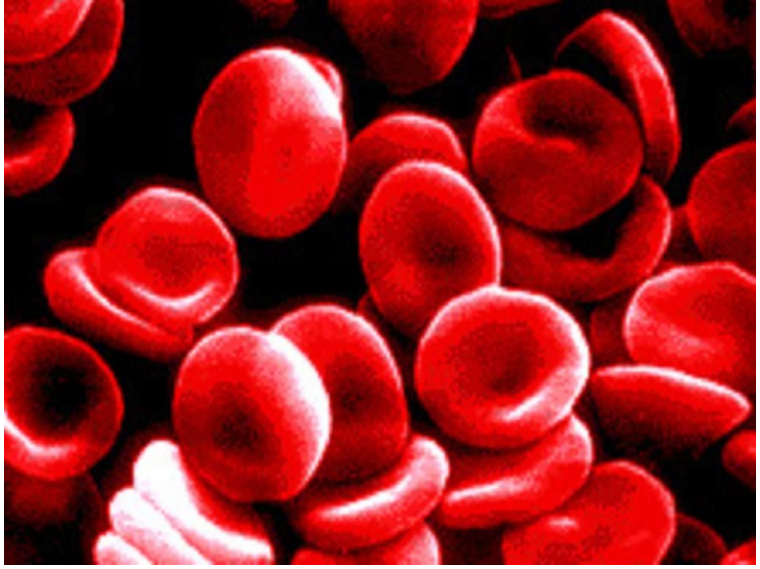

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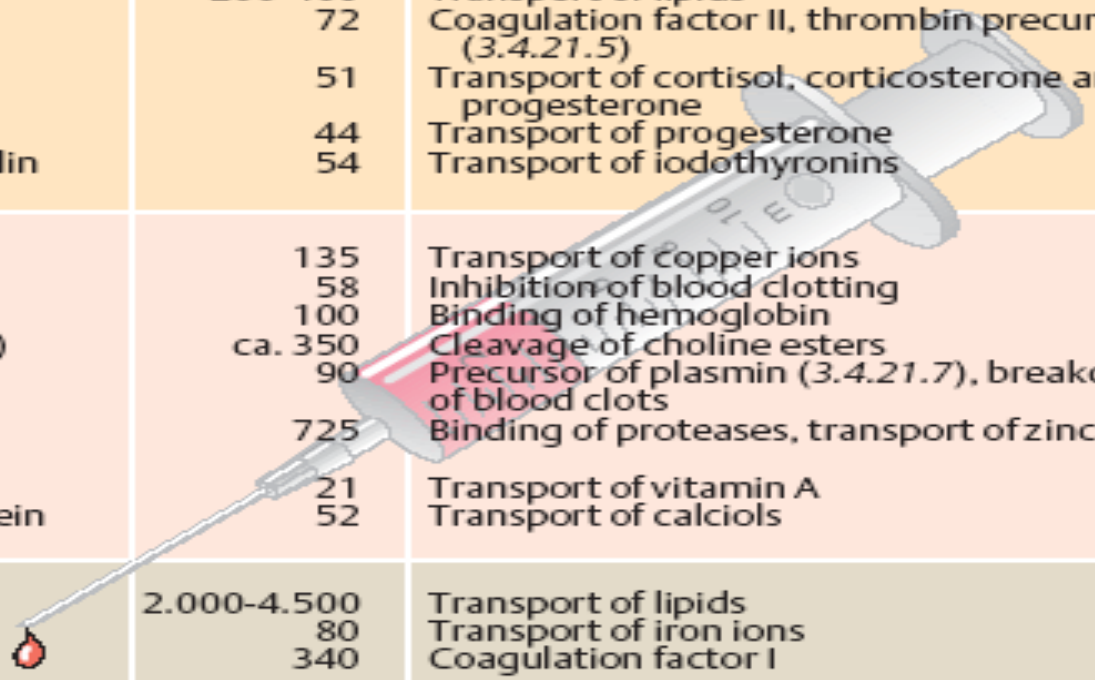
BLOOD plasma proteins

TEST-ALL SLIDES

Plasma Proteins

- Plasma contains a large variety of proteins including albumin, immunoglobulins, and clotting proteins such as fibrinogen. Albumin constitutes about 60% of the total protein in plasma and is present at concentrations between 35 and 55 mg/mL. It is the main contributor to osmotic pressure of the blood and it functions as a carrier molecule for molecules with low water solubility such as lipid soluble hormones, enzymes, fatty acids, metal ions, and pharmaceutical compounds. Albumin is structurally stable due to its seventeen disulfide bonds and unique in that it has the highest water solubility and the lowest isoelectric point (pI) of the plasma proteins. Due to the structural integrity of albumin it remains stable under conditions where most other proteins denature.

Group	Protein	M_r in kDa	Function
Albumins:	Transthyretin	50-66	Transport of thyroxin and triiodothyronin
	Albumin: 45 g · l^{-1}	67	Maintenance of osmotic pressure; transport fatty acids, bilirubin, bile acids, steroid hormones, pharmaceuticals and inorganic ions.
α_1-Globulins:	Antitrypsin	51	Inhibition of trypsin and other proteases
	Antichymotrypsin	58-68	Inhibition of chymotrypsin
	Lipoprotein (HDL)	200-400	Transport of lipids
	Prothrombin	72	Coagulation factor II, thrombin precursor (*3.4.21.5*)
	Transcortin	51	Transport of cortisol, corticosterone and progesterone
	Acid glycoprotein	44	Transport of progesterone
	Thyroxin-binding globulin	54	Transport of iodothyronins
α_2-Globulins:	Ceruloplasmin	135	Transport of copper ions
	Antithrombin III	58	Inhibition of blood clotting
	Haptoglobin	100	Binding of hemoglobin
	Cholinesterase (3.1.1.8)	ca. 350	Cleavage of choline esters
	Plasminogen	90	Precursor of plasmin (*3.4.21.7*), breakdown of blood clots
	Macroglobulin	725	Binding of proteases, transport of zinc ions
	Retinol-binding protein	21	Transport of vitamin A
	Vitamin D-binding protein	52	Transport of calciols
β-Globulins:	Lipoprotein (LDL)	2.000-4.500	Transport of lipids
	Transferrin	80	Transport of iron ions
	Fibrinogen	340	Coagulation factor I
	Sex hormone-binding globulin	65	Transport of testosterone and estradiol
	Transcobalamin	38	Transport of vitamin B_{12}
	C-reactive protein	110	Complement activation
γ-Globulins:	IgG	150	Late antibodies
	IgA	162	Mucosa-protecting antibodies
	IgM	900	Early antibodies
	IgD	172	B-lymphocyte receptors
	IgE	196	Reagins



Examples of Plasma Components for Clinical Use

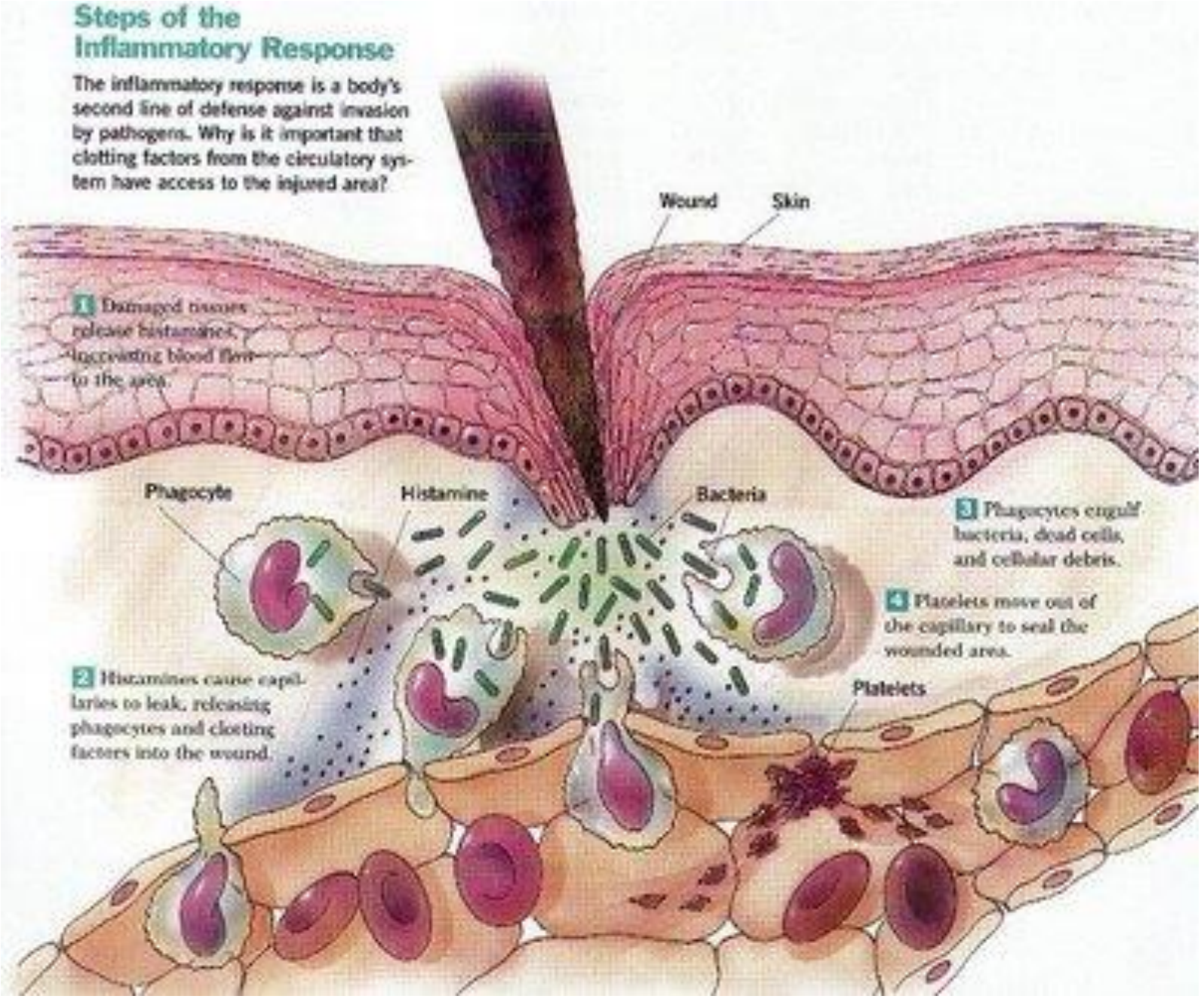
- **Plasma Component:**
- factor VIII (hemophilia A)
- factor IX complex (hemophilia B, anticoagulant overdose,
- factor II and factor X deficiencies, liver disease)
- Immunoglobulin (passive prophylaxis some types of immune thrombocytopenic purpura)
- antithrombin III (congenital deficiency, disseminated intravascular coagulation)
- alpha-I-antitrypsin (hereditary deficiencies emphysema and COPD, cirrhosis)

Acute-phase proteins

- Inflammation also induces high systemic levels of acute-phase proteins. In acute inflammation, these proteins prove beneficial, however in chronic inflammation they can contribute to amyloidosis. These proteins include C-reactive protein, serum amyloid A, and serum amyloid P, vasopressin, which cause a range of systemic effects including:
- Fever
- Increased blood pressure
- Decreased sweating
- Malaise
- Loss of appetite
- Somnolence

C-reactive protein (CRP)

- **C-reactive protein** (**CRP**) is a protein found in the blood, the levels of which rise in response to inflammation (an acute-phase protein). Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via c1q.
- CRP is synthesized by the liver in response to factors released by fat cells (adipocytes). It is a member of the pentraxin family of proteins. It is not related to C-peptide or protein C.


Steps of the Inflammatory Response
The inflammatory response is a body's second line of defense against invasion by pathogens. Why is it important that clotting factors from the circulatory system have access to the injured area?
Wound
Skin
1 Damaged tissues release histamines, increasing blood flow to the area.
Phagocyte
Histamine
Bacteria
3 Phagocytes engulf bacteria, dead cells, and cellular debris.
4 Platelets move out of the capillary to seal the wounded area.
2 Histamines cause capillaries to leak, releasing phagocytes and clotting factors into the wound.
Platelets

Serum amyloid A (SAA)

- **Serum amyloid A** (SAA) proteins are a family of apolipoproteins associated with high-density lipoprotein(HDL) in plasma. Different isoforms of SAA are expressed constitutively (constitutive SAAs) at different levels or in response to inflammatory stimuli. These proteins are produced predominantly by the liver. The conservation of these proteins throughout invertebrates and vertebrates suggests that SAAs play a highly essential role in all animals.
- Acute-phase serum amyloid A proteins (A-SAAs) are secreted during the acute phase of inflammation. These proteins have several roles, including the transport of cholesterol to the liver for secretion into the bile, the recruitment of immune cells to inflammatory sites, and the induction of enzymes that degrade extracellular matrix. A-SAAs are implicated in several chronic inflammatory diseases, such as amyloidosis, atherosclerosis, and rheumatoid arthritis. Three acute-phase SAA isoforms have been reported in mice, called SAA1, SAA2, and SAA3. During inflammation, SAA1 and SAA2 are expressed and induced principally in the liver, whereas SAA3 is induced in many distinct tissues. SAA1 and SAA2 genes are regulated in liver cells by the proinflammatory cytokines IL-1, IL-6, and TNF-α. Both SAA1 and SAA2 are induced up to a 1000-fold in mice under acute inflammatory conditions following exposure to bacterial lipopolysaccharide (LPS). Three A-SAA genes have also been identified in humans[4], although the third gene, *SAA3*, is believed to represent a pseudogene that does not generate messenger RNA or protein

The main classes of lipoproteins

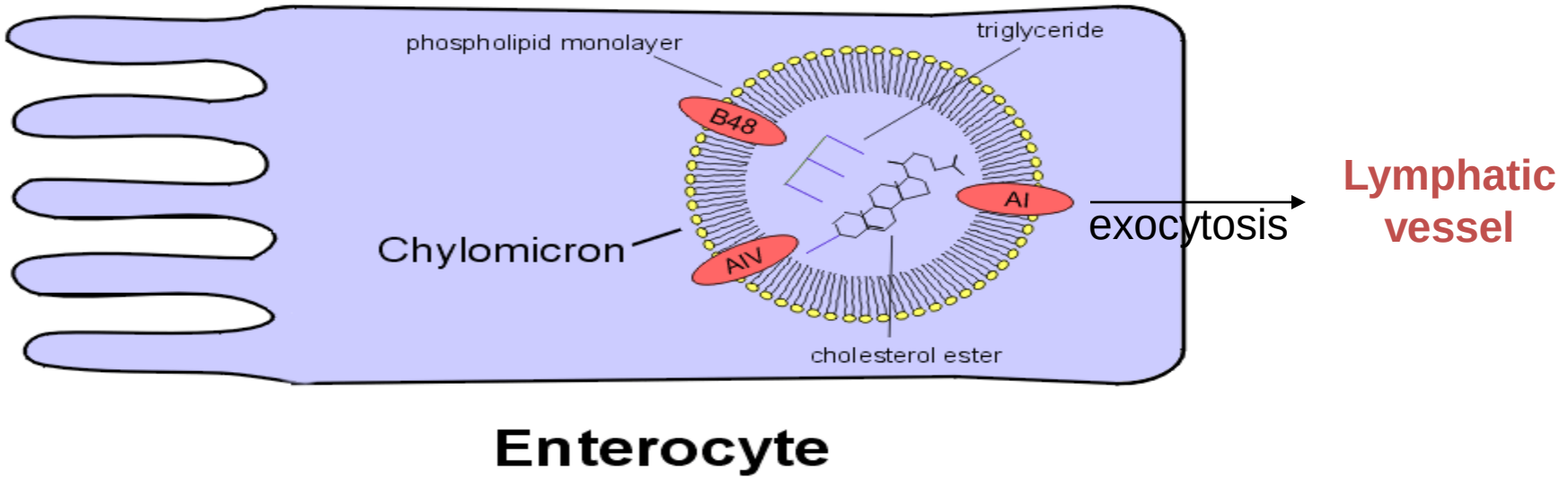
1. Chylomicrons.
2. Very low density lipoproteins (VLDL).
3. Intermediate density lipoproteins (IDL).
4. Low density lipoproteins (LDL).
5. High density lipoproteins (HDL).

Lipoproteins in human plasma

	Chylomicrons	VLDLs	IDLs	LDLs	HDLs
Molecular weight $\times 10^{-6}$	>400	10–80	5–10	2.3	0.18–0.36
Density ($g\,cm^{-3}$)	<0.95	0.95–1.006	1.006–1.019	1.019–1.063	1.063–1.210
Chemical composition (%)					
Protein	2	10	18	25	33
Triacylglycerol	85	50	31	10	8
Cholesterol	4	22	29	45	30
Phospholipid	9	18	22	20	29

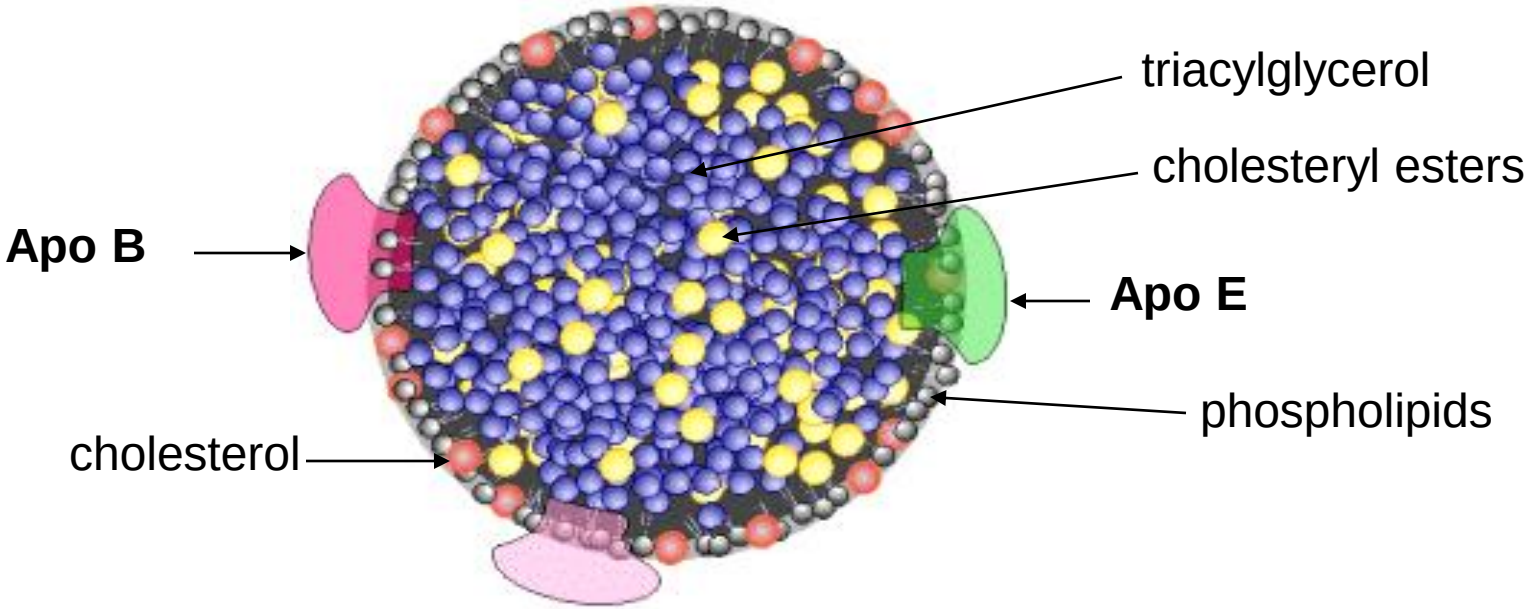
Chylomicrons

- are the **largest lipoproteins** (180 to 500 nm in diameter)
- are **synthesized in the ER of intestinal cells**
- contain 85 % of TGs (it is the **main transport form of dietary TGs**).
- **apoprotein B-48 (apo B-48)** is the main protein component
- deliver TGs from the intestine (via lymph and blood) to tissues (**muscle** for energy, **adipose** for storage).
- bind to membrane-bound ***lipoprotein lipase*** (at adipose tissue and muscle), where the triacylglycerols are **again degraded into free fatty acids and monoacylglycerol** for transport into the tissue
- are present in blood only after feeding



VLDL

- are **formed in the liver**
- contain 50 % of TGs and 22 % of cholesterol
- two lipoproteins — **apo B-100** and **apo E**
- the **main transport form of TGs synthesized in the organism (liver)**
- deliver the TGs from liver to peripheral tissue (**muscle** for energy, **adipose** for storage)
- bind to membrane-bound ***lipoprotein lipases*** (triacylglycerols are **again degraded into free fatty acids and monoacylglycerol)**



Lipoproteinlipase – **enzyme which is located within capillaries of muscles and adipose tissue**

Function: ***hydrolyses of TGs of chylomicrons and VLDL. Formed free fatty acids and glycerol pass into the cells***

Chylomicrons and VLDL which gave up TGs are called **remnants of chylomicrons** and **remnants of VLDL**

Remnants are rich in cholesterol esters

Remnants of chylomicrons **are captured by liver**

Remnants of VLDL are also called **intermediate density lipoproteins (IDL)**

Fate of the IDL:
- some **are taken by the liver**
- others are **degraded to the low density lipoproteins (LDL)** (by the removal of more triacylglycerol)

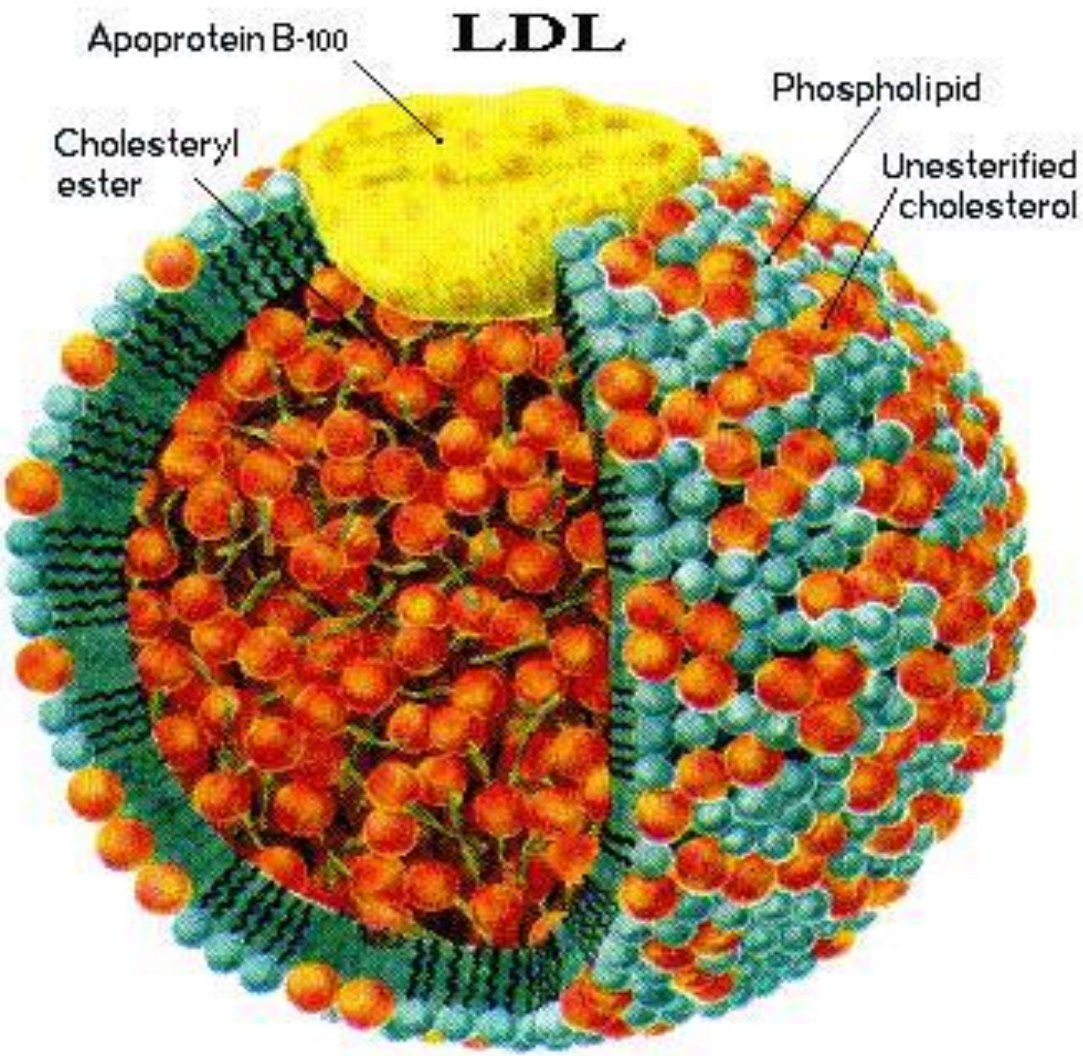
LDL

LDL are **formed in the blood from IDL** and **in liver from IDL** (enzyme – ***liver lipase***)

LDL are enriched in cholesterol and cholesteryl esters (contain **about 50 % of cholesterol**)

Protein component - **apo B-100**

LDL is the **major carrier of cholesterol (transport cholesterol to peripheral tissue)**



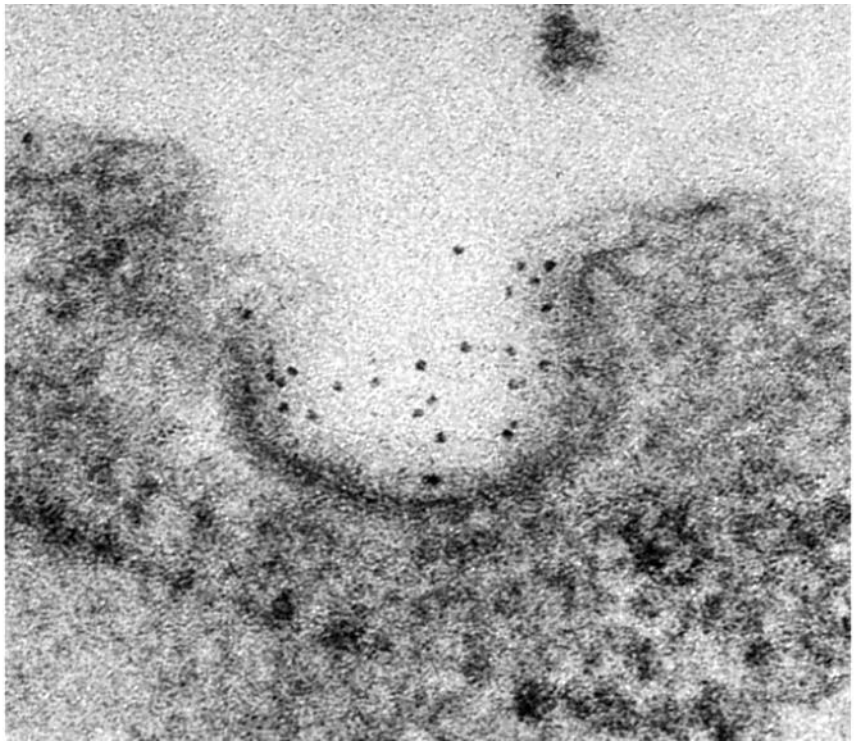
Cells of all organs have **LDL receptors**

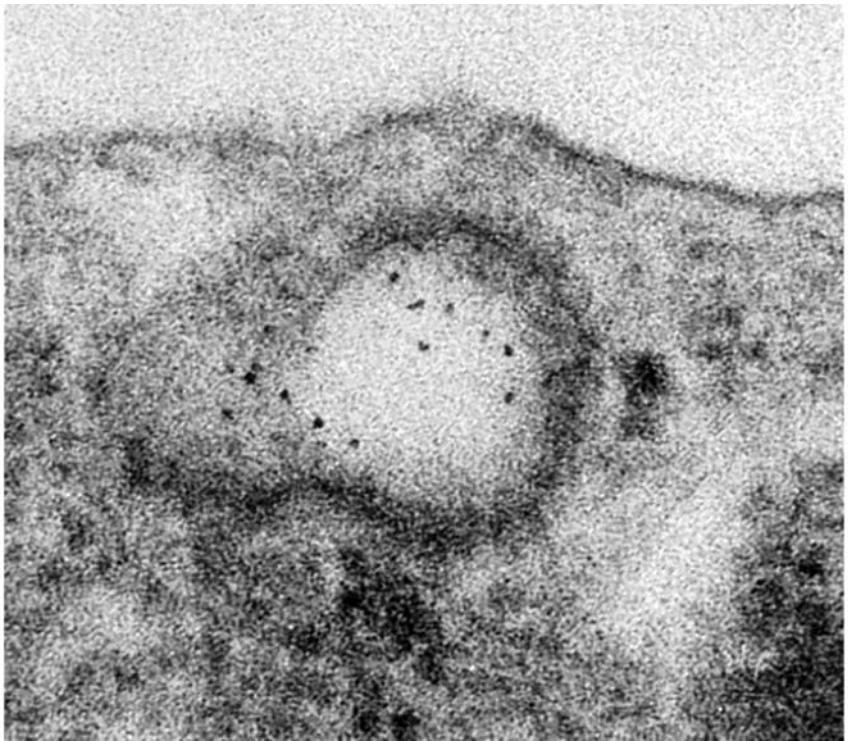
Receptors for LDL are localized in specialized regions called ***coated pits***, which contain a specialized protein called ***clathrin***

Apo B-100 on the surface of an LDL **binds to the receptor**

Receptor-LDL complex enters the cell by **endocytosis**.

Endocytic vesicle is formed





Vesicle **fuse with lysosomes**

Lysosomal ***lipases*** and ***proteases*** degrade LDL

LDL receptor itself **returns to the plasma membrane**

Apo B-100 is hydrolyzed to **amino acids**

Cholesteryl esters are hydrolyzed to **free cholesterol** and **fatty acids**

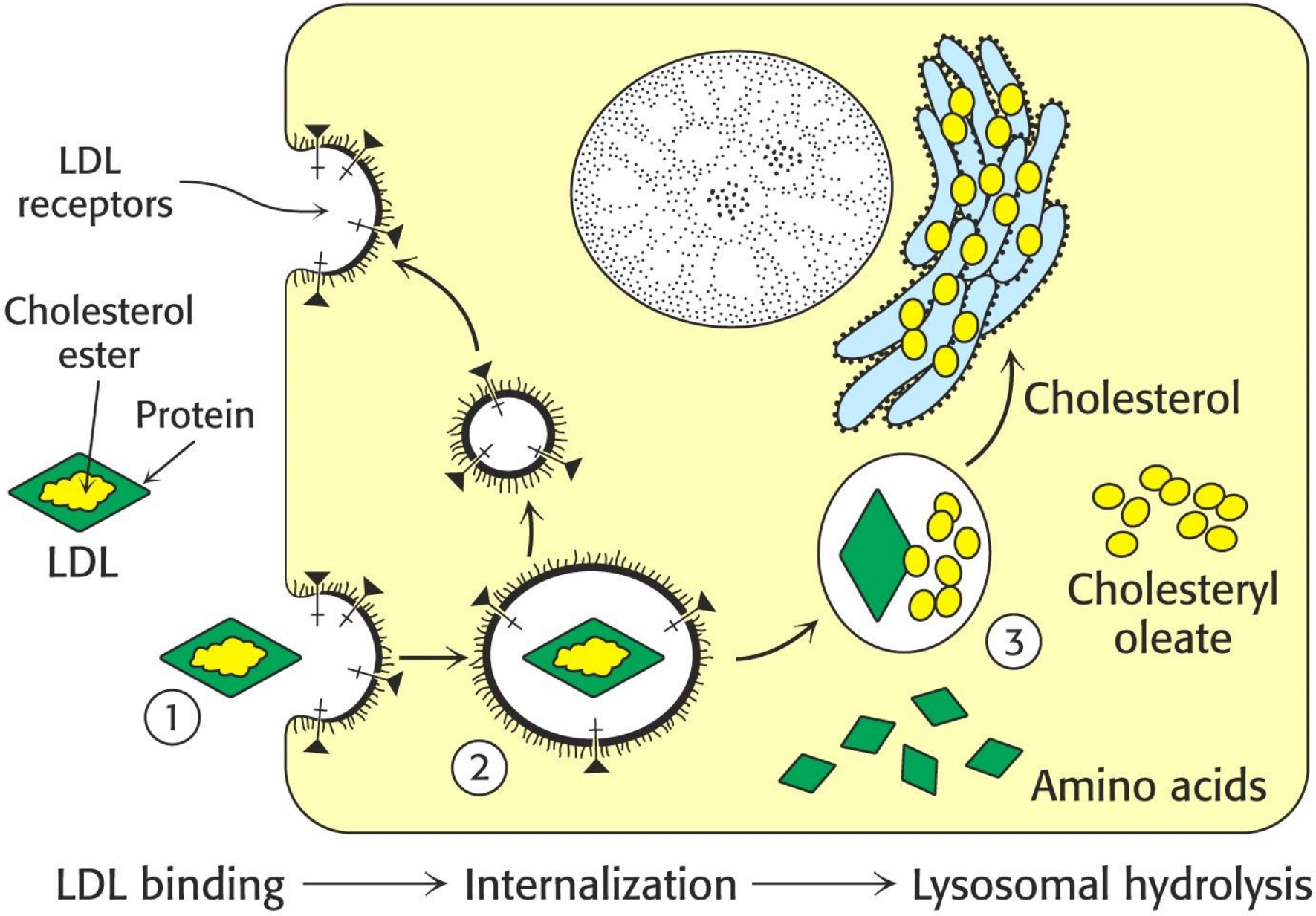
Released free cholesterol:

- **is incorporated into the membranes** or
- **is reesterified** for storage inside the cell by the enzyme ***acyl CoA:cholesterol acyltransferase (ACAT)***

Feedback regulation:

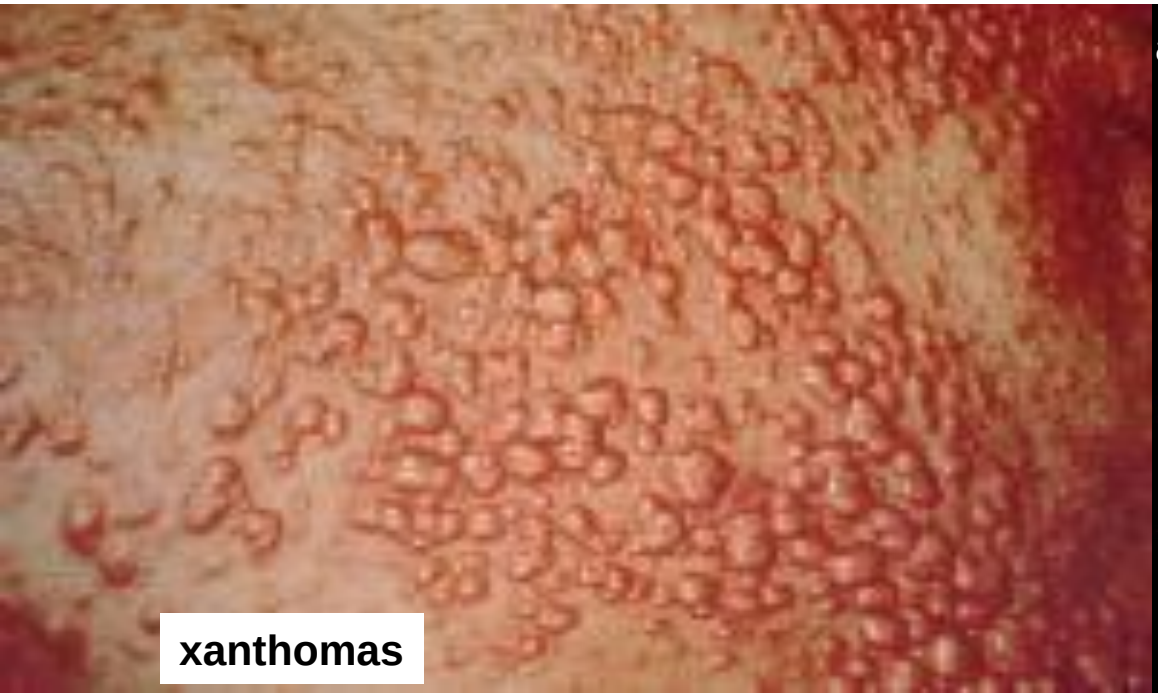
abundance of intracellular cholesterol suppresses the synthesis of LDL receptors and so the uptake of additional cholesterol from plasma LDL is blocked

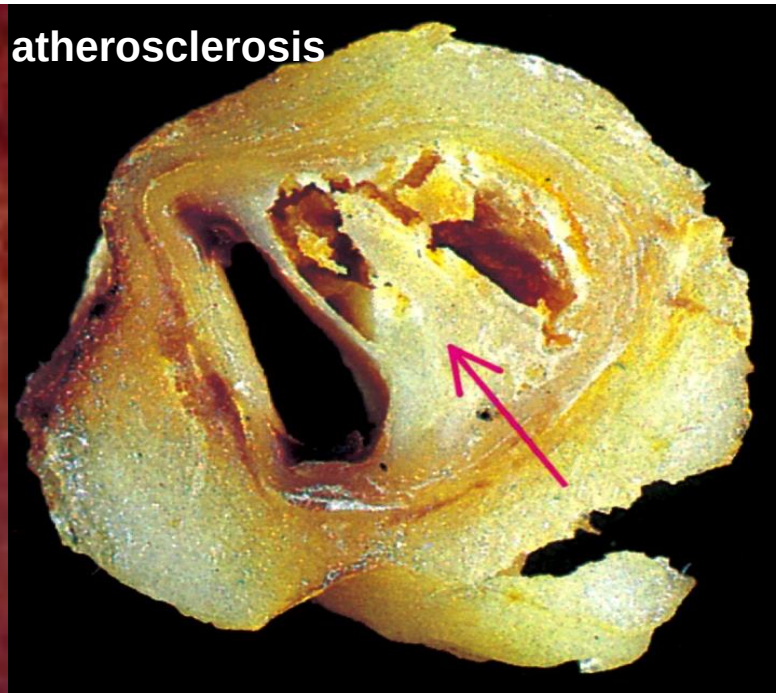
LDL uptake by *receptor-mediated endocytosis*



Familial hypercholesterolemia

- **congenital disease** when **LDL receptor are not synthesized** (mutation at a single autosomal locus)
- the **concentration of cholesterol in blood markedly increases**
- severe **atherosclerosis** is developed (deposition of cholesterol in arteries)
- nodules of cholesterol called **xanthomas** *are* prominent in skin and tendons
- most homozygotes die of coronary artery disease in childhood
- the disease in heterozygotes (1 in 500 people) has a milder and more variable clinical course

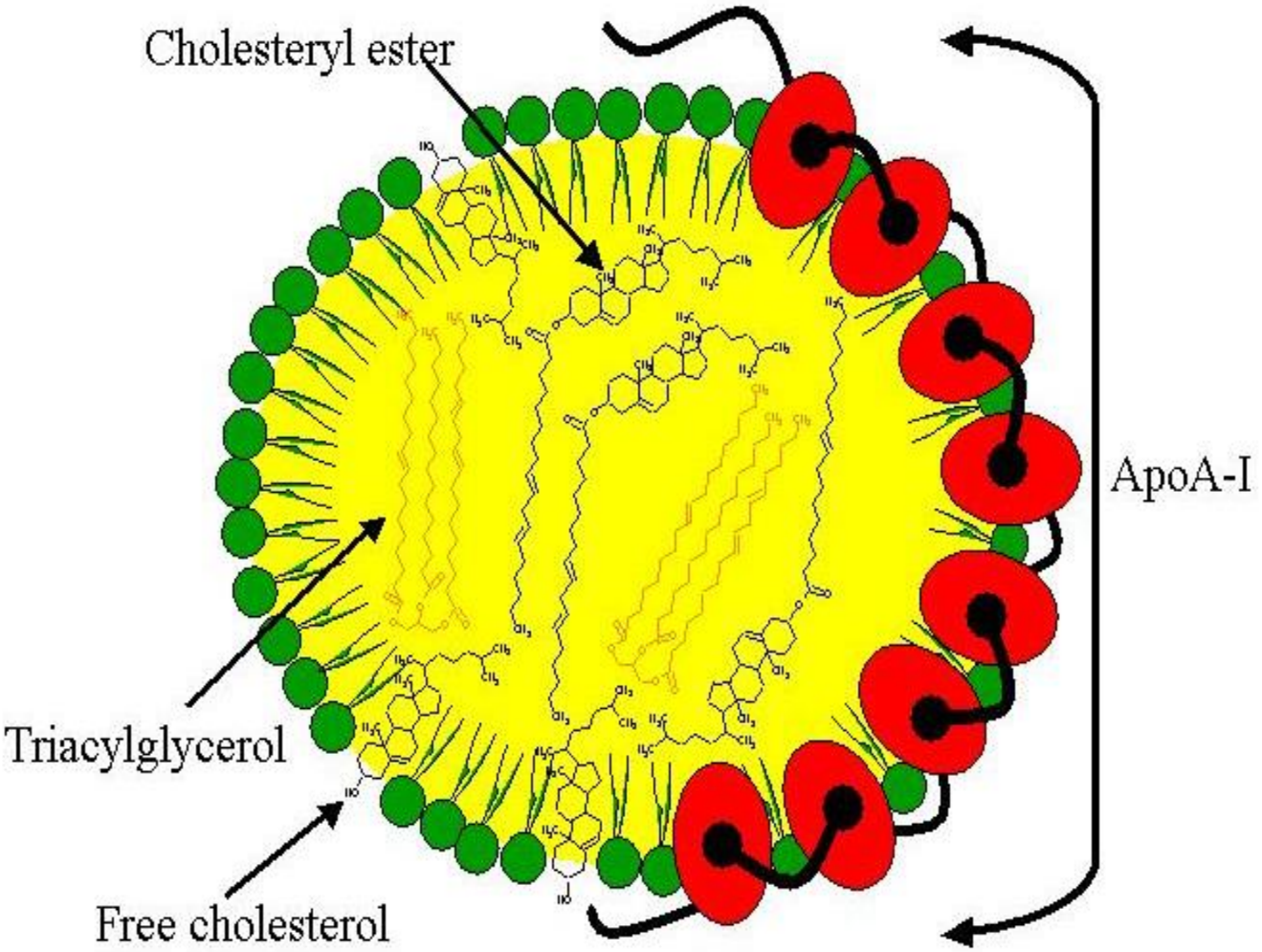


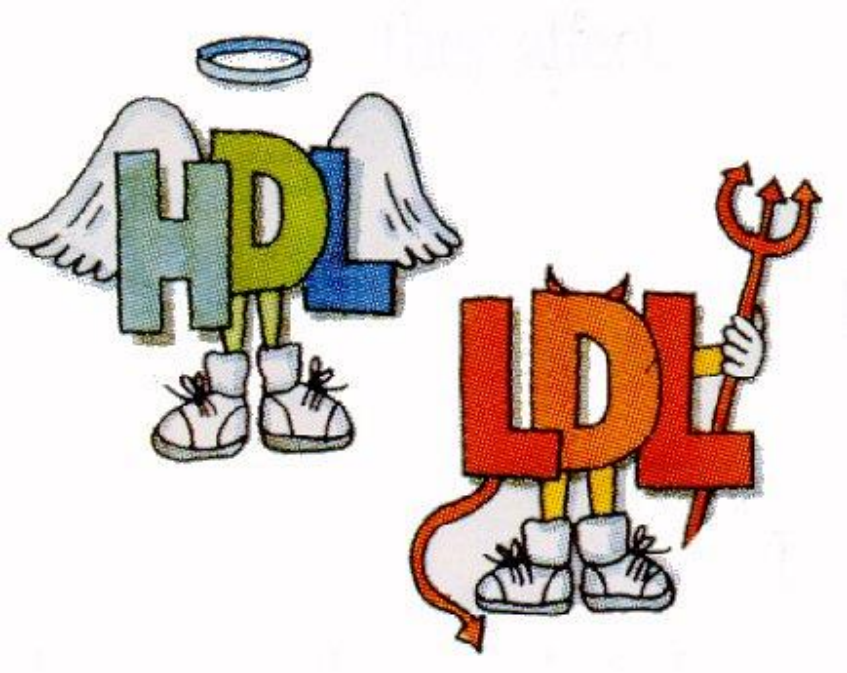


HDL

- are **formed in the liver** and partially in **small intestine**
- contain the great amount of **proteins (about 40 %)**

- **pick up the cholesterol from peripheral tissue,** chylomicrons and VLDL
- enzyme ***acyltransferase*** in HDL esterifies cholesterols, convert it to cholesterol esters and transport to the liver



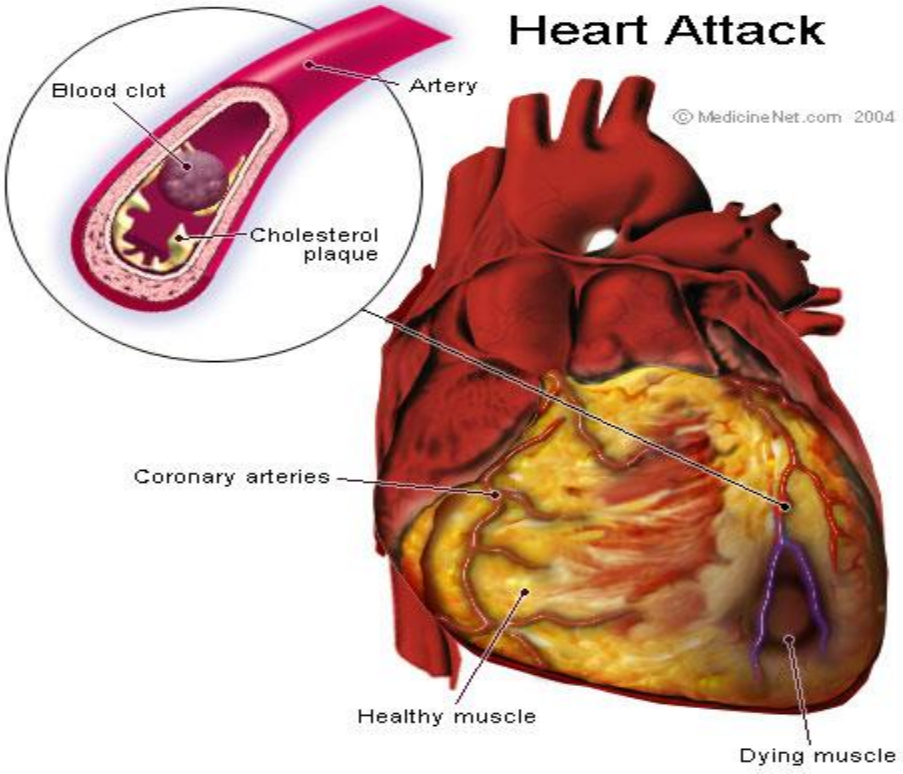


High serum levels of cholesterol cause disease and death by contributing to development of **atherosclerosis**

Cholesterol which is present in the form of the **LDL** is so-called **"bad cholesterol."**

Cholesterol in the form of **HDL** is referred to as **"good cholesterol"**

HDL functions as a shuttle that moves cholesterol throughout the body



LDL/HDL Ratio

The **ratio** of cholesterol in the form of **LDL** to that in the form of **HDL** can be used to evaluate **susceptibility to the development of atherosclerosis**

For a healthy person, the LDL/HDL ratio is 3.5

Transport Forms of Lipids