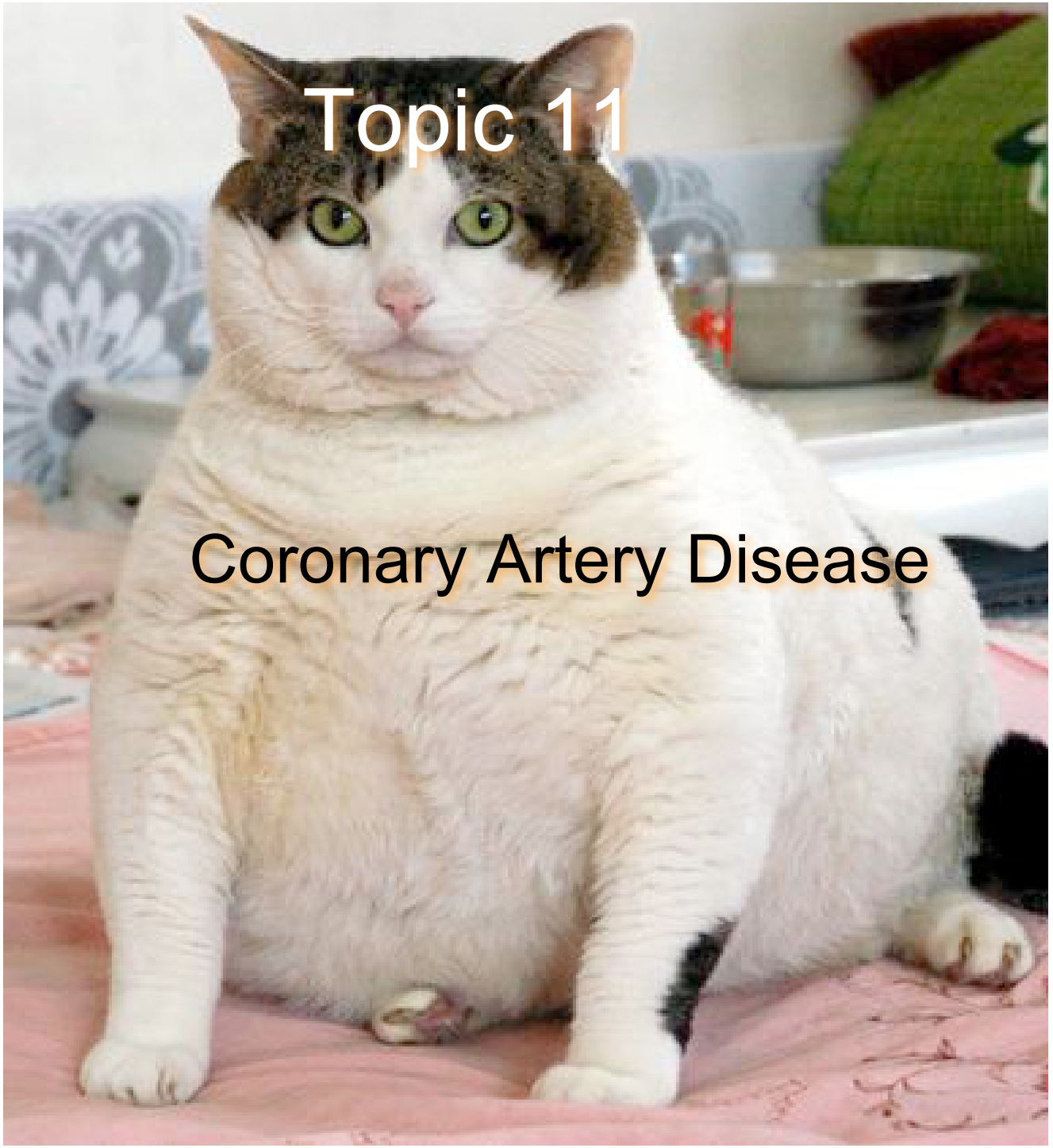

Topic 11
Coronary Artery Disease

Lipid metabolism

Page last updated at 06:38 GMT, Tuesday, 29 April 2008 07:38 UK

Scientists make weight loss claim

Nick Bryant
BBC News, Sydney

Australian scientists believe they may have discovered how to help people lose weight without cutting back on food.

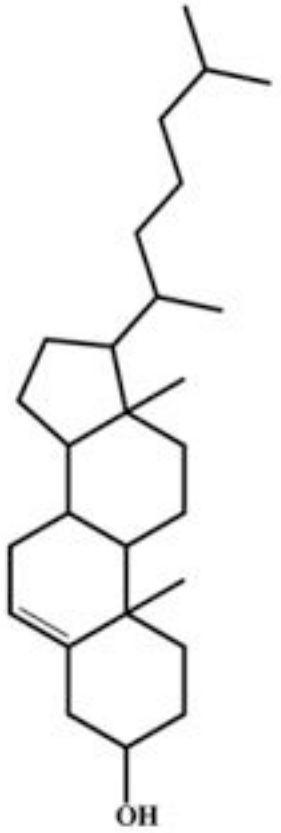
Researchers in Melbourne found that by manipulating fat cells in mice they were able to speed up metabolism.

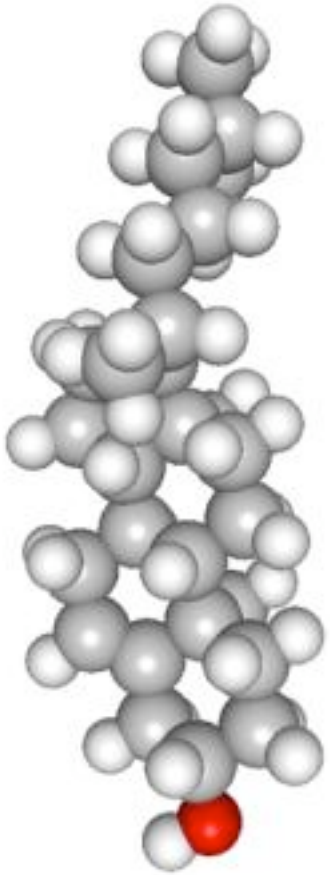
SEE ALSO
- 'Gym pill' trips fat-burning gene
  29 Apr 07 | Health
- Clear obesity gene link 'found'
  12 Apr 07 | Health
- 'Gym pill' for a no-work six-pack
  31 Aug 06 | Health
- 'Marathon' mouse keeps on runnin
  24 Aug 04 | Science/Nature

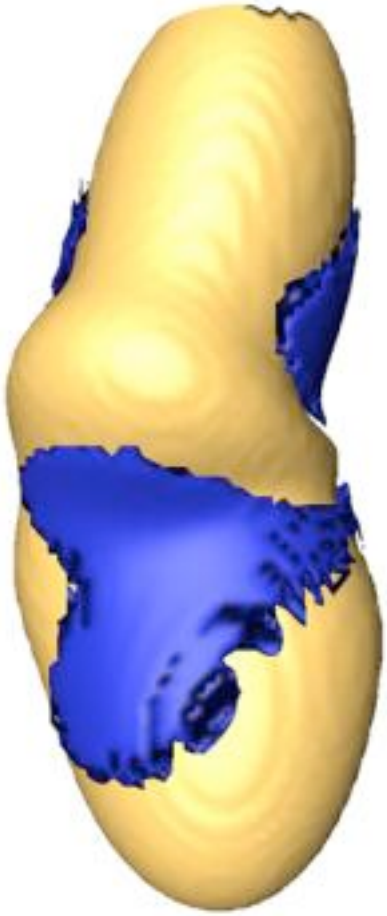
RELATED INTERNET LINKS
- Melbourne Howard Florey Institute

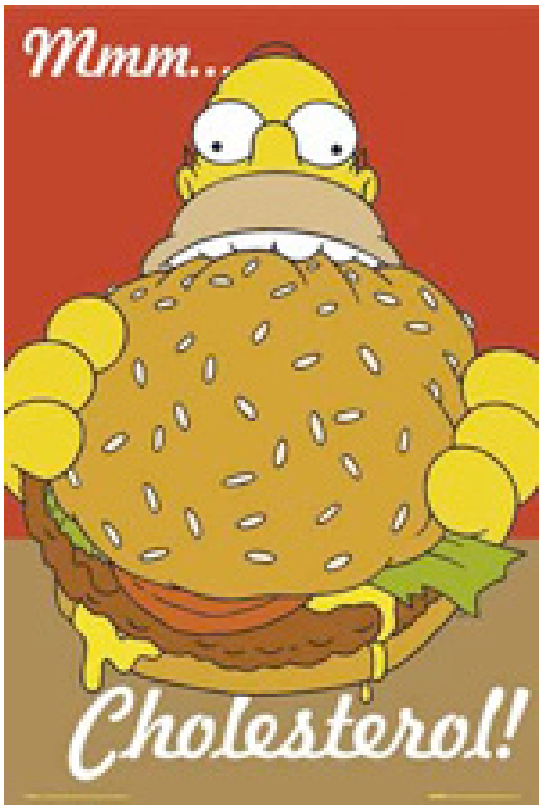
http://news.bbc.co.uk/2/hi/health/7372495.stm

Sterol Metabolism and Coronary Artery Disease









Big Picture: Exogenous Cholesterol and Fat Metabolism

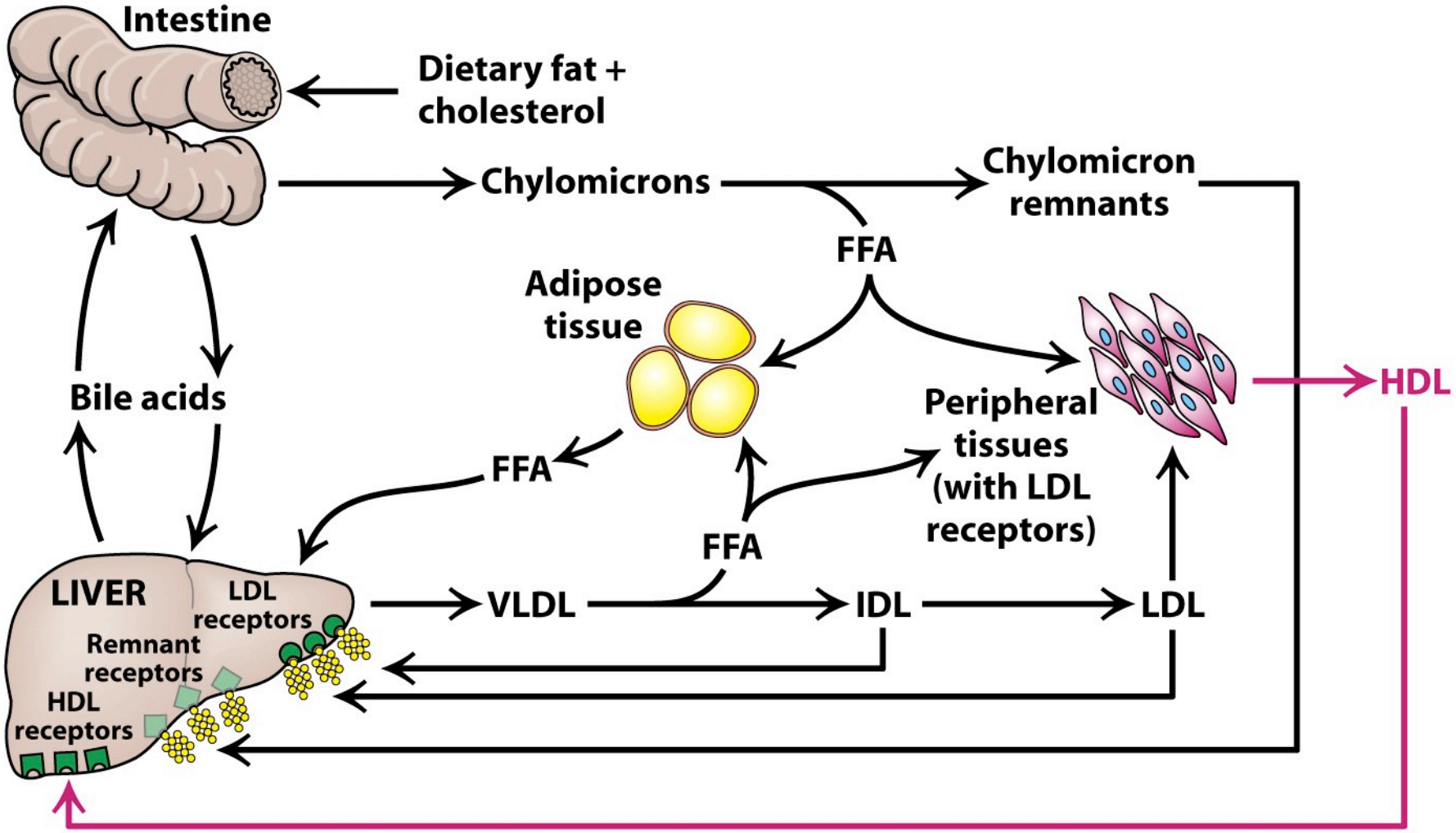
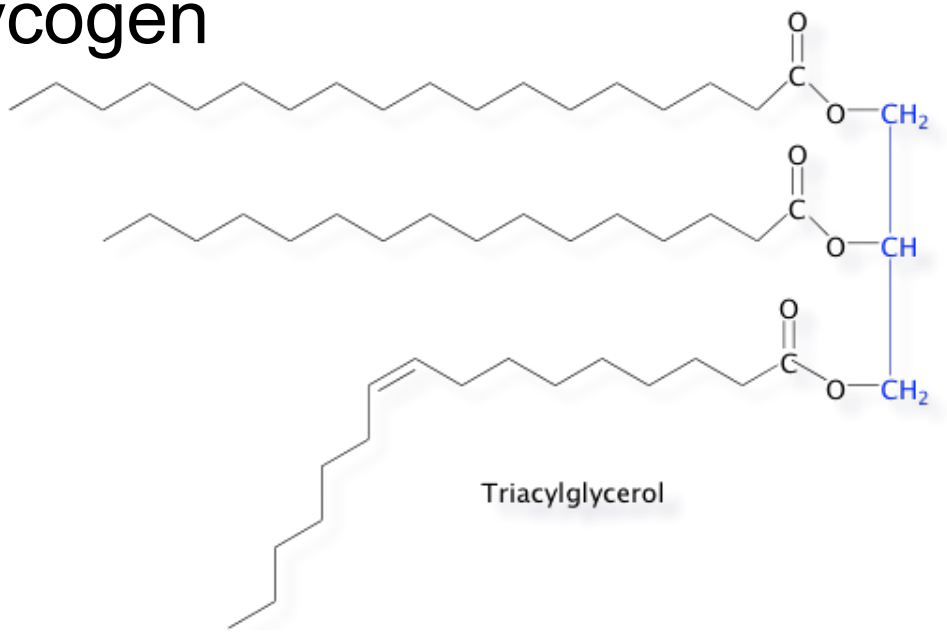


Figure 26-16
Biochemistry, Sixth Edition

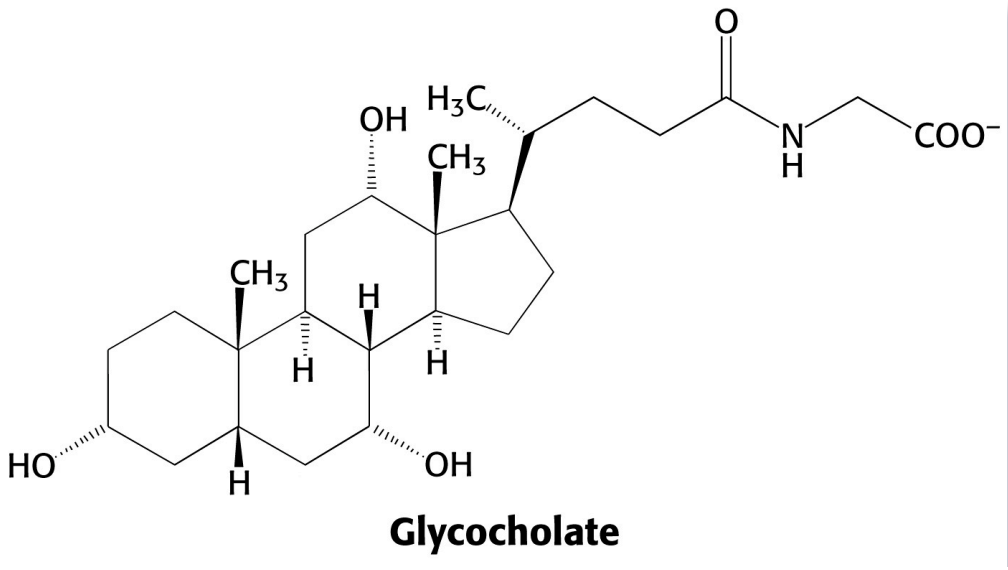
Fats-Triglycerides

- Triglycerides are a highly concentrated store of energy
  - 9 kcal/g *vs* 4 kcal/g for glycogen
  - Glycogen is also highly hydrated, 2 g H_2O/g glycogen



Pancreatic Lipases

- Dietary triacylglycerols must be broken down before being absorbed by the intestines.
- Bile salts, which act as detergents, are used to solublize the triacylglycerols



Glycocholate

Pancreatic Lipases

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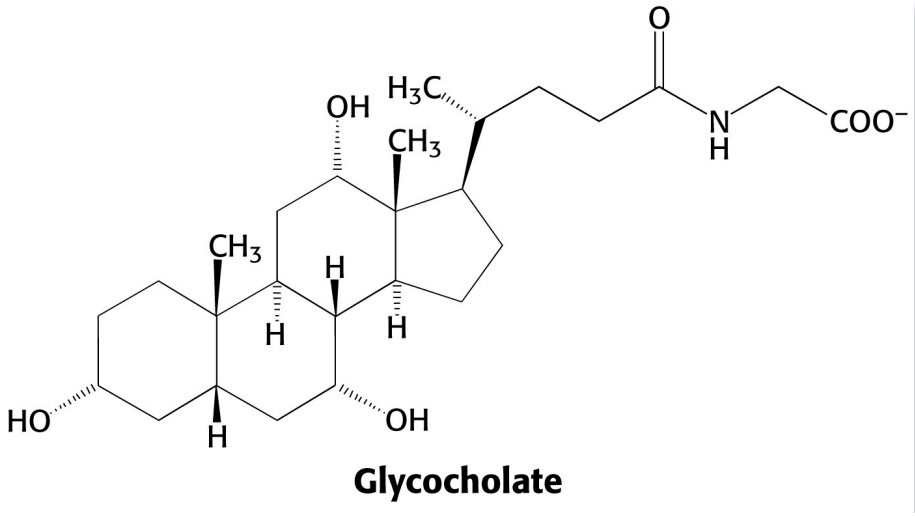
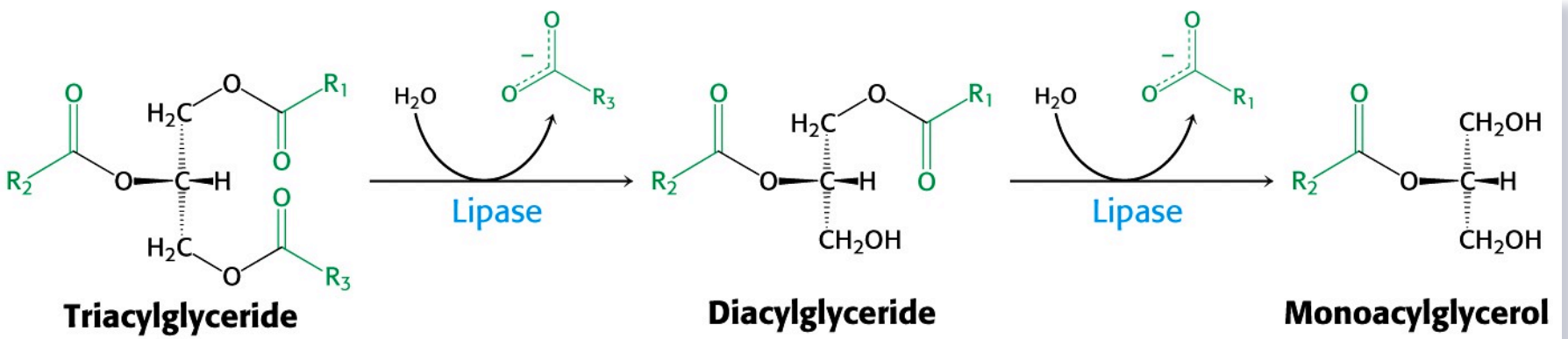


Glycocholate

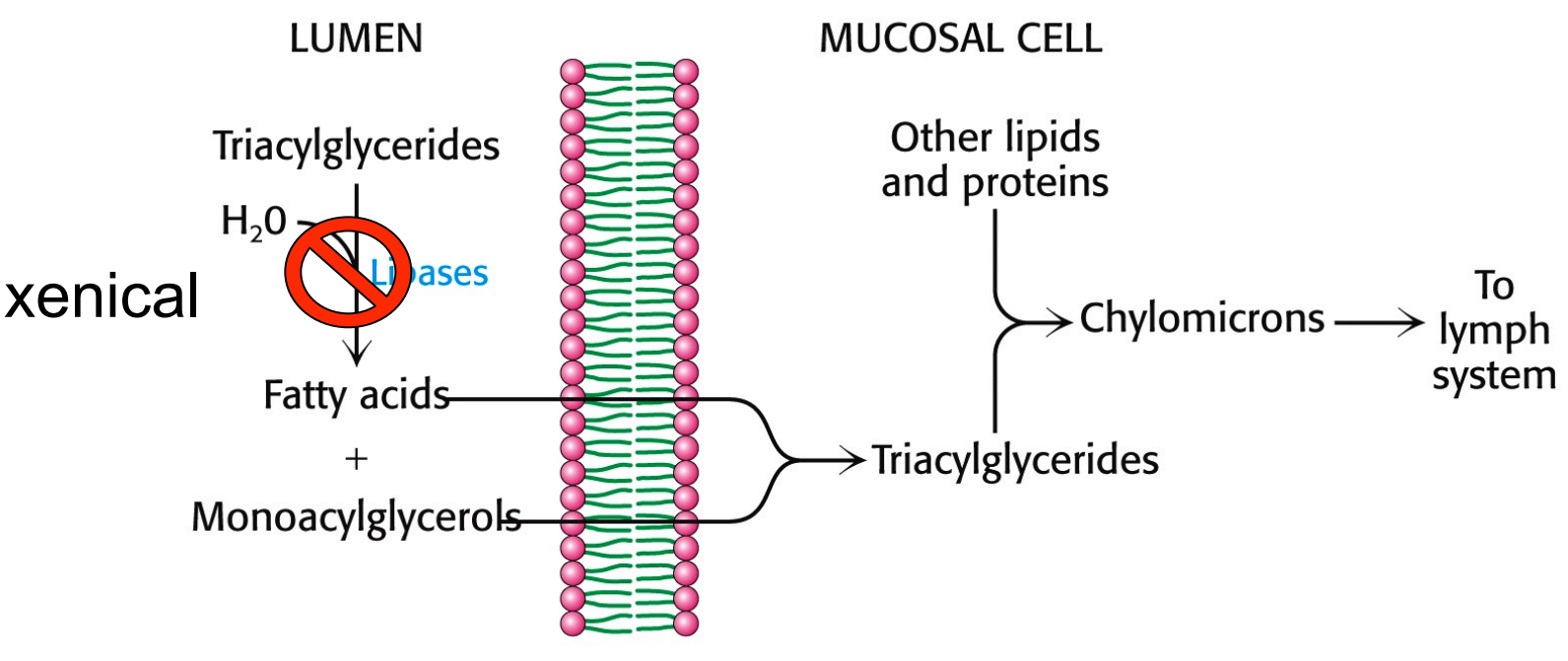
Pancreatic Lipases

- Pancreatic lipases hydrolyze the ester bonds of the triacylglycerols while in the



Chylomicrons

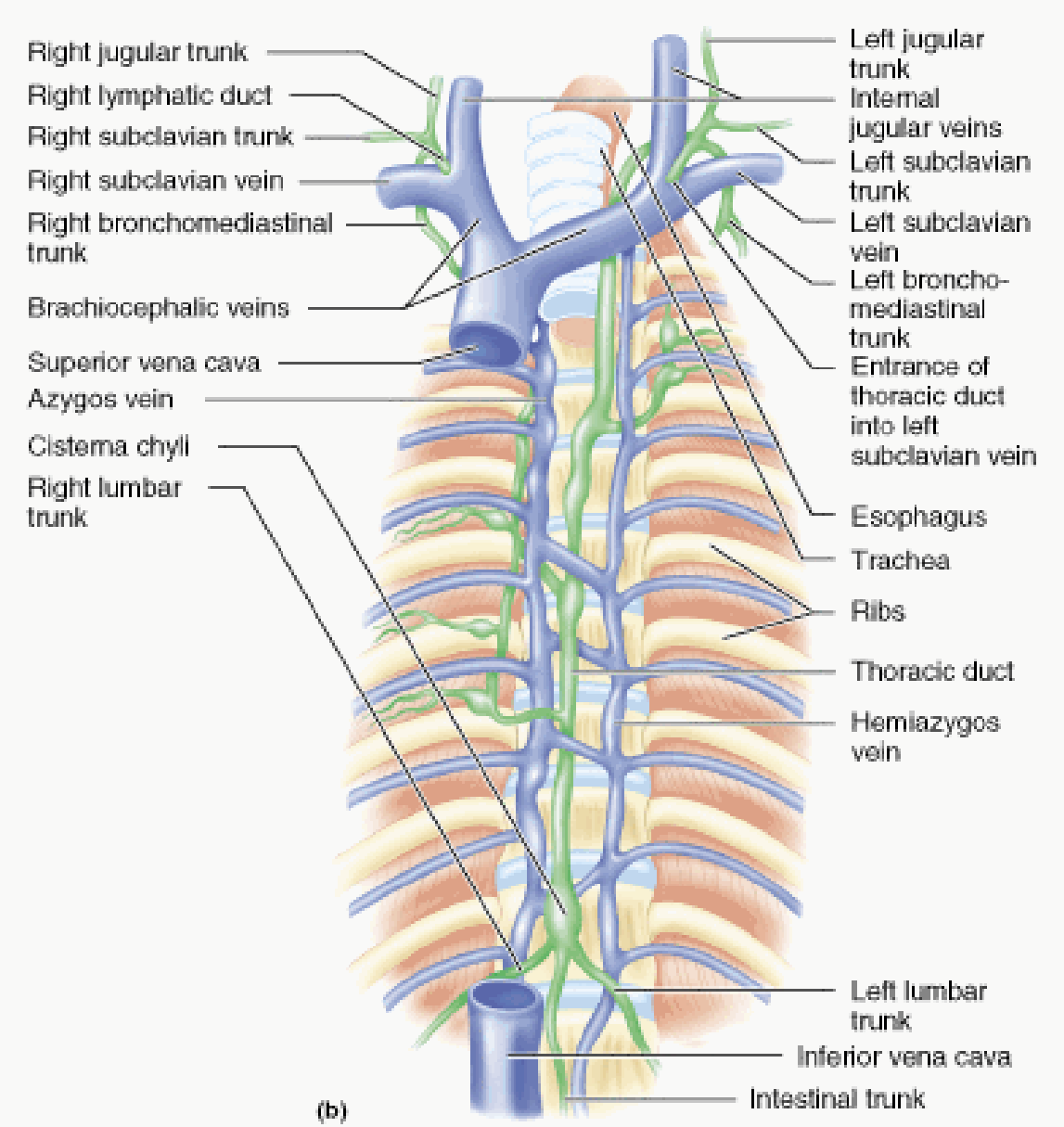
- In the intestinal mucosal cells, the fatty acids and monoacylglycerides are resynthesized into triacylglycerides and packaged into *chylomicrons*. Chylomicrons and lymph are dumped via the thoracic duct into the left subclavian vein



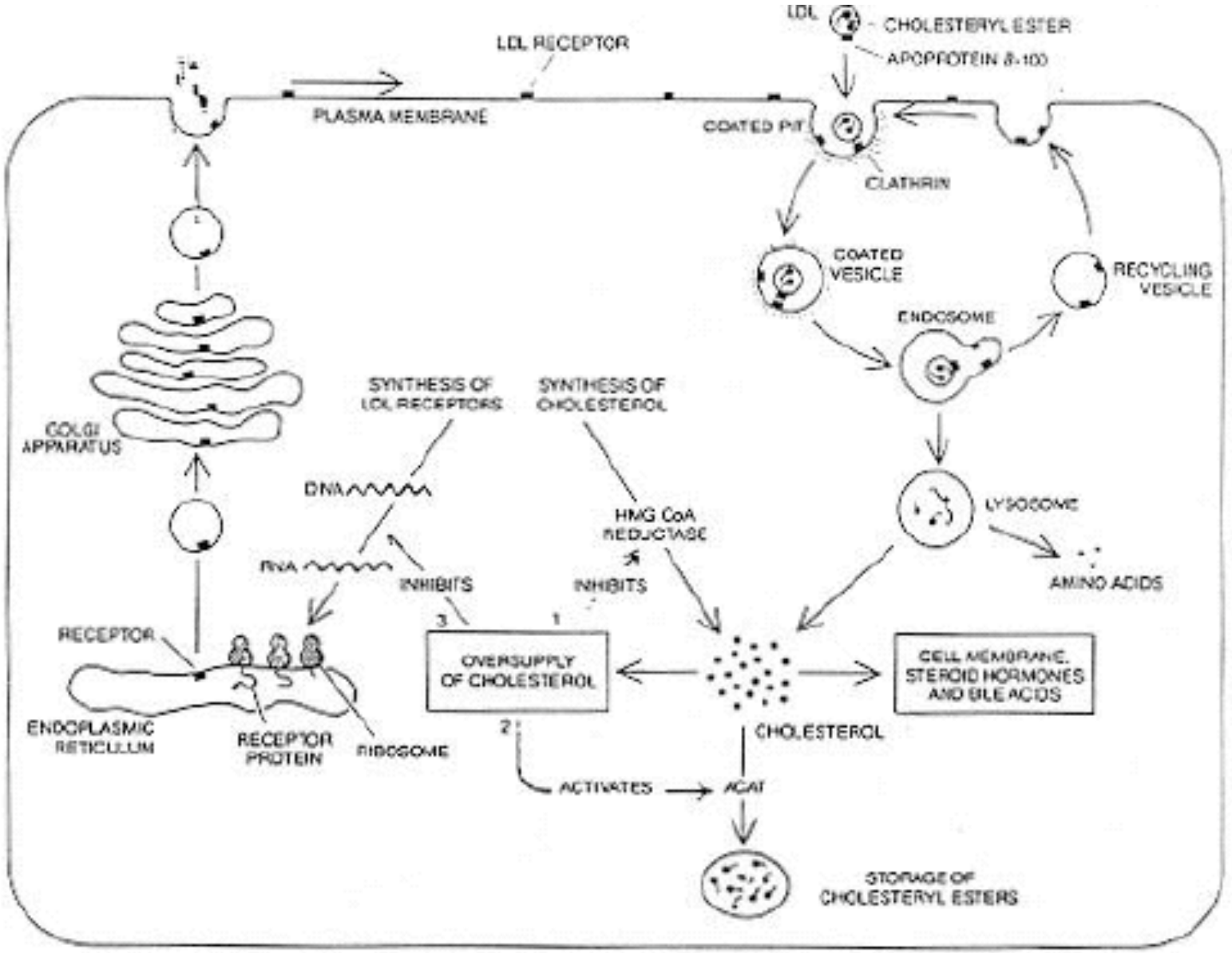
Chylomicrons

Chylomicrons and lymph are dumped via the thoracic duct into the left subclavian vein.

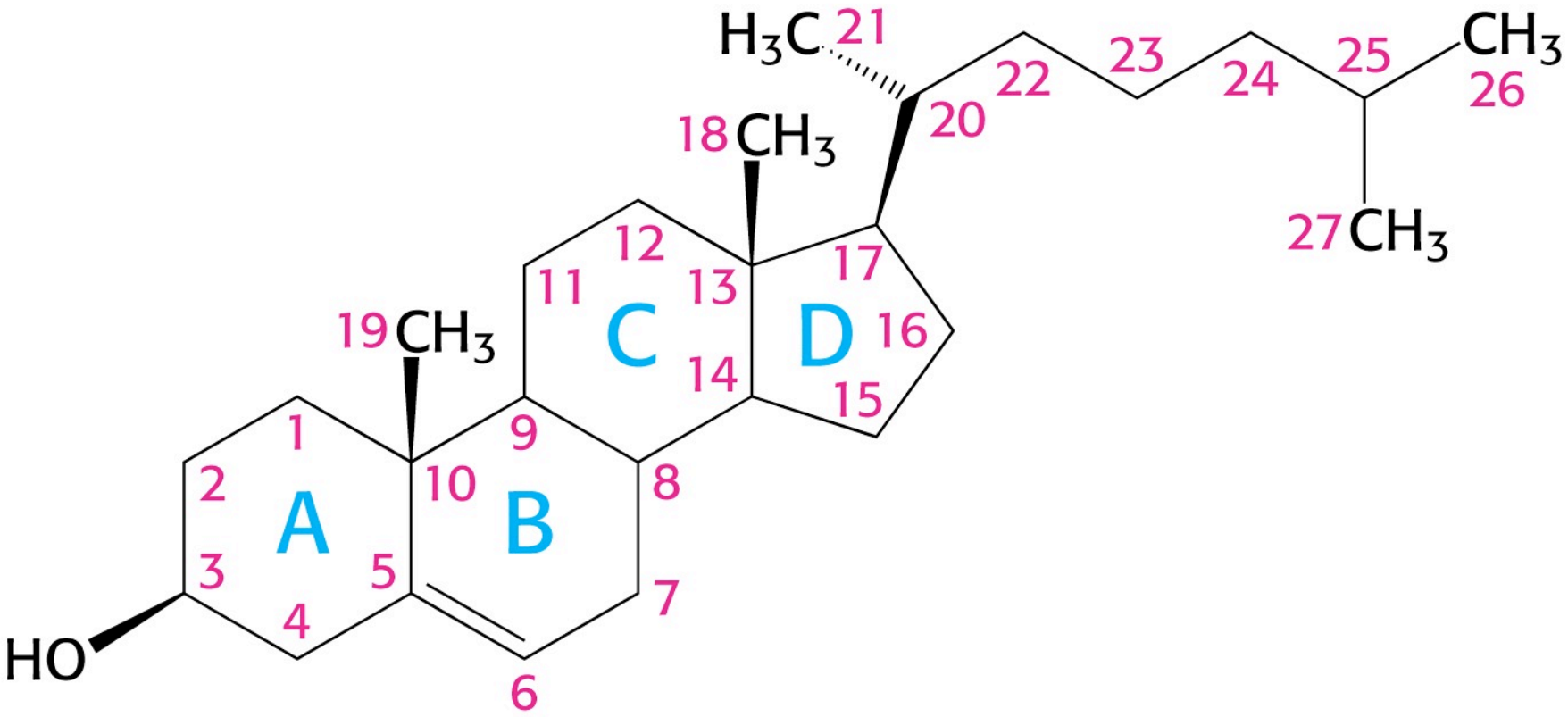
Want to know more about lymphatic system?
Try here:
http://owensboro.kctcs.edu/gcaplan/anat2/notes/Notes7%20Lymphatic%20Anatomy.htm

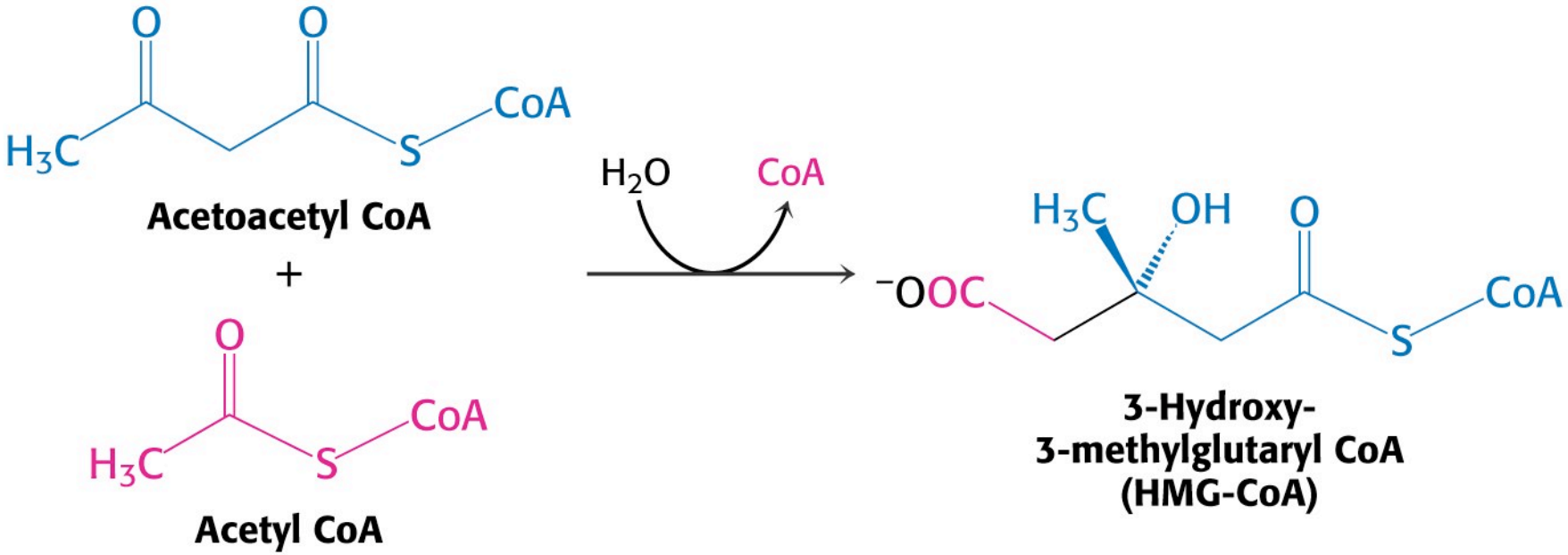


Big Picture: Endogenous and Exogenous Cholesterol Metabolism

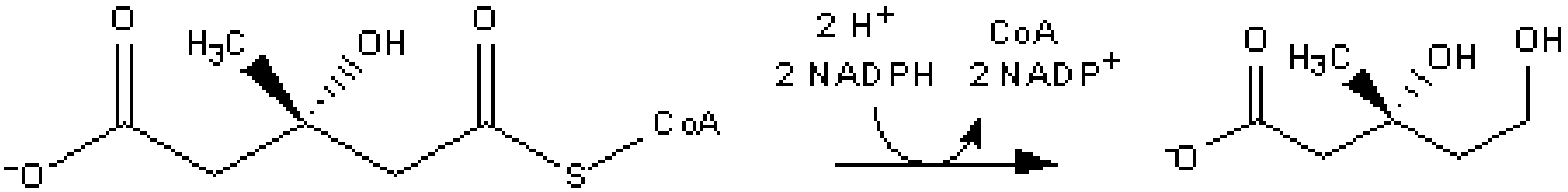


Cholesterol Synthesis

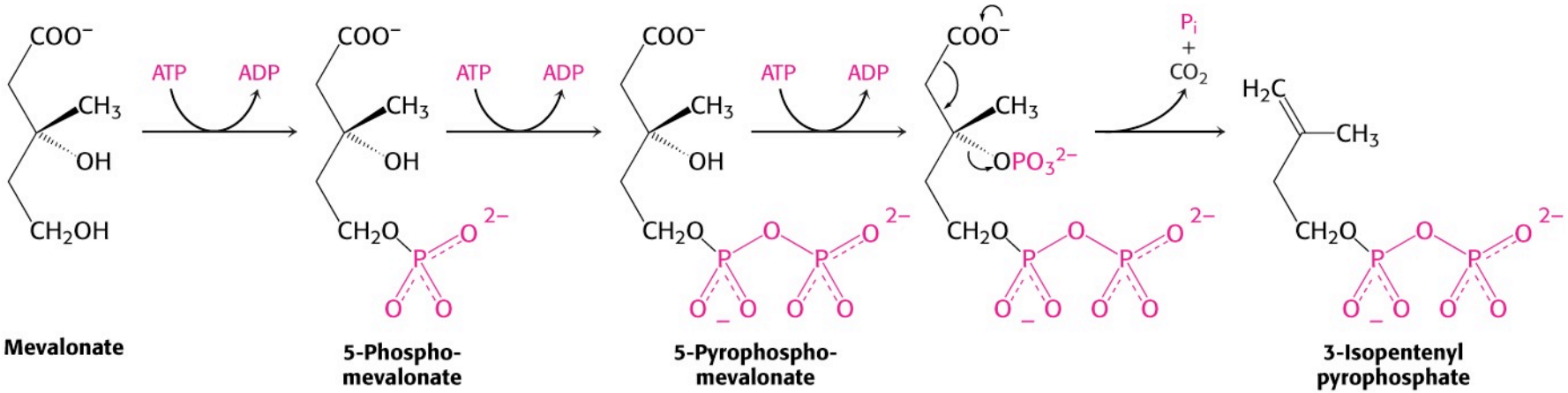


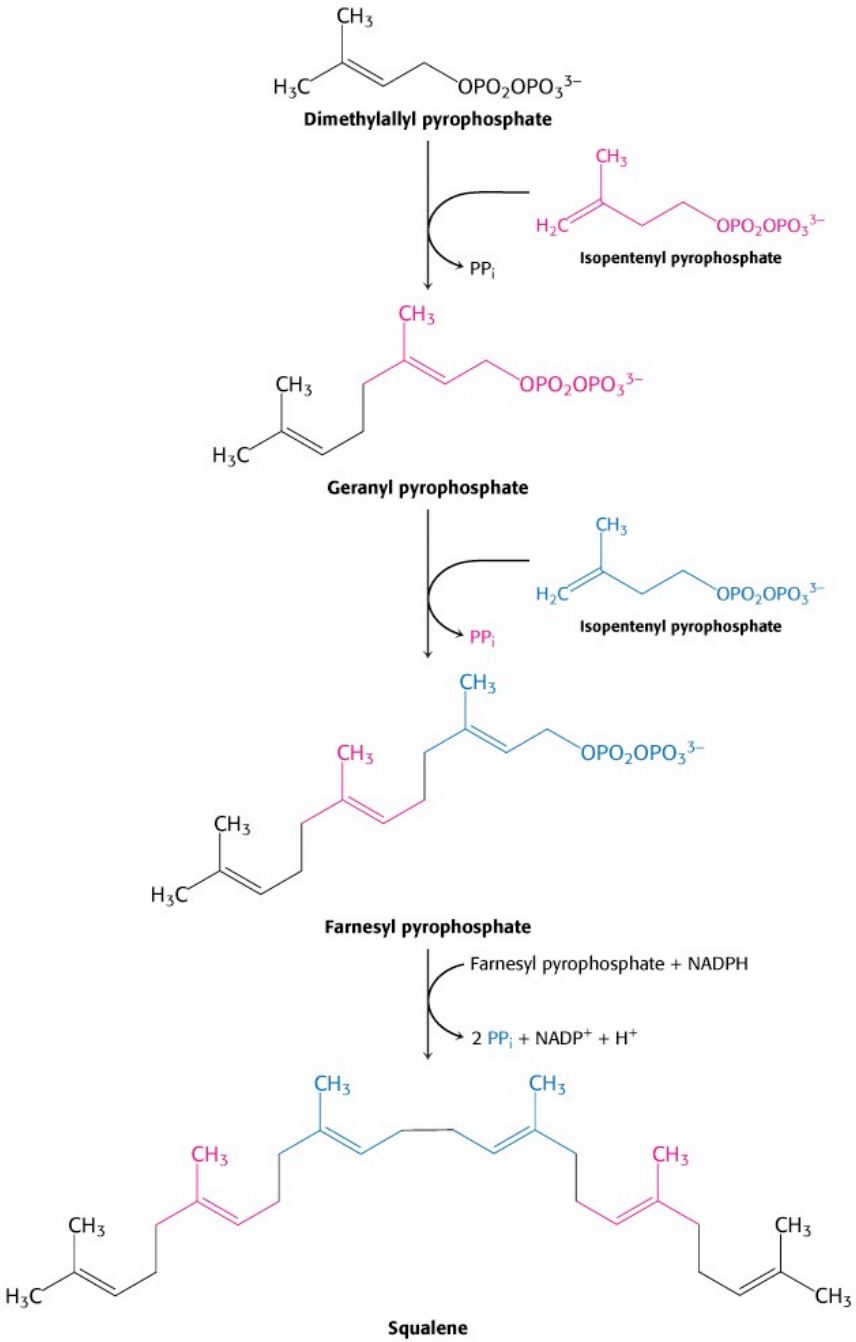


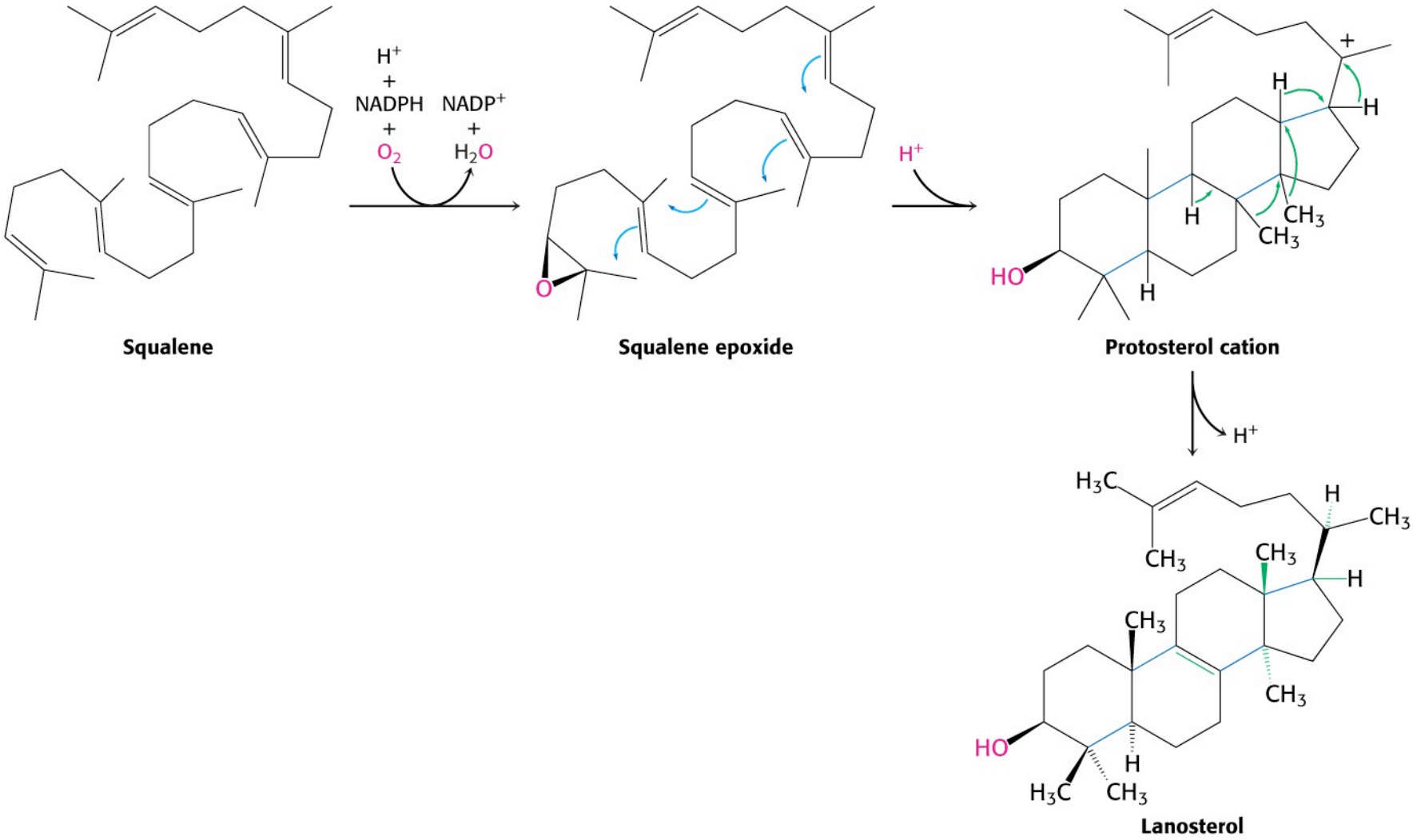
HMG-CoA Reductase



Mevalonic acid


ATP
ADP
ATP
ADP
ATP
ADP
Pi
+
CO2
Mevalonate
5-Phospho-
mevalonate
5-Pyrophospho-
mevalonate
3-Isopentenyl
pyrophosphate


CH3
H3C
OPO2OPO3 3–
Dimethylallyl pyrophosphate
CH3
H2C
OPO2OPO3 3–
Isopentenyl pyrophosphate
PPi
CH3
CH3
H3C
OPO2OPO3 3–
Geranyl pyrophosphate
CH3
H2C
OPO2OPO3 3–
Isopentenyl pyrophosphate
PPi
CH3
CH3
CH3
H3C
OPO2OPO3 3–
Farnesyl pyrophosphate
Farnesyl pyrophosphate + NADPH
2 PPi + NADP+ + H+
CH3
CH3
CH3
CH3
CH3
CH3
H3C
CH3
Squalene

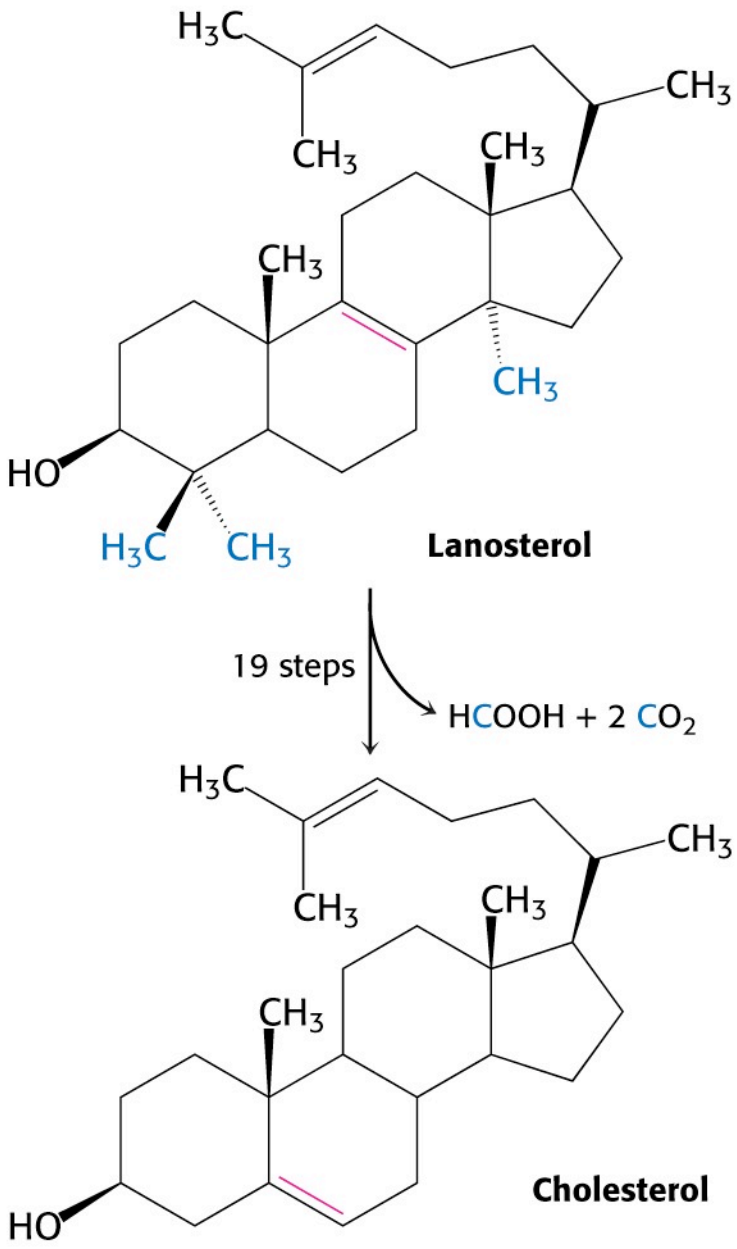


Squalene

Squalene epoxide

Protosterol cation

Lanosterol


H3C
CH3
CH3
CH3
CH3
CH3
HO
H3C
CH3
Lanosterol
19 steps
HCOOH + 2 CO2
H3C
CH3
CH3
CH3
CH3
HO
Cholesterol

Regulation of Cholesterol Metabolism: HMG-CoA reductase

1. Reductase mRNA; SREBP pathway
2. mRNA translation
3. Reductase degradation; sensing membrane cholesterol
4. Reductase Phosphorylation

Regulation of Cholesterol Metabolism: HMG-CoA reductase (SREBP)

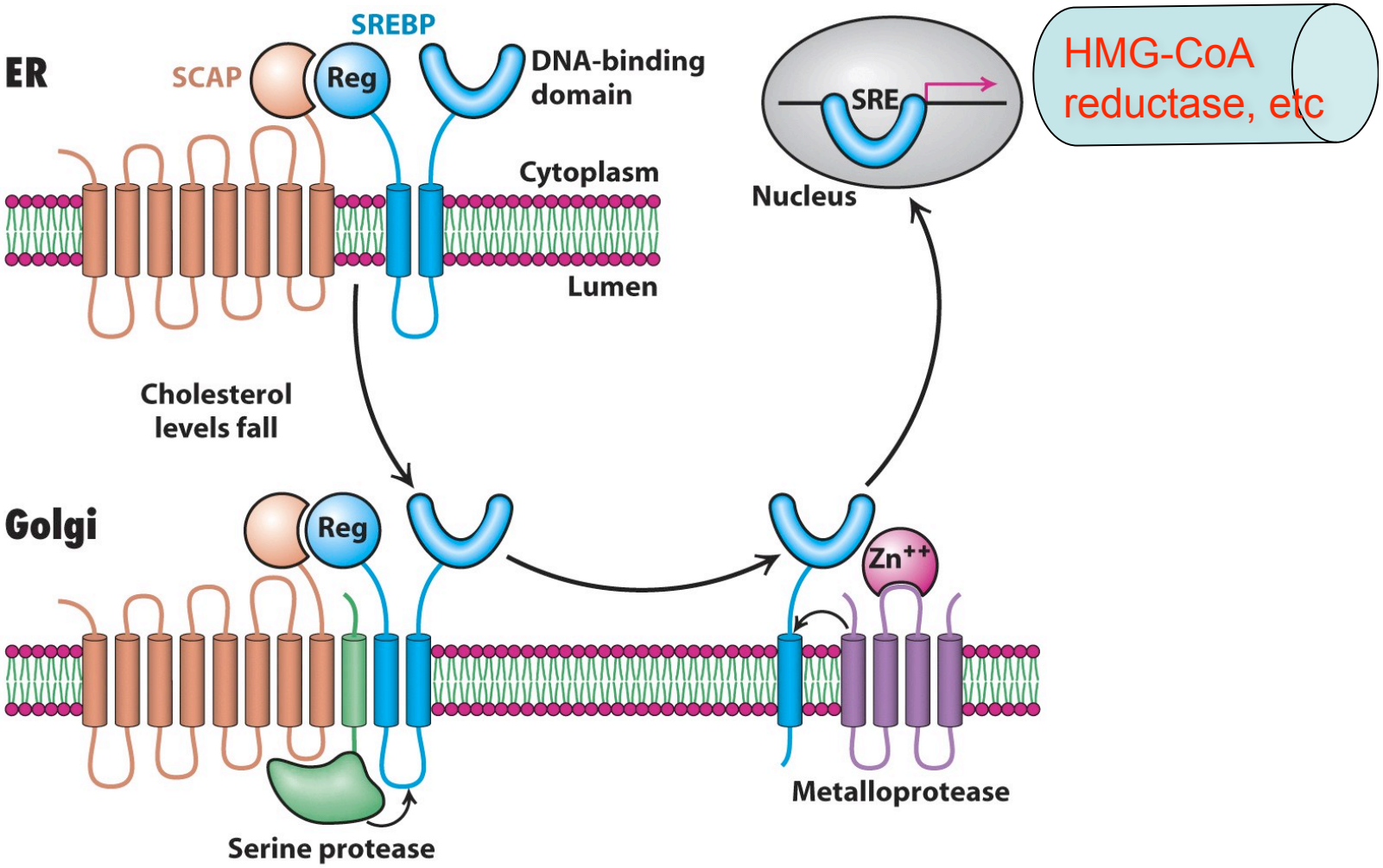
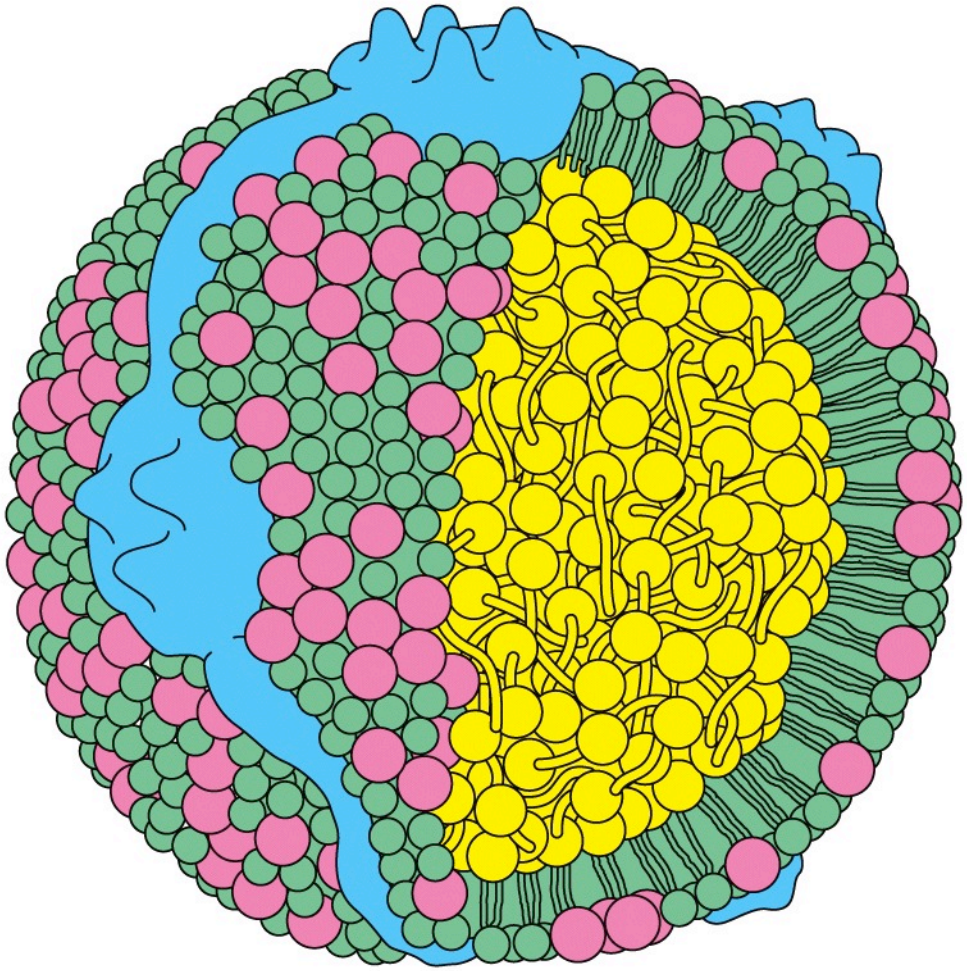


Figure 26-13
Biochemistry, Sixth Edition

Lipid Transport-LDL



Unesterified cholesterol
Phospholipid
Cholesteryl ester
Apoprotein B-100

Lipid Transport

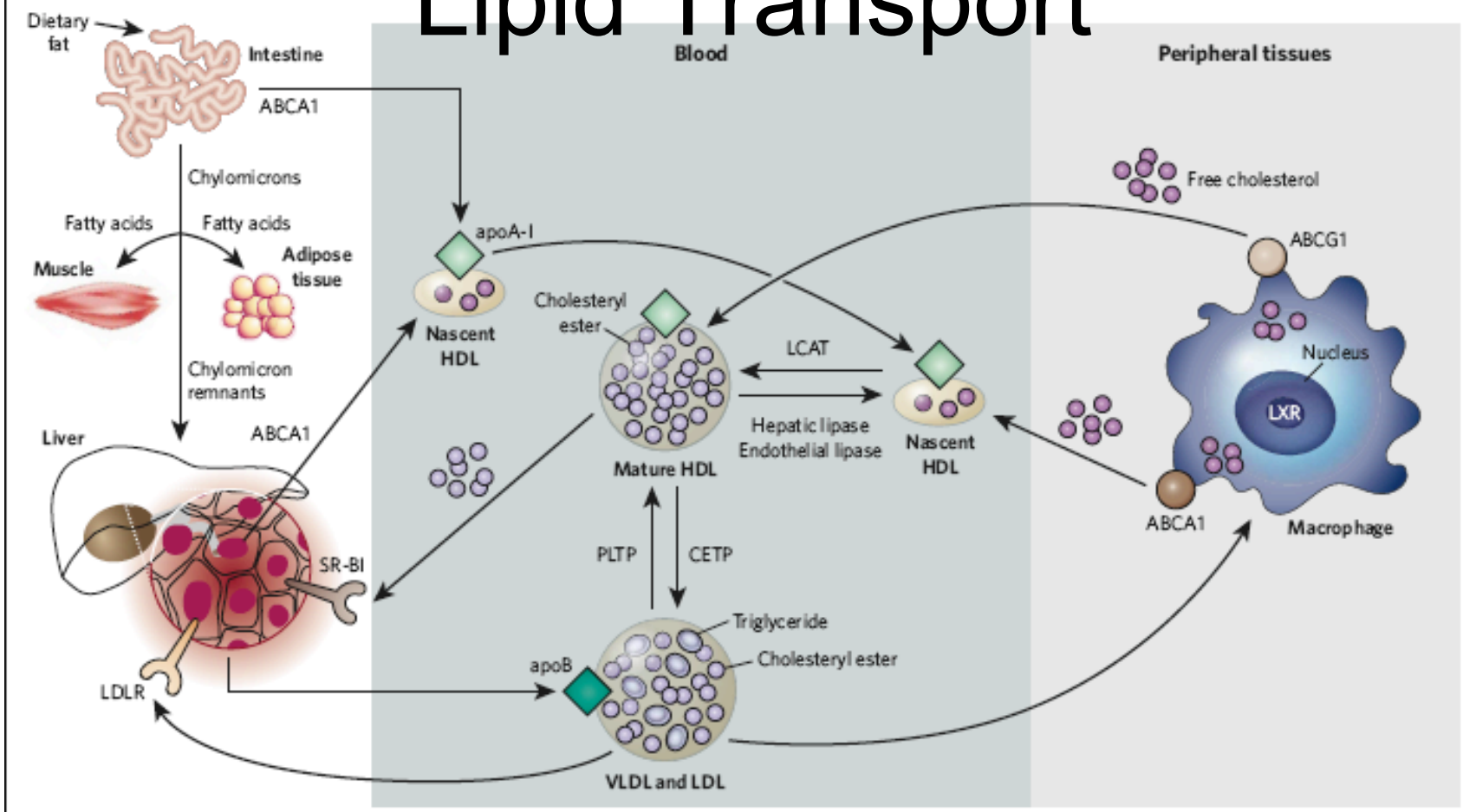


Figure 2 | Lipoprotein metabolism. Lipoprotein metabolism has a key role in atherogenesis. It involves the transport of lipids, particularly cholesterol and triglycerides, in the blood. The intestine absorbs dietary fat and packages it into chylomicrons (large triglyceride-rich lipoproteins), which are 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 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

Lipid Transport-Other lipoproteins

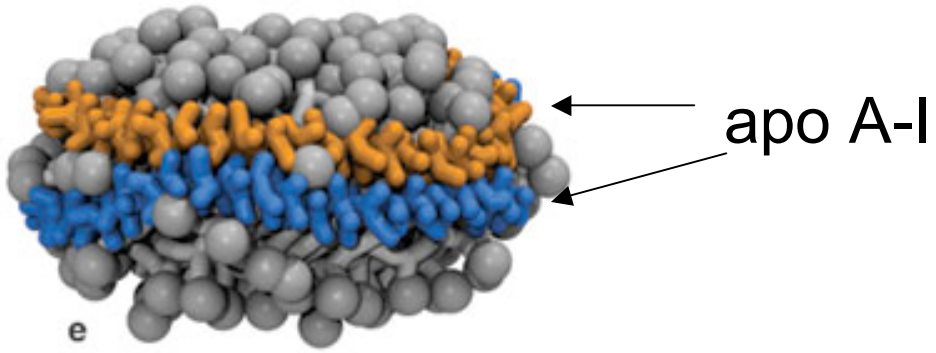
TABLE 26.1 Properties of plasma lipoproteins

Plasma lipoproteins	Density (g ml^{-1})	Diameter (nm)	Apolipoprotein	Physiological role	Composition (%) TAG	CE	C	PL	P
Chylomicron	<0.95	75–1200	B48, C, E	Dietary fat transport	86	3	1	8	2
Very low density lipoprotein	0.95–1.006	30–80	B100, C, E	Endogenous fat transport	52	14	7	18	8
Intermediate-density lipoprotein	1.006–1.019	15–35	B100, E	LDL precursor	38	30	8	23	11
Low-density lipoprotein	1.019–1.063	18–25	B100	Cholesterol transport	10	38	8	22	21
High-density lipoprotein	1.063–1.21	7.5–20	A	Reverse cholesterol transport	5–10	14–21	3–7	19–29	33–57

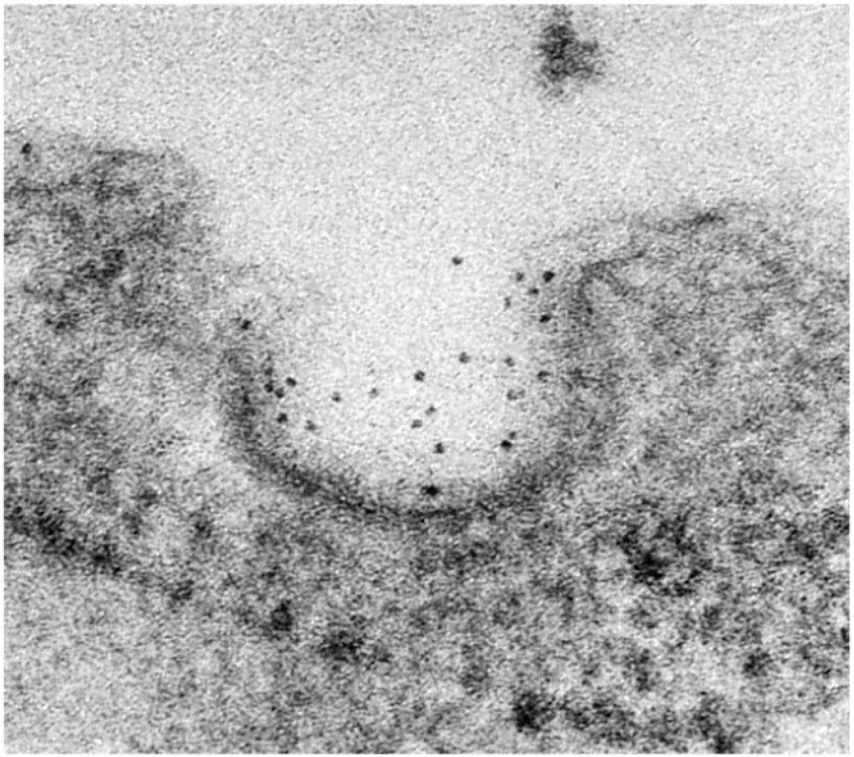
Abbreviations: TAG, triacylglyerol; CE, cholesterol ester; C, free cholesterol; PL, phospholipid; P, protein.

Table 26-1
Biochemistry, Sixth Edition

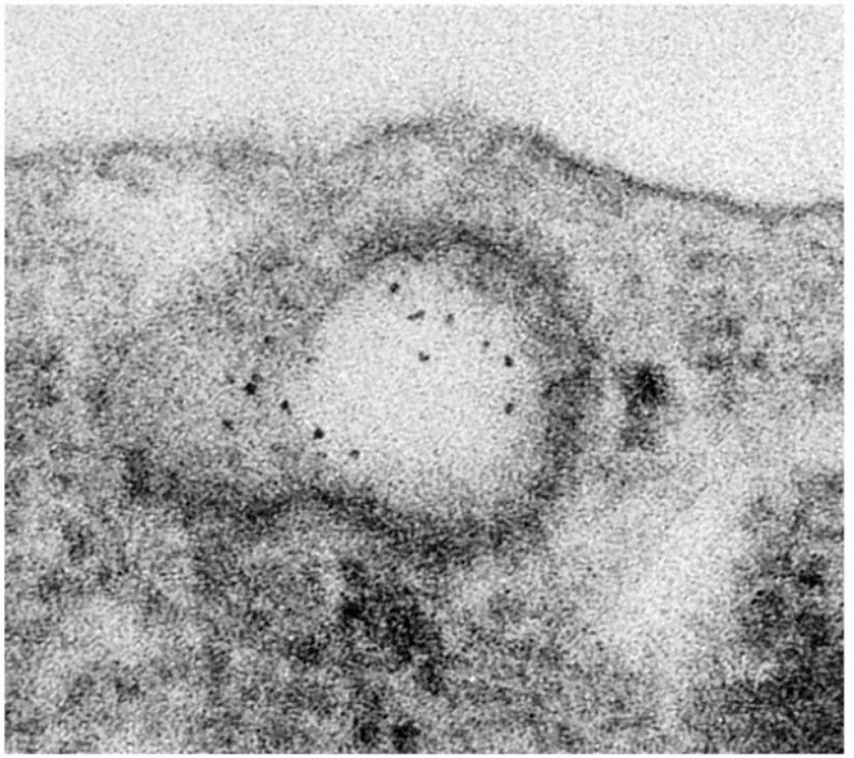
[See HDL Structure]



The LDL receptor



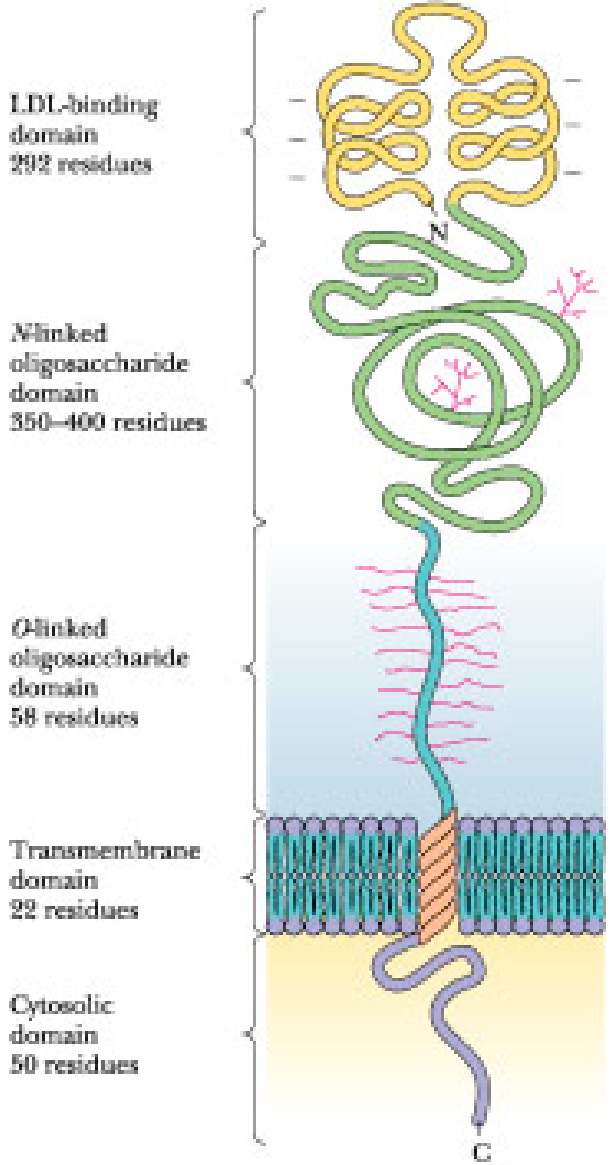
(A)



(B)

See Clathrin Structure Here

The LDL receptor



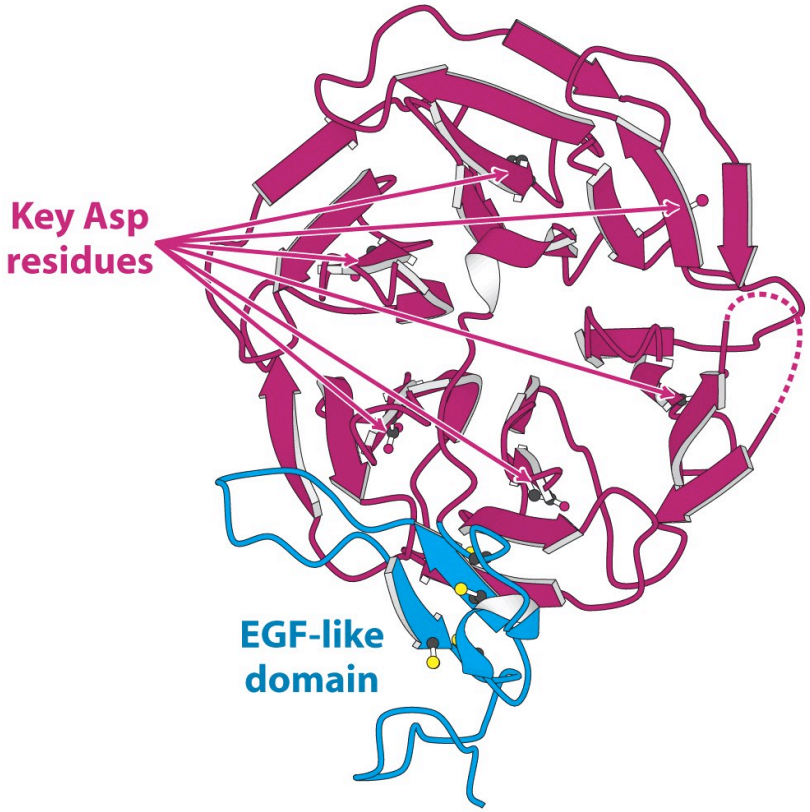


Figure 26-19
Biochemistry, Sixth Edition

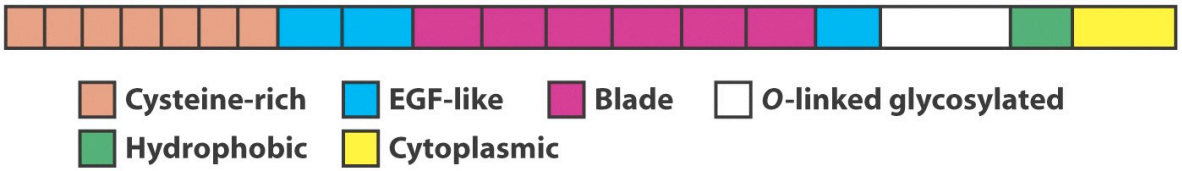


Figure 26-18
Biochemistry, Sixth Edition

Cholesterol and CORONARY ARTERY DISEASE

HOW DOES IT HAPPEN AND HOW CAN YOU STOP IT?

CAD-Risk Factors

- High [LDL]
  - DIET
  - PARENTS (see Science 18 May 2001: Vol. 292. no. 5520, pp. 1310 - 1312)
- Smoking
- Type I and II diabetes
- High Blood Pressure

But it’s not straightforward…

To understand where this complexity can lead in a simple example, consider a steak--to be precise, a porterhouse, select cut, with a half-centimeter layer of fat, the nutritional constituents of which can be found in the Nutrient Database for Standard Reference at the USDA Web site. After broiling, this porterhouse reduces to a serving of almost equal parts fat and protein. Fifty-one percent of the fat is monounsaturated, of which virtually all (90%) is oleic acid, the same healthy fat that's in olive oil. Saturated fat constitutes 45% of the total fat, but a third of that is stearic acid, which is, at the very least, harmless. The remaining 4% of the fat is polyunsaturated, which also improves cholesterol levels. In sum, well over half--and perhaps as much as 70%--of the fat content of a porterhouse will improve cholesterol levels compared to what they would be if bread, potatoes, or pasta were consumed instead. The remaining 30% will raise LDL but will also raise HDL. All of this suggests that eating a porterhouse steak rather than carbohydrates might actually improve heart disease risk, although no nutritional authority who hasn't written a high-fat diet book will say this publicly.

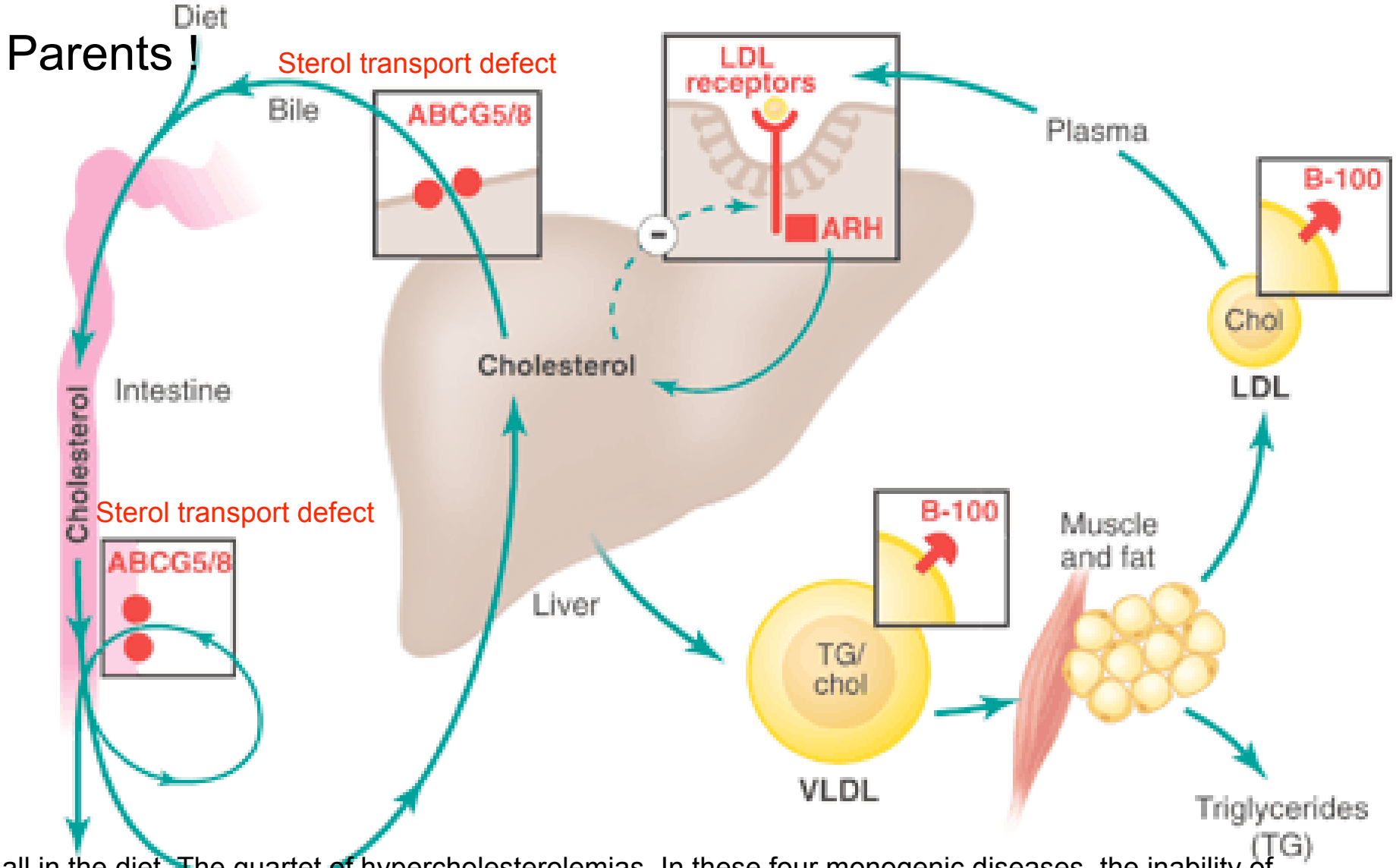
Science 30 March 2001:
Vol. 291. no. 5513, pp. 2536 - 2545

Parents !

FOUR MONOGENIC DISEASES THAT ELEVATE PLASMA LDL AND CAUSE HEART ATTACKS

Human disease	Prevalence in population	Typical plasma LDL-cholesterol level*	Mutant gene product	Mechanism for decreased LDL receptor function
		mg/dl		
Familial hypercholesterolemia			LDL receptor	Nonfunctional receptors
Heterozygous	1 per 500†	300		
Homozygous	1 per million†	650		
Familial ligand defective apoB-100			apoB-100	Decreased binding of LDL to receptors
Heterozygous	1 per 1000‡	270		
Homozygous	<1 per million ‡	320		
Autosomal recessive hypercholesterolemia	<1 per 10 million§	470	ARH	? Altered location of receptors in liver
Sitosterolemia	<1 per 10 million	100 to 600 depending on diet	ABCG5 and/or ABCG8	Suppression of receptor gene transcription

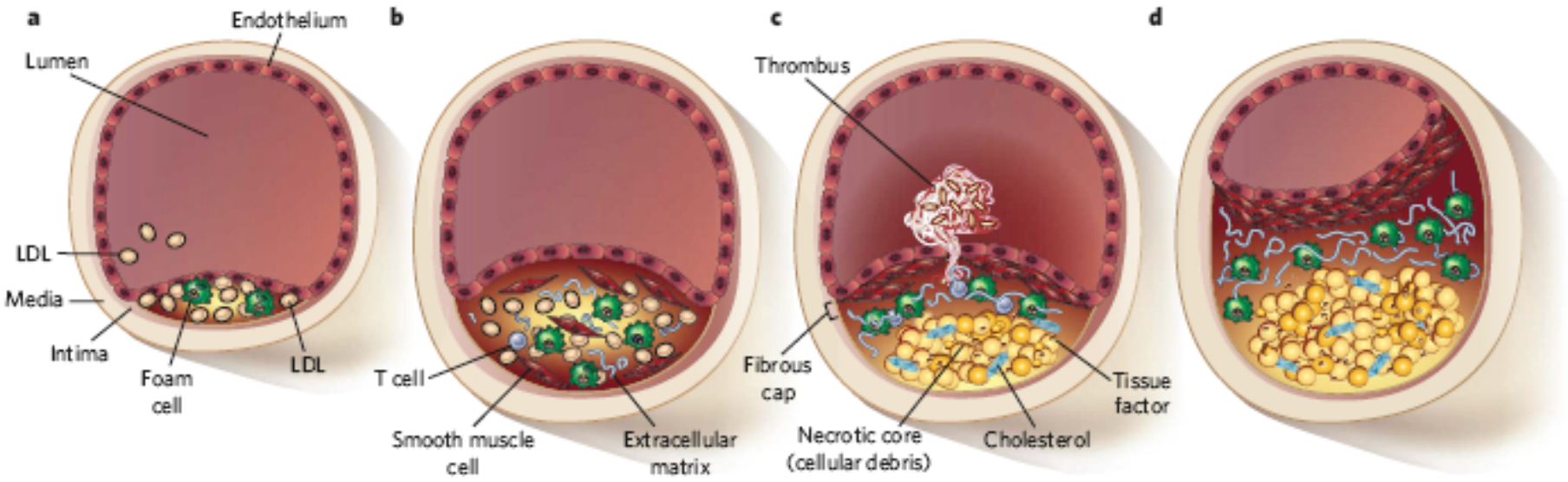
*Typical adult plasma LDL-cholesterol is 120 mg/dl in the United States (6). †All populations. ‡ Primarily in individuals of European descent. §Primarily in individuals of Italian and Middle Eastern descent.



Not all in the diet. The quartet of hypercholesterolemias. In these four monogenic diseases, the inability of defective LDLRs to remove cholesterol-carrying LDLs from plasma causes an increase in plasma LDL and the deposition of atherosclerotic fatty plaques in arteries, leading to heart disease. The mutant gene products of the cholesterol quartet are shown in red; also depicted are the points where their normal counterparts act in the cholesterol pathway. [Not shown are the intermediate density lipoproteins (IDL), which are highly atherogenic intermediates in the conversion of VLDL to LDL (Science 18 May 2001: Vol. 292. no. 5520, pp. 1310 - 1312).]

Coronary Artery Disease

NATURE|Vol 451|21 February 2008 INSIGHT REVIEW



ATHEROSCLEROSIS INDUCED BY HYPERCHOLESTEROLEMIA

Classic Model Circulation. 1997 Feb 18;95(4):1062-71.

CIRCULATING T-LYMPHOCYTES

CIRCULATING MONOCYTES

CIRCULATING LDL

8. Adhesion and penetration

1. Adhesion to aortic endothelium
   a) Changes in monocytes
   b) Changes in endothelial cells
2. Penetration into intima
   Chemoattractants
3. Phenotypic modulation in subendothelial space
4. Replication

6. Increased rate of entry; decreased rate of exit

ARTERIAL T-CELLS

ARTERIAL TISSUE MACROPHAGES

INTIMAL LDL

5. Uptake of modified LDL and accumulation of cholesterol ester doplets

7. Oxidation, aggregation or other modifications

MODIFIED LDL

FATTY STREAK LESION

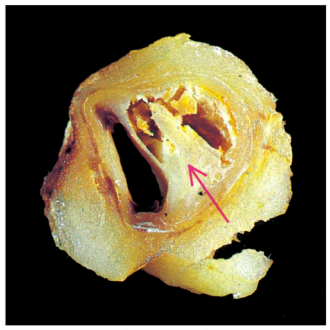
ARTERIAL MACROPHAGE-DERIVED FOAM CELLS
ARTERIAL SMOOTH MUSCLE-DERIVED FOAM CELLS

SMC UPTAKE OF MODIFIED LDL

9. SMC growth (Smooth muscle cells)
10. Synthesis and secretion of CT matrix (connective tissue)

Cytokines and growth factors

Migration of SMC into intima



5 mm

FIBROUS PLAQUE LESION

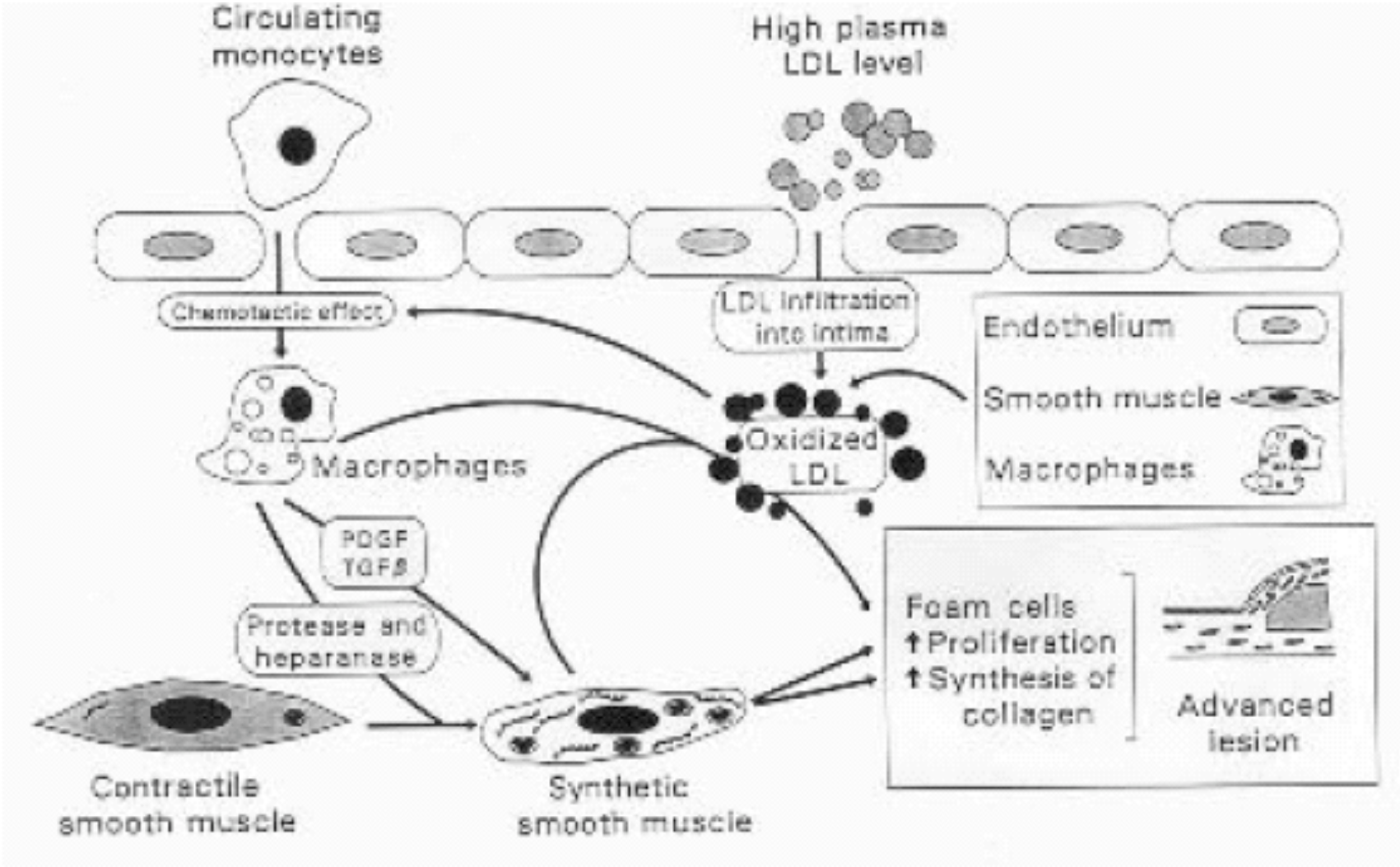
Death and necrosis of foam cells
Death and necrosis of SMC

COMPLEX LESION WITH NECROTIC CORE

PLAQUE RUPTURE

THROMBOSIS AND INFARCTION

Coronary Artery Disease



Coronary Artery Disease

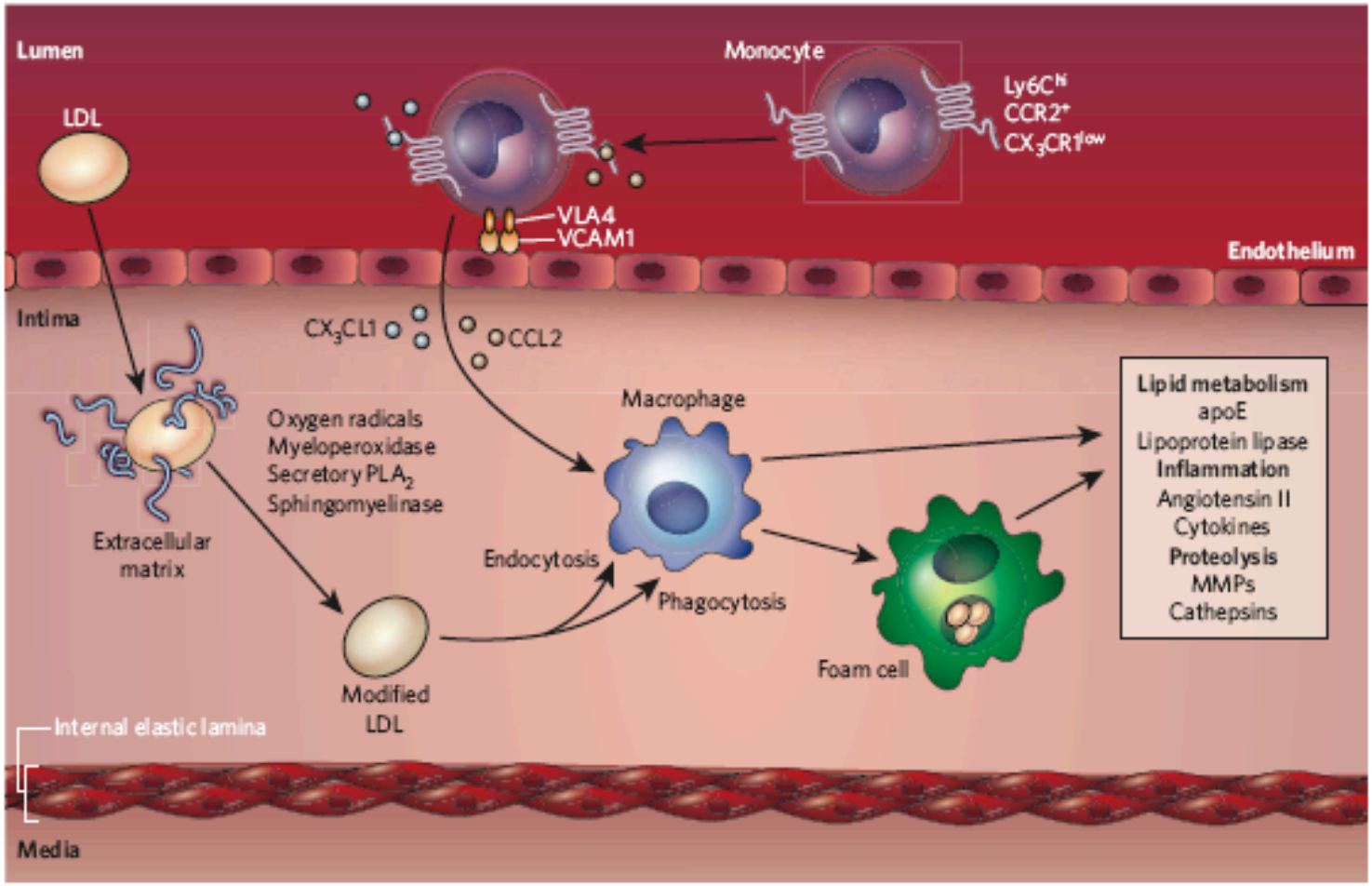


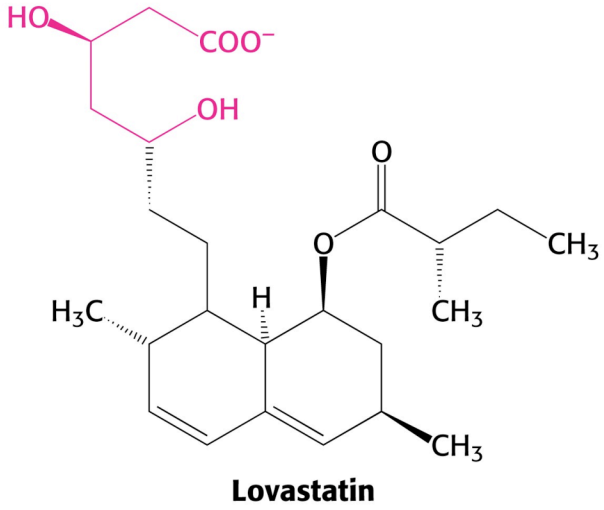
Figure 3 | Recruitment of monocytes and formation of foam cells. LDLs in the blood enter the intima, where they are retained through binding to the extracellular matrix. LDLs are then modified by oxygen radicals, myeloperoxidase, secretory phospholipase A_2 and sphingomyelinase. This results in the generation of pro-inflammatory biologically active lipids that initiate and maintain an active inflammatory process in the intima (not CX_3CL1 and CCL2, which recruit subsets of monocytes to the intima. These monocytes then differentiate into macrophages, which take up modified LDL through endocytosis or phagocytosis and become foam cells (which are loaded with cholesterol). Macrophages secrete various factors involved in propagating the atherosclerotic plaque, including factors involved in lipid metabolism, inflammation and proteolysis. VLA4, very late activation

Coronary Artery Disease-

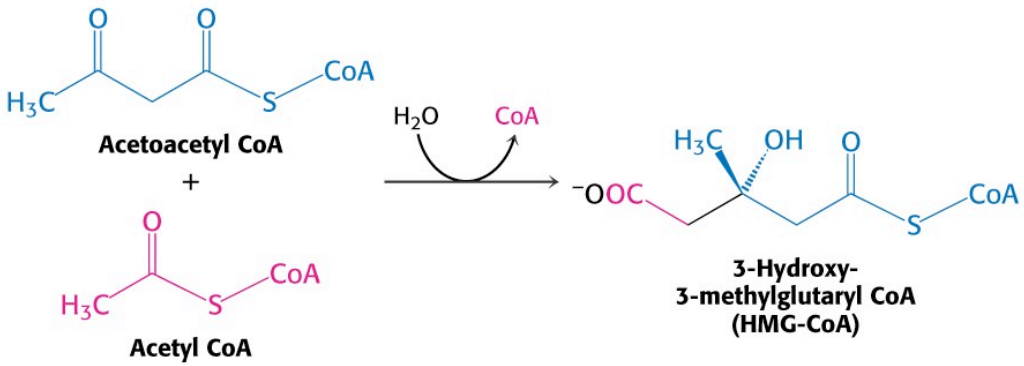
Treatments

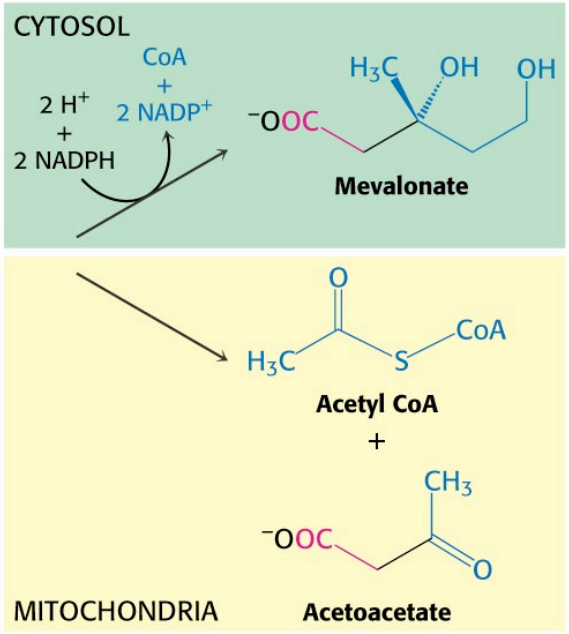
- Statins-

HMG CoA reductase inhibitors



Lovastatin

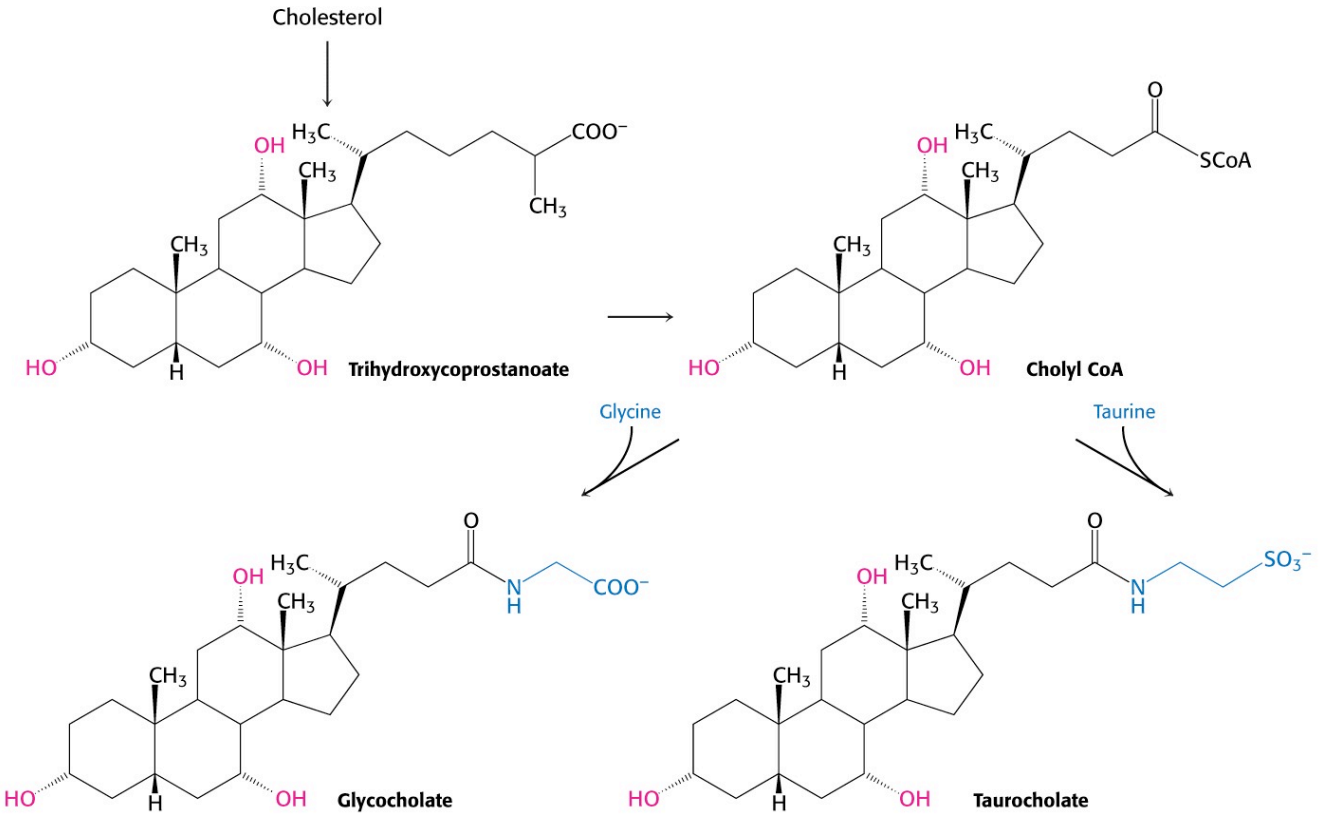




Coronary Artery Disease-

Treatments

- Fiber/Cholestyramine/etc.



Coronary Artery Disease-

Treatments

- Niacin-Incr. HDL, lower LDL-good with statins
  - http://www.mayoclinic.com/health/niacin/NS_patient-niacin
- Antiinflammatories-blood clotting decr., lower inflammation(CRP)
- Blood Pressure-β-blockers, exercise, weight
- DIET!!! (sat/trans fats)-raise LDL, reduce HDL/LDL
- Don't smoke!-oxidation, blood vessel constriction
- others