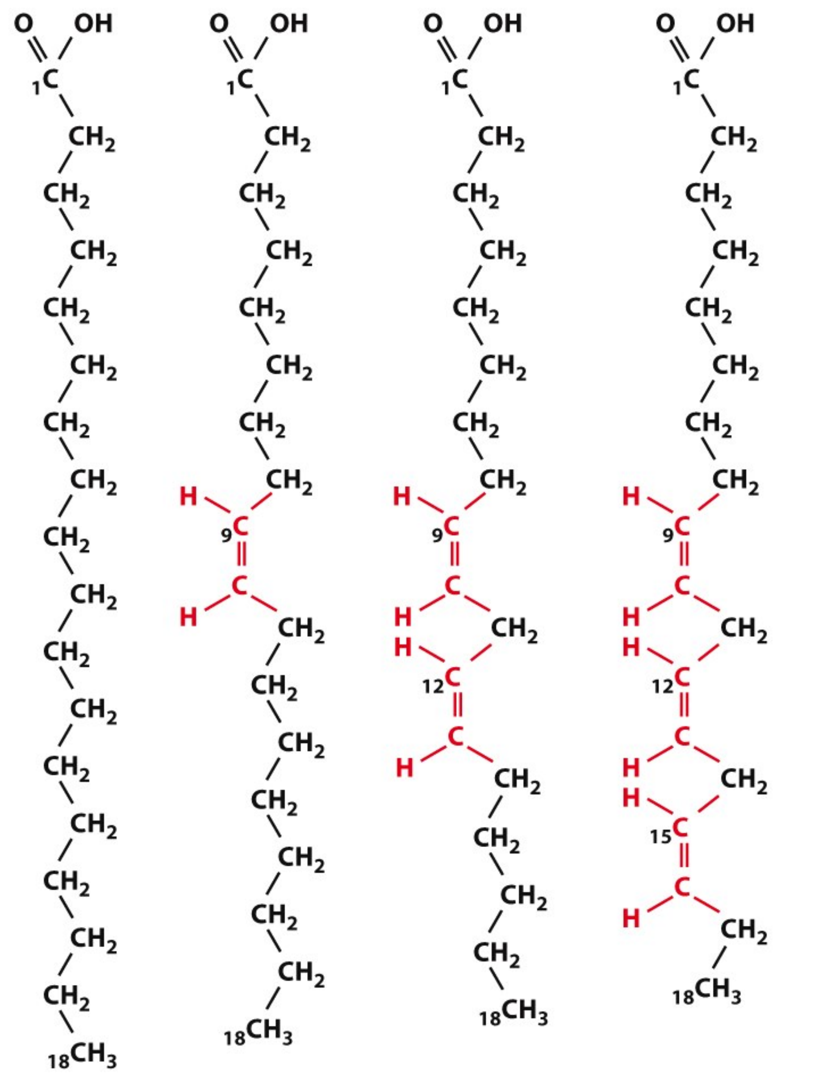
Lipids, Membrane Structure and Membrane Proteins

CHEM 420 – Principles of Biochemistry
Instructor – Anthony S. Serianni

Chapter 12: Voet/Voet, *Biochemistry*, 2011
Fall 2015

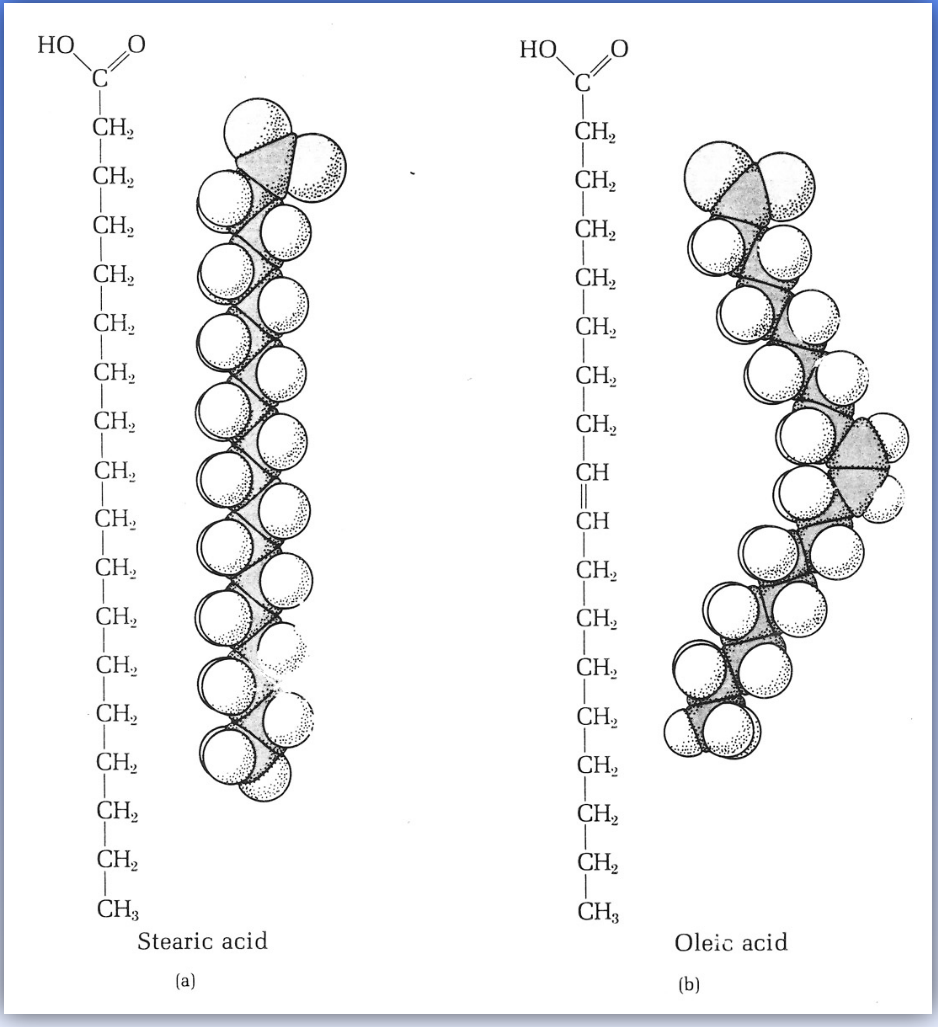
October 26 & 28



Stearic acid | Oleic acid | Linoleic acid | α-Linolenic acid

Figure 12-1

Fatty acids are the basic <u>building blocks</u> used to create lipids. Fatty acids are long-chain carboxylic acids. Most lipids contain at least one fatty acid constituent. Fatty acids can be <u>saturated</u> (no C-C double bonds) or can contain one or more C-C double bonds (<u>unsaturated</u>).



Saturated fatty acids are linear-extended molecules.

The introduction of a *cis* C-C double bond into the fatty acid chain causes the molecule to assume a bent conformation.

Table 12-1 **The Common Biological Fatty Acids**

Symbol[a]	Common Name	Systematic Name	Structure	mp (°C)
Saturated fatty acids				
12:0	Lauric acid	Dodecanoic acid	$CH_3(CH_2)_{10}COOH$	44.2
14:0	Myristic acid	Tetradecanoic acid	$CH_3(CH_2)_{12}COOH$	52
16:0	Palmitic acid	Hexadecanoic acid	$CH_3(CH_2)_{14}COOH$	63.1
18:0	Stearic acid	Octadecanoic acid	$CH_3(CH_2)_{16}COOH$	69.6
20:0	Arachidic acid	Eicosanoic acid	$CH_3(CH_2)_{18}COOH$	75.4
22:0	Behenic acid	Docosanoic acid	$CH_3(CH_2)_{20}COOH$	81
24:0	Lignoceric acid	Tetracosanoic acid	$CH_3(CH_2)_{22}COOH$	84.2
Unsaturated fatty acids (all double bonds are cis)				
16:1*n*–7	Palmitoleic acid	9-Hexadecenoic acid	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$	−0.5
18:1*n*–9	Oleic acid	9-Octadecenoic acid	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	13.4
18:2*n*–6	Linoleic acid	9,12-Octadecadienoic acid	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COOH$	−9
18:3*n*–3	α-Linolenic acid	9,12,15-Octadecatrienoic acid	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COOH$	−17
18:3*n*–6	γ-Linolenic acid	6,9,12-Octadecatrienoic acid	$CH_3(CH_2)_4(CH{=}CHCH_2)_3(CH_2)_3COOH$	
20:4*n*–4	Arachidonic acid	5,8,11,14-Eicosatetraenoic acid	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COOH$	−49.5
20:5*n*–3	EPA	5,8,11,14,17-Eicosapentaenoic acid	$CH_3CH_2(CH{=}CHCH_2)_5(CH_2)_2COOH$	−54
22:6*n*–3	DHA	4,7,10,13,16,19-Docosahexenoic acid	$CH_3CH_2(CH{=}CHCH)_6CH_2COOH$	
24:1*n*–9	Nervonic acid	15-Tetracosenoic acid	$CH_3(CH_2)_7CH{=}CH(CH_2)_{13}COOH$	39

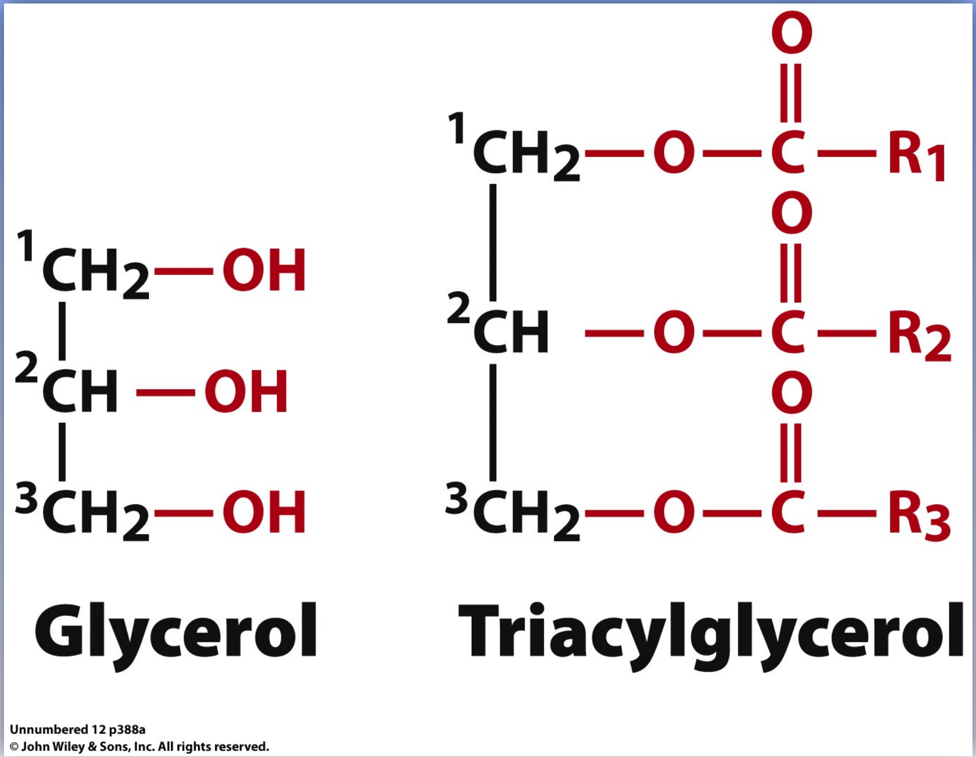
[a]Number of carbon atoms: number of double bonds. For unsaturated fatty acids, *n* is the number of carbon atoms, *n* − *x* is the double-bonded carbon atom, and *x* is the number of that carbon atom counting from the methyl terminal (ω) end of the chain.

Source: Dawson, R.M.C., Elliott, D.C., Elliott, W.H., and Jones, K.M., *Data for Biochemical Research* (3rd ed.), Chapter 8, Clarendon Press (1986).

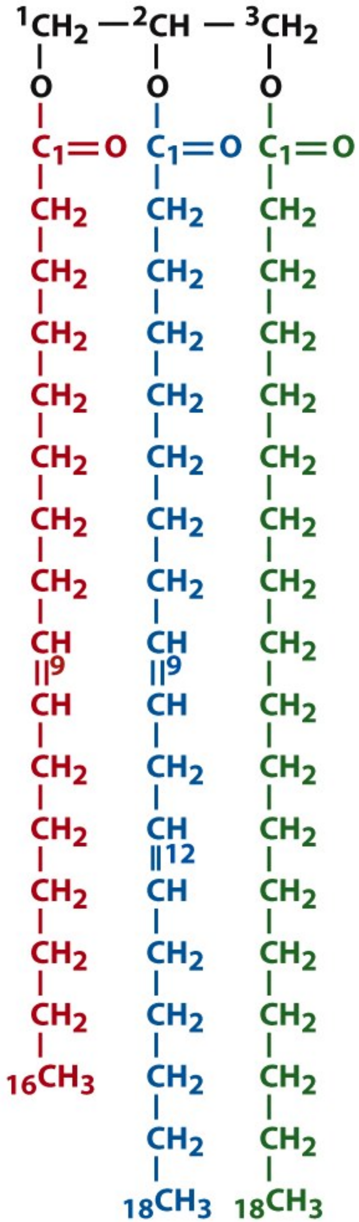
Table 12-1

Lipid types: Triacylglycerols (triglycerides, neutral fats)

Triacylglycerols are composed of a glycerol molecule to which are esterified three (3) fatty acids.



1-Palmitoleoyl-2-linoleoyl-3-stearoyl-glycerol



Unnumbered 12 p388b

An example of a triglyceride. These lipids are structurally diverse because many different types of fatty acids can be esterified to the glycerol core. Triglycerides are mainly located in the adipocytes (fat cells) in the human body.

Lipid types: Glycerophospholipids

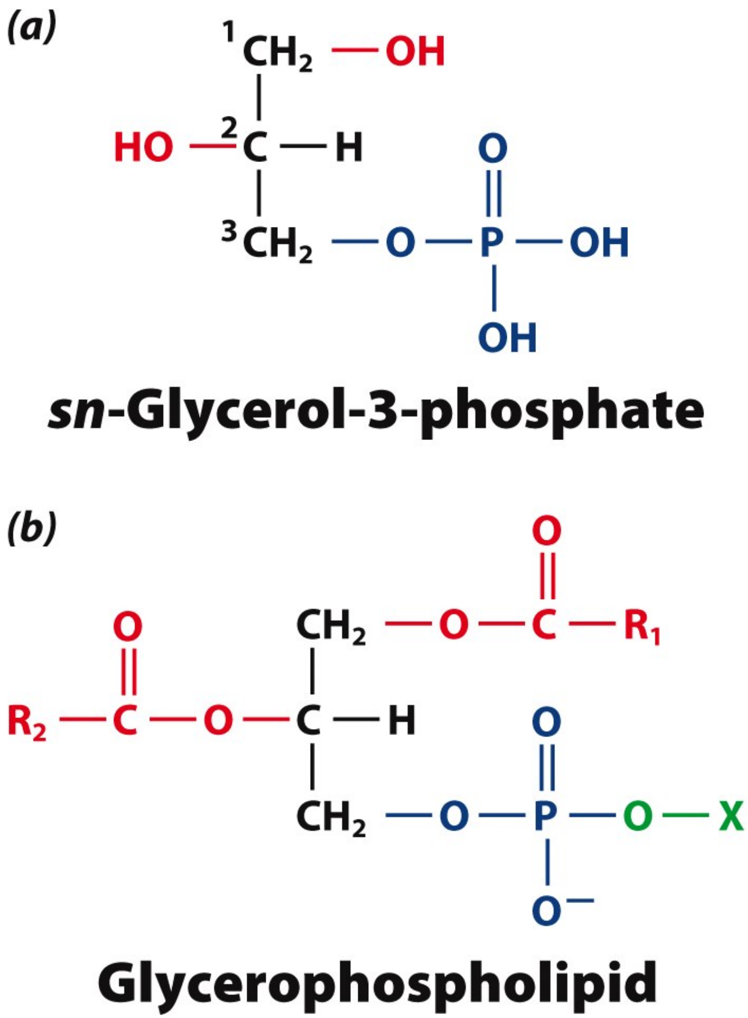
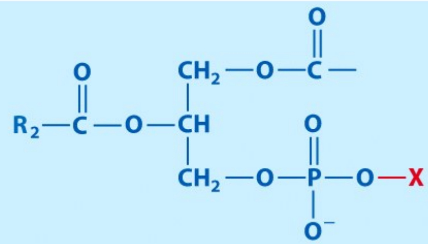


Figure 12-3

These lipids are composed of glycerol, two fatty acids, and a variable phosphate-containing head group. Phosphatidic acid lacks the head group substituent.

Different phosphate-containing head group in glycerophospholipids

Table 12-2 The Common Classes of Glycerophospholipids



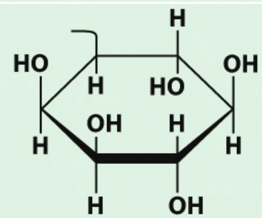
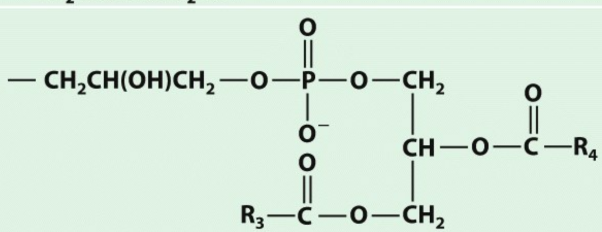
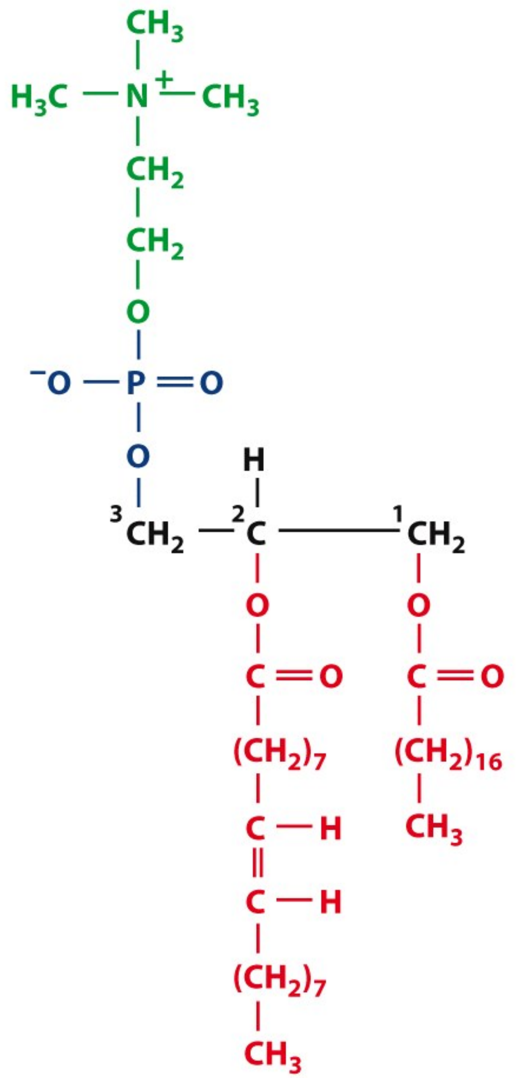
Name of X—OH	Formula of —X	Name of Phospholipid
Water	—H	Phosphatidic acid
Ethanolamine	$—CH_2CH_2NH_3^+$	Phosphatidylethanolamine
Choline	$—CH_2CH_2N(CH_3)_3^+$	Phosphatidylcholine (lecithin)
Serine	$—CH_2CH(NH_3^+)COO^-$	Phosphatidylserine
myo-Inositol		Phosphatidylinositol
Glycerol	$—CH_2CH(OH)CH_2OH$	Phosphatidylglycerol
Phosphatidylglycerol (cardiolipin)		Diphosphatidylglycerol

Table 12-2

An example of a glycerophospholipid: phosphatidylcholine



1-Stearoyl-2-oleoyl-3-phosphatidylcholine

Figure 12-4a

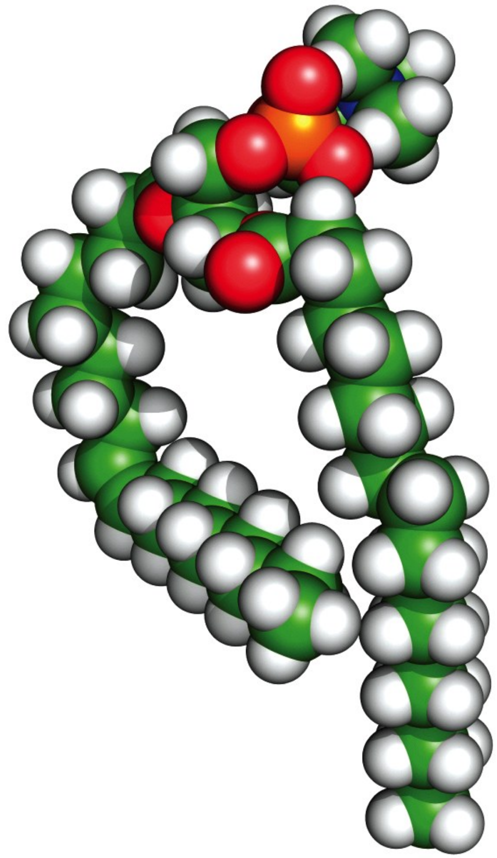
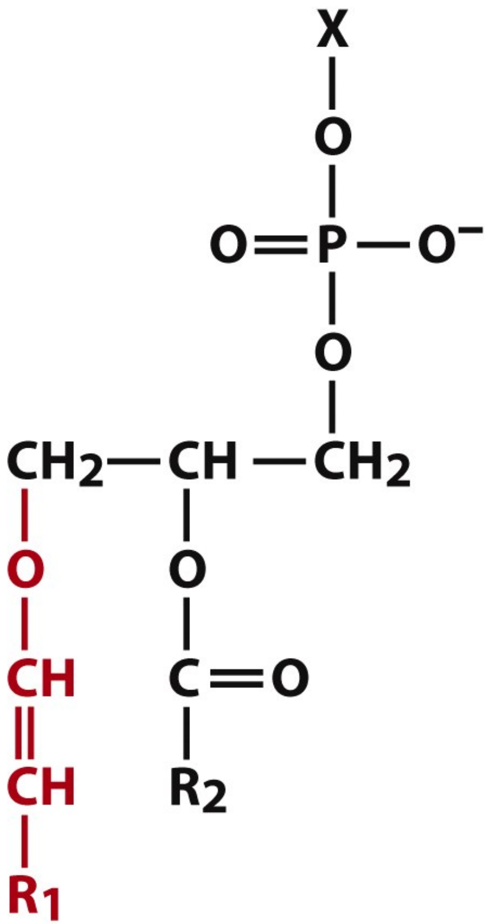


Figure 12-4b

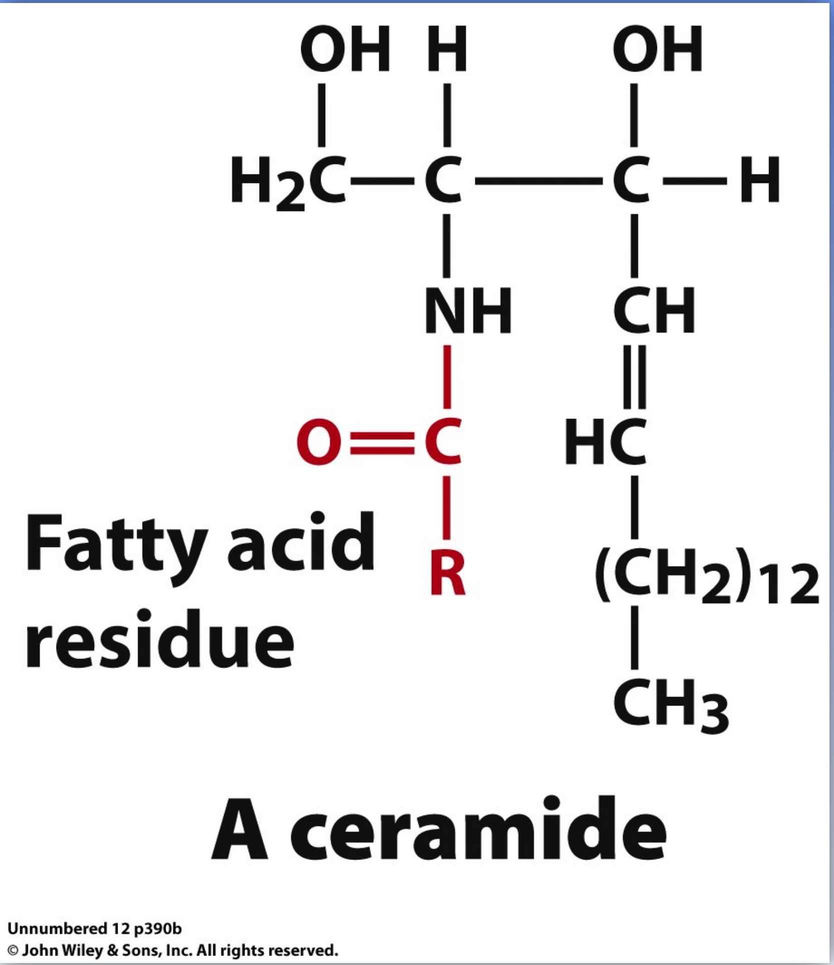


A plasmalogen

A special type of glycerophospholipid

Plasmalogen: contains a phosphate-containing head group at C3 of glycerol, a fatty acyl ester at C2 of glycerol, and an ether linkage at C1 of glycerol. The double bond in the long-chain substituent at C1 is always *cis*.

Lipid types: Sphingolipids



Sphingolipids are built from a common sphingosine or dihydrosphingosine core. A ceramide is composed of sphingosine to which is attached a fatty acid via amide linkage.

The sphingosine and dihydrosphingosine cores of sphingolipids: Note that the double bond in sphingosine is always trans.

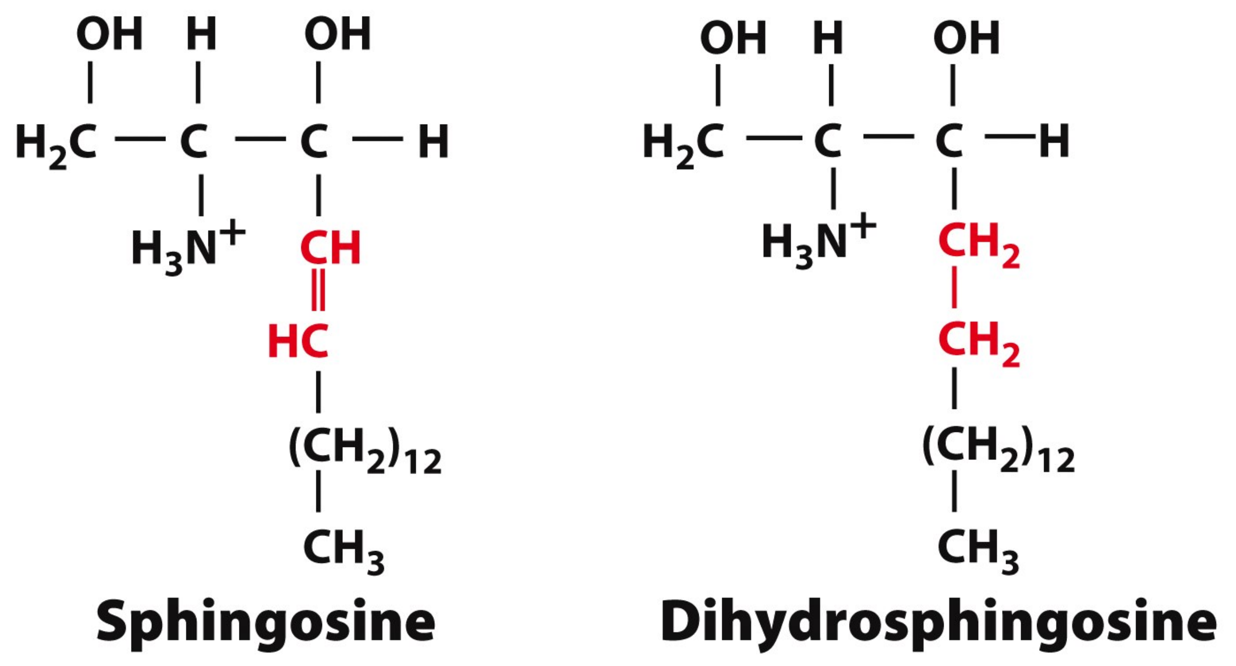
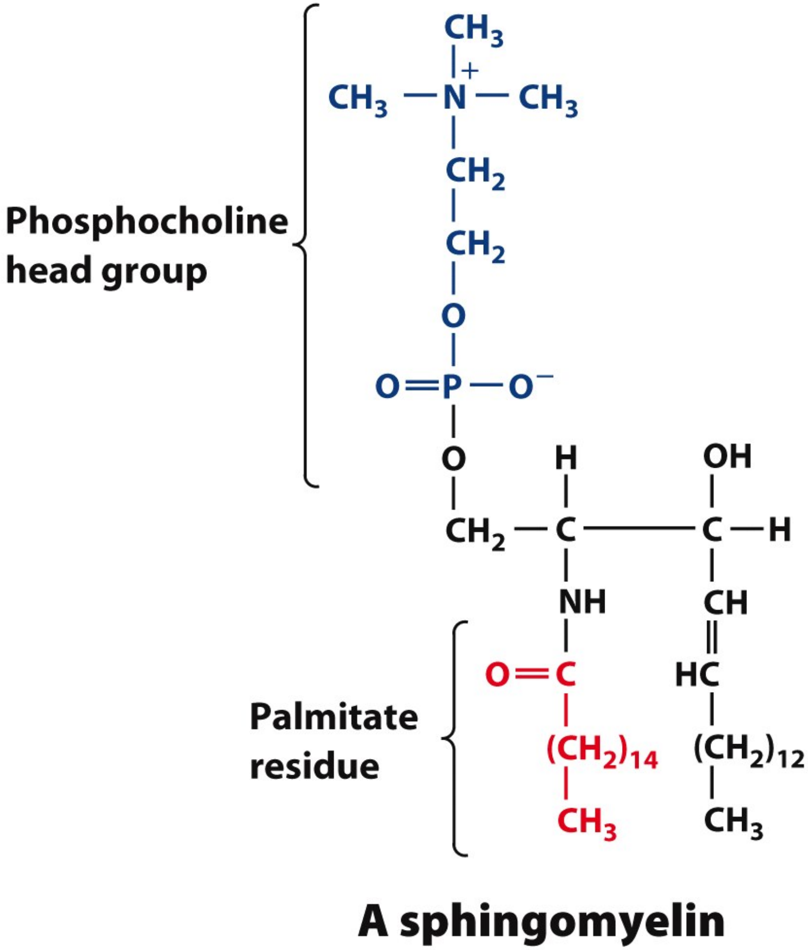


Figure 12-5

Sphingomyelins are the most common type of sphingolipid. This lipid is commonly found as a major constituent of the <u>myelin sheath</u> of nerve cells.



A sphingomyelin

Figure 12-6a

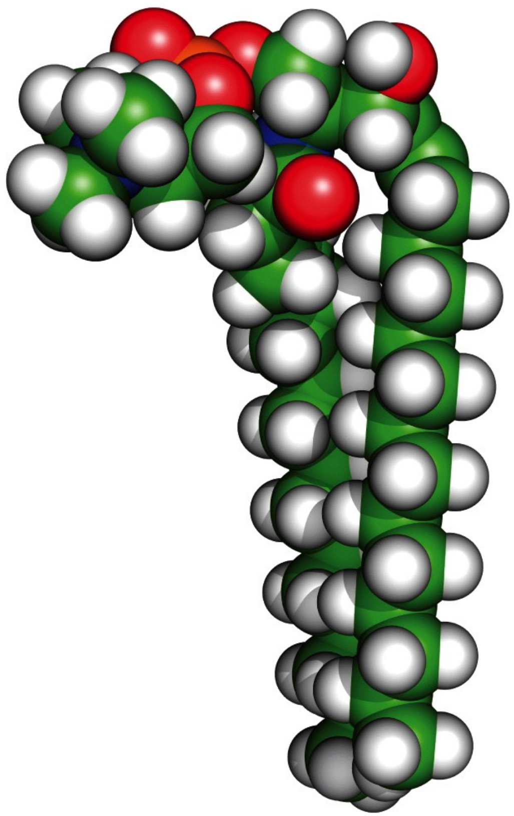


Figure 12-6b

Sphingolipids: **<u>Cerebrosides</u>** – have a single sugar linked to the primary hydroxyl group of ceramide.

Sphingolipids: **<u>Gangliosides</u>** – have an oligosaccharide linked to the primary hydroxyl group of ceramide.

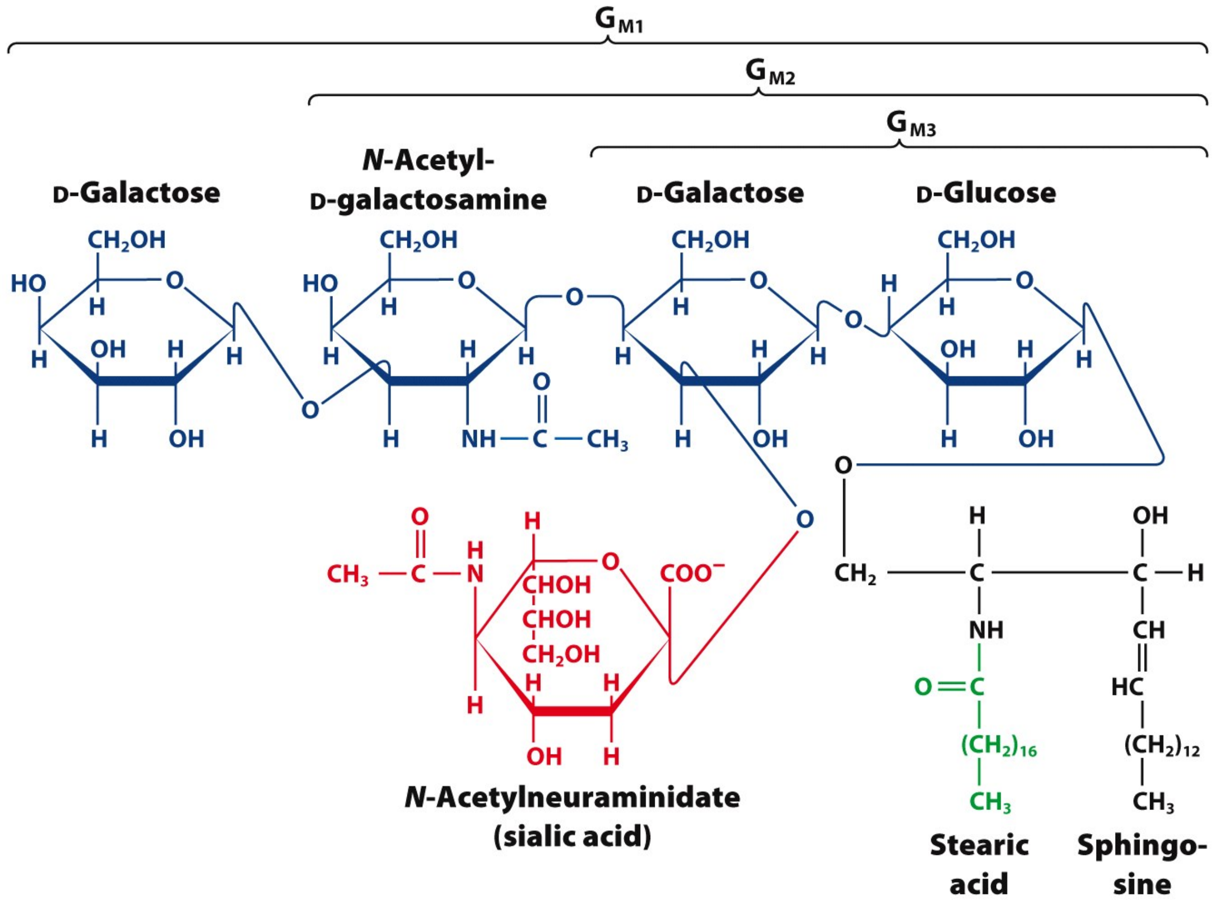


Figure 12-7a

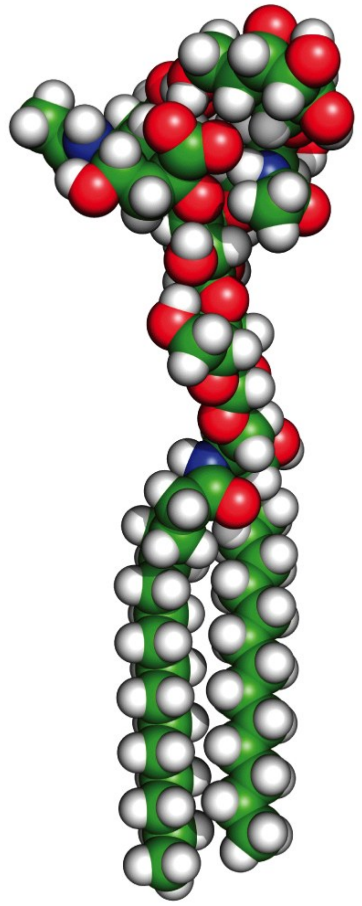


Figure 12-7b

Lipid types: Steroids

Comprised of a fused four-ring (A-D) core

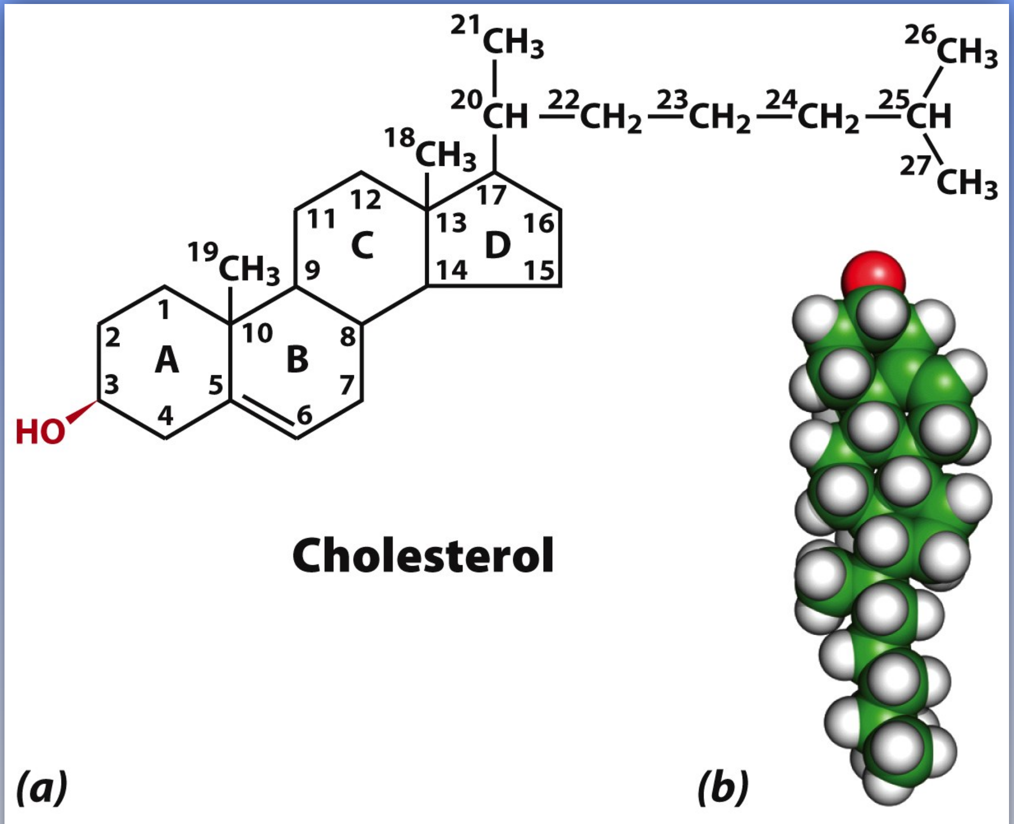
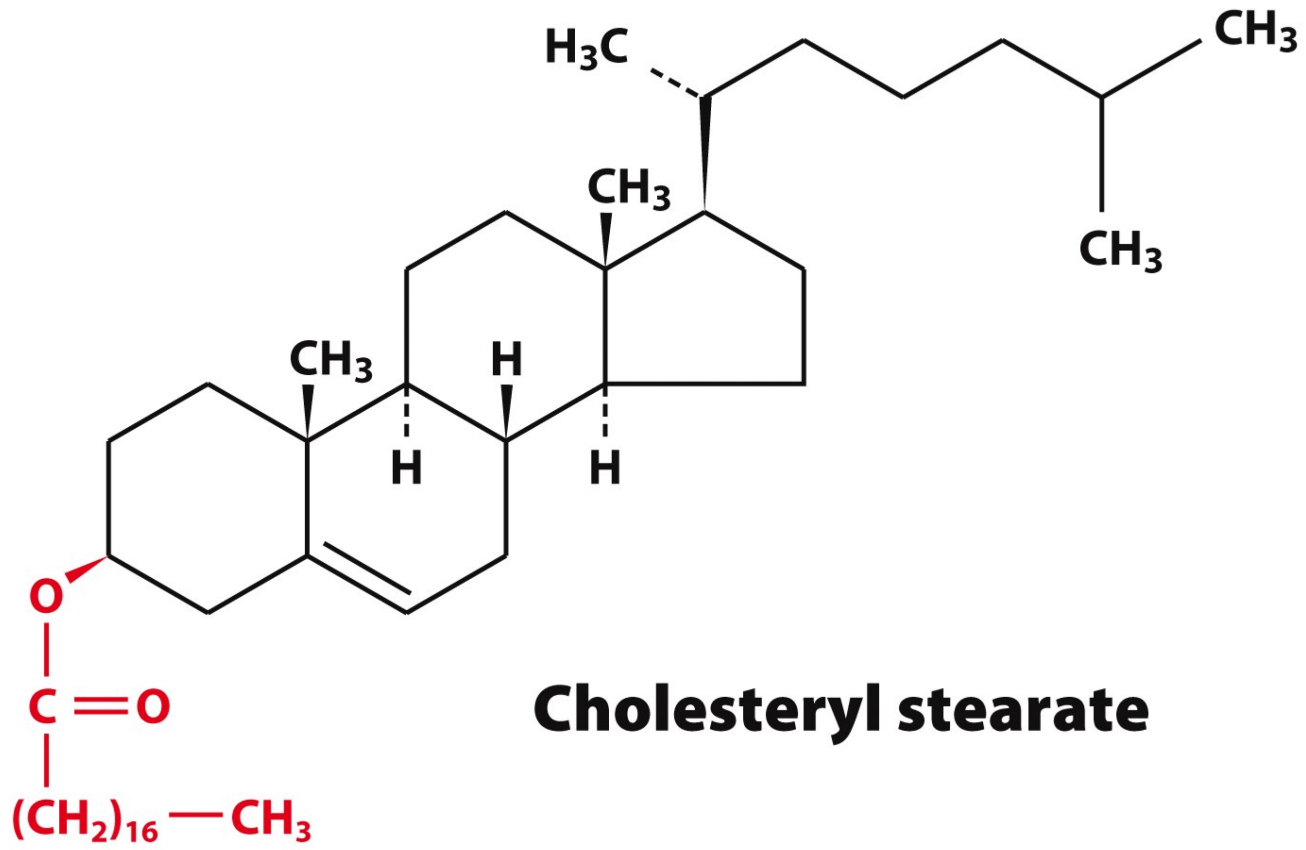


Figure 12-9

Cholesterol is a sterol, and is a major component of biological membranes, often in the form of a fatty acyl ester. Cholesterol is the metabolic precursor in the biosynthesis of steroid hormones in humans.

An example of a fatty acyl ester of cholesterol



Cholesteryl stearate

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Physical properties of lipids: Aggregation (self-assembly) in aqueous solution

Figure 12-11a

The conical van der Waals envelope of single-tailed lipids

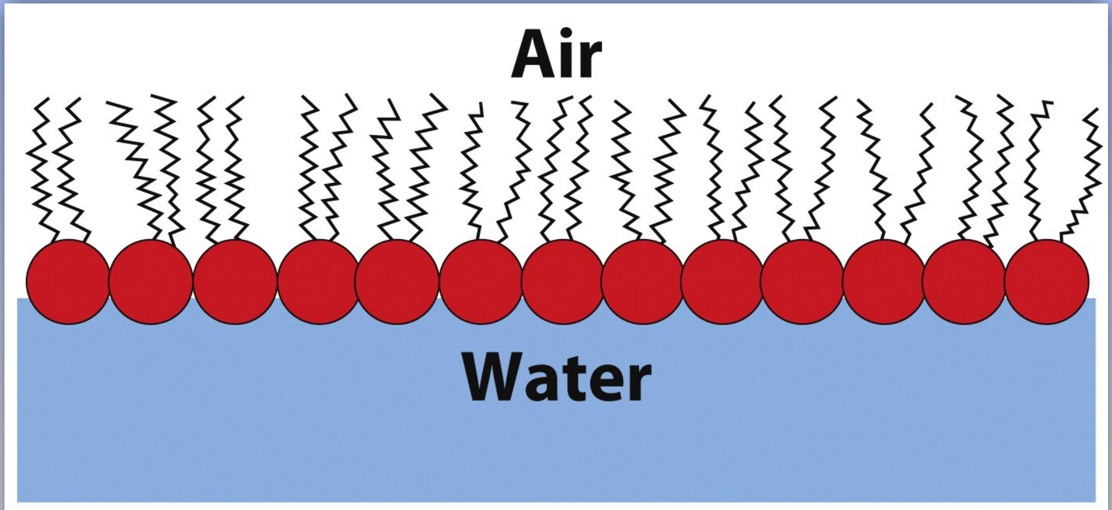


Figure 12-10

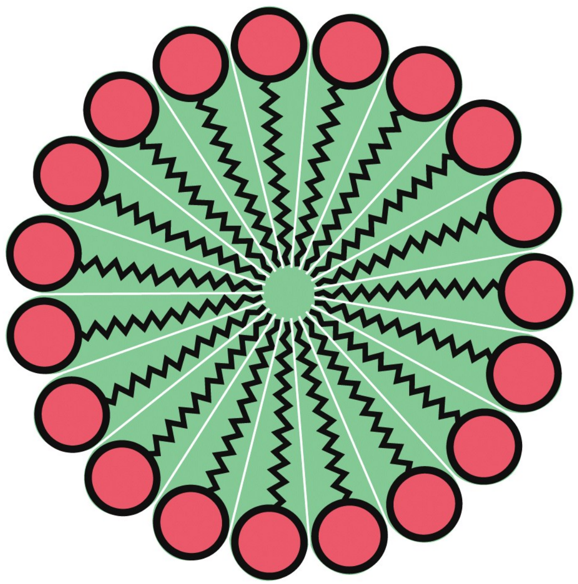


Figure 12-11b

A spheroidal micelle

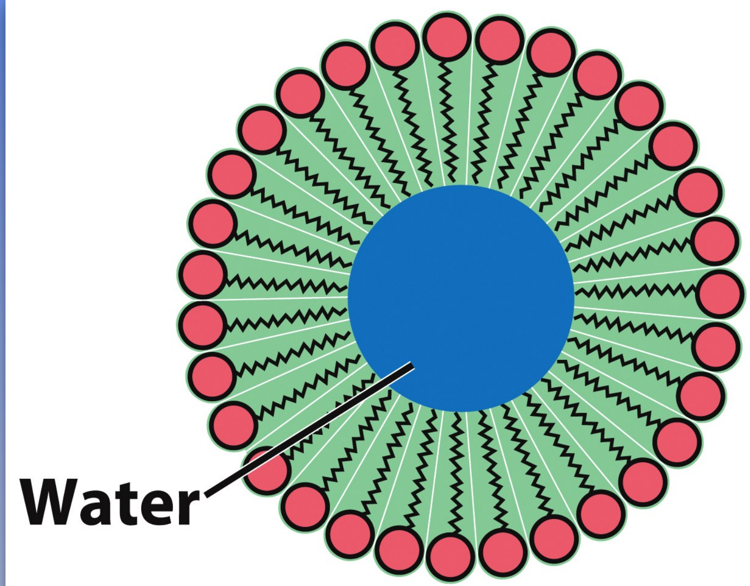


Figure 12-11c

Unfavorable micelle with a water center

Collapse of a spheroidal water-centered micelle

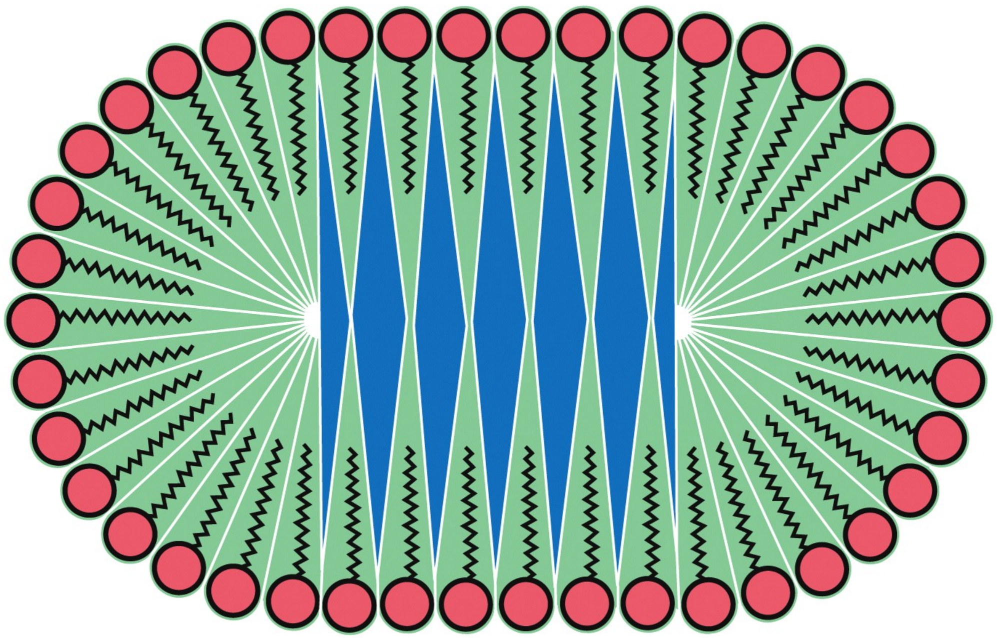


Figure 12-11d

Disk-like micelles with bilayer structure

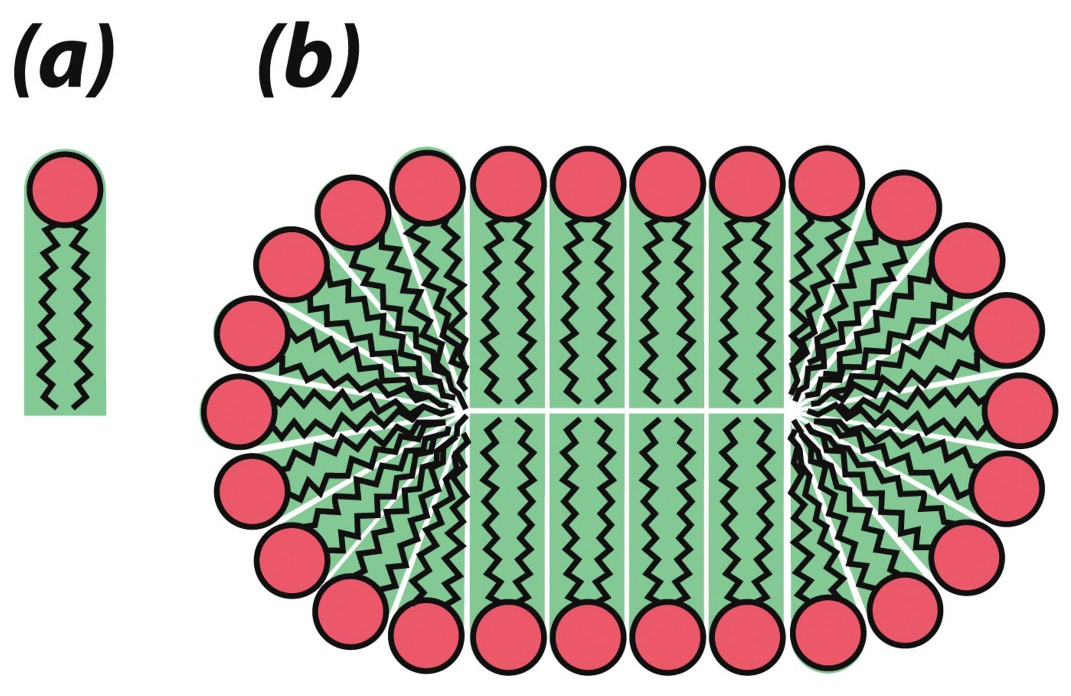


Figure 12-12

Types of motional behaviors of lipids in bilayers

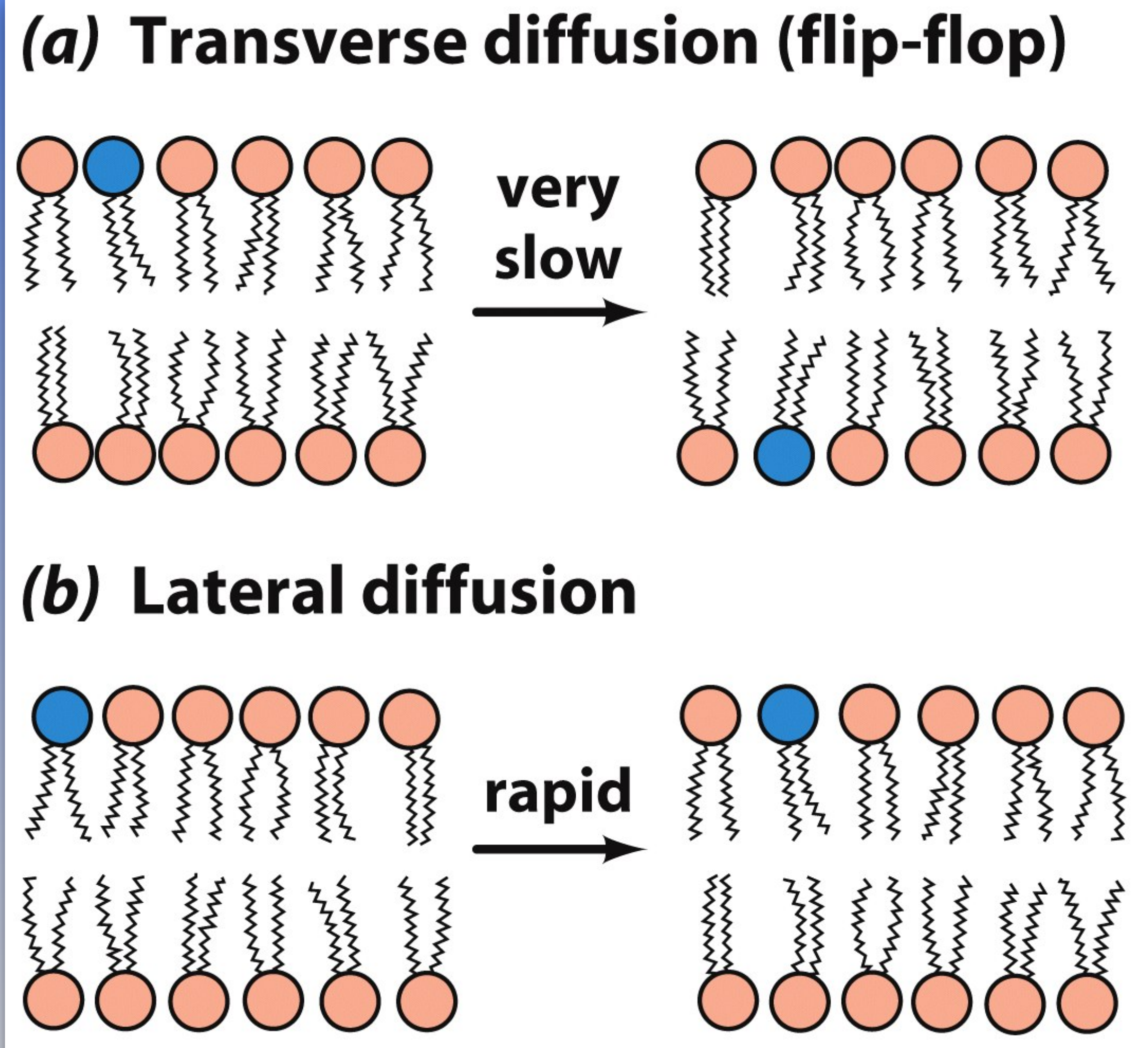


Figure 12-14

Bilayer fluidity

As a lipid bilayer cools below a characteristic transition temperature, it undergoes a phase change – an order-disorder transition – in which it becomes a gel-like solid.

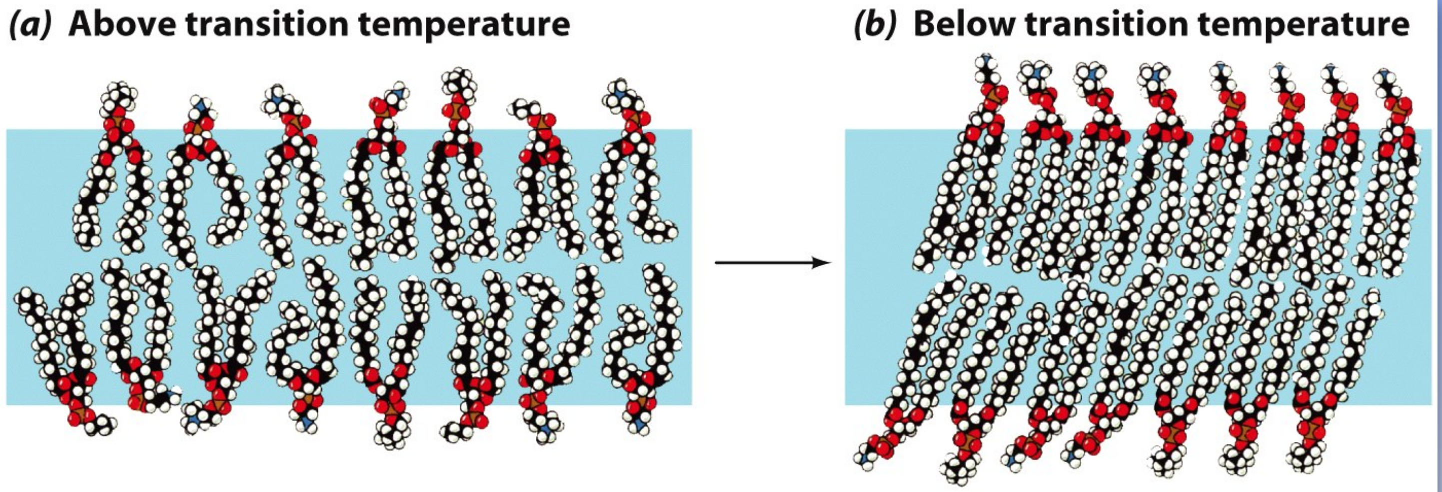


Figure 12-17

The transition temperature increases with the chain length and degree of saturation of the bilayer's component fatty acid residues.

Cholesterol as a membrane "plasticizer"

Cholesterol decreases membrane fluidity near the membrane surface. Its rigid steroid ring system interferes with the motions of the fatty acid tails, causing them to become more ordered.

Cholesterol acts as a spacer that facilitates increased mobility of the fatty acid tails near their methyl ends.

Cholesterol broadens the temperature range of the order-disorder transition, and abolishes it at high concentrations by inhibiting the "crystallization" of fatty acid tails.

Biological membranes are composed of proteins associated with a lipid bilayer matrix.

Table 12-3 **Lipid Compositions of Some Biological Membranes**[a]

Lipid	Human Erythrocyte	Human Myelin	Beef Heart Mitochondria	*E. coli*
Phosphatidic acid	1.5	0.5	0	0
Phosphatidylcholine	19	10	39	0
Phosphatidylethanolamine	18	20	27	65
Phosphatidylglycerol	0	0	0	18
Phosphatidylinositol	1	1	7	0
Phosphatidylserine	8.5	8.5	0.5	0
Cardiolipin	0	0	22.5	12
Sphingomyelin	17.5	8.5	0	0
Glycolipids	10	26	0	0
Cholesterol	25	26	3	0

[a]The values given are weight percent of total lipid.

Source: Tanford, C., *The Hydrophobic Effect, p.* 109, Wiley (1980).

Table 12-3

Protein-lipid ratios in biological membranes vary widely with membrane function.

Table 12-4 **Compositions of Some Biological Membranes**

Membrane	Protein (%)	Lipid (%)	Carbohydrate (%)	Protein to Lipid Ratio
Plasma membranes:				
Mouse liver cells	46	54	2–4	0.85
Human erythrocyte	49	43	8	1.1
Amoeba	52	42	4	1.3
Rat liver nuclear membrane	59	35	2.0	1.6
Mitochondrial outer membrane	52	48	(2–4)[a]	1.1
Mitochondrial inner membrane	76	24	(1–2)[a]	3.2
Myelin	18	79	3	0.23
Gram-positive bacteria	75	25	(10)[a]	3.0
Halobacterium purple membrane	75	25		3.0

[a]Deduced from the analyses.

Source: Guidotti, G., *Annu. Rev. Biochem.* **41**, 732 (1972).

Table 12-4

Types of membrane proteins: Integral (tightly bound by hydrophobic forces and can be separated from the membrane only by membrane disruption)

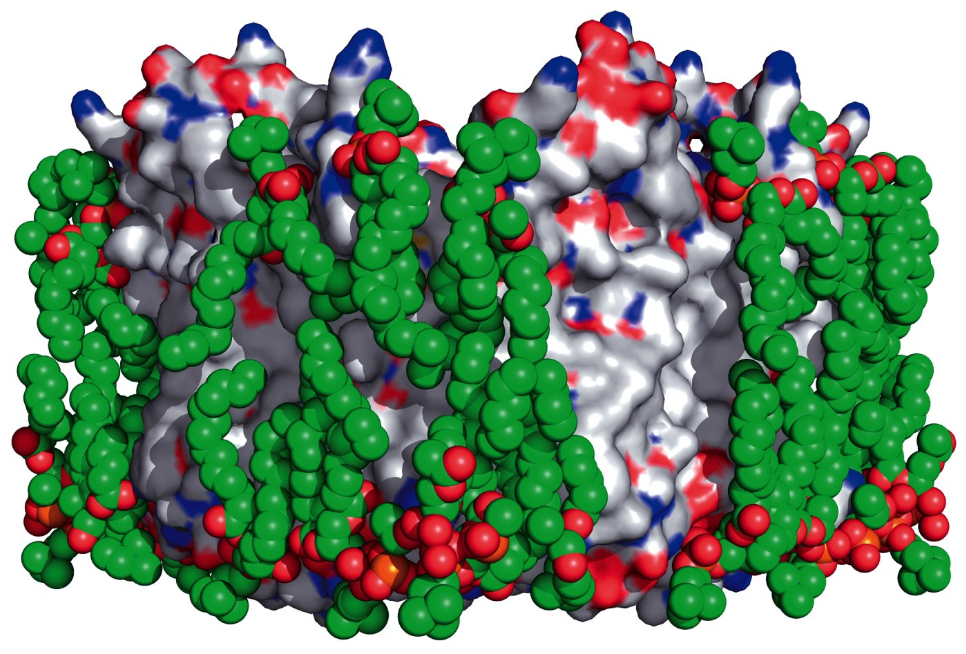


Figure 12-18

Detergents used to extract integral proteins from membranes

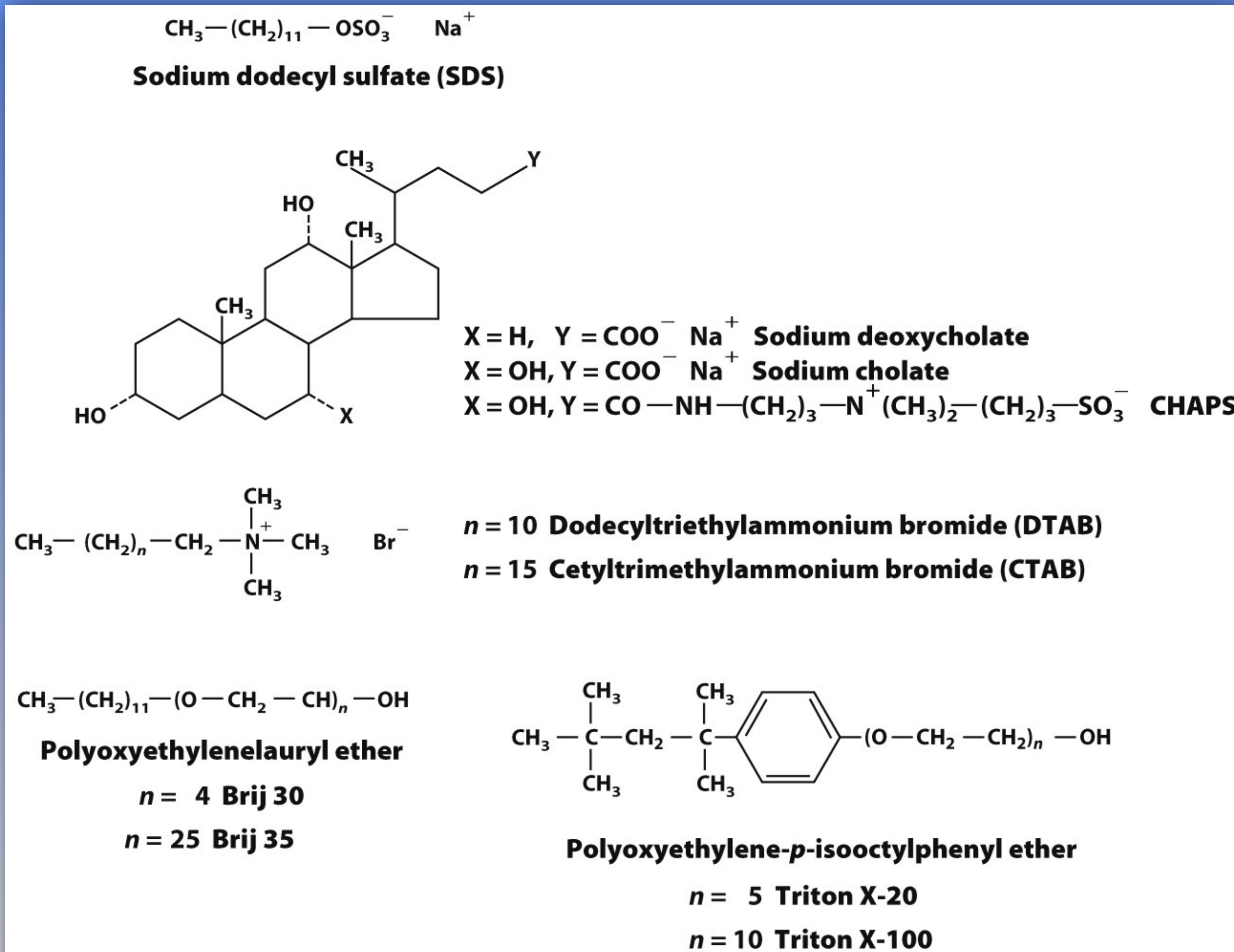


Figure 12-19

<u>Types of membrane proteins</u>: peripheral (extrinsic) proteins – are dissociated from membranes by relatively mild procedures that leave the membrane intact.

Diagram of a plasma membrane showing intrinsic and peripheral proteins and membrane asymmetry

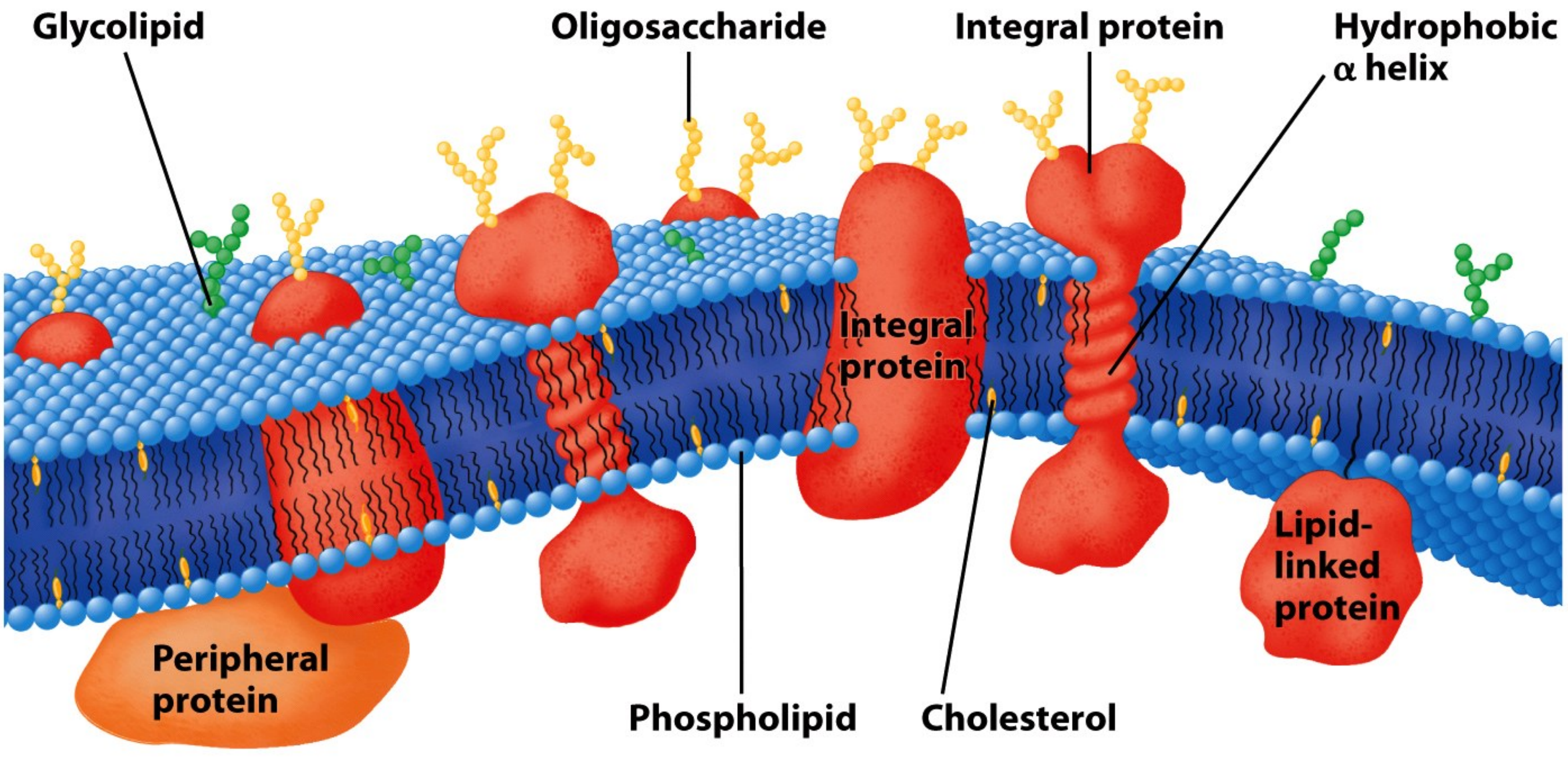


Figure 12-20

An example of an integral protein – glycophorin A (erythrocyte)

All integral proteins are amphiphilic – the embedded sequence(s) is hydrophobic and the exposed sequence(s) is hydrophilic. Integral proteins are often highly glycosylated (exterior side).

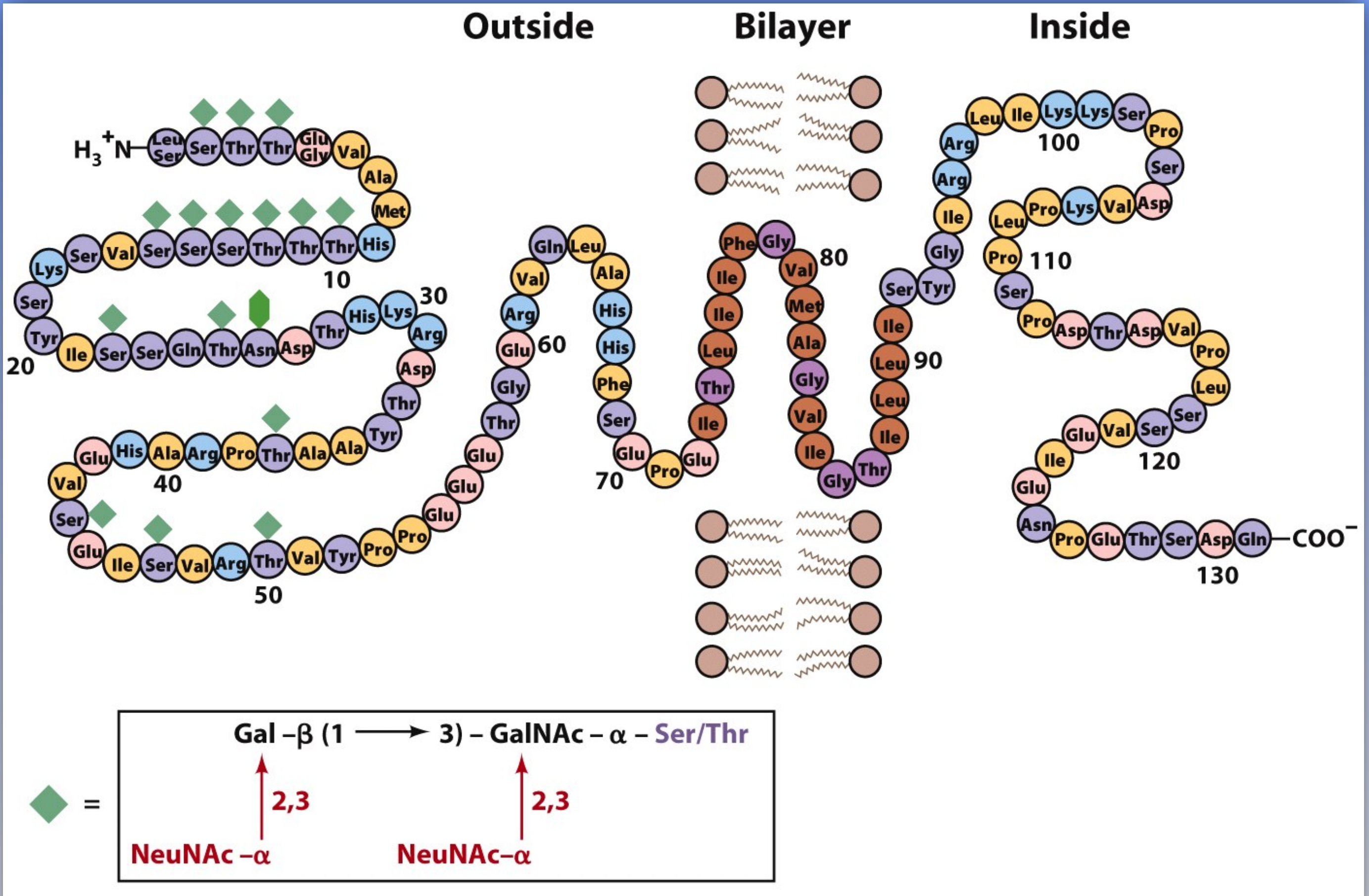


Figure 12-21

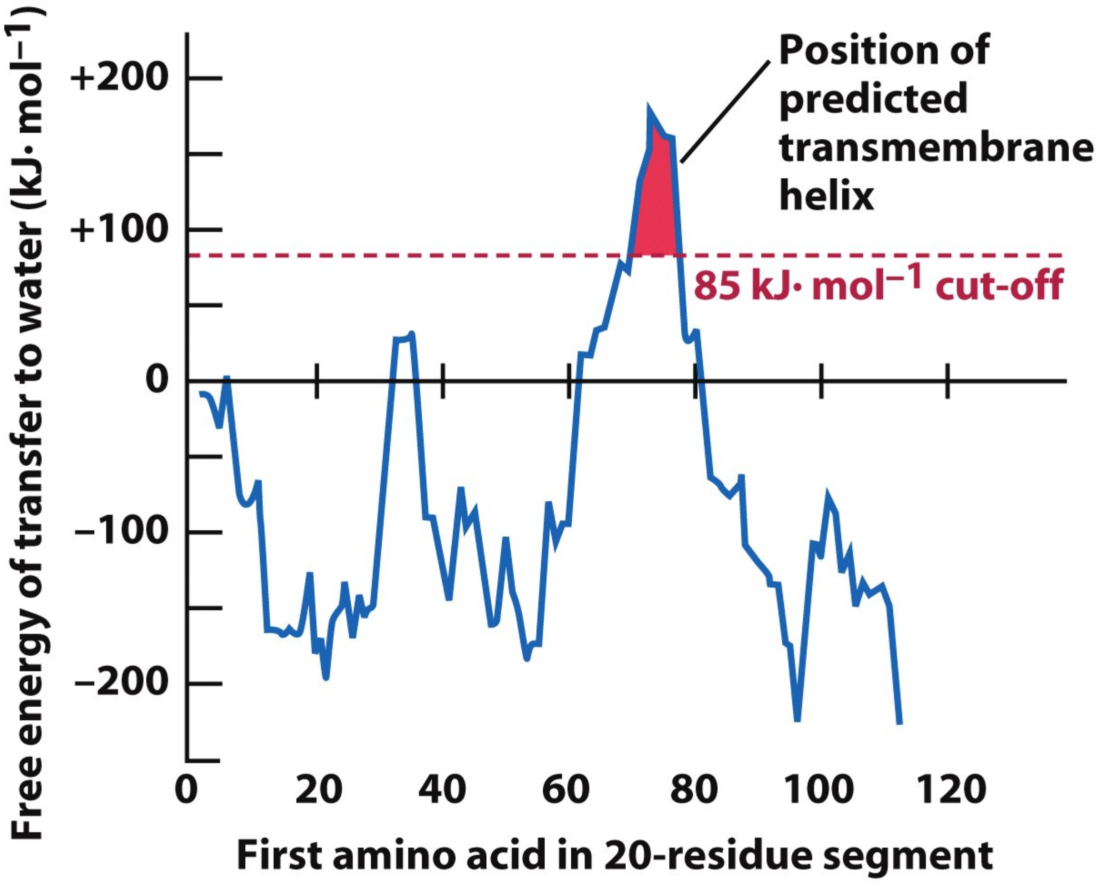


Figure 12-22

Plot of free energy of transfer to water for 20-residue segments of glycophorin A. As values become more positive (less favorable), there is a greater propensity of the segment to reside in the membrane.

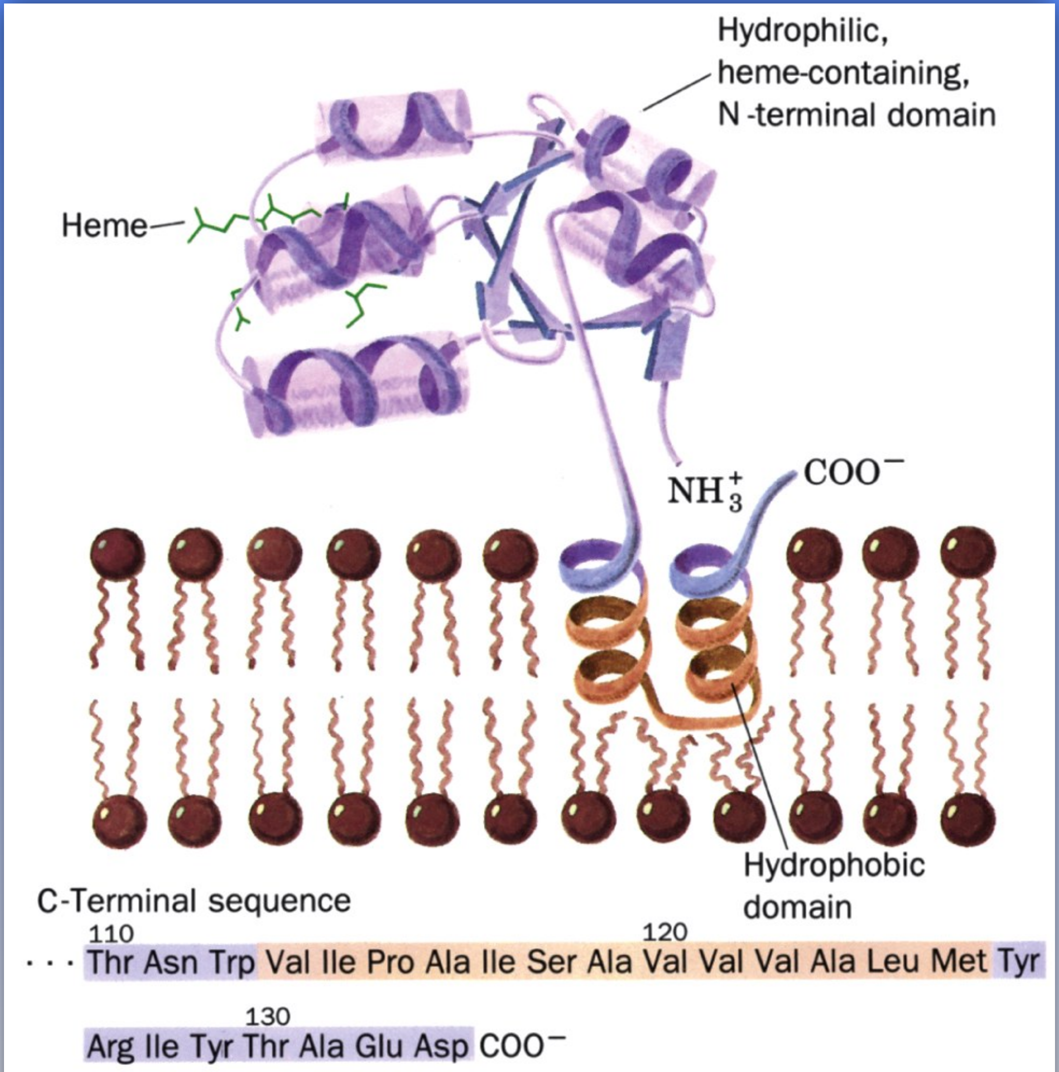


Figure 12-23

Another example of an integral membrane protein:

Cytochrome b_5. The hydrophobic segments anchor the active region of the protein to the membrane.

Porins are channel-forming proteins that contain transmembrane β barrels – they are present in the outer membranes of mitochondria and chloroplasts.

These proteins allow the membrane to become permeable to small polar molecules and ions.

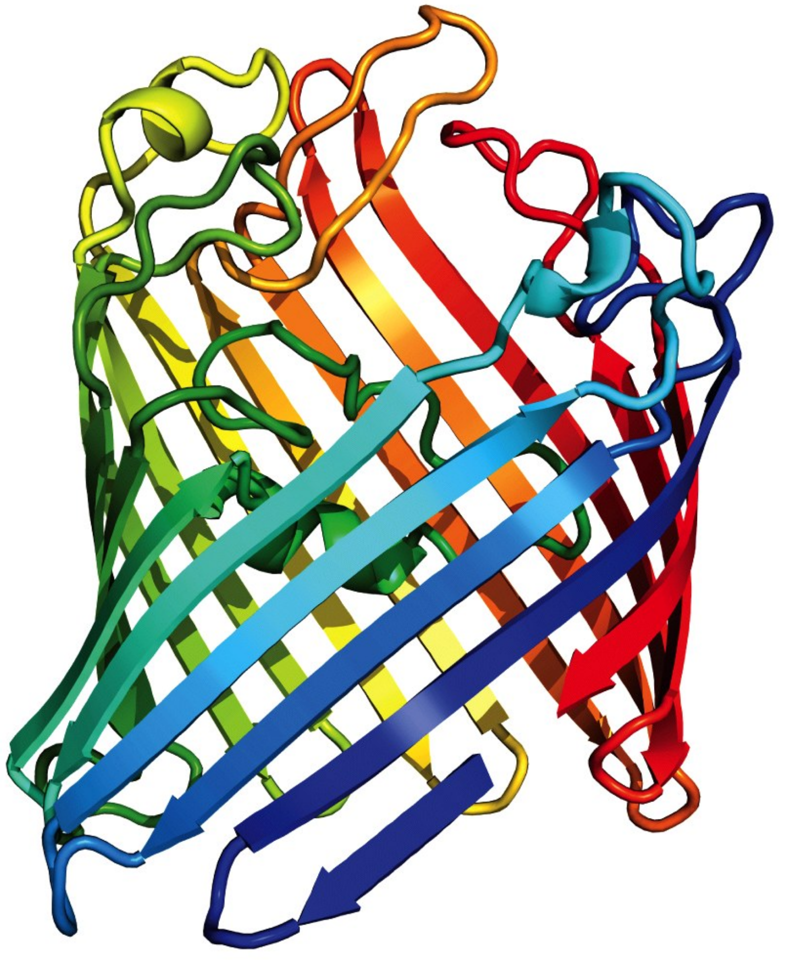


Figure 12-27a

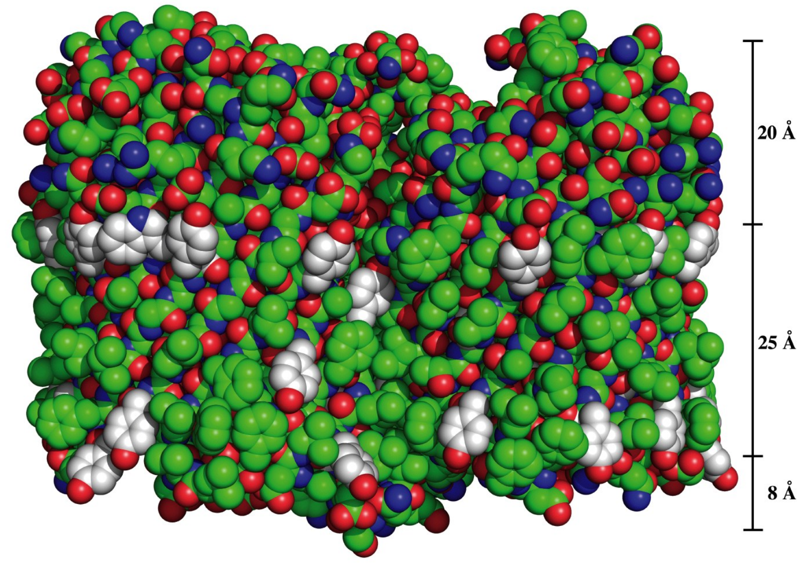


Figure 12-27c

Lipid-linked proteins: Lipids are covalently linked to the protein; the lipid portion anchors the attached protein to membranes and mediates protein-protein interactions in the membrane.

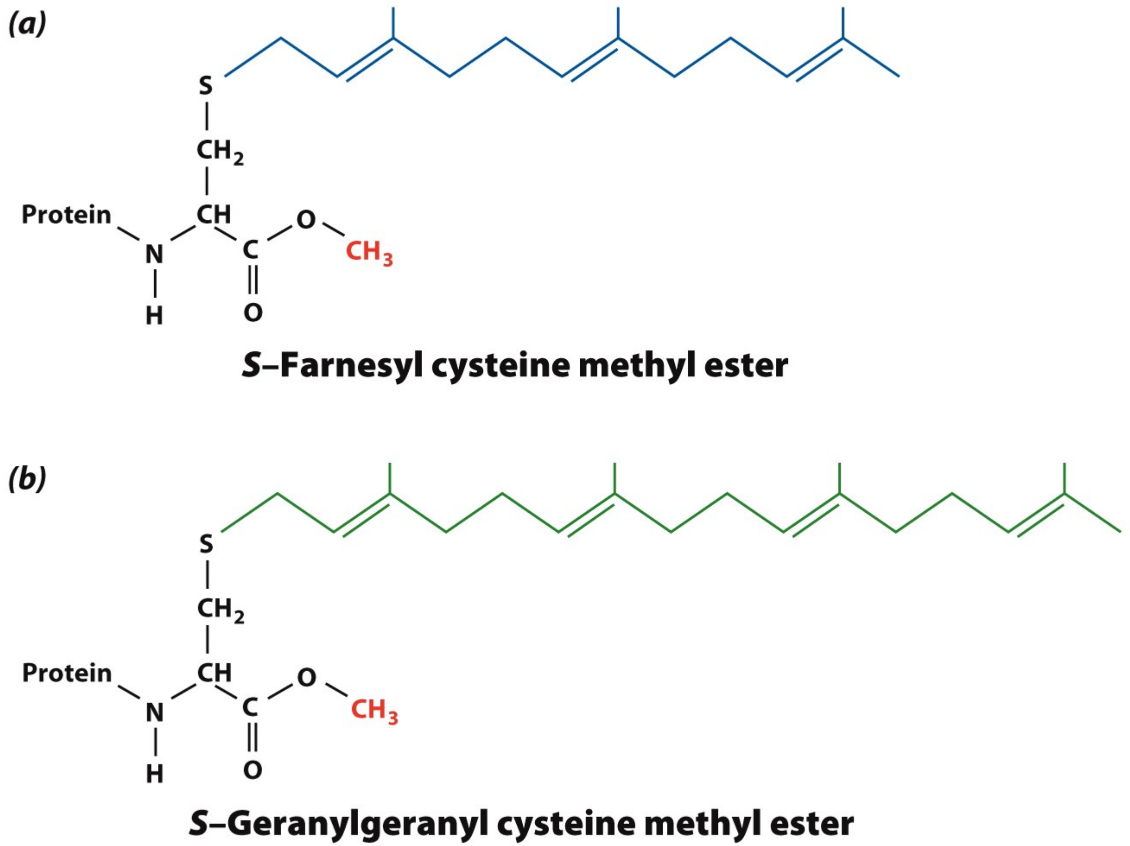
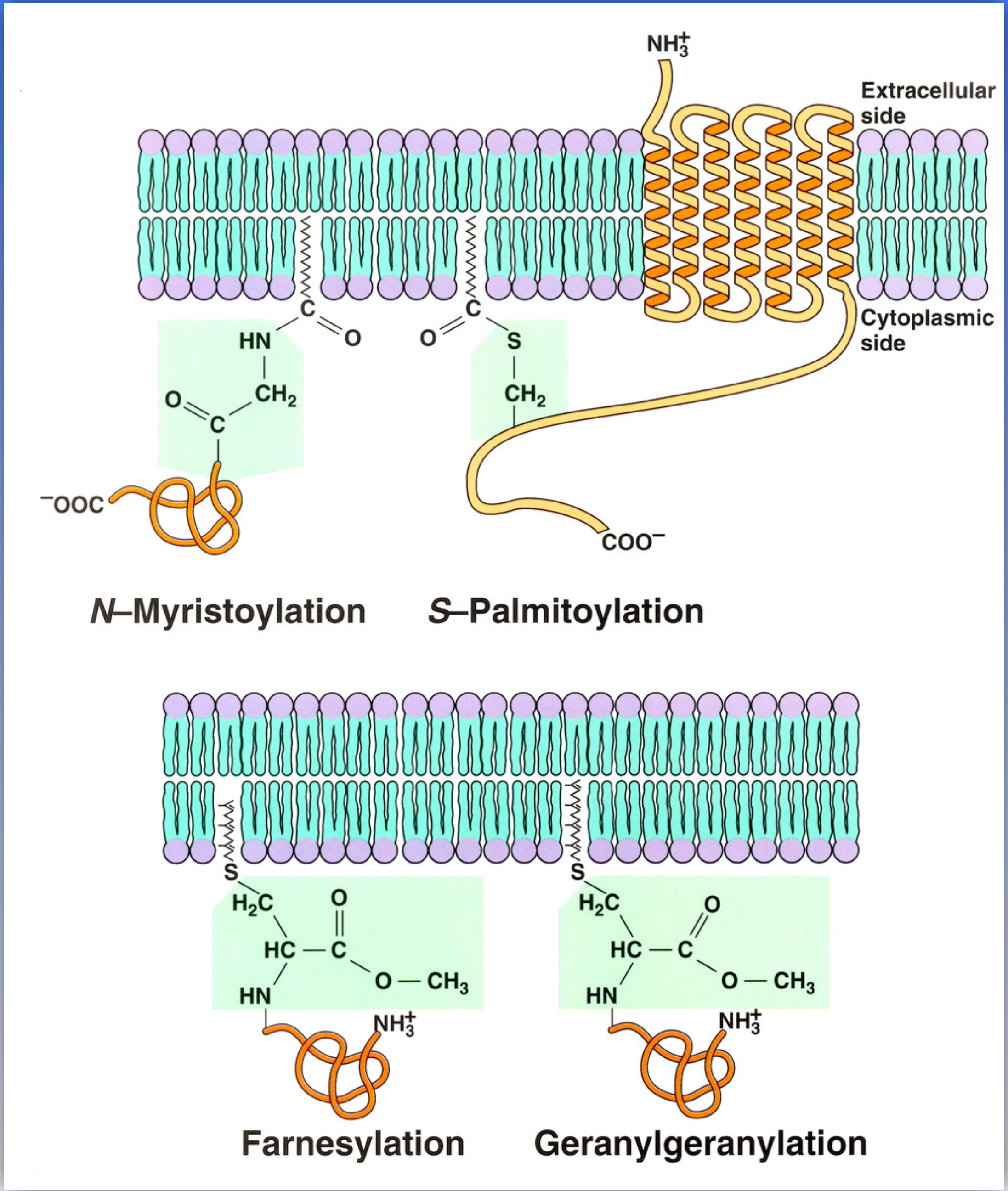


Figure 12-29

Prenylated proteins



Fatty acylated proteins

Lipid-linked proteins: GPI-linked proteins

Glycosylphosphatidylinositol groups function to anchor a wide variety of proteins to the exterior surface of eukaryotic plasma membrane (PM) - provide an alternative to transmembrane polypeptide domains in binding proteins to the PM.

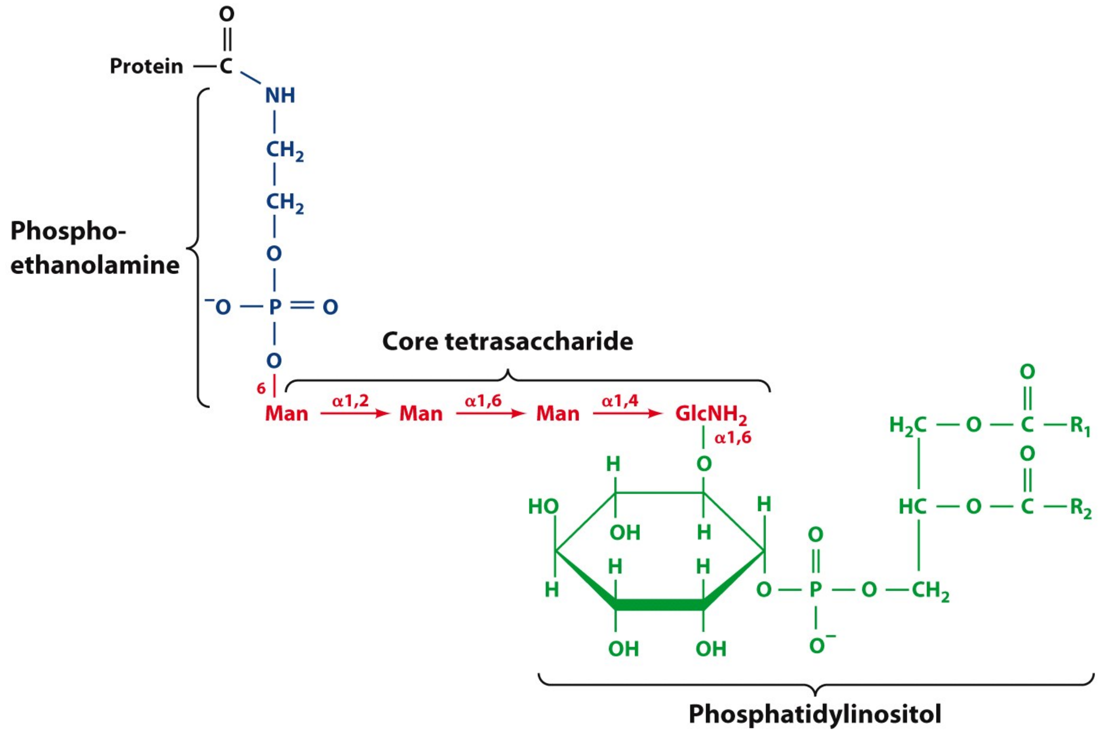


Figure 12-30

Occur on the exterior surface of the PM (asymmetric display)

The <u>fluid-mosaic</u> model of membrane structure has been experimentally verified.

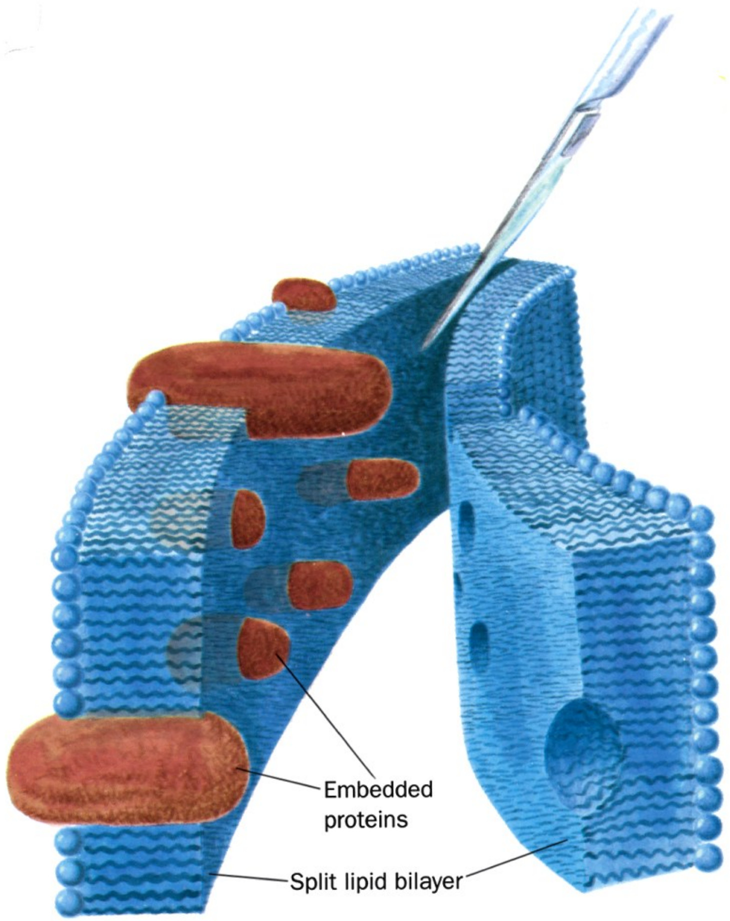


Figure 12-32

<u>The freeze-fracture technique</u>:

Splitting the membrane exposes the interior of the lipid bilayer and its embedded proteins.

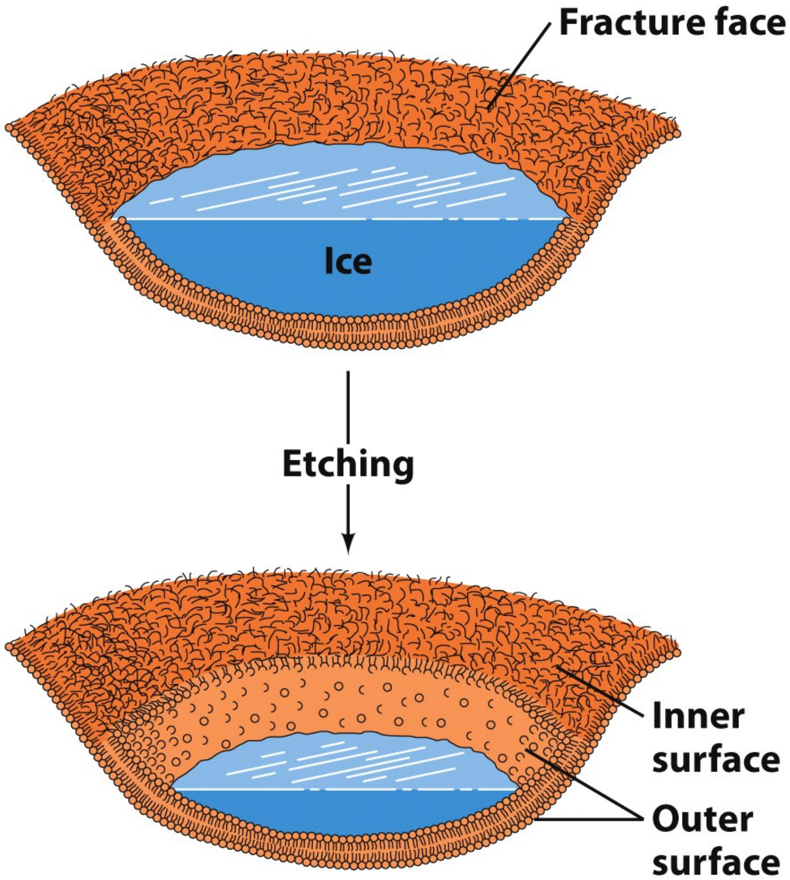


Figure 12-33

The freeze-etch procedure:

Ice that encases a freeze-fractured membrane is partially sublimed away so as to expose the outer membrane surface for electron microscopy.

The asymmetric distribution of phospholipids in the human erythrocyte membrane

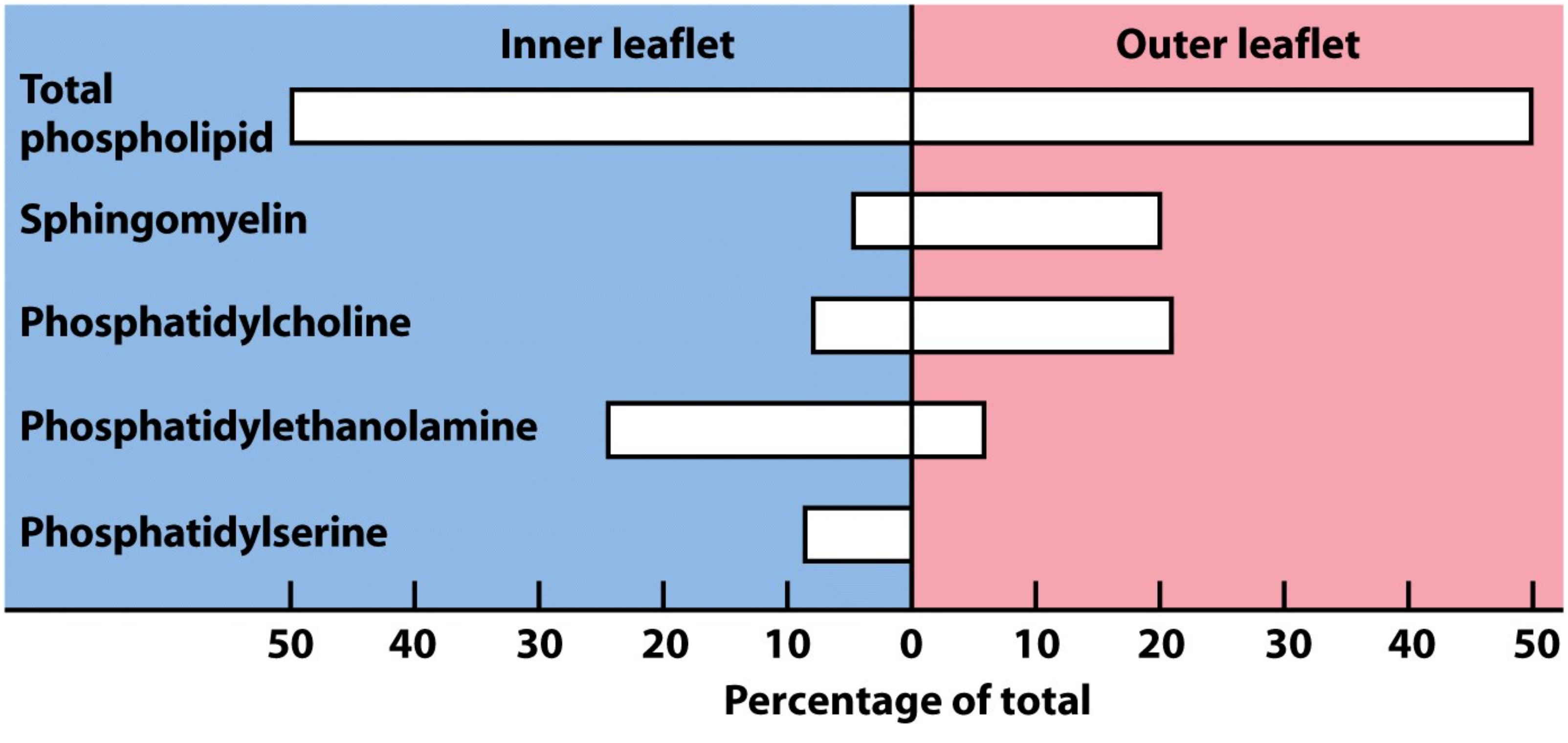


Figure 12-35

Lipids within the PM segregate to form microdomains that contain only certain types of lipids and proteins (*e.g.*, glyco-sphingolipid "rafts")

Lipid motion in membranes: hop diffusion

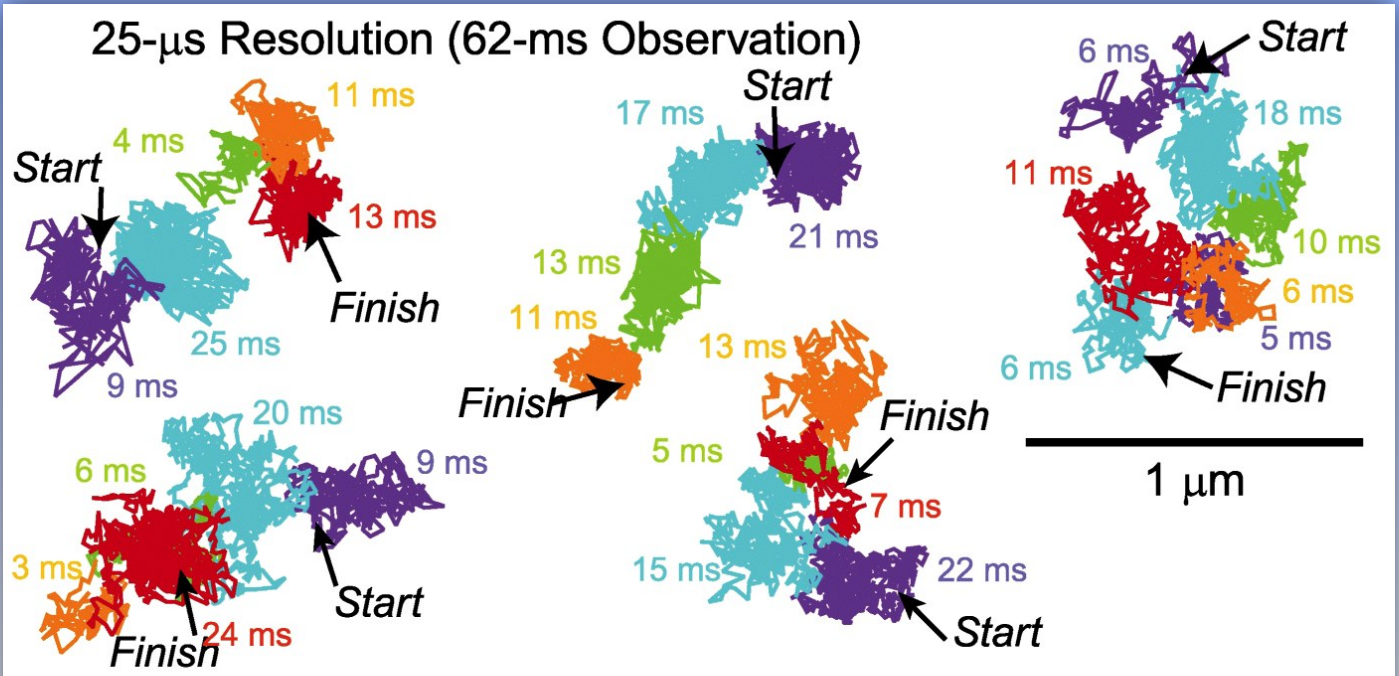


Figure 12-36
Courtesy of Akihiro Kasumi, Nagoya University, Japan

Structure of the human erythrocyte membrane

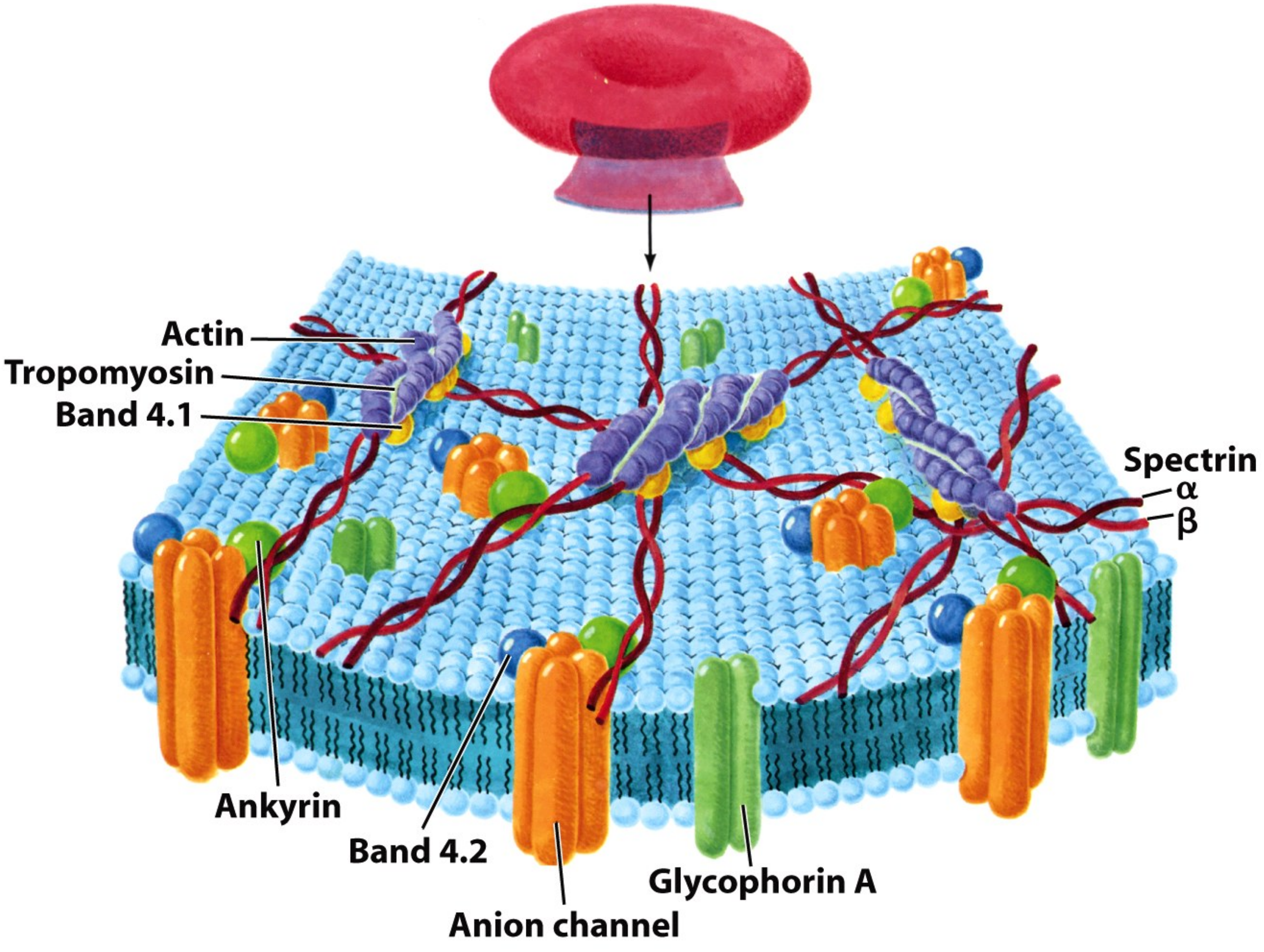


Figure 12-38d

The ABO blood group substances are carbohyrates attached to erythrocyte surface sphingoglycolipids.

Table 12-5 **Structures of the A, B, and H Antigenic Determinants in Erythrocytes**

Type	Antigen
H	Galβ(1 → 4)GlcNAc··· ↑ 1,2 L-Fucα
A	GalNAcα(1 → 3)Galβ(1 → 4)GlcNAc··· ↑ 1,2 L-Fucα
B	Galα(1 → 3)Galβ(1 → 4)GlcNAc··· ↑ 1,2 L-Fucα

Abbreviations: Gal = galactose, GalNAc = *N*-acetylgalactosamine, GlcNAc = *N*-acetylglucosamine, L-Fuc = L-fucose.

Table 12-5

Gap junctions: join discrete regions of neighboring PMs – allow the passage of small molecules between cells – an important form of intercellular communication

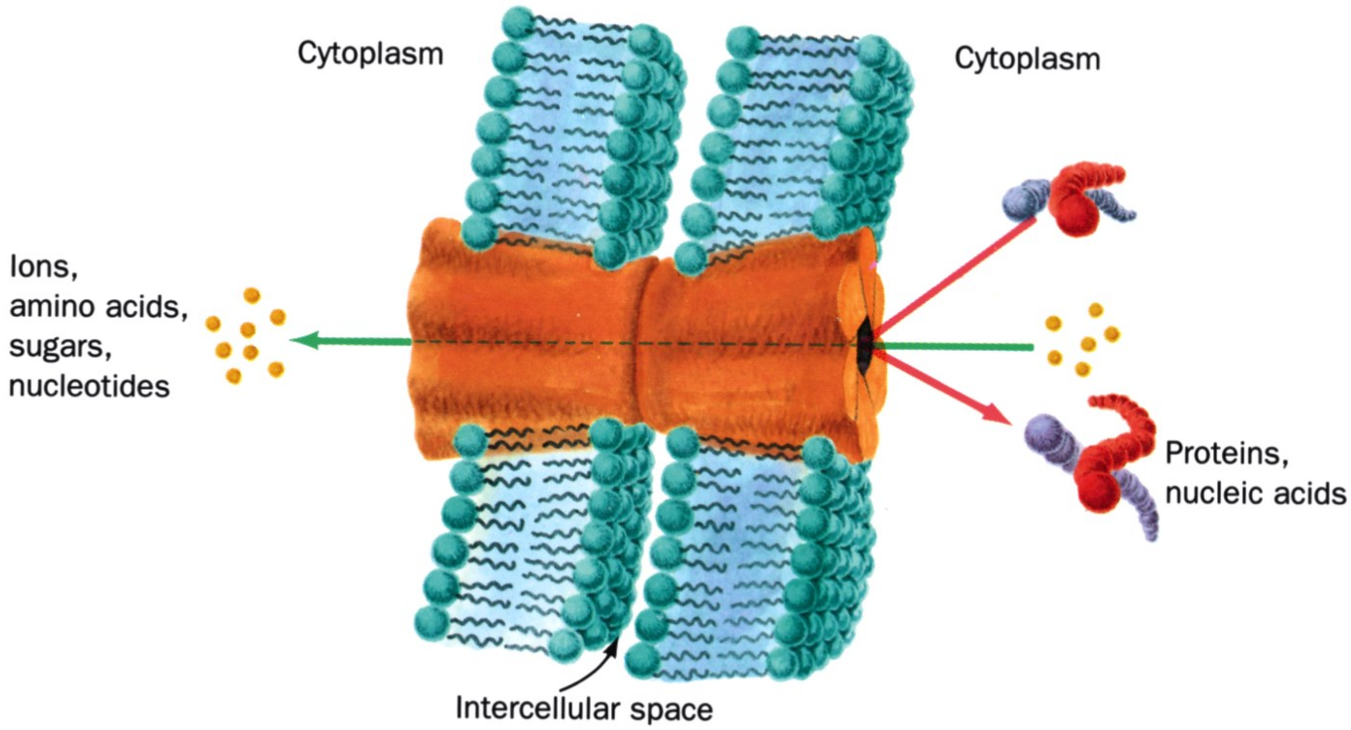


Figure 12-41

Lipoproteins in human plasma

Table 12-6 **Characteristics of the Major Classes of Lipoproteins in Human Plasma**

	Chylomicrons	VLDL	IDL	LDL	HDL
Density ($g \cdot cm^{-3}$)	<0.95	<1.006	1.006–1.019	1.019–1.063	1.063–1.210
Particle diameter (Å)	750–12,000	300–800	250–350	180–250	50–120
Particle mass (kD)	400,000	10,000–80,000	5000–10,000	2300	175–360
% Protein[a]	1.5–2.5	5–10	15–20	20–25	40–55
% Phospholipids[a]	7–9	15–20	22	15–20	20–35
% Free cholesterol[a]	1–3	5–10	8	7–10	3–4
% Triacylglycerols[b]	84–89	50–65	22	7–10	3–5
% Cholesteryl esters[b]	3–5	10–15	30	35–40	12
Major apolipoproteins	A-I, A-II, B-48, C-I, C-II, C-III, E	B-100, C-I, C-II, C-III, E	B-100, C-I, C-II, C-III, E	B-100	A-I, A-II, C-I, C-II, C-III, D, E

[a]Surface components.
[b]Core lipids.

Table 12-6

In lipoproteins, the lipid and the protein associate non-covalently. Lipoproteins serve in the blood plasma as transport vehicles for triacylglycerols and cholesterol.

Lipoproteins are globular micelle-like particles that consist of a nonpolar core of triacylglycerols and cholesterol esters surrounded by an amphiphilic coating of protein, phospholipid and cholesterol.

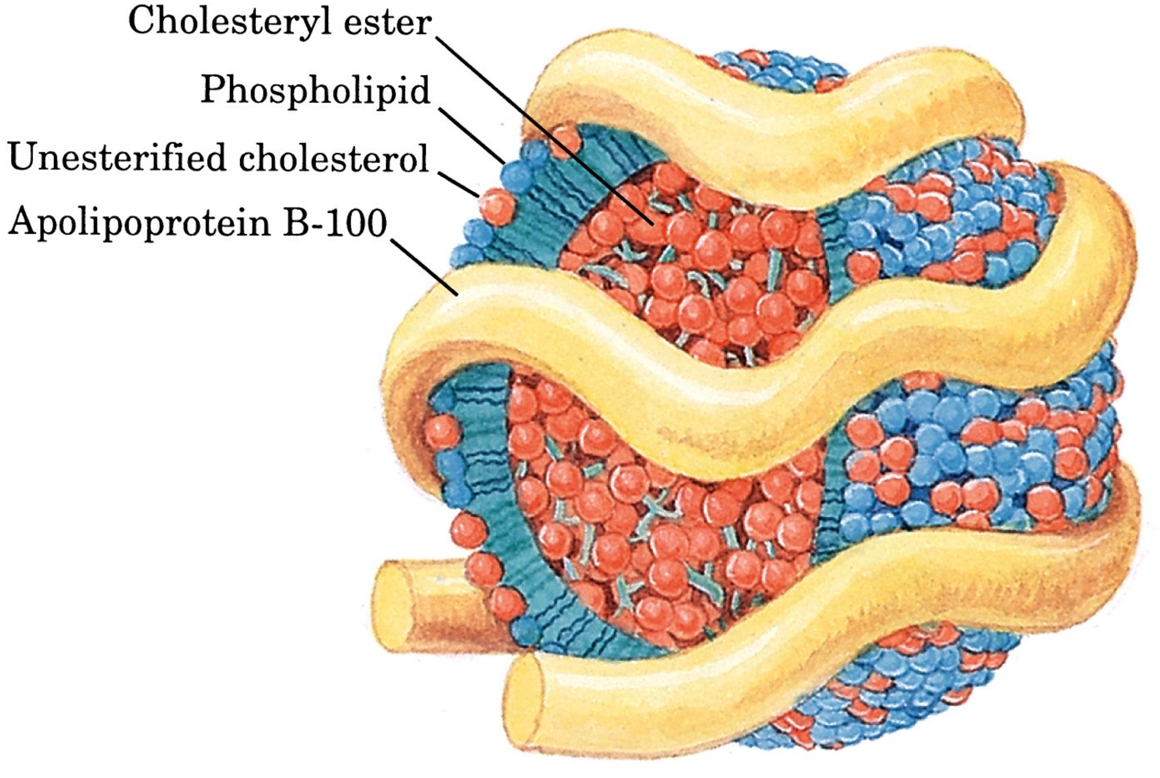


Figure 12-83

An example: low density lipoprotein (LDL)

Table 12-7 Properties of the Major Species of Human Apolipoproteins

Apolipoprotein	Number of Residues	Molecular Mass[a] (kD)	Function
A-I	243	29	Activates LCAT[b]
A-II	77	17	Inhibits LCAT, activates hepatic lipase
B-48	2152	241	Cholesterol clearance
B-100	4536	513	Cholesterol clearance
C-I	56	6.6	Activates LCAT?
C-II	79	8.9	Activates LPL[c]
C-III	79	8.8	Inhibits LPL, activates LCAT?
D	169	19	Unknown
E	299	34	Cholesterol clearance

[a]All apolipoproteins are monomers but apoA-II, which is a disulfide-linked dimer.
[b]LCAT = lecithin–cholesterol acyltransferase.
[c]LPL = lipoprotein lipase.

Table 12-7

Apolipoproteins have amphipathic helices that coat lipoprotein surfaces.

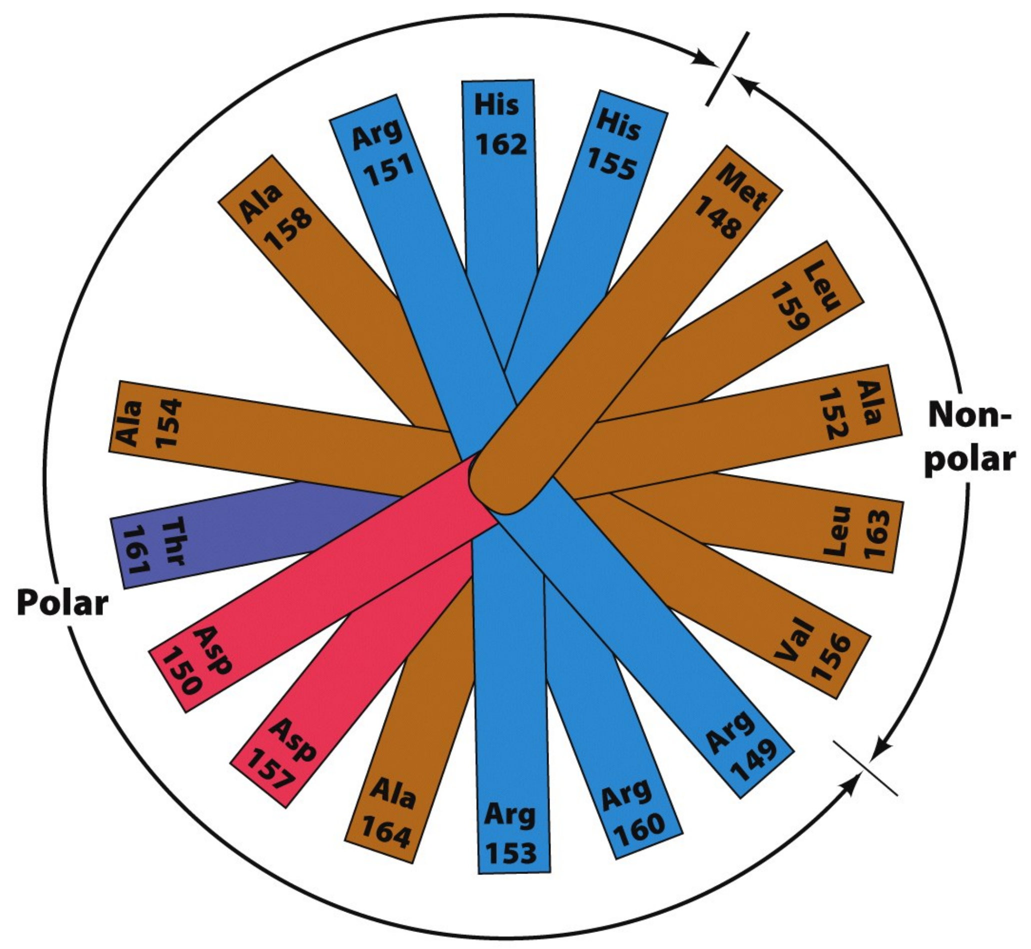


Figure 12-84

Helical wheel projection of the amphipathic α-helix constituting residues 148-164 of apolipoprotein A-I

Model for plasma triacylglycerol and cholesterol transport in humans

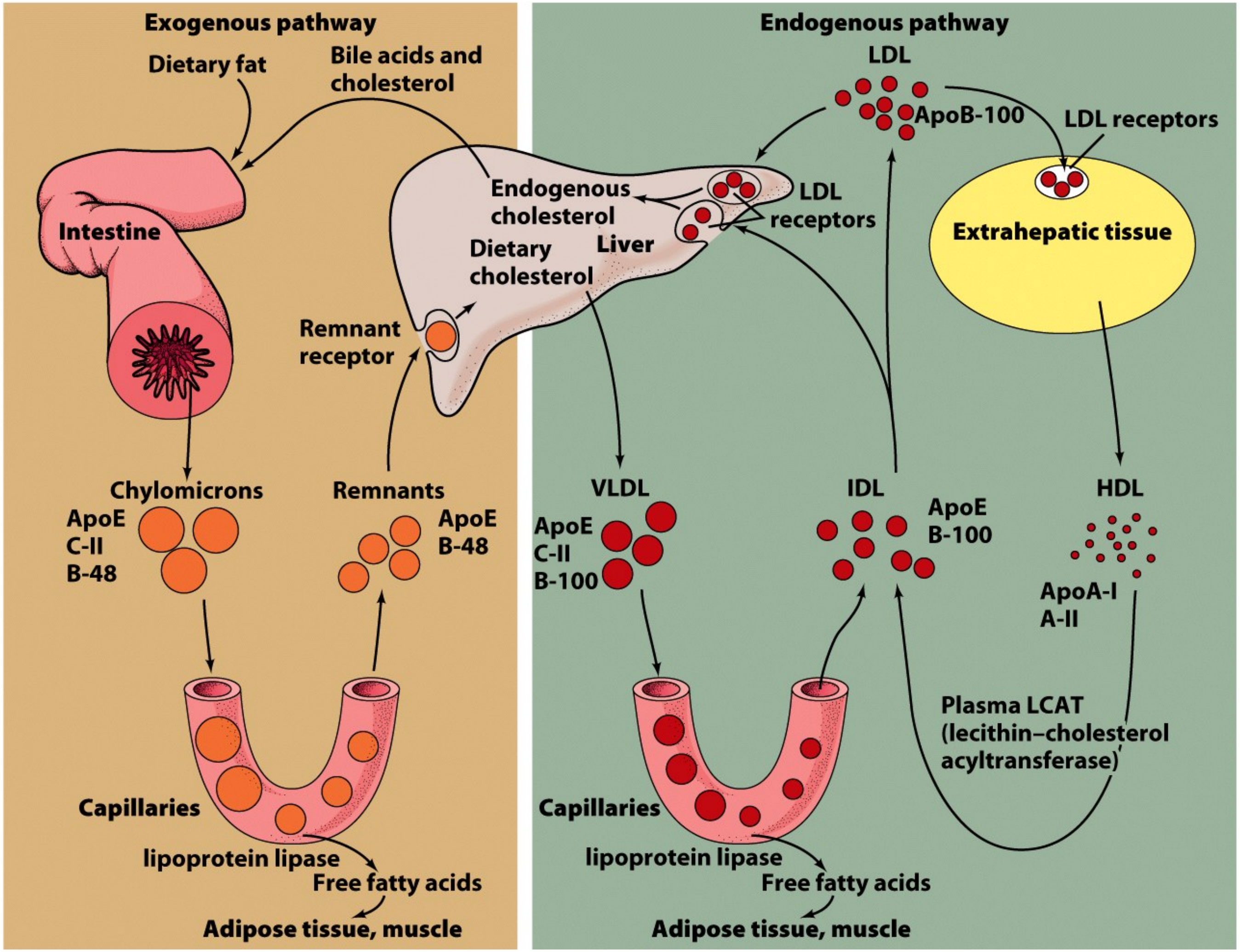
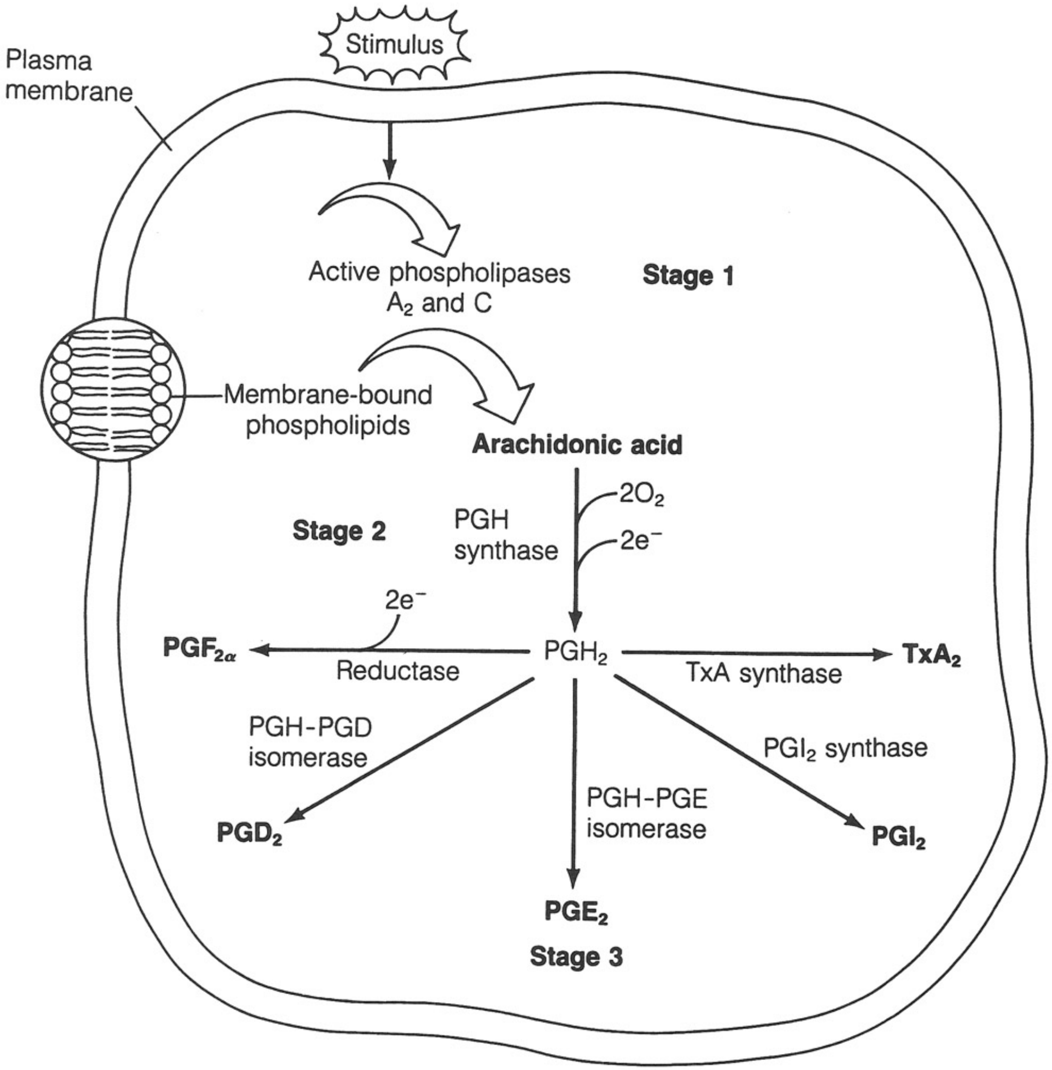
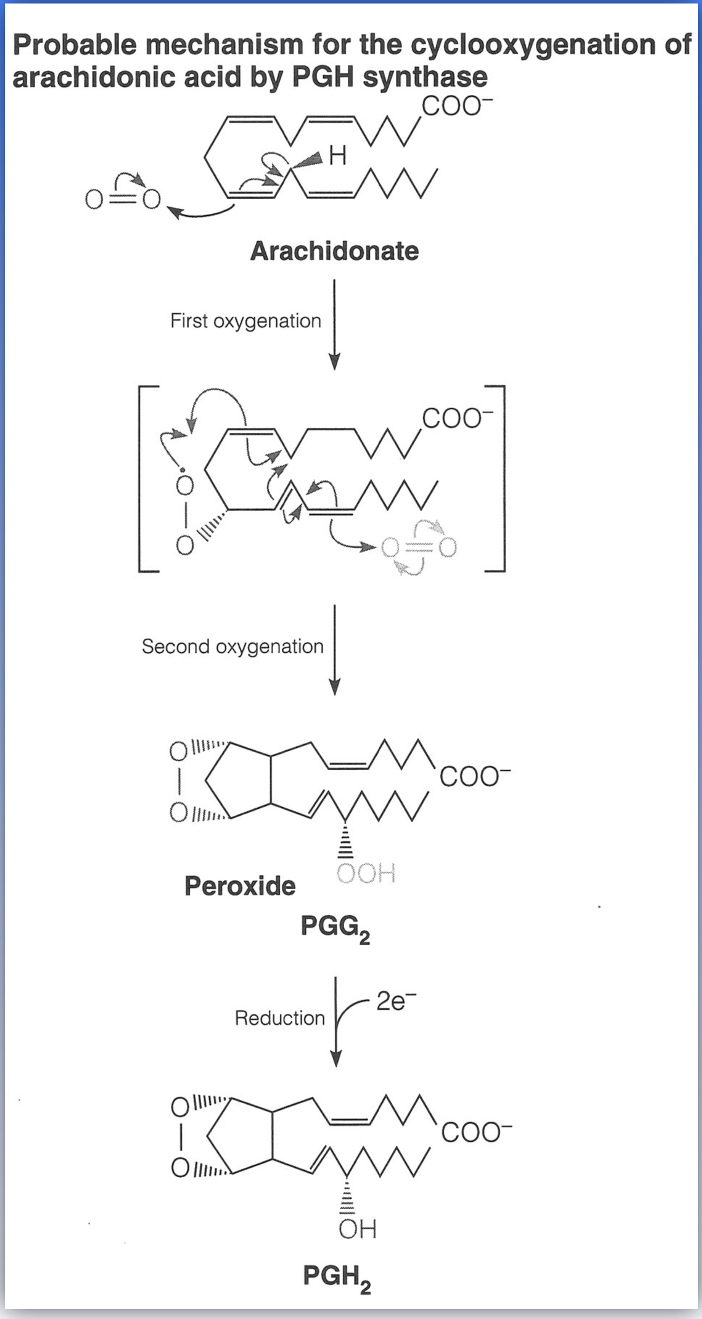


Figure 12-86

Summary of biosynthetic routes to the major prostaglandins and thromboxane A_2



The unsaturated fatty acid, arachidonic acid, is the key precursor in the biosynthesis of prostaglandins and thromboxanes.



Proposed mechanism for the conversion of arachidonate to PGG_2 and PGH_2 by the enzyme, PGH synthase. This enzyme is inhibited by aspirin.