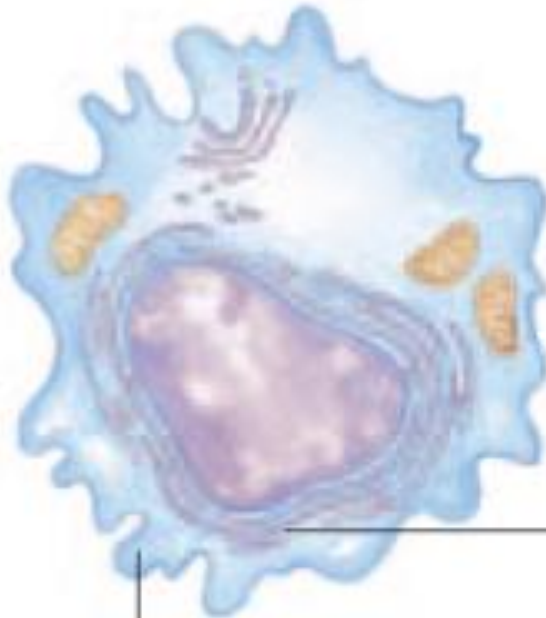


BIOSYNTHESIS OF CHOLESTEROL

Animal cells



Endoplasmic reticulum

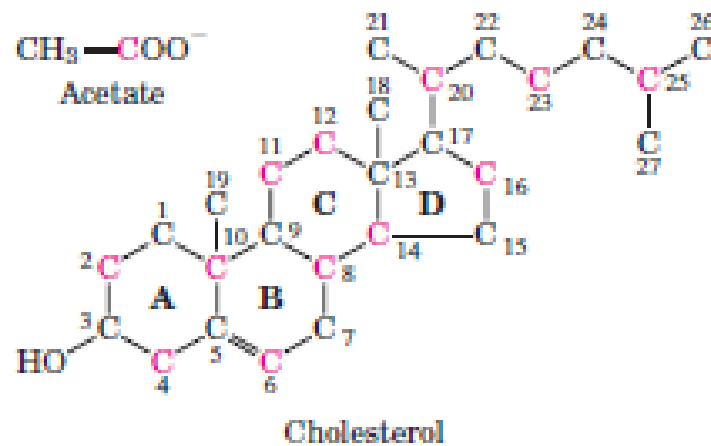
- Sterol synthesis (late stages)

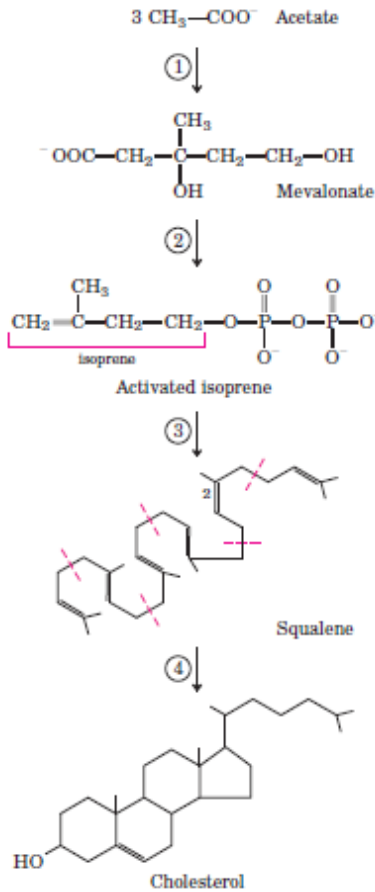
Cytosol

- Isoprenoid and sterol synthesis (early stages)

Origin of the carbon atoms of cholesterol

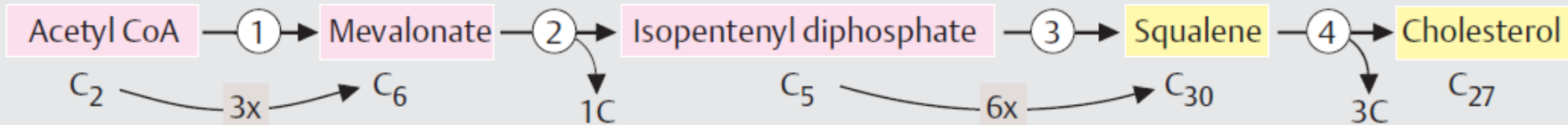
This can be deduced from tracer experiments with acetate labeled in the methyl carbon (black) or the carboxyl carbon (red). The individual rings in the fused-ring system are designated A through D.

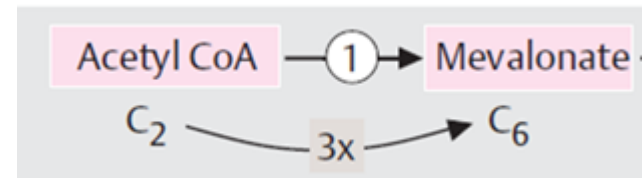
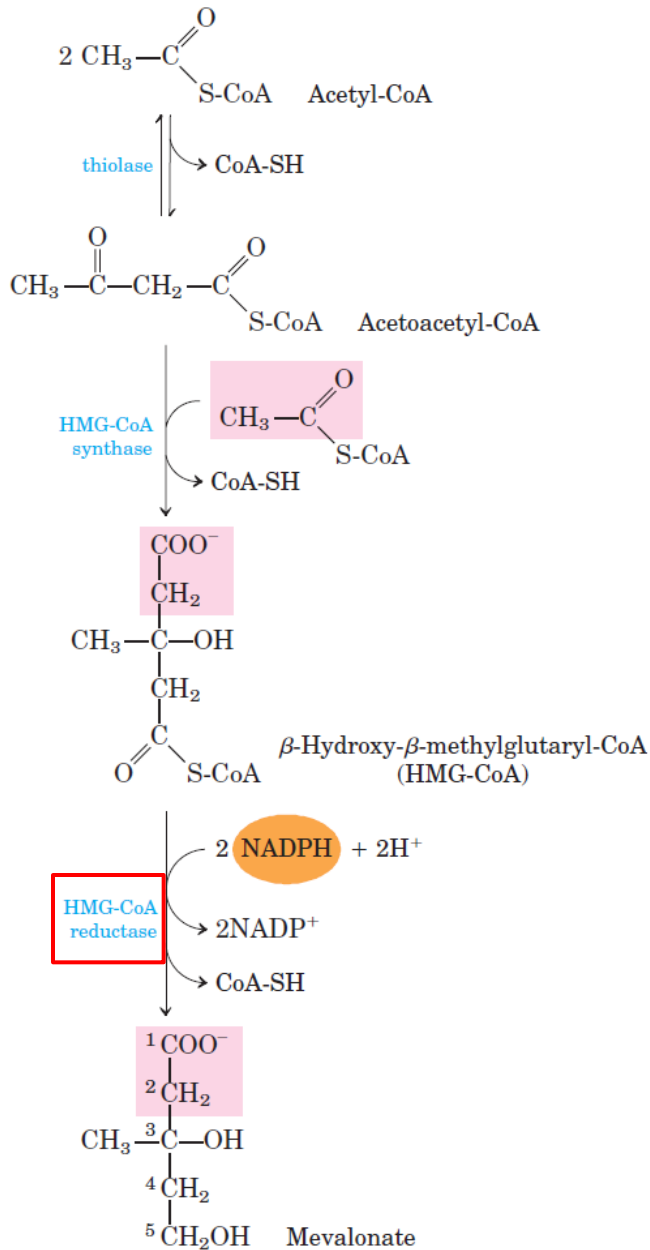




Summary of cholesterol biosynthesis

Isoprene units in squalene are set off by red dashed lines.





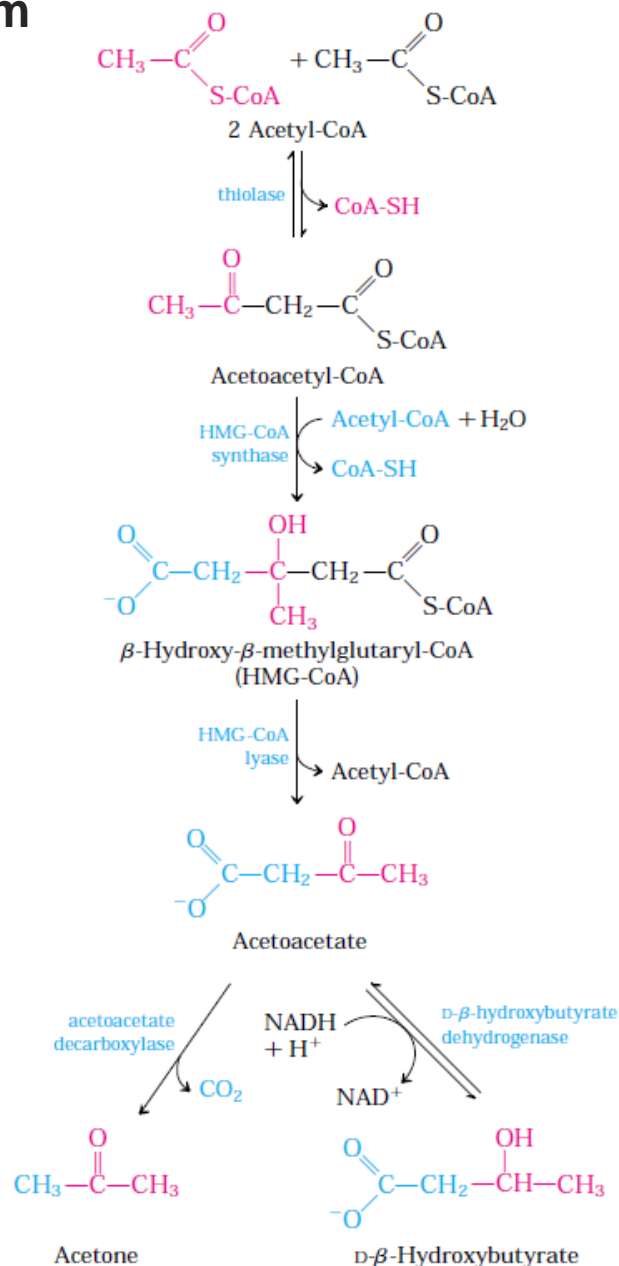
Formation of mevalonate from acetyl-CoA

The origin of C-1 and C-2 of mevalonate from acetyl-CoA is shown in pink.

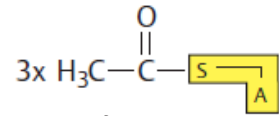
Remember: Formation of ketone bodies from acetyl-CoA.

Healthy, well-nourished individuals produce ketone bodies at a relatively low rate. When acetyl-CoA accumulates (e.g. in starvation or untreated diabetes), thiolase catalyzes the condensation of two acetyl-CoA molecules to acetoacetyl-CoA, the parent compound of the three ketone bodies. The reactions of ketone body formation occur in the matrix of liver mitochondria.

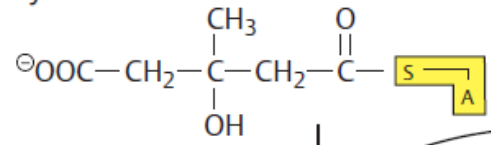
The six-carbon compound β -hydroxy- β -methylglutaryl-CoA (HMG-CoA) is also an intermediate of sterol biosynthesis, but the enzyme that forms HMG-CoA in that pathway is cytosolic. HMG-CoA lyase is present only in the mitochondrial matrix.



Acetyl CoA



3-Hydroxy-3-methylglutaryl CoA

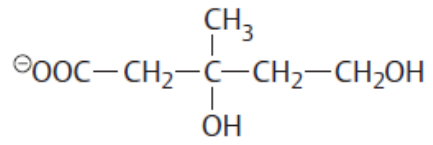


Insulin
Thyroxin
Glucagon

HMG-CoA reductase
1.1.1.34

Cholesterol

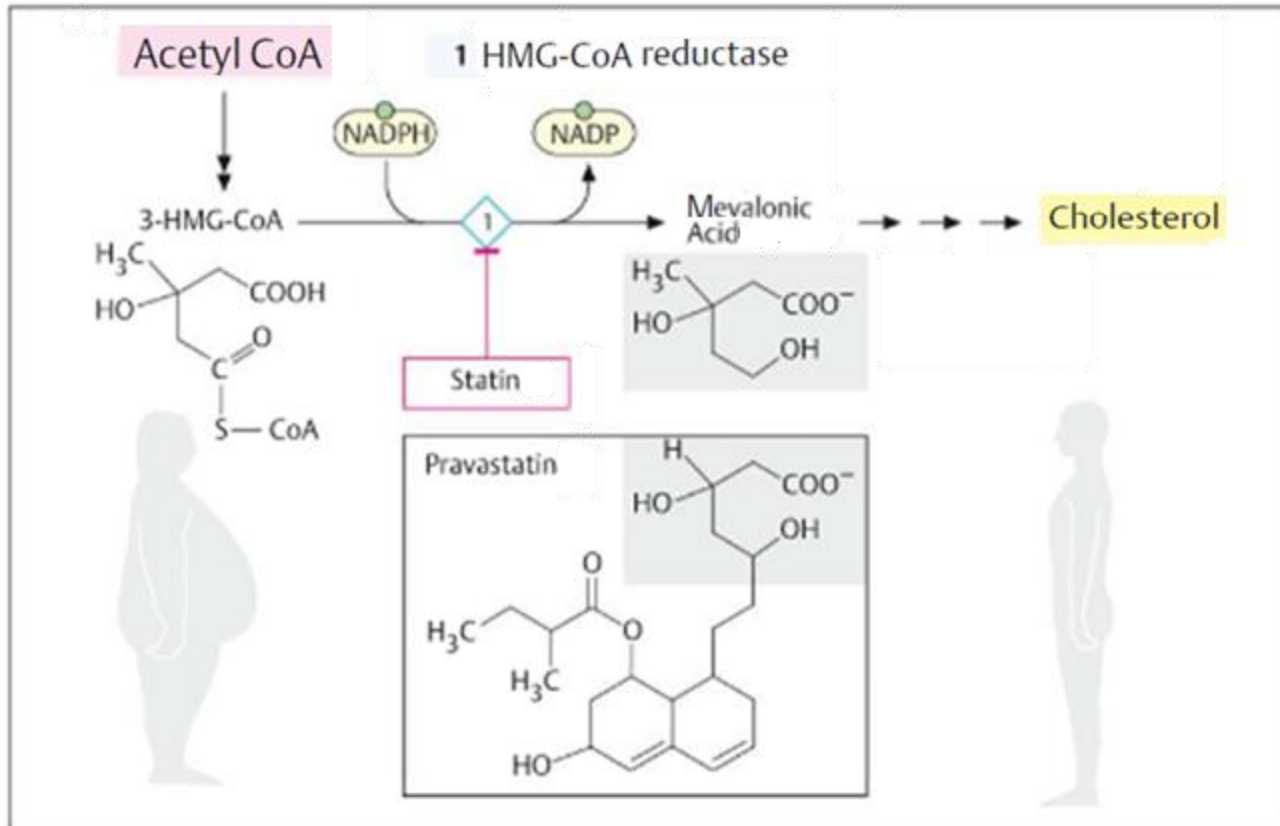
Key enzyme

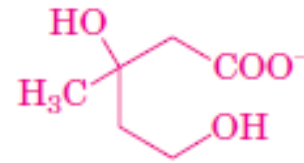
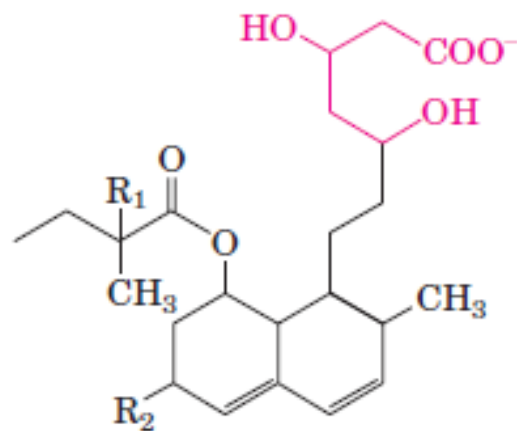


Mevalonate



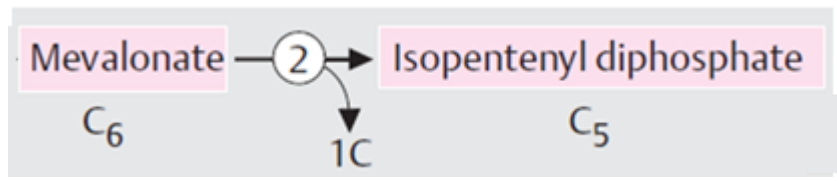
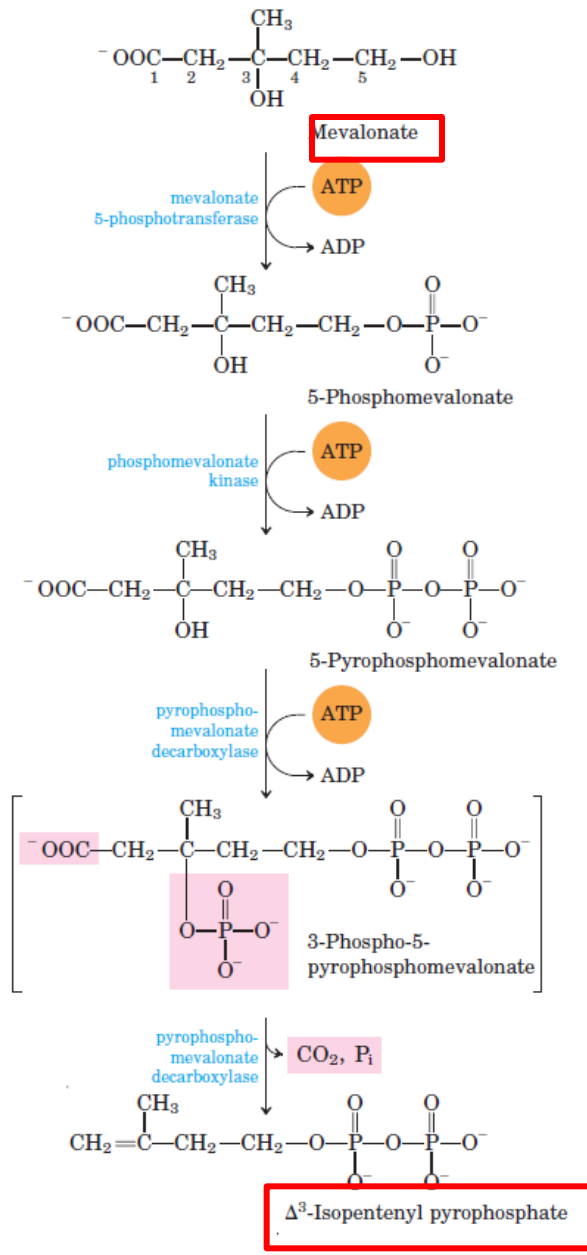
①





Mevalonate

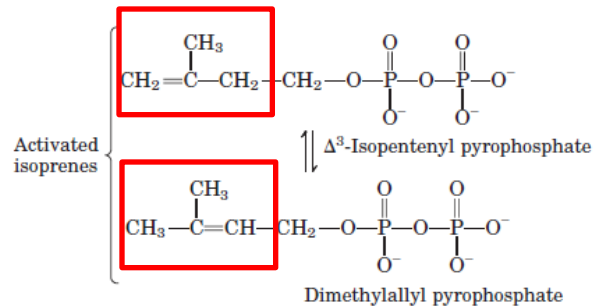
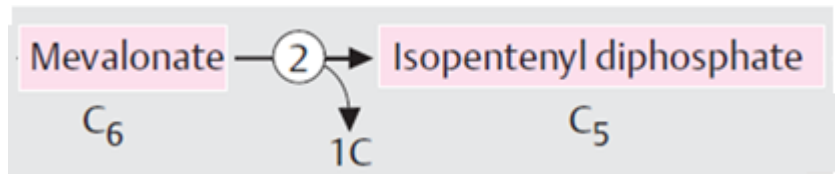
$R_1 = H$	$R_2 = H$	Compactin
$R_1 = CH_3$	$R_2 = CH_3$	Simvastatin (Zocor)
$R_1 = H$	$R_2 = OH$	Pravastatin (Pravachol)
$R_1 = H$	$R_2 = CH_3$	Lovastatin (Mevacor)



Conversion of mevalonate to activated isoprene units

Three phosphate groups are transferred from three ATP molecules to mevalonate.

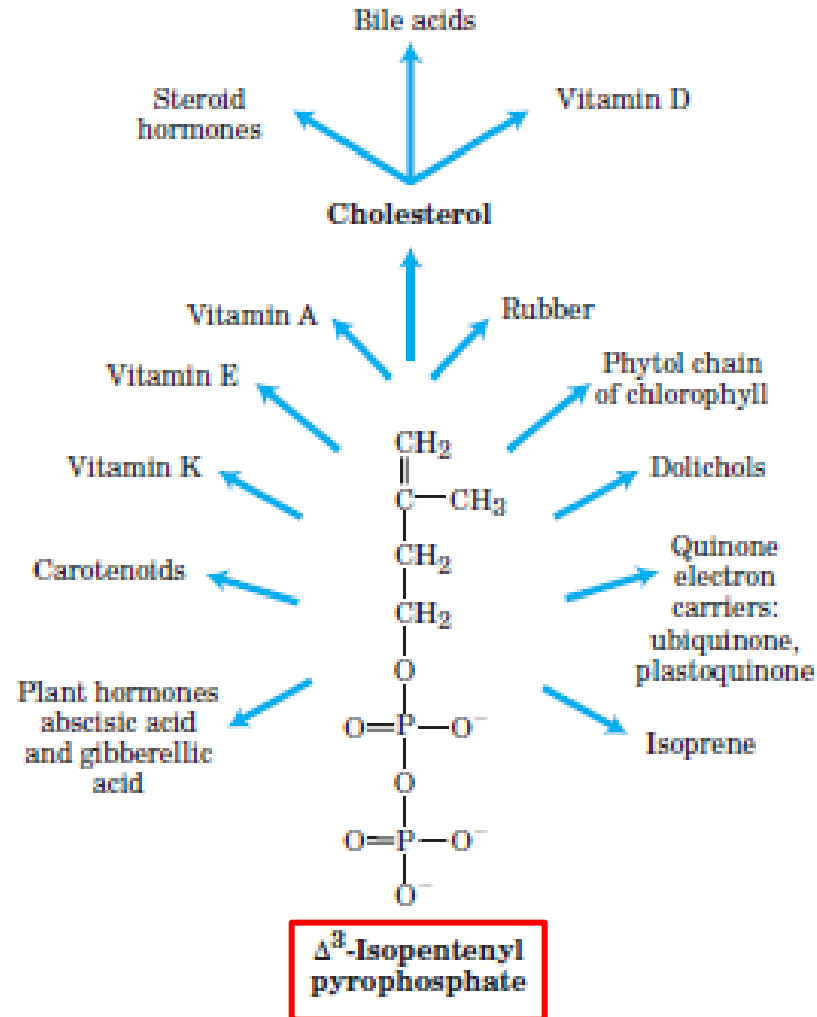
C-3 phosphate and the nearby carboxyl group leave, producing a double bond in the five-carbon product, Δ³-isopentenyl pyrophosphate.

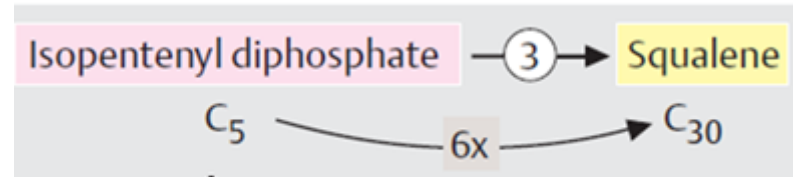
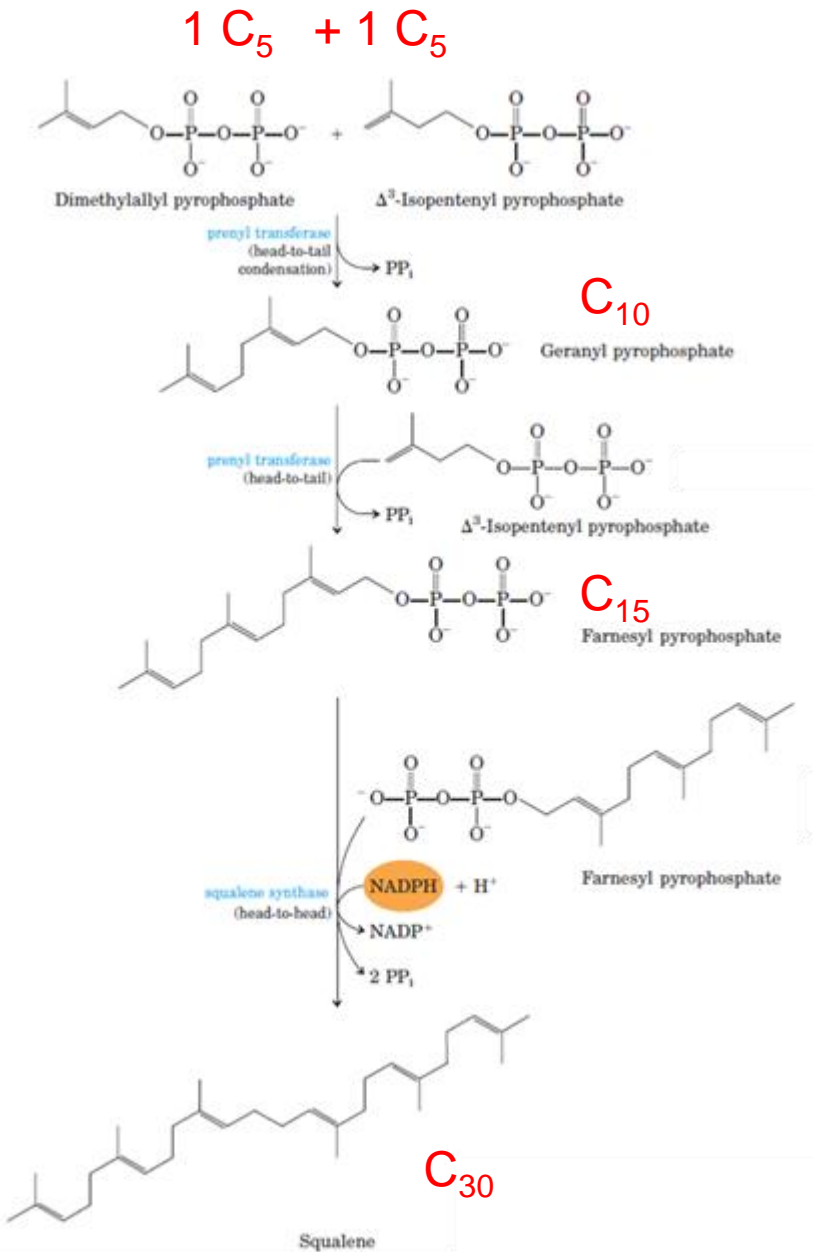


Isomerization of Δ^3 -isopentenyl pyrophosphate yields a second activated isoprene, **dimethylallyl pyrophosphate**.

*Isoprenoids (or Terpenes), are hydrocarbon containing secondary metabolites

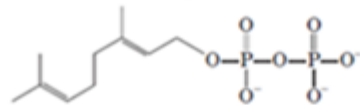
Overview of isoprenoid derivatives



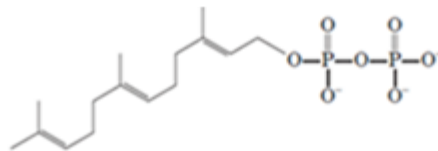


Condensation of six activated isoprene units to form squalene

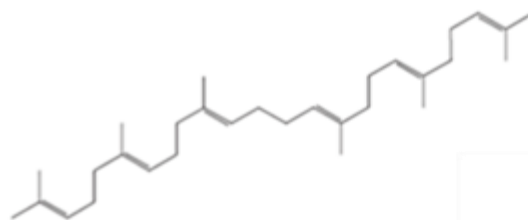
Isopentenyl pyrophosphate and dimethylallyl pyrophosphate undergo a head-to-tail condensation, in which one pyrophosphate group is displaced and a 10-carbon chain, **geranyl** pyrophosphate, is formed. (The “head” is the end to which pyrophosphate is joined.) Geranyl pyrophosphate undergoes another head-to-tail condensation with isopentenyl pyrophosphate yielding the 15-carbon intermediate **farnesyl** pyrophosphate. Finally, two molecules of farnesyl pyrophosphate join head to head, with the elimination of both pyrophosphate groups, to form **squalene**.



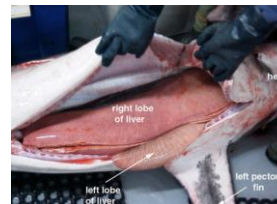
Geranyl pyrophosphate



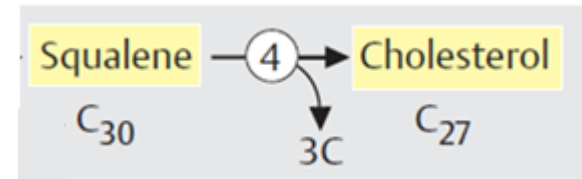
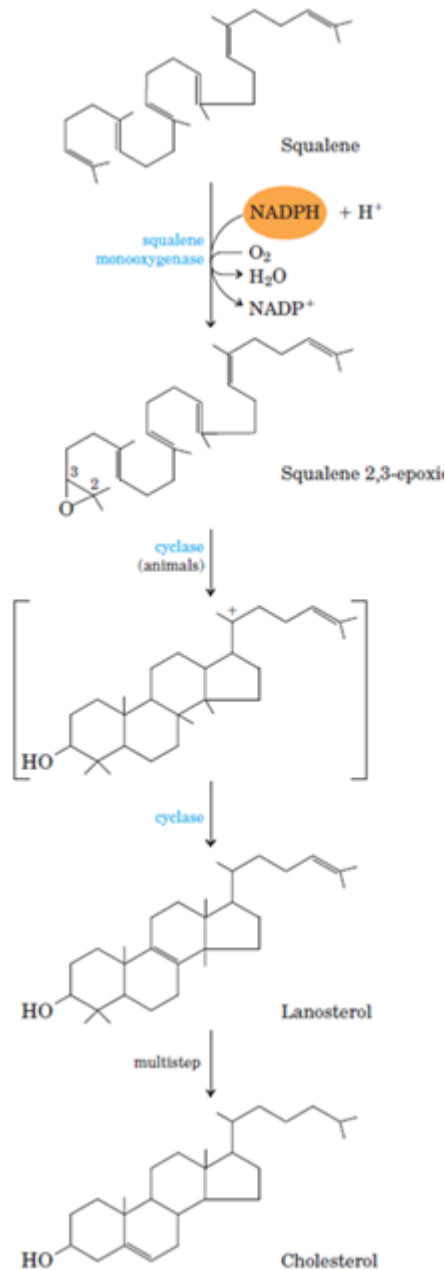
Farnesyl pyrophosphate



Squalene



Isoprenoids (or Terpenes), are hydrocarbon containing biomolecules made up of multiples of the isoprene unit.



Ring closure converts linear squalene to the condensed steroid nucleus

The first step in this sequence is catalyzed by a mixed-function oxidase (a monooxygenase), for which the cosubstrate is NADPH.

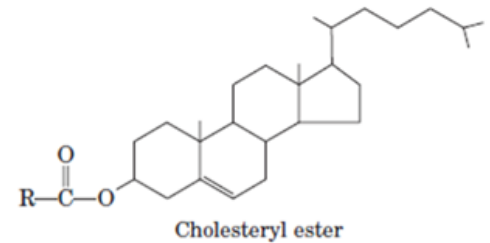
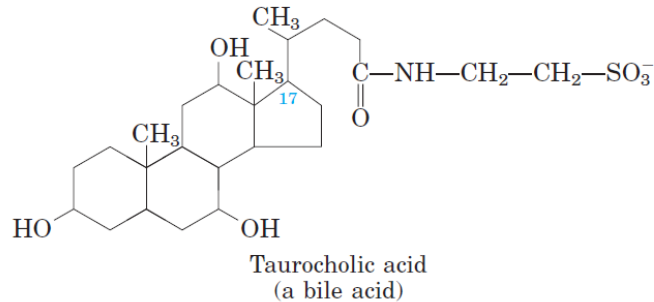
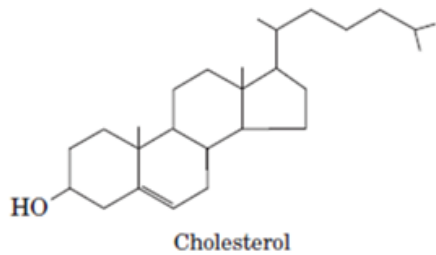
The product is an epoxide*, which in the next step is cyclized to the steroid nucleus. The final product of these reactions in animal cells is cholesterol;

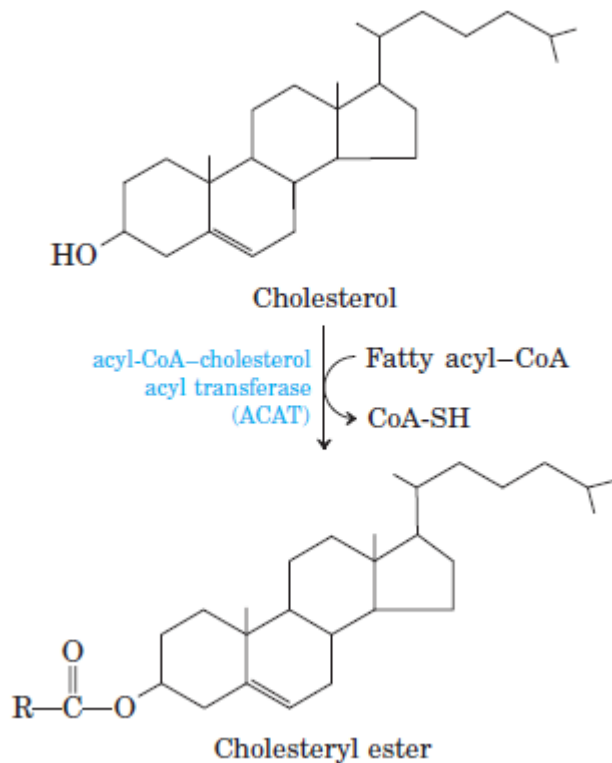
in other organisms, slightly different sterols (stigmasterol in plants, ergosterol in fungi) are produced.

*in organic chemistry, an epoxide is a *cyclic ether*, where the ether forms a three-atom ring: two atoms of carbon and one atom of oxygen

Much of the cholesterol synthesis in vertebrates takes place in the liver. A small fraction of the cholesterol made there is incorporated into the membranes of hepatocytes

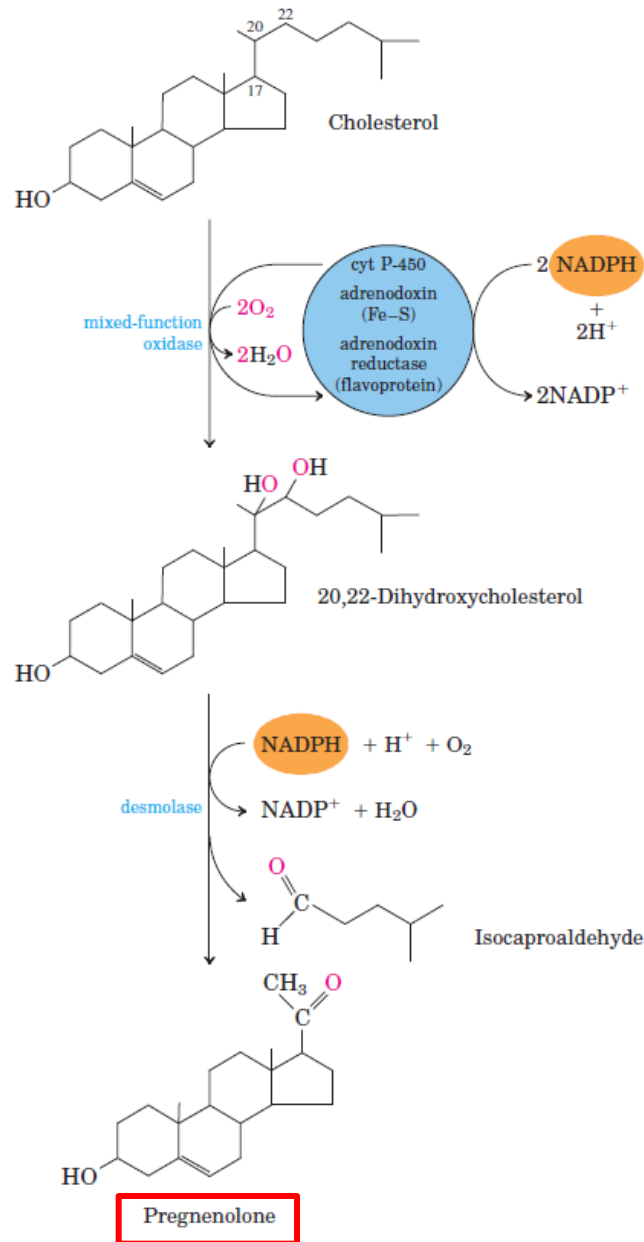
Most of it is exported in one of three forms: biliary cholesterol, bile acids, or cholesteryl esters.





Cholesteryl esters are formed in the liver through the action of **acyl-CoA-cholesterol acyl transferase (ACAT)**

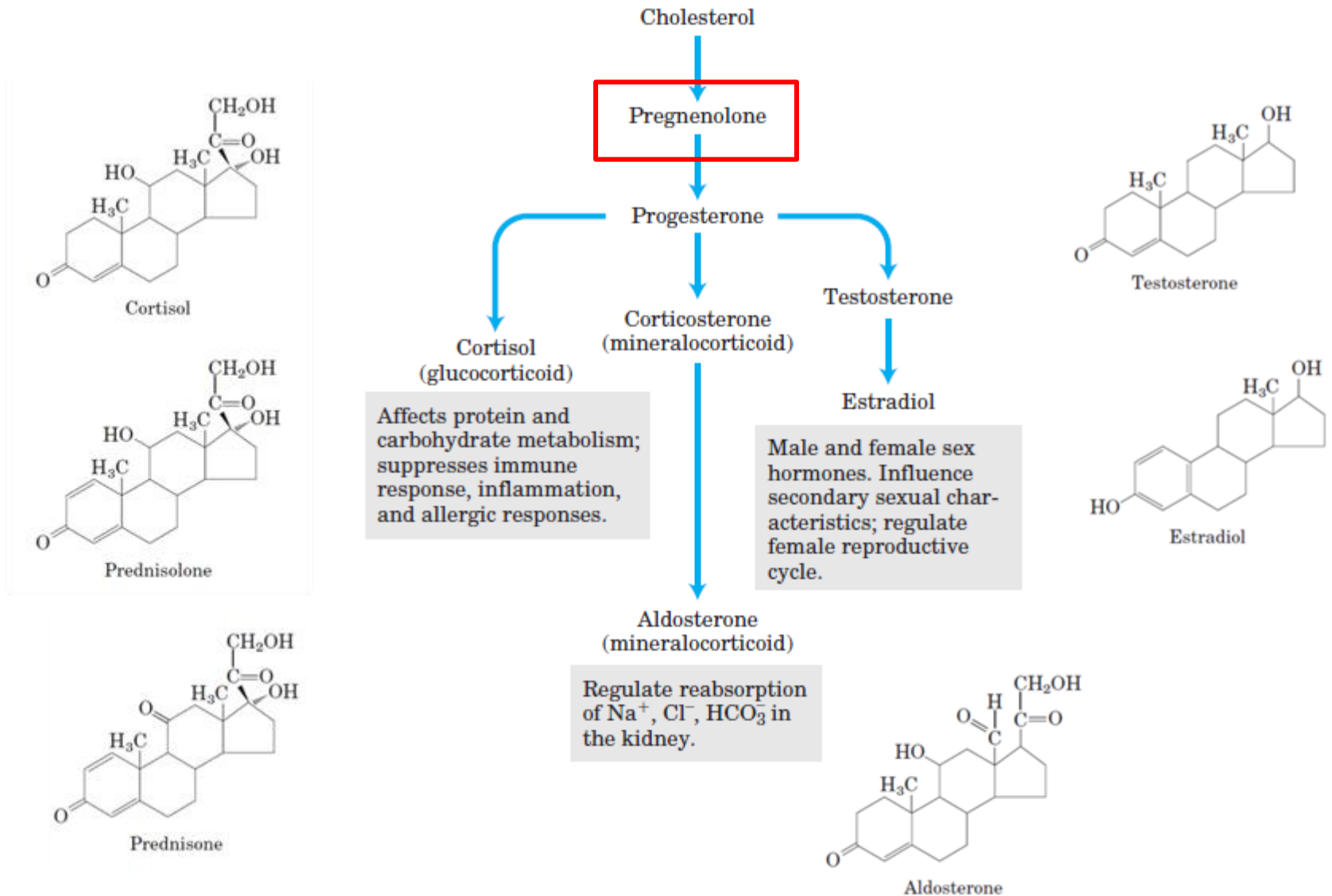
This enzyme catalyzes the transfer of a fatty acid from coenzyme A to the hydroxyl group of cholesterol, converting the cholesterol to a more hydrophobic form. Cholesteryl esters are transported in secreted lipoprotein particles to other tissues that use cholesterol, or they are stored in the liver.



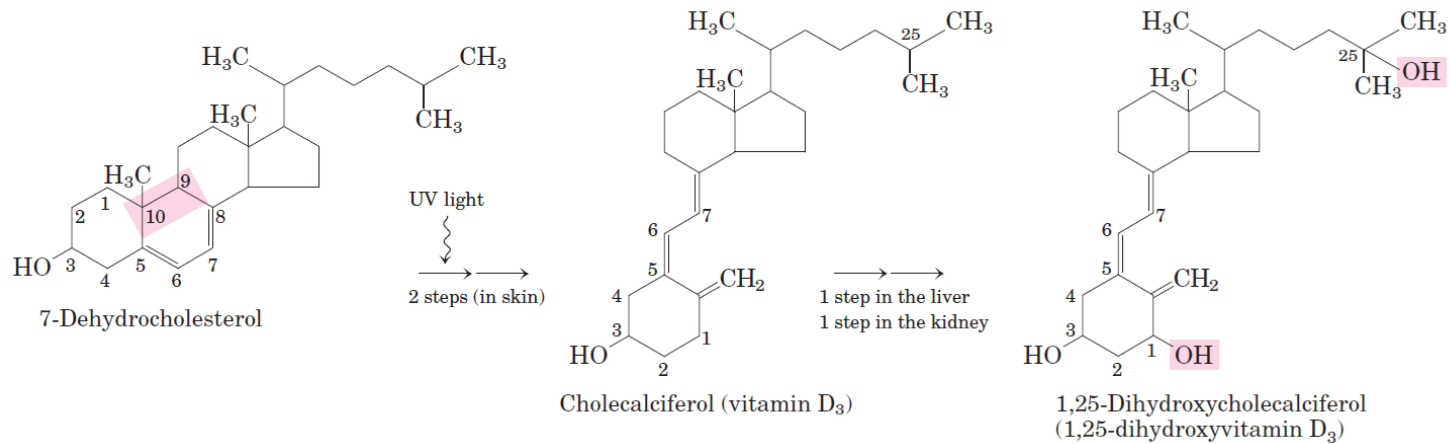
Side-chain cleavage in the synthesis of steroid hormones

Cytochrome P-450 acts as electron carrier in this mixed function oxidase system that oxidizes adjacent carbons. The process also requires the electron-transferring proteins adrenodoxin and adrenodoxin reductase. This system for cleaving side chains is found in mitochondria of the adrenal cortex, where active steroid production occurs. Pregnenolone is the precursor of all other steroid hormones.

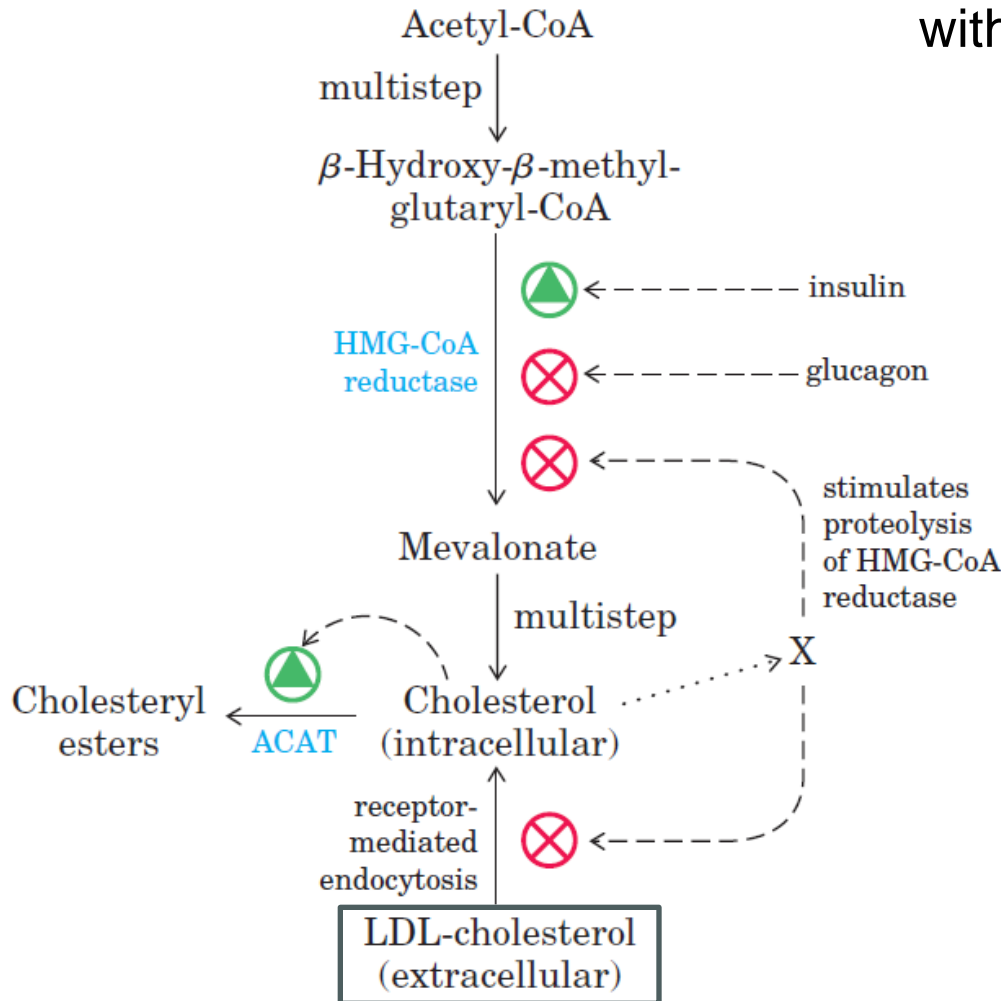
Some organs (adrenal gland and gonads, for example) use cholesterol as a precursor for steroid hormone production



Cholesterol is also a precursor of vitamin D



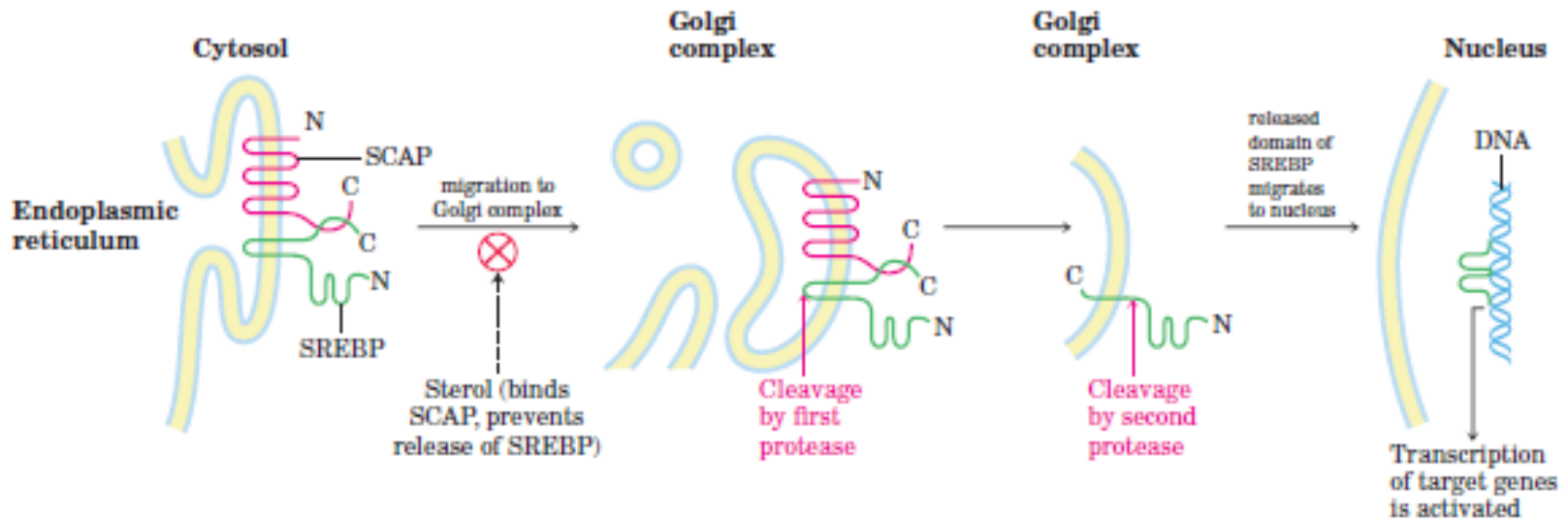
Regulation of cholesterol formation balances synthesis with dietary uptake



Glucagon promotes phosphorylation (inactivation) of HMG-CoA reductase; insulin promotes dephosphorylation (activation).

X represents unidentified metabolites of cholesterol that stimulate proteolysis of HMG-CoA reductase.

Sterol regulatory element-binding proteins (SREBPs)



SREBP are embedded in the ER when first synthesized, in a complex with the protein SREBP cleavage-activating protein (SCAP).

When bound to SCAP, SREBPs are inactive.

When sterol levels decline, the complex migrates to the Golgi complex, and SREBP is cleaved by two different proteases in succession.

The liberated amino-terminal domain of SREBP migrates to the nucleus, where it activates transcription of sterol-regulated genes, such as the gene encoding HMG-CoA reductase.