NATURE OF LIPIDS. Lipids have a hydrophobic nature because of the predominance of hydrocarbon chains ($—CH_2—CH_2—CH_2—$) in their structure. They are insoluble or only poorly soluble in water, but readily soluble in nonpolar solvents such as ether and benzene.

Some common classifications of lipids and their general biologic functions

Lipid	Primary Functions
Fatty acids	Energy sources, biosynthetic precursors
Triacylglycerols	Storage, transport
Phosphoglycerides	Membrane components
Ketone bodies	Energy sources
Sphingolipids	Membrane components
Eicosanoids	Modulators of physiologic activity
Cholesterol	Membrane component
Steroid hormones	Modulators of physiologic activity

Fatty acids are water-insoluble, saturated or unsaturated, long-chain hydrocarbons with a carboxyl group at the end of the chain

Predominant Fatty Acids Found in Mammalian Tissues

Common Name	Systematic Name	No. Carbon Atoms	No. Double Bonds	Melting Point (°C)
Lauric	Dodecanoic	12	0	43.5
Myristic	Tetradecanoic	14	0	54.4
Palmitic	Hexadecanoic	16	0	62.8
Stearic	Octadecanoic	18	0	69.6
Pamitoleic	cis-Δ^9-Hexadecenoic	16	1	1.0
Oleic	cis-Δ^9-Octadecenoic	18	1	13.0
Linoleic	all cis-Δ^9,Δ^{12}-Octadecadienoic	18	2	-11.0
Linolenic	all cis-$\Delta^9,\Delta^{12},\Delta^{15}$-Octadecatrienoic	18	3	-11.2
Arachidonic	all cis-$\Delta^5,\Delta^8,\Delta^{11},\Delta^{14}$-Eicosatetraenoic	20	4	-49.5

1. **Saturated fatty acids** do not have double bonds in the chain.
    a. **Nomenclature. The systematic name** gives the number of carbons, with the suffix *-anoic* appended. Palmitic acid, for example, has 16 carbons and has the systematic name hexadecanoic acid.
    b. **Structure. The general formula** of saturated fatty acids is CH_3—$(CH_2)_n$-COOH, where *n* is the number of methylene groups between the methyl and carboxyl carbons.
2. **Unsaturated fatty acids** have one or more double bonds. In naturally occurring fatty acids, these bonds are always in a cis as opposed to a *trans* configuration (i.e., the single hydrogens bonded to each carbon are oriented in the same direction). The most commonly used system for designating the position of double bonds in an unsaturated fatty acid is the delta (Δ) numbering system.
    a. **Numbering system.** The terminal carboxyl carbon is designated C-1, and the double bond is given the number of the carbon on the carboxyl side of the double bond. For example, palmitoleic acid, which has 16 carbons and a double bond between C-9 and C-10, is designated $16:1:\Delta^9$, or 16:1:9.
    b. The **systematic name** gives the number of carbon atoms, number of double bonds (unless it has only one), and bears the suffix *-enoic*. Thus, linoleic acid, with 18 carbons and two c/s double bonds, is cis-Δ^9,Δ^{12}-octadecadienoic acid.

Source of fatty acids

1. Nonessential fatty acids. Nonessential fatty acids can be synthesized from products of glucose oxidation and do not, therefore, have to be included in the diet.

2. Essential fatty acids. Fatty acids of the linoleic ($18:2:\Delta^{9,12}$) and linolenic ($18:3:\Delta^{9,12,15}$) families must be obtained from the diet.

Physical properties

1. Fatty acids are detergent-like because of their **amphipathic nature.** They have non-polar (CH_3) and polar (—COOH) ends. In biphasic systems, they orient with the polar end associated with water and the nonpolar end associated with the hydrophobic phase.

2. The melting point of fatty acids is related to chain length and degree of unsaturation. The longer the chain length, the higher the melting point; the greater the number of double bonds, the lower the melting point.

Triacylglycerols (triglycerides)

1. **Structure.** Triacylglycerols are triesters of glycerol and three fatty acids.
2. **Function.** Fatty acids are converted to triacylglycerols for transport between tissues and for storage of metabolic fuel. a. The main stores of metabolic fuel in humans are the fat deposits in fat cells **(adipocytes).** These serve long-term needs for metabolic fuel.

   a. Triacylglycerols have two major advantages over other forms of metabolic fuel.

   (1) Triacylglycerols provide a concentrated form of fuel because their complete combustion to carbon dioxide (CO_2) and water releases 9 kcal/g as opposed to 4 kcal/g for carbohydrate.
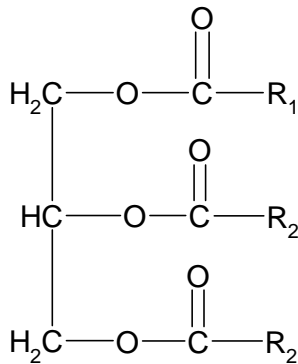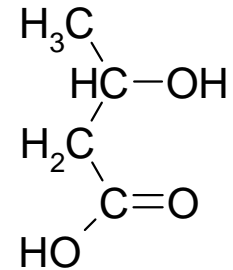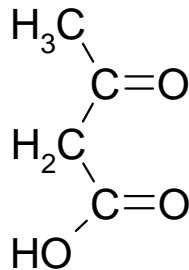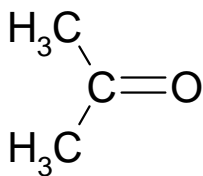

$R = $ a fatty acid

   (2) Because they are water insoluble, triacylglycerols present no osmotic problems to the cell when stored in large amounts.

   b. **Lipolysis** involves the **hydrolysis of triacylglycerols to free glycerol and free fatty acids** (also known as **nonesterified fatty acids**) with both products leaving the adipocyte. The appearance of fatty acids in the blood during fasting is due to the mobilization of fat stores by this process.

   (1) **Utilization of fatty acids.** Fatty acids are used by most tissues, except the brain, as a metabolic fuel.
   (2) **Utilization of glycerol.** Glycerol is used by the liver as a substrate for gluconeogenesis .

1. **Ketone bodies,** which are formed from fatty acids and carbohydrates, include acetone, acetoacetate, and β-hydroxybutyrate.

$$\begin{array}{ccc} H_3C & H_3C & H_3C \\ \searrow & \searrow & \searrow \\ C=O & C=O & HC-OH \\ \nearrow & \nearrow & | \\ H_3C & H_2C & H_2C \\ & \searrow & \searrow \\ & C=O & C=O \\ & \nearrow & \nearrow \\ & HO & HO \end{array}$$

  a. Ketone bodies are synthesized in liver mitochondria and released into the blood for use as metabolic fuel by other tissues. **The liver does not use ketone bodies.**
  b. Levels of synthesis are high when the rate of fatty acid oxidation is high and carbohydrate utilization is low. This occurs during fasting, starvation, untreated diabetes, and prolonged alcohol abuse.
2. **Ketoacidosis** is an imbalance of blood pH caused by the excessive accumulation of acetoacetate or β-hydroxybutyrate, which are weak acids.
  a. **Ketosis** refers to **ketonuria** (high urine levels of ketone bodies) and **ketonemia** (high blood levels of ketone bodies).
  b. During starvation, ketone bodies are the only source of fuel, so they are consumed by the body, and there is no excess to accumulate. In contrast, in untreated diabetes, blood levels of ketone bodies may become high enough to produce life-threatening ketoacidosis.

PHOSPHOLIPIDS are the major lipid constituents of cellular membranes. They comprise approximately 40% of the lipids in the erythrocyte membrane and more than 95% of the lipids in the inner mitochondrial membrane.

Phosphoglycerides are triesters of glycerol-3-phosphate in which two esters have been formed between the two hydroxyl groups and fatty acid side chains (R_1 and R_2), and a third ester has been formed between the phosphate group and a hydroxyl-containing compound, X.

(structure diagram)	R = a fatty acid; X = a hydroxy-containing compound.
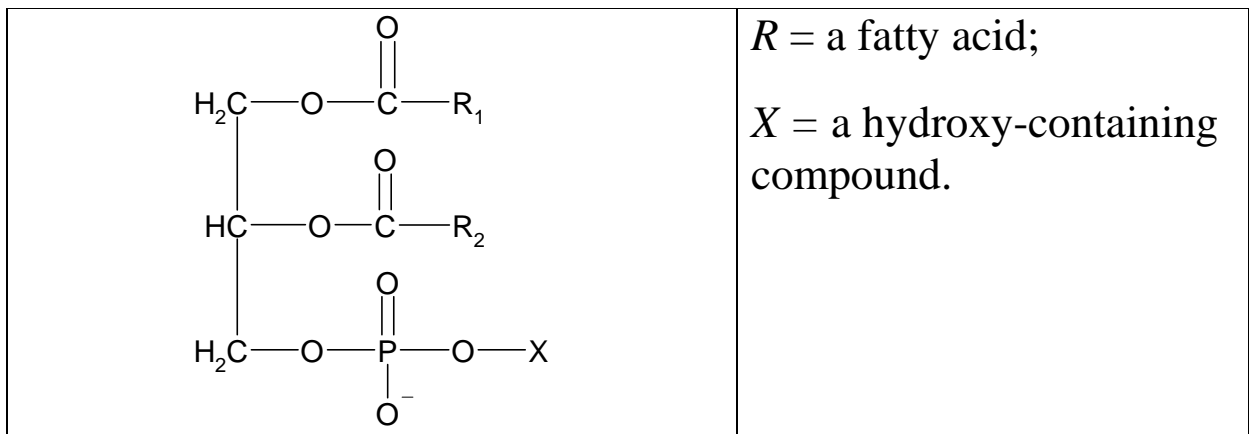
Classification of phosphoglycerides. Phosphoglycerides include the following compounds:

1. **Phosphatidylcholine** (lecithin)
2. **Phosphatidylethanolamine** (a cephalin)
3. **Phosphatidylserine** (a cephalin)
4. **Phosphatidylinositol**
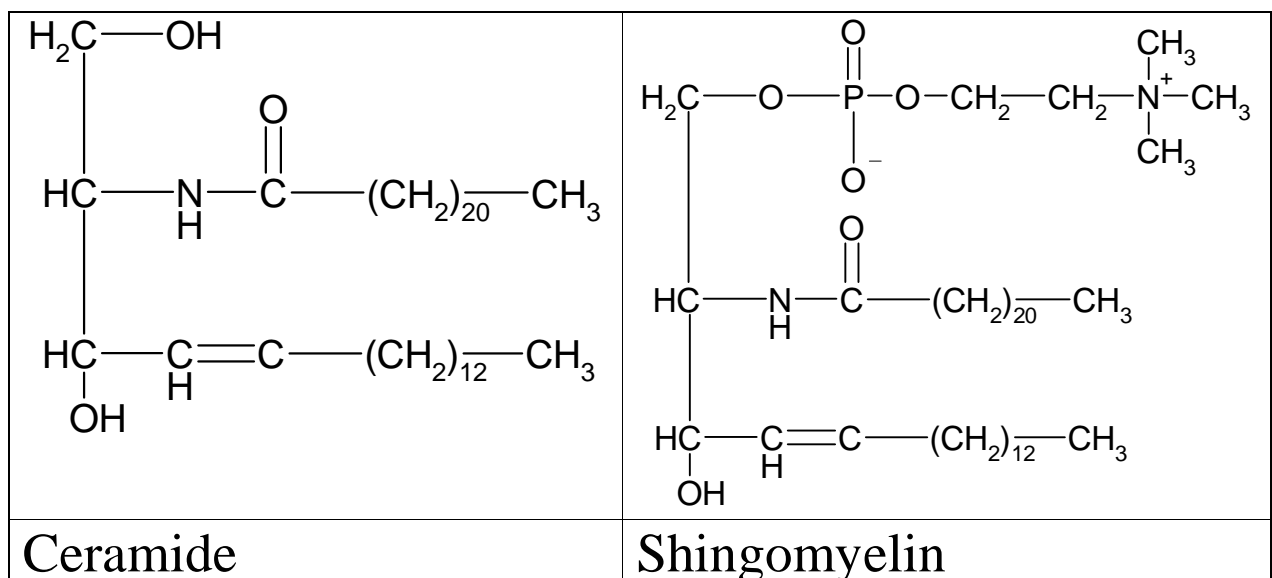5. **Cardiolipin,** which comprises approximately 20% of the lipids of the inner mitochondrial membrane

Characteristics of phosphoglycerides

1. Phosphoglycerides are the most polar lipids and are **amphipathic,** possessing **both hydrophilic and hydrophobic groups.** They inhabit transition regions between aqueous and nonaqueous phases.
3. Phosphoglycerides are **amphoteric,** bearing **both negatively and positively charged groups.**

SPHINGOLIPIDS are present in nearly all human tissues. The greatest concentration of sphingolipids is found in the central nervous system (CMS), particularly in white matter.

1. Function. Sphingomyelin is the major phospholipid component of membranes in neural tissues.

2. Structure. Sphingomyelin, which is derived from the amino alcohol, sphingosine, is the only sphingolipid that contains phosphate and has no sugar moiety. It is formed from **ceramide,** which is the **core structure** of naturally occurring sphingolipids, including the glycosphingolipids.

Ceramide	Shingomyelin
H_2C—OH HC—NH—$C(=O)$—$(CH_2)_{20}$—CH_3 HC—CH=C—$(CH_2)_{12}$—CH_3 OH	H_2C—O—$P(=O)(O^-)$—O—CH_2—CH_2—$N^+(CH_3)_3$ HC—NH—$C(=O)$—$(CH_2)_{20}$—CH_3 HC—CH=C—$(CH_2)_{12}$—CH_3 OH

Glycosphingolipids are sphingolipids that contain carbohydrate moieties.

1. Cerebrosides are ceramide monohexosides, the most important being **galactocerebroside and glucocerebroside.** Cerebrosides are found in neural tissue membranes, particularly the myelin sheath.
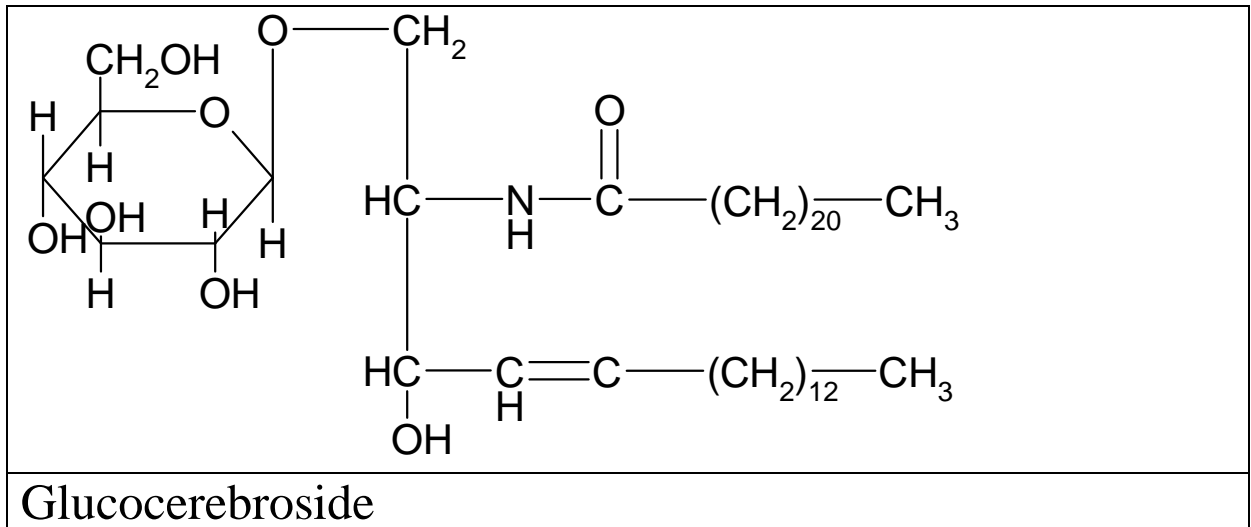
Glucocerebroside

2. Sulfatides are Cerebrosides that contain sulfated sugars. (b-**Sulfogalactocerebroside** accounts for approximately 15% of the lipids in white matter of the brain.

3. Globosides are ceramide oligosaccharides that contain two or more sugar molecules, most often galactose, glucose, or N-acetylgalactosamine, attached to ceramide. They are found in serum, the spleen, the liver, and erythrocytes. For example, **lactosylceramide** is found in erythrocyte membranes.

4. Gangliosides

a. Nature

Gangliosides are glycosphingolipids that contain one or more neuraminic acid residues, usually as the N-acetyl derivative [i.e., **N-acetylneuraminic acid** (NANA)], which is **sialic acid.** They are found in high concentration in ganglion cells of the CNS and in lower concentration in the membranes of most cells.

b. Nomenclature

(1) The letter G is used to denote a ganglioside, with M, D, T, or Q to indicate, respectively, mono-, di-, tri-, or quatrosialic acid contents. Numerical subscripts are based on their chromatographic migration. For example:

GM_1 = Gal-(N-AcGal)-Gal-Glc-Cer

GM_2 = (N-AcGal)-Gal-Glc-Cer

GM_3 = Gal-Glc-Cer

where *Cer* = ceramide, *Glc* = glucose, *Gal* = galactose, and *N-AcGal* = N-acetylgalactosamine.

(2) For example, the GM_2 ganglioside is:

(N-AcGal)-Gal-Glc-Cer
 |
 |
NANA
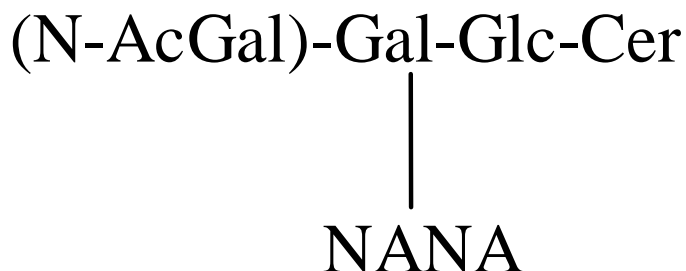
Sphingolipidoses are inherited genetic disorders referred to as **lipid storage diseases,** in which there is a deficiency of an enzyme that is involved in the normal catabolism of a particular sphingolipid. This results in the intracellular accumulation of that lipid to harmful levels.

Sphingolipidoses

| Disease	Lipid Accumulated	Enzyme Deficiency	Primary Organ Affected
Niemann-Pick	Sphingomyelin	Sphingomyelinase	Brain, liver, spleen
Gaucher's	Glucocerebroside	β-Glucosidase	Brain, liver, spleen
Krabbe's	Galactocerebroside	β-Galactosidase	Brain
Metachromatic leukodystrophy	β-Sulfogalacto-cerebroside	Sulfatide sulfatase	Brain
Fabry's	Ceramide trihexoside	α-Galactosidase	Kidneys
Tay-Sachs	Ganglioside GM_2	Hexosaminidase A	Brain

Digestion of lipids

1. **Triacylglycerol** is the major dietary lipid of nutritional value.
2. **Emulsification**
   a. Digestion of lipids begins in the duodenum, when the entrance of the **acid chyme** from the stomach stimulates secretion of enteric hormones by the duodenal mucosa.
   b. **Bile salts and phosphatidylcholine** act as detergents in the duodenum due to their amphipathic structures. They aid in formation of mixed micelles (which have a large surface area) from fat globules (which have a small surface area).
   c. The micellar associations of lipids are the substrates for hydrolyzing enzymes.
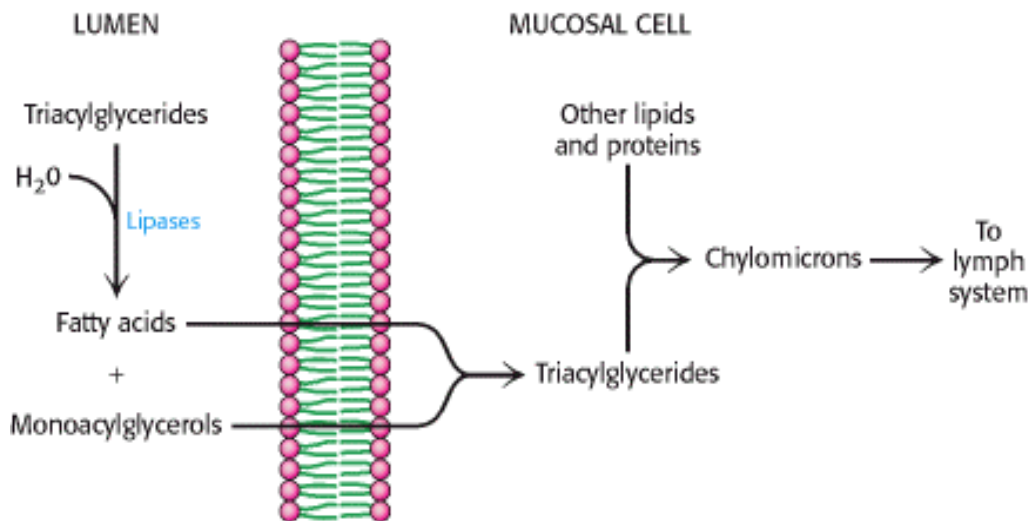3. **Hydrolysis of triacylglycerols is effected by three enzymes.**
   a. **Pancreatic lipase** cleaves triacylglycerols to 2-monoacylglycerol and two fatty acids.
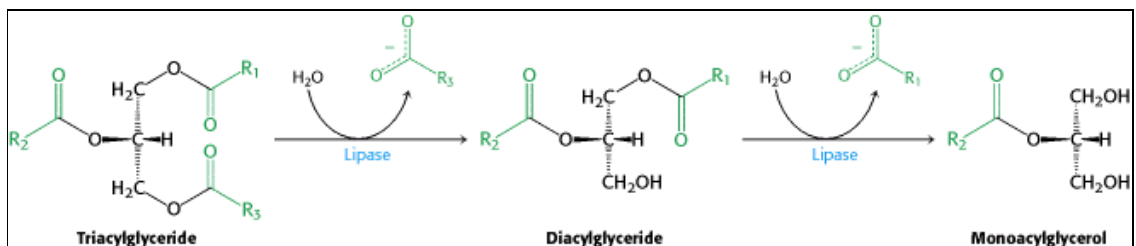

   b. **Cholesterol esterase** hydrolyzes cholesterol esters to cholesterol plus a fatty acid.
   c. **Phospholipase** A_2 hydrolyzes phospholipid.

CHYLOMICRON FORMATION

Free fatty acids and monoacylglycerols are absorbed by intestinal epithelial cells. Triacylglycerols are resynthesized and packaged with other lipids and apoprotein B-48 to form chylomicrons, which are then released into the lymph system.

LUMEN   MUCOSAL CELL

Triacylglycerides

H_2O

Lipases

Fatty acids
+
Monoacylglycerols

Other lipids and proteins

Chylomicrons → To lymph system

Triacylglycerides

Schematic Model of Low-Density Lipoprotein. The LDL particle is approximately 22 nm (220 Å) in diameter.
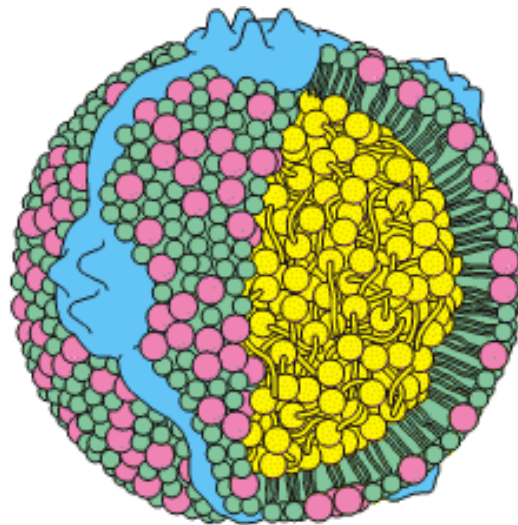
Unesterified cholesterol
Phospholipid
Cholesteryl ester
Apoprotein B-100

Sites of lipoprotein formation and transport

1. The liver is the formation site of:
   a. **Very low-density lipoproteins (VLDL),** which transport triacylglycerols from the liver to other tissues
   b. **High-density lipoproteins (HDL),** which transport excess cholesterol from other tissues to the liver and are sometimes referred to as "good" cholesterol
2. **The intestine** is the site of **chylomicron formation.** Chylomicrons are triacylglycerols that are given a coat composed of protein, phospholipids, and cholesterol esters.
   a. Chylomicrons are transported in membrane-bound vesicles to membranes of mucosal cells, where they are released by exocytosis into the extracellular space. Once chylomicrons are in the plasma, most of the lipids contained in the chylomicrons are removed by lipoprotein lipase, forming **chylomicron remnants,**
   b. Chylomicron remnants deliver dietary fat to the liver. The chylomicron remnants that remain after delipidation are enriched in cholesterol and cholesterol ester. They are cleared by the liver, where most of the cholesterol is used for bile acid synthesis.
3. **The plasma** is the formation site of:
   a. **Intermediate-density lipoproteins (IDL),** which are the initial product of VLDL degradation
   b. **Low-density lipoproteins (LDL),** which transport cholesterol esters
   c. **Chylomicron remnants**

Properties of Major Plasma Lipoproteins

	HDL	LDL	IDL	VLDL	Chylomicron
Density (g/ml)	1.06-1.2	1.02-1.06	1.01-1.02	0.95-1.01	<0.95
Diameter (nm)	5-20	20-25	25-30	30-90	90-1 000
% Lipid	50-55	75-80	80-85	90-95	98
% Total lipid as:					
Cholesterol (free)	3-4	7-10	8	5-10	1-3
Cholesterol ester	12	35-40	22	10-12	3-5
Phospholipid	20-25	15-20	22	15-20	7-9
Triacylglycerol	3	7-10	30	50-65	84-89
% Protein content	45-50	20-25	15-20	5-10	2
% Total protein as apoprotein (Apo):					
ApoA-1,A-2,A-4	90-95	0	0	0-3	0-3
ApoB-48,B-100	0-2	95-100	50-60	40-50	20-22
ApoC-1,C-2,C-3	4-6	0-5	20	35-40	60-65
ApoD	0-2	0	0	0	1
ApoE	0-5	0	15-20	5-10	5

HDL = high-density lipoprotein; *IDL* = intermediate-density lipoprotein; *LDL* = low-density lipoprotein; *VLDL* = very low-density lipoprotein; *nm* = nanometer.
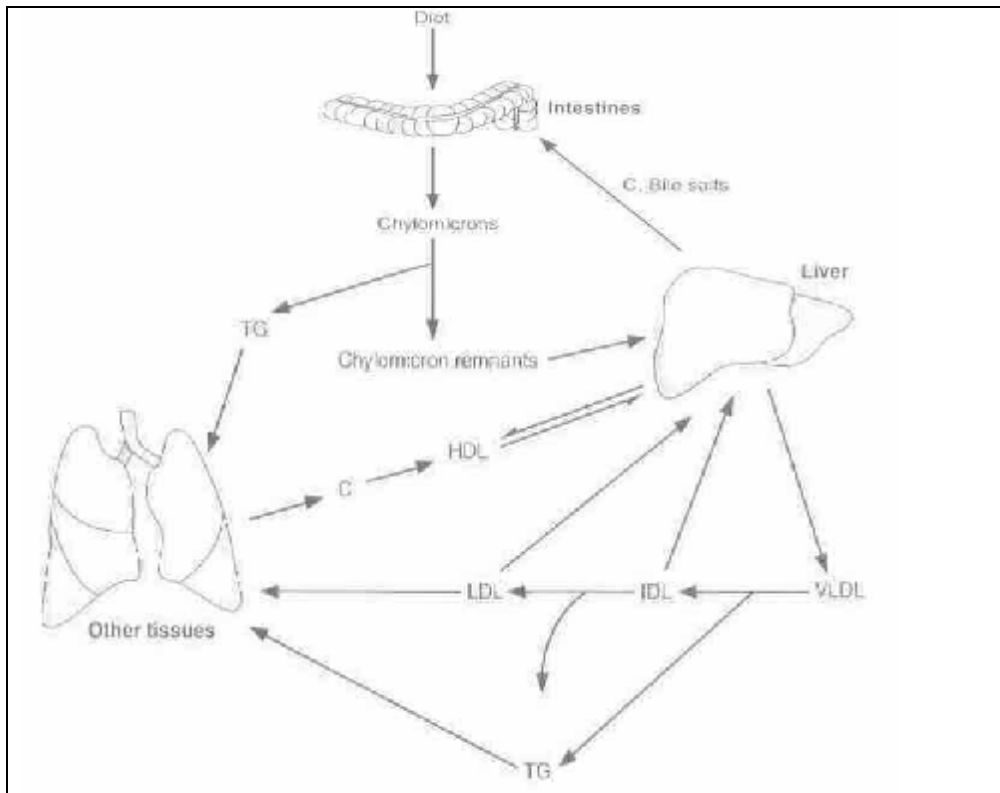
The metabolism and transport of plasma lipoproteins. C= cholesterol; *HDL* - high-density lipoprotein; *IDL* = intermediate-density lipoprotein; *LDL* = low-density lipoprotein; *TC* = triacylglycerols; *VLDL —* very low-density lipoprotein.

Receptor-Mediated Endocytosis.
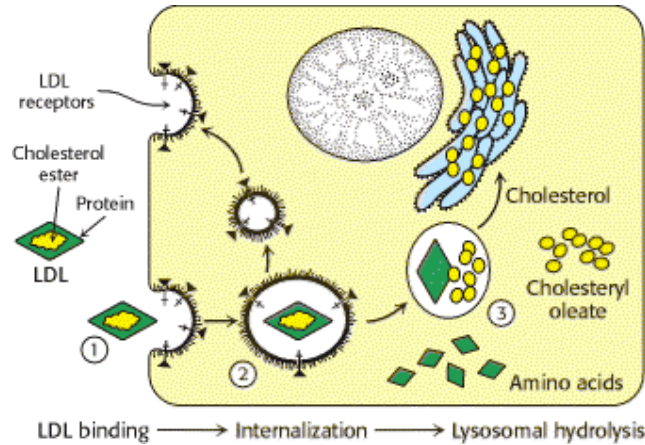
The process of receptor-mediated endocytosis is illustrated for the cholesterol-carrying complex, low-density lipoprotein (LDL): (1) LDL binds to a specific receptor, the LDL receptor; (2) this complex invaginates to form an internal vesicle; (3) after separation from its receptor, the LDL-containing vesicle fuses with a lysosome, leading to degradation of the LDL and release of the cholesterol.
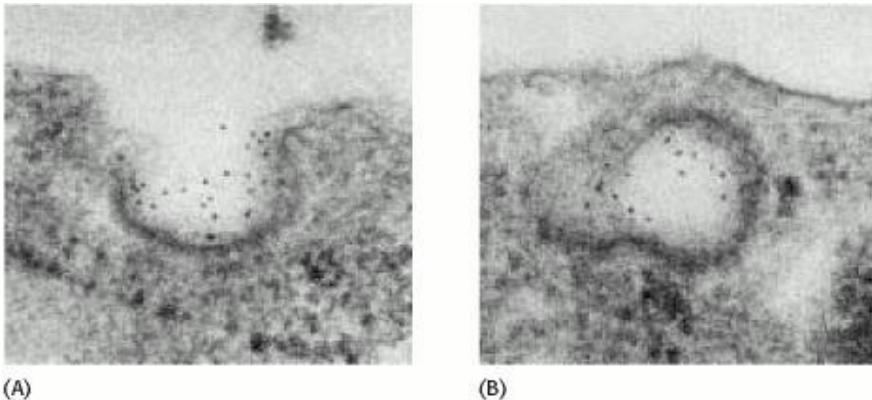
Endocytosis of LDL Bound to Its Receptor. (A) Electron micrograph showing LDL (conjugated to ferritin for visualization, dark spots) bound to a coated-pit region on the surface of a cultured human fibroblast cell. (B) Micrograph showing this region invaginating and fusing to form an endocytic vesicle

Disorders of lipoprotein metabolism

Hyperlipidemias represent an abnormally high level of plasma lipoproteins. The most serious consequence of hyperlipidemias is increased risk of **atherosclerosis,** an arterial disease that causes heart attacks and stroke.

Types of Hyperlipidemias

Type	Generic Classification	Increased Lipoprotein	Increased Lipid
I	Lipoprotein lipase deficiency	Chylomicrons	Triacylglycerols
IIa	Hypercholesterolemia (LDL receptor deficiency)	LDL	Cholesterol
IIb	Combined hyperlipidemia	LDL, VLDL	Triacylglycerols, cholesterol
III	Dysbetalipoproteinemia	β-VLDL	Triacylglycerols, cholesterol
IV	Hypertriglyceridemia	VLDL	Triacylglycerols
V	Mixed hyperlipidemia	VLDL, chylomicrons	Triacylglycerols

AN ATHEROSCLEROTIC PLAQUE.

A plaque (marked by an arrow) blocks most of the lumen of this blood vessel. The plaque is rich in cholesterol.
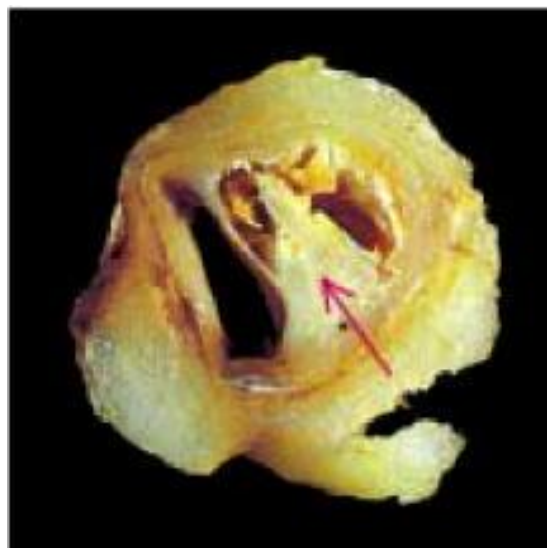
5 mm

Hypolipidemias are caused by a deficiency of one or more of the plasma lipoproteins.

   a. **Hypobetalipoproteinemia** (abetalipoproteinemia) is a genetic disorder characterized by neurologic symptoms, including ataxia and mental retardation.
      (1) Plasma triacylglycerol and cholesterol levels are decreased.
      (2) There is a complete absence of (3-lipoproteins (no chylomicrons or VLDLs).
      (3) Absorption of fat is greatly reduced.
   b. **HDL deficiency (Tangier disease)** is characterized by recurrent polyneuropathy, lymphadenopathy, tonsillar hyperplasia, and hepatosplenomegaly (from storage of cholesterol in reticuloendothelial cells).
      (1) Plasma cholesterol levels are low; triacylglycerols are normal or increased.
      (2) There is a marked decrease in plasma HDLs.