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A premature baby in an incubator.

18

Lipids and Their Functions in Biochemical Systems

BIOCHEMISTRY

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Learning Goals

1. Discuss the physical and chemical properties and biological function of each of the families of lipids.
2. Write the structures of saturated and unsaturated fatty acids.
3. Compare and contrast the structure and properties of saturated and unsaturated fatty acids.
4. Write equations representing the reactions that fatty acids undergo.
5. Describe the functions of prostaglandins.
6. Discuss the mechanism by which aspirin reduces pain.
7. Draw the structure of a phospholipid and discuss its amphipathic nature.
8. Discuss the general classes of sphingolipids and their functions.
9. Draw the structure of the steroid nucleus and discuss the functions of steroid hormones.
10. Describe the function of lipoproteins in triglyceride and cholesterol transport in the body.
11. Draw the structure of the cell membrane and discuss its functions.
12. Discuss passive and facilitated diffusion of materials through a cell membrane.
13. Explain the process of osmosis.
14. Describe the mechanism of action of a Na^+-K^+ ATPase.

CHEMISTRY CONNECTION

Lifesaving Lipids

In the intensive-care nursery the premature infant struggles for life. Born three and a half months early, the baby weighs only 1.6 pounds, and the lungs labor to provide enough oxygen to keep the tiny body alive. Premature infants often have respiratory difficulties because they have not yet begun to produce *pulmonary surfactant*.

Pulmonary surfactant is a combination of phospholipids and proteins that reduces surface tension in the alveoli of the lungs. (Alveoli are the small, thin-walled air sacs in the lungs.) This allows efficient gas exchange across the membranes of the alveolar cells; oxygen can more easily diffuse from the air into the tissues and carbon dioxide can easily diffuse from the tissues into the air.

Without pulmonary surfactant, gas exchange in the lungs is very poor. Pulmonary surfactant is not produced until early in the sixth month of pregnancy. Premature babies born before they have begun secretion of natural surfactant suffer from *respiratory distress syndrome (RDS)*, which is caused by the severe difficulty they have obtaining enough oxygen from the air that they breathe.

Until recently, RDS was a major cause of death among premature infants, but now a lifesaving treatment is available. A fine aerosol of an artificial surfactant is administered directly into the trachea. The Glaxo-Wellcome Company product EXOSURF Neonatal contains the phospholipid lecithin to reduce surface tension; 1-hexadecanol, which spreads the lecithin; and a polymer called tyloxapol, which disperses both the lecithin and the 1-hexadecanol.

Artificial pulmonary surfactant therapy has dramatically reduced premature infant death caused by RDS and appears to have reduced overall mortality for all babies born weighing less than 700 g (about 1.5 pounds). Advances such as this have come about as a result of research on the makeup of body tissues and secretions in both healthy and diseased individuals. Often, such basic research provides the information needed to develop effective therapies.

In this chapter we will study the chemistry of lipids with a wide variety of structures and biological functions. Among these are the triglycerides that stock our adipose tissue, pain-producing prostaglandins, and steroids that determine our secondary sexual characteristics.

Introduction

Lipids seem to be the most controversial group of biological molecules, particularly in the fields of medicine and nutrition. One concern is the use of anabolic steroids by athletes. Although these hormones increase muscle mass and enhance performance, we are just beginning to understand the damage they cause to the body.

We are concerned about what types of dietary fat we should consume. We hear frequently about the amounts of saturated fats and cholesterol in our diets because a strong correlation has been found between these lipids and heart disease. Large quantities of dietary saturated fats may also predispose an individual to colon, esophageal, stomach, and breast cancers. As a result, we are advised to reduce our intake of cholesterol and saturated fats.

Nonetheless, lipids serve a wide variety of functions essential to living systems and are required in our diet. Standards of fat intake have not been experimentally determined. However, the most recent U.S. Dietary Guidelines recommend that dietary fat not exceed 30% of the daily caloric intake, and no more than 10% should be saturated fats.

18.1 Biological Functions of Lipids

Learning Goal 1

The term **lipids** actually refers to a collection of organic molecules of varying chemical composition. They are grouped together on the basis of their solubility in nonpolar solvents. Lipids are commonly subdivided into four main groups:

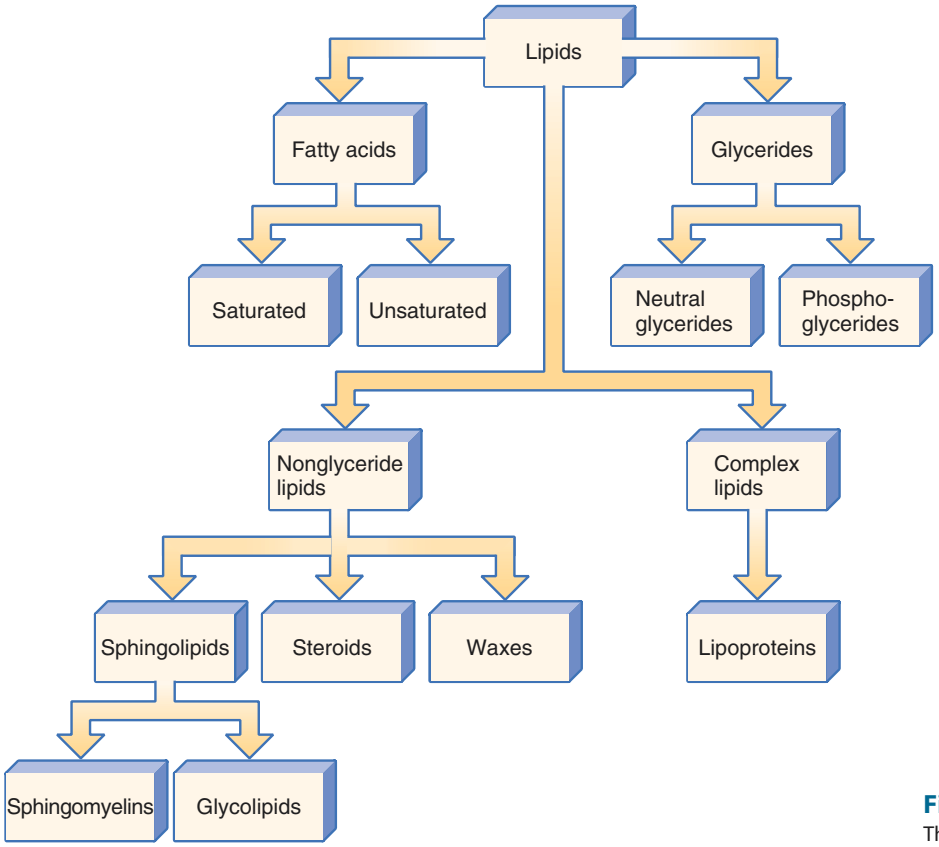


Figure 18.1
The classification of lipids.

1. *Fatty acids* (saturated and unsaturated)
2. *Glycerides* (glycerol-containing lipids)
3. *Nonglyceride lipids* (sphingolipids, steroids, waxes)
4. *Complex lipids* (lipoproteins)

In this chapter we examine the structure, properties, chemical reactions, and biological functions of each of the lipid groups shown in Figure 18.1.

As a result of differences in their structures, lipids serve many different functions in the human body. The following brief list will give you an idea of the importance of lipids in biological processes:

- *Energy source.* Like carbohydrates, lipids are an excellent source of energy for the body. When oxidized, each gram of fat releases 9 kcal of energy, or more than twice the energy released by oxidation of a gram of carbohydrate.
- *Energy storage.* Most of the energy stored in the body is in the form of lipids (triglycerides). Stored in fat cells called *adipocytes,* these fats are a particularly rich source of energy for the body.
- *Cell membrane structural components.* Phosphoglycerides, sphingolipids, and steroids make up the basic structure of all cell membranes. These membranes control the flow of molecules into and out of cells and allow cell-to-cell communication.
- *Hormones.* The steroid hormones are critical chemical messengers that allow tissues of the body to communicate with one another. The prostaglandins exert strong biological effects on both the cells that produce them and other cells of the body.

Lipid-soluble vitamins are discussed in detail in Appendix E.

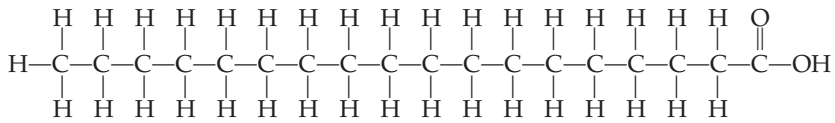
- *Vitamins.* The lipid-soluble vitamins, A, D, E, and K, play a major role in the regulation of several critical biological processes, including blood clotting and vision.
- *Vitamin absorption.* Dietary fat serves as a carrier of the lipid-soluble vitamins. All are transported into cells of the small intestine in association with fat molecules. Therefore a diet that is too low in fat can result in a deficiency of these four vitamins.
- *Protection.* Fats serve as a shock absorber, or protective layer, for the vital organs. About 4% of the total body fat is reserved for this critical function.
- *Insulation.* Fat stored beneath the skin (subcutaneous fat) serves to insulate the body from extremes of cold temperatures.

18.2 Fatty Acids

Structure and Properties

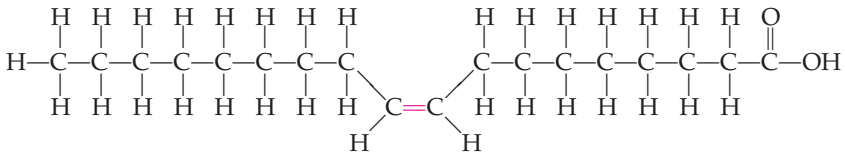
Learning Goal 2

Fatty acids are long-chain monocarboxylic acids. As a consequence of their biosynthesis, fatty acids generally contain an *even number* of carbon atoms. The general formula for a **saturated fatty acid** is $CH_3(CH_2)_nCOOH$, in which n in biological systems is an even integer. If $n = 16$, the result is an 18-carbon saturated fatty acid, stearic acid, having the following structural formula:



The saturated fatty acids may be thought of as derivatives of alkanes, the saturated hydrocarbons described in Chapter 11.

Note that each of the carbons in the chain is bonded to the maximum number of hydrogen atoms. To help remember the structure of a saturated fatty acid, you might think of each carbon in the chain being "saturated" with hydrogen atoms. Examples of common saturated fatty acids are given in Table 18.1. An example of an **unsaturated fatty acid** is the 18-carbon unsaturated fatty acid oleic acid, which has the following structural formula:



The unsaturated fatty acids may be thought of as derivatives of the alkenes, the unsaturated hydrocarbons discussed in Chapter 12.

In the case of unsaturated fatty acids there is at least one carbon-to-carbon double bond. Because of the double bonds, the carbon atoms involved in these bonds are not "saturated" with hydrogen atoms. The double bonds found in almost all naturally occurring unsaturated fatty acids are in the *cis* configuration. In addition, the double bonds are not randomly located in the hydrocarbon chain. Both the placement and the geometric configuration of the double bonds are dictated by the enzymes that catalyze the biosynthesis of unsaturated fatty acids. Examples of common unsaturated fatty acids are also given in Table 18.1.

EXAMPLE 18.1 ***Writing the Structural Formula of an Unsaturated Fatty Acid***

Draw the structural formula for palmitoleic acid.

Solution

The I.U.P.A.C. name of palmitoleic acid is *cis*-9-hexadecenoic acid. The name tells us that this is a 16-carbon fatty acid having a carbon-to-carbon

Continued—

Table 18.1 Common Saturated and Unsaturated Fatty Acids

Common Saturated Fatty Acids

Common Name	I.U.P.A.C. Name	Melting Point (°C)	RCOOH Formula	Condensed Formula
Capric	Decanoic	32	$C_9H_{19}COOH$	$CH_3(CH_2)_8COOH$
Lauric	Dodecanoic	44	$C_{11}H_{23}COOH$	$CH_3(CH_2)_{10}COOH$
Myristic	Tetradecanoic	54	$C_{13}H_{27}COOH$	$CH_3(CH_2)_{12}COOH$
Palmitic	Hexadecanoic	63	$C_{15}H_{31}COOH$	$CH_3(CH_2)_{14}COOH$
Stearic	Octadecanoic	70	$C_{17}H_{35}COOH$	$CH_3(CH_2)_{16}COOH$
Arachidic	Eicosanoic	77	$C_{19}H_{39}COOH$	$CH_3(CH_2)_{18}COOH$

Common Unsaturated Fatty Acids

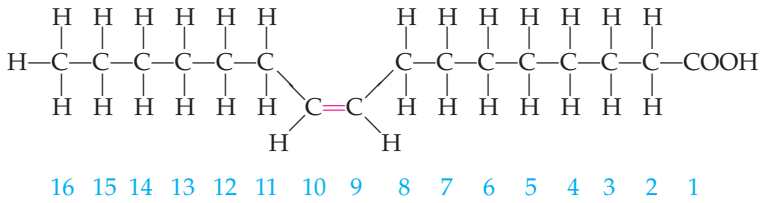
Common Name	I.U.P.A.C. Name	Melting Point (°C)	RCOOH Formula	Number of Double Bonds	Position of Double Bonds
Palmitoleic	*cis*-9-Hexadecenoic	0	$C_{15}H_{29}COOH$	1	9
Oleic	*cis*-9-Octadecenoic	16	$C_{17}H_{33}COOH$	1	9
Linoleic	*cis,cis*-9,12-Octadecadienoic	5	$C_{17}H_{31}COOH$	2	9, 12
Linolenic	All *cis*-9,12,15-Octadecatrienoic	−11	$C_{17}H_{29}COOH$	3	9, 12, 15
Arachidonic	All *cis*-5,8,11,14-Eicosatetraenoic	−50	$C_{19}H_{31}COOH$	4	5, 8, 11, 14

Condensed Formula

Palmitoleic	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$
Oleic	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
Linoleic	$CH_3(CH_2)_4CH{=}CH{-}CH_2{-}CH{=}CH(CH_2)_7COOH$
Linolenic	$CH_3CH_2CH{=}CH{-}CH_2{-}CH{=}CH{-}CH_2{-}CH{=}CH(CH_2)_7COOH$
Arachidonic	$CH_3(CH_2)_4CH{=}CH{-}CH_2{-}CH{=}CH{-}CH_2{-}CH{=}CH{-}CH_2{-}CH{=}CH{-}(CH_2)_3COOH$

EXAMPLE 18.1 *—Continued*

double bond between carbons 9 and 10. The name also reveals that this is the *cis* isomer.



Examination of Table 18.1 and Figure 18.2 reveals several interesting and important points about the physical properties of fatty acids.

- The melting points of saturated fatty acids increase with increasing carbon number, as is the case with alkanes. Saturated fatty acids containing ten or more carbons are solids at room temperature.
- The melting point of a saturated fatty acid is greater than that of an unsaturated fatty acid of the same chain length. The reason is that saturated fatty acid chains tend to be fully extended and to stack in a regular structure, thereby causing increased intermolecular attraction. Introduction of a *cis*

Learning Goal 3

The relationship between alkane chain length and melting point is described in Section 11.2.

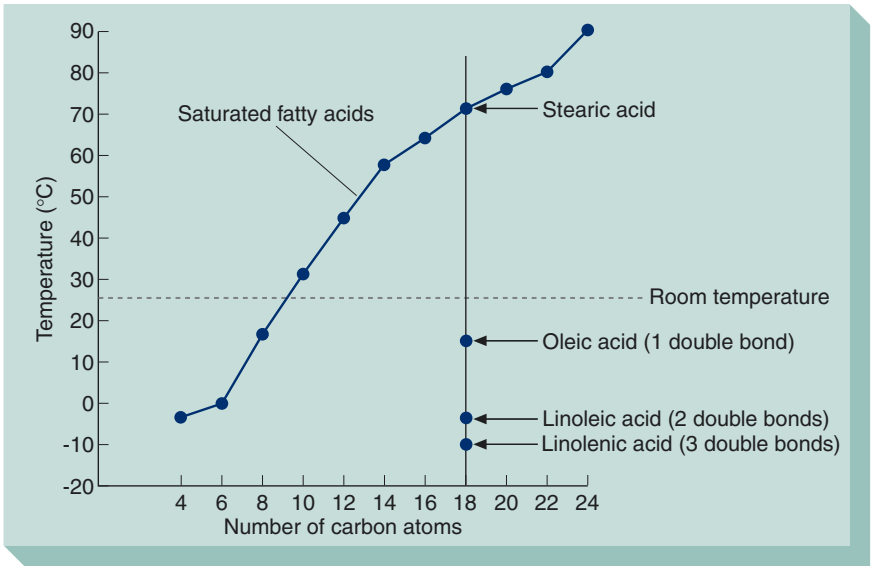


Figure 18.2
The melting points of fatty acids. Melting points of both saturated and unsaturated fatty acids increase as the number of carbon atoms in the chain increases. The melting points of unsaturated fatty acids are lower than those of the corresponding saturated fatty acid with the same number of carbon atoms. Also, as the number of double bonds in the chain increases, the melting points decrease.

double bond into the hydrocarbon chain produces a rigid 30° bend. Such "kinked" molecules cannot stack in an organized arrangement and thus have lower intermolecular attractions and lower melting points.

- As in the case for saturated fatty acids, the melting points of unsaturated fatty acids increase with increasing hydrocarbon chain length.

The relationship between alkene chain length and melting point is described in Section 12.1.

EXAMPLE 18.2 *Examining the Similarities and Differences between Saturated and Unsaturated Fatty Acids*

Construct a table comparing the structure and properties of saturated and unsaturated fatty acids.

Solution

Property	Saturated Fatty Acid	Unsaturated Fatty Acid
Chemical composition	Carbon, hydrogen, oxygen	Carbon, hydrogen, oxygen
Chemical structure	Hydrocarbon chain with a terminal carboxyl group	Hydrocarbon chain with a terminal carboxyl group
Carbon-carbon bonds within the hydrocarbon chain	Only C—C single bonds	At least one C—C double bond
Hydrocarbon chains are characteristic of what group of hydrocarbons	Alkanes	Alkenes
"Shape" of hydrocarbon chain	Linear, fully extended	Bend in carbon chain at site of C—C double bond
Physical state at room temperature	Solid	Liquid
Melting point for two fatty acids of the same hydrocarbon chain length	Higher	Lower
Relationship between melting point and chain length	Longer chain length, higher melting point	Longer chain length, higher melting point

Question 18.1

Draw formulas for each of the following fatty acids:

a. Oleic acid
b. Lauric acid
c. Linoleic acid
d. Stearic acid

Question 18.2

What is the I.U.P.A.C. name for each of the fatty acids in Question 18.1? (*Hint:* Review the naming of carboxylic acids in Section 15.1 and Table 18.1.)

Chemical Reactions of Fatty Acids

Learning Goal 4

The reactions of fatty acids are identical to those of short-chain carboxylic acids. The major reactions that they undergo include esterification, acid hydrolysis of esters, saponification, and addition at the double bond.

Esterification

In **esterification,** fatty acids react with alcohols to form esters and water according to the following general equation:

Esterification is described in Sections 15.1 and 15.2.

$$\underset{\text{Fatty acid}}{R^1{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH} + \underset{\text{Alcohol}}{HOR^2} \xrightarrow{H^+,\ \text{heat}} \underset{\text{Ester}}{R^1{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OR^2} + \underset{\text{Water}}{H{-}OH}$$

Acid Hydrolysis

Recall that hydrolysis is the reverse of esterification, producing fatty acids from esters:

Acid hydrolysis is discussed in Section 15.2.

$$\underset{\text{Ester}}{R^1{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OR^2} + \underset{\text{Water}}{HO{-}H} \xrightarrow{H^+,\ \text{heat}} \underset{\text{Fatty acid}}{R^1{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH} + \underset{\text{Alcohol}}{R^2OH}$$

Saponification

Saponification is the base-catalyzed hydrolysis of an ester:

Saponification is described in Section 15.2.

$$\underset{\text{Ester}}{R^1{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OR^2} + \underset{\text{Base}}{NaOH} \longrightarrow \underset{\text{Salt}}{R^1{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O^-Na^+} + \underset{\text{Alcohol}}{R^2OH}$$

The role of soaps in removal of dirt and grease is described in Section 15.2.

Examples of micelles are shown in Figures 15.4 and 23.1.

The product of this reaction, an ionized salt, is a soap. Because soaps have a long uncharged hydrocarbon tail and a negatively charged terminus (the carboxylate group), they form micelles that dissolve oil and dirt particles. Thus the dirt is emulsified and broken into small particles, and can be rinsed away.

Problems can arise when "hard" water is used for cleaning because the high concentrations of Ca^{2+} and Mg^{2+} in such water cause fatty acid salts to precipitate. Not only does this interfere with the emulsifying action of the soap, it also leaves a hard scum on the surface of sinks and tubs.

$$2R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O^- + Ca^{2+} \longrightarrow (R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O^-)_2Ca^{2+}(s)$$

Reaction at the Double Bond (Unsaturated Fatty Acids)

Hydrogenation is an example of an addition reaction. The following is a typical example of the addition of hydrogen to the double bonds of a fatty acid:

Hydrogenation is discussed in Section 12.5.

A HUMAN PERSPECTIVE

Mummies Made of Soap

In the Smithsonian Museum of Natural History in Washington, D.C., one can find a great many wonders of the natural world. None is quite as macabre as the corpse made of soap. The man in question died of yellow fever in the eighteenth century and was buried near Boston. Actually, he was buried alongside a woman, perhaps the love of his life, who has been dubbed "Soap Woman." She, too, died of yellow fever. However, the couple has been separated for quite some time, because Soap Woman has been on display at the Mutter Museum at the College of Physicians in Philadelphia since 1874.

Recently Soap Woman became a television celebrity when a CT Scan done to examine the body was filmed for "The Mummy Road Show," a presentation of the National Geographic Channel. One reason for the examination was to try to understand the conditions that caused this chemical conversion. At the present time, no one is precisely sure how these two people turned to soap. One clue resides in the environment of the burial site. Apparently the groundwater running through the graves was very basic. Another clue to the mystery is that our soap couple was overweight. Certainly these two factors contributed to the saponification reactions that converted this chubby couple into blocks of soap.

Soap Woman.

$$\underset{\text{Linoleic acid}}{CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH} \xrightarrow{2H_2,\ Ni} \underset{\text{Stearic acid}}{CH_3(CH_2)_{16}COOH}$$

Hydrogenation is used in the food industry to convert polyunsaturated vegetable oils into saturated solid fats. *Partial hydrogenation* is carried out to add hydrogen to some, but not all, double bonds in polyunsaturated oils. In this way liquid vegetable oils are converted into solid form. Crisco is one example of a hydrogenated vegetable oil.

Hydrogenation of vegetable oils produces a mixture of *cis* and *trans* unsaturated fatty acids. The *trans* unsaturated fatty acids are thought to contribute to atherosclerosis (hardening of the arteries).

Margarine is also produced by partial hydrogenation of vegetable oils, such as corn oil or soybean oil. The extent of hydrogenation is carefully controlled so that the solid fat will be spreadable and have the consistency of butter when eaten. If too many double bonds were hydrogenated, the resulting product would have the undesirable consistency of animal fat. Artificial color is added to the product, and it may be mixed with milk to produce a butterlike appearance and flavor.

EXAMPLE 18.3 *Writing Equations Representing the Chemical Reactions of Fatty Acids*

Write an equation for each of the following reactions and indicate the I.U.P.A.C. names of each of the organic reactants and products:

a. The esterification of capric acid with propyl alcohol

Continued—

EXAMPLE 18.3 *—Continued*

Solution

$$\underset{\text{Decanoic acid}}{CH_3(CH_2)_8{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH} + \underset{\text{Propanol}}{CH_3CH_2CH_2OH} \xrightarrow{H^+,\ \text{heat}} \underset{\text{Propyl decanoate}}{CH_3(CH_2)_8{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}CH_2CH_2CH_3} + H_2O$$

b. The acid hydrolysis of methyl decanoate

Solution

$$\underset{\text{Methyl decanoate}}{CH_3(CH_2)_8{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}CH_3} + H_2O \xrightarrow{H^+,\ \text{heat}} \underset{\text{Methanol}}{CH_3OH} + \underset{\text{Decanoic acid}}{CH_3(CH_2)_8{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH}$$

c. The base-catalyzed hydrolysis of ethyl dodecanoate

Solution

$$\underset{\text{Ethyl dodecanoate}}{CH_3(CH_2)_{10}{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}CH_2CH_3} + NaOH \longrightarrow \underset{\text{Sodium dodecanoate}}{CH_3(CH_2)_{10}{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O^-Na^+} + \underset{\text{Ethanol}}{CH_3CH_2OH}$$

d. Hydrogenation of oleic acid

Solution

$$\underset{\textit{cis}\text{-9-Octadecenoic acid}}{CH_3(CH_2)_7CH{=}CH(CH_2)_7{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH} \xrightarrow{H_2,\ Ni} \underset{\text{Octadecanoic acid}}{CH_3(CH_2)_{16}{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH}$$

Question 18.3

Write the complete equation for each of the following reactions:

a. Esterification of lauric acid and ethanol
b. Reaction of oleic acid with NaOH
c. Hydrogenation of arachidonic acid

Question 18.4

Write the complete equation for each of the following reactions:

a. Esterification of capric acid and 2-pentanol
b. Reaction of lauric acid with KOH
c. Hydrogenation of palmitoleic acid

Eicosanoids: Prostaglandins, Leukotrienes, and Thromboxanes

Some of the unsaturated fatty acids containing more than one double bond cannot be synthesized by the body. For many years it has been known that linolenic acid and linoleic acid, called the **essential fatty acids,** are necessary for specific biochemical functions and must be supplied in the diet (see Table 18.1). The function of linoleic acid became clear in the 1960s when it was discovered that linoleic acid is required for the biosynthesis of **arachidonic acid,** the precursor of a class of hormonelike molecules known as **eicosanoids.** The name is derived from the Greek word *eikos*, meaning "twenty," because they are all derivatives of twenty-carbon fatty acids. The eicosanoids include three groups of structurally related compounds: the prostaglandins, the leukotrienes, and the thromboxanes.

A hormone is a chemical signal that is produced by a specialized tissue and is carried by the bloodstream to target tissues. Eicosanoids are referred to as hormonelike because they affect the cells that produce them, as well as other target tissues.

Prostaglandins are extremely potent biological molecules with hormonelike activity. They received the name *prostaglandins* because they were originally isolated from seminal fluid produced in the prostate gland, but more recently they also have been isolated from most animal tissues. Prostaglandins are unsaturated carboxylic acids consisting of a twenty-carbon skeleton that contains a five-carbon ring.

Learning Goal 5 Learning Goal 6

Several general classes of prostaglandins are grouped under the designations A, B, E, and F, among others. The nomenclature of prostaglandins is based on the arrangement of the carbon skeleton and the number and orientation of double bonds, hydroxyl groups, and ketone groups. For example, in the name PGF_2, PG stands for prostaglandin, F indicates a particular group of prostaglandins with a hydroxyl group bonded to carbon-9, and 2 indicates that there are two carbon-carbon double bonds in the compound. The examples in Figure 18.3 illustrate the general structure of prostaglandins and the current nomenclature system.

Prostaglandins are made in most tissues, and exert their biological effects on the cells that produce them and on other cells in the immediate vicinity. The extraordinary range of prostaglandin functions includes

- stimulation of smooth muscle,
- regulation of steroid biosynthesis,
- inhibition of gastric secretion,
- inhibition of hormone-sensitive lipases,
- inhibition of platelet aggregation,
- stimulation of platelet aggregation,
- regulation of nerve transmission,
- sensitization to pain, and
- mediation of the inflammatory response.

Because the prostaglandins and the closely related leukotrienes and thromboxanes affect so many body processes and because they often cause opposing effects in different tissues, it can be difficult to keep track of their many regulatory functions. The following is a brief summary of some of the biological processes that are thought to be regulated by the prostaglandins, leukotrienes, and thromboxanes.

1. **Blood clotting.** Blood clots form when a blood vessel is damaged, yet such clotting along the walls of undamaged vessels could result in heart attack or stroke. *Thromboxane* A_2 (Figure 18.4) is produced by platelets in the blood and stimulates constriction of the blood vessels and aggregation of the platelets. Conversely, PGI_2 (prostacyclin) is produced by the cells lining the blood vessels and has precisely the opposite effect of thromboxane A_2. Prostacyclin inhibits platelet aggregation and causes dilation of blood vessels and thus prevents the untimely production of blood clots.
2. **The inflammatory response.** The inflammatory response is another of the body's protective mechanisms. When tissue is damaged by mechanical injury, burns, or invasion by microorganisms, a variety of white blood cells descend on the damaged site to try to minimize the tissue destruction. The result of this response is swelling, redness, fever, and pain. Prostaglandins

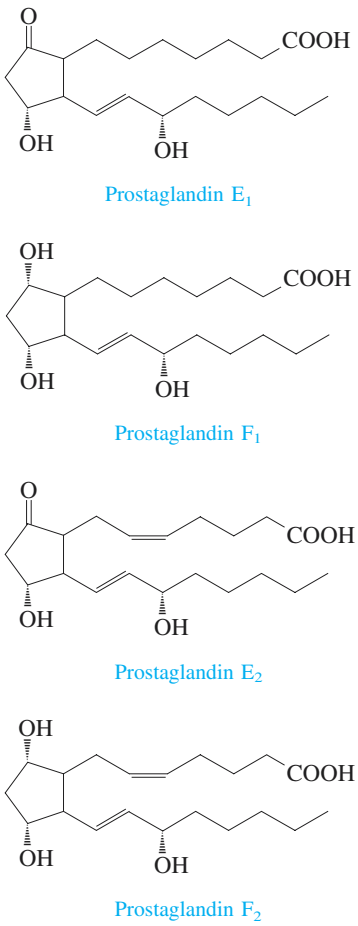


Figure 18.3
The structures of four prostaglandins.

are thought to promote certain aspects of the inflammatory response, especially pain and fever. Drugs such as aspirin block prostaglandin synthesis and help to relieve the symptoms. We will examine the mechanism of action of these drugs later in this section.

3. **Reproductive system.** PGE_2 stimulates smooth muscle contraction, particularly uterine contractions. An increase in the level of prostaglandins has been noted immediately before the onset of labor. PGE_2 has also been used to induce second trimester abortions. There is strong evidence that dysmenorrhea (painful menstruation) suffered by many women may be the result of an excess of two prostaglandins. Indeed, drugs, such as ibuprofen, that inhibit prostaglandin synthesis have been approved by the FDA and are found to provide relief from these symptoms.
4. **Gastrointestinal tract.** Prostaglandins have been shown to both inhibit the secretion of acid and increase the secretion of a protective mucus layer into the stomach. In this way, prostaglandins help to protect the stomach lining. Consider for a moment the possible side effect that prolonged use of a drug such as aspirin might have on the stomach—ulceration of the stomach lining. Because aspirin inhibits prostaglandin synthesis, it may actually encourage stomach ulcers by inhibiting the formation of the normal protective mucus layer, while simultaneously allowing increased secretion of stomach acid.
5. **Kidneys.** Prostaglandins produced in the kidneys cause the renal blood vessels to dilate. The greater flow of blood through the kidney results in increased water and electrolyte excretion.
6. **Respiratory tract.** Eicosanoids produced by certain white blood cells, the *leukotrienes* (see Figure 18.4), promote the constriction of the bronchi associated with asthma. Other prostaglandins promote bronchodilation.

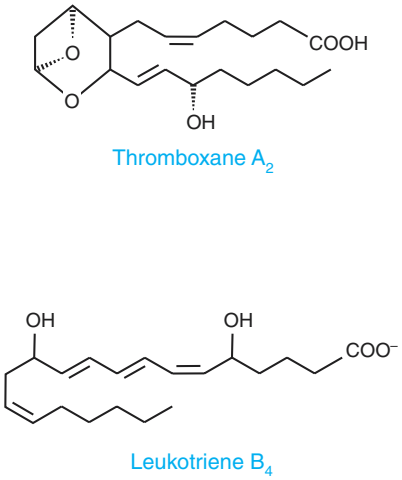


Figure 18.4
The structures of thromboxane A_2 and leukotriene B_4.

As this brief survey suggests, the prostaglandins have numerous, often antagonistic effects. Although they do not fit the formal definition of a hormone (a substance produced in a specialized tissue and transported by the circulatory system to target tissues *elsewhere* in the body), the prostaglandins are clearly strong biological regulators with far-reaching effects.

As mentioned, prostaglandins stimulate the inflammatory response and, as a result, are partially responsible for the cascade of events that cause pain. Aspirin has long been known to alleviate such pain, and we now know that it does so by inhibiting the synthesis of prostaglandins (Figure 18.5).

The first two steps of prostaglandin synthesis (Figure 18.6), the release of arachidonic acid from the membrane and its conversion to PGH_2 by the enzyme cyclooxygenase, occur in all tissues that are able to produce prostaglandins. The conversion of PGH_2 into the other biologically active forms is tissue specific and requires the appropriate enzymes, which are found only in certain tissues.

Aspirin works by inhibiting the cyclooxygenase, which catalyzes the first step in the pathway leading from arachidonic acid to PGH_2. The acetyl group of aspirin becomes covalently bound to the enzyme, thereby inactivating it (Figure 18.5). Because the reaction catalyzed by cyclooxygenase occurs in all cells, aspirin effectively inhibits synthesis of all of the prostaglandins.

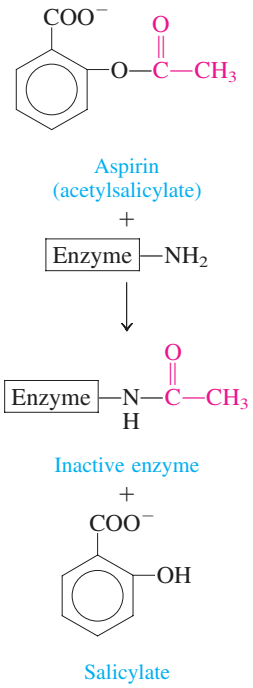


Figure 18.5
Aspirin inhibits the synthesis of prostaglandins by acetylating the enzyme cyclooxygenase. The acetylated enzyme is no longer functional.

18.3 Glycerides

Neutral Glycerides

Glycerides are lipid esters that contain the glycerol molecule and fatty acids. They may be subdivided into two classes: neutral glycerides and phosphoglycerides. Neutral glycerides are nonionic and nonpolar. Phosphoglyceride molecules have a polar region, the phosphoryl group, in addition to the nonpolar fatty acid tails. The structures of each of these types of glycerides are critical to their function.

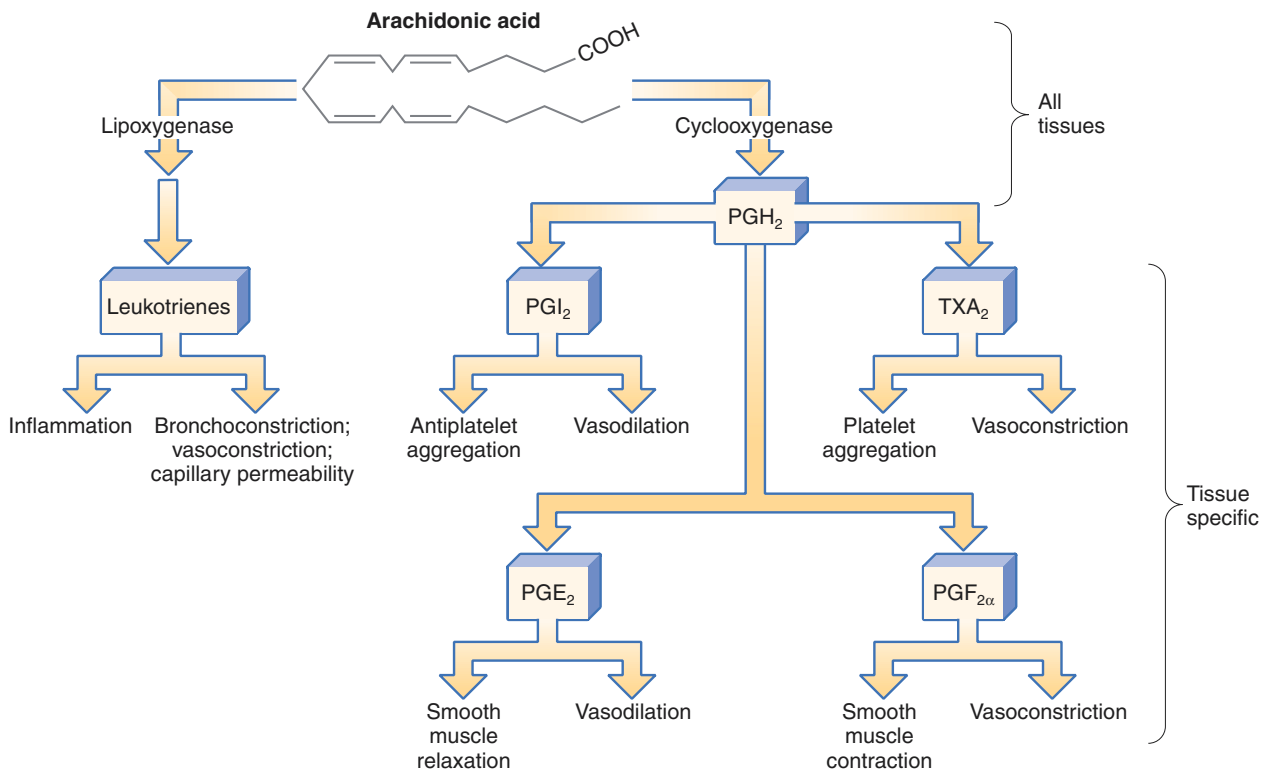


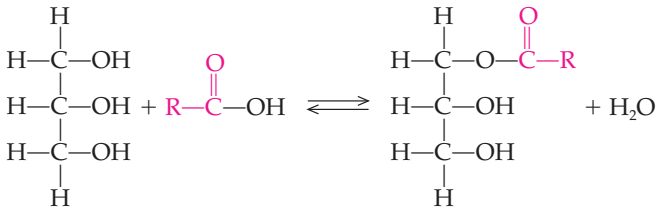
Figure 18.6
A summary of the synthesis of several prostaglandins from arachidonic acid.

The esterification of glycerol with a fatty acid produces a **neutral glyceride.** Esterification may occur at one, two, or all three positions, producing **monoglycerides, diglycerides,** or **triglycerides.** You will also see these referred to as *mono-*, *di-*, or *triacylglycerols.*

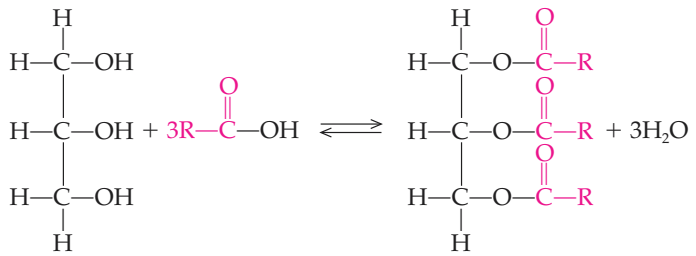
EXAMPLE 18.4 ***Writing an Equation for the Synthesis of a Monoglyceride***

Write a general equation for the esterification of glycerol and one fatty acid.

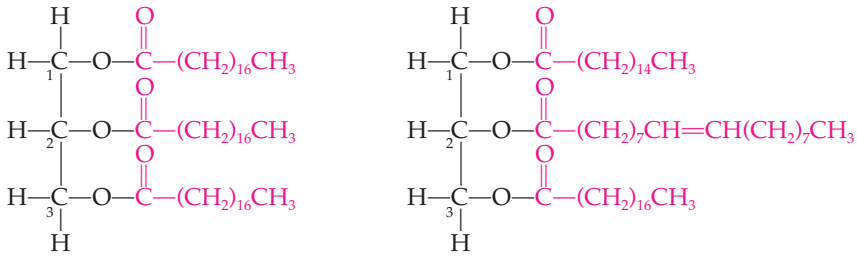
Solution



Although monoglycerides and diglycerides are present in nature, the most important neutral glycerides are the triglycerides, the major component of fat cells. The triglyceride consists of a glycerol backbone (shown in black) joined to three fatty acid units through ester bonds (shown in red). The formation of a triglyceride is shown in the following equation:



Triglycerides (triacylglycerols) are named by using the "backbone" name, *glycerol,* as the suffix. The name(s) of the fatty acyl group(s) are placed before it. The fatty acyl group is named by dropping the ending *-ic acid* and replacing it with the ending *-oyl.* In the examples below, the name of the triglyceride on the left is tristearoylglycerol. The prefix *tri-* tells us that there are three stearic acyl groups attached to the glycerol backbone. The triglyceride on the right is a *mixed triglyceride;* that is, there are three different fatty acyl groups attached to the glycerol backbone. They are listed according to their placement along the glycerol backbone.



Because there are no charges (+ or −) on these molecules, they are called *neutral glycerides.* These long molecules readily stack with one another and constitute the majority of the lipids stored in the body's fat cells.

The principal function of triglycerides in biochemical systems is the storage of energy. If more energy-rich nutrients are consumed than are required for metabolic processes, much of the excess is converted to neutral glycerides and stored as triglycerides in fat cells of *adipose tissue.* When energy is needed, the triglycerides are metabolized by the body, and energy is released. For this reason, exercise, along with moderate reduction in caloric intake, is recommended for overweight individuals. Exercise, an energy-demanding process, increases the rate of metabolism of fats and results in weight loss.

Lipid metabolism is discussed in Chapter 23.

See A Human Perspective: Losing Those Unwanted Pounds of Adipose Tissue in Chapter 23.

Phosphoglycerides

Learning Goal 7

Phospholipids are a group of lipids that are phosphate esters. The presence of the phosphoryl group results in a molecule with a polar head (the phosphoryl group) and a nonpolar tail (the alkyl chain of the fatty acid). Because the phosphoryl group ionizes in solution, a charged lipid results.

The most abundant membrane lipids are derived from glycerol-3-phosphate and are known as **phosphoglycerides.** Phosphoglycerides contain acyl groups derived from long-chain fatty acids at C-1 and C-2 of glycerol-3-phosphate. At C-3 the phosphoryl group is joined to glycerol by a phosphoester bond. The simplest phosphoglyceride contains a free phosphoryl group and is known as a **phosphatidate** (Figure 18.7). When the phosphoryl group is attached to another hydrophilic molecule, a more complex phosphoglyceride is formed. For example, *phosphatidylcholine*

Phosphoesters are described in Section 15.4.

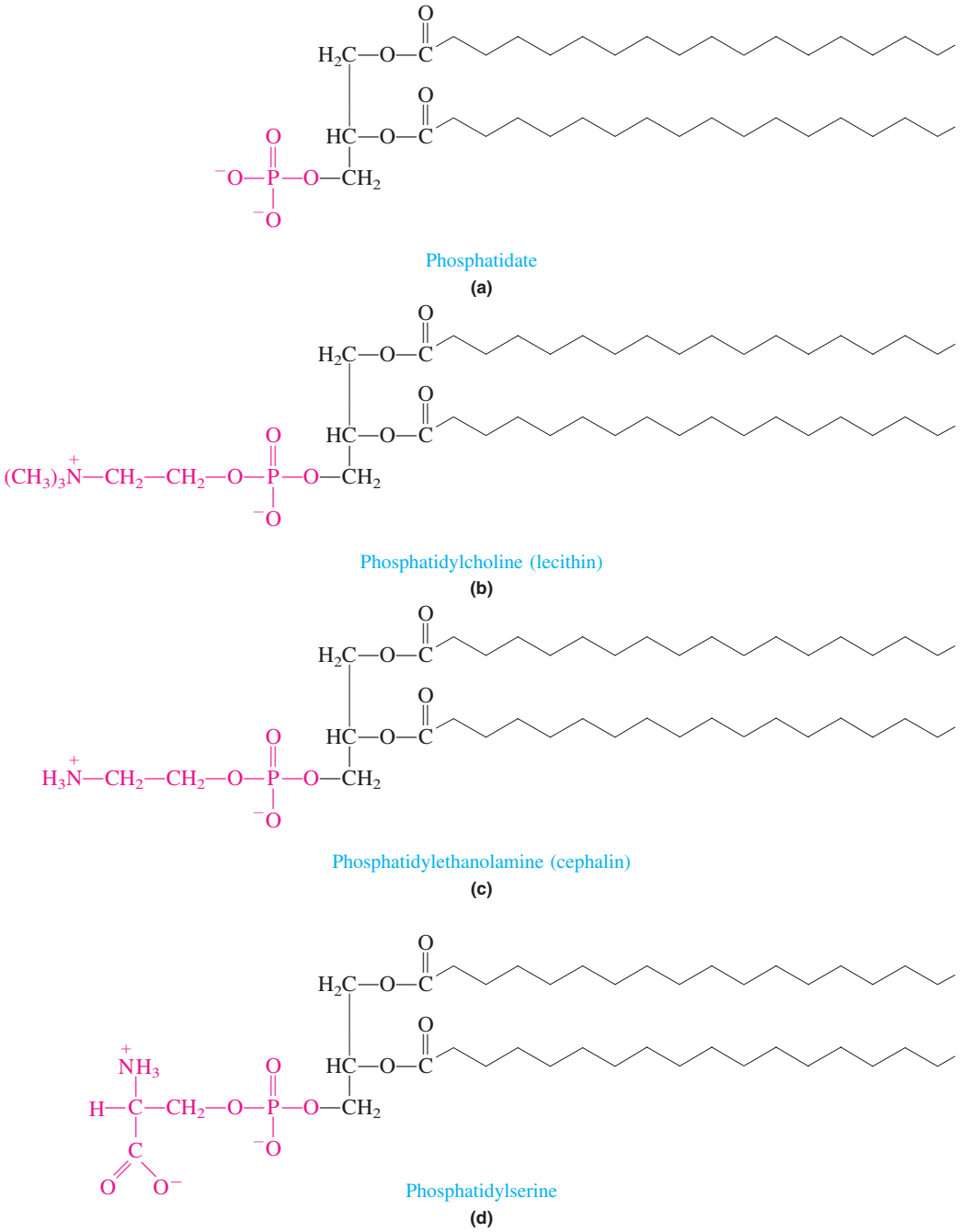


Figure 18.7
The structures of (a) phosphatidate and the common membrane phospholipids, (b) phosphatidylcholine (lecithin), (c) phosphatidylethanolamine (cephalin), and (d) phosphatidyl serine.

(lecithin) and *phosphatidylethanolamine (cephalin)* are found in the membranes of most cells (Figure 18.7).

Lecithin possesses a polar "head" and a nonpolar "tail." Thus, it is an *amphipathic* molecule. This structure is similar to that of soap and detergent molecules, discussed earlier. The ionic "head" is hydrophilic and interacts with water molecules, whereas the nonpolar "tail" is hydrophobic and interacts with nonpolar molecules. This amphipathic nature is central to the structure and function of cell membranes.

In addition to being a component of cell membranes, lecithin is the major phospholipid in pulmonary surfactant. It is also found in egg yolks and soybeans and is used as an emulsifying agent in ice cream. An **emulsifying agent** aids in the suspension of triglycerides in water. The amphipathic lecithin serves as a bridge, holding together the highly polar water molecules and the nonpolar triglycerides. Emulsification occurs because the hydrophilic head of lecithin dissolves in water and its hydrophobic tail dissolves in the triglycerides.

Cephalin is similar in general structure to lecithin; the amine group bonded to the phosphoryl group is the only difference.

See the Chemistry Connection: Lifesaving Lipids, at the beginning of this chapter.

Question 18.5

Using condensed formulas, draw the mono-, di-, and triglycerides that would result from the esterification of glycerol with each of the following acids.

a. Oleic acid
b. Capric acid
c. Palmitic acid
d. Lauric acid

Question 18.6

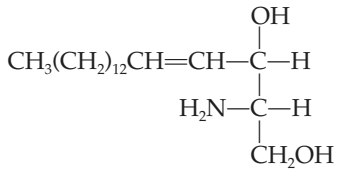
Name the triglycerides that are produced in the reactions discussed in Question 18.5.

18.4 Nonglyceride Lipids

Sphingolipids

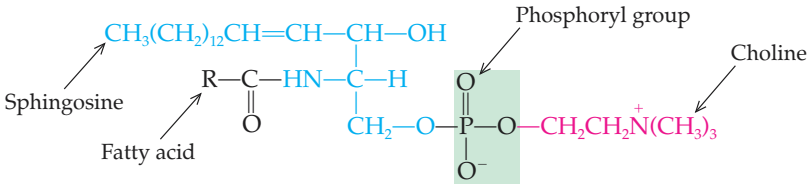
Learning Goal 8

Sphingolipids are lipids that are not derived from glycerol. Like phospholipids, sphingolipids are amphipathic, having a polar head group and two nonpolar fatty acid tails, and are structural components of cellular membranes. They are derived from sphingosine, a long-chain, nitrogen-containing (amino) alcohol:



Sphingosine

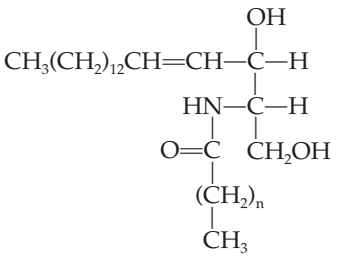
The sphingolipids include the sphingomyelins and the glycosphingolipids. The **sphingomyelins** are the only class of sphingolipids that are also phospholipids:



Sphingomyelin

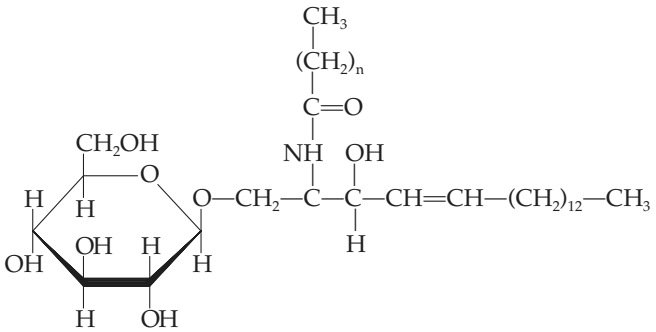
Sphingomyelins are located throughout the body, but are particularly important structural lipid components of nerve cell membranes. They are found in abundance in the myelin sheath that surrounds and insulates cells of the central nervous system. In humans, about 25% of the lipids of the myelin sheath are sphingomyelins. Their role is essential to proper cerebral function and nerve transmission.

Glycosphingolipids, or *glycolipids*, include the cerebrosides, sulfatides, and gangliosides and are built on a ceramide backbone structure, which is a fatty acid amide derivative of sphingosine:

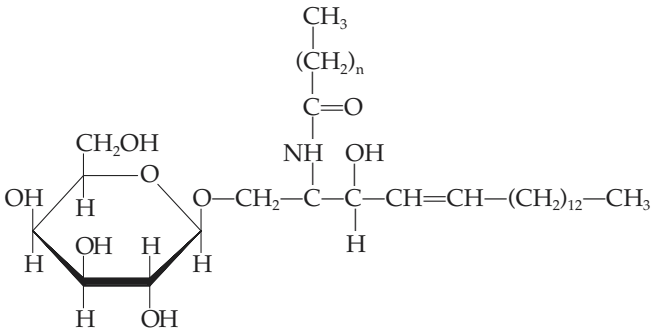


Ceramide

The *cerebrosides* are characterized by the presence of a single monosaccharide head group. Two common cerebrosides are glucocerebroside, found in the membranes of macrophages (cells that protect the body by ingesting and destroying foreign microorganisms) and galactocerebroside, found almost exclusively in the membranes of brain cells. Glucocerebroside consists of ceramide bonded to the hexose glucose; galactocerebroside consists of ceramide joined to the monosaccharide galactose.



Glucocerebroside



Galactocerebroside

Sulfatides are derivatives of galactocerebroside that contain a sulfate group. Notice that they carry a negative charge at physiological pH.

A CLINICAL PERSPECTIVE

Disorders of Sphingolipid Metabolism

There are a number of human genetic disorders that are caused by a deficiency in one of the enzymes responsible for the breakdown of sphingolipids. In general, the symptoms are caused by the accumulation of abnormally large amounts of these lipids within particular cells. It is interesting to note that three of these diseases, Niemann-Pick disease, Gaucher's disease, and Tay-Sachs disease are found much more frequently among Ashkenazi Jews of Northern European heritage than among other ethnic groups.

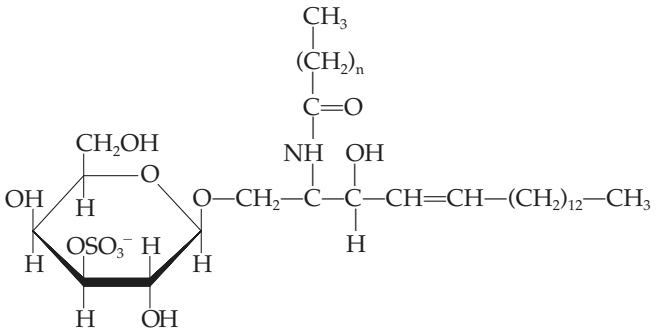
Of the four subtypes of Niemann-Pick disease, type A is the most severe. It is inherited as a recessive disorder (i.e., a defective copy of the gene must be inherited from each parent) that results in an absence of the enzyme sphingomyelinase. The absence of this enzyme causes the storage of large amounts of sphingomyelin and cholesterol in the brain, bone marrow, liver, and spleen.

Symptoms may begin when a baby is only a few months old. The parents may notice a delay in motor development and/or problems with feeding. Although the infants may develop some motor skills, they quickly begin to regress as they lose muscle strength and tone, as well as vision and hearing. The disease progresses rapidly and the children typically die within the first few years of life.

Tay-Sachs disease is a lipid storage disease caused by an absence of the enzyme hexosaminidase, which functions in ganglioside metabolism. As a result of the enzyme deficiency, the ganglioside, shown in Section 18.4, accumulates in the cells of the brain causing neurological deterioration. Like Niemann-Pick disease, it is an autosomal recessive genetic trait that becomes apparent in the first few months of the life of an infant and rapidly progresses to death within a few years. Symptoms include listlessness, irritability, seizures, paralysis, loss of muscle tone and function, blindness, deafness, and delayed mental and social skills.

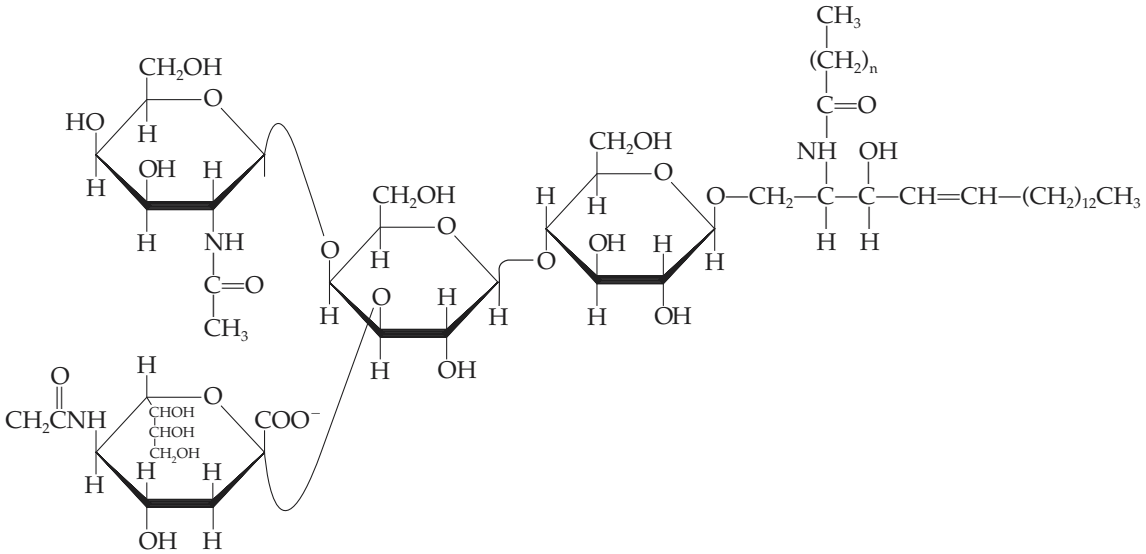
Gaucher's disease is an autosomal recessive genetic disorder resulting in a deficiency of the enzyme glucocerebrosidase. In the normal situation, this enzyme breaks down glucocerebroside, which is an intermediate in the synthesis and degradation of complex glycosphingolipids found in cellular membranes. In Gaucher's disease, glucocerebroside builds up in macrophages found in the liver, spleen, and bone marrow. These cells become engorged with excess lipid and displace healthy, normal cells in bone marrow. The symptoms of Gaucher's disease include severe anemia, thrombocytopenia (reduction in the number of platelets), and hepatosplenomegaly (enlargement of the spleen and liver). There can also be skeletal problems including bone deterioration and secondary fractures.

Fabry's disease is an X-linked inherited disorder caused by the deficiency of the enzyme α-galactosidase A. This disease afflicts as many as fifty thousand people worldwide. Typically, symptoms, including pain in the fingers and toes and a red rash around the waist, begin to appear when individuals reach their early twenties. A preliminary diagnosis can be confirmed by determining the concentration of the enzyme α-galactosidase A. Patients with Fabry's disease have an increased risk of kidney and heart disease, and a reduced life expectancy. Because this is an X-linked disorder, it is more common among males than females.



A sulfatide of galactocerebroside

Gangliosides are glycolipids that possess oligosaccharide groups, including one or more molecules of *N*-acetylneuraminic acid (sialic acid). First isolated from membranes of nerve tissue, gangliosides are found in most tissues of the body.



A ganglioside associated with Tay-Sachs disease

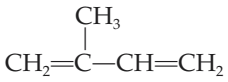
Steroids

Learning Goal 9

Lipid digestion is described in Section 23.1.

Steroids are a naturally occurring family of organic molecules of biochemical and medical interest. A great deal of controversy has surrounded various steroids. We worry about the amount of cholesterol in the diet and the possible health effects. We are concerned about the use of anabolic steroids by athletes wishing to build muscle mass and improve their performance. However, members of this family of molecules derived from cholesterol have many important functions in the body. The bile salts that aid in the emulsification and digestion of lipids are steroid molecules, as are the sex hormones testosterone and estrone.

The steroids are members of a large, diverse collection of lipids called the *isoprenoids*. All of these compounds are built from one or more five-carbon units called *isoprene*.

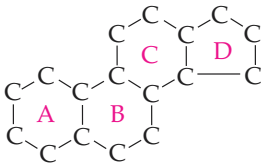


Isoprene

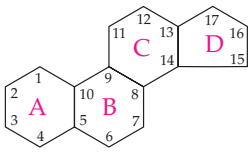
The structure and function of the lipid-soluble vitamins are found in Appendix E, Lipid-Soluble Vitamins.

Terpene is the general term for lipids that are synthesized from isoprene units. Examples of terpenes include the steroids and bile salts, the lipid-soluble vitamins, chlorophyll, and certain plant hormones.

All steroids contain the steroid nucleus (steroid carbon skeleton) as shown here:



Carbon skeleton of the steroid nucleus



Steroid nucleus

The steroid carbon skeleton consists of four fused rings. Each ring pair has two carbons in common. Thus two fused rings share one or more common bonds as part of their ring backbones. For example, rings A and B, B and C, and C and D are all fused in the preceding structure. Many steroids have methyl groups attached to carbons 10 and 13, as well as an alkyl, alcohol, or ketone group attached to carbon-17.

Cholesterol, a common steroid, is found in the membranes of most animal cells. It is an amphipathic molecule and is readily soluble in the hydrophobic re-

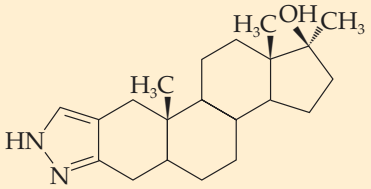
A HUMAN PERSPECTIVE

Anabolic Steroids and Athletics

In the 1988 Summer Olympics, Ben Johnson of Canada ran the fastest 100-meter race in history, 9.79 seconds, and was awarded the Gold Medal. Little more than two days later, Michele Verdier of the International Olympic Committee stood at a press conference and read the following statement: "The urine sample of Ben Johnson, Canada, Athletics, 100 meters, collected Saturday, 24th September 1988, was found to contain metabolites of a banned substance, namely stanozolol, an anabolic steroid." Johnson was disqualified, and Carl Lewis of the United States became the Olympic Gold Medalist in the 100-meter race.

Why do athletes competing in power sports take anabolic steroids? Use of anabolic steroids has a number of desirable effects for the athlete. First, they help build the muscle mass needed to succeed in sprints or weight lifting. They hasten the healing of muscle damage caused by the intense training of the competitive athlete. Finally, anabolic steroids may help the athlete maintain an aggressive attitude, not just during the competition but also throughout training.

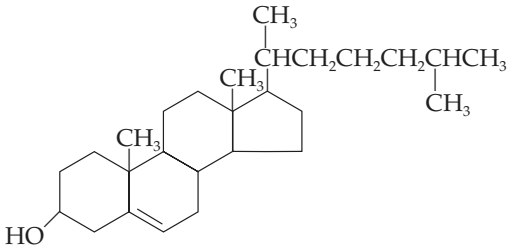
If these hormones have such beneficial effects, why not allow all athletes to use them? Unfortunately, the beneficial effects are far outweighed by the negative side effects. These include kidney and liver damage, stroke, impotence and infertility, an increase in cardiovascular disease, and extremely aggressive behavior.



Stanozolol

Even though these life-threatening side effects are well known, athletes continue to use anabolic steroids. The temptation must have been too great for Ben Johnson. After a period of suspension from amateur athletics, Johnson again entered competition. In March 1993, testing before a track meet revealed that he had used anabolic steroids to enhance his performance. As a result, he was forever banned from amateur competition.

gion of membranes. It is involved in regulation of the fluidity of the membrane as a result of the nonpolar fused ring. However, the hydroxyl group is polar and functions like the polar heads of sphingolipids and phospholipids. There is a strong correlation between the concentration of cholesterol found in the blood plasma and heart disease, particularly **atherosclerosis** (hardening of the arteries). Cholesterol, in combination with other substances, contributes to a narrowing of the artery passageway. As narrowing increases, more pressure is necessary to ensure adequate blood flow, and high blood pressure (*hypertension*) develops. Hypertension is also linked to heart disease.

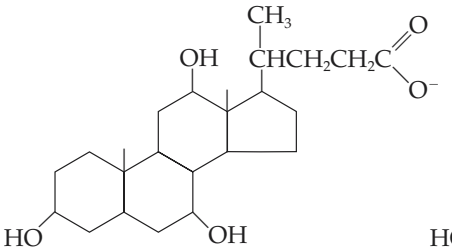


Cholesterol

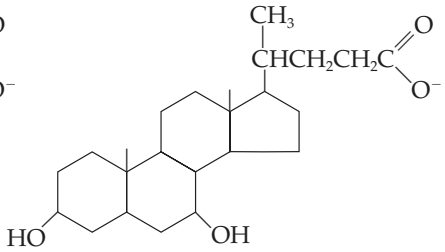
Egg yolks contain a high concentration of cholesterol, as do many dairy products and animal fats. As a result, it has been recommended that the amounts of these products in the diet be regulated to moderate the dietary intake of cholesterol.

Bile salts are amphipathic derivatives of cholesterol that are synthesized in the liver and stored in the gallbladder. The principal bile salts in humans are cholate and chenodeoxycholate.

Bile salts are described in greater detail in Section 23.1.



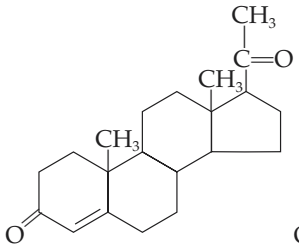
Cholate



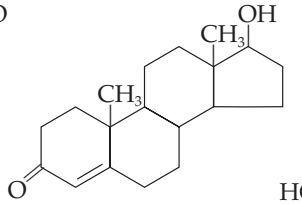
Chenodeoxycholate

Bile salts are emulsifying agents whose polar hydroxyl groups interact with water and whose hydrophobic regions bind to lipids. Following a meal, bile flows from the gallbladder to the duodenum (the uppermost region of the small intestine). Here the bile salts emulsify dietary fats into small droplets that can be more readily digested by lipases (lipid digesting enzymes) also found in the small intestine.

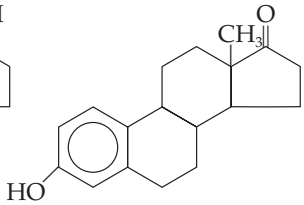
Steroids play a role in the reproductive cycle. In a series of chemical reactions, cholesterol is converted to the steroid *progesterone*, the most important hormone associated with pregnancy. Produced in the ovaries and in the placenta, progesterone is responsible for both the successful initiation and the successful completion of pregnancy. It prepares the lining of the uterus to accept the fertilized egg. Once the egg is attached, progesterone is involved in the development of the fetus and plays a role in the suppression of further ovulation during pregnancy.



Progesterone



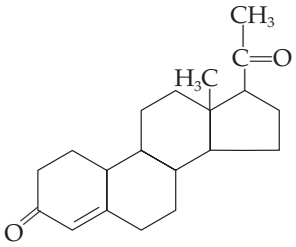
Testosterone



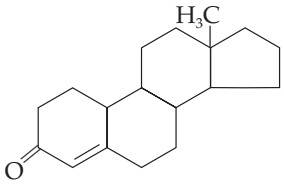
Estrone

Testosterone, a male sex hormone found in the testes, and *estrone*, a female sex hormone, are both produced by the chemical modification of progesterone. These hormones are involved in the development of male and female sex characteristics.

Many steroids, including progesterone, have played important roles in the development of birth control agents. 19-Norprogesterone was one of the first synthetic birth control agents. It is approximately ten times as effective as progesterone in providing birth control. However, its utility was severely limited because this compound could not be administered orally and had to be taken by injection. A related compound, norlutin (chemical name: 17-α-ethynyl-19-nortestosterone), was found to provide both the strength and the effectiveness of 19-norprogesterone and could be taken orally.



19-Norprogesterone



Norlutin

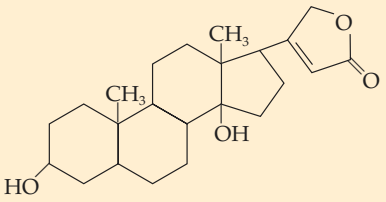
Currently "combination" oral contraceptives are prescribed most frequently. These include a progesterone and an estrogen. These newer products confer better contraceptive protection than either agent administered individually. They are also used to regulate menstruation in patients with heavy menstrual bleeding. First investigated in the late 1950s and approved by the FDA in 1961, there are at least thirty combination pills currently available. In addition, a transdermal patch for the treatment of postmenopausal osteoporosis is being investigated.

All of these compounds act by inducing a false pregnancy, which prevents ovulation. When oral contraception is discontinued, ovulation usually returns within

A CLINICAL PERSPECTIVE

Steroids and the Treatment of Heart Disease

The foxglove plant (*Digitalis purpurea*) is an herb that produces one of the most powerful known stimulants of heart muscle. The active ingredients of the foxglove plant (digitalis) are the so-called cardiac glycosides, or *cardiotonic steroids*, which include digitoxin, digosin, and gitalin.



Digitoxin

The structure of digitoxin, one of the cardiotonic steroids produced by the foxglove plant.

Digitalis purpurea, the foxglove plant.

These drugs are used clinically in the treatment of congestive heart failure, which results when the heart is not beating with strong, efficient strokes. When the blood is not propelled through the cardiovascular system efficiently, fluid builds up in the lungs and lower extremities (edema). The major symptoms of congestive heart failure are an enlarged heart, weakness, edema, shortness of breath, and fluid accumulation in the lungs.

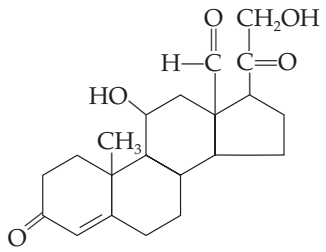
This condition was originally described in 1785 by a physician, William Withering, who found a peasant woman whose folk medicine was famous as a treatment for chronic heart problems. Her potion contained a mixture of more than twenty herbs, but Dr. Withering, a botanist as well as physician, quickly discovered that foxglove was the active ingredient in the mixture. Withering used *Digitalis purpurea* successfully to treat congestive heart failure and even described some cautions in its use.

The cardiotonic steroids are extremely strong heart stimulants. A dose as low as 1 mg increases the stroke volume of the heart (volume of blood per contraction), increases the strength of the contraction, and reduces the heart rate. When the heart is pumping more efficiently because of stimulation by digitalis, the edema disappears.

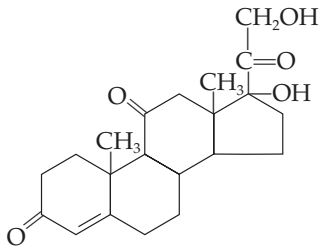
Digitalis can be used to control congestive heart failure, but the dose must be carefully determined and monitored because the therapeutic dose is close to the dose that causes toxicity. The symptoms that result from high body levels of cardiotonic steroids include vomiting, blurred vision and lightheadedness, increased water loss, convulsions, and death. Only a physician can determine the initial dose and maintenance schedule for an individual to control congestive heart failure and yet avoid the toxic side effects.

three menstrual cycles. Although there have been problems associated with "the pill," it appears to be an effective and safe method of family planning for much of the population.

Cortisone is also important to the proper regulation of a number of biochemical processes. For example, it is involved in the metabolism of carbohydrates. Cortisone is also used in the treatment of rheumatoid arthritis, asthma, gastrointestinal disorders, many skin conditions, and a variety of other diseases. However, treatment with cortisone is not without risk. Some of the possible side effects of cortisone therapy include fluid retention, sodium retention, and potassium loss that can lead to congestive heart failure. Other side effects include muscle weakness, osteoporosis, gastrointestinal upsets including peptic ulcers, and neurological symptoms, including vertigo, headaches, and convulsions.



Aldosterone



Cortisone

Aldosterone is a steroid hormone produced by the adrenal cortex and secreted into the bloodstream when blood sodium ion levels are too low. Upon reaching its target tissues in the kidney, aldosterone activates a set of reactions that cause sodium ions and water to be returned to the blood. If sodium levels are elevated, aldosterone is not secreted from the adrenal cortex and the sodium ions filtered out of the blood by the kidney will be excreted.

Question 18.7

Draw the structure of the steroid nucleus. Note the locations of the A, B, C, and D steroid rings.

Question 18.8

What is meant by the term *fused ring?*

Waxes

$$CH_3(CH_2)_{14}-\overset{\overset{\displaystyle O}{\|}}{C}-O-(CH_2)_{29}CH_3$$

Myricyl palmitate (beeswax)

$$CH_3(CH_2)_{14}-\overset{\overset{\displaystyle O}{\|}}{C}-O-(CH_2)_{15}CH_3$$

Cetyl palmitate (whale oil)

Waxes are derived from many different sources and have a variety of chemical compositions, depending on the source. Paraffin wax, for example, is composed of a mixture of solid hydrocarbons (usually straight-chain compounds). The natural waxes generally are composed of a long-chain fatty acid esterified to a long-chain alcohol. Because the long hydrocarbon tails are extremely hydrophobic, waxes are completely insoluble in water. Waxes are also solid at room temperature, owing to their high molecular weights. Two examples of waxes are myricyl palmitate, a major component of beeswax, and whale oil (spermaceti wax), from the head of the sperm whale, which is composed of cetyl palmitate.

Naturally occurring waxes have a variety of uses. Lanolin, which serves as a protective coating for hair and skin, is used in skin creams and ointments. Carnauba wax is used in automobile polish. Whale oil was once used as a fuel, in ointments, and in candles. However, synthetic waxes have replaced whale oil to a large extent, because of efforts to ban the hunting of whales.

18.5 Complex Lipids

Learning Goal 10

Complex lipids are lipids that are bonded to other types of molecules. The most common and important complex lipids are plasma lipoproteins, which are responsible for the transport of other lipids in the body.

Lipids are only sparingly soluble in water, and the movement of lipids from one organ to another through the bloodstream requires a transport system that uses **plasma lipoproteins.** Lipoprotein particles consist of a core of hydrophobic lipids surrounded by amphipathic proteins, phospholipids, and cholesterol (Figure 18.8).

There are four major classes of human plasma lipoproteins:

- **Chylomicrons,** which have a density of less than 0.95 g/mL, carry dietary triglycerides from the intestine to other tissues. The remaining lipoproteins are classified by their densities.

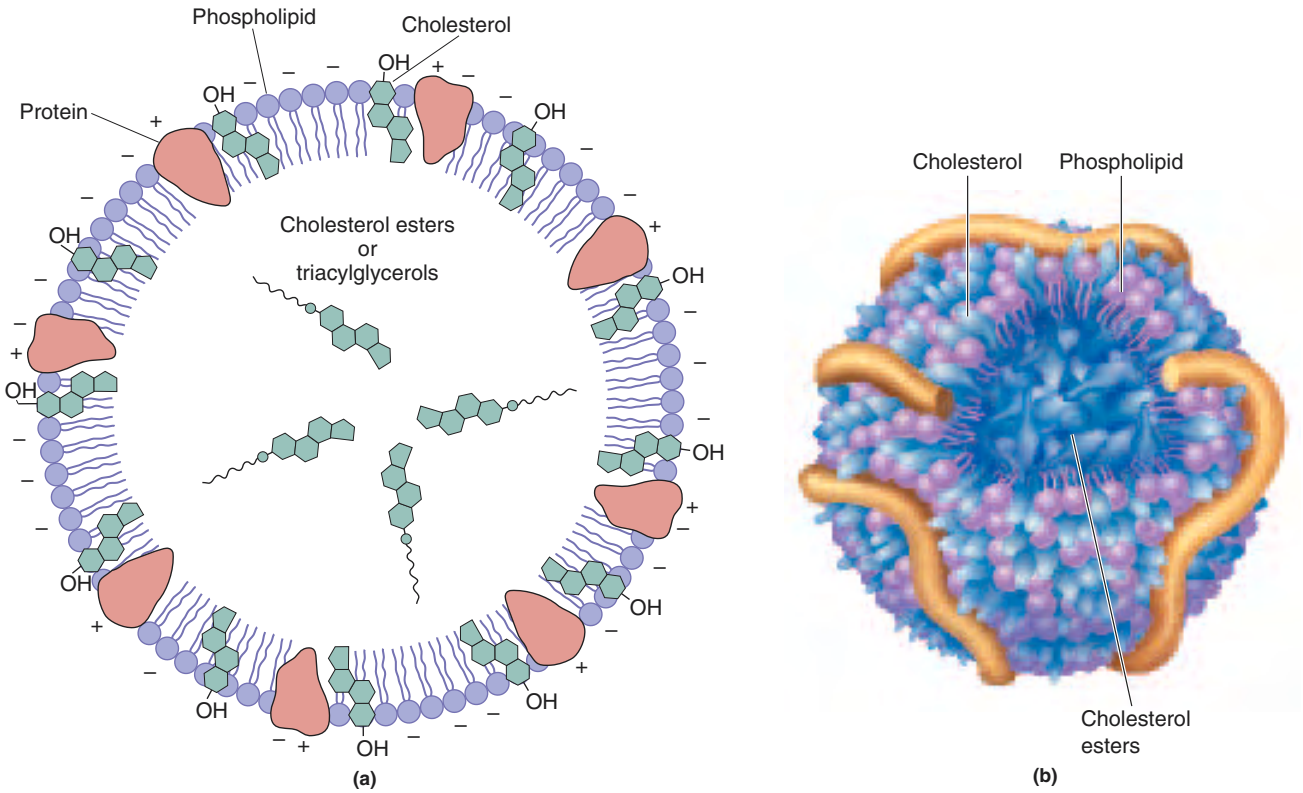


Figure 18.8
A model for the structure of a plasma lipoprotein. The various lipoproteins are composed of a shell of protein, cholesterol, and phospholipids surrounding more hydrophobic molecules such as triglycerides or cholesterol esters (cholesterol esterified to fatty acids). (a) Cross section, (b) three-dimensional view.

- **Very low density lipoproteins (VLDL)** have a density of 0.95–1.019 g/mL. They bind triglycerides synthesized in the liver and carry them to adipose and other tissues for storage.
- **Low-density lipoproteins (LDL)** are characterized by a density of 1.019–1.063 g/mL. They carry cholesterol to peripheral tissues and help regulate cholesterol levels in those tissues. These are richest in cholesterol, frequently carrying 40% of the plasma cholesterol.
- **High-density lipoproteins (HDL)** have a density of 1.063–1.210 g/mL. They are bound to plasma cholesterol; however, they transport cholesterol from peripheral tissues to the liver.

A summary of the composition of each of the plasma lipoproteins is presented in Figure 18.9.

Chylomicrons are aggregates of triglycerides and protein that transport dietary triglycerides to cells throughout the body. Not all lipids in the blood are derived directly from the diet. Triglycerides and cholesterol are also synthesized in the liver and also are transported through the blood in lipoprotein packages. Triglycerides are assembled into VLDL particles that carry the energy-rich lipid molecules either to tissues requiring an energy source or to adipose tissue for storage. Similarly, cholesterol is assembled into LDL particles for transport from the liver to peripheral tissues.

Entry of LDL particles into the cell is dependent on a specific recognition event and binding between the LDL particle and a protein receptor embedded within the membrane. Low-density lipoprotein receptors (LDL receptors) are found in the membranes of cells outside the liver and are responsible for the uptake of cholesterol

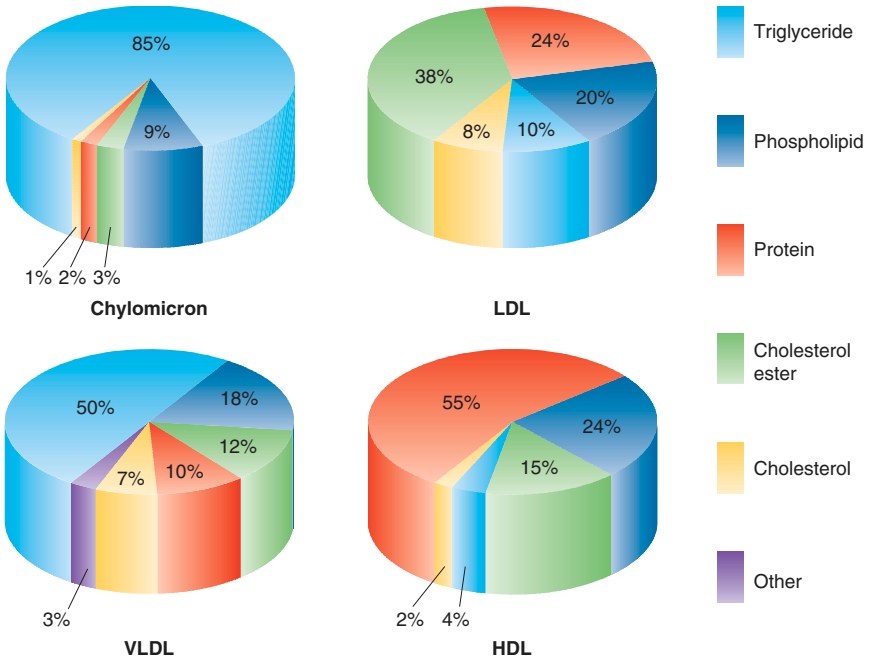


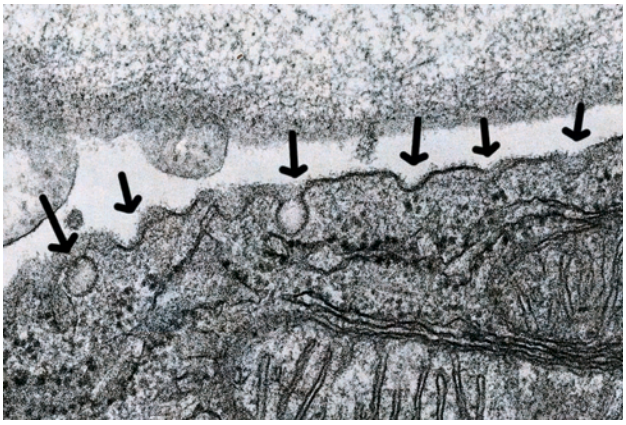
Figure 18.9
A summary of the relative amounts of cholesterol, phospholipid, protein, triglycerides, and cholesterol esters in the four classes of lipoproteins.

by the cells of various tissues. LDL (lipoprotein bound to cholesterol) binds specifically to the LDL receptor, and the complex is taken into the cell by a process called *receptor-mediated endocytosis* (Figure 18.10). The membrane begins to be pulled into the cell at the site of the LDL receptor complexes. This draws the entire LDL particle into the cell. Eventually, the portion of the membrane surrounding the LDL particles pinches away from the cell membrane and forms a membrane around the LDL particles. As we will see in Section 18.6, membranes are fluid and readily flow. Thus they can form a vesicle or endosome containing the LDL particles.

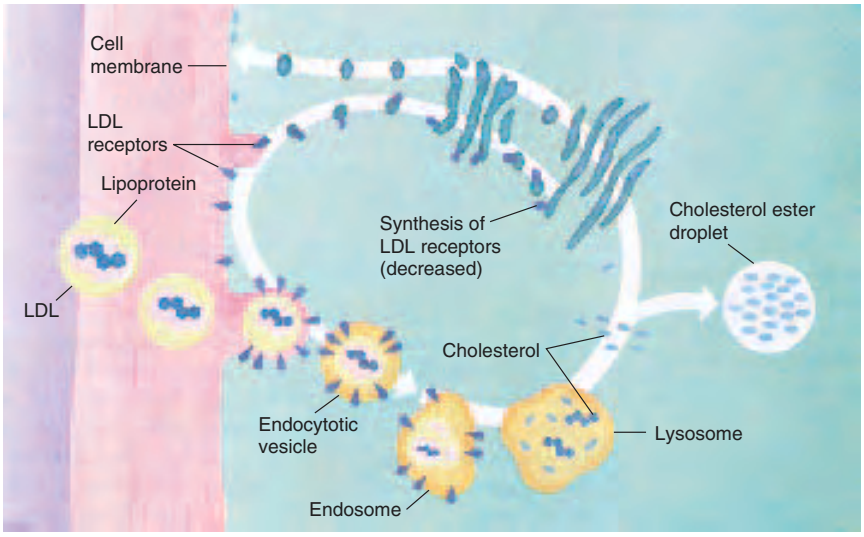
Cellular digestive organelles known as *lysosomes* fuse with the endosomes. This fusion is accomplished when the membranes of the endosome and the lysosome flow together to create one larger membrane-bound body or vesicle. Hydrolytic enzymes from the lysosome then digest the entire complex to release cholesterol into the cytoplasm of the cell. There, cholesterol inhibits its own biosynthesis and activates an enzyme that stores cholesterol in cholesterol ester droplets. High concentrations of cholesterol inside the cell also inhibit the synthesis of LDL receptors to ensure that the cell will not take up too much cholesterol. People who have a genetic defect in the gene coding for the LDL receptor do not take up as much cholesterol. As a result they accumulate LDL cholesterol in the plasma. This excess plasma cholesterol is then deposited on the artery walls, causing atherosclerosis. This disease is called *hypercholesterolemia.*

Liver lipoprotein receptors enable large amounts of cholesterol to be removed from the blood, thus ensuring low concentrations of cholesterol in the blood plasma. Other factors being equal, the person with the most lipoprotein receptors will be the least vulnerable to a high-cholesterol diet and have the least likelihood of developing atherosclerosis.

There is also evidence that high levels of HDL in the blood help reduce the incidence of atherosclerosis, perhaps because HDL carries cholesterol from the peripheral tissues back to the liver. In the liver, some of the cholesterol is used for bile synthesis and secreted into the intestines, from which it is excreted.



(a)



(b)

Figure 18.10
Receptor-mediated endocytosis.
(a) Electron micrographs of the process of receptor-mediated endocytosis.
(b) Summary of the events of receptor-mediated endocytosis of LDL.

A final correlation has been made between diet and atherosclerosis. People whose diet is high in saturated fats tend to have high levels of cholesterol in the blood. Although the relationship between saturated fatty acids and cholesterol metabolism is unclear, it is known that a diet rich in unsaturated fats results in decreased cholesterol levels. In fact, the use of unsaturated fat in the diet results in a decrease in the level of LDL and an increase in the level of HDL. With the positive correlation between heart disease and high cholesterol levels, the current dietary recommendations include a diet that is low in fat and the substitution of unsaturated fats (vegetable oils) for saturated fats (animal fats).

Recently an inflammatory protein, the C-reactive protein, has been implicated in atherosclerosis. A test for the level of this protein in the blood is being suggested as a way to predict the risk of heart attack. It is hoped that a sensitive test will be available within a year.

What is the mechanism of uptake of cholesterol from plasma? **Question 18.9**

What is the role of lysosomes in the metabolism of plasma lipoproteins? **Question 18.10**

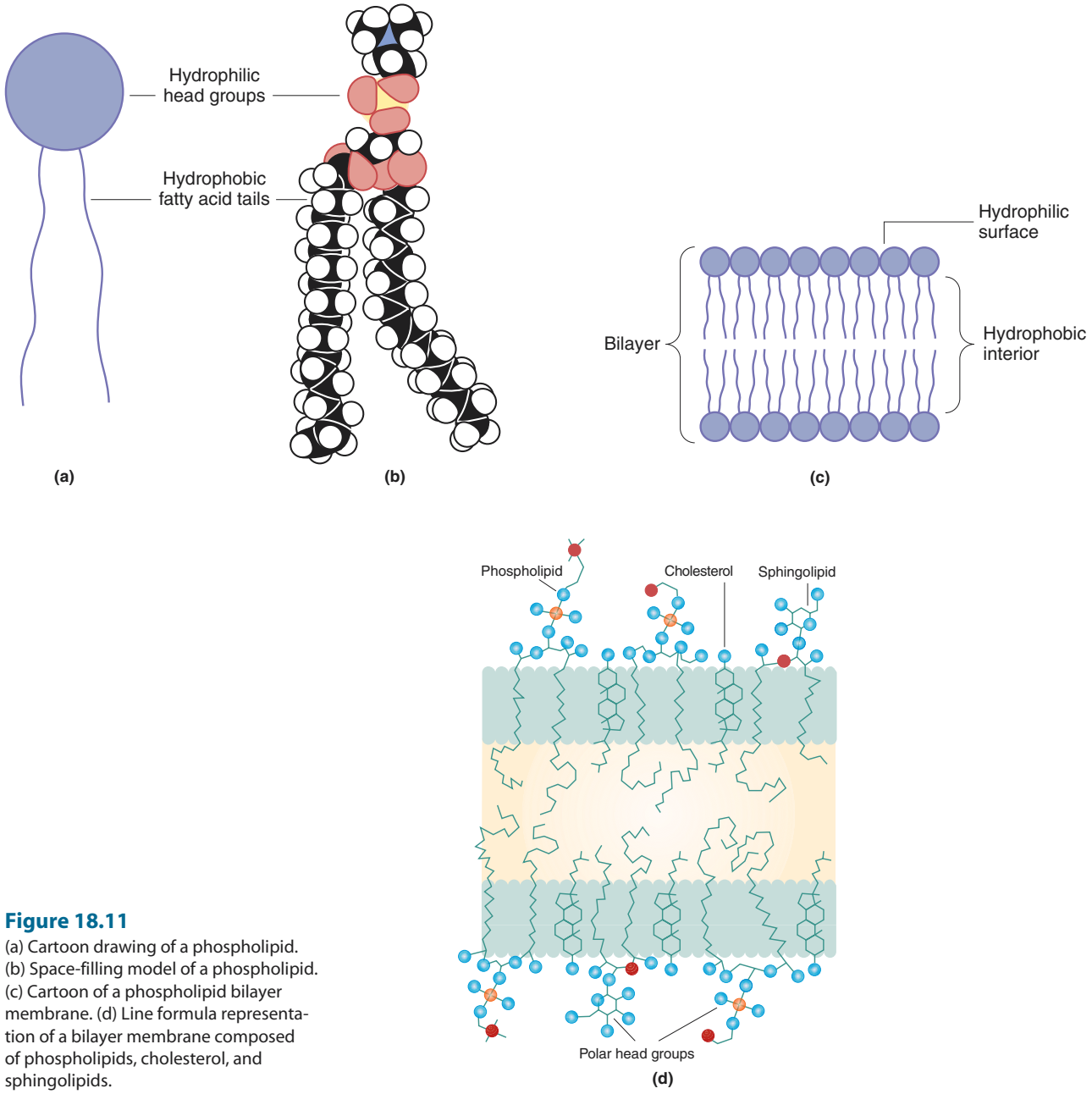


Figure 18.11
(a) Cartoon drawing of a phospholipid. (b) Space-filling model of a phospholipid. (c) Cartoon of a phospholipid bilayer membrane. (d) Line formula representation of a bilayer membrane composed of phospholipids, cholesterol, and sphingolipids.

18.6 The Structure of Biological Membranes

Learning Goal 11

Biological membranes are *lipid bilayers* in which the hydrophobic hydrocarbon tails are packed in the center of the bilayer and the ionic head groups are exposed on the surface to interact with water (Figure 18.11). The hydrocarbon tails of membrane phospholipids provide a thin shell of nonpolar material that prevents mixing of molecules on either side. The nonpolar tails of membrane phospholipids thus provide a barrier between the interior of the cell and its surroundings. The polar heads of lipids are exposed to water, and they are highly solvated. Little exchange, known colloquially as "flip-flop," occurs between lipids on the outer and

inner halves of the bilayers (Figure 18.12). The movement of a lipid molecule within one sheath of the bilayer, by contrast, is rapid. A bacterial cell is about 2 μm long, and a lipid molecule diffuses from one end of the cell to the other in a second.

The two layers of the phospholipid bilayer membrane are not identical in composition. For instance, in human red blood cells, approximately 80% of the phospholipids in the outer layer of the membrane are phosphatidylcholine and sphingomyelin; whereas phosphatidylethanolamine and phosphatidylserine make up approximately 80% of the inner layer. In addition, carbohydrate groups are found attached only to those phospholipids found on the outer layer of a membrane. Here they participate in receptor and recognition functions.

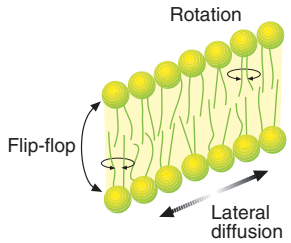


Figure 18.12
Lateral diffusion in a biological membrane is rapid, but "flip-flop" across the membrane almost never occurs.

Fluid Mosaic Structure of Biological Membranes

As we have just noted, membranes are not static; they are composed of molecules in motion. The fluidity of biological membranes is determined by the proportions of saturated and unsaturated fatty acid groups in the membrane phospholipids. About half of the fatty acids that are isolated from membrane lipids from all sources are unsaturated.

The unsaturated fatty acid tails of the phospholipids contribute to membrane fluidity because of the bends introduced into the hydrocarbon chain by the double bonds. Because of these "kinks," the fatty acid tails do not pack together tightly.

We also find that the percentage of unsaturated fatty acid groups in membrane lipids is inversely proportional to the temperature of the environment. Bacteria, for example, have different ratios of saturated and unsaturated fatty acids in their membrane lipids, depending on the temperatures of their surroundings. For instance, the membranes of bacteria that grow in the Arctic Ocean have high levels of unsaturated fatty acids so that their membranes remain fluid even at these frigid temperatures. Conversely, the organisms that live in the hot springs of Yellowstone National Park, with temperatures near the boiling point of water, have membranes with high levels of saturated fatty acids. This flexibility in fatty acid content enables the bacteria to maintain the same membrane fluidity over a temperature range of almost 100°C.

Generally, the body temperatures of mammals are quite constant, and the fatty acid composition of their membrane lipids is therefore usually very uniform. One interesting exception is the reindeer. Much of the year the reindeer must travel through ice and snow. Thus the hooves and lower legs must continue to function at much colder temperatures than the rest of the body. Because of this, the percentage of unsaturation in the membranes varies along the length of the reindeer leg. We find that the proportion of unsaturated fatty acid groups increases closer to the hoof. The lower freezing points and greater fluidity of lipids that contain a high proportion of unsaturated fatty acid groups permit the membranes to function in the low temperatures of ice and snow to which the lower leg is exposed.

Thus membranes are fluid, regardless of the environmental temperature conditions. In fact, it has been estimated that membranes have the consistency of olive oil.

Although the hydrophobic barrier created by the fluid lipid bilayer is an important feature of membranes, the proteins embedded within the lipid bilayer are equally important and are responsible for critical cellular functions. The presence of these membrane proteins was revealed by an electron microscopic technique called *freeze-fracture*. Cells are frozen to very cold temperatures and then fractured with a very fine diamond knife. Some of the cells are fractured between the two layers of the lipid bilayer. When viewed with the electron microscope, the membrane appeared to be a mosaic, studded with proteins. Because of the fluidity of membranes and the appearance of the proteins seen by electron microscopy, our concept of membrane structure is called the **fluid mosaic model** (Figure 18.13).

Some of the observed proteins, called **peripheral membrane proteins,** are bound only to one of the surfaces of the membrane by interactions between ionic

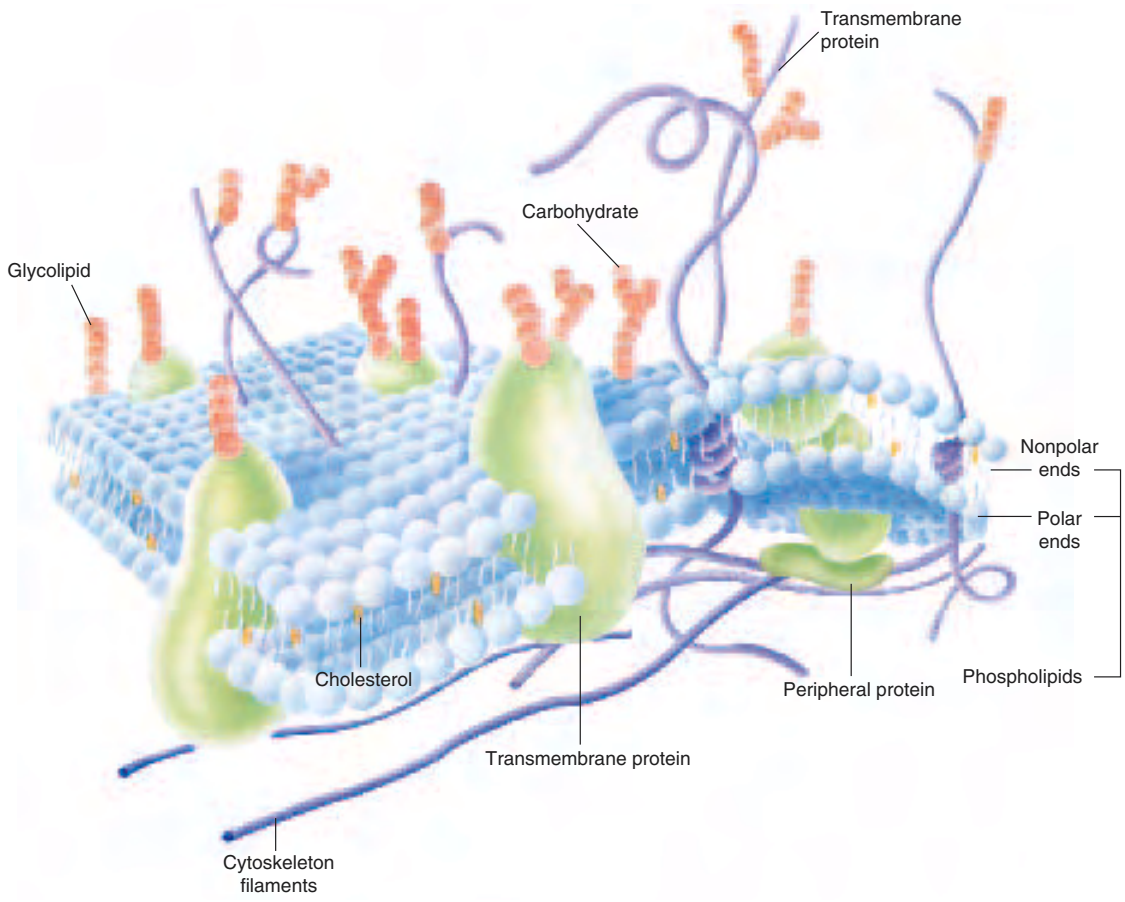


Figure 18.13
The fluid mosaic model of membrane structure.

head groups of the membrane lipids and ionic amino acids on the surface of the peripheral protein. Other membrane proteins, called **transmembrane proteins,** are embedded within the membrane and extend completely through it, being exposed both inside and outside the cell.

Just as the phospholipid composition of the membrane is asymmetric, so too is the orientation of transmembrane proteins. Each transmembrane protein has hydrophobic regions that associate with the fatty acid tails of membrane phospholipids. Each also has a unique hydrophilic domain that is always found associated with the outer layer of the membrane and is located on the outside of the cell. This region of the protein typically has oligosaccharides covalently attached. Hence these proteins are *glycoproteins.* Similarly, each transmembrane protein has a second hydrophilic domain that is always found associated with the inner layer of the membrane and projects into the cytoplasm of the cell. Typically this region of the transmembrane protein is attached to filaments of the cytoplasmic skeleton.

Because the lipid bilayer is fluid, there can be rapid lateral diffusion of membrane proteins through the lipid bilayer; but membrane proteins, like membrane lipids, do not "flip-flop" across the membrane or turn in the membrane like a revolving door of a department store.

Membranes are dynamic structures, as we may infer from our knowledge about the mobility of membrane proteins and lipids. The mobility of proteins embedded in biological membranes was studied by labeling certain proteins in human and mouse cell membranes with red and green fluorescent dyes. The human and mouse cells were fused; in other words, special techniques were used to cause the membranes of

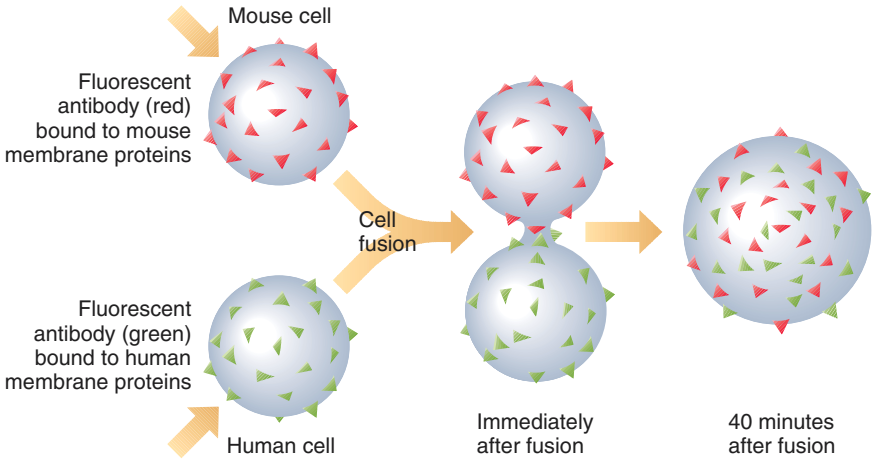


Figure 18.14
Demonstration that membranes are fluid and that proteins move freely in the plane of the lipid bilayer.

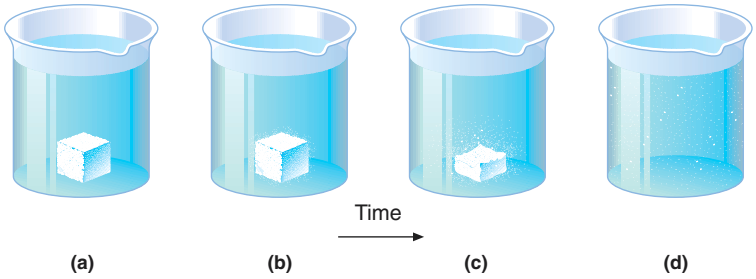


Figure 18.15
Diffusion results in the *net* movement of sugar and water molecules from the area of high concentration to the area of low concentration. Eventually, the concentrations of sugar and water throughout the beaker will be equal.

the mouse and human cell to flow together to create a single cell. The new cell was observed through a special ultraviolet or fluorescence microscope. The red and green patches were localized within regions of their original cell membranes when the experiment began. An hour later the color patches were uniformly distributed in the fused cellular membrane (Figure 18.14). This experiment suggests that we can think of the fluid mosaic membrane as an ocean filled with mobile, floating icebergs.

Membrane Transport

Learning Goal 12

The cell membrane mediates the interaction of the cell with its environment and is responsible for the controlled passage of material into and out of the cell. The external cell membrane controls the entrance of fuel and the exit of waste products. Internal cellular membranes partition metabolites among cell organelles. Most of these transport processes are controlled by transmembrane transport proteins. These transport proteins are the cellular gatekeepers, whose function in membrane transport is analogous to the function of enzymes in carrying out cellular chemical reactions. However, some molecules pass through the membranes unassisted, by the **passive transport** processes of diffusion and osmosis. These are referred to as passive processes because they do not require any energy expenditure by the cell.

Passive Diffusion: The Simplest Form of Membrane Transport

If we put a teaspoon of instant iced tea on the surface of a glass of water, the molecules soon spread throughout the solution. The molecules of both the solute (tea) and the solvent (water) are propelled by random molecular motion. The initially concentrated tea becomes more and more dilute. This process of the *net* movement of a solute with the gradient (from an area of high concentration to an area of low concentration) is called *diffusion* (Figure 18.15).

A CLINICAL PERSPECTIVE

Liposome Delivery Systems

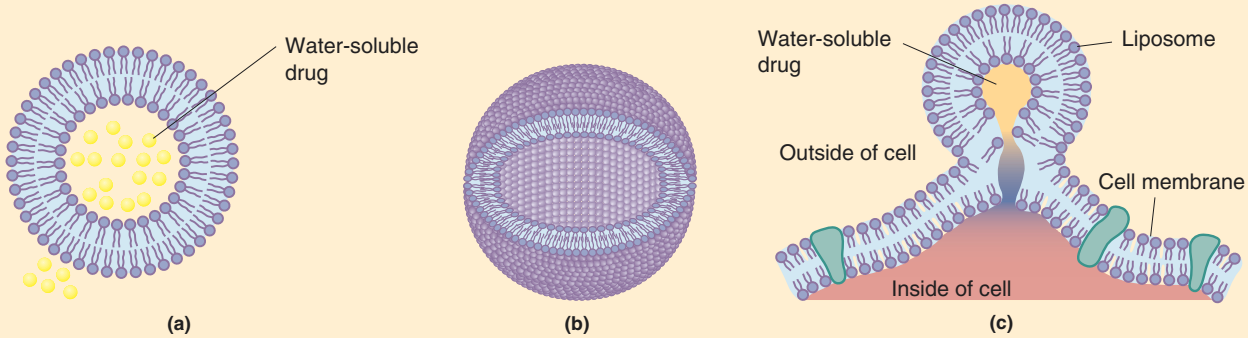
Liposomes were discovered by Dr. Alec Bangham in 1961. During his studies on phospholipids and blood clotting, he found that if he mixed phospholipids and water, tiny phospholipid bilayer sacs, called liposomes, would form spontaneously. Since that first observation, liposomes have been developed as efficient delivery systems for everything from antitumor and antiviral drugs, to the hair-loss therapy minoxidil!

If a drug is included in the solution during formation of liposomes, the phospholipids will form a sac around the solution. In this way the drug becomes encapsulated within the phospholipid sphere. These liposomes can be injected intravenously or applied to body surfaces. Sometimes scientists include hydrophilic molecules in the surface of the liposome. This increases the length of time that they will remain in circulation in the bloodstream. These so-called stealth liposomes are being used to carry anticancer drugs, such as doxorubicin and mitoxantrone. Liposomes are also being used as carriers for the antiviral drugs, such as AZT and ddC, that are used to treat human immunodeficiency virus infection.

A clever trick to help target the drug-carrying liposome is to include an antibody on the surface of the liposome. These antibodies are proteins designed to bind specifically to the surface of a tumor cell. Upon attaching to the surface of the tumor cell, the liposome "membrane" fuses with the cell membrane. In this way the deadly chemicals are delivered only to those cells targeted for destruction. This helps to avoid many of the unpleasant side effects of chemotherapy treatment that occur when normal healthy cells are killed by the drug.

Another application of liposomes is in the cosmetics industry. Liposomes can be formed that encapsulate a vitamin, herbal agent, or other nutritional element. When applied to the skin, the liposomes pass easily through the outer layer of dead skin, delivering their contents to the living skin cells beneath. As with the pharmaceutical liposomes, these liposomes, sometimes called cosmeceuticals, fuse with skin cells. Thus, they directly deliver the beneficial cosmetic agent directly to the cells that can benefit the most.

Since their accidental discovery forty years ago, much has been learned about the formation of liposomes and ways to engineer them for more efficient delivery of their contents. This is another example of the marriage of serendipity, an accidental discovery, with scientific research and technological application. As the development of new types of liposomes continues, we can expect that even more ways will be found to improve the human condition.



(a) cross-section of a liposome, (b) three-dimensional view of a liposome, and (c) liposome fusing with cell membrane.

Diffusion is one means of passive transport across membranes. Let's now suppose that a biological membrane is present and that a substance is found at one concentration outside the membrane and at half that concentration inside the membrane. If the solute can pass through the membrane, diffusion will occur with net transport of material from the region of initial high concentration to the region of initial low concentration, and the substance will equilibrate across the cell membrane (Figure 18.16). After a while, the concentration of the substance will be the same on both sides of the membrane; the system will be at equilibrium, and no more net change will occur.

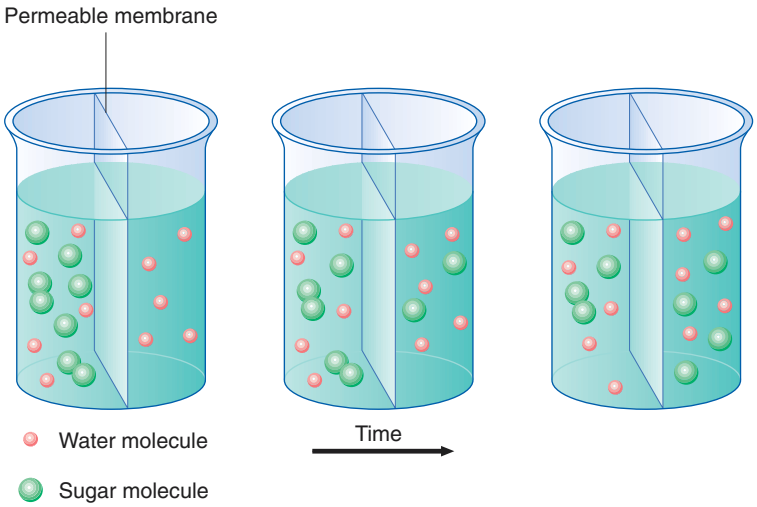


Figure 18.16
Diffusion of a solute through a membrane.

Of what practical value is the process of diffusion to the cell? Certainly, diffusion is able to distribute metabolites effectively throughout the interior of the cell. But what about the movement of molecules through the membrane? Because of the lipid bilayer structure of the membrane, only a few molecules are able to diffuse freely across a membrane. These include small molecules such as O_2 and CO_2. Any large or highly charged molecules or ions are not able to pass through the lipid bilayer directly. Such molecules require an assist from cell membrane proteins. Any membrane that allows the diffusion of some molecules but not others is said to be *selectively permeable.*

Facilitated Diffusion: Specificity of Molecular Transport

Most molecules are transported across biological membranes by specific protein carriers known as *permeases.* When a solute diffuses through a membrane from an area of high concentration to an area of low concentration by passing through a channel within a permease, the process is known as **facilitated diffusion.** No energy is consumed by facilitated diffusion; thus it is another means of passive transport, and the direction of transport depends upon the concentrations of metabolite on each side of the membrane.

Transport across cell membranes by facilitated diffusion occurs through pores within the permease that have conformations, or shapes, that are complementary to those of the transported molecules. The charge and conformation of the pore define the specificity of the carrier (Figure 18.17). Only molecules that have the correct shape can enter the pore. As a result, the rate of diffusion for any molecule is limited by the number of carrier permease molecules in the membrane that are responsible for the passage of that molecule.

The transport of glucose illustrates the specificity of carrier permease proteins. D-Glucose is transported by the glucose carrier, but its enantiomer, L-glucose, is not. Thus the glucose permease exhibits stereospecificity. In other words, the solute to be brought into the cell must "fit" precisely, like a hand in a glove, into a recognition site within the structure of the permease. In Chapter 20 we will see that enzymes that catalyze the biochemical reactions within cells show this same type of specificity.

Enzyme specificity is discussed in Section 20.5.

The rate of transport of metabolites into the cell has profound effects on the net metabolic rate of many cells. Insulin, a polypeptide hormone synthesized by the islet β-cells of the pancreas, increases the maximum rate of glucose transport by a factor of three to four. The result is that the metabolic activity of the cell is greatly increased.

The metabolic effects of insulin are described in Sections 21.7 and 23.6.

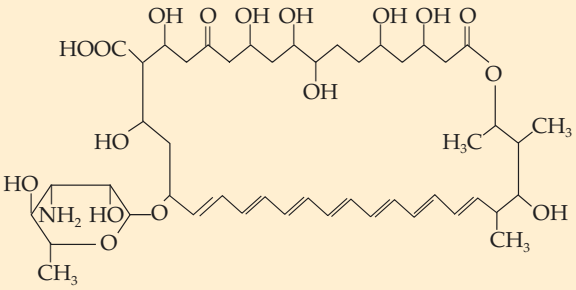
A CLINICAL PERSPECTIVE

Antibiotics That Destroy Membrane Integrity

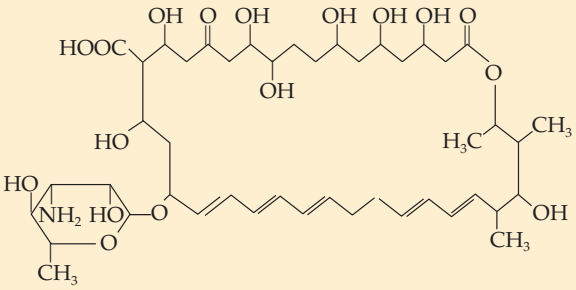
The "age of antibiotics" began in 1927 when Alexander Fleming discovered, quite by accident, that a product of the mold *Penicillium* can kill susceptible bacteria. We now know that penicillin inhibits bacterial growth by interfering with cell wall synthesis. Since Fleming's time, hundreds of antibiotics, which are microbial products that either kill or inhibit the growth of susceptible bacteria or fungi, have been discovered. The key to antibiotic therapy is to find a "target" in the microbe, a metabolic process or structure that the human does not have. In this way the antibiotic will selectively inhibit the disease-causing organism without harming the patient.

Many antibiotics disrupt cell membranes. The cell membrane is not an ideal target for antibiotic therapy because all cells, human and bacterial, have membranes. Therefore both types of cells are damaged. Because these antibiotics exhibit a wide range of toxic side effects when ingested, they are usually used to combat infections topically (on body surfaces). In this way, damage to the host is minimized but the inhibitory effect on the microbe is maximized.

Polymyxins are antibiotics produced by the bacterium *Bacillus polymyxa.* They are protein derivatives having one end that is hydrophobic because of an attached fatty acid. The opposite end is hydrophilic. Because of these properties, the polymyxins bind to membranes with the hydrophobic end embedded within the membrane, while the hydrophilic end remains outside the cell. As a result, the integrity of the membrane is disrupted, and leakage of cellular constituents occurs, causing cell death.



Amphotericin B



Nystatin

The structures of amphotericin B and nystatin, two antifungal antibiotics.

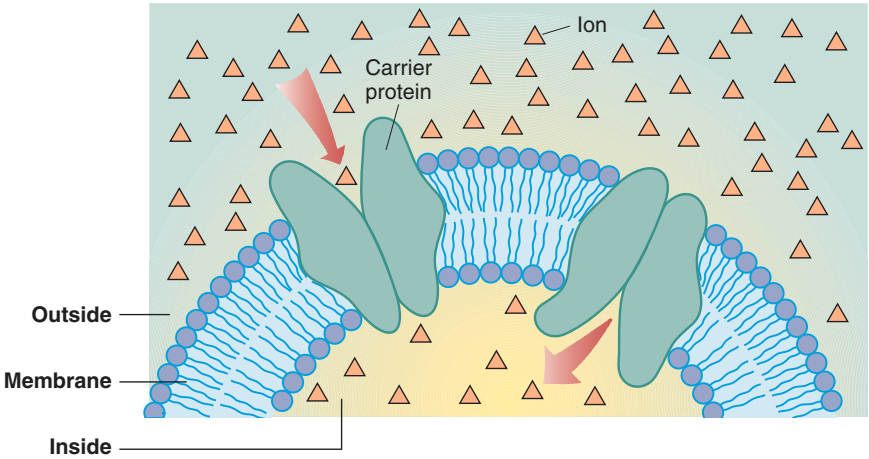
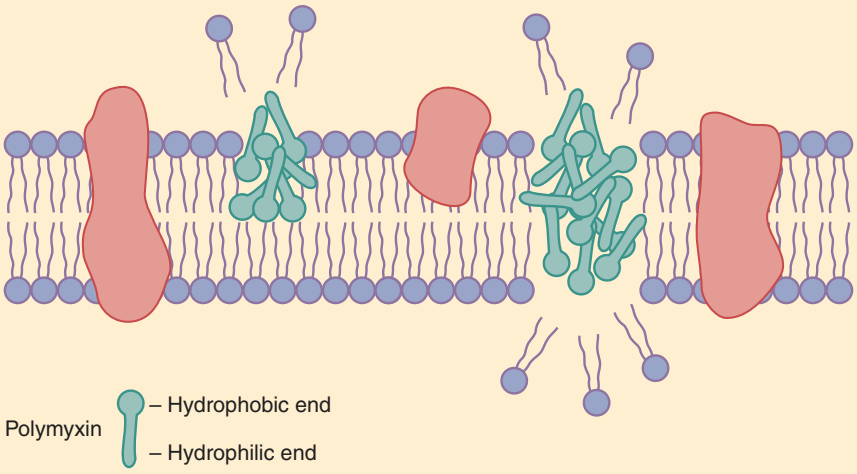


Figure 18.17
Transport by facilitated diffusion occurs through pores in the transport protein whose size and shape are complementary to those of the transported molecule.



Polymyxins act like detergents, disrupting membrane integrity and killing the cell.

Although the polymyxins have been found to be useful in treating some urinary tract infections, pneumonias, and infections of burn patients, other antibiotics are now favored because of the toxic effects of the polymyxins on the kidney and central nervous system. Polymyxin B is still used topically and is available as an over-the-counter ointment in combination with two other antibiotics, neomycin and bacitracin.

Two other antibiotics that destroy membranes, amphotericin B and nystatin, are large ring structures that are used in treating serious systemic fungal infections. These antibiotics form complexes with ergosterol in the fungal cell membrane, and they disrupt the membrane permeability and cause leakage of cellular constituents. Neither is useful in treating bacterial infections because most bacteria have no ergosterol in their membranes. Both amphotericin B and nystatin are extremely toxic and cause symptoms that include nausea and vomiting, fever and chills, anemia, and renal failure. It is easy to understand why the use of these drugs is restricted to treatment of life-threatening fungal diseases.

Red blood cells use the same anion channel to transport Cl^- into the cell in exchange for HCO_3^- ions (Figure 18.18). This two-way transport is known as *antiport.* This transport occurs by facilitated diffusion so that Cl^- flows from a high exterior concentration to a low interior one, and bicarbonate flows from a high interior concentration to a low exterior one.

Osmosis: Passive Movement of a Solvent Across a Membrane

Learning Goal 13

Because a cell membrane is selectively permeable, it is not always possible for solutes to pass through it in response to a concentration gradient. In such cases the solvent diffuses through the membrane. Such membranes, permeable to solvent but not to solute, are specifically called **semipermeable membranes. Osmosis** is the diffusion of a solvent (water in biological systems) through a semipermeable membrane in response to a water concentration gradient.

Recall that there is an inverse relationship between the osmotic (solute) concentration of a solution and the water concentration of that solution, as discussed in Chapter 7.

Suppose that we place a 0.5 *M* glucose solution in a dialysis bag that is composed of a membrane with pores that allow the passage of water molecules but not glucose molecules. Consider what will happen when we place this bag into a beaker of pure water. We have created a gradient in which there is a higher concentration of glucose inside the bag than outside, but the glucose cannot diffuse through the bag to achieve equal concentration on both sides of the membrane.

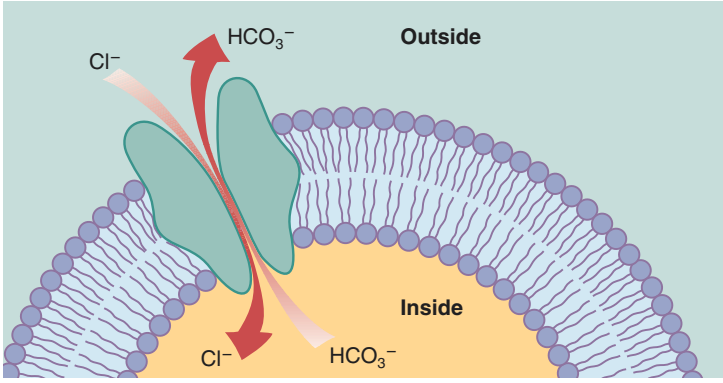


Figure 18.18
Transport of Cl^- and HCO_3^- ions in opposite directions across the red blood cell membrane.

Now let's think about this situation in another way. We have a higher concentration of water molecules outside the bag (where there is only pure water) than inside the bag (where some of the water molecules are occupied in the hydration of solute particles and are consequently unable to move freely in the system). Because water can diffuse through the membrane, a net diffusion of water will occur through the membrane into the bag. This is the process of osmosis (Figure 18.19).

As you have probably already guessed, this system can never reach equilibrium (equal concentrations inside and outside the bag) because regardless of how much water diffuses into the bag, diluting the glucose solution, the concentration of glucose will always be higher inside the bag (and the accompanying free water concentration will always be lower).

What happens when the bag has taken in as much water as it can, when it has expanded as much as possible? Now the walls of the bag exert a force that will stop the *net* flow of water into the bag. **Osmotic pressure** is the pressure that must be exerted to stop the flow of water across a selectively permeable membrane by osmosis. Stated more precisely, the osmotic pressure of a solution is the net pressure with which water enters it by osmosis from a pure water compartment when the two compartments are separated by a semipermeable membrane.

Osmotic concentration or *osmolarity* is the term used to describe the osmotic strength of a solution. It depends only on the ratio of the number of solute particles to the number of solvent particles. Thus the chemical nature and size of the solute are not important, only the concentration, expressed in molarity. For instance, a 2 *M* solution of glucose (a sugar of molecular weight 180) has the same osmolarity as a 2 *M* solution of albumin (a protein of molecular weight 60,000).

Blood plasma has an osmolarity equivalent to a 0.30 *M* glucose solution or a 0.15 *M* NaCl solution. This latter is true because in solution NaCl dissociates into Na^+ and Cl^- and thus contributes twice the number of solute particles as a molecule that does not ionize. If red blood cells, which have an osmolarity equal to blood plasma, are placed in a 0.30 *M* glucose solution, no net osmosis will occur because the osmolarity and water concentration inside the red blood cell are equal to those of the 0.30 *M* glucose solution. The solutions inside and outside the red blood cell are said to be **isotonic** (*iso* means "same," and *tonic* means "strength") **solutions.** Because the osmolarity is the same inside and outside, the red blood cell will remain the same size (Figure 18.20b).

What happens if we now place the red blood cells into a **hypotonic solution,** in other words, a solution having a lower osmolarity than the cytoplasm of the cell? In this situation there will be a net movement of water into the cell as water diffuses down its concentration gradient. The membrane of the red blood cell does not have the strength to exert a sufficient pressure to stop this flow of water, and

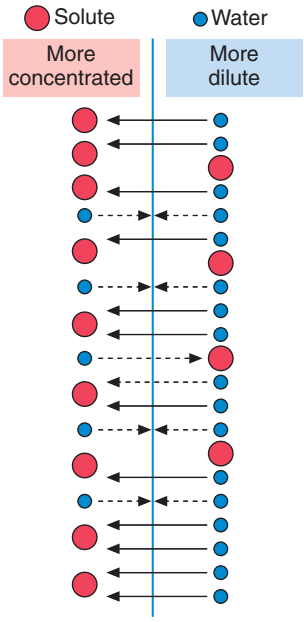


Figure 18.19
Osmosis across a membrane. The solvent, water, diffuses from an area of lower solute concentration to an area of higher solute concentration.

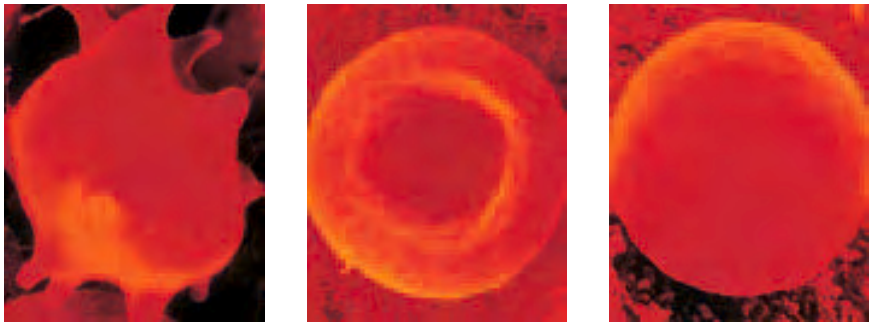


Figure 18.20
Scanning electron micrographs of red blood cells exposed to (a) hypertonic, (b) isotonic, and (c) hypotonic solutions.

the cell will swell and burst (Figure 18.20c). Alternatively, if we place the red blood cells into a **hypertonic solution** (one with a greater osmolarity than the cell), water will pass out of the cells, and they will shrink dramatically in size (Figure 18.20a).

These principles have important applications in the delivery of intravenous (IV) solutions into an individual. Normally, any fluids infused intravenously must have the correct osmolarity; they must be isotonic with the blood cells and the blood plasma. Such infusions are frequently either 5.5% dextrose (glucose) or "normal saline." The first solution is composed of 5.5 g of glucose per 100 mL of solution (0.30 *M*), and the latter of 9.0 g of NaCl per 100 mL of solution (0.15 *M*). In either case they have the same osmotic pressure and osmolarity as the plasma and blood cells and can therefore be safely administered without upsetting the osmotic balance between the blood and the blood cells.

Energy Requirements for Transport

Learning Goal 14

Simple diffusion, facilitated diffusion, and osmosis involve the spontaneous flow of materials from a region of higher concentration to an area of lower concentration (a concentration gradient). To survive, cells often must move substances "uphill," against a concentration gradient. This phenomenon, called **active transport,** requires energy. Many ions and food molecules are imported through the cell membrane by active transport. The energy used for this process may consume more than half of the total energy harvested by cellular metabolism.

A good example of active transport is the Na^+-K^+ ATPase, which moves these ions into and out of the cell against their gradients (Figure 18.21). Cells must maintain a high concentration of Na^+ outside the cell and a high concentration of K^+ inside the cell. This requires a continuous supply of cellular energy in the form of adenosine triphosphate (ATP). Over one-third of the total ATP produced by the cell is used to maintain these Na^+ and K^+ concentration gradients across the cell membrane. Thus, the name *Na^+-K^+ ATPase* refers to the enzymatic activity that hydrolyzes ATP. The hydrolysis of ATP releases the energy needed to move Na^+ and K^+ ions across the cell membrane. For each ATP molecule hydrolyzed, three Na^+ are moved out of the cell and two K^+ are transported into the cell.

How does membrane transport resemble enzyme catalysis? **Question 18.11**

Why is D-glucose transported by the glucose transport protein whereas L-glucose is not? **Question 18.12**

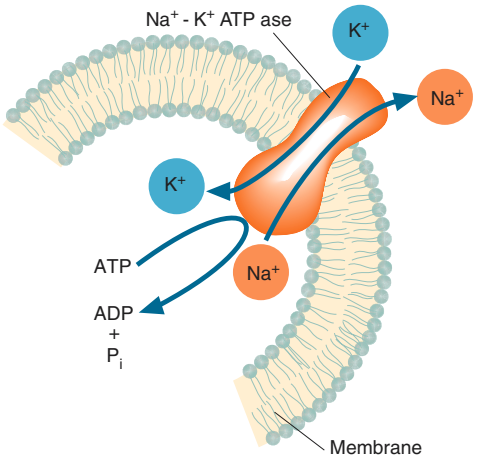


Figure 18.21
Schematic diagram of the operation of Na^+-K^+ ATPase.

Summary

18.1 Biological Functions of Lipids

Lipids are organic molecules characterized by their solubility in nonpolar solvents. Lipids are subdivided into classes based on structural characteristics: *fatty acids*, *glycerides*, nonglycerides, and *complex lipids*. Lipids serve many functions in the body, including energy storage, protection of organs, insulation, and absorption of vitamins. Other lipids are energy sources, hormones, or vitamins. Cells store chemical energy in the form of lipids, and the cell membrane is a lipid bilayer.

18.2 Fatty Acids

Fatty acids are *saturated* and *unsaturated* carboxylic acids containing between twelve and twenty-four carbon atoms. Fatty acids with even numbers of carbon atoms occur most frequently in nature. The reactions of fatty acids are identical to those of carboxylic acids. They include esterification, production by acid hydrolysis of esters, saponification, and addition at the double bond. *Prostaglandins*, thromboxanes, and leukotrienes are derivatives of twenty-carbon fatty acids that have a variety of physiological effects.

18.3 Glycerides

Glycerides are the most abundant lipids. The triesters of glycerol (*triglycerides*) are of greatest importance. Neutral triglycerides are important because of their ability to store energy. The ionic *phospholipids* are important components of all biological membranes.

18.4 Nonglyceride Lipids

Nonglyceride lipids consist of *sphingolipids*, *steroids*, and *waxes*. *Sphingomyelin* is a component of the myelin sheath around cells of the central nervous system. The *steroids* are important for many biochemical functions: *Cholesterol* is a membrane component; testosterone, progesterone, and estrone are sex hormones; and cortisone is an anti-inflammatory steroid that is important in the regulation of many biochemical pathways.

18.5 Complex Lipids

Plasma lipoproteins are complex lipids that transport other lipids through the bloodstream. *Chylomicrons* carry dietary triglycerides from the intestine to other tissues. *Very low density lipoproteins* carry triglycerides synthesized in the liver to other tissues for storage. *Low-density lipoproteins* carry cholesterol to peripheral tissues and help regulate blood cholesterol levels. *High-density lipoproteins* transport cholesterol from peripheral tissues to the liver.

18.6 The Structure of Biological Membranes

The *fluid mosaic model* of membrane structure pictures biological membranes that are composed of lipid bilayers in which proteins are embedded. Membrane lipids contain polar head groups and nonpolar hydrocarbon tails. The hydrocarbon tails of phospholipids are derived from saturated and unsaturated long-chain fatty acids containing an even number of carbon atoms. The lipids and proteins diffuse rapidly in the lipid bilayer but seldom cross from one side to the other.

The simplest type of membrane transport is passive diffusion of a substance across the lipid bilayer from the region of higher concentration to that of lower concentration. Many metabolites are transported across biological membranes by permeases that form pores through the membrane. The conformation of the pore is complementary to that of the substrate to be transported. Cells use energy to transport molecules across the plasma membrane against their concentration gradients, a process known as *active transport*.

The Na^+-K^+ ATPase hydrolyzes one molecule of ATP to provide the driving force for pumping three Na^+ out of the cell in exchange for two K^+.

Key Terms

active transport (18.6)
arachidonic acid (18.2)
atherosclerosis (18.4)
cholesterol (18.4)
chylomicron (18.5)
complex lipid (18.5)
diglyceride (18.3)
eicosanoid (18.2)
emulsifying agent (18.3)
essential fatty acid (18.2)
esterification (18.2)
facilitated diffusion (18.6)
fatty acid (18.2)
fluid mosaic model (18.6)
glyceride (18.3)
high-density lipoprotein (HDL) (18.5)
hydrogenation (18.2)
hypertonic solution (18.6)
hypotonic solution (18.6)
isotonic solution (18.6)
lipid (18.1)
low-density lipoprotein (LDL) (18.5)
monoglyceride (18.3)
neutral glyceride (18.3)
osmosis (18.6)
osmotic pressure (18.6)
passive transport (18.6)
peripheral membrane protein (18.6)
phosphatidate (18.3)
phosphoglyceride (18.3)
phospholipid (18.3)
plasma lipoprotein (18.5)
prostaglandin (18.2)
saponification (18.2)
saturated fatty acid (18.2)
semipermeable membrane (18.6)
sphingolipid (18.4)
sphingomyelin (18.4)
steroid (18.4)
terpene (18.4)
transmembrane protein (18.6)
triglyceride (18.3)
unsaturated fatty acid (18.2)
very low density lipoprotein (VLDL) (18.5)
wax (18.4)

Questions and Problems

Biological Functions of Lipids

18.13 List the four main groups of lipids.
18.14 List the biological functions of lipids.

Fatty Acids

18.15 What is the difference between a saturated and an unsaturated fatty acid?
18.16 Write the structure for a saturated and an unsaturated fatty acid.
18.17 As the length of the hydrocarbon chain of saturated fatty acids increases, what is the effect on the melting points?
18.18 As the number of carbon-carbon double bonds in fatty acids increases, what is the effect on the melting points?
18.19 Draw the structures of each of the following fatty acids:
a. Decanoic acid
b. Stearic acid
c. *trans*-5-Decenoic acid
d. *cis*-5-Decenoic acid
18.20 What are the common and I.U.P.A.C. names of each of the following fatty acids?
a. $C_{15}H_{31}COOH$
b. $C_{11}H_{23}COOH$
c. $CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$
d. $CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
18.21 Write an equation for each of the following reactions:
a. Esterification of glycerol with three molecules of myristic acid
b. Acid hydrolysis of tristearoyl glycerol
c. Reaction of decanoic acid with KOH
d. Hydrogenation of linoleic acid
18.22 Write an equation for each of the following reactions:
a. Esterification of glycerol with three molecules of palmitic acid
b. Acid hydrolysis of trioleoyl glycerol
c. Reaction of stearic acid with KOH
d. Hydrogenation of oleic acid
18.23 What is the function of the essential fatty acids?
18.24 What molecules are formed from arachidonic acid?
18.25 What is the biochemical basis for the effectiveness of aspirin in decreasing the inflammatory response?
18.26 What is the role of prostaglandins in the inflammatory response?
18.27 List four effects of prostaglandins.
18.28 What are the functions of thromboxane A_2 and leukotrienes?

Glycerides

18.29 Draw the structure of the triglyceride molecule formed by esterification at C-1, C-2, and C-3 with hexadecanoic acid, *trans*-9-hexadecenoic acid, and *cis*-9-hexadecenoic acid, respectively.
18.30 Draw one possible structure of a triglyceride that contains the three fatty acids stearic acid, palmitic acid, and oleic acid.
18.31 Draw the structure of the phosphatidate formed between glycerol-3-phosphate that is esterified at C-1 and C-2 with capric and lauric acids, respectively.
18.32 Draw the structure of a lecithin molecule in which the fatty acyl groups are derived from stearic acid.
18.33 What are the structural differences between triglycerides (triacylglycerols) and phospholipids?
18.34 How are the structural differences between triglycerides and phospholipids reflected in their different biological functions?

Nonglyceride Lipids

18.35 What is a sphingolipid?
18.36 What is the function of sphingomyelin?
18.37 What is the role of cholesterol in biological membranes?
18.38 How does cholesterol contribute to atherosclerosis?
18.39 What are the biological functions of progesterone, testosterone, and estrone?
18.40 How has our understanding of the steroid sex hormones contributed to the development of oral contraceptives?
18.41 What is the medical application of cortisone?
18.42 What are the possible side effects of cortisone treatment?
18.43 A wax found in beeswax is myricyl palmitate. What fatty acid and what alcohol are used to form this compound?
18.44 A wax found in the head of sperm whales is cetyl palmitate. What fatty acid and what alcohol are used to form this compound?
18.45 What are isoprenoids?
18.46 What is a terpene?
18.47 List some important biological molecules that are terpenes.
18.48 Draw the five-carbon isoprene unit.

Complex Lipids

18.49 What are the four major types of plasma lipoproteins?
18.50 What is the function of each of the four types of plasma lipoproteins?

18.51 What is the relationship between atherosclerosis and high blood pressure?
18.52 How is LDL taken into cells?
18.53 How does a genetic defect in the LDL receptor contribute to atherosclerosis?
18.54 What is the correlation between saturated fats in the diet and atherosclerosis?

The Structure of Biological Membranes

18.55 How will the properties of a biological membrane change if the fatty acid tails of the phospholipids are converted from saturated to unsaturated chains?
18.56 What is the function of unsaturation in the hydrocarbon tails of membrane lipids?
18.57 What is the basic structure of a biological membrane?
18.58 Describe the fluid mosaic model of membrane structure.
18.59 Describe peripheral membrane proteins.
18.60 Describe transmembrane proteins and list some of their functions.
18.61 What is the major effect of cholesterol on the properties of biological membranes?
18.62 Why do the hydrocarbon tails of membrane phospholipids provide a barrier between the inside and outside of the cell?
18.63 What experimental observation shows that proteins diffuse within the lipid bilayers of biological membranes?
18.64 Why don't proteins turn around in biological membranes like revolving doors?

Biological Membranes: Transport

18.65 Explain the difference between simple diffusion across a membrane and facilitated diffusion.
18.66 Explain what would happen to a red blood cell placed in each of the following solutions:
a. hypotonic **c.** hypertonic
b. isotonic
18.67 How does active transport differ from facilitated diffusion?
18.68 By what mechanism are Cl^- and HCO_3^- ions transported across the red blood cell membrane?
18.69 What is the meaning of the term *antiport?*
18.70 How does insulin affect the transport of glucose?
18.71 What properties of a transport protein (permease) determine its specificity?
18.72 Why is the function of the Na^+-K^+ ATPase an example of active transport?
18.73 What is the stoichiometry of the Na^+-K^+ ATPase?
18.74 How will the Na^+ and K^+ concentrations of a cell change if the Na^+-K^+ ATPase is inhibited?
18.75 What is meant by the term *active transport?*

Critical Thinking Problems

1. Olestra is a fat substitute that provides no calories, yet has all the properties of a naturally occurring fat. It has a creamy, tongue-pleasing consistency. Unlike other fat substitutes, olestra can withstand heating. Thus, it can be used to prepare foods such as potato chips and crackers. Olestra is a sucrose polyester and is produced by esterification of six, seven, or eight fatty acids to molecules of sucrose. Draw the structure of one such molecule having eight stearic acid acyl groups attached.
2. Liposomes can be made by vigorously mixing phospholipids (like phosphatidylcholine) in water. When the mixture is allowed to settle, spherical vesicles form that are surrounded by a phospholipid bilayer "membrane." Pharmaceutical chemists are trying to develop liposomes as a targeted drug delivery system. By adding the drug of choice to the mixture described above, liposomes form around the solution of drug. Specific proteins can be incorporated into the mixture that will end up within the phospholipid bilayers of the liposomes. These proteins are able to bind to targets on the surface of particular kinds of cells in the body. Explain why injection of liposome encapsulated pharmaceuticals might be a good drug delivery system.
3. "Cholesterol is bad and should be eliminated from the diet." Do you agree or disagree? Defend your answer.
4. Why would a phospholipid such as lecithin be a good emulsifying agent for ice cream?
5. When a plant becomes cold-adapted, the composition of the membranes changes. What changes in fatty acid and cholesterol composition would you predict? Explain your reasoning.
6. In terms of osmosis, explain why it would be preferable for a cell to store 10,000 molecules of glycogen each composed of 10^5 molecules of glucose rather than to store 10^9 individual molecules of glucose.