Biochemistry of Lipids

1

Classification.
Digestion and absorption.
Membrane structure and functions.

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PhD, assistant

Lipid: Definition

Biological molecules that are insoluble in aqueous solutions and soluble in organic solvents are classified as **lipids**.

Lipids have diverse structures, but are similar in that they are insoluble in water.

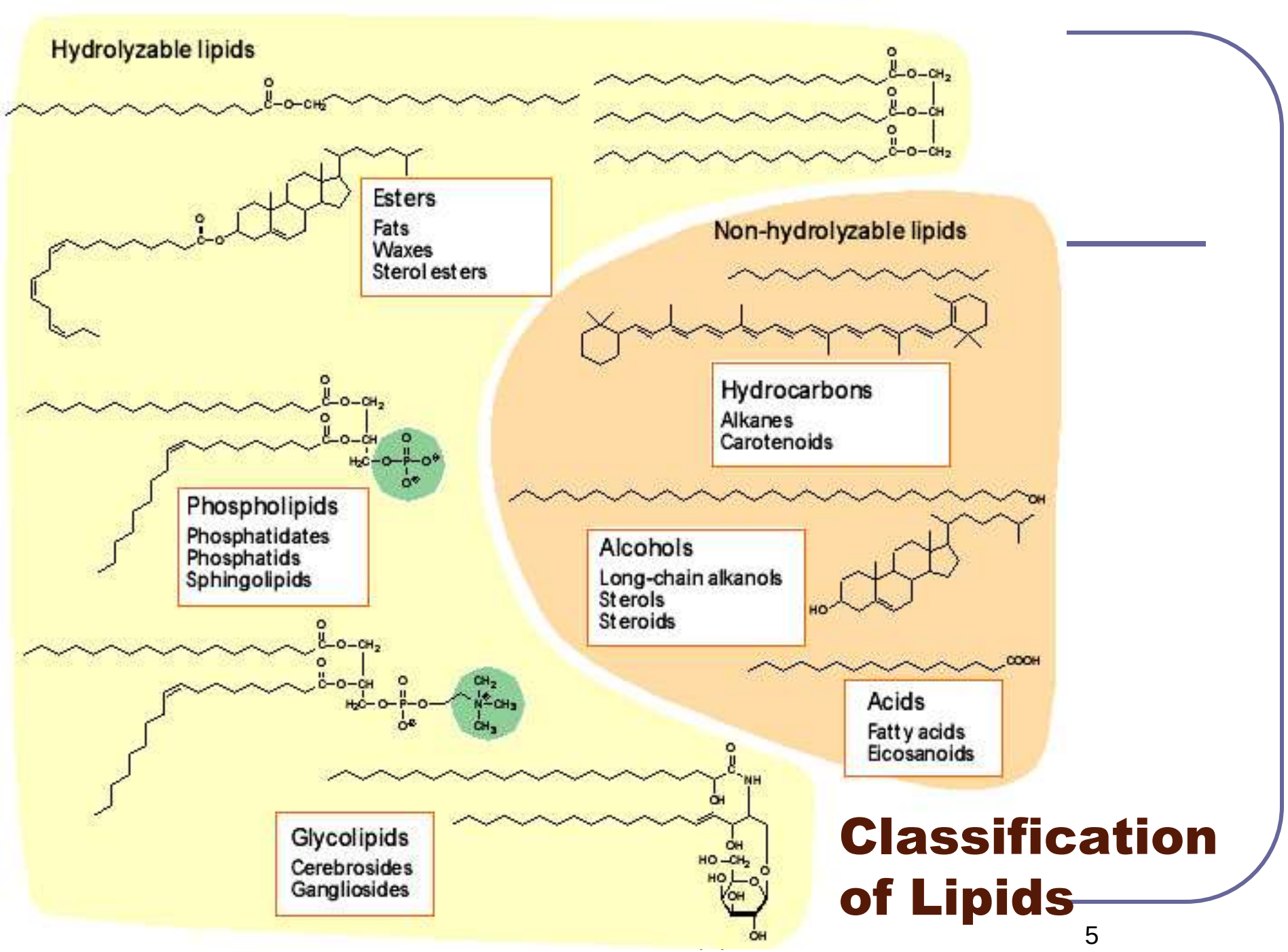
Major Roles of Biological Lipids

The lipids of physiological importance for humans have **four major functions**:

1. Structural components of biological membranes
2. Energy reserves (triacylglycerols)
3. Vitamins and hormones
4. Lipid solubilization (bile acids)

Fatty acids

- **Fatty acids** are long-chain hydrocarbon molecules containing a carboxylic acid moiety at one end.
  - usually even number of carbon atoms (16 – 20) lenght
  - saturated or unsaturated (*see lipids.pdf*)
- The numbering of carbons in fatty acids begins with the carbon of the *carboxylate* group.
  - Carboxyl group is ionized, fatty acids become negatively charged.

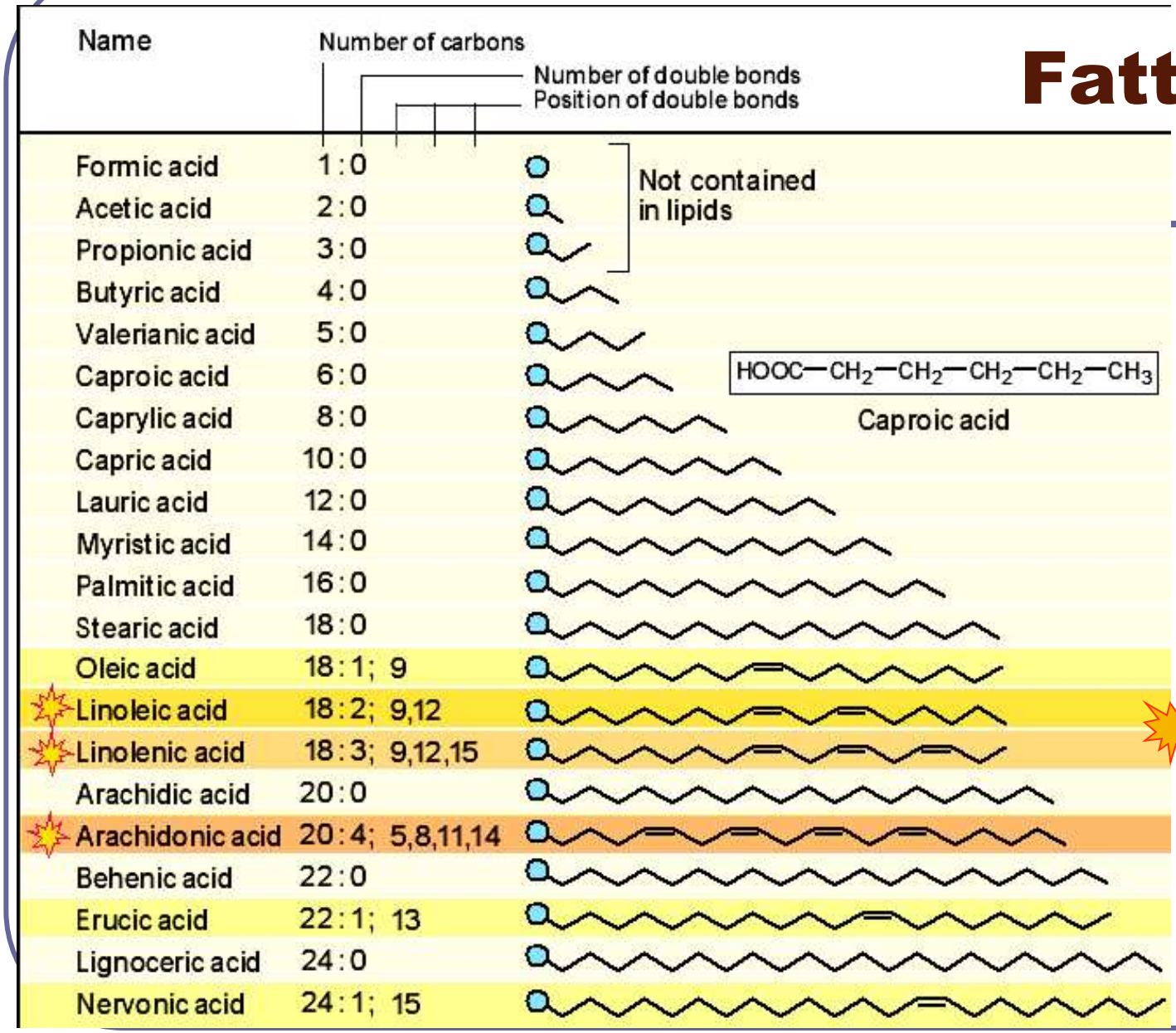


Classification of Lipids

Fatty Acids: Role

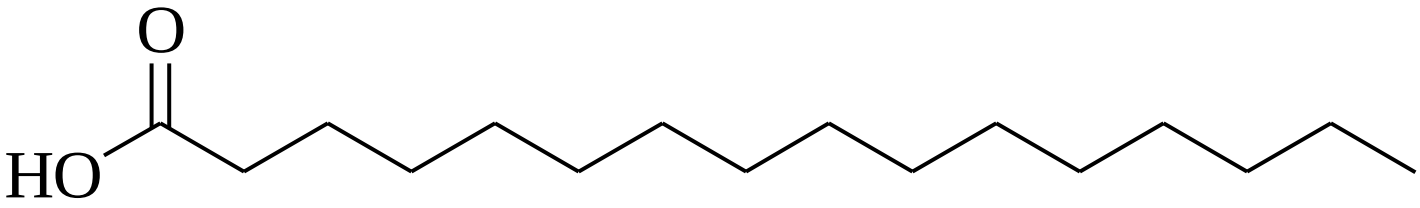
- **Fatty acids (FA)** fill two major roles in the body:
  1. as the components of more complex membrane lipids.
  2. as the major components of stored fat in the form of triacylglycerols.

Fatty Acids Table

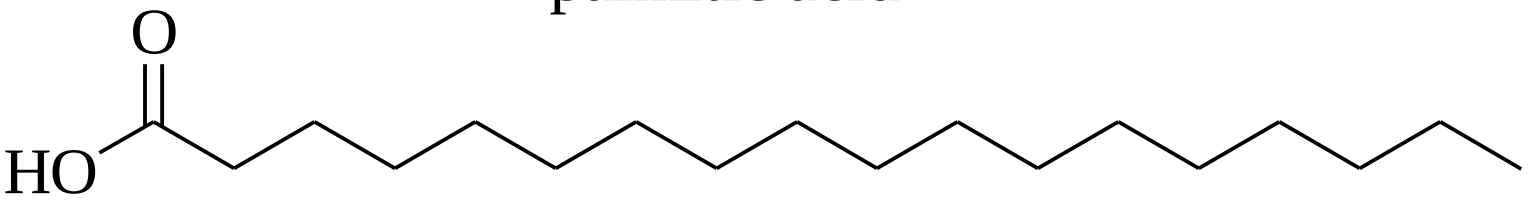


ω-3 & ω-6 unsaturated FA are essential in human nutrition

Numeric Designations Used for Fatty Acids (1)



palmitic acid

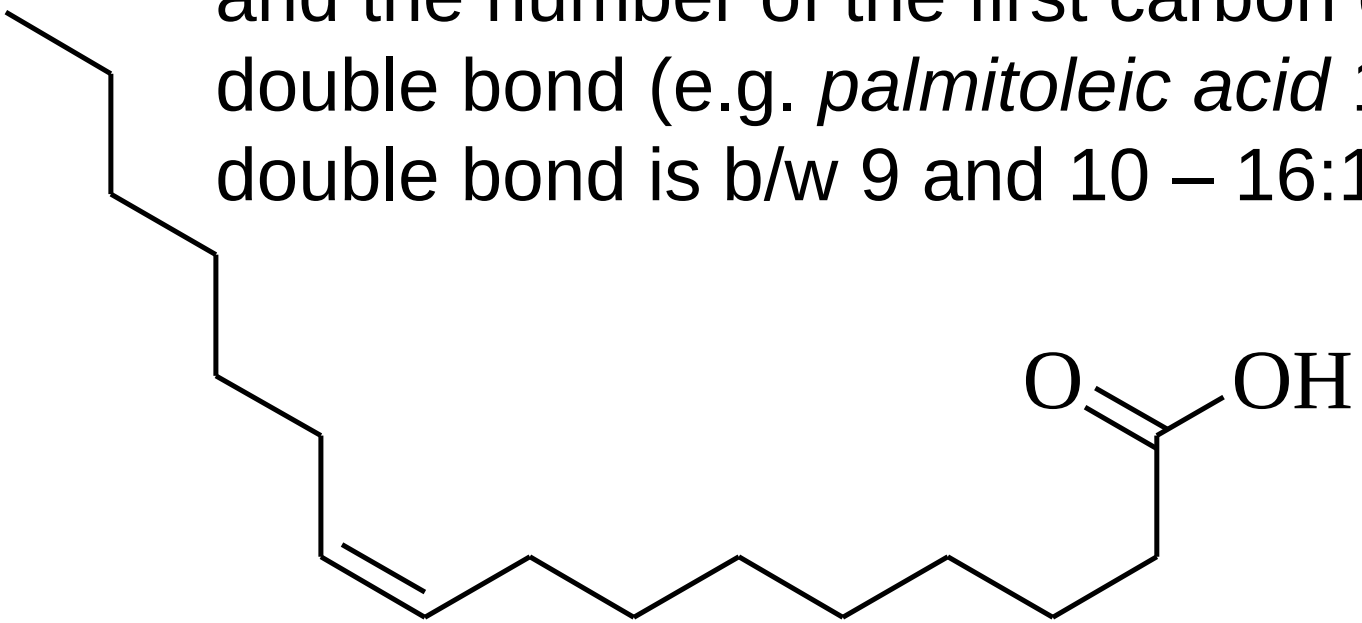


stearic acid

- **Number of carbon atoms**, number of sites of unsaturation (eg, *palmitic acid* is a 16-C FA with no unsaturation and is designated by 16:0).
- Stearic acid – 18:0.

Numeric Designations Used for Fatty Acids (2)

- **The site of unsaturation** is indicated by Δ and the number of the first carbon of the double bond (e.g. *palmitoleic acid* 16-C, double bond is b/w 9 and 10 – $16:1^{\Delta 9}$).

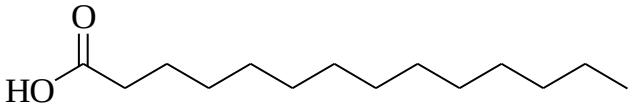
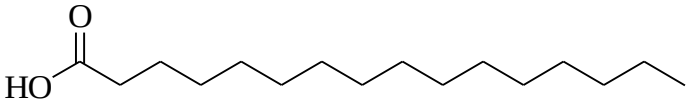
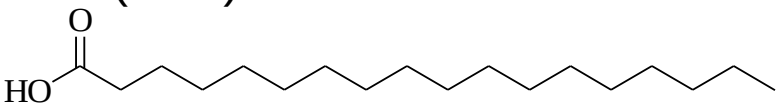


palmitoleic acid

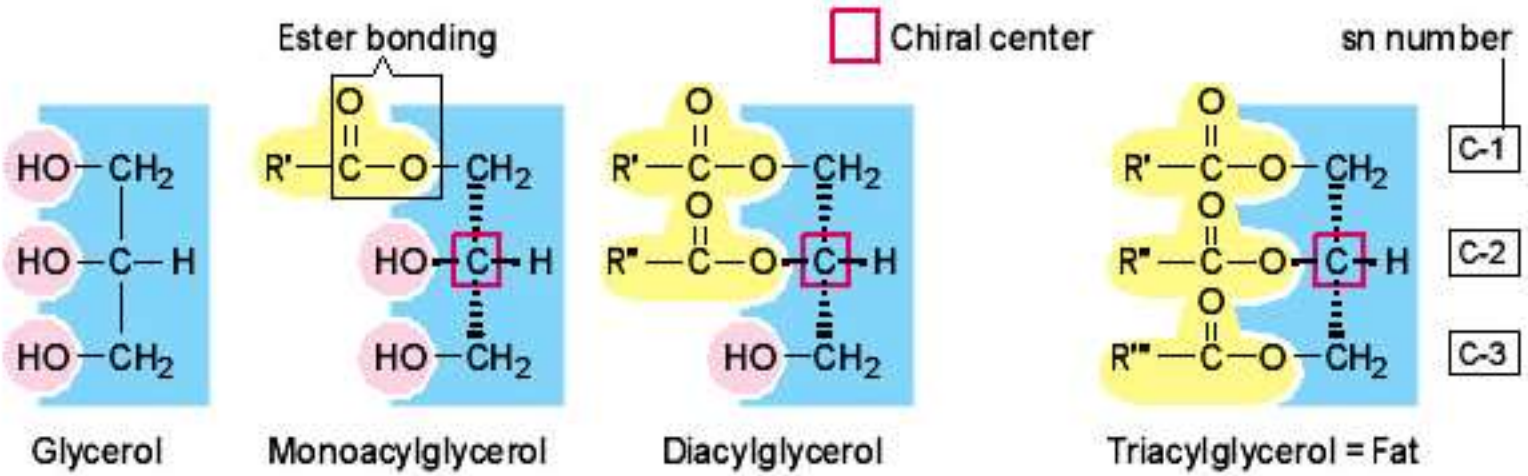
Physical Properties of Fatty Acids

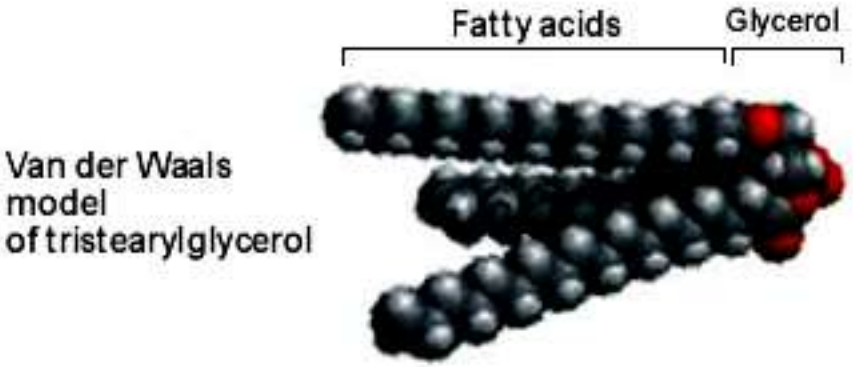
- Saturated FA of less than 8 C atoms are liquid at physiological °t, more than 10 – solid.
- The presence of double bonds in FA lowers the melting point relative to a saturated FA.

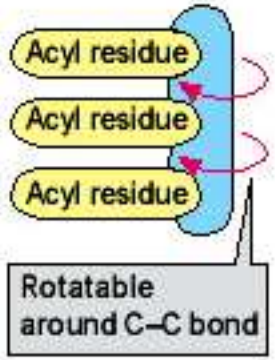
Physiologically Relevant Fatty Acids

Num Symbol	Common Name	Structure	Comments
14:0	Myristic acid	$CH_3(CH_2)_{12}COOH$ 	Often found attached to the N-term. of plasma memb.-assoct'd cytoplasmic proteins
16:0	Palmitic acid	$CH_3(CH_2)_{14}COOH$ 	End product of mammalian fatty acid synthesis
$16:1^{\Delta 9}$	Palmitoleic acid	$CH_3(CH_2)_5C{=}C(CH_2)_7COOH$	
18:0	Stearic acid	CH3(CH2)16COOH 	

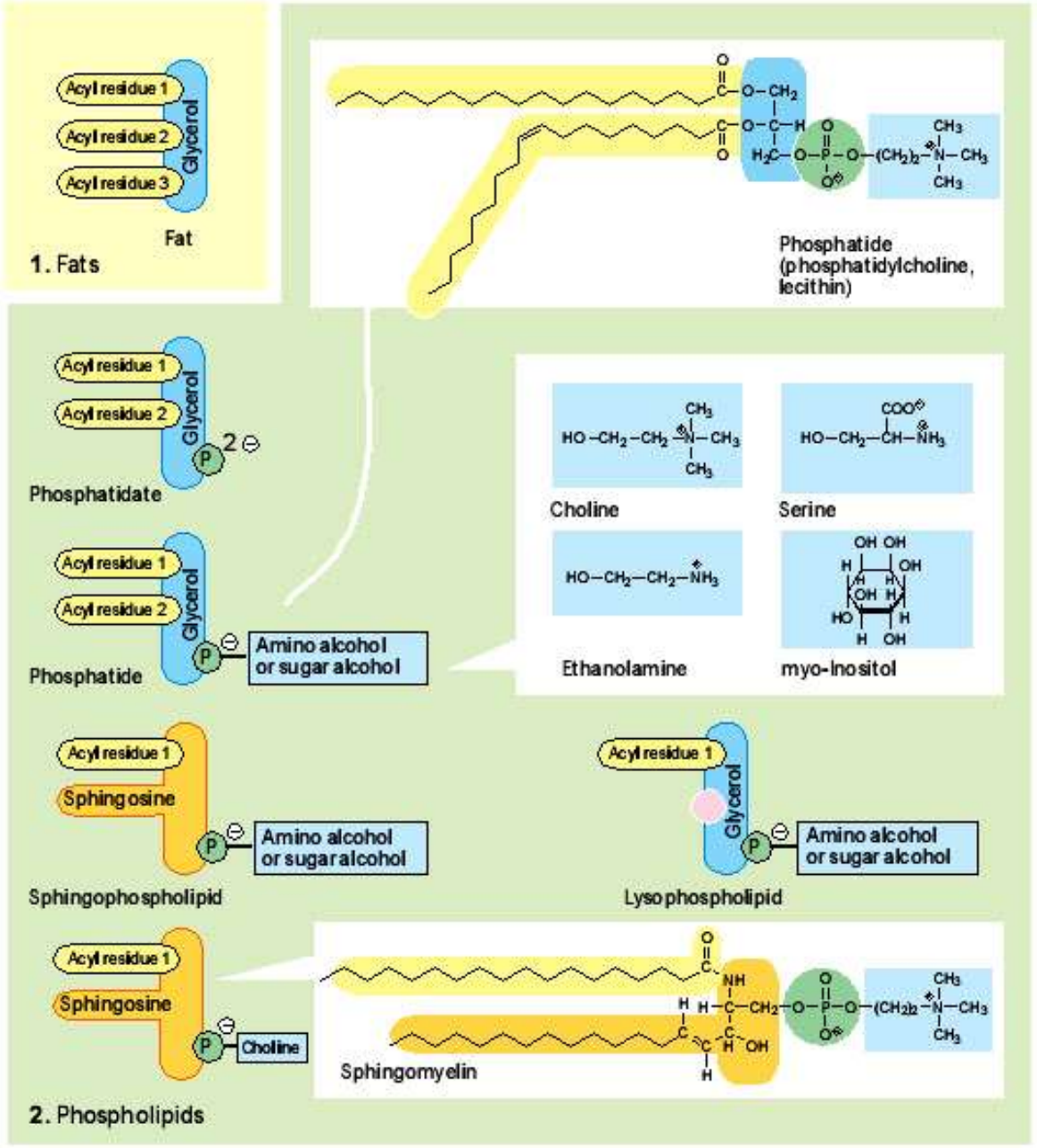
Structure of Fats





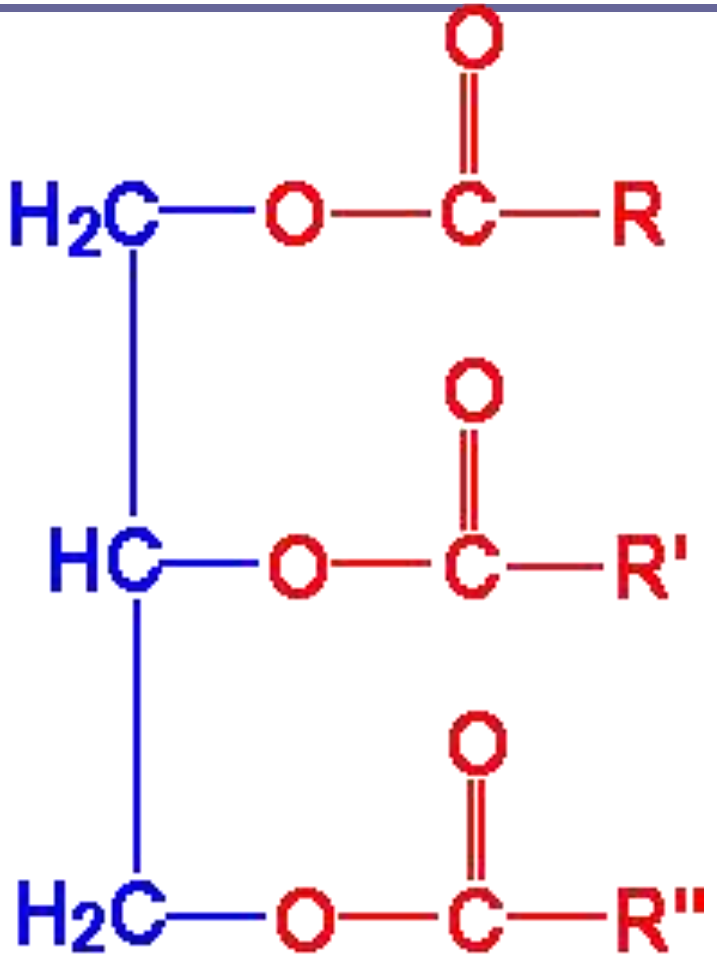


Structure of Fats and Phospho-lipids



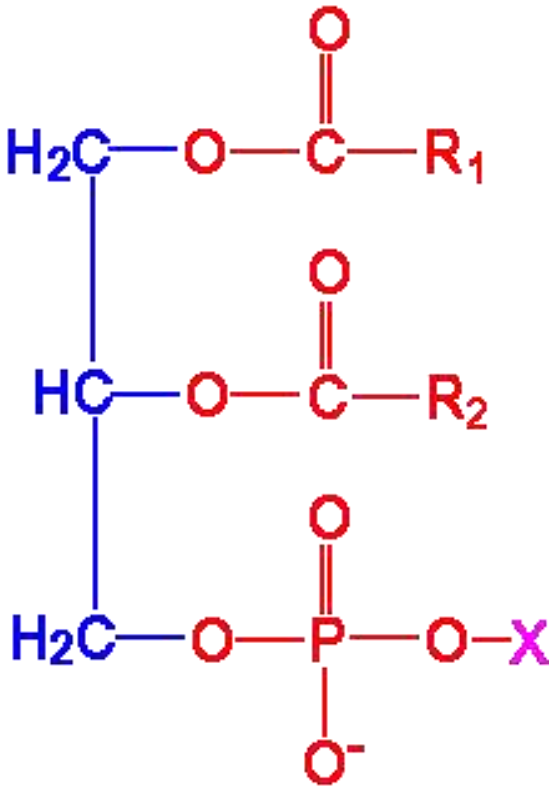
Basic Structure of Triacylglycerides

- Triacylglycerides are composed of a glycerol backbone to which 3 fatty acids are esterified.
  - Basic composition of a triacylglyceride. The glycerol backbone is in blue.



Basic Structure of Phospholipids

- The basic structure of phospolipids is very similar to that of the triacylglycerides except that C-3 of the glycerol backbone is esterified to phosphoric acid. The building block of the phospholipids is **phosphatidic acid** which results when the X substitution in the basic structure is a hydrogen atom.
  - Basic composition of a phospholipid. X can be a number of different substituents.

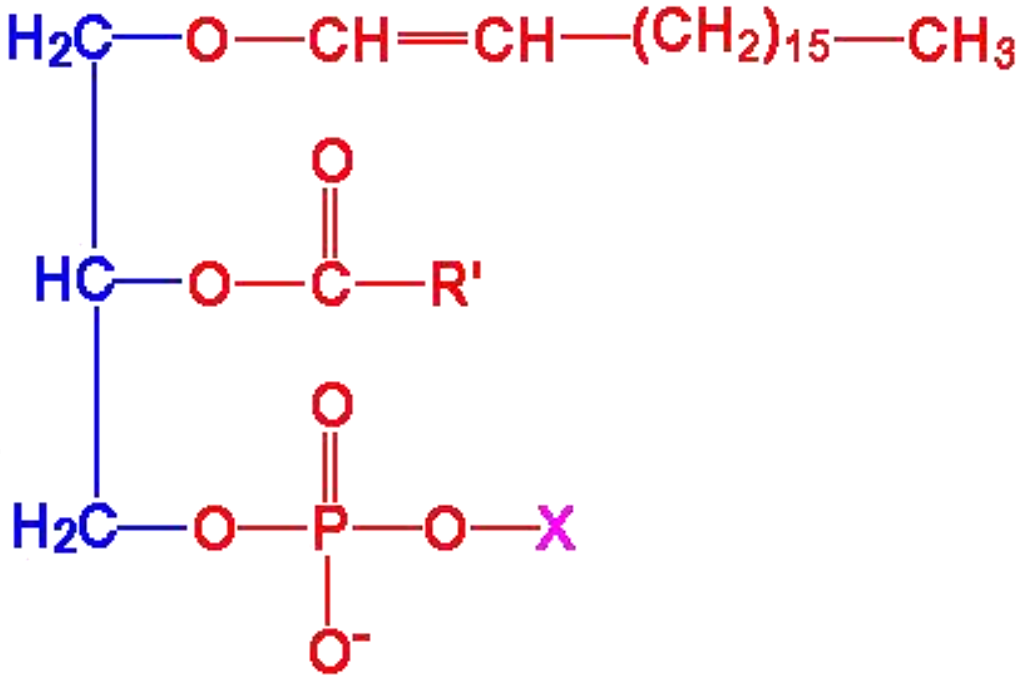


Phospholipids: Types

- Substitutions include
  - ethanolamine (**phosphatidylethanolamine**),
  - choline (**phosphatidylcholine**, also called **lecithins**),
  - serine (**phosphatidylserine**),
  - glycerol (**phosphatidylglycerol**),
  - myo-inositol (**phosphatidylinositol**).
- these compounds can have a variety in the numbers of inositol alcohols that are phosphorylated generating polyphosphatidylinositols), and phosphatidylglycerol (diphosphatidylglycerol more commonly known as **cardiolipins**).

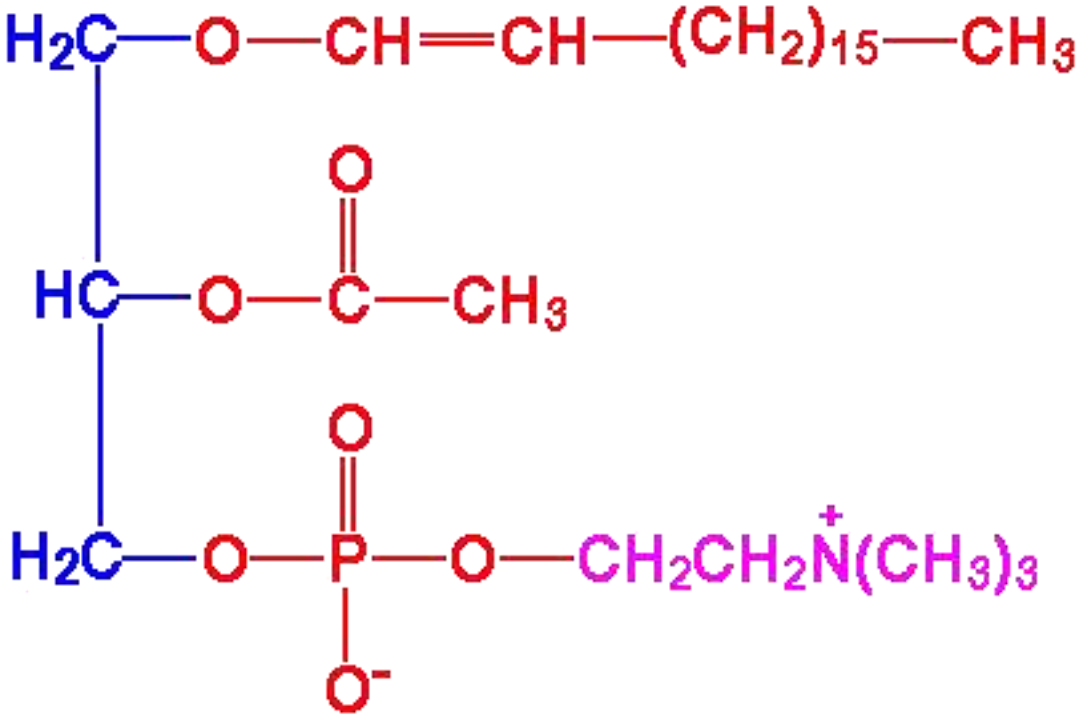
Basic Structure of Plasmalogens

- Plasmalogens are complex membrane lipids that resemble phospholipids, principally phosphatidylcholine. The major difference is that the fatty acid at C-1 of glycerol contains either an O-alkyl or O-alkenyl ether species.
  - basic composition of *O*-alkenyl plasmalogens

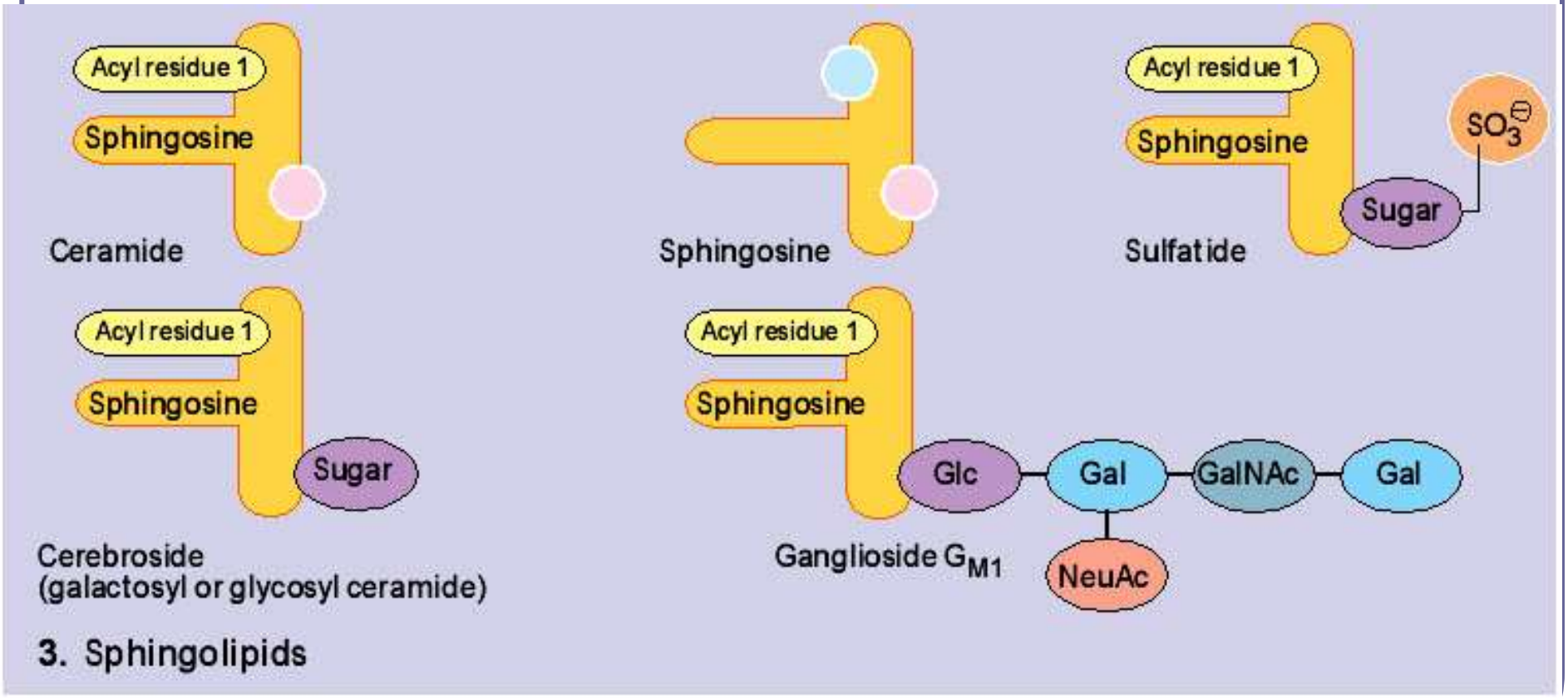


Platelet Activating Factor

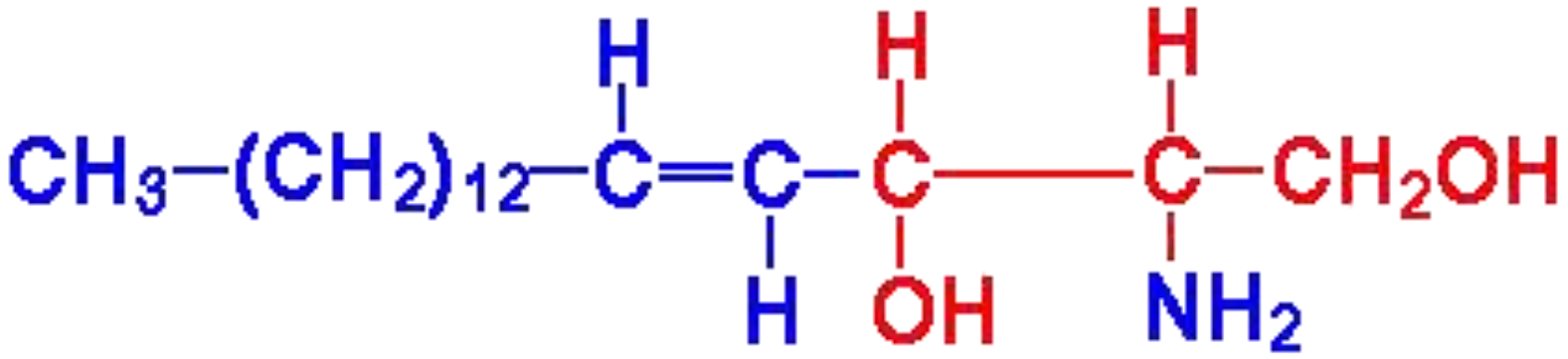
- One of the most potent biological molecules is **platelet activating factor** (PAF) which is a choline plasmalogen in which the C-2 position of glycerol is esterified with an acetyl group instead of a long chain fatty acid.
  - structure of PAF



Structure of Sphingolipids

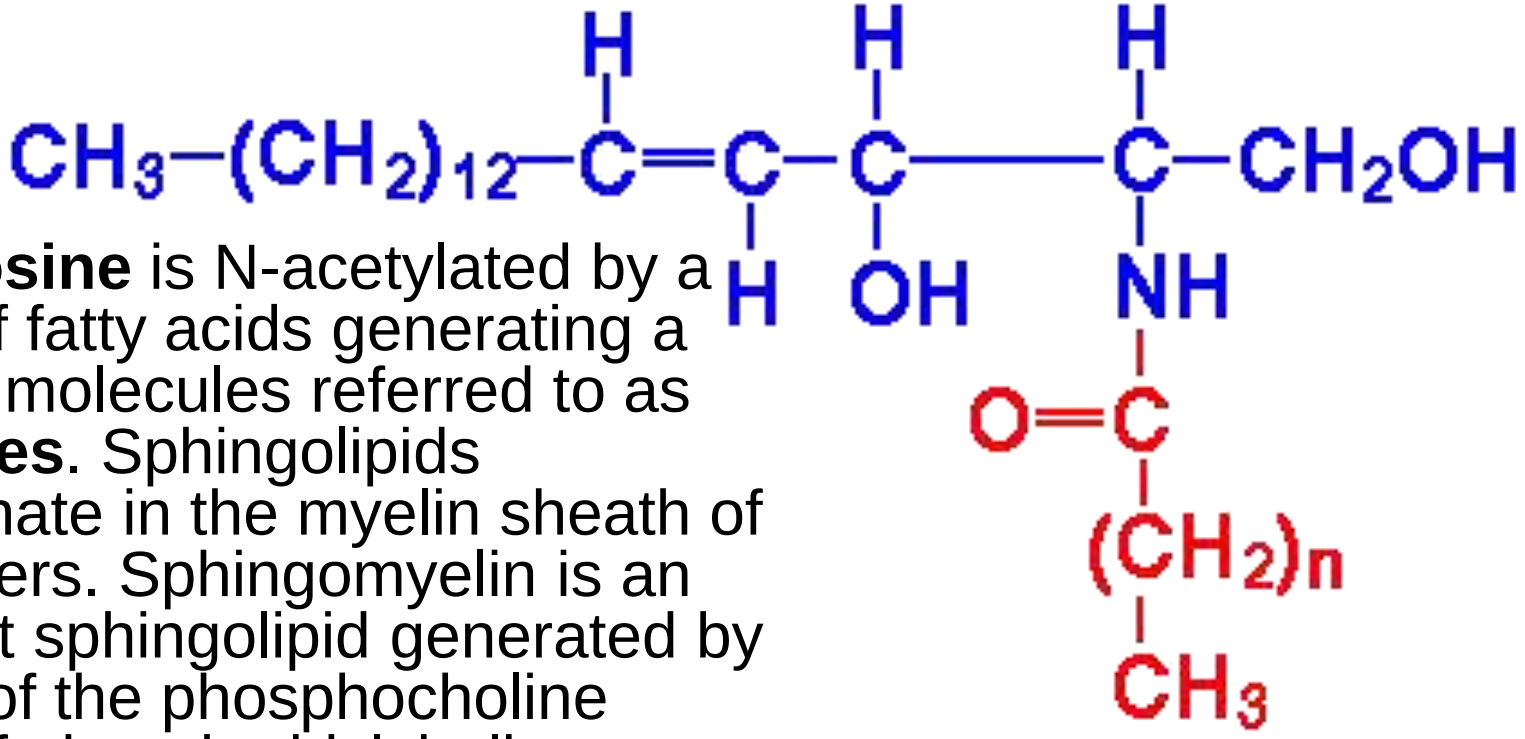


Basic Structure of Sphingolipids



- Sphingolipids are composed of a backbone of **sphingosine** which is derived itself from glycerol.

Basic composition of a ceramide

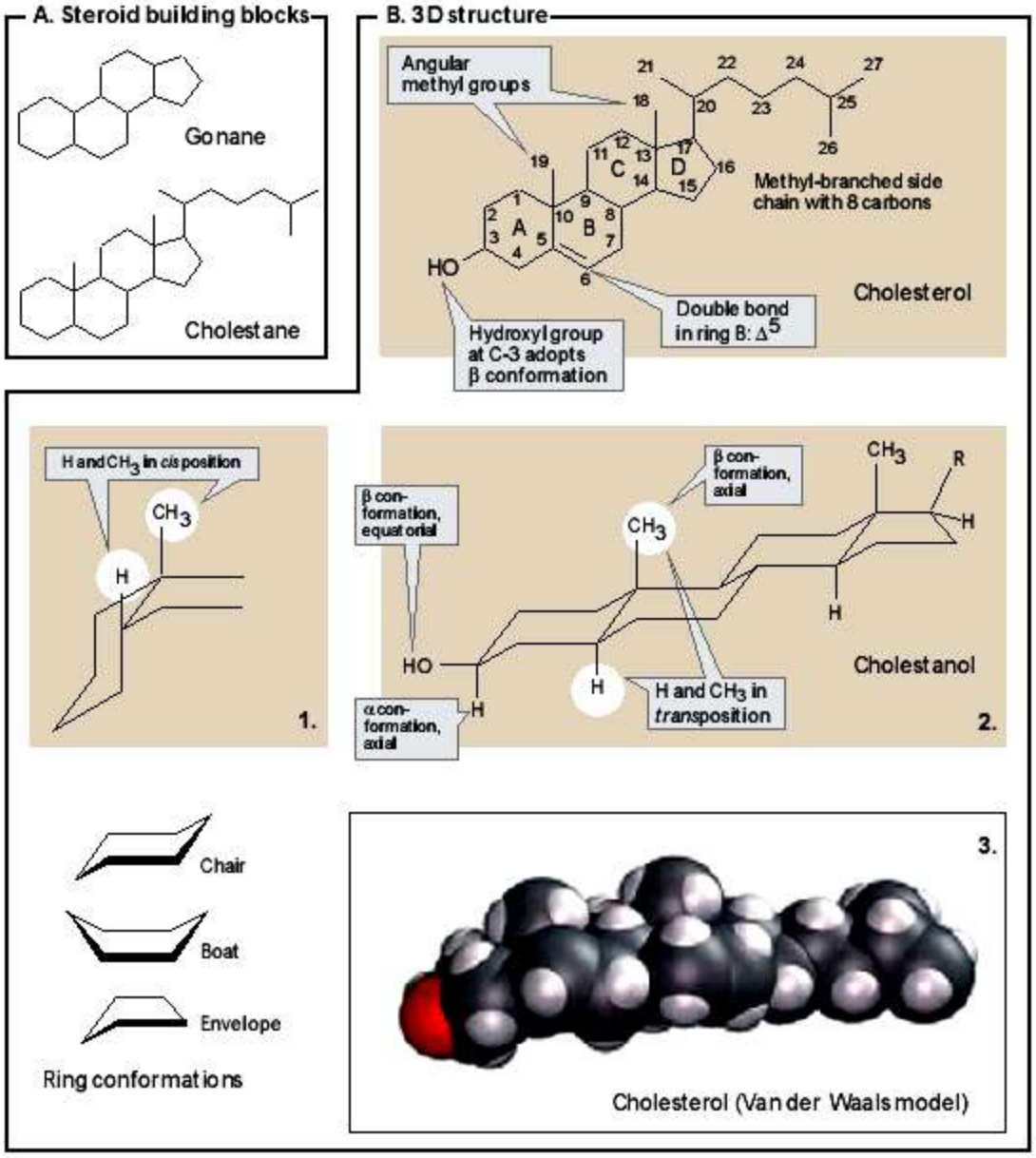


- **Sphingosine** is N-acetylated by a variety of fatty acids generating a family of molecules referred to as **ceramides**. Sphingolipids predominate in the myelin sheath of nerve fibers. Sphingomyelin is an abundant sphingolipid generated by transfer of the phosphocholine moiety of phosphatidylcholine to a ceramide, thus sphingomyelin is a unique form of a phospholipid.

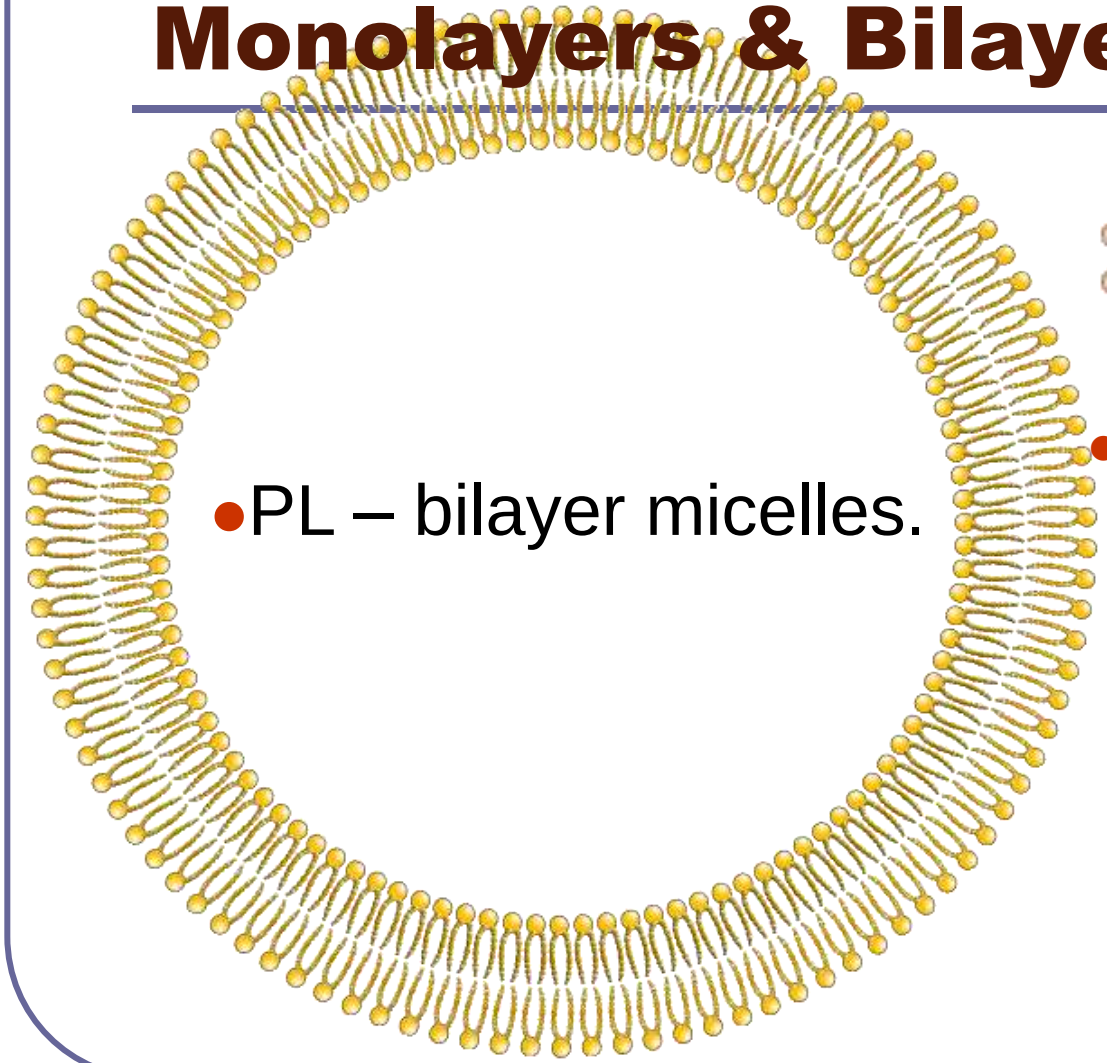
Sphingolipids: Glycosphingolipids

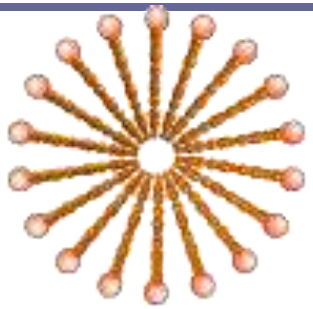
- The other major class of sphingolipids (besides the sphingomyelins) are the **glycosphingolipids** generated by substitution of carbohydrates to the 1-st carbon of the glycerol backbone of a ceramide. There are 4 major classes of glycosphingolipids:
  - **Cerebrosides:** contain a single moiety, principally galactose.
  - **Sulfatides:** sulfuric acid esters of galactocerebrosides.
  - **Globosides:** contain 2 or more sugars.
  - **Gangliosides:** similar to globosides except also contain sialic acid

Structure of Steroids

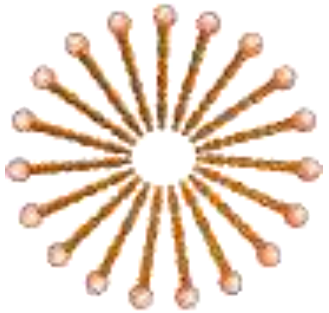


Monolayers & Bilayers

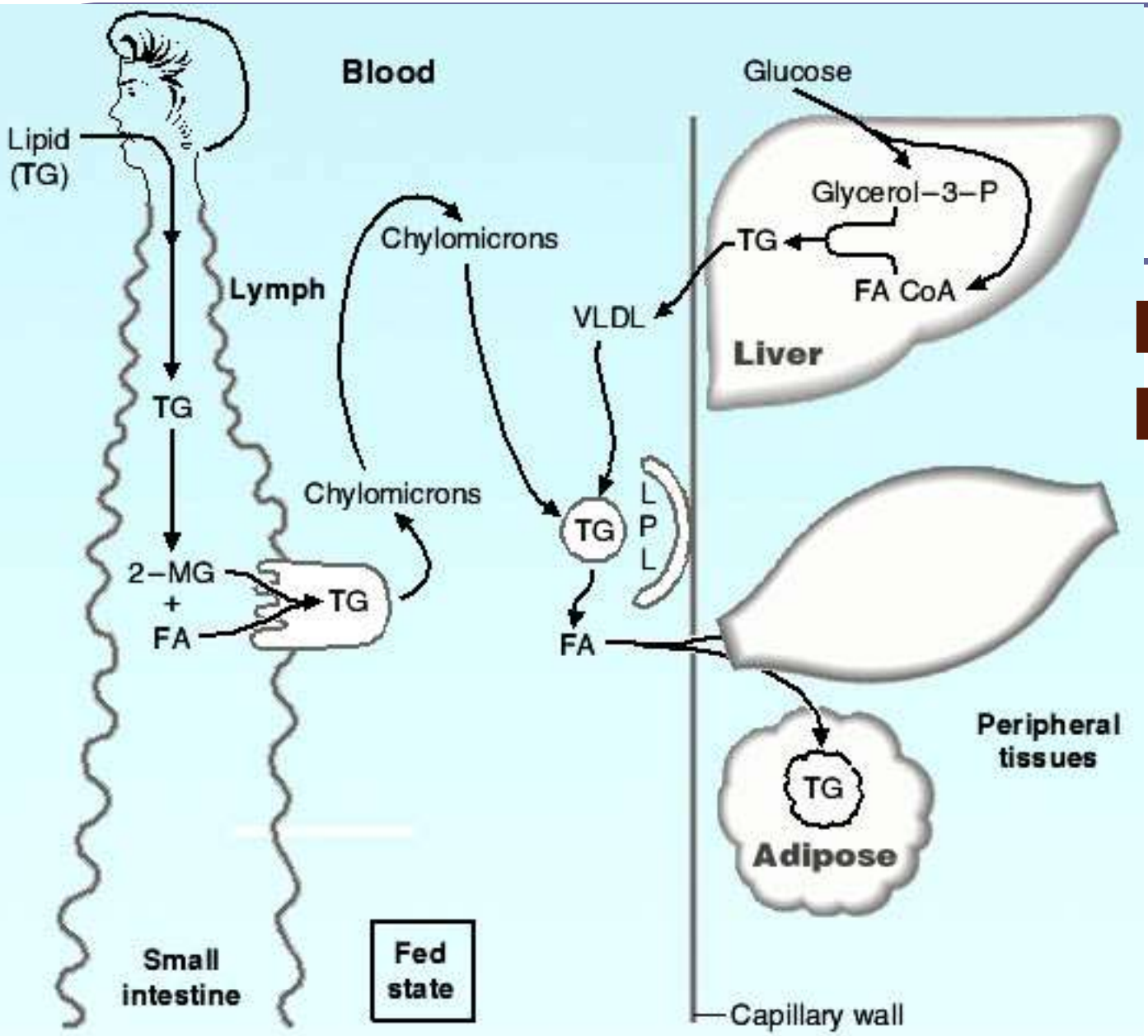




- PL – bilayer micelles.
- FA mainly produces monolayer micelles.



Lipid Digestion



Fatty Acids Digestion

The majority of body FA are acquired in the diet.

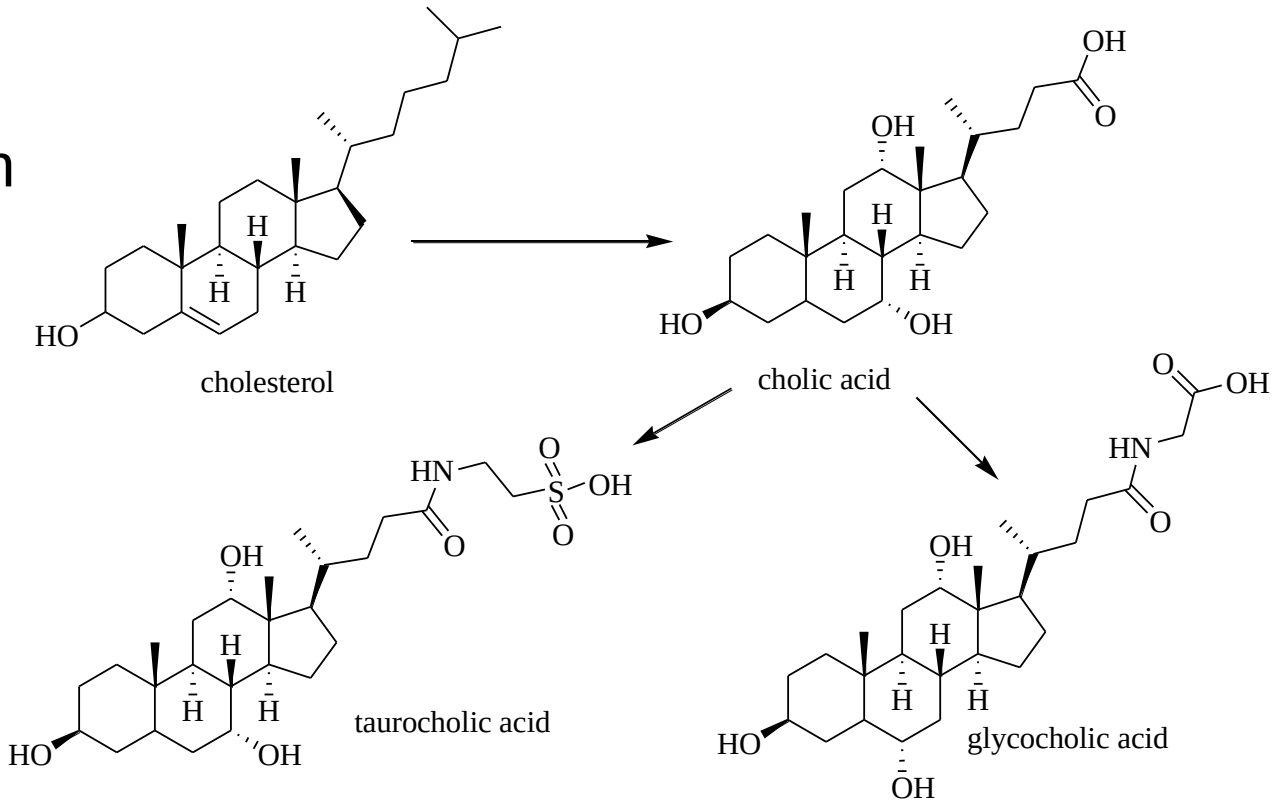
1. The human organism can synthesize all the various FA.
   - Linoleic acid and linolenic acid, containing unsaturation sites beyond carbons 9 and 10, and cannot be synthesized in the body, must be in the diet: **essential FA**.
2. Plants are capable of synthesizing linoleic and linolenic acid, so humans should consume various plants or eat the meat of animals that have consumed these plant fats.

Intestinal Uptake of Lipids

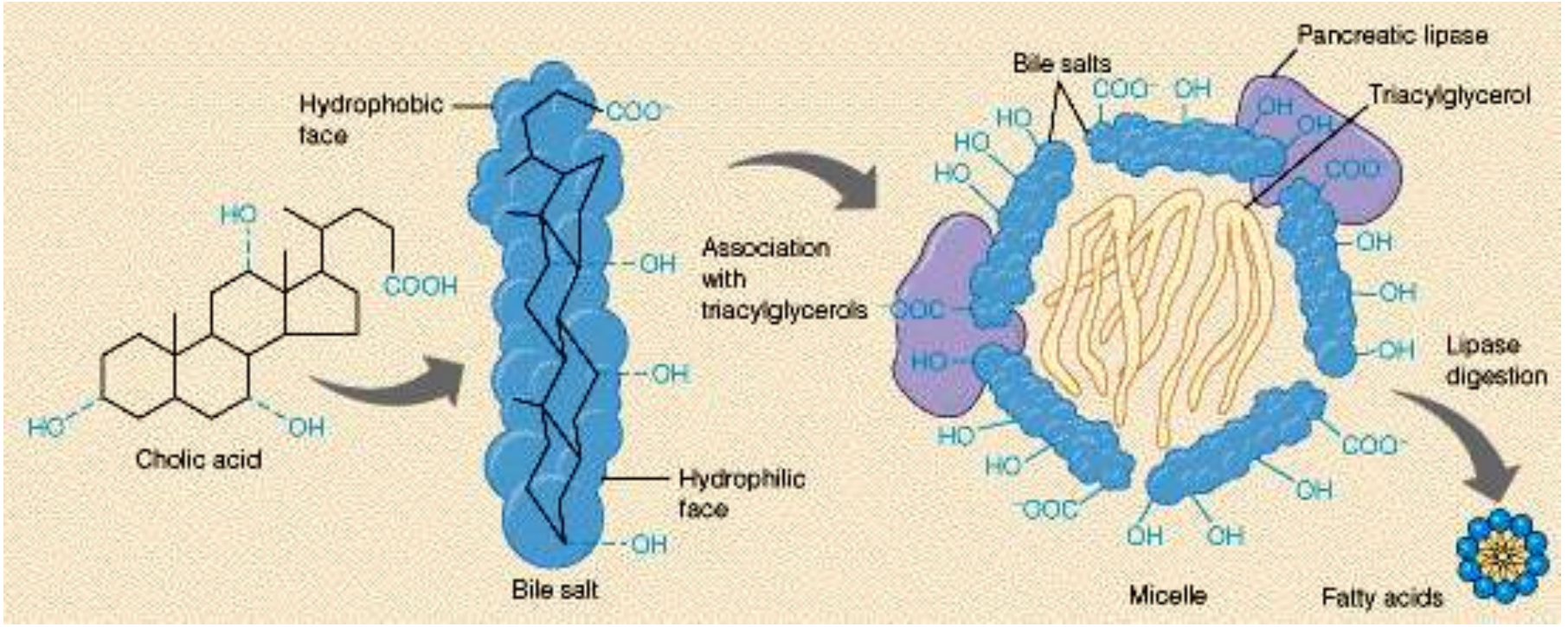
- Dietary lipids must be absorbed from the small intestine.
  - These molecules are insoluble in the intestine.
  - The *solubilization* (or *emulsification*) of dietary lipids is accomplished by means of **bile salts.**

Bile Salts

- synthesized from cholesterol in the liver.
- stored in the gallbladder;
- secreted following the ingestion of fat.



Action of bile salts in emulsifying fats in the intestine



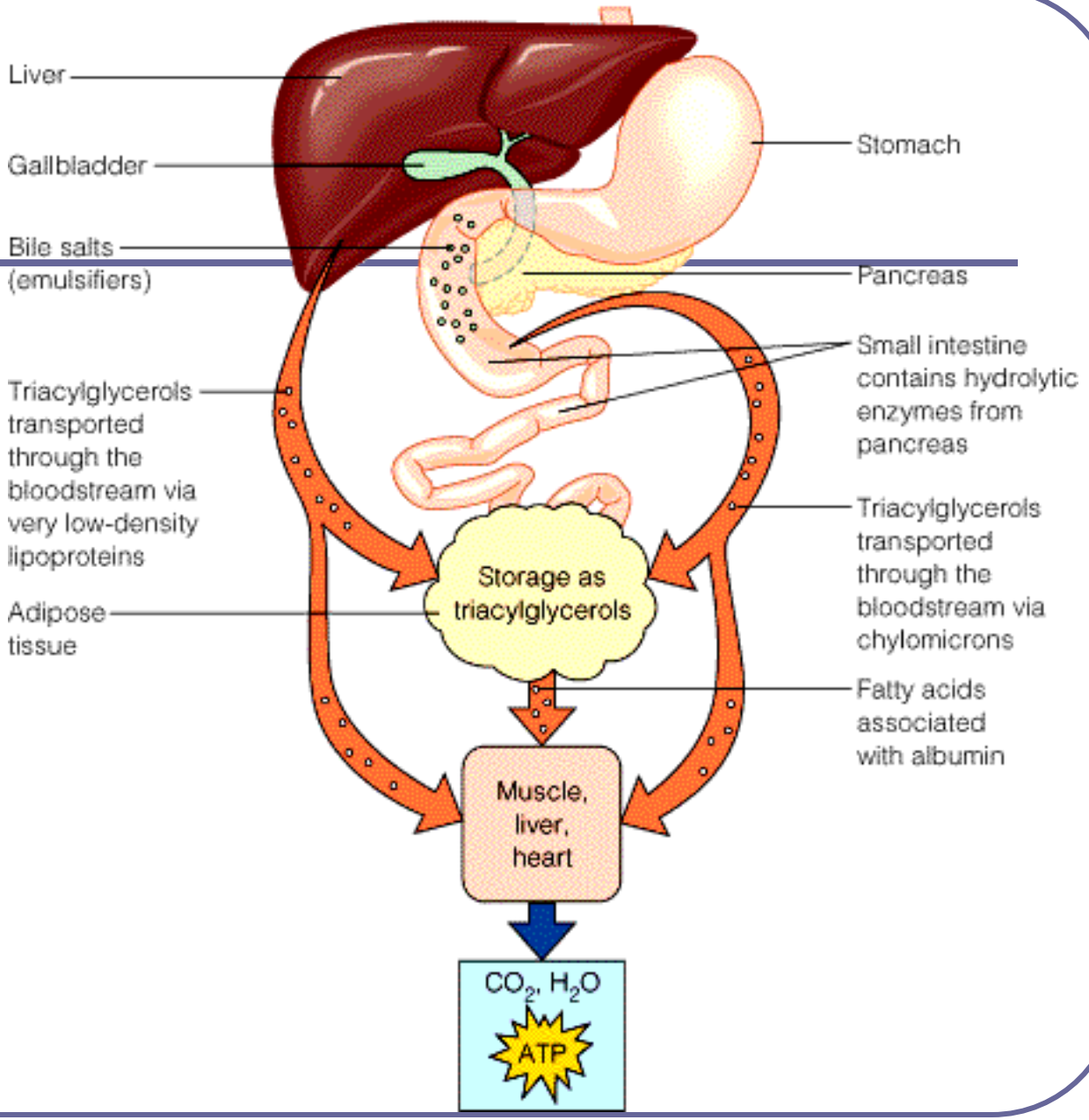
Lipases

- The emulsification of dietary fats renders them accessible to pancreatic lipases (primarily **lipase** and **phospholipase A_2**).
  - the enzymes are secreted the pancreas, generate *free fatty acids* (FFA), *mono*- and *diacylglycerols* from dietary triacylglycerols.
- Pancreatic **lipase** degrades triacylglycerols to 1,2-diacylglycerols and 2-acylglycerols.

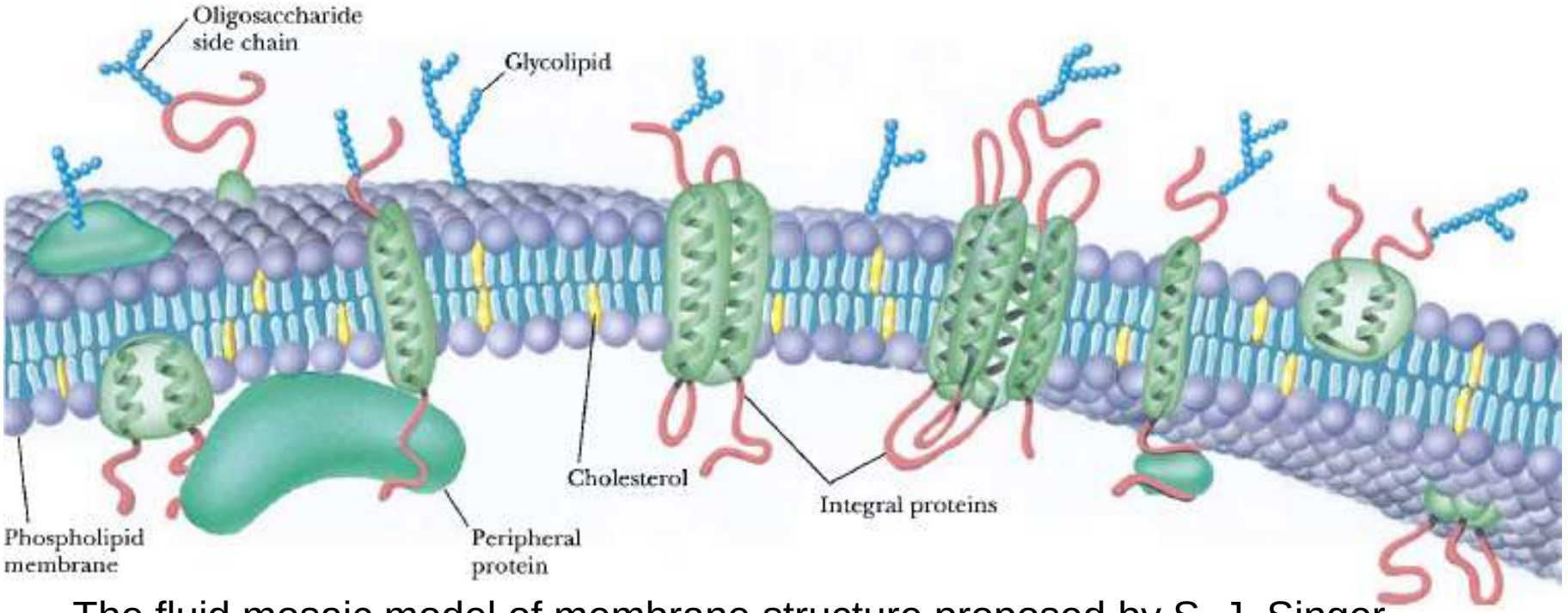
Pancreatic Phospholipase A_2

- Phospholipids are degraded at the 2 position by pancreatic phospholipase A_2 releasing a free fatty acid and the lysophospholipid.
- The products of pancreatic lipases then diffuse into the intestinal epithelial cells, where the re-synthesis of triacyglycerols occurs.

Overview of fat digestion, absorption, storage, and mobilization in the human

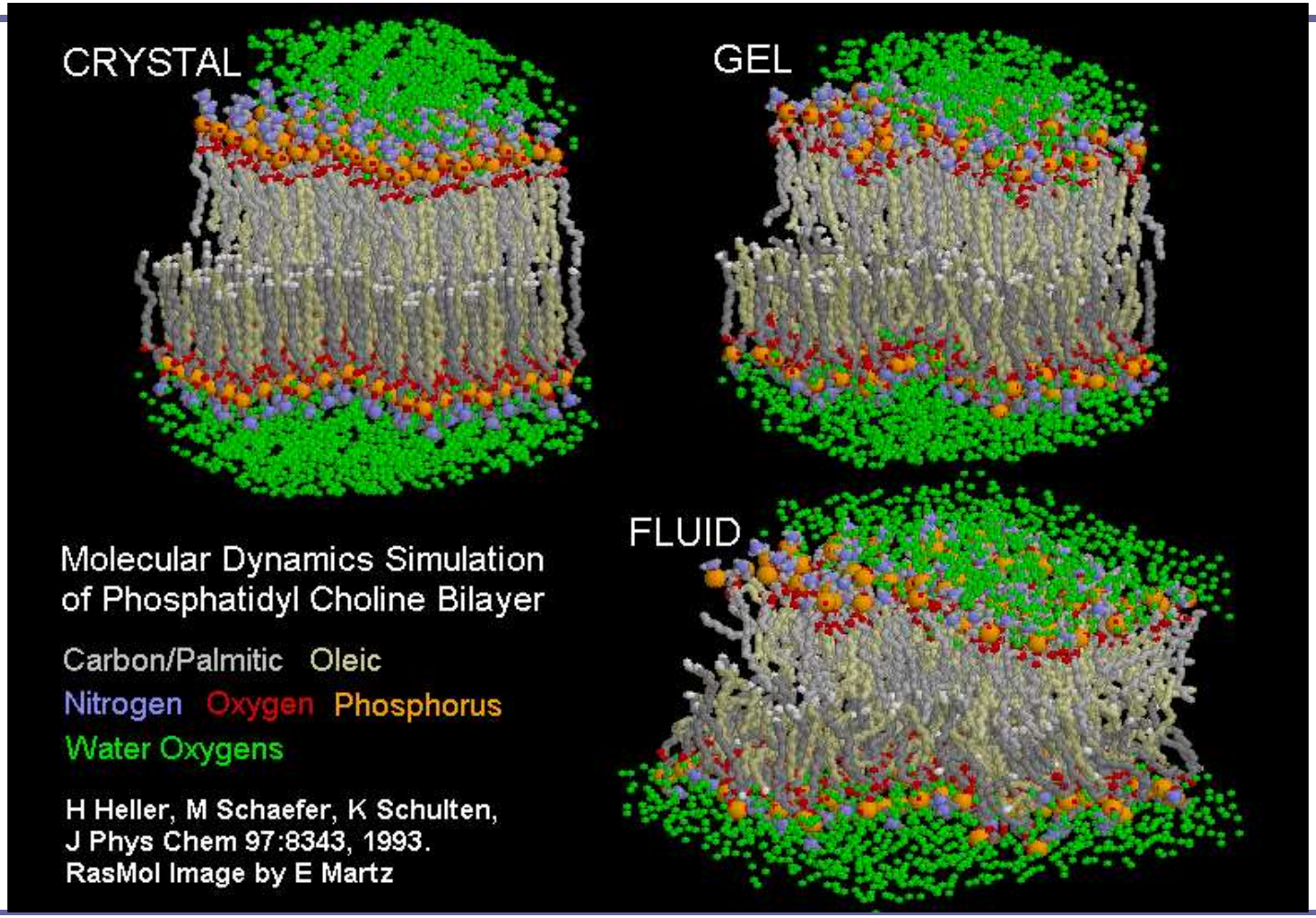


Membrane Structure and Functions

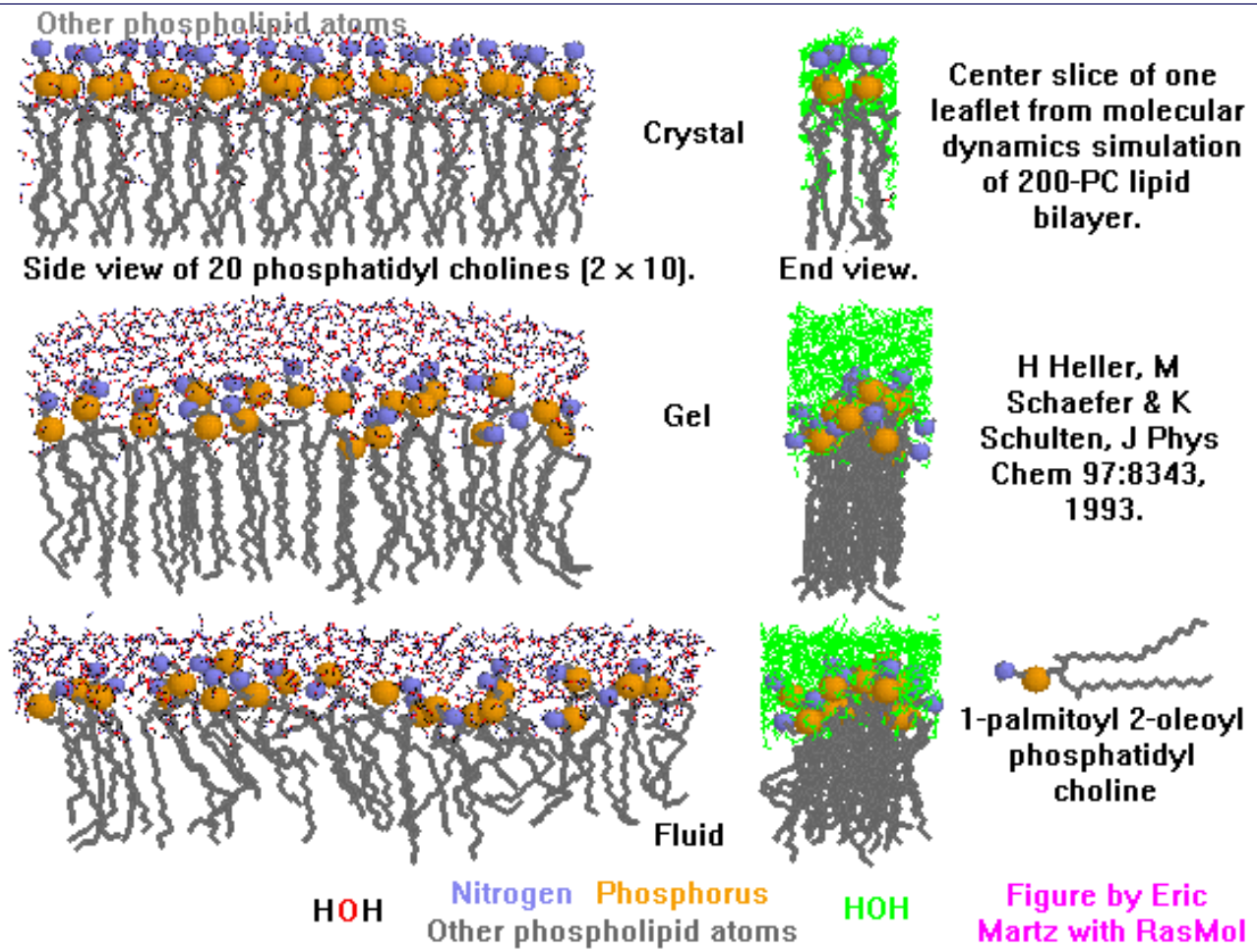


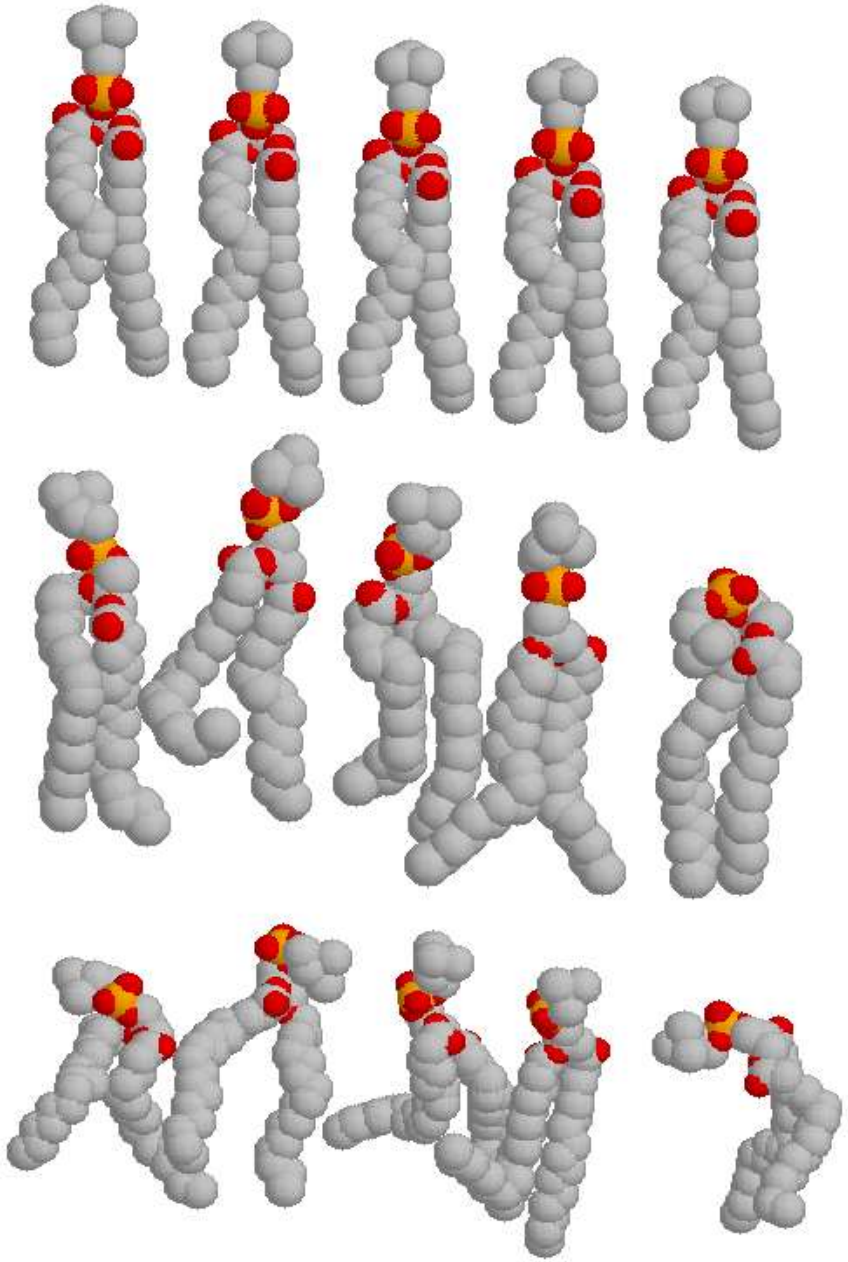
The fluid mosaic model of membrane structure proposed by S. J. Singer and G. L. Nicolson. In this model, the lipids and proteins are assumed to be mobile, so that they can move rapidly and laterally in the plane of the membrane. Transverse motion may also occur, but it is much slower.
(from Garreth&Grisham)

Crystal, Gel, and Fluid Phases



Phospholipids in Bilayers





Crystal

Gel

Fluid

Phosphatidyl cholines taken from model lipid bilayers simulated by Heller et al., J. Phys. Chem. 97:8343, 1993.

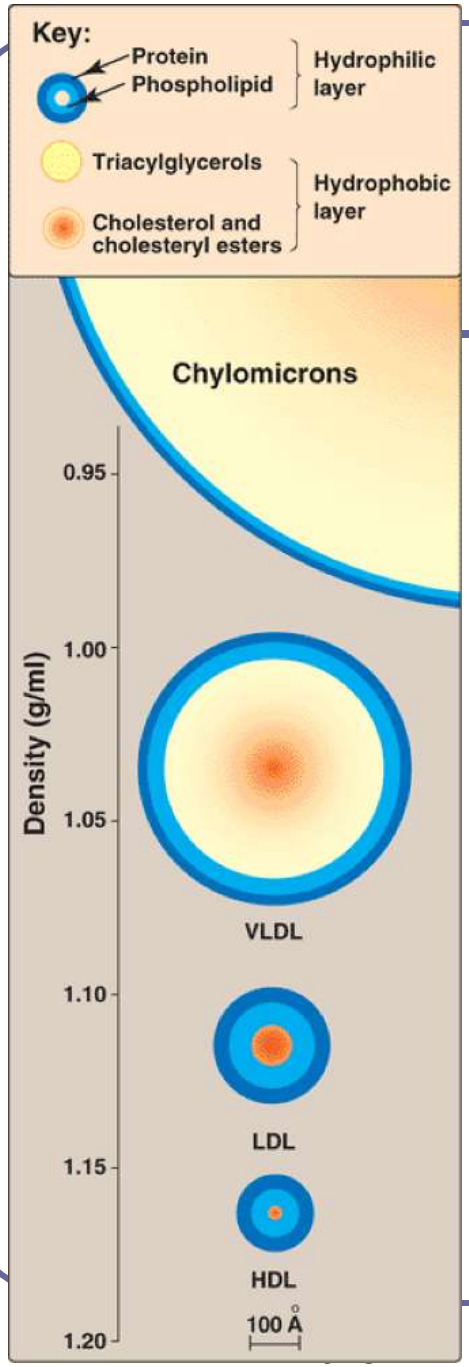
Image by Eric Martz with RasMol

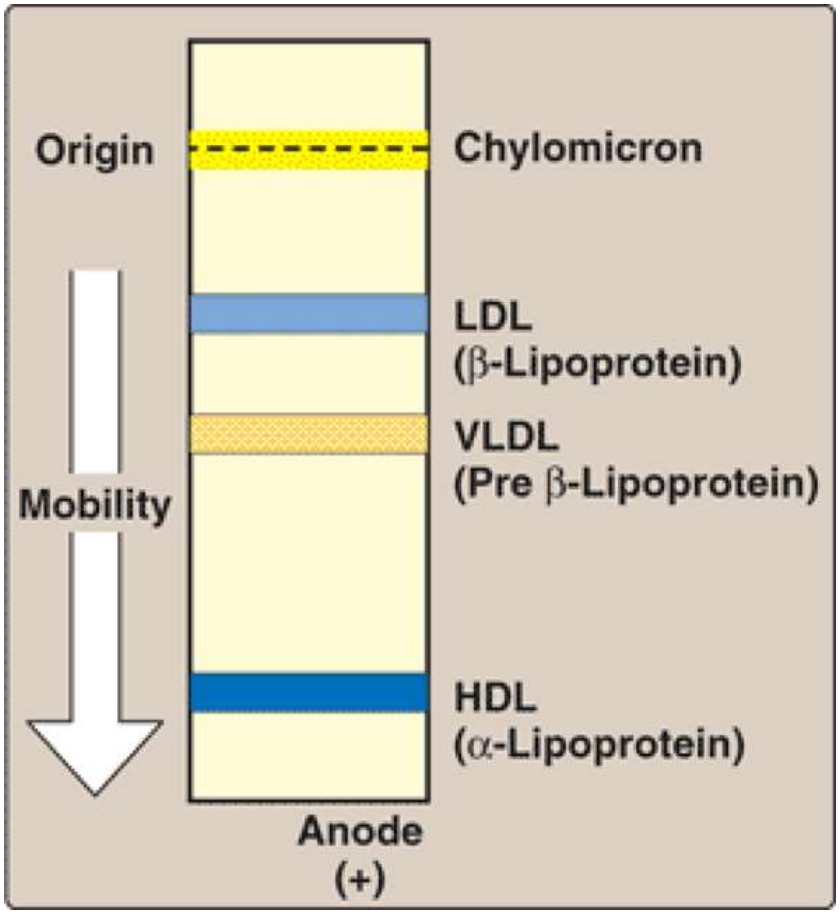
Lipoprotein metabolism

Lipoproteins

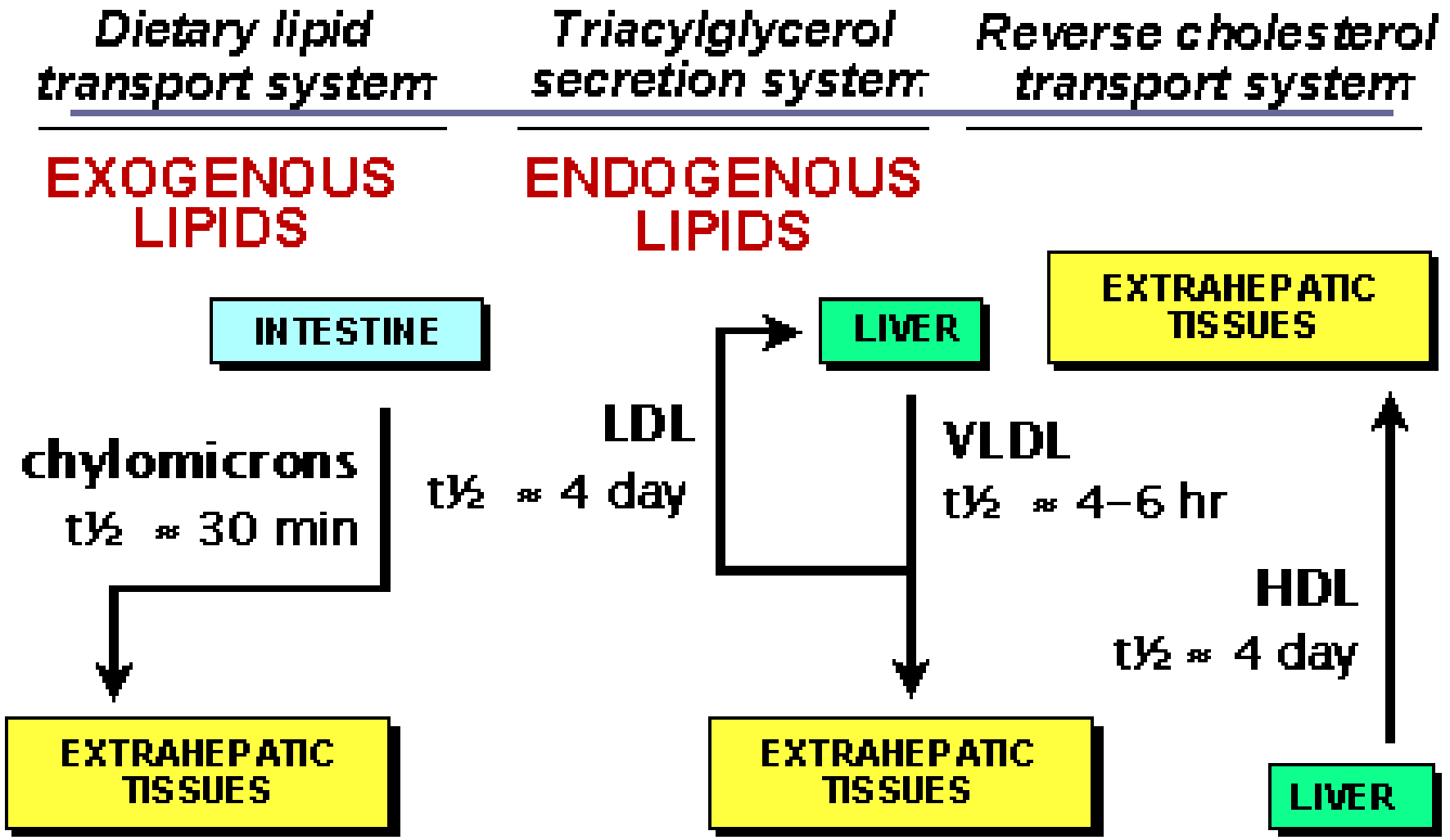
- Dietary triacylglycerols (TG) and cholesterol (CS) (or synthesized by the liver), are solubilized in lipid-protein complexes.
  - contain TG lipid droplets and cholesteryl esters surrounded by the polar phospholipids (PL) and proteins identified as **apolipoproteins**.
  - vary in their content of lipid and protein.
    - *26102004\Lipid Digestion and Lipoproteins.htm*

Types of Lipoproteins

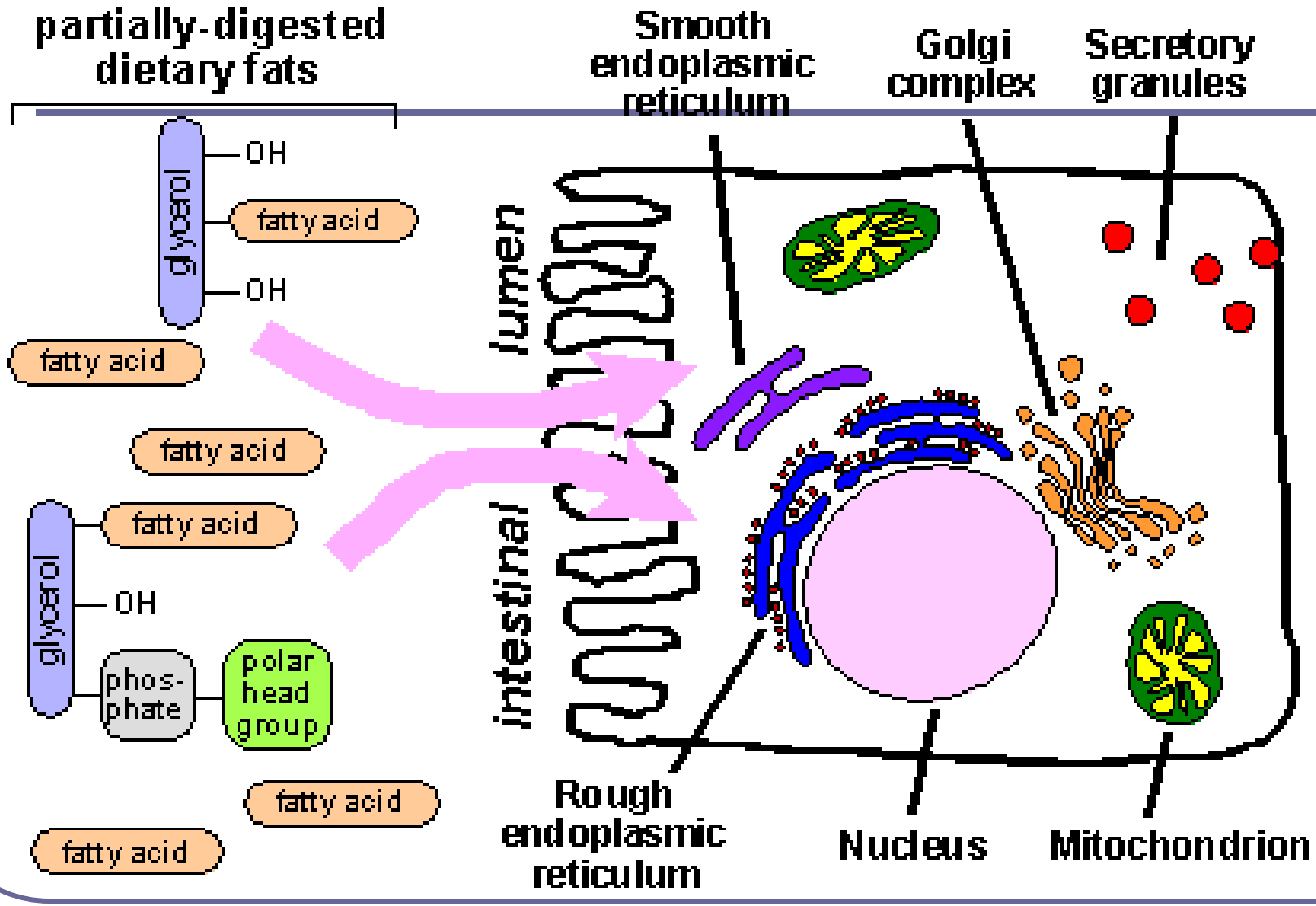




Overview of Lipoprotein Functions

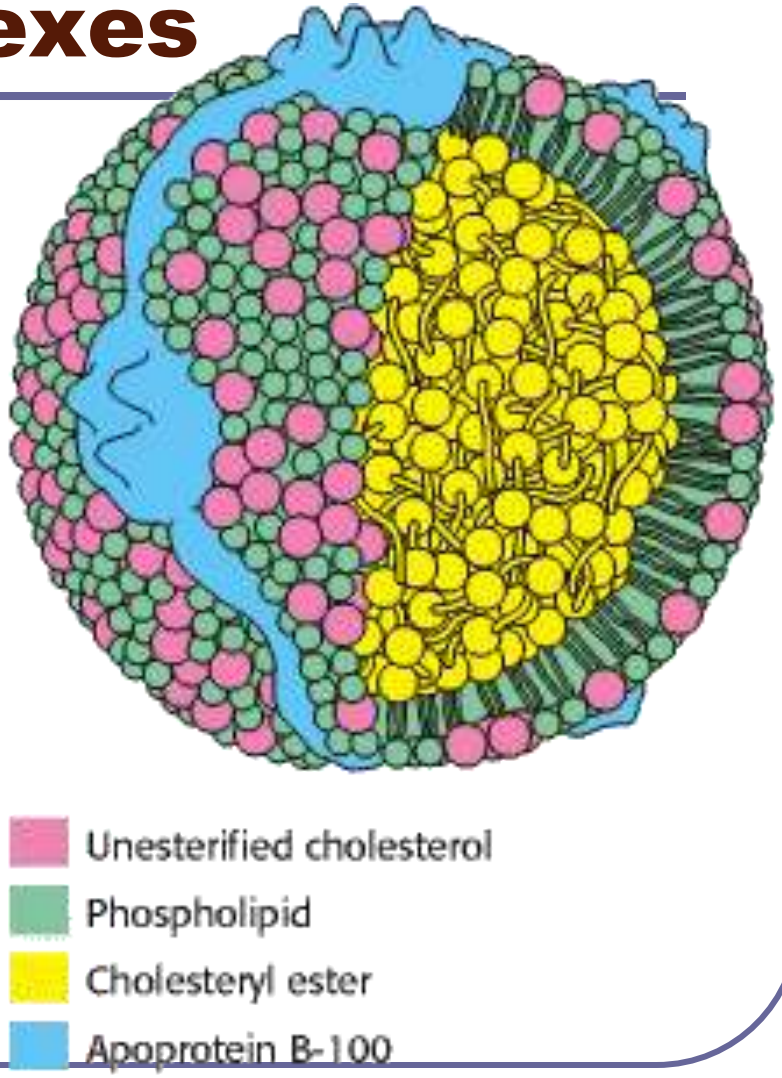


Lipid Uptake by Intestinal Epithelial Cells

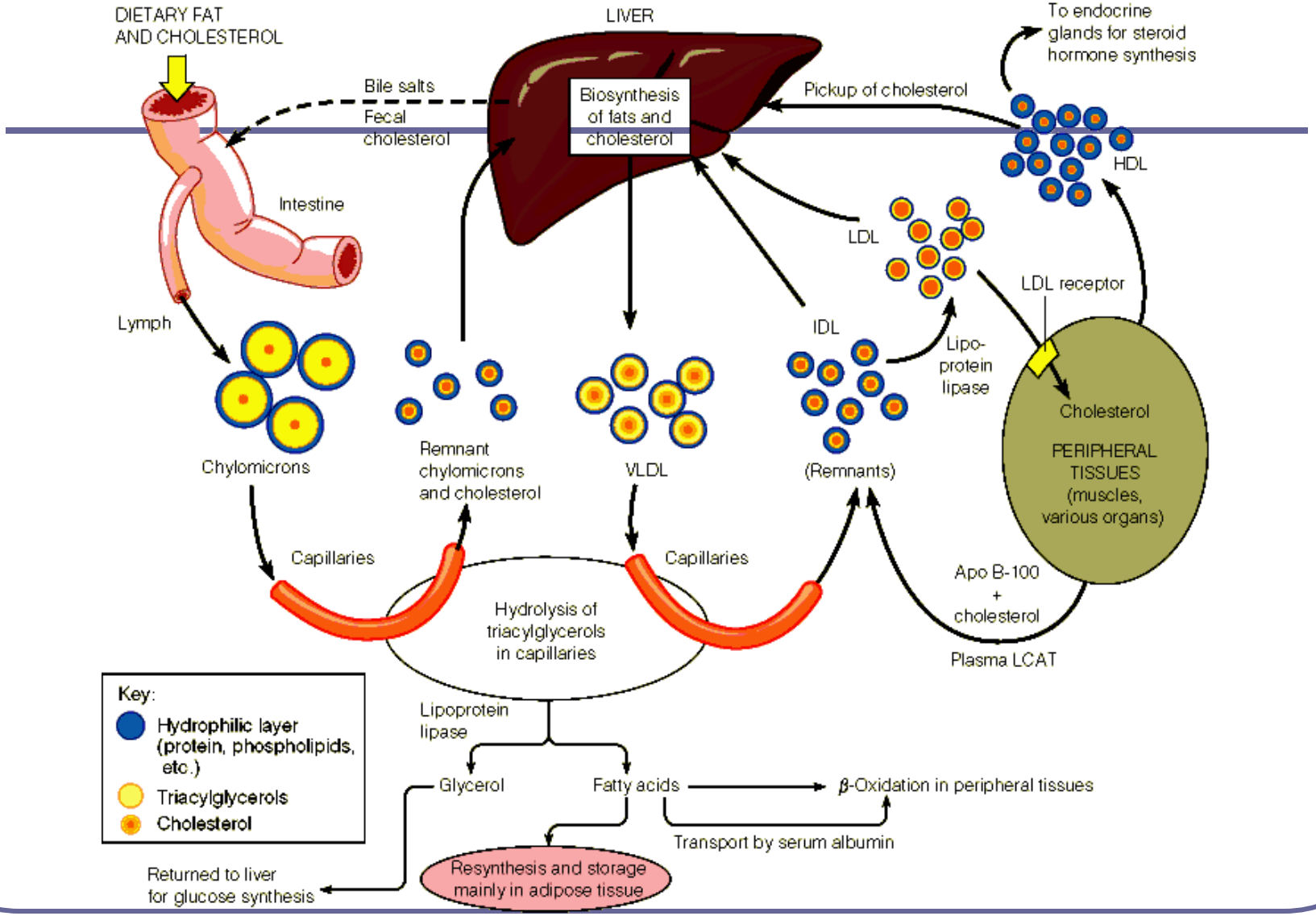


Composition of the Major Lipoprotein Complexes

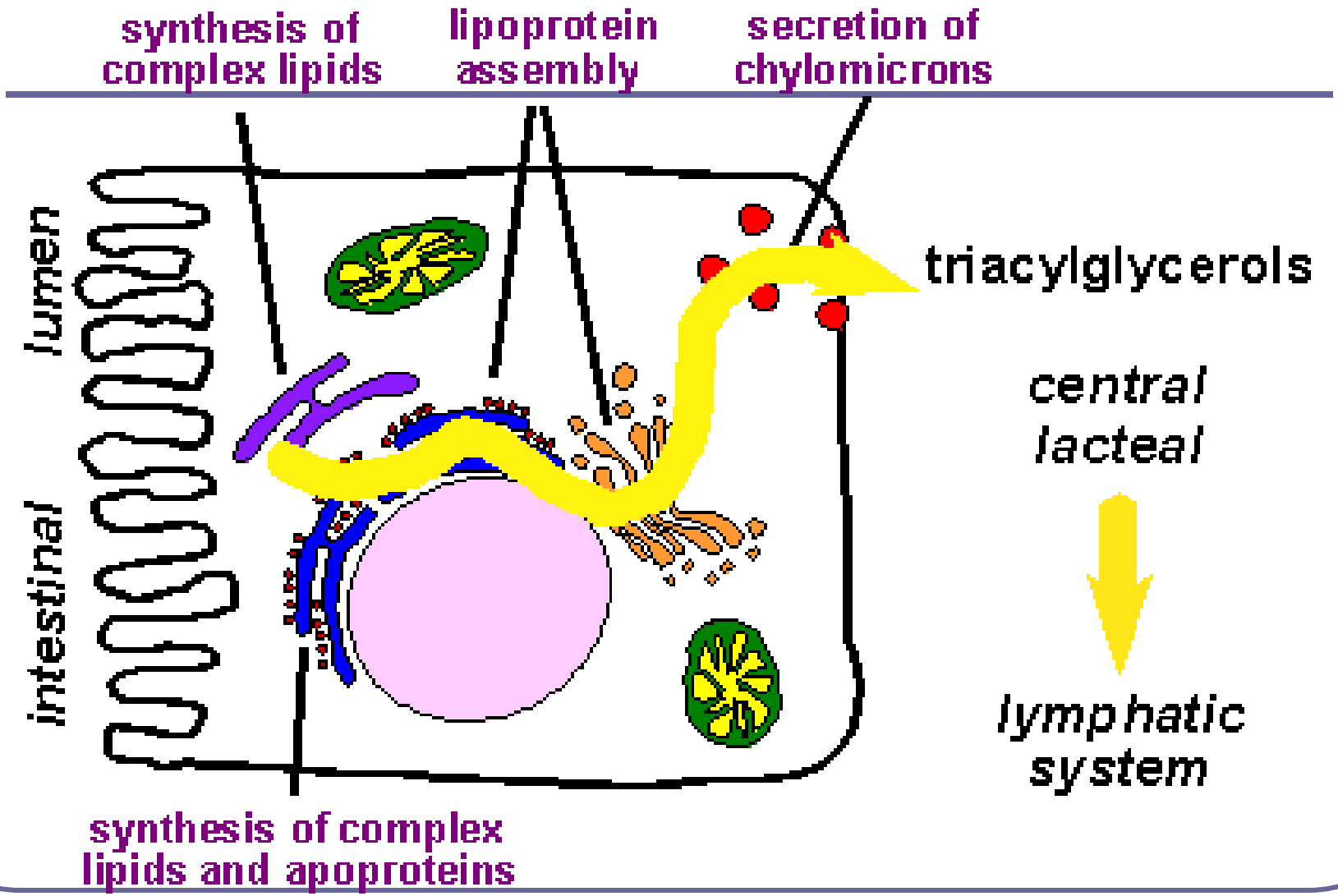
- Schematic model of low-density lipoprotein
  - *26102004\Lipid Digestion and Lipoproteins.htm*

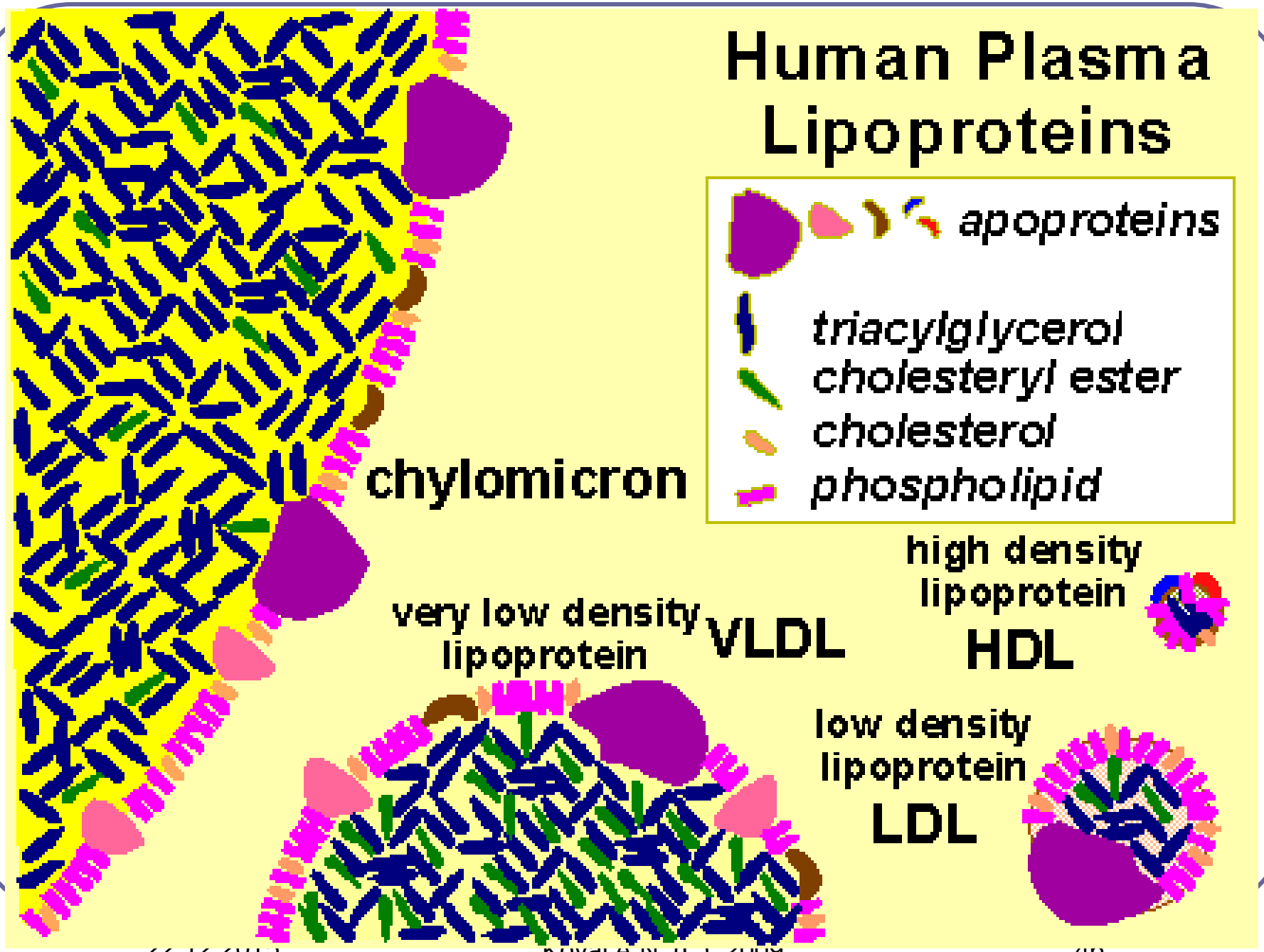


Overview of lipoprotein transport pathways and fates

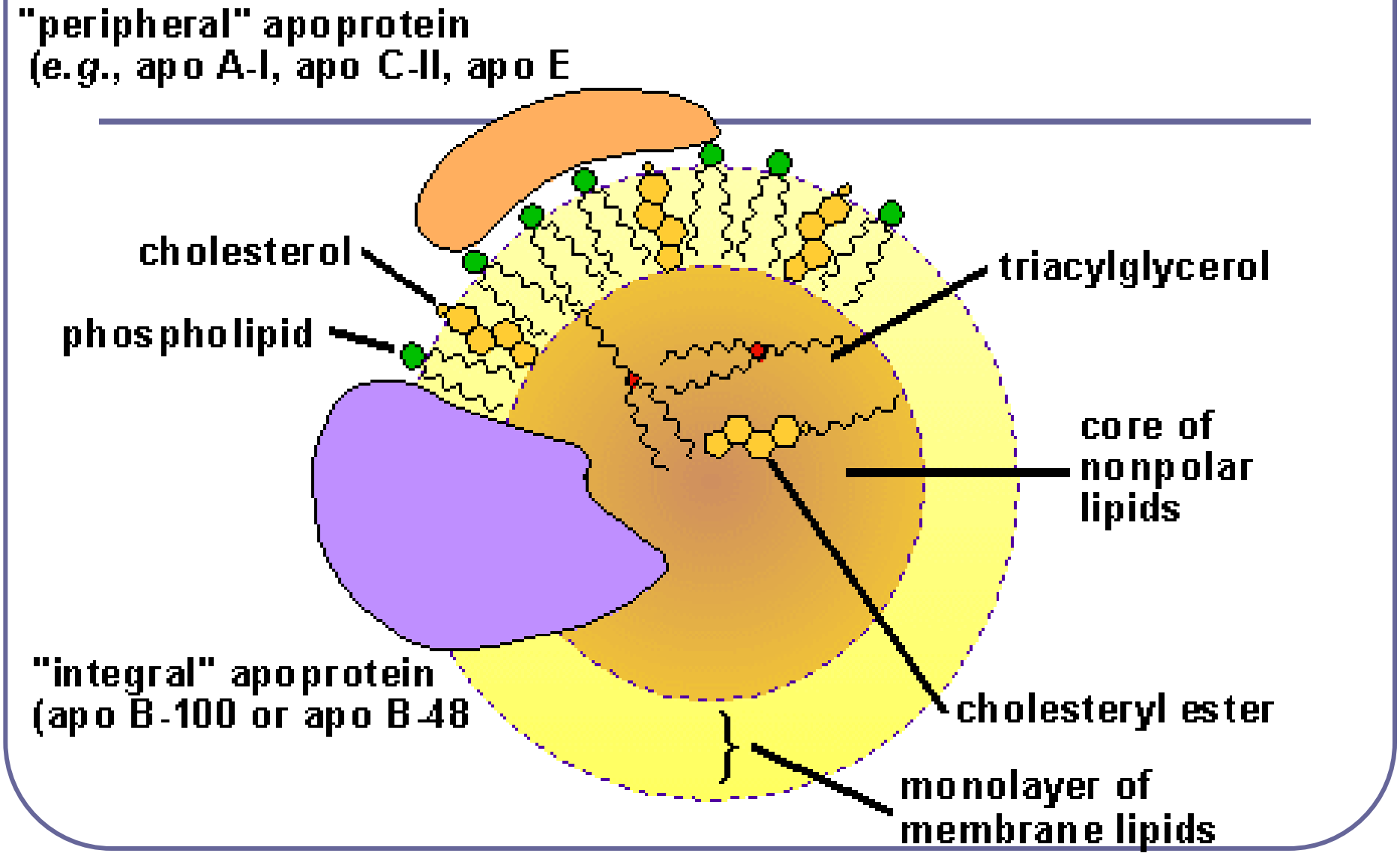


Lipid Export from Intestinal Epithelial Cells




Human Plasma Lipoproteins
apoproteins
triacylglycerol
cholesteryl ester
cholesterol
phospholipid
chylomicron
very low density lipoprotein
VLDL
high density lipoprotein
HDL
low density lipoprotein
LDL

General Structure of a Plasma Lipoprotein



Major Human Plasma Apolipoproteins

Protein	Distribution	Function
apo A-I	HDL2, HDL3, chylomicron	activator of LCAT; structural role
apo B-100	VLDL, LDL	ligand for receptor; structural role
apo B-48	chylomicron	structural role
apo C-II	chylomicron, VLDL, HDL2	cofactor with lipoprotein lipase
apo E	chylomicron, VLDL, apo-E-rich HDL	ligand for receptor

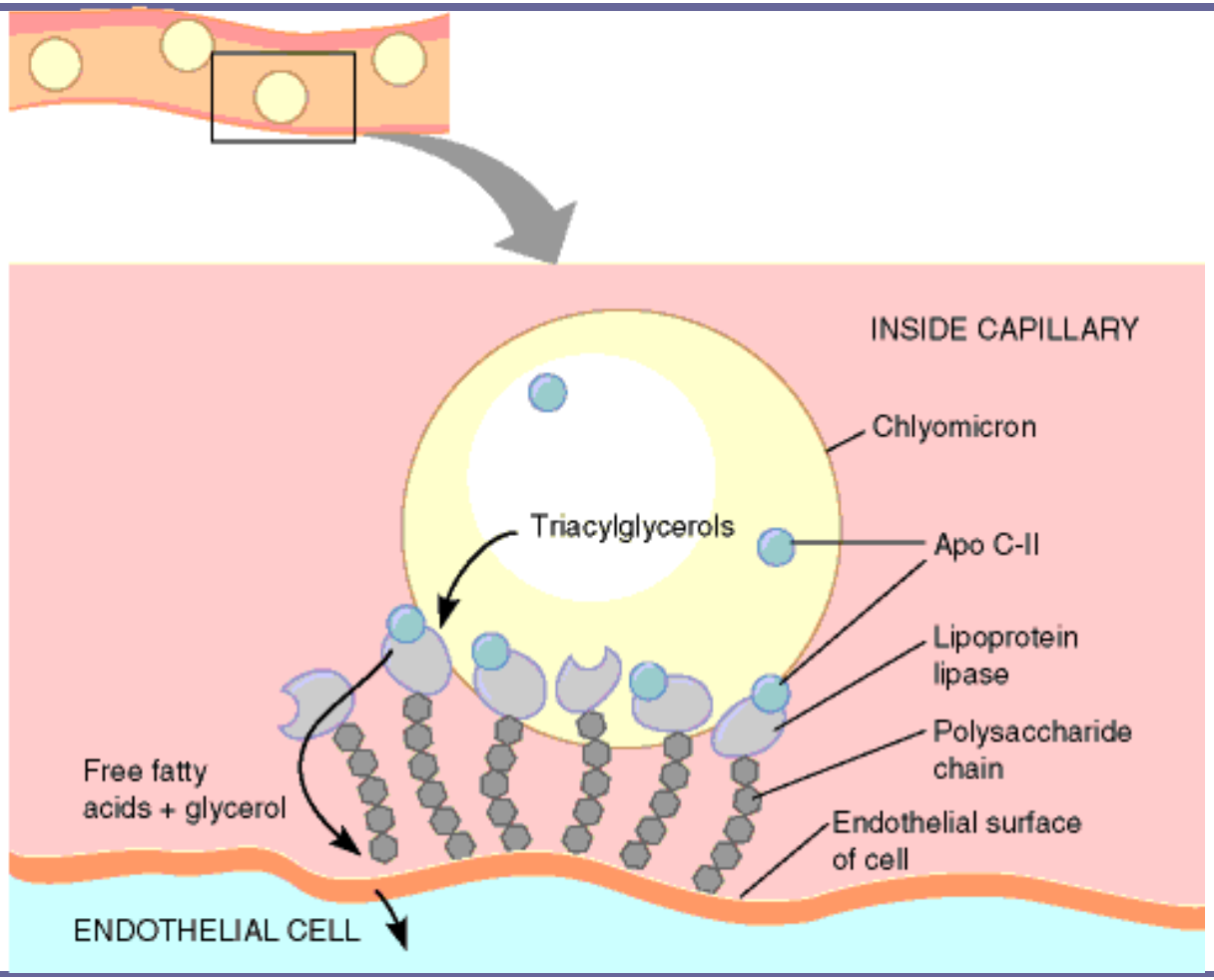
Chylomicrons

- **Chylomicrons** are assembled in the intestinal mucosa as a means to transport dietary (exogenous) *cholesterol* and *triacylglycerols* to the rest of the body.
  - predominant lipids – triacylglycerols.
  - Initially predominating apolipoproteins – apoB-48 and apoA-I, -A-II and IV.
- **ApoB-48 combines only with chylomicrons.**

Chylomicrons metabolism

- Chylomicrons leave the intestine via the lymphatic system and enter the circulation at the left subclavian vein.
  - In the bloodstream, chylomicrons acquire apoC-II and apoE from plasma HDLs.
  - In the capillaries of adipose tissue and muscle, the fatty acids of chylomicrons are removed from the triacylglycerols by the action of lipoprotein lipase (LPL), which is found on the surface of the endothelial cells of the capillaries.
  - The apoC-II in the chylomicrons activates LPL in the presence of phospholipid.

Binding of a chylomicron to lipoprotein lipase on the inner surface of a capillary



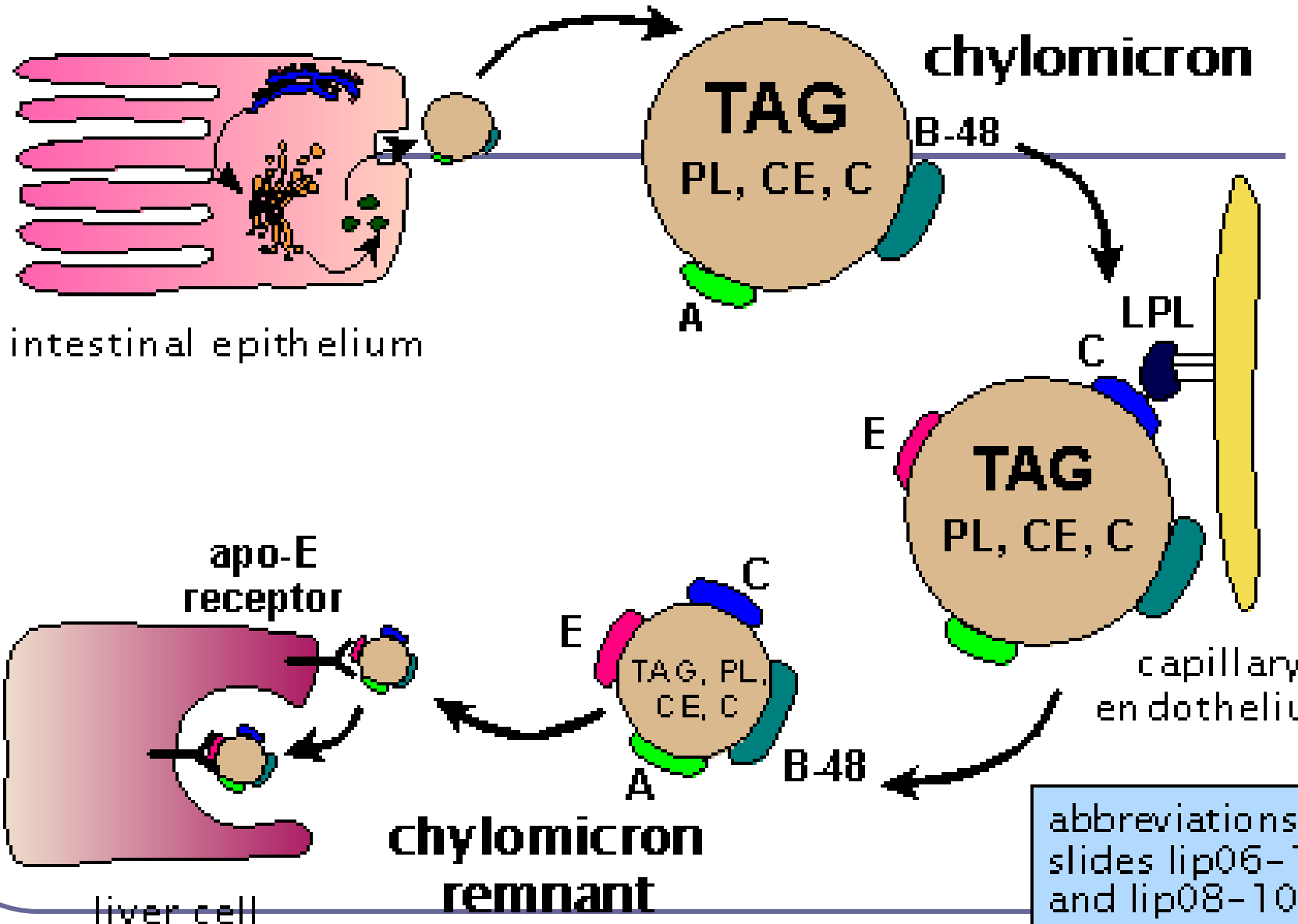
Chylomicrons metabolism (cont'd)

- The free fatty acids are then absorbed by the tissues and the glycerol backbone of the triacylglycerols is returned, via the blood, to the liver and kidneys.
- Glycerol is converted to the glycolytic intermediate dihydroxyacetone phosphate (DHAP).
- During the removal of fatty acids, a substantial portion of phospholipid, apoA and apoC is transferred to HDLs. The loss of apoC-II prevents LPL from further degrading the **chylomicron remnants**.

Chylomicron remnants

- Chylomicron remnants – containing primarily cholesterol, apoE and apoB-48 – are then delivered to, and taken up by, the liver through interaction with the chylomicron remnant receptor.
- The recognition of chylomicron remnants by the hepatic remnant receptor requires apoE. Chylomicrons function to deliver dietary triacylglycerols to adipose tissue and muscle and dietary cholesterol to the liver.

Metabolism of Chylomicrons



abbreviations:
slides lip06-16
and lip08-10

Chylomicron Remnants (1)

- The **free fatty acids** are absorbed by the tissues.
- Glycerol is converted to the glycolytic intermediate *dihydroxyacetone phosphate* (DHAP).
  - During the removal of fatty acids, a substantial portion of phospholipid, apoA and apoC is transferred to HDLs.
- The loss of apoC-II prevents LPL from further degrading the chylomicron remnants.

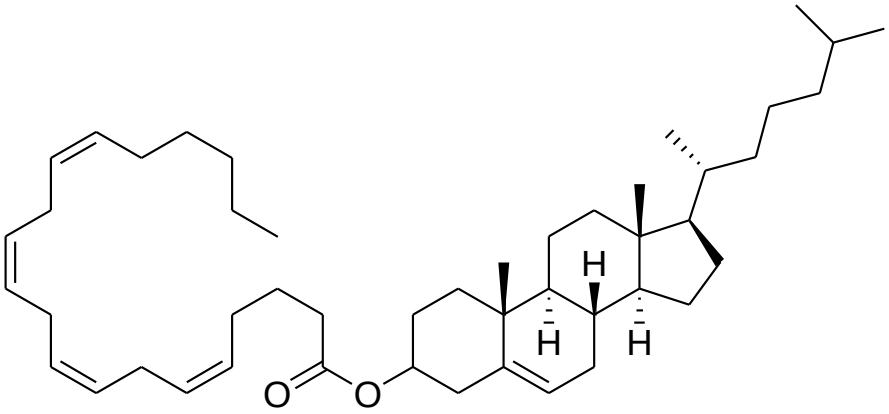
Chylomicron remnants (2)

- **Chylomicron remnants** – containing primarily cholesterol, apoE and apoB-48.
  - Liver interacts with the *chylomicron remnant receptor*.
- The recognition of chylomicron remnants by the hepatic remnant receptor requires apoE.
- Chylomicrons function to deliver dietary triacylglycerols to adipose tissue and muscle and dietary cholesterol to the liver.

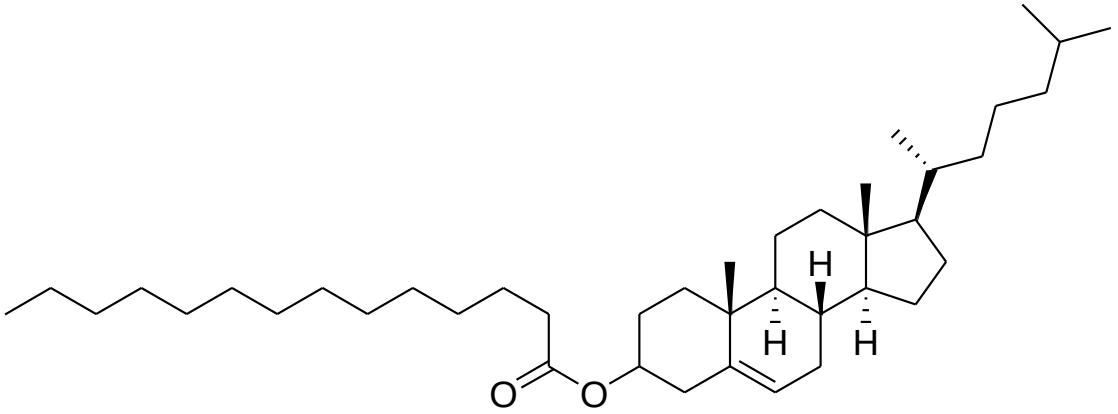
Very Low Density Lipoproteins, VLDLs

- The dietary fat and carbohydrate in excess leads to their conversion into triacylglycerols (TAG) in the liver.
  - TAG are packaged into VLDLs, released for delivery to the various tissues (primarily muscle and adipose tissue) for storage or production of energy.
- VLDLs are formed endogenously derived TAGs to extra-hepatic tissues.
  - VLDLs contain also some cholesterol and cholesteryl esters and the apoproteins, apoB-100, apoC-I, apoC-II, apoC-III and apoE.
- Like nascent chylomicrons, newly released VLDLs acquire apoCs and apoE from circulating HDLs.

Cholesterol Esters (examples)



O-arachidonoyl-cholesterol



O-myristoyl-cholesterol

- Cholesterol esters formation in lipoproteins is catalyzed by **LCAT** (*lecithyn-cholesterol acyl transferase*)

From VLDLs to IDLs

- The fatty acid portion of VLDLs is released to adipose tissue and muscle in the same way as for chylomicrons, through the action of lipoprotein lipase.
- The action of lipoprotein lipase coupled to a loss of certain apoproteins (the apoCs) converts VLDLs to intermediate density lipoproteins (IDLs), also termed VLDL remnants.
- The apoCs are transferred to HDLs. The predominant remaining proteins are apoB-100 and apoE. Further loss of triacylglycerols converts IDLs to LDLs.

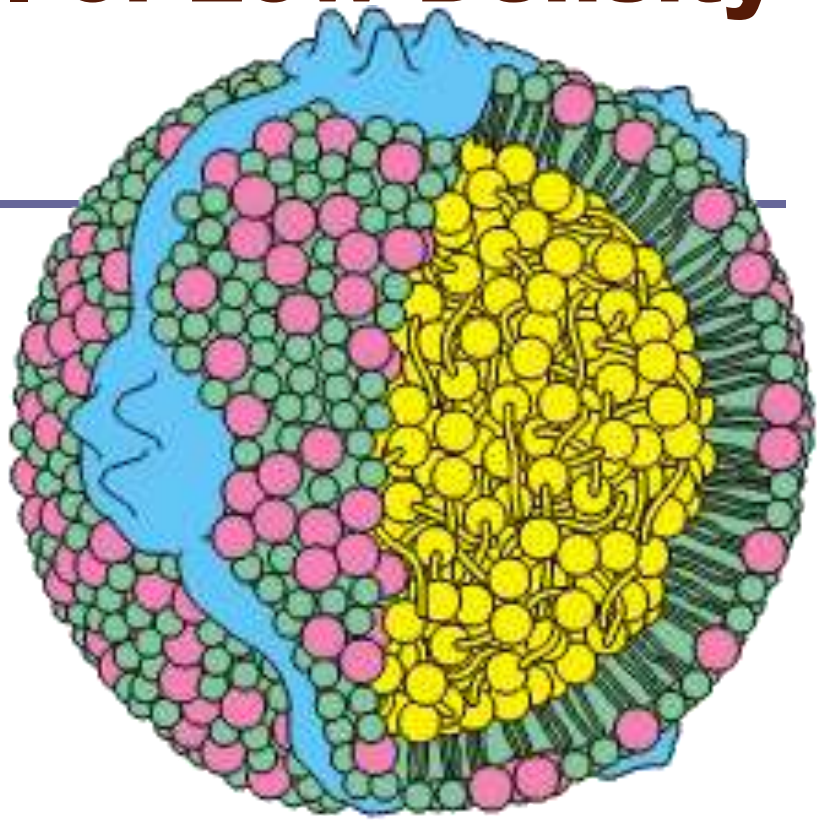
Intermediate Density Lipoproteins, IDLs

- IDLs are formed as triacylglycerols are removed from VLDLs.
  - The fate of IDLs is either conversion to LDLs or direct uptake by the liver.
- Conversion of IDLs to LDLs occurs as more triacylglycerols are removed.
- The liver takes up IDLs after they have interacted with the LDL receptor to form a complex, which is endocytosed by the cell.

Low Density Lipoproteins, LDLs

- The cellular requirement for cholesterol as a membrane component is satisfied in one of two ways: either it is synthesized *de novo* within the cell, or it is supplied from extra-cellular sources, namely, chylomicrons and LDLs.

Schematic Model of Low-Density Lipoprotein



LDL and VLDL Interactions

- As indicated above, the dietary cholesterol that goes into chylomicrons is supplied to the liver by the interaction of chylomicron remnants with the remnant receptor.
- In addition, cholesterol synthesized by the liver can be transported to extra-hepatic tissues if packaged in VLDLs.
  - In the circulation VLDLs are converted to LDLs through the action of lipoprotein lipase.
  - LDLs are the primary plasma carriers of cholesterol for delivery to all tissues.

LDLs

- The exclusive apolipoprotein of LDLs is **apoB-100**.
- The uptake of LDLs occurs in liver (75%), adrenals and adipose tissue.
- interaction of LDLs with LDL receptors requires apoB-100.
- The endocytosed membrane vesicles (endosomes) fuse with lysosomes, cholesteryl esters are hydrolyzed to yield free CS.
- The CS is incorporated into the plasma membranes.
- Excess intracellular CS is re-esterified by **acyl-CoA-cholesterol acyltransferase (ACAT)**, for intracellular storage.
- The activity of **ACAT** is enhanced by the presence of intracellular CS.

LDLs metabolism regulation

- Insulin and tri-iodothyronine (T3) increase the binding of LDLs to liver cells.
- Glucocorticoids (e.g., dexamethasone) have the opposite effect.
- These effects may explain the hypercholesterolemia and increased risk of atherosclerosis that have been shown to be associated with uncontrolled diabetes or hypothyroidism.

Lipoprotein-X

- An abnormal form of LDL, identified as **lipoprotein-X (Lp-X),** predominates in the circulation of patients suffering from lecithin-cholesterol acyl transferase (**LCAT**, see HDL discussion for LCAT function) deficiency or cholestatic liver disease.
- There is an elevation in the level of circulating free CS and PL.

High Density Lipoproteins, HDLs

- HDLs are synthesized de novo in the liver and small intestine.
- These newly formed HDLs are nearly devoid of any CS and cholesteryl esters.
- The primary apoproteins of HDLs are apoA-I, apoC-I, apoC-II and apoE.
- In fact, a major function of HDLs is to act as circulating stores of apoC-I, apoC-II and apoE.

High Density Lipoproteins, HDLs (2)

- HDLs are converted into spherical lipoprotein particles through the accumulation of cholesteryl esters.
- This accumulation converts nascent HDLs to HDL_2 and HDL_3.
- Any free CS present in chylomicron remnants and VLDL remnants (IDLs) can be esterified through by the HDL-associated enzyme, **lecithin:cholesterol acyltransferase, LCAT.**
- **LCAT** is synthesized in the liver and so named because it transfers a fatty acid from lecithin to the CS, generating a cholesteryl ester and lysolecithin.
- The activity of LCAT requires interaction with apoA-I, which is found on the surface of HDLs.

HDLs in Reverse Cholesterol Transport

- CS-rich HDLs return to the liver, where they are endocytosed.
- Hepatic uptake of HDLs, or **reverse cholesterol transport**, may be mediated through an HDL-specific apoA-I receptor or through lipid-lipid interactions.
- Macrophages also take up HDLs through apoA-I receptor interaction.
- HDLs can then acquire CS and apoE from the macrophages; CS-enriched HDLs are then secreted from the macrophages.
- The added apoE in these HDLs leads to an increase in their uptake and catabolism by the liver.

LDL Receptors

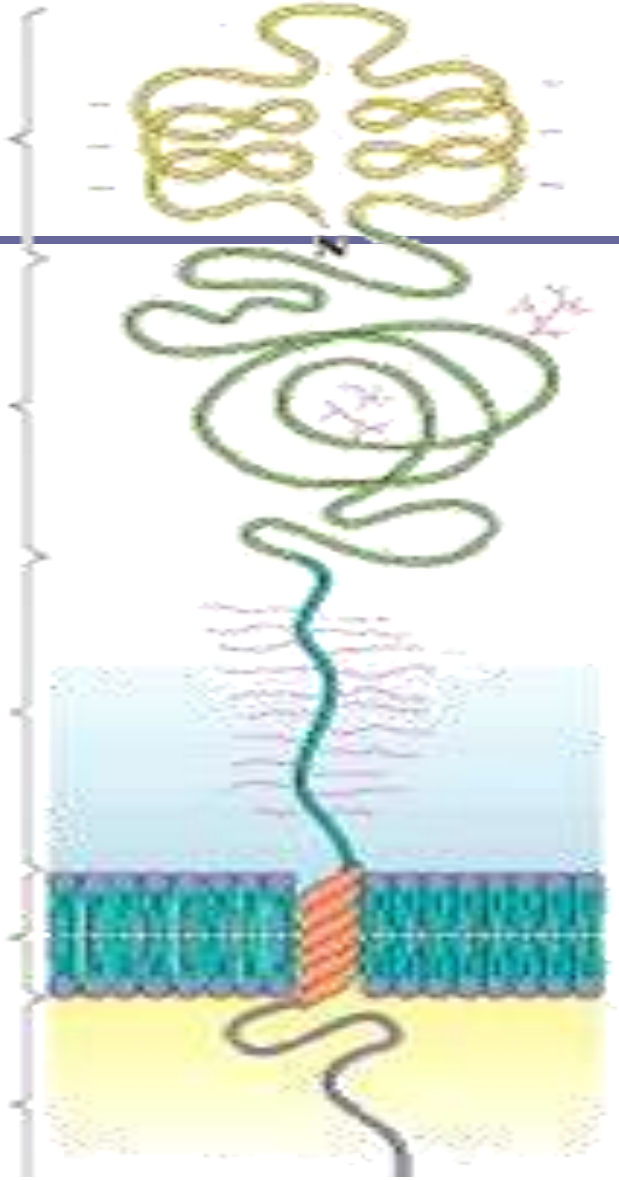
- LDLs are the principal plasma carriers of cholesterol delivering cholesterol from the liver (via hepatic synthesis of VLDLs) to peripheral tissues, primarily the adrenals and adipose tissue.
- LDLs also return cholesterol to the liver.

LDL Receptors (2)

- The cellular uptake of cholesterol from LDLs occurs following the interaction of LDLs with the LDL receptor (also called the apoB-100/apoE receptor).
- The sole apoprotein present in LDLs is apoB-100, which is required for interaction with the LDL receptor.

LDL receptor (3)

- The LDL receptor is a polypeptide of 839 amino acids that spans the plasma membrane.
  - An extracellular domain is responsible for apoB-100/apoE binding.
  - The intracellular domain is responsible for the clustering of LDL receptors into regions of the plasma membrane termed **coated pits.**



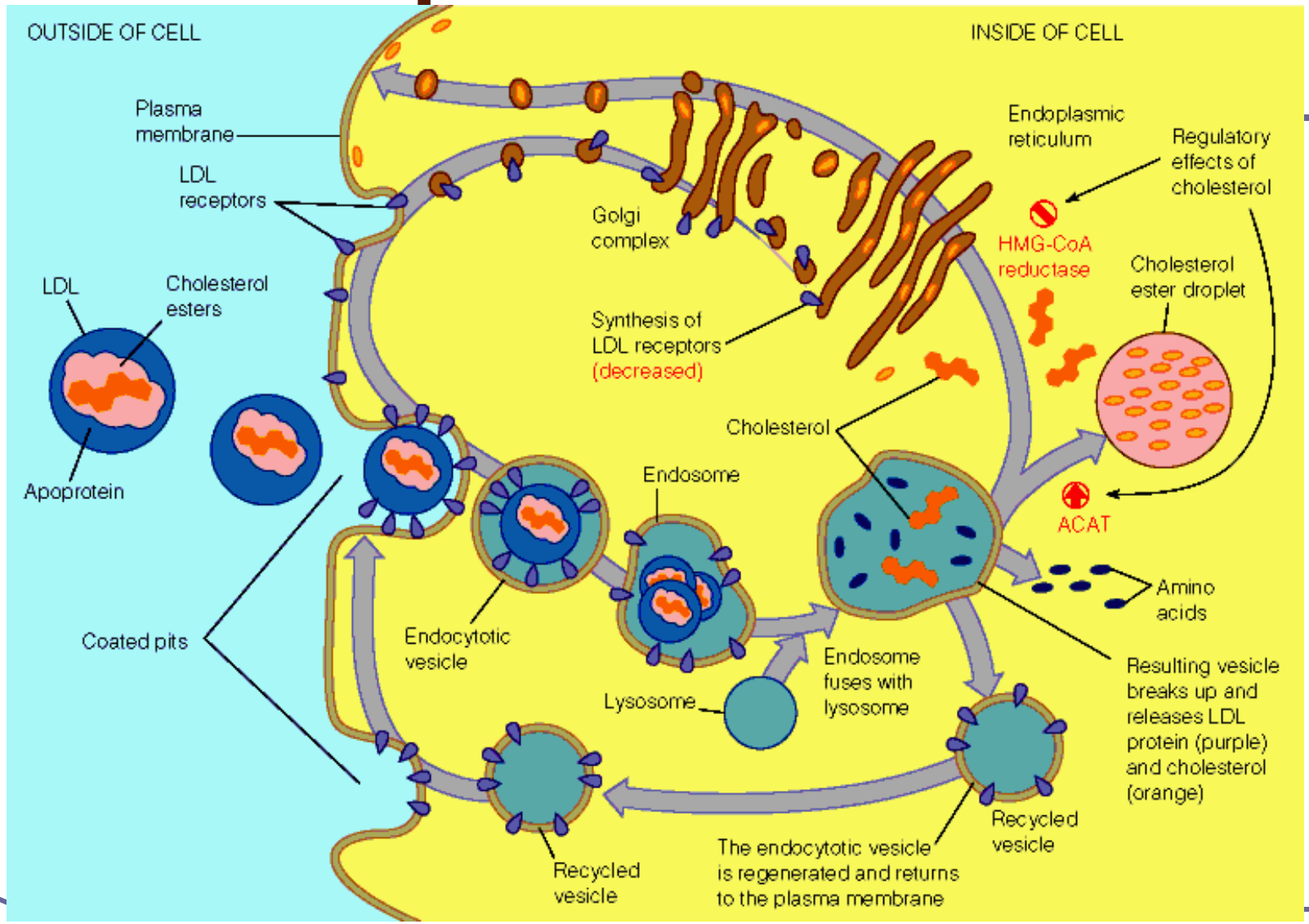
LDL receptors (4)

- Once LDL binds the receptor, the complexes are rapidly internalized (endocytosed).
- ATP-dependent proton pumps lower the pH in the endosomes, which results in dissociation of the LDL from the receptor.
- The portion of the endosomal membranes harboring the receptor are then recycled to the plasma membrane and the LDL-containing endosomes fuse with lysosomes.
- Acid hydrolases of the lysosomes degrade the apoproteins and release free fatty acids and cholesterol.
- As indicated above, the free cholesterol is either incorporated into plasma membranes or esterified (by ACAT) and stored within the cell.

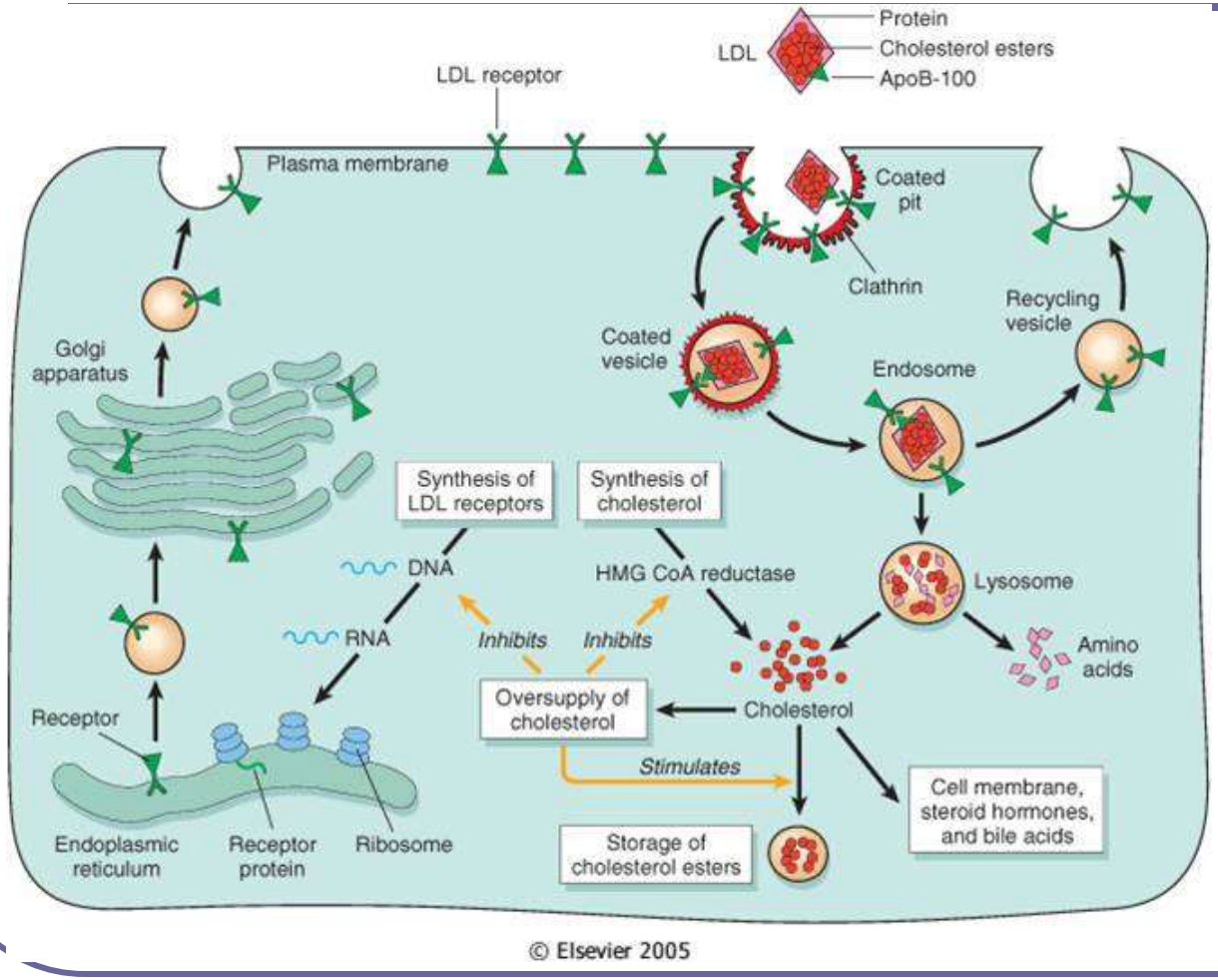
LDL Receptors (5)

- The level of intracellular cholesterol is regulated through cholesterol-induced suppression of LDL receptor synthesis and cholesterol-induced inhibition of cholesterol synthesis.
  - The increased level of intracellular cholesterol that results from LDL uptake has the additional effect of activating ACAT, thereby allowing the storage of excess cholesterol within cells.
  - However, the effect of cholesterol-induced suppression of LDL receptor synthesis is a decrease in the rate at which LDLs and IDLs are removed from the serum.
  - This can lead to excess circulating levels of cholesterol and cholesteryl esters when the dietary intake of fat and cholesterol exceeds the needs of the body.
  - The excess cholesterol tends to be deposited in the skin, tendons and (more gravely) within the arteries, leading to **atherosclerosis.**

Involvement of LDL receptors in cholesterol uptake and metabolism



Endocytosis of LDL Bound to Its Receptor



Apoprotein Classifications: Apo A family

Apoprotein - MW (Da)	Lipoprotein Association	Function and Comments
apoA-I - 29,016	Chylomicrons, HDL	major protein of HDL, activates lecithin:cholesterol acyltransferase, LCAT
apoA-II - 17,400	Chylomicrons, HDL	primarily in HDL, enhances hepatic lipase activity
apoA-IV - 46,000	Chylomicrons and HDL	present in triacylglycerol rich lipoproteins

Apoprotein Classifications: Apo B family

Apoprotein - MW (Da)	Lipoprotein Association	Function and Comments
apoB-48 - 241,000	Chylomicrons	exclusively found in chylomicrons, derived from apoB-100 gene by RNA editing in intestinal epithelium; lacks the LDL receptor-binding domain of apoB-100
apoB-100 - 513,000	VLDL, IDL and LDL	major protein of LDL, binds to LDL receptor; one of the longest known proteins in humans

Apoprotein Classifications: Apo C family

Apoprotein - MW (Da)	Lipoprotein Association	Function and Comments
apoC-I - 7,600	Chylomicrons, VLDL, IDL and HDL	may also activate LCAT
apoC-II - 8, 916	Chylomicrons, VLDL, IDL and HDL	activates lipoprotein lipase
apoC-III - 8,750	Chylomicrons, VLDL, IDL and HDL	inhibits lipoprotein lipase

Apoprotein Classifications: Apo D, CETP, Apo E, Apo H.

Apoprotein - MW (Da)	Lipoprotein Association	Function and Comments
apoD, 33,000	HDL	closely associated with LCAT
cholesterol ester transfer protein, **CETP**	HDL	exclusively associated with HDL, cholesteryl ester transfer
apoE - 34,000 (at least 3 alleles [E2, E3, E4] each of which have multiple isoforms)	Chylomicron remnants, VLDL, IDL and HDL	binds to LDL receptor, $apoE_{\varepsilon\text{-}4}$ allele amplification associated with late-onset Alzheimer's disease
apoH - 50,000 (also known as β-2-glycoprotein I)	Chylomicrons	triacylglycerol metabolism

Apoprotein Classifications:

Apoprotein - MW (Da)	Lipoprotein Association	Function and Comments
apo(a) - at least 19 different alleles; protein ranges in size from 300,000 - 800,000	LDL	disulfide bonded to apoB-100, forms a complex with LDL identified as lipoprotein(a), Lp(a); strongly resembles plasminogen; may deliver cholesterol to sites of vascular injury, high risk association with premature coronary artery disease and stroke

Clinical Significances of Lipoprotein Metabolism

- Few individuals carry the inherited defects in lipoprotein metabolism: hyper- or hypolipoproteinemias.
  - Persons suffering from diabetes mellitus, hypothyroidism and kidney disease often exhibit abnormal lipoprotein metabolism as a result of secondary effects of their disorders.
    - For example, because lipoprotein lipase (LPL) synthesis is regulated by insulin, LPL deficiencies leading to Type I hyperlipoproteinemia may occur as a secondary outcome of diabetes mellitus.
  - Additionally, insulin and thyroid hormones positively affect hepatic LDL-receptor interactions; therefore, the hypercholesterolemia and increased risk of athersclerosis associated with uncontrolled diabetes or hypothyroidism is likely due to decreased hepatic LDL uptake and metabolism.

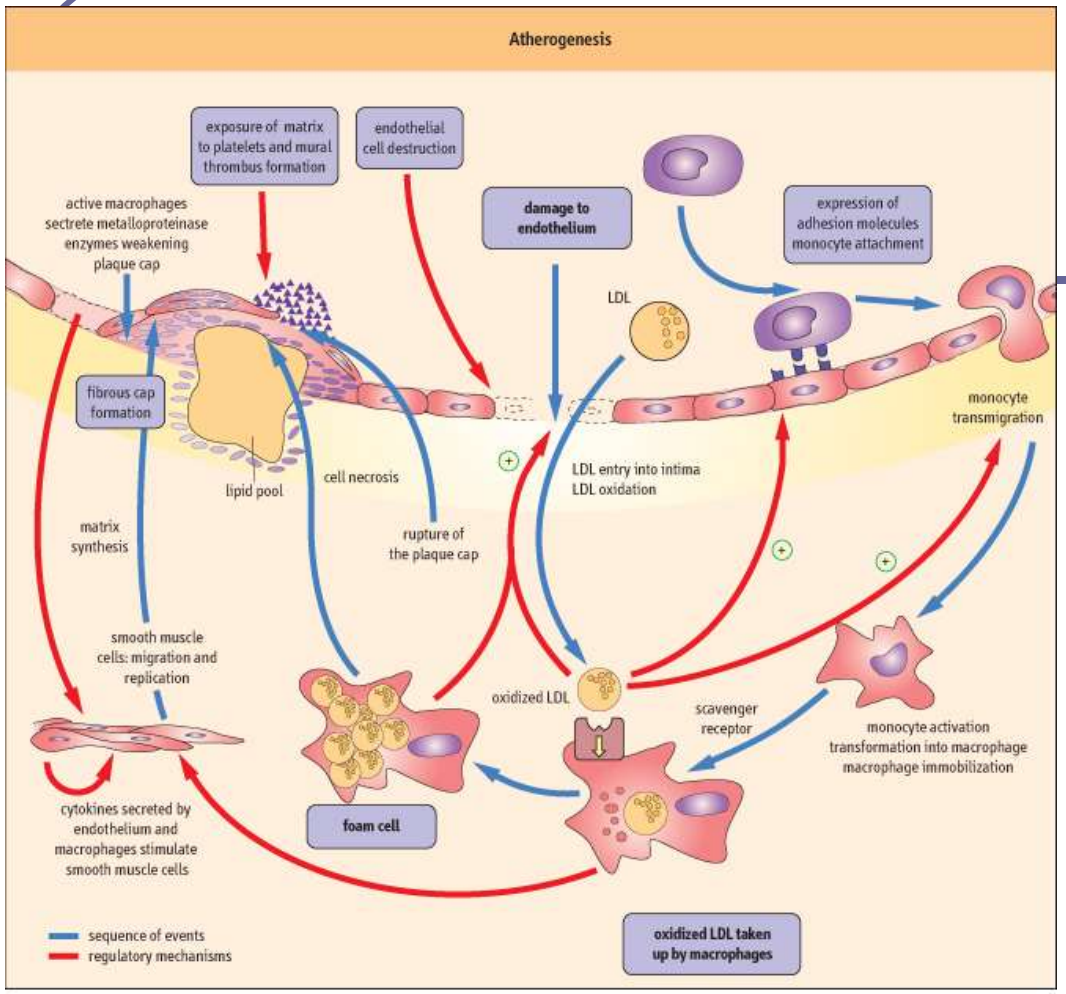
Familial Hypercholesterolemia

- Of the many disorders of lipoprotein metabolism, familial hypercholesterolemia (FH) may be the most prevalent in the general population.
  - Heterozygosity at the FH locus occurs in 1:500 individuals, whereas, homozygosity is observed in 1:1,000,000 individuals.

Phenotypic classification of dyslipidemia (by Fredrickson)

Dyslipidemia type (Fredrickson)	Increased electrophoretic fraction (lipoproteins)	Increased cholesterol	Increased triglyceride
I	chylomicrons	yes	yes
IIa	beta (LDL)	yes	no
IIb	pre-beta & beta (VLDL & LDL)	yes	yes
III	'broad beta' band (IDL)	yes	yes
IV	pre-beta (VLDL)	no	yes
V	pre-beta (VLDL) plus chylomicrons	yes	yes

Atherogenes is: Process &Stages



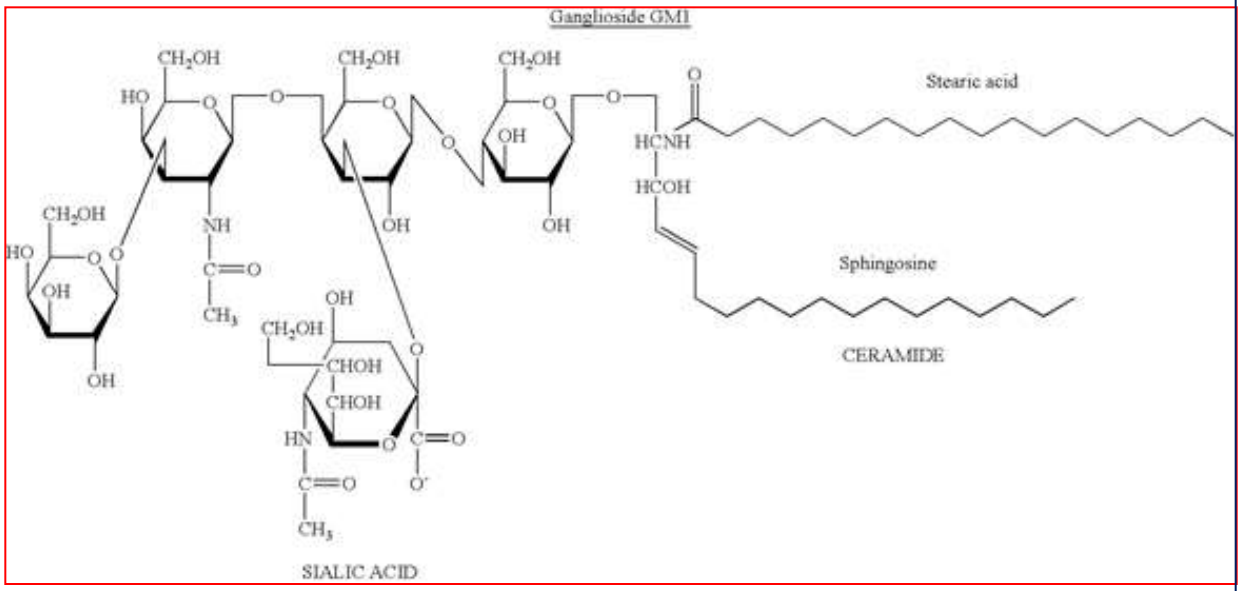
MCP-1: monocyte chemoattractant protein 1, VCAM-1: vascular cell adhesion molecule 1, ICAM-1: intracellular cell adhesion molecule 1, TNFβ: tumor necrosis factor beta, TNFα: tumor necrosis factor alpha, IFNγ: interferon gamma, NO: nitric oxide, PDGF: platelet-derived growth factor, bFGF: basic fibroblast growth factor, IGF-1: insulin-like growth factor 1, EGF: epidermal growth factor, TGFβ: transforming growth factor beta, IL-1: interleukin 1.

Atherogenesis is driven by signals mediated by cytokines and growth factors generated by all the major types of cells participating in the process: endothelial cells, macrophages, T lymphocytes and vascular smooth muscle cells (VSMC).

Multiple activation paths:

- the expression of MCP-1 and VCAM-1 may be stimulated by signals generated macrophages as well as by the oxidized LDL.
- VSMC may be stimulated by the dysfunctional endothelial cells, by macrophages, and by T lymphocytes (also the autocrine activation).
- Note that a hormone, angiotensin II also participates in these processes.

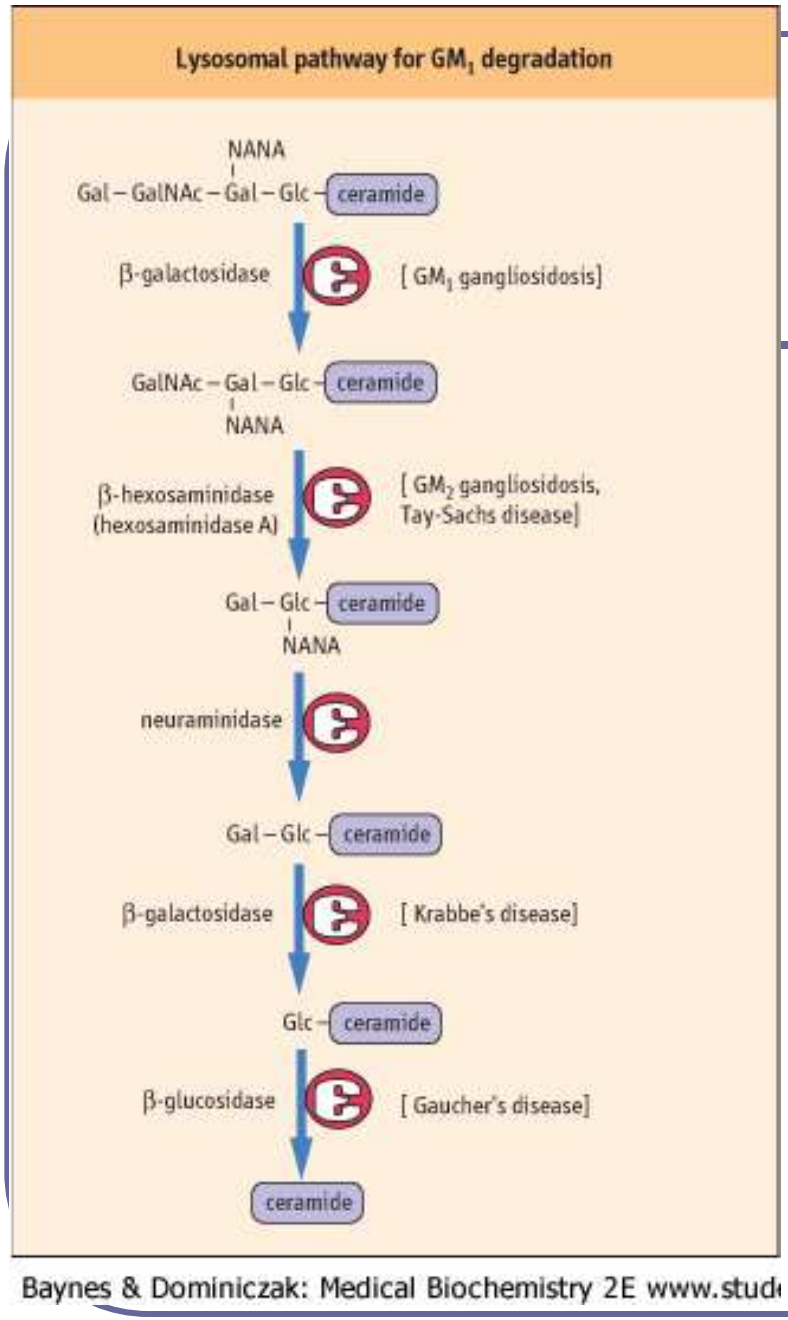
Structure of GM1 Ganglioside



Gangliosides: These are the most complex glycosphingolipids, and are found primarily in the ganglion cells of the central nervous system, particularly at the nerve endings. They are derivatives of ceramide oligosaccharides, and contain one or more molecules of NANA.

The notation for these compounds is G (for ganglioside) plus a subscript M, D, T, or Q to indicate whether there is one (mono), two, three, or four (quatro) molecules of NANA in the ganglioside, respectively. Additional numbers and letters in the subscript designate the sequence of the carbohydrate attached to the ceramide.

Gangliosides are of medical interest because several lipid storage disorders involve the accumulation of NANA-containing glycosphingolipids in cells.

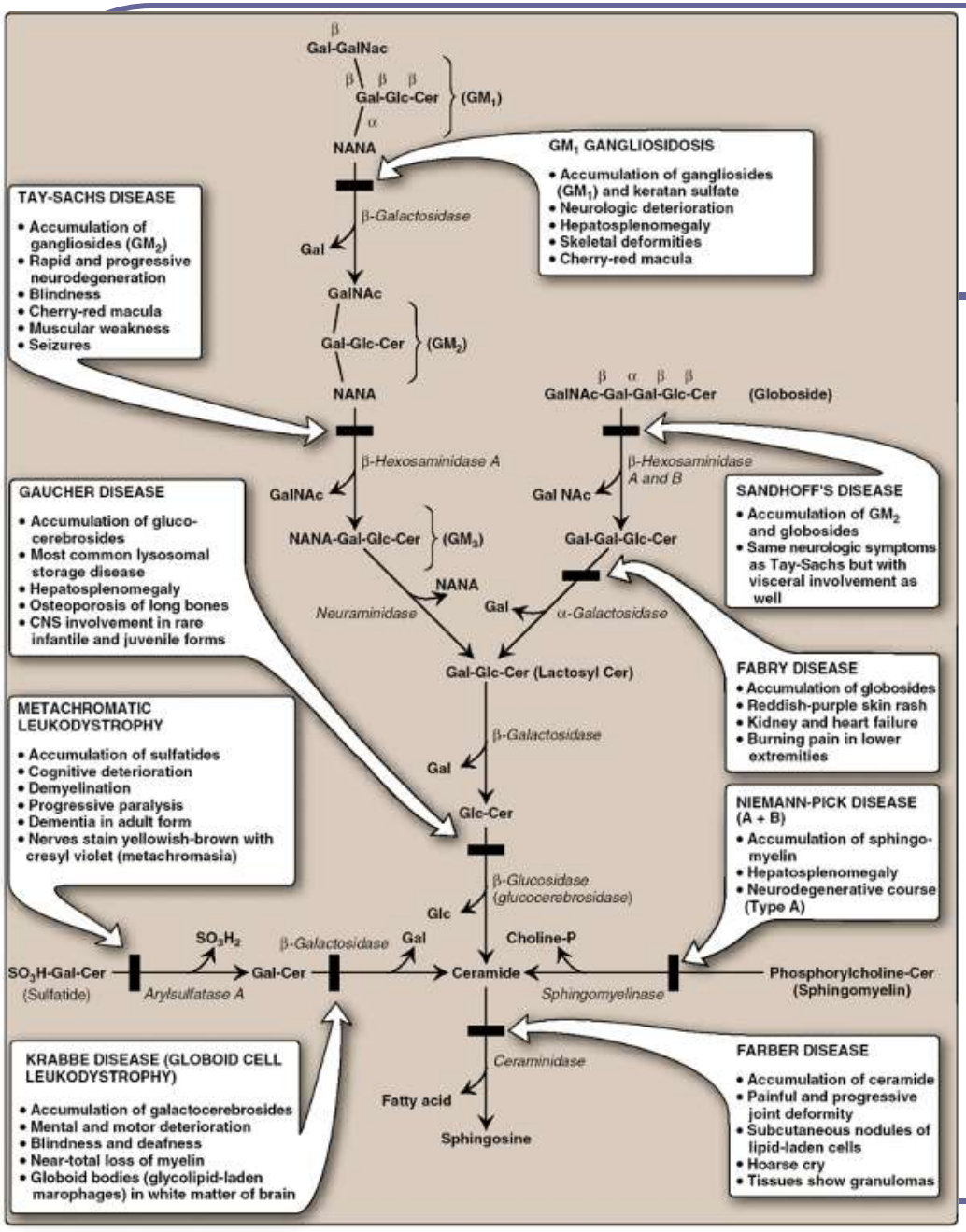


Lysosomal pathway for turnover of ganglioside GM1 in human cells

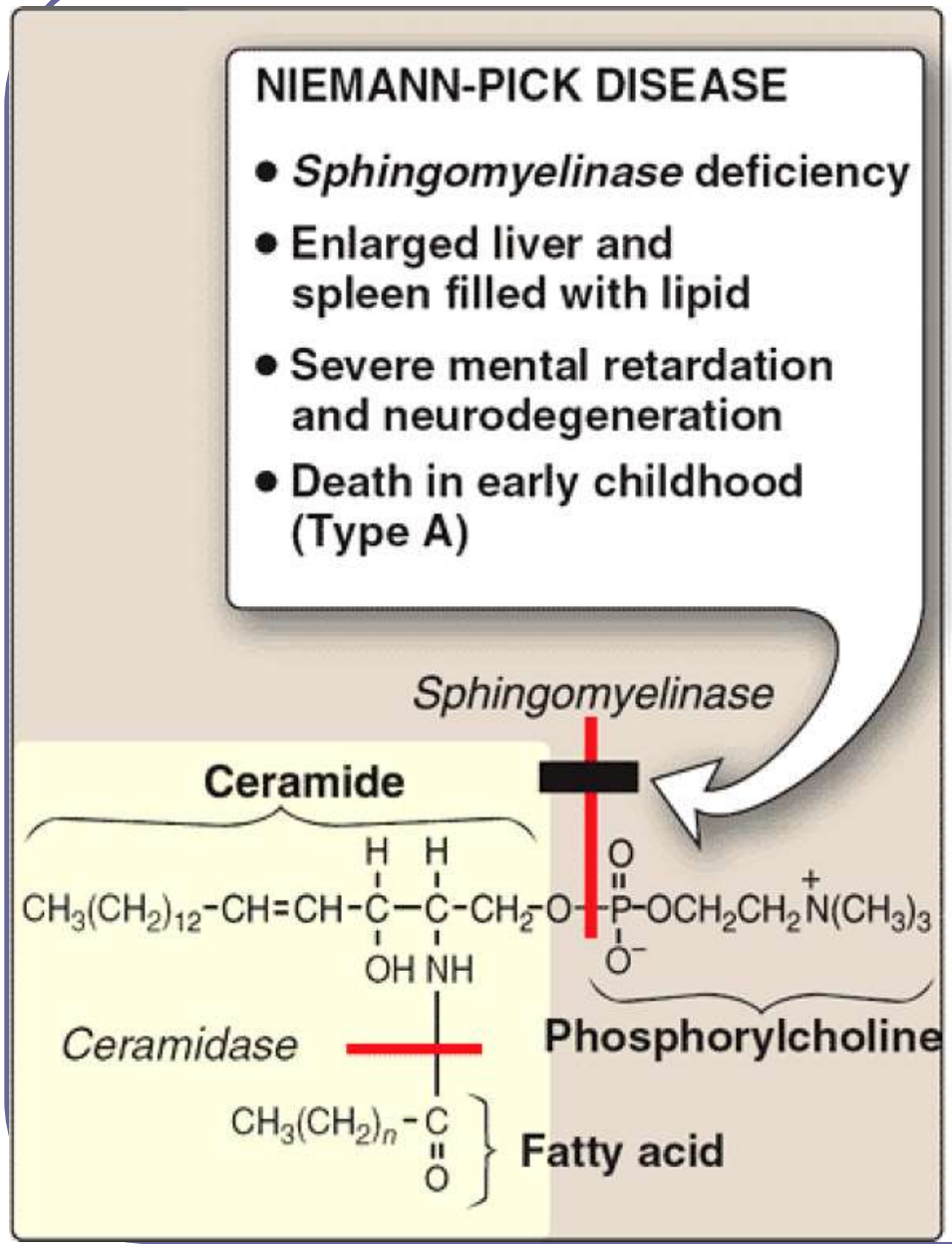
Various enzymes may be missing in specific lipid storage diseases.

- Gal, galactose;
- GalNAc, N-acetylgalactosamine;
- Glc, glucose;
- NANA, n-acetyl neuraminic acid.

Lipidoses: Sphingolipidoses & Gangliosidoses



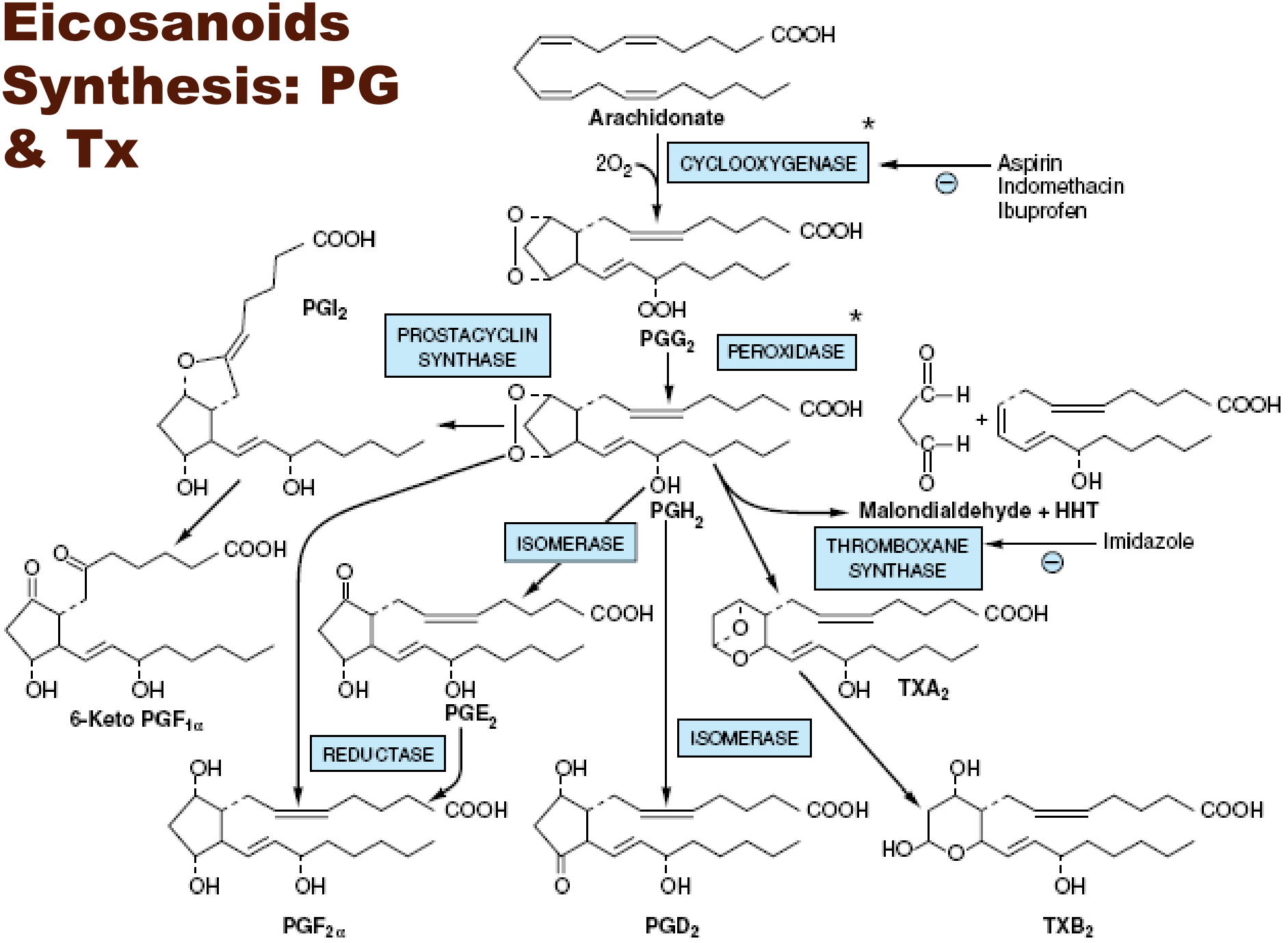
- Degradation of sphingolipids showing the enzymes affected in related genetic diseases, the sphingolipidoses.
- All of the diseases are autosomal recessive except Fabry disease, which is X-linked, and all can be fatal in early life.
- Cer = ceramide.



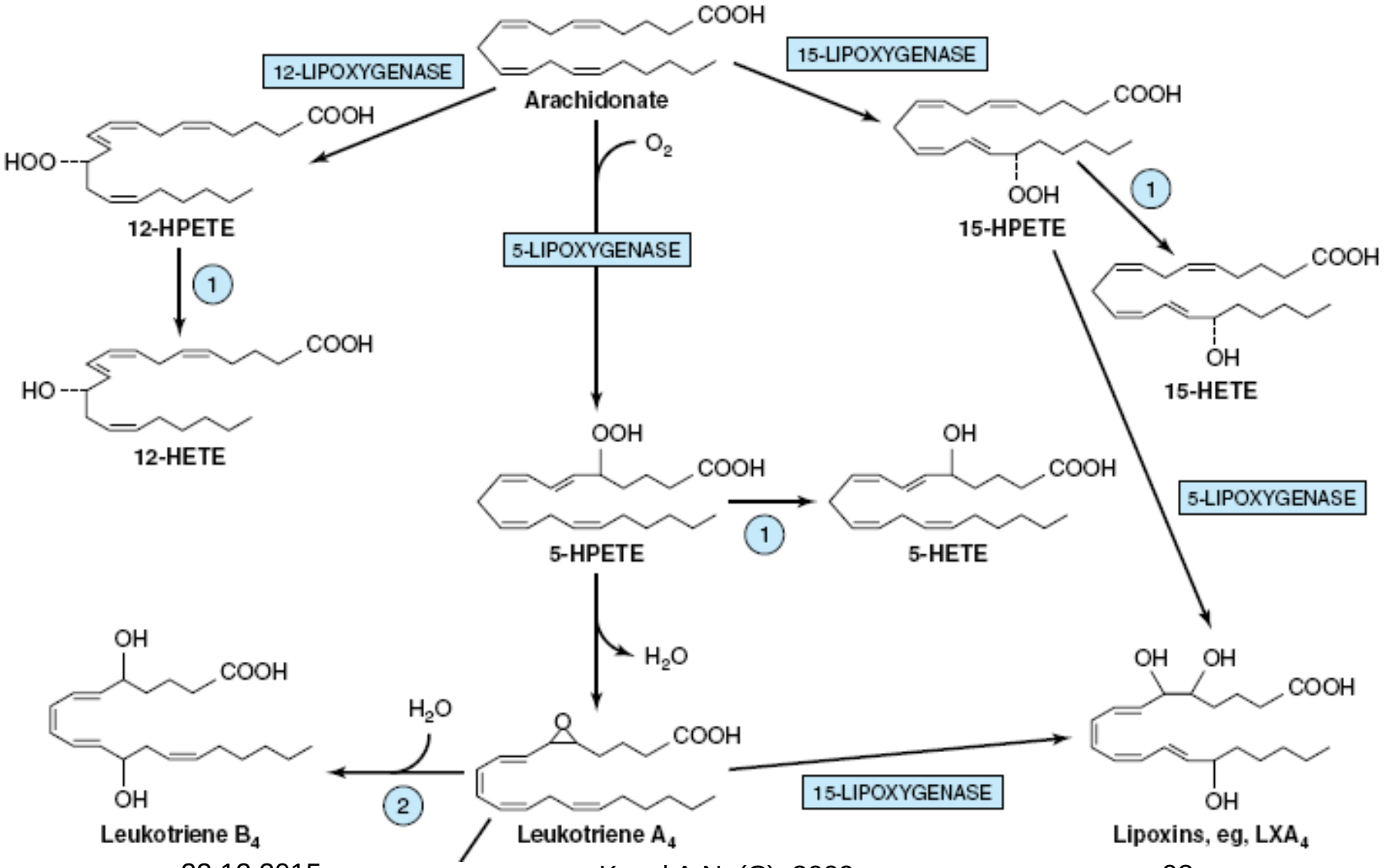
Niemann-Pick Disease

- Niemann-Pick disease (Types A and B) is an autosomal recessive disease caused by the inability to degrade sphingomyelin.
- Type A:
  - The deficient enzyme is sphingomyelinase - a type of phospholipase C. In the severe infantile form (Type A - less than 1% normal activity), the liver and spleen are the primary sites of lipid deposits and are, therefore, tremendously enlarged.
  - The lipid consists primarily of the sphingomyelin that cannot be degraded.
  - Infants with this disease experience rapid and progressive neurodegeneration as a result of deposition of sphingomyelin in the central nervous system, and they die in early childhood.
- Type B:
  - A less severe variant (Type B - 5% or more) causes little to no damage to neural tissue, but lungs, spleen, liver, and bone marrow are affected, resulting in a chronic form of the disease, with a life expectancy into adulthood.
- Niemann-Pick disease occurs with greater frequency in the Ashkenazi Jewish population.

Eicosanoids Synthesis: PG & Tx



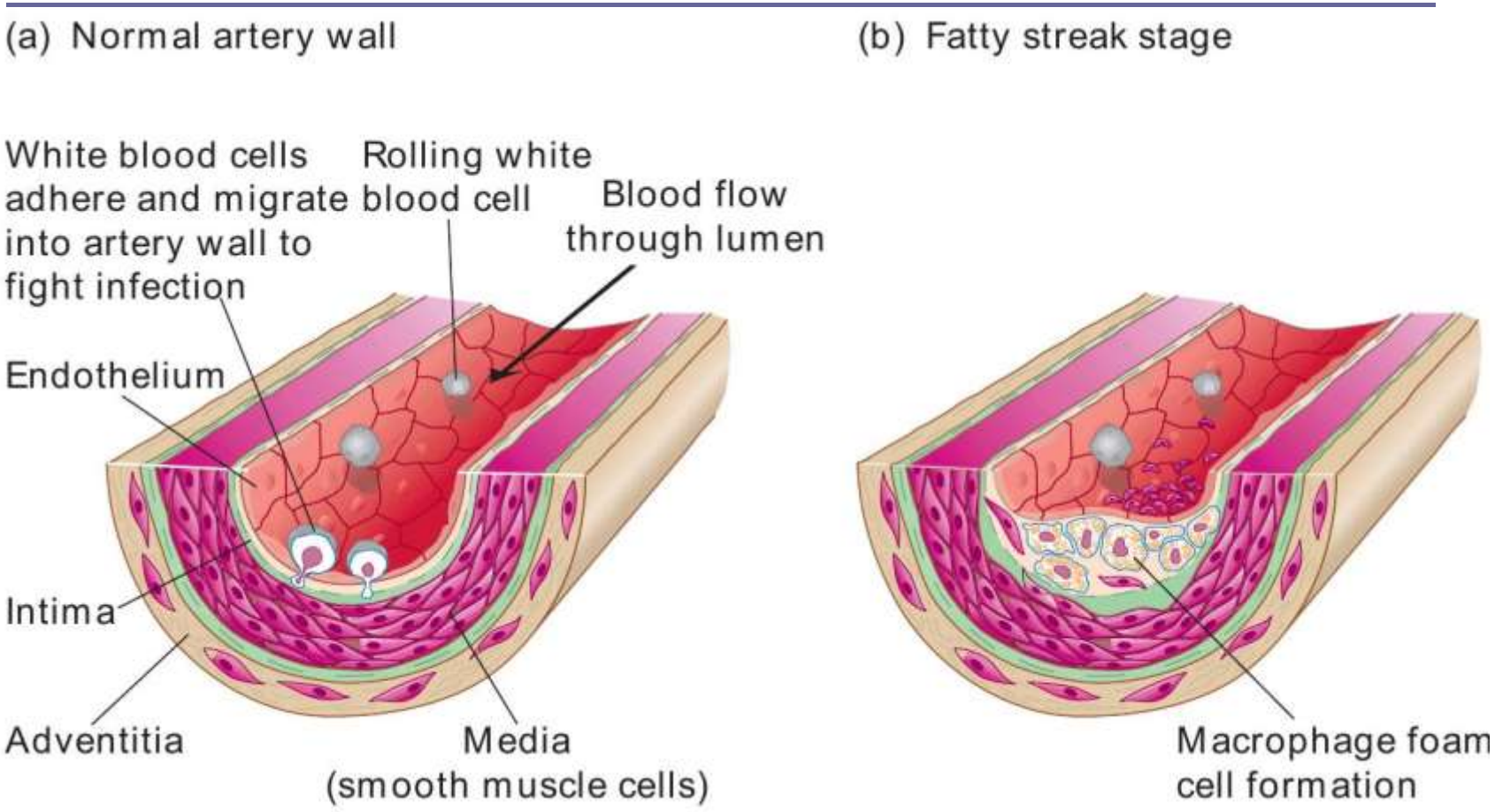
Eicosanoids: Leukotriens



Eicosanoids: Leukotriens (2)

PATHOLOGY OF LIPID METABOLISM. ATHEROGENESIS

Normal Artery and Fatty Streak Stage



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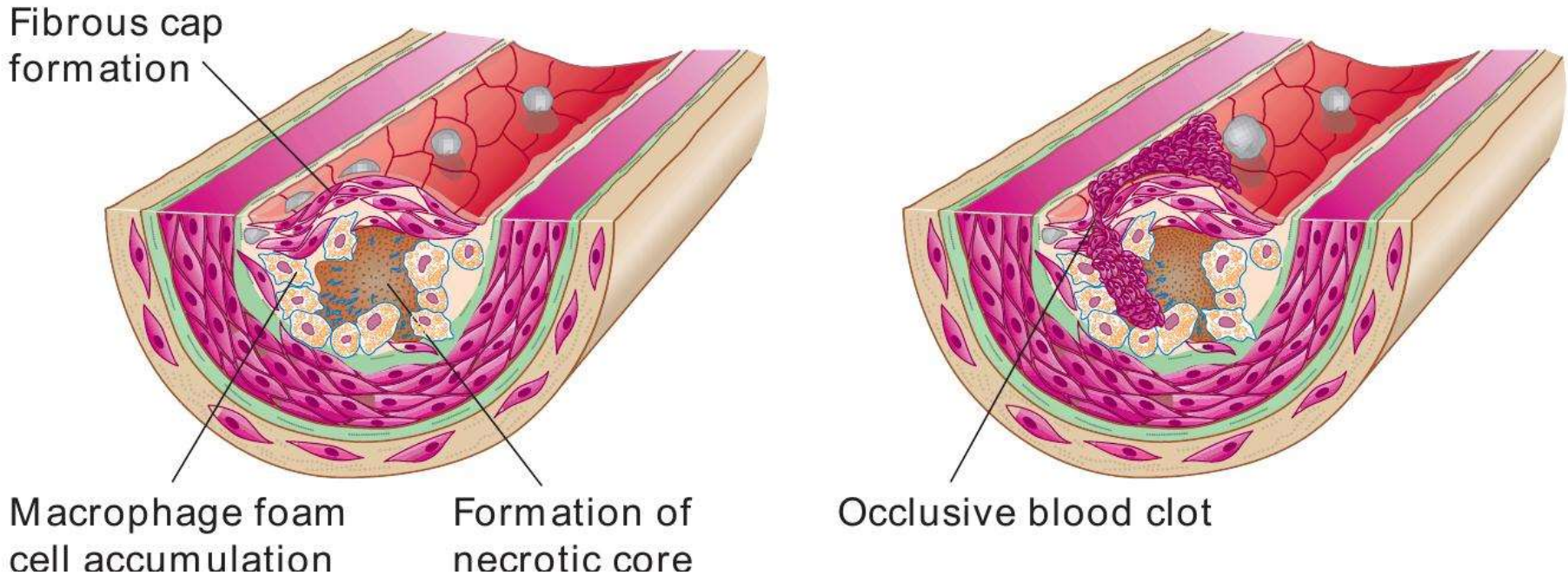
Plaque Stage and Rupture of Endothelium With Blood Clot Formation

(c) Atherosclerotic plaque stage

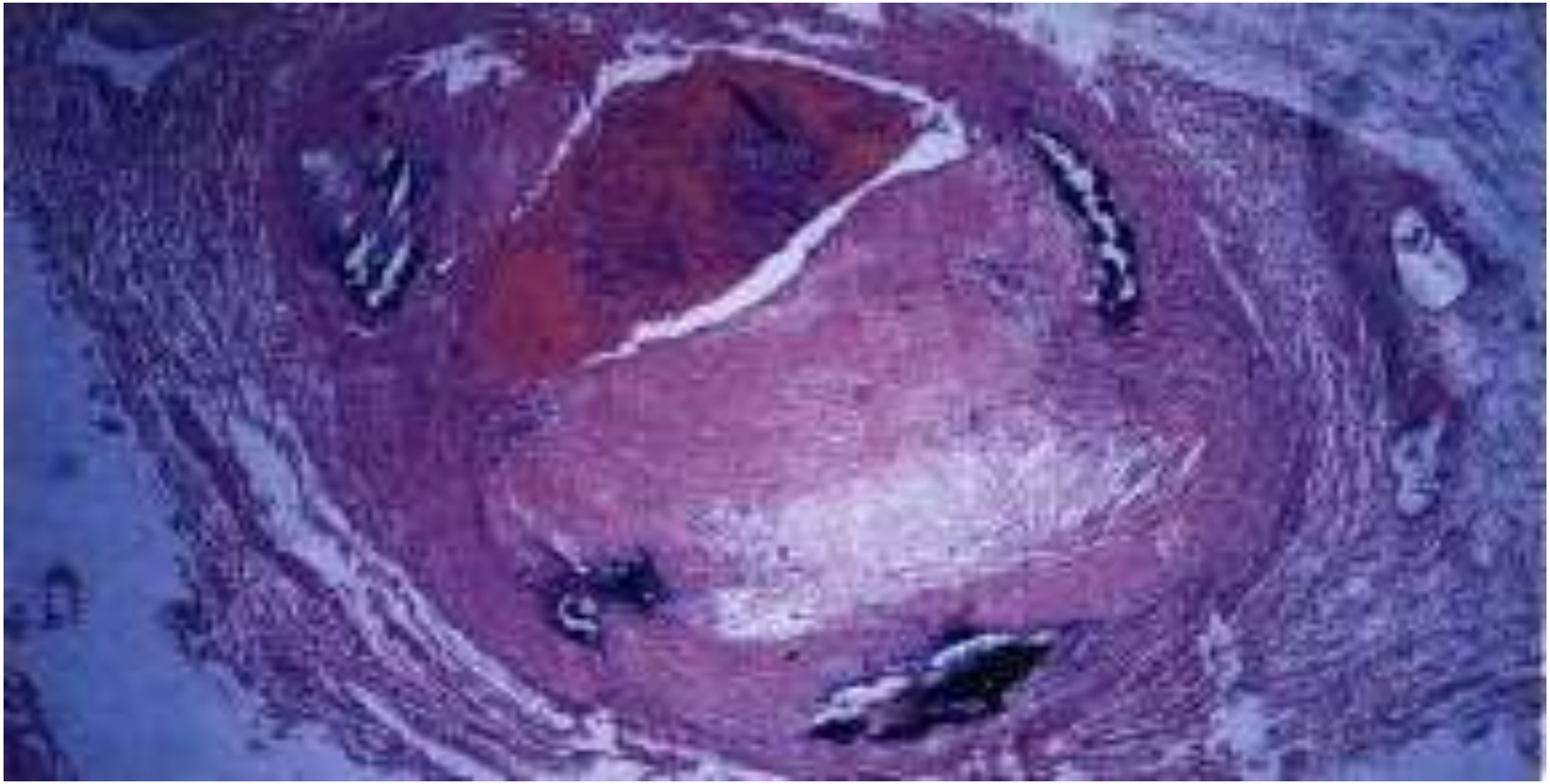
(d) Rupture of endothelium and occlusive blood clot formation



Molecular Cell Biology Lodish 5Th Ed

Artery in Health Man

Plaque Formation: Artery Blocked



Genetic Basis of Familial Hypercholesterolemia

- FH is an inherited disorder comprising four different classes of mutation in the LDL receptor gene.
  - The class 1 defect (the most common) results in a complete loss of receptor synthesis.
  - The class 2 defect results in the synthesis of a receptor protein that is not properly processed in the Golgi apparatus and therefore is not transported to the plasma membrane.
  - The class 3 defect results in an LDL receptor that is incapable of binding LDLs.
  - The class 4 defect results in receptors that bind LDLs but do not cluster in coated pits and are, therefore, not internalized.

Hyperlipoproteinemias

Disorder	Defect	Comments
Type I (familial LPL deficiency, familial hyperchylomicronemia)	(a) deficiency of LPL; (b) production of abnormal LPL; (c) apoC-II deficiency	slow chylomicron clearance, reduced LDL and HDL levels; treated by low fat/complex carbohydrate diet; no increased risk of coronary artery disease
Type II (familial hypercholesterolemia, FH)	4 classes of LDL receptor defect	reduced LDL clearance leads to hypercholesterolemia, resulting in athersclerosis and coronary artery disease
Type III (familial dysbetalipoproteinemia , remnant removal disease, broad beta disease, apolipoprotein E deficiency)	hepatic remnant clearance impaired due to apoE abnormality; patients only express the $apoE_2$ isoform that interacts poorly with the apoE receptor	causes xanthomas, hypercholesterolemia and athersclerosis in peripheral and coronary arteries due to elevated levels of chylomicrons and VLDLs

Lipid Peroxidation Is Source Of Free Radicals

- Peroxidation **(auto-oxidation)** of lipids is responsible for deterioration of foods **(rancidity);** for damage to tissues in vivo, where it may be a cause of **cancer**, **inflammatory diseases, atherosclerosis, and aging.**
- The deleterious effects are considered to be caused by **free radicals** (ROO•, RO•, OH•) produced during peroxide formation from fatty acids containing methylene-interrupted double bonds, ie, those found in the naturally occurring polyunsaturated fatty acids.

Lipid Peroxidation Is a Chain Reaction: Initiation

- Lipid peroxidation is a chain reaction providing a continuous supply of free radicals that initiate further peroxidation. The whole process can be depicted as follows:
- **(1)** Initiation:

$$ROOH + Metal^{(n)+} \rightarrow ROO^{\bullet} + Metal^{(n-1)+} + H^{+}$$

$$X^{\bullet} + RH \rightarrow R^{\bullet} + XH$$

Lipid Peroxidation: Propagation and Termination

- Propagation: $R^{\bullet} + O_2 \rightarrow ROO^{\bullet}$

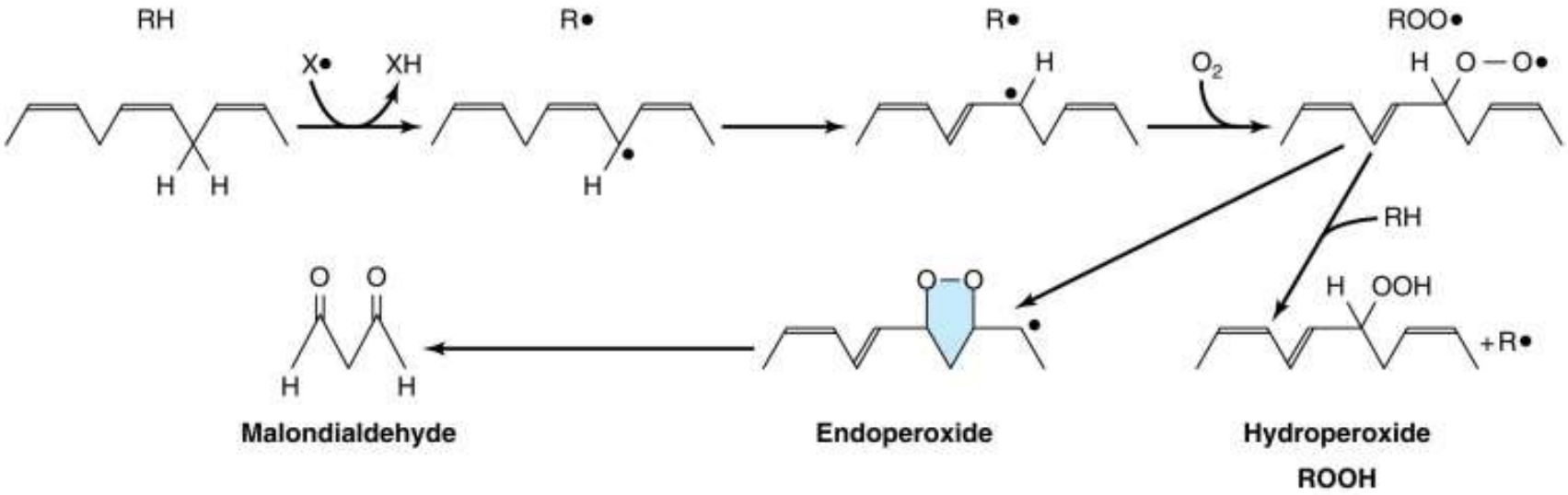
  $ROO^{\bullet} + RH \rightarrow ROOH + R^{\bullet}$, etc

- Termination: $ROO^{\bullet} + ROO^{\bullet} \rightarrow ROOR + O_2$

  $ROO^{\bullet} + R^{\bullet} \rightarrow ROOR$

  $R^{\bullet} + R^{\bullet} \rightarrow RR$

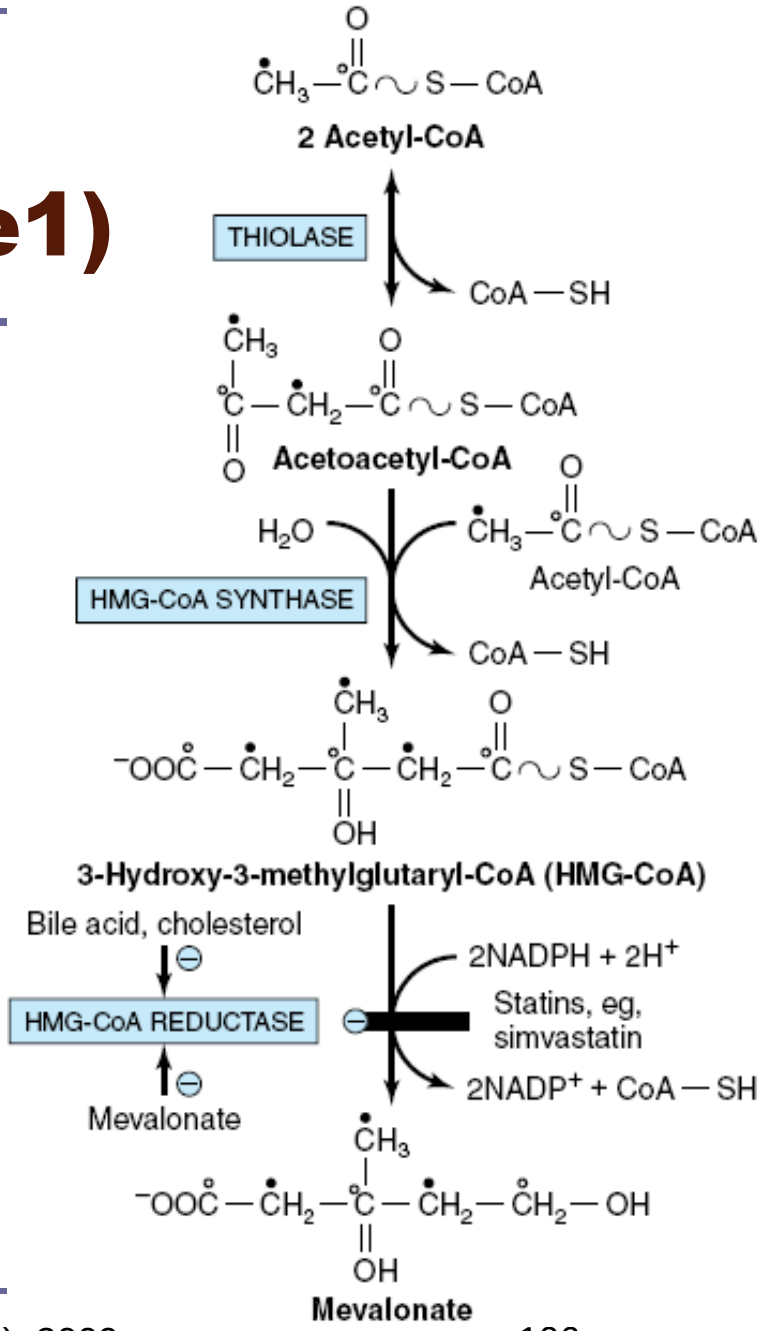
Lipid Peroxidation



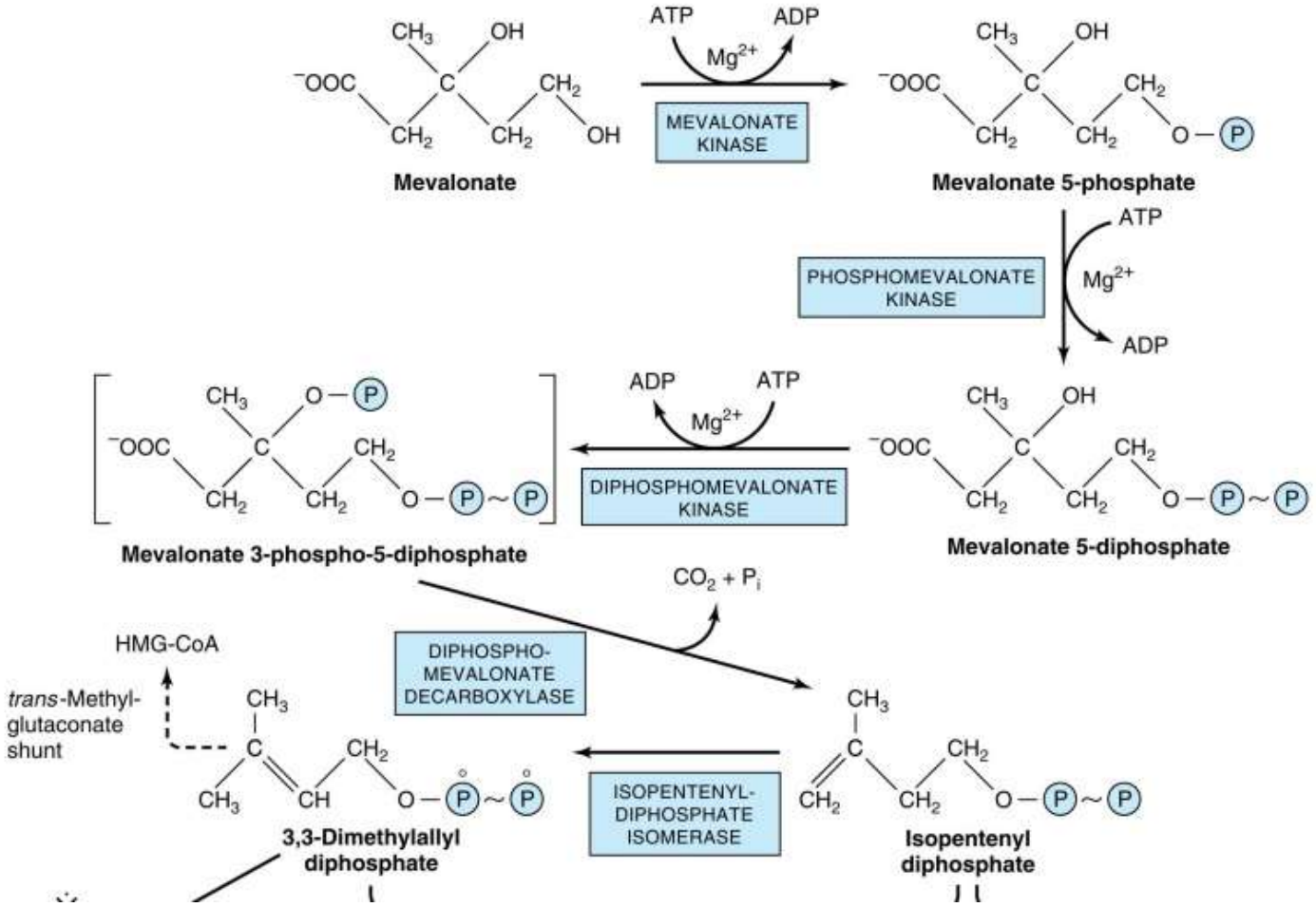
Lipid peroxidation. The reaction is initiated by an existing free radical (X•), by light, or by metal ions. Malondialdehyde is only formed by fatty acids with three or more double bonds and is used as a measure of lipid peroxidation together with ethane from the terminal two carbons of ω3 fatty acids and pentane from the terminal five carbons of ω6 fatty acids.

(from Marry, Grenner et al. "Harpers Illustrated Biochemistry", 2004)

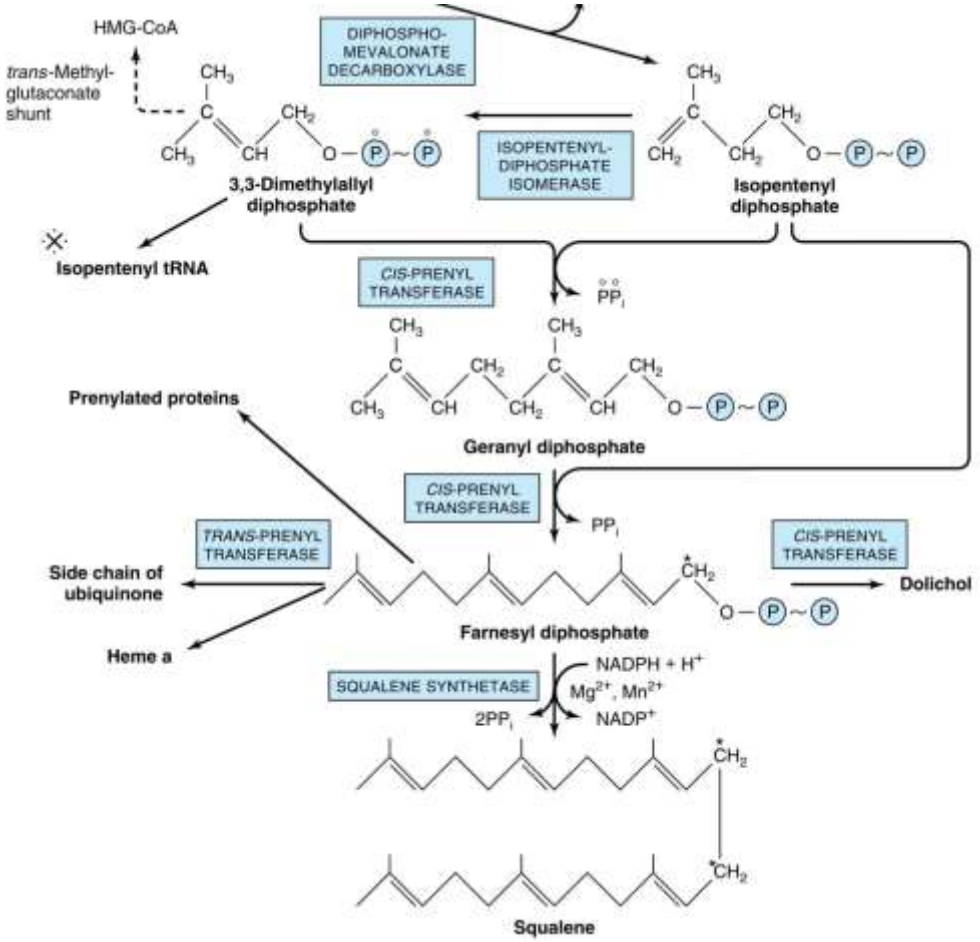
Cholesterol Biosynthesis (stage1)



Cholesterol Biosynthesis (stage 2)



Cholesterol Biosynthesis (stage 3)



Next time…

- …we'll start the new topic "Protein and Nucleic Acid Biochemistry" and discuss:
  - protein digestion in gastro-intestinal tract
  - amino acid absorption in the intestine.


Thank you
for your attention!