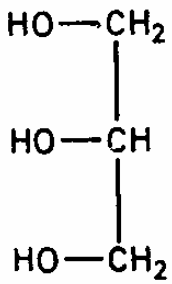
Volné radikály a ateroskleróza

Tuky

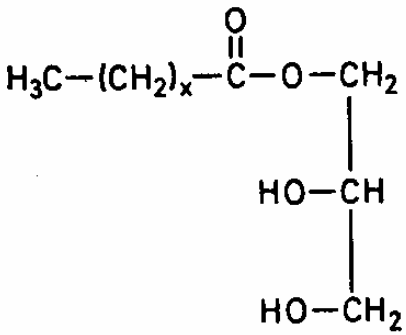
jsou složené sloučeniny
Chemickým charakterem patří k esterům

Z kyselin obsahují nerozvětvené alifatické kyseliny
Alkoholickou složkou je glycerol

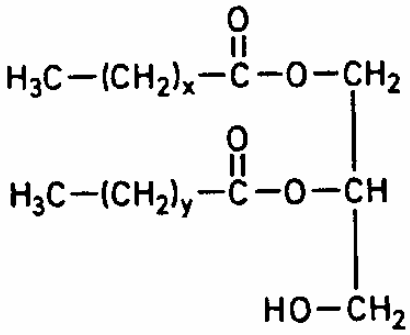
Glycerol jako trojsytný alkohol může tvořit **mono-, di- a triacylglyceroly**
(v dřívější terminologii mono-, di- a triglyceridy)



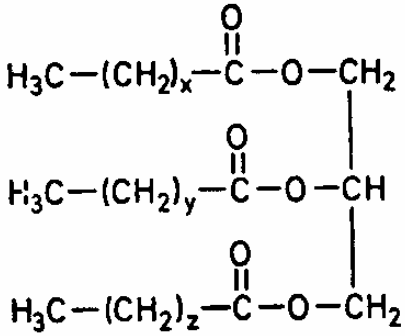
glycerol



monoacylglycerol

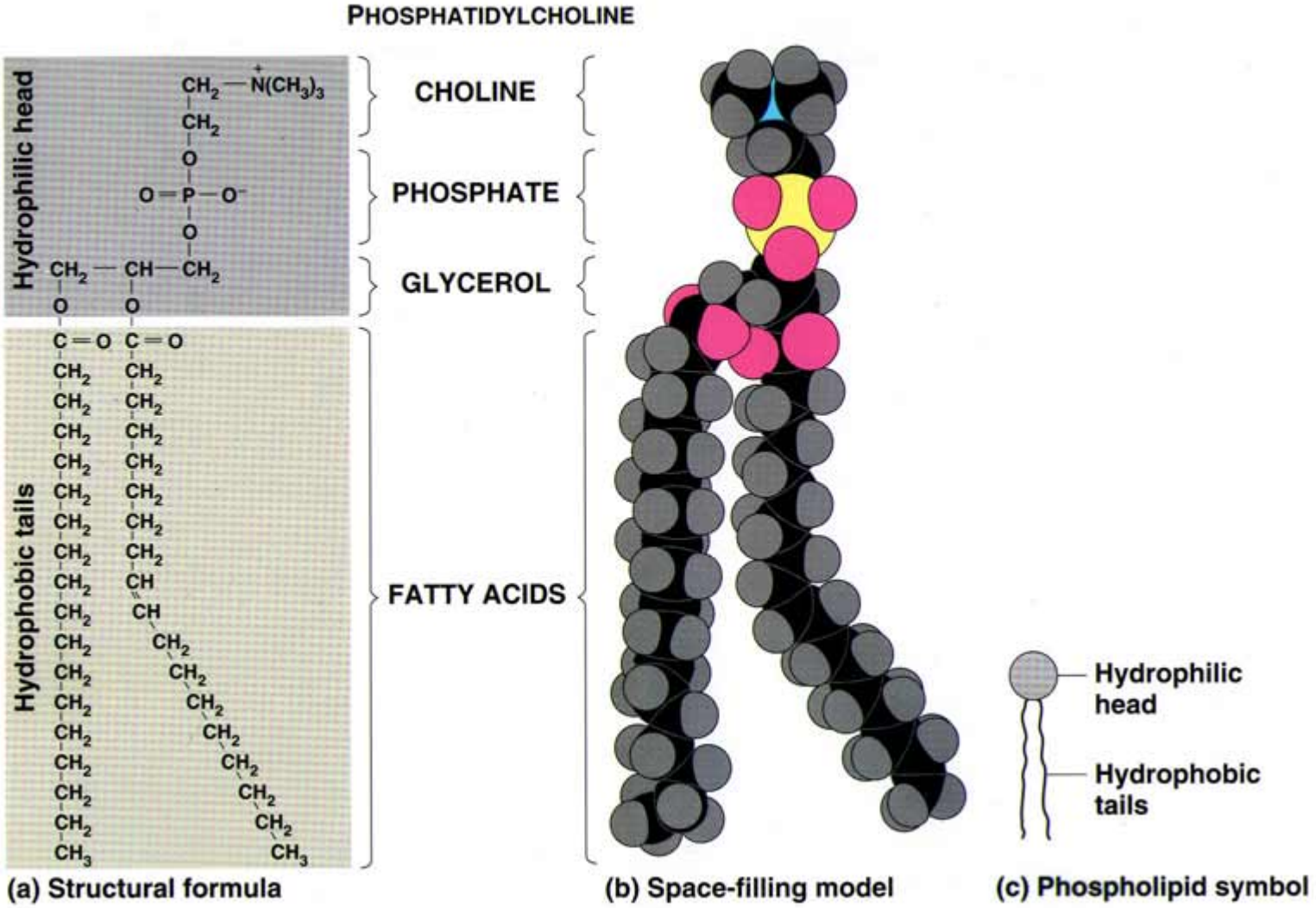


diacylglycerol



triacylglycerol

The structure of a phospholipid



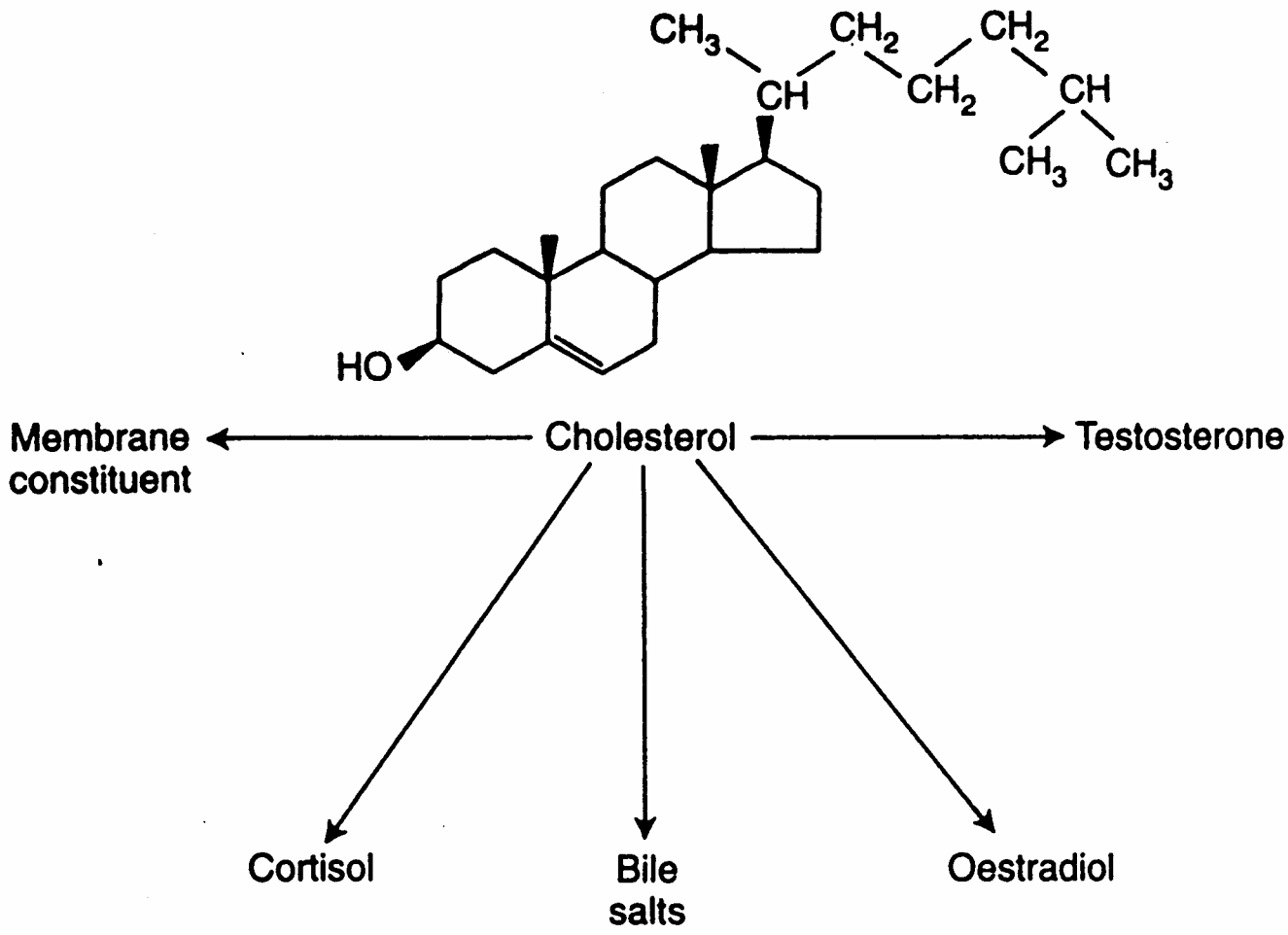
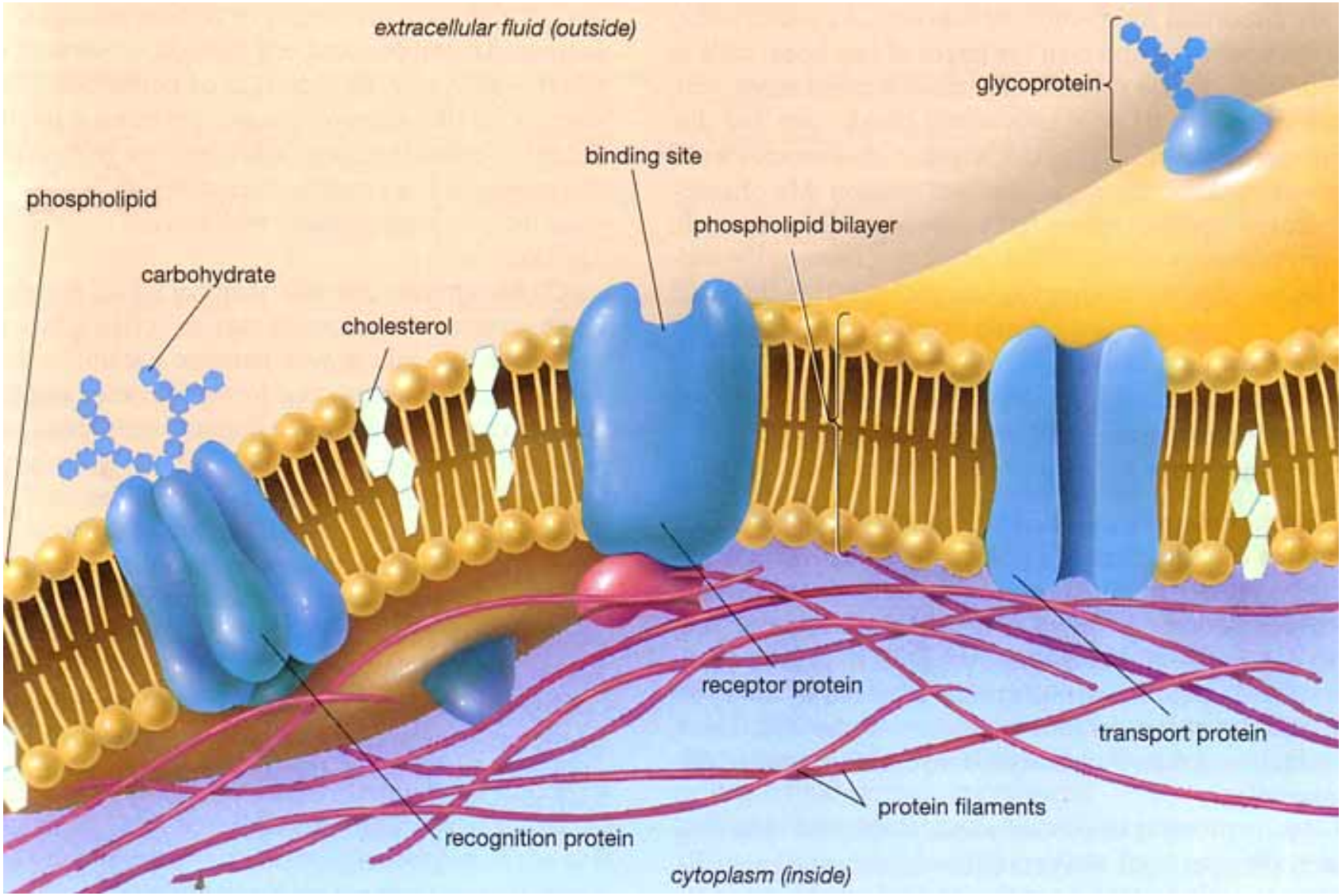


Figure A3. The structure of cholesterol.


extracellular fluid (outside)
glycoprotein
binding site
phospholipid
phospholipid bilayer
carbohydrate
cholesterol
receptor protein
transport protein
protein filaments
recognition protein
cytoplasm (inside)

Shrnutí

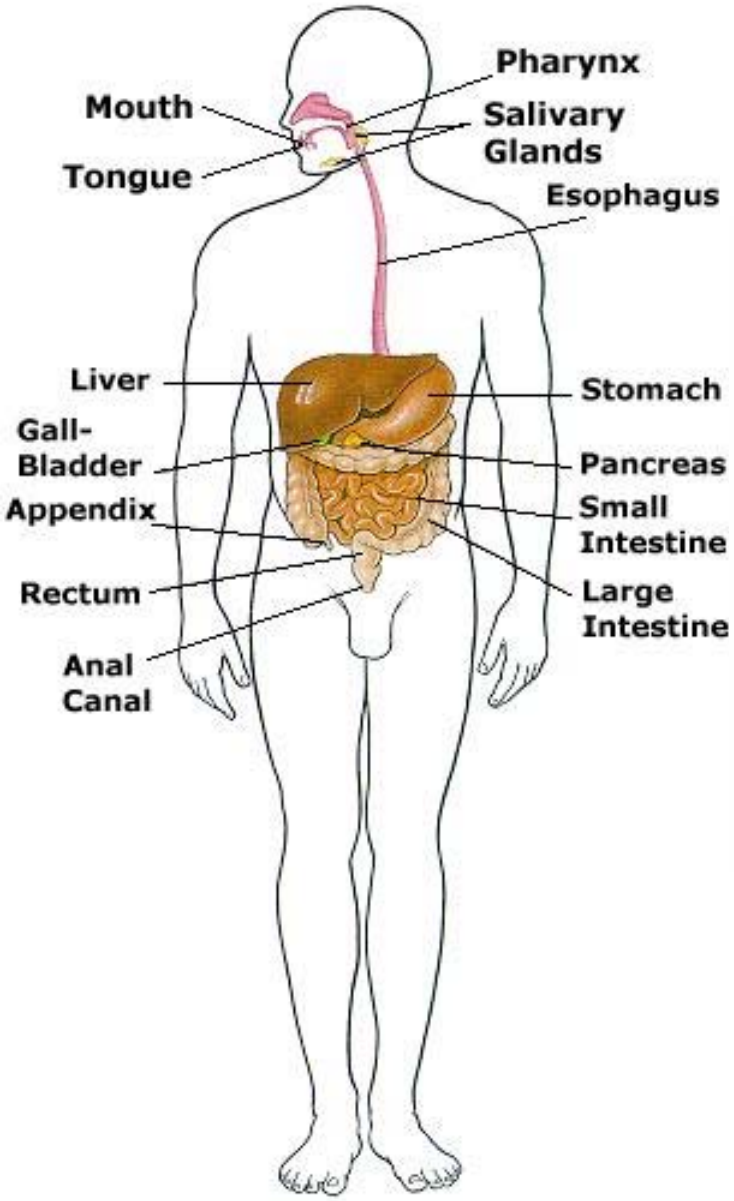
Potravou jsou přijímány tyto základní látky tukovité povahy:

triacylglyceroly

cholesterol a jeho estery

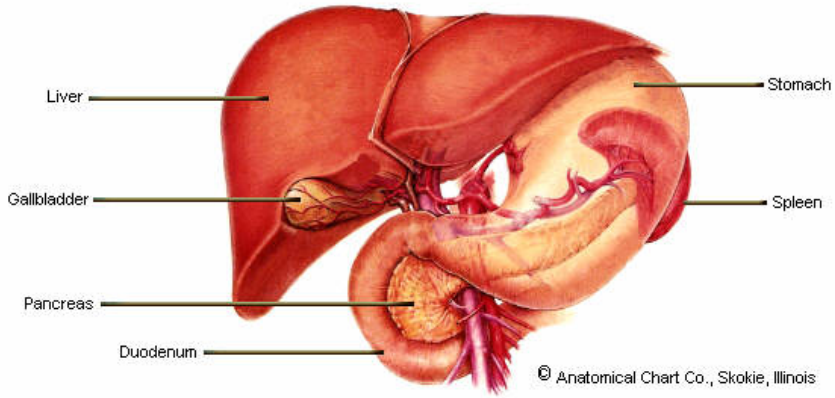
fosfolipidy (především lecithin)

Major Digestive Organs



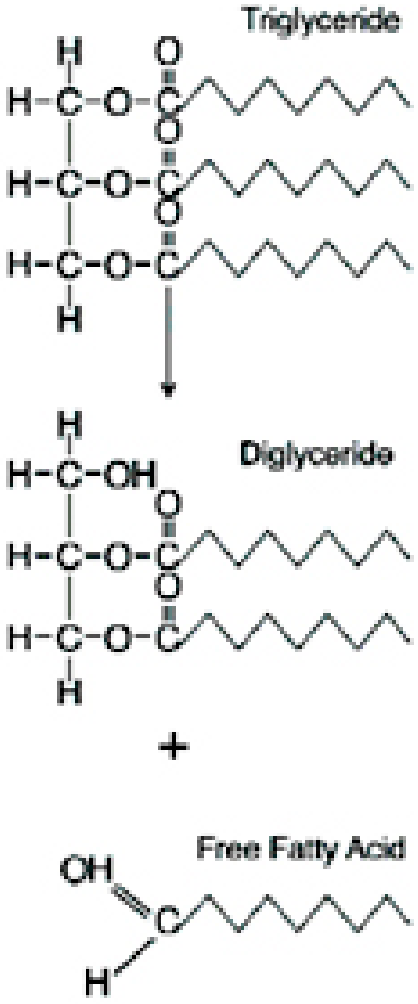
adapted from Thibodeau

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

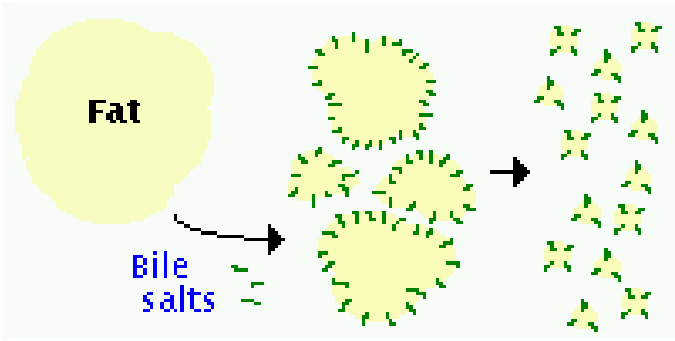


Štěpení tuků v tenkém střevě

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

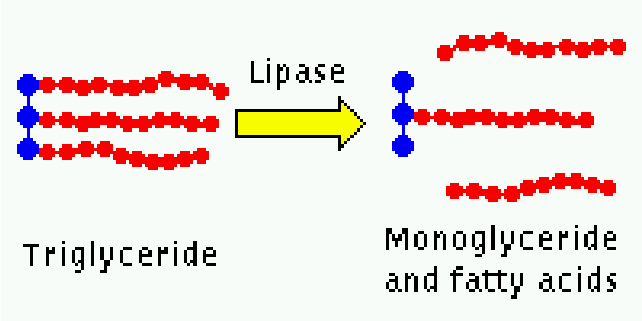


Pancreatic Lipase Action

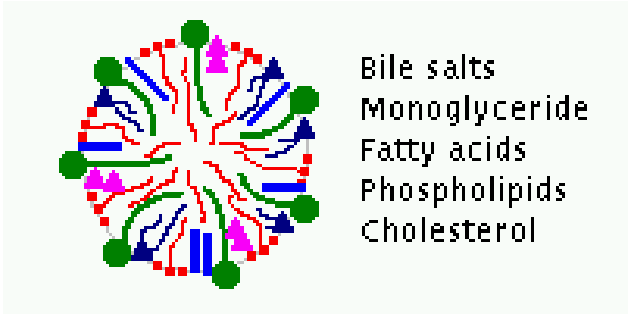


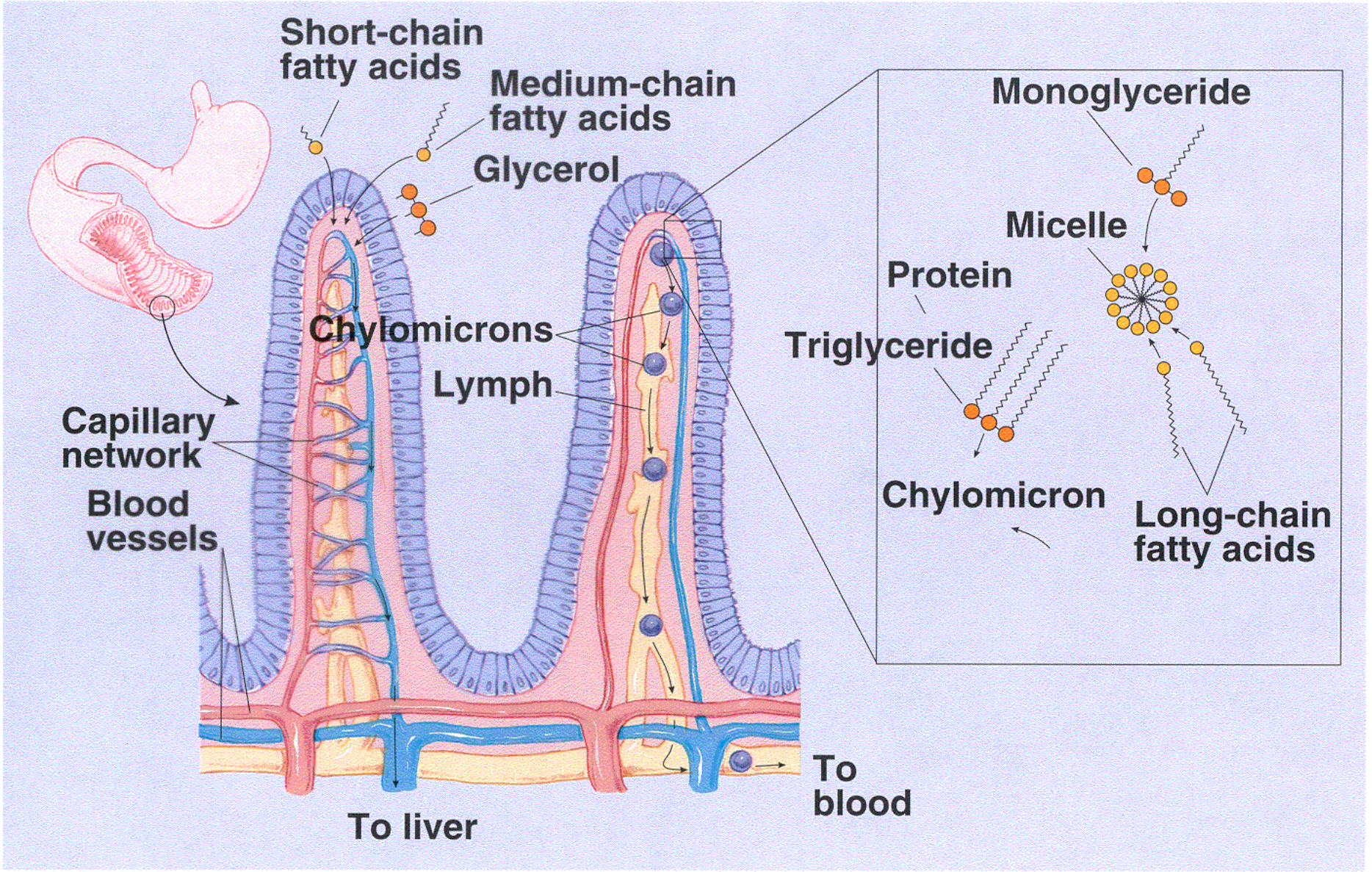
Hydrofobní části žlučových kyselin se vnoří do tukových kapének, hydrofilní části zůstávají na povrchu, to vede ke štěpení. Čím menší kapénky, tím lepší účinek pankreatické lipázy

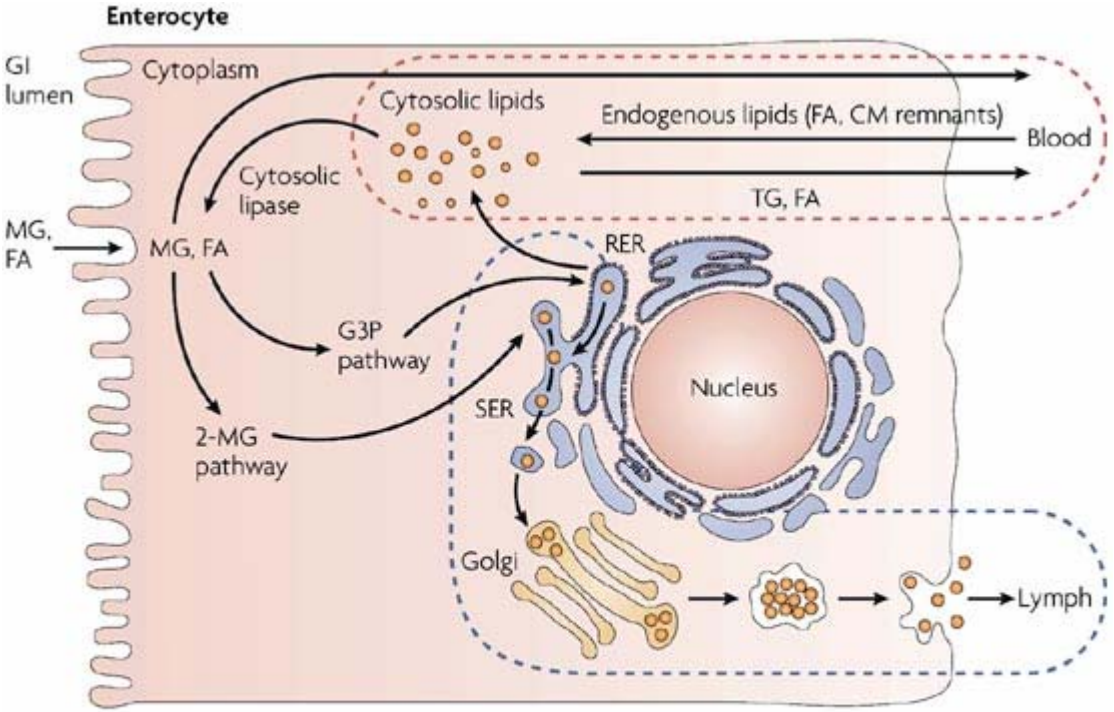
Hydrolýza triacylglycerolů pankreatickou lipázou. Látka orlistat (Xenical) inhibuje PL – léčba obezity



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.



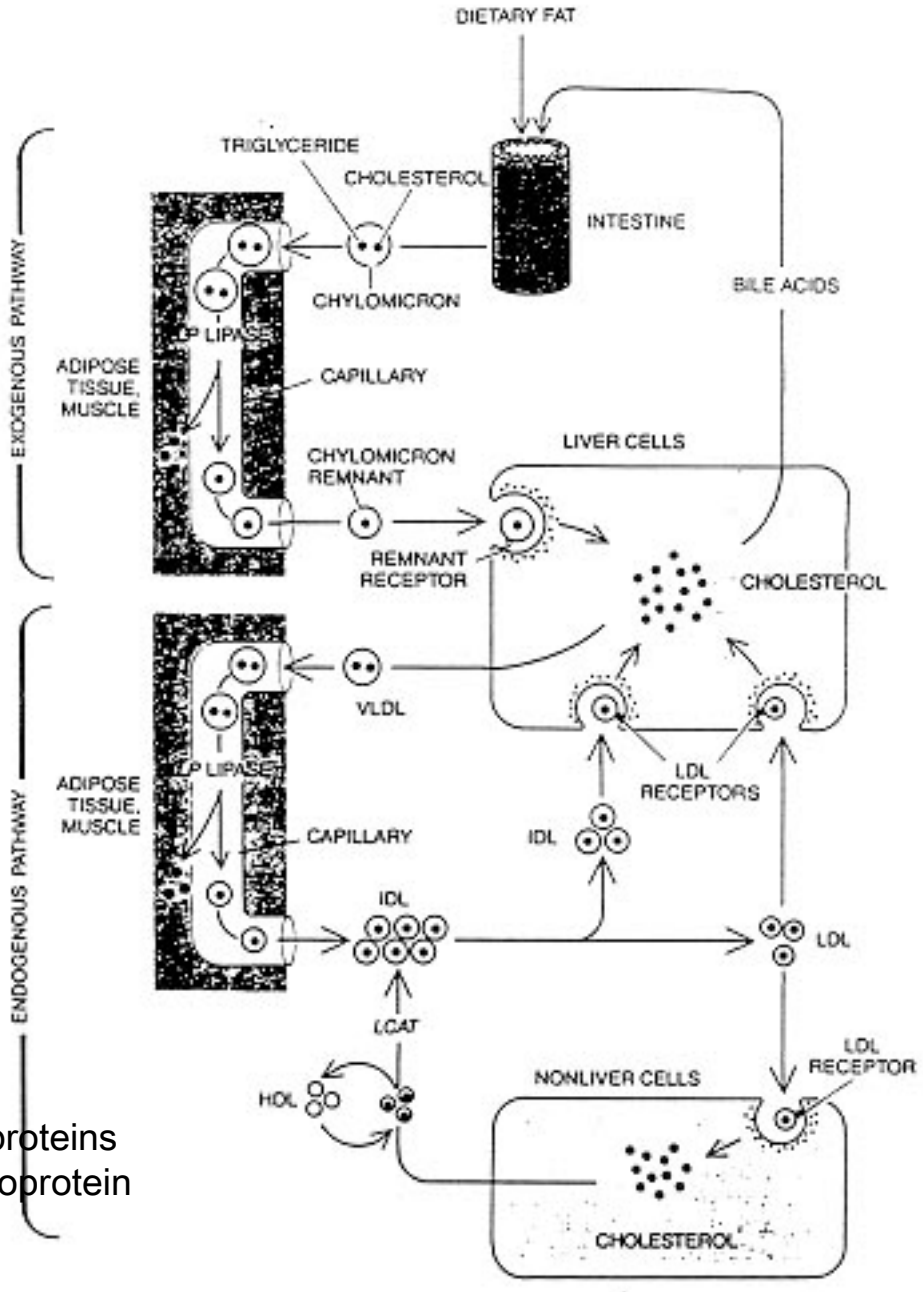

Short-chain fatty acids
Medium-chain fatty acids
Glycerol
Chylomicrons
Lymph
Capillary network
Blood vessels
To liver
To blood
Monoglyceride
Micelle
Protein
Triglyceride
Chylomicron
Long-chain fatty acids



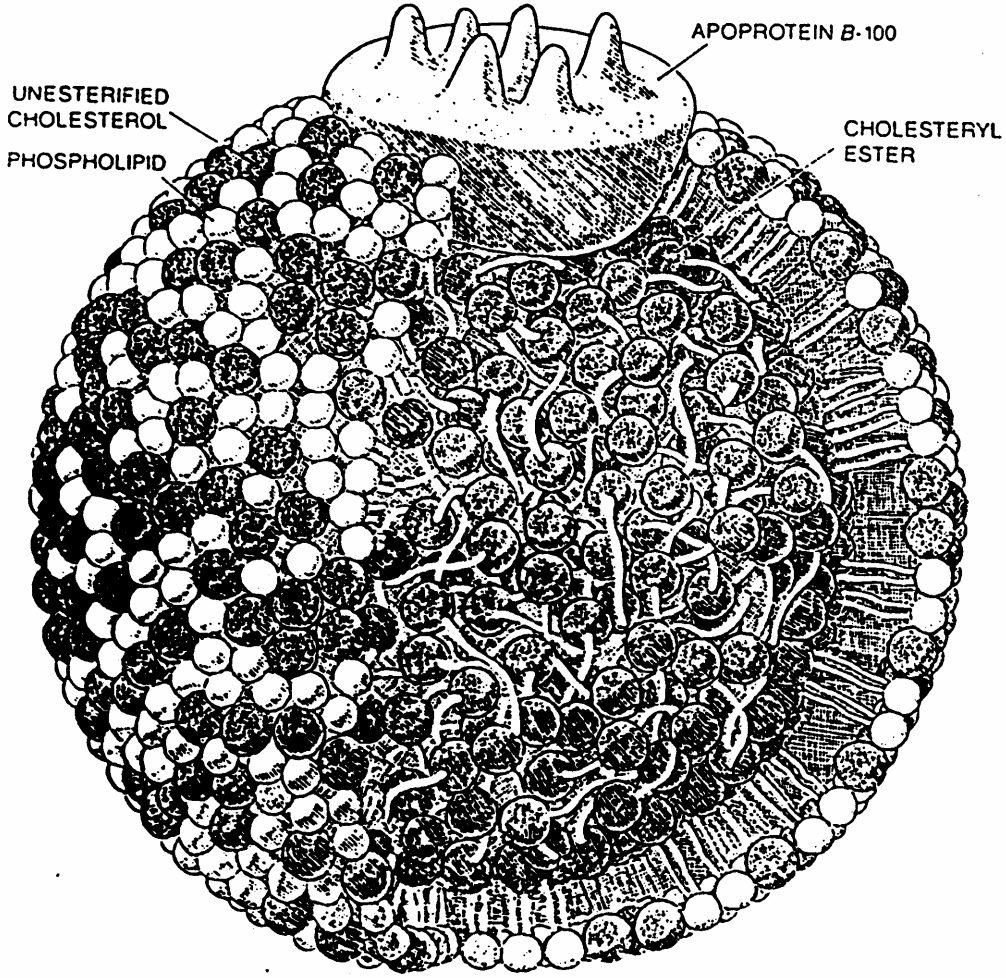
Following uptake across the apical membrane of the enterocyte, the products of gastrointestinal (GI) lumen lipid digestion — monoglyceride (MG) and fatty acid (FA) — can either diffuse across the enterocyte and enter the portal vein blood or be re-synthesized to triglyceride (TG) by either the 2-monoglyceride (2-MG) pathway associated with the smooth endoplasmic reticulum (SER) or the a-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.

Porter *et al*. *Nature Reviews Drug Discovery* **6**, 231–248 (March 2007) | doi:10.1038/nrd2197

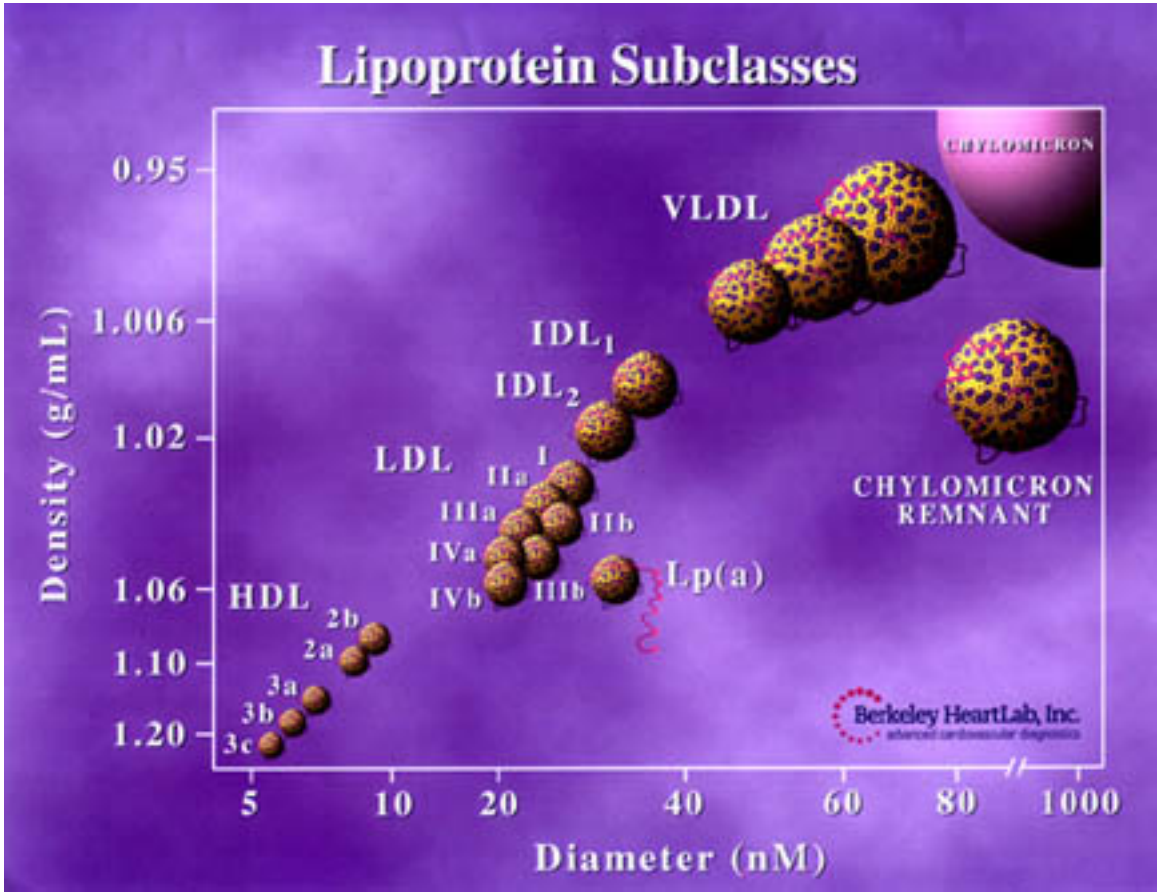
LP – lipoproteinová lipáza. Štěpí triglyceridy, mastné kyseliny vstřebány, zbytek bohatý na cholesterol do jater.

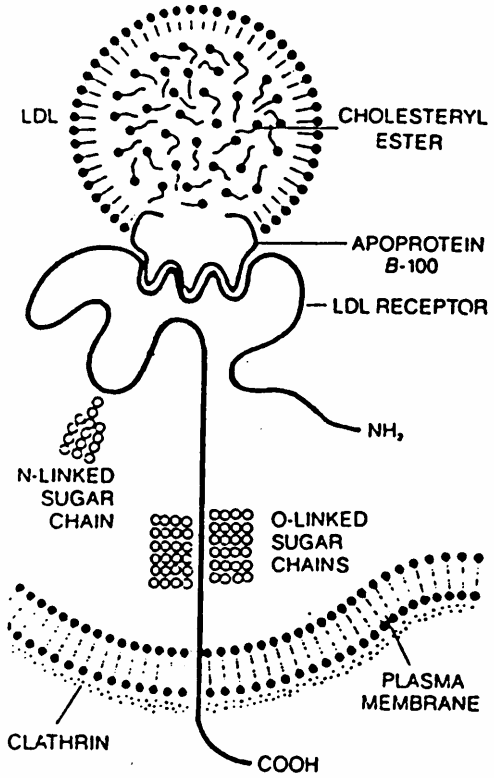


VLDL – very low density lipoproteins
IDL – intermediate density lipoprotein
LDL – low density lipoprotein
HDL – high density lipoprotein

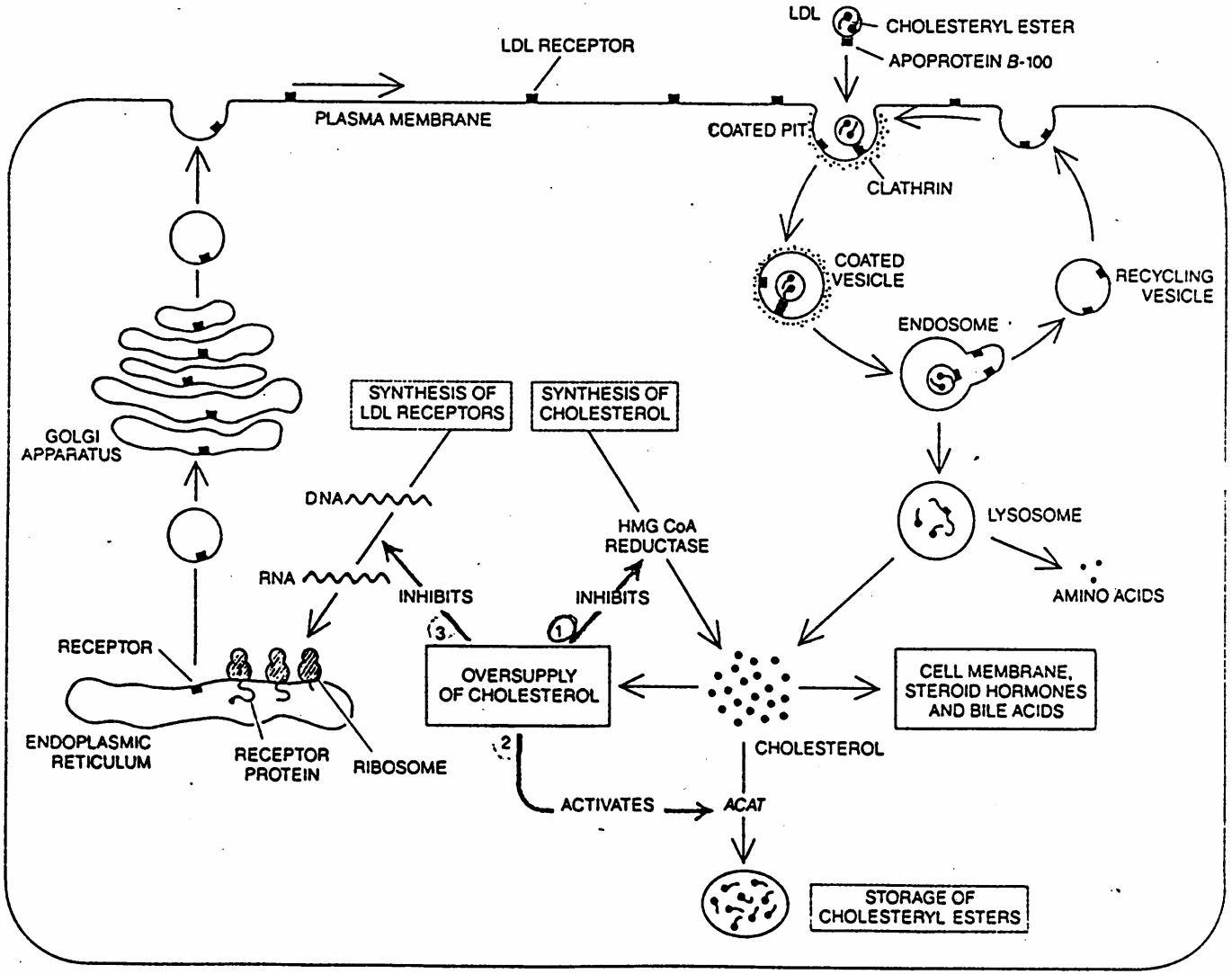


LDL, MAJOR CHOLESTEROL CARRIER in the bloodstream, is a spherical particle with a mass of three million daltons and a diameter of 22 nanometers (millionths of a millimeter). Its core consists of some 1,500 cholesteryl esters, each a cholesterol molecule attached by an ester linkage to a long fatty acid 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
CHYLOMICRON
VLDL
IDL1
IDL2
LDL
I
IIa
IIb
IIIa
IIIb
IVa
IVb
Lp(a)
HDL
2b
2a
3a
3b
3c
CHYLOMICRON REMNANT
Berkeley HeartLab, Inc.
Density (g/mL)
0.95
1.006
1.02
1.06
1.10
1.20
5
10
20
40
60
80
1000
Diameter (nM)



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.



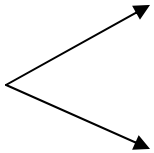
CIRCULATING LDL (*top right*) **is taken into a cell by receptor-mediated endocytosis. LDL is bound by a receptor in a coated pit, which invaginates and pinches off to form a coated vesicle. Fusion of several vesicles gives rise to an endosome, in whose acidic environment the LDL dissociates from the 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 Mϕ = 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:

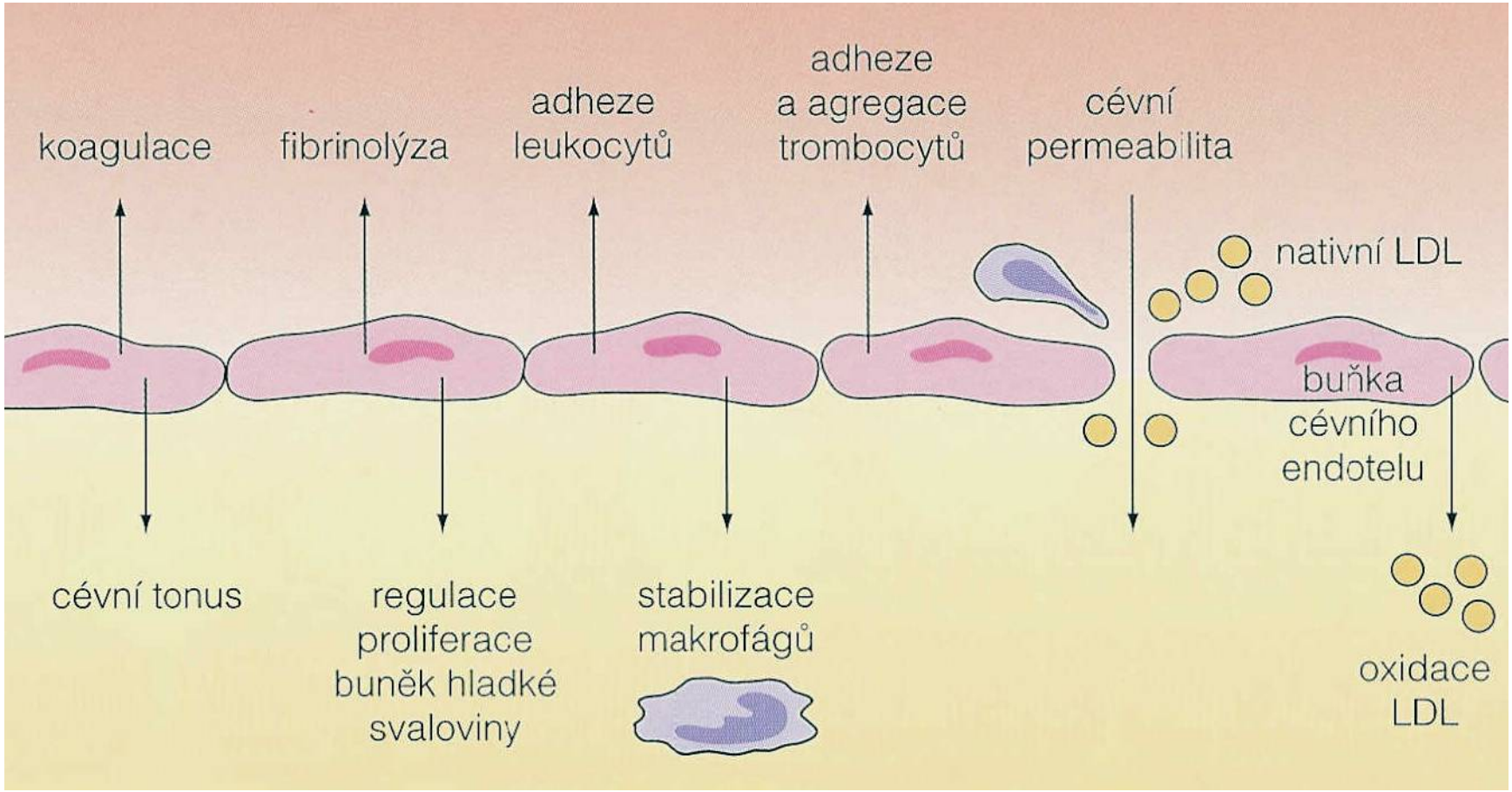
„Abnormální“ lipidy, hypertense, nikotin, DM, hypercholesterolemie, genetické dispozice, faktory srážení krve, homocystein, …

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 apoproteinu B a PL
- Vazba aldehydu na aminoskupinu Lys (glc, malondialdehyd) – glykace usnadňuje oxidaci LDL $\Rightarrow$ oxidace glykovaných bílkovin vede k tvorbě AGEs (advanced glycation end-products)
- Vícemodifikované LDL nejsou rozpoznávány LDL receptory (pohlcovány makrofágy a ukládány v podobě kapének $\Rightarrow$ pěnové buňky

Dalších 5 obrázků

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Inflammation, Atherosclerosis, and Coronary Artery Disease

Göran K. Hansson, M.D., Ph.D.

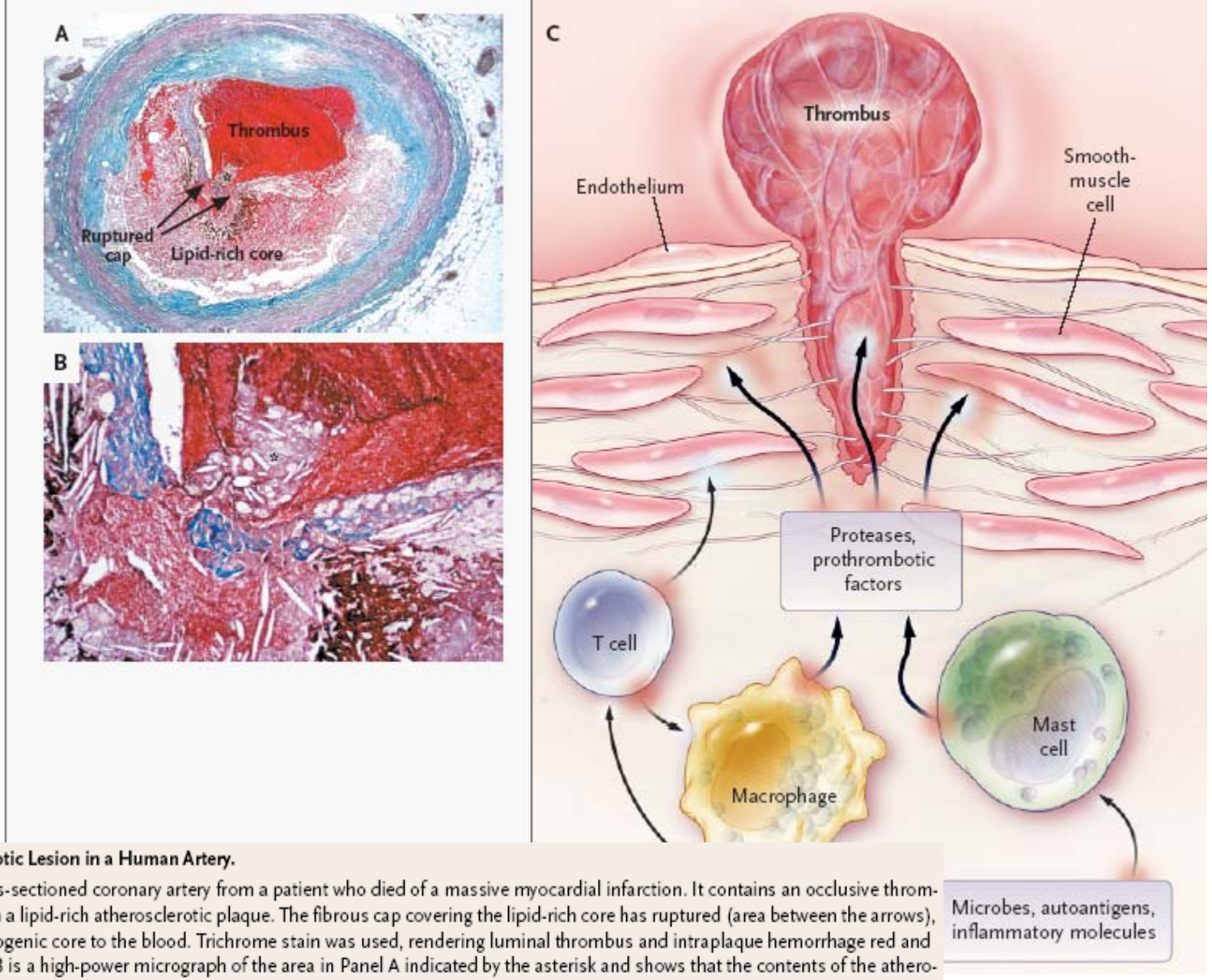


Figure 1. Atherosclerotic Lesion in a Human Artery.

Panel A shows a cross-sectioned coronary artery from a patient who died of a massive myocardial infarction. It contains an occlusive thrombus superimposed on a lipid-rich atherosclerotic plaque. The fibrous cap covering the lipid-rich core has ruptured (area between the arrows), exposing the thrombogenic core to the blood. Trichrome stain was used, rendering luminal thrombus and intraplaque hemorrhage red and collagen blue. Panel B is a high-power micrograph of the area in Panel A indicated by the asterisk and shows that the contents of the atheromatous plaque have seeped through the gap in the cap into the lumen, suggesting that plaque rupture preceded thrombosis (the asterisk indicates cholesterol crystals). (Panels A and B courtesy of Dr. Erling Falk, University of Aarhus, Aarhus, Denmark.) Panel C illustrates the consequences of the activation of immune cells in a coronary plaque. Microbes, autoantigens, and various inflammatory molecules can activate T cells, macrophages, and mast cells, leading to the secretion of inflammatory cytokines (e.g., interferon-γ and tumor necrosis factor) that reduce the stability of plaque. The activation of macrophages and mast cells also causes the release of metalloproteinases and cysteine proteases, which directly attack collagen and other components of the tissue matrix. These cells may also produce prothrombotic and procoagulant factors that directly precipitate the formation of thrombus at the site of plaque rupture.

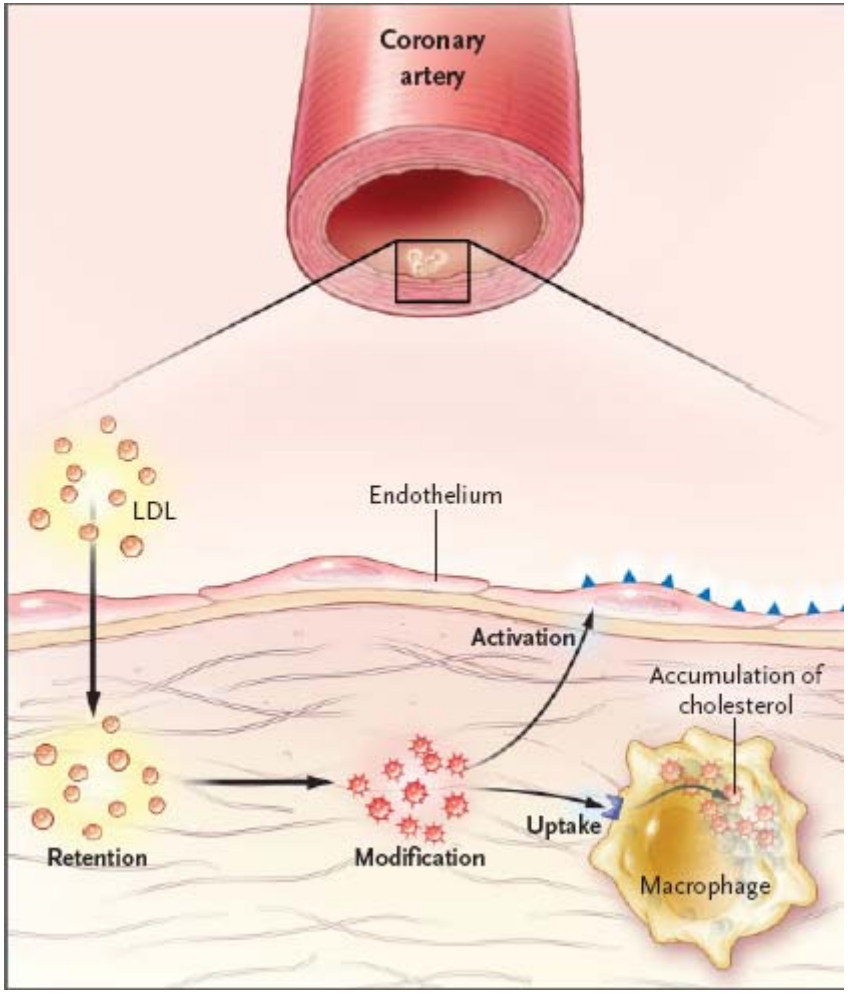


Figure 2. Activating Effect of LDL Infiltration on Inflammation in the Artery.
In patients with hypercholesterolemia, excess LDL infiltrates the artery and is retained in the intima, particularly at sites of hemodynamic strain. Oxidative and enzymatic modifications lead to the release of inflammatory 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.

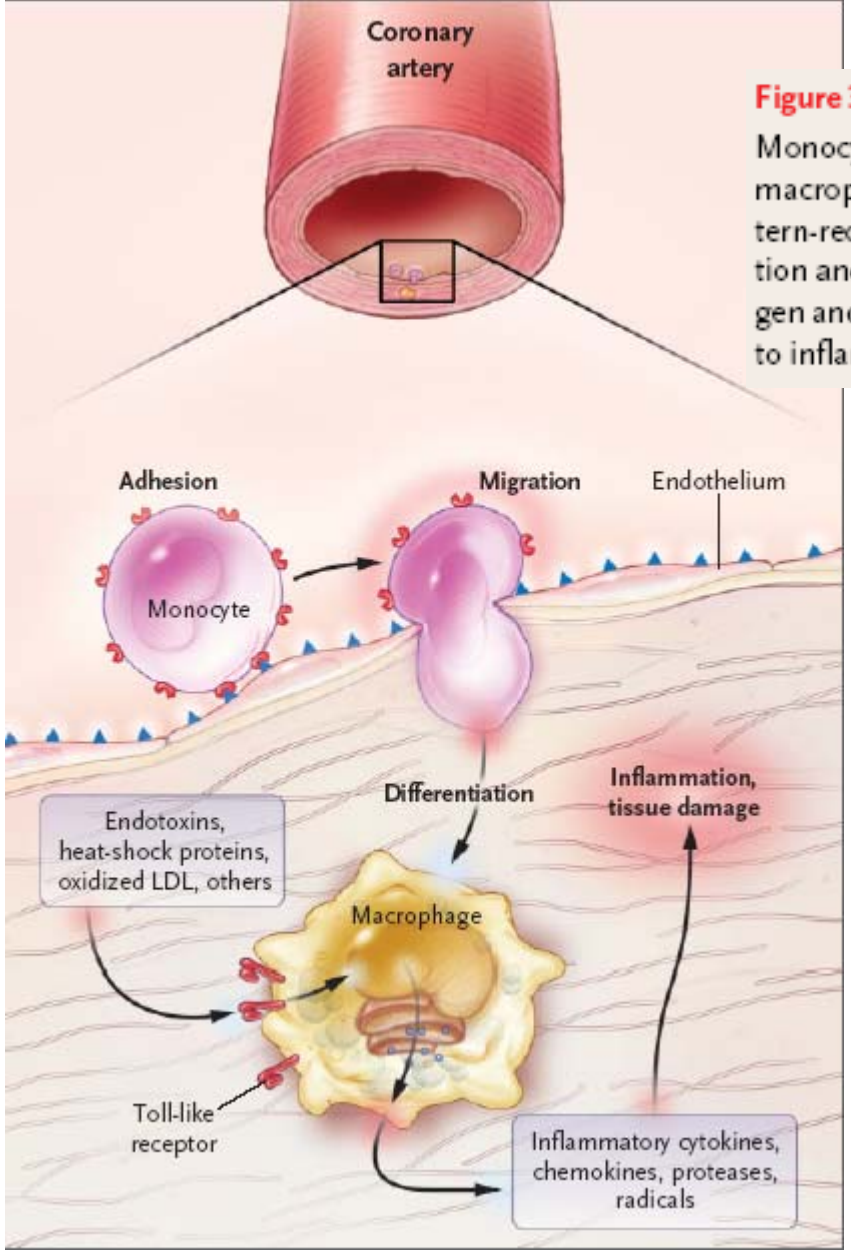


Figure 3. Role of Macrophage Inflammation of the Artery.

Monocytes recruited through the activated endothelium differentiate into macrophages. Several endogenous and microbial molecules can ligate pattern-recognition receptors (toll-like receptors) on these cells, inducing activation and leading to the release of inflammatory cytokines, chemokines, oxygen and nitrogen radicals, and other inflammatory molecules and, ultimately, to inflammation and tissue damage.

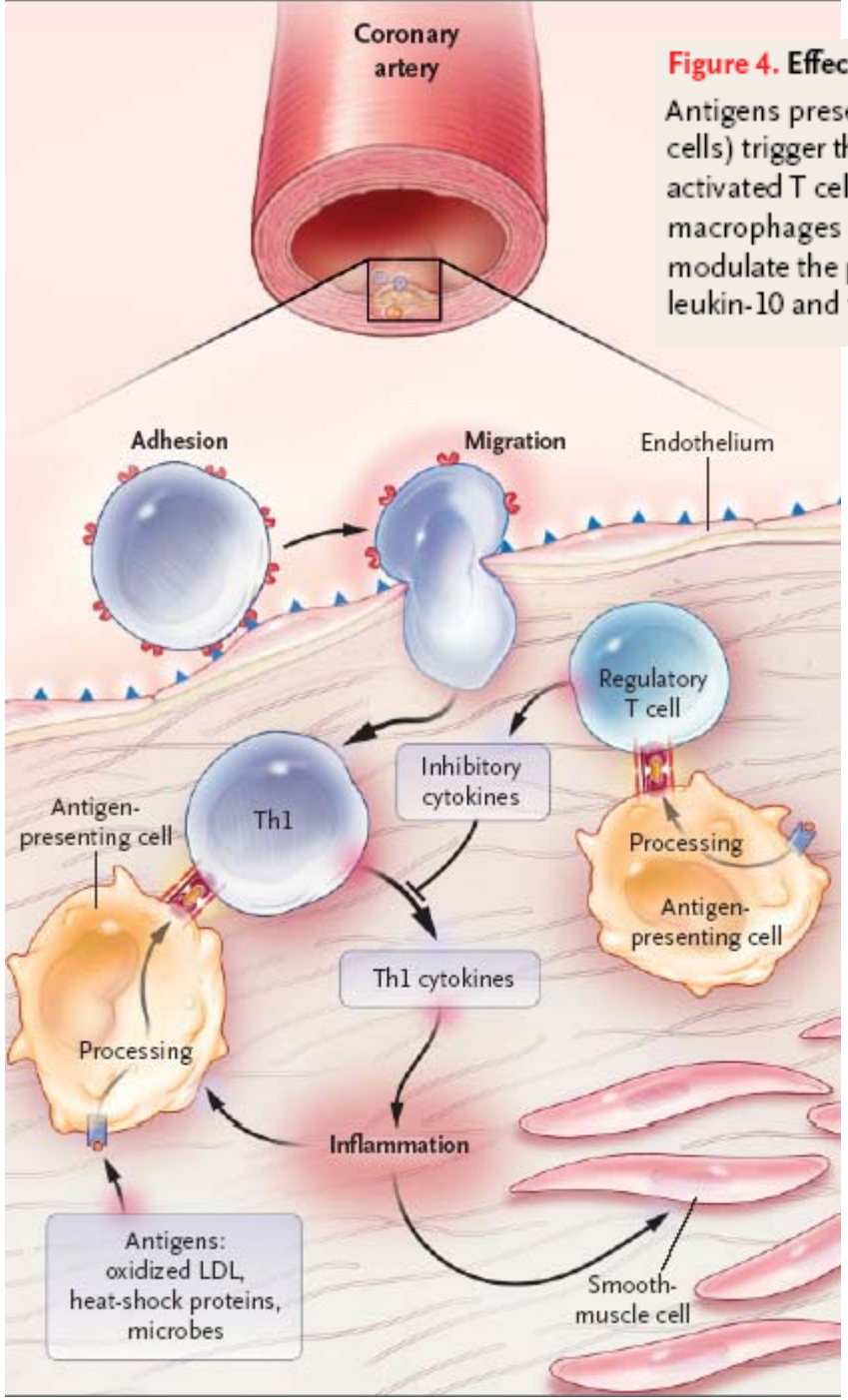
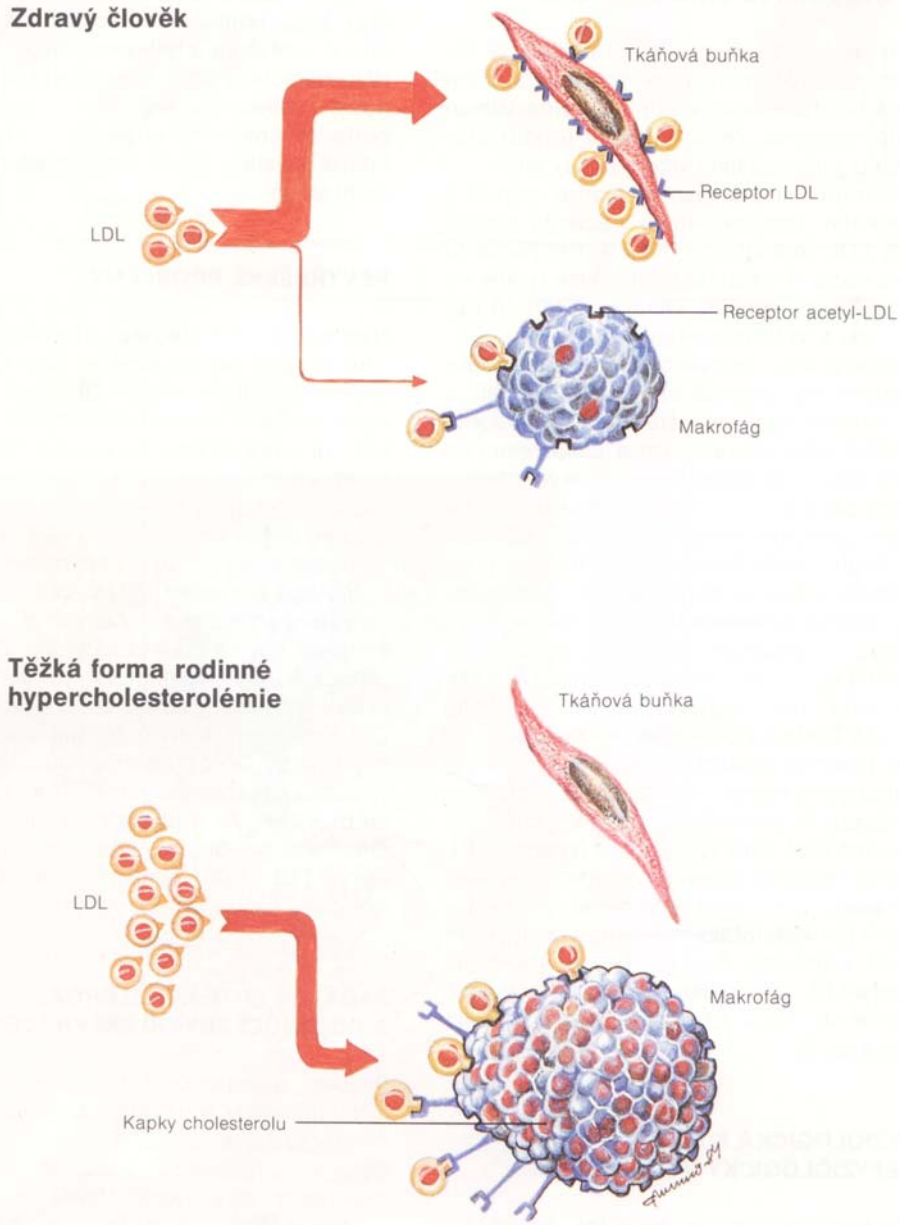
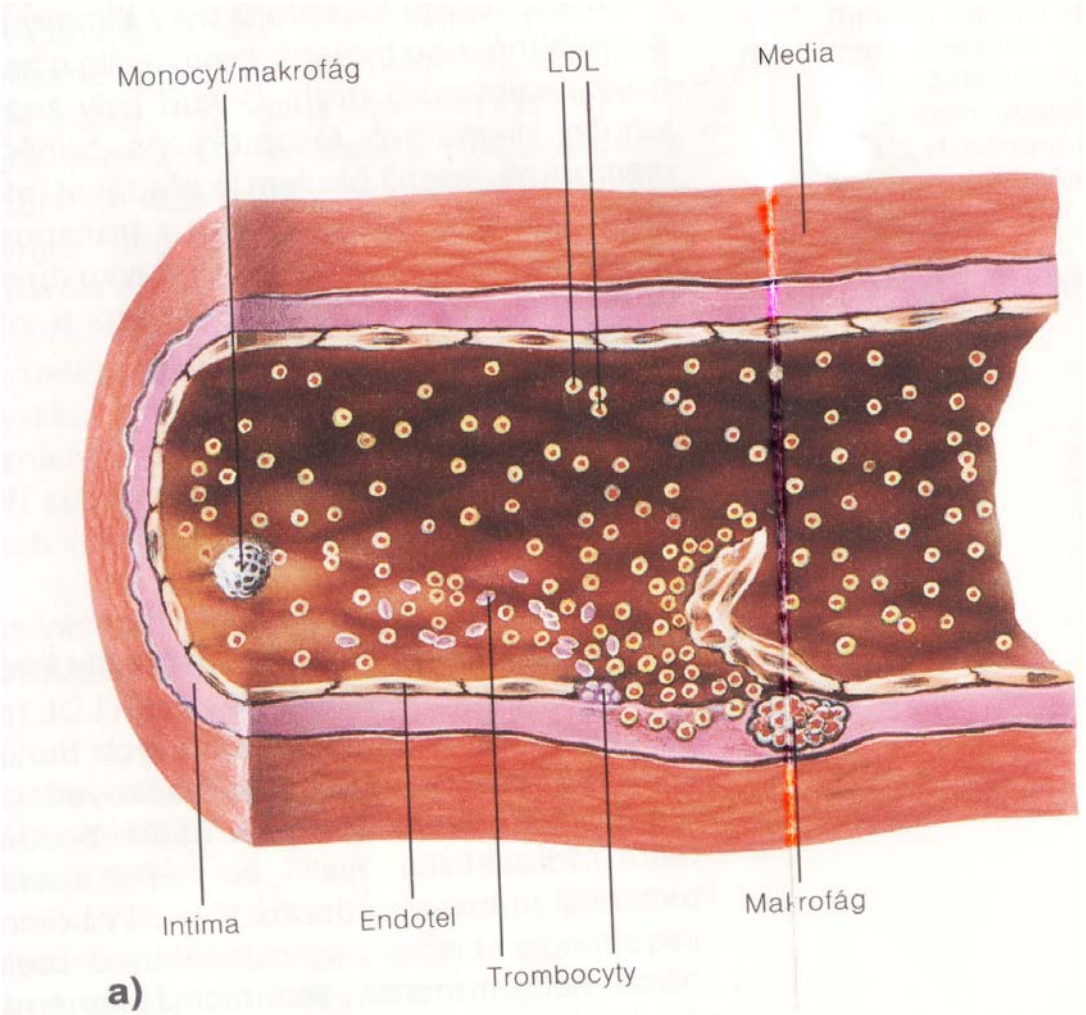
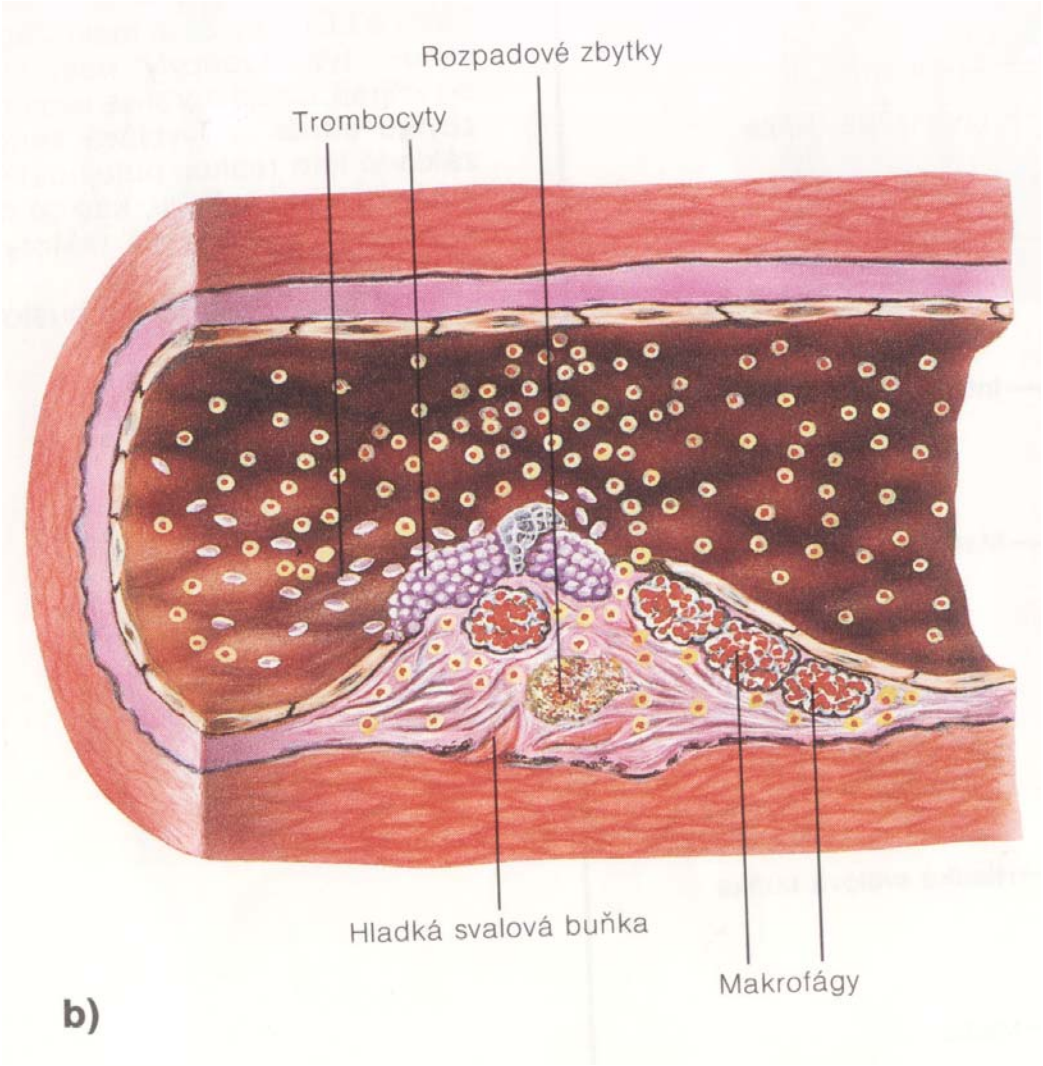


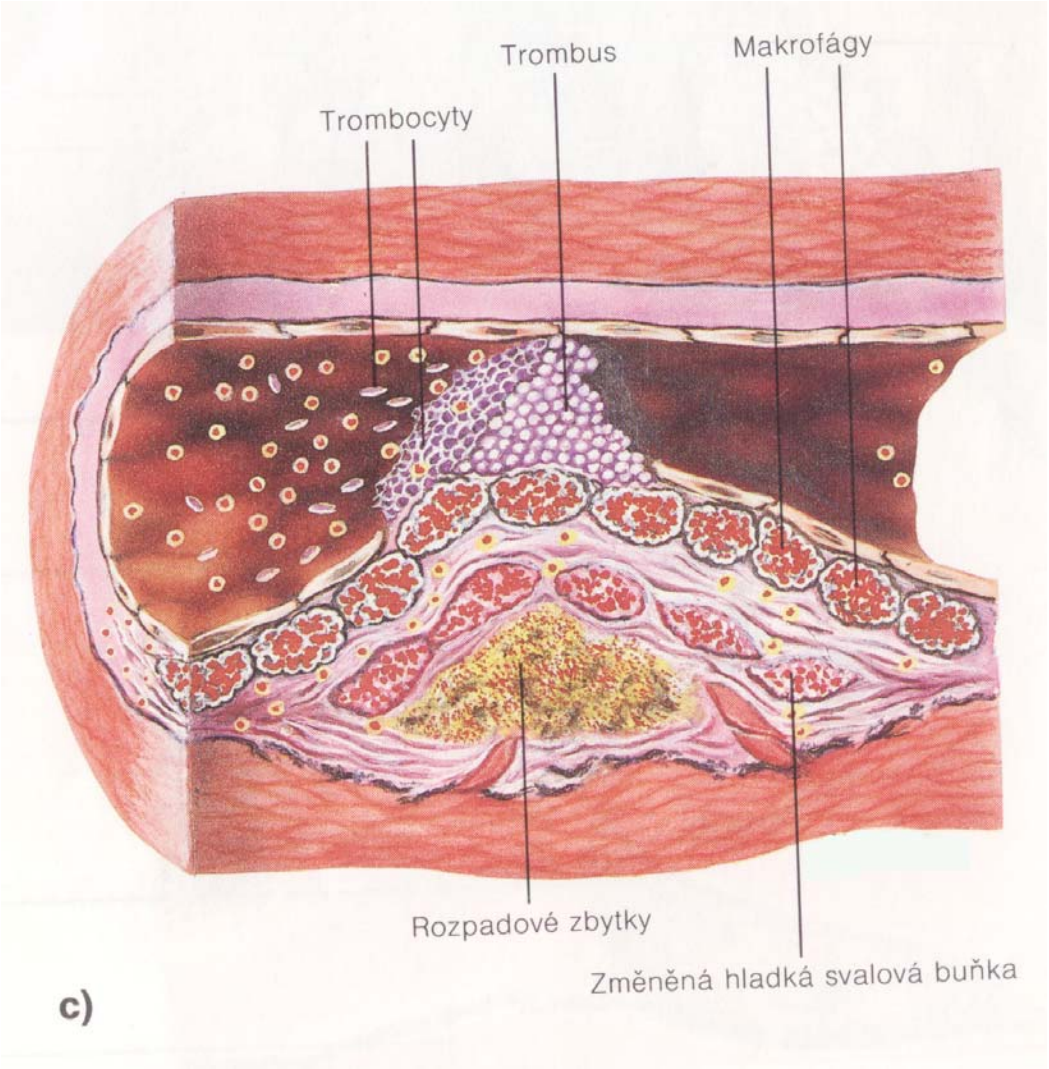
Figure 4. Effects of T-Cell Activation on Plaque Inflammation.

Antigens presented by macrophages and dendritic cells (antigen-presenting cells) trigger the activation of antigen-specific T cells in the artery. Most of the activated T cells produce Th1 cytokines (e.g., interferon-γ), which activate macrophages and vascular cells, leading to inflammation. Regulatory T cells modulate the process by secreting antiinflammatory cytokines (such as interleukin-10 and transforming growth factor β).


Zdravý člověk
Tkáňová buňka
Receptor LDL
LDL
Receptor acetyl-LDL
Makrofág
Těžká forma rodinné hypercholesterolémie
Tkáňová buňka
LDL
Makrofág
Kapky cholesterolu


Monocyt/makrofág
LDL
Media
Intima
Endotel
Trombocyty
Makrofág
a)


Rozpadové zbytky
Trombocyty
Hladká svalová buňka
Makrofágy
b)


Trombus
Makrofágy
Trombocyty
Rozpadové zbytky
Změněná hladká svalová buňka
c)

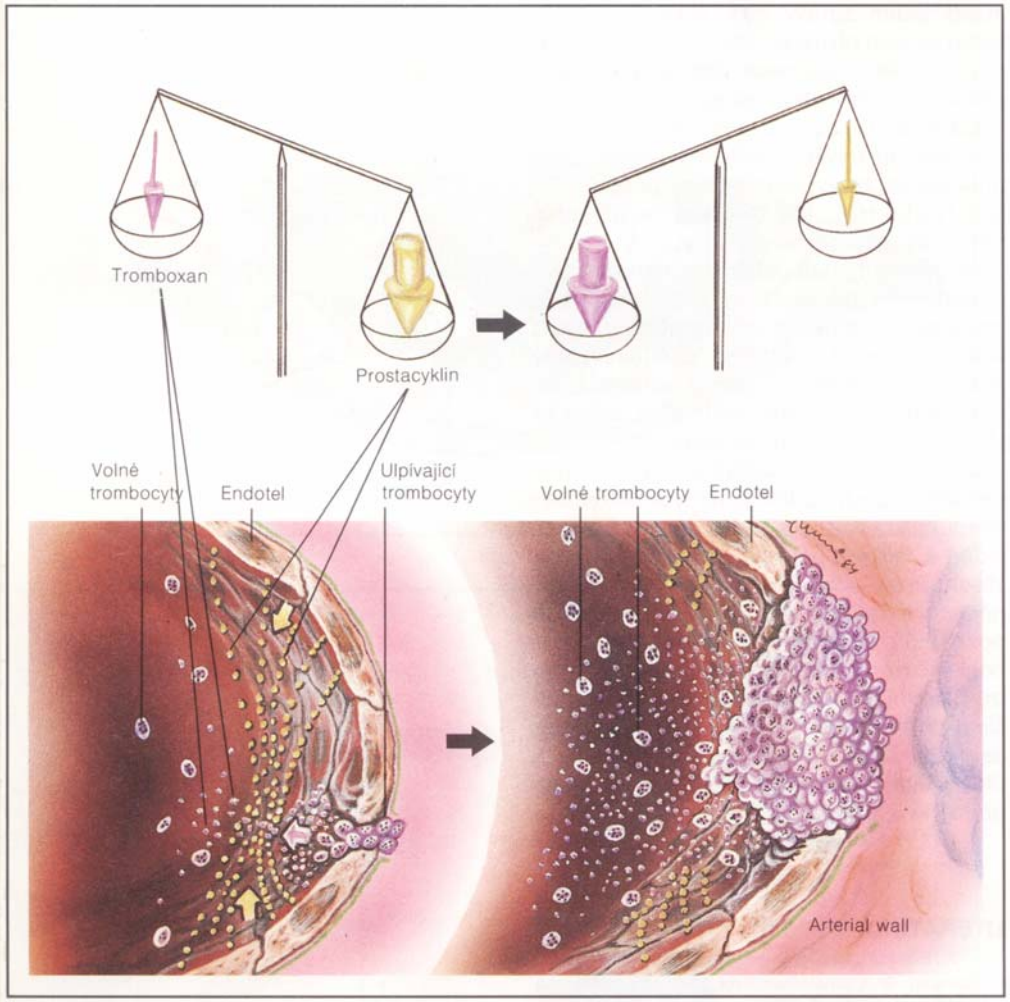
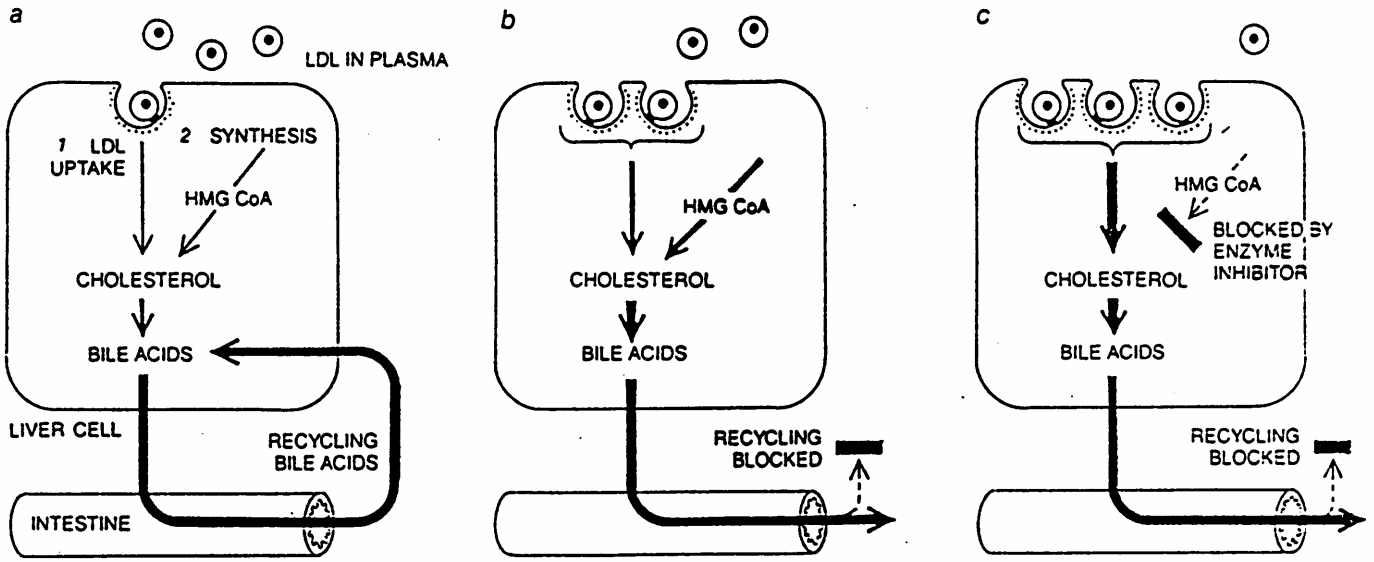

Tromboxan
Prostacyklin
Volné trombocyty
Endotel
Ulpívající trombocyty
Volné trombocyty
Endotel
Arterial wall

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

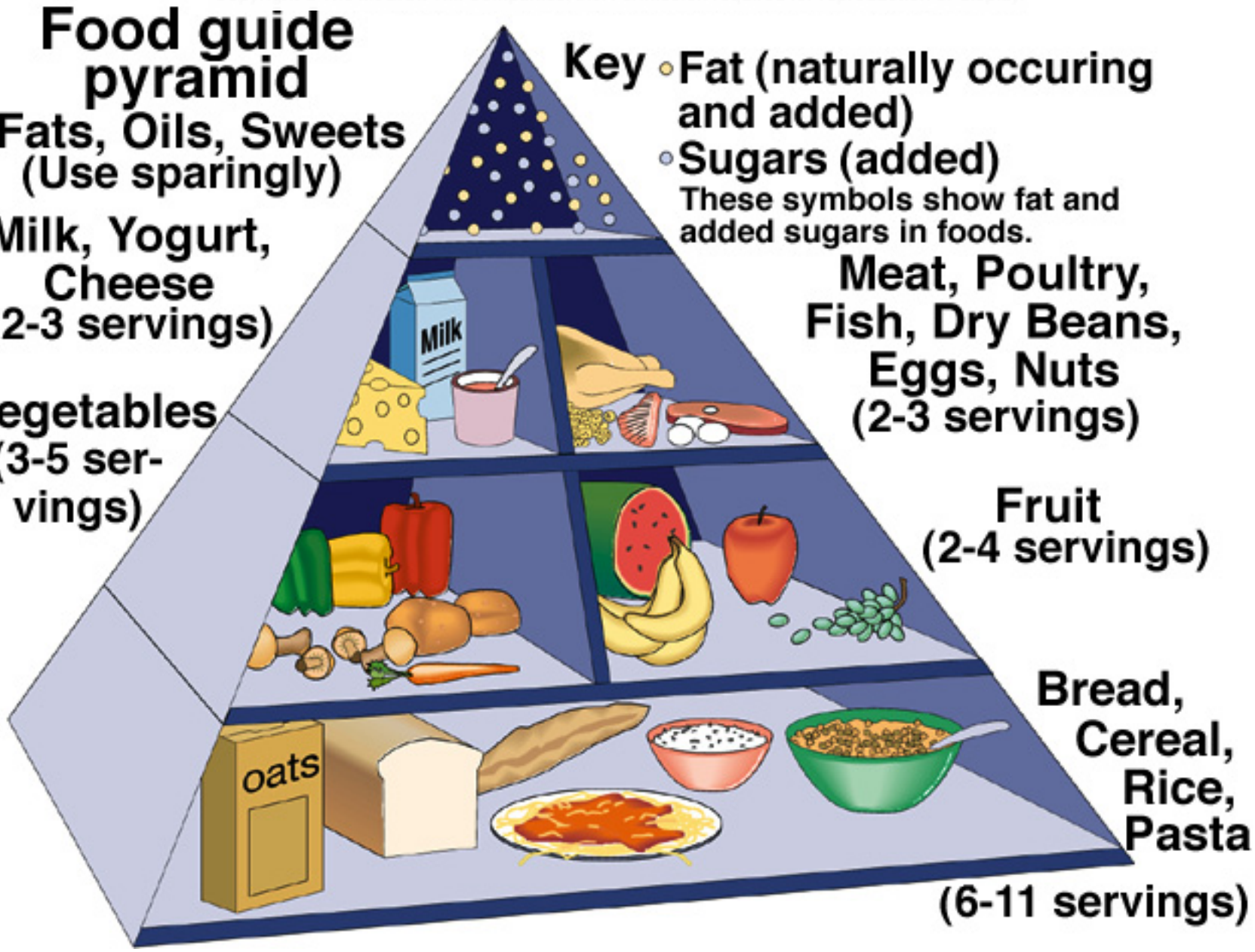
Cholesterol Level	Initial Classification
Total Cholesterol	
< 200 mg/dl (5.2 mmol/L)	Desirable blood cholesterol
200-239 mg/dl (5.2-6.2mmol/L) cholesterol	Borderline high blood
240 mg/dl (6.2 mmol/L) or greater	High blood cholesterol
HDL Cholesterol	
< 35 mg/dl (0.9 mmol/L)	Low HDL cholesterol

*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.



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.

Table 2. *Recommended dietary allowances (RDAs)[†] or Reference Nutrient Intakes (RNI) for various nutrients (values are quantities needed per day to meet the known nutritional needs of healthy persons)*

	UK		USA	
	Males	Females	Males	Females
Vitamin A	700 μg	600 μg	1000 μg	800 μg
Vitamin E*	>4 mg	>3 mg	10 mg (15 IU)	8 mg
Vitamin C[†]	40 mg	40 mg	60 mg	60 mg
β-Carotene	not set	not set	not set	not set
Selenium	75 μg	60 μg	50–200 μg	
Iron	8.7 mg	14.8 mg	10 mg	
Zinc	9.5 mg	7.0 mg	15 mg	
Copper	1.2 mg	1.2 mg	2–3 mg	
Fibre[†]	12–14 g		20–35 g	

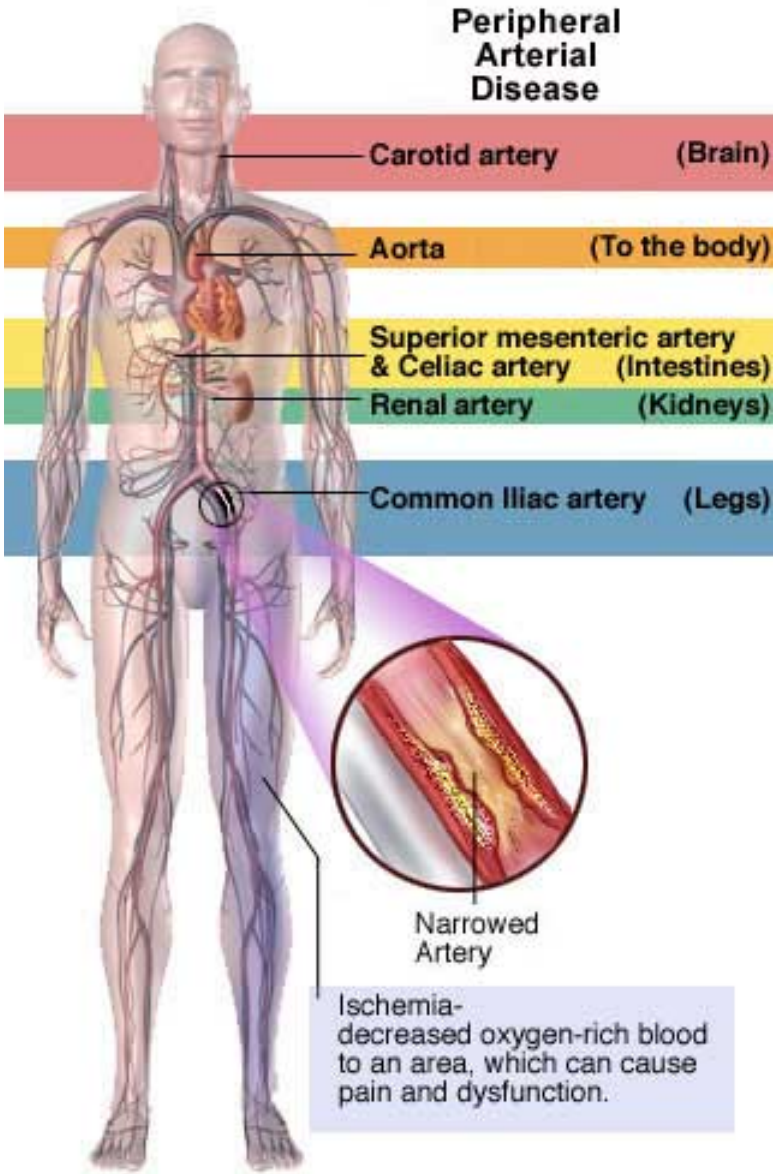
Vitamin C – test tube experiments – also pro-oxidative properties. Why do these pro-oxidant effects of ascorbic acid not usually happen *in vivo*? Because under most circumstances free iron and copper are not available in the extracellular fluids.

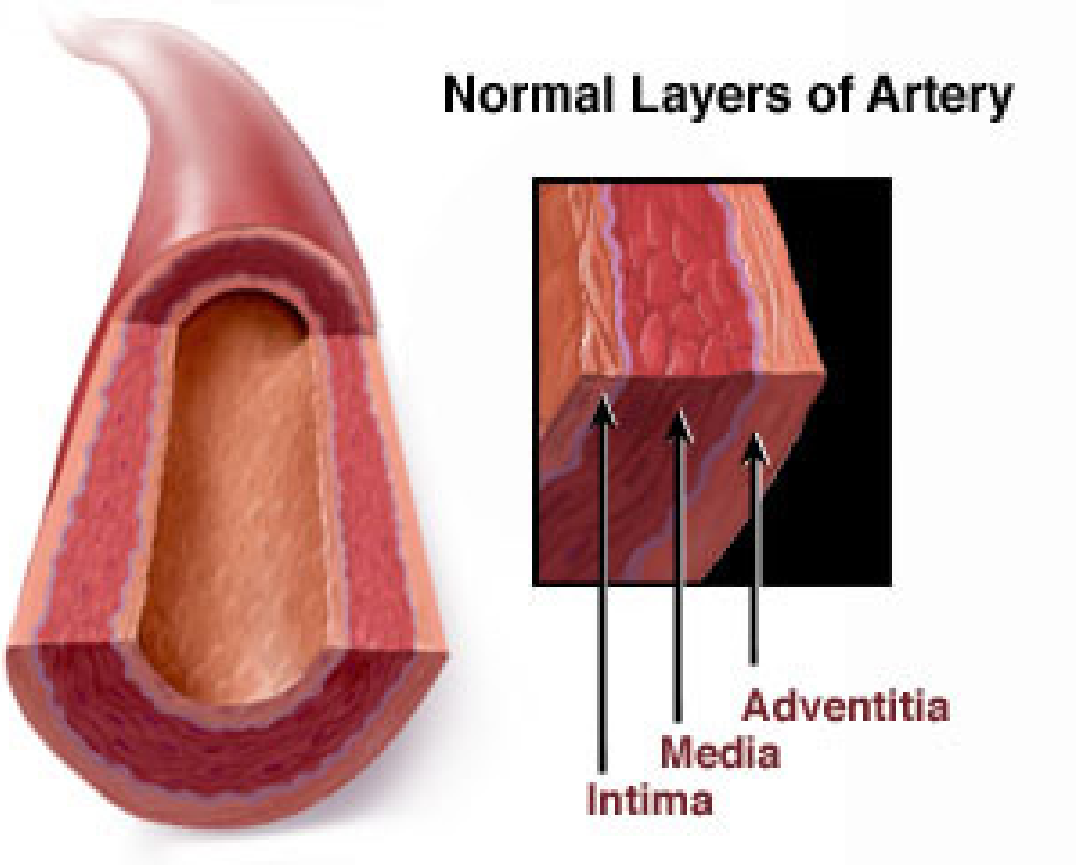
Positive Risk Factors

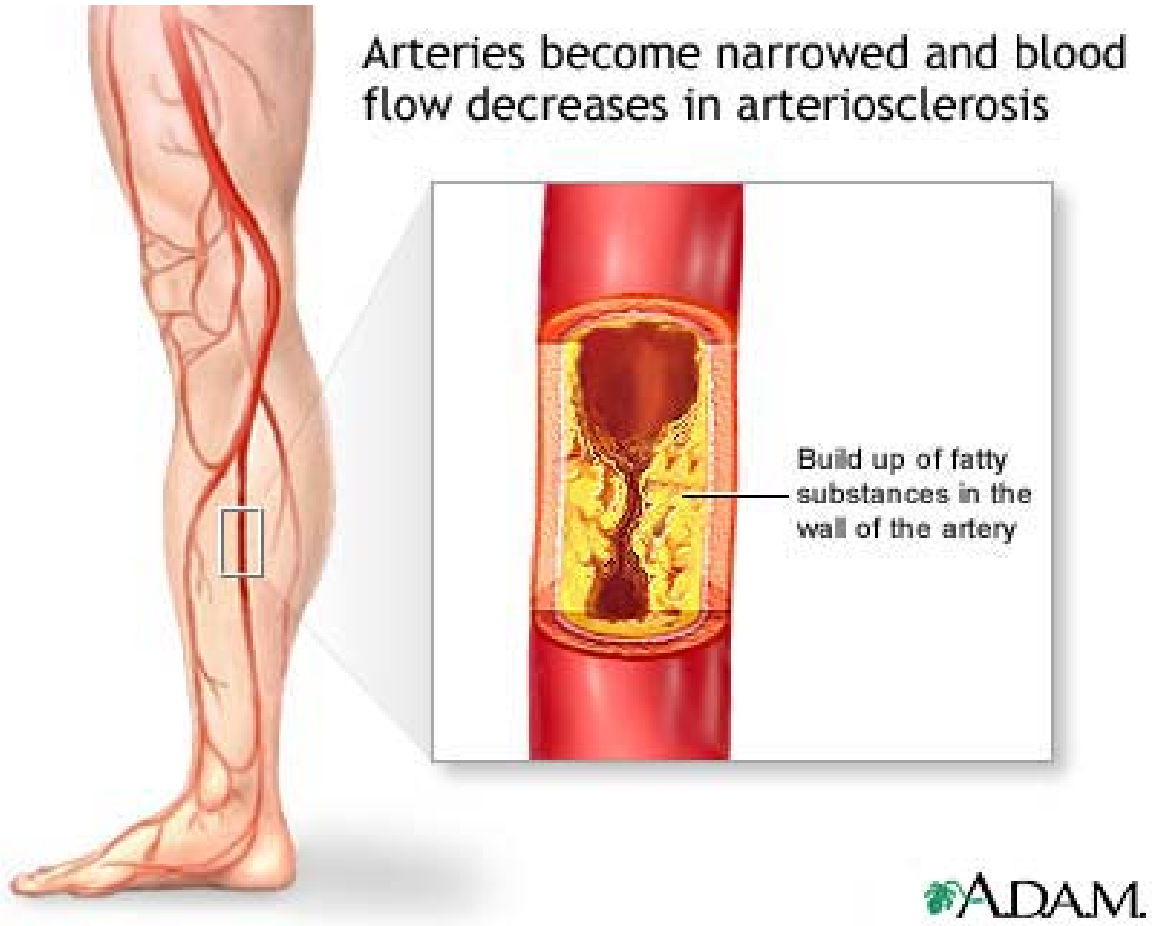
Age
Male 45 or older
Estrogen Status
Female 55 or older (or premature menopause) without estrogen replacement therapy
Family history of premature CHD
definite myocardial infarction or sudden death before 55 y of age in father or other first-degree relative
Current cigarette smoking
Hypertension
blood pressure 140/90 or greater** or taking antihypertensive medication
Low HDL cholesterol
35 mg/dl [0.9 mmol/L] or less**

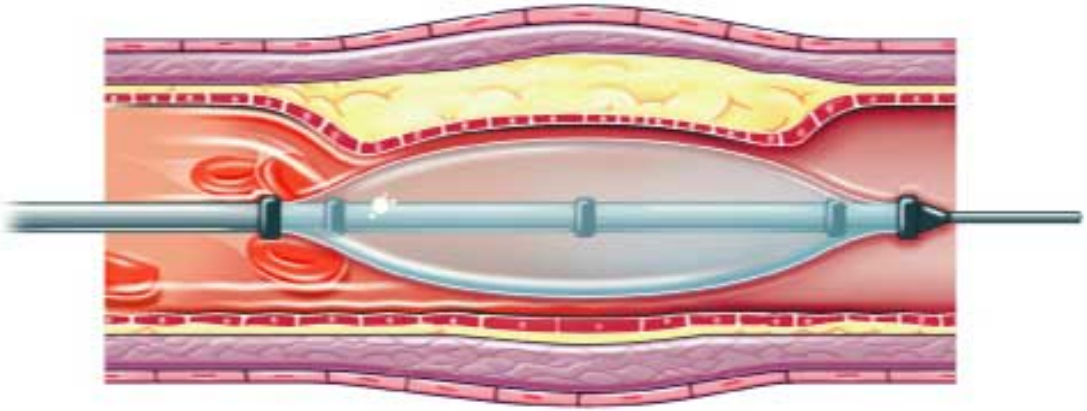
Negative Risk Factors***

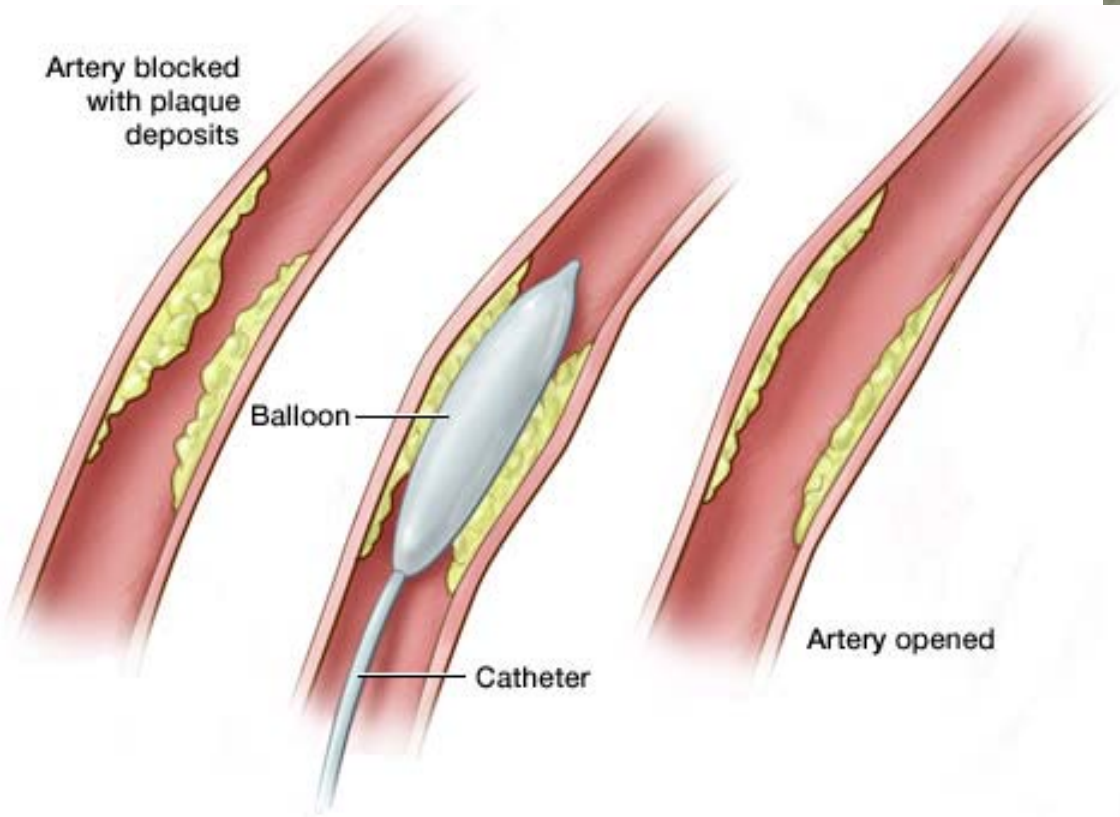
High HDL cholesterol (60 mg/dl [1.6 mmol/L] or greater)


Peripheral Arterial Disease
Carotid artery (Brain)
Aorta (To the body)
Superior mesenteric artery & Celiac artery (Intestines)
Renal artery (Kidneys)
Common Iliac artery (Legs)
Narrowed Artery
Ischemia- decreased oxygen-rich blood to an area, which can cause pain and dysfunction.


Normal Layers of Artery
Adventitia
Media
Intima

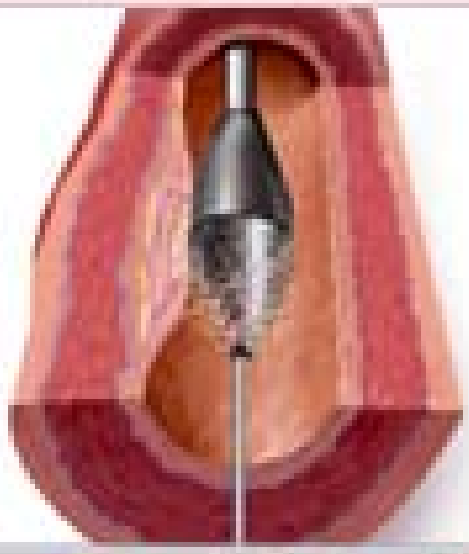

Arteries become narrowed and blood flow decreases in arteriosclerosis
Build up of fatty substances in the wall of the artery
A.D.A.M.




Artery blocked with plaque deposits
Balloon
Catheter
Artery opened


1
2
3

Atherectomy



For more info...

HeartCenterOnline