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BIOMEDICAL IMPORTANCE

The lipids are a heterogeneous group of compounds, including fats, oils, steroids, waxes, and related compounds, which are related more by their physical than by their chemical properties. They have the common property of being (1) relatively **insoluble in water** and (2) **soluble in nonpolar solvents** such as ether and chloroform. They are important dietary constituents not only because of their high energy value but also because of the fat-soluble vitamins and the essential fatty acids contained in the fat of natural foods. Fat is stored in **adipose tissue**, where it also serves as a thermal insulator in the subcutaneous tissues and around certain organs. Nonpolar lipids act as **electrical insulators**, allowing rapid propagation of depolarization waves along **myelinated nerves**. Combinations of lipid and protein (lipoproteins) are important cellular constituents, occurring both in the cell **membrane** and in the mitochondria, and serving also as the means of **transporting lipids** in the blood. Knowledge of lipid biochemistry is necessary in understanding many important biomedical areas, eg, **obesity**, **diabetes mellitus**, **atherosclerosis**, and the role of various **polyunsaturated fatty acids** in nutrition and health.

LIPIDS ARE CLASSIFIED AS SIMPLE OR COMPLEX

1. **Simple lipids:** Esters of fatty acids with various alcohols.
 - a. **Fats:** Esters of fatty acids with glycerol. **Oils** are fats in the liquid state.
 - b. **Waxes:** Esters of fatty acids with higher molecular weight monohydric alcohols.
2. **Complex lipids:** Esters of fatty acids containing groups in addition to an alcohol and a fatty acid.
 - a. **Phospholipids:** Lipids containing, in addition to fatty acids and an alcohol, a phosphoric acid residue. They frequently have nitrogen-containing bases and other substituents, eg, in **glycerophospholipids** the alcohol is glycerol and in **sphingophospholipids** the alcohol is sphingosine.
 - b. **Glycolipids (glycosphingolipids):** Lipids containing a fatty acid, sphingosine, and carbohydrate.

c. **Other complex lipids:** Lipids such as sulfolipids and aminolipids. Lipoproteins may also be placed in this category.

3. **Precursor and derived lipids:** These include fatty acids, glycerol, steroids, other alcohols, fatty aldehydes, and ketone bodies (Chapter 22), hydrocarbons, lipid-soluble vitamins, and hormones.

Because they are uncharged, acylglycerols (glycerides), cholesterol, and cholesteryl esters are termed **neutral lipids**.

FATTY ACIDS ARE ALIPHATIC CARBOXYLIC ACIDS

Fatty acids occur mainly as esters in natural fats and oils but do occur in the unesterified form as **free fatty acids**, a transport form found in the plasma. Fatty acids that occur in natural fats are usually straight-chain derivatives containing an even number of carbon atoms. The chain may be **saturated** (containing no double bonds) or **unsaturated** (containing one or more double bonds).

Fatty Acids Are Named After Corresponding Hydrocarbons

The most frequently used systematic nomenclature names the fatty acid after the hydrocarbon with the same number and arrangement of carbon atoms, with **-oic** being substituted for the final **-e** (Genevan system). Thus, saturated acids end in **-anoic**, eg, octanoic acid, and unsaturated acids with double bonds end in **-enoic**, eg, octadecenoic acid (oleic acid).

Carbon atoms are numbered from the carboxyl carbon (carbon No. 1). The carbon atoms adjacent to the carboxyl carbon (Nos. 2, 3, and 4) are also known as the α , β , and γ carbons, respectively, and the terminal methyl carbon is known as the ω or n-carbon.

Various conventions use Δ for indicating the number and position of the double bonds (Figure 14–1); eg, Δ^9 indicates a double bond between carbons 9 and 10 of the fatty acid; $\omega 9$ indicates a double bond on the ninth carbon counting from the ω -carbon. In animals, additional double bonds are introduced only between the existing double bond (eg, $\omega 9$, $\omega 6$, or $\omega 3$) and the

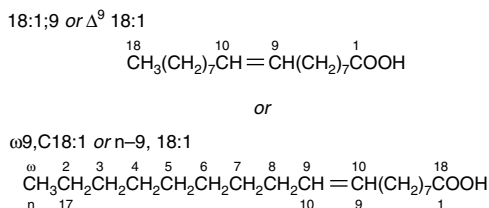


Figure 14–1. Oleic acid. $n - 9$ (n minus 9) is equivalent to $\omega 9$.

carboxyl carbon, leading to three series of fatty acids known as the $\omega 9$, $\omega 6$, and $\omega 3$ families, respectively.

Saturated Fatty Acids Contain No Double Bonds

Saturated fatty acids may be envisaged as based on acetic acid ($\text{CH}_3\text{—COOH}$) as the first member of the series in which $\text{—CH}_2\text{—}$ is progressively added between the terminal $\text{CH}_3\text{—}$ and —COOH groups. Examples are shown in Table 14–1. Other higher members of the series are known to occur, particularly in waxes. A few branched-chain fatty acids have also been isolated from both plant and animal sources.

Table 14–1. Saturated fatty acids.

Common Name	Number of C Atoms	
Acetic	2	Major end product of carbohydrate fermentation by rumen organisms ¹
Propionic	3	An end product of carbohydrate fermentation by rumen organisms ¹
Butyric	4	In certain fats in small amounts (especially butter). An end product of carbohydrate fermentation by rumen organisms ¹
Valeric	5	
Caproic	6	
Lauric	12	Spermaceti, cinnamon, palm kernel, coconut oils, laurels, butter
Myristic	14	Nutmeg, palm kernel, coconut oils, myrtles, butter
Palmitic	16	Common in all animal and plant fats
Stearic	18	

¹Also formed in the cecum of herbivores and to a lesser extent in the colon of humans.

Unsaturated Fatty Acids Contain One or More Double Bonds (Table 14–2)

Fatty acids may be further subdivided as follows:

- (1) **Monounsaturated** (monoethenoid, monoenoic) acids, containing one double bond.
- (2) **Polyunsaturated** (polyethenoid, polyenoic) acids, containing two or more double bonds.
- (3) **Eicosanoids**: These compounds, derived from eicosa- (20-carbon) polyenoic fatty acids, comprise the **prostanoids**, **leukotrienes (LTs)**, and **lipoxins (LXs)**. Prostanoids include **prostaglandins (PGs)**, **prostacyclins (PGIs)**, and **thromboxanes (TXs)**.

Prostaglandins exist in virtually every mammalian tissue, acting as local hormones; they have important physiologic and pharmacologic activities. They are synthesized *in vivo* by cyclization of the center of the carbon chain of 20-carbon (eicosanoic) polyunsaturated fatty acids (eg, arachidonic acid) to form a cyclopentane ring (Figure 14–2). A related series of compounds, the **thromboxanes**, have the cyclopentane ring interrupted with an oxygen atom (oxane ring) (Figure 14–3). Three different eicosanoic fatty acids give rise to three groups of eicosanoids characterized by the number of double bonds in the side chains, eg, PG_1 , PG_2 , PG_3 . Different substituent groups attached to the rings give rise to series of prostaglandins and thromboxanes, labeled A, B, etc—eg, the “E” type of prostaglandin (as in PGE_2) has a keto group in position 9, whereas the “F” type has a hydroxyl group in this position. The **leukotrienes** and **lipoxins** are a third group of eicosanoid derivatives formed via the lipoxygenase pathway (Figure 14–4). They are characterized by the presence of three or four conjugated double bonds, respectively. Leukotrienes cause bronchoconstriction as well as being potent proinflammatory agents and play a part in **asthma**.

Most Naturally Occurring Unsaturated Fatty Acids Have *cis* Double Bonds

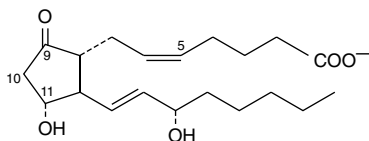
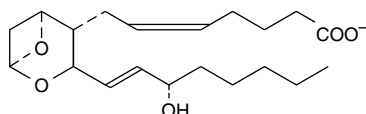
The carbon chains of saturated fatty acids form a zigzag pattern when extended, as at low temperatures. At higher temperatures, some bonds rotate, causing chain shortening, which explains why biomembranes become thinner with increases in temperature. A type of **geometric isomerism** occurs in unsaturated fatty acids, depending on the orientation of atoms or groups around the axes of double bonds, which do not allow rotation. If the acyl chains are on the same side of the bond, it is *cis*-, as in oleic acid; if on opposite sides, it is *trans*-, as in elaidic acid, the *trans* isomer of oleic acid (Fig-

Table 14–2. Unsaturated fatty acids of physiologic and nutritional significance.

Number of C Atoms and Number and Position of Double Bonds	Family	Common Name	Systematic Name	Occurrence
Monoenoic acids (one double bond)				
16:1;9	ω 7	Palmitoleic	<i>cis</i> -9-Hexadecenoic	In nearly all fats.
18:1;9	ω 9	Oleic	<i>cis</i> -9-Octadecenoic	Possibly the most common fatty acid in natural fats.
18:1;9	ω 9	Elaidic	<i>trans</i> -9-Octadecenoic	Hydrogenated and ruminant fats.
Dienoic acids (two double bonds)				
18:2;9,12	ω 6	Linoleic	all- <i>cis</i> -9,12-Octadecadienoic	Corn, peanut, cottonseed, soybean, and many plant oils.
Trienoic acids (three double bonds)				
18:3;6,9,12	ω 6	γ -Linolenic	all- <i>cis</i> -6,9,12-Octadecatrienoic	Some plants, eg, oil of evening primrose, borage oil; minor fatty acid in animals.
18:3;9,12,15	ω 3	α -Linolenic	all- <i>cis</i> -9,12,15-Octadecatrienoic	Frequently found with linoleic acid but particularly in linseed oil.
Tetraenoic acids (four double bonds)				
20:4;5,8,11,14	ω 6	Arachidonic	all- <i>cis</i> -5,8,11,14-Eicosatetraenoic	Found in animal fats and in peanut oil; important component of phospholipids in animals.
Pentaenoic acids (five double bonds)				
20:5;5,8,11,14,17	ω 3	Timnodonic	all- <i>cis</i> -5,8,11,14,17-Eicosapentaenoic	Important component of fish oils, eg, cod liver, mackerel, menhaden, salmon oils.
Hexaenoic acids (six double bonds)				
22:6;4,7,10,13,16,19	ω 3	Cervonic	all- <i>cis</i> -4,7,10,13,16,19-Docosahexaenoic	Fish oils, phospholipids in brain.

ure 14–5). Naturally occurring unsaturated long-chain fatty acids are nearly all of the *cis* configuration, the molecules being “bent” 120 degrees at the double bond. Thus, oleic acid has an L shape, whereas elaidic acid remains “straight.” Increase in the number of *cis* double bonds in a fatty acid leads to a variety of possible spatial configurations of the molecule—eg, arachidonic acid, with four *cis* double bonds, has “kinks” or a

U shape. This has profound significance on molecular packing in membranes and on the positions occupied by fatty acids in more complex molecules such as phospholipids. *Trans* double bonds alter these spatial relationships. *Trans* fatty acids are present in certain foods, arising as a by-product of the saturation of fatty acids during hydrogenation, or “hardening,” of natural oils in the manufacture of margarine. An additional small

**Figure 14–2.** Prostaglandin E_2 (PGE_2).**Figure 14–3.** Thromboxane A_2 (TXA_2).

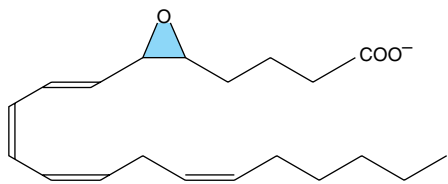


Figure 14–4. Leukotriene A_4 (LTA_4).

contribution comes from the ingestion of ruminant fat that contains *trans* fatty acids arising from the action of microorganisms in the rumen.

Physical and Physiologic Properties of Fatty Acids Reflect Chain Length and Degree of Unsaturation

The melting points of even-numbered-carbon fatty acids increase with chain length and decrease according to unsaturation. A triacylglycerol containing three saturated fatty acids of 12 carbons or more is solid at body temperature, whereas if the fatty acid residues are 18:2, it is liquid to below 0 °C. In practice, natural acylglycerols contain a mixture of fatty acids tailored to suit their functional roles. The membrane lipids, which must be fluid at all environmental temperatures, are

more unsaturated than storage lipids. Lipids in tissues that are subject to cooling, eg, in hibernators or in the extremities of animals, are more unsaturated.

TRIACYLGLYCEROLS (TRIGLYCERIDES)* ARE THE MAIN STORAGE FORMS OF FATTY ACIDS

The triacylglycerols (Figure 14–6) are esters of the trihydric alcohol glycerol and fatty acids. Mono- and diacylglycerols wherein one or two fatty acids are esterified with glycerol are also found in the tissues. These are of particular significance in the synthesis and hydrolysis of triacylglycerols.

Carbons 1 & 3 of Glycerol Are Not Identical

To number the carbon atoms of glycerol unambiguously, the *-sn-* (stereochemical numbering) system is used. It is important to realize that carbons 1 and 3 of glycerol are not identical when viewed in three dimensions (shown as a projection formula in Figure 14–7). Enzymes readily distinguish between them and are nearly always specific for one or the other carbon; eg, glycerol is always phosphorylated on *sn*-3 by glycerol kinase to give glycerol 3-phosphate and not glycerol 1-phosphate.

PHOSPHOLIPIDS ARE THE MAIN LIPID CONSTITUENTS OF MEMBRANES

Phospholipids may be regarded as derivatives of **phosphatidic acid** (Figure 14–8), in which the phosphate is esterified with the —OH of a suitable alcohol. Phosphatidic acid is important as an intermediate in the synthesis of triacylglycerols as well as phosphoglycerols but is not found in any great quantity in tissues.

Phosphatidylcholines (Lecithins) Occur in Cell Membranes

Phosphoacylglycerols containing choline (Figure 14–8) are the most abundant phospholipids of the cell mem-

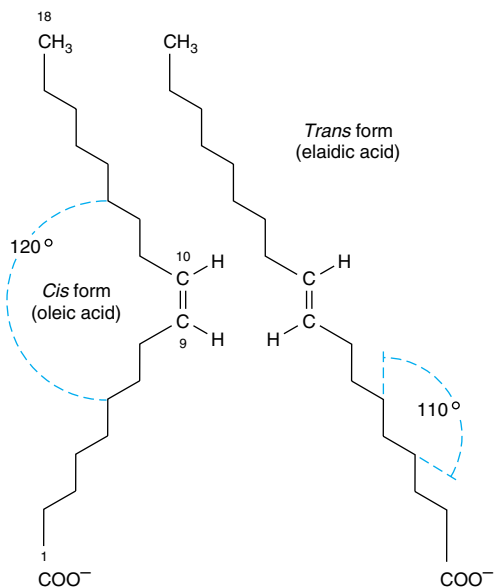


Figure 14–5. Geometric isomerism of Δ^9 , 18:1 fatty acids (oleic and elaidic acids).

* According to the standardized terminology of the International Union of Pure and Applied Chemistry (IUPAC) and the International Union of Biochemistry (IUB), the monoglycerides, diglycerides, and triglycerides should be designated monoacylglycerols, diacylglycerols, and triacylglycerols, respectively. However, the older terminology is still widely used, particularly in clinical medicine.

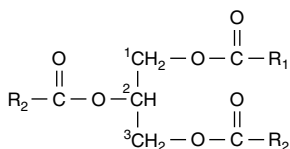


Figure 14–6. Triacylglycerol.

brane and represent a large proportion of the body's store of choline. Choline is important in nervous transmission, as acetylcholine, and as a store of labile methyl groups. **Dipalmitoyl lecithin** is a very effective surface-active agent and a major constituent of the **surfactant** preventing adherence, due to surface tension, of the inner surfaces of the lungs. Its absence from the lungs of premature infants causes **respiratory distress syndrome**. Most phospholipids have a saturated acyl radical in the *sn*-1 position but an unsaturated radical in the *sn*-2 position of glycerol.

Phosphatidylethanolamine (cephalin) and **phosphatidylserine** (found in most tissues) differ from phosphatidylcholine only in that ethanolamine or serine, respectively, replaces choline (Figure 14–8).

Phosphatidylinositol Is a Precursor of Second Messengers

The inositol is present in **phosphatidylinositol** as the stereoisomer, **myoinositol** (Figure 14–8). **Phosphatidylinositol 4,5-bisphosphate** is an important constituent of cell membrane phospholipids; upon stimulation by a suitable hormone agonist, it is cleaved into **diacylglycerol** and **inositol trisphosphate**, both of which act as internal signals or second messengers.

Cardiolipin Is a Major Lipid of Mitochondrial Membranes

Phosphatidic acid is a precursor of **phosphatidylglycerol** which, in turn, gives rise to **cardiolipin** (Figure 14–8).

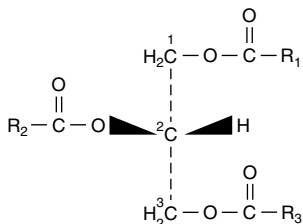
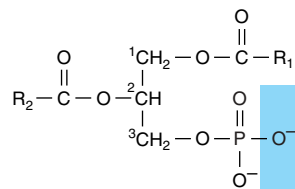


Figure 14–7. Triacyl-*sn*-glycerol.



Phosphatidic acid

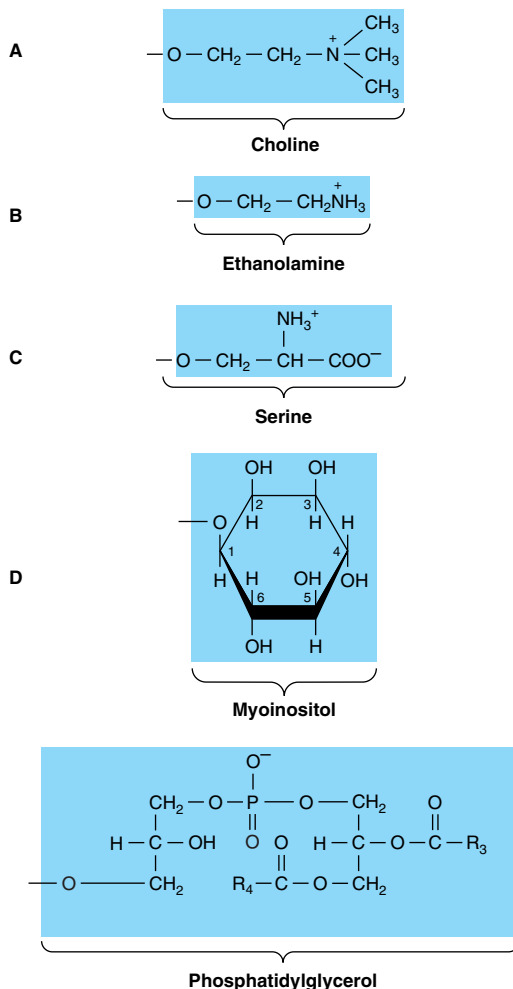


Figure 14–8. Phosphatidic acid and its derivatives. The O^- shown shaded in phosphatidic acid is substituted by the substituents shown to form in **(A)** 3-phosphatidylcholine, **(B)** 3-phosphatidylethanolamine, **(C)** 3-phosphatidylserine, **(D)** 3-phosphatidylinositol, and **(E)** cardiolipin (diphosphatidylglycerol).

Lysophospholipids Are Intermediates in the Metabolism of Phosphoglycerols

These are phosphoacylglycerols containing only one acyl radical, eg, **lysophosphatidylcholine (lysolecithin)**, important in the metabolism and interconversion of phospholipids (Figure 14–9). It is also found in oxidized lipoproteins and has been implicated in some of their effects in promoting **atherosclerosis**.

Plasmalogens Occur in Brain & Muscle

These compounds constitute as much as 10% of the phospholipids of brain and muscle. Structurally, the plasmalogens resemble phosphatidylethanolamine but possess an ether link on the *sn*-1 carbon instead of the ester link found in acylglycerols. Typically, the alkyl radical is an unsaturated alcohol (Figure 14–10). In some instances, choline, serine, or inositol may be substituted for ethanolamine.

Sphingomyelins Are Found in the Nervous System

Sphingomyelins are found in large quantities in brain and nerve tissue. On hydrolysis, the sphingomyelins yield a fatty acid, phosphoric acid, choline, and a complex amino alcohol, **sphingosine** (Figure 14–11). No glycerol is present. The combination of sphingosine plus fatty acid is known as **ceramide**, a structure also found in the glycosphingolipids (see below).

GLYCOLIPIDS (GLYCOSPHINGOLIPIDS) ARE IMPORTANT IN NERVE TISSUES & IN THE CELL MEMBRANE

Glycolipids are widely distributed in every tissue of the body, particularly in nervous tissue such as brain. They occur particularly in the outer leaflet of the plasma membrane, where they contribute to **cell surface carbohydrates**.

The major glycolipids found in animal tissues are glycosphingolipids. They contain ceramide and one or more sugars. **Galactosylceramide** is a major glyco-

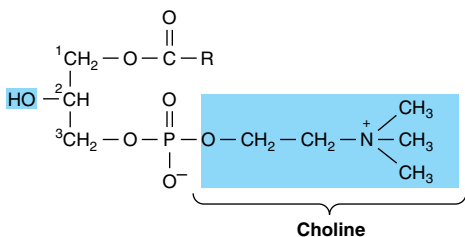


Figure 14–9. Lysophosphatidylcholine (lysolecithin).

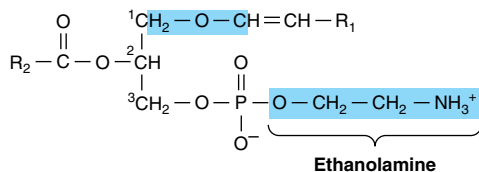


Figure 14–10. Plasmalogen.

sphingolipid of brain and other nervous tissue, found in relatively low amounts elsewhere. It contains a number of characteristic C₂₄ fatty acids, eg, cerebronic acid. Galactosylceramide (Figure 14–12) can be converted to sulfogalactosylceramide (**sulfatide**), present in high amounts in myelin. Glucosylceramide is the predominant simple glycosphingolipid of extraneural tissues, also occurring in the brain in small amounts. **Gangliosides** are complex glycosphingolipids derived from glucosylceramide that contain in addition one or more molecules of a **sialic acid**. Neuraminic acid (NeuAc; see Chapter 13) is the principal sialic acid found in human tissues. Gangliosides are also present in nervous tissues in high concentration. They appear to have receptor and other functions. The simplest ganglioside found in tissues is G_{M3}, which contains ceramide, one molecule of glucose, one molecule of galactose, and one molecule of NeuAc. In the shorthand nomenclature used, G represents ganglioside; M is a monosialo-containing species; and the subscript 3 is a number assigned on the basis of chromatographic migration. G_{M1} (Figure 14–13), a more complex ganglioside derived from G_{M3}, is of considerable biologic interest, as it is known to be the receptor in human intestine for cholera toxin. Other gangliosides can contain anywhere from one to five molecules of sialic acid, giving rise to di-, trisialogangliosides, etc.

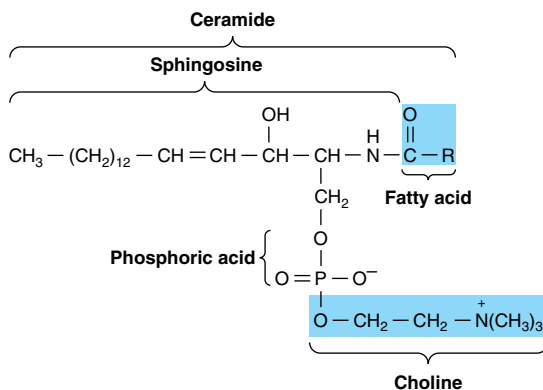


Figure 14–11. A sphingomyelin.

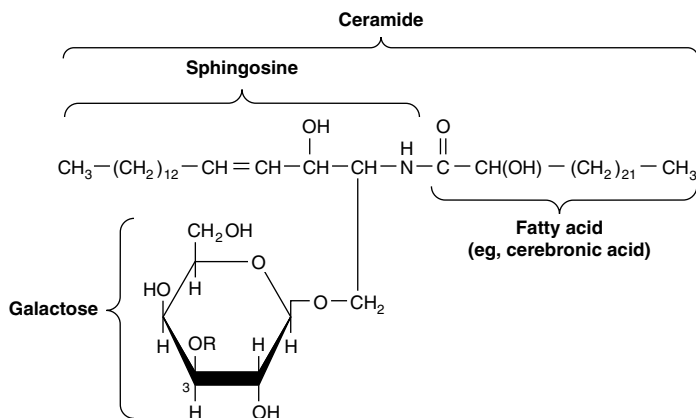


Figure 14–12. Structure of galactosylceramide (galactocerebroside, R = H), and sulfogalactosylceramide (a sulfatide, R = SO_4^{2-}).

STERIODS PLAY MANY PHYSIOLOGICALLY IMPORTANT ROLES

Cholesterol is probably the best known steroid because of its association with **atherosclerosis**. However, biochemically it is also of significance because it is the precursor of a large number of equally important steroids that include the bile acids, adrenocortical hormones, sex hormones, D vitamins, cardiac glycosides, sosterols of the plant kingdom, and some alkaloids.

All of the steroids have a similar cyclic nucleus resembling phenanthrene (rings A, B, and C) to which a cyclopentane ring (D) is attached. The carbon positions on the steroid nucleus are numbered as shown in Figure 14–14. It is important to realize that in structural formulas of steroids, a simple hexagonal ring denotes a completely saturated six-carbon ring with all valences satisfied by hydrogen bonds unless shown otherwise; ie, it is not a benzene ring. All double bonds are shown as such. Methyl side chains are shown as single bonds unattached at the farther (methyl) end. These occur typically at positions 10 and 13 (constituting C atoms 19 and 18). A side chain at position 17 is usual (as in cholesterol). If the compound has one or more hydroxyl

groups and no carbonyl or carboxyl groups, it is a **sterol**, and the name terminates in -ol.

Because of Asymmetry in the Steroid Molecule, Many Stereoisomers Are Possible

Each of the six-carbon rings of the steroid nucleus is capable of existing in the three-dimensional conformation either of a “chair” or a “boat” (Figure 14–15). In naturally occurring steroids, virtually all the rings are in the “chair” form, which is the more stable conformation. With respect to each other, the rings can be either *cis* or *trans* (Figure 14–16). The junction between the A and B rings can be *cis* or *trans* in naturally occurring steroids. That between B and C is *trans*, as is usually the C/D junction. Bonds attaching substituent groups above the plane of the rings (β bonds) are shown with bold solid lines, whereas those bonds attaching groups below (α bonds) are indicated with broken lines. The A ring of a 5α steroid is always *trans* to the B ring, whereas it is *cis* in a 5β steroid. The methyl groups attached to C_{10} and C_{13} are invariably in the β configuration.

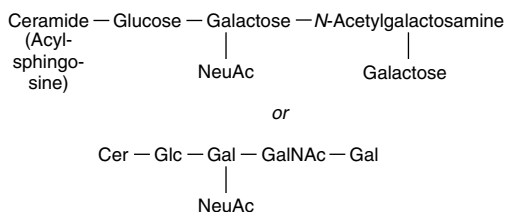


Figure 14–13. G_{M1} ganglioside, a monosialoganglioside, the receptor in human intestine for cholera toxin.

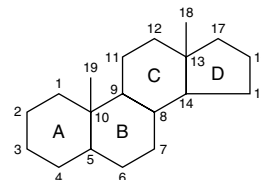


Figure 14–14. The steroid nucleus.

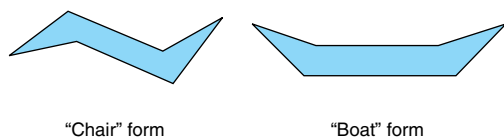


Figure 14-15. Conformations of stereoisomers of the steroid nucleus.

Cholesterol Is a Significant Constituent of Many Tissues

Cholesterol (Figure 14-17) is widely distributed in all cells of the body but particularly in nervous tissue. It is a major constituent of the plasma membrane and of plasma lipoproteins. It is often found as **cholesteryl ester**, where the hydroxyl group on position 3 is esterified with a long-chain fatty acid. It occurs in animals but not in plants.

Ergosterol Is a Precursor of Vitamin D

Ergosterol occurs in plants and yeast and is important as a precursor of vitamin D (Figure 14-18). When irradiated with ultraviolet light, it acquires antirachitic properties consequent to the opening of ring B.

Polyprenoids Share the Same Parent Compound as Cholesterol

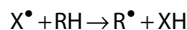
Although not steroids, these compounds are related because they are synthesized, like cholesterol (Figure 26-2), from five-carbon isoprene units (Figure 14-19). They include **ubiquinone** (Chapter 12), a member of the respiratory chain in mitochondria, and the long-

chain alcohol **dolichol** (Figure 14-20), which takes part in glycoprotein synthesis by transferring carbohydrate residues to asparagine residues of the polypeptide (Chapter 47). Plant-derived isoprenoid compounds include rubber, camphor, the fat-soluble vitamins A, D, E, and K, and β -carotene (provitamin A).

LIPID PEROXIDATION IS A SOURCE OF FREE RADICALS

Peroxidation (**auto-oxidation**) of lipids exposed to oxygen is responsible not only for deterioration of foods (**rancidity**) but also for damage to tissues *in vivo*, where it may be a cause of cancer, inflammatory diseases, atherosclerosis, and aging. The deleterious effects are considered to be caused by free radicals (ROO^\bullet , RO^\bullet , OH^\bullet) produced during peroxide formation from fatty acids containing methylene-interrupted double bonds, ie, those found in the naturally occurring polyunsaturated fatty acids (Figure 14-21). Lipid peroxidation is a chain reaction providing a continuous supply of free radicals that initiate further peroxidation. The whole process can be depicted as follows:

(1) Initiation:



(2) Propagation:

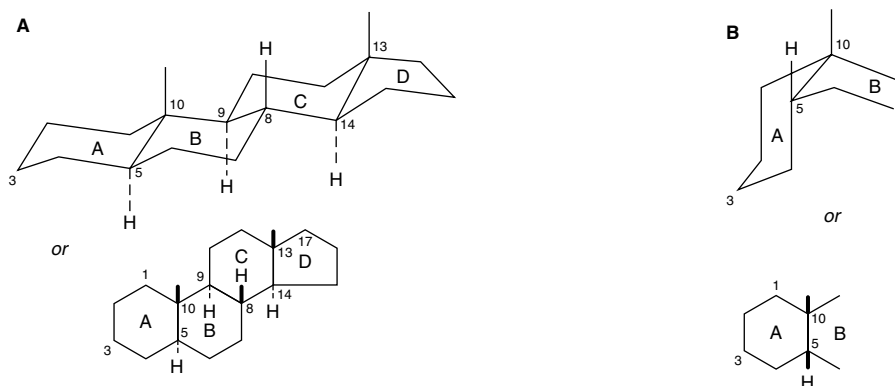
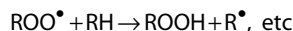
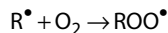


Figure 14-16. Generalized steroid nucleus, showing (A) an all-*trans* configuration between adjacent rings and (B) a *cis* configuration between rings A and B.

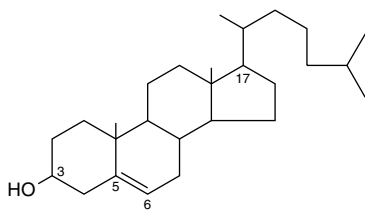
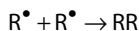
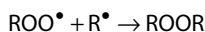
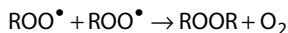


Figure 14–17. Cholesterol, 3-hydroxy-5,6-cholestene.

(3) Termination:



Since the molecular precursor for the initiation process is generally the hydroperoxide product ROOH, lipid peroxidation is a chain reaction with potentially devastating effects. To control and reduce lipid peroxidation, both humans in their activities and nature invoke the use of **antioxidants**. Propyl gallate, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT) are antioxidants used as food additives. Naturally occurring antioxidants include vitamin E (tocopherol), which is lipid-soluble, and urate and vitamin C, which are water-soluble. Beta-carotene is an antioxidant at low PO_2 . Antioxidants fall into two classes: (1) preventive antioxidants, which reduce the rate of chain initiation; and (2) chain-breaking antioxidants, which interfere with chain propagation. Preventive antioxidants include catalase and other peroxidases that react with ROOH and chelators of metal ions such as EDTA (ethylenediaminetetraacetate) and DTPA (diethylenetriaminepentaacetate). In vivo, the principal chain-breaking antioxidants are superoxide dismutase, which acts in the aqueous phase to trap superoxide free radicals ($\text{O}_2^{\bullet-}$); perhaps urate; and vitamin E, which acts in the lipid phase to trap ROO^\bullet radicals (Figure 45–6).

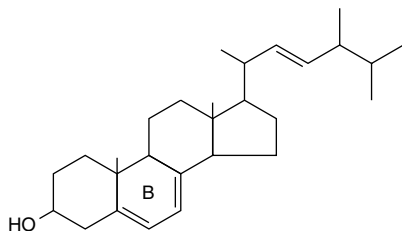


Figure 14–18. Ergosterol.

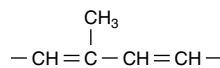


Figure 14–19. Isoprene unit.

Peroxidation is also catalyzed in vivo by heme compounds and by **lipoxygenases** found in platelets and leukocytes. Other products of auto-oxidation or enzymic oxidation of physiologic significance include **oxysterols** (formed from cholesterol) and **isoprostanes** (prostanoids).

AMPHIPATHIC LIPIDS SELF-ORIENT AT OIL:WATER INTERFACES

They Form Membranes, Micelles, Liposomes, & Emulsions

In general, lipids are insoluble in water since they contain a predominance of nonpolar (hydrocarbon) groups. However, fatty acids, phospholipids, sphingolipids, bile salts, and, to a lesser extent, cholesterol contain polar groups. Therefore, part of the molecule is **hydrophobic**, or water-insoluble; and part is **hydrophilic**, or water-soluble. Such molecules are described as **amphipathic** (Figure 14–22). They become oriented at oil:water interfaces with the polar group in the water phase and the nonpolar group in the oil phase. A bilayer of such amphipathic lipids has been regarded as a basic structure in biologic membranes (Chapter 41). When a critical concentration of these lipids is present in an aqueous medium, they form **micelles**. Aggregations of bile salts into micelles and liposomes and the formation of mixed micelles with the products of fat digestion are important in facilitating absorption of lipids from the intestine. Liposomes may be formed by sonicating an amphipathic lipid in an aqueous medium. They consist of spheres of lipid bilayers that enclose part of the aqueous medium. They are of potential clinical use—particularly when combined with tissue-specific antibodies—as carriers of drugs in the circulation, targeted to specific organs, eg, in cancer therapy. In addition, they are being used for gene transfer into vascular cells and as carriers for topical and transdermal

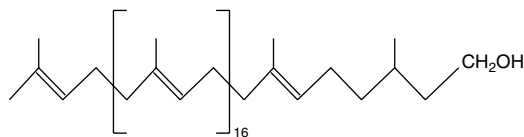


Figure 14–20. Dolichol—a C_{95} alcohol.

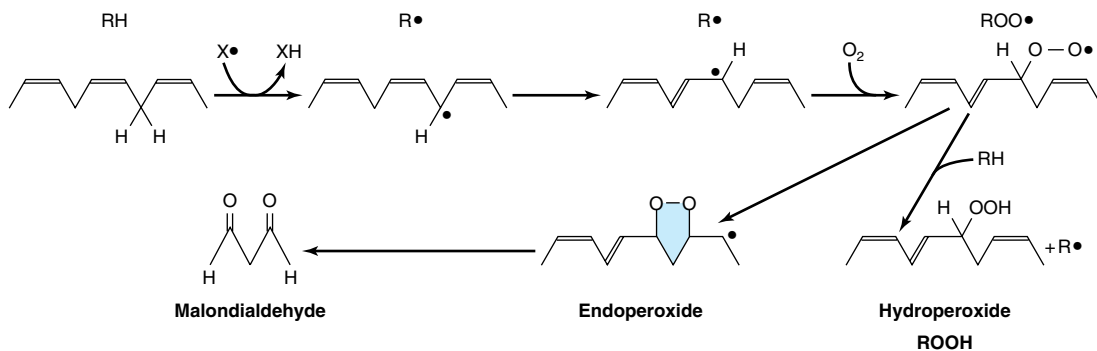


Figure 14–21. Lipid peroxidation. The reaction is initiated by an existing free radical (X^\bullet), by light, or by metal ions. Malondialdehyde is only formed by fatty acids with three or more double bonds and is used as a measure of lipid peroxidation together with ethane from the terminal two carbons of $\omega 3$ fatty acids and pentane from the terminal five carbons of $\omega 6$ fatty acids.

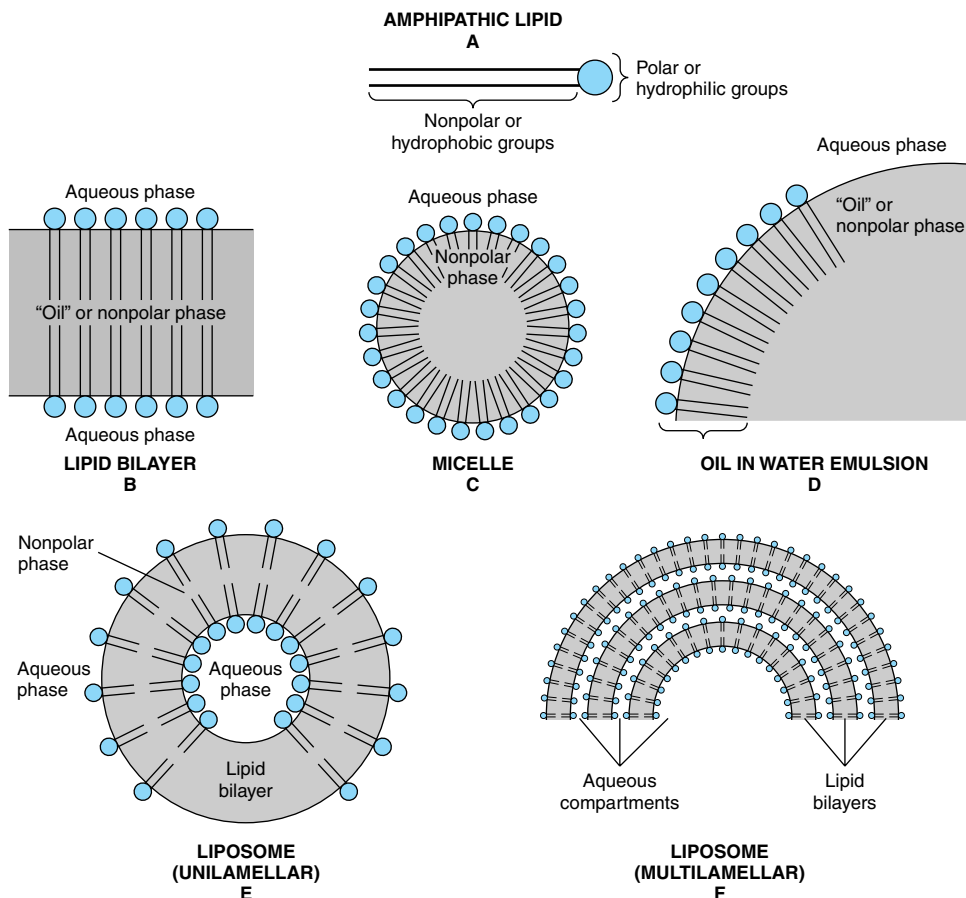


Figure 14–22. Formation of lipid membranes, micelles, emulsions, and liposomes from amphipathic lipids, eg, phospholipids.

delivery of drugs and cosmetics. **Emulsions** are much larger particles, formed usually by nonpolar lipids in an aqueous medium. These are stabilized by emulsifying agents such as amphipathic lipids (eg, lecithin), which form a surface layer separating the main bulk of the nonpolar material from the aqueous phase (Figure 14–22).

SUMMARY

- Lipids have the common property of being relatively insoluble in water (hydrophobic) but soluble in nonpolar solvents. Amphipathic lipids also contain one or more polar groups, making them suitable as constituents of membranes at lipid:water interfaces.
- The lipids of major physiologic significance are fatty acids and their esters, together with cholesterol and other steroids.
- Long-chain fatty acids may be saturated, monounsaturated, or polyunsaturated, according to the number of double bonds present. Their fluidity decreases with chain length and increases according to degree of unsaturation.
- Eicosanoids are formed from 20-carbon polyunsaturated fatty acids and make up an important group of physiologically and pharmacologically active compounds known as prostaglandins, thromboxanes, leukotrienes, and lipoxins.
- The esters of glycerol are quantitatively the most significant lipids, represented by triacylglycerol (“fat”), a major constituent of lipoproteins and the storage form of lipid in adipose tissue. Phosphoacylglycerols

are amphipathic lipids and have important roles—as major constituents of membranes and the outer layer of lipoproteins, as surfactant in the lung, as precursors of second messengers, and as constituents of nervous tissue.

- Glycolipids are also important constituents of nervous tissue such as brain and the outer leaflet of the cell membrane, where they contribute to the carbohydrates on the cell surface.
- Cholesterol, an amphipathic lipid, is an important component of membranes. It is the parent molecule from which all other steroids in the body, including major hormones such as the adrenocortical and sex hormones, D vitamins, and bile acids, are synthesized.
- Peroxidation of lipids containing polyunsaturated fatty acids leads to generation of free radicals that may damage tissues and cause disease.

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