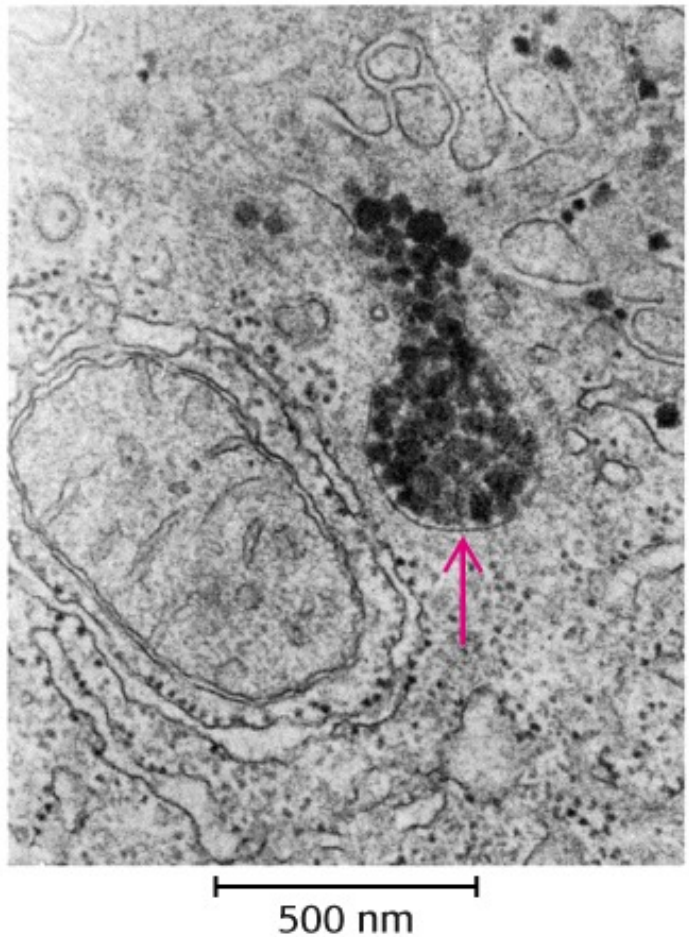
Cholesterol Metabolism

- **Structure**
- **Synthesis**
- **Regulation**
- **Transport of Cholesterol**
- **Hypercholesterolemia**



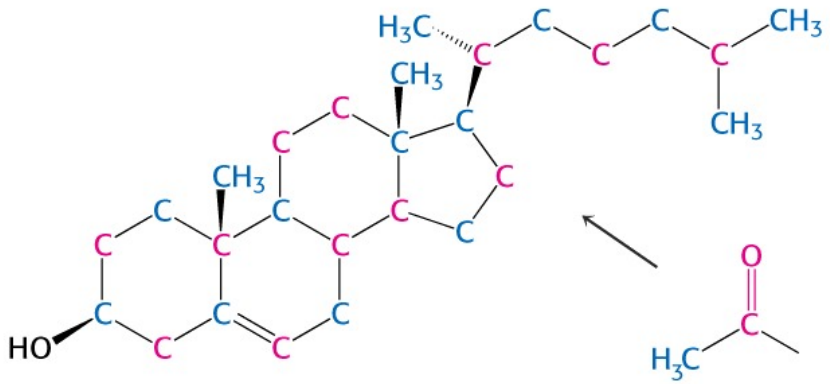
Liver cell synthesis of VLDL

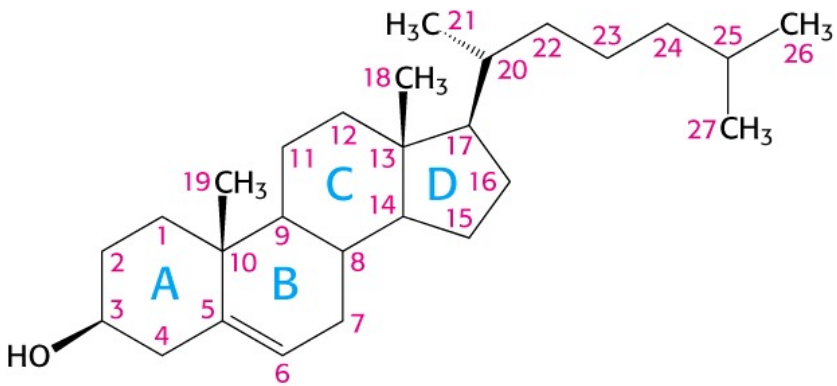
Functions of Cholesterol

- Component of Cell membranes
- Precursor of steroid hormones/bile acids
- Sources: diet (.3 g/day) and biosynthesis (1g/d)
- Excrete 1100 mg sterol
- Plants and fungus contain sitosterols and erogsterols

Structure

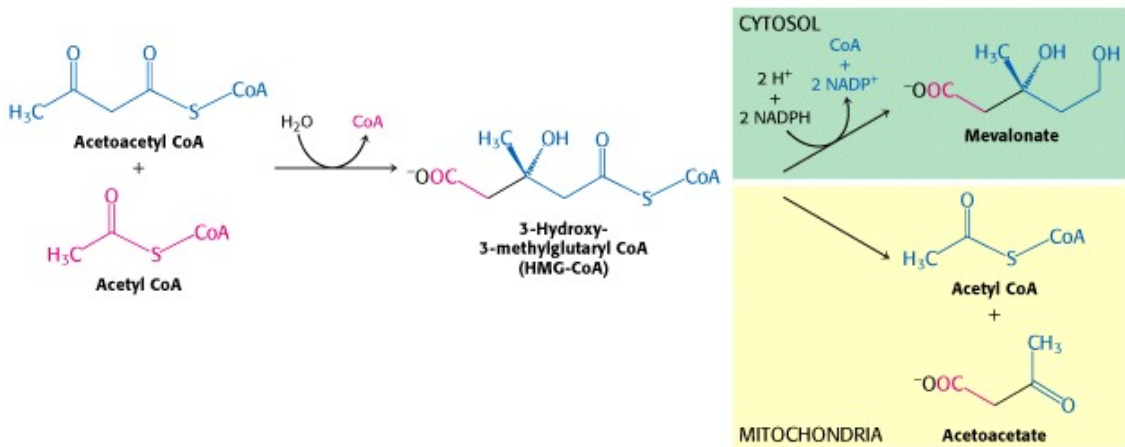
- **3-hydroxy-5,6 cholestene**
- **3 six member rings**
- **1 five member ring**
- **tail**
- **-OH group off C3**
- **from Isopentenyl pyrophosphate**
- **produces quinones, carotenoids, vitamin A,D,E,K, steroid hormones, and bile salts**





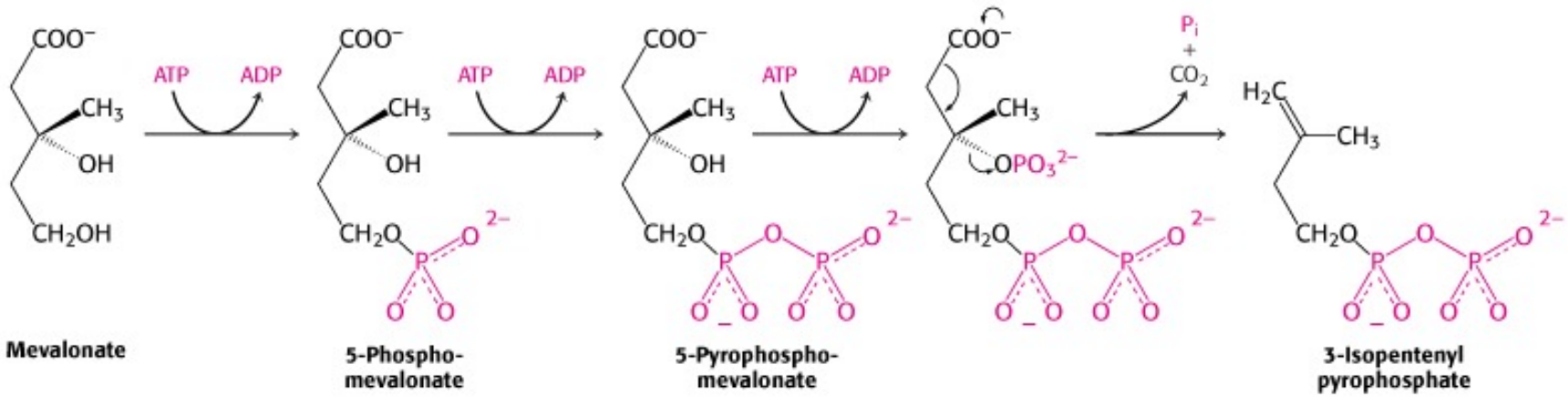
Synthesis

- Acetyl CoA units
- cytolosic pathway
- uses HMG-CoA synthetase
- new HMG-CoA reductase, committed step



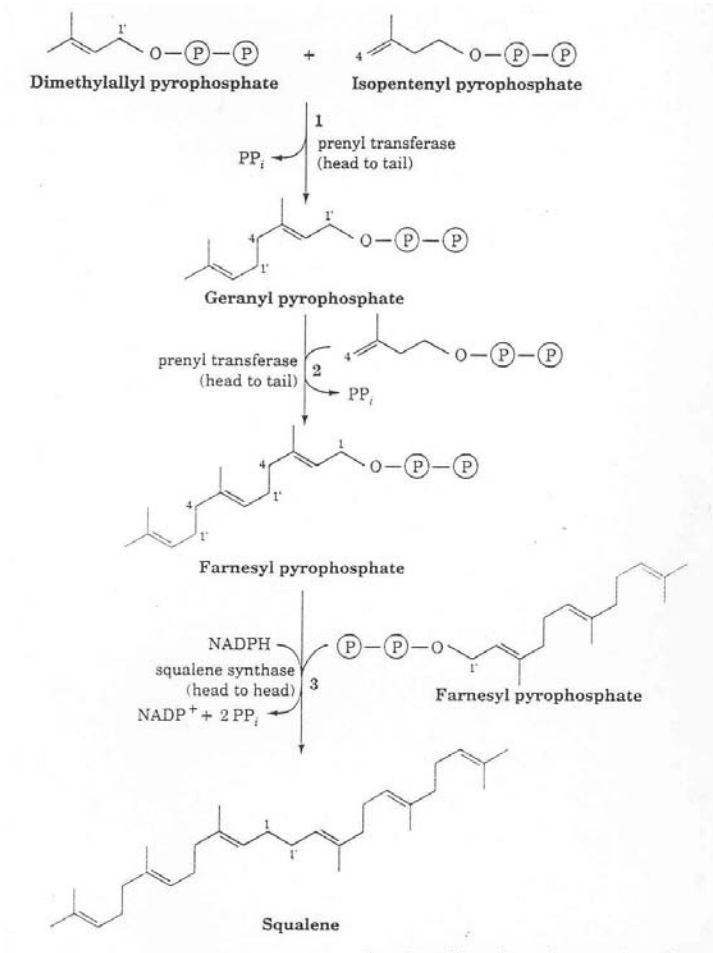
Synthesis of Isopentenyl pyrophosphate

- produce mevalonate
- produce Isopentenyl pyrophosphate & Dimethylallyl pyrophosphate



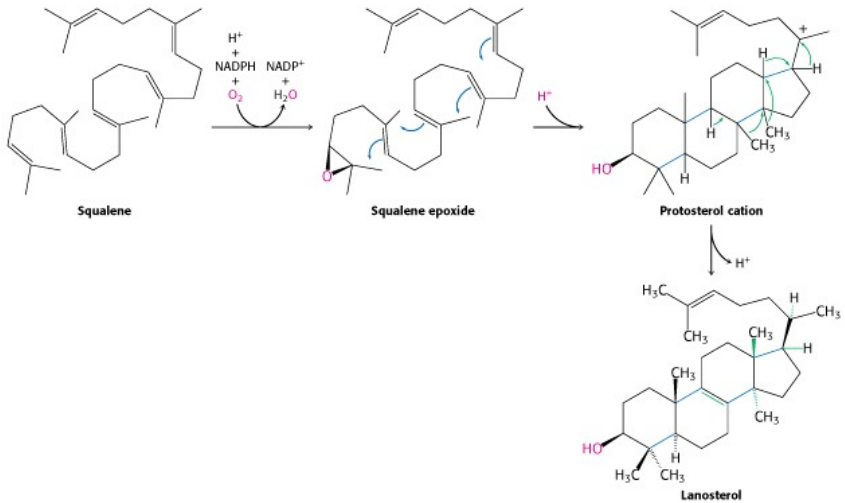
Condensation Reactions

- Condensation of 5 carbon units to produce
- geranyl pyrophosphate
- farnesyl pyrophosphate
- squalene



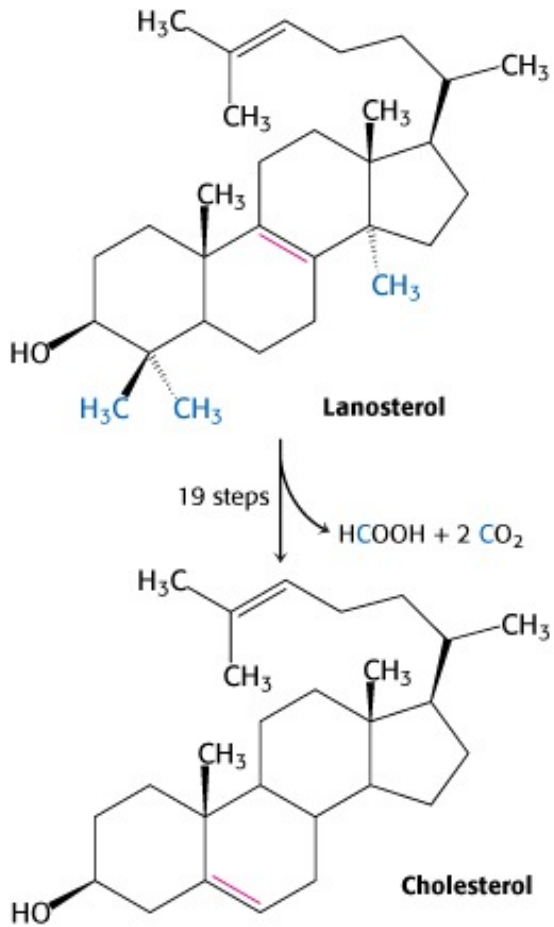
Cyclization

- Squalene monooxgenase leads to cyclization to lanosterol (1st sterol)
- lanosterol to cholesterol
- Cholesterol to bile acids



Cholesterol

- lanosterol to cholesterol
- Cholesterol to bile acids



Regulation

Positive – Insulin, dephosphorylation
Negative -- glucagon

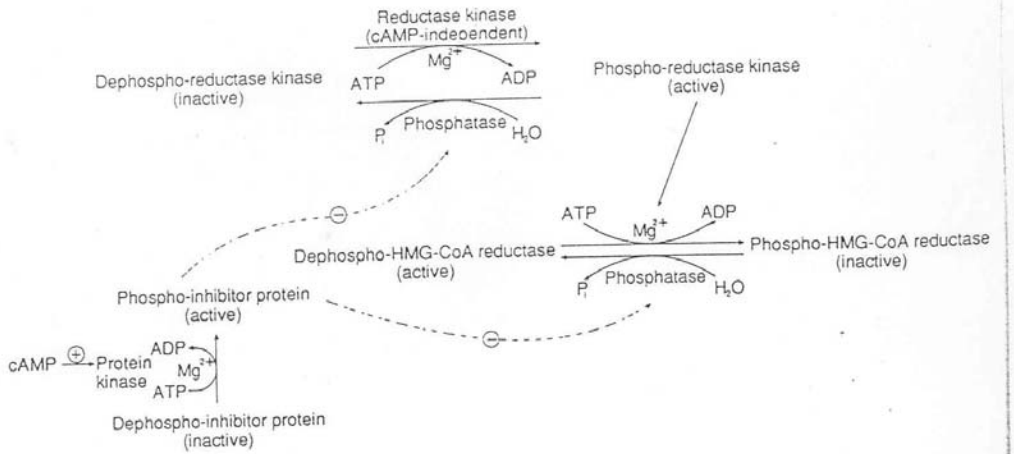


FIGURE 19–11
Regulation of HMG-CoA reductase by phosphorylation-dephosphorylation; phosphorylation leads to loss of catalytic activity. The two phosphatases are identical and are inhibited by an inhibitor protein that is more active when phosphorylated by a cAMP-dependent protein kinase. Phosphorylation of reductase kinase is not cAMP-dependent.

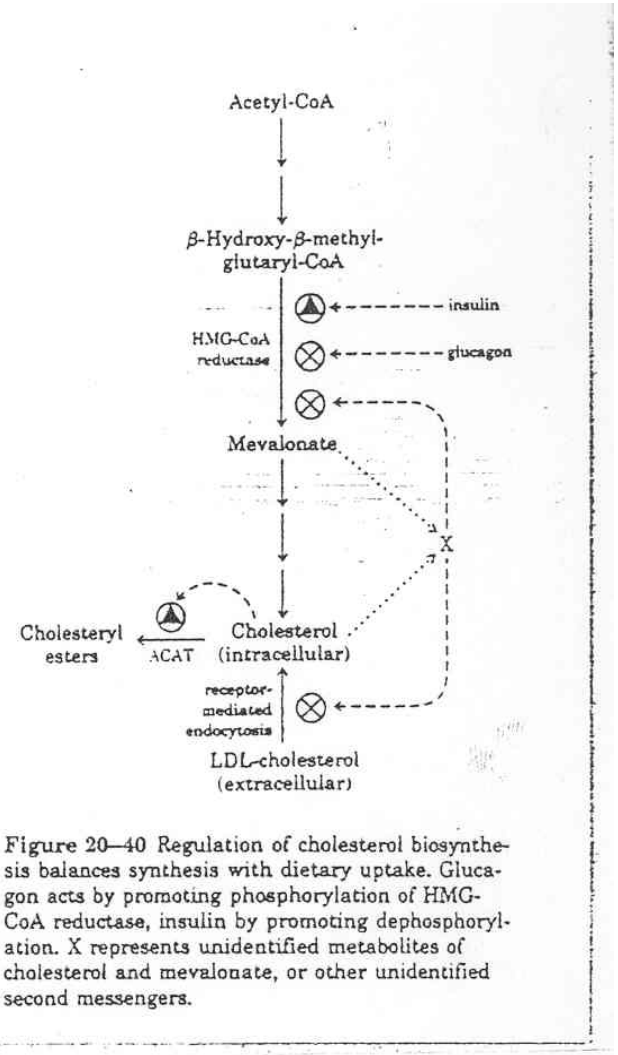
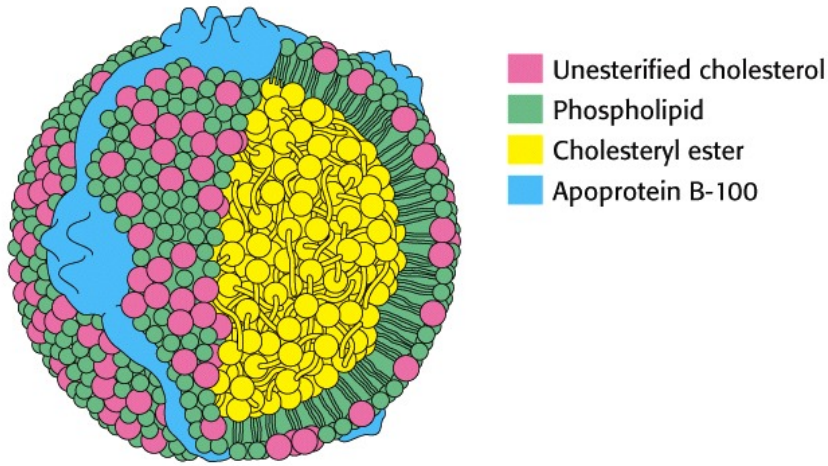


Figure 20–40 Regulation of cholesterol biosynthesis balances synthesis with dietary uptake. Glucagon acts by promoting phosphorylation of HMG-CoA reductase, insulin by promoting dephosphorylation. X represents unidentified metabolites of cholesterol and mevalonate, or other unidentified second messengers.

Transport of Cholesterol

- **Transported from Liver to other parts of body**
- **Plasma lipoproteins**
- **Composed of proteins, phospholipids, hydrophobic core**
- **4 major groups**
- **Chylomicrons: transport of triacylglycerols**
- **VLDL: transport of stored fat/fat from carbohydrate**
- **LDL: transport of cholesterol esters to peripheral tissue**
- **HDL: transport of cholesterol esters from peripheral tissue to liver**



Plasma lipoproteins

TABLE 26.1 Properties of plasma lipoproteins

Lipoproteins	Major core lipids	Apoproteins	Mechanism of lipid delivery
Chylomicron	Dietary triacylglycerols	B-48, C, E	Hydrolysis by lipoprotein lipase
Chylomicron remnant	Dietary cholesterol esters	B-48, E	Receptor-mediated endocytosis by liver
Very low density lipoprotein (VLDL)	Endogenous triacylglycerols	B-100, C, E	Hydrolysis by lipoprotein lipase
Intermediate-density lipoprotein (IDL)	Endogenous cholesterol esters	B-100, E	Receptor-mediated endocytosis by liver and conversion into LDL
Low-density lipoprotein (LDL)	Endogenous cholesterol esters	B-100	Receptor-mediated endocytosis by liver and other tissues
High-density lipoprotein (HDL)	Endogenous cholesterol esters	A	Transfer of cholesterol esters to IDL and LDL

Source: After M. S. Brown and J. L. Goldstein, *The Pharmacological Basis of Therapeutics*. 7th ed., A. G. Gilman, L. S. Goodman, T. W. Rall, and F. Murad, Eds. (Macmillan, 1985), p. 828.

Lipoproteins

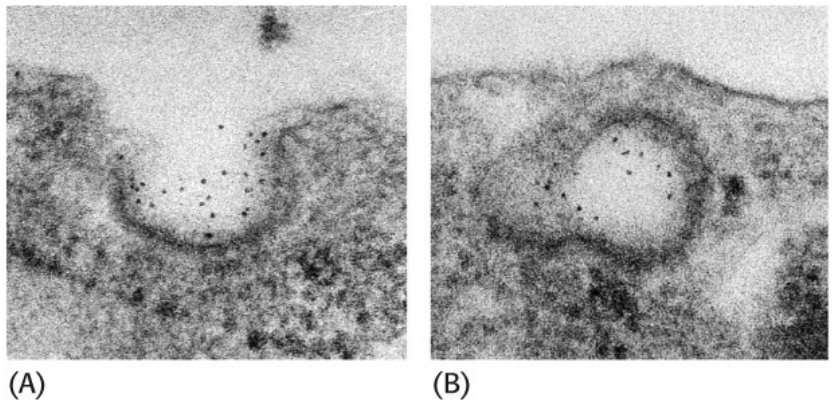
Table 20–2 Major classes of human plasma lipoproteins: some properties

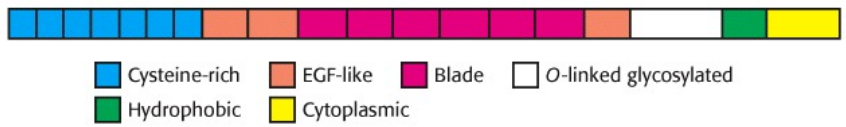
Lipoprotein	Density (g/mL)	Composition (wt %)				
		Protein	Free cholesterol	Cholesteryl esters	Phospholipids	Triacylglycerols
Chylomicrons	<1.006	2	1	3	9	85
VLDL	0.95–1.006	10	7	12	18	50
LDL	1.006–1.063	23	8	37	20	10
HDL	1.063–1.210	55	2	15	24	4

Source: Modified from Kritchevsky, D. (1986) Atherosclerosis and nutrition. *Nutr. Int.* 2, 290–297.

Cellular Uptake

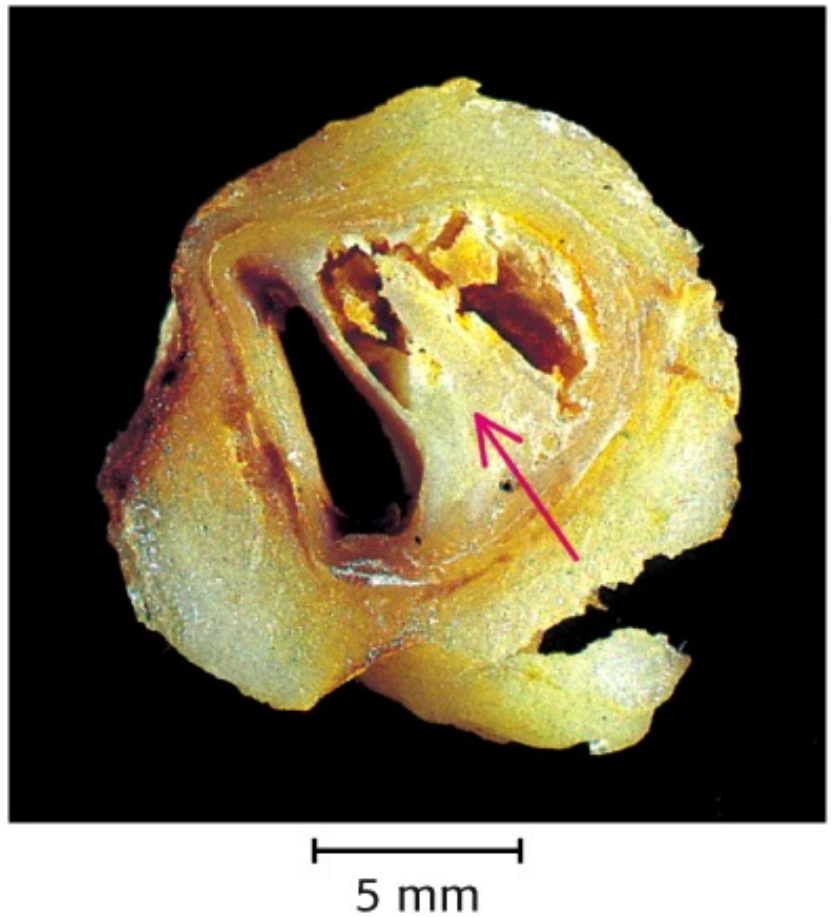
- **Uptake to cell receptor mediated endocytosis**
- **coated pits**
- **gene regulated: cellular concentration of cholesterol**
- **Removal of cholesterol: Active transport out of cell to HDL**
- **LCAT (Lecithin-cholesterol acyltransferase): esterfies fatty acid to cholesterol**
- **HDL transported to liver and to VLDL and LDL, remove from blood**





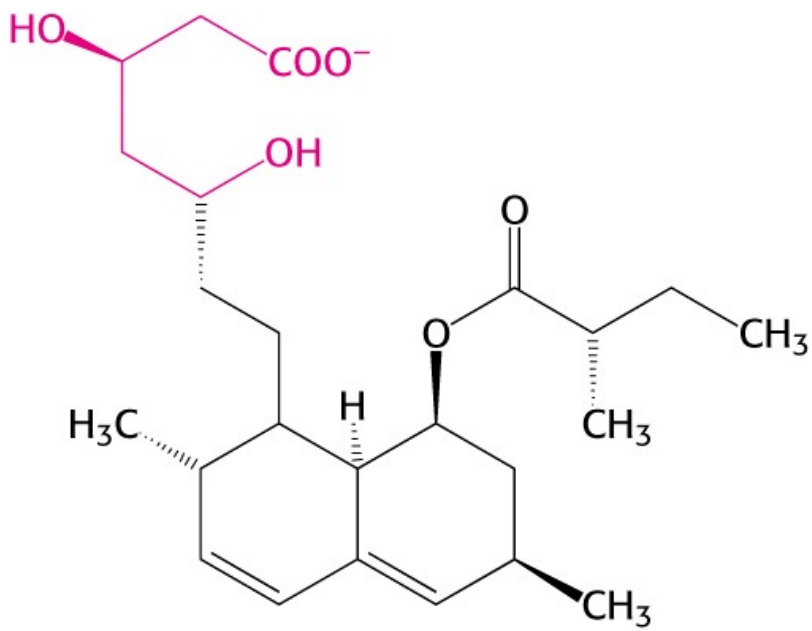
Hypercholesterolemias

- **Familial Hypercholesterolemias: Genetic defect**
- **Five classes of mutations**
- **no receptor synthesized**
- **receptor not transported to cell surface**
- **receptor does not bind LDL**
- **receptor may not cluster in pits**
- **receptor may not release LDL in the cell**
- **autosomal dominant disorder**
- **Heterozygote plasma levels of LDL: 320-500 mg/dL, increased residence time in blood**
- **Homozygous plasma levels of LDL: 600-1000 mg/dL**



Treatment

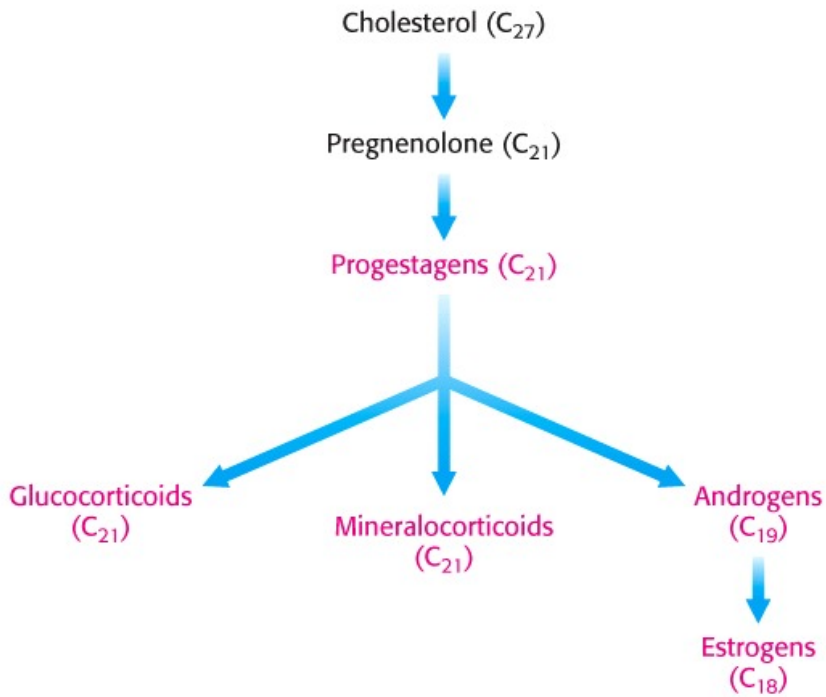
- **Treatments:**
- **Diet: no animal foods**
- **Pharmocogical treatment**
  - **use of statins**
  - **affect HMG-CoA reductase**
  - **competitive inhibition**
  - **Km for statins1 um vs 10 um for HMG-CoA**
  - **Lovastatin, simvastatin, pravastatin**
- **use of statins increases enzyme expression**
- **total body cholesterol reduced 20-40%**
- **increased expression of LDL receptors**
- **clears blood serum of cholesterol**
- **can have other effects on liver/pathway**



Lovastatin

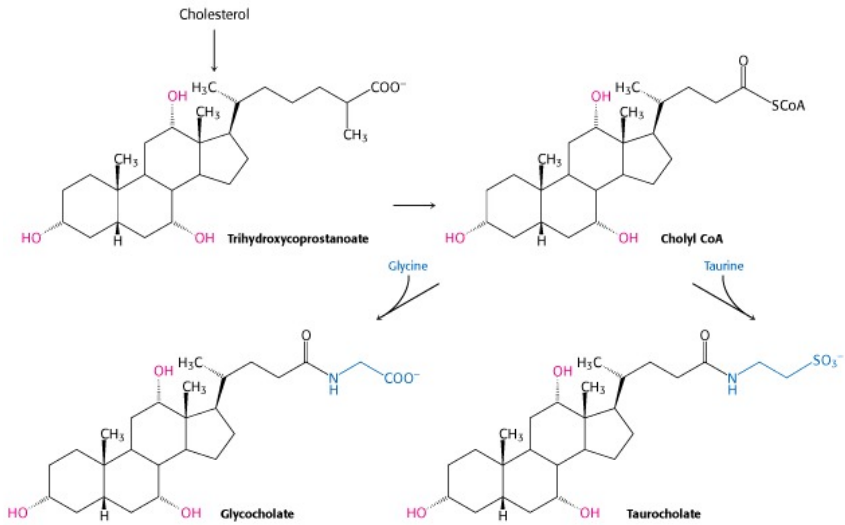
Derivatives of Cholesterol

- **Steroid hormones**
- **Androgens**
- **Estrogens**
- **Mineralocorticoids**
- **Glucocorticoids**
- **Progestagens**
- **Transcription activating factors**
- **Regulate gene expression**



Bile Salts

- Detergents
- Help absorb lipid soluble vitamins
- .8- 1 g/day produced and lost in feces
- Circulate 15-20 g/day
- Produced from HDL
- Stored in gall bladder
- Reabsorb 90% from intestine



Vitamin D

- Precursor of vitamin D
- 7-dehydrocholesterol photolyzed by UV light
- Pre-vitamin D
- Spontaneous isomerization to Vit D
- Rickets– inadequate calcification of bones