

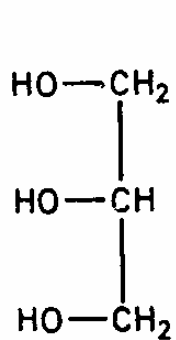
Volné radikály a ateroskleróza

Tuky

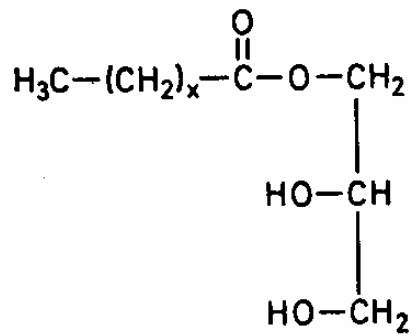
jsou složené sloučeniny
Chemickým charakterem patří k esterům

Z kyselin obsahují nerozvětvené alifatické kyseliny
Alkoholickou složkou je glycerol

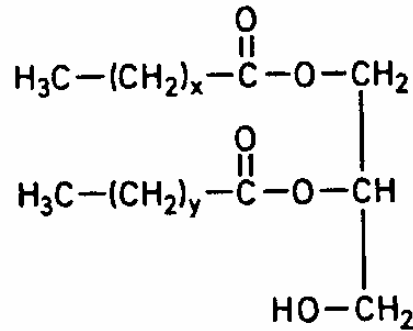
Glycerol jako trojsytný alkohol může tvořit **mono-, di- a triacylglyceroly**
(v dřívější terminologii mono-, di- a triglyceridy)



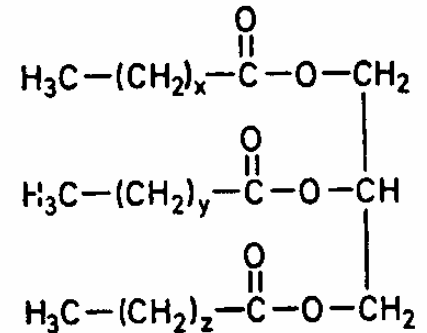
glycerol



monoacylglycerol



diacylglycerol



triacylglycerol

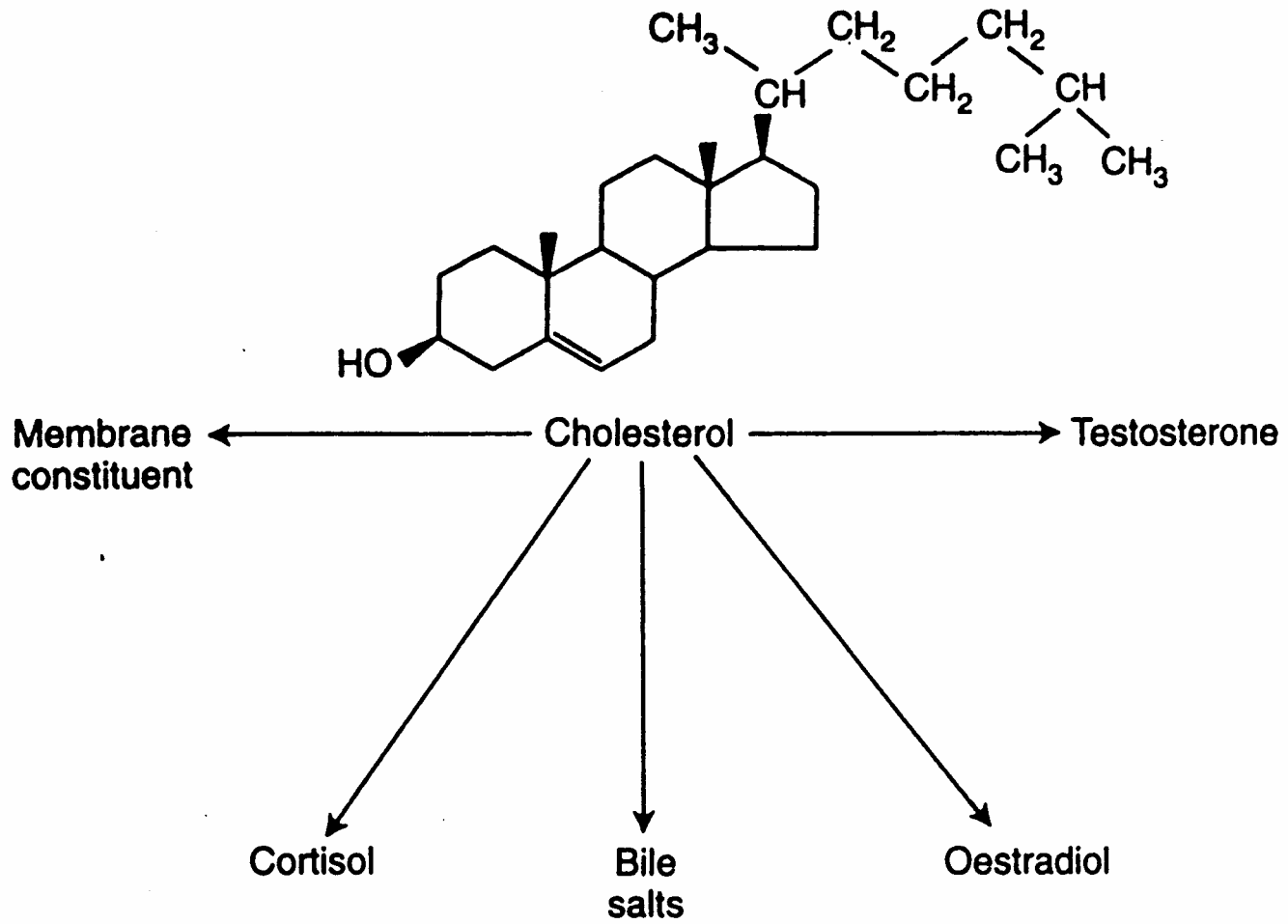
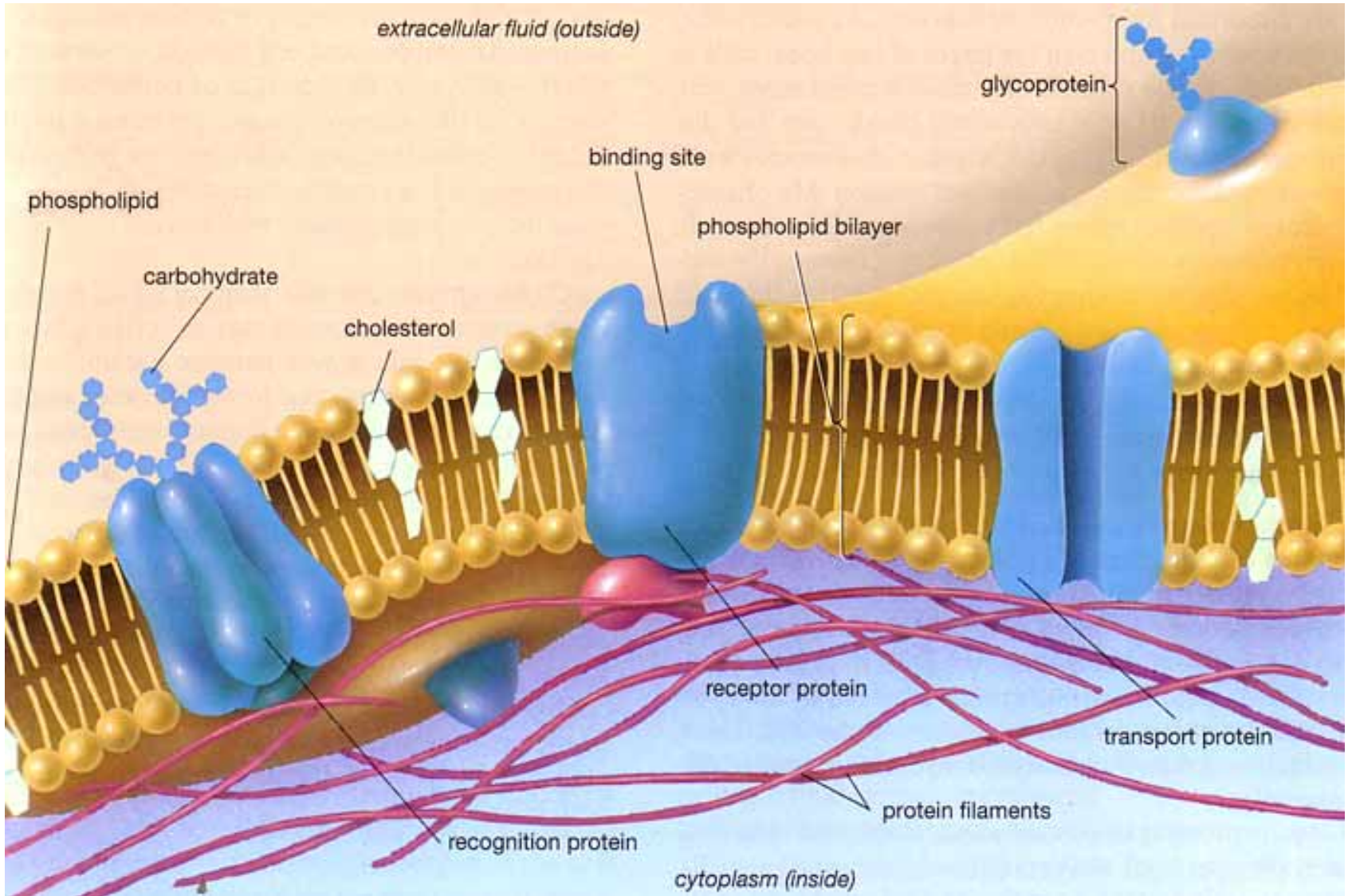


Figure A3. The structure of cholesterol.



Shrnutí

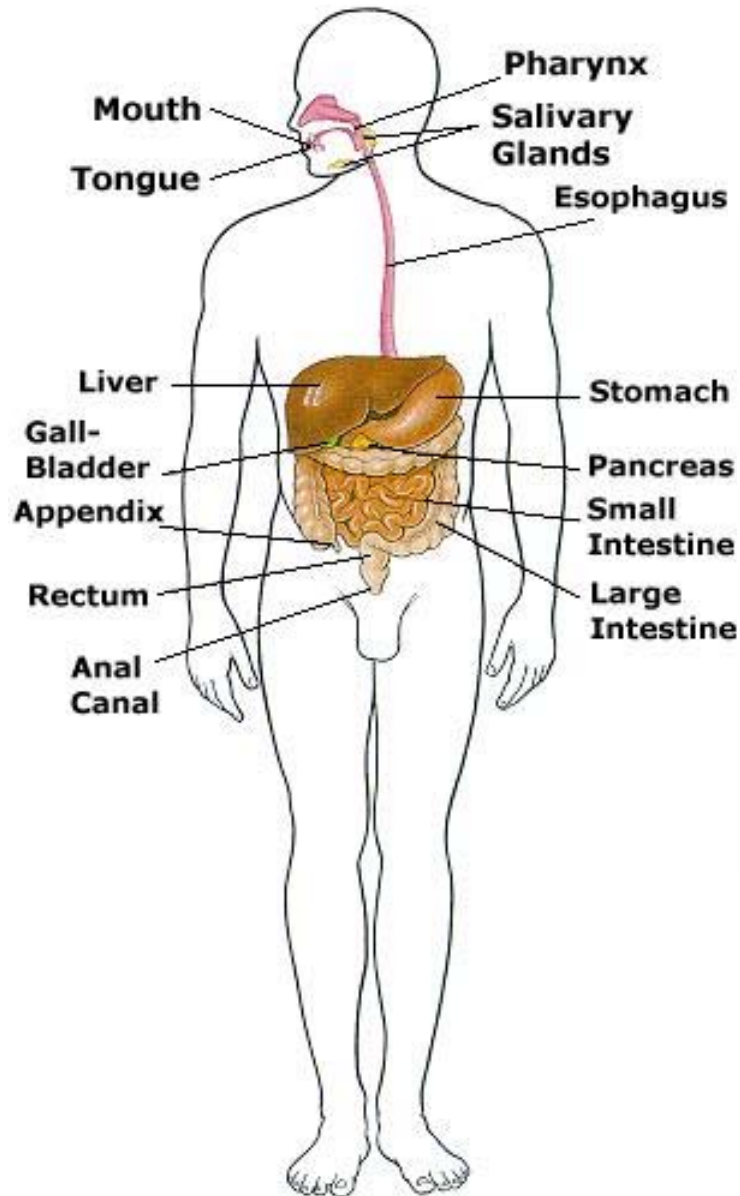
Potravou jsou přijímány tyto základní látky tukovité povahy:

triacylglyceroly

cholesterol a jeho estery

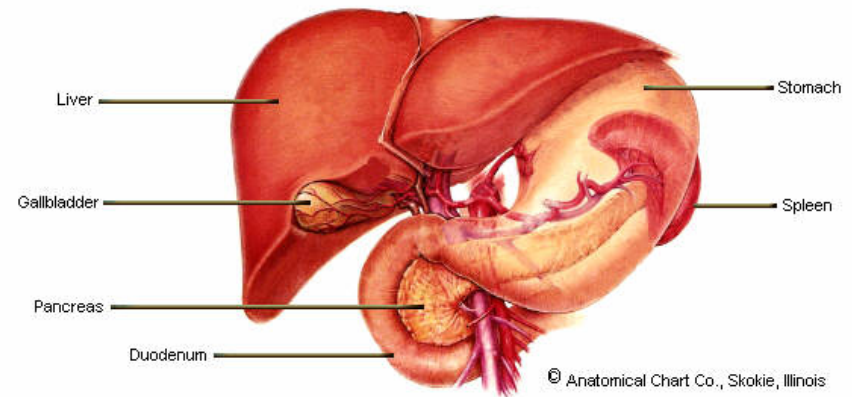
fosfolipidy (především lecithin)

Major Digestive Organs



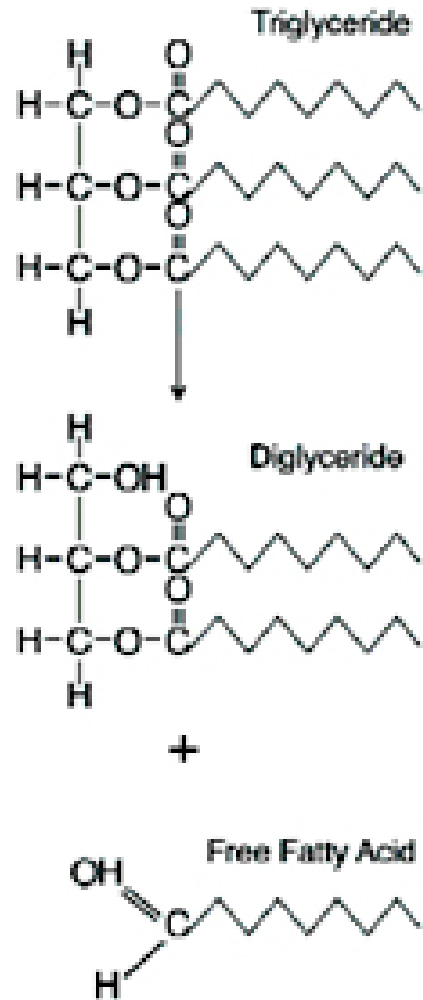
adapted from Thibodeau

Healthy liver, gall bladder, duodenum,
pancreas, spleen, and stomach.

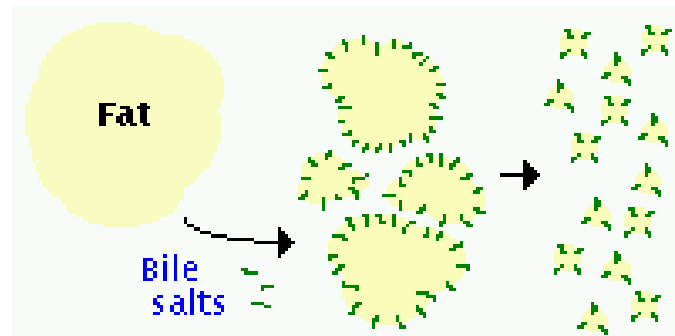


Štěpení tuků v tenkém střevě

	Enzym	Substrát	Optim. podmínky	Konečný produkt
DUODENUM	pankreatická lipasa	triacylglyceroly	soli žlučových kyselin	diacylglyceroly monoacylglyceroly mastné kyseliny glycerol
	fosfolipasa	fosfolipidy (lecithin= fosfatidylcholin)		masné kyseliny (lysolecithin)
	cholesterol esterasa	estery cholesterolu s mastnými kyselinami		volný cholesterol
Další oddíly tenkého střeva	střevní lipasa	monoacylglyceroly		glycerol mastné kyseliny

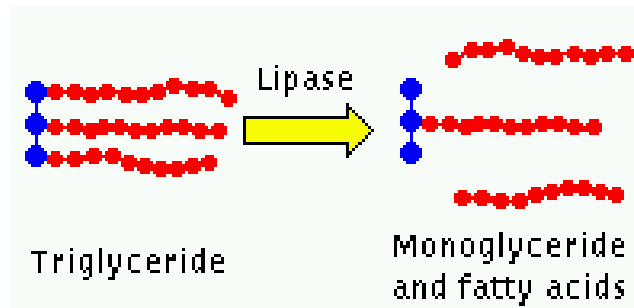


Pancreatic Lipase Action

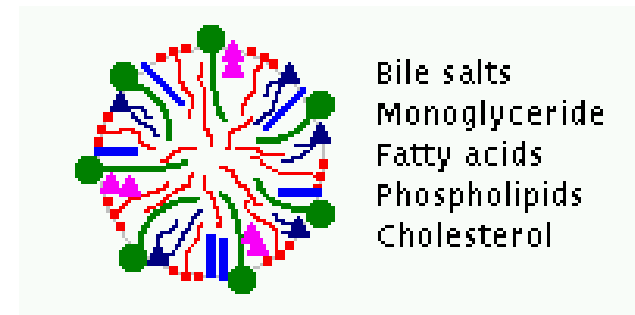


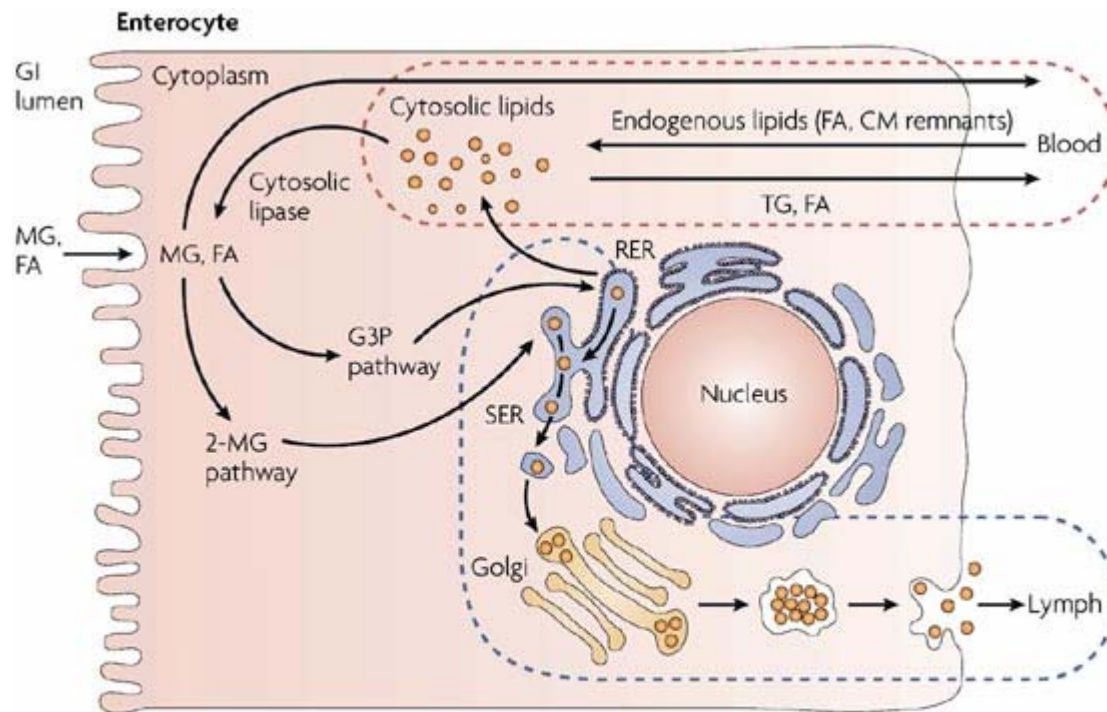
Hydrofobní části žlučových kyselin se vnoří do tukových kapének, hydrofilní části zůstávají na povrchu, to vede ke štěpení. Čím menší kapénky, tím lepší účinek pankreatické lipázy

Hydrolýza triacylglycerolů pankreatickou lipázou. Látka orlistat (Xenical) inhibuje PL – léčba obezity



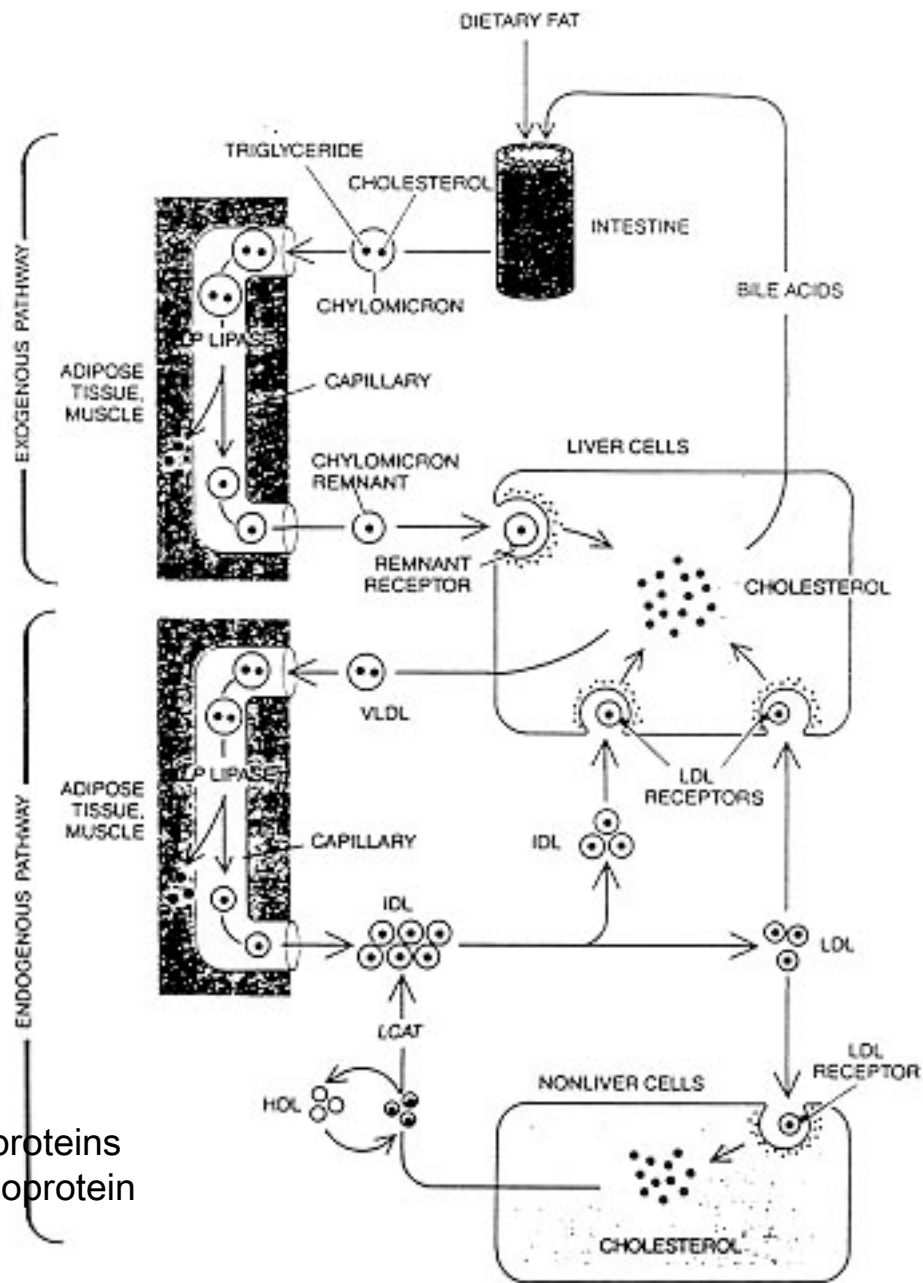
Micely – malé agregáty lipidů a žlučových kyselin. Micely přilnou k povrchu epiteliálních buněk a tuky jsou absorbovány prostou difuzí nebo pomocí transportního proteinu. Mastné kyseliny a monoacylglyceroly jsou transportovány do ER, kde jsou resyntetizovány triacylglyceroly. Poté jsou v GA tvořeny chylomikra a exocytózou jsou vypuzeny ven do lymfy. Tou se následně dostávají do krve.



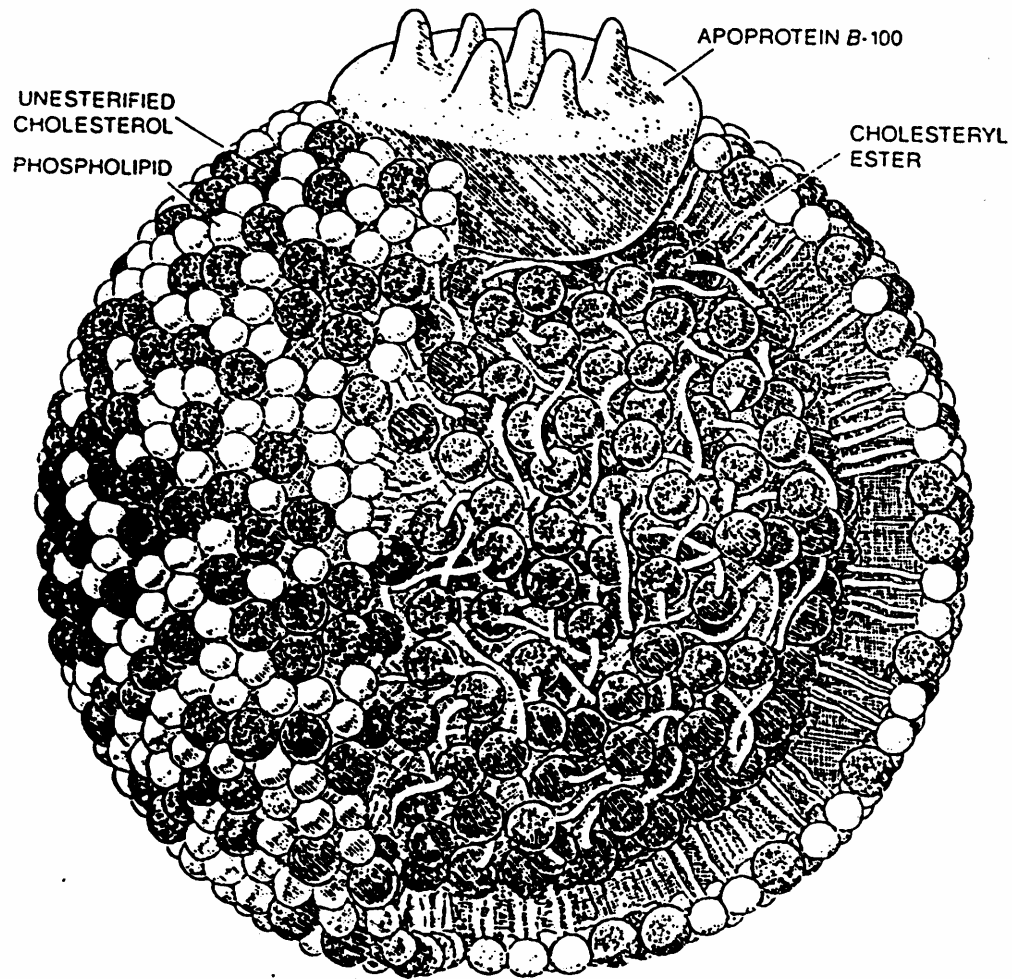


Following uptake across the apical membrane of the enterocyte, the products of gastrointestinal (GI) lumen lipid digestion — monoglyceride (MG) and fatty acid (FA) — can either diffuse across the enterocyte and enter the portal vein blood or be re-synthesized to triglyceride (TG) by either the 2-monoglyceride (2-MG) pathway associated with the smooth endoplasmic reticulum (SER) or the α-glycerol-3 phosphate (G3P) pathway associated with the rough endoplasmic reticulum (RER). TG formed by these pathways typically enters the ER lumen and is assembled into lipoproteins (LPs; represented by orange circles). LPs are then transported to the Golgi, exocytosed from the enterocyte and taken up into the intestinal lymphatic system. As lipid contained within the lipoprotein assembly pathways and the Golgi is destined for transport to the systemic circulation by the intestinal lymphatic system, this pool of lipids is referred to as the **lymph lipid precursor pool** (dashed blue line). A cytosolic pool of lipids is also located within the enterocyte. This lipid pool comprises excess TG formed by the G3P pathway and endogenous lipids taken up from the intestinal blood supply in the form of either FA or chylomicron (CM) remnants. The cytosolic lipids are subject to hydrolysis by cytosolic lipase and the digestion products formed can be re-circulated into TG assembly pathways. However, the majority of lipids from this pool exit the enterocyte in the form of TG or free FA and are taken up into portal vein blood. The pool of lipids that is transported from the enterocyte by the portal vein is therefore referred to as the **portal lipid precursor pool** (dashed red line). Recent evidence suggests that the trafficking and pooling of lipids within the enterocyte have a significant influence on the intracellular disposition of lipophilic drugs.

LP – lipoproteinová lipáza.
 Štěpí triglyceridy, mastné kyseliny vstřebány, zbytek bohatý na cholesterol do jater.

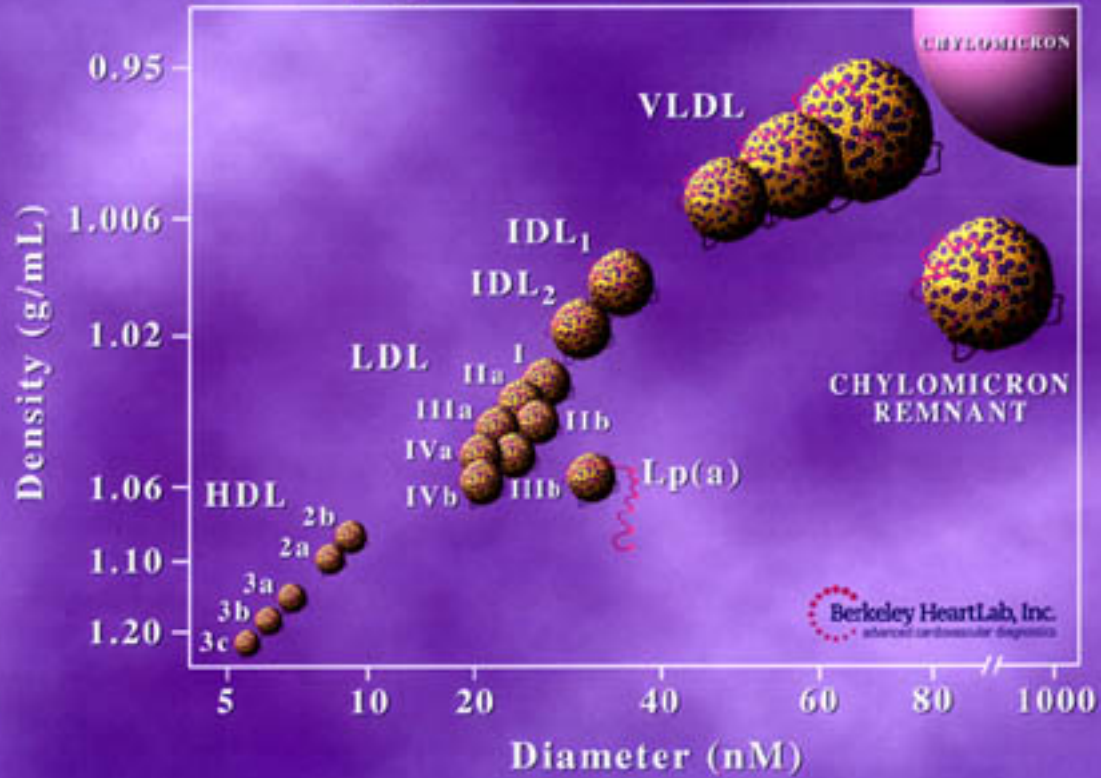


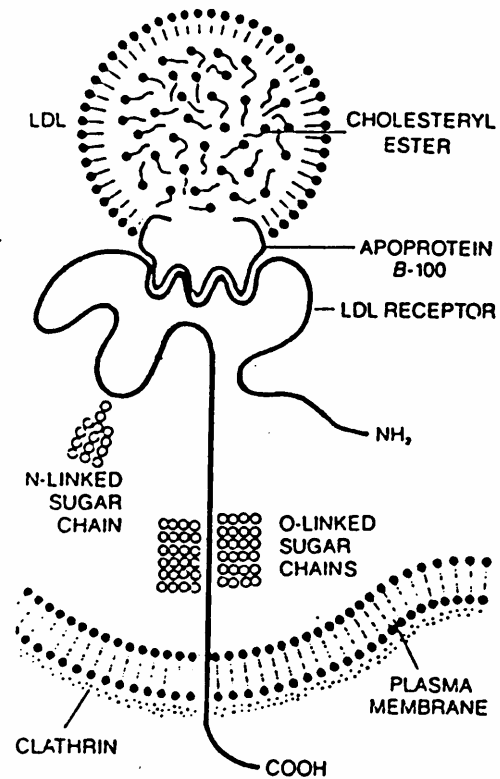
VLDL – very low density lipoproteins
 IDL – intermediate density lipoprotein
 LDL – low density lipoprotein
 HDL – high density lipoprotein



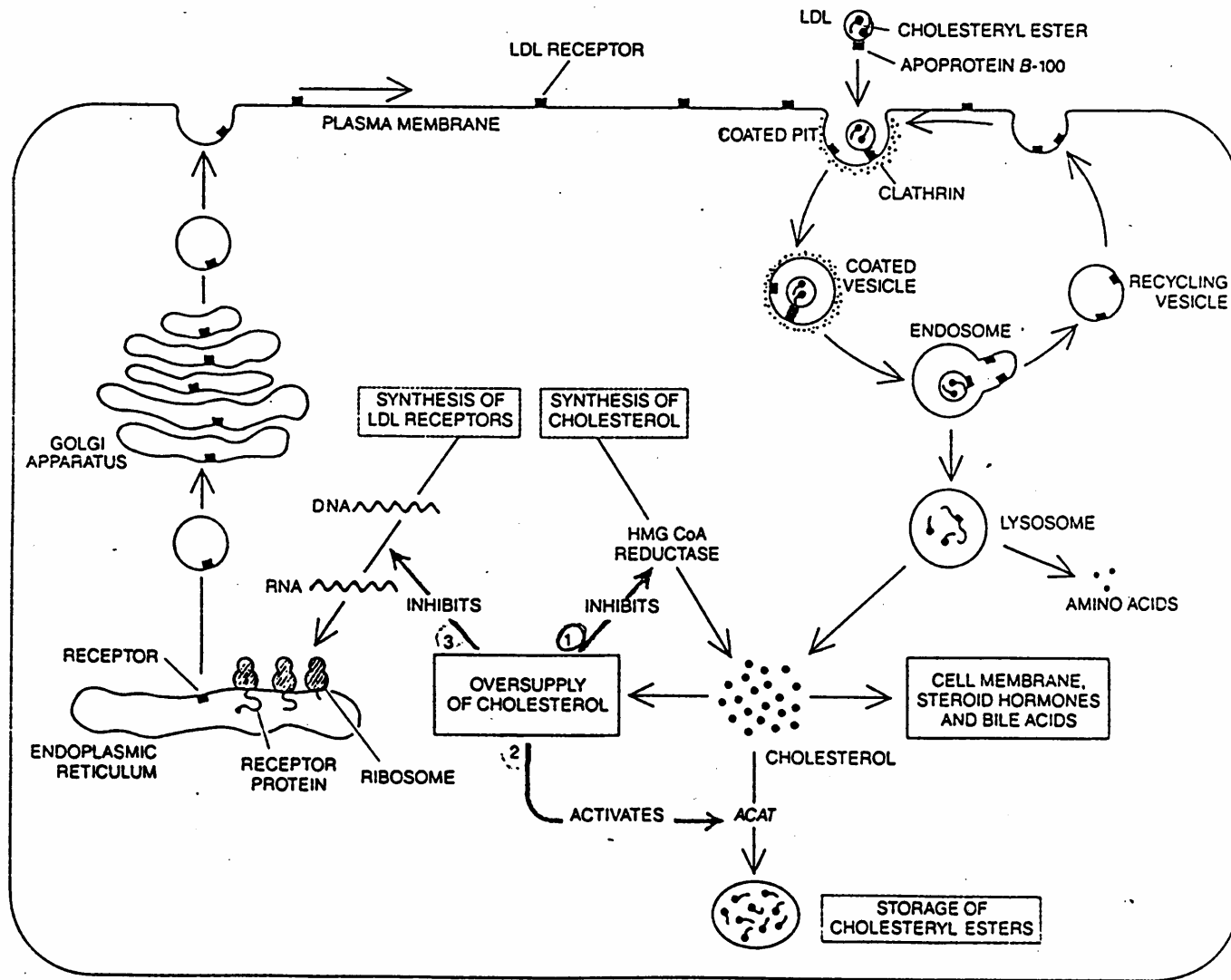
LDL, MAJOR CHOLESTEROL CARRIER in the bloodstream, is a spherical particle with a mass of three million daltons and a diameter of 22 nanometers (millionths of a millimeter). Its core consists of some 1,500 cholesteryl esters, each a cholesterol molecule attached by an ester linkage to a long fatty acid chain. The oily core is shielded from the aqueous plasma by a detergent coat composed of 800 molecules of phospholipid, 500 molecules of unesterified cholesterol and one large protein molecule, apoprotein *B-100*. When blood cholesterol is elevated, increasing the risk of atherosclerosis, the reason is almost always an increase in circulating LDL.

Lipoprotein Subclasses





LDL RECEPTOR, a glycoprotein embedded in the plasma membrane of most body cells, was purified from the adrenal gland by Wolfgang J. Schneider in the authors' laboratory. David W. Russell and Tokuo Yamamoto cloned complementary DNA derived from its messenger RNA. The DNA's nucleotide sequence was determined and from it the 839-amino-acid sequence of the receptor's protein backbone was deduced. Sites of attachment of sugar chains to nitrogen (N) and oxygen (O) atoms were identified, as was a stretch likely to traverse the membrane. The actual shape of the receptor is not yet known; the drawing is a highly schematic representation.



CIRCULATING LDL (top right) is taken into a cell by receptor-mediated endocytosis. LDL is bound by a receptor in a coated pit, which invaginates and pinches off to form a coated vesicle. Fusion of several vesicles gives rise to an endosome, in whose acidic environment the LDL dissociates from the receptor, which is recycled to the cell surface. The LDL is delivered to a lysosome, where enzymes break down the apoprotein B-100 into amino acids and cleave the ester bond to yield unesterified cholesterol for membrane synthesis

and other cellular needs. The cellular level of cholesterol is self-regulating. An oversupply of cholesterol has three metabolic effects. It inhibits the enzyme HMG CoA reductase, which controls the rate of cholesterol synthesis (1); it activates the enzyme ACAT, which esterifies cholesterol for storage (2), and it inhibits the manufacture of new LDL receptors by suppressing transcription of the receptor gene into messenger RNA (3), which would ordinarily be translated on ribosomes of the endoplasmic reticulum to make the receptor protein.

LDL receptor na jaterních a jiných buňkách =
zpětnovazebná regulace

Scavenger receptor na $M\phi$ = fagocytóza bez regulace =
vznik pěnových buněk = základ aterosklerózy

(Brown a Goldstein – Nobelova cena)

Atherosklerosa  atherogenese
trombogenese

= zúžení až uzávěr cév.

Nemá jedinou příčinu (> 200), více
spolupůsobících faktorů:

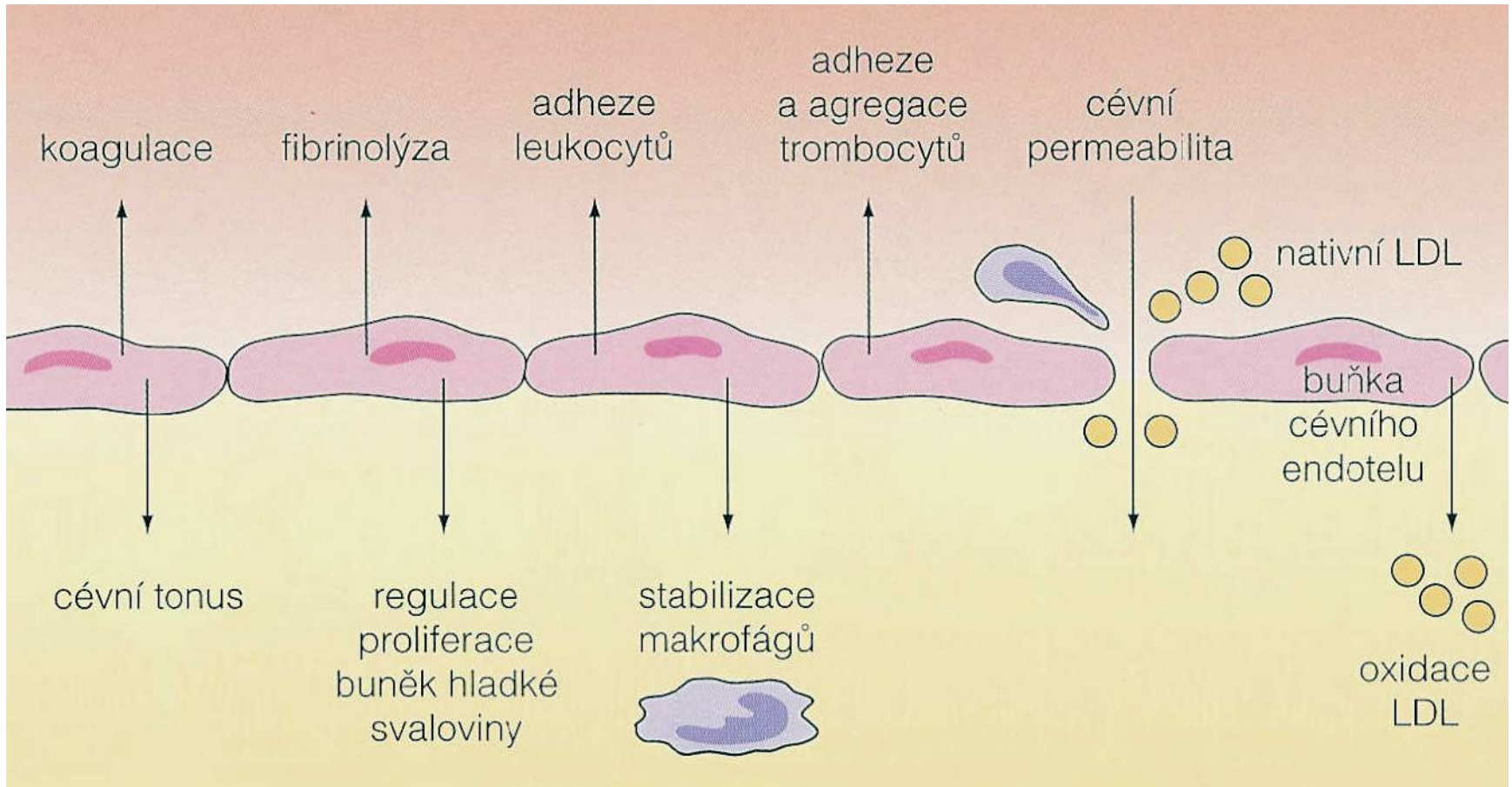
„Abnormální“ lipidy, hypertense, nikotin, DM,
hypercholesterolemie, genetické dispozice, faktory srážení
krve, homocystein, ...

Cévní endotel

Klíčové postavení v ochraně cévní stěny před atherosklerotickými změnami

- Kontrola permeability
- Kontrola optimálního průtoku
- Zajištění nesmáčivosti povrchu (zabránění adheze a agregace trombocytů)
- Aktivace koagulace
- Kontrola fibrinolýzy, angiogeneze

Působení endotelu



Modifikace LDL

- Přímá oxidace apoproteinů B a PL
- Vazba aldehydu na aminoskupinu Lys = glykace usnadňuje oxidaci LDL

Další obrázky

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Inflammation, Atherosclerosis, and Coronary Artery Disease

Göran K. Hansson, M.D., Ph.D.

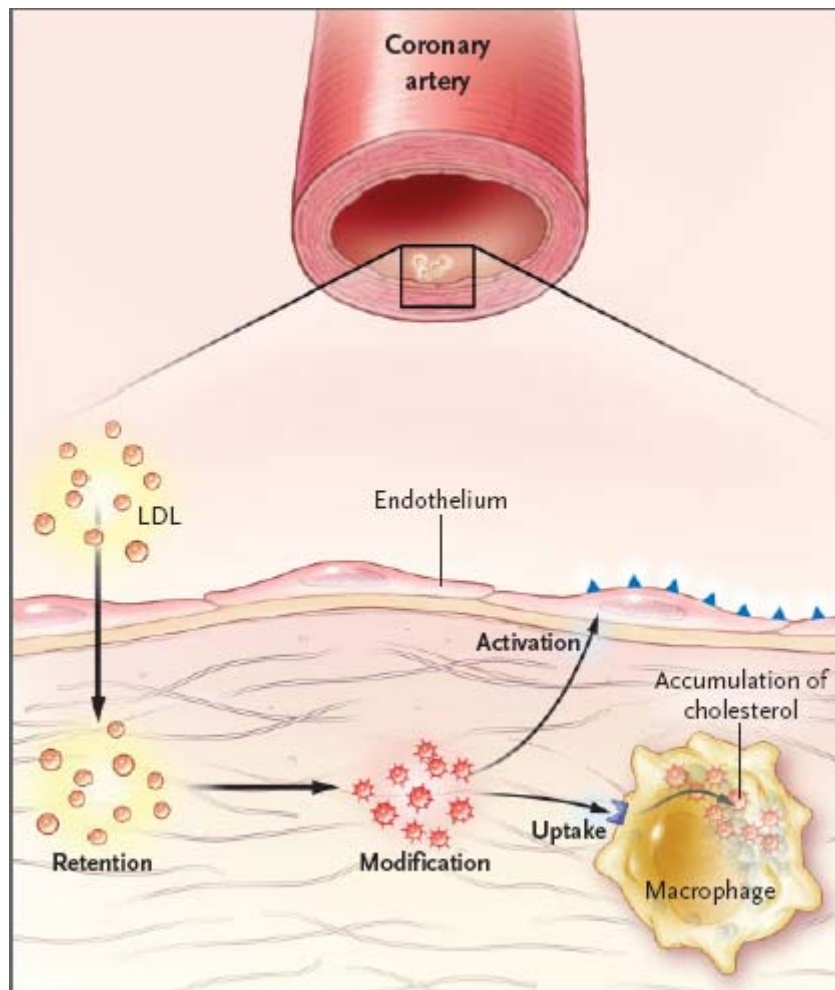
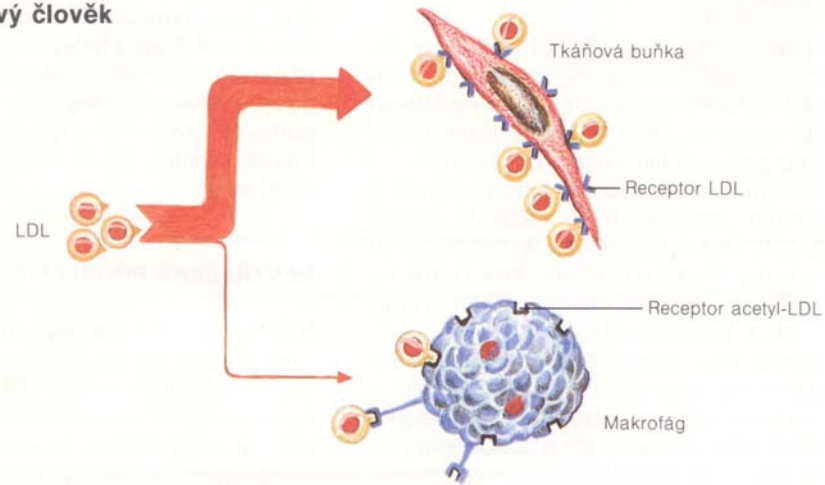


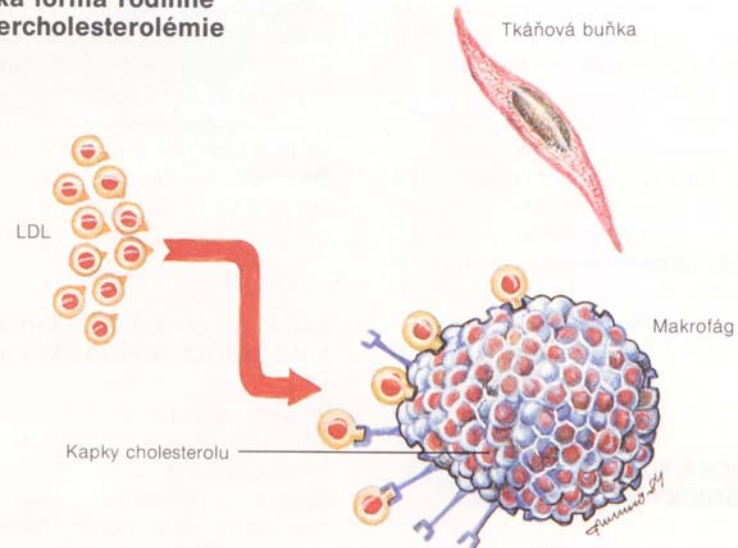
Figure 2. Activating Effect of LDL Infiltration on Inflammation in the Artery.

In patients with hypercholesterolemia, excess LDL infiltrates the artery and is retained in the intima, particularly at sites of hemodynamic strain. Oxidative and enzymatic modifications lead to the release of inflammatory lipids that induce endothelial cells to express leukocyte adhesion molecules. The modified LDL particles are taken up by scavenger receptors of macrophages, which evolve into foam cells.

Zdravý člověk



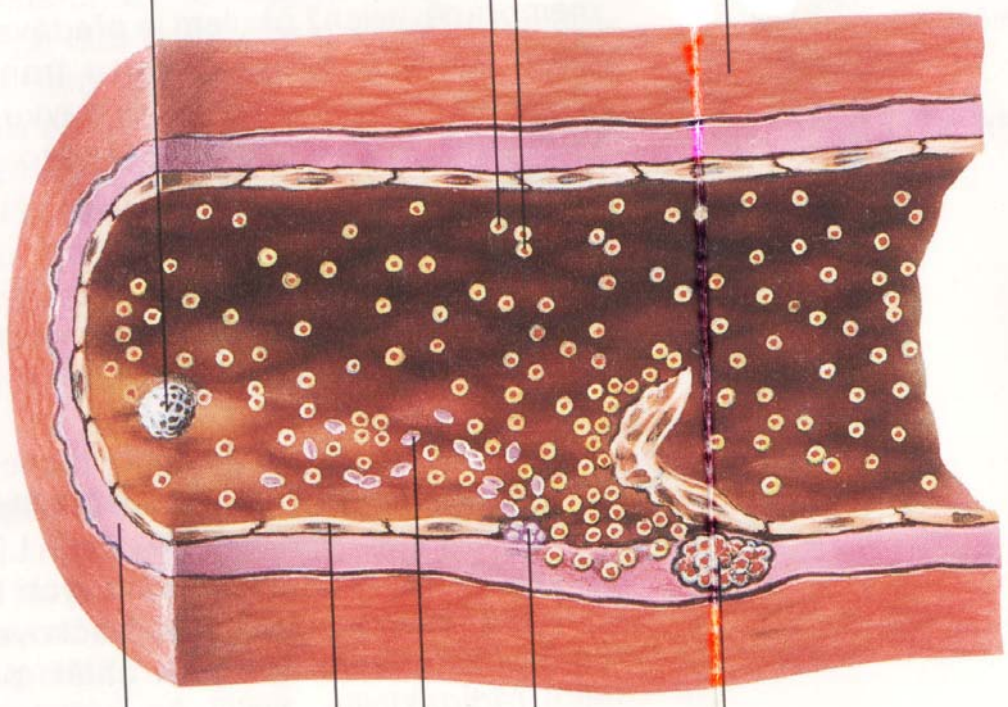
Těžká forma rodinné hypercholesterémie



Monocyt/makrofág

LDL

Media



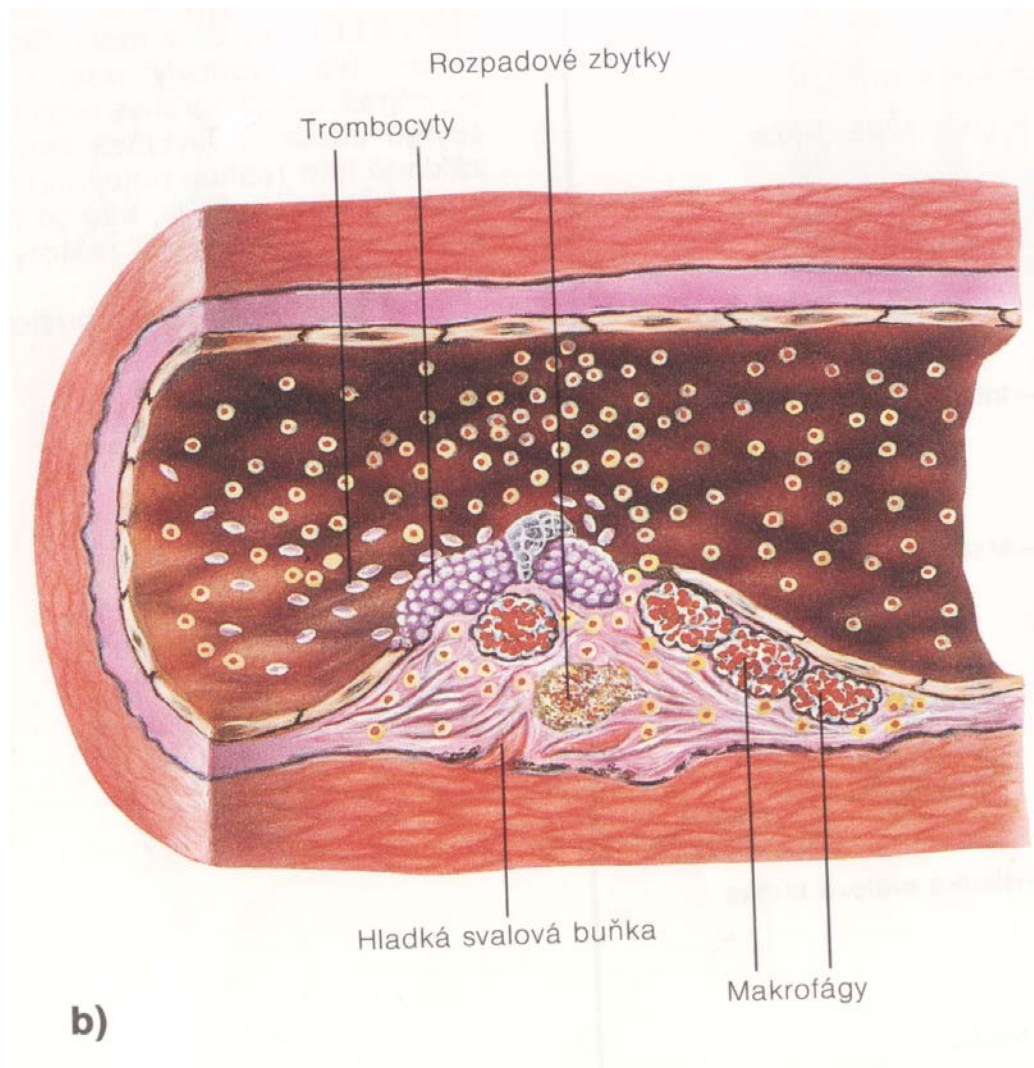
Intima

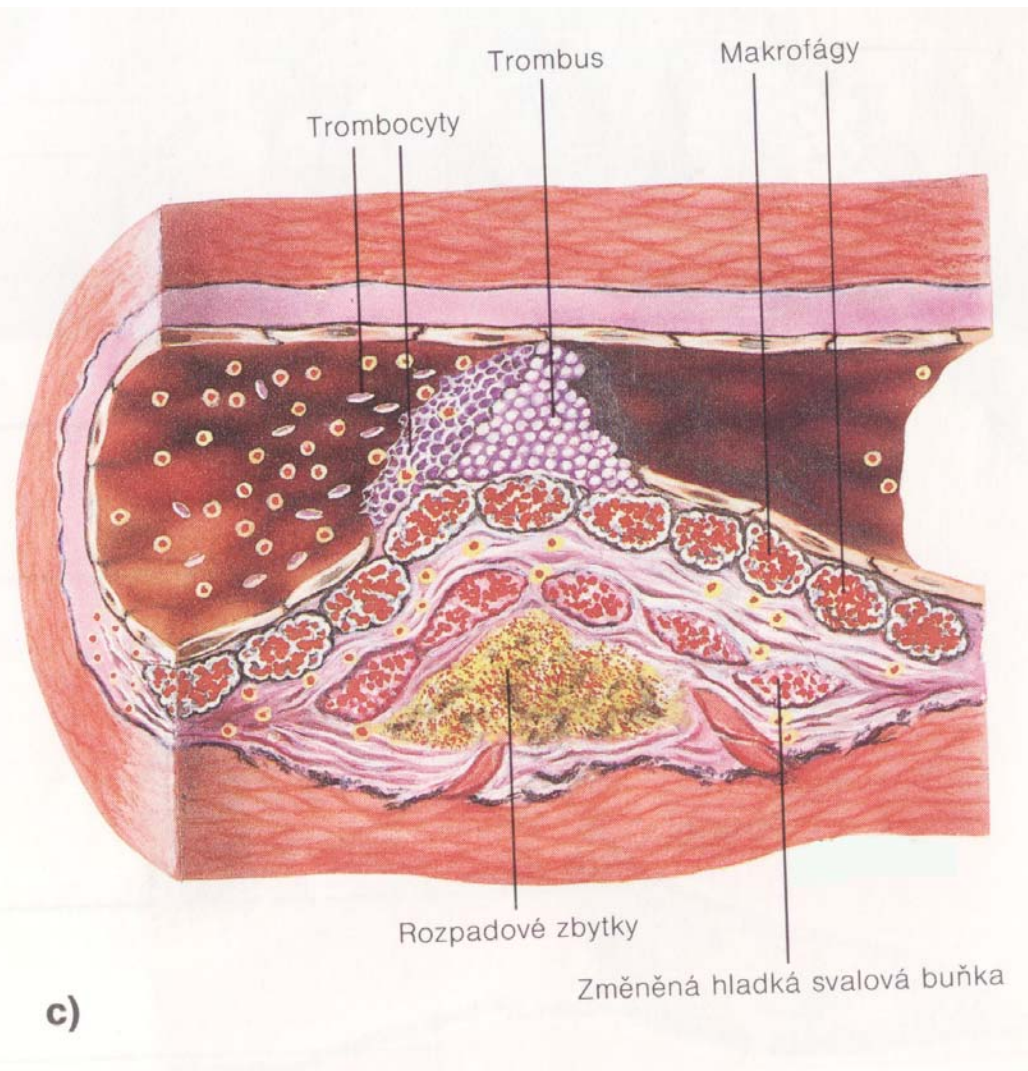
Endotel

Trombocyty

Makrofág

a)





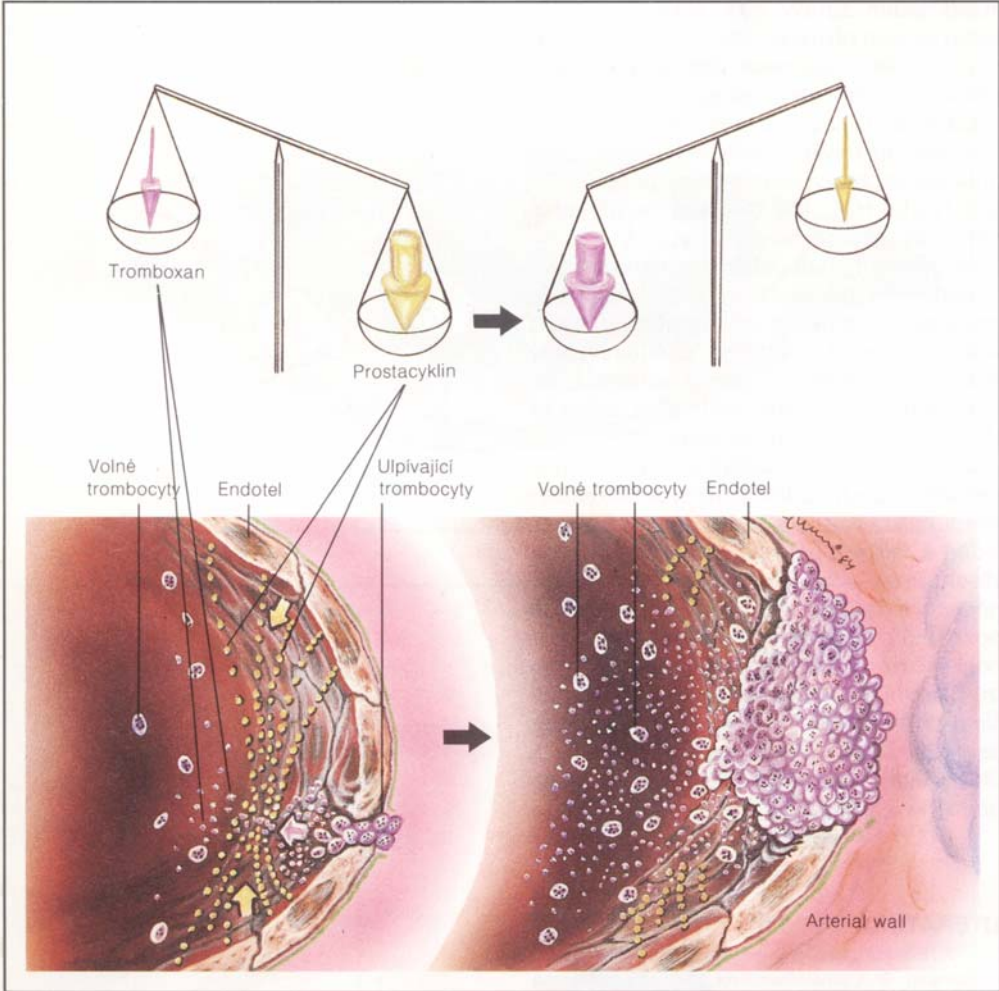


Table 2 -Initial Classification Based on Total Cholesterol and HDL Levels*

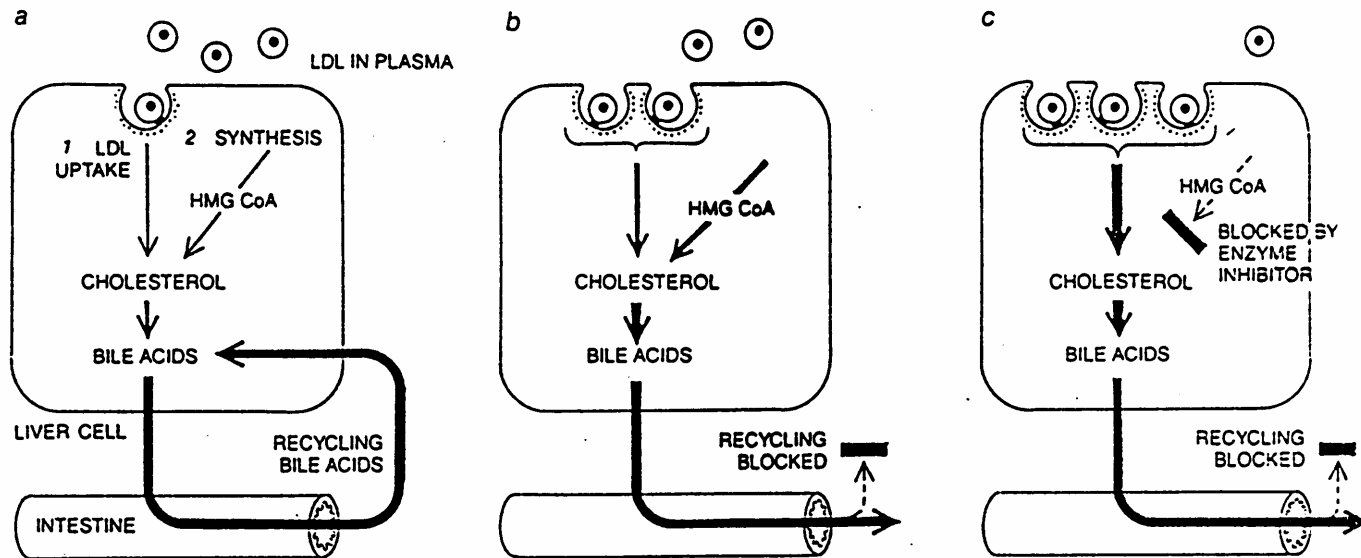
Cholesterol Level	Initial Classification
Total Cholesterol	
< 200 mg/dl (5.2 mmol/L)	Desirable blood cholesterol
200-239 mg/dl (5.2-6.2mmol/L) cholesterol	Borderline high blood
240 mg/dl (6.2 mmol/L) or greater	High blood cholesterol

HDL Cholesterol

< 35 mg/dl (0.9 mmol/L)	Low HDL cholesterol
-------------------------	---------------------

***HDL indicates high-density lipoprotein**

Terapie vysoké hladiny cholesterolu



LIVER GETS CHOLESTEROL for conversion into bile acids from IDL and LDL taken up from the circulation (1) or by synthesizing it de novo (2). A key step in the long synthetic pathway is reduction of HMG CoA to mevalonic acid, a reaction catalyzed by the enzyme

HMG CoA reductase. The enzyme is inhibited by the drugs compactin or mevinolin, whose side chain is so similar to that of HMG CoA (colored frames) that it blocks the enzyme's active site. Enzyme inhibition leaves liver dependent on uptake of IDL and LDL.

Food guide pyramid

Fats, Oils, Sweets
(Use sparingly)

Milk, Yogurt,
Cheese
(2-3 servings)

Vegetables
(3-5 servings)

Fruit
(2-4 servings)

Bread,
Cereal,
Rice,
Pasta

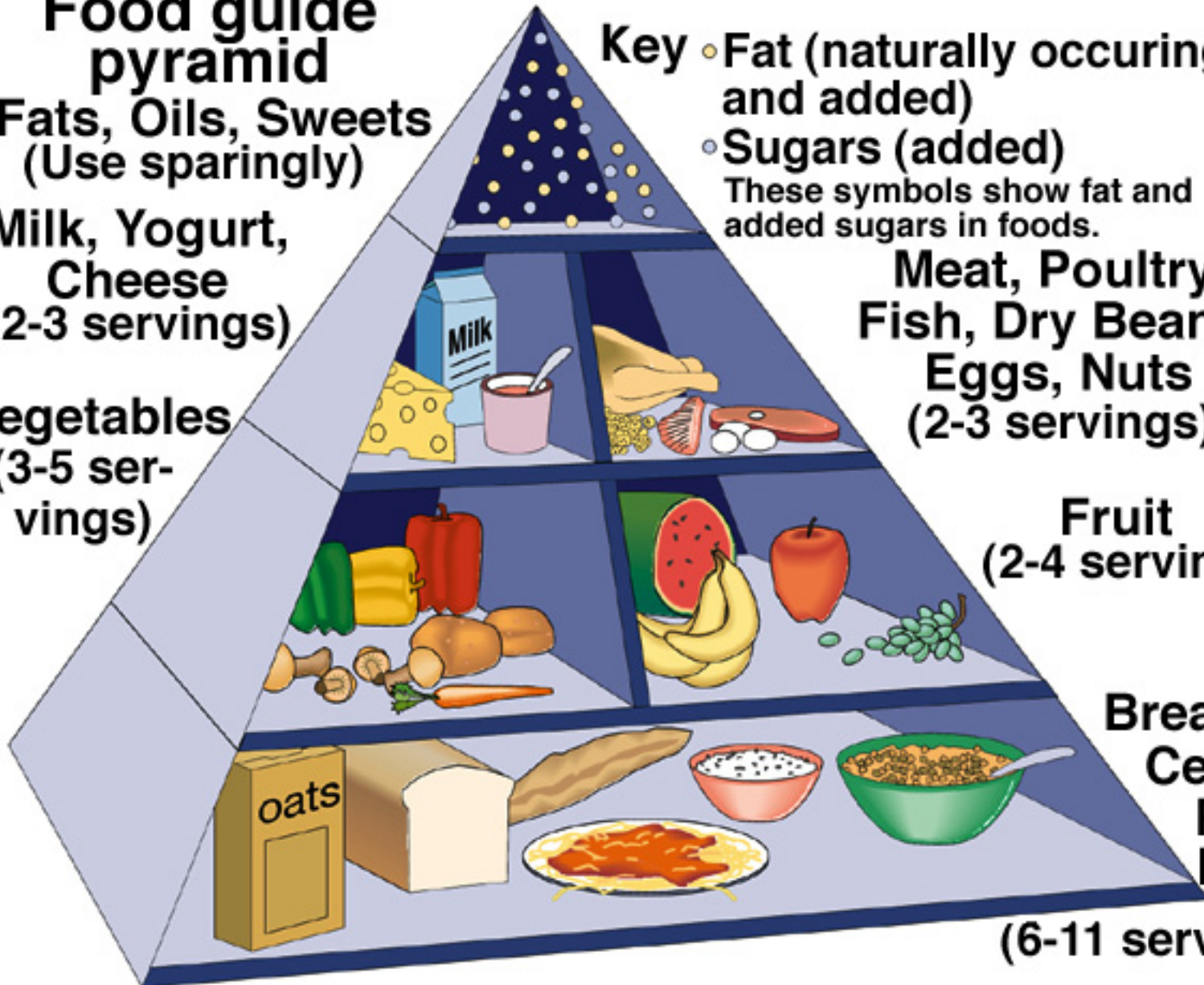
(6-11 servings)

Key • Fat (naturally occurring and added)

◦ Sugars (added)

These symbols show fat and added sugars in foods.

Meat, Poultry,
Fish, Dry Beans,
Eggs, Nuts
(2-3 servings)



dietary recommendations

Eat plenty of fresh fruit and vegetables, at least five different portions per day.

Minimize intake of fats and red meats, but do not become paranoid about it. Don't worry about polyunsaturates versus saturates.

Check your cholesterol level. If 200 mg/100 ml or below don't worry. If at or above 250 mg/100 ml seek medical advice.

Consume no more than 300 units (200 mg) of vitamin E (d- α -tocopherol, *not* dl- α -tocopherol) per day from a reliable source such as the 'own brand' of a reputable chain drug store. Take with food as you need fat to absorb it.

If you wish, consume up to 250 mg of vitamin C per day. Again, select a reputable supplier (e.g. the 'own brand' of a reputable chain drug-store). If you smoke, stop. If you can't, eat plenty of fruits and vegetables and consider supplementing with more vitamin C (Table 2, p. 67).

Do not take any form of iron supplements unless there is a clearly identified medical need monitored by laboratory tests.

We see no case at present for consuming β -carotene supplements.

Positive Risk Factors

Age

Male 45 or older

Estrogen Status

Female 55 or older (or premature menopause) **without** estrogen replacement therapy

Family history of premature CHD

definite myocardial infarction or sudden death **before** 55 y of age in father or other first-degree relative

Current cigarette smoking

Hypertension

blood pressure 140/90 or greater** or taking antihypertensive medication

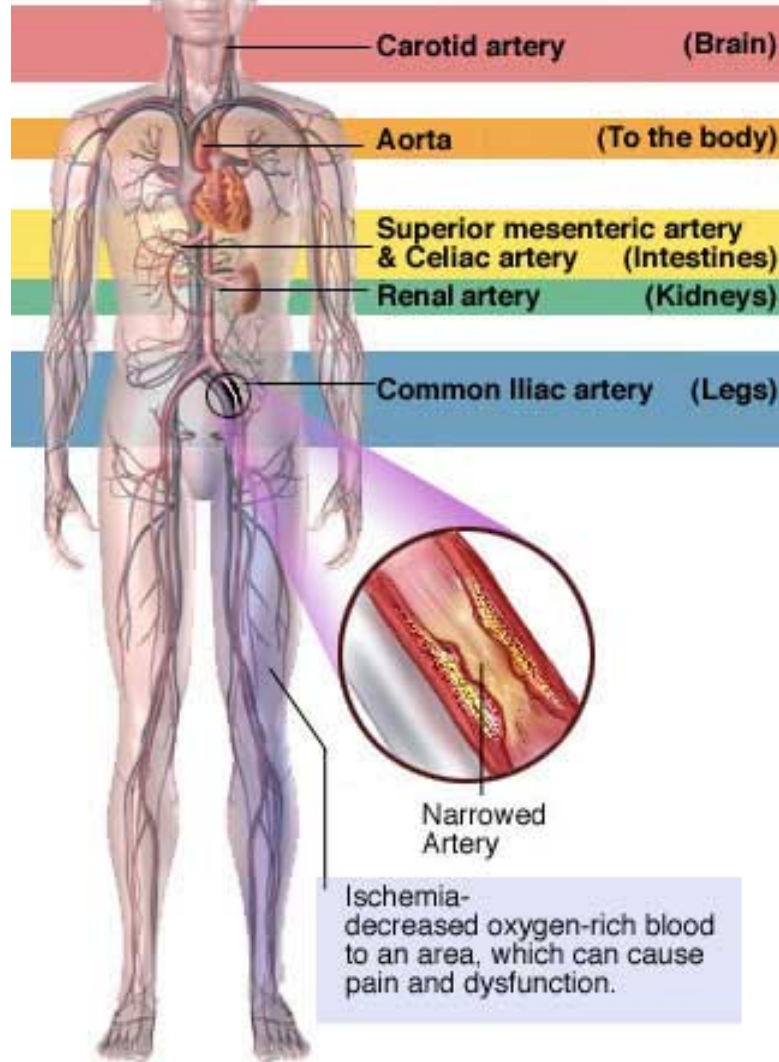
Low HDL cholesterol

35 mg/dl [0.9 mmol/L] or less**

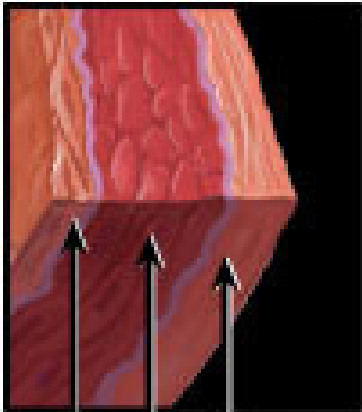
Negative Risk Factors***

High HDL cholesterol (60 mg/dl [1.6 mmol/L] or greater)

Peripheral Arterial Disease

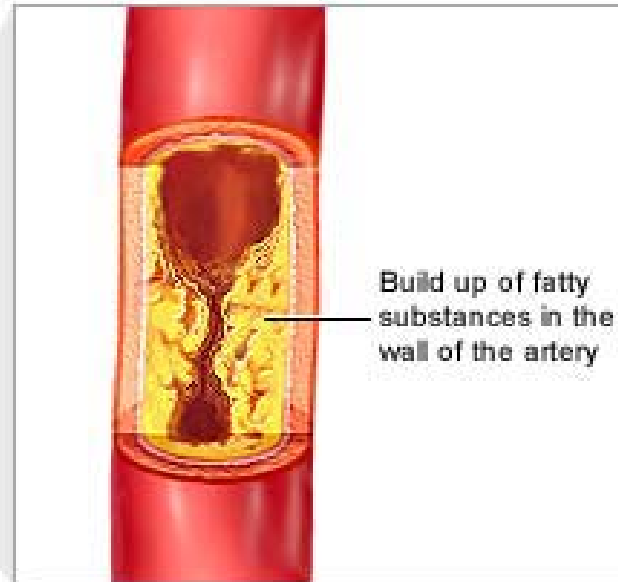
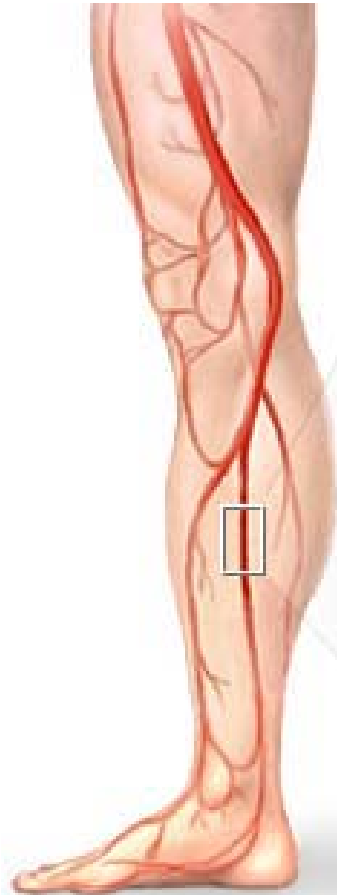


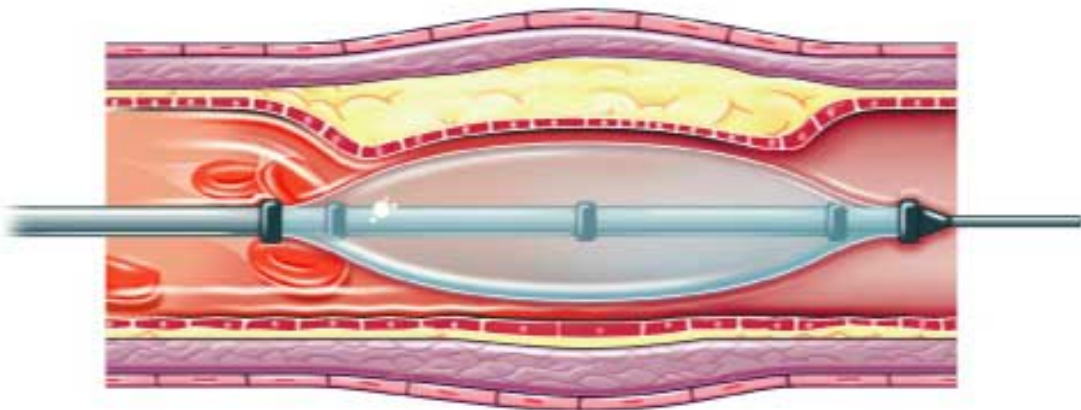
Normal Layers of Artery



Intima
Media
Adventitia

Arteries become narrowed and blood flow decreases in arteriosclerosis





Artery blocked with plaque deposits

Balloon

Catheter

Artery opened



Atherectomy

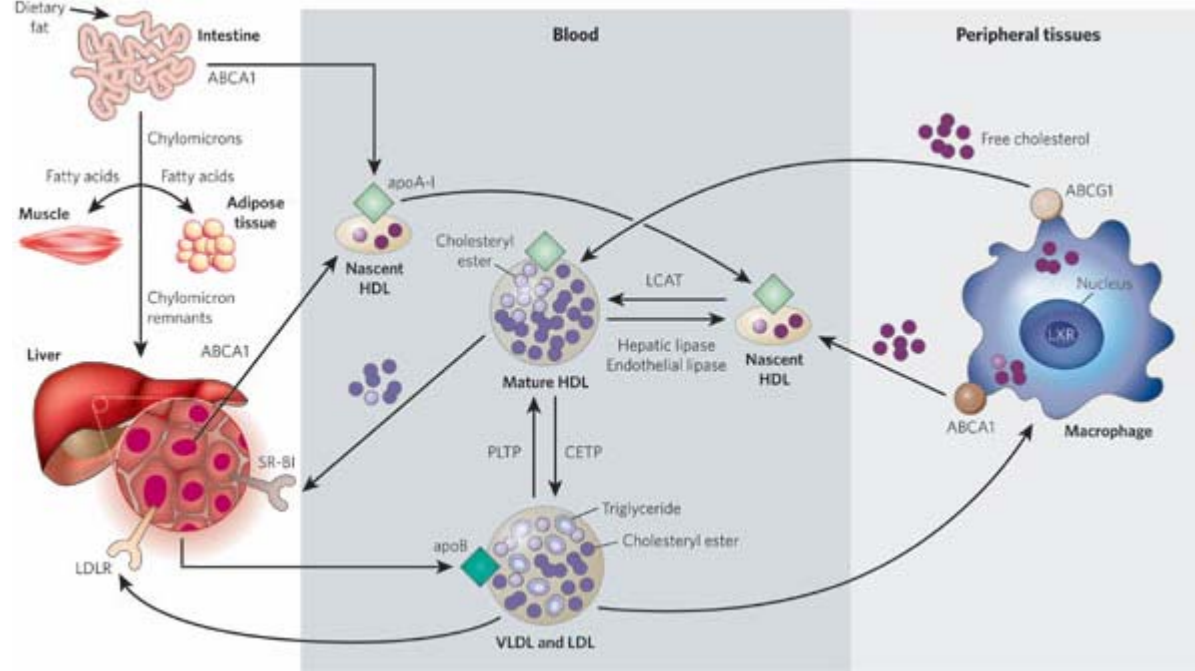


For
more
info...



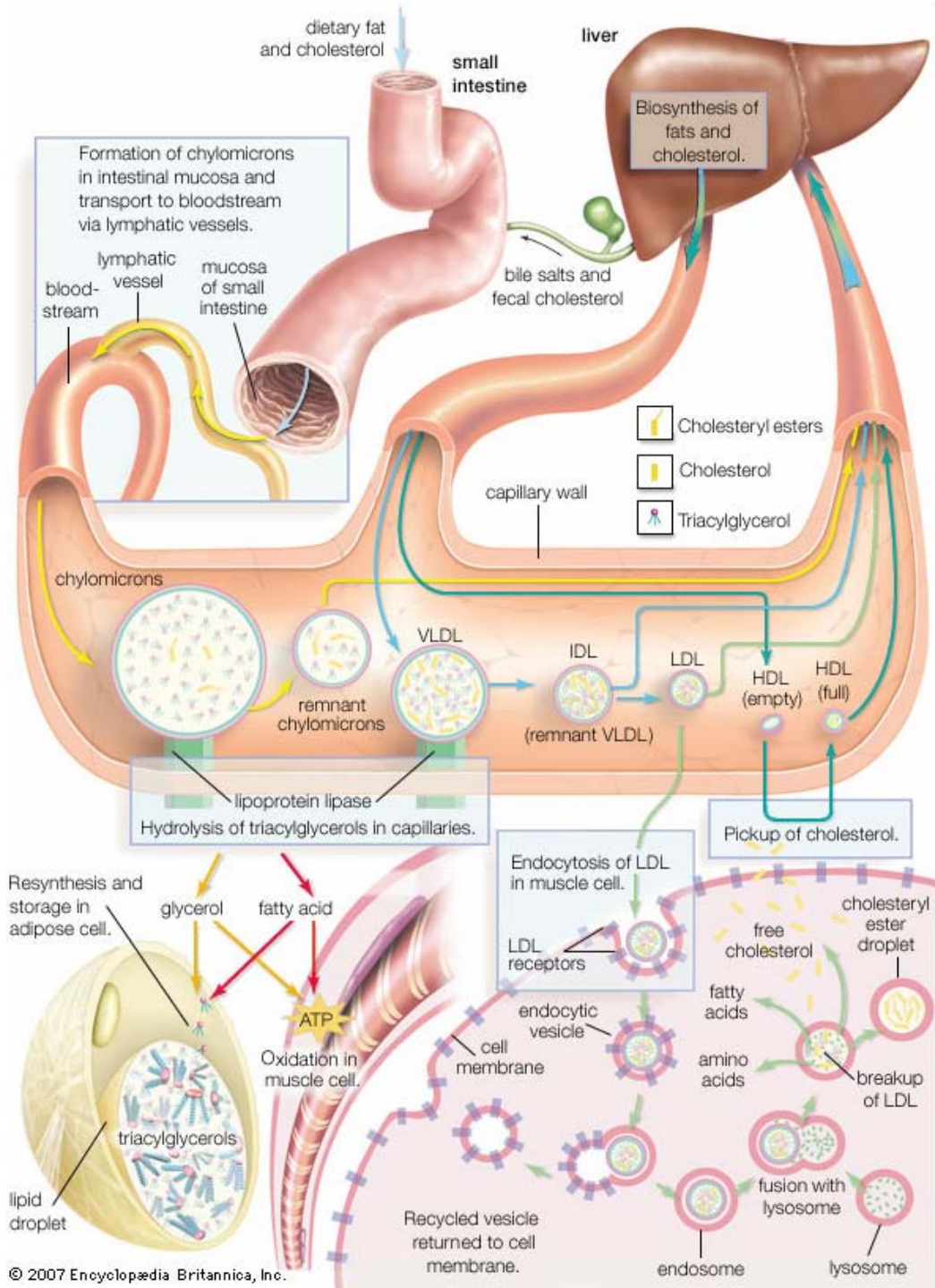
HeartCenterOnline





Lipoprotein metabolism has a key role in atherogenesis. It involves the transport of lipids, particularly cholesterol and triglycerides, in the blood. The intestine absorbs dietary fat and packages it into chylomicrons (large triglyceride-rich lipoproteins), which are transported to peripheral tissues through the blood. In muscle and adipose tissues, the enzyme lipoprotein lipase breaks down chylomicrons, and fatty acids enter these tissues. The chylomicron remnants are subsequently taken up by the liver. The liver loads lipids onto apoB and secretes very-low-density lipoproteins (VLDLs), which undergo lipolysis by lipoprotein lipase to form low-density lipoproteins (LDLs). LDLs are then taken up by the liver through binding to the LDL receptor (LDLR), as well as through other pathways. By contrast, high-density lipoproteins (HDLs) are generated by the intestine and the liver through the secretion of lipid-free apoA-I. ApoA-I then recruits cholesterol from these organs through the actions of the transporter ABCA1, forming nascent HDLs, and this protects apoA-I from being rapidly degraded in the kidneys. In the peripheral tissues, nascent HDLs promote the efflux of cholesterol from tissues, including from macrophages, through the actions of ABCA1. Mature HDLs also promote this efflux but through the actions of ABCG1. (In macrophages, the nuclear receptor LXR upregulates the production of both ABCA1 and ABCG1.) The free (unesterified) cholesterol in nascent HDLs is esterified to cholesteryl ester by the enzyme lecithin cholesterol acyltransferase (LCAT), creating mature HDLs. The cholesterol in HDLs is returned to the liver both directly, through uptake by the receptor SR-BI, and indirectly, by transfer to LDLs and VLDLs through the cholesteryl ester transfer protein (CETP). The lipid content of HDLs is altered by the enzymes hepatic lipase and endothelial lipase and by the transfer proteins CETP and phospholipid transfer protein (PLTP), affecting HDL catabolism.

www.nature.com/.../images/nature06796-f3.2.jpg



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