = white eyes

The possible genotypes and phenotypes in both males and females are as follows:

Genotype	*Phenotype*
X^RX^R	red-eyed female
X^RX^r	red-eyed female
X^rX^r	white-eyed female
X^RY	red-eyed male
X^rY	white-eyed male

Notice that there are three possible genotypes for females but only two for males. Females can be heterozygous X^RX^r, in which case they are carriers. Carriers usually do not show a recessive abnormality, but they are capable of passing on a recessive allele for an abnormality. But unlike autosomal traits, males cannot be carriers for X-linked traits; if the dominant allele is on the single X chromosome, they show the dominant phenotype, and if the recessive allele is on the single X chromosome, they show the recessive phenotype. For this reason, males are considered **hemizygous** for X-linked traits, because a male possesses only one allele for the trait and, therefore, expresses whatever allele is present on the X chromosome.

We know that male fruit flies have white eyes when they receive the mutant recessive allele from the female parent. What is the inheritance pattern when females have white eyes? Females can have white eyes only when they receive a recessive allele from both parents.

Human X-linked Disorders

Several X-linked recessive disorders occur in humans, including color blindness, Menkes syndrome, muscular dystrophy, adrenoleukodystrophy, and hemophilia.

Color Blindness. In humans, the receptors for color vision in the retina of the eyes are three different classes of cone cells. Only one type of pigment protein is present in each class of cone cell; there are blue-sensitive, red-sensitive, and green-sensitive cone cells. The allele for the blue-sensitive protein is autosomal, but the alleles for the red- and green-sensitive pigments are on the X chromosome. About 8% of Caucasian men have red-green color blindness. Most of these see brighter greens as tans, olive greens as browns, and reds as reddish browns. A few cannot tell reds from greens at all. They see only yellows, blues, blacks, whites, and grays.

Pedigrees can also reveal the unusual inheritance pattern seen in sex-linked traits. For example, the pedigree in Figure 2.19 shows the usual pattern of inheritance for color blindness. More males than females have the trait, because recessive alleles on the X chromosome are expressed in males. The disorder often passes from grandfather to grandson through a carrier daughter.

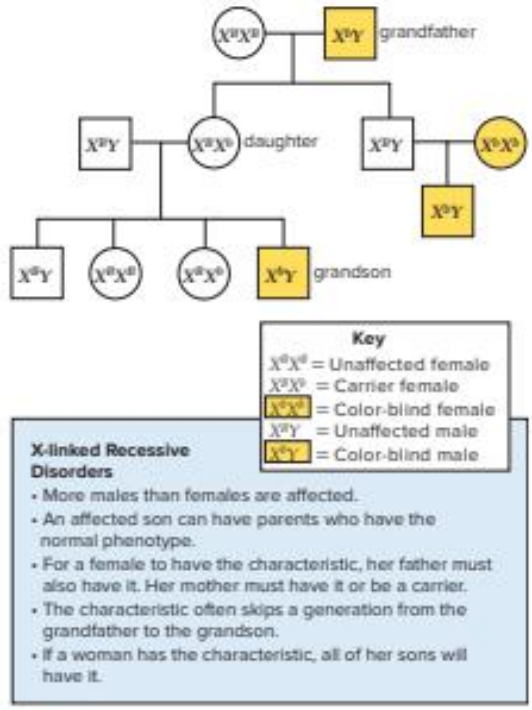


Figure 2.19 X-linked recessive pedigree. This pedigree for color blindness exemplifies the inheritance pattern of an X-linked recessive disorder. The list gives various ways of recognizing the X-linked recessive pattern of inheritance.

Menkes Syndrome. Menkes syndrome, or kinky hair syndrome, is caused by a defective allele on the X chromosome. Normally, the gene product controls the movement of the metal copper into and out of cells. The symptoms of Menkes syndrome are due to an accumulation of copper in some parts of the body, and the lack of the metal in other parts.

Symptoms of Menkes syndrome include poor muscle tone, seizures, abnormally low body temperature, skeletal anomalies, and the characteristic brittle, steely hair associated with the disorder. Although the condition is relatively rare, affecting approximately 1 in 100,000, mostly males, the prognosis for people with Menkes syndrome is poor, and most individuals die within the first few years of life. In recent years, some people with Menkes syndrome have been treated with injections of copper directly underneath the skin, but with mixed results, and treatment must begin very early in life to be effective.

Muscular Dystrophy. Muscular dystrophy, as the name implies, is characterized by a wasting away of the muscles. The most common form, Duchenne muscular dystrophy, is X-linked and occurs in about 1 out of every 3,600 male births. Symptoms such as waddling gait, toe walking, frequent falls, and difficulty in rising may appear as soon as the child starts to walk. Muscle weakness intensifies until the individual is confined to a wheelchair. Death usually occurs by age 20; therefore, affected males are rarely fathers. The recessive allele remains in the population through passage from carrier mother to carrier daughter.

The allele for Duchenne muscular dystrophy has been isolated, and it has been discovered that the absence of a protein called dystrophin causes the disorder. Much investigative work has determined that dystrophin is involved in the release of calcium from

Nature of Science

Hemophilia and the Royal Families of Europe

About 1 in 10,000 males is a hemophiliac. There are two common types of hemophilia: Hemophilia A is due to the absence or minimal presence of a clotting factor known as factor VIII, and hemophilia B is due to the absence of clotting factor IX. Hemophilia is called the bleeder's disease because the affected person's blood either does not clot or clots very slowly. Although hemophiliacs bleed externally after an injury, they also bleed internally, particularly around joints. Hemorrhages can be stopped with transfusions of fresh blood (or plasma) or concentrates of the clotting protein. Also, clotting factors are available as biotechnology products.

The pedigree in Figure 2A shows why hemophilia is often referred to as "the royal disease." Queen Victoria of England, who reigned from 1837 to 1901, was the first of the royals to carry the gene. From her, the disease eventually spread to the Prussian, Spanish, and Russian royal families. In that era, monarchs arranged marriages between their children to consolidate political alliances. This practice allowed the gene for hemophilia to spread throughout the royal families. It is assumed that a spontaneous mutation arose either in Queen Victoria after her conception or in one of the gametes of her parents. However, in the book *Queen Victoria's Gene* by D. M. Potts, the author postulates that Edward Augustus, Duke of Kent, may not have been Queen Victoria's father. Potts suggests that Victoria may have instead been the illegitimate child of a hemophiliac male.

Of Queen Victoria's 26 grandchildren, 4 grandsons had hemophilia and 4 granddaughters were carriers. Because none of Queen Victoria's brothers and sisters were affected, it seems that the faulty allele she carried arose by mutation either in Victoria or in one of her parents. Her carrier daughters, Alice and Beatrice, introduced the allele into the ruling houses of Russia, Prussia, and Spain, respectively. Alexi, the last heir to the Russian throne before the Russian Revolution, was a hemophiliac. There are no hemophiliacs in the present British royal family, because Victoria's eldest son, King Edward VII, did not receive the allele.

Questions to Consider

1. How may a pedigree pattern be used to determine if a disease is autosomal dominant or autosomal recessive?
2. Assume that the mutation for hemophilia did not originate with Victoria. What does this tell you about the genotypes of her parents?

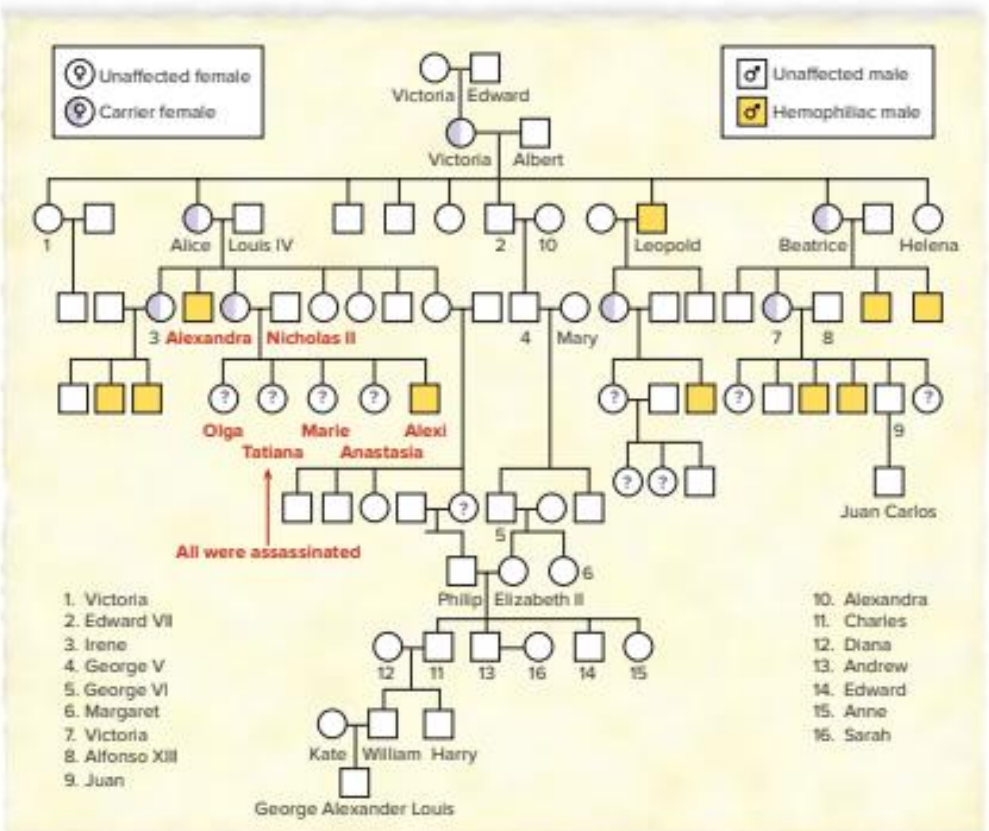


Figure 2A Hemophilia: an X-linked trait. Queen Victoria was a carrier, so each of her sons had a 50% chance of having the disorder, and each of her daughters had a 50% chance of being a carrier. This pedigree shows only the affected descendants.

the sarcoplasmic reticulum in muscle fibers. The lack of dystrophin causes calcium to leak into the cell, which promotes the action of an enzyme that dissolves muscle fibers. When the body attempts to repair the tissue, fibrous tissue forms, and this cuts off the blood supply, so more and more cells die.

A test is now available to detect carriers of Duchenne muscular dystrophy. Also, various treatments have been tried. Immature muscle cells can be injected into muscles, and for every 100,000 cells injected, dystrophin production occurs in 30–40% of muscle fibers. The allele for dystrophin has been inserted into thigh muscle cells, and about 1% of these cells then have produced dystrophin.

Adrenoleukodystrophy. Adrenoleukodystrophy, or ALD, is an X-linked recessive disorder due to the failure of a carrier protein to move either an enzyme or a very long-chain fatty acid (24–30 carbon atoms) into peroxisomes. As a result, these fatty acids are not broken down, and they accumulate inside the cell; the result is severe nervous system damage.

Children with ALD fail to develop properly after age 5, lose adrenal gland function, exhibit very poor coordination, and show a progressive loss of hearing, speech, and vision. The condition is usually fatal, with no known cure, but the onset and severity of symptoms in patients not yet showing symptoms may be mitigated by treatment with a mixture of lipids derived from olive oil. The disease was made well known by the 1992 movie *Lorenzo's Oil*, detailing a mother's and father's determination to devise a treatment for their son who was suffering from ALD.

Check Your Progress 2.4

1. Summarize why incomplete dominance does not support blending.
2. Summarize how to identify an X-linked trait from an autosomal trait.
3. Explain how a trait may be both polygenic and multifactorial.

Reviewing *the* BIG IDEAS

BIG IDEA 1

Individuals with genes that when expressed confer favorable variations are more likely to survive and produce more offspring. Genes provide the raw material for natural selection. 1.A.1.c,e

The persistence of genetic disease over evolutionary time may confer some biological benefit to humans. 1.A.1.c,e; *3.A.3.c, IE*

BIG IDEA 3

Understanding the chromosomal basis of inheritance allows us to understand the pattern of the passage of genes from parent to offspring. 3.A.3.a,b; 3.A.2.c

The inheritance patterns of many traits cannot be explained by simple Mendelian genetics. 3.A.4.a-c

With the help of Mendel's model of the inheritance of traits, pedigree analysis, and statistics, scientists have been able to link many human diseases to specific genes on certain chromosomes. Many ethical, social, and medical issues surround human genetic diseases. 3.A.3.a,d; 3.A.4.a-c

SUMMARIZE

AP Answering the Essential Questions

The science of genetics explains the stability of inheritance (why you are human, as are your parents) as well as variations between offspring from one generation to the next (why you have a different combination of traits than your parents). Austrian Gregor Mendel came up with a model in the 1860s to explain these patterns. An understanding of inheritance has always been important to agriculture and medicine. However, today humans' ability to manipulate genetic information raises ethical questions.

Previously, we studied how mitosis and meiosis allow for the passage of genetic information from parent to offspring, preserving existing information with great fidelity. We also learned that changes in genetic information can produce variations that are more favorable for a species' survival when environmental conditions change. Genes (and DNA) provide the raw material for natural selection and evolution. In sexually-reproducing organisms, meiosis followed by fertilization provides a spectrum of traits in offspring and on which natural selection operates; meiosis explains the patterns of inheritance observed by Mendel and his famous pea plants.

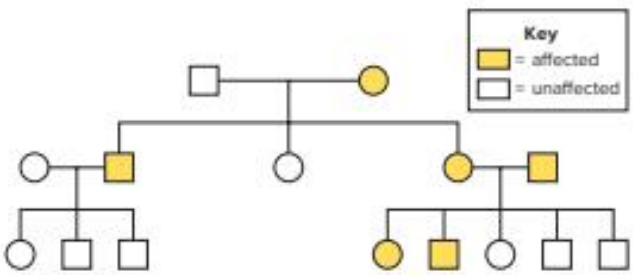
Mendel's experiments As you likely studied in a previous biology course, Mendel selected certain phenotypes to track by controlling pollination in his pea plants. To review, Mendel began by crossing plants that were true-breeding for a trait that occurred in two distinct but alternative forms, such as purple or white flower color (monohybrid cross). When Mendel observed offspring from the parental (P) cross, all offspring in this F1 generation expressed only one trait such as purple flower color. The other phenotype (e.g., white flower color) disappeared, which Mendel probably found perplexing. Allowing these F1 hybrids to self-pollinate (or cross-breed with other F1 hybrids) produced an F2 generation in which the disappearing phenotype reappeared (sounds like magic!) in about 1/4 (25%) of the F2 plants or in a phenotypic ratio of 3:1 (e.g., 3 purple: 1 white). Mendel used the terms **recessive** to describe the trait that had disappeared in the F1 generation and **dominant** to the trait that had not. **Heterozygous** describes a trait whose gene combination (genotype) consists of one dominant allele and one recessive allele. Thus, when Mendel crossed two heterozygous plants, the offspring almost always expressed a 3:1 phenotypic ratio of dominant to recessive. This allowed Mendel to propose his **law of segregation**—which takes us right back to meiosis.

Mendel's law of segregation states that the individual has two alleles (Mendel used the word "factors") for each trait, and the alleles

segregate with equal probability into the gametes during meiosis. Although Mendel didn't know it at the time of his work, the variations in the traits were due to the variations in genes. Each gene has a specific location, or locus, on a chromosome, and dominant alleles mask the expression of recessive alleles.

Mendel carried his work a step further by investigating dihybrid crosses, in which the F1 individuals showed dominant characteristics for two traits, but there were four phenotypes in a 9:3:3:1 ratio among the F2 offspring. This allowed Mendel to deduce the **law of independent assortment,** which states that the members of one pair of alleles separate independently of those of another pair. Therefore, all possible combinations of parental alleles can occur in the gametes, and the laws of probability and constructing **Punnett squares** help us predict the chances of producing gametes and offspring. Mendel's laws hold because of the events of meiosis. As we studied previously, because homologous pairs of chromosomes line up randomly at the equator of the cell during meiosis, dominant alleles can separate (segregate) with other dominant alleles or other recessive alleles. In other words, homologous chromosomes, and alleles they carry, segregate independently during gamete formation, creating an assortment of alleles in the gametes.

Beyond Mendelian inheritance Many human traits and genetic disorders can be explained on the basis of simple Mendelian inheritance. When studying human genetic disorders, biologists often construct **pedigrees** to show the pattern of inheritance of a characteristic (trait) within a family. The particular pattern indicates the manner in which a characteristic is inherited, such as autosomal dominant or autosomal recessive. Additional support for the chromosome theory of inheritance came when Thomas Hunt Morgan and his group determined that certain traits are located on sex chromosomes such as X and Y. Morgan's organism of choice was the common fruit fly, *Drosophila*, which, unlike Mendel's pea plants, has males and females. Typically, females have two X chromosomes (XX), and males have one X chromosome and one Y chromosome (XY). Alleles on the X chromosome are called **X-linked** alleles; the Y chromosome does not carry those alleles. The Y chromosome does not carry these genes, and, because males inherit only one copy of an allele for an X-linked trait, they cannot be heterozygous for the traits. Examples of X-linked traits in humans include color blindness, hemophilia, and sickle cell anemia. In addition to X-linked traits, other patterns of inheritance have been discovered since Mendel's original contribution. For example, some genes have multiple alleles although each individual has only two alleles (e.g., human blood types), and some traits results from the expression of nonnuclear DNA. Through evolution, sometimes a genetic disease can benefit an individual or a population; for example, sickle cell anemia can provide protection against malaria. It should be noted that many ethical, social, and medical issues surround human genetics such as privacy issues associated with ownership of genetic information or reproductive issues.



ASSESS

Choose the best answer for each question.

2.1 Gregor Mendel

1. Mendel's work supported which of the following?
   a. blending theory of inheritance
   b. particulate theory of inheritance
   c. theory of acquired characteristics
   d. All of these are correct.
2. Mendel's success was based on
   a. use of the pea plant as a model organism.
   b. his ability to apply statistics to his studies.
   c. careful planning of his experiments.
   d. All of these are correct.

2.2 Mendel's Laws

3. The law of segregation states all of the following except
   a. factors separate during formation of the gametes.
   b. each individual has two factors for each trait.
   c. gametes contain a single factor for each trait.
   d. factors assort independently of each other by meiosis.
4. In peas, yellow seed (*Y*) is dominant over green seed (*y*). In the F_2 generation of a monohybrid cross that begins when a dominant homozygote is crossed with a recessive homozygote, you would expect
   a. three plants with yellow seeds to every plant with green seeds.
   b. plants with one yellow seed for every green seed.
   c. only plants that produce green seeds.
   d. only plants that produce yellow seeds.
5. In guinea pigs, smooth coat (*S*) is dominant over rough coat (*s*), and black coat (*B*) is dominant over white coat (*b*). In the cross *SsBb* × *SsBb*, how many of the offspring will have a smooth black coat, on average?
   a. ¼
   b. about 9/16
   c. 1/16
   d. 6/16
6. In horses, *B* = black coat, *b* = brown coat, *T* = trotter, and *t* = pacer. A black trotter that has a brown pacer offspring has which of the following genotypes?
   a. *BT*
   b. *BbTt*
   c. *bbtt*
   d. *BBtt*

2.3 Mendelian Patterns of Inheritance and Human Disease

7. Which of the following is not correct for an autosomal recessive pedigree?
   a. Males inherit the trait 50% of the time.
   b. Heterozygous individuals are carriers.
   c. Only homozygous recessive individuals express the trait.
   d. Homozygous dominant individuals and heterozygotes have the same phenotype.
8. Cystic fibrosis is an example of a/an _____ trait.
   a. autosomal dominant
   b. autosomal recessive
   c. X-linked
   d. incomplete dominant

9. When analyzing a pedigree, you notice that two unaffected parents have produced a child that is affected by the trait. This suggests which of the following patterns of inheritance?
   a. autosomal dominant
   b. X-linked
   c. autosomal recessive
   d. All of these are correct.

2.4 Beyond Mendelian Inheritance

For questions 10–14, match the statements to the items in the key.

Key:
   a. multiple alleles
   b. polygenic trait
   c. pleiotropic gene
   d. incomplete dominance

10. A single gene produces a variety of phenotypes.
11. Multiple genes are involved, and the distribution resembles a bell-shaped curve.
12. In humans, there are three possible alleles at the chromosomal locus that determine blood type.
13. A cross of two heterozygous individuals produces an intermediate phenotype.
14. The environment may influence the phenotypic distribution of the trait.

ENGAGE

AP Applying the Big Ideas

1. BIG IDEA 1 Inheritance of genes within a population is a cornerstone of species' ability to change over time.
   a. **Describe** TWO kinds of data that could be collected by scientists to provide a direct answer to the question, how can scientists investigate the role of natural selection in evolution?
   b. **Explain** how the data you suggested in part (a) would provide a direct answer to the question.

2. BIG IDEA 3 Methemoglobinemia is an autosomal recessive disorder. If a man and a woman are both carriers of the recessive allele, what is the **probability** of each of the following (show all work):
   a. All three of their offspring will be of normal phenotype?
   b. All three of their offspring will have methemoglobinemia?

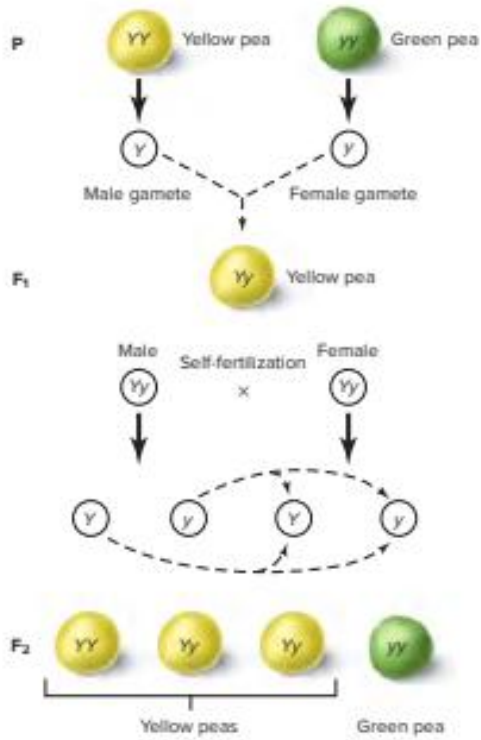
AP Applying the Science Practices

Analyze the Data

How can dominant traits be determined? Botanists discover a rare new species of plant and find that all individuals in the species display a desirable ability to withstand high heat and appear to be avoided by most large herbivores.

Data and Observations

Scientists have determined that the leaves have either sharp, serrated edges or smooth margins, and blooms that are either yellow or white.



Think Critically SP 1 SP 5 SP 6

1. **Design** an investigation that would determine whether serrated or smooth margins were the dominant trait for the leaves of this plant, and whether yellow or white blossoms are the dominant trait for the flowers.
2. Assuming serrated margins and white flowers are the dominant traits, **determine** what fraction of the offspring of two heterozygous plants would be expected to have serrated margins and yellow blooms?

The diversity of life is dependent on variations in genes.

3

Molecular Biology of the Gene

Chapter Outline

AP All life on Earth contains the four bases of DNA—A, G, C, and T. Different combinations of these bases make up genes, and every species has its own unique collection and combination of genes. These bases are molecules and code for biological "parts," such as the proteins that make skin, bones, eyes, leaves, and flowers.

MC1R is one of several genes that contribute to skin, hair, and eye color in humans, and studies of this gene have led to major insights into the evolution of human skin pigmentation. *MC1R* is a specific sequence of genetic instructions found in the nucleus of every cell in the human body. The gene is conserved every time a cell divides.

Humans have variation in their *MC1R* and other pigment genes that stem from their ancestry. A few differences in the placement of an adenine (A) or a cytosine (C) in the gene, for example, can alter gene expression—when and how much of the melanin is produced. So although everyone has melanin genes that become replicated with each cell division, each individual's gene expression is determined from the information that DNA transmits to the protein-making machinery.

As you read through the chapter, think about these Essential Questions:

1. How did historical experiments help identify DNA as the carrier of genetic information? 1.B.1.a.1 3.A.1.a.4.i-ii
2. How does the chemical structure of DNA as defined by the Watson and Crick model determine DNA's ability to store and transmit genetic information? 3.A.1 3.A.1.b.1-3
3. How does genetic information stored in DNA flow from a sequence of nucleotides in a gene to a sequence of amino acids in a protein? 3.A.1.a.5.i-ii 3.A.1.c.3 3.A.1.c.4.i-vii 3.A.1.d

Following the BIG IDEAS

BIG IDEA 1 DNA stores and transmits genetic information in all organisms.

BIG IDEA 3 Genetic information in the form of a coded sequence of nucleotides dictates the sequence of amino acids which will make a protein.

3.1 The Genetic Material

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the properties a substance must possess in order to serve as the genetic material.
2. Examine how historical researchers demonstrated that DNA is the genetic material.
3. Explain the chemical structure of DNA as defined by the Watson and Crick model.

The middle of the twentieth century was an exciting period of scientific discovery. On one hand, geneticists were busy determining that *DNA* (*deoxyribonucleic acid*) is the genetic material of all living organisms. On the other hand, biochemists were in a frantic race to describe the structure of DNA. The classic experiments performed during this era set the stage for an explosion in our knowledge of modern molecular biology.

When researchers began their work, they knew that the genetic material must be

1. Able to *store information* that pertains to the development, structure, and metabolic activities of the cell or organism
2. Stable, so that it *can be replicated* with high accuracy during cell division and be transmitted from generation to generation
3. Able to *undergo rare changes*, called mutations, that provide the genetic variability required for evolution to occur

This chapter will show, as the researchers of the twentieth century did, that DNA can fulfill these functions.

Transformation of Bacteria

During the late 1920s, the bacteriologist Frederick Griffith (1879–1941) was attempting to develop a vaccine against *Streptococcus pneumoniae* (pneumococcus), which causes pneumonia in mammals. In 1931, he performed a classic experiment with the bacterium. He noticed that when these bacteria are grown on culture plates, some, called S strain bacteria, produce shiny, smooth colonies and others, called R strain bacteria, produce colonies that have a rough appearance. Under the microscope, S strain bacteria have a capsule (mucous coat) that makes them smooth, but R strain bacteria do not.

When Griffith injected mice with the S strain of bacteria, the mice died, but when he injected mice with the R strain, the mice did not die (Fig. 3.1). In an effort to determine whether the capsule alone was responsible for the virulence (ability to kill) of the S strain bacteria, he injected mice with heat-killed S strain bacteria. The mice did not die.

Finally, Griffith injected the mice with a mixture of heat-killed S strain and live R strain bacteria. Most unexpectedly, the mice died—and living S strain bacteria were recovered from the bodies! Griffith concluded that some substance necessary for the bacteria to produce a capsule and be virulent must have passed from the dead S strain bacteria to the living R strain bacteria, so that the R strain bacteria were *transformed* (Fig. 3.1*d*). This change in the phenotype of the R strain bacteria must have been due to a change in their genotype. Indeed, couldn't the transforming substance that passed from S strain to R strain be genetic material? Reasoning such as this prompted investigators at the time to begin looking for the transforming substance to determine the chemical nature of the genetic material.

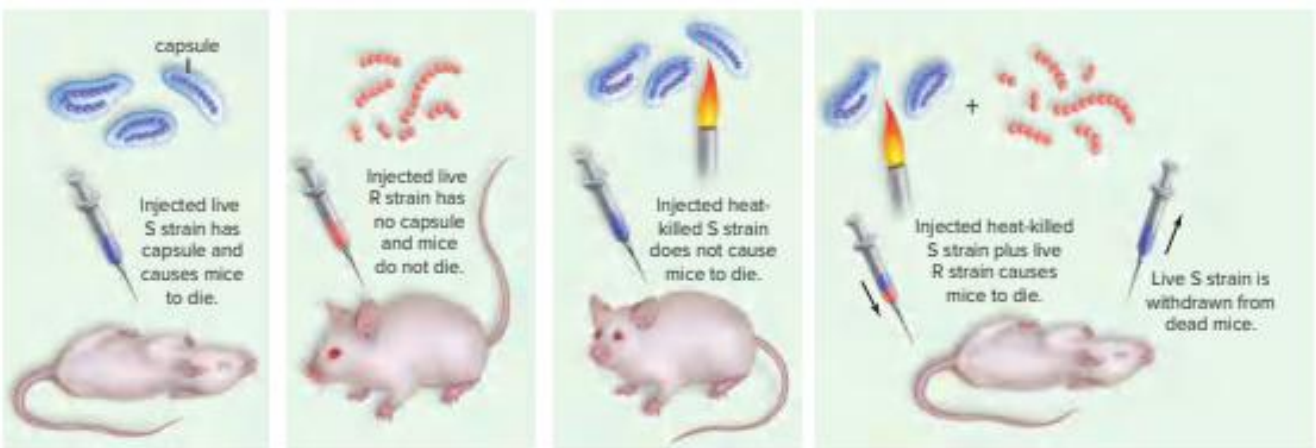


Figure 3.1 Griffith's transformation experiment. **a.** Encapsulated S strain is virulent and kills mice. **b.** Nonencapsulated R strain is not virulent and does not kill mice. **c.** Heat-killed S strain bacteria do not kill mice. **d.** If heat-killed S strain and R strain are both injected into mice, they die, because the R strain bacteria have been transformed into the virulent S strain.

DNA: The Transforming Substance

By the time the next group of investigators, led by Oswald Avery (1877–1955) in the 1940s, began their work, it was known that the genes are on the chromosomes and that the chromosomes contain both proteins and nucleic acids. Investigators were having a very heated debate about whether protein or DNA was the genetic material. Many thought that the protein component of chromosomes must be the genetic material because proteins contain up to 20 different amino acids that can be sequenced in any particular way. On the other hand, nucleic acids—DNA and RNA—contain only four types of nucleotides as basic building blocks. Some argued that DNA did not have enough variability to be able to store information and be the genetic material.

In 1944, after 16 years of research, Oswald Avery and his coinvestigators, Colin MacLeod and Maclyn McCarty, published a paper demonstrating that the transforming substance that allows *Streptococcus* to produce a capsule and be virulent is DNA. This meant that DNA is the genetic material. Here is what they found out:

1. DNA from S strain bacteria causes R strain bacteria to be transformed, so that they can produce a capsule and be virulent.
2. The addition of DNase, an enzyme that digests DNA, prevents transformation from occurring. This supports the hypothesis that DNA is the genetic material.
3. The molecular weight of the transforming substance is large. This suggests the possibility of genetic variability.
4. The addition of enzymes that degrade proteins has no effect on the transforming substance, nor does RNase, an enzyme that digests RNA. This shows that neither protein nor RNA is the genetic material.

These experiments showed that DNA is the transforming substance and, therefore, the genetic material. Although some scientists remained skeptical, many felt that the evidence for DNA being the genetic material was overwhelming.

An experiment by Alfred Hershey and Martha Chase in the early 1950s helped to firmly establish DNA as the genetic material. Hershey and Chase used a virus called a T phage, composed of radioactively labeled DNA and capsid coat proteins, to infect *E. coli* bacteria. They discovered that the radioactive tracers for DNA, but not protein, ended up inside the bacterial cells, causing them to become transformed. Since only the genetic material could have caused this transformation, Hershey and Chase determined that DNA must be the genetic material (Fig. 3.2).

The Structure of DNA

By the early 1950s, DNA was widely accepted as the genetic material of all living organisms. However. the structure of DNA was not known. How can a molecule with only four different nucleotides produce the great diversity of life on Earth?

To understand the structure of DNA, we need to understand how the bases in DNA are composed. Investigators knew that DNA contains four different types of nucleotides: two with *purine* bases, **adenine** (**A**) and **guanine** (**G**), which have a double ring; and two with *pyrimidine* bases, **thymine** (**T**) and **cytosine** (**C**), which have a single ring (Fig. 3.3*a, b*). Erwin Chargaff used new chemical techniques developed in the 1940s to analyze in detail the base content of DNA.

A sample of Chargaff's data is seen in Figure 3.3*c*. You can see that while some species—*E. coli* and *Zea mays* (corn), for example—do

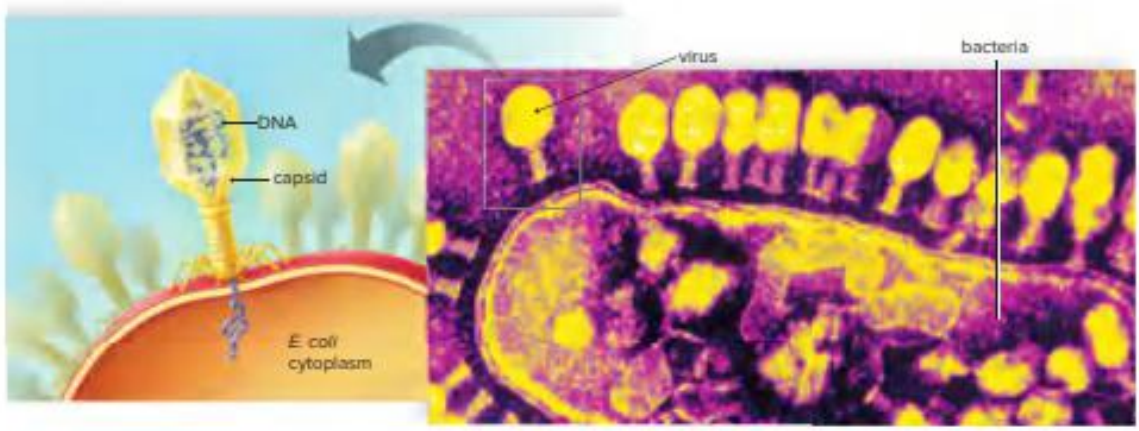
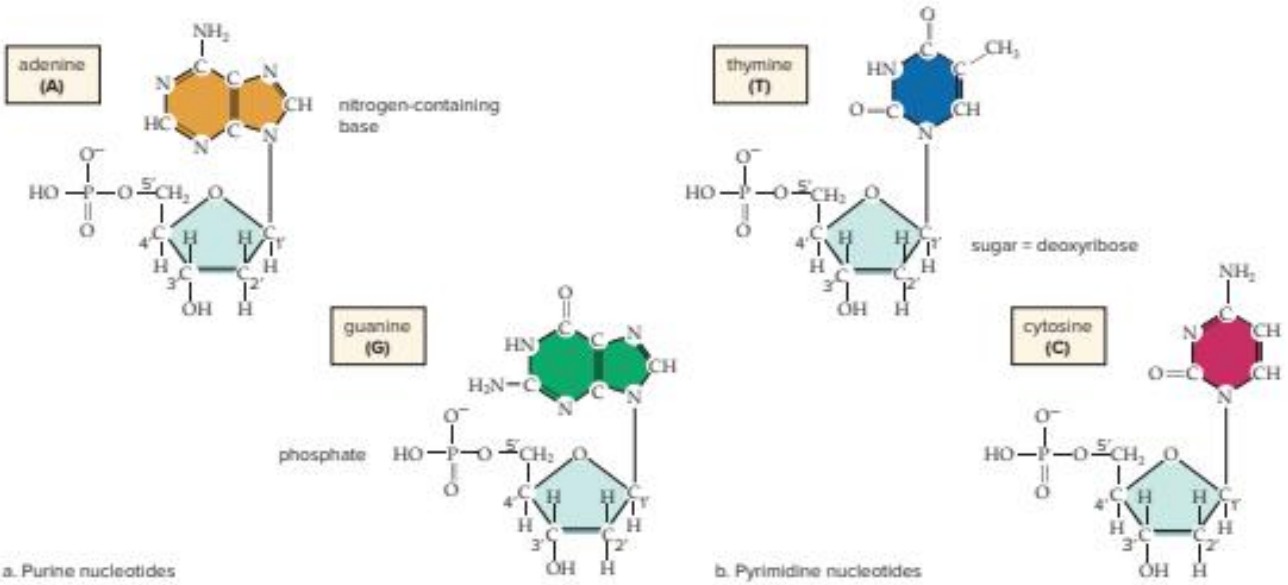


Figure 3.2 The tools of Hershey and Chase. **a.** Drawing of a T phage showing the protein coat (capsid) and DNA. **b.** An electron micrograph showing T phage infecting bacteria. The DNA was labeled with radioactivity, allowing Hershey and Chase to follow its progress into a bacterial cell and eventually provide a blueprint to make new phages.



DNA Composition in Various Species (%)				
Species	**A**	**T**	**G**	**C**
Homo sapiens (human)	31.0	31.5	19.1	18.4
Drosophila melanogaster (fruit fly)	27.3	27.6	22.5	22.5
Zea mays (corn)	25.6	25.3	24.5	24.6
Neurospora crassa (fungus)	23.0	23.3	27.1	26.6
Escherichia coli (bacterium)	24.6	24.3	25.5	25.6
Bacillus subtilis (bacterium)	28.4	29.0	21.0	21.6

c. Chargaff's data

Figure 3.3 Nucleotide composition of DNA. All nucleotides contain phosphate, a 5-carbon sugar, and a nitrogen-containing base. In DNA, the sugar is called deoxyribose, because it lacks an oxygen atom in the 2′ position, compared to ribose. The nitrogen-containing bases are **(a)** the purines adenine and guanine, which have a double ring, and **(b)** the pyrimidines thymine and cytosine, which have a single ring. **c.** Chargaff's data show that the DNA of various species differs. For example, in humans the A and T percentages are about 31%, but in fruit flies these percentages are about 27%.

have approximately 25% of each type of nucleotide, most do not. Further, the percentage of each type of nucleotide differs from species to species. Therefore, the nucleotide content of DNA is not fixed across species, and DNA does have the *variability* between species required for it to be the genetic material.

Within each species, however, DNA was found to have the *constancy* required of the genetic material—that is, all members of a species have the same base composition. Also, the percentage of A always equals the percentage of T, and the percentage of G equals the percentage of C. It follows that if the percentage of A + T equals 40%, then the percentage of G + C equals 60%. These relationships are called Chargaff's rules.

Chargaff's rules:

1. The amount of A, T, G, and C in DNA varies from species to species.
2. In each species, the amount of A = T and the amount of G = C.

Although only one of four bases is possible at each nucleotide position in DNA, the sheer number of bases and the length of most DNA molecules are more than sufficient to provide for variability. For example, it has been calculated that each human chromosome typically contains about 140 million base pairs. This provides for a staggering number of possible sequences of nucleotides. Because any of the four possible nucleotides can be present at each nucleotide position, the total number of possible nucleotide sequences is $4^{(140 \times 10^6)}$, or $4^{140,000,000}$. No wonder each species has its own unique base percentages!

X-Ray Diffraction of DNA

Rosalind Franklin (Fig. 3.4*a*), a researcher at King's College in London, studied the structure of DNA using X-rays. She found that if a concentrated, viscous solution of DNA is made, it can be separated into fibers. Under the right conditions, the fibers are enough like a crystal (a solid substance whose atoms are arranged in a definite manner) that when X-rayed, an X-ray diffraction pattern results (Fig. 3.4*b*).

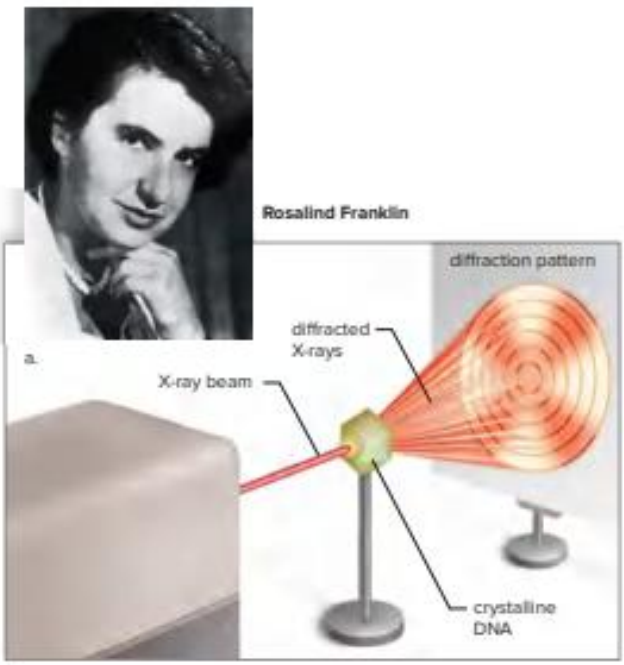


Figure 3.4 X-ray diffraction of DNA. **a.** Rosalind Franklin (1920–1958). **b.** When a crystal is X-rayed, the way in which the beam is diffracted reflects the pattern of the molecules in the crystal. The closer together two repeating structures are in the crystal, the farther from the center the beam is diffracted. **c.** The diffraction pattern of DNA produced by Rosalind Franklin. The crossed (X) pattern in the center told investigators that DNA is a helix, and the dark portions at the top and the bottom told them that some feature is repeated over and over. Watson and Crick determined that this feature was the hydrogen-bonded bases.

The X-ray diffraction pattern of DNA shows that DNA is a double helix. The helical shape is indicated by the crossed (X) pattern in the center of the photograph in Figure 3.4c. The dark portions at the top and bottom of the photograph indicate that some portion of the helix is repeated. Maurice H. F. Wilkins, a colleague of Franklin's, showed one of her crystallographic patterns to James Watson, who immediately grasped its significance.

The Watson and Crick Model

James Watson, an American, was on a postdoctoral fellowship at Cavendish Laboratories in Cambridge, England, when he began to work with the biophysicist Francis H. C. Crick. Using the data provided from X-ray diffraction and other sources, they constructed a model of DNA, for which they received a Nobel Prize in 1962.

Based on previous work of other scientists, Watson and Crick knew that DNA is a polymer of nucleotides, but they did not know how the nucleotides were arranged within the molecule. However, they deduced that DNA is a **double helix** with sugar-phosphate backbones on the outside and paired bases on the inside. This arrangement fits the mathematical measurements provided by Franklin's X-ray diffraction data for the spacing between the base pairs (0.34 nm) and for a complete turn of the double helix (3.4 nm).

According to Watson and Crick's model, the two DNA strands of the double helix are *antiparallel*, meaning that the sugar-phosphate groups that are chained together to make each strand are oriented in opposite directions. As seen in Figure 3.5, each nucleotide possesses a phosphate group located at the 5′ position of the sugar. Nucleotides are joined together by linking the 5′ phosphate of one nucleotide to a free hydroxyl (–OH) located at the 3′ position on the sugar of the preceding nucleotide, giving the molecule directionality. *Antiparallel* simply means that while one DNA strand runs 5′ to 3′, the other strand runs in a parallel but opposite direction.

This model also agreed with Chargaff's rules, which state that A = T and G = C. Figure 3.5 shows that A is hydrogen-bonded to T, and G is hydrogen-bonded to C. This **complementary base pairing** means that a purine (large, two-ring base) is always bonded to a pyrimidine (smaller, one-ring base). This antiparallel pairing arrangement of the two strands ensures that the bases are oriented properly, so that they can interact. The consistent spacing between the two strands of the DNA was detected by Franklin's X-ray

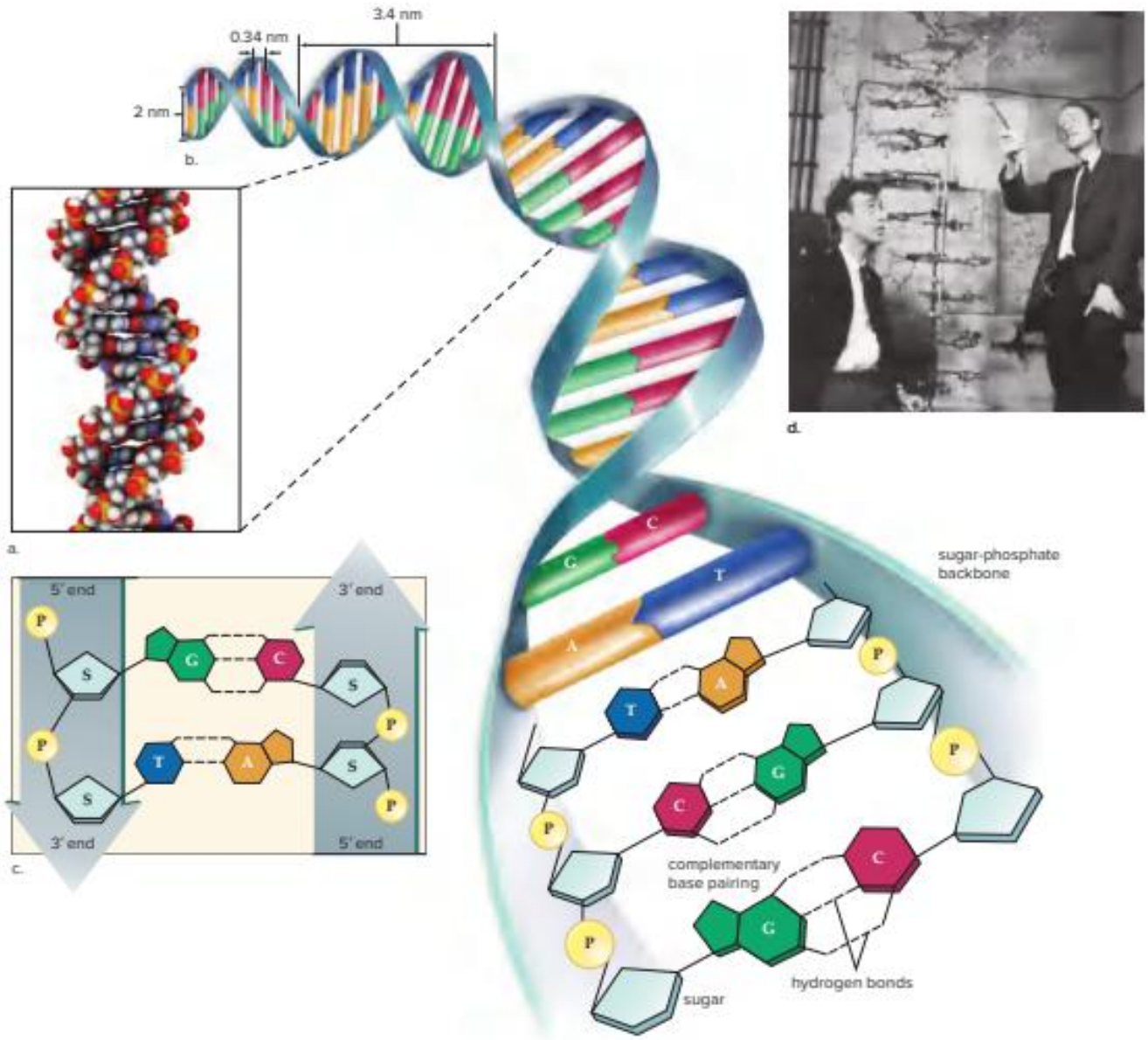


Figure 3.5 Watson and Crick model of DNA.
a. Space-filling model of DNA. **b.** The double helix molecules. **c.** The two strands of the molecule are antiparallel. The direction of the strand is said to be 5′ to 3′ when going from top to bottom. The 5′ end of a DNA strand has a phosphate group, while the 3′ end has an –OH group (not shown). **d.** James Watson (*left*) and Francis Crick (*right*) deduced the molecular configuration of DNA.

diffraction pattern, because two pyrimidines together are too narrow, and two purines together are too wide.

The information stored within DNA must always be read in the 5′ to 3′ direction. Thus, a DNA strand is usually replicated in a 5′ to 3′ direction.

Check Your Progress 3.1

1. Explain the major features of DNA structure.
2. Explain the roles of Erwin Chargaff and Rosalind Franklin in elucidating the final structure of DNA.

3.2 Replication of DNA

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain why the replication of DNA is semiconservative.
2. Describe the enzymes and proteins involved in DNA replication.
3. Contrast DNA replication in eukaryotes and prokaryotes.

The term **DNA replication** refers to the process of copying a DNA molecule. Following replication, there is usually an exact copy of the parental DNA double helix. As soon as Watson and Crick developed their double helix model, they commented, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

A **template** is most often a mold used to produce a shape complementary to itself. During DNA replication, each DNA strand of the parental double helix serves as a template for a new strand in a daughter molecule. DNA replication is termed **semiconservative replication,** because each daughter DNA double helix contains an old strand from the parental DNA double helix and a new strand. In Figure 3.6, the backbones of the parental DNA molecule are blue. Following replication, the daughter molecules each have a green backbone (new strand) and a blue backbone (old strand). Because A pairs with T, and G pairs with C, a daughter DNA double helix has the same sequence of bases as the parental DNA double helix had originally.

DNA replication requires three main steps: unwinding, complementary base pairing, and joining. At the molecular level, several enzymes and proteins participate in the synthesis of the new DNA strands (Fig. 3.7 and Table 3.1).

Unwinding

A **DNA helicase** enzyme unwinds DNA and separates the parental strands. This creates two replication forks that move away from each other. These separated strands now become the template to create two new DNA molecules. DNA is chemically stable as a helix, but not as single strands. **Single-stranded binding proteins** (**SSB**) attach to newly separated DNA and prevent it from re-forming the helix so replication can occur.

Table 3.1 Proteins Involved in DNA Replication

Protein Name	Function
DNA helicase	Separates double-stranded DNA into single strands
Single-stranded binding protein (SSB)	Binds to single-stranded DNA and prevents it from re-forming a double helix
DNA primase	Synthesizes short RNA primers
DNA polymerase	Synthesizes DNA in the leading and lagging strands, removes RNA primers filling the gaps with more DNA, and proofreads newly made DNA
DNA ligase	Covalently attaches adjacent Okazaki fragments in the lagging strand

Complementary Base Pairing

DNA replication needs a *primer,* a short strand of RNA, to put in place before replication can begin. **DNA primase** places short primers on the strands to be replicated. DNA polymerase recognizes this RNA target and begins DNA synthesis, allowing new nucleotides to form complementary base pairs with the old strand and connecting the new nucleotides together in a chain. DNA polymerase also proofreads the strands and can correct any mistakes.

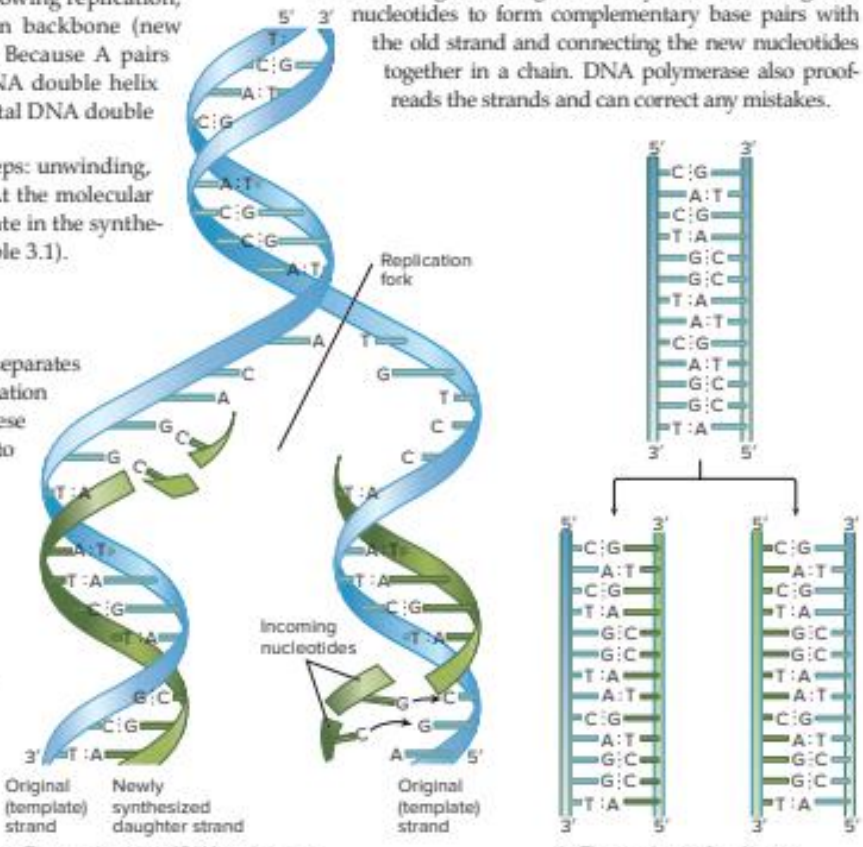


Figure 3.6 Semiconservative replication (simplified). After the DNA double helix unwinds, each parental strand serves as a template for the formation of the new daughter strands. Complementary free nucleotides hydrogen bond to a matching base (e.g., A with T; G with C) in each parental strand and are joined to form a complete daughter strand. Two helices, each with a daughter and parental strand, are produced following replication.

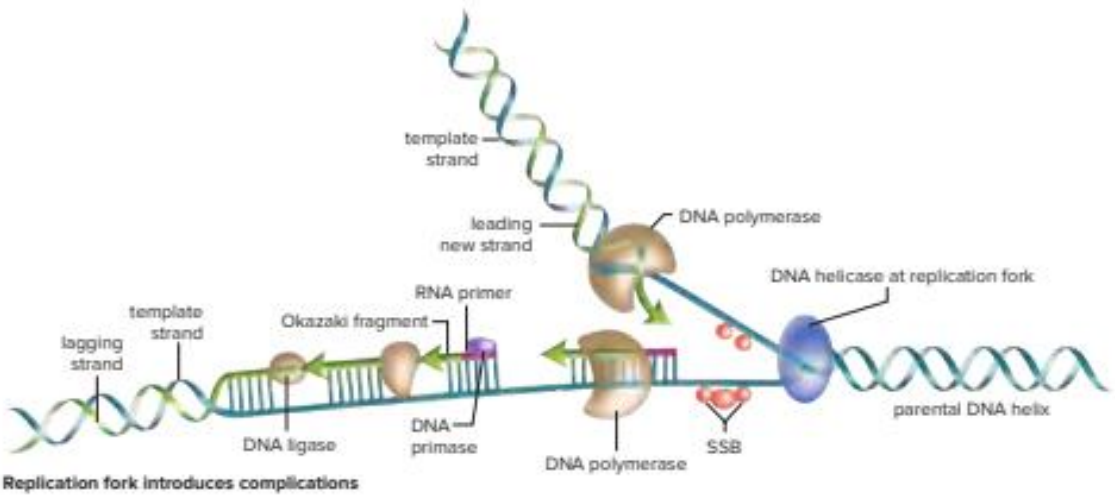


Figure 3.7 Enzymes in DNA replication. The major enzymes involved in DNA replication. Note that the synthesis of the new DNA molecules occurs in opposite directions due to the orientation of the original DNA strands.

The parental strands are antiparallel to each other, and each of the new daughter strands must also be antiparallel to its matching parental strand—which creates a problem. DNA can only be synthesized in a 5′ to 3′ direction (see Fig. 3.5c). One strand, the *leading strand*, is exposed so that synthesis in a 5′ to 3′ direction is easier and replication is continuous. The other new strand in the fork must be synthesized in the opposite direction, requiring DNA polymerase to synthesize the new strand in short 5′ to 3′ segments with periodic starts and stops. This strand is called the *lagging strand*. Replication of the lagging strand is therefore made in segments called *Okazaki fragments*, after Japanese scientist Reiji Okazaki, who discovered them.

Joining

After both new strands are made, DNA polymerase has yet another role by converting the short RNA sequences, laid down by the primase, into DNA.

Finally, the enzyme **DNA ligase** is the "glue" that mends all the Okazaki fragments together, resulting in the two double helix molecules that are identical to each other and to the original molecule.

The DNA is copied during S phase of the cell cycle before the start of mitosis or meiosis. Because the goal of these processes is either to create an exact cell copy (mitosis) or to make a gamete for reproduction (meiosis), in either case you have to double the DNA before you can separate it during cell division. DNA replication must occur before a cell can divide. Cancer, which is characterized by rapid, uncontrolled cell division, is sometimes treated with chemotherapeutic drugs that mimic one of the four nucleotides in DNA. When these are mistakenly used by the cancer cells to synthesize DNA, replication stops and the cells die off.

Prokaryotic Versus Eukaryotic Replication

The process of DNA replication is distinctly different in prokaryotic and eukaryotic cells, although many of these organisms' basic functions are similar (Fig. 3.8).

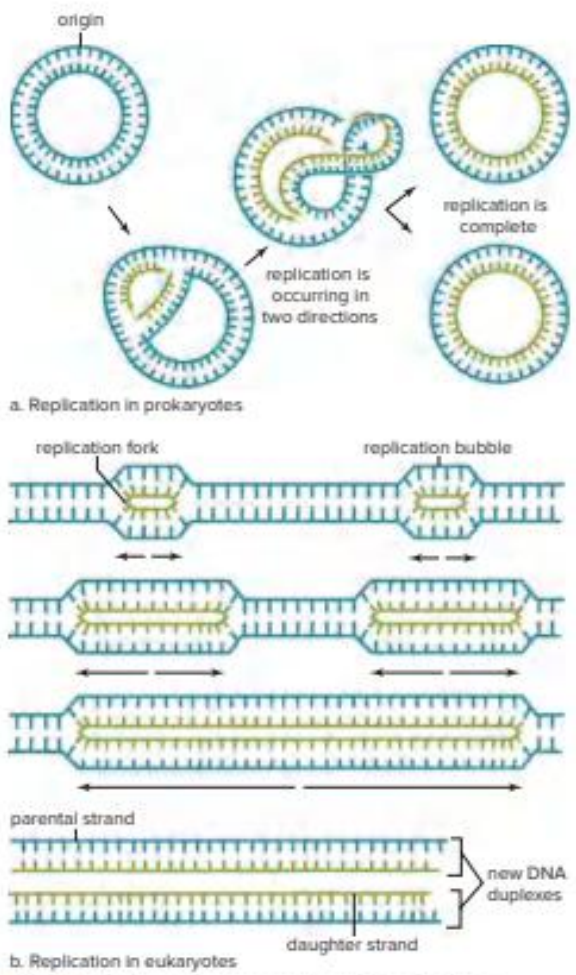


Figure 3.8 Prokaryotic versus eukaryotic replication.
a. In prokaryotes, replication can occur in two directions at once, because the DNA molecule is circular. **b.** In eukaryotes, replication occurs at numerous replication bubbles, each with two forks. The forks move away from each other until they meet again and the two new daughter helices have been completed.

Prokaryotic DNA Replication

Bacteria have a single circular loop chromosome, whose DNA must be replicated before the cell divides. In some circular DNA molecules, replication moves around the DNA molecule in one direction only. In others, as shown in Figure 3.8*a*, replication occurs in two directions. The process always occurs in the 5′ to 3′ direction.

The process begins at the *origin of replication*, a specific site on the bacterial chromosome. The strands are separated and unwound, and a DNA polymerase enzyme binds to each side of the opening and begins the copying process. When the two DNA polymerases meet at a termination region, replication is halted, and the two copies of the chromosome are separated.

Bacterial cells require about 40 minutes to replicate the complete chromosome. Because bacterial cells are able to divide as often as once every 20 minutes, it is possible for a new round of DNA replication to begin even before the previous round is completed!

Eukaryotic DNA Replication

In eukaryotes, DNA replication begins at numerous origins of replication along the length of the linear chromosome, and replication bubbles spread bidirectionally until they meet. Notice in Figure 3.8*b* that there is a V shape wherever DNA is being replicated. This is called a **replication fork.**

The chromosomes of eukaryotes are long, making replication a more time-consuming process. Eukaryotes replicate their DNA at a slower rate—500 to 5,000 base pairs per minute—but there are many individual origins of replication to accelerate the process. Therefore, eukaryotic cells complete the replication of the diploid amount of DNA (in humans, over 6 billion base pairs) in a matter of hours!

The linear chromosomes of eukaryotes also pose another problem: DNA polymerase is unable to replicate the ends of the chromosomes. The ends of eukaryotic chromosomes are composed of telomeres, which are short DNA sequences that are repeated over and over. Telomeres are not copied by DNA polymerase; rather, they are added by an enzyme called telomerase, which adds the correct number of repeats after the chromosome is replicated. In stem cells, this process preserves the ends of the chromosomes and prevents the loss of DNA after successive rounds of replication. Unregulated telomerase activity can negatively affect cell function, as seen with uncontrolled cell division in cancer cells.

Accuracy of Replication

A DNA polymerase is very accurate and makes a mistake approximately once per 100,000 base pairs at most. This error rate, however, would result in many errors accumulating over the course of several cell divisions. DNA polymerase is also capable of checking for accuracy, or proofreading the daughter strand it is making. It can recognize a mismatched nucleotide and remove it from a daughter strand by reversing direction and removing several nucleotides. Once it has removed the mismatched nucleotide, it changes direction again and resumes making DNA. Overall, the error rate for the bacterial DNA polymerase is only 1 in 100 million base pairs!

Check Your Progress 3.2

1. Explain the three major steps in DNA replication.
2. Explain why replication must occur differently on the leading and lagging strands.
3. Compare DNA replication in prokaryotes and eukaryotes.

3.3 The Genetic Code of Life

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain the function of transcription and translation.
2. Explain how the mRNA nucleotides determine the sequence of amino acids in a polypeptide.

Evidence began to mount in the 1900s that metabolic disorders can be inherited. An English physician, Sir Archibald Garrod, called them "inborn errors of metabolism." Investigators George Beadle and Edward Tatum, working with red bread mold, proposed what they called the "one gene, one enzyme hypothesis," based on the observation that a defective gene caused a defective enzyme.

This and many other examples illustrate the flow of genetic information from DNA to RNA to protein to an observed trait. We now turn our attention to the transfer of information from DNA to RNA, the next component in the system.

RNA Carries the Information

Like DNA, *RNA* (*ribonucleic acid*) is a polymer composed of nucleotides. The nucleotides in RNA, however, contain the sugar ribose and the bases adenine (A), cytosine (C), guanine (G), and **uracil** (U). In RNA, the base uracil replaces the thymine found in DNA. Finally, RNA is single-stranded and does not form a double helix in the same manner as DNA (Table 3.2 and Fig. 3.9).

There are three major classes of RNA. Each class has a unique size, shape, and function in protein synthesis.

Messenger RNA (**mRNA**) takes a message from DNA in the nucleus to the ribosomes in the cytoplasm.
Transfer RNA (**tRNA**) transfers amino acids to the ribosomes.
Ribosomal RNA (**rRNA**), along with ribosomal proteins, makes up the ribosomes, where polypeptides are synthesized.

Table 3.2 RNA Structure Compared to DNA Structure

	RNA	DNA
Sugar	Ribose	Deoxyribose
Bases	Adenine, guanine, uracil, cytosine	Adenine, guanine, thymine, cytosine
Strands	Single-stranded	Double-stranded with base pairing
Helix	No	Yes

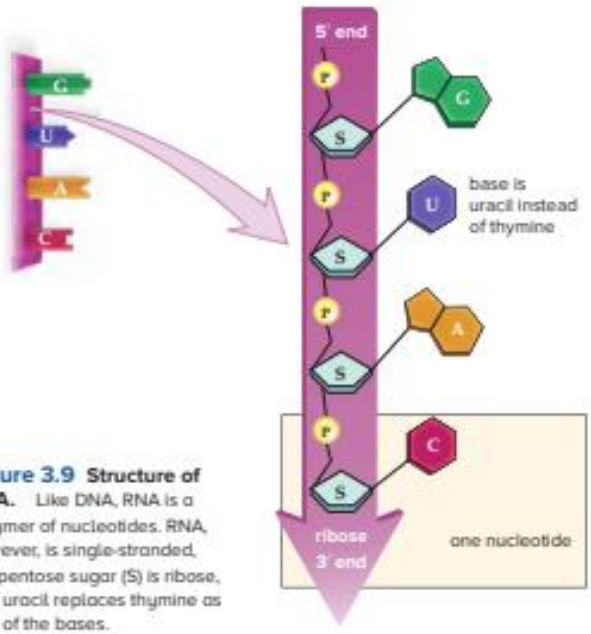


Figure 3.9 Structure of RNA. Like DNA, RNA is a polymer of nucleotides. RNA, however, is single-stranded, the pentose sugar (S) is ribose, and uracil replaces thymine as one of the bases.

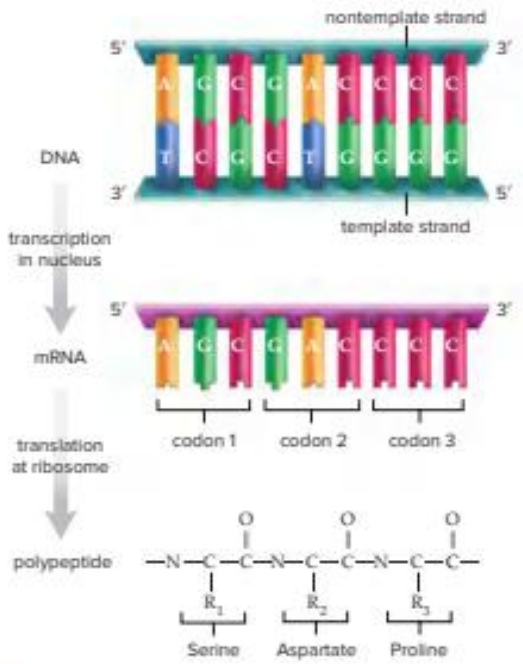


Figure 3.10 The flow of genetic information in a cell. One strand of DNA acts as a template for mRNA synthesis, and the sequence of bases in mRNA determines the sequence of amino acids in a polypeptide.

The Genetic Code

In the genetic flow of information, two major steps are needed to convert the information stored in DNA into a protein that supports body function (Fig. 3.10). First, the DNA undergoes **transcription** (L. *trans,* "across"; *scriptio,* "a writing"), a process by which an RNA molecule is produced based on a DNA template. DNA is transcribed, or copied base by base, into mRNA, tRNA, and rRNA.

Second, during **translation** (L. *trans,* "across"; *latus,* "carry or bear"), the mRNA transcript is read by a ribosome and converted into the sequence of amino acids in a polypeptide. Like a translator who understands two languages, the cell changes a nucleotide sequence into an amino acid sequence. Together, the flow of information from DNA to RNA to protein to trait is known as the **central dogma** of molecular biology.

Now that we know that the DNA sequence within a gene is transcribed into an RNA molecule and, for genes that code for proteins, the mRNA sequence determines the sequence of amino acids in a protein, it becomes necessary to identify the specific **genetic code** for each of the 20 amino acids found in proteins. Although scientists knew that DNA somehow directed protein production, they did not initially know specifically how the code was translated. This discovery was made in the 1960s.

Finding the Genetic Code

Logically, the genetic code would have to be at least a **triplet code;** that is, each coding unit, or **codon,** would need to be made up of three nucleotides. The reason is that fewer nucleotides would not provide sufficient variety to encode 20 different amino acids.

In 1961, Marshall Nirenberg and J. Heinrich Matthei performed an experiment that laid the groundwork for cracking the genetic code. First, they found that a cellular enzyme could be used to construct a synthetic RNA (one that does not occur in cells), and then they found that the synthetic RNA polymer could be translated in a test tube that contained the cytoplasmic contents of a cell. Their first synthetic RNA was composed only of uracil, and the protein that resulted was composed only of the amino acid phenylalanine. Therefore, the mRNA codon for phenylalanine was known to be UUU. Later, they were able to translate just three nucleotides at a time; in that way, it was possible to assign an amino acid to each of the mRNA codons (Fig. 3.11).

Like the periodic table and other major works, the genetic code seen in Figure 3.11 is a masterpiece of scientific discovery, because it is a key that unlocks the very basis of biological life. Here are some of its features:

1. The genetic code is *degenerate.* This term means that most amino acids have more than one codon; leucine, serine, and arginine have six different codons, for example. The degeneracy (redundancy) of the code helps protect against potentially harmful mutations.
2. The genetic code is *unambiguous.* Each triplet codon has only one meaning.
3. The code has *start and stop signals.* There is only one start signal, but there are three stop signals.

The Code Is Universal

With a few exceptions, the genetic code (Fig. 3.11) is universal to all living organisms. In 1979, however, researchers discovered

First Base	Second Base				Third Base
	U	C	A G		
U	UUU phenylalanine	UCU serine	UAU tyrosine	UGU cysteine	U
	UUC phenylalanine	UCC serine	UAC tyrosine	UGC cysteine	C
	UUA leucine	UCA serine	UAA stop	UGA stop	A
	UUG leucine	UCG serine	UAG stop	UGG tryptophan	G
C	CUU leucine	CCU proline	CAU histidine	CGU arginine	U
	CUC leucine	CCC proline	CAC histidine	CGC arginine	C
	CUA leucine	CCA proline	CAA glutamine	CGA arginine	A
	CUG leucine	CCG proline	CAG glutamine	CGG arginine	G
A	AUU isoleucine	ACU threonine	AAU asparagine	AGU serine	U
	AUC isoleucine	ACC threonine	AAC asparagine	AGC serine	C
	AUA isoleucine	ACA threonine	AAA lysine	AGA arginine	A
	AUG (start) methionine	ACG threonine	AAG lysine	AGG arginine	G
G	GUU valine	GCU alanine	GAU aspartate	GGU glycine	U
	GUC valine	GCC alanine	GAC aspartate	GGC glycine	C
	GUA valine	GCA alanine	GAA glutamate	GGA glycine	A
	GUG valine	GCG alanine	GAG glutamate	GGG glycine	G

Figure 3.11 Messenger RNA codons. Notice that in this chart each of the codons (in boxes) is composed of three letters representing the first base, second base, and third base. For example, find the box where C for the first base and A for the second base intersect. You will see that U, C, A, or G can be the third base. The bases CAU and CAC are codons for histidine; the bases CAA and CAG are codons for glutamine.

that the genetic code used within the mitochondria, chloroplasts, and some archaebacteria, differs slightly from the more familiar genetic code.

The universal nature of the genetic code provides strong evidence that all living organisms share a common evolutionary heritage. Because the same genetic code is used by all living organisms, it is possible to transfer genes from one organism to another. Many commercial and medicinal products, such as human insulin, can be produced in this manner. The Nature of Science feature, "Moving Genes Between Species: Green Fluorescent Protein and Cells," on page 219 demonstrates that the gene for GFP could be transferred from jellyfish to a number of other organisms to cause a fluorescent green color. This is made possible only because the genetic code is universal.

Check Your Progress 3.3

1. Examine the flow of genetic information in a cell.
2. Describe the three major classes of RNA; what is the function of each class?
3. Explain why the genetic code is said to be degenerate.

3.4 First Step: Transcription

Learning Outcomes

Upon completion of this section, you should be able to

1. Distinguish among the events of transcription that occur during formation of an mRNA molecule.
2. Describe how eukaryotic mRNA molecules are processed and exported to the cytoplasm.

During *transcription*, a segment of the DNA serves as a template for the production of an RNA molecule. Although mRNA, tRNA, and rRNA are all produced by transcription, we focus here on transcription to make mRNA, the type of RNA that eventually leads to building a protein.

Messenger RNA Is Produced

The sequences of bases in a gene are transcribed into an mRNA molecule based on complementary base pairing: The T base in the DNA pairs with A in the mRNA, G with C, and A with U (note that uracil replaces T in the newly formed mRNA) (Fig. 3.12). When a gene is transcribed, a segment of the DNA helix unwinds and unzips, and complementary RNA nucleotides pair with DNA nucleotides of the strand opposite the gene. This strand is known as the *template strand;* the other strand is the gene strand. An **RNA polymerase** joins the nucleotides together in the 5′ to 3′ direction. Like DNA polymerase, an RNA polymerase adds a nucleotide only to the 3′ end of the polymer under construction.

Transcription begins when RNA polymerase attaches to a region of DNA called a promoter (Fig. 3.12). A **promoter** defines the start of transcription, the direction of transcription, and the strand to be transcribed. The binding of RNA polymerase to the promoter is the *initiation* of transcription. The RNA-DNA association is not as stable as the two strands in the DNA helix. Therefore, only the newest portion of an RNA molecule that is associated with RNA polymerase is bound to the DNA, and the rest dangles off to the side.

Elongation of the mRNA molecule occurs as the RNA polymerase reads down the DNA template strand in a 5′ to 3′ direction and continues until RNA polymerase comes to a DNA stop sequence, where *termination* occurs. The stop sequence causes RNA polymerase to stop transcribing the DNA and to release the mRNA molecule, now called an **mRNA transcript.**

It is not necessary for RNA polymerase to finish making one mRNA transcript before it starts another. As long as they have access to the gene's promoter, many RNA polymerase molecules can be working one after the other to produce mRNA transcripts at the same time (Fig. 3.13*a*). This allows the cell to produce many thousands of copies of the same mRNA molecule, and eventually many copies of the same protein, within a shorter period of time than if a single mRNA copy were used to direct protein synthesis. This ability to rapidly express the gene enables the cell (and the organism) to better respond to changing environmental conditions and have a greater chance at survival.

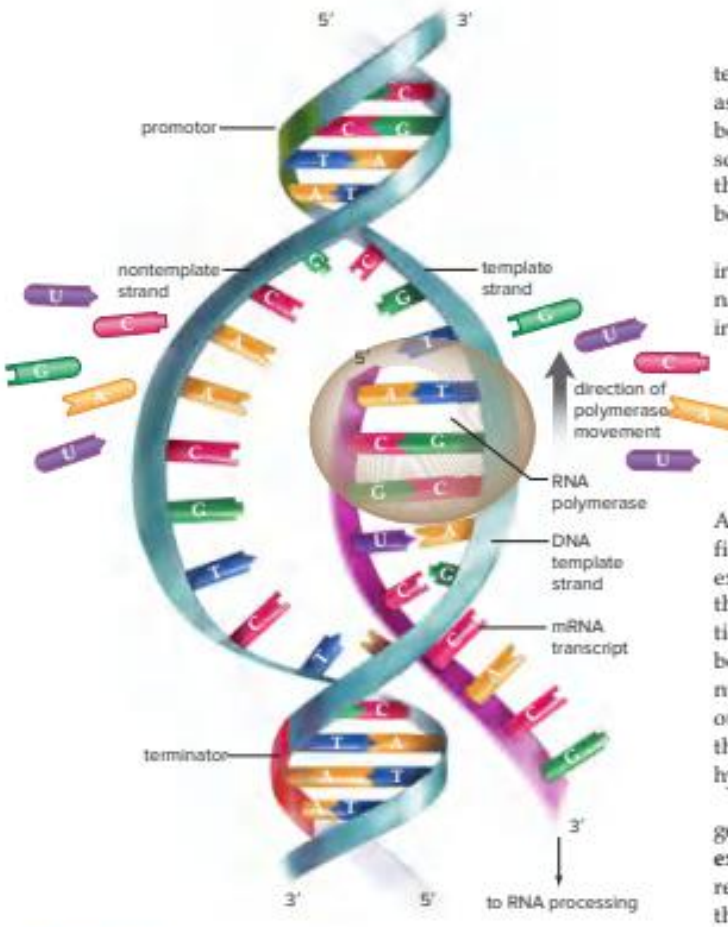


Figure 3.12 Transcription. During transcription, the complementary mRNA is made from a DNA template. At the point of attachment of RNA polymerase, the DNA helix unwinds and unzips, and complementary RNA nucleotides are joined together. After RNA polymerase has passed by, the DNA strands rejoin and the mRNA transcript dangles to the side.

Note that, for a given gene, either strand of the DNA can be a template strand. In Figure 3.12, RNA polymerase uses one strand as the template, but for another gene, the opposite strand may be the template. Assuming both genes are on the same chromosome, and therefore the same piece of DNA, can you think what the orientation of the template strand in the second gene might be? (*Hint:* Consider the directionality of RNA polymerase.)

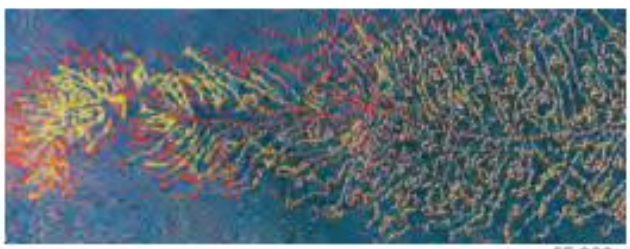
Some species of *Amanita* mushrooms, such as the Destroying Angel and Death Cap, are so named because of their toxic nature. The *Amanita* produces a toxin called α-amanitin, which inhibits the function of RNA polymerase (Fig. 3.13*b*). The *Amanita* mushrooms are responsible for 95% of all mushroom poisonings and can often lead to a quick death due to the destruction of a person's liver.

RNA Molecules Undergo Processing

A newly formed RNA transcript, called a pre-mRNA, is modified or processed before leaving the eukaryotic nucleus. For example, the molecule receives a cap at the 5′ end and a tail at the 3′ end (Fig. 3.14). The *cap* is a modified guanine (G) nucleotide that helps tell a ribosome where to attach when translation begins. The tail consists of a chain of 150–200 adenine (A) nucleotides. This *poly-A tail* facilitates the transport of mRNA out of the nucleus, helps initiate loading of ribosomes and the start of translation, and delays degradation of mRNA by hydrolytic enzymes.

When the mRNA is first made by RNA polymerase from the gene, it is in a rough form. Called pre-mRNA, it contains a mix of **exons** (protein-coding regions) and **introns** (non-protein-coding regions), particularly in multicellular eukaryotes. Because only the exons of the pre-mRNA will be contained in the mature mRNA, the introns, which occur in between the exons, must be spliced out. An easy way to remember this is with the phrase "exons are *expressed* and introns are *in the way*."

In lower eukaryotes, introns are removed by "self-splicing"—that is, the intron itself has the capability of enzymatically splicing



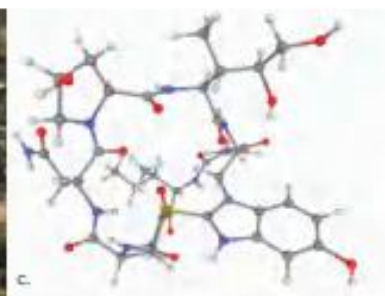


Figure 3.13 RNA polymerase. **a.** Numerous RNA transcripts extend from a horizontally oriented gene in an amphibian egg cell. The strands get progressively longer because transcription begins to the left. **b.** The α-amanitin toxin from *Amanita* mushrooms inhibits the activity of (**c**) RNA polymerase.

BIG IDEA 3: Information Storage, Transmission, and Response

Moving Genes Between Species: Green Fluorescent Protein and Cells

Most cells lack any significant pigmentation. Thus, cell biologists frequently rely on dyes to produce enough contrast to resolve (view) organelles and other cellular structures. The first of these dyes was developed in the nineteenth century from chemicals used to stain clothes in the textile industry. Since then, significant advances have occurred in the development of cellular stains.

In 2008, three scientists—Martin Chalfie, Roger Y. Tsien, and Osamu Shimomura—earned the Nobel Prize in Chemistry or Medicine for their work with a protein called *green fluorescent protein*, or *GFP*. GFP is a bioluminescent protein found in the jellyfish *Aequorea victoria*, commonly called the crystal jelly (Fig. 3A*a*). The crystal jelly is a native of the West Coast of the United States. This jellyfish is normally transparent, but when disturbed it releases a fluorescent protein called aequorin, which fluoresces with a green color. The scientists were able to isolate the fluorescent protein from the jellyfish and develop it as a molecular tag. The molecular tag works by inserting the *GFP* gene just after the promoter region of another gene in a different organism. RNA polymerase binds to the promoter and initiates transcription of that gene. If the *GFP* gene is inserted correctly, it can be expressed (glow) in organisms other than the crystal jellyfish.

These tags can be generated for almost any protein within the cell, revealing not only its cellular location but also how its distribution within the cell may change as a result of a response to its environment. Figure 3A*b* shows fluorescent GloFish®, first developed to glow in the presence of water pollution. They are now widely available for purchase as pets. Figure 3A*c* shows how a GFP-labeled antibody can be used to identify the cellular location of the actin proteins in a human cell. Actin is one of the prime components of the cell's microfilaments, which in turn are part of the cytoskeleton of the cell. This image shows the distribution of actin in a human cell.

Questions to Consider

1. Discuss how a researcher might use a GFP-labeled protein to study cancer.
2. Should this technology be applied to any type of pet?

a. b. c.

Figure 3A GFP as molecular tags. **a.** The jellyfish *Aequorea victoria*. **b.** GFP and other fluorescent proteins used to modify fish. **c.** Human cells tagged with a GFP-labeled antibody to the actin protein.

itself out of a pre-mRNA. In higher eukaryotes, the RNA splicing is done by spliceosomes, which contain *small nuclear RNAs* (*snRNAs*). By means of complementary base pairing, snRNAs are capable of identifying the introns to be removed. A spliceosome utilizes a **ribozyme** (enzyme made of RNA rather than just protein) to cut and remove the introns. Following splicing of the exons together and the addition of the 5′ cap and 3′ poly-A tail, an mRNA is ready to leave the nucleus and be translated into a protein.

Function of Introns

For many years, scientists thought that introns were simply wasted space within genes. Now, we realize they serve several key functions in the cell. The presence of introns allows a cell to choose which exons will go into a particular mRNA. Just because an mRNA has all the exons in its pre-mRNA doesn't mean they will all make it to the final product. For example, if a gene has three exons, then depending on cell need and environmental conditions, it may produce an mRNA with exons 1 and 2 only, or 1 and 3 only, or 1, 2, and 3. This ability is called *alternative mRNA splicing*, and it increases the flexibility and efficiency of the cell. The snRNAs of the spliceosomes that excise the introns play an important role in alternative splicing in eukaryotes.

Some introns give rise to *microRNAs* (*miRNAs*), which are small molecules involved in regulating the translation of mRNAs. These molecules bind with the mRNA through complementary base pairing and, in that way, prevent translation from occurring.

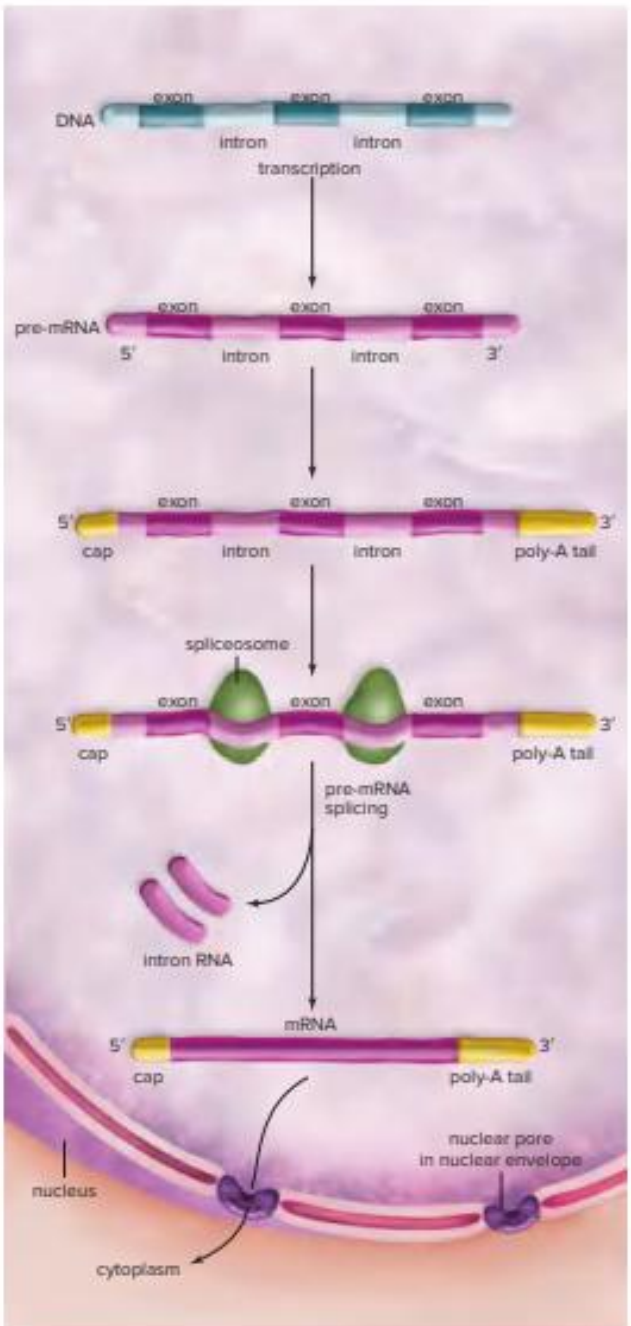


Figure 3.14 Messenger RNA (mRNA) processing in eukaryotes. DNA contains both exons (protein-coding sequences) and introns (non-protein-coding sequences). Both of these are transcribed and are present in pre-mRNA. During processing, a cap and a poly-A tail (a series of adenine nucleotides) are added to the molecule. Also, introns get cut out and the exons get spliced together by complexes called spliceosomes. Once processing is complete, the mRNA molecule is ready to leave the nucleus.

It is also possible that the presence of introns encourages crossing-over during meiosis, and this permits a phenomenon termed *exon shuffling*, which can play a role in the evolution of new genes.

Check Your Progress 3.4

1. Explain the role of RNA polymerase.
2. Describe the three major modifications that occur during the processing of an mRNA.
3. Distinguish between the introns and exons of a gene.
4. Explain the potential evolutionary benefits of alternative mRNA splicing.

3.5 Second Step: Translation

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the roles of mRNA, tRNA, and rRNA in translating the genetic code.
2. Examine the stages of translation and the events that occur during each stage.

Translation, which takes place in the cytoplasm of eukaryotic cells, is the second step needed to express a gene into a protein. During translation, the sequence of codons (nucleotide triplets) in the mRNA is read by a ribosome, which connects the sequence of amino acids dictated by the mRNA into a polypeptide. The process is called translation because it requires the conversion of information from a nucleic acid language (DNA and RNA) into an amino acid language (protein).

The Role of Transfer RNA

Transfer RNA (tRNA) molecules transfer amino acids to the ribosomes. A tRNA molecule is a single-stranded nucleic acid that doubles back on itself to create regions where complementary bases are hydrogen-bonded to one another. The structure of a tRNA molecule is generally drawn as a flat cloverleaf (Fig. 3.15*a*), but a space-filling model shows the molecule's actual three-dimensional shape (Fig. 3.15*b*).

There is at least one tRNA molecule for each of the 20 amino acids found in proteins. The amino acid binds to the 3′ end. The opposite end of the molecule contains an **anticodon,** a group of three bases that is complementary and antiparallel to a specific mRNA codon. For example, a tRNA that has the anticodon 5′ AAG 3′ binds to the mRNA codon 5′ CUU 3′ and carries the amino acid leucine. In the genetic code, 61 codons specify amino acids; the other 3 serve as stop sequences (see Fig. 3.11).

Approximately 40 different tRNA molecules are found in most cells. There are fewer tRNAs than codons, because some tRNAs can pair with more than one codon. In 1966, Francis Crick observed this phenomenon and called it the *wobble hypothesis*. He stated that the first two positions in a tRNA anticodon pair obey the A–U/G–C configuration rule. However, the third position can be variable.

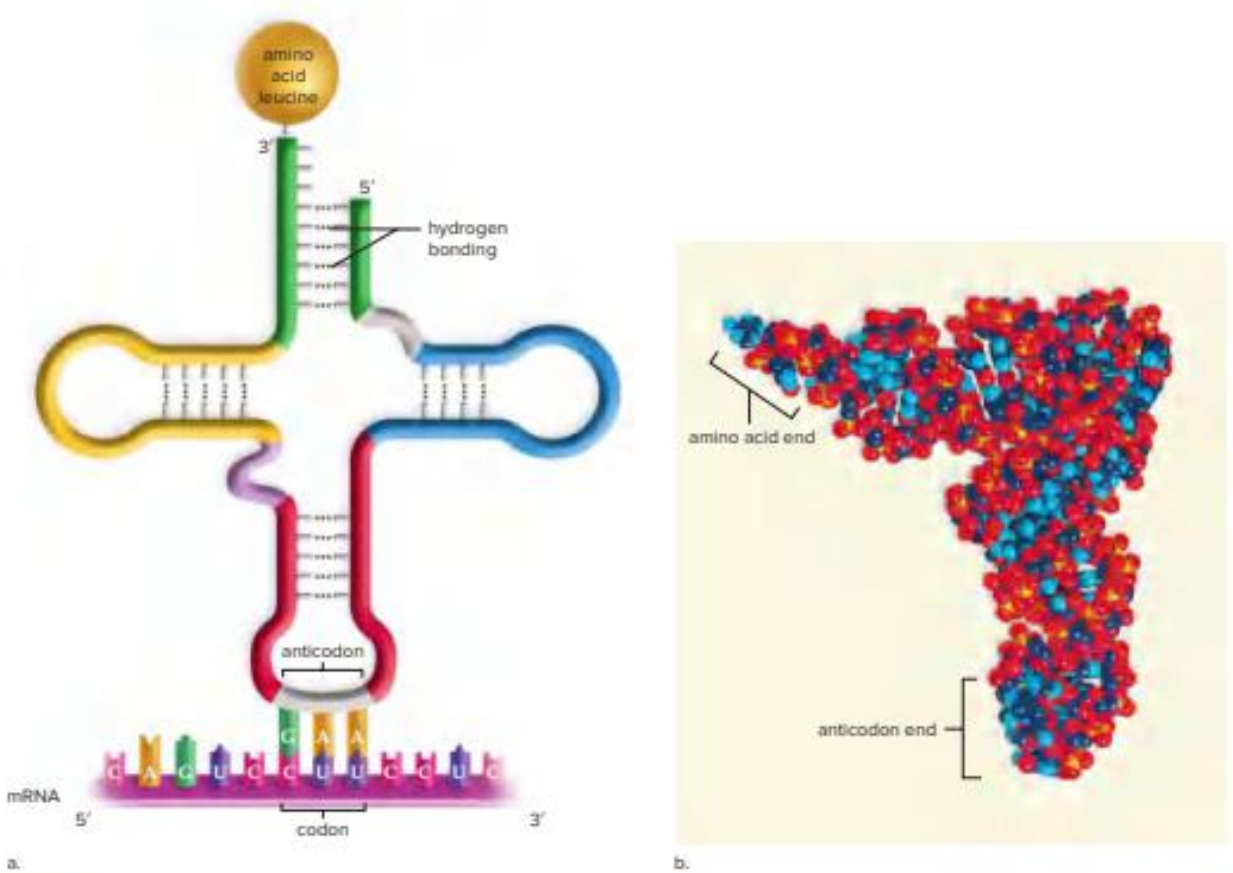


Figure 3.15 Structure of a transfer RNA (tRNA) molecule. **a.** Complementary base pairing indicated by hydrogen bonding occurs between nucleotides within the molecule, and this causes it to form its characteristic loops. The anticodon that base-pairs with a particular messenger RNA (mRNA) codon occurs at one end of the folded molecule; the other two loops help hold the molecule at the ribosome. An appropriate amino acid is attached at the 3′ end of the molecule in the cytoplasm by a tRNA charging enzyme. For this mRNA codon and tRNA anticodon, the specific amino acid is leucine. **b.** Space-filling model of tRNA molecule.

Some tRNA molecules can recognize as many as four separate codons differing only in the third nucleotide. The wobble effect helps ensure that despite changes in DNA base sequences, the resulting sequence of amino acids will produce a correct protein. This is one of the reasons the genetic code is said to be degenerate.

How does the correct amino acid become attached to the correct tRNA molecule? This task is carried out by amino acid–charging enzymes, generically called aminoacyl-tRNA synthetases. Just as a key fits a lock, each enzyme has a recognition site for a particular amino acid to be joined to a specific tRNA. For example, leucine-tRNA synthetase attaches the leucine amino acid to a tRNA with the correct anticodon. This is an energy-requiring process that uses ATP. A tRNA with its amino acid attached is termed a *charged tRNA*. Once the amino acid–tRNA complex is formed, it is added to the large pool of charged tRNAs that exist in the cytoplasm, where it can now be accessed by a ribosome during protein synthesis.

The Role of Ribosomal RNA

As with so many cellular structures, the structure of a ribosome is essential to its function.

Structure of a Ribosome

In eukaryotes, ribosomal RNA (rRNA) is produced from a DNA template in the nucleolus of a nucleus. The rRNA is packaged with a variety of proteins into two ribosomal subunits, one of which is larger than the other. The subunits then move separately through nuclear envelope pores into the cytoplasm, where they join together at the start of translation (Fig. 3.16*a*). Once translation begins, ribosomes can remain in the cytoplasm, or they can become attached to endoplasmic reticulum.

Function of a Ribosome

Both prokaryotic and eukaryotic cells contain thousands of ribosomes per cell, because they play such a significant role in protein synthesis. Ribosomes have a binding site for mRNA and three binding sites for transfer RNA (tRNA) molecules (Fig. 3.16*b*). The tRNA binding sites facilitate complementary base pairing between tRNA anticodons and mRNA codons. The large ribosomal subunit has enzyme activity from rRNA (a ribozyme) that creates the peptide bond between adjacent amino acids. This peptide bond is created many times to produce a polypeptide, which

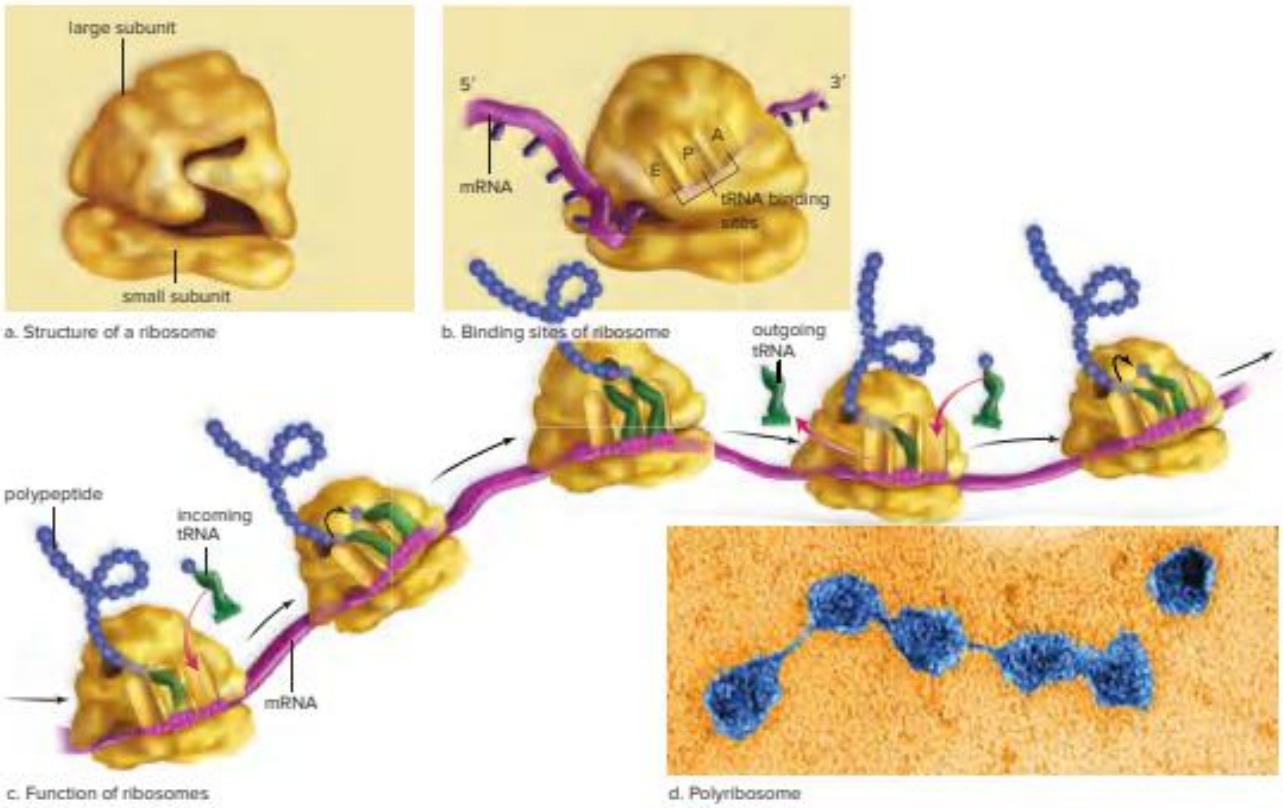


Figure 3.16 Ribosome structure and function. **a.** Side view of a ribosome shows a small subunit and a large subunit. **b.** Frontal view of a ribosome shows its binding sites. mRNA is bound to the small subunit, and the large subunit has three binding sites for tRNAs. **c.** Overview of protein synthesis. The tRNA bearing the growing polypeptide passes the entire chain to the new amino acid carried by the tRNA occupying the A site. The ribosome shifts, and freed of its burden, the "empty" tRNA exits. The new peptide-bearing tRNA moves over one binding site, making the A site accessible once again to a new tRNA. This cycle is repeated until the ribosome reaches the termination codon. **d.** Electron micrograph of a polyribosome, a number of ribosomes all translating the same mRNA molecule.

in turn folds into its three-dimensional shape and becomes a protein.

When a ribosome moves down an mRNA molecule, the polypeptide increases by one amino acid at a time (Fig. 3.16*c*). Translation terminates at a stop codon. Once translation is complete, the polypeptide dissociates from the translation complex and folds into its normal shape. Recall hat a polypeptide twists and bends into a definite shape based on the makeup of its amino acids. This folding process begins as soon as the polypeptide emerges from a ribosome. Chaperone molecules that are often present in the cytoplasm and the ER ensure that protein folding proceeds as it should. For proteins that contain more than one polypeptide, each subunit is folded first, and then subunits join together into a final, functional protein complex.

Like RNA polymerase during transcription, multiple ribosomes often attach and translate the same mRNA at one time. As soon as the initial portion of mRNA has been translated by one ribosome, and the ribosome has begun to move down the mRNA, another ribosome can attach to the mRNA. The entire complex of mRNA and multiple ribosomes is called a **polyribosome** (Fig. 3.16*d*), and it greatly increases the efficiency of translation.

Translation Requires Three Steps

During translation, the codons of an mRNA base-pair with the anticodons of tRNA molecules carrying specific amino acids. The order of the codons determines the order of the tRNA molecules at a ribosome and the corresponding sequence of amino acids in a polypeptide. The process of translation must be extremely orderly, so that the amino acids of a polypeptide are sequenced correctly. Even a single amino acid change has the potential to dramatically affect a protein's function, as is the case with individuals who carry the alleles for sickle-cell disease.

Protein synthesis involves three steps: initiation, elongation, and termination. Enzymes are required for each of the three steps to function properly. The first two steps, initiation and elongation, require energy.

Initiation

Initiation is the step that brings all the translation components together. Proteins called initiation factors are required to assemble the small ribosomal subunit, mRNA, initiator tRNA, and the large ribosomal subunit for the start of protein synthesis.

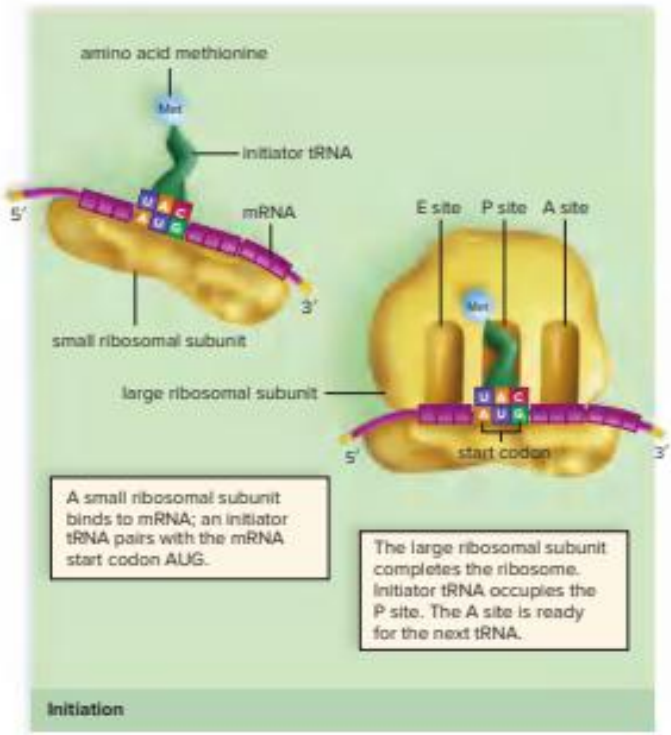


Figure 3.17 Initiation. In prokaryotes, participants in the translation process assemble as shown. The first amino acid is typically a special form of methionine.

Initiation is shown in Figure 3.17. In prokaryotes, a small ribosomal subunit attaches to the mRNA in the vicinity of the *start codon* (AUG). The first, or initiator, tRNA pairs with this codon. Then, a large ribosomal subunit joins to the small subunit (Fig. 3.17). Although similar in many ways, initiation in eukaryotes is much more complex.

As already discussed, a ribosome has three binding sites for tRNAs. One of these is called the E (for "exit") site, second is the P (for "peptide") site, and the third is the A (for "amino acid") site. The initiator tRNA binds to the P site, even though it carries only the amino acid methionine (see Fig. 3.11). The A site is where tRNA carrying the next amino acid enters the ribosome, and the E site is for any tRNAs that are leaving a ribosome. Following initiation, translation continues with elongation and then termination.

Elongation

Elongation is the stage during protein synthesis when a polypeptide increases in length one amino acid at a time. In addition to the necessary tRNAs, elongation requires elongation factors, which facilitate the binding of tRNA anticodons to mRNA codons within a ribosome.

Elongation is shown in Figure 3.18, where a tRNA with an attached peptide is already at the P site, and a tRNA carrying its appropriate amino acid is just arriving at the A site. Once a ribosome has verified that the incoming tRNA matches the codon and is firmly in place at the A site, the entire growing peptide will be transferred to the amino acid on the tRNA in the A site. A ribozyme, an rRNA-based enzyme that is a part of the large ribosomal subunit, uses energy to transfer the growing peptide and create a new peptide bond. Following peptide bond formation, the peptide is one amino acid longer than it was before. Next, *translocation* occurs: The ribosome moves forward, and the peptide-bearing

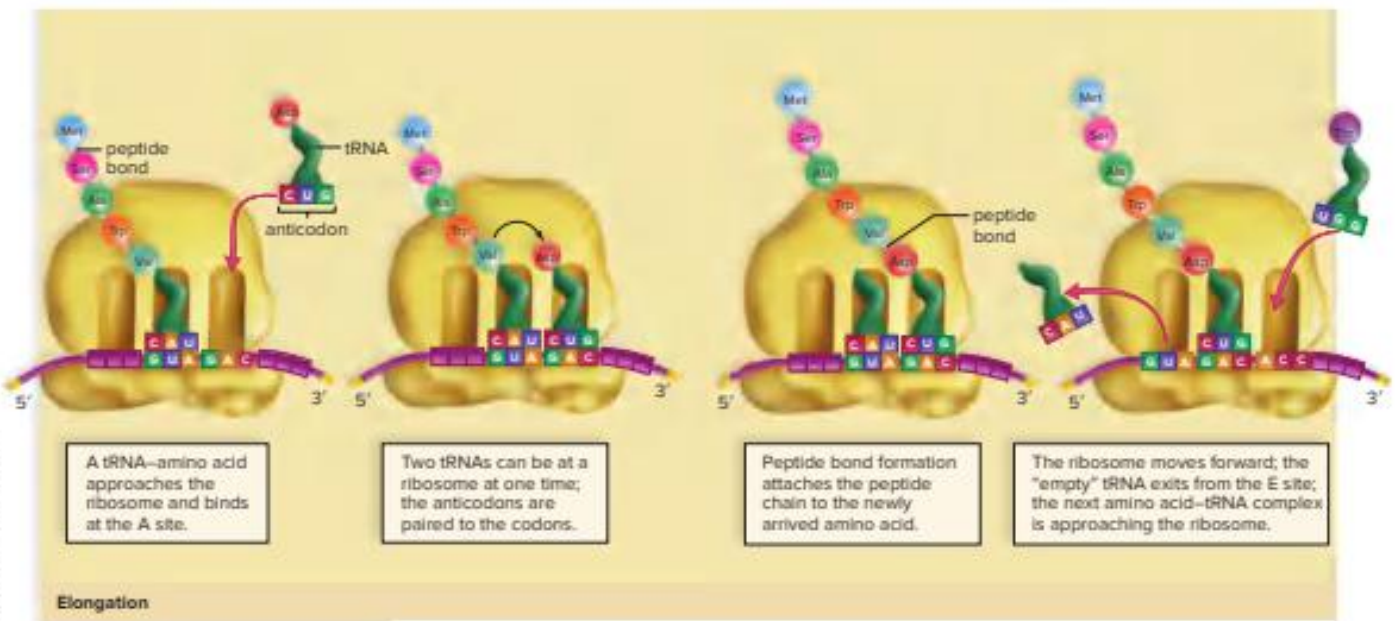


Figure 3.18 Elongation. Note that a polypeptide is already at the P site. During elongation, polypeptide synthesis occurs as amino acids are added one at a time to the growing chain.

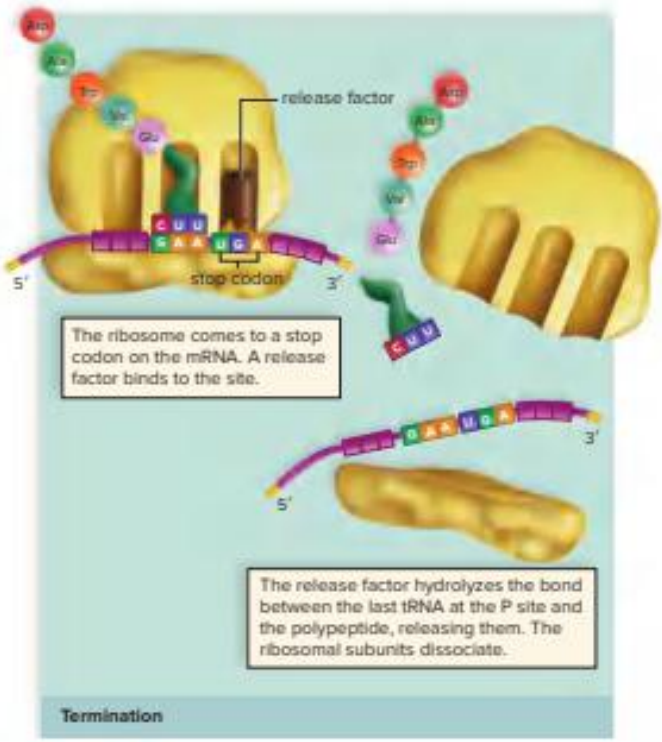


Figure 3.19 Termination. During termination, the finished polypeptide is released, as are the mRNA and the last tRNA.

tRNA is now in the P site of the ribosome. The spent tRNA, now at the E site, exits the ribosome. A new codon is now exposed at the A site and is ready to receive another tRNA.

The complete cycle—complementary base pairing of new tRNA, transfer of peptide chain, and translocation—is repeated at a rapid rate (about 15 times each second in the bacterium *Escherichia coli*).

Eventually, the ribosome reaches a stop codon, and termination occurs, during which the polypeptide is released.

Termination

Termination is the final step in protein synthesis. During termination, as shown in Figure 3.19, the polypeptide and the assembled components that carried out protein synthesis are separated from one another.

Termination of polypeptide synthesis occurs at a *stop codon*—that is, a codon that does not code for an amino acid. Termination requires a protein called a release factor, which can bind to a stop codon and cleave the polypeptide from the last tRNA. After this occurs, the polypeptide is set free and begins to fold and take on its three-dimensional shape. The ribosome dissociates into its two subunits, which are returned to the cytoplasmic pool of large and small subunits, to be used again as necessary.

Overall, proteins do the work of the cell, whether they reside in a membrane within the cell or are free in the cytoplasm. A new

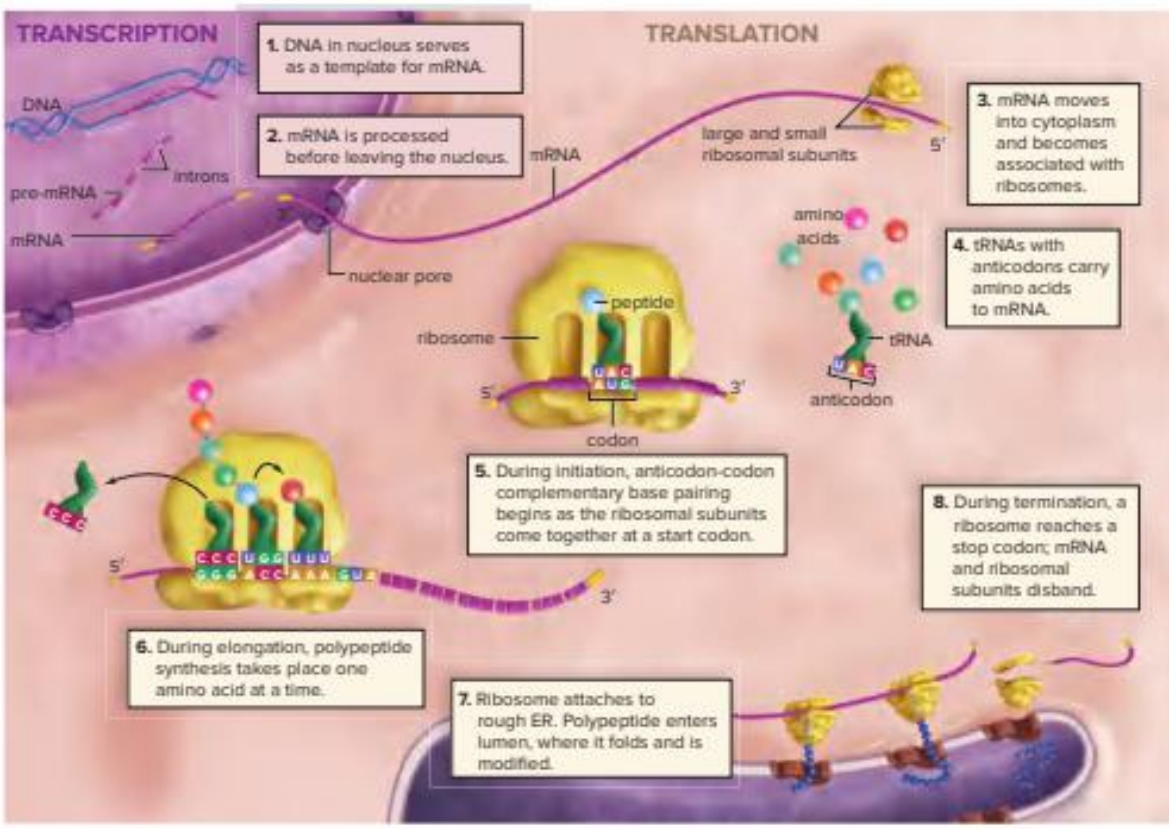


Figure 3.20 Summary of protein synthesis in eukaryotes.

field of biology called **proteomics** is dedicated to understanding the structure of proteins and how they function in metabolic pathways. One of the important goals of proteomics is to understand how proteins are modified in the endoplasmic reticulum and the Golgi apparatus.

Gene Expression

A gene has been expressed once its product, a protein (or an RNA), is made and is operating in the cell. For a protein, gene expression requires transcription and translation (Fig. 3.20), and it requires that the protein be active.

Translation occurs at ribosomes. Some ribosomes (polyribosomes) remain free in the cytoplasm, and some become attached to rough ER. The first few amino acids of a polypeptide act as a signal peptide that indicates where the polypeptide belongs in the cell or if it is to be secreted from the cell. Polypeptides that are to be secreted enter the lumen of the ER by way of a channel and are then folded and further processed by the addition of sugars, phosphates, or lipids. Transport vesicles carry the proteins between organelles and to the plasma membrane as appropriate for that protein.

Check Your Progress 3.5

1. Explain the role of transfer RNA in translation.
2. Describe how the structure of a ribosome contributes to polypeptide synthesis.
3. Examine the events that occur during the three major steps of translation.

REVIEWING *the* BIG IDEAS

BIG IDEA 1

The use of DNA and RNA as sources of genetic information and machinery molecules to synthesize proteins is seen universally in all domains of life; a common genetic code points to a common ancestor for all organisms. 1.B.1.a.1; 1.D.2.b.2

BIG IDEA 3

Scientists worked to identify DNA as the genetic material of life and to discover its double helix structure. 3.A.1.a.4.i-ii

DNA and RNA have different structures and functions, but complementary base pairing and enzyme facilitation are essential in replication, transcription and translation. 3.A.1; 3.A.1.b.1-3

DNA replication is a semi-conservative process, with one stranding serving as the template for a new, complementary strand. 3.A.1.a.5.i-ii

RNA molecules differ in structure and function, facilitating their role in synthesizing proteins; following transcription, RNA molecules are often modified. 3.A.1.b.4.i-iv; 3.A.1.c.1-2

Following transcription, mRNA carries a triplet code for an amino acid sequence to a ribosome; translation of information carried by mRNA occurs when codons are matched with tRNA molecules carrying specific amino acids, creating a protein chain. 3.A.1c.3; 3.A.1.c.4.i-vii

Activities of translated proteins results in the physical phenotypes of organisms. 3.A.1.d.*IE*

SUMMARIZE

AP Answering the Essential Questions

The middle of the twentieth century was an exciting period for scientific discovery. Geneticists were busy identifying DNA (*deoxyribonucleic acid*) as the genetic material of all living organisms, and biochemists were in a race to describe the structure of DNA. Several classic experiments performed during this era set the stage for an explosion in our knowledge of modern biology. In 1928 Fredrick Griffith's work in developing a vaccine against pneumonia identified a mysterious substance that could cause hereditary changes in bacteria. Later work by Avery, McCarty, and MacLeod, and Hershey and Chase identified this substance as DNA, not protein as other scientists had hypothesized.

The structure of DNA Further evidence determining DNA as the genetic material was provided when Erwin Chargaff performed a chemical analysis of DNA from a variety of organisms and noticed regularity in the ratios of nitrogenous bases. Previously we learned that DNA is composed of nucleotides which, in turn, are composed of three subunits: a five-carbon sugar (deoxyribose), a phosphate group, and one of four nitrogenous bases. Among the different organisms Chargaff studied, the number of adenines (A) approximately equaled the number of thymines (T), and the number of cytosines (C) equaled the number of guanines (G) or **A=T** and **C=G.** Rosalind Franklin used X-ray crystallography to photograph DNA, showing that the molecule is a double helix with repeating structural features and certain dimensions. Now it was up to James Watson and Francis Crick to put the puzzle pieces together by building a model of DNA in which sugar-phosphate molecules made up the sides of a twisted ladder, and the **complementary base pairs** (A and T, and C and G) formed rungs connected across the middle by hydrogen bonds. In addition, the two strands of the double helix have directionality, from the 5′ end (with the phosphate group) to the 3′ end (with the –OH group of the sugar); the two strands run antiparallel to each other, one strand from 3′ to 5′ and the complementary strand from 5′ to 3′—sort of like a divided highway. The directionality of DNA will become important when we explore how DNA copies itself during mitosis and meiosis.

The Watson and Crick model suggested a method by which DNA could be replicated. Basically, the two strands unwind and unzip at the hydrogen bonds, and each parental strand acts as a **template** for a new daughter strand that is **complementary** to the template. The process is called **semiconservative replication** because the original

information coded in the sequences of nucleotides of the parental DNA strand—the genes formed using A, T, C, and G—is kept or conserved in one strand of the daughter molecule.

DNA replication But—you guessed it—the process is a bit more complicated than this simple description and involves several different enzymes. However, with the exception of the enzymes that are in bold below, you are not expected to know the names and roles of other enzymes involved in replication. Replication of a chromosome begins at particular sites called **origins of replication** consisting of short stretches of DNA having a specific sequence of nucleotides. The *E. coli* chromosome, like other bacterial chromosomes, is circular and has a single origin. Proteins that initiate DNA replication recognize this sequence and open a replication "bubble" bordered on each side by a replication fork; because of the directionality of the DNA molecule, replication occurs in both directions, and the bubbles grow until the entire molecule is copied. Replication in prokaryotes typically proceeds in both directions from one point of origin to a termination region until there are two copies of the circular chromosomes. Replication in eukaryotes has many points of origin and many bubbles (places where the DNA strands are separating and replication is occurring.)

To begin replication, **DNA helicase** opens the double-stranded DNA at the hydrogen bonds between complementary nucleotides on each side of the helix, and other proteins ensure the strands stay apart. Because the untwisting of the double helix causes tighter twisting ahead of the replication fork, **topoisomerase** helps relieve this strain. Before replication can get underway, DNA needs to be primed. **DNA polymerase** initiates synthesis, but only can add DNA nucleotides to the end of an existing chain that is based-paired with the template strand. **Primase** gets replication started by adding a few RNA primers. Once these primers are recognized by DNA polymerase, replication can begin.

As we noted, the two ends of a DNA molecule run in opposite directions. DNA polymerase recognizes the 3′ –OH end of the DNA template strand. Consequently, the two new strands are synthesized in opposite directions; the original parental strand is read from 3′ to 5′, whereas the new daughter strand is made from 5′ to 3′. DNA replication on the leading strand is continuous, with DNA polymerase adding nucleotides one-by-one; however, replication of the other strand—called the lagging strand—requires making many fragments, called Okazaki fragments. Think of the activities on the lagging strand as like trying to move up an escalator that is moving down. Fragments are mended together by **DNA ligase,** resulting in two helices identical to the parental DNA.

Transcription and translation Genetic information encoded in DNA flows from a sequence of nucleotides in a gene to a sequence of amino acids in a protein. The **central dogma** of molecular biology says that the flow of genetic information is from DNA → RNA → protein. RNA is a nucleic acid that uses the nucleotide **uracil (U)** instead of thymine (T). **Messenger RNA (mRNA), transfer RNA (tRNA),** and **ribosomal RNA (rRNA)** are specialized RNAs needed to make proteins through **transcription** and **translation.** More specifically, (1) DNA is a template for its own replication and forms mRNA formation during transcription, and (2) the sequence of nucleotides in mRNA directs the correct sequence of amino acid of a polypeptide during translation. The **genetic code** is a **triplet code,** and each **codon** consists of three bases. For example, the **codon ACC** on DNA codes from the amino acid tryptophan. The codon is degenerate—that is, more than one codon exists for most amino acids, sort of like synonyms you studied in your English class (different word, same meaning). There are also one start and three stop codons. The genetic code is considered universal to all organisms but with a few exceptions. The synthesis of a protein occurs in two steps: transcription and translation.

During transcription, the enzyme RNA polymerase reads the DNA molecule in the 3′ to 5′ direction, similar to how DNA polymerase works in replication. However, because a molecule of RNA is synthesized, U, not T, pairs with A. Transcription begins when RNA polymerase attaches to the **promoter** of a gene and continues until RNA polymerase reaches a stop sequence. An **mRNA transcript** is made and then processed following transcription. Processing includes the addition of a GTP cap to the 5′ end the mRNA transcript and a poly-A tail to the 3′ end. **Introns** are removed in eukaryotes by spliceosomes containing ribozymes, and **exons** are kept and their information expressed in a protein. Small nuclear RNAs (snRNAs) present in spliceosomes help identify the introns to be removed. These snRNAs also play a role in **alternative mRNA splicing,** which allows a single eukaryotic gene to code for different proteins, depending on which segments of the gene serve as introns and which serve as exons. In addition, some introns serve as **microRNAs (miRNAs),** which help regulate the translation of mRNAs. Research is now directed at discovering the many ways small RNAs influence the production of proteins in a cell.

After all this information, you might want to take a deep breath. Rest assured, the synthesis of a protein is almost done. The last step is assembling a polypeptide. Translation requires mRNA, transfer RNA (tRNA), and ribosomal RNA (rRNA). A tRNA molecule is often depicted as a cloverleaf, with an **anticodon** on one end, and an amino acid at the other; amino acid-charging enzymes ensure that the correct amino acid is attached to the correct tRNA. For example, the anticodon CCG on tRNA corresponds to the codon GGC on mRNA, or the amino acid glycine (hint: You need to be familiar with various charts of mRNA codons and the amino acids for which they code). When tRNAs bind with their codon at a ribosome, the amino acids are correctly sequenced in a polypeptide, according to the order predetermined by DNA and transcribed to mRNA. In the cytoplasm, many ribosomes—which are composed of rRNA and protein—move along the same mRNA at a time. Translation requires three steps: During **initiation,** mRNA, the first (initiator) tRNA, and the two subunits of a ribosome come together in the proper orientation at a start codon. During **elongation,** as the tRNA anticodons bind to their codons, the growing peptide chain is transferred by peptide bonding to the next amino acid in a polypeptide. During **termination** at a stop codon, the polypeptide is cleaved from the last tRNA and the ribosome dissociates. Once a polypeptide is synthesized, its role as a protein is determined such as determining the physical phenotypes of organisms. The field of proteomics studies how proteins are made, function, and are modified by other organelles.

ASSESS

Choose the best answer for each question.

3.1 The Genetic Material

1. Transformation occurs when
   a. DNA is transformed into RNA.
   b. DNA is transformed into protein.
   c. bacteria cannot grow on penicillin.
   d. organisms receive foreign DNA and thereby acquire a new characteristic.
2. The double helix model of DNA resembles a twisted ladder in which the rungs of the ladder are
   a. a purine paired with a pyrimidine.
   b. A paired with G and C paired with T.
   c. sugar-phosphate paired with sugar-phosphate.
   d. a 5′ end paired with a 3′ end.
3. If 30% of an organism's DNA is thymine, then
   a. 70% is purine.
   b. 15% is guanine.
   c. 30% is adenine.
   d. 70% is pyrimidine.

4. If the sequence of bases in one strand of DNA is 5′ TAGCCT 3′, then the sequence of bases in the other strand is
   a. 3′ TCCGAT 5′.
   b. 3′ ATCGGA 5′.
   c. 3′ TAGCCT 5′.
   d. 3′ AACGGUA 5′.

3.2 Replication of DNA

5. DNA replication is said to be semiconservative because
   a. one of the new molecules conserves both of the original DNA strands.
   b. the new DNA molecule contains two new DNA strands.
   c. both of the new molecules contain one new strand and one old strand.
   d. DNA polymerase conserves both of the old strands.
6. The enzyme responsible for separating double-stranded DNA into single-stranded DNA is
   a. DNA helicase.
   b. DNA primase.
   c. DNA polymerase.
   d. DNA ligase.

3.3 The Genetic Code of Life

7. The central dogma of molecular biology
   a. states that DNA is a template for all RNA production.
   b. states that DNA is a template only for DNA replication.
   c. states that translation precedes transcription.
   d. states that RNA is a template for DNA replication.
8. If the sequence of DNA on the template strand of a gene is AAA, the mRNA codon produced by transcription will be _____ and will specify the amino acid _____ .
   a. AAA, lysine
   b. AAA, phenylalanine
   c. TTT, arginine
   d. UUU, phenylalanine

3.4 First Step: Transcription

9. If the sequence of bases in the coding strand of a DNA molecule is TAGC, then the sequence of bases in the mRNA will be
   a. AUCG.
   b. TAGC.
   c. UAGC.
   d. ATCG.
10. The portion of the mRNA transcript that gets removed during RNA processing is the
    a. exons.
    b. introns.
    c. poly-A tails.
    d. 5′ caps.

3.5 Second Step: Translation

11. During protein synthesis, an anticodon on transfer RNA (tRNA) pairs with
    a. DNA nucleotide bases.
    b. ribosomal RNA (rRNA) nucleotide bases.
    c. messenger RNA (mRNA) nucleotide bases.
    d. other tRNA nucleotide bases.
3. This is a segment of a DNA molecule. What are (a) the RNA codons, (b) the matching tRNA anticodons, and (c) the sequence of amino acids in the eventual protein?

ENGAGE

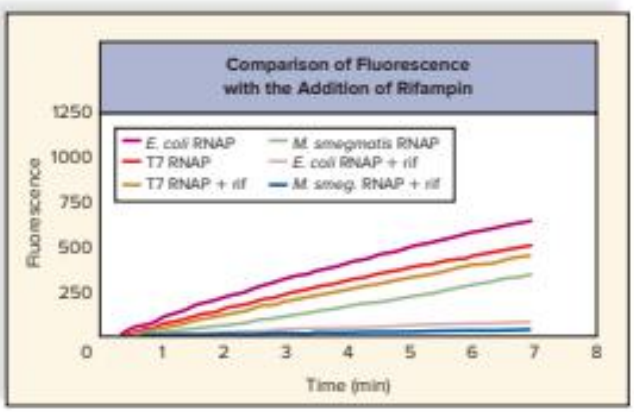
AP Applying the Big Ideas

1. BIG IDEA 1 Organisms share many conserved core processes and features that evolved and are widely distributed among organisms today. Major features of the genetic code are shared by all modern living systems.
   a. **Describe** TWO specific examples of conserved core biological processes and features involved in the molecular biology of genes.
   b. **Explain** how the examples you described for part (a) support the concept of common ancestry for all organisms.

2. BIG IDEA 3 The proof that DNA is the carrier of genetic information involved a number of important historical experiments.
   a. **Describe** TWO of these historical investigations that answer the question: How can we know that DNA is the source of heritable information?
   b. **Justify** how the data from these experiments answer the question from part (a).

AP Applying the Science Practices

How can a virus affect transcription? To study RNA synthesis, a group of scientists used a fluorescent molecular beacon to trace molecules. This beacon becomes fluorescent when it binds to newly synthesized RNA. The fluorescence increases as the RNA chain lengthens. Thus, the beacon can be used to follow RNA synthesis. In this experiment, scientists added the antibiotic rifampin (rif) to RNA polymerase from a virus (T7 RNAP), *Escherichia coli* (*E. coli* RNAP), and *Mycobacterium smegmatis* (*M. smegmatis* RNAP) and followed RNA synthesis.



*Data obtained from: Marras, Salvatore A.E., et al. 2004. Real-time measurement of *in vitro* transcription. *Nucleic Acids Research* 32 9.e: 72.

Think Critically SP 1 SP 5

1. **Describe** the relationship between the fluorescence level and time in each experiment not exposed to rifampin.
2. **Infer** what the relationship between fluorescence level and time indicates is happening in each case where rifampin was added.
3. **Interpret** which organism's RNA synthesis is affected most by the antibiotic rifampin.

4

Regulation of Gene Expression

The health of an individual may be affected by social status. Researchers are using female rhesus macaques, seen here, to study the effects of gene expression in social groups.

Chapter Outline

AP Social status can affect what genes are turned on and off in fish, honeybees, and insects. A recent study found a similar effect in macaque monkeys. Scientists interested in gene regulation worked with 49 female rhesus macaques housed at the Yerkes National Primate Research Center at Emory University. At the center, new enclosures were created to house the females in a group to create a "social unit." The females that had been in the social unit earlier had a higher-ranking social status, and the females introduced later were lower-ranking.

Blood samples taken from the macaques showed that high-ranking females had stronger immune systems with a higher production of white blood cells, while lower-ranking females had fewer white blood cells. The DNA of high-ranking versus low-ranking females was also different in how certain genes were expressed—some genes were turned on or off.

Gene expression is the information in DNA transcribed and translated into a protein. Gene expression needs to be controlled or regulated, and there are many mechanisms that do this.

As you read through the chapter, think about these Essential Questions:

1. How do changes in DNA lead to variation in phenotypes that are subject to natural selection? 1.A.1.c 1.C.3.b
2. How does the operon model explain how gene expression is regulated in prokaryotes? 3.B.1.a-c
3. How do regulatory genes, molecules, and transcription factors control gene expression in eukaryotes? 3.B.1.a.1 *IE* 3.B.1.c.1-3
4. How can cells specialize when they contain the same set of genetic instructions? 4.A.3.a-c

Following *the* BIG IDEAS

BIG IDEA 1	Random changes in DNA can lead to phenotypic variation that can be acted upon by natural selection.
BIG IDEA 3	Regulation of prokaryotic genes is often at the operon level, while eukaryotes fine tune gene expression and modify gene products.
BIG IDEA 4	Regulation of gene activity involves intricate interactions with internal and external factors.

4.1 Prokaryotic Regulation

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the structure of an operon and state the role of each component of the operon.
2. Explain how the *trp* and *lac* operons of prokaryotes are regulated.
3. Distinguish between a repressible operon and an inducible operon.

Because their environment is ever changing, bacteria do not always need to express their entire complement of enzymes and proteins. In 1961, French microbiologists François Jacob and Jacques Monod showed that *Escherichia coli* is capable of regulating the expression of its genes. They observed that the genes in a metabolic pathway, called **structural genes,** are grouped on a chromosome and transcribed at the same time.

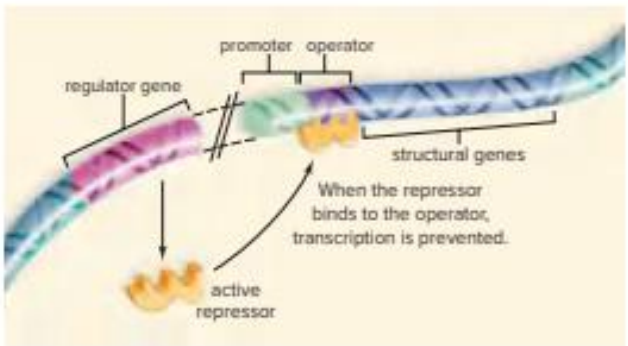
Jacob and Monod, therefore, proposed the **operon** (L. *opera,* "works") model to explain gene regulation in prokaryotes. They later received a Nobel Prize for their investigations.

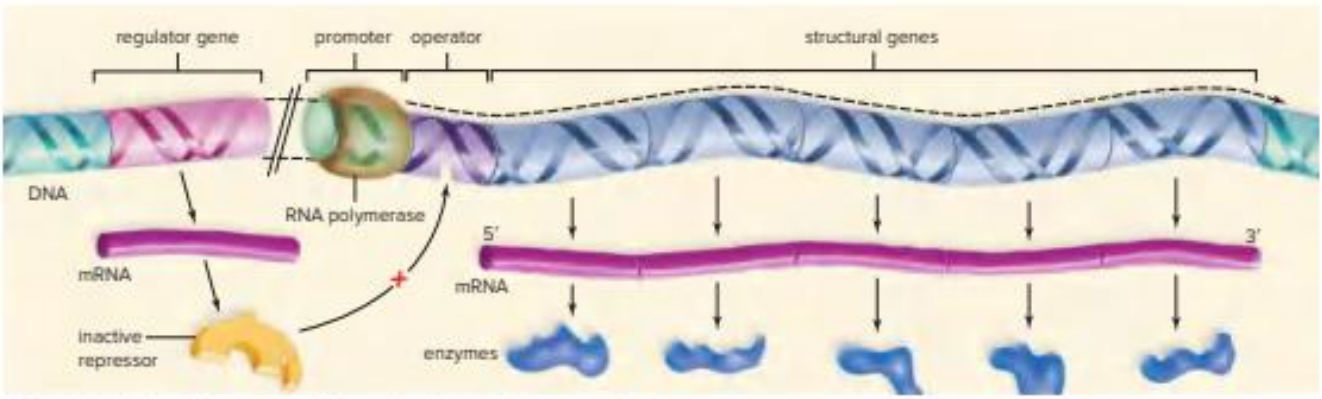
An operon (Fig. 4.1) typically includes the following parts:

Regulator gene—Normally located outside the operon, this codes for a DNA-binding protein that acts as a **repressor.** The repressor controls whether the operon is active or not.

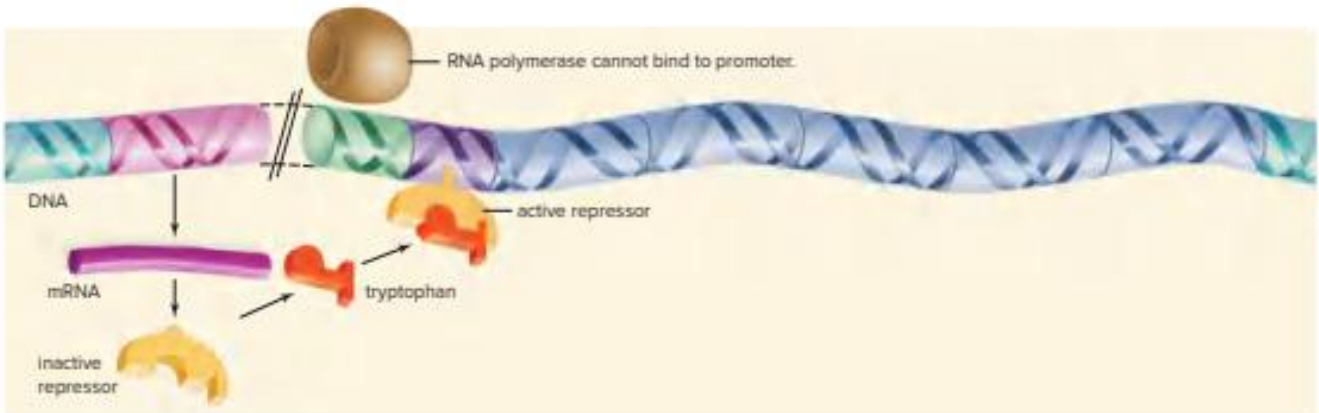
Promoter—A short sequence of DNA where RNA polymerase first attaches to begin transcription of the grouped genes. Basically, a promoter signals the start of the operon and the location where transcription begins.

Operator—A short portion of DNA located before the structural genes. If a repressor is attached to the operator, then transcription cannot occur; conversely, if a repressor is not attached,





a. **Tryptophan absent.** Enzymes needed to synthesize tryptophan are produced.



b. **Tryptophan present.** Presence of tryptophan prevents production of enzymes used to synthesize tryptophan.

Figure 4.1 The *trp* operon. **a.** The regulator gene codes for a repressor protein that is normally inactive. RNA polymerase attaches to the promoter, and the structural genes are expressed. **b.** When the nutrient tryptophan is present, it binds to the repressor, changing its shape. Now the repressor is active and can bind to the operator. RNA polymerase cannot attach to the promoter, and the structural genes are not expressed.

then transcription can occur. In this way, the operator controls transcription of structural genes.

Structural genes—These genes code for the enzymes and proteins that are involved in the metabolic pathway of the operon. The structural genes are transcribed as a unit.

Next, we will briefly review the findings of Jacob and Monod in their studies of two *E. coli* operons: the *trp* operon and the *lac* operon.

The *trp* Operon

Tryptophan is an essential amino acid synthesized by the enzymes coded for in the *trp* operon. Many investigators, including Jacob and Monod, found that some operons in *E. coli* usually exist in the "on" rather than "off" condition. For example, in the *trp* operon, the regulator codes for a repressor that ordinarily is unable to attach to the operator. Therefore, RNA polymerase can bind to the promoter, and the structural genes of the operon are ordinarily expressed (Fig. 4.1). Their products, five different enzymes, are part of an anabolic pathway for the synthesis of the amino acid tryptophan.

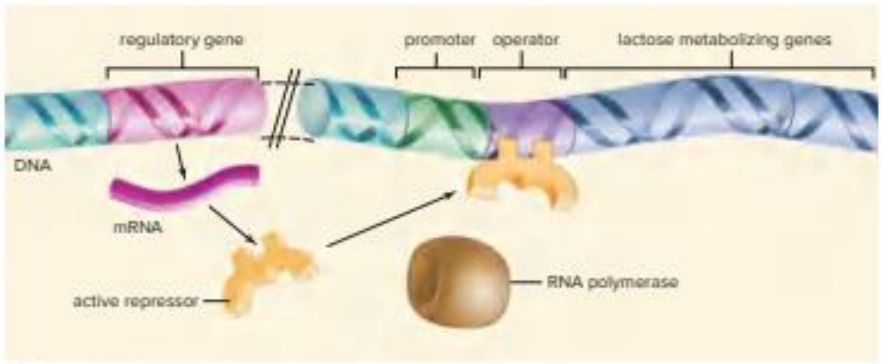
If tryptophan happens to be already present in the medium, the cell does not need these enzymes, and the operon is turned off by the following method. Tryptophan binds to the repressor. A change in shape now allows the repressor to bind to the operator and prevent RNA polymerase from binding to the promoter, and the structural genes are not expressed. The enzymes are said to be repressible (can be turned "off"), and the entire unit is called a *repressible operon*. Tryptophan is called the **corepressor.** Repressible operons are usually involved in anabolic pathways that synthesize a substance needed by the cell.

The *lac* Operon

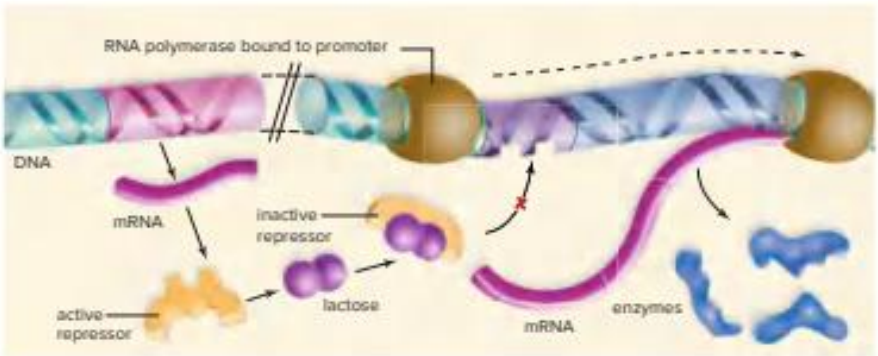
Bacteria metabolism is remarkably efficient; if proteins or enzymes are needed for metabolism, then the structural genes are expressed. If no metabolism is necessary, then genes are not expressed. For example, if the milk sugar lactose is not present, there is no need to express genes for enzymes involved in lactose catabolism. But when only lactose is present, the cell immediately begins to make the three enzymes needed for lactose metabolism.

The enzymes that break down lactose are encoded by three genes (Fig. 4.2): One gene is for an enzyme called β-galactosidase, which breaks down the disaccharide lactose to glucose and galactose; a second gene codes for a permease that facilitates the entry of lactose into the cell; and a third gene codes for an enzyme called transacetylase, which has an accessory function in lactose metabolism.

The three structural genes are adjacent to one another on the chromosome and are under the control of a single promoter and a single operator. The regulator gene codes for a *lac* operon repressor



a. Operon when lactose is absent.



b. Operon when lactose is present.

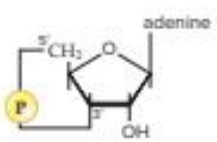
Figure 4.2 The *lac* operon.
a. The regulator gene codes for a repressor that is normally active. When it binds to the operator, RNA polymerase cannot attach to the promoter, and structural genes are not expressed. **b.** When lactose is present, it binds to the repressor, changing its shape, so that it is inactive and cannot bind to the operator. Now RNA polymerase binds to the promoter, and the structural genes are expressed.

that ordinarily binds to the operator and prevents transcription of the three genes. When only lactose (more correctly, allolactose, an isomer formed from lactose) is present, lactose binds to the repressor, and the repressor undergoes a change in shape that prevents it from binding to the operator. Because the repressor is unable to bind to the operator, RNA polymerase is better able to bind to the promoter. After RNA polymerase carries out transcription, the three enzymes of lactose metabolism are synthesized.

Because the presence of lactose brings about expression of genes, it is called an **inducer** of the *lac* operon: The enzymes are said to be inducible enzymes (can be turned "on"), and the entire unit is called an *inducible operon*. Inducible operons are usually found in catabolic pathways that break down a nutrient. Why is that beneficial? Because these enzymes need to be active only when the nutrient is present.

Further Control of the lac *Operon*

If both glucose and lactose are present, then *E. coli* preferentially breaks down glucose. The bacterium has a way to ensure that the lactose operon is fully turned on only when glucose is absent. A molecule called *cyclic AMP* (*cAMP*) accumulates when glucose is absent. Cyclic AMP, which is derived from ATP, has only one phosphate group, which is attached to ribose at two locations:

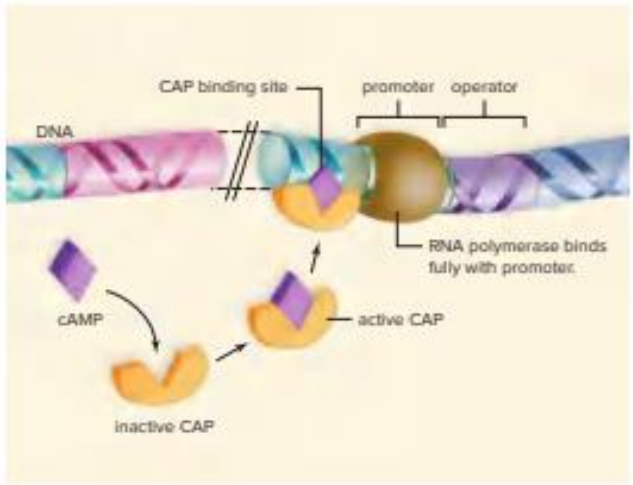


cyclic AMP
(cAMP)

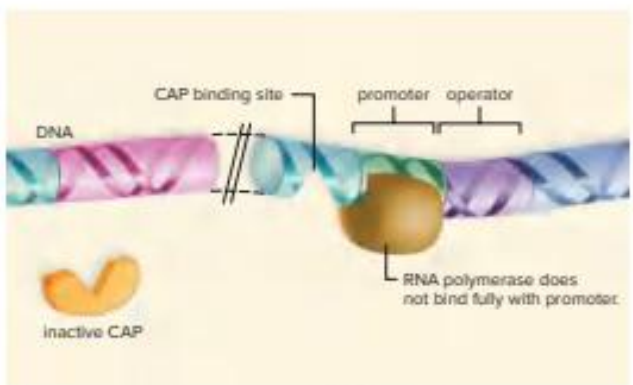
Cyclic AMP binds to a molecule called a *catabolite activator protein* (*CAP*), and the complex attaches to a CAP binding site next to the *lac* promoter. When CAP binds to DNA, DNA bends, exposing the promoter to RNA polymerase. RNA polymerase is now better able to bind to the promoter, so that the *lac* operon structural genes are transcribed, leading to their expression (Fig. 4.3).

When glucose is present, there is little cAMP in the cell; CAP is inactive, and the lactose operon does not function maximally. CAP affects other operons as well and takes its name for activating the catabolism of various other metabolites when glucose is absent. A cell's ability to encourage the metabolism of lactose and other metabolites when glucose is absent provides a backup system for survival when the preferred energy source, glucose, is absent.

The CAP protein's regulation of the *lac* operon is an example of positive control. Why? When this molecule is active, it promotes the activity of an operon. The use of repressors, on the other hand, is an example of negative control, because when active they shut down an operon. A positive control mechanism allows the cell to fine-tune its response. In the case of the *lac* operon, the operon is only maximally active when glucose is absent and lactose is present. If both glucose and lactose are present, the cell preferentially metabolizes glucose.



a. **Lactose present, glucose absent (cAMP level high)**



b. **Lactose present, glucose present (cAMP level low)**

Figure 4.3 Action of CAP. When active CAP binds to its site on DNA, the RNA polymerase is better able to bind to the promoter, so that the structural genes of the *lac* operon are expressed. **a.** CAP becomes active in the presence of cAMP, a molecule that is prevalent when glucose is absent. Therefore, transcription of lactose enzymes increases, and lactose is metabolized. **b.** If glucose is present, CAP is inactive, and RNA polymerase does not completely bind to the promoter. Therefore, transcription of lactose enzymes decreases, and less metabolism of lactose occurs.

Check Your Progress 4.1

1. Explain the difference between the roles of the promoter and operator of an operon.
2. Summarize how gene expression differs in an inducible operon versus a repressible operon, and give an example of each.
3. Describe the difference between positive control and negative control of gene expression.
4. Explain which operon discussed in this section is catabolic and which operon is anabolic.

4.2 Eukaryotic Regulation

Learning Outcomes

Upon completion of this section, you should be able to

1. List the levels of control of gene expression in eukaryotes.
2. Summarize how chromatin structure may be involved in regulation of gene expression in eukaryotes.
3. Identify the mechanisms of transcriptional, posttranscriptional, and translational control of gene expression.

With a few minor exceptions, each cell of a multicellular eukaryote has a complete complement of genes; the differences in cell types are determined by the different genes that are actively expressed in each cell. For example, in muscle cells a different set of genes is turned on in the nucleus and a different set of proteins is active in the cytoplasm, compared to nerve or liver cells.

Like prokaryotic cells, a variety of mechanisms regulate gene expression in eukaryotic cells. These mechanisms can be grouped under five primary levels of control; three of them pertain to the nucleus, and two pertain to the cytoplasm (Fig. 4.4). In other words, control of gene activity in eukaryotes extends from transcription to protein activity. The following types of control in eukaryotic cells can modify the amount of the gene product:

1. *Chromatin structure:* Chromatin packing is used as a way to keep genes turned off. If genes are not accessible to RNA polymerase, they cannot be transcribed. Chromatin structure is one method of *epigenetic inheritance* (Gk. *epi,* "besides"), the transmission of genetic information outside the coding sequences of a gene.
2. *Transcriptional control:* The degree to which a gene is transcribed into mRNA determines the amount of gene product. In the nucleus, transcription factors may promote or repress transcription, the first step in gene expression.
3. *Posttranscriptional control:* Posttranscriptional control involves mRNA processing and how fast mRNA leaves the nucleus.
4. *Translational control:* Translational control occurs in the cytoplasm and affects when translation begins and how long it continues. Small RNA molecules (siRNA) are known to regulate translation. In addition, any condition that can cause the persistence of the 5′ cap and 3′ poly-A tail can affect the length of translation. Excised introns may also have effects on the life span of mRNA.
5. *Posttranslational control:* Posttranslational control, which also takes place in the cytoplasm, occurs after protein synthesis. Only a functional protein is an active gene product.

We now explore each of these types of control in greater depth.

Chromatin Structure

The DNA in eukaryotes is always associated with a variety of proteins, and together they make up a stringy material called **chromatin.** Chromatin is most evident in the nucleus during interphase of the cell cycle.

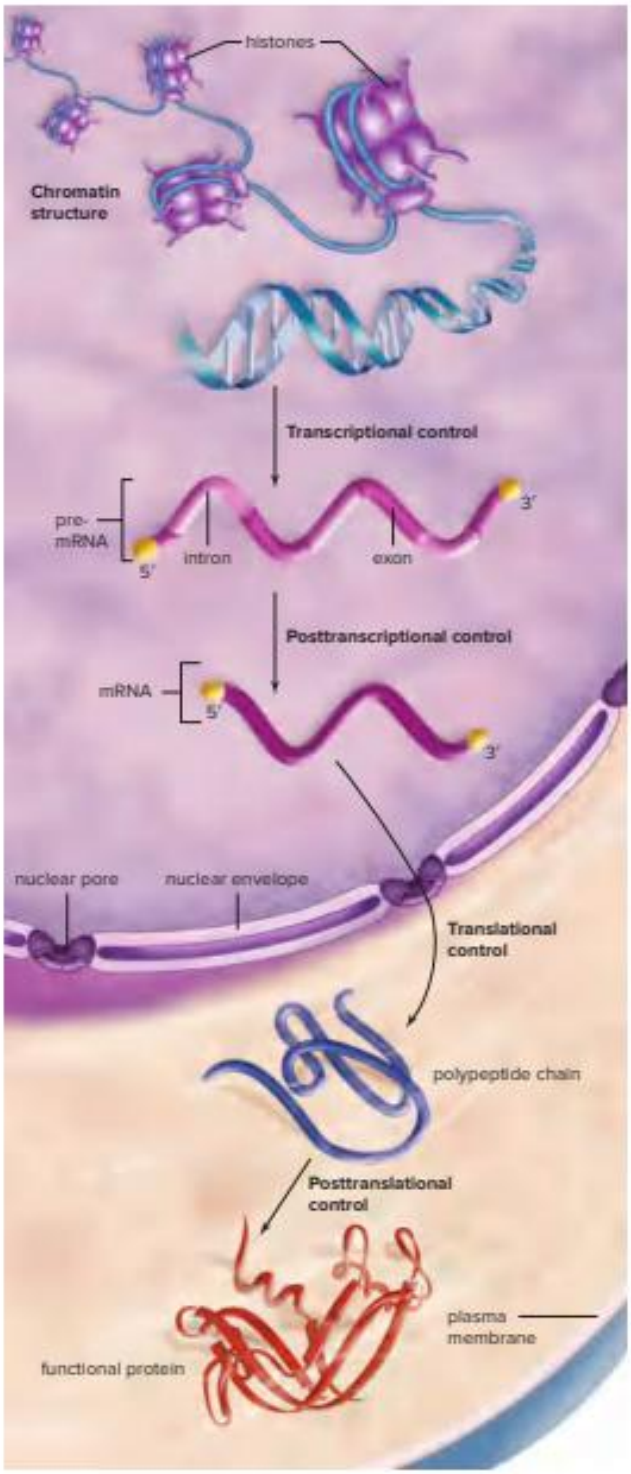


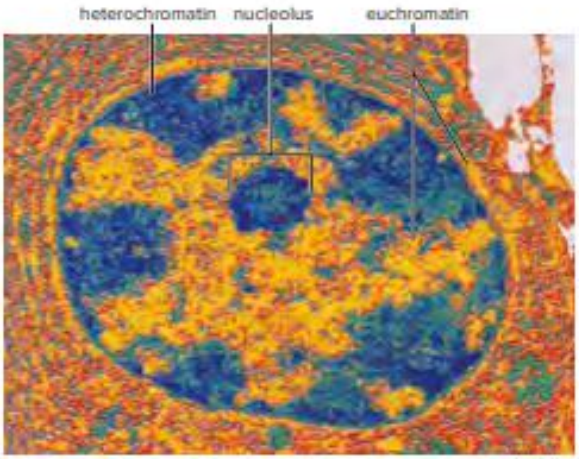
Figure 4.4 Levels at which control of gene expression occurs in eukaryotic cells. The five levels of control are (1) chromatin structure, (2) transcriptional control, and (3) posttranscriptional control, which occur in the nucleus; and (4) translational and (5) posttranslational control, which occur in the cytoplasm.

You learned that one class of these DNA-associated proteins consists of the histones. Histones play an important role in the compaction of the DNA, as well as in eukaryotic gene regulation. Without histones, the DNA would not fit inside the nucleus. Each human cell contains around 2 meters of DNA, yet the nucleus is only 5 to 8 micrometers (μm) in diameter.

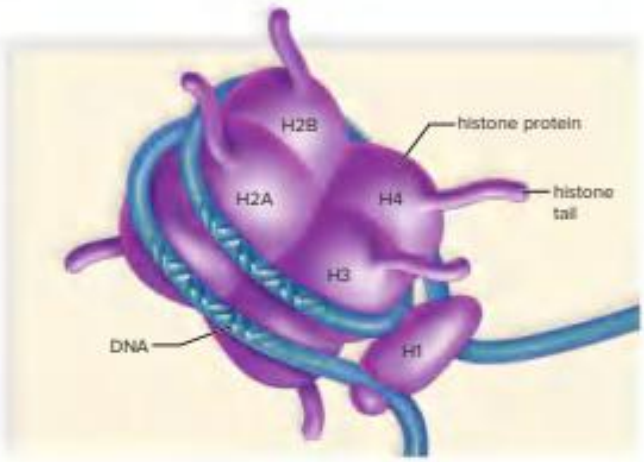
The degree to which chromatin is compacted greatly affects the accessibility of the chromatin to the transcriptional machinery of the cell, and thus the expression levels of the genes. Active genes in eukaryotic cells are associated with more loosely packed chromatin called *euchromatin,* while the more tightly packed DNA, called *heterochromatin,* contains mostly inactive genes. Under a microscope, the more densly compacted heterochromatin stains darker than euchromatin (Fig. 4.5*a*).

What regulates whether chromatin exists as heterochromatin or euchromatin? You learned that a *nucleosome* consists of a portion of DNA wrapped around a group of histone molecules. Histone molecules have *tails,* strings of amino acids that extend beyond the main portion of a nucleosome (Fig. 4.5*b*). In heterochromatin, the histone tails tend to bear methyl groups ($-CH_3$); in euchromatin, the histone tails tend to be acetylated and have attached acetyl groups ($-COCH_3$).

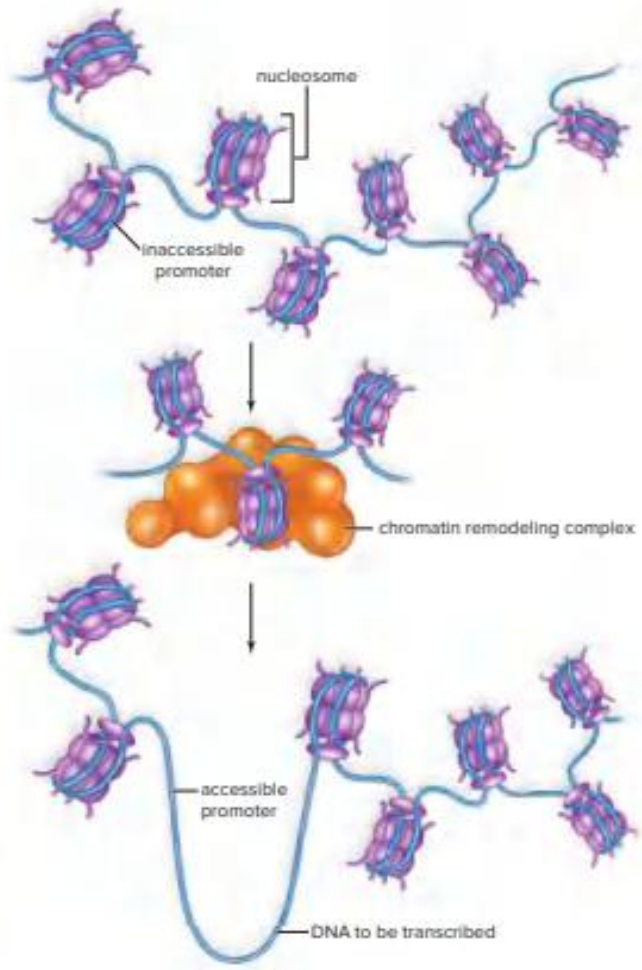
Histones regulate accessibility to DNA; euchromatin becomes genetically active when histones no longer block access to DNA. When DNA in euchromatin is transcribed, a group of proteins called the *chromatin remodeling complex* pushes aside, or *unpacks,* the histone portion of a nucleosome, so that access to DNA is not blocked and transcription can begin (Fig. 4.5*c*). After unpacking occurs, many decondensed loops radiate from the central axis of the chromosome. These chromosomes have been named lampbrush chromosomes, because their feathery appearance resembles the brushes that were once used to clean kerosene lamps.



a. Darkly stained heterochromatin and lightly stained euchromatin



b. A nucleosome



c. DNA unpacking

Figure 4.5 Chromatin structure regulates gene expression. **a.** A eukaryotic nucleus contains highly condensed heterochromatin (darkly stained) and euchromatin (lightly stained), which is not as condensed. **b.** Nucleosomes ordinarily prevent access to DNA, so that transcription cannot take place. If histone tails are acetylated, access can be achieved; if the tails are methylated, access is more difficult. **c.** A chromatin remodeling complex works on euchromatin to make the DNA available and thus the promoter accessible for transcription.

In addition to physically moving nucleosomes aside to expose promoters, chromatin remodeling complexes may also affect gene expression by adding acetyl or methyl groups to histone tails.

Heterochromatin Is Not Transcribed

In general, highly condensed heterochromatin is inaccessible to RNA polymerase, and the genes contained within are seldom or never transcribed. A dramatic example of heterochromatin is the **Barr body** in mammalian females. This small, darkly staining mass of condensed chromatin adhering to the inner edge of the nuclear membrane is an inactive X chromosome. To compensate for the fact that female mammals have two X chromosomes (XX), whereas males have only one (XY), one of the X chromosomes in the cells of female embryos undergoes inactivation. The inactive X chromosome does not produce gene products, allowing both males and females to produce the same amount of gene product from a single X chromosome.

How do we know that Barr bodies are inactive X chromosomes that are not producing gene products? In a heterozygous female, 50% of the cells have one X chromosome active, and 50% have the other X chromosome active. The body of a heterozygous female is therefore a mosaic, with "patches" of genetically different cells. Investigators have discovered that human females who are heterozygous for an X-linked recessive form of ocular albinism have patches of pigmented and nonpigmented cells at the back of the eye.

As other examples, women who are heterozygous for X-linked hereditary absence of sweat glands have patches of skin lacking sweat glands. And the female calico cat exhibits a difference in X-inactivation in its cells. In these cats, an allele for black coat color is on one X chromosome, and a corresponding allele for orange coat color is on the other. The patches of black and orange in the coat can be related to which X chromosome is in the Barr bodies of the cells found in the patches (Fig. 4.6).

Epigenetic Inheritance

Histone modification is sometimes linked to a phenomenon termed **epigenetic inheritance,** in which variations in the pattern of inheritance are not due to changes in the sequence of the DNA nucleotides. For example, when histones are methylated, sometimes the DNA itself becomes methylated as well.

During *genomic imprinting,* either the mother's or the father's gene (but not both) is methylated during gamete formation. If an inherited allele is highly methylated, the gene is not expressed, even if it is a normal gene in every other respect. For traits that exhibit genomic imprinting, the expression of the gene depends on whether the unmethylated allele was inherited from the mother or the father.

The term *epigenetic inheritance* is now used broadly for other inheritance patterns that do not depend on the genes themselves. Epigenetic inheritance explains unusual inheritance patterns and may play an important role in growth, aging, and cancer. As discussed in the Biological Systems feature, "Same but Not the Same—the Role of Epigenetics," researchers are hopeful that it will be easier to develop drugs to modify this level of inheritance, rather than trying to change the DNA itself.

Transcriptional Control

Although eukaryotes have various levels of genetic control (see Fig. 4.4), **transcriptional control** remains the most critical of these levels. The first step toward transcription is availability of DNA, which involves chromatin structure. Transcriptional control also involves the participation of transcription factors, activators, and repressors.

Transcription Factors, Activators, and Repressors

Although some operons like those of prokaryotic cells have been found in eukaryotic cells, transcription in eukaryotes is still controlled by DNA-binding proteins. Every cell contains many different types of **transcription factors,** proteins that help regulate transcription by assisting the binding of the RNA polymerase to the promotor. A cell has many different types of transcription factors, and a variety of transcription factors may be active at a single promoter. Thus, the absence of one can prevent transcription from occurring.

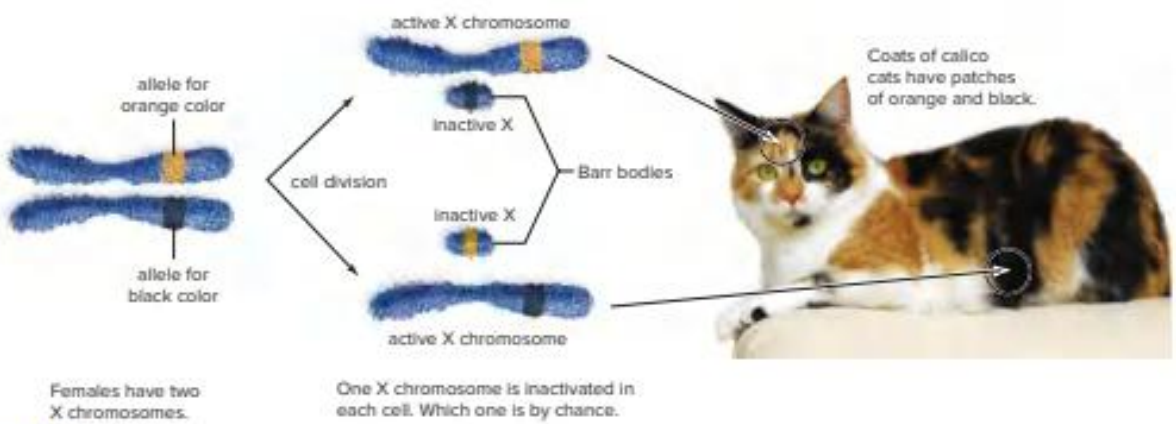


Figure 4.6 X-inactivation in mammalian females. In cats, the alleles for black or orange coat color are carried on the X chromosomes. Random X-inactivation occurs in females. Therefore, in heterozygous females, 50% of the cells have an allele for black coat color and 50% of the cells have an allele for orange coat color. The result is calico cats that have coats with patches of both black and orange.

Even if all the transcription factors are present, transcription may not begin without the assistance of a DNA-binding protein called a **transcription activator.** These bind to regions of DNA called **enhancers,** which may be located some distance from the promoter. A hairpin loop in the DNA brings the transcription activators attached to the enhancer into contact with the transcription factor complex (Fig. 4.7). Likewise, the binding of repressors within the promoter may prohibit the transcription of certain genes. Most genes are subject to regulation by both activators and repressors.

The promoter structure of eukaryotic genes is often very complex, and a large variety of regulatory proteins may interact with each other and with transcription factors to affect a gene's transcription level. Mediator proteins act as a bridge between transcription factors and transcription activators at the promoter. Now RNA polymerase can begin the transcription process (Fig. 4.7). Such protein-to-protein interactions are a hallmark of eukaryotic gene regulation. Together, these mechanisms can fine-tune a gene's transcription level in response to a large variety of conditions. For example, all the cells in a corn plant contain the gene for the pigment anthocyanin, but where and when anthocyanin is made is transcriptionally controlled. UV light induces anthocyanin production in the leaves where it is controlled by one set of transcription factors. Later, organ development cues anthocyanin production in the kernels controlled by a different set of transcription factors.

Posttranscriptional Control

Posttranscriptional control of gene expression occurs in the nucleus and includes alternative mRNA splicing and controlling the speed with which mRNA leaves the nucleus.

Recall that during pre-mRNA splicing, introns (noncoding regions) are excised and exons (expressed regions) are joined together to form an mRNA. When introns are removed from pre-mRNA, differential splicing of exons can occur, and this affects gene expression. For example, an exon that is normally included in an mRNA transcript may be skipped, and it is excised along with the flanking introns (Fig. 4.8). The resulting mature mRNA has an altered sequence, and the protein it encodes is altered. Sometimes introns remain in an mRNA transcript; when this occurs, the protein-coding sequence is also changed.

Examples of alternative pre-mRNA splicing abound. Both the hypothalamus and the thyroid gland produce a protein hormone called calcitonin, but the mRNA that leaves the nucleus is not the same in both types of cells. This results in the thyroid's releasing a slightly different version of calcitonin than does the hypothalamus.

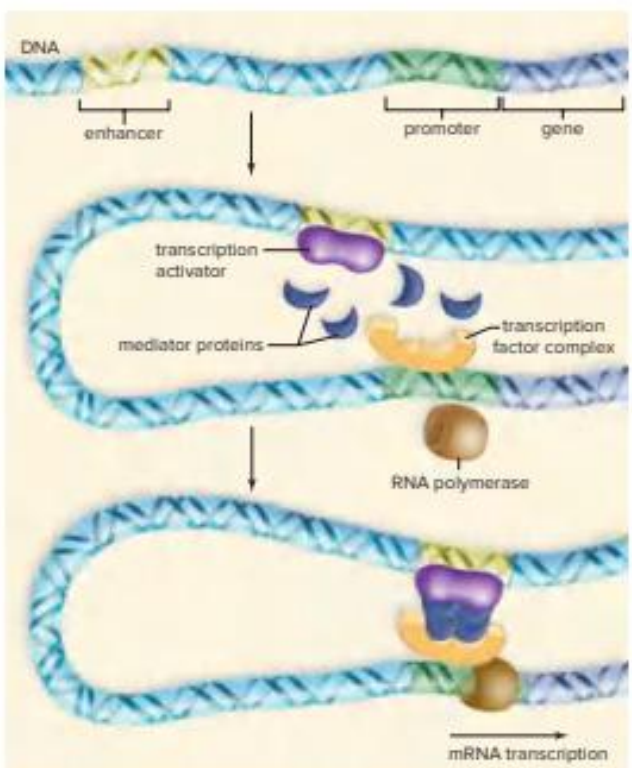
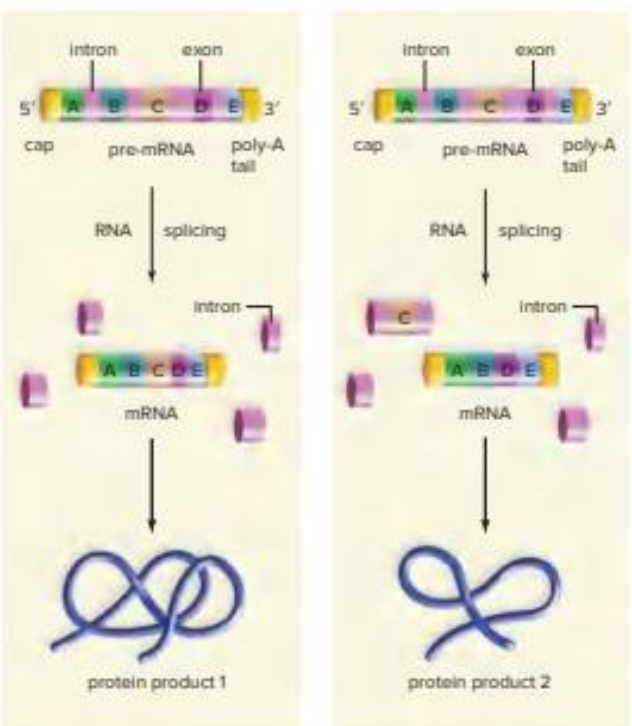


Figure 4.7 Eukaryotic transcription factors. Transcription in eukaryotic cells requires that transcription factors bind to the promoter and transcription activators bind to an enhancer. The enhancer may be far from the promoter, but the DNA loops and mediator proteins act as a bridge joining activators to factors. Only then does transcription begin.



a. b.

Figure 4.8 Alternative processing of pre-mRNA. Because the pre-mRNAs are processed differently in these two cells (**a** and **b**), distinct proteins result. This is a form of posttranscriptional control of gene expression.

Evidence of alternative mRNA splicing is found in other cells, such as those that produce neurotransmitters, muscle regulatory proteins, and antibodies.

Alternative pre-mRNA splicing allows humans and other complex organisms to recombine their genes in novel ways to create the great variety of proteins found in these organisms. Researchers are busy determining how small nuclear RNAs (snRNAs) affect the splicing of pre-mRNA. Alternative mRNA splicing can also result in the inclusion of an intron that brings about destruction of the mRNA before it leaves the nucleus.

Further posttranscriptional control of gene expression is achieved by modifying the speed of transport of mRNA from the nucleus into the cytoplasm. Evidence indicates there is a difference in the length of time it takes various mRNA molecules to pass through a nuclear pore, affecting the amount of gene product realized per unit of time following transcription.

Small RNA (sRNA) Molecules Regulate Gene Expression

For a long time, scientists were faced with a mystery: A cell appeared to contain vastly more DNA than was needed to account for the number of expressed proteins. The DNA that was not expressed as proteins was initially termed "junk" DNA, but recently scientists have begun to understand the role of this DNA in the cell. Although only about 1.5% of the transcribed DNA codes for protein, the remainder is used to form small RNA (sRNA) molecules. We now know that these sRNA molecules represent an important form of gene regulation that functions at multiple levels of gene expression.

Let's take a closer look at how these RNA molecules regulate gene expression (Fig. 4.9).

1. The transcribed RNA can form loops as hydrogen bonding occurs between its bases.
2. The double-stranded RNA (dsRNA) is diced up by enzymes in the cell to form sRNA molecules.
3. Some of these sRNA molecules regulate transcription, while others are involved in the regulation of translation. Various ways have been found by which sRNA may regulate gene expression. sRNA molecules have been known to alter the compaction of DNA, so that some genes are inaccessible to the transcription machinery of the cell.
4. Small RNAs are the source of **microRNAs** (**miRNAs**), small snippets of RNA that can bind to and disable the translation of mRNA in the cytoplasm.
5. Small RNAs are also the source of **small-interfering RNAs** (**siRNAs**) that join with an enzyme (an RNA-induced silencing complex, or RISC) to form an active silencing complex. This activated complex targets specific mRNAs in the cell for breakdown, preventing them from being expressed.

By using a combination of miRNA and siRNA molecules, a cell can fine-tune the amount of product being expressed from a gene, much as a dimmer switch on a light regulates the brightness of the room. Because both miRNA and siRNA molecules interfere with the normal gene expression pathways, the process is often referred to as **RNA interference.**

The first scientists to artifically construct miRNA and siRNA molecules to suppress the expression of a specific gene were Andrew Fire and Craig Mello. Following this discovery, medical scientists recognized that it may be possible to use sRNA molecules as therapeutic agents to suppress the expression of disease-causing genes. For their discovery, Fire and Mello received the 2006 Nobel Prize in Physiology and Medicine.

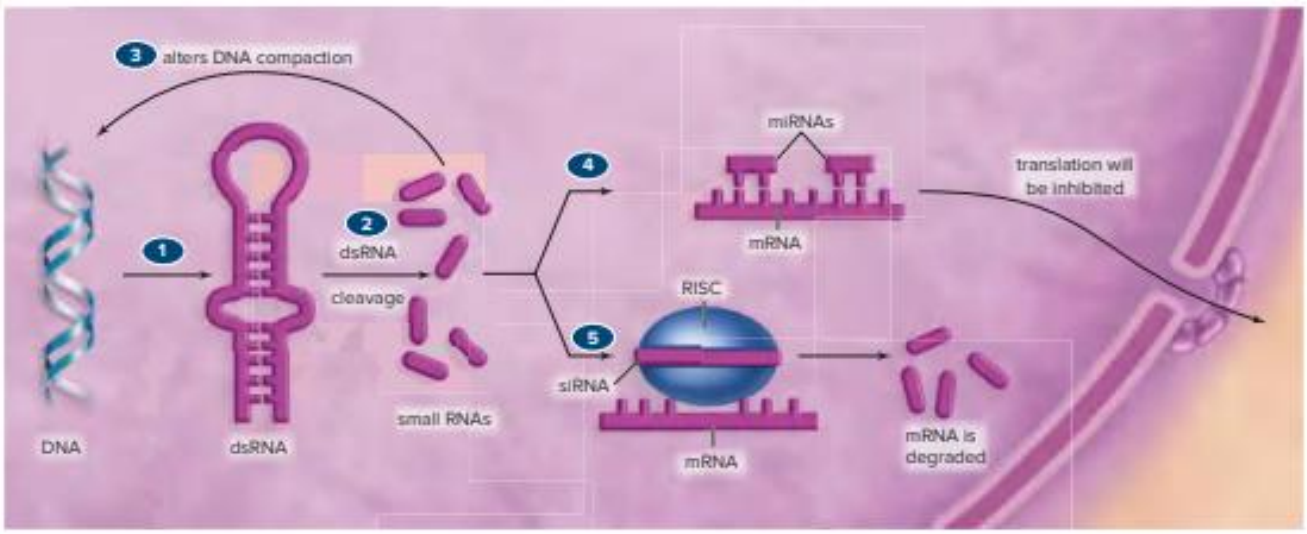


Figure 4.9 Function of small RNA molecules. Transcription of the DNA (1) may lead to looped and double-stranded RNA (dsRNA). (2) The cleavage of the dsRNA produces many small RNA (sRNA) molecules. (3) An sRNA can double-back to increase DNA compaction, or it may become an miRNA or siRNA. (4) miRNA reduces translation by binding to complementary mRNA molecules. (5) siRNA forms a complex with RISC, which then degrades any mRNA with a sequence of bases that are complementary to the siRNA.

BIG IDEA 4: Interdependent Relationships

Same but Not the Same—the Role of Epigenetics

Mia and Emma are identical twins in their early 20s. They both have a dimpled chin and blonde hair, and they wear the same-size clothes and shoes. As little girls, their parents emphasized their similarities by dressing them the same and giving them both the same opportunities to play piano and do gymnastics. As teenagers, things began to change. Their clothing styles were different—Mia preferred the current trends, whereas Emma loved black clothing. Mia was also more outgoing and popular; Emma was more reserved and thoughtful.

How is it possible that two people with the same genes and raised alike can be so different? Many scientists attribute a person's outcome to two factors: nature and nurture. Nature, your genes, gives you traits for eye color, hair color, and blood type. Nurture is based on your lifestyle and environment, including diet, rearing, and education. But is there a third force at work that can affect a person's overall health and well-being? Researchers working with identical twins believe there is a bridge between nature and nurture in the form of epigenetics (Gk. *epi-*, "upon, over").

The specific chemical reactions, or epigenetic "tags," can come in different forms but are often associated with DNA methylation, in which a methyl group attaches to the cytosine base of DNA (Fig. 4B). With a methyl group attached, transcription cannot occur. The methyl group interferes with transcription factors and other proteins in the transcription machinery, thereby silencing or weakening a gene. Over time, the differences in these tags accumulate, making twins increasingly different from each other (Fig. 4C).

Epigenetics are heritable changes in gene expression without changing the DNA sequence. Chemical reactions due to environmental exposure influence how genes are turned off or on, how they are weakened or strengthened, how they change our immune systems, and how they build muscle, brains, and all other body parts. Identical twins present a unique opportunity to study epigenetics, because they are clones resulting from a split in a single fertilized egg (Fig. 4A). Assuming a similar upbringing, their gradual differences over time can therefore be attributed to their disparate control of genes.

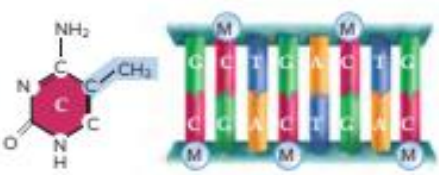
Epigenetics has important implications for medicine. The appearance of tags on genes helps scientists discover the cause of some illnesses that cannot be explained by DNA or genetic mutations alone. Identical twins discordant (different) for autism, psychiatric disorders, and cancer have been shown to have different DNA methylation on certain genes.

In addition, the epigenetic changes are reversible. A study using rats showed that rat pups that are licked and nurtured by their mothers become calm adults. Rat pups that are not nurtured are anxious. Injecting a calm rat with a drug that adds methyl groups creates an anxious rat. Conversely, injecting an anxious rat with a different drug that removes methyl groups creates a calm rat. In drug development, epigenetic medicines could be used to correct or reverse the particular effect of a tag.

Questions to Consider

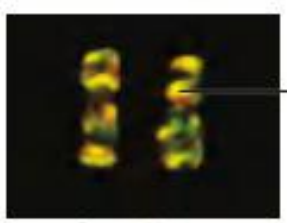
1. How does epigenetics affect transcription and translation?
2. What lifestyle choices most likely negatively impact a person's epigenetics?

Figure 4A Identical twins. Identical twins come from a single fertilized egg that splits in two. Their genes are the same.



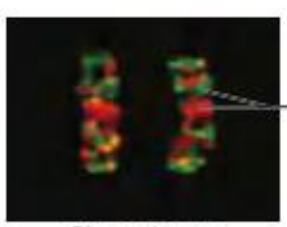
DNA methylation is the addition of a methyl group (M) to the DNA base cytosine (C).

Figure 4B DNA methylation. DNA is methylated when a methyl group attaches to the cytosine nucleotide.



Yellow shows where the twins have epigenetic tags in the same place.

3-year-old twins



Red and green show where the twins have epigenetic tags in different places.

50-year-old twins

Figure 4C Comparison of twin's chromosomes. One twin's epigenetic tags are dyed green, and the other twin's tags are dyed red. An overlap in green and red shows up as yellow. The 50-year-old twins have more epigenetic tags in different places than do the 3-year-old twins.

Translational Control

Translational control begins when the processed mRNA molecule reaches the cytoplasm and before there is a protein product. Translational control involves the activity of mRNA for translation at the ribosome.

The presence or absence of the 5′ cap and the length of the poly-A (adenine nucleotide) tail at the 3′ end of a mature mRNA transcript can determine whether translation takes place and how long the mRNA is active. The long life of mRNAs that code for hemoglobin in mammalian red blood cells is attributed to the persistence of their 5′ end caps and their long 3′ poly-A tails. Therefore, any condition that affects the length of the poly-A tail or leads to removal of the cap may trigger the destruction of an mRNA.

Posttranslational Control

Posttranslational control begins once a protein has been synthesized and has become active. Posttranslational control represents the last chance a cell has for influencing gene expression.

If all the proteins produced by a cell during its lifetime remained in the cell, serious problems would arise. Thus, proteins are continually being synthesized and then degraded.

Proteins only needed for a short time can be altered chemically, leaving them nonfunctional. Proteins may not be folded correctly or they may change shape over time, leading them to behave erratically or stick to one another and form aggregates. In fact, a number of neurodegenerative diseases, such as Alzheimer dementia, Parkinson disease, and mad cow disease, are related to proteins that aggregate, forming plaques in the brain. Thus, in addition to normal turnover of proteins, cells need a way to get rid of old, unused, and incorrectly folded proteins.

Just how long a protein remains active in a cell is usually regulated by the use of **proteases,** enzymes that break down proteins. To protect the cell, proteases are typically confined to the lysosomes or special structures called **proteasomes.** For a protein to enter a proteasome, it has to be tagged with a signaling protein that is recognized by the proteasome cap (Fig. 4.10). When the cap recognizes the tag, it opens and allows the protein to enter the core of the structure, where it is digested to peptide fragments. Notice that proteasomes help regulate gene expression because they help control the amount of protein product in the cytoplasm.

Check Your Progress 4.2

1. Describe the five levels of genetic control in eukaryotes.
2. Explain how chromatin structure influences gene expression.
3. Discuss how small RNA molecules and proteasomes regulate gene expression.

4.3 Gene Mutations

Learning Outcomes

Upon completion of this section, you should be able to

1. Distinguish between spontaneous and induced mutations.
2. Identify how mutations influence protein structure.
3. Summarize how mutations may cause cancer.

A **gene mutation** is a permanent change in the sequence of bases in DNA. The effect of a DNA base sequence change on protein activity can range from no effect to complete inactivity. Germ-line mutations are those that occur in sex cells and can be passed to subsequent generations. Somatic mutations occur in body cells and, therefore, may affect only a small number of cells in a tissue. Somatic mutations are not passed on to future generations, but they can lead to the development of cancer.

Causes of Mutations

Some mutations are spontaneous—they happen for no apparent reason—whereas others are induced by environmental influences. In most cases, **spontaneous mutations** arise as a result of abnormalities in normal biological processes. **Induced mutations** may result from exposure to toxic chemicals or radiation, which induce (cause) changes in the base sequence of DNA.

Spontaneous Mutations

Spontaneous mutations can be associated with any number of normal processes. For example, a movable piece of DNA, termed a *transposon,* may jump from one location to another, disrupting

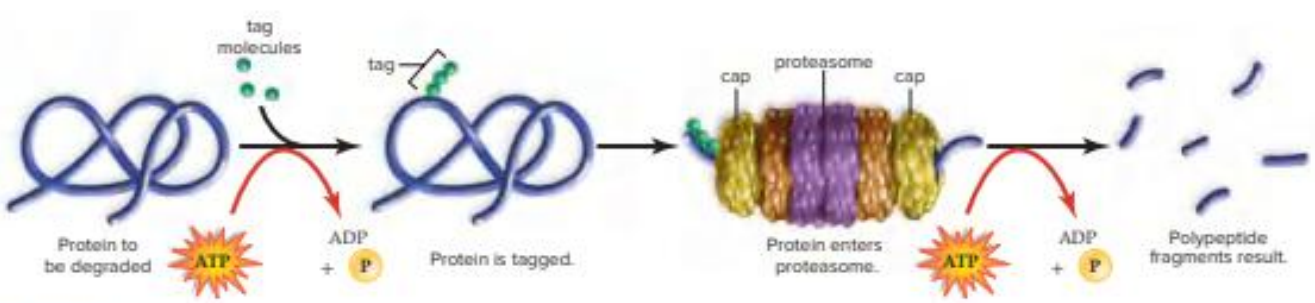


Figure 4.10 Proteasomes degrade proteins in a cell. Proteins to be degraded are first tagged with a signaling molecule. They then enter the proteasome, where they are broken down to polypeptide fragments.

one or more genes and leading to an abnormal product. On rare occasions, a base in DNA can undergo a chemical change that leads to a mispairing during replication. A subsequent base-pair change may be carried forth in future generations. Spontaneous mutations due to DNA replication errors, however, are rare. DNA polymerase, the enzyme that carries out replication, proofreads the new strand against the old strand and detects any mismatched nucleotides, and each is usually replaced with a correct nucleotide. In the end, only about one mistake occurs for every 1 billion nucleotide pairs replicated.

Induced Mutations

Induced mutations are caused by **mutagens,** environmental factors that can alter the base composition of DNA. Among the best-known mutagens are radiation and organic chemicals. Many mutagens are also **carcinogens** (cancer-causing mutagens).

Chemical mutagens are present in many sources, including some of the food we eat and many industrial chemicals. The mutagenic potential of AF-2, a food additive once widely used in Japan, and of safrole, a flavoring agent, caused them to be banned. Surprisingly, many naturally occurring substances—like aflatoxin, produced in moldy grain and peanuts (and present in peanut butter at an average level of 2 parts per billion), and acrylamide, a natural product found in french fries—are also suspected mutagens.

Tobacco smoke contains a number of organic chemicals that are known carcinogens, and it is estimated that one-third of all cancer deaths can be attributed to smoking. Lung cancer is the most frequent lethal cancer in the United States, and smoking is implicated in the development of cancers of the mouth, larynx, bladder, kidney, and pancreas. The greater the number of cigarettes smoked per day, the earlier the habit starts, and the higher the tar content, the greater is the possibility of these cancers.

Scientists use the Ames test for mutagenicity to hypothesize that a chemical can be carcinogenic (Fig. 4.11). In the Ames test, a histidine-requiring strain of bacteria is exposed to a chemical. If the chemical is mutagenic, the bacteria can grow without histidine. A large number of chemicals used in agriculture and industry give a positive Ames test. Examples are ethylene dibromide (EDB), which is added to leaded gasoline (to vaporize lead deposits in the engine and send them out the exhaust), and ziram, which is used to prevent fungal disease on crops. Some drugs, such as isoniazed (used to prevent tuberculosis), are mutagenic according to the Ames test.

Aside from chemicals, certain forms of radiation, such as X-rays and gamma rays, are called ionizing radiation, because they create free radicals, ionized atoms with unpaired electrons. Free radicals react with and alter the structure of other molecules, including DNA. Ultraviolet (UV) radiation is easily absorbed by the pyrimidines in DNA. Wherever there are two thymine molecules next to one another, ultraviolet radiation may cause them to bond together, forming *thymine dimers.* A kink results in the DNA. Usually, these dimers are removed by **DNA repair enzymes,** which constantly monitor DNA and fix any irregularities. One enzyme excises a portion of DNA that contains the dimer; another makes a new section by using the other strand as a template; and still another seals the new section in place.

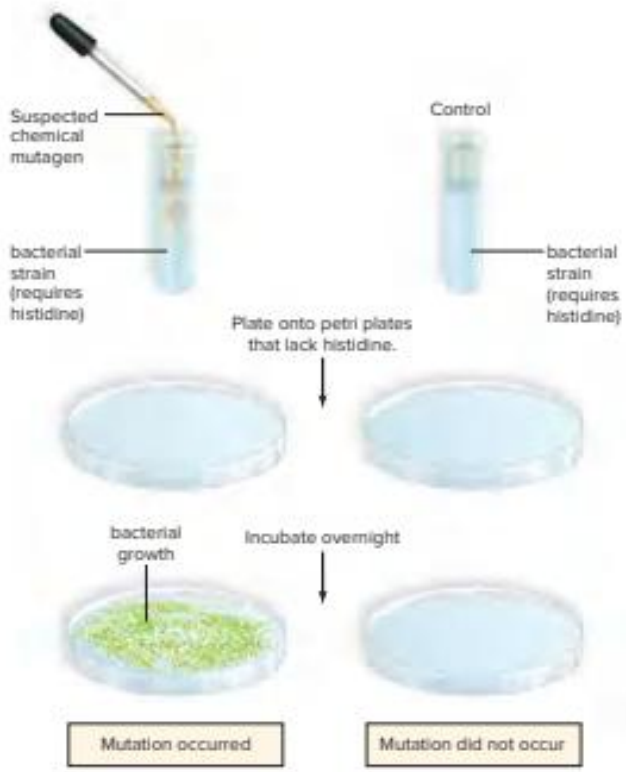
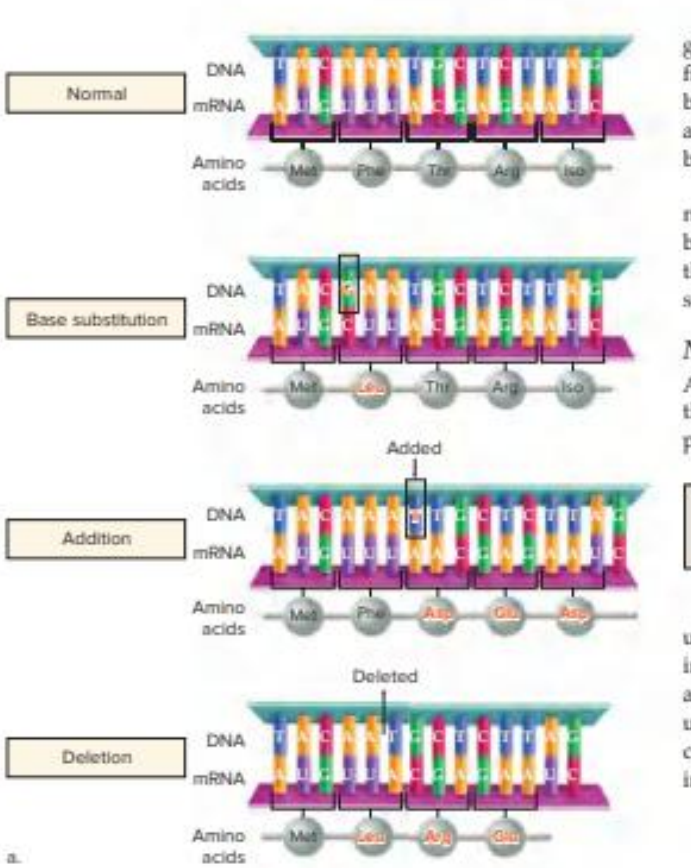


Figure 4.11 The Ames test for mutagenicity. A bacterial strain that requires histidine as a nutrient is exposed to a suspected chemical mutagen, but a control is not exposed. The bacteria are plated on a medium that lacks histidine; only the bacteria exposed to the chemical show growth. A mutation allowed the bacteria to grow; therefore, the chemical can be carcinogenic.

The importance of these repair enzymes is exemplified by individuals with the condition known as xeroderma pigmentosum. They lack some of the repair enzymes, and as a consequence, these individuals have a high incidence of skin cancer because of the large number of mutations that accumulate over time. Also, repair enzymes can fail, as when skin cancer develops because of excessive sunbathing or prolonged exposure to X-rays.

Effect of Mutations on Protein Activity

Point mutations involve a change in a single DNA nucleotide. That change alters transcription and possibly changes the specific amino acid. One type of point mutation is a *base substitution* resulting in one DNA nucleotide being replaced with another incorrect nucleotide. Notice the base difference in the second row of Figure 4.12*a* and how it changes the resultant amino acid sequence. Sometimes a base substitution has little or no effect on the final protein produced, but in some cases early stop codons can be introduced or coding for the wrong amino acid can severely alter the protein shape. Such is the case with the genetic disorder sickle-cell disease (Fig. 4.12*b*). In this gene, there is a base substitution that alters the mRNA codon for



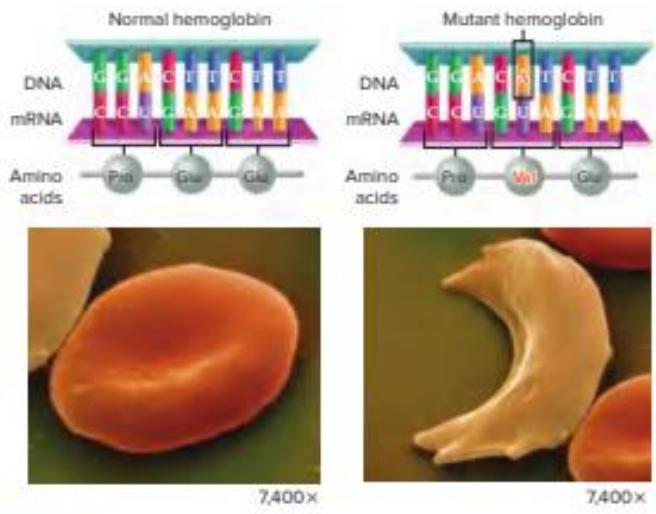


Figure 4.12 Point mutations. The effect of a point mutation can vary. **a.** Starting at the *top:* Normal sequence of bases results in a normal sequence of amino acids; next, a base substitution can result in the wrong amino acid; in the final two rows, an addition or deletion can result in a frameshift mutation altering all the codons downstream of the point mutation. **b.** Due to a base substitution in the hemoglobin gene, the DNA now codes for valine instead of glutamic acid, and the result is that normal red blood cells become sickle-shaped.

glutamic acid. Instead, the codon for valine is present, altering the final shape of hemoglobin—the protein that carries oxygen in the blood. The abnormal hemoglobin molecules form semirigid rods, and the red blood cells become sickle-shaped, resulting in decreased blood flow through tiny blood vessels.

Frameshift mutations occur most often when one or more nucleotides are either added or deleted from DNA (Fig. 4.12*a*, bottom two lines). Because all the codons downstream of the mutation are now shifted, the result is a completely new sequence of codons, yielding a nonfunctional protein.

Nonfunctional Proteins

A single nonfunctioning protein can have a dramatic effect on the phenotype, because enzymes are often a part of metabolic pathways. One metabolic pathway in cells is as follows:

If a faulty code for enzyme E_A is inherited, a person is unable to convert the molecule A to B. Phenylalanine builds up in the system, and the excess causes an intellectual disability and the other symptoms of the genetic disorder phenylketonuria (PKU). In the same pathway, if a person inherits a faulty code for enzyme E_B, then B cannot be converted to C, and the individual is an albino.

A rare condition called androgen insensitivity is due to a faulty receptor for androgens, which are male sex hormones, such as testosterone. In a male with this condition, plenty of testosterone is present in the blood, but the cells are unable to respond to it. Female instead of male external genitals form, and female instead of male secondary sex characteristics occur at puberty. The individual, who appears to be a normal female, may be prompted to seek medical advice when menstruation never occurs. The karyotype is that of a male rather than a female, and the individual does not have the internal sexual organs of a female.

Mutations Can Cause Cancer

It is estimated that one in three people will develop cancer at some time in their lives. Of these affected individuals, one-third of the females and one-fourth of the males will die due to cancer. In the United States, the three deadliest forms of cancer are lung cancer, colon and rectal cancer, and breast cancer.

The development of cancer involves a series of accumulating mutations that can be different for each type of cancer. As discussed, tumor suppressor genes ordinarily act as brakes on cell division, especially when it begins to occur abnormally. Proto-oncogenes stimulate cell division but are usually turned off in fully differentiated, nondividing cells. When proto-oncogenes mutate, they become oncogenes that are active all the time. Carcinogenesis begins with the loss of tumor suppressor gene activity and/or the gain of oncogene activity. When tumor suppressor genes are inactive and oncogenes are active, cell division occurs uncontrollably, because a cell signaling

pathway that reaches from the plasma membrane to the nucleus no longer functions as it should (Figs. 4.13 and 4.14).

It often happens that tumor suppressor genes and proto-oncogenes code for transcription factors or proteins that control transcription factors. As we have seen, transcription factors are a part of the rich and diverse types of mechanisms that control gene expression in cells. They are of fundamental importance to DNA replication and repair, cell growth and division, control of apoptosis, and cellular differentiation. Therefore, it is not surprising that inherited or acquired defects in transcription factor structure and function contribute to the development of cancer.

For example, the tumor suppressor gene called *p53* is more frequently mutated in human cancers than is any other known gene. It has been found that the p53 protein acts as a transcription factor, and as such it is involved in turning on the expression of genes whose products are cell cycle inhibitors. *p53* also promotes apoptosis (programmed cell death) when it is needed. The retinoblastoma protein (RB) controls the activity of a transcription factor for cyclin D and other genes whose products promote entry into the S stage of the cell cycle. When the tumor suppressor gene *p16* mutates, the RB protein is always available, and the result is too much active cyclin D in the cell.

Mutations in many other genes also contribute to the development of cancer. Several proto-oncogenes code for ras proteins, which are needed for cells to grow, to make new DNA, and to not grow out of control. A point mutation is sufficient to turn a normally functioning *ras* proto-oncogene into an oncogene, and abnormal growth results.

Check Your Progress 4.3

1. List some common causes of spontaneous and induced mutations.
2. Explain how a frameshift mutation may disrupt a gene's function.
3. Discuss how a mutation in a tumor suppressor gene and in proto-oncogenes disrupts the cell cycle.

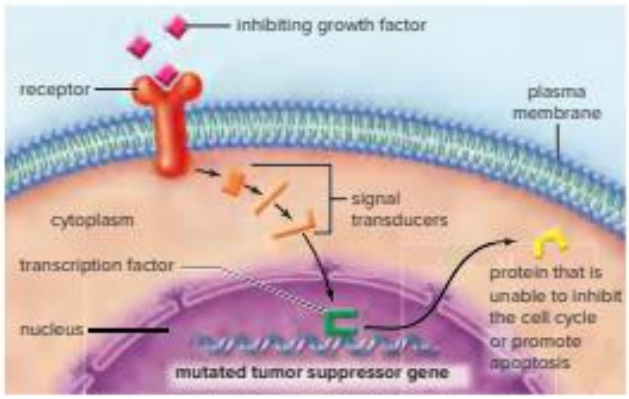


Figure 4.13 Cell signaling pathway that stimulates a mutated tumor suppressor gene. A mutated tumor suppressor gene codes for a product that directly or indirectly stimulates the cell cycle.

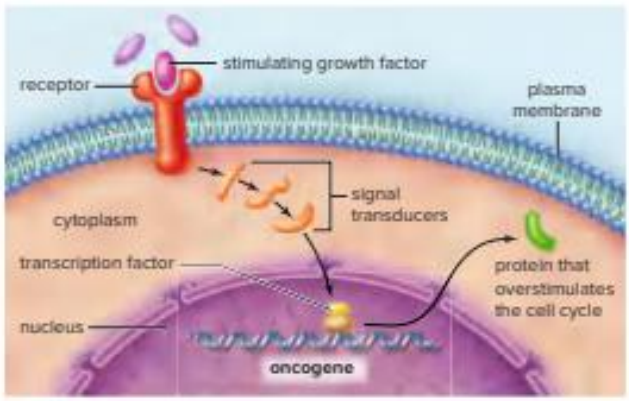


Figure 4.14 Cell signaling pathway that stimulates an oncogene. An oncogene codes for a product that either directly or indirectly overstimulates the cell cycle.

Reviewing *the* BIG IDEAS

BIG IDEA 1

Living organisms are subject to genetic mutations or changes in the nucleotide sequence of DNA; this source of variation, if expressed as a phenotype, is acted upon by natural selection, allowing for evolutionary change over time. 1.A.2.b; *3.C.1.d*

RNA may play a prominent role in the regulation of the genome, thus providing evidence that RNA may have preceded DNA in the evolutionary history of cells. 1.D.1.a.5

BIG IDEA 3

Prokaryotes use direct mechanisms to control their operons and gene expression; eukaryotes employ many level of regulation. 3.B.1.a-c

Regulatory DNA sequences, molecules, and transcription factors function to control gene expression. 3.B.1.a.1 *IE*; 3.B.1.c.1-3

Specialized RNA regulates by alternative gene splicing and message silencing. Identical genes may produce different phenotypes due to differing gene regulation. 3.B.1.a.2; 3.B.1.d

DNA repair enzymes correct irregularities and environmental damage; errors in correct systems may lead to mutations with many effects. 3.C.1.a-b

BIG IDEA 4

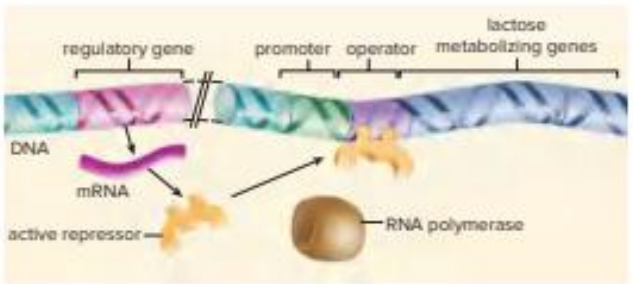
Environmental and internal cues may affect gene regulation, which ultimately determines cells differentiation and function. 4.A.3.a-c

SUMMARIZE

AP Answering the Essential Questions

Structure and function in biology result from the presence of genetic information and the correct expression of this information. How does a cell know when to express genes? Many mechanisms determine when and how this happens, such as adding methyl groups to DNA or regulating RNA polymerase. Simply the type of chromosome a gene is on can alter its expression. Mutations in the DNA sequence and even nongenetic factors such as the external environment can play a role. By understanding how cells regulate gene expression, we can better understand the basis of many human diseases, including cancer.

Gene regulation in prokaryotes Regulation of gene expression in prokaryotes occurs primarily by controlling transcription. Bacteria often organize genes involved in a common process or pathway into **operons** in which genes are coordinately regulated. For example, in *E. coli*, the genes that are involved in lactose metabolism are located together on the bacterial chromosome. The operon model of gene expression states that a **regulator gene** codes for a **repressor**, a protein that binds to the **operator**. When the repressor binds to the operator, RNA polymerase—the enzyme that transcribes mRNA from DNA—is unable to bind to the **promoter**, and transcription of the **structural genes** of the operon (genes that are translated into protein products) cannot occur. Operons may be regulated by both activators and repressors (positive or negative control), depending on whether or not the protein products are needed by the cell.



The *trp* operon is an example of a repressible operon, because when the amino acid tryptophan, the **corepressor**, is present, it binds to the repressor, allowing the repressor to bind to the operator. The operator is blocked, and RNA polymerase cannot transcribe the structural genes needed to synthesize tryptophan (the cell likely has a supply of tryptophan and does not need to make more). The *lac* operon is an example of an inducible operon, because when lactose, the **inducer**, is present it binds to the repressor. In this case, the repressor is unable to bind to the operator; RNA polymerase moves along the DNA, and the structural genes are transcribed and ultimately translated into enzymes needed to metabolize lactose. When lactose is absent, the repressor is activated, it binds to the operator, and the operon is switched off. To conserve resources, the structural genes in the *lac* operon are not maximally expressed unless lactose is present and glucose is absent. Both the *trp* and *lac* operons exhibit negative control because a repressor is involved.

Gene regulation in eukaryotes Eukaryotic cells are more complex than prokaryotic cells so their gene expression and control is more complex—with regulatory genes, regulatory elements, and transcription factors acting in concert. Unlike the operon which controls gene expression at the level of transcription in bacteria, eukaryotes have multiple levels of gene regulation: chromatin structure, transcriptional control, posttranscriptional control, translational control, and posttranslational control.

Chromatin structure helps regulate transcription because highly condensed heterochromatin is genetically inactive, whereas less-condensed euchromatin is genetically active. Chemical modifications to chromosomes can alter gene expression. Adding methyl groups to DNA can prevent transcription, while adding acetyl groups to histones can promote transcription. In addition, regulatory proteins called **transcription factors**, as well as DNA sequences called enhancers, play a role in controlling transcription by binding to the promoter. Transcription activators bind to an enhancer. Small RNA molecules, such as **microRNAs** and **small-interfering RNAs** (siRNAs), are involved in RNA interference and thus play a role in gene expression at the level of transcription. The involvement of RNA in gene regulation provides evidence that RNA may have preceded DNA in the evolutionary history of cells. **Posttranscriptional control** is achieved by creating variations in messenger RNA (mRNA) splicing—removing introns and piecing together different arrangements of exons—which may yield multiple RNA messages from the same gene, thus producing a large number of proteins from a relatively small number of genes. Splicing may also alter the speed with which a particular mRNA leaves the nucleus prior to translation.

Translational control affects mRNA translation, especially the length of time it takes to translate mRNA into a polypeptide, by altering the stability of an mRNA transcript. **Posttranslational control** affects whether or not an enzyme is active and how long it is active. Gene regulation in eukaryotes accounts for some of the phenotypic differences among cells and organisms with similar genes. In other words, even though almost all cells in your body contain the same DNA and the same genes, what makes a liver cell different from a muscle cell is the expression of different genes in different cell types. Often this is referred to as **differential gene expression**.

Mutations All living organisms are subject to genetic mutations, or changes, in the nucleotide sequences of DNA. Mutation is the source of genetic variability that is acted on by natural selection, allowing for evolutionary change over time. Some mutations are detrimental to the organism, and DNA repair mechanisms have evolved to reduce the negative impact of mutations. For example, DNA repair enzymes monitor and fix irregularities in DNA caused when the molecule is exposed to UV. Mutations can be spontaneous, occurring for no apparent reason, or induced by environmental factors such as radiation and toxins. Carcinogens are mutation-inducing factors (mutagens) that cause cancer. **Point mutations**—in which one nucleotide base in a gene sequence is incorrect—can have a range of effects, depending on the particular codon change. Sickle-cell disease is an example of a point mutation that affects the ability of hemoglobin, a protein in red blood cells, to carry oxygen. **Frameshift mutations** result when one or more bases are added or deleted, and the result is usually a nonfunctional protein that drastically can affect the phenotype. Most cases of cystic fibrosis, albinism, and androgen insensitivity are due to nonfunctional proteins. As we studied, cancer can result due to an accumulation of genetic mutations among genes that code for proteins that regulate the cell cycle. The cell cycle occurs inappropriately when proto-oncogenes become oncogenes and tumor suppressor genes are no longer effective. Mutations that affect transcription and other regulators of gene expression also are associated with cancer.

ASSESS

Choose the best answer for each question.

4.1 Prokaryotic Regulation

1. In regulation of the *lac* operon, when lactose is present and glucose is absent,
   a. there is a low level of cAMP present.
   b. there is a high level of cAMP present.
   c. transcription of structural genes occurs.
   d. transcription of lactose occurs.
2. In regulation of the *trp* operon, when tryptophan is present,
   a. the repressor is able to bind to the operator.
   b. the repressor is unable to bind to the operator.
   c. transcription of the repressor in inhibited.
   d. transcription of the structural genes, operator, and promoter occurs.
3. In operon models, the function of the promoter is to
   a. code for the repressor protein.
   b. bind with RNA polymerase.
   c. bind to the repressor.
   d. code for the regulator gene.

4.2 Eukaryotic Regulation

4. Which of the following regulate(s) gene expression in the eukaryotic nucleus?
   a. transcriptional control
   b. translational control
   c. posttranscriptional control
   d. Both a and c are correct.
5. Which of the following mechanisms may create multiple mRNAs from the same gene?
   a. posttranslational control
   b. alternative mRNA splicing
   c. binding of a transcription factor
   d. chromatin remodeling
6. Translational control of gene expression occurs within the
   a. nucleus.
   b. cytoplasm.
   c. nucleolus.
   d. mitochondria.
7. Barr bodies are
   a. genetically active X chromosomes in males.
   b. genetically inactive X chromosomes in females.
   c. genetically active Y chromosomes in males.
   d. genetically inactive Y chromosomes in females.

4.3 Gene Mutations

8. A mutation in a DNA molecule involving the replacement of one nucleotide base pair with another is called a(n)
   a. frameshift mutation.
   b. transposon.
   c. deletion mutation.
   d. base substitution.
9. THE COW ATE THE HAY. If the letter *C* is deleted from this sentence, shifting the reading frame, we read THE OWA TET HEH AY. Which of the following mutations *best* explains this example?
   a. spontaneous mutation
   b. frameshift mutation
   c. induced mutation
   d. base substitution
10. A cell is cancerous. You might find an abnormality in
    a. a proto-oncogene.
    b. a tumor suppressor gene.
    c. regulation of the cell cycle.
    d. All of these are correct.
11. A tumor suppressor gene
    a. inhibits cell division.
    b. opposes oncogenes.
    c. is subject to mutations.
    d. All of these are correct.

ENGAGE

AP Applying the Big Ideas

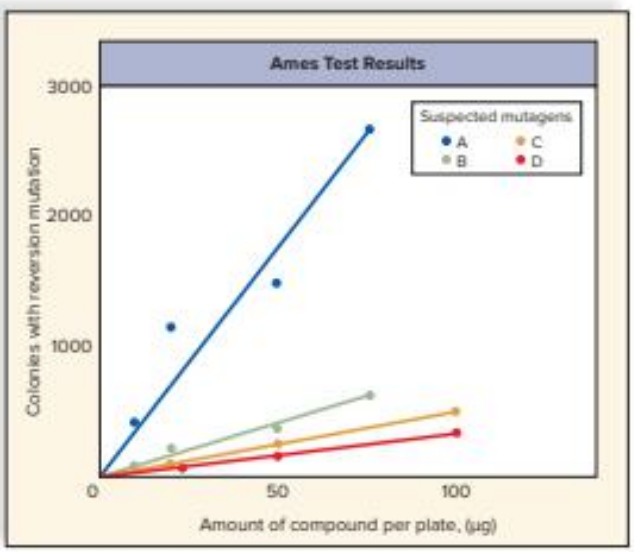
1. BIG IDEA 1 Scientists claim that organisms share many conserved core processes and features that evolved and are widely distributed among organisms today. **Defend this claim** using THREE pieces of evidence from the mechanisms for the regulation of gene expression.

2. BIG IDEA 3 Eukaryotes have evolved a variety of regulatory mechanisms that allow them to fine-tune gene expression and produce a large number of proteins from a relatively small number of genes. **Explain** how THREE regulatory mechanisms of gene expression support efficient cell function.

3. BIG IDEA 4 Your classmate is able to recite that external and internal cues affect gene regulation, but is unable to explain what is meant by the statement. Improve on their understanding by explaining the phenomena using THREE examples to illustrate what it means.

AP Applying the Science Practices

How can we know if a compound is a mutagen? The Ames test is used to identify mutagens. The test uses a strain of bacteria that cannot make the amino acid histidine. The bacteria are exposed to a suspected mutagen and grow on a medium without histidine. The bacteria that grow have a mutation called a reversion because they reverted to the natural condition of making histidine. The compounds in the graph were Ames tested.



*Data obtained from: Ames, B.N. 1979. Identifying environmental chemicals causing mutations and cancer. *Science*. 204: 587–593.

Think Critically SP 5 SP 6

1. **Describe** the relationship between the amount of the compound and the mutation.
2. **Analyze** which compound is the strongest mutagenic compound.

5

Biotechnology and Genomics

Combating tooth decay with traditional methods may one day be a thing of the past.

Chapter Outline

AP Dental disease in cats is one of the most common medical conditions seen by veterinarians. Approximately two thirds of all cats over the age of 3 are estimated to have some form of gum or tooth decay. The oral cavity of cats is a perfect incubator for many kinds of bacteria, and as these bacteria multiply, they form an invisible layer called plaque. Toxins produced by some of these bacteria could be absorbed into the cat's bloodstream, produce infections, and cause damage to organs.

In an effort to combat dental disease, researchers have been modifying tobacco plants to produce vaccines against the decay-causing bacterium *Streptococcus mutans*. These vaccines could reduce painful and costly dental procedures, and they have both veterinary and human applications. Another approach is the genetic engineering of the *Streptococcus mutans* itself. Tooth decay arises when this bacterium releases lactic acid on teeth, creating the holes in the enamel that become cavities. Scientists are creating strains that cannot produce lactic acid and would simply wash away with saliva.

The tobacco plants and bacteria were altered through a process called biotechnology—the manipulation of living organisms that results in a desired process or product. Other bacteria can be modified to make insulin or to eat pollutants. Crop plants can be altered to have higher vitamin content, or to be more resistant to pests. Even animals are being genetically modified and cloned to produce specific proteins in their milk. Gene therapies also exist in humans, where a DNA change can cure or slow down a disease.

As you read through the chapter, think about these Essential Questions:

1. How can DNA analysis and genome comparison allow us to better understand the evolution of species? 1.A.4.b.3
2. How can genetic engineering techniques be used to benefit human society? 3.A.1.e.*IE*
3. How can the manipulation of DNA by humans affect the evolution of species, and what are the ethical, medical, or social implications? 3.A.1.f.*IE*

Following *the* BIG IDEAS

BIG IDEA 1 — The field of comparative genomics is yielding valuable new insights into the relationships between species, impacting taxonomy and evolutionary biology.

BIG IDEA 3 — Genetic engineering allows beneficial changes to be made in DNA and RNA sequences, improving the products or the actions of these molecules.

5.1 DNA Cloning

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the steps involved in making a recombinant DNA molecule.
2. Explain the purpose of the polymerase chain reaction (PCR).
3. Identify how PCR may be used to analyze DNA.

In biology, **cloning** is the production of genetically identical copies of DNA, cells, or organisms through some asexual means. When an underground stem or root sends up new shoots, the resulting plants are clones of one another. The members of a bacterial colony on a petri dish are clones, because they all came from the division of a single original cell. Human identical twins are also considered clones. Early in embryonic development the cells separate, and each becomes a complete individual.

DNA cloning can be done to produce many identical copies of the same gene—that is, for the purpose of **gene cloning.** Scientists clone genes for a number of reasons. They might want to determine the difference in base sequence between a normal gene and a mutated gene. Or they might use the genes to genetically modify organisms in a beneficial way. When cloned genes are used to modify a human, the process is called **gene therapy.** Otherwise, the organisms are called **transgenic organisms** (L. *trans,* "across, through"; Gk. *genic,* "producing"). Transgenic organisms are frequently used today to produce a product desired by humans.

Recombinant DNA (rDNA) technology and the polymerase chain reaction (PCR) are two procedures that scientists can use to clone DNA.

Recombinant DNA Technology

Recombinant DNA (**rDNA**) contains DNA from two or more different sources, such as a human cell and a bacterial cell, as shown in Figure 5.1. To make rDNA, a technician needs a **vector** (L. *vehere,* "to carry") by which rDNA will be introduced into a host cell. One common vector is a plasmid. **Plasmids** are small accessory rings of DNA found in bacteria; they were first discovered in the bacterium *Escherichia coli* (*E. coli*). The ring is not part of the main bacterial chromosome; it replicates on its own and can be easily removed from or introduced into a bacterial cell.

Two enzymes are needed to introduce foreign DNA into vector DNA: (1) a **restriction enzyme,** which cleaves (cuts) DNA, and (2) an enzyme called **DNA ligase** (L. *ligo,* "bind"), which seals DNA into an opening created by the restriction enzyme. Hundreds of restriction enzymes occur naturally in bacteria, and they cut up any viral DNA that enters the cell. They are called restriction enzymes because they *restrict* the growth of viruses. Scientists take advantage of these enzymes and use them as molecular scissors to cleave any piece of DNA at a specific site.

Notice that the restriction enzyme creates a puzzlelike gap in the DNA (Fig. 5.2), into which a piece of foreign DNA can be placed if its ends are complementary to those exposed by the restriction enzyme. The single-stranded, but complementary, ends of the two DNA molecules are called "sticky ends" because they can bind a piece of foreign DNA by complementary base-pairing. Sticky ends facilitate the insertion of foreign DNA into vector DNA as long as both are cleaved by the same restriction enzyme.

Next, genetic engineers use the enzyme DNA ligase to seal the foreign piece of DNA into the vector. DNA splicing is now complete; an rDNA molecule has been prepared (see Fig. 5.1). Bacterial cells take up recombinant plasmids, when they are treated to make their plasma membranes more permeable. Thereafter, as the plasmid replicates, DNA is cloned.

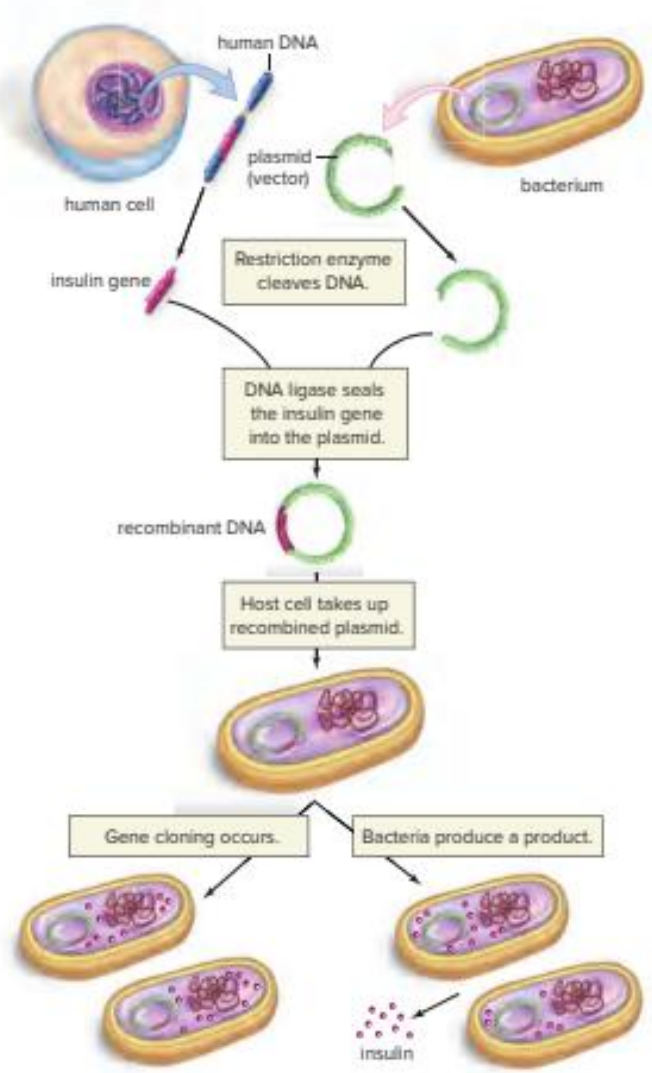


Figure 5.1 Cloning a human gene. This figure shows the basic steps in the cloning of a human gene. Human DNA and plasmid DNA are cleaved by a specific type of restriction enzyme. Then the human DNA, perhaps containing the insulin gene, is spliced into a plasmid by the enzyme DNA ligase. Gene cloning is achieved after a bacterium takes up the plasmid. If the gene functions normally, as expected, the product (e.g., insulin) may also be retrieved.

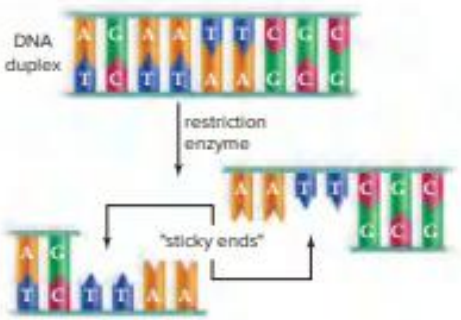


Figure 5.2 Restriction enzymes cut DNA at specific locations. Each restriction enzyme recognizes a specific sequence of nucleotides. After the enzyme cuts the DNA, "sticky ends" may be formed that are useful in the cloning of DNA sequences.

The Polymerase Chain Reaction

Another revolution in molecular biology was the development of the **polymerase chain reaction (PCR)**. American biochemist Kary Mullis developed PCR in 1983, and in 1993, he was awarded the Nobel Prize in Chemistry for his discovery. PCR can accelerate the pace of genetic engineering by quickly creating many clones of a piece of DNA without first inserting it into a plasmid. The process mimics DNA replication in the cell (see section 3.2), except that PCR is very specific—it amplifies (makes copies of) only a targeted DNA sequence. The targeted sequence can be less than one part in a million of the total DNA sample!

PCR requires the use of DNA polymerase, the enzyme that carries out DNA replication, and a supply of nucleotides for the new DNA strands. The DNA polymerase used in the reaction is a heat-stable (thermostable) polymerase that has been extracted from the bacterium *Thermus aquaticus*, which lives in hot springs. The enzyme can withstand the high temperature used to separate double-stranded DNA; therefore, replication does not have to be interrupted by the need to add more enzyme. PCR is a chain reaction because the targeted DNA is repeatedly replicated as long as the process continues. The colors in Figure 5.3 distinguish the old strand from the new DNA strand, but keep in mind that all the newly synthesized strands are identical (clones). Notice that the amount of DNA doubles with each replication cycle.

Analyzing DNA

DNA amplified by PCR can be analyzed for various purposes. For example, mitochondrial DNA taken from modern living populations was used to decipher the evolutionary history of human populations. For identification purposes, DNA taken from a corpse burned beyond recognition can be matched to that on the bristles of the person's toothbrush!

Analysis of DNA following PCR has undergone improvements over the years. At first, the entire genome was treated with restriction enzymes, resulting in a unique collection of different-sized fragments, because each person has his or her own restriction enzyme sites. A process called **gel electrophoresis,** which separates DNA fragments according to their size, was then employed; the result of fragment sorting was a pattern of distinctive bands that identified the person.

DNA fingerprinting (also called **DNA profiling**) is a technology that can identify and distinguish among individuals based on variations in their DNA. Like the human fingerprint, the DNA of each individual is different and can be used for identification. When subjected to DNA fingerprinting, selected fragments of chromosomal DNA produce a series of bands on a gel (Fig. 5.4*a*). The unique pattern of these bands is usually a distinguishing feature of each individual.

In the past two decades, the technique of DNA fingerprinting has become automated and is now done using PCR, which amplifies

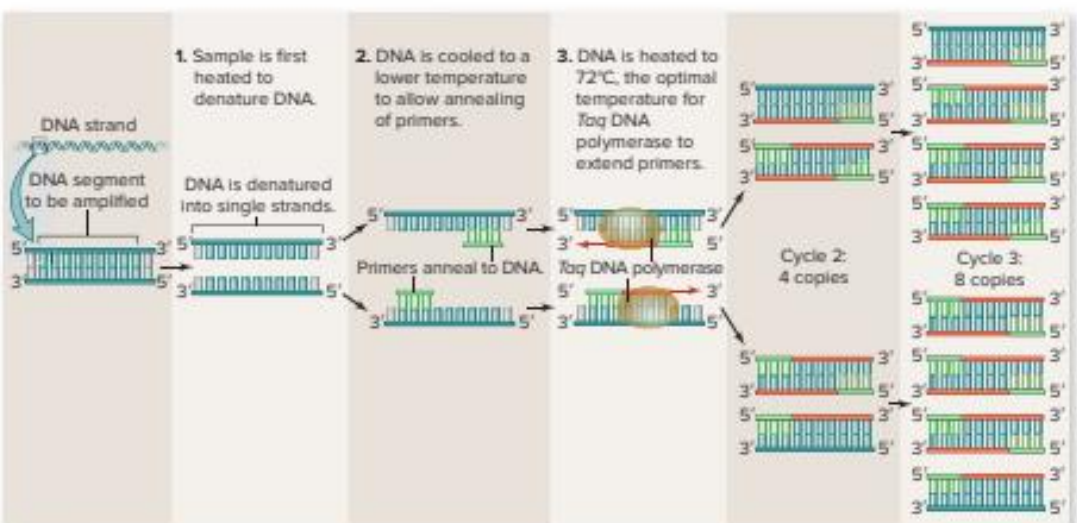


Figure 5.3 Polymerase chain reaction (PCR). PCR allows the production of many identical copies of a specific sequence of DNA in a laboratory setting.

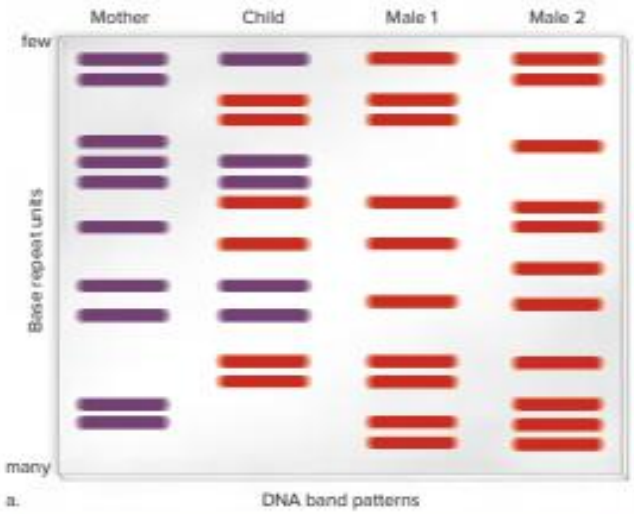


Figure 5.4 DNA fingerprinting using STRs to establish paternity. **a.** In this method, DNA fragments containing STRs are separated by gel electrophoresis. Male 1 is the father. **b.** Each person's DNA fingerprint (only one is shown) can also be printed out by a machine that detects fluorescence.

short tandem repeat sequences (**STRs**)—short DNA sequences that are repeated many times in a row. Such tandem repeat sequences, which are noncoding regions of chromosomal DNA, are found at specific locations in the genomes of all species. The number of repeats at each location tends to vary from one individual to the next. For example, humans have the sequence GATA on chromosome 7. One person may have this sequence 10 times, while another may have 15 repeats. The person with the higher number of repeats will have a larger DNA fragment.

The newest method of producing DNA fingerprints does away with the need to use gel electrophoresis: The DNA fragments are fluorescently labeled. A laser then excites the fluorescent STRs, and a detector records the amount of emission for each DNA fragment in terms of peaks and valleys. Therefore, the greater the fluorescence, the greater the number of repeats at a location. The printout, such as the one shown in Figure 5.4*b*, is the DNA fingerprint, and each person has his or her own unique printout. Currently, the Federal Bureau of Investigation (FBI) uses 13 STR locations on various chromosomes that are now routinely used in the identification of individuals in the United States.

Other Applications

Applications of PCR are limited only by the imagination.

- A viral infection, a genetic disorder, or cancer can be confirmed when the DNA tested matches that of a known virus or mutated gene.
- DNA fingerprinted from blood or tissues at a crime scene has been successfully used in screening suspects, convicting criminals, and exonerating those wrongly convicted.
- DNA fingerprinting through STR profiling has been extensively used to identify the victims of natural disasters, such as tsunamis in Indonesia and Japan.
- Relatives can be found, paternity suits can be settled (Fig. 5.4*a*), genetic disorders can be detected, and illegally poached ivory and fish can be recognized using this technology.
- PCR has also shed new light on evolutionary studies by comparing extracted DNA from ancient specimens with that of living organisms or by comparing DNA of two living species to study their genetic relatedness.

Check Your Progress **5.1**

1. Explain the purpose of restriction enzymes in creating an rDNA molecule.
2. Contrast how gene cloning is different between recombinant technology and PCR.
3. Explain how DNA fingerprinting distinguishes individuals.

5.2 Biotechnology Products

Learning Outcomes

Upon completion of this section, you should be able to

1. Identify the benefits of genetically modified bacteria, plants, and animals to human society.
2. Describe the steps involved in the production of a transgenic animal.

Today, transgenic bacteria, plants, and animals are often called **genetically modified organisms** (**GMOs**), and the products they produce are called **biotechnology products.**

Genetically Modified Bacteria

Many uses have been found for genetically modified bacteria, besides the production of proteins. Biotechnology products from bacteria include insulin, clotting factor VIII, human growth hormone, t-PA (tissue plasminogen activator), and hepatitis B vaccine.

Transgenic bacteria have many other uses as well. Some have been produced to promote the health of plants. For example, bacteria that normally live on plants and encourage the formation of ice crystals have been changed from frost-plus to frost-minus bacteria. As a result, new crops, such as frost-resistant strawberries,

are being developed. Also, a bacterium that normally colonizes the roots of corn plants has now been endowed with genes (from another bacterium) that code for an insect toxin. The toxin protects the roots from insects.

Bacteria can be selected for their ability to degrade a particular substance, and this ability can then be enhanced by bioengineering. *Bioremediation* is the process that uses microorganisms or other organisms, such as plants, to detoxify pollutants in the environment. For instance, naturally occurring bacteria that eat oil have been genetically engineered to clean up beaches (Fig. 5.5) after oil spills, such as the 2010 Deep Water Horizon spill in the Gulf of Mexico. Bacteria can also remove sulfur from coal before it is burned and help clean up toxic waste dumps. One such strain was given genes that allowed it to clean up levels of toxins that would have killed other strains. Further, these bacteria were given "suicide" genes that caused them to self-destruct when the job had been accomplished.

Organic chemicals are often synthesized by having catalysts act on precursor molecules or by using bacteria to carry out the synthesis. Today, it is possible to go one step further and manipulate the genes that code for these enzymes. For instance, biochemists discovered a strain of bacteria that is especially good at producing phenylalanine, an organic chemical needed to make aspartame, the dipeptide sweetener better known as NutraSweet®. They isolated, altered, and formed a vector for the appropriate genes, so that various other bacteria could be genetically engineered to produce phenylalanine.

Genetically Modified Plants

Techniques have been developed to introduce foreign genes into immature plant embryos or into plant cells called *protoplasts* that have had the cell wall removed. The protoplasts are treated with an electric current while they are suspended in a liquid containing foreign DNA. The current creates tiny, self-sealing holes in the plasma membrane, through which the DNA can enter. These treated protoplasts go on to develop into mature plants.

Foreign genes transferred to strains of cotton, corn, potato, and even bananas have made these plants resistant to pests such as fungi and insects, because their cells now produce a chemical that is toxic to the pest species. Similarly, soybeans have been made resistant to a common herbicide. Some corn and cotton plants are both pest- and herbicide-resistant. A new strain of rice called Golden Rice has been engineered to have a higher vitamin A content. These and other genetically modified crops are now sold commercially, with the goal of increased yields and better nutrient content. Like bacteria, plants are also being engineered to produce human proteins, such as hormones, clotting factors, and antibodies, in their seeds. One type of antibody made by corn can deliver radioisotopes to tumor cells; another, made by soybeans, can be used to treat genital herpes. Currently, tobacco plants are being used to develop a vaccine against tooth decay.

Figure 5.5 Bioremediation. Bacteria capable of decomposing oil have been engineered and patented by researchers such as Dr. Chakrabarty.

Genetically Modified Animals

Techniques have been developed to insert genes into the eggs of animals. It is possible to microinject foreign genes into eggs by hand, but another method uses vortex mixing. The eggs are placed in an agitator with DNA and silicon-carbide needles, and the needles make tiny holes through which the DNA can enter. When these eggs are fertilized, the resulting offspring are transgenic animals. Through this technique, many types of animal eggs have taken up the gene for bovine growth hormone (bGH). The procedure has been used to produce larger fishes, cows, rabbits, and sheep.

Gene pharming, the use of transgenic farm animals to produce pharmaceuticals, is being pursued by a number of firms. Genes that code for therapeutic and diagnostic proteins are incorporated into an animal's DNA, and the proteins appear in the animal's milk. Trials are under way for drugs that treat cystic fibrosis, cancer, blood diseases, and other disorders. Figure 5.6*a* outlines the procedure for producing transgenic mammals: DNA containing the gene of interest is injected into donor eggs. Following in vitro fertilization, the zygotes are placed in host females, where they develop. After female offspring mature, the product is secreted in their milk.

Cloning Transgenic Animals

For many years, researchers believed that adult vertebrate animals could not be cloned, because cloning requires that all the genes of an adult cell be turned on if development is to proceed normally. This had long been thought impossible.

In 1997, however, Scottish scientists announced that they had produced a cloned sheep, which they called Dolly. Since then, calves, goats, rabbits, and even cats have also been cloned. The techniques can be applied to produce populations of transgenic animals.

As shown in Figure 5.6*b*, after enucleated eggs from a donor are microinjected with 2n nuclei from a single transgenic animal, they are coaxed to begin development in vitro. Development

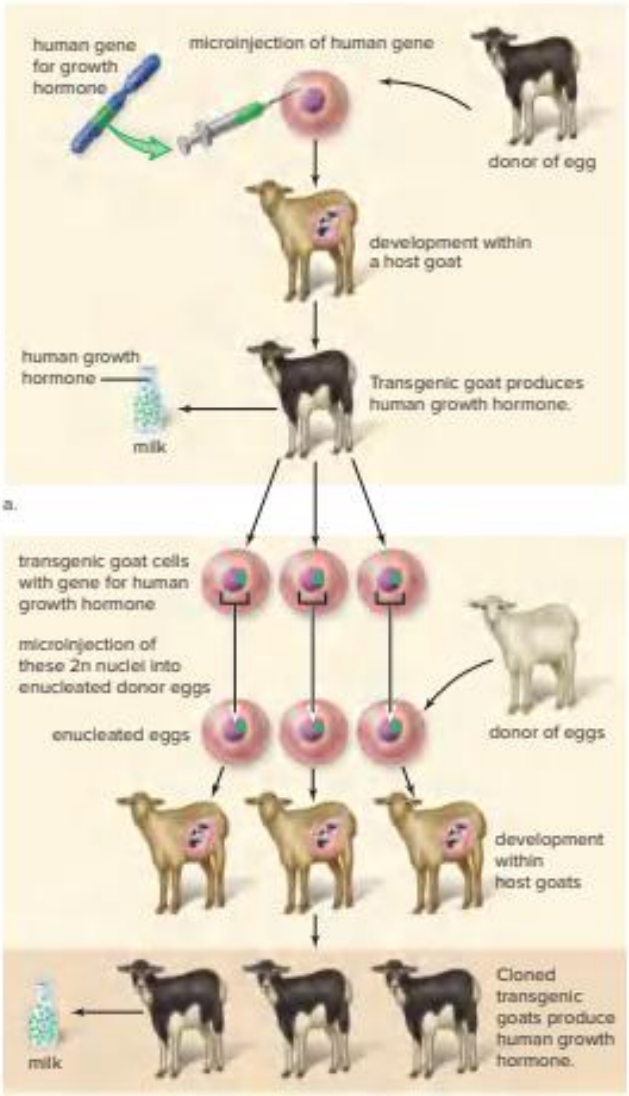


Figure 5.6 Transgenic mammals produce a product. This figure illustrates the basic procedure for generating a transgenic animal. **a.** A bioengineered egg develops in a host to create a transgenic goat, which produces a biotechnology product in its milk. **b.** Nuclei from the transgenic goat are transferred into donor eggs, which develop into cloned transgenic goats.

continues in host females until the clones are born. The female clones have the same product in their milk as does the original transgenic animal. Now that scientists have a way to clone animals, this procedure will undoubtedly be used routinely to procure biotechnology products. However, animal cloning is a difficult process with a low success rate (usually 1 or 2 viable embryos per 100 attempts). The vast majority of cloning attempts are unsuccessful, resulting in the early death of the clone.

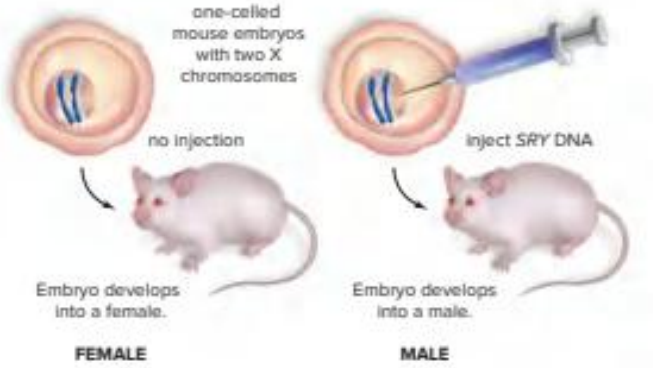


Figure 5.7 Experimental use of mice. Bioengineered mice showed that maleness is due to *SRY* DNA.

Compared with the production of proteins in bacteria, one advantage of molecular pharming is that certain proteins are more likely to function properly when expressed in mammals. This may be due to specific protein folding or other modifications that occur in mammals but not in bacteria. In addition, certain proteins may be degraded rapidly or folded improperly when expressed in bacteria. Furthermore, the yield of recombinant proteins in milk can be quite large. Each dairy cow, for example, produces about 10,000 liters of milk per year. In some cases, a transgenic cow can produce appoximately 1 gram per liter (g/L) of the transgenic protein in its milk.

Applications of Transgenic Animals

Researchers are using transgenic mice for many different research projects. Figure 5.7 shows how this technology has demonstrated that a section of DNA called *SRY* (sex determining region of the *Y* chromosome) produces a male animal. The *SRY* gene was cloned, and then one copy was injected into single-celled mouse embryos. Injected embryos developed into males, but any that were not injected developed into females.

Eliminating a gene is another way to study a gene's function. A *knockout mouse* has had both alleles of a gene removed or made nonfunctional. For example, scientists have constructed a knockout mouse lacking the *CFTR* gene, the same gene mutated in cystic fibrosis patients. The mutant mouse has a phenotype similar to that of a human with cystic fibrosis and can be used to test new drugs for the treatment of the disease.

Check Your Progress 5.2

1. List some of the beneficial applications of transgenic bacteria, animals, and plants.
2. Distinguish between a transgenic animal and a cloned animal.

5.3 Gene Therapy

Learning Outcomes

Upon completion of this section, you should be able to

1. Distinguish between in vivo and ex vivo gene therapy in humans.
2. List examples of how in vivo and ex vivo gene therapy has been used to treat human disease.

The manipulation of an organism's genes can be extended to humans in a process called **gene therapy.** Gene therapy is an accepted therapy for the treatment of a disorder and has been used to cure inborn errors of metabolism, as well as to treat more generalized disorders, such as cardiovascular disease and cancer.

Viruses genetically modified to be safe can be used to transport a normal gene into the body. Sometimes the gene is injected directly into a particular region of the body. In the following sections, we discuss examples of **ex vivo gene therapy,** in which the gene is inserted into cells that have been removed and then returned to the body, and **in vivo gene therapy,** in which the gene is delivered directly into the body.

ex vivo – a process that takes place outside of a living organism
in vivo – a process that takes place inside of a living organism

Ex Vivo Gene Therapy

Children who have SCID (severe combined immunodeficiency) lack the enzyme ADA (adenosine deaminase), which is involved in the maturation of immune cells. Therefore, these children are prone to constant infections and may die unless they receive treatment. To carry out gene therapy, bone marrow stem cells are removed from the bone marrow of the patient and are infected with a virus that carries a normal gene for the enzyme into their DNA. Then the cells are returned to the patient, where it is hoped they will divide to produce more blood cells with the same genes.

One of the earliest uses of ex vivo gene therapy was for familial hypercholesterolemia, a condition that develops when liver cells lack a receptor protein for removing cholesterol from the blood. The high levels of blood cholesterol make the patient subject to fatal heart attacks at a young age. In this procedure, a small portion of the liver was surgically excised and then infected with a virus containing a normal gene for the receptor before being returned to the patient. Patients experienced lowered serum cholesterol levels following this procedure. Scientists are investigating using ex vivo gene therapy to treat other human diseases, including some forms of hemophilia.

One type of ex vivo gene therapy is gene transfer by modified blood cells. This is used in the skin to treat skin cancer. Another example is gene transfer by modified implants, such as is used in the liver to treat familial hypercholesterolemia. In enothelium, or blood vessel lining, gene transfer by implantation of modified implants is used to treat hemophilia and diabetes mellitus. And gene transfer by implantation of modified stem cells is used in bone marrow to treat SCID and sickle-cell disease.

In Vivo Gene Therapy

Cystic fibrosis patients lack a gene that codes for a transmembrane carrier of the chloride ion. They often suffer from numerous and potentially deadly infections of the respiratory tract. In gene therapy trials, the gene needed to cure cystic fibrosis is sprayed into the nose or delivered to the lower respiratory tract by adenoviruses. Another method of delivery is to enclose the gene in a lipid globule called a liposome. So far, this treatment has resulted in limited success, but recent advances in the use of lentiviral vectors is promising. Lentiviruses have a long incubation period and have been shown to be effective in infecting lung tissue.

In cancer patients, genes are being used to make healthy cells more tolerant of, and tumors more vulnerable to, chemotherapy. The gene *p53* brings about apoptosis, and there is much interest in introducing it into cancer cells that no longer have the gene and in that way killing them off.

Sites for in vivo gene therapy include the brain, lungs, blood, and muscle. In the brain, gene transfer by injection is used to treat Huntington disease, Alzheimer disease, Parkinson disease, and brain tumors. The same therapy is used in muscles to treat Duchenne muscular dystrophy. In the lungs, gene transfer by aerosol spray is used to treat cystic fibrosis and hereditary emphysema. Gene transfer by bone marrow transplant is used in the blood to treat sickle-cell disease.

Check Your Progress 5.3

1. Describe the methods that are being used to introduce genes into humans for gene therapy.
2. Discuss an example of ex vivo and of in vivo gene therapy.

5.4 Genomics

Learning Outcomes

Upon completion of this section, you should be able to

1. Distinguish among the sciences of genomics, proteomics, and bioinformatics.
2. Identify the function of repetitive elements, transposons, and unique noncoding DNA sequences in the human genome.
3. Explain how DNA microarrays are used in the study of genomics.

In the preceding century, researchers discovered the structure of DNA, how DNA replicates, and how DNA and RNA are involved in the process of protein synthesis. Genetics in the twenty-first century concerns **genomics**, the study of genomes—our complete genetic makeup and that of other organisms. Knowing the sequence of bases in genomes is the first step, and thereafter we want to understand the function of our genes and their introns, as well as the intergenic sequences. The enormity of the task can be appreciated by knowing that there are approximately 6 billion base nucleotides in the 2n human genome. Many other organisms have a larger number of protein-coding genes but fewer noncoding regions compared to the human genome.

Sequencing the Genome

We now know the order of the base pairs in the human genome. This feat, which has been likened to arriving at the periodic table of the elements in chemistry, was accomplished by the **Human Genome Project (HGP)**, a 13-year effort that involved both university and private laboratories around the world.

In the beginning, investigators developed a laboratory procedure that would allow them to decipher a short sequence of base pairs, and then instruments became available that could carry out sequencing automatically. Over the 13-year span, DNA sequencers were constantly improved, and now modern instruments can automatically analyze up to 2 million base pairs of DNA in a 24-hour period.

Sperm DNA was the material of choice for analysis, because it has a much higher ratio of DNA to protein than other types of cells. (Recall that sperm do provide both X and Y chromosomes.) However, white blood cells from female donors were also used in order to include female-originated samples. The male and female donors were of European, African, American (both North and South), and Asian ancestry.

Many small regions of DNA that vary among individuals, termed polymorphisms, were identified during the HGP. Most of these are *single nucleotide polymorphisms* (*SNPs*); they vary by only one nucleotide. Many SNPs have no effect; others may contribute to enzymatic differences affecting the phenotype. It's possible that certain SNP patterns change an individual's susceptibility to disease and alter his or her response to medical treatments (see Chapter 16).

Determining the number of genes in the human genome required a number of techniques, many of which relied on identifying RNAs in cells and then working backward to find the DNA that can pair with each RNA. **Structural genomics**—knowing the sequence of the bases and how many genes we have—is now being followed by functional genomics.

Estimates place the number of human genes between 21,000 and 23,000. The majority of these genes are expected to code for proteins. However, much of the human genome was formerly described as "junk," because it does not specify the order of amino acids in a polypeptide. However, recall from Chapter 12 that it is possible for RNA molecules to have a regulatory effect in cells. We examine this in more detail in the next section.

Structure of the Eukaryotic Genome

Historically, genes were defined as discrete units of heredity that corresponded to a locus on a chromosome (see Fig. 2.4). Prokaryotes typically possess a single circular chromosome with genes that are packed together very closely; eukaryotic chromosomes, in contrast, are much more complex: The genes are seemingly randomly distributed along the length of a chromosome and are fragmented into exons, with intervening sequences called introns scattered throughout the length of the gene (Fig. 5.9).

In general, more complex organisms have more complex genes with more and larger introns. In humans, 95% or more of the average protein-coding gene is introns. Once a gene is transcribed, the introns must be removed and the exons joined together to form a functional mRNA transcript (see Fig. 3.14).

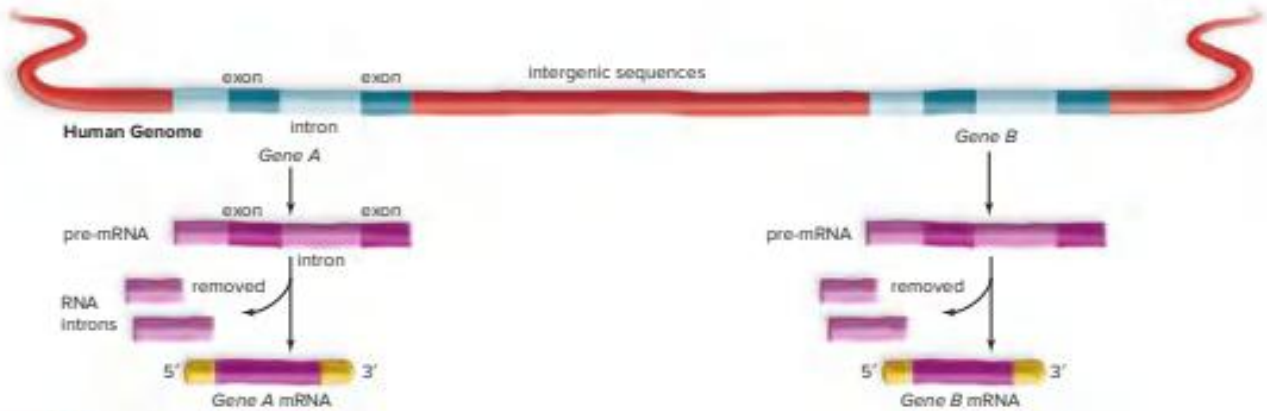
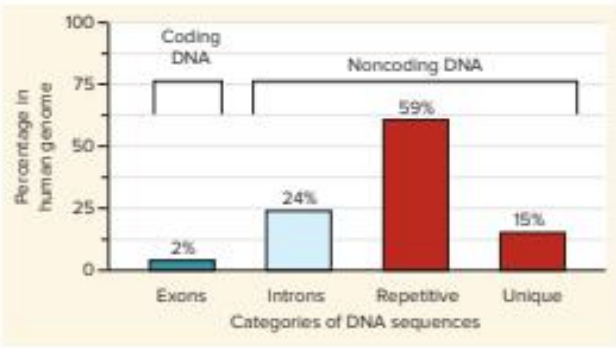


Figure 5.9 Chromosomal DNA. A genome contains protein-coding DNA (exons) and noncoding DNA, including introns (light blue) and other intergenic sequences (red). Only the exons are present in mRNA and specify protein synthesis.

Once regarded as merely intervening sequences, introns are now attracting attention as regulators of gene expression. The presence of introns allows exons to be put together in various sequences, so that different mRNAs and proteins can result from a single gene. Introns might also regulate gene expression and help determine which genes are to be expressed and how they are to be spliced. In fact, entire genes have been found embedded within the introns of other genes.

Intergenic Sequences

DNA sequences occur between genes and are referred to as **intergenic sequences** (Fig. 5.9). In general, as the complexity of an organism increases, so does the proportion of its noncoding DNA sequences. Intergenic sequences are now known to comprise the vast majority of human chromosomes, and protein-coding genes represent only about 1.5–2.0% of our total DNA. The remainder of this DNA, once dismissed as "junk DNA," is now thought to serve many important functions. Several basic types of intergenic sequences are found in the human genome, including (1) repetitive elements, (2) transposons, and (3) unique noncoding DNA. The majority of intergenic sequences belong to this last class.



Repetitive DNA Elements

Repetitive DNA elements occur when a sequence of two or more nucleotides is repeated many times along the length of one or more chromosomes. Repetitive elements are very common—comprising nearly half of the human genome—therefore, many scientists believe that their true significance has yet to be discovered. Although many scientists still dismiss them as having no function, others point out that the centromeres and telomeres of chromosomes are composed of repetitive elements, suggesting that repetitive DNA elements may not be as useless as once thought. For one thing, repetitive DNA of the centromere could possibly help with segregating the chromosomes during cell division.

Repetitive DNA elements include tandem repeats and interspersed repeats. **Tandem repeat** means that the repeated sequences are next to each other on the chromosome. Tandem repeats are often referred to as satellite DNA, because they have a different density than the rest of the DNA within the chromosome. The number and types of tandem repeats may vary significantly from one individual to another, making them invaluable as indicators of heritage. One type of tandem repeat sequence, referred to as *short tandem repeats*, or *STRs*, has become a standard method in forensic science for distinguishing one individual from another and for determining familial relationships (see page 247).

The second type of repetitive DNA element is called an **interspersed repeat,** meaning that the repetitions may be placed intermittently along a single chromosome or across multiple chromosomes. For example, a repetitive DNA element, known as the *Alu* sequence, is interspersed every 5,000 base pairs in human DNA and comprises nearly 5–6% of total human DNA. Because of their common occurrence, interspersed repeats are thought to play a role in the evolution of new genes.

Transposons

Transposons are specific DNA sequences that have the remarkable ability to move within and between chromosomes. Their movement to a new location sometimes alters neighboring genes, particularly decreasing their expression. In other words, a transposon sometimes acts as a regulator gene. The movement of transposons throughout the genome is thought to be a driving force in the evolution of living organisms. The *Alu* repetitive element is an example of a transposon. In fact, many scientists now think that many repetitive DNA elements were originally derived from transposons.

Although Barbara McClintock first described these "movable elements" in corn over 60 years ago, it took time for the scientific community to fully appreciate this revolutionary idea. In fact, their significance was only realized within the past few decades. Transposons, sometimes termed "jumping genes," have now been discovered in bacteria, fruit flies, humans, and many other organisms. McClintock received a Nobel Prize in 1983 for her discovery of transposons and for her pioneering work in genetics (Fig. 5.10).

Unique Noncoding DNA

Genes constitute an estimated 1.5% of the human genome, and repetitive DNA elements make up about 44%; the function of the remaining half, or *unique noncoding DNA*, remains a mystery. Even though this DNA does not appear to contain any protein-coding genes, it has been highly conserved through evolution. In the many millions of years that separate humans from mice, large tracts of this mysterious DNA have remained almost unchanged. But if this DNA has no relevant function, then why has it been so meticulously maintained?

Recently, scientists observed that between 74% and 93% of the genome is transcribed into RNA, including many of these unknown sequences. Thus, what was once thought to be a vast "junk DNA wasteland" may be much more important than once thought and may play active roles in the cell. Small-sized RNAs may be able to carry out regulatory functions more easily than proteins at times. Therefore, a previously overlooked RNA signaling network may be what allows humans, for example, to achieve structural complexity far beyond anything seen in the unicellular world. Together, these findings have revealed a much more complex, dynamic genome than was envisioned merely a few decades ago.

Revisiting the Definition of a Gene

Perhaps the modern definition of a gene should take the emphasis away from the chromosome and place it on the results of transcription. Previously, molecular genetics considered a gene to

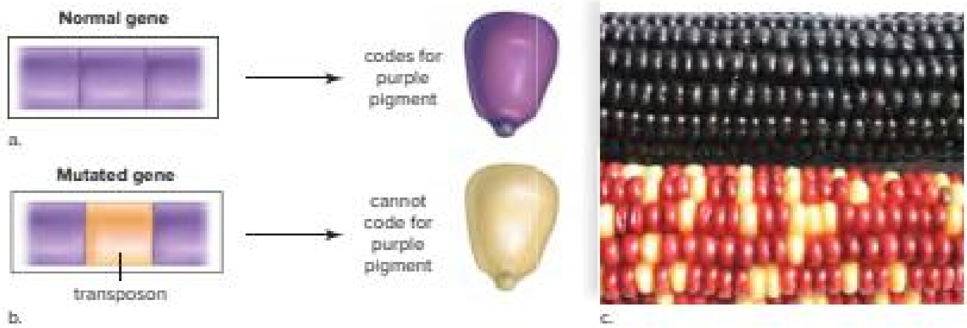


Figure 5.10 Transposons may cause gene mutations. **a.** A purple-coding gene ordinarily codes for a purple pigment. **b.** A transposon "jumps" into the purple-coding gene. This mutated gene is unable to code for purple pigment, and a white kernel results. **c.** Indian corn displays a variety of colors and patterns due to transposon activity.

be a nucleic acid sequence that codes for the sequence of amino acids in a protein. In contrast to this definition, geneticists have known for some time that all three types of RNA are transcribed from DNA, and that these RNAs are useful products. We also know that protein-coding regions can be interrupted by regions that do not code for a protein but do produce RNAs with various functions. This knowledge expands on the central dogma of genetics and recognizes that a gene product need not be a protein, and a gene need not be on one locus on a chromosome. The DNA sequence that results in a gene product can be split and be present on one or several chromosomes. Also, any DNA sequence can result in one or more products. Furthermore, some prokaryotes have RNA genes. In other words, the genetic material need not be DNA. Again, we can view this as a simple expansion of the central dogma of genetics.

Functional and Comparative Genomics

Since we now know the structure of our genome, the emphasis today is on functional genomics and on comparative genomics. The aim of **functional genomics** is to understand the exact role of the genome in cells or organisms.

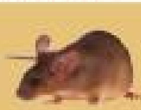
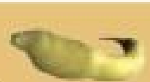
The Nature of Science feature, "Testing for Genetic Disorders," on page 90, discusses the importance of a new technology that can be used to monitor the expression of thousands of genes simultaneously. **DNA microarrays,** also known as DNA chips or genome chips, contain microscopic amounts of known DNA sequences fixed onto a small glass slide or silicon chip in known locations (see Fig. 5A). The use of a microarray can tell you what genes are turned on in a specific cell or organism at a particular time and under what environmental circumstances. When mRNA molecules of a cell or an organism bind through complementary base pairing with the various DNA sequences on an array, then that gene is active in the cell.

DNA microarrays are increasingly available that rapidly identify all the mutations in the genome of an individual. This information is called the person's **genetic profile.** The genetic profile can indicate if any genetic illnesses are likely and what type of drug therapy for an illness might be most appropriate for that individual.

The aim of **comparative genomics** is to compare the human genome to the genome of other organisms, such as the model organisms listed in Table 5.1. Model organisms are used in genetic analysis because they have many genetic mechanisms and cellular pathways in common with each other and with humans. Functional genomics has also been advanced through the study of these genomes.

Much has been learned by genetically modifying mice; however, other model organisms can also be used. Scientists inserted

Table 5.1 Comparison of Sequenced Genomes

Organism	 *Homo sapiens* (human)	 *Mus musculus* (mouse)	 *Drosophila melanogaster* (fruit fly)	 *Arabidopsis thaliana* (flowering plant)	 *Caenorhabditis elegans* (roundworm)	 *Saccharomyces cerevisiae* (yeast)
Estimated Size	3,300 million bases	2,800 million bases	180 million bases	125 million bases	97 million bases	12 million bases
Estimated Number of Genes	~23,000	~23,000	13,600	25,500	21,700	5,700
Chromosome Number	46	40	8	10	12	32

Nature of Science

Testing for Genetic Disorders

Genetic testing is required if prospective parents are concerned about being carriers for autosomal recessive disorders. If a woman is already pregnant, the parents may want to know if the unborn child has a disorder. If the woman is not pregant, the parents may opt for testing of an embryo or egg before she does become pregnant. One way to detect genetic disorders is to test the DNA for mutated genes.

Testing the DNA

DNA testing typically uses procedures that test for a specific genetic marker, or probe the genome for sequences of interest using DNA microarrays. Testing for a genetic marker is similar to the traditional procedure for DNA fingerprinting, as discussed earlier. As an example, consider that individuals with Huntington disease have an abnormality in the sequence of bases at a particular location on a chromosome. An unusually long STR can be found, which in turn causes a frameshift mutation in a gene. The length of the STR can be detected with PCR.

DNA Microarrays

With advances in robotic technology, it is now possible to place the entire human genome onto a single microarray (Fig. 5A). The mRNA from the organism or the cell to be tested is labeled with a fluorescent dye and added to a chip. When the mRNAs bind to the microarray, a fluorescent pattern results and is recorded by a computer. Now the scientist knows what DNA is active in that cell or organism. A researcher can use this method to determine the difference in gene expression between two different cell types, such as between liver cells and muscle cells.

A mutation microarray, the most common type, can be used to generate a person's genetic profile. The microarray contains hundreds to thousands of known diseases-associated mutant gene alleles. Genomic DNA from the individual to be tested is labeled with a fluorescent dye, then added to a microarray. The spots on the microarray fluoresce if the individual's DNA binds to the mutant genes on the chip, indicating that the individual may have a particular disorder or is at risk for developing it later in life. This technique can generate a genetic profile quicker than the older methods of DNA sequencing.

DNA microarrays can also identify genes associated with diseased tissues. The investigator applies the mRNA from normal and abnormal tissue to the microarray. The intensity of fluorescense from a spot on the microarray indicates the amount of mRNA originating from that gene in the diseased tissue relative to the normal tissue. If a gene is activated in the disease, more copies of mRNA will bind to the microarray than the control tissue, and the spot will appear more red than green.

Genomic microarrays are also used to identify links between disease and chromosomal variations. In this case, the chip contains genomic DNA that is cut into fragments. Each spot on the microarray corresponds to a known chromosomal location. Labeled genomic DNA from diseased tissues and control tissues bind to the DNA on the chip, and the fluorescense from both dyes is determined. If the number of copies of any particular target DNA has increased, more sample DNA will bind to that spot on the microarray relative to the control DNA, and a difference in fluorescence of the two dyes will be detected.

Home kits are now available to consumers who want their genetic profile. An individual would submit a DNA sample and receive a report with over 240 possible conditions and traits, including carrier status for various diseases. Currently, the U.S. Federal Drug Administration (FDA) is concerned about "false" positives that may cause consumers to undergo unnecessary medical procedures or undue stress and is working with these companies to improve the product and the information relayed to consumers.

Questions to Consider

1. What benefits are there when using a DNA microarray over a genetic marker such as an STR?
2. Why might a researcher want to know what genes are being expressed in different cell types?
3. How might the information from a DNA microarray be used to develop new medicines to treat disease?

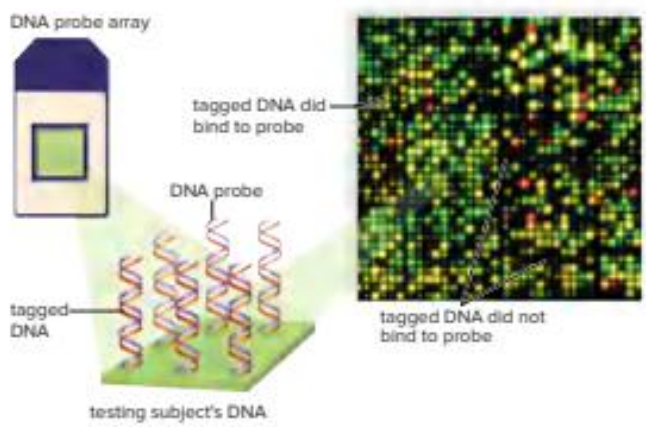


Figure 5A Use of a DNA microarray to test for a genetic disorder. This DNA chip contains rows of DNA sequences for mutations that indicate the presence of particular genetic disorders. If DNA fragments derived from an individual's DNA bind to a sequence representing a mutation on the DNA chip, that sequence fluoresces, and the individual has the mutation.

a human gene associated with early-onset Parkinson disease into *Drosophila melanogaster,* and the flies showed symptoms similar to those seen in humans with the disorder. This outcome suggested that we might be able to use these organisms instead of mice to test therapies for Parkinson disease.

Comparative genomics also offers a way to study changes in a genome over time, because the model organisms have a shorter generation time than humans. Comparing genomes can also help us understand the evolutionary relationships between organisms. One surprising discovery is that the genomes of all vertebrates are highly similar. Researchers were not surprised to find that the genes of chimpanzees and humans are 98% alike, but they did not expect to find that our sequence is also 85% like that of a mouse. Genomic comparisons will likely reveal evolutionary relationships between organisms never previously considered.

Proteomics

The entire collection of a species' proteins is the **proteome.** At first, it may be surprising to learn that the proteome is larger than the genome until we consider all the many regulatory mechanisms, such as alternative pre-mRNA splicing, that increase the number of possible proteins in an organism.

Proteomics is the study of the structure, function, and interaction of cellular proteins. Specific regulatory mechanisms differ between cells, and these differences account for the specialization of cells. One goal of proteomics is to identify and determine the function of the proteins within a particular cell type. Each cell produces thousands of different proteins, which can vary not only between cells but also within each cell, depending on circumstances. Therefore, the goal of proteomics is an overwhelming endeavor. Microarray technology can assist with this project, as can today's supercomputers.

Computer modeling of the three-dimensional shape of cellular proteins is also an important part of proteomics. If the primary structure of a protein is known, it should be possible to predict its final three-dimensional shape, and even the effects of DNA mutations on the protein's shape and function.

The study of protein function is viewed as essential to the discovery of new and better drugs. Also, it may be possible in the future to correlate drug treatment to the particular proteome of the individual to increase its efficiency and decrease side effects.

Bioinformatics

Bioinformatics is the application of computer technologies, specially developed software, and statistical techniques to the study of biological information, particularly databases that contain much genomic and proteomic information (Fig. 5.11). The new, raw data produced by structural genomics and proteomics are stored in databases that are readily available to research scientists. They are called raw data because, as yet, they have little meaning. Functional genomics and proteomics are dependent on computer analysis to find significant patterns in the raw data. For example, BLAST, which stands for *b*asic *l*ocal *a*lignment search *t*ool, is a computer program that can identify homologous genes among the genomic sequences of model organisms. **Homologous genes** are genes that code for the same proteins, although the base sequences may be slightly different. Finding these differences can help trace the history of evolution among a group of organisms.

Figure 5.11 Bioinformatics. New computer programs are being used to make sense of the raw data generated by genomics and proteomics. Bioinformatics allows researchers to study both functional and comparative genomics in a meaningful way.

Bioinformatics also has various applications in human genetics. For example, researchers found the function of the protein that causes cystic fibrosis by using the computer to search for genes in model organisms that have the same sequence. Because they knew the function of this gene in model organisms, they could deduce the function in humans. This was a necessary step toward possibly developing specific treatments for cystic fibrosis.

The human genome has 3 billion known base pairs, and without the computer it would be almost impossible to make sense of these data. For example, it is now known that an individual's genome often contains multiple copies of a gene. But individuals may differ as to the number of copies—called *copy number variations.* It seems that the number of copies in a genome can be associated with specific diseases. The computer can help make correlations between genomic differences among large numbers of people and disease.

It is safe to say that, without bioinformatics, progress in determining the function of DNA sequences, comparing our genome to model organisms, knowing how genes and proteins interact in cells, and so forth would be extremely slow. The Evolution feature, "Metagenomics," on page 92, discusses the use of bioinformatics in the new field of metagenomics.

Check Your Progress 5.4

1. Distinguish between the genome and the proteome of a cell.
2. Summarize the difference between a short tandem repeat and a transposon.
3. Explain how the use of microarrays and bioinformatics aids in the study of genomics and proteomics.

BIG IDEA 1: Evolution

Metagenomics

In Figure 5B, a microbiologist dips a hand in a pond to extract a muddy substance teeming with life. What microorganisms are in this sample? How do the various microbes interact, and how are they all adapted to living in this environment? These are just a few of many questions that can be answered in the field of metagenomics. Metagenomics studies metagenomes—genetic material obtained directly from environmental samples. A broad sample of collected organisms allows investigators to determine evolutionary interactions in a particular environment by revealing the hidden biodiversity of microscopic life.

Traditionally, if a scientist wanted to know what microbial species were present in a sample, he or she would have had to isolate one species from another and be able to culture it in a laboratory to obtain enough DNA for sequencing. Only the most abundant species would be isolated and cultured, resulting in a loss of the true biodiversity that actually existed in the sample. Methods have been developed to address this shortcoming.

Shotgun Sequencing

One of the methods employed in metagenomics is the use of shotgun sequencing, a technique also used in the Human Genome Project. Shotgun sequencing got its name from the broad trajectory of buckshot a shotgun blast produces. Shotgun sequencing can be likened to putting ten copies of this textbook in a shredder, then taking those pieces out and reassembling a complete book. The approach randomly shears DNA, sequences the short fragments, then reassembles these sequences into the correct order in what is called a consensus sequence (Fig. 5C).

When studying microbial biodiversity, the scientist feeds the sequence information into a computer, and bioinformatics software begins the filtering process. Eukaryotic DNA can be identified and removed, leaving the microbial DNA behind for analysis. The biggest challenge scientists face working in metagenomics is the enormous size of the fragmented data. Genes isolated from the microorganisms in the human gut revealed 3.3 million genes, requiring close to 570 gigabases of sequence data. Collecting and analyzing data sets of this size is a difficult computational challenge. Many of these challenges are being met by software developers working in bioinformatics.

Studies Using Metagenomics

Investigators working with the San Diego Zoo were interested in the gut microbes that inhabit various species of mammals. They asked, does each type of mammal have its own community of microbes? The study analyzed the fecal DNA from 34 mammalian species, including humans, and determined what microbes lived in the gut of each species. Most of the fecal samples were obtained from zoo animals with closely monitored diets, as well as humans who kept a strict food diary. The results showed that the *diet* of mammals, not the specific species of that mammal, determines what microorganims live in the gut. The collection of gut microbes is conserved across mammalian species, depending on what they eat. If a mammal is an herbivore, one set of microbes exists in the gut compared with the mammals that are omnivores or carnivores.

Metagenomics can also be used as a diagnostic tool to discover causative agents of diseases. Researchers working on a disease affecting boa constrictors suspected that a virus was to blame. DNA from affected and healthy snakes was obtained, and all the snake DNA was filtered out using a computer. The resulting DNA sequences revealed arenaviruses and a virus that was a hybrid of two previously identified viruses. The results not only confirmed that the snake disease was viral but also had larger implications for viral evolution—arenaviruses were only previously known to infect mammals and had never been identified in reptiles. This discovery opened up many questions about host range, evolution, and mechanisms of pathogenesis of viruses.

Questions to Consider

1. Why is metagenomics used versus traditional genomic techniques?
2. Why is shotgun sequencing used in this field of study?
3. Why is metagenomics closely tied to evolutionary biology?

Figure 5B Obtaining an environmental sample. Scientists interested in microbial diversity can collect a sample of mixed species and use metagenomics to analyze what species and genes are present.

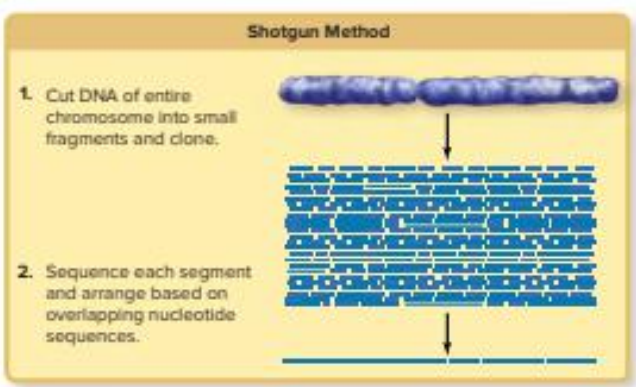


Figure 5C Shotgun sequencing method. The metagenome of an environmental sample is fragmented into small clones and sequenced. Computers assemble and analyze DNA sequences.

REVIEWING *the* BIG IDEAS

BIG IDEA 1 Modern technology allows comparisons of genomes of organisms from every domain, revealing interesting and sometimes unexpected relationships. 1.A.4.b.3

BIG IDEA 3 Genes from virtually every organism can be cloned using *in vivo* plasmid-based transformation technology; multiple copies of a DNA sequences can be produced *in vitro* using PCR. 3.A.1.e.*IE*

Electrophoresis and restriction enzymes are widely used for DNA analysis. 3.A.1.e.*IE*

Genetically modified organisms (GMOs), including transgenic and cloned animals and plants, have been engineered to add beneficial characteristics or to produce novel protein products such as pharmaceuticals. 3.A.1.f.*IE*

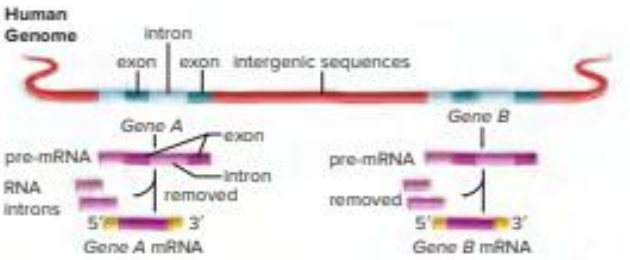
SUMMARIZE

AP Answering the Essential Questions

Genetic engineering techniques enable scientists to manipulate the heritable information stored in DNA and, in special cases, RNA. Using model organisms as a guide, geneticists are able to recombine DNA molecules, clone animals and plants, and produce transgenic organisms such as trees (or mice) that fluoresce in the dark. We likely have eaten genetically modified foods, and you may know someone who has received gene therapy to treat a disease. We certainly have seen examples of how DNA analysis is used to solve crimes. From an evolutionary standpoint, the field of comparative genomics is yielding valuable new insights into the relationship among species.

DNA biotechnology One example of DNA technology involves **cloning**. Cloning produces genetically identical copies of DNA, cells, or organisms. **Gene cloning** results when a gene is isolated and many copies are produced. The gene can be studied in the laboratory or inserted into a bacterium, plant, or an animal, creating **transgenic organisms**. Then, this gene may be transcribed and translated to produce a protein, which can become a commercial product or a medicine such as human insulin. When a gene is inserted into a human, the process is called **gene therapy**. Gene therapy has been used in the fight against cancer, cystic fibrosis, and cardiovascular disease.

Two methods are currently available for making copies of DNA: **recombinant DNA** technology and the **polymerase chain reaction (PCR)**. Recombinant DNA contains DNA from two different sources. A **restriction enzyme** is used to cut or cleave **plasmid** (vector) DNA and foreign (donor) DNA at specific regions. The resulting "sticky ends" facilitate the insertion of foreign DNA into vector DNA, and the foreign gene is sealed into the vector DNA by DNA ligase. Both bacterial plasmids and viruses can be used as vectors to carry foreign genes into bacterial host cells. PCR uses the enzyme DNA polymerase (which we studied in Chapter 3) to quickly make multiple copies of a specific piece (target) of DNA. PCR is a chain reaction because in the lab the targeted DNA can be replicated over and over again. Analysis of DNA segments using **gel electrophoresis** following PCR has all sort of uses from assisting genomic research to doing **DNA fingerprinting** for the purposes of identifying individuals and confirming paternity. Even more precise DNA fingerprinting can be accomplished by taking advantage of **short tandem repeats (STR)** present in the genomes of all organisms.



Another example of how biotechnology is used is the creation of transgenic organisms, also called **genetically modified organisms (GMOs)**, which have had a foreign gene inserted into them. Genetically modified bacteria, agricultural plants such as corn, and farm animals now produce biotechnology products of interest to humans, such as hormones and vaccines. Bacteria usually secrete the product, and the seeds of plants and the milk of animals contain the product. Transgenic bacteria have been engineered to promote the health of plants, extract minerals, produce chemicals, and perform bioremediation (solving environmental issues such as contamination). Transgenic crops that are engineered to resist herbicides and pests are commercially available. Questions emerge from these technologies, including the safety of genetically modified foods.

Genomics Using biotechnology, researchers in the field of **genomics** know the sequence of all the base pairs along the length of human chromosomes. This achievement, known at the **Human Genome Project**, helped researchers identify around 21,000 genes that code for proteins—about 1.5% of the human genome. The rest of our DNA consists of regions that do not code for protein, and the information that was once considered "junk DNA" (e.g., tandem repeats and transposons) is now believed to be more active in genome evolution than once thought. Other noncoding regions may be involved in regulating gene expression. Through genomics, scientists are working to understand the function of the protein-coding regions and noncoding regions of our genomes. Comparative genomics has revealed that little difference exists between the DNA sequence of our bases and those of many other organisms, increasing our knowledge of evolutionary relationships among species.

ASSESS

Choose the best answer for each question.

5.1 DNA Cloning

1. Restriction enzymes in bacterial cells are ordinarily used
   a. during DNA replication.
   b. to degrade the bacterial cell's DNA.
   c. to degrade viral DNA that enters the cell.
   d. to attach pieces of DNA together.
2. Using the key, put the phrases in the correct order to form a plasmid-carrying recombinant DNA.

Key:

1. use restriction enzymes
2. use DNA ligase
3. remove plasmid from parent bacterium
4. introduce plasmid into new host bacterium

   a. 1, 2, 3, 4
   b. 4, 3, 2, 1
   c. 3, 1, 2, 4
   d. 2, 3, 1, 4
3. The polymerase chain reaction
   a. uses RNA polymerase.
   b. takes place in huge bioreactors.
   c. uses a temperature-insensitive enzyme.
   d. makes lots of nonidentical copies of DNA.

5.2 Biotechnology Products

4. Bacteria are able to successfully transcribe and translate human genes because
   a. both bacteria and humans contain plasmid vectors.
   b. bacteria can replicate their DNA, but humans cannot.
   c. human and bacterial ribosomes are vastly different.
   d. the genetic code is nearly universal.
5. Which of these is an incorrect statement?
   a. Bacteria usually secrete the biotechnology product into the medium.
   b. Plants are being engineered to have human proteins in their seeds.
   c. Animals are engineered to have a human protein in their milk.
   d. Animals can be cloned, but plants and bacteria cannot.
6. Which is not a correct association with regard to bioengineering?
   a. plasmid as a vector—bacteria
   b. protoplast as a vector—plants
   c. RNA virus as a vector—human stem cells
   d. All of these are correct.

5.3 Gene Therapy

7. When a cloned gene is used to modify a human disease, the process is called
   a. bioremediation.
   b. gene therapy.
   c. genetic profiling.
   d. gene pharming.
8. Which of the following delivery methods is not used in gene therapy?
   a. virus
   b. nasal sprays
   c. liposomes
   d. electric currents

5.4 Genomics

9. A genetic profile can
   a. assist an individual in maintaining good health.
   b. show how many genes are normal.
   c. be accomplished utilizing a microarray.
   d. Both a and c are correct.
10. Which is a true statement?
    a. Genomics would be slow going without bioinformatics.
    b. Genomics is related to the field of proteomics.
    c. Genomics shows that we are related to all other organisms tested so far.
    d. All of these are correct.
11. Which of the following was used to find the function of the cystic fibrosis gene?
    a. microarray
    b. proteomics
    c. comparative genomics and bioinformatics
    d. sequencing of the gene
12. Repetitive DNA elements
    a. may be tandem or spread across several chromosomes.
    b. are found in centromeres and telomeres.
    c. make up nearly half of human chromosomes.
    d. All of these are correct.
13. Bioinformatics can
    a. assist genomics and proteomics.
    b. compare our genome to that of a primate.
    c. depend on computer technology.
    d. All of these are correct.
14. Proteomics is used to discover
    a. what proteins are active in what cells.
    b. the structure and function of proteins.
    c. how proteins interact.
    d. All of these are correct.

ENGAGE

AP Applying the Big Ideas

1. BIG IDEA 1 The field of comparative genomics is yielding valuable new insights into the relationships between species, impacting taxonomy and evolutionary biology.
   a. **Describe** TWO kinds of data that could be collected by scientists to provide a direct answer to the question, how is the concept of biological evolution supported by genomics?
   b. **Explain** how the data you suggested in part (a) would provide a direct answer to the question.

2. BIG IDEA 3 Identify and describe at least TWO commonly used genetic engineering technologies used by scientists to manipulate heritable information.

AP Applying the Science Practices

How can DNA microarrays be used to classify types of prostate cancer? The gene expression profiles between normal prostate cells and prostate cancer cells can be compared using DNA microarray technology.

Data and Observations

The diagram shows a subset of the data obtained.

*Data obtained from: Lapointe, et al. 2004. Gene expression profiling identifies clinically relevant subtypes of prostate cancer. *PNAS* 101: 811–816.

Think Critically

1. **Calculate** the percentage of spots that are yellow. Then calculate the percentage of green spots and red spots.
2. **Explain** why some of the spots are black.
3. **Apply Concepts** How would you choose a gene to study as a cause of prostate cancer?

My Notes