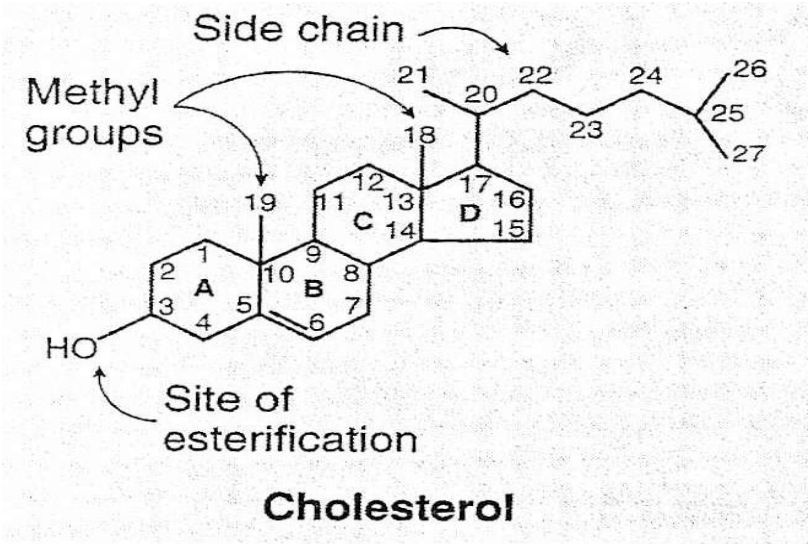

بسم الله الرحمن الرحيم

Cholesterol Synthesis & Metabolism



Dr Nabila Sher
KGMC 2022

BY THE END OF THIS LESSON THE STUDENT WILL BE ABLE TO….

Inform Learner of Objectives

KNOW

- Chemical structure of cholesterol
- Cholesterol biosynthesis
- Derivatives of cholesterol
- Regulation of cholesterol synthesis
- Disorder of cholesterol


KEEP
CALM
AND
ACTIVATE PRIOR
KNOWLEDGE

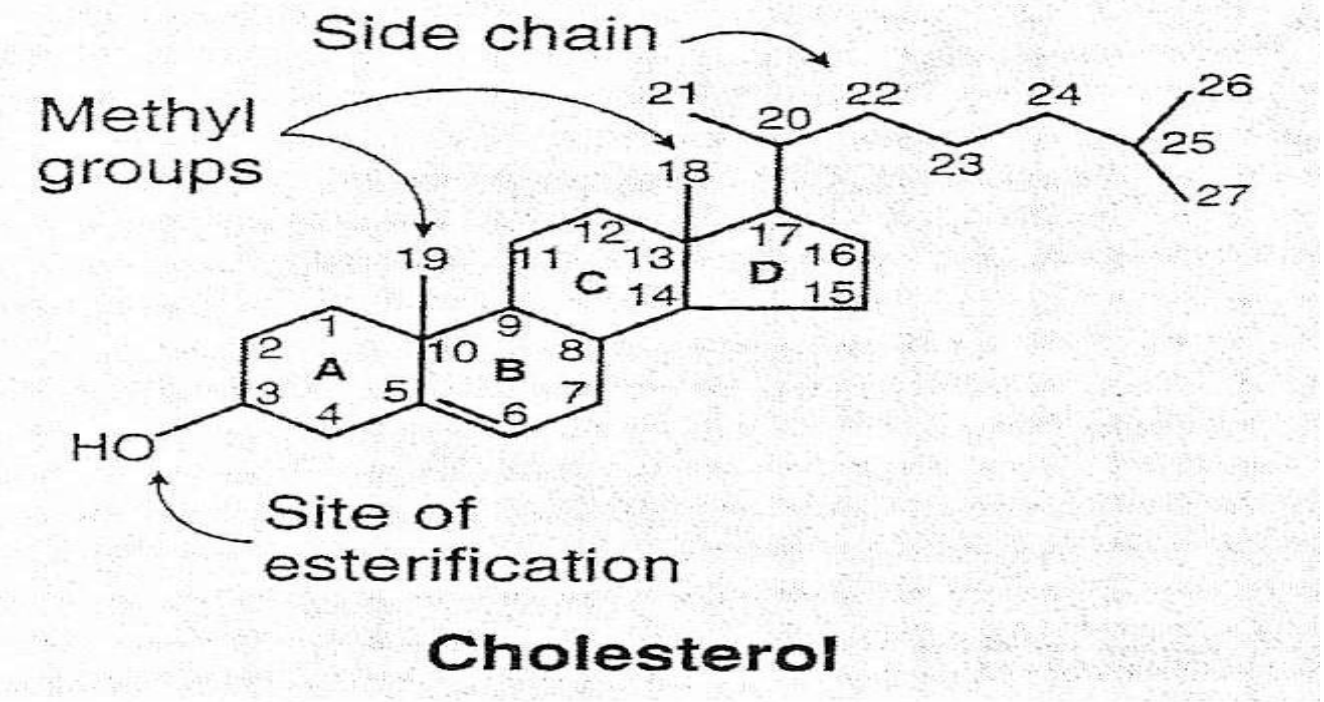
- What is cholesterol
- What is the chemical name of cholesterol
- What is the chemical formula of cholesterol

Cholesterol

cyclopentano-perhydro-phenantrene

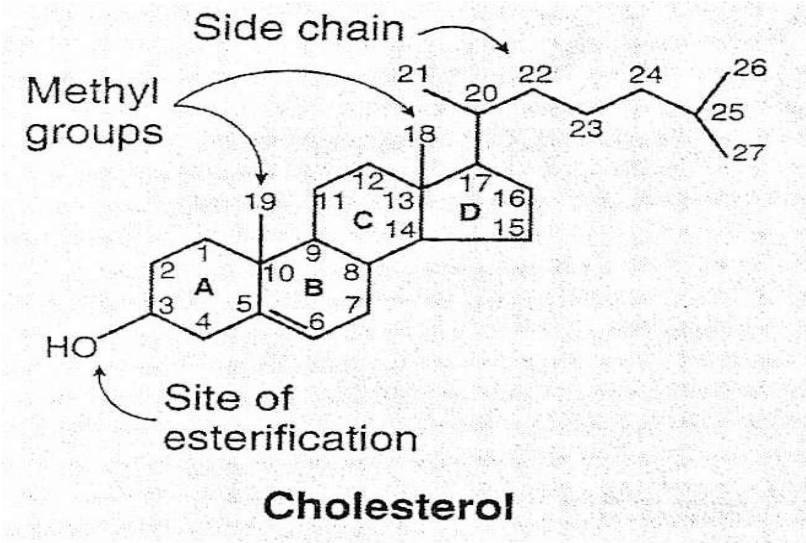
A+B+C= Phenantrene rings

D =Cyclopentane (C27H46O)



Cholesterol(animal sterol)

cyclopentanoperhydrophenantrene



Cholesterol

The most important sterol in human body. Its molecular formula is C27 H45 OH.

Source:

Exogenous:

Dietary cholesterol, approx 0.3 gm/ day. Diet rich in cholesterol are butter, cream, milk, egg yolk, meat, etc. A hen's egg weighing 2 oz gives 250 mg cholesterol.

Endogenous:

Synthesized in the body from acetyl CoA, approximately 1.0 gm/day.

Cholesterol

Occurrence:

It is widely present in body tissues brain and nervous tissue 2%, liver 0.3%, skin 0.3% , intestinal mucosa 0.2% , adrenal cortex 10% or more, corpus luteum is also rich in cholesterol.

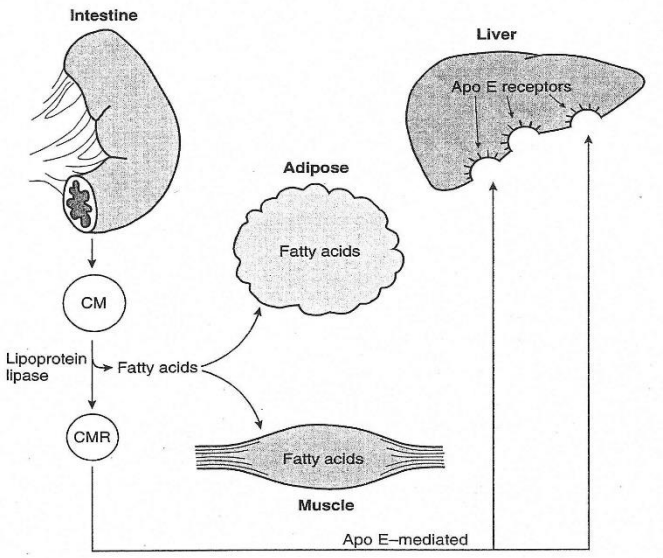
Forms of Cholesterol:

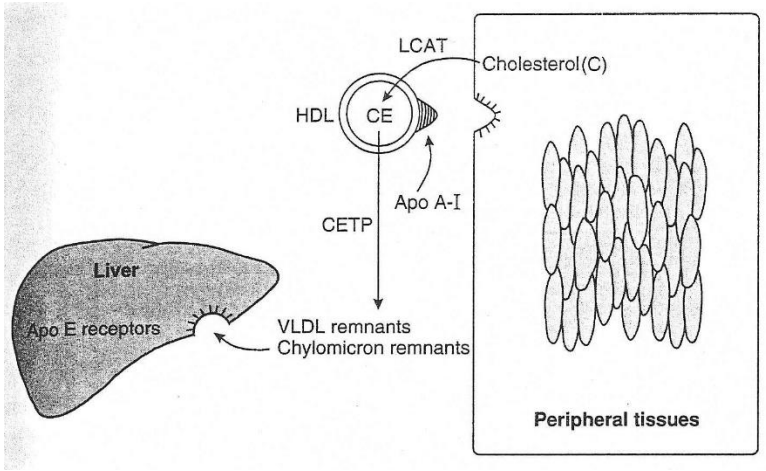
Cholesterol occurs both in free form and in ester form, in which it is esterified with fatty acids at – OH group at C3 position.

Free cholesterol is equally distributed between plasma and red blood cells, brain and nervous tissue.

Sources of hepatic cholesterol

- Dietary cholesterol
  - From chylomicron remnants
- Cholesterol from extra-hepatic tissues
  - Reverse cholesterol transport via HDL
    - Chylomicron remnants
    - IDL
- De novo synthesis





Central Role of the Liver in Cholesterol Balance:
Fate of hepatic cholesterol

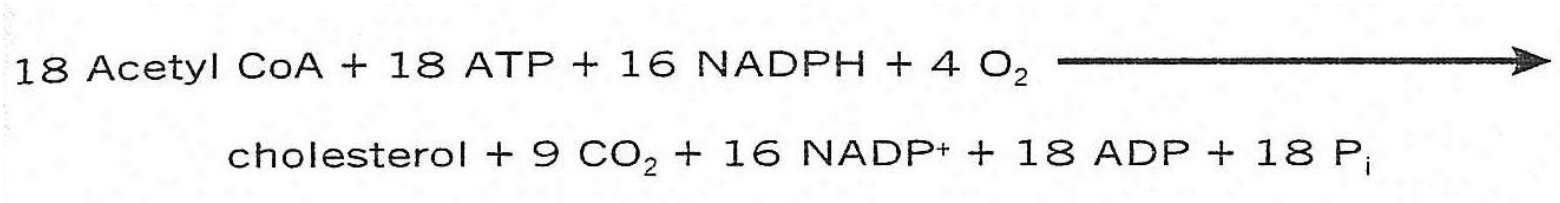
- VLDL , LDL
  - Transport to extra-hepatic tissues
- Direct excretion into bile
  - Gallstones commonly are precipitates of cholesterol
    - Occurs when bile becomes supersaturated with cholesterol
      - Obesity, biliary stasis
- Bile acid synthesis and excretion into bile

Cholesterol Biosynthesis

- Cholesterol (sterol) present in our body about 2g/kg, 1g is synthesized/day in adults.
- Amphipathic in nature.
- All the tissues participate in cholesterol biosynthesis 50% in liver, 15% in intestine, the rest in skin, adrenal cortex and reproductive tissues etc.
- The enzymes involved are found in cytosol and microsomal fraction of the cells.

De novo Synthesis of Cholesterol

- Primary site: liver (~1g/d)
  - Secondary sites: adrenal cortex, ovaries, testes
- Overall equation:



Cholesterol biosynthesis

Location of pathway

1. The pathway is located in the cytosol, beginning with acetyl-CoA.
2. Most cells can make cholesterol, but liver is most active.

Cholesterol biosynthesis

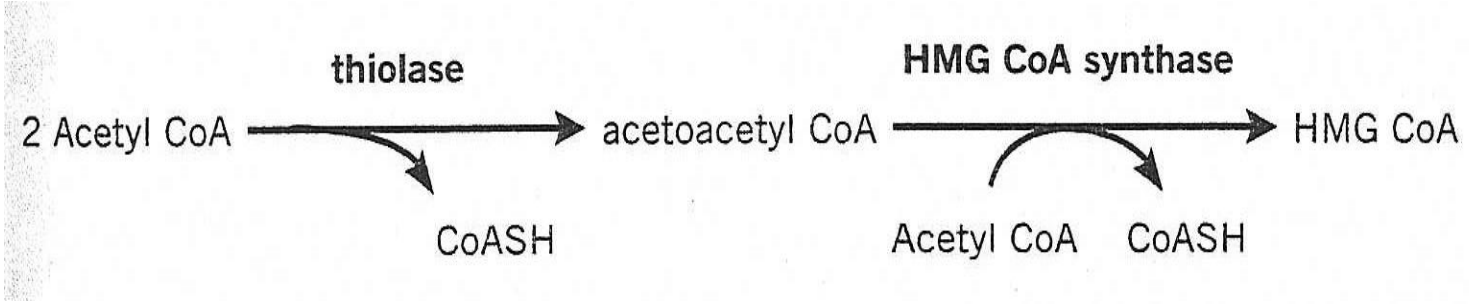
Five stages (summary)

1. Formation of HMG CoA
2. Formation of mevalonate (6C)
3. Conversion of mevalonate into activated isoprene(5C)
4. Polymerization of six 5-carbon isoprene units (30 carbons) to form squalene
5. Cyclization of squalene to create the steroid nucleus Cholesterol(27C)

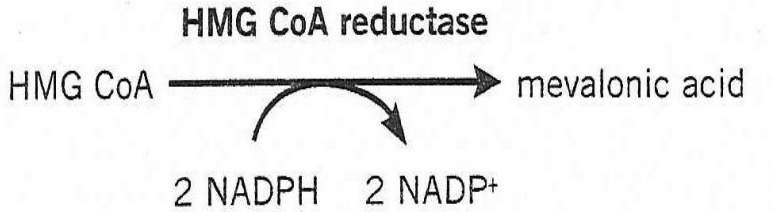
De novo Synthesis of Cholesterol

1.Formation of β Hydroxy β Methylglutaryl CoA

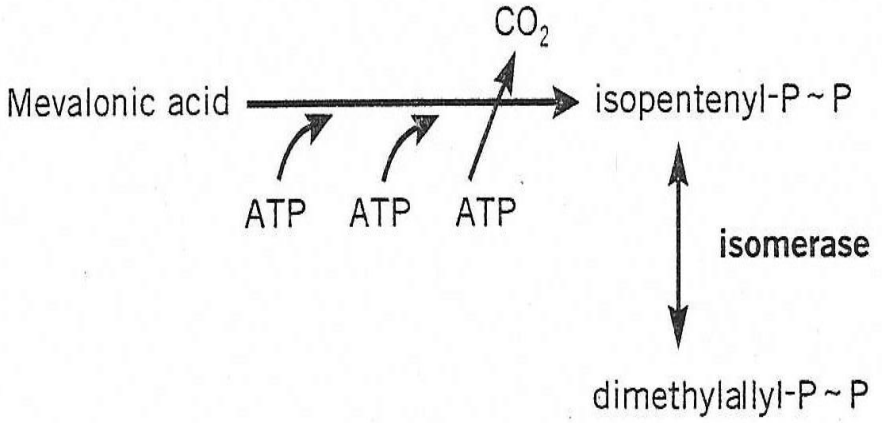
– Analogous to KB synthesis (mito)



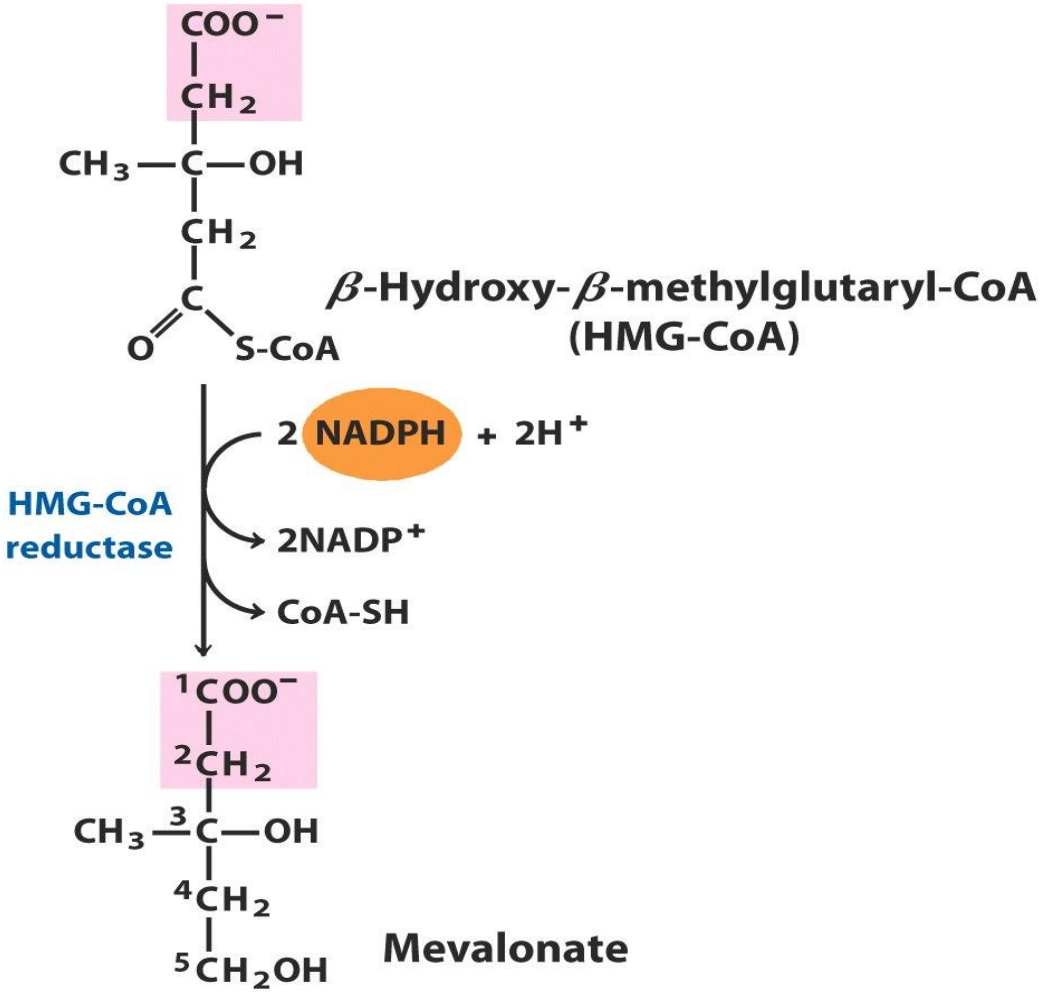
2.Formation of mevalonic acid.



3.Conversion of mevalonic acid to activated isoprenoids



HMG-CoA Reductase



Key control step in cholesterol biosynthesis

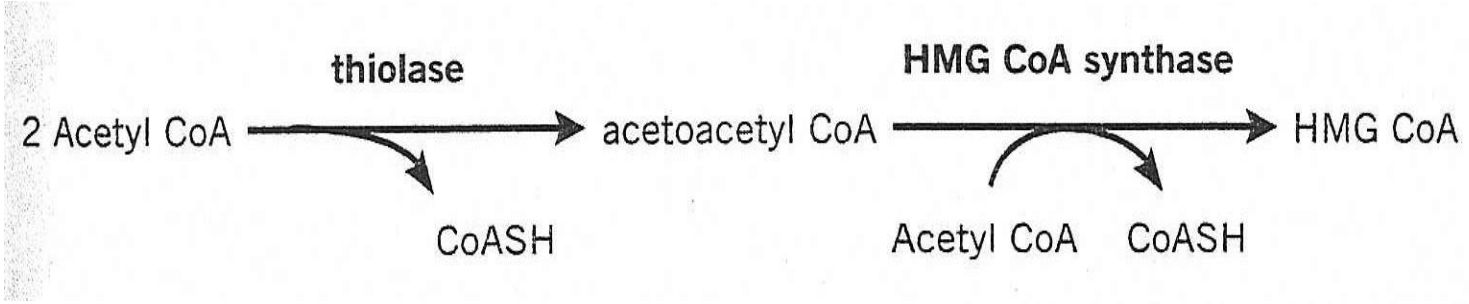
HMG-CoA reductase

1. Integral membrane protein in the ER
2. Carries out an irreversible reaction
3. Is an important regulatory enzyme in cholesterol synthesis

De novo Synthesis of Cholesterol

1.Formation of β Hydroxy β Methylglutaryl CoA

– Analogous to KB synthesis (mito)



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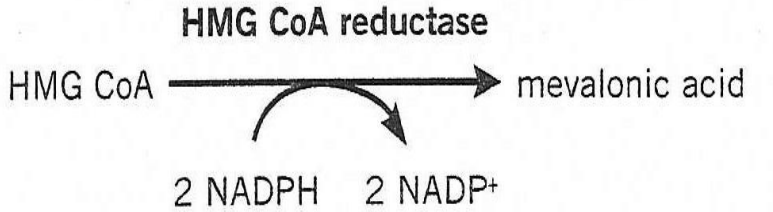

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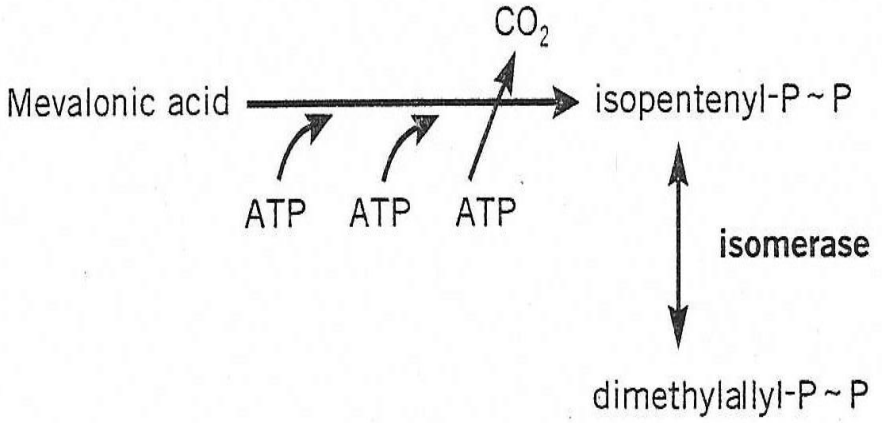
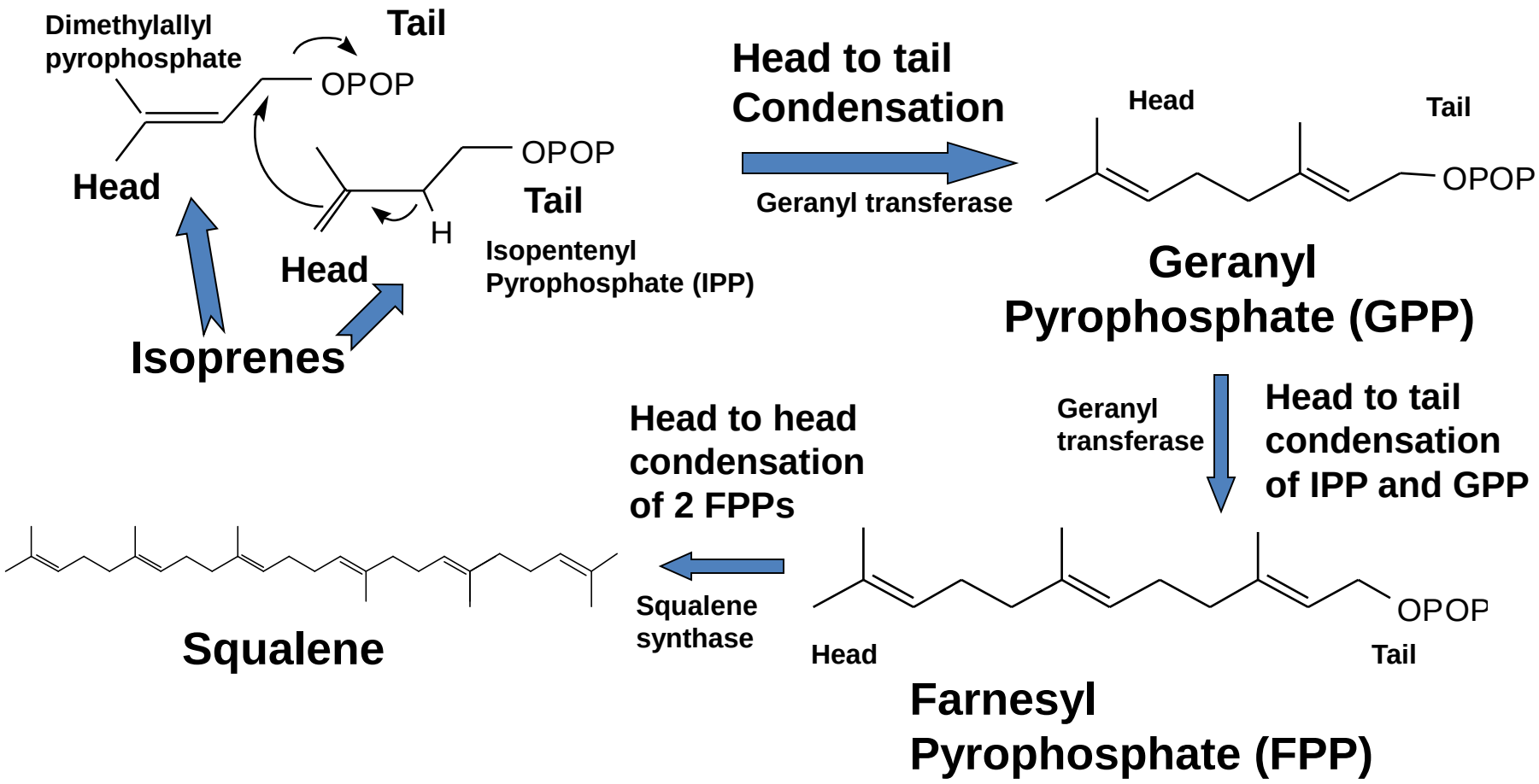
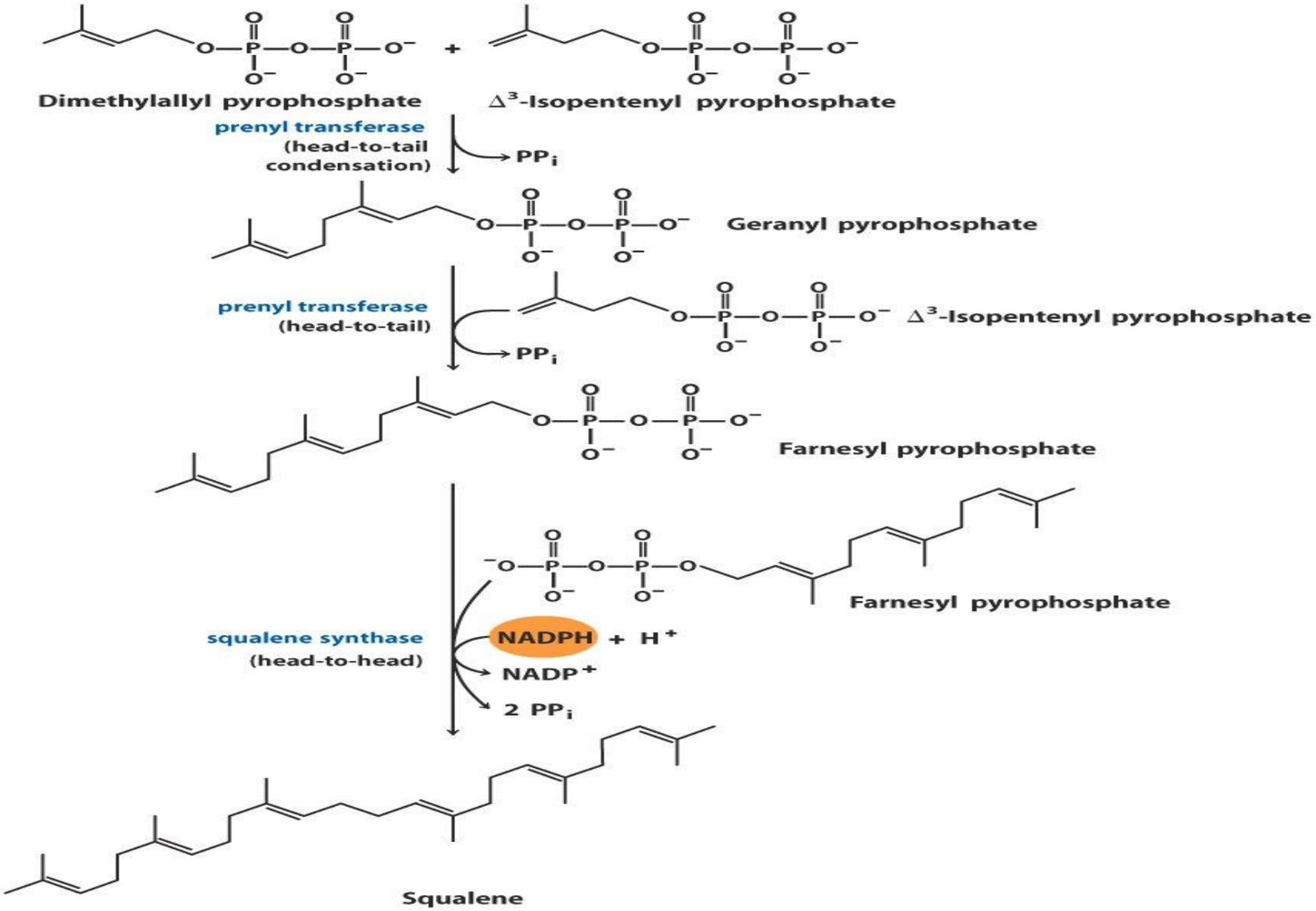


Cholesterol Biosynthesis: 4-Isoprenoid Condensation



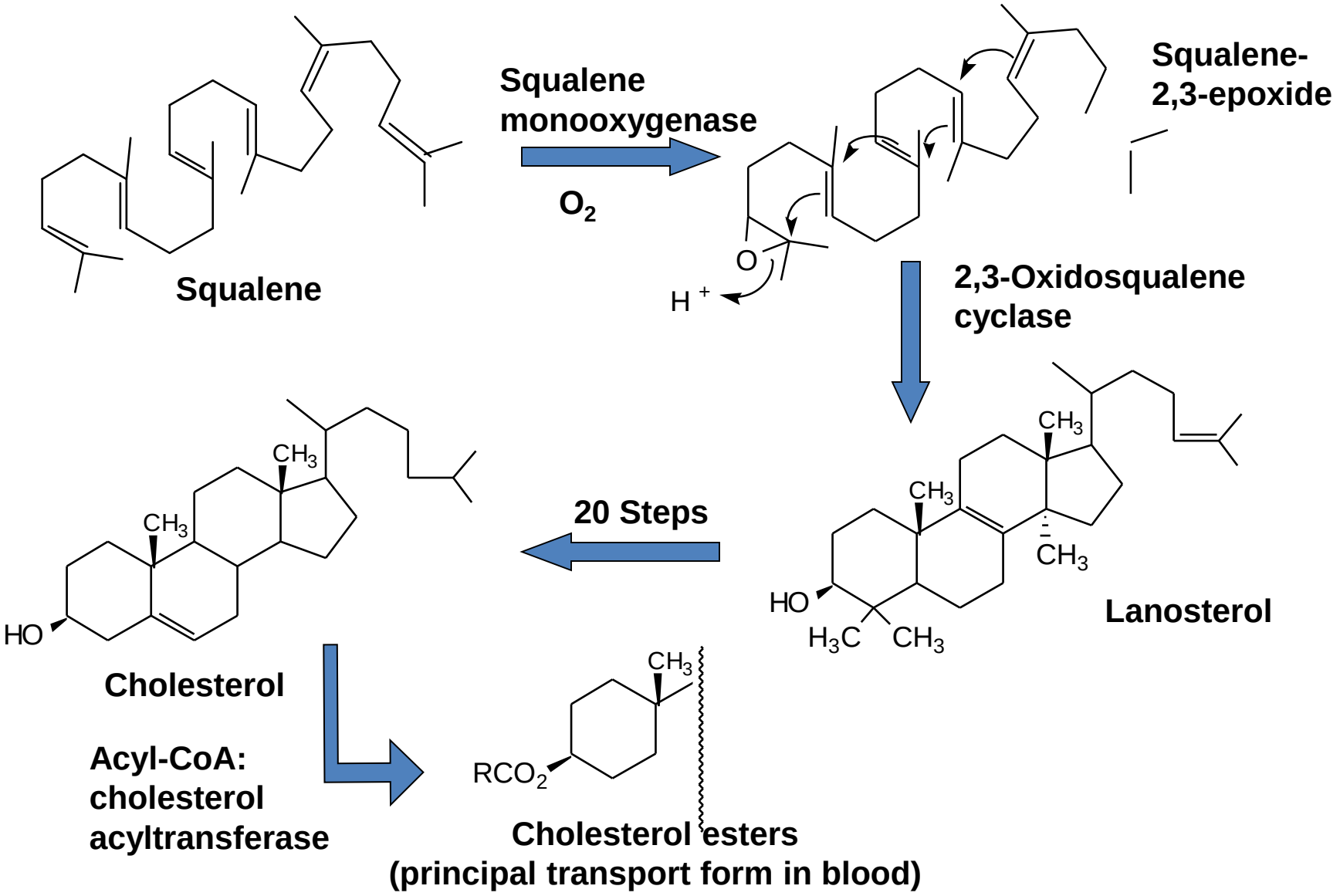
Cholesterol Synthesis: Stage 3



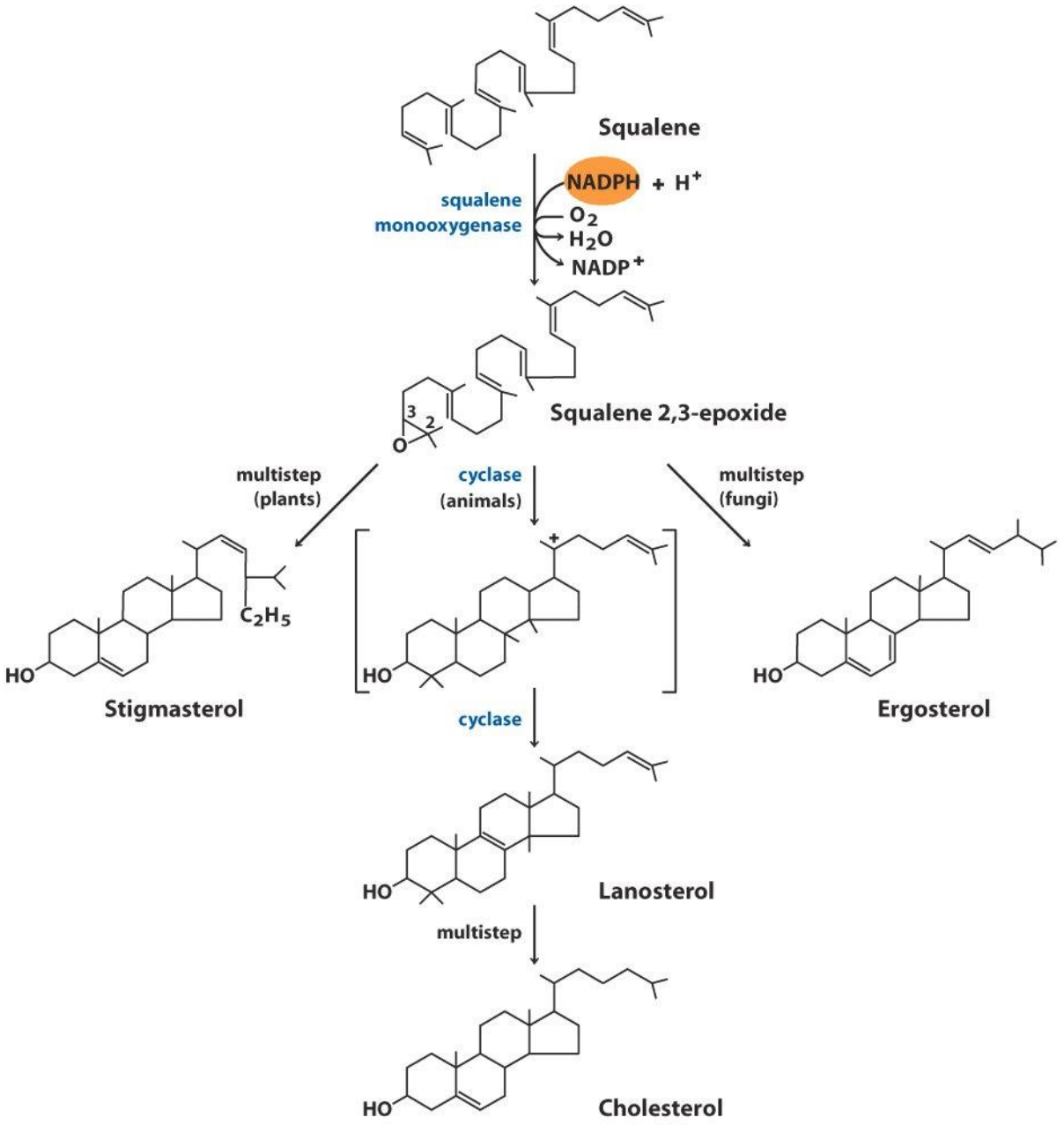
Conversion of squalene to cholesterol

- Squalene.....hydroxylation & cyclization..... Using O2 & NADPH..... Lanosterol.
- Lanosterol..... Cholesterol by 20 rxn.
- Reducing C atoms 30-27.
- By removal of methyl groups from C4 & C14.
- Shift of double bonds from 8-5C.

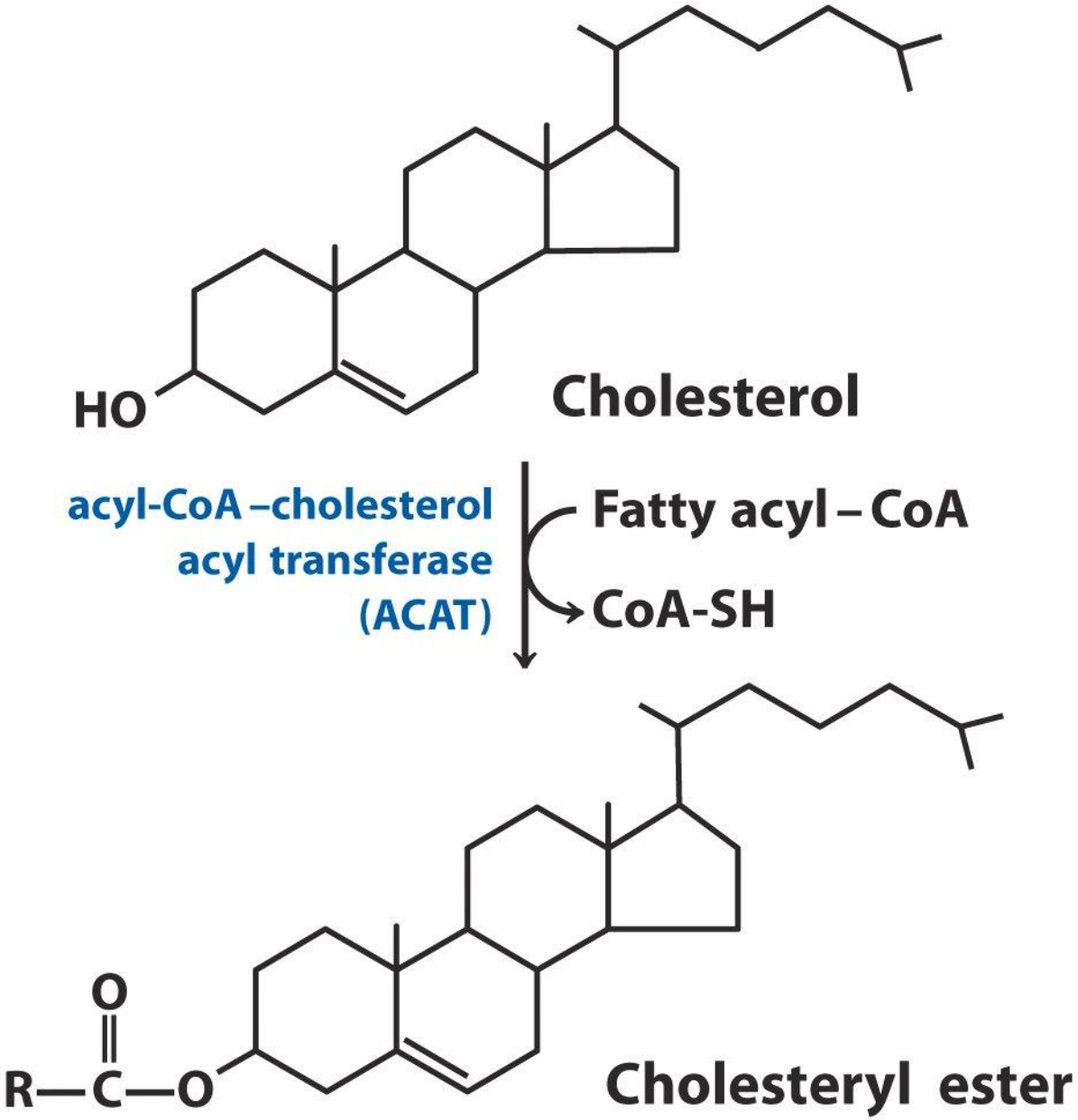
Conversion of Squalene to Cholesterol



Cholesterol Synthesis: Stage 5



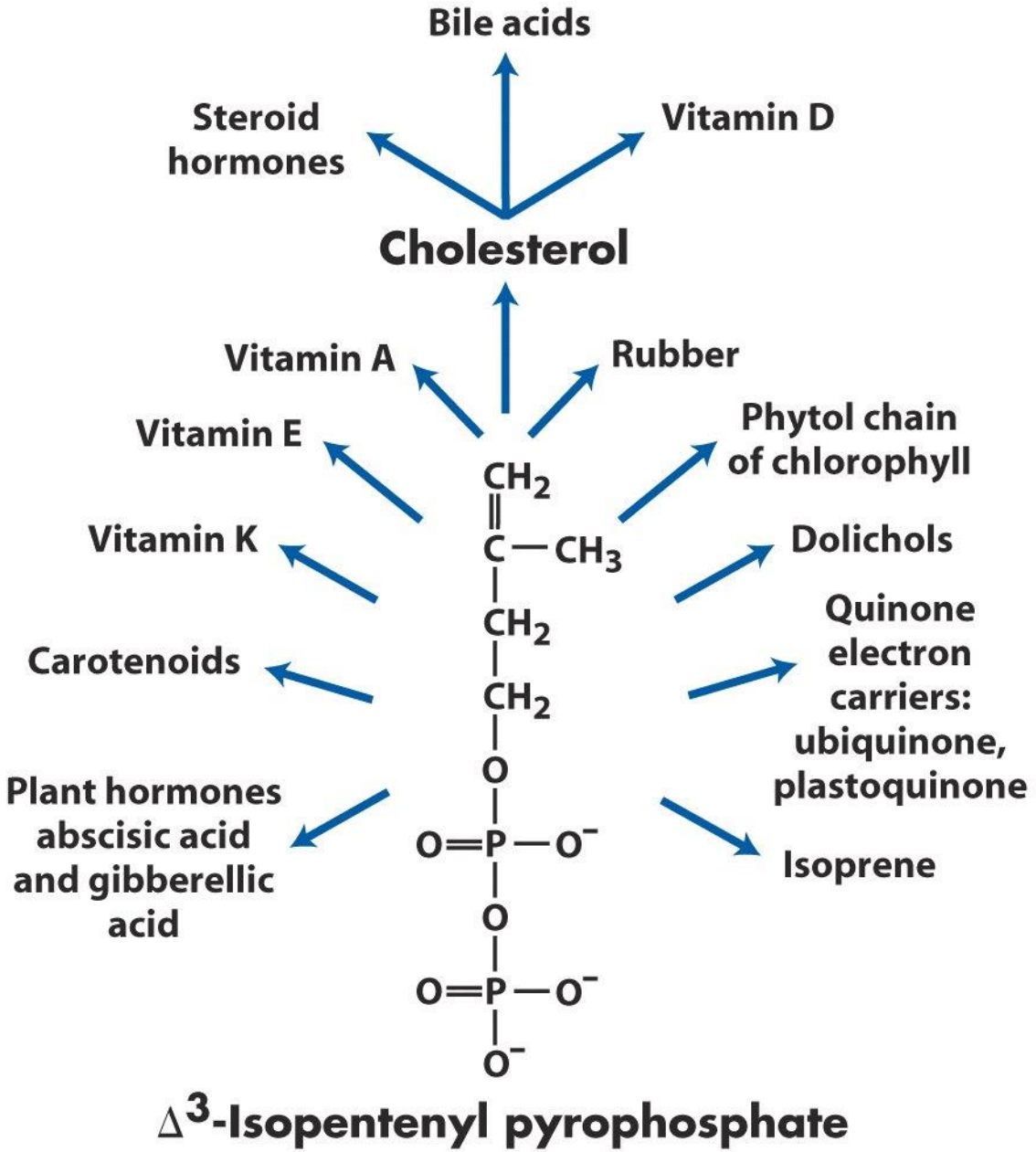
Synthesis of Cholesterol Esters



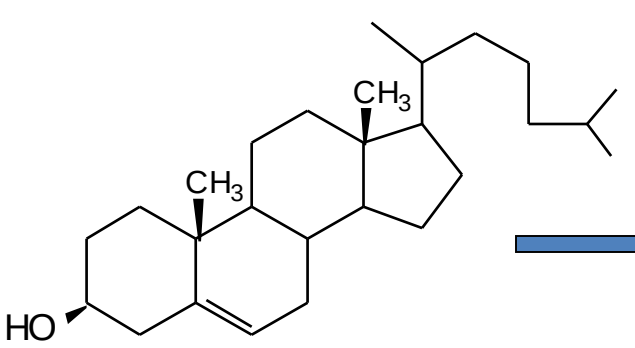
Export of Cholesterol Synthesized in Liver

- Secreted into the small intestine via the bile fluid.
- Conversion to bile acids followed by secretion into the small intestine in the bile fluid. (Bile acids function to emulsify dietary lipid.)
- Conversion to cholesterol esters, packaging into lipoproteins and export into the blood.

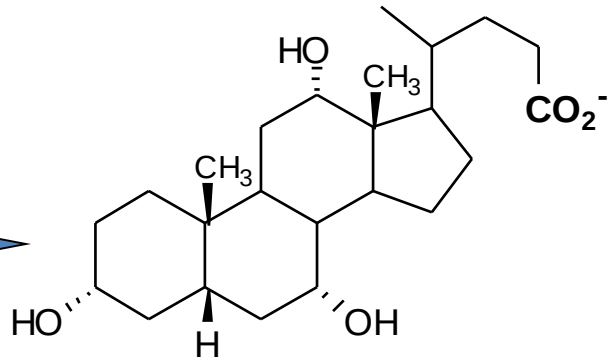
Natural Products Derived from Activated Isoprene Units



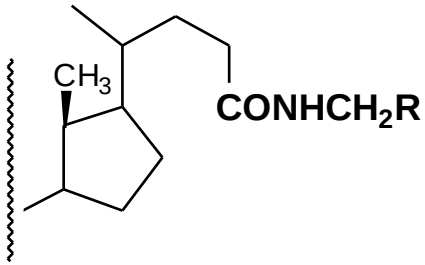
Transformations of Cholesterol: Bile Salts



Cholesterol



Cholic acid

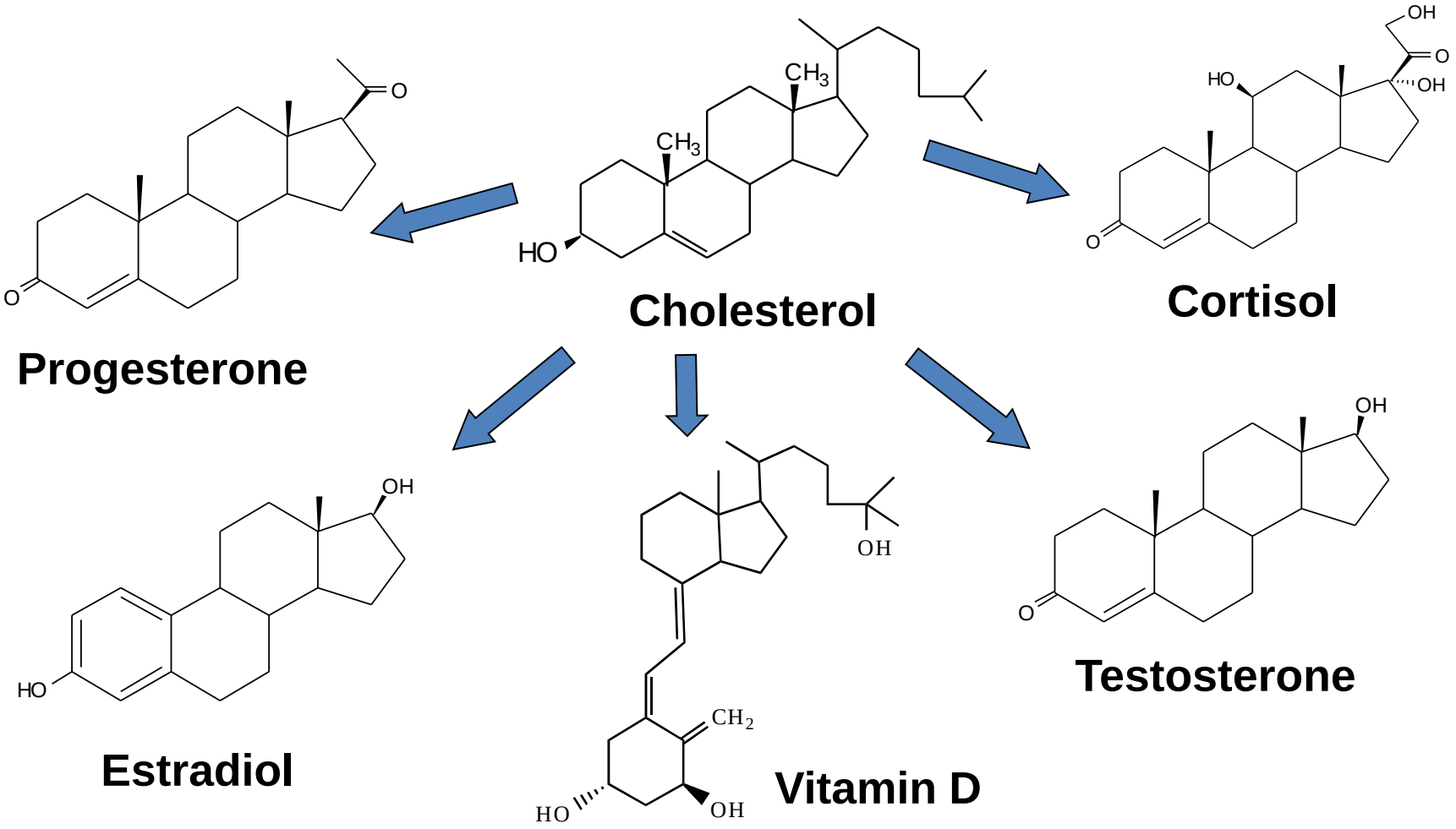


R = $CH_2SO_3^-$ Taurocholate

R = CO_2^- Glycocholate

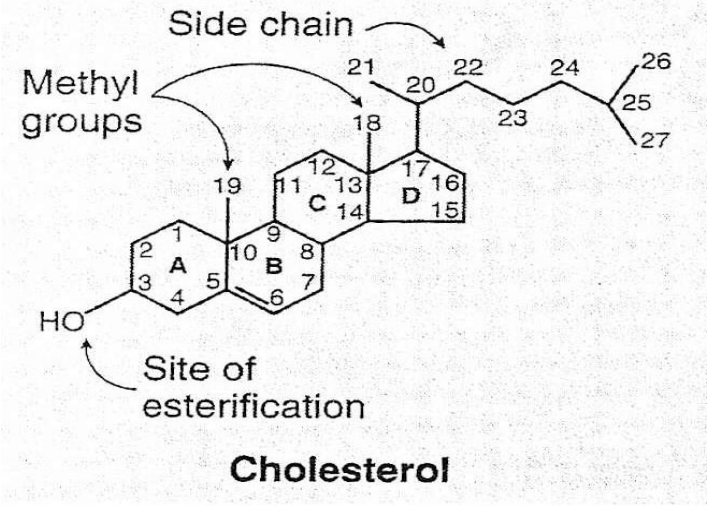
Detergents

Transformations of Cholesterol: Steroid Hormones



Cholesterol Functions

- Membrane component
- Precurser to
  - Bile acids
  - Vitamin D
  - Steroid hormones



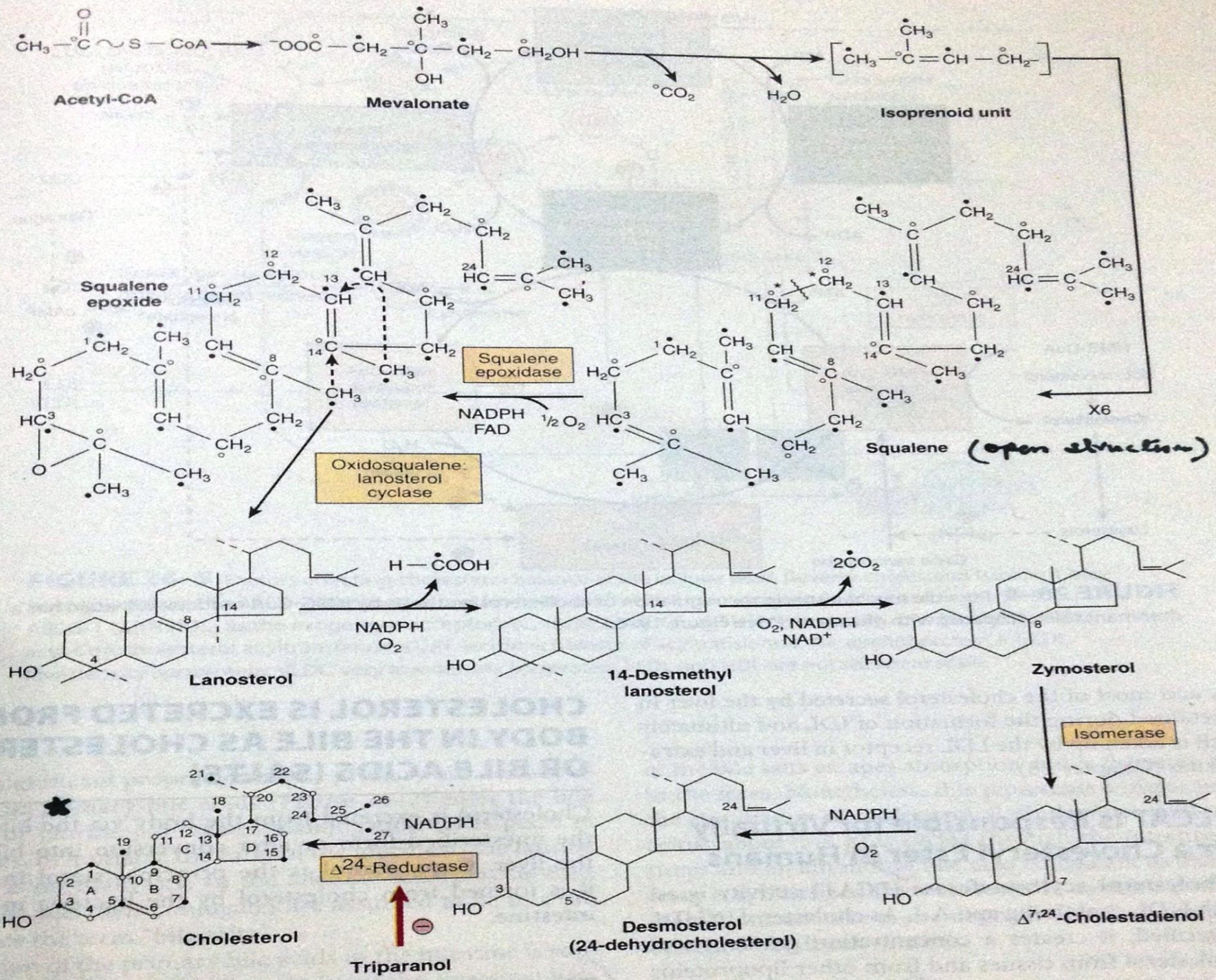
- Essential ingradient of lipoprotein
- Cholesterol esters provides FA to liver for oxidation
- Ubiquinone.

Regulation of cholesterol synthesis

- cholesterol synthesis is controlled by HMG-CoA reductase.
- feed back control
- Hormonal regulation

Glucagon and glucocorticoids favours inactive HMG CoA while insulin and thyroxine increase active HMG CoA

- Inhibition by drugs
- Bile acids
- fasting


Acetyl-CoA
Mevalonate
CO_2
H_2O
Isoprenoid unit
X6
Squalene
(open structure)
Squalene epoxide
Squalene epoxidase
NADPH
FAD
½ O_2
Oxidosqualene: lanosterol cyclase
Lanosterol
NADPH
O_2
H—COOH
14-Desmethyl lanosterol
O_2, NADPH
NAD^+
$2CO_2$
Zymosterol
Isomerase
$\Delta^{7,24}$-Cholestadienol
NADPH
O_2
Desmosterol (24-dehydrocholesterol)
NADPH
Δ^{24}-Reductase
Cholesterol
Triparanol

EXCRETION OF CHOLESTREROL

- Cholesterol is excreted in faeces
- Cannot be destroyed by oxidation to CO_2 and H_2O, because of absence of enzyme capable of catabolising the steroid nucleus
- About 1gm of cholesterol is eliminated from the body per day

DISORDER OF CHOLESTEROL METABOLISM

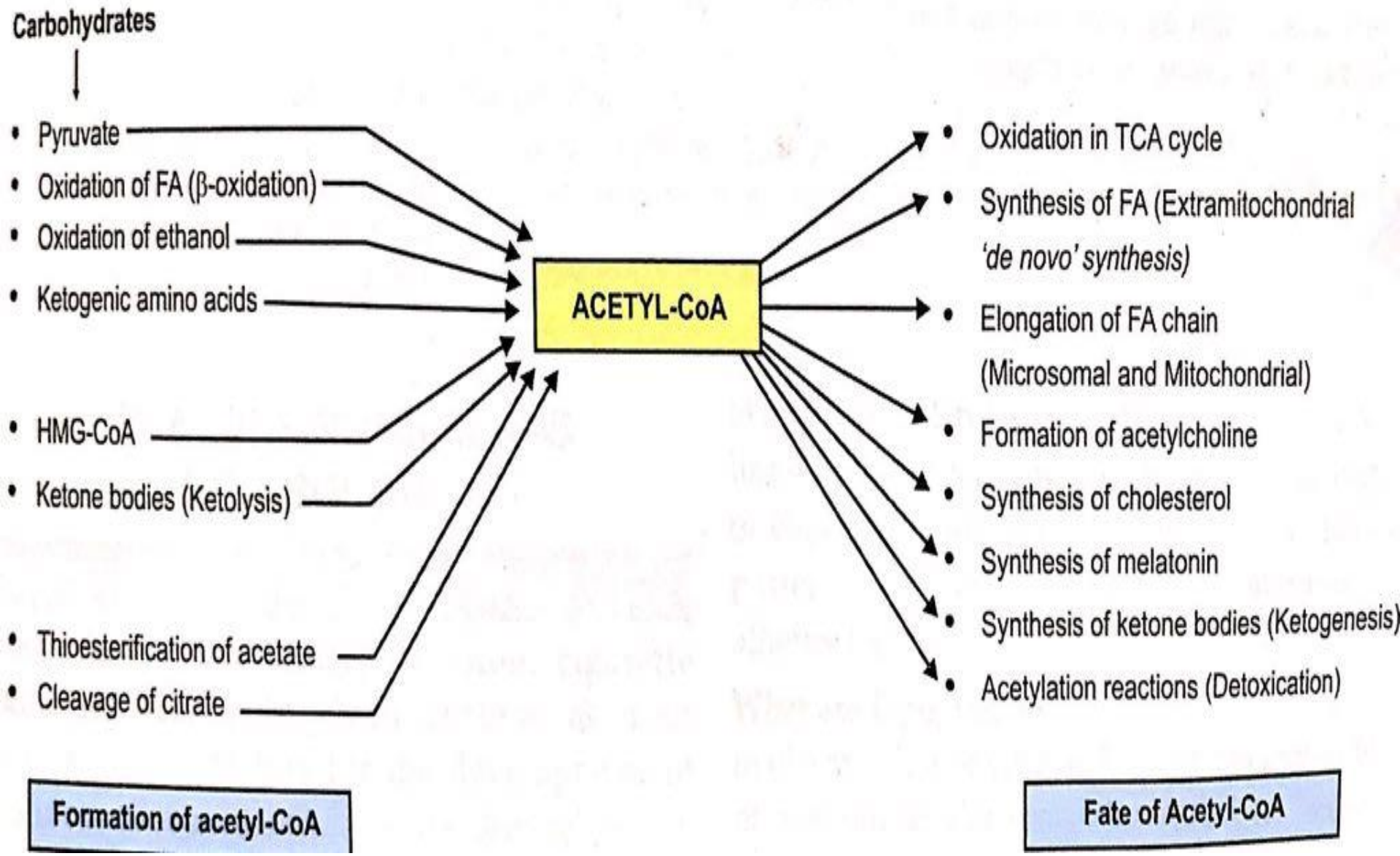
FAMILIAL HYPERCHOLESTEROLAEMIA

- Deficiency or malfunction of LDL receptors
- Plasma LDL & cholesterol level are elevated

ATHEROSCLEROSIS

- Deposition of cholesterol and other lipids in the arterial wall
- Leads to formation of plaque→endothelial damage→IHD

Sources and utilization of acetyl CoA



ANY QUESTION

- **CHATTERJEA BIOCHEMISTRY**
- **LIPPINCOTT BIOCHEMISTRY**
- **HARPERS BIOCHEMISTRY**
- **SATYANARAYANA BIOCHEMIST**
- **INTERNET**

Thank you