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C H A P T E R

13

Lipids–II
Classification

(a)

(b)

Lipids

(a) **Fat.** A European brown bear ready to hibernate. Fat is an efficient way to store energy. If this bear stored the same amount of energy in carbohydrates instead of fat, she probably would be unable to walk!
(b) **Wax.** Wax is a highly saturated lipid that remains very firm at normal outdoor temperatures. Its rigidity allows it to be used to form the strong but thin-walled hexagons of this honeycomb.

Bloor (1943) has proposed the following classification of lipids based on their chemical composition.

A.   Simple lipids or **Homolipids.** These are esters of fatty acid with farious alcohols.

1.   *Fats and oils (triglycerides, triacylglycerols).* These are esters of fatty acids with a trihydroxy alcohol, glycerol. A fat is solid at ordinary room temperature wheras an oil is liquid.

2.   *Waxes.* These are esters of fatty acids with high molecular weight monohydroxy alcohols.

B.   Compound lipids or **Heterolipids.** These are esters of fatty acids with alcohol and possess additional group(s) also.

1.   *Phospholipids (phosphatids)*, These are compounds containing, in addition to fatty acids and glycerol, a phosphoric acid, nitrogen bases and other substituents.

2.   *Glycolipids (cerebrosides).* These are the compounds of fatty acids with carbohydrates and contain nitrogen but no phosphoric acid. The glycolipids also include certain structurally-related compounds comprising the groups, gangliosides, sulfolipids and sulfatids.

C.   Derived lipids. These are the substances derived from simple and compound lipids by hydrolysis. These include fatty acids, alcohols, mono- and diglycerides, steroids, terpenes and carotenoids.

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Glycerides and cholesterol esters, because of their uncharged nature, are also called *neutral lipids.*

However, Conn and Stumpf (1976) have traditionally classified lipids into following 6 classes :

1. Acyl glycerols
2. Waxes
3. Phospholipids
4. Sphingolipids
5. Glycolipids
6. Terpenoid lipids including carotenoids and steroids

SIMPLE LIPIDS

FATS AND OILS
(= Triglycerides or Triacylglycerols)

The triglycerides are the most abundant of all lipids. They constitute about 98% of total dietary lipids ; the remaining 2% consists of phospholipids and cholesterol and its esters. They are the major components of storage or depot fats in plant and animal cells but are not normally found in membranes. They are nonpolar, hydrophobic molecules since they contain no electrically charged or highly polar functional groups. In animals, the *fat cells* or *adipocytes* contain very large quantities of triglycerides in the form of fat droplets, which fill almost the entire cell volume (Fig. 13-1). Adipocytes are abundantly found under the skin, in the abdominal cavity and in the mammary glands. Triglycerides can be stored in quantities, sufficient to supply the energy needs of the body for many months, as in the case of obese persons. On the contrary, the body can store the carbohydrate glycogen in

Fig 13-1. A scanning electron micrograph of adipocytes

Each adipocyte contains a fat globule that occupies nearly the entire cell.

(*Courtesy* : *Fred E. Hossler*)

meagre amounts, sufficient to supply energy need of a day only. *Triglycerides are much better adapted than glycogen to serve as storage form of energy.* They are not only stored in large amounts but also yield over twice as much energy as carbohydrates. Since fats tend to remain in the stomach longer than carbohydrates and are digested more slowly, they also have greater satiety value than carbohydrates. The arctic and antarctic animals (Fig. 13-2) such as whales, seals, walruses and penguins are amply padded with triglycerides to serve both as energy storage depots and as an insulation against very low temperatures. Most fats and oils, upon hydrolysis, yield several fatty acids as well as glycerol. However, the milk of spiny anteater is an exception in that it comprises almost pure triolein. Human body contains enough fat to make 7 bars of soap !
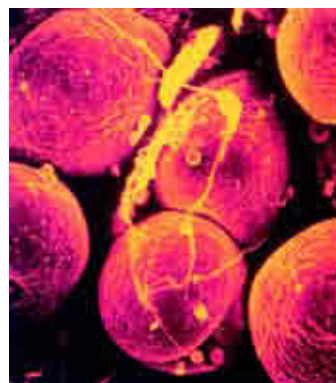

Fig 13-2. Insulating blubber of whales and the fat molecules

Fat such as the triacylglycerol molecule (lower) are widely used to store excess energy for later use and to fulfill other purposes, illustrated by the insulating blubber of whales. The natural tendency of fats to exist in nearly water-free forms makes these molecules well-suited for these roles.

[*Courtesy : (Upper) Francois Cohier*)

In a normal man, weighing 70 kg, at least 10-20% of the body weight is lipid, the bulk of which is triacylglycerol (TAG). TAG is found in all organs of the human body, particularly in adipose

tissue, in which droplets of triacylglycerols may represent more than 90% of the cytoplasm of the cells. Body lipid is a reservoir of potential chemical energy. About 100 times more energy is stored as mobilizable lipid than as mobilizable carbohyldrate in the normal human being. TAG is stored in a relatively water-free state in the tissue, in comparison to carbohydrate, which is heavily hydrated.

Chemically, triglycerides are esters of glycerol with 3 fatty acid molecules. Their generic formula is shown in Fig. 13–3.
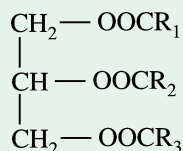
$$CH_2 - OOCR_1$$
$$CH - OOCR_2$$
$$CH_2 - OOCR_3$$

Fig. 13–3. Generic formula of triglycerides

Obviously, when the groups attached to carbon 1 and 3 differ, a centre of asymmetry is created at C 2. The 2 optical isomers may, thus, be represented as shown in Fig. 13–4. *The naturally-occurring fats are of L-type.*
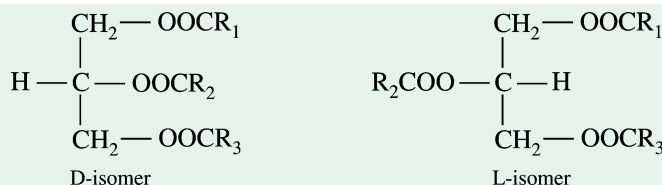
$$CH_2 - OOCR_1$$
$$H - C - OOCR_2$$
$$CH_2 - OOCR_3$$
D-isomer

$$CH_2 - OOCR_1$$
$$R_2COO - C - H$$
$$CH_2 - OOCR_3$$
L-isomer

Fig. 13–4. Two optical isomers of triglycerides

A fat molecule contains 3 moles of fatty acids which may be similar or dissimilar. Those containing a single kind of fatty acid in all 3 positions (α, β, α') are called *simple* (or *symmetrical*) *triglycerides* ; they are named after the fatty acids they contain (Fig. 13–5). Examples are tripalmitin, tristearin
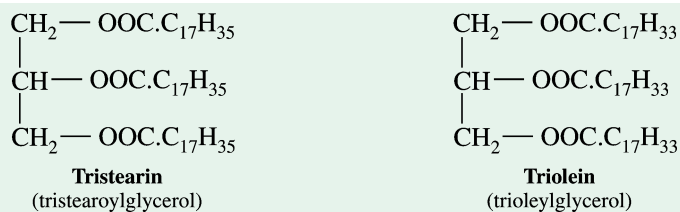
$$CH_2 - OOC.C_{17}H_{35}$$
$$CH - OOC.C_{17}H_{35}$$
$$CH_2 - OOC.C_{17}H_{35}$$
Tristearin
(tristearoylglycerol)

$$CH_2 - OOC.C_{17}H_{33}$$
$$CH - OOC.C_{17}H_{33}$$
$$CH_2 - OOC.C_{17}H_{33}$$
Triolein
(trioleylglycerol)

Fig. 13–5. Two simple triglycerides

and triolein. They occur very infrequently in natural fats. Such simple triglycerides have, however, been synthesized in the laboratory *e.g.*, tristearin and triolein.

Most of the triglycerides of nature are mixed (or asymmetrical) triglycerides, i.e., they contain 2 or 3 different fatty acid units in the molecule. Representatives of such mixed triglycerides are oleodipalmitin and oleopalmitostearin (Fig. 13–6).
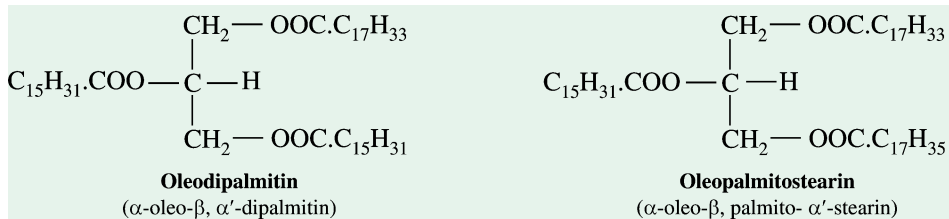
$$CH_2 - OOC.C_{17}H_{33}$$
$$C_{15}H_{31}.COO - C - H$$
$$CH_2 - OOC.C_{15}H_{31}$$
Oleodipalmitin
(α-oleo-β, α'-dipalmitin)

$$CH_2 - OOC.C_{17}H_{33}$$
$$C_{15}H_{31}.COO - C - H$$
$$CH_2 - OOC.C_{17}H_{35}$$
Oleopalmitostearin
(α-oleo-β, palmito- α'-stearin)

Fig. 13–6. Two mixed triglycerides

Most **animal fats** such as those from meat, milk and eggs are relatively rich in saturated fatty acids but contain a rather low content of polyunsaturated fatty acids (Table 13–1) ; two exceptions

are chicken fat and fish fat. The large proportion of saturated fatty acids (*esp*., palmitic and stearic) with high melting point confers solid state to the animal fats. The **plant fats**, on the other hand, contain a large proportion of unsaturated fatty acids (*esp*., polyunsaturated). The unsaturated fatty acids have low melting point and confer liquid state to the plant fats.

Table 13–1.   Fatty acid composition of important animal and plant fats

Fat/Oil	*Percentage of total fatty acids*		
	Saturated	*Monounsaturated*	*Polyunsaturated*
Animal fats			
Butter fat	60	36	4
Pork fat	59	39	2
Beef fat	53	44	2
Chicken fat	39	44	21
Plant fats			
Olive oil*	20	26	54
Corn oil	15	31	53
Soybean oil	14	24	53
Soft margarine	23	22	52

*   data not confirmed.

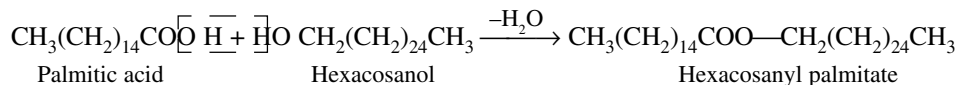The differences between the animal and plant fats are presented in Table 13–2.

Waxes

Far less spread but equally important are the waxes. The term `wax' originates in the Old English word weax, meaning "the material of the honeycomb", reminding of beeswax, the honeycomb is made of. These are esters of long-chain saturated and unsaturated fatty acids with long-chain monohydroxy alcohols. The fatty acids range in between C_{14} and C_{36} and the alcohols range from C_{16} to C_{36}. In vertebrates, waxes are secreted by cutaneous glands as a protective coating to keep the skin pliable, lubricated and water-proof. Hair, wool and fur are also coated with wax. Birds, particularly waterfowl, secrete waxes in their preen glands to make their feathers water-repellent. The leaves of many plants such as *Rhododendron, Calotropis* etc., are shiny because of the deposition of protective waxy coating. Waxes also serve as the chief storage form of fuel in planktons. Since marine organisms (whale, herring, salmon) consume planktons in large quantities, waxes act as major food and storage lipids in them.

**Table 13–2.   Differences between animal and plant fats**

Animal fat	*Plant fat*
1. Relatively rich in saturated fatty acids, *esp*., C_{16} and C_{18} acids.	1. Relatively rich in unsaturated fatty acids, *esp*., polyunsaturated acids.
2. Solid at ordinary room temperature.	2. Liquid at ordinary room temperaure.
3. These have usually low iodine number.	3. These have usually high iodine number.
4. These have usually high Reichert-Meissl . number	4. These have usually low Reichert-Miessl number.
5. These are stored mainly in liver and bone marrow	5. These are stored mainly in seeds and fruits.
6. Oxidative rancidity is observed more frequently.	6. Oxidative rancidity is observed less frequently.
Examples– Butterfat, Beef fat, Tallow	**Examples–** Olive oil, Castor oil, Soybean oil, Corn oil

Most of the waxes are mixtures of esters. Thus, *sperm whale wax* (spermaceti) and *beeswax* are composed mainly of palmitic acid esterified with either hexacosanol, $CH_3(CH_2)_{24}.CH_2OH$ or triacontanol, $CH_3(CH_2)_{28}.CH_2OH$.

$$CH_3(CH_2)_{14}CO\underline{O\ H} + \underline{H}O\ CH_2(CH_2)_{24}CH_3 \xrightarrow{-H_2O} CH_3(CH_2)_{14}COO—CH_2(CH_2)_{24}CH_3$$

Palmitic acid   Hexacosanol   Hexacosanyl palmitate

Moreover, sperm whale wax is also rich in cetyl palmitate and the beeswax in myricyl palmitate.

$$CH_3(CH_2)_{14}COO—CH_2(CH_2)_{14}CH_3 \qquad\qquad CH_3(CH_2)_{14}COO—CH_2(CH_2)_{28}CH_3$$

Cetyl palmitate   **Myricyl palmitate**
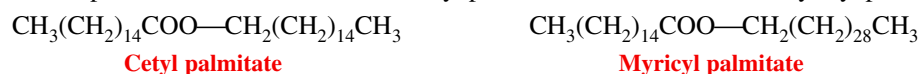
Carnauba wax, the hardest known wax, consists mainly of fatty acids esterified with tetracosanol, $CH_3(CH_2)_{22}.CH_2OH$ and tetratriacontanol, $CH_3(CH_2)_{32}.CH_2OH$.

The waxes from the conifers contain polymers formed by the ester-linking of many ω-hydroxy acids, such as juniperic acid, with each other.

$$HOOC.(CH_2)_{14}.CH_2OH$$

Juniperic acid
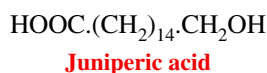
There are certain waxes which have a characteristic odour. This is due to the presence of hydroxy acids in the form of lactones in them. For example, a wax named *ambretolide*, which is extracted from the seeds of lady's finger, *Abelmoschus esculentus*, has a characteristic musky smell.

Ambretolide
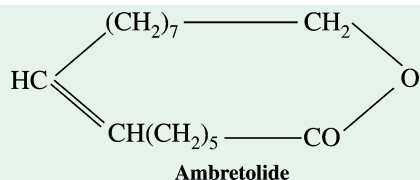
Lipids of marine organisms such as starfish, squid and shark contain fatty alcohols that are long-chain alkyl ethers of glycerol. Three such *glyceryl ethers* (Fig. 13–7), as they are called have been isolated from shark oil.
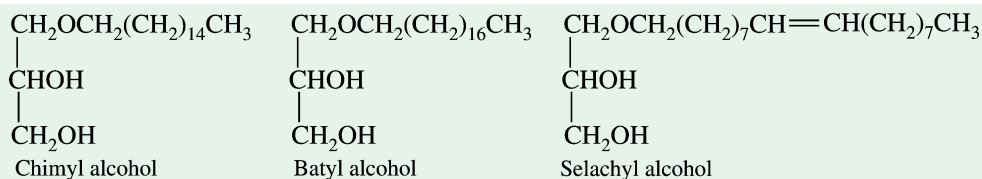
Fig. 13–7. Some glyceryl ethers

Waxes are unusually inert due to their saturated nature of the hydrocarbon chain. However, they can be split slowly with hot alcoholic KOH. They are insoluble in water and highly resistant to atmospheric oxidation. Hence, these are used in polishing furnitures and automobiles and also in wax-coated paper used to wrap perishable food products such as biscuits, cakes, etc. Lanolin (from lamb's wool), beeswax (from honeycomb), carnauba wax (from a Brazilian palm tree) and spermaceti oil (from sperm whales) are widely used in the manufacture of lotions, ointments and polishes.

COMPOUND LIPIDS

PHOSPHOLIPIDS
(= Phosphatids)

Phospholipids are the most abundant membrane lipids. They serve primarily as structural components of membranes and are never stored in large quantities. As their name implies, phospholipids contain phosphorus in the form of phosphoric acid groups. They differ from triglycerides in possessing usually one hydrophilic polar "head" group and usually two hydrophobic nonpolar "tails". For this reason, they are often called *polar lipids*. Thus, *phospholipids are amphipathic, whereas the storage*

lipids (triglycerides and waxes) are not. In phospholipids, two of the OH groups in glycerol are linked to fatty acids while the third OH group is linked to phosphoric acid. The phosphate is further linked to one of a variety of small polar head groups (alcohols). Folch and Sperry (1955) have classified phospholipids into phosphoglycerides, phosphoinositides and phosphosphingosides.

A.   Phosphoglycerides

These are the major phospholipids found in membranes and contain two fatty acid molecules or "tails" esterified to the first and second hydroxyl groups of glycerol. The third hydroxyl group of glycerol forms an ester linkage with phosphoric acid. In addition, phosphoglycerides contain a second alcohol, which is also esterified to the phosporic acid. This is referred to as 'head alcohol group' as it is present at one end ('head') of the long phosphoglyceride molecule.

The various phosphoglycerides differ in their head alcohol groups. However, all of them contain two nonpolar tails, each consisting of a long chain (usually C_{16} or C_{18}) fatty acid. Usually one of the fatty acids is saturated and the other unsaturated ; the latter is always esterified to the middle or β-hydroxy group of glycerol. A noteworthy feature of the phosphoglycerides is that they contain an asymmetric carbon atom at position 2 in the glycerol part of their molecule. It has the L-configuration since it is related to L-glyceraldehyde. All phosphoglycerides have a negative charge on phosphoric group at pH 7. In addition, the head alcohol group may also have one or more electric charges at pH 7.

1.   *Lecithins* (= *phosphatidyl cholines*) – Lecithins (*likithos*[G] = yolk) are widely distributed in nature. Various oil seeds like soybean and the yeasts are important sources from plant world. In animals, the glandular and nervous tissues are rich in these lipids. The lecithins are required for the normal transport and utilization of as other lipids *esp*., in the liver of animals. In their absence, accumulation of lipids occurs in the liver to as much as 30% against a normal value of 3-4%, giving rise to a condition called "*fatty liver*". This fatty infiltration may lead to fibrotic changes, characteristic of the liver disease *cirrhosis*.

In addition to glycerol and 2 moles of fatty acids, the lecithins (Fig. 13–8) also contain phosphoric acid and a nitrogen base choline at either the end or middle carbon atom of glycerol unit. Accordingly, two forms of lecithins, α and β are recognized.

Fig. 13–8. Structure of α-lecithin

On complete hydrolysis, lecithin yields choline, phosphoric acid, glycerol and 2 moles of fatty acids. But partial hydrolysis of lecithins by *lecithinases* (active principles found in snake venoms) causes removal of only one fatty acid to yield substances called **lysolecithins** (Fig. 13–9). These, therefore, contain only one acyl radical. When subjected into the blood stream by sting as a result of snake bite or by needle, the lysolecithins cause rapid rupture (hemolysis) of the red blood corpuscles.

Fig. 13–9. Structure of α-lysolecithin

2.   *Cephalins* – The cephalins (*kephalus*^{G} = head) are closely associated with lecithins in animal tissues. These have also been identified from soybean oil. These are similar in structure to the lecithins except that the choline is replaced by either ethanolamine or serine. Serine is the biochemical precursor of ethanolamine.

$$HO — CH_2— CH_2— NH_2 \qquad\qquad HO — CH_2— CH — NH_2$$
$$COOH$$

Ethanolamine   **Serine**
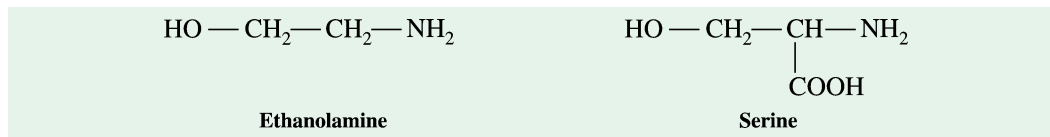
Accordingly, two types of cephalins are recognized, phosphatidyl ethanolamine and phosphatidyl serine. Like lecithins, the cephalins (Fig. 13–10) also exist in 2 forms, α and β, depending upon the relative positions of the two substituent fatty acids.

Glycerol + Fatty acid ¦ Phosphoric acid ¦ Ethanolamine   Glycerol + Fatty acid ¦ Phosphoric acid ¦ Serine

α-**phosphatidyl ethanolamine**   α-**phosphatidyl serine**
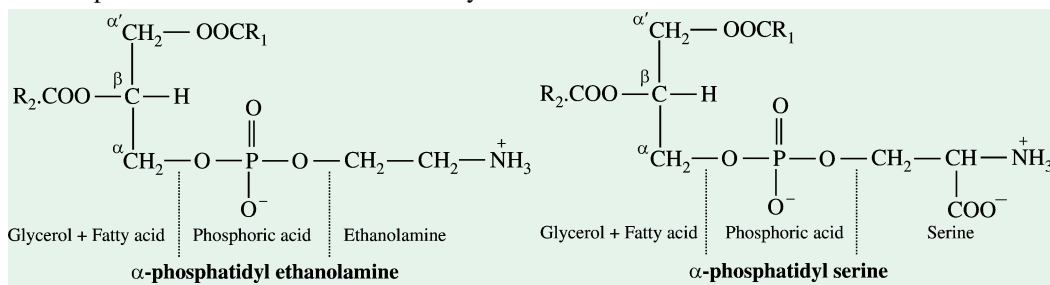
Fig. 13–10. The two cephalins

Since the primary amino group of ethanolamine is a weaker base than the quaternary ammonium group of choline, *the cephalins are more acidic than lecithins.* Moreover, the cephalins are comparatively less souble in alcohol than lecithins.

Venoms containing lecithinases also split off fatty acids from cephalins, leaving hemolytic **lysocephalins.**

3.   *Plasmalogens* (=*Phosphoglyceracetals*) − Plasmalogens constitute about 10% of the phospholipids of the brain and muscle. These are apparently not found in significant quantities in plant tissues. Structurally, these resemble lecithins and cephalins but have one of the fatty acids replaced by an unsaturated ether. Since the nitrogen base can be choline, ethanolamine or serine, three types of plasmalogens (Fig. 13−11) are accordingly distinguished : phosphatidal choline, phosphatidal ethanolamine and phosphatidal serine.

Phosphatidal choline

Phosphatidal ethanolamine   **Phosphatidal serine**

Fig. 13–11. The three plasmalogens

B.   Phosphoinositides (=Phosphatidyl inositols)

Phosphoinositides (Fig. 13–12) have been found to occur in phospholipids of brain tissue and of soybeans and are of considerable importance because of their role in transport processes in cells. These are phospholipids where a cyclic hexahydroxy alcohol called inositol replaces base. The inositol is present as the stereoisomer, *myo*-inositol. On hydrolysis, the phosphoinositides yield 1 mole of glycerol, two moles of fatty acid, 1 mole of inositol and 1, 2, or 3 moles of phosphoric acid. Accordingly, mono-, di- or triphosphoinositides are found.

Monophosphoinositide

ⓅP = phosphate

Triphosphoinositide
(1-phosphatidyl-L-*myo*-inositol-4, 5 diphosphate)
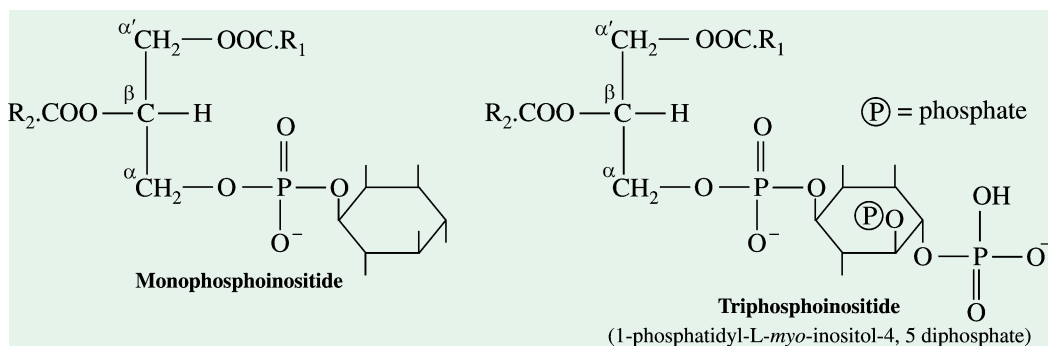
Fig. 13–12. The two phosphoinositides

Phosphoinositides are also classified as glycolipids, in as much as they contain carbohydrate residue.

C.   Phosphosphingosides (=Sphingomyelins)

These compounds are commonly found in nerve tissue *esp*., in the myelin sheath of the nerve (hence their name, sphingomyelins) and apparently lack in plants and the microorganisms. In a *syndrome* called *Niemann–Pick* disease, the sphingomyelins are stored in the brain in large quantities. These differ from other phospholipids in their lack of glycerol and the presence of another nitrogenous base sphingosine or a closely related dihydrosphingosine, besides choline, in place of glycerol. Sphingomyelins are electrically charged molecules and contain phosphocholine as their polar head groups.

A **syndrome** (*syn*^{G} = together; *dramein*^{G} = to run) is a group of symptoms associated with a particular disease or abnormality, although not every symptom is necessarily shown by every patient with the disease.

CLINICAL IMPLICATIONS

Niemann–Pick disease (= sphingomyelin lipidosis) is a rare genetic disorder, inherited as an autosomal recessive condition. The disease is caused by a deficiency of the enzyme *sphingomyelinase*, which cleaves ceramide-phosphocholine bond of sphingomyelin. As a result, sphingomyelin accumulates in large amounts in the reticuloendothelial system since their synthesis is normal in rate but their degradation is interrupted. Niemann–Pick cells (prototype of 'foam cells') are found in the bone marrow, spleen, lymphoid tissues, liver, lung and tissues, of virtually any organ. Clinically, the disease manifests itself in two forms :

(a)   *Early or infantile form.* This is characterized by hepatos-plenomegaly, macular degeneration, cherry-red retinal spot (= macula) in nearly half of the cases, mental retardation and blindness. Death ensues by two years of age.

(b)   *Late or adult form.* This perhaps is the most common of the two forms and reveals intellectual impairment during late infancy, slow evolution of the disease, no changes in the ocular fundi and survival beyond the age of five. However, death of the patient occurs by the second decade.

$$CH_3(CH_2)_{12}CH = CH - CH - CH - CH_2OH$$

OH NH_2

Sphingosine or **4-sphingenine**
(1, 3-dihydroxy-2-amino-*trans*-octadec-4-ene)

$$CH_3(CH_2)_{14}CH - CH - CH - CH_2OH$$

OH NH_2
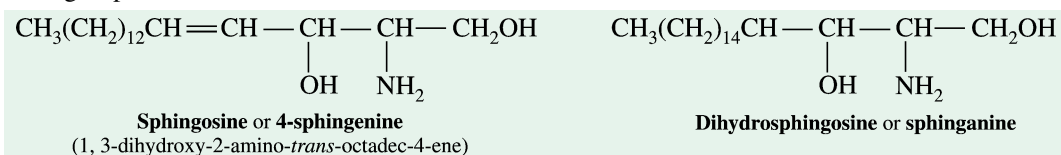
Dihydrosphingosine or **sphinganine**

On hydrolysis, the phosphosphingosides yield equimolar amounts of fatty acid, phosphoric acid, choline and sphingosine or dihydrosphingosine but no glycerol. Thus, in these compounds the atomic ratio N/P is 2, in contrast to phosphoglycerides where this ratio equals unity. Phosphoinositides, however, do not contain a nitrogen base.
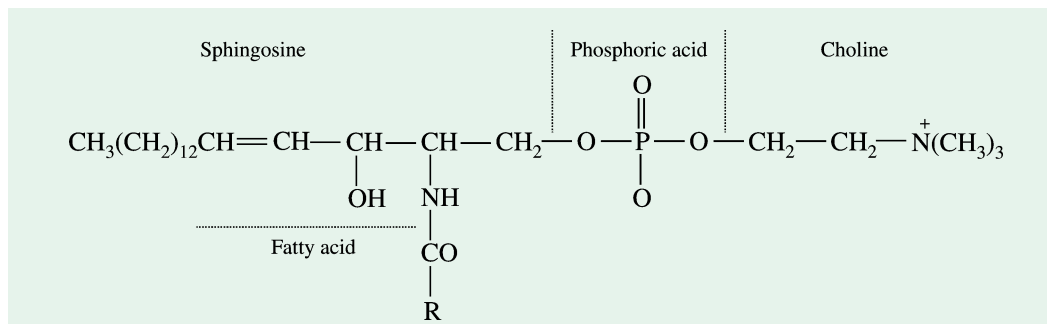
$$CH_3(CH_2)_{12}CH=CH-\underset{\underset{OH}{|}}{CH}-\underset{\underset{NH}{|}}{CH}-CH_2-O-\underset{\underset{O}{\overset{O}{\underset{|}{\overset{\|}{P}}}}}{}-O-CH_2-CH_2-\overset{+}{N}(CH_3)_3$$

Sphingosine | Phosphoric acid | Choline

Fatty acid — CO — R

Fig. 13–13. Structure of sphingomyelin

It may be observed from the formula of sphingomyelin (Fig. 13–13) that sphingosine carries the phosphoric acid on its primary alcohol group and the fatty acid by amide linkage on its primary amino group.

GLYCOLIPIDS
(= Cerebrosides or Glycosphingosides)

The cerebrosides, as the name suggests, are important constituent of brain where they amount to about 8% of the solid matter. These may also occur in tissues other than brain. Since the head group characteristically consists of one or more sugar units, cerebrosides are often called glycosphingosides. Like phospholipids, glycolipids are composed of a hydrophobic region, containing 2 long hydrocarbon tails, and a polar region, which now contains one or more sugar residues and no phosphate. Both phospholipids and glycolipids form self-sealing lipid bilayers that are the basis for all cellular membranes. In Gaucher disease, the cerebrosides appear in relatively large amount in the liver and the spleen. They are also present in large amount in the brain in Niemann–Pick disease. These are present in much higher concentration in medullated than in nonmedullated nerve fibres. There is evidence that they also occur in some plant organs.

The structure of cerebrosides (Fig. 13–14) is somewhat similar to that of phosphosphingosides. They contain a high molecular weight fatty acid, sphingosine and either galactose or glucose instead of choline but no phosphoric acid. They have no electric charge since their polar head groups are neutral. In general properties, they resemble sphingomyelins.

CLINICAL IMPLICATIONS

Gaucher disease (= glucocerebrosidosis) is a not-so-rare, autosomal recessive, hereditary syndrome, often familial and of Jewish origin. It is 30 times more prevalent among the Ashkenazic Jews, with 1 case in 2,500 births. The disease is due to a deficiency of the enzyme *glucosyl ceramide hydrolase* (= *glucocerebrosidase*), which cleaves ceramide from ceramide trihexoside, causing deposition of the later. Gaucher's cells (pale lipid-containing cells) are found in abundance in all the organs specifically in the lungs and bone marrow, resulting in marked hepatosplenomegaly. Thus, the disease affects the lungs and causes destruction of bones. Clinically, two patterns of the disease have been reported :

(a) *Infantile or acute form.* In this, the symptoms appear early with hepatosplenomegaly, mental retardation, hypertonicity and signs of respiratory involvement. Most patients die during infancy.

(b) *Adult or chronic form.* This is more common a form of this disease. There is slow evolution of the disease with hepatosplenomegaly, hypersplenism, pathological fractures and often no neurological deficit.
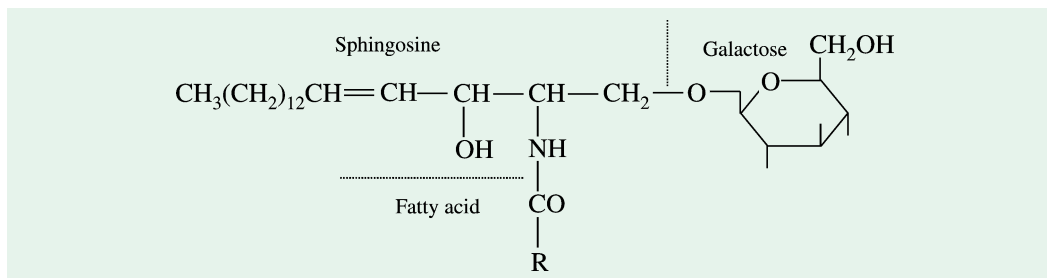
$$CH_3(CH_2)_{12}CH = CH - CH - CH - CH_2 - O$$

Sphingosine

Galactose CH_2OH

OH   NH

Fatty acid   CO

R

Fig. 13–14. Structure of a cerebroside

The name **ceramide** is commonly used to designate the sphingosine–fatty acid (or N-acylsphingosine) portion of the cerebrosides. Here again the sphingosine carries the galactose by glycosidic linkage on its primary alcohol group and the fatty acid by an amide linkage on its primary amino group.

Individual cerebrosides are differentiated on the basis of their fatty acid component (Fig. 13–15). The various classes, so differentiated, are as follows :

(*a*) Kerasin–contains saturated C 24 lignoceric acid.

(*b*) Phrenosin (cerebron)–contains a 2-hydroxy derivative of lignoceric acid called cerebronic acid.

$$CH_3(CH_2)_{22}COOH$$
Lignoceric acid

$$CH_3(CH_2)_{21}\, CH(OH)COOH$$
Cerebronic acid

$$CH_3(CH_2)_7\, CH = CH(CH_2)_{13}\, COOH$$
Nervonic acid

$$CH_3(CH_2)_7\, CH = CH(CH_2)_{12}\, CH(OH)COOH$$
Oxynervonic acid
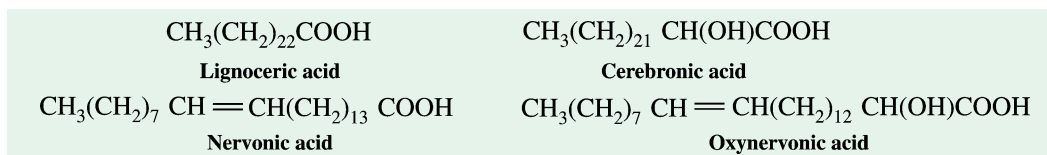
Fig. 13–15. Characteristic fatty acids of cerebrosides

(*c*) Nervon–contains an unsaturated homologue of lignoceric acid called nervonic acid,

(*d*) Oxynervon–contains a 2-hydroxy derivative of nervonic acid called oxynervonic acid.

Gangliosides

In 1955, Klenk isolated a new type of glycolipid from brain tissue and named it as **ganglioside.** These are found in significant concentrations in ganglion cells of nervous tissue (hence so named) and also in most parenchymatous tissues like spleen and erythrocytes. They make up about 6% of the membrane lipids in the gray matter of the brain. They are also found in lesser amounts in the membranes of most nonneural tissues. Gangliosides are thought to act as receptors for toxic agents like the pathogens, *Vibrio cholerae* influenza virus and tetanus toxin. They are also implicated to play a role in cell-cell interaction.

The structure of gangliosides (Fig. 13–16) is complex and related to that of cerebrosides in that they contain a ceramide (N-acylsphingosine) linked to a carbohydrate (galactose or glucose).

Ceramide $\xrightarrow{\beta\text{-}1 \to 1'}$ Glucose $\xrightarrow{\beta\text{-}1 \to 4}$ Galactose $\xrightarrow{\beta\text{-}1 \to 4}$ N-acetyl-galactosamine $\xrightarrow{\beta\text{-}1 \to 3}$ Galactose

$\alpha\text{-}2 \to 3$

N-acetyl-neuraminic acid

G_{M_1}

G_{M_2}

G_{M_3}
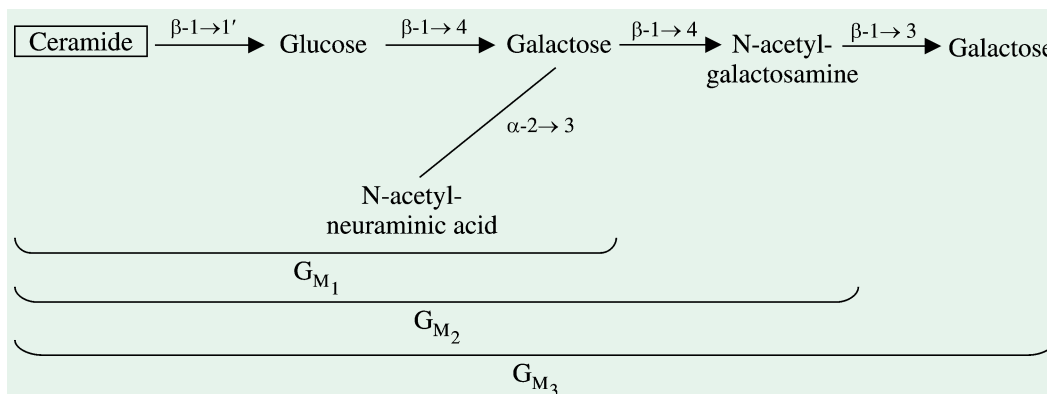
Fig. 13–16. The three gangliosides

In addition to these, the gangliosides also generally contain 2 additional moles of carbohydrates, 1 mole of N-acetylgalactosamine and from 1 to 5 moles of N-acetylneuraminic acid (NANA). In Tay–Sachs disease, the gangliosides are stored in relatively large amounts in the brain and spleen.

CLINICAL IMPLICATIONS

Tay-Sachs disease (named after an English physician Warren Tay who first described the disease and an American neurologist Bernard Sachs who worked out its details), also called G_{M2} **gangliosidosis,** was first described in 1881. This is the oldest medically described lipid storage disease or lipidosis. It is a common hereditary disorder. Although the disease is rare in the population at large (1 in 3,00,000 births), it has a very high incidence (1 in 3,600 births) in Ashkenazic Jews, who make up about 90% of the Jewish population in America. One in 30 Ashkenazic Jews carries the defective gene in recessive form (*i.e.*, the carrier rate is 1/30), whereas the carrier rate is 1/300 in non-Jewish Americans. Consequently, the incidence of the disease is about 100 times higher in Jewish Americans. When both parents are carrier, their children are likely to develop Tay-Sachs disease even though the parents show no symptoms of the disease. Because the disease is irreversible and needs intensive care, genetic counseling of parents has become important in averting its consequences. The disease is caused due to a deficiency of the enzyme N-*acetylgalactosaminidase* (= *hexosaminidase A*), which cleaves a specific bond (β-8→4) between an N-acetyl-D-galactosamine and a D-galactose residue in the polar head of the ganglioside, G_{M2}. In effect, G_{M2} is not degraded to G_{M1}. With the result, G_{M2}, which is also called as Tay–Sachs ganglioside, is accumulated in large amounts in the lysosomes, particularly in the brain cells to the tune of 100-300 times the normal G_{M2} content, causing degeneration of the nervous system. In Tay–Sachs disease, the symptoms are evident before an affected infant is a year old. Weakness, retardation in development and difficulty in eating are typical early symptoms. Mental retardation and blindness usually follow a few months later; death, between two and five years, is inevitable. Over 90% of the patients have a characteristic cherry-red spot in the retina. Tay–Sachs disease can be diagnosed during fetal development. Amniotic fluid is obtained by amniocentesis and assayed for b-N-acetylgalactosaminidase activity. As mentioned, Tay–sachs disease shares the tragic element of Niemann–Pick and Gaucher diseases in that the affected child seldom lives beyond age three.

More than 15 different gangliosides have been characterized and their structures determined. These are commonly abbreviated by the letter G, with a subscript $_M$, $_D$ or $_T$ to designate that they contain one, two or three sialic acid and (N-acetylneuraminate or N-glycolyl neuraminate) residues respectively, and a number or letter to distinguish different members of a group from one another. In essence, they consist of an oligosaccharide chain attached to ceramide (N-acylsphingosine) by a sugar residue which is usually glucose. They lack phosphoric acid.
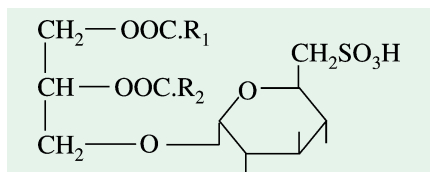
Sulfolipids.

A glycolipid that contains sulfur is widely distributed in plants. It is localized in the chloroplasts but is also found in the chromatophores of photosynthetic bacteria. As the sulfur in this compound is present as a sulfonic group in a hexose, this may be included under a class of compounds called sulfolipids. Its structure is given in Fig. 13–17.

Sulfatides.

A sulfate ester analogue of phrenosin, abundant in white matter of brain, is another sulfur-containing glycolipid. In it, the sulfate is present in ester linkage at C 3 of the galactose portion of the molecule. Members of this group of cerebroside sulfuric esters have been designated as sulfatides.

Fig. 13–17. Structure of a sulfolipid (6-sulfo-6-deoxy-α-glucosyl monoglyceride)

The classification of compound lipids as presented here is now becoming obsolete. It is, however, more logical to classify them according to the main alcohol component (refer Table 13–3). According to this system, the compound lipids fall under 2 categories : one in which the main alcohol component is glycerol **(glycerophosphatides)** and the other in which sphingosine is the main alcohol component **(sphingolipids).** The further classification of these two categories depends on the nature of the other alcohol components.

Table 13–3. **Classification of compound lipids**

Name	Main alcohol component(s)	Other alcohol component(s)*	N:P ratio
Glycerophos-phatides			
Phosphatidic acids	Diglyceride (= glycerol diester)	—	0 : 1
Lecithins	Diglyceride (= glycerol diester)	Choline	1 : 1
Cephalins	Diglyceride (= glycerol diester)	Ethanolamine, serine	1 : 1
Inositides	Diglyceride (= glycerol diester)	Inositol	0 : 1
Plasmalogens	Monoglyceride (= glycerol ester) + Enol ether	Choline, ethanolamine, serine	1 : 1
Sphingolipids			
Sphingomyelins	N-acylsphingosine	Choline	2 : 1
Cerebrosides	N-acylsphingosine	Galactose, glucose	1 : 0
Sulfatides	N-acylsphingosine	Galactose	$(1H_2SO_4)$
Gangliosides	N-acylsphingosine	Galactose, glucose	No P
		+	
		N-acetylgalactosamine	
		+	
		N-acetylneuraminic acid	

*   The other alcohol components in all the sphingolipids except sphingomyelins are not present as phosphoric esters, but rather in glycosidic linkages. For this reason, these sphingolipids are grouped under glycolipids.

DERIVED LIPIDS

The group derived lipids is a **"catch all" group** in Bloor's classification. It includes the hydrolysis products of simple and compound lipids and also various other compounds such as steroids, terpenes, fatty acids, alcohols, fatty aldehydes, ketones etc.

STEROIDS

The steroids (*stereos*[G] = solid) are one of the most studied classes of biological compounds and are often found in association with fat. Since they contain no fatty acids, they are *nonsaponifiable*, *i.e.*, cannot be hydrolyzed by heating with alkali to yield soaps of their fatty acid components. Fats, on the other hand, are saponifiable and form soaps when hydrolyzed with alkali. The steroids may be separated from the fat after the latter is saponified since they occur in 'nonsaponifiable residue'. All steroids may be considered as derivatives of a fused and fully saturated ring system called **cyclopentanoperhydrophenanthrene** or **sterane.** This system consists of 3 cyclohexane rings (A, B and C) fused in nonlinear or phenanthrene manner and a terminal cyclopentane ring (D). The sterane nucleus along with the conventional numbering of the carbon atoms is shown in Fig. 13−18.
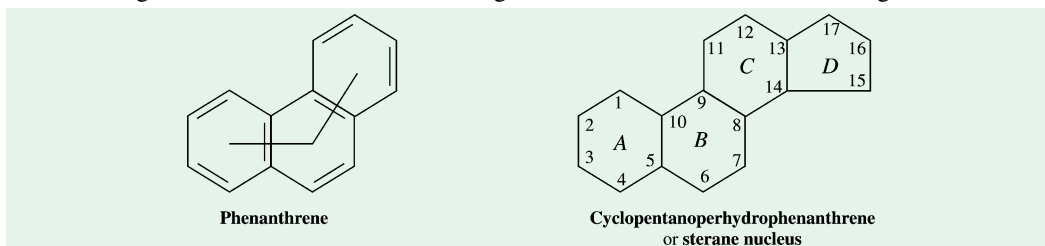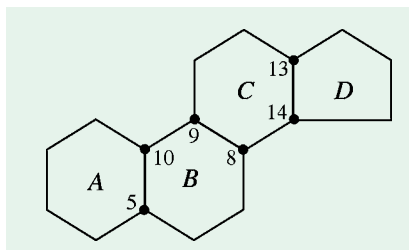

Phenanthrene

Cyclopentanoperhydrophenanthrene
or **sterane nucleus**

Fig. 13–18. Phenanthrene and sterane nucleus

It may, however, be emphasized that in steroids the hexagonal rings are not the benzene rings as in them the valences of C atoms are fully satisfied by hydrogen bonds, unless shown otherwise.
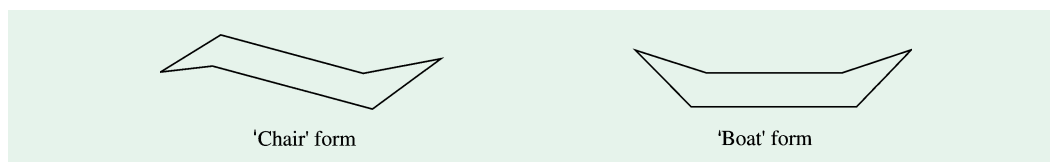

Fig. 13–19. Asymmetric centres in sterane (= gonane) nucleus

(shown by solid black circles)

The double bonds, if present, are shown as such. The 'angular' methyl groups occur typically at positions 10 and 13 and constitute carbon atoms 19 and 18 respectively. The steroids may have one or more hydroxyl groups, one OH group being present usually on C 3. A side chain at C 17 is usual. This side chain serves as a convenient basis for classification of steroids. For example, the side chain contains 8, 9 or 10 C atoms in sterols, 5 C atoms in bile acids, 2 C atoms in adrenal cortical steroids and in progesterone and none in naturally occurring estrogens and androgens.

Stereochemical considerations of steroids. Without even considering the substituent groups, there are 6 possible asymmetric centres present in the steroid nucleus (Fig. 13−19). Consequently, the steroids have many potential stereoisomers. Each of 3 cyclohexane rings, on the basis of the tetrahedral theory, is capable of existing in 3-dimensional conformation either of a **'chair'** or of a **'boat'** (Fig. 13−20).

Steroids containing hydroxyl groups (hydroxy steroids) are often referred to as **sterols**. Broadly speaking, the various sterols fall under 2 groups based on their source : the animal sterols or *zoosterols* (cholesterol, cholestanol, coprostanol) and the plant sterols or *phytosterols* (ergosterol, stigmasterol, spinasterol). A third group of sterols, which are obtained from fungi including yeasts, is sometimes separately referred to as *mycosterols*. This classification, however, is not rigid as some sterols are obtained from more than one of these sources.

These 2 forms are aplanar and strainless and were first proposed by Sachse in 1890. The 'chair' form is *rigid* (in the sense that it resists distortion) and when it is changed to the 'boat' form, some angular deformity invariably takes place. The 'chair' conformation of cyclohexane itself is more *stable* than the 'boat' conformation. The 'chair' and 'boat' forms are both free from angle strain but because of differences in steric strain and bond opposition strain, the two forms differ in energy content (Finar, 1975).

'Chair' form   'Boat' form

Fig. 13–20. Two types of conformation of a cyclohexane ring

In naturally occurring steroids, all the rings are in 'chair' form. With respect to each other, the rings can be either -*cis* or -*trans* (Fig. 13−21). The junction between the rings A and B (A/B junction) in naturally-occurring steroids may be either -*cis* or -*trans*. But the B/C and C/D junctions are, with certain exceptions, always in -*trans* form. The idea of -*cis* and -*trans* forms with respect to A/B junction may be explained as below. The hydrogen atom on C 5 may be either on the same side of the plane of molecule as the methyl group on C 10 or on the opposite side. In the former case, rings A and B will be -*cis* to each other and the molecule is said to belong to **normal configuration.** If the hydrogen atom and the methyl group are on the opposite sides, the rings A and B are -*trans* to each other and the molecule is of **allo configuration.**
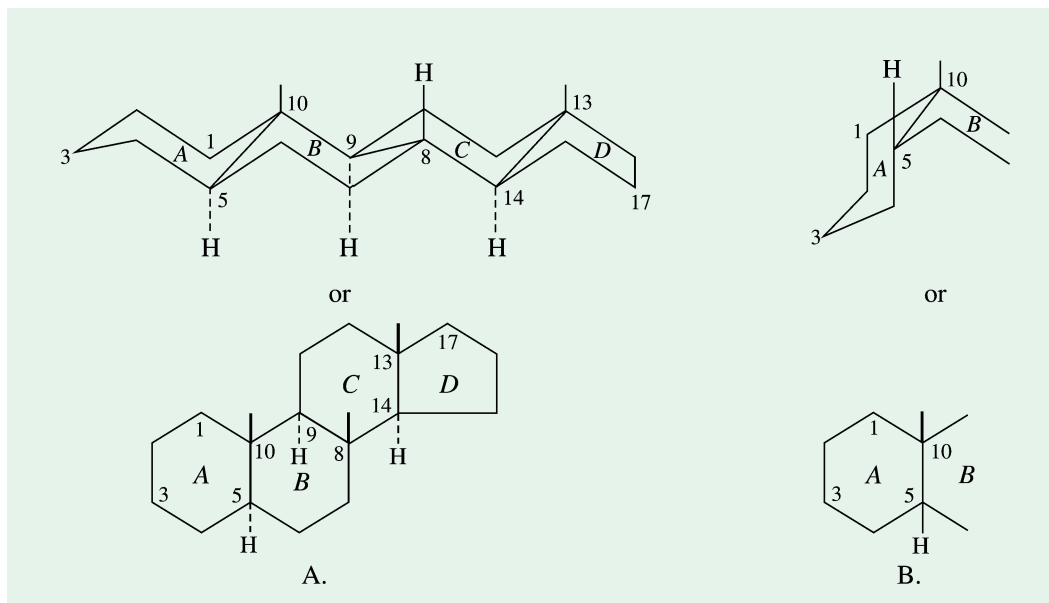
Fig. 13–21. Stereochemical aspects of steroid nucleus, A. all - *trans* configuration between adjacent rings, B. a -*cis* configuration between rings A and B

In the structural representation of the steroids, substituents that are above the plane of the ring (or β-**oriented**) are shown with solid lines, while those which are below the plane of the ring (or α-**oriented**) are represented with broken lines. The methyl groups at C 10 and C 13, the hydroxyl group on C 3 and the side chain at C 17 are all β-oriented.

Certain common steroids are described below.

C 29, C 28 and C 27 Steroids

1. Cholesterol (*chole*^{G} = bile). Cholesterol is undoubtedly the most publicized lipid in nature, because of the strong correlation between high levels of cholesterol in the blood and the incidence of diseases of the cardiovascular system in humans. It is not only an important component of some cell membranes and of plasma lipoproteins but also the precursor of many other biologically important steroids, such as bile acids and various steroid hormones. It is the principal sterol of higher animals and is especially abundant in nerve tissues and in gallstones. In occurs either free or as fatty esters in all animal cells. It was first isolated in 1784, from human gallstones which consist almost entirely of cholesterol and hence so named (cholesterol literally means 'solid alcohol from bile'). Its main sources are fish liver oils and the brain and spinal cord of cattle. White matter contains as much as 14%, gray matter 5%, spinal

Cholesterol is generally believed to be notorious as a major cause of heart disease. There are 2 types of cholesterol, the low-density lipoprotein cholesterol. (LDL-C) and the high-density lipoprotein cholesterol (HDL-C). The LDL-C grows with intake of eggs and dairy products and triggers heart trouble. However, in a study conducted by Dr. Ian Craig of the Goteborg University, Sweden in the early 70s showed that patients with heart trouble such as myocardial infarction had low levels of HDL-C, as compared to other people. He pointed out that most of the preventive heart attack studies have so far been aimed at lowering the LDL-C levels through drugs and diet, but it seemed that normal variations in diet made little difference in HDL-C levels. Also, HDL-C levels were generally found higher in women than men. Perhaps this is the reason why fewer women than men have heart attacks. There are, thus, hopeful signs that incidence of heart disease may be lowered by increasing the HDL-C level in heart patients.

cord 12% and liver about 1% cholesterol. *Cholesterol is , however, not found in plant fats.* Its parent hydrocarbon is cholestane, $C_{27}H_{48}$. The structure of cholesterol was determined by the German chemist, Adolph Windaus (LT, 1879 – 1959), who received 1928 Nobel Prize in Chemistry. Cholesterol (Fig. 13–22) has a molecular formula, $C_{27}H_{45}OH$. In addition to an OH group at C3, there is a double bond at C5. The hydroxyl group constitutes its polar head, the rest of the molecule is hydrophobic. It is a white crystalline solid and is optically active, $[\alpha]_D$ 39°. The crystals are rhombic plates with one of the angles broken. It has a melting point of 149°C. Konrad S. Bloch, a Germany-born American biochemist, elucidated the biosynthetic pathway of cholesterol synthesis, one of the most complex known, for which he received the coveted Nobel Prize in Chemistry along with Feodor Lynen, a German and John Cornforth, a Briton, in 1964. Bloch combined work and pleasure by traveling to Bimini for collection of shark livers.
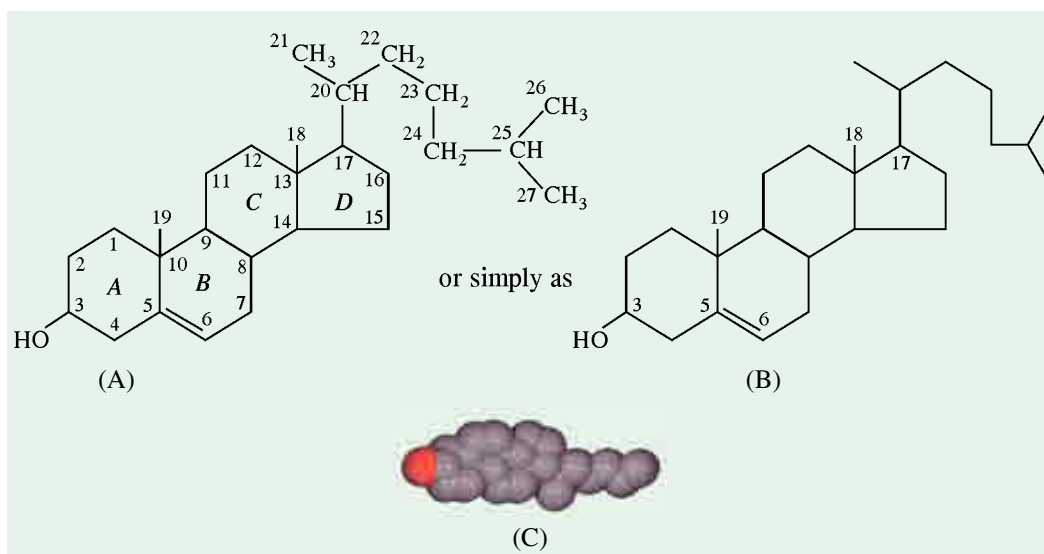
Fig. 13–22. Structure of cholesterol

(3-hydroxy-5, 6-cholestane)

(A) : **Molecular representation.** The individual rings in the fused-ring system are designated A through D.

(B) : **Simplified version.** It is customary to write steroid structure in the manner shown here, without, however, the methyl substituents.

(C) : **Space-filling model.** The C is shown with grey, vinyl C with yellow, O with red, N with blue and P with green. H is not shown.

[*Courtesy : (C) Richard Pastor and Richard Venable*]

On receiving the Nobel Prize in 1985 for their work on cholesterol, Michael Brown and Joseph Goldstein recounted in their lecture the extraordianry history of cholesterol :

"Cholesterol is the most highly decorated small molecule in biology. **Thirteen Nobel Prizes** have been awarded to scientists who devoted major parts of their careers to cholesterol. Ever since it was isolated from gallstones in 1784, cholesterol has exerted an almost hypnotic fascination for scientists from the most diverse areas of science and medicine.... Cholesterol is a Janus-faced molecule. The very property that makes it useful in cell membranes, namely its absolute insolubility in water, also makes it lethal."

(Courtesy : The Nobel Foundation, 1985)

Table 13-4 provides data on fat and cholesterol contents of some notable animal foods.

Table 13-4.	**Fat and cholesterol content of some animal foods***		
Food Item	*Fat* *g/100 g*	*Saturated fatty acids* *g/100 g*	*Cholesterol* *mg/100 g*
Butter	80	50	250
Ghee	100	65	300
Milk (cow)	4	2	14
Milk (buffalo)	8	4	16
Milk (skimmed)	0.1	—	2
Milk (condensed)	10	6	40
Cream	13	8	40
Cheese	25	15	100
Egg (whole)	11	4	400
Egg (yolk)	30	9	1120
Chicken (with skin)	18	6	100
Chicken (without skin)	4	1	60
Beef	16	8	70
Mutton	13	7	65
Pork	35	13	90
Organ meats			
Brain	6	2	2000
Heart	5	2	150
Kidney	2	1	370
Liver	9	3	300

*   The data are based on per 100 g edible portion of the food item.

No vegetable oil contains any cholesterol; hence, it is misleading for oil manufacturers to advertise any oil as 'low cholesterol' oil. Saturated fats of animals origin (such as butter, ghee and lard) do contain cholesterol but *vanaspati,* which is derived from vegetable oils, does not contain cholesterol. Only a little portion of the body cholesterol is derived from diet. The bulk of it is synthesized in the body. Unsaturated fatty acids lower blood cholesterol levels by controlling cholesterol's synthesis as well as its elimination from the body. Thus, vegetable oils when consumed within the recommended amounts help to maintain proper levels of lipids in the blood than do the saturated fats like butter, ghee, lard and vanaspati. These saturated fats elevate blood lipids (cholesterol and triglycerides) and reduce the ratio of good to bad cholesterol even when consumed within the recommended limits. High intake of dietary cholesterol can probably raise blood cholesterol levels and hence should be avoided, esp., by the elderly people and those having high blood cholesterol.

The level of cholesterol in the blood is measured in milligrams per decilitre (mg/dl, which is equivalent to parts per 1,00,000). The levels range from less than 50 in infants to an average of 215 in adults to 1,200 or more in individuals suffering from a rare inherited disease called *familial cholesterolemia.* For those persons in the normal range, about two-thirds of their cholesterol is transported as LDLs. Most of the rest is carried by HDLs.

An often-posed question relates to the consumption of eggs and meat, and sometimes even milk, because of the relatively high content of cholesterol in these foods. Milk is no doubt a very good and safe food. Persons aspiring to control their cholesterol intake (and calories) must use defatted or skimmed milk. Egg and meat proteins are of high grade and desirable especially for the growing children. Those desirous of reducing their cholesterol intake should eat only the white of egg and lean on white meat like chicken and fish. Nutritionally, fish is a very good food since it has high-quality

protein (fish fat is rich in *n*-3 PUFA) and its flesh has very little cholesterol. Organ meats like brain and liver are rich in cholesterol and should hence be avoided by those wanting to restrict cholesterol.

The notion that cholesterol is a poisonous substance in the body is misleading. It is the parent hydrocarbon from which many important hormones (corticosteroids and sex steroids, for example) are synthesized. The problem creates when blood cholesterol level rise and the level of LDL-cholesterol, which carries cholesterol to the tissues, goes below the desired level. HDL-cholesterol or good cholesterol removes cholesterol from the tissues and helps eliminating it from the body. High blood cholesterol results in the deposition of cholesterol in the arteries and narrows the passage, a condition called *atherosclerosis.* Also, the arterial surface roughens due to cholesterol deposition, which leads to frequent blood clotting or *thrombosis.* Both are major health hazards. Studies, however, point out that even very low levels of blood cholesterol are too not desirable. *The thumb rule, therefore, is moderation.* Both too much and too little of fat may be harmful.

In blood about two-thirds of the cholesterol is esterified mainly to unsaturated fatty acids, the remaining portion occurring as the free alcohol. Reduction of the double bond gives rise to 2 products, coprostanol and cholestanol.

2. Coprostanol (= coprosterol). It occurs in feces and is produced in the intestine as a result of bacterial action on the double bond of cholesterol. The A/B junction is -*cis* in coprostanol in contrast to -*trans* in cholesterol.

3. Cholestanol. It occurs as a minor constituent of the sterols of blood and other tissues. Here the A/B junction is in -*trans* form.

4. Ergosterol. It is present in ergot (hence its nomenclature), yeast and the mould *Neurospora.* Its parent hydrocarbon is ergostane, $C_{28}H_{50}$. Ergosterol (Fig. 13–23) has a molecular formula, $C_{28}H_{43}OH$ with one OH group at C_3 and 3 double bonds at C_5, C_7 and C_{22}. It is also optically active, $[\alpha]_D$ -135°.

Rupture of the ring B by UV radiation produces vitamin D_2 which is chemically known as ergocalciferol. A similar compound cholecalciferol (or vitamin D_3) is, however, obtained from 7-dehydrocholesterol on irradiation with UV light (refer Chapter 32).
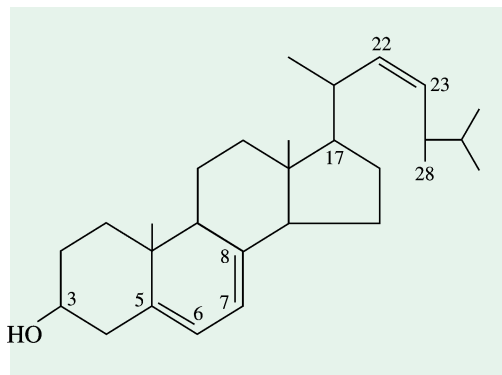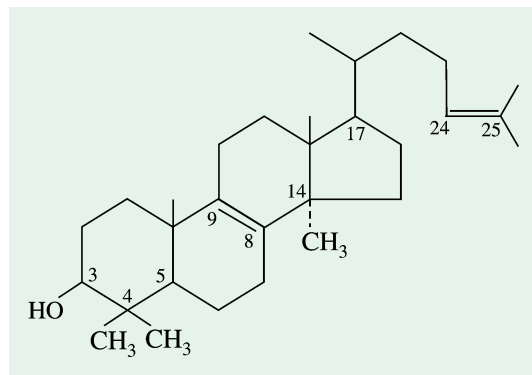

Fig. 13–23. **Structure of ergosterol**

Fig. 13–24. **Structure of lanosterol**

5. Lanosterol (= cryptosterol). It is a major constituent of wool fat and is also present in minor quantities in liver and yeast. Lanosterol (Fig. 13–24) is a C 30 compound with twin methyl groups at C 4 and a third angular methyl group on C 14. There are 2 double bonds at C_8 and C_{24}. It is an intermediate in the biosynthesis of cholesterol.

A number of sterols have also been obtained from various plant and animal sources, for example **stigmasterol** (from soybean and wheat germ oils), **spinasterol** (spinach and cabbage), **sitosterol** (many higher plants), **ostreasterol** (oysters) and **chondrillasterol** (marine sponges).

C 24 Steroids or Bile Acids

The bile acids are the important end products of cholesterol metabolism in higher plants. About 20 natural bile acids have been characterized (Table 13–4). All these are derived from a C 24 parent steroid, cholanic acid and resemble coprostanol in having rings A and B in cis form. The most abundant bile acids in human bile are cholic acid (25-60% of the total bile acids), chenodeoxycholic acid (30-50%) and deoxycholic acid (5-25%). Various bile acids differ from each other in the number and position of OH groups which are all in a configuration. In the bile acids, the number of OH group(s) may be 1, 2, or 3 and the position of OH group(s) may be any of the following : 3, 6, 7, 11, 12 and 23. The side chain is usually made up of 5 carbon atoms and bears the carboxyl group.

Table 13–5.   **Some important natural bile acids**

Name	Formula	Melting point, 0ºC	Position of OH group(s)	Source
Monohydroxycholanic acid	$C_{23}H_{38}(OH).COOH$			
Lithocholic acid		186	3	Man, Ox
Dihydroxycholanic acids	$C_{23}H_{37}(OH)_2.COOH$			
Deoxycholic acid		172	3, 12	Man, Ox
Chenodeoxycholic acid		140	3, 7	Man, Ox, Hen
α-hydrodeoxycholic acid		197	3, 6	Pig
Trihydroxycholanic acid	$C_{23}H_{36}(OH)_3.COOH$			
Cholanic acid		195	3, 7, 12	Man, Ox

The structure of two principal bile acids is given in Fig. 13–25.

Cholic acid
(3α, 7α, 12α-trihydroxycholanic acid)

Chenodeoxycholic acid
(3α, 7α,-dihydroxycholanic acid)
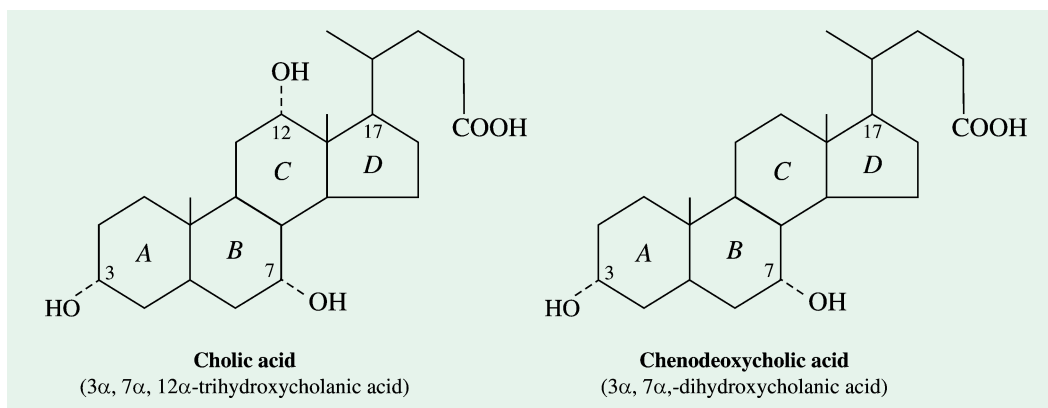
Fig. 13–25. Two principal bile acids

These acids are coupled in amide linkage to the amino acids glycine (NH_2—CH_2—COOH) and taurine (NH_2—CH_2—CH_2—SO_3H) to form glycocholic and taurocholic acids respectively (Fig. 13–26). The reaction is characteristic of COOH group and involves the side chain only. The salts of these conjugated acids have high surface activity and hence promote the intestinal absorption of lipids like cholesterol. They are water-soluble and are powerful detergents.

CO — NH — CH$_2$ — COOH

Glycocholic acid
(= cholylglycine)

CO — NH — CH$_2$ — CH$_2$ — SO$_3$H

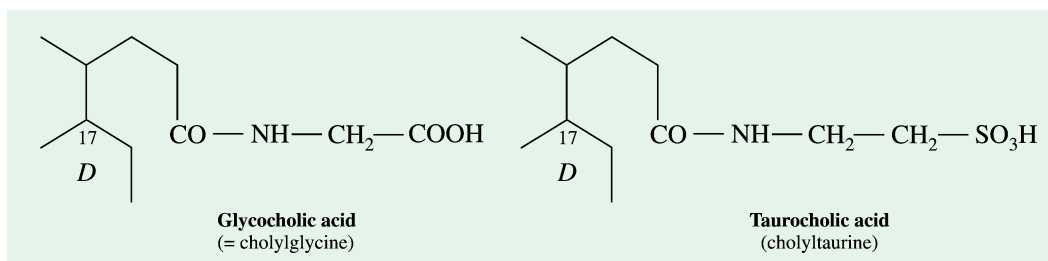**Taurocholic acid**
(cholyltaurine)

Fig. 13–26. Side chain of two bile-acid amides

C 21, C 19 and C 18 Steroids

On account of their hormonal role, these have been described in Chapter 30.

Several important poisons are based on the steroid structure. **Digitoxior digitalin** (Fig. 13-27 *a*, *b*) is present in the foxglove plant (*Digitalis purpurea*) and has a powerful heart stimulating action. Another cardiac glycoside, **Quabain**, (Fig. 13-27 *c*) is isolated from the East African Ouabio tree and has the sugar, rhamnose, attached to a modified sterol nucleus. It is of interest to note that it is a powerful inhibitor of the 'sodium pump', a device which normally ensures that the cell content of potassium is higher and that of sodium is lower than in the circumambient fluid.

(*a*)　　　　(*b*)　　　　(*c*)
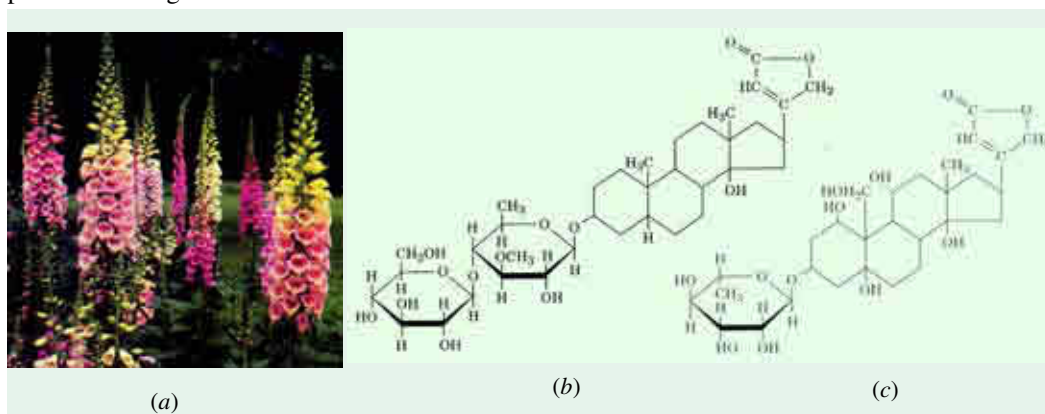
Fig. 13.27. The foxglove plant and two most-commonly prescribed cardiac drugs

(*a*) **The foxglove plant, Digitalis purpurea.** The leaves of purple foxglove plant are the source of the popular heart muscle stimulant, digitalis.

(*b*) **Digitoxin.** It is extracted from the dried leaves of foxglove plant and is the major component of digitalis, one of the most-widely used cardiac muscle stimulant.

(*c*) **Quabain**. It is a cardiac glycoside, isolated from the East African Quabio tree.

(Courtesy : (a) Derek Fell)

Table 13–6 lists the occurrence and biological role of some important steroids.

Table 13–6. **Some steroids and their biological roles**

Group	Representative	Formula	Occurrence	Biological role
Sterols				
C$_{30}$	Lanosterol	C$_{30}$H$_{51}$O	Wool fat	Biosynthesis of cholesterol
C$_{28}$	Ergosterol	C$_{28}$H$_{44}$O	Yeast	Provitamin D
C$_{27}$	Cholesterol	C$_{27}$H$_{46}$O	Animal fats	Structural component and precursor

	7-dehydro-cholesterol	$C_{27}H_{44}O$	Skin	Provitamin D
Bile acids				
C_{24}	Cholic acid	$C_{24}H_{40}O_5$	Intestine and gall-bladder	Absorption of fats
	Chenodeoxycholic acid	$C_{24}H_{40}O_4$	Intestine and gall-bladder	Absorption of fats
Hormones				
C_{21}	Progesterone	$C_{21}H_{30}O_2$	Corpus luteum	Hormone
	Deoxycorticosterone	$C_{21}H_{30}O_3$	Adrenal cortex	Hormone
	Cortisol	$C_{21}H_{30}O_5$	Adrenal cortex	Hormone
C_{19}	Testosterone	$C_{19}H_{28}O_2$	Testes	Hormone
C_{18}	Estradiol	$C_{18}H_{24}O_2$	Ovaries	Hormone

TERPENES

Among the nonsaponifiable lipids found in plants are many hydrocarbons known as terpenes (from *turpentine*). In general, these hydrocarbons and their oxygenated derivatives have lesser than 40 carbon atoms. The simplest terpenes are called *monoterpenes* and conform to the formula $C_{10}H_{16}$ (equivalent to 2 isoprene units, Fig. 13–28), those with the formula $C_{15}H_{24}$ are called as *sesquiterpenes,* with $C_{20}H_{32}$ as *diterpenes* and with $C_{30}H_{48}$ as *triterpenes*. Terpenes with 40 carbon atoms (or *tetraterpenes*) include compounds called carotenoids (refer Chapter 32).
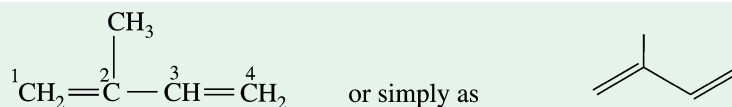
Fig. 13–28. Structure of isoprene
(2-methyl-1, 3-butadiene)

In fact, O. Wallach (1910 Nobel Laureate in Chemistry) was the first to point out, in 1887, that nearly all the terpenoids are made of varying number of repetitive units (C_5H_8), called isoprene units. His finding later came to be known **isoprene rule.** Structurally, isoprene is a 5-carbon diene. The carbon skeletons of open-chain monoterpenoids and sesquiterpenoids are :

Monoterpenoid

Sesquiterpenoid
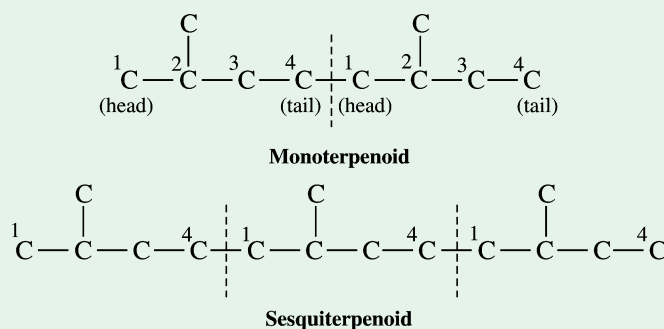
Even not only the presence of isoprene units but their special type of arrangement is found to be present in nearly all the terpenoids. Ingold, in 1925, formulated this observation under another rule, the **special isoprene rule**, according to which the isoprene units in terpenoids are usually joined in *head-to-tail linkages* or 1,4 linkages (the branched end of the isoprene unit was considered as the head).

Cryptone
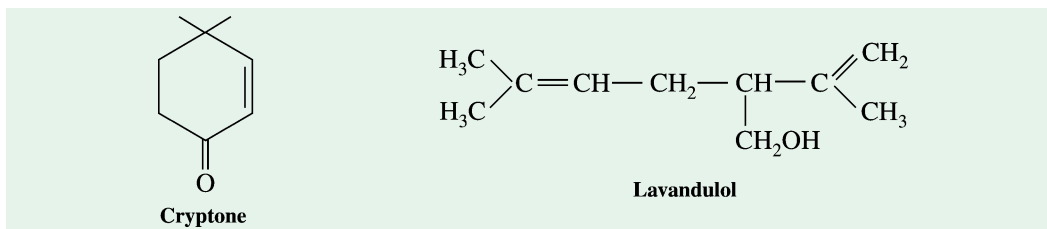
Lavandulol

Exceptions, however, do occur for these two isoprene rules. For example, *cryptone*, a natural terpenoid, contains only 9 carbon atoms instead of 10. Also, in *lavandulol*, the 2 isoprene units are not joined in head-to-tail manner, and in *carotenoids*, the two halves (each with 4 isoprene units) are linked with each other by *tail-to-tail* at the centre.

Monoterpenes and Sesquiterpenes

The fragrances of many plants arise from volatile C_{10} and C_{15} terpenes. These and their oxygenated derivatives occur as components of the essential oils, some of which are used as perfumes. Important monoterpenes (Fig. 13–29) are *myrcene* (from oil of bay), *geraniol* (from rose oil), *limonene* (from lemon oil) and *menthol* (from peppermint oil).

Myrcene, $C_{10}H_{16}$

Geraniol, $C_{10}H_{18}O$

Limonene, $C_{10}H_{16}$

Menthol, $C_{10}H_{20}O$
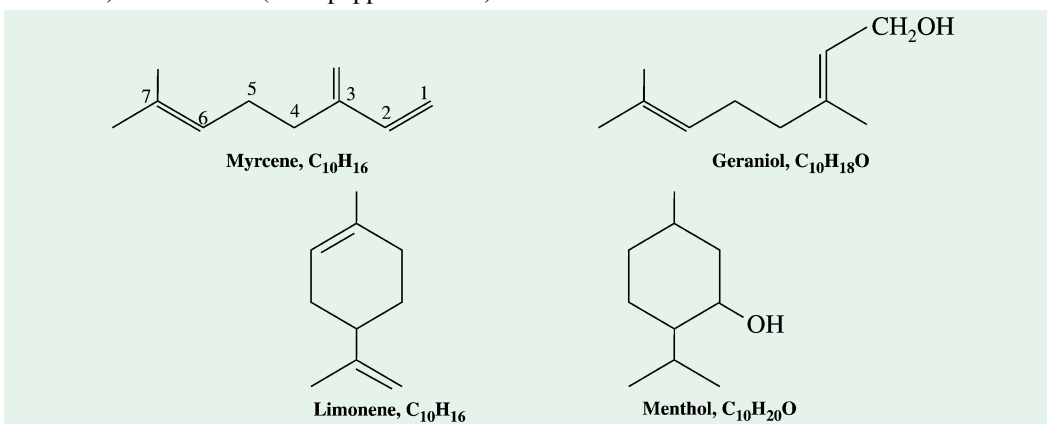
Fig. 13–29. Four important monoterpenes

Among the sesquiterpenes, farnesol (Fig. 13–30) is widely distributed but is present in essential oils in small amounts.
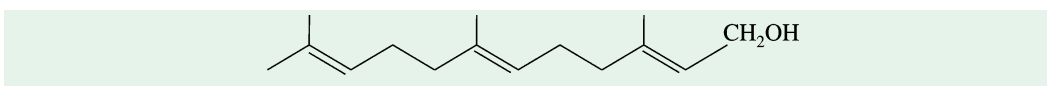
Fig. 13–30. Structure of farnesol

Diterpenes

These are usually found as substituents of the resins and balsams. The two resin acids, **abietic** and **sapietic** (Fig. 13–31) are the best known tricyclic diterpenes.

Abietic acid, $C_{20}H_{30}O_2$

Sapietic acid
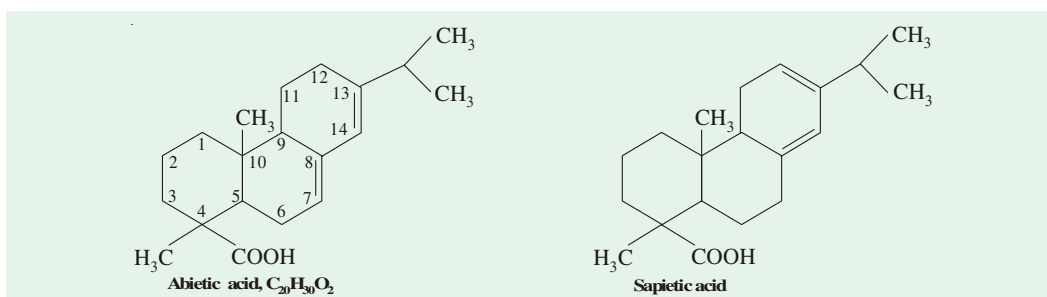
Fig. 13–31. Two best known diterpenes

Vitamins A_1 and A_2 and their aldehydes called retinenes are important monocyclic derivatives of diterpenes.

Phytol.

($C_{20}H_{40}O$; b.p. 145°C) is an acyclic diterpene and is obtained from the hydrolysis of chlorophyll. It was isolated from nettles by Paul Karrer *et al* in 1943. The phytol molecule

Paul Karrer, a Swiss, received his doctorate in 1911 from the University of Zurich. He was awarded **1937 Nobel Prize in Chemistry** for his researches into the constitution of carotenoids, flavins and vitamins A and B, along with Walter Norman Haworth of England. Karrer's contributions include: synthesis of squalene, structure and synthesis of α and β carotenes, and synthesis of riboflavin, α-tocopherol and perhydrovitamin A.

(Fig. 13–32) has 2 chiral (= asymmetric) centres, 7 and 11. Natural phytol is very weakly dextrorotatory.
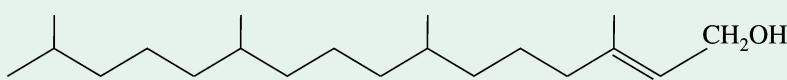
Fig. 13–32. Structure of phytol

Triterpenes

These are not widespread in nature but are significant in that some of them are intermediates in the biosynthesis of cholesterol. Two such compounds are : a tetracyclic alcohol, **lanosterol** (see page 260) and an acyclic hydrocarbon, **squalene**. Squlaene ($C_{30}H_{50}$; b.p. 240–242°C) was first isolated from the liver of sharks (genus *Squalus*), hence so named. The olive oil and several other vegetable oils are other sources. It has also been detected in the leaves. Each squalene molecule (Fig. 13–33) has 6 double bonds. The double-bond system present is of nonconjugated type. The conjugated double bonds are, however, absent from the molecule.
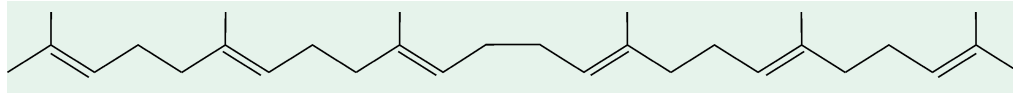

Fig. 13–33. Structure of squalene

Polyterpene

Mention, however, should also be made of **rubber** (MW = ca 3,00,000), a polyterpene present in the latex of many tropical plants. A molecule of rubber (Fig. 13–34) is composed of about 500 to 5,000 isoprene units joined in a long straight chain. When the bark of the rubber tree is cut, latex slowly exudes from the cut. Addition of acetic acid coagulates the rubber, which is then separated from the liquor and either processed into blocks or rolled into sheets, and finally dried in a current of warm air, or smoked.
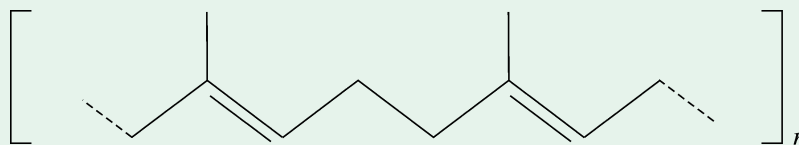

Fig. 13–34. Structure of rubber
(*cis* configuration about double bonds)

Carotenoids

The carotenoids are tetraterpenes. These are widely distributed in both the plant and animal kingdoms but are exclusively of plant origin. These occur in unsaponifiable residue of plant and animal lipids. They are isoprene derivatives with a high degree of unsaturation. Because of the presence of many conjugated double bonds, they are coloured red or yellow. As an example, the pigment of

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tomato (*lycopene*) and that of carrot (α- and β-*carotene*) are red while many oxygen-containing carotenoids are yellow (*xanthophylls*). Since the olefinic (= double) bonds permit *cis-trans* isomerism, numerous forms are possible. *Most carotenoids, however, exist in all-trans form.* The presence of long hydrocarbon chain in carotenoids makes them lipid-soluble; they are hence also called *lipochromes* or *chromolipids*.

Lycopene

Lycopene ($C_{40}H_{56}$) is the main pigment of tomato, paprika and many other fruits. It is a highly unsaturated, unbranched, long chain hydrocarbon (a polyene) and is composed of two identical units ($C_{20}H_{28}$), joined by a double bond between C_{15} and $C_{15'}$. Each of these units may, in turn, be considered to have been derived from 4 isoprene units ($C_5 H_8$). A molecule of lycopene (Fig. 13–35) in all contains as many as 13 double bonds, of which 11 are conjugated.
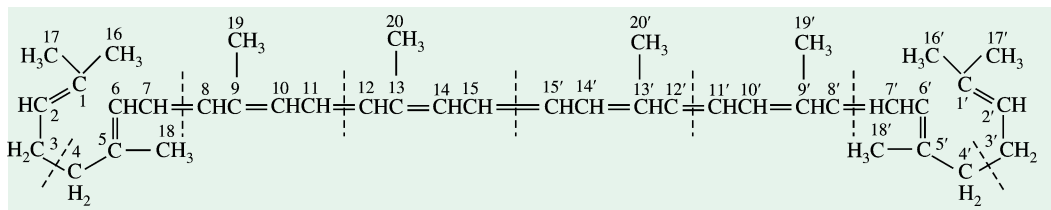

Fig. 13–35. Structure of lycopene
(Dotted lines mark the positions where various isoprene-like sements are joined with each other.)

Carotene

Another group of naturally occurring carotenoids, with the same molecular formula as that of lycopene, is **carotene**. Carotene was first isolated by Wackenroder (1831) from carrots (this was the origin of the name *carotin*, which was later on modified to *carotene*). The 3 types of carotenes are :

1. α-carotene– violet crystals ; m.p. 187°C ; optically active (dextrorotatory).
2. β-carotone– red crystals ; m.p. 183°C ; optically inactive.
3. γ-carotene– dark red crystals ; m.p. 152–154°C; optically inactive.

(The prefixes α, β and γ in the carotenes were assigned not on the basis of structural properties but rather as a result of observations of their elution patterns on a $CaCO_3$ chromatographic column, eluted with petroleum ether).

The carotenes are obtained commercially by chromatography. The two best sources are carrots and alfalfa. Their relative proportion, however, varies with the source; for example carrots contain 15% α-, 85% β- and 0.1% γ-form. These are unstable to air, heat, acids and alkalies.

It is to be noted that the ends of the lycopene chain can easily close up to form rings, with the disappearance of the double bonds. Ring closure on only one end results in the production of
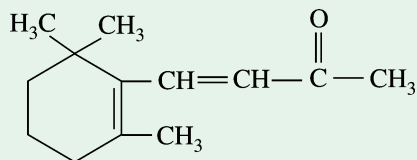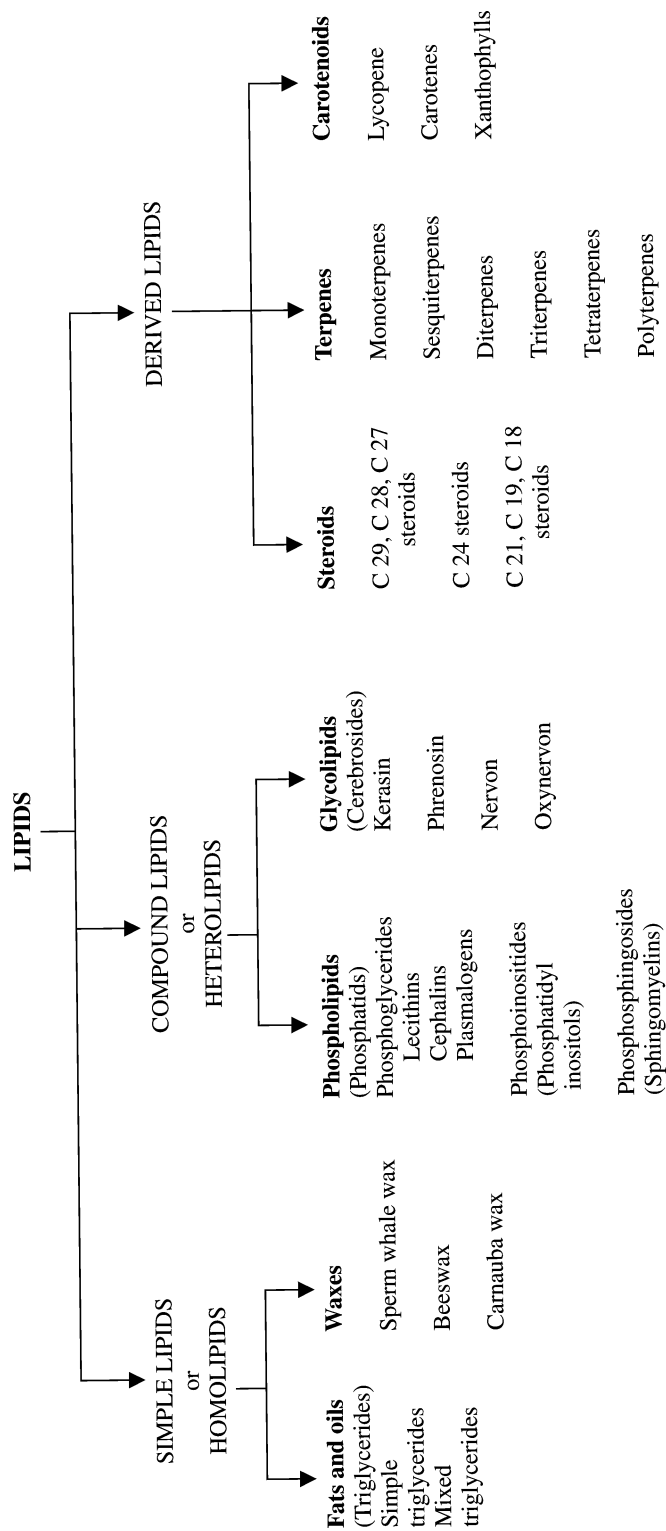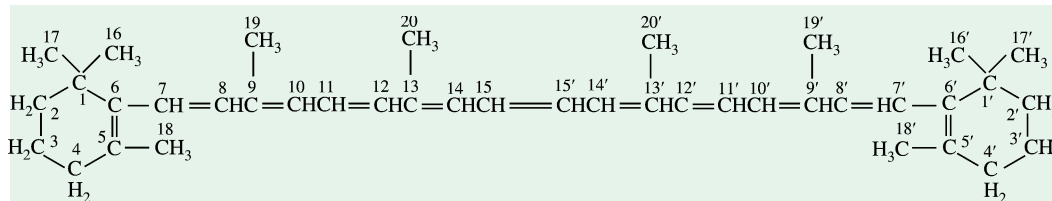

Fig. 13–36. Structure of β-ionone

γ-carotene while closure of the ring at both ends produces β- and α-carotenes which differ from each other in the position of the double bonds in the rings. The ring is structurally related to the ionones. (Fig. 13–36). In β-carotene, both annular double bonds are in conjugation with the system of double bonds of the long chain (β-ionone structure). In α-carotene, one of the annular double bonds is removed from the system of conjugation by one position (α-ionone structure). Of particular interest is β-carotene (Fig. 13–37), which is precursor of vitamin A.

LIPIDS

SIMPLE LIPIDS or HOMOLIPIDS

Fats and oils
(Triglycerides)
Simple triglycerides
Mixed triglycerides

Waxes
Sperm whale wax
Beeswax
Carnauba wax

COMPOUND LIPIDS or HETEROLIPIDS

Phospholipids
(Phosphatids)
Phosphoglycerides
Lecithins
Cephalins
Plasmalogens

Phosphoinositides
(Phosphatidyl inositols)

Phosphosphingosides
(Sphingomyelins)

Glycolipids
(Cerebrosides)
Kerasin
Phrenosin
Nervon
Oxynervon

DERIVED LIPIDS

Steroids
C 29, C 28, C 27 steroids
C 24 steroids
C 21, C 19, C 18 steroids

Terpenes
Monoterpenes
Sesquiterpenes
Diterpenes
Triterpenes
Tetraterpenes
Polyterpenes

Carotenoids
Lycopene
Carotenes
Xanthophylls

Fig. 13–37. Structure of β-carotene

Xanthophylls

Xanthophylls are characterized by the presence of hydroxyl groups in the ionone rings of carotenes, in the para position to the long chain. The xanthophyll of the leaf (*lutein*, $C_{40}H_{56}O_2$, Fig. 13–38) is derived from α-carotene while that of corn (*zeaxanthine*) from β-carotene. The xanthophyll of crustaceans (*astaxanthine*) is, however, more rich in oxygen. Astaxanthine is responsible for the appetizing redness of boiled lobsters.
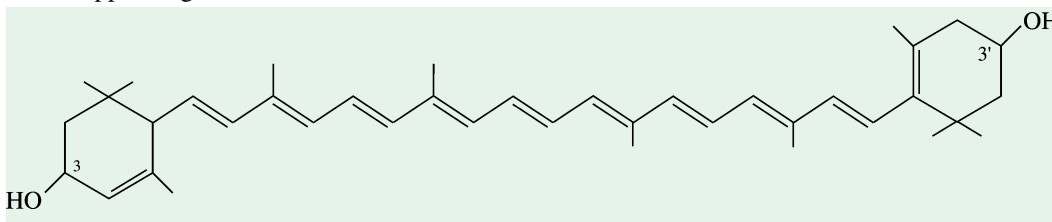

Fig. 13–38. Structure of lutein

(3, 3′-dihydroxy-α-carotene)

The classification of lipids described above may be summarized as depicted on page 252.

REFERENCES

See list following Chapter 14.

PROBLEMS

1. A common structural feature of membrane lipid molecules is their amphipathic nature. For example, in phosphatidylcholine, the two fatty acid chains are hydrophobic and the phosphocholine head group is hydrophilic. For each of the following membrane lipids, name the components that serve as the hydrophobic and hydrophilic units :

   (*a*) phosphatidylethanolamine

   (*b*) sphingomyelin

   (*c*) galactosylcerebroside

   (*d*) cholesterol

2. Which of the following could not be classified as a lipid ?

   (*a*) steroids

   (*b*) fats and oils

   (*c*) waxes

   (*d*) photosynthetic pigments

   (*e*) anthocyanin pigments