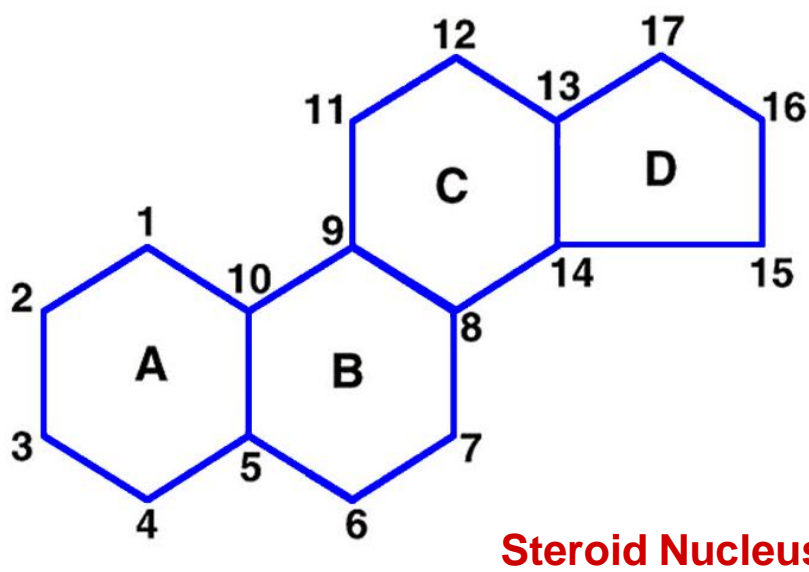
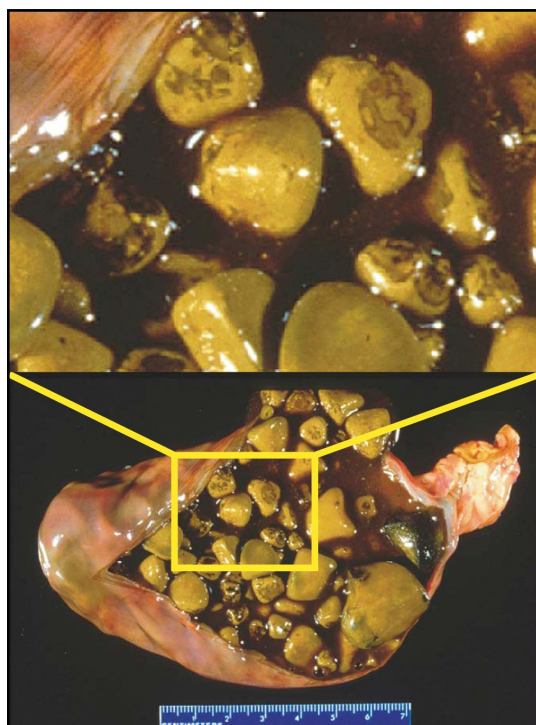
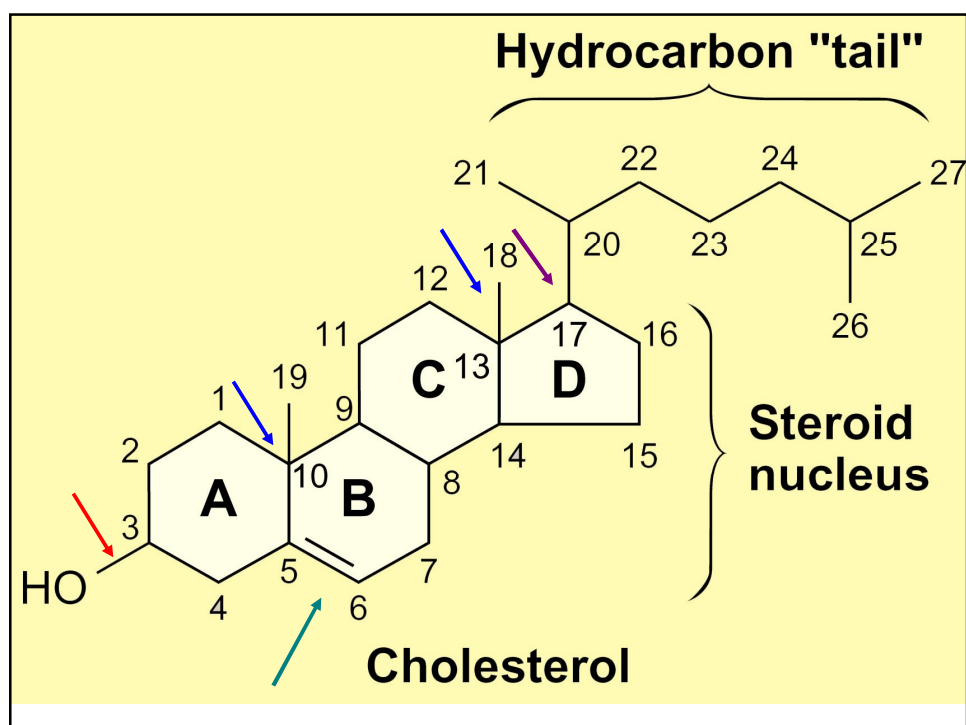


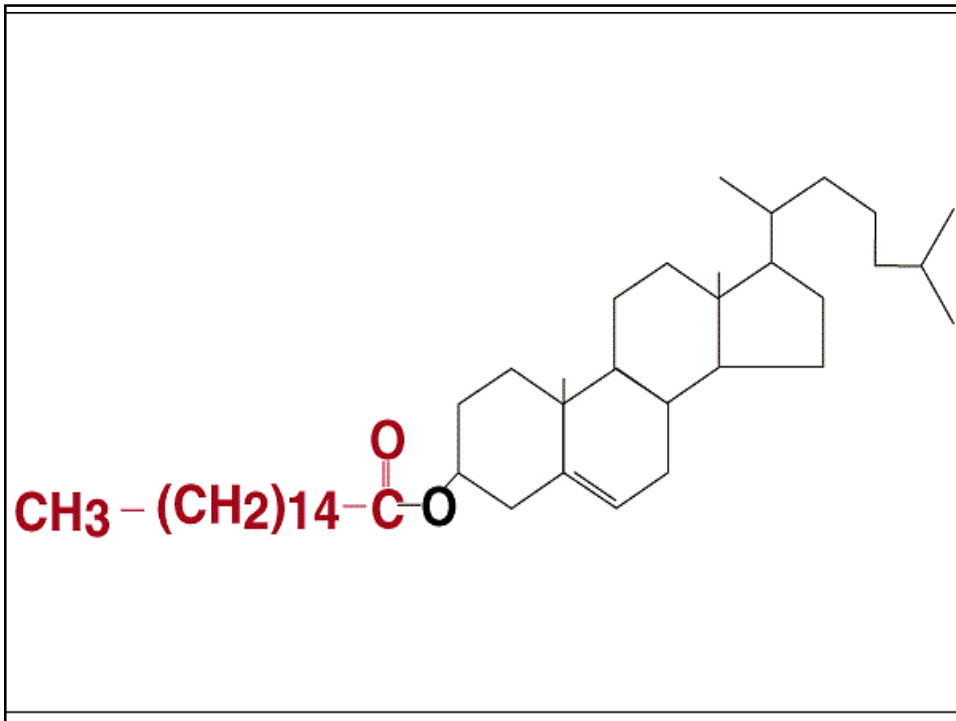
Cholesterol Metabolism

Lippincott's Illustrated Review
Chapter 18





Cholesterol was
isolated from gall
bladder stones
in 1774



Sources and Elimination of Cholesterol

Synthesis: ≈ 1000 mg

Liver, Small Intestine, Adrenal Cortex ...

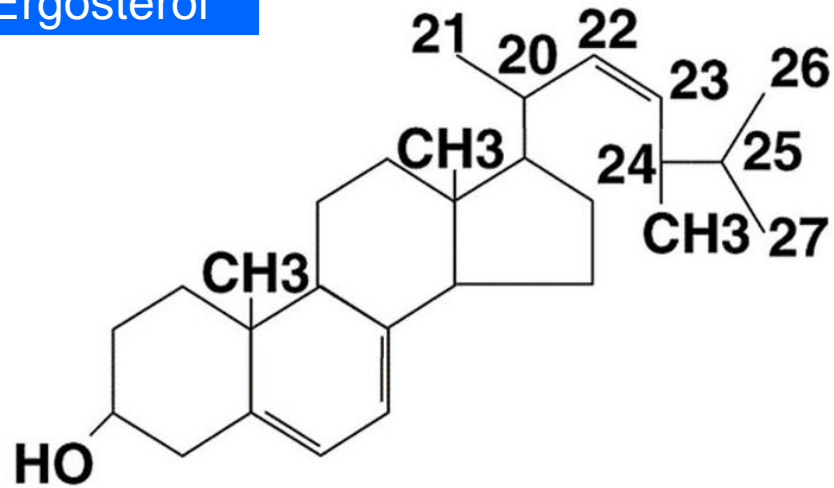
Dietary: ≈ 300 mg

(Low Cholesterol Diet)

Elimination: Via the Bile

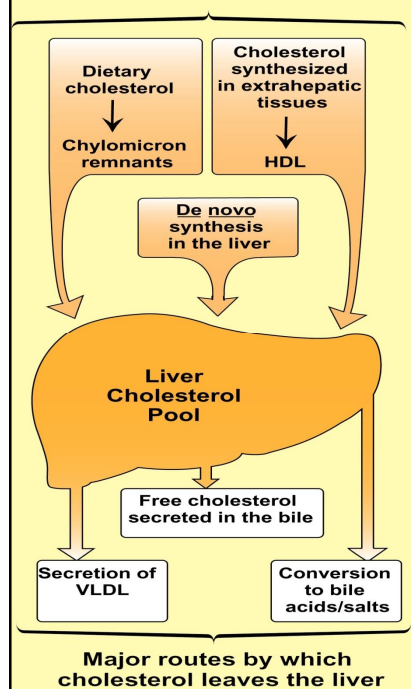
Cholesterol, Bile Salts

Ergosterol



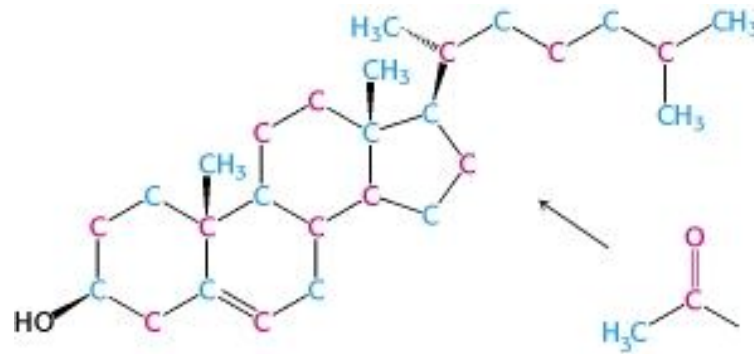
Plant Sterols are Poorly Absorbed by Human

Major sources of liver cholesterol

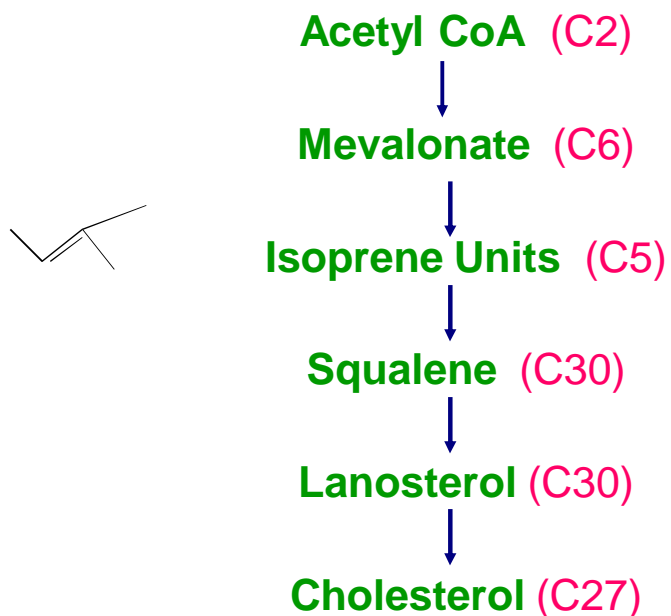


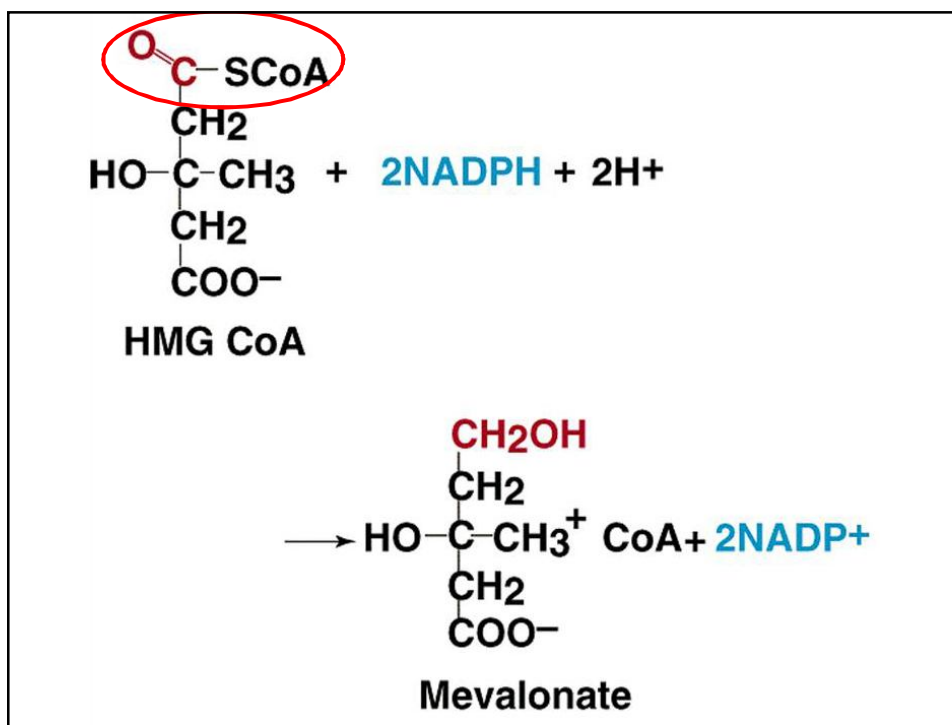
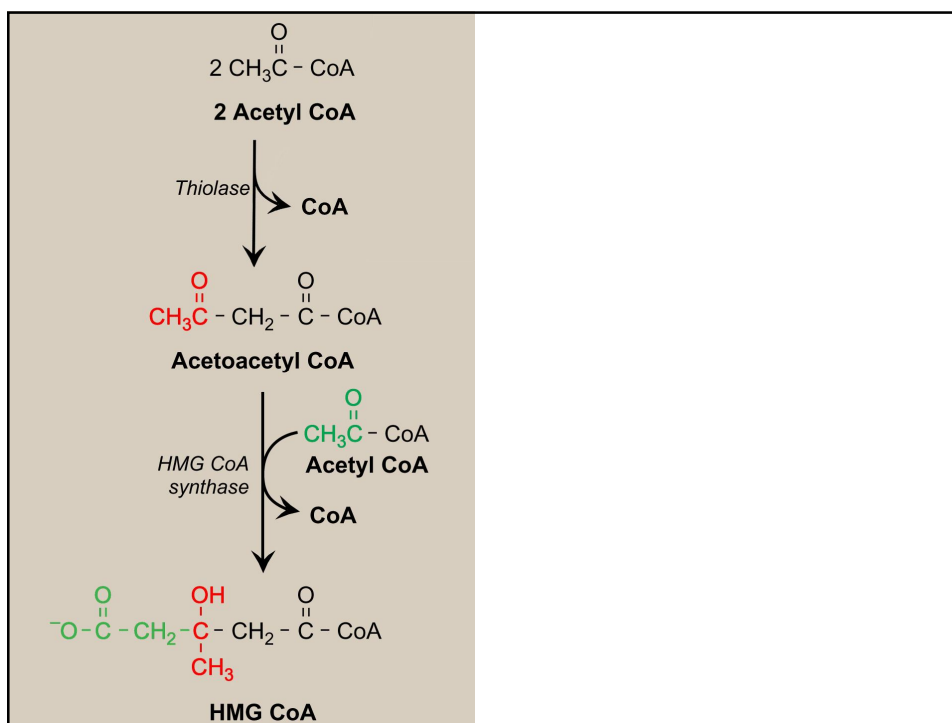
Cholesterol Synthesis Requires

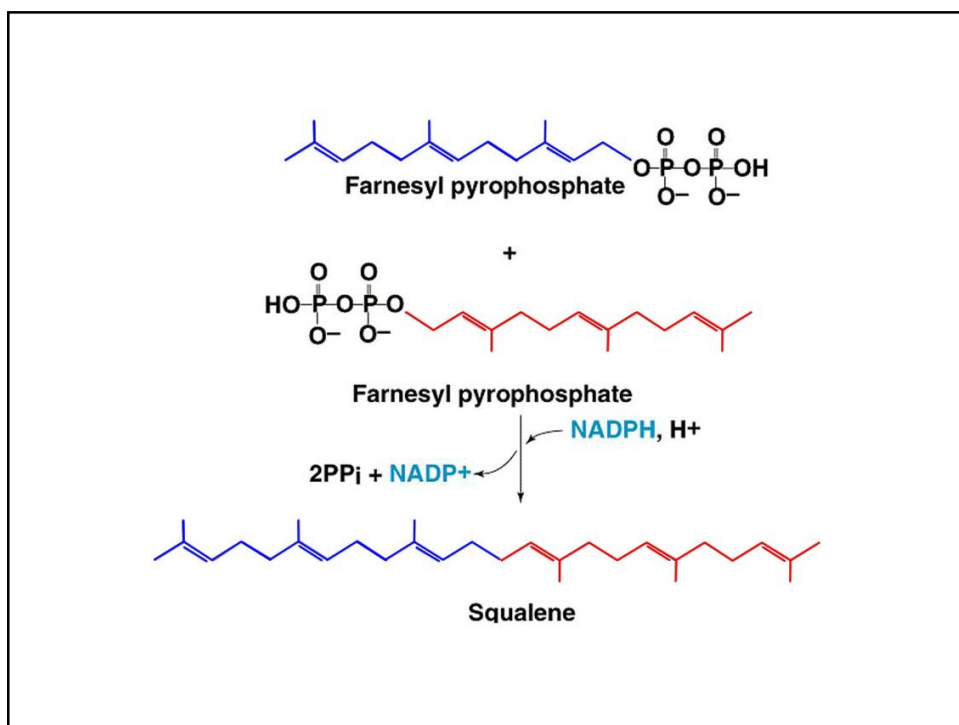
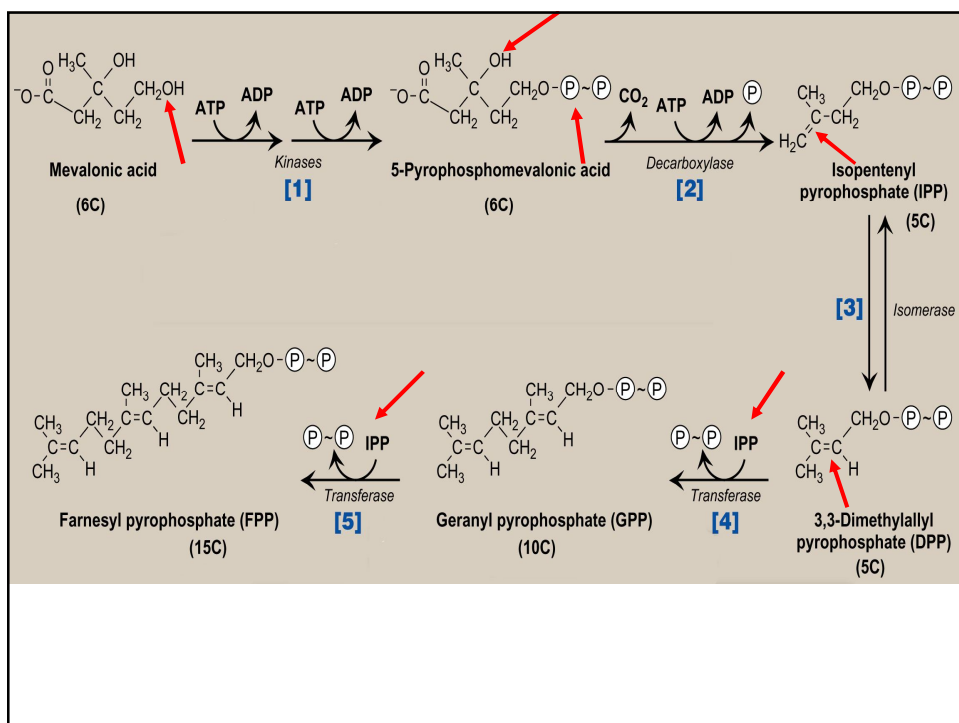
- Carbon Source: Acetyl CoA
- Energy: ATP
- Reducing Power: NADPH
- O_2

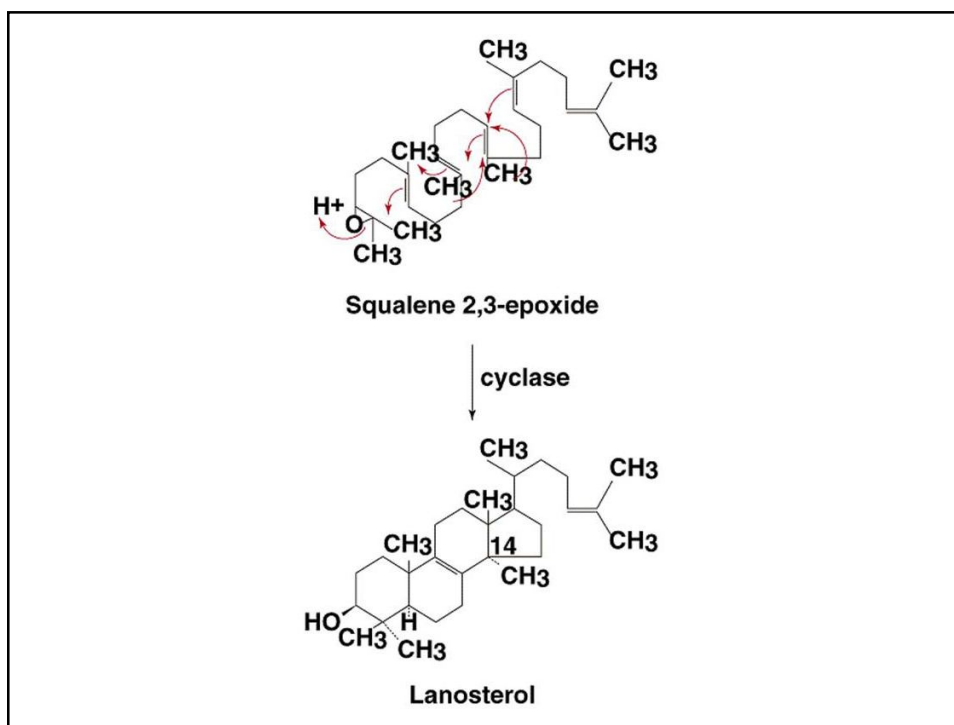
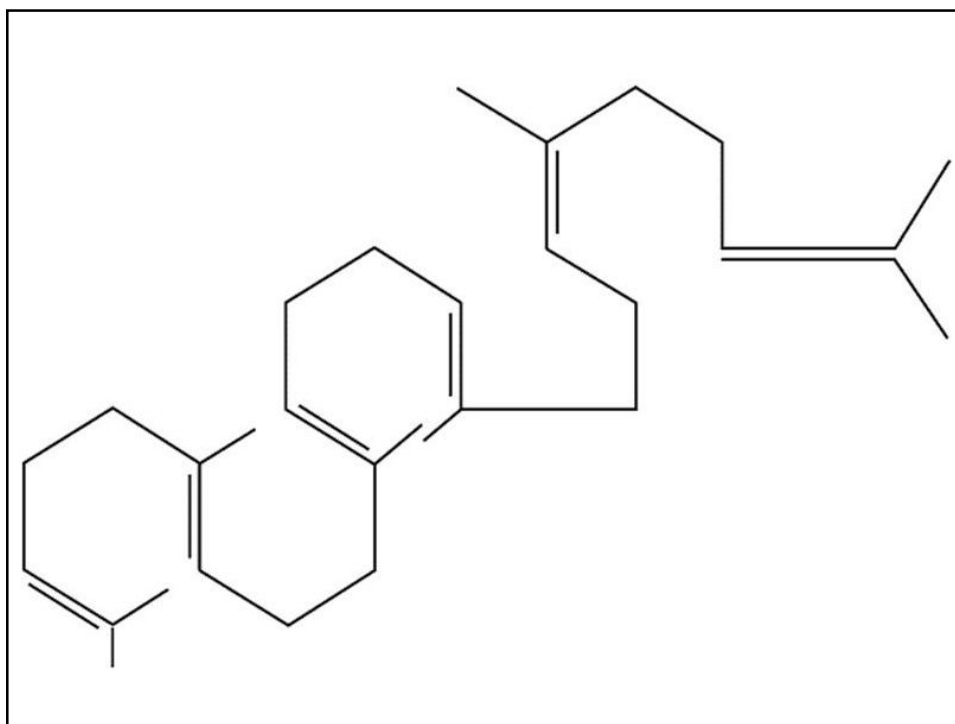


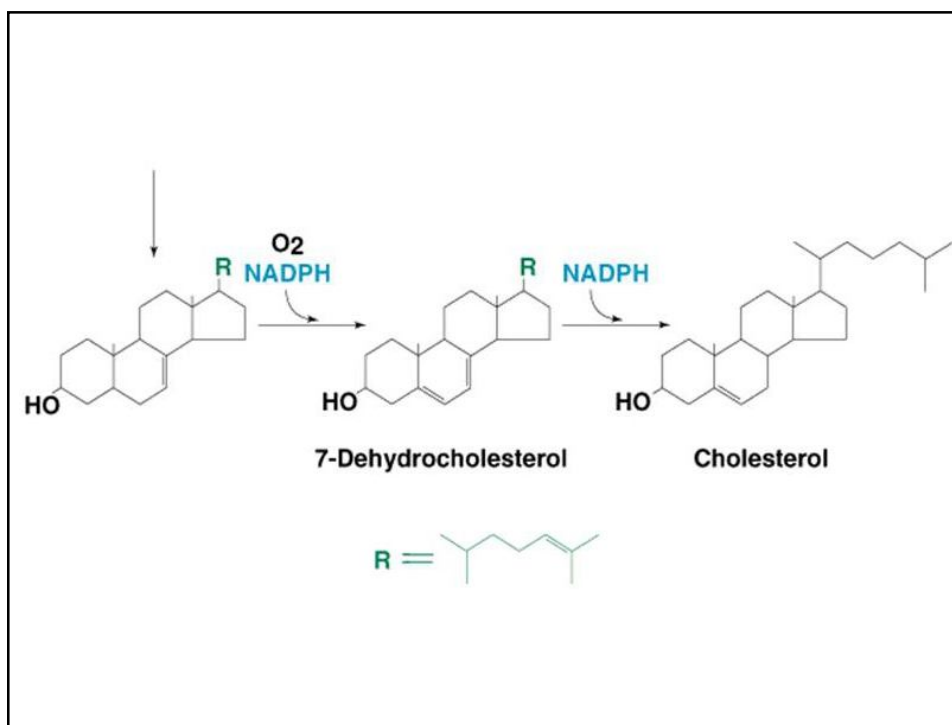
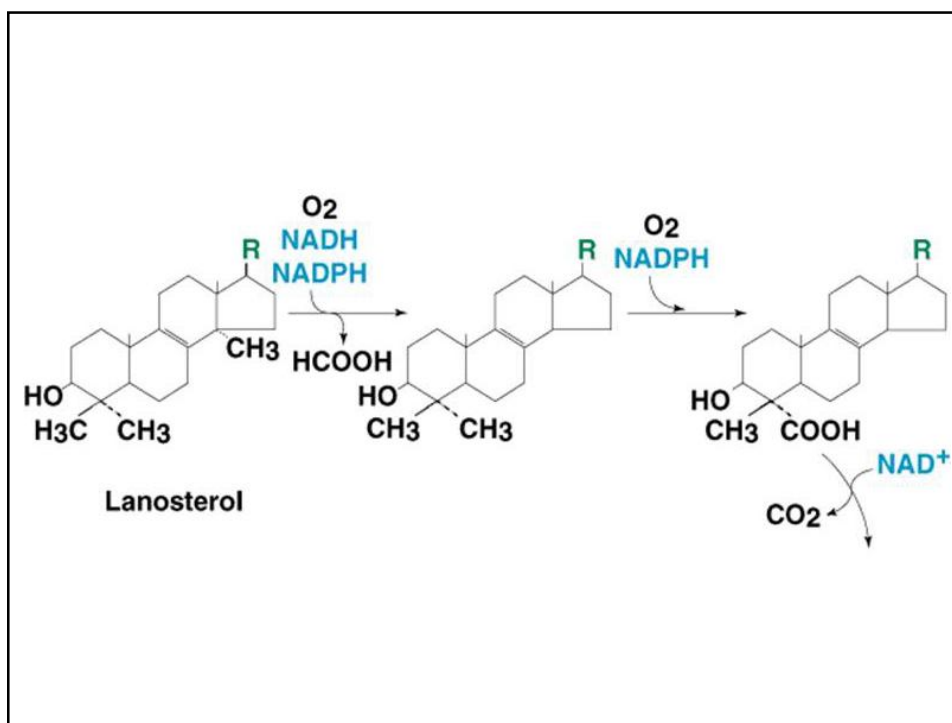
Stages in Cholesterol Synthesis

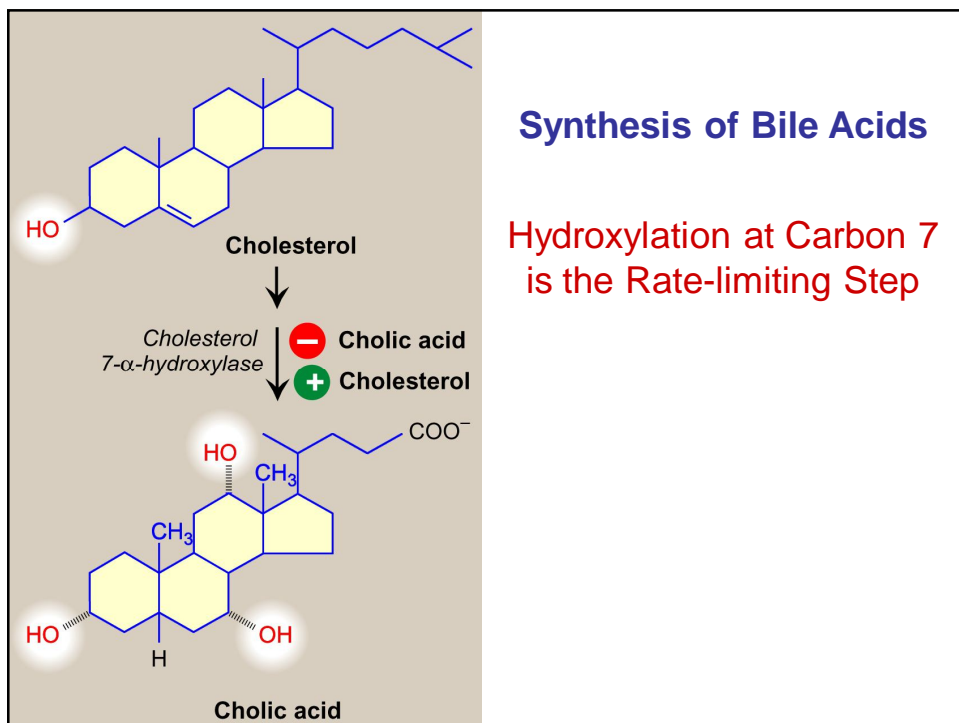
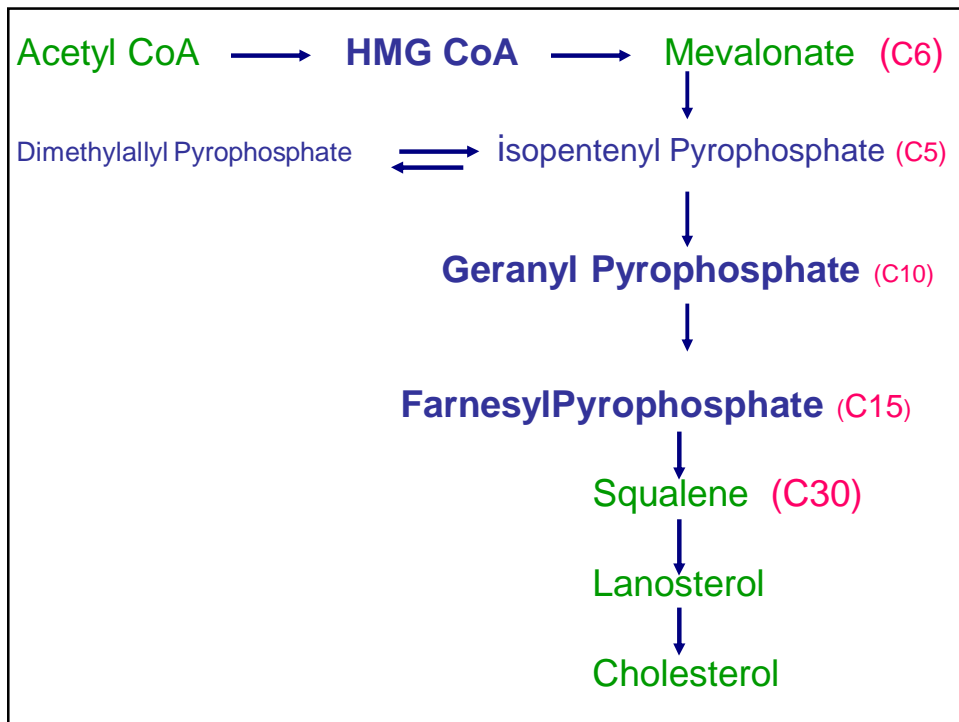


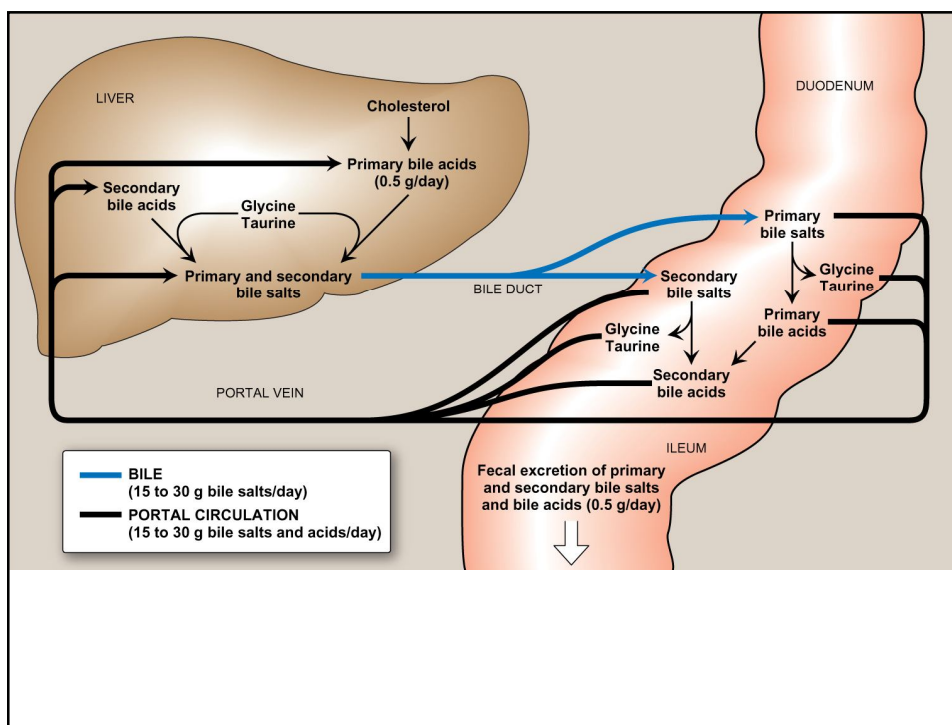
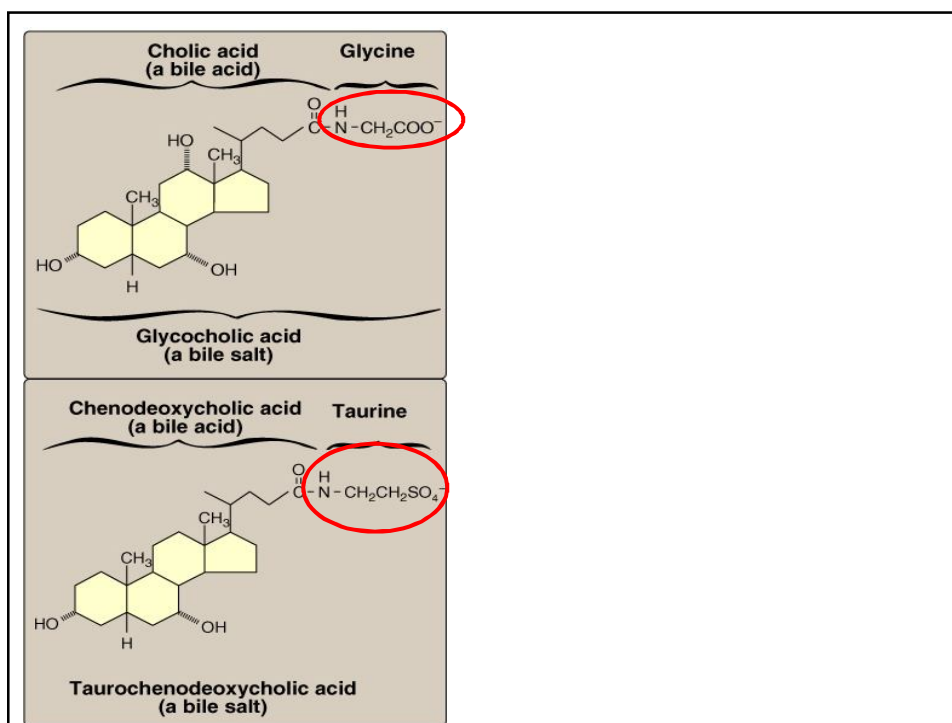






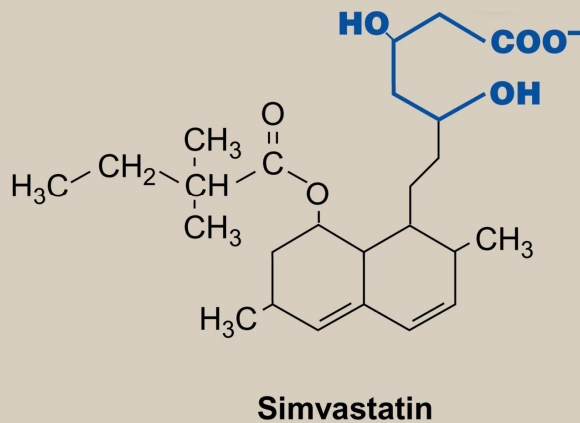
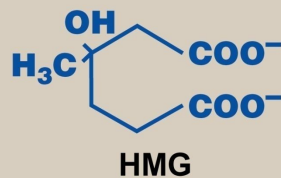






Lowering Cholesterol Level

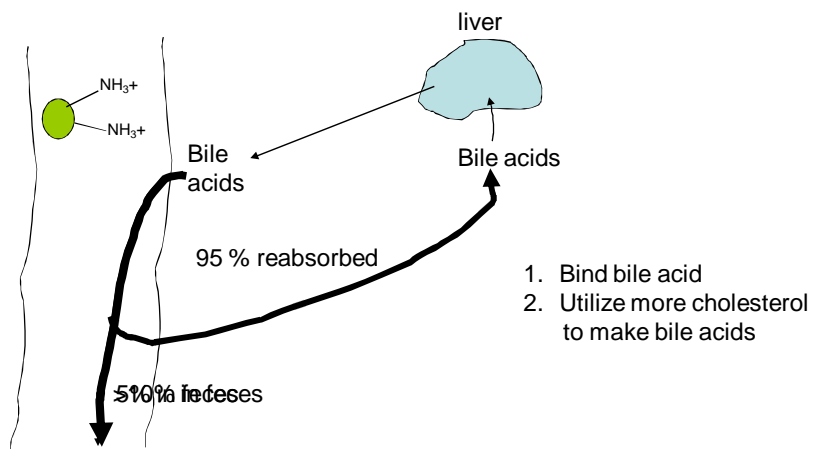
- Dietary
 - ↓ Cholesterol intake
 - ↑ PUSFA / SFA
 - ↑ Fiber
 - Daily Ingestion of Plant Steroid Esters
- Inhibition of Synthesis
- ↓ Enterohepatic Circulation of Bile Acids

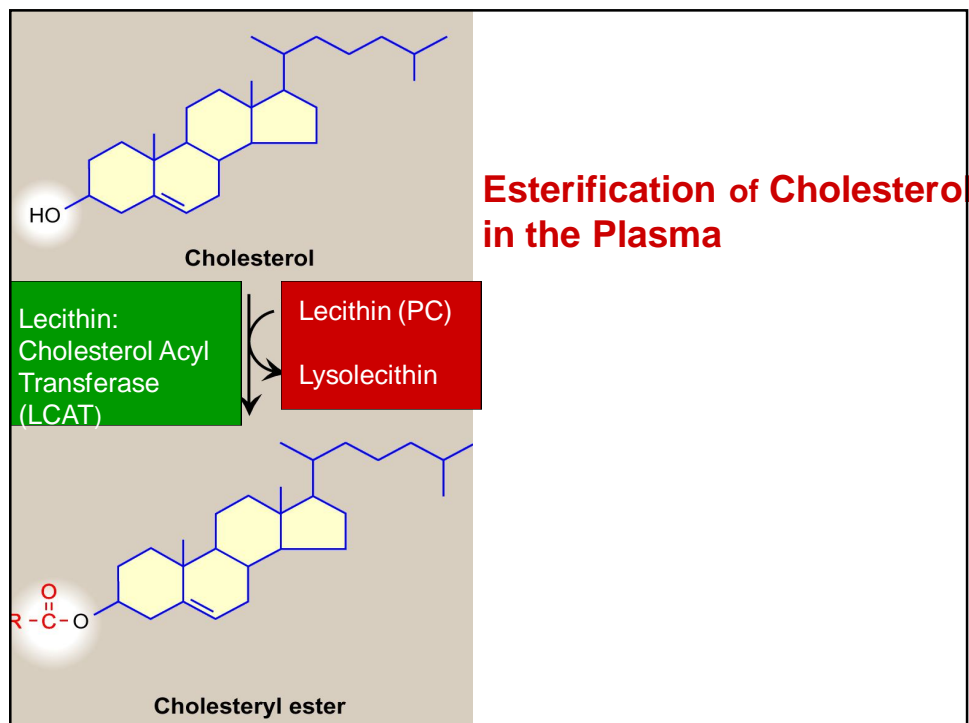
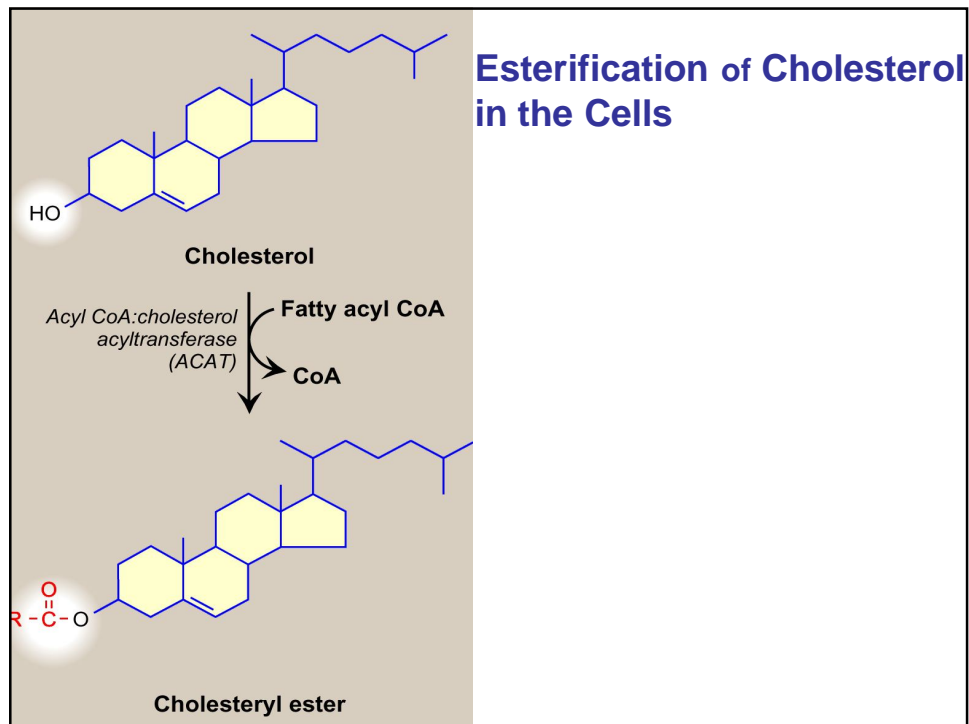




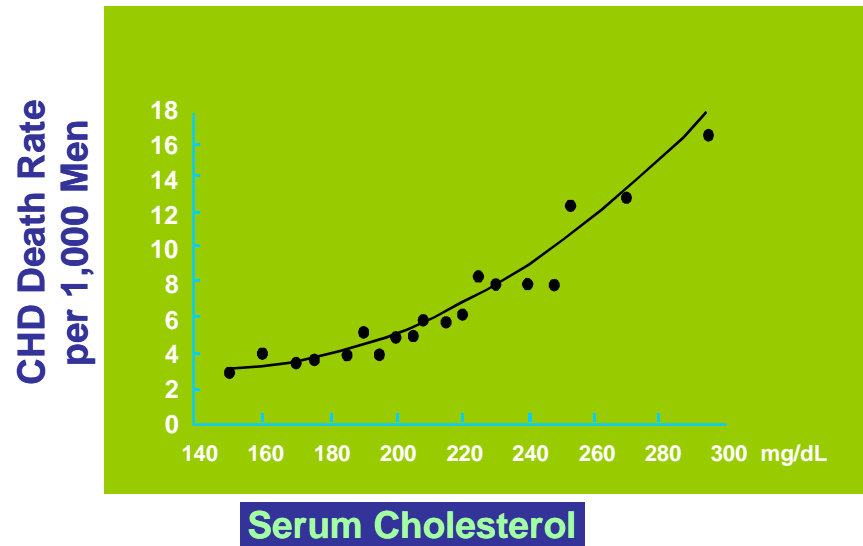
Lowering Cholesterol

- Bile sequestering agents





Serum Cholesterol and CHD



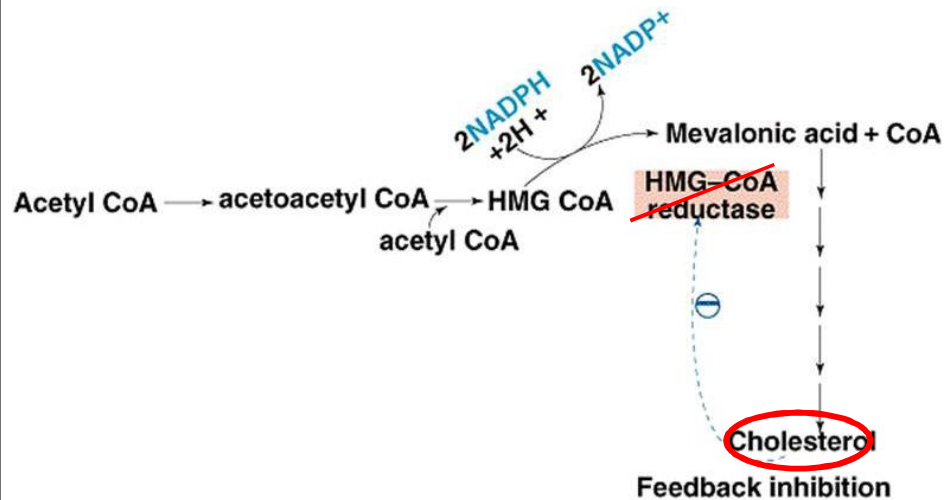
Martin M. Lancet 1986;11:933



Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- Covalent Modification
- Hormonal Regulation
- Proteolytic Regulation

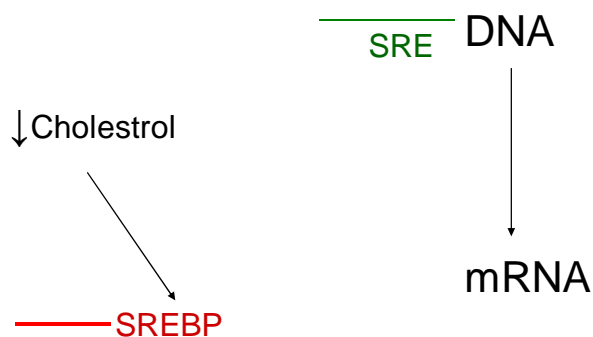
Regulation of Cholesterol Synthesis



Regulation of Cholesterol Synthesis

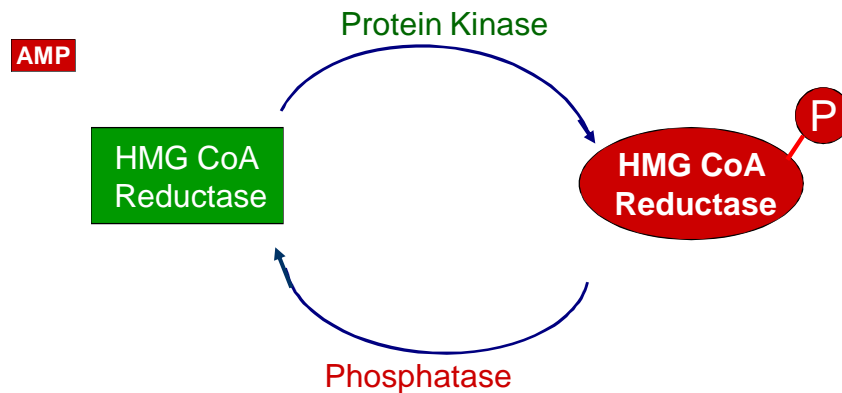
- Regulation of Gene Expression

Expression of the HMG CoA Reductase Gene
Requires a Transcriptional Factor (Protein):



Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- **Covalent Modification**



Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- Covalent Modification

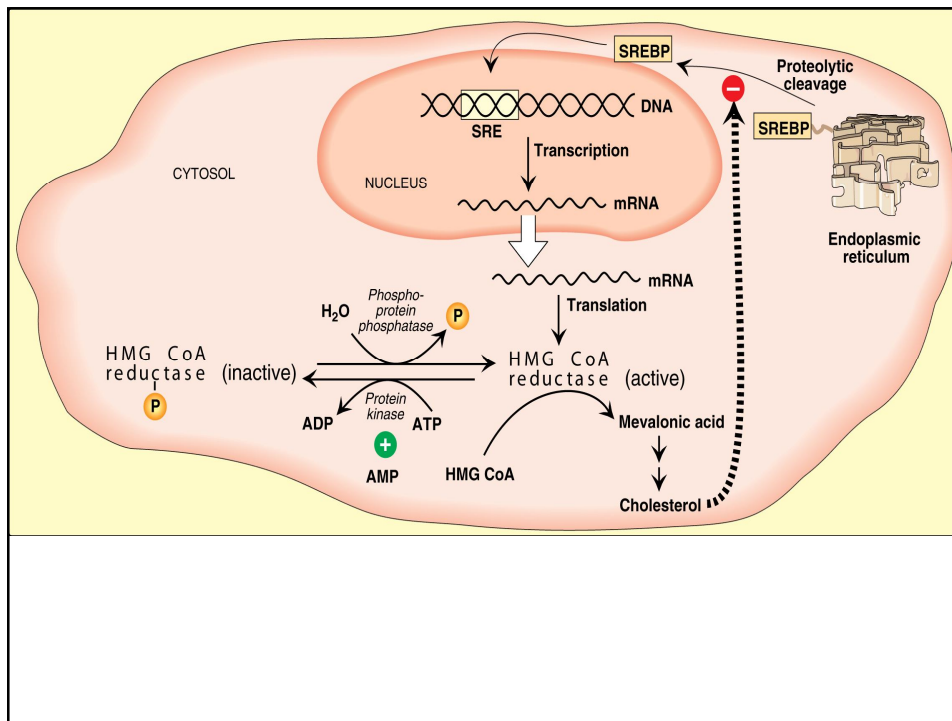
- **Hormonal Regulation**

Glucagon: ↑ Phosphorylated Form

Insulin: ↑ Dephosphorylated Form (↑ Phosphatase)

Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- Covalent Modification
- Hormonal Regulation
- **Proteolytic Regulation**



Transport of Cholesterol in the Blood

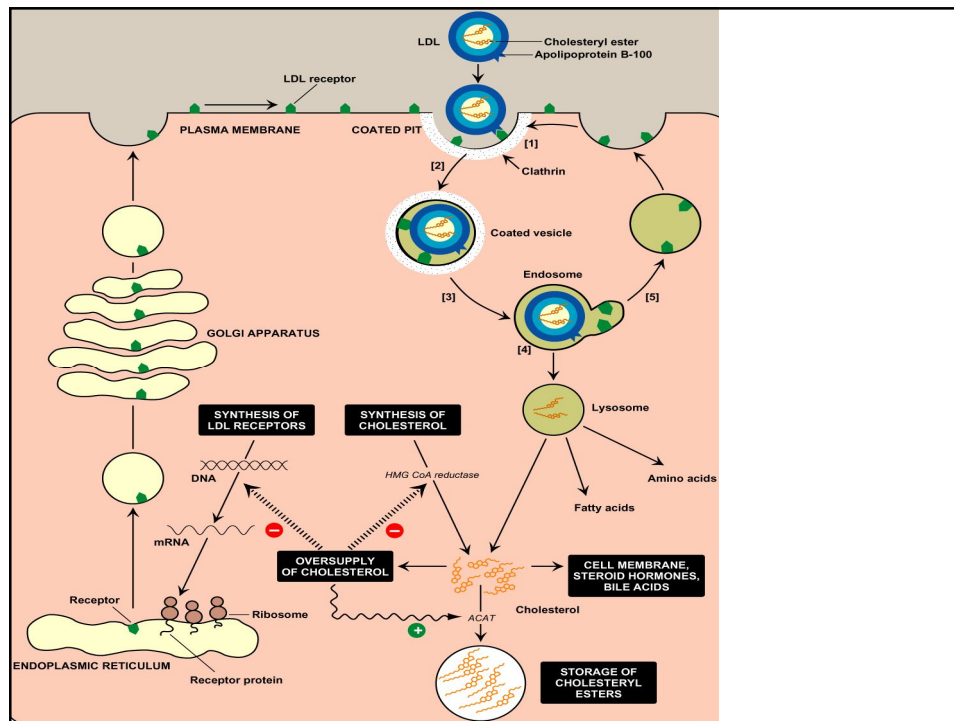
Chylomicrons → remenats

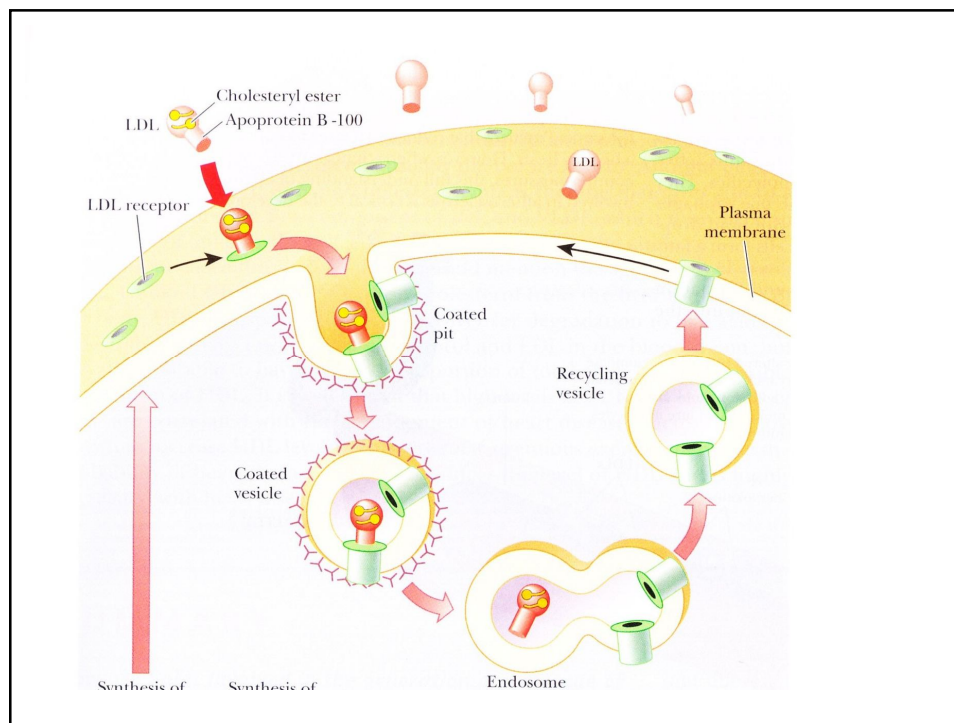
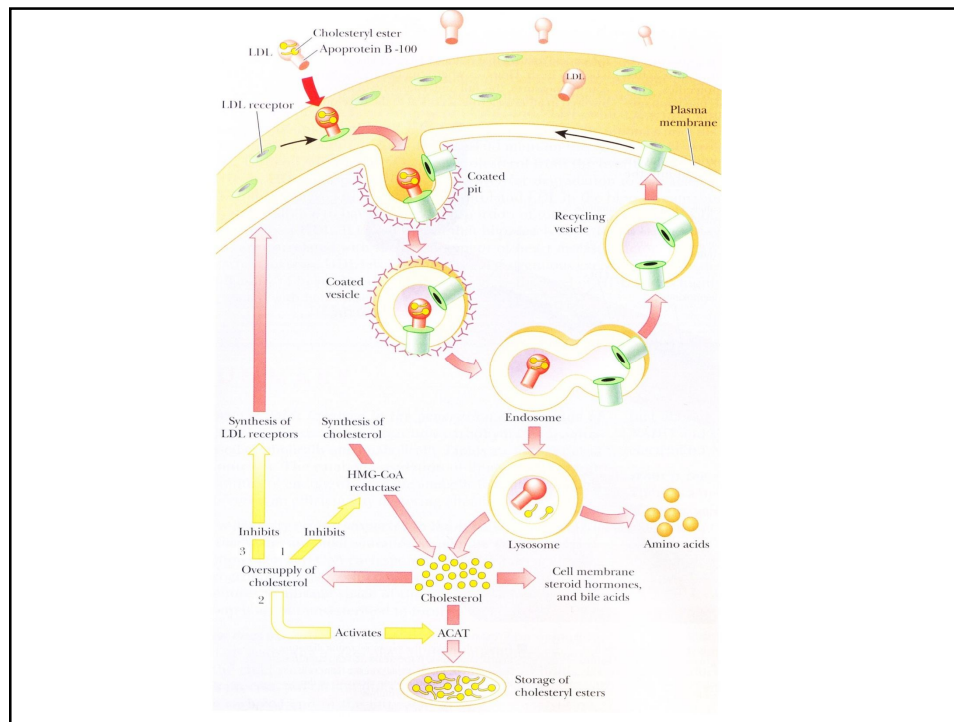
VLDL → IDL → LDL
 ↓ ↓ ↓
 Liver Liver extrahepatic tissues

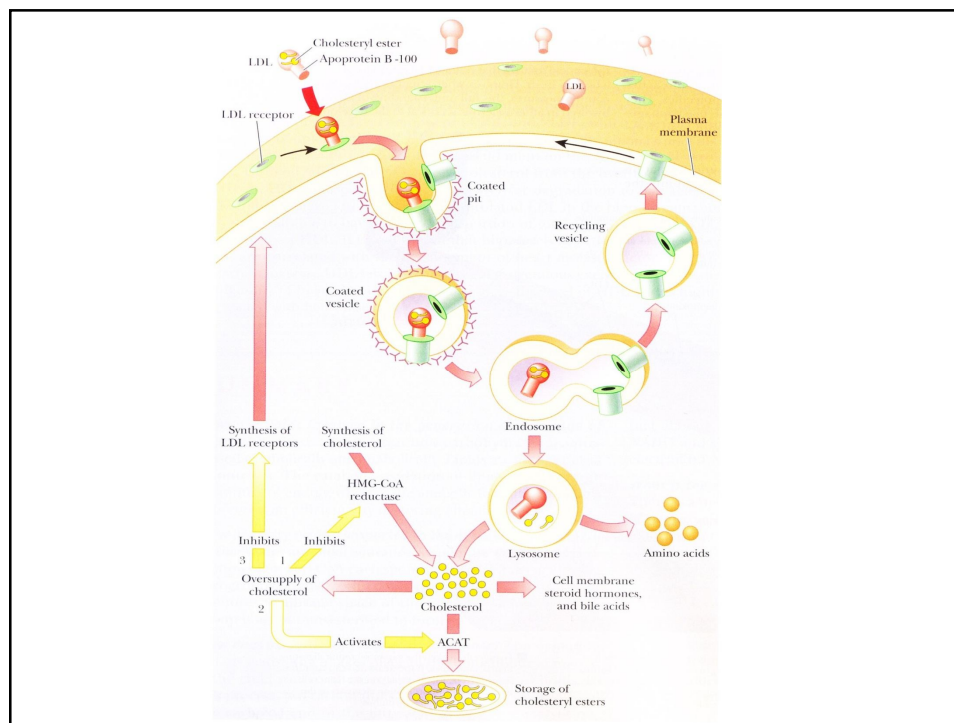
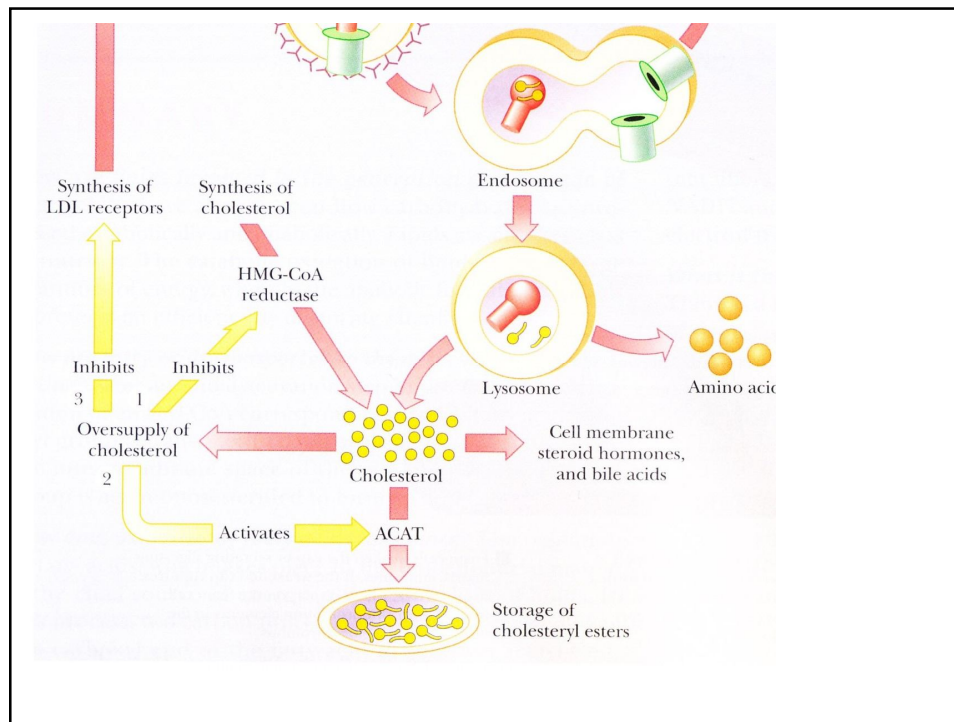
HDL

Importance Vital **or lethal** ?

Risk factor for coronary heart disease.





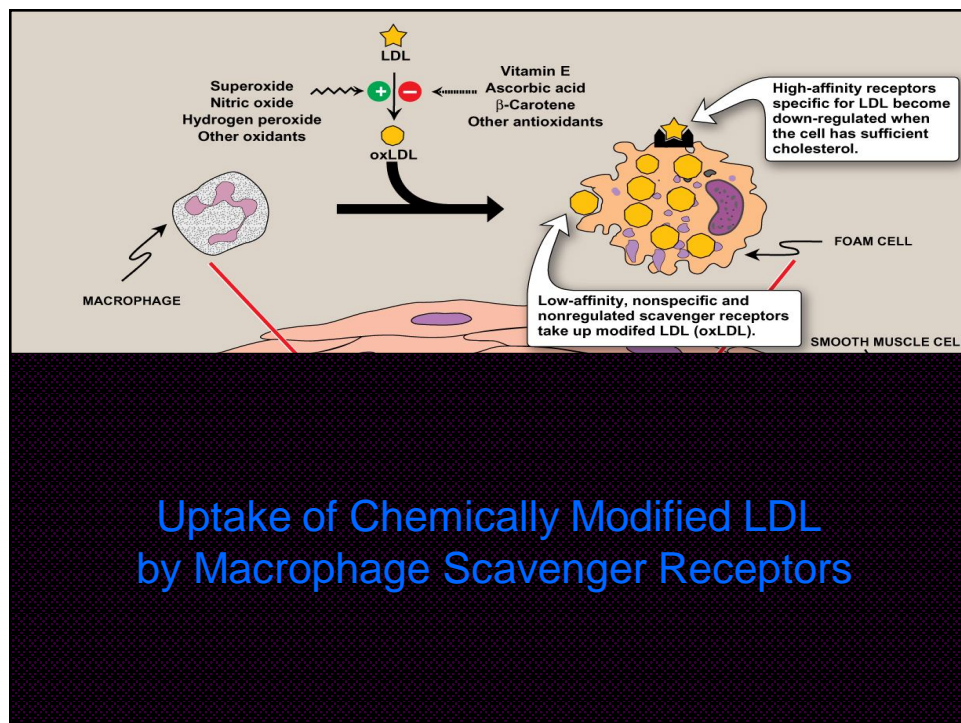
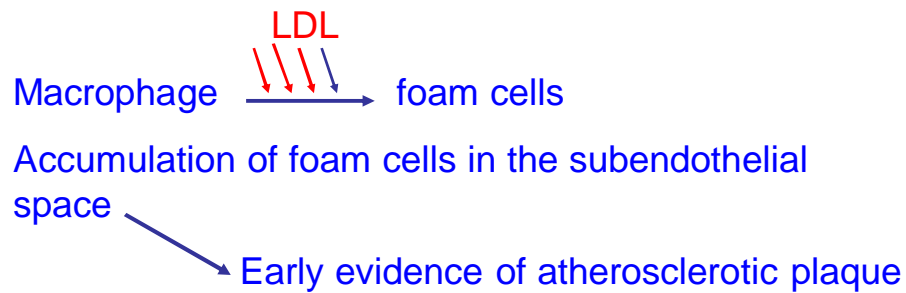


Macrophage Scavenger Receptor

Non specific

modified (damaged) LDL

No down regulation



Modifiable and non-modifiable CAD risk factors

Cigarette smoking	Males > 45 years Females > 55 years
Obesity	Males
Hypertension (blood pressure \geq 140 / 90 mmHg)	Family history of coronary artery disease
Physical inactivity	
Kidney disease	
Diabetes mellitus	
Alcohol consumption	
Stress	
Elevated LDL	
Reduced HDL	

Familial Hypercholesterolemia

Homozygotes 680 mg/dl

Heterozygotes 300 mg/dl

Absence of LDL receptor / Abnormal Receptor

Homozygotes No Receptors

Hetero $\frac{1}{2}$ Normal Number

Accumulation of IDL more IDL \longrightarrow LDL

Cholesterol deposition in tissues

Atherosclerosis Death in childhood