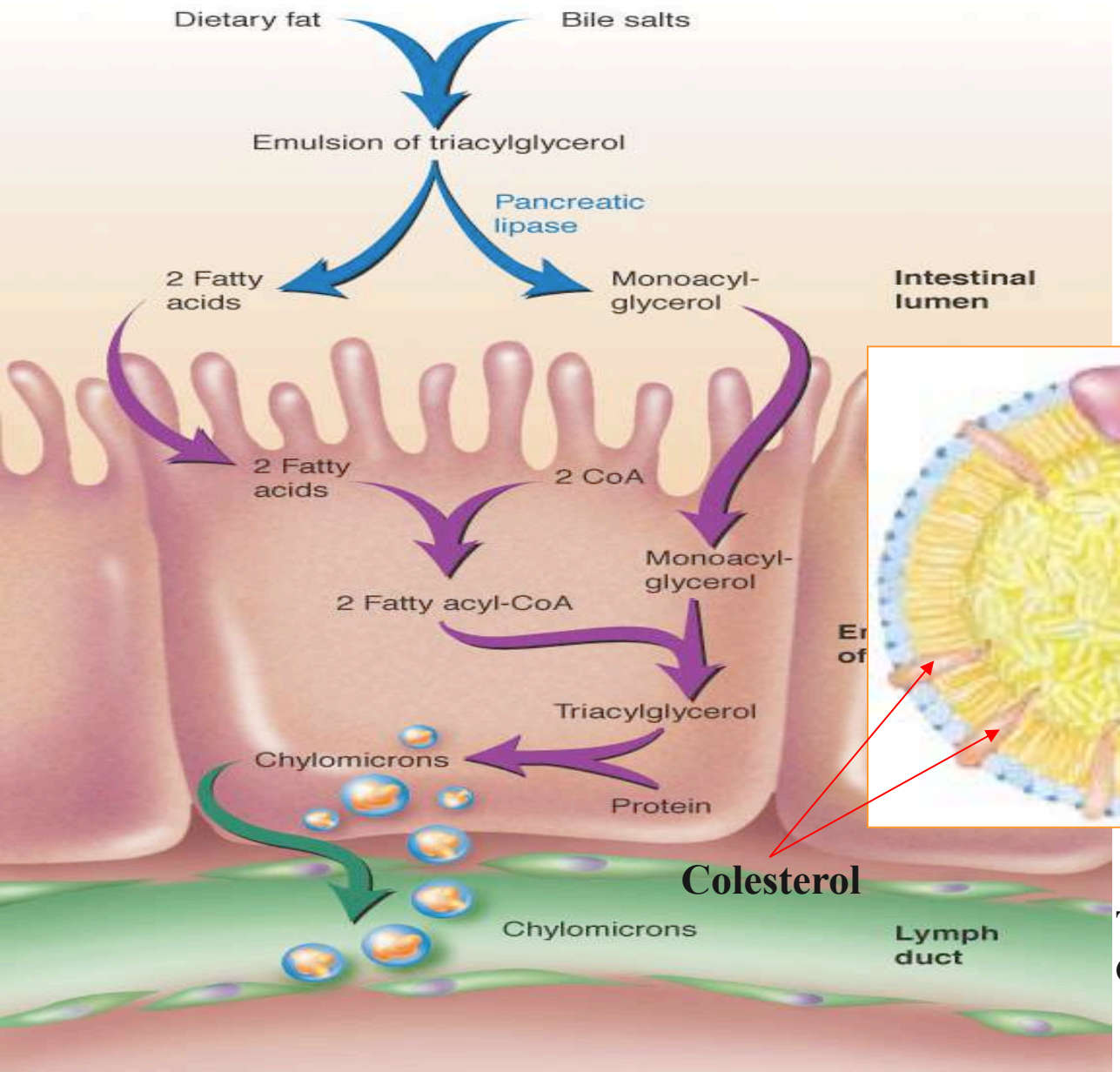
Universidad Mayor de San Andrés
Facultad de Medicina
Bioquímica y Biología Molecular
La Paz. Bolivia

Capítulo 9.7
Colesterol: síntesis, transporte y excreción

Prof. Ricardo Amaru MD. PD. ACAD.

Nota: Esta presentación es una recopilación de diversos autores, algunas diapositivas han sido modificadas y rediseñadas por el prof. Ricardo Amaru.

Digestión y absorción



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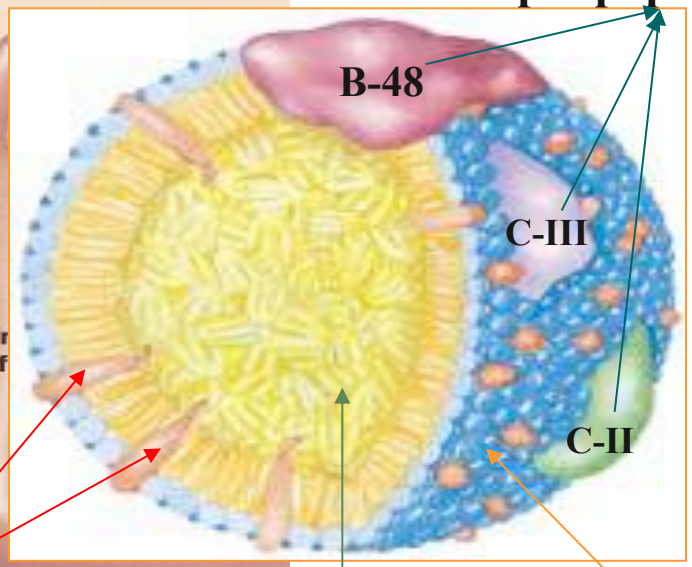
Apolipoproteínas

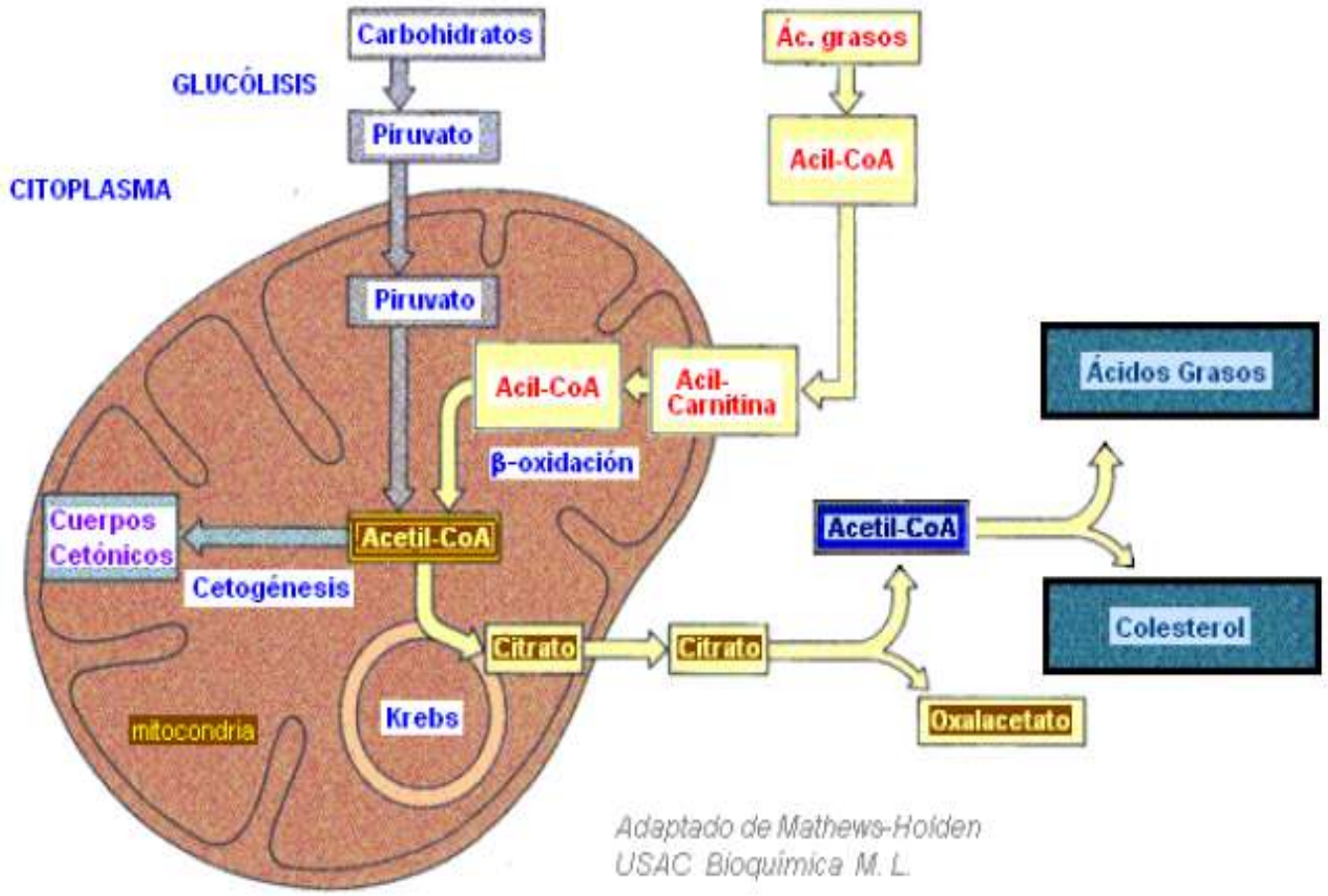


Colesterol

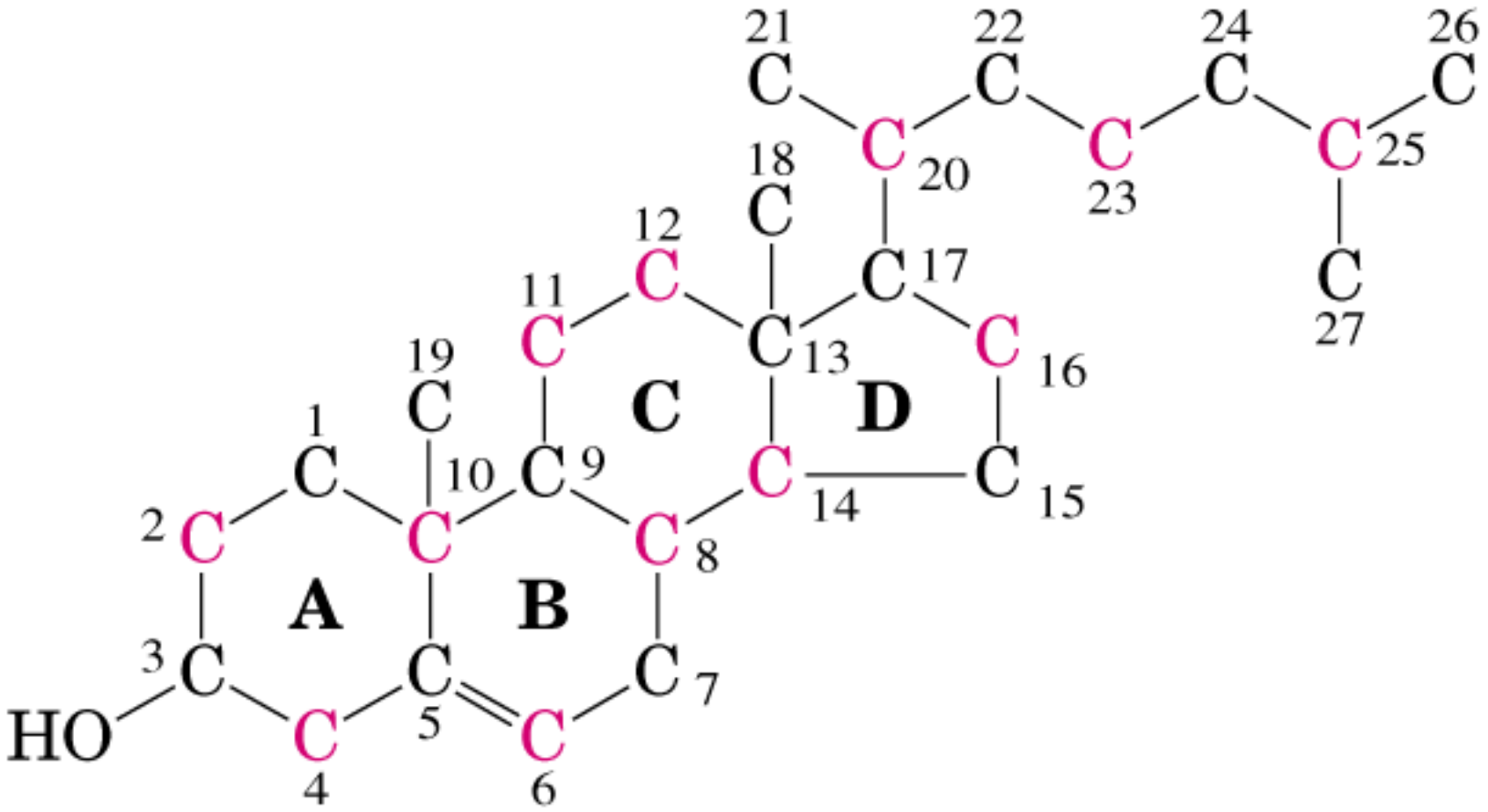
Fosfolípidos

Triacilgliceroles y ésteres de Colesterol.

Biosíntesis de colesterol



Colesterol


HO
A
B
C
D
1
2
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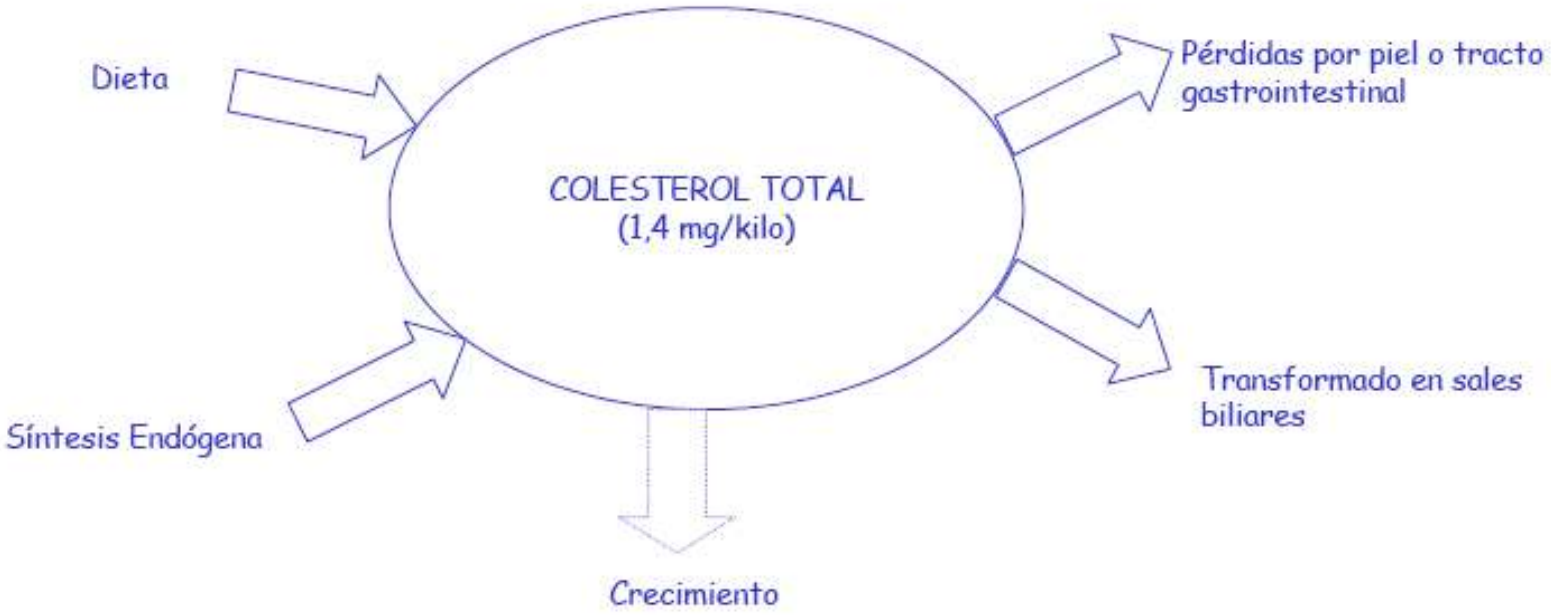
Metabolismo del Colesterol



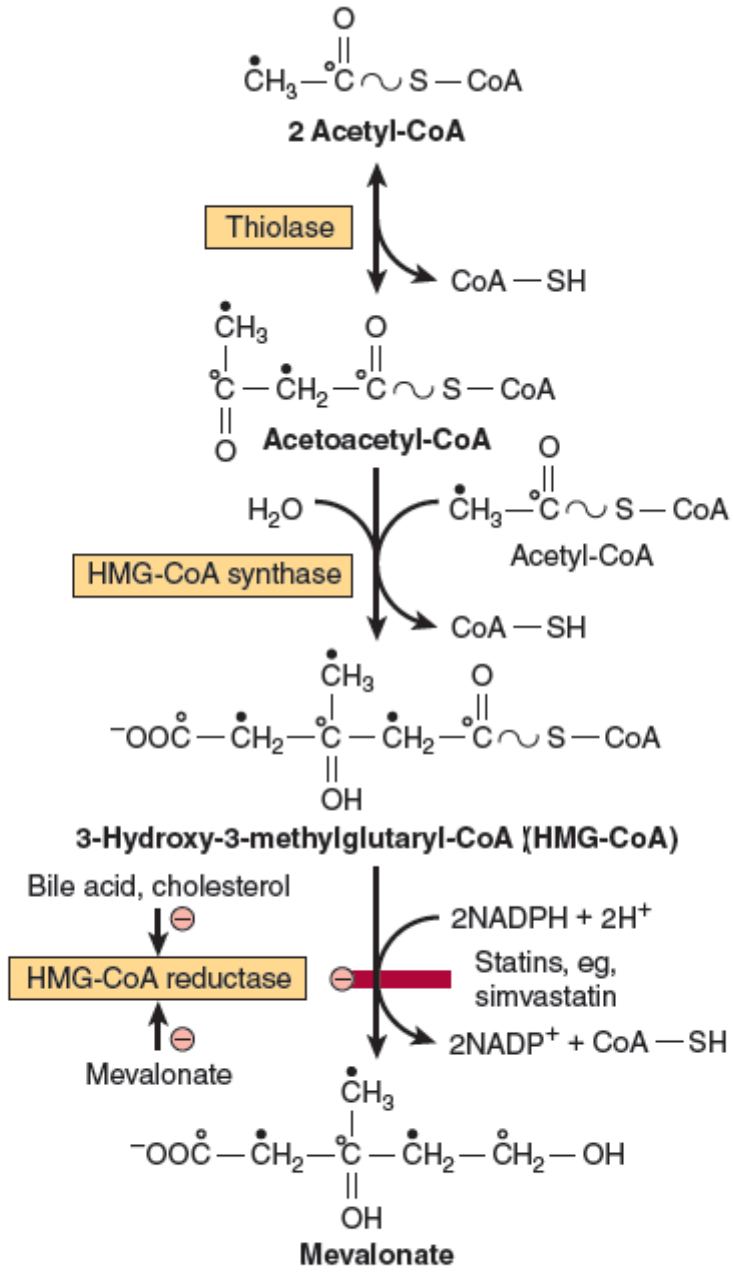
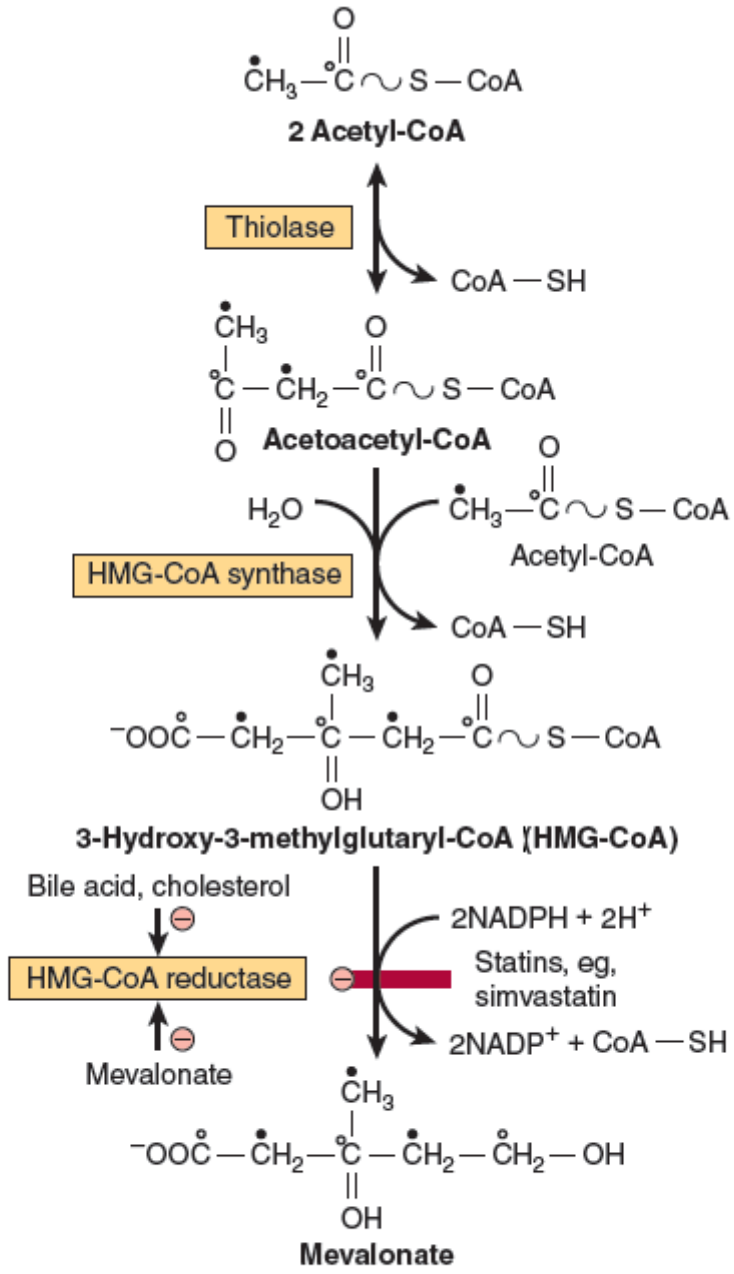


FIGURE 26–1 **Biosynthesis of mevalonate.** HMG-CoA reductase is inhibited by statins. The open and solid circles indicate the fate of each of the carbons in the acetyl moiety of acetyl-CoA.



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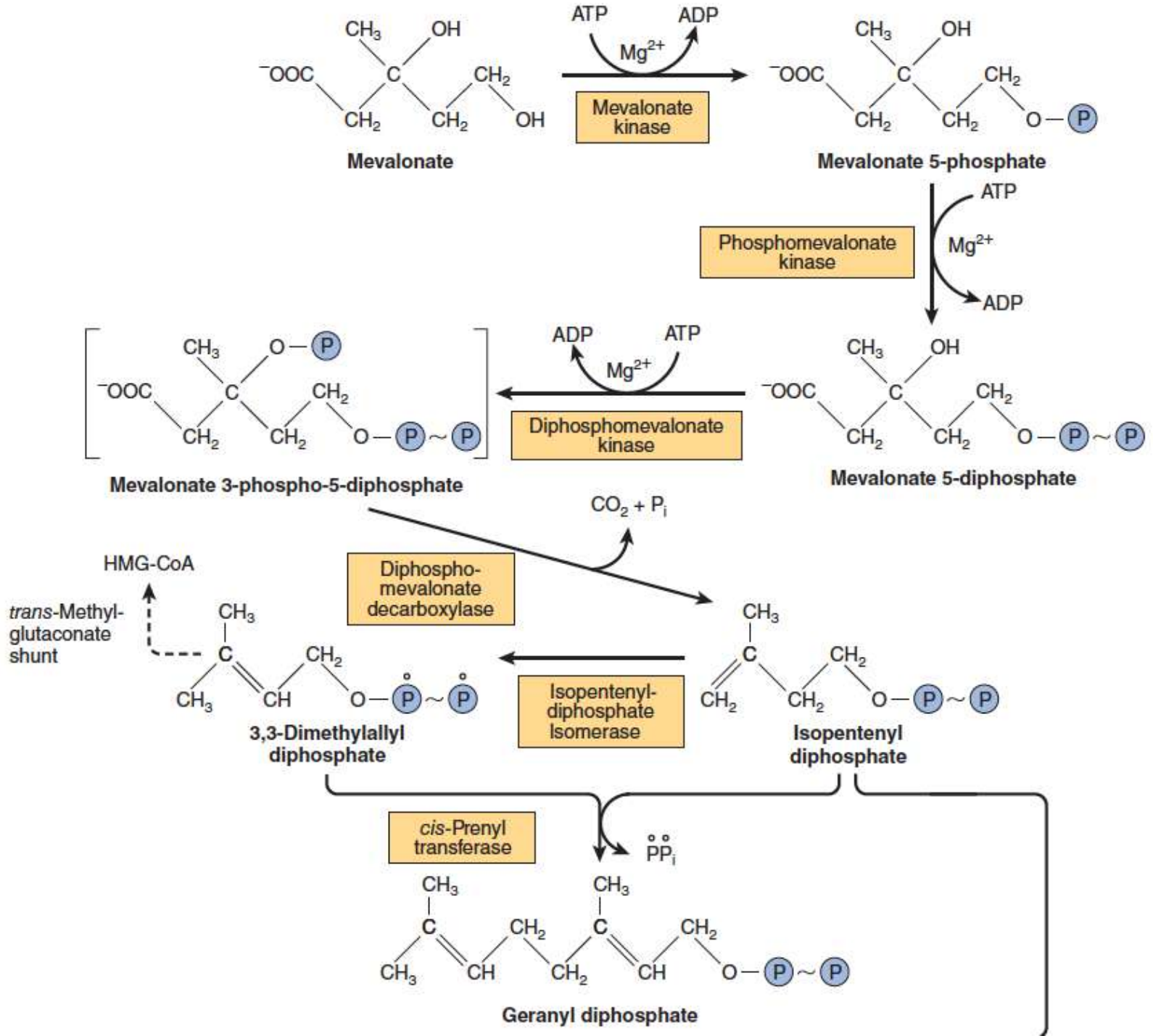
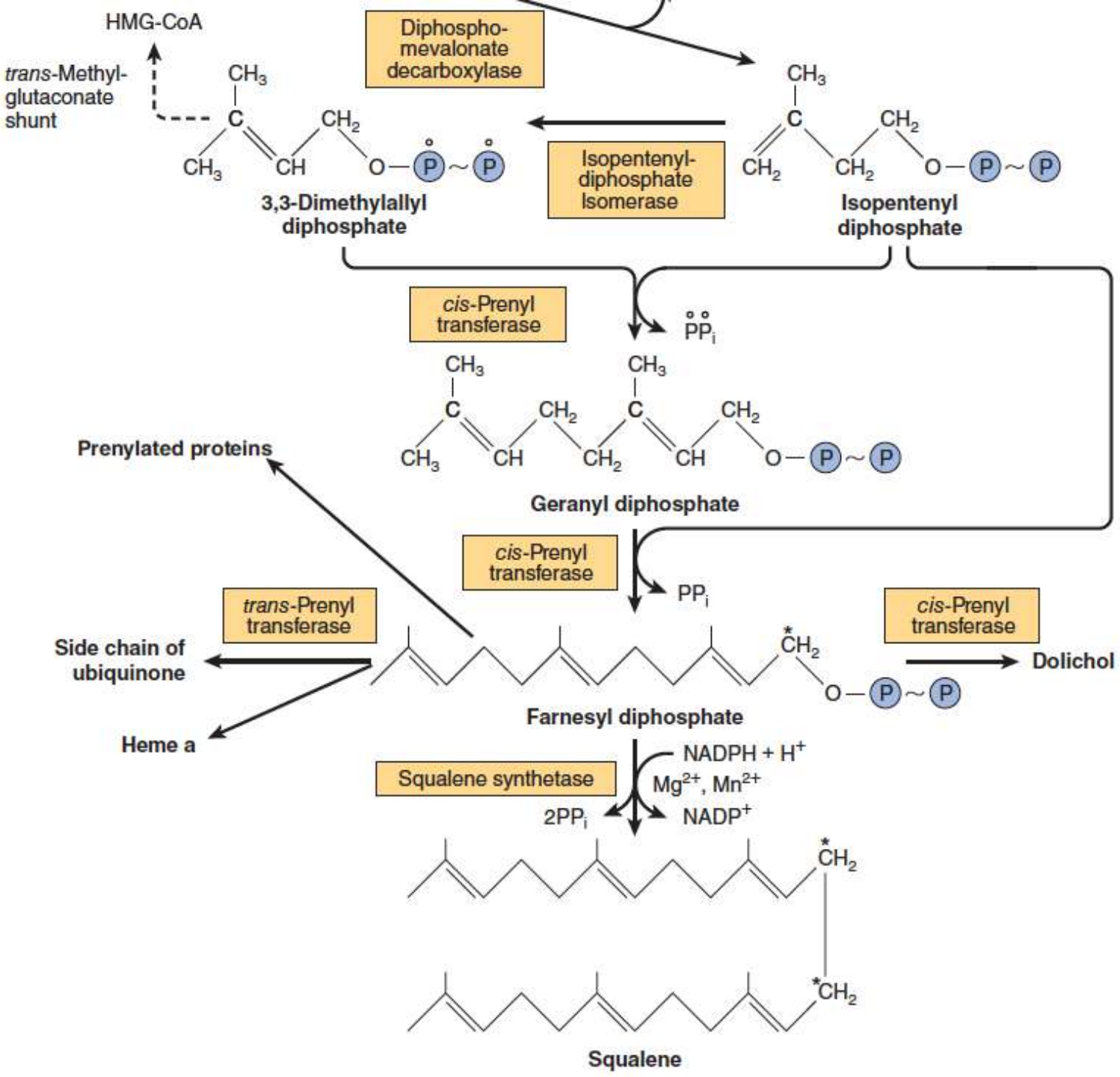

ATP
ADP
Mg2+
Mevalonate kinase
Mevalonate
Mevalonate 5-phosphate
Phosphomevalonate kinase
ATP
Mg2+
ADP
Diphosphomevalonate kinase
Mevalonate 3-phospho-5-diphosphate
Mevalonate 5-diphosphate
CO2 + Pi
Diphospho-mevalonate decarboxylase
HMG-CoA
trans-Methyl-glutaconate shunt
Isopentenyl-diphosphate Isomerase
3,3-Dimethylallyl diphosphate
Isopentenyl diphosphate
cis-Prenyl transferase
PPi
Geranyl diphosphate


HMG-CoA
trans-Methyl-glutaconate shunt
Diphospho-mevalonate decarboxylase
Isopentenyl-diphosphate Isomerase
3,3-Dimethylallyl diphosphate
Isopentenyl diphosphate
cis-Prenyl transferase
PPi
Geranyl diphosphate
Prenylated proteins
cis-Prenyl transferase
PPi
trans-Prenyl transferase
cis-Prenyl transferase
Side chain of ubiquinone
Dolichol
Heme a
Farnesyl diphosphate
NADPH + H+
Squalene synthetase
Mg2+, Mn2+
2PPi
NADP+
Squalene

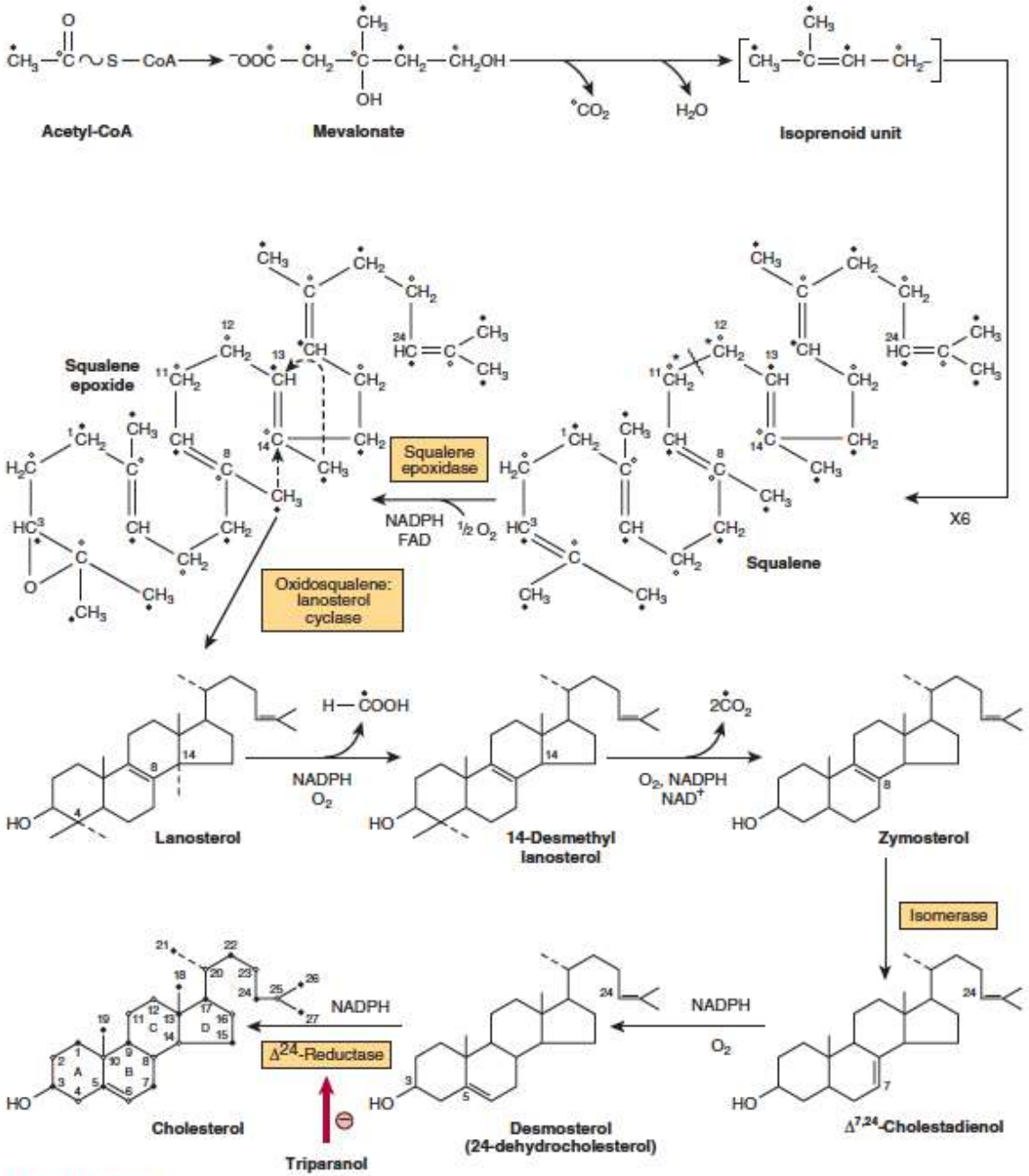
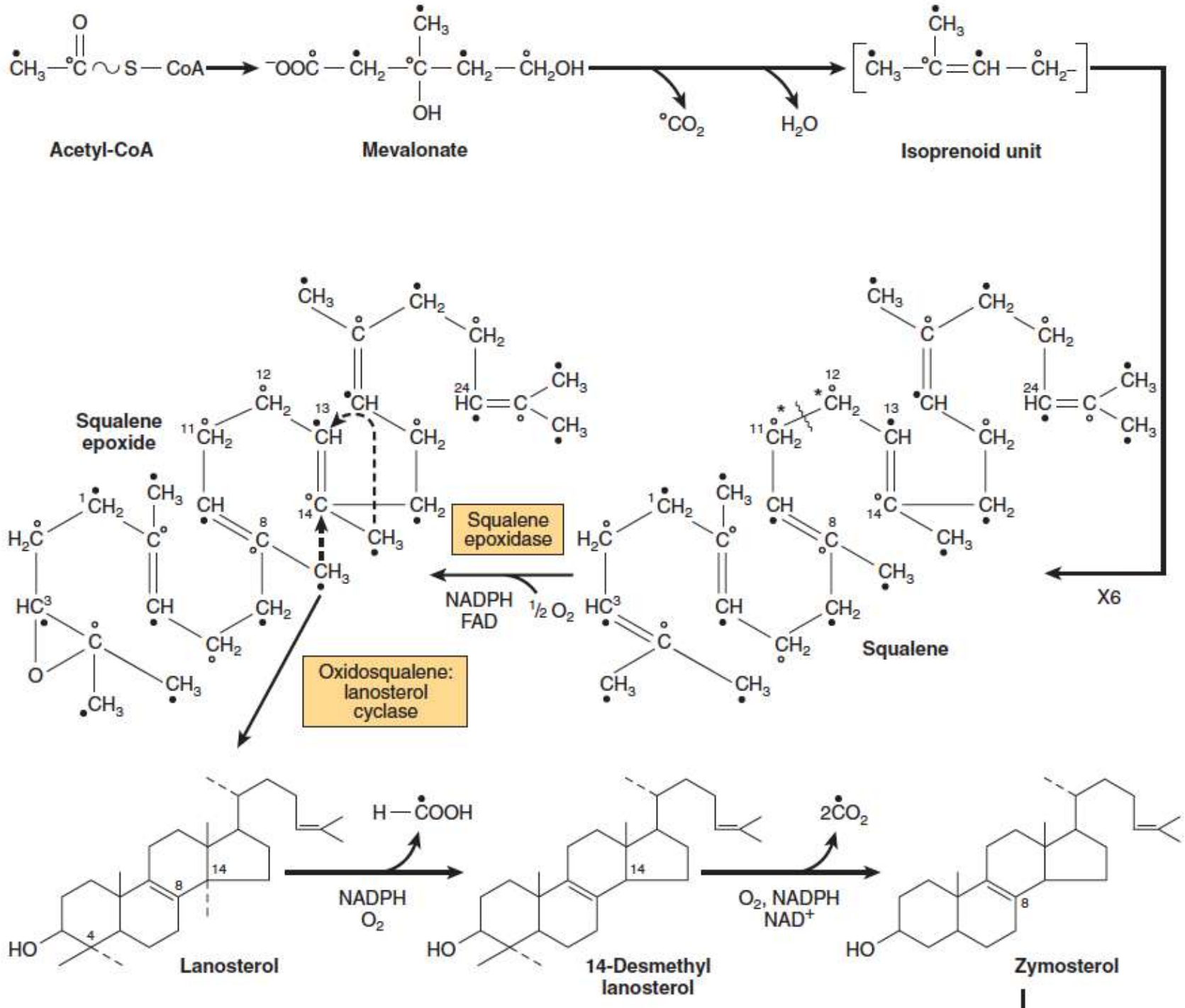
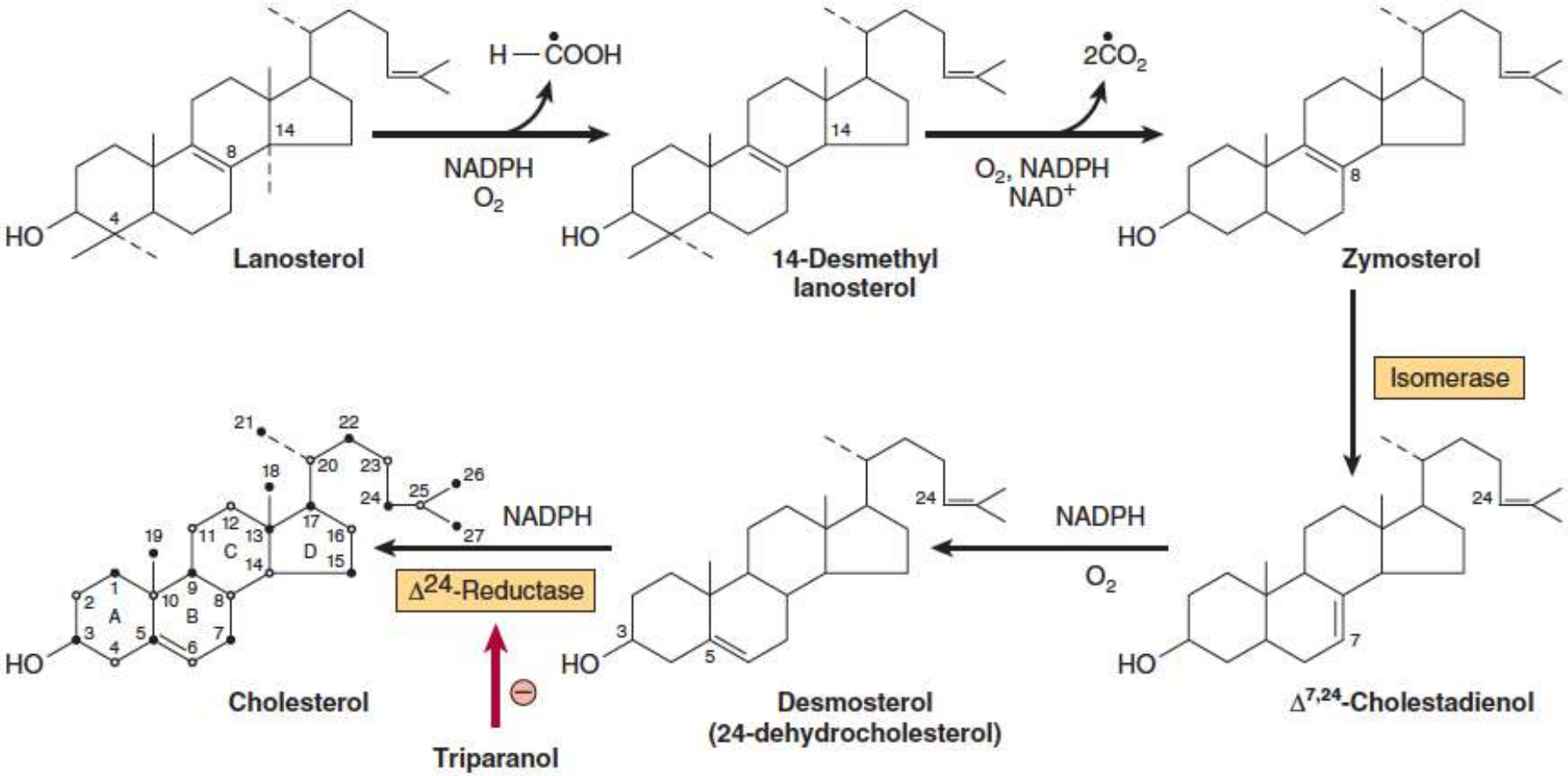


FIGURE 26–3 **Biosynthesis of cholesterol.** The numbered positions are those of the steroid nucleus and the open and solid circles indicate the fate of each of the carbons in the acetyl moiety of acetyl-CoA. (*Refer to labeling of squalene in Figure 26–2.)


Acetyl-CoA
Mevalonate
$^{\circ}CO_2$
H_2O
Isoprenoid unit
X6
Squalene
Squalene epoxidase
NADPH
FAD
$\frac{1}{2}\ O_2$
Squalene epoxide
Oxidosqualene: lanosterol cyclase
Lanosterol
NADPH
O_2
H—COOH
14-Desmethyl lanosterol
$2CO_2$
O_2, NADPH
NAD^+
Zymosterol


Lanosterol
H—ĊOOH
NADPH
O2
14-Desmethyl lanosterol
2ĊO2
O2, NADPH
NAD+
Zymosterol
Isomerase
Δ7,24-Cholestadienol
NADPH
O2
Desmosterol (24-dehydrocholesterol)
NADPH
Δ24-Reductase
Triparanol
Cholesterol
HO
A
B
C
D

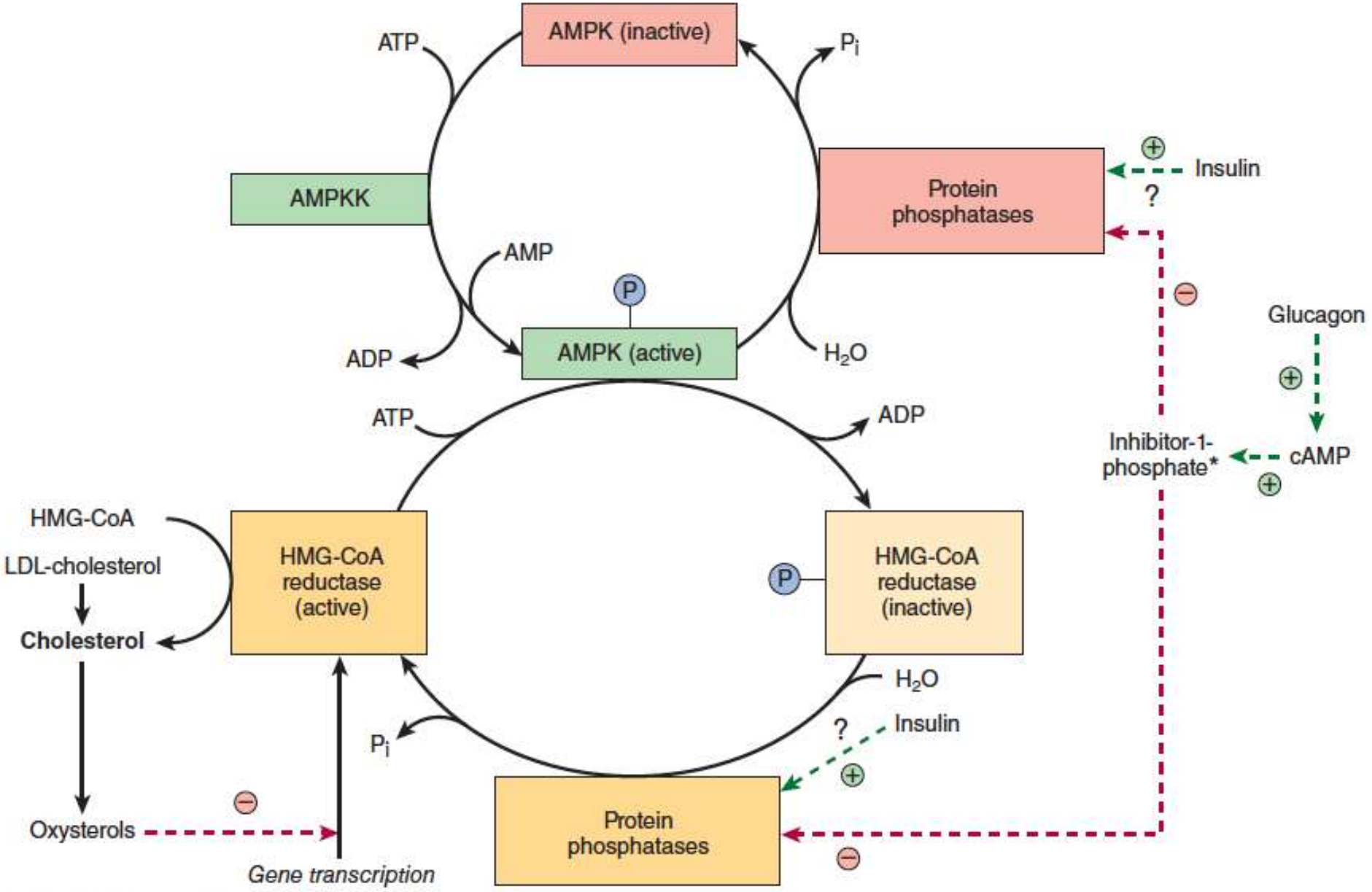


FIGURE 26–4 Possible mechanisms in the regulation of cholesterol synthesis by HMG-CoA reductase. Insulin has a dominant role compared with glucagon. (AMPK, AMP activated protein kinase; AMPKK, AMP activated protein kinase kinase.) *See Figure 18–6.

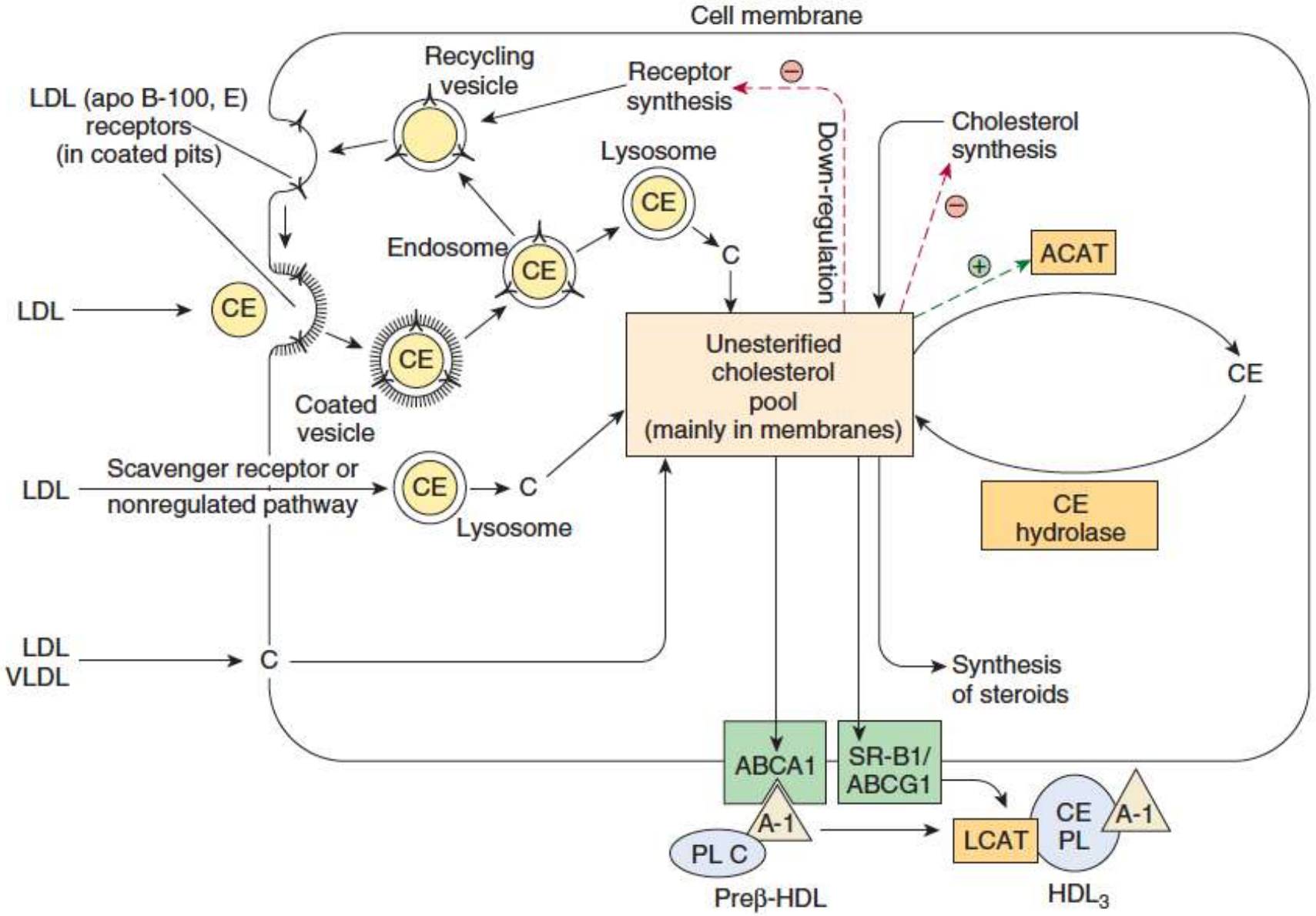


FIGURE 26–5 **Factors affecting cholesterol balance at the cellular level.** Reverse cholesterol transport may be mediated via the ABCA-1 transporter protein (with preβ-HDL as the exogenous acceptor) or the SR-B1 or ABCG-1 (with HDL_3 as the exogenous acceptor). (C, cholesterol; CE, cholesteryl ester; PL, phospholipid; ACAT, acyl-CoA:cholesterol acyltransferase; LCAT, lecithin:cholesterol acyltransferase; A-I, apolipoprotein A-I; LDL, low-density lipoprotein; VLDL, very low density lipoprotein.) LDL and HDL are not shown to scale.

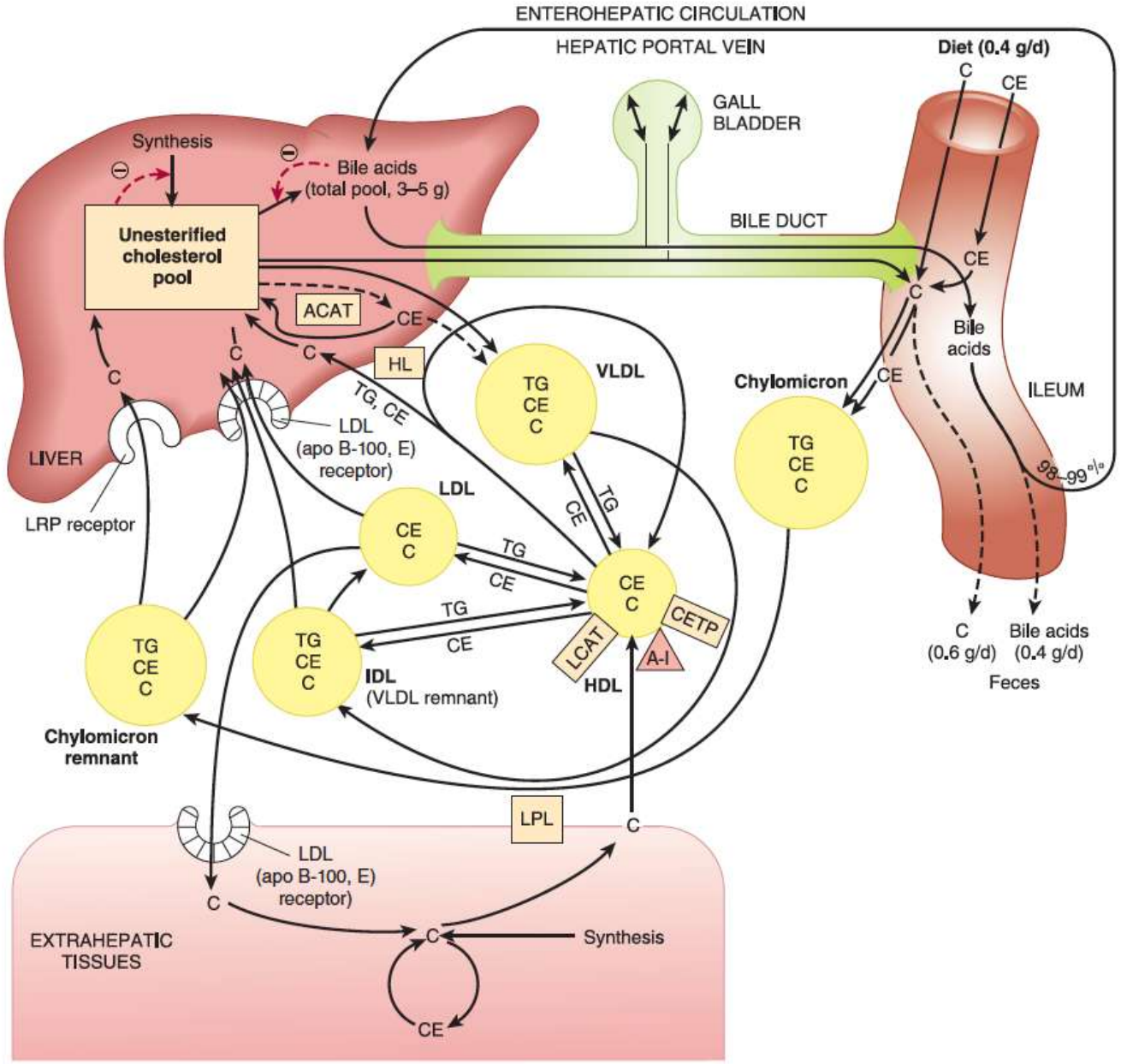


FIGURE 26–6 **Transport of cholesterol between the tissues in humans.** (ACAT, acyl-CoA:cholesterol acyltransferase; C, unesterified cholesterol; CE, cholesteryl ester; TG, triacylglycerol; VLDL, very low density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LCAT, lecithin:cholesterol acyltransferase; A-I, apolipoprotein A-I; CETP, cholesteryl ester transfer protein; LPL, lipoprotein lipase; HL, hepatic lipase; LRP, LDL receptor-related protein-1.)

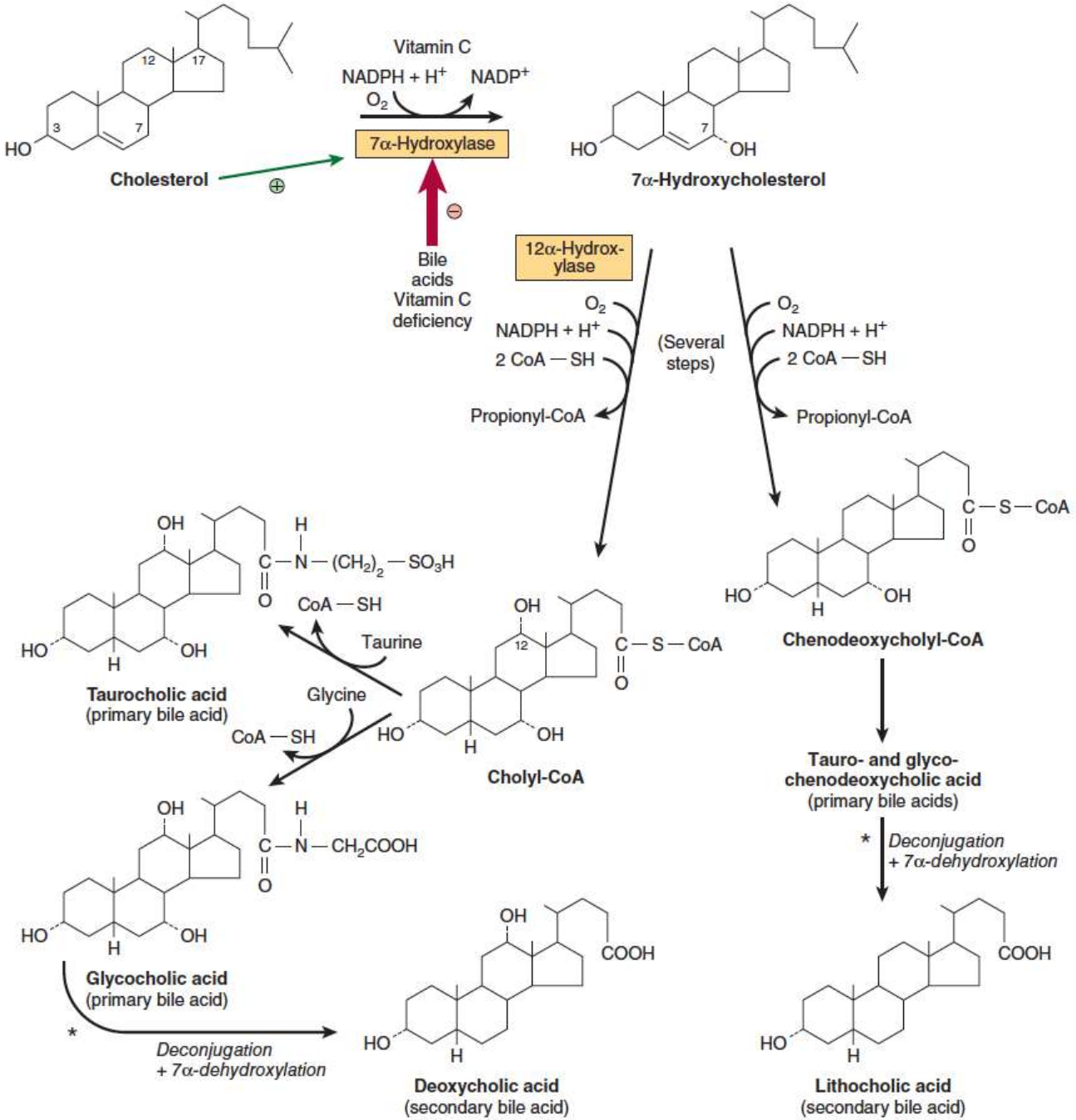
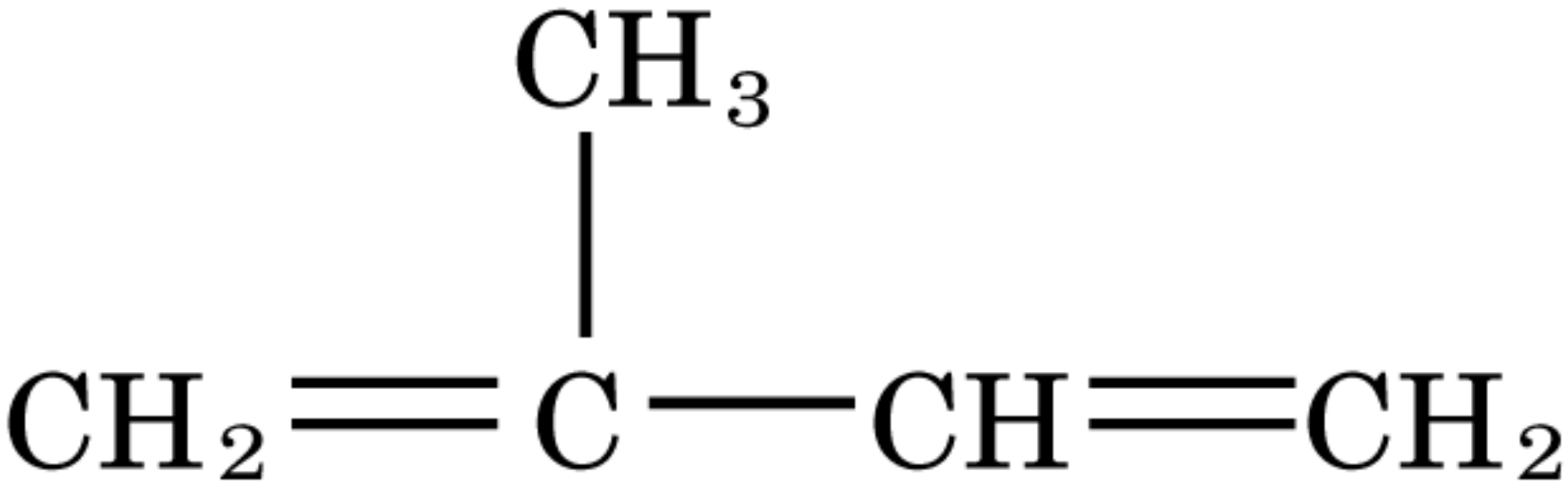


FIGURE 26–7 **Biosynthesis and degradation of bile acids.** A second pathway in mitochondria involves hydroxylation of cholesterol by sterol 27-hydroxylase. *Catalyzed by microbial enzymes.

TABLE 26-1 Primary Disorders of Plasma Lipoproteins (Dyslipoproteinemias)

Name	Defect	Remarks
Hypolipoproteinemias Abetalipoproteinermia	No chylomicrons, VLDL, or LDL are formed because of defect in the loading of apo B with lipid.	Rare; blood acylglycerols low; intestine and liver accumulate acylglycerols. Intestinal malabsorption. Early death avoidable by administration of large doses of fat-soluble vitamins, particularly vitamin E.
Familial alpha-lipoprotein deficiency Tangier disease Fish-eye disease Apo-A-I deficiencies	All have low or near absence of HDL.	Tendency toward hypertriacylglycerolemia as a result of absence of apo C-II, causing inactive LPL. Low LDL levels. Atherosclerosis in the elderly.
Hyperlipoproteinemias Familial lipoprotein lipase deficiency (type I)	Hypertriacylglycerolemia due to deficiency of LPL, abnormal LPL, or apo C-II deficiency causing inactive LPL.	Slow clearance of chylomicrons and VLDL. Low levels of LDL and HDL. No increased risk of coronary disease.
Familial hypercholesterolemia (type IIa)	Defective LDL receptors or mutation in ligand region of apo B-100.	Elevated LDL levels and hypercholesterolemia, resulting in atherosclerosis and coronary disease.
Familial type III hyperlipoproteinemia (broad beta disease, remnant removal disease, familial dysbetalipoproteinemia	Deficiency in remnant clearance by the liver is due to abnormality in apo E. Patients lack isoforms E3 and E4 and have only E2, which does not react with the E receptor.[a]	Increase in chylomicron and VLDL remnants of density <1.019 (β-VLDL). Causes hypercholesterolemia, xanthomas, and atherosclerosis.
Familial hypertriacylglycerolemia (type IV)	Overproduction of VLDL often associated with glucose intolerance and hyperinsulinemia.	Cholesterol levels rise with the VLDL concentration. LDL and HDL tend to be subnormal. This type of pattern is commonly associated with coronary heart disease, type II diabetes mellitus, obesity, alcoholism, and administration of progestational hormones.
Familial hyperalphalipoproteinemia	Increased concentrations of HDL.	A rare condition apparently beneficial to health and longevity.
Hepatic lipase deficiency	Deficiency of the enzyme leads to accumulation of large triacylglycerolrich HDL and VLDL remnants.	Patients have xanthomas and coronary heart disease.
Familial lecithin:cholesterol acyltransferase (LCAT) deficiency	Absence of LCAT leads to block in reverse cholesterol transport. HDL remains as nascent disks incapable of taking up and esterifying cholesterol.	Plasma concentrations of cholesteryl esters and lysolecithin are low. Present is an abnormal LDL fraction, lipoprotein X, found also in patients with cholestasis. VLDL is abnormal (β-VLDL).
Familial lipoprotein(a) excess	Lp(a) consists of 1 mol of LDL attached to 1 mol of apo(a). Apo(a) shows structural homologies to plasminogen.	Premature coronary heart disease due to atherosclerosis, plus thrombosis due to inhibition of fibrinolysis.

[a]There is an association between patients possessing the apo E4 allele and the incidence of Alzheimer disease. Apparently, apo E4 binds more avidly to β-amyloid found in neuritic plaques.

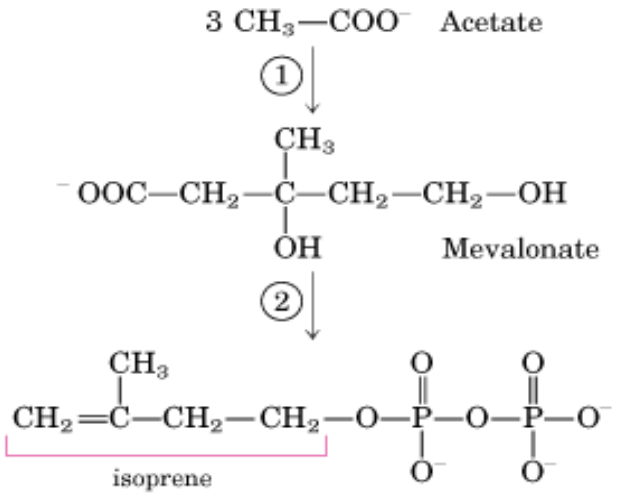


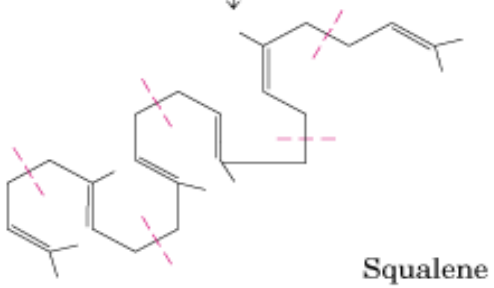
Isopreno

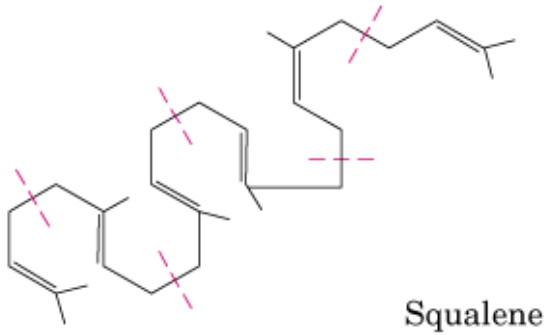
Biosíntesis de colesterol

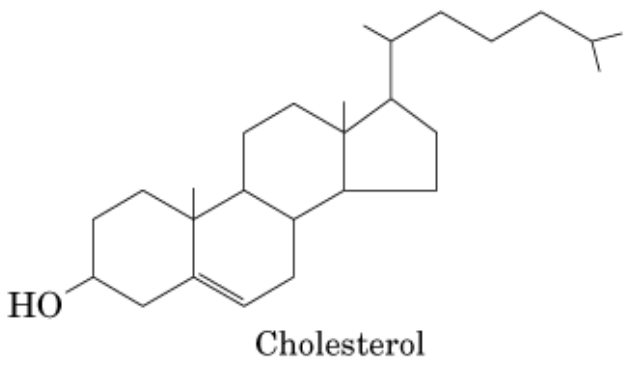
Síntesis de:

1. Mevalonato
2. Isoprenoide
3. Escualeno
4. Lanosterol
5. Colesterol









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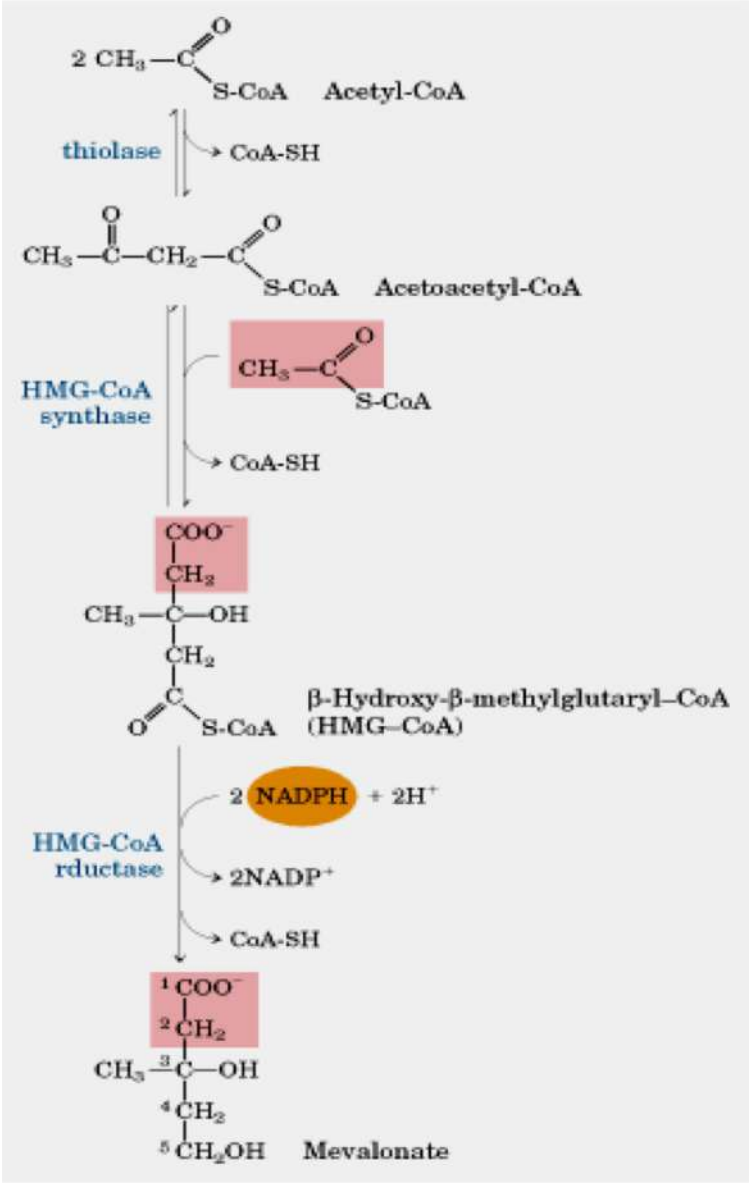
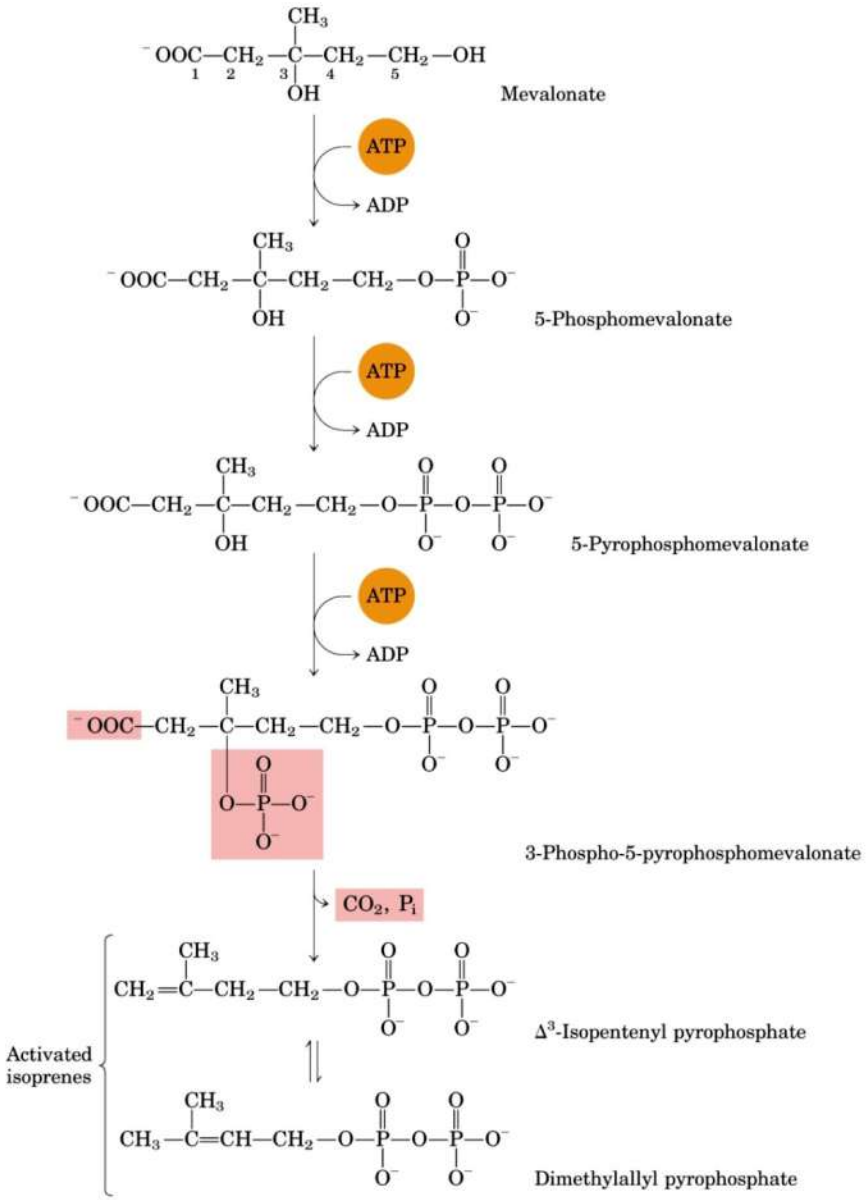
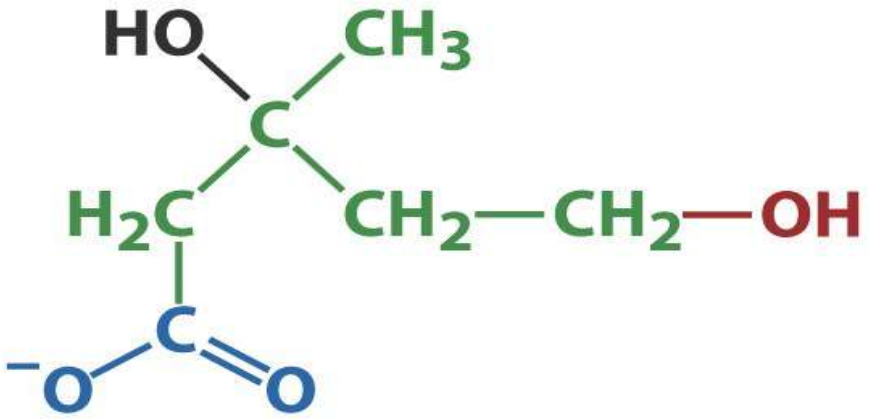


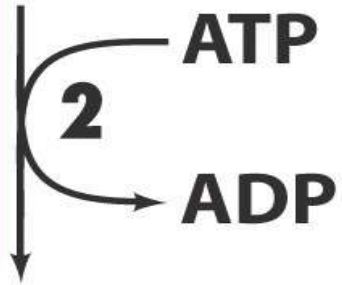
2. Síntesis de Isoprenilo

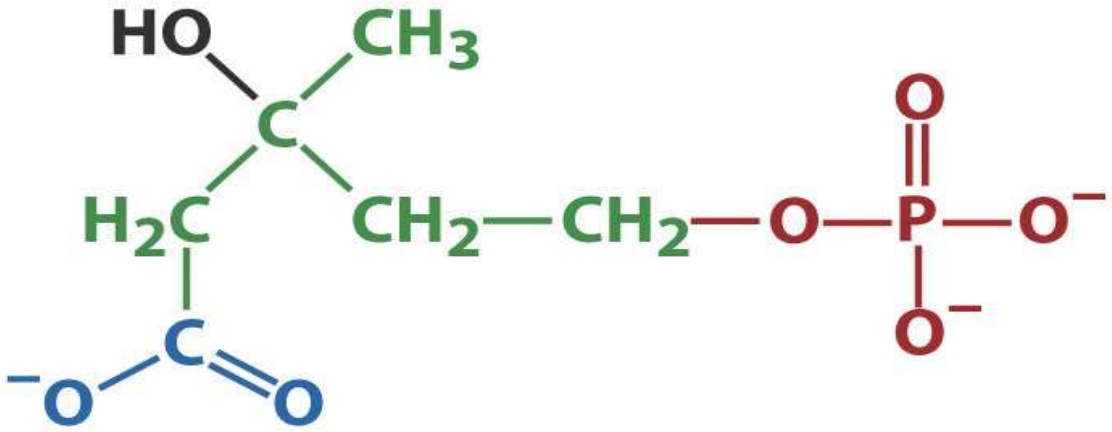




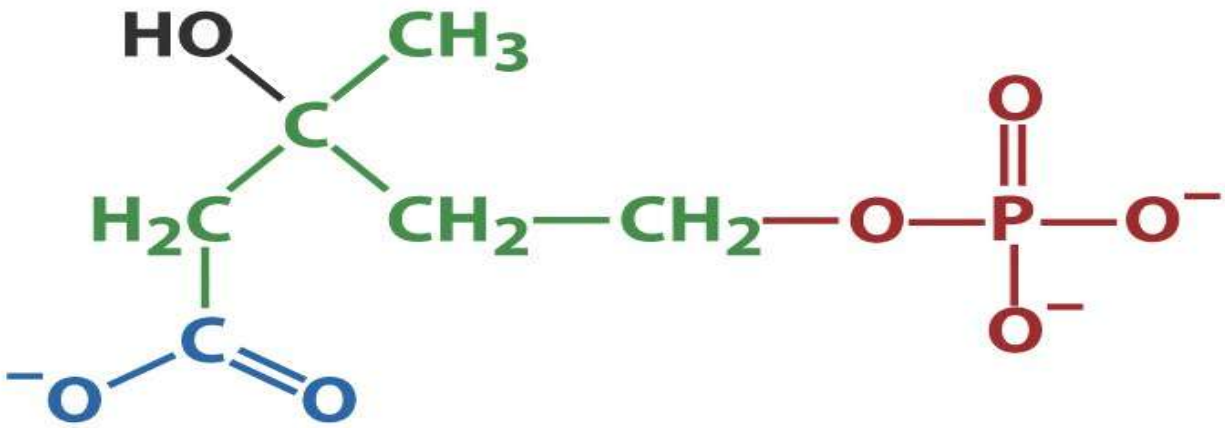
Mevalonato

Mevalonato-5-fosfotransferasa





Fosfomevalonato



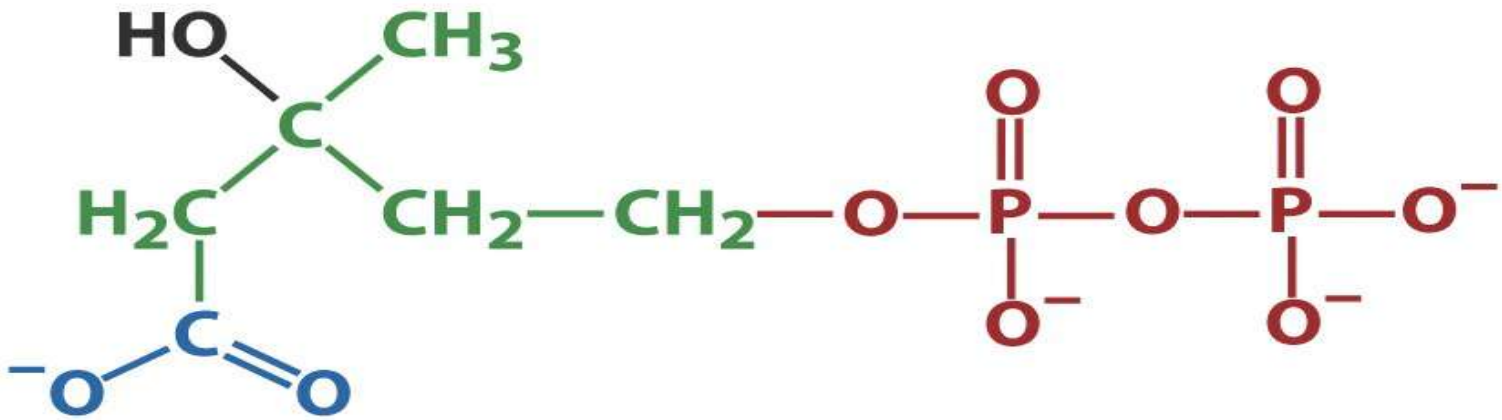
5-Fosfomevalonato

Fosfomevalonato Cinasa

ATP

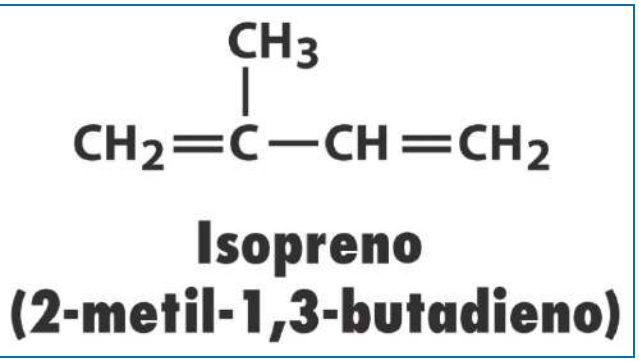
3

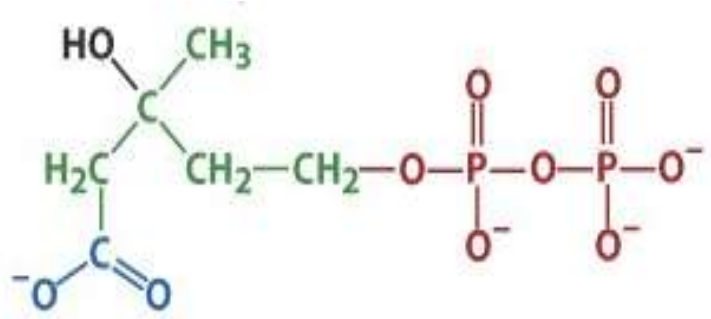
ADP



5-Pirofosfomevalonato

2. Síntesis de Isoprenoide





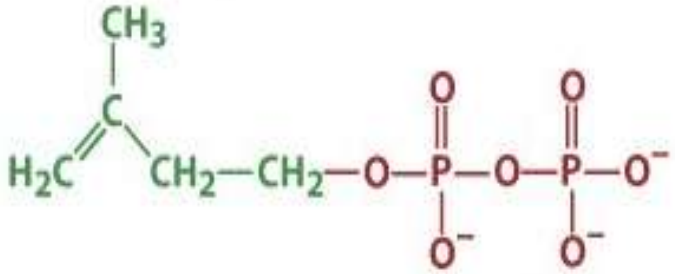
5-pirofosfomevalonato

Pirofosfomevalonato descarboxilasa

ATP

4

ADP + P_i + CO_2



Isopentenil pirofosfato

3. Síntesis de Escualeno

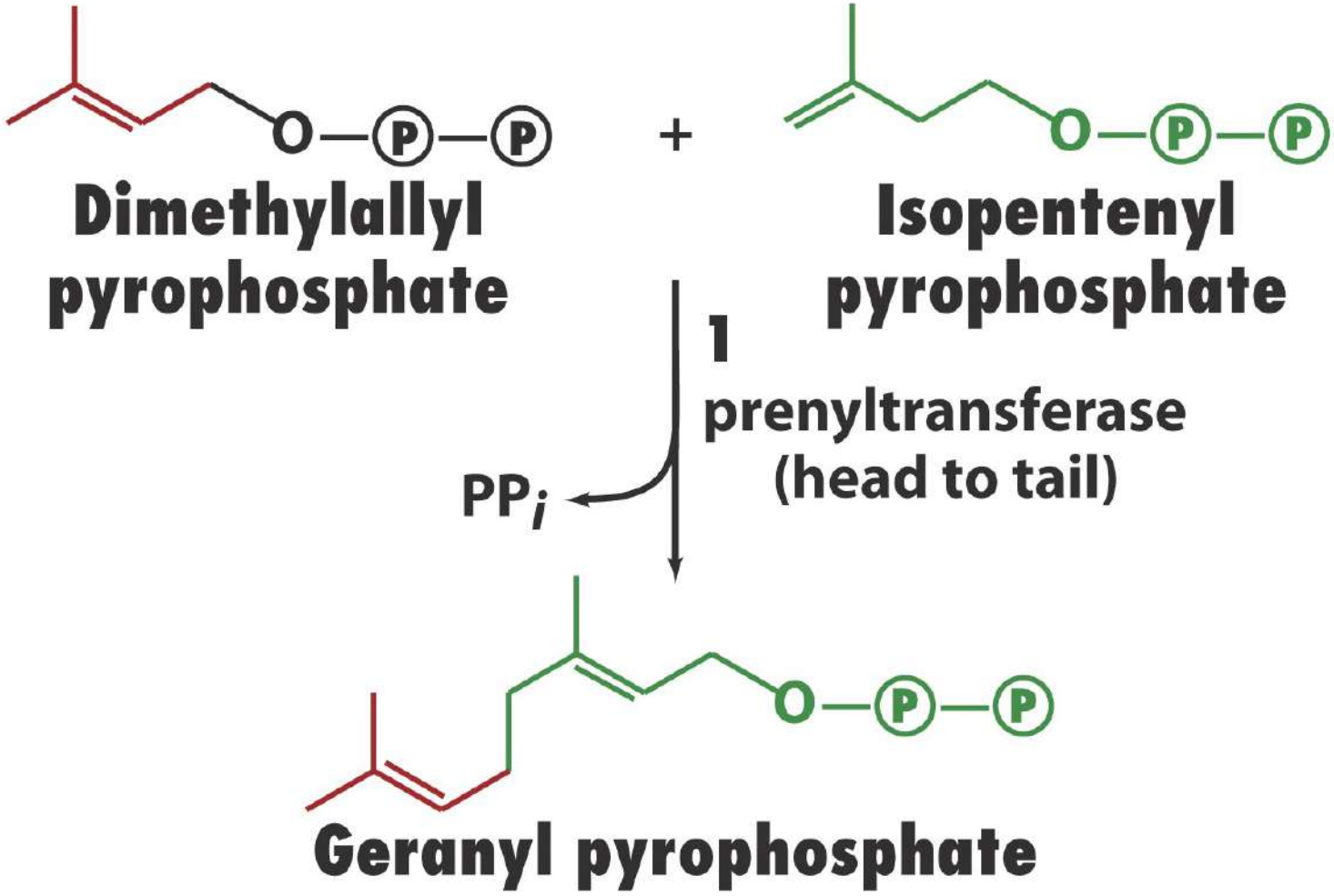
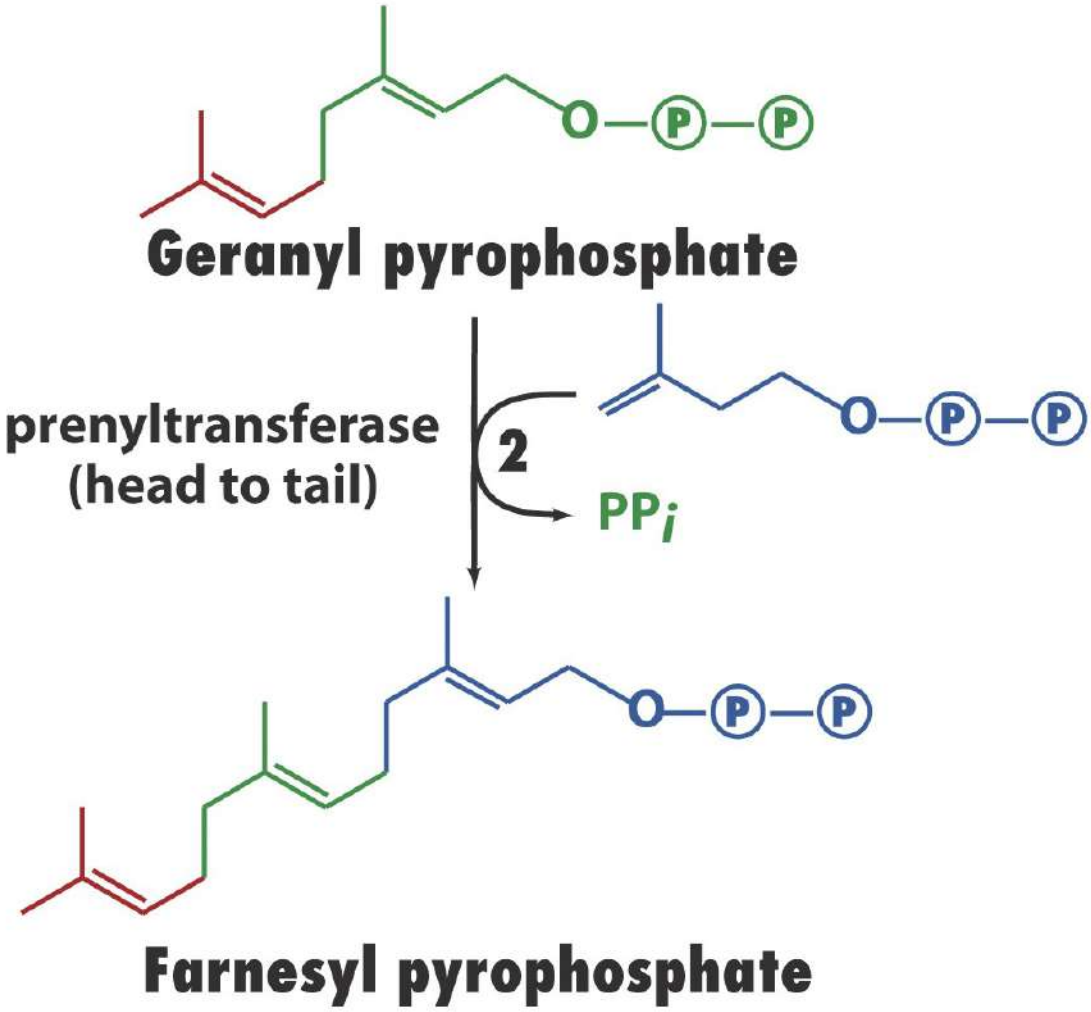
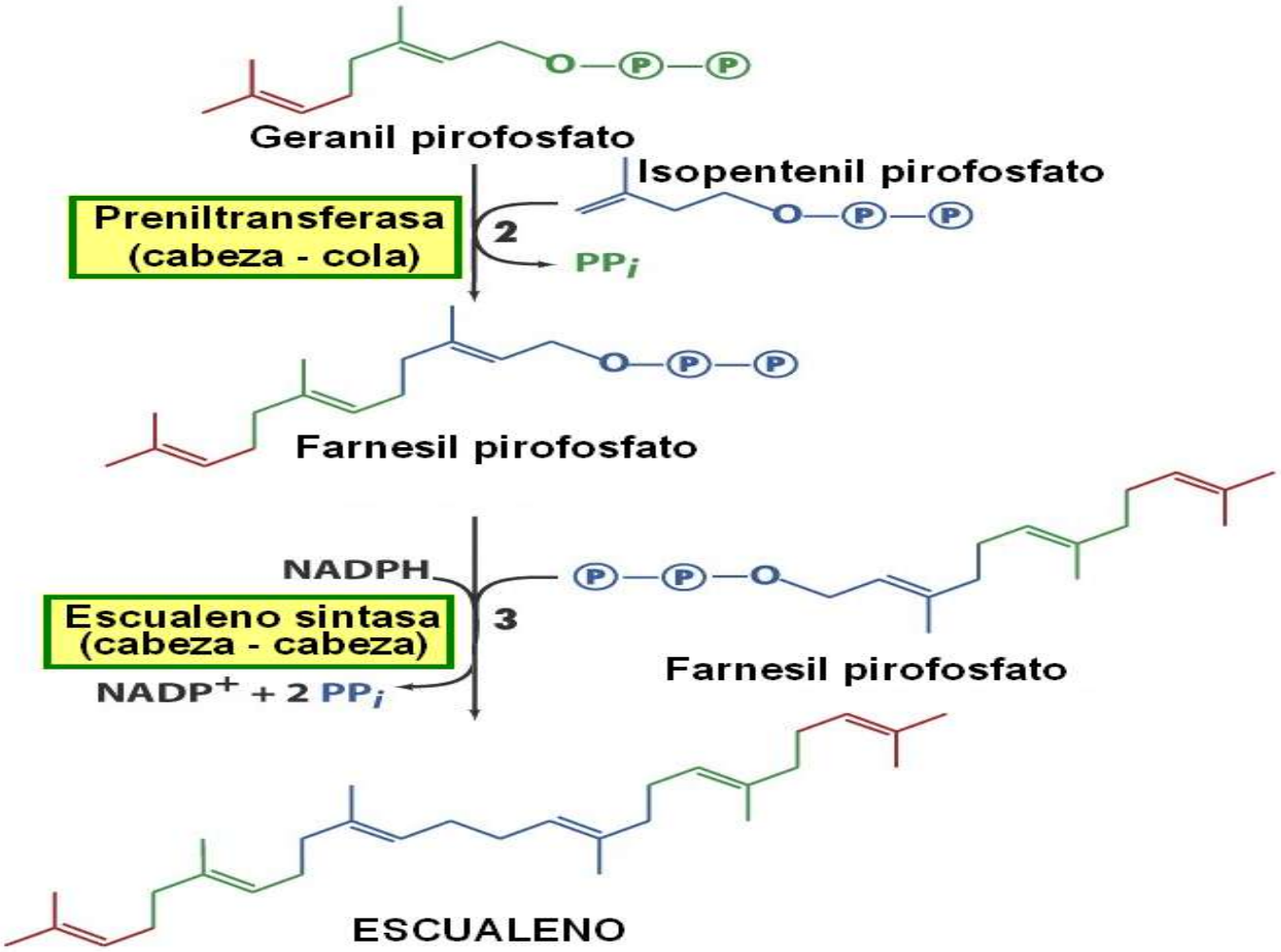


Figure 19-39 part 1 Fundamentals of Biochemistry, 2/e

3. Síntesis de Escualeno



3. Síntesis de Escualeno



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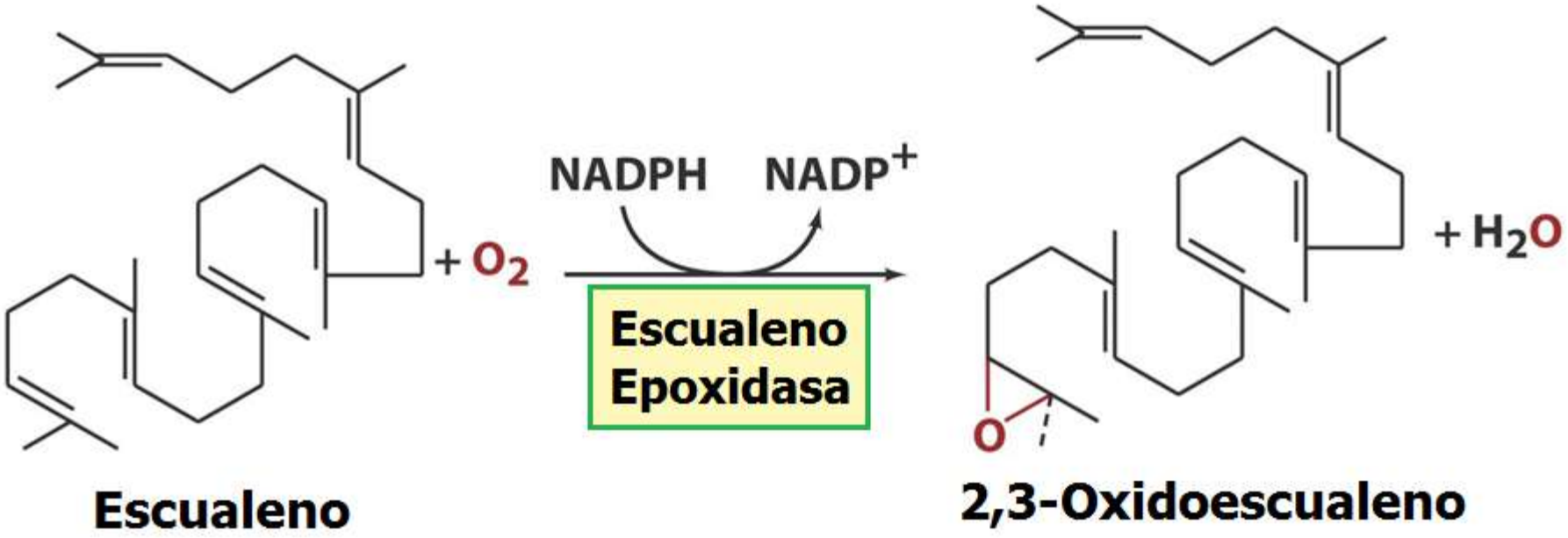

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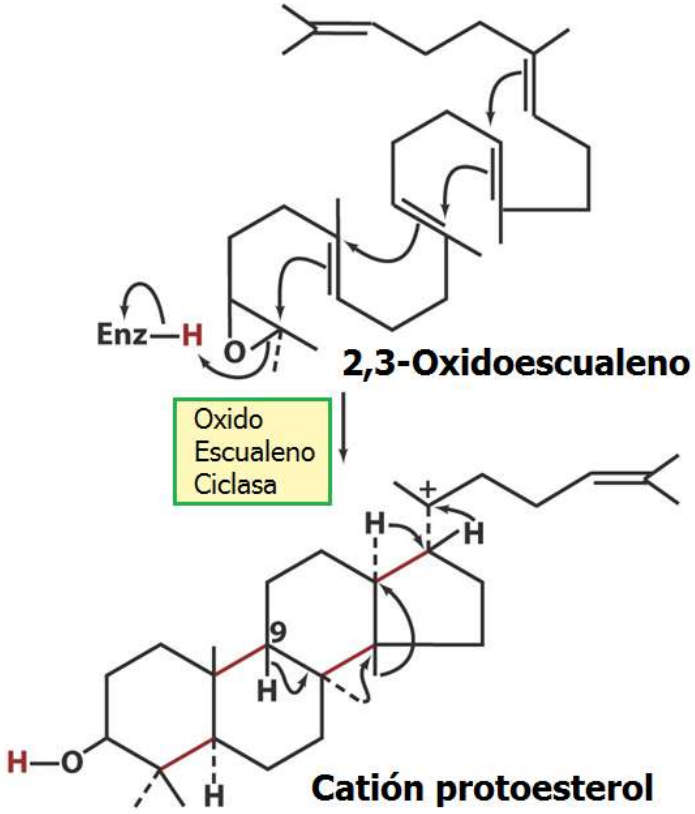
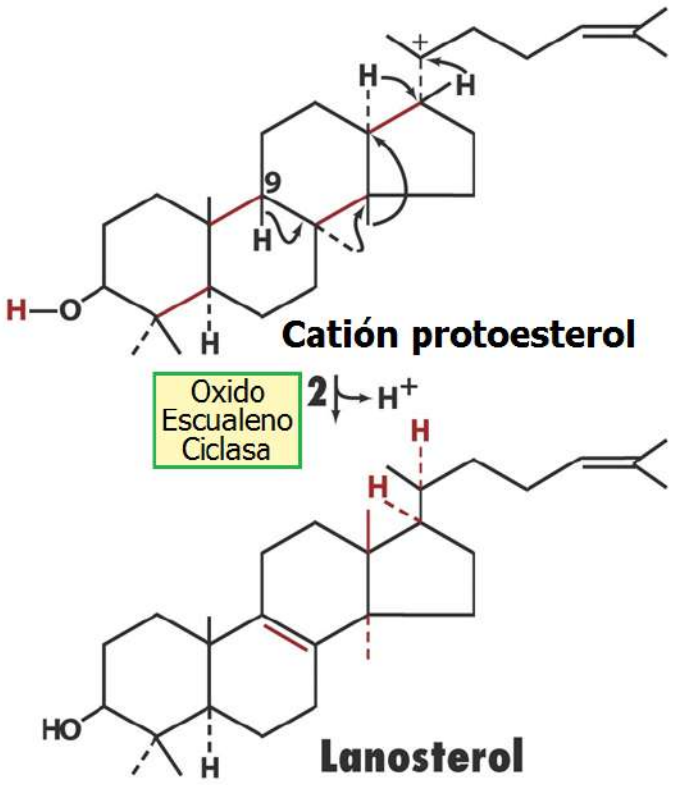


Oxidoescualeno Ciclasa:

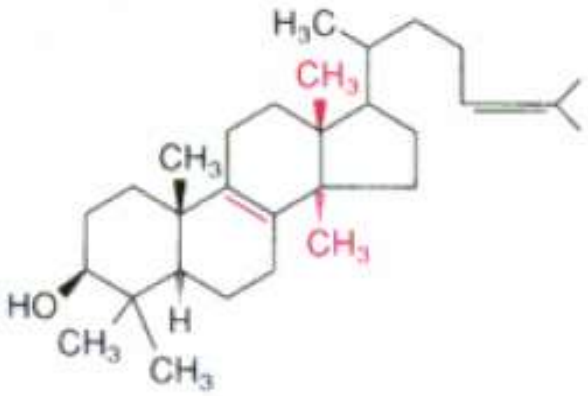
4. Síntesis de Lanosterol



Oxidoescualeno Ciclasa:

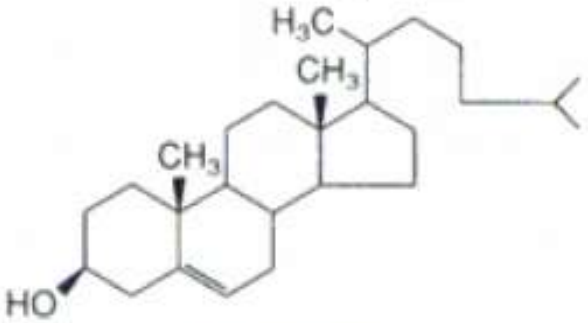
Síntesis de COLESTEROL

Lanosterol + NADPH O2
→ 14des-metil-lanosterol
+ O2 NADP NAD
14des-metil-lanosterol + O2 NADP NAD
→ Cimosterol
Cimosterol
→ *ISOMERASA*
→ Δ7-24 -colestadienol
Δ7-24 -colestadienol + NADP O2
→ Desmosterol
(24-Dehidrocolesterol)
Desmosterol + NADPH
→ Δ24 –*REDUCTASA*
→ Colesterol



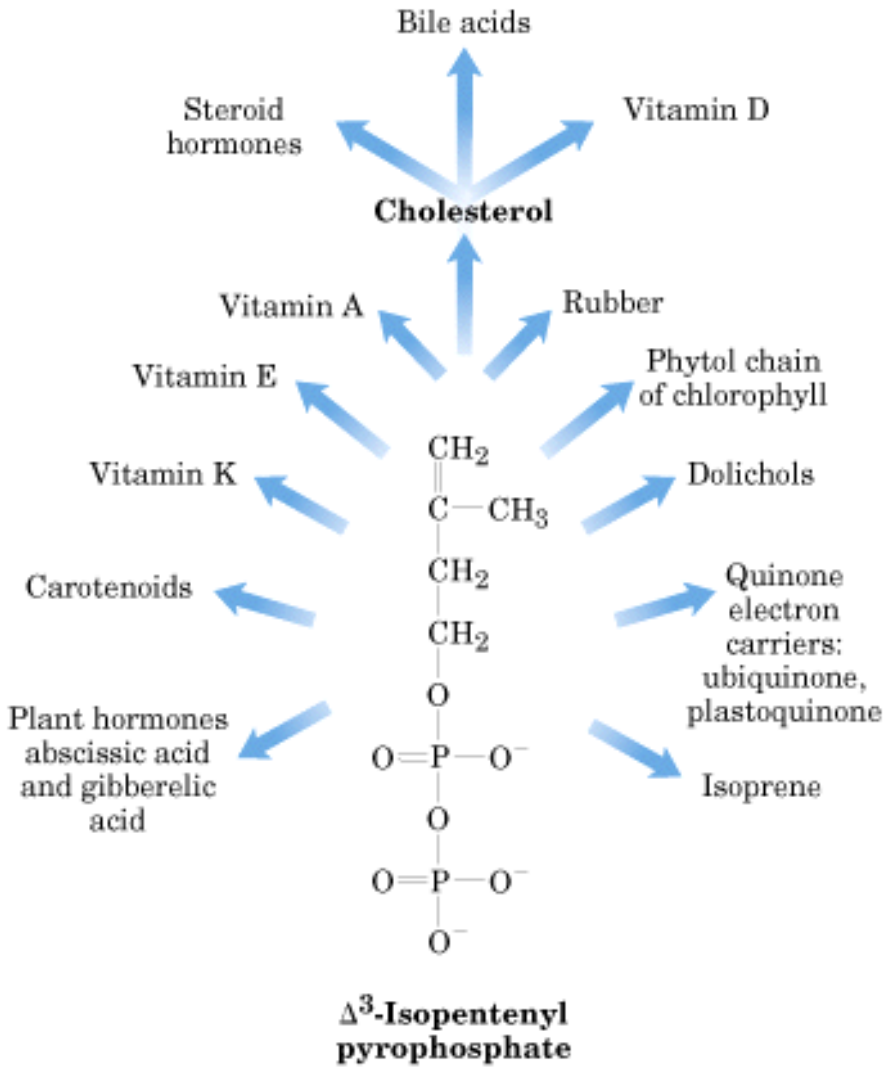
Lanosterol

Varias reacciones

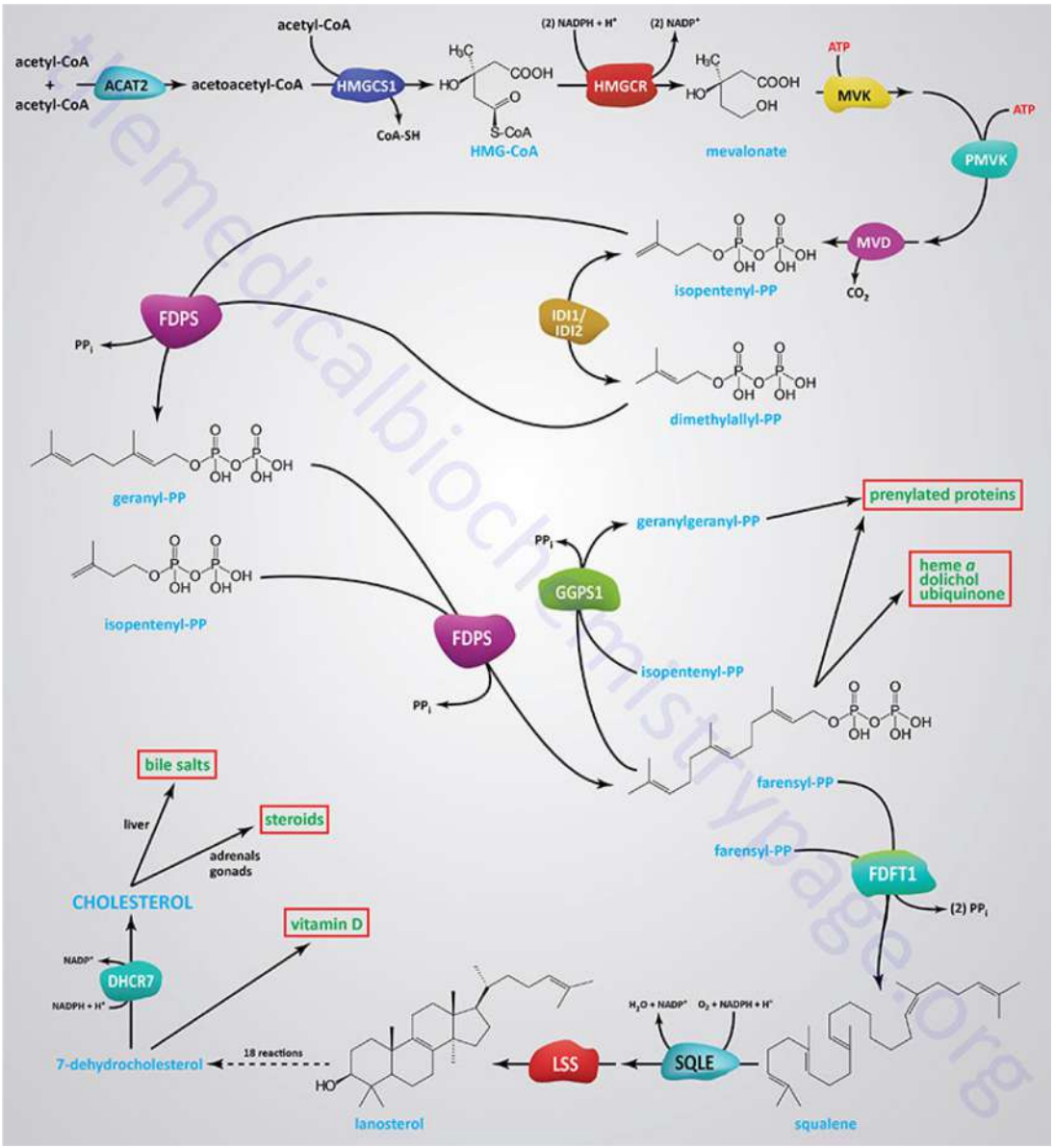


Colesterol

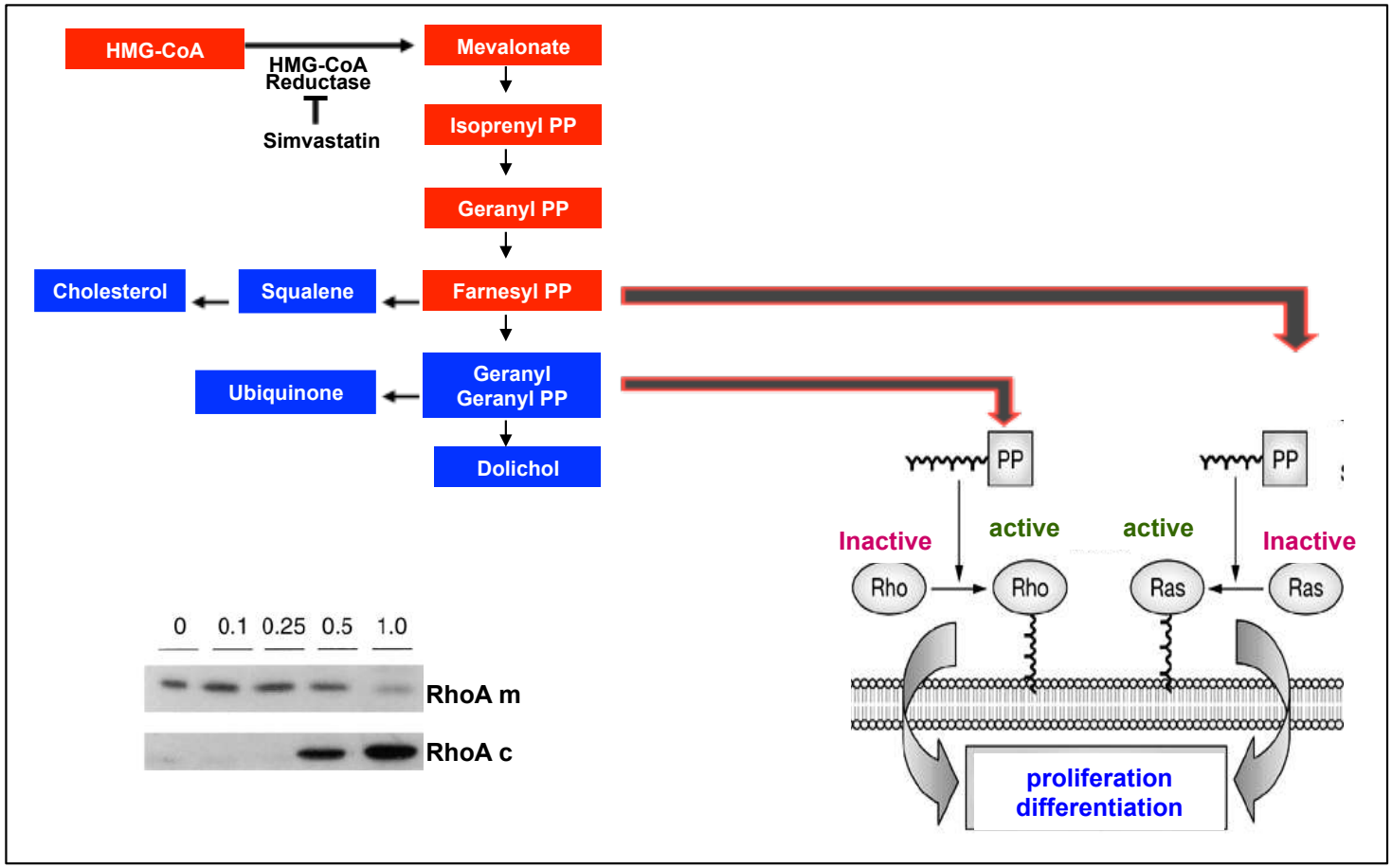
Destino de Isoprenilo



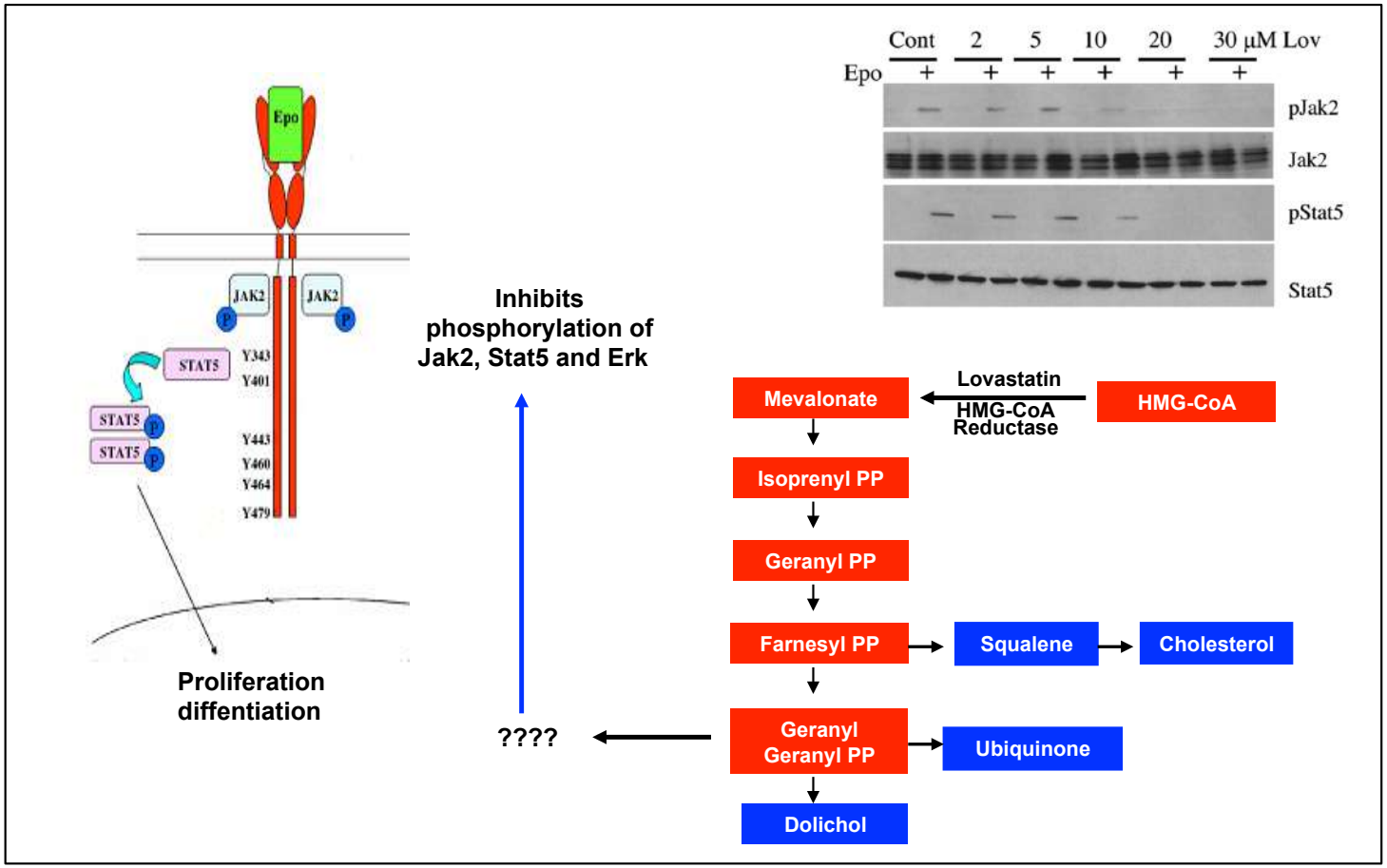
Vía del mevalonato



La simvastatina inhibe la isoprenilación de Rho and Ras

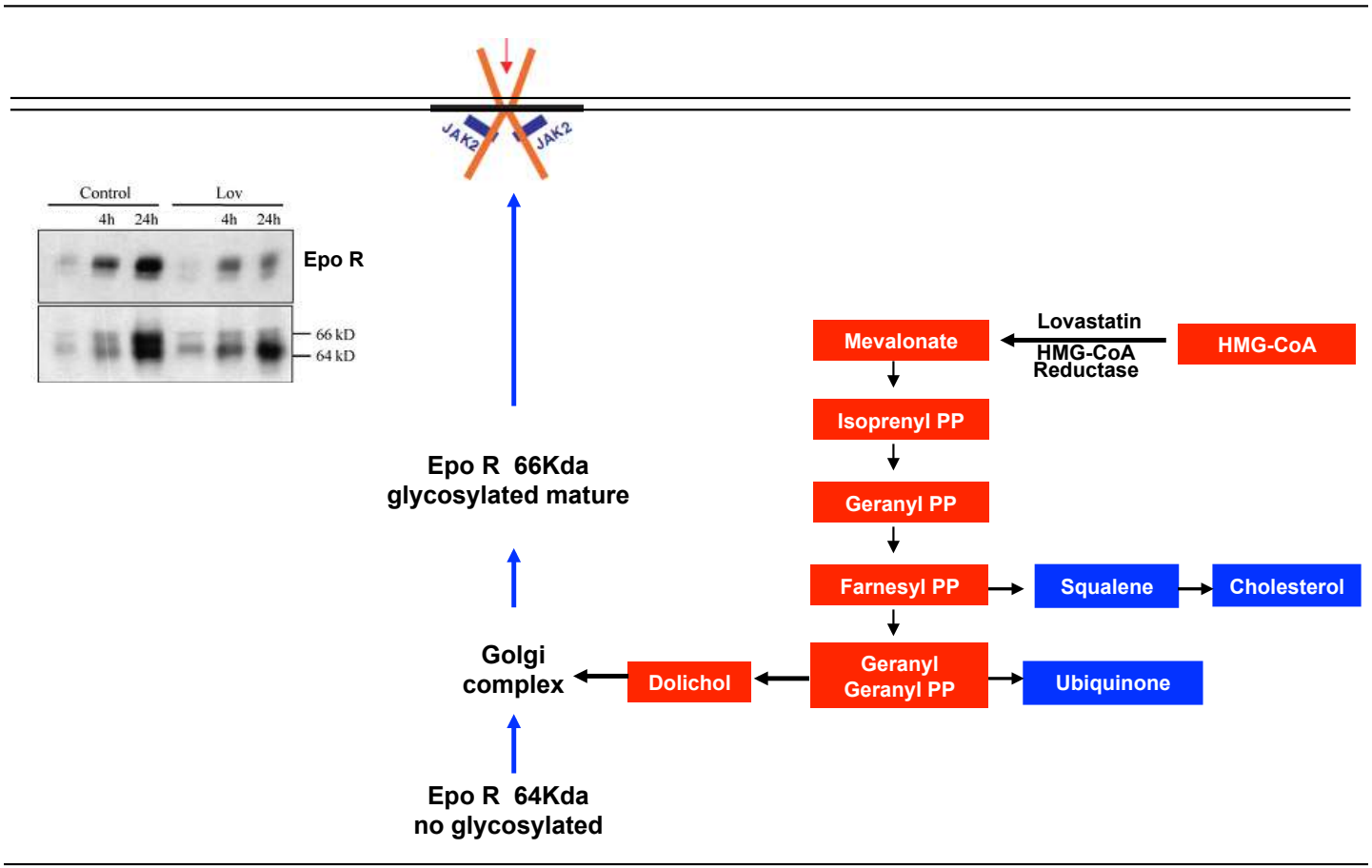


La lovastatina inhibe la fosforilación de Jak2 y Stat5



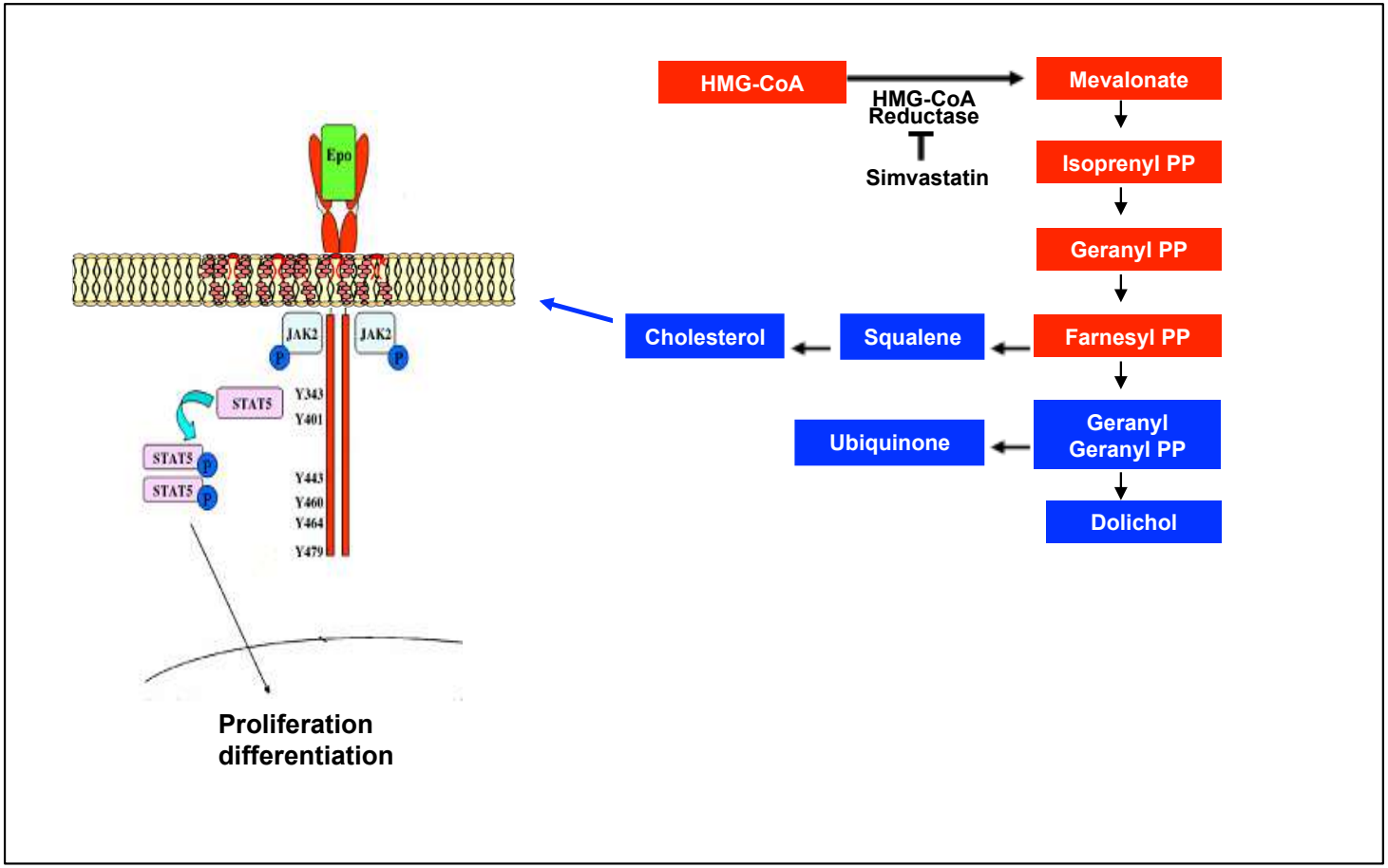
Sumaya N et al. JPET 2006;316:403-409

La lovastatina inhibe la maduración de Epo-R

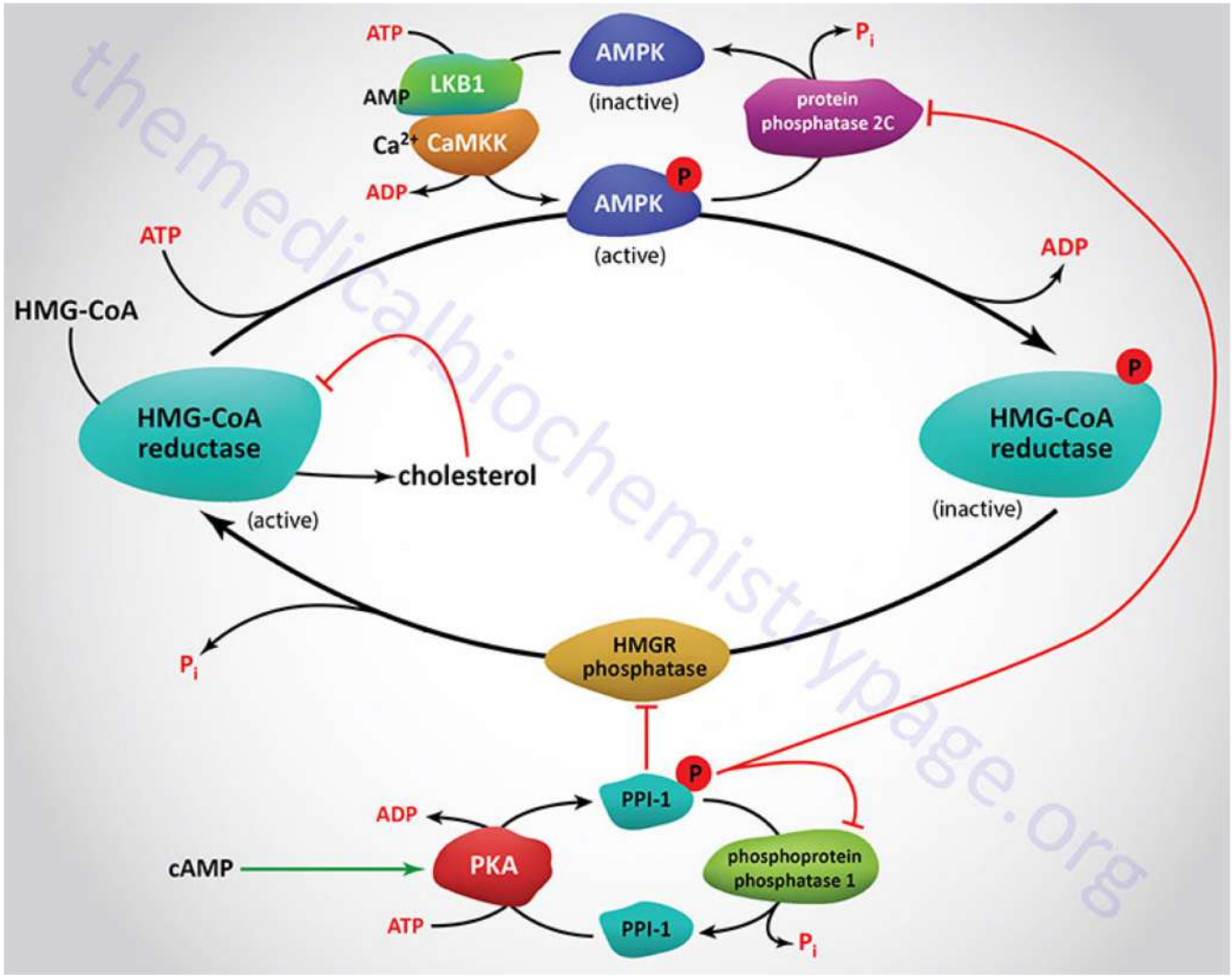


Sumaya N. Biochemical pharmacology 2007;74:590-600

La simvastatina altera la isla “lipid rafts” e inhibe la señal enviada a través de JAK2^{V617F}



Regulación de HMG-CoA reductasa



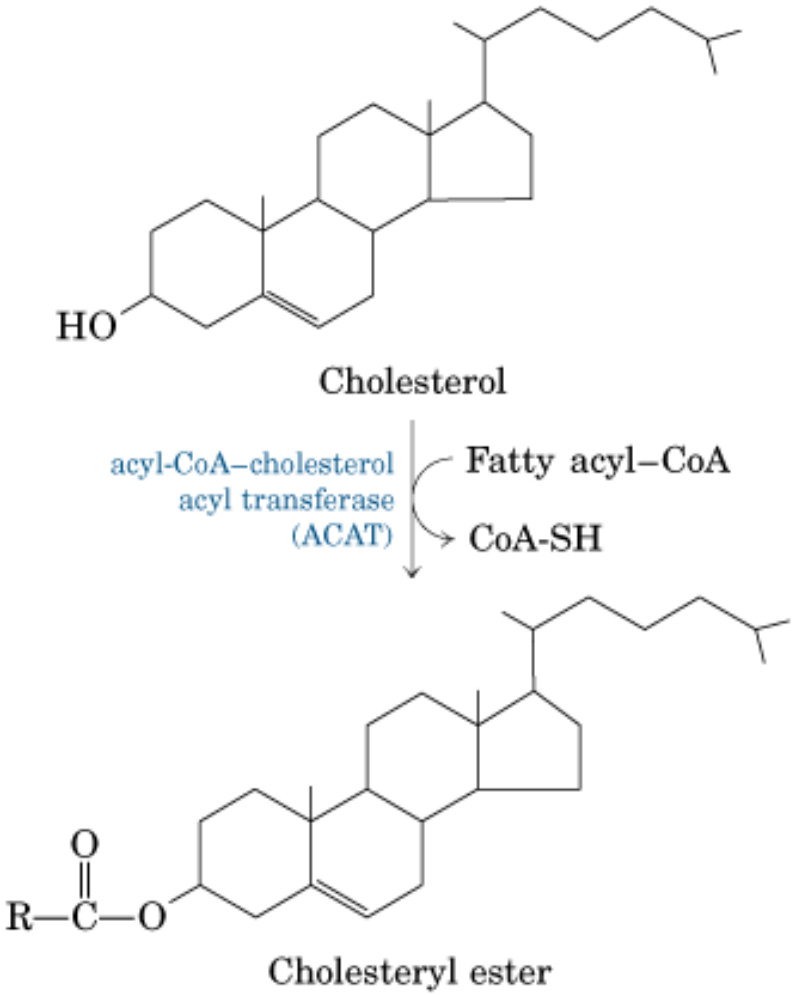
Destinos del Colesterol

a. Esterificación para su almacenamiento

b. Formación de hormonas esteroideas

c. Formación de Sales Biliares para emulsificación de los lípidos y excreción de colesterol

a. Esterificación del Colesterol



Catabolismo de colesterol

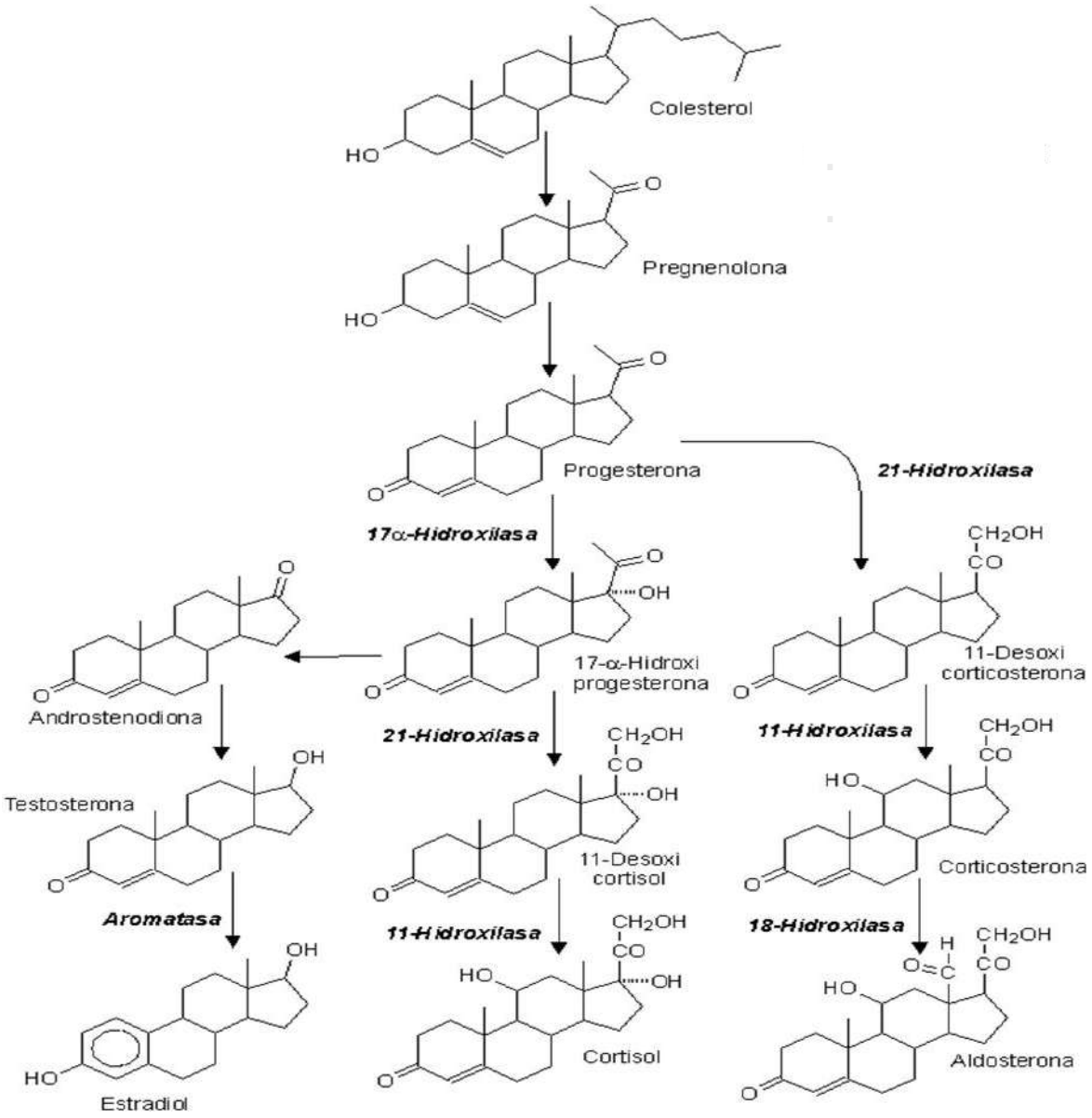
El organismo carece de enzimas para degradar al ciclopentanoperhidrofenantreno

Se elimina a través del Hígado, una parte se transforma en ácidos biliares.

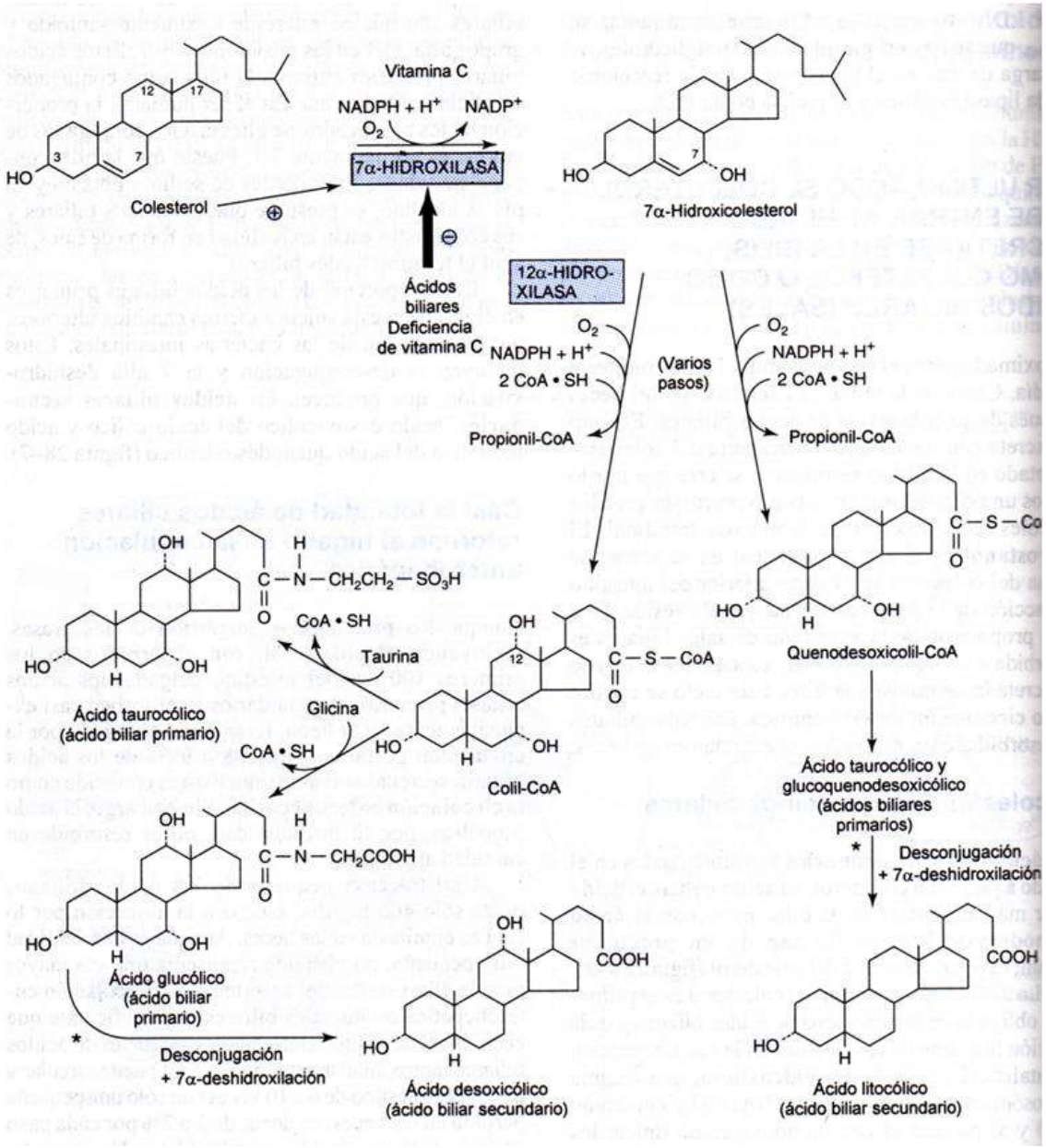
En el intestino son reabsorbidos y los que no se reabsorben, por acción de bacterias de la flora normal, se convierte en Coprostanol

Existe equilibrio entre las cantidades sintetizadas y excretadas.

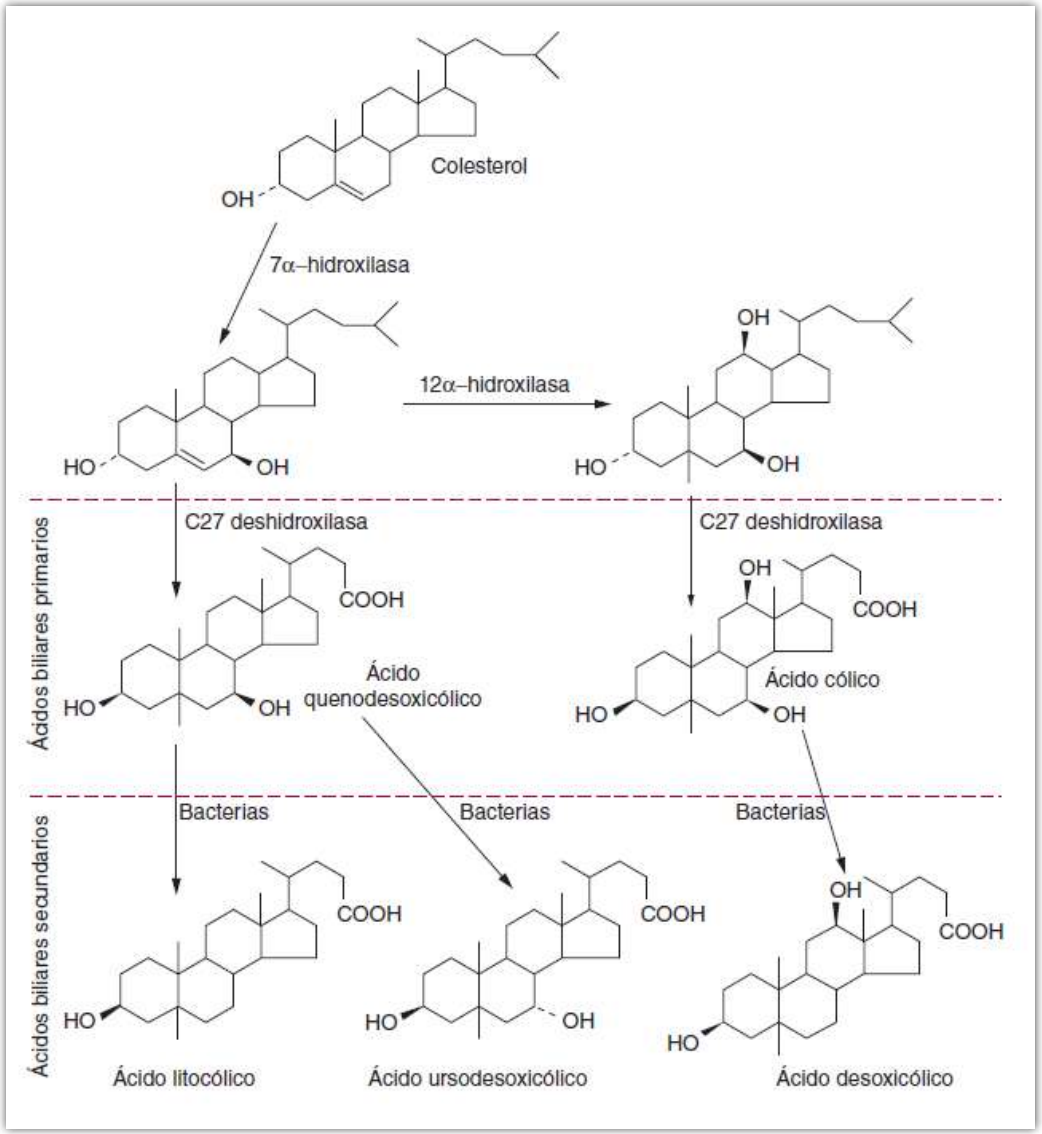
Biosíntesis del hormonas esteroidales



c. Síntesis de ácidos biliares

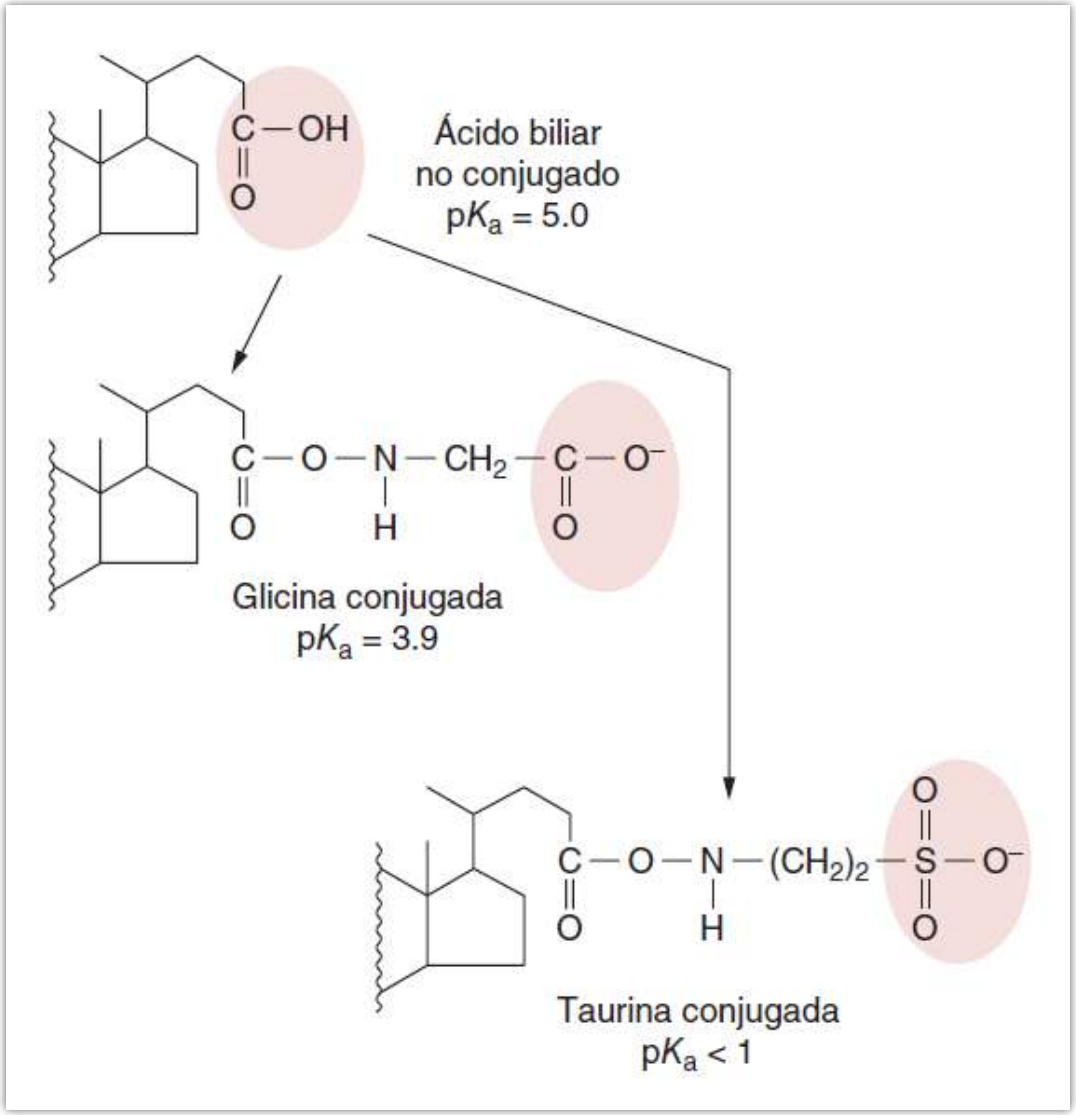


c. Síntesis de ácidos biliares



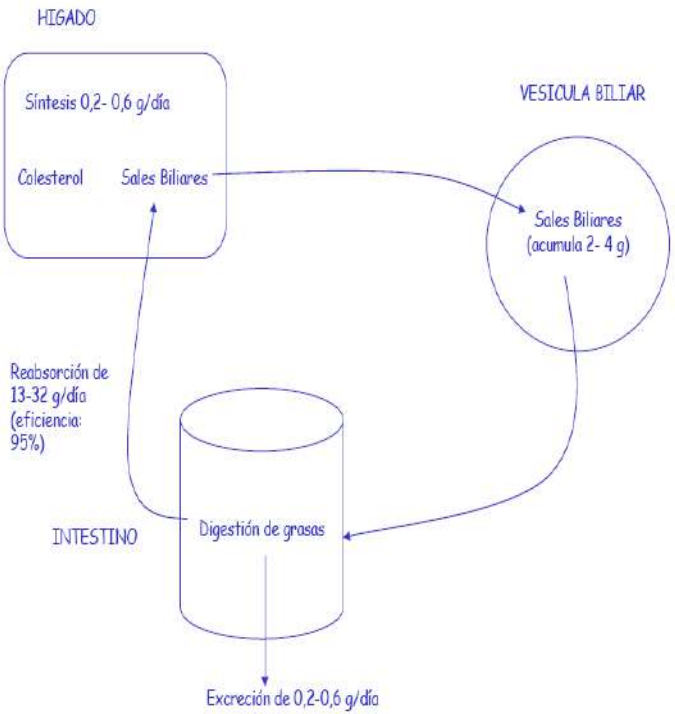
Los ácidos biliares primarios son sintetizados en el hígado, Y los ácidos biliares secundarios en el colon por enzimas bacterianas.

Conjugación de ácidos biliares



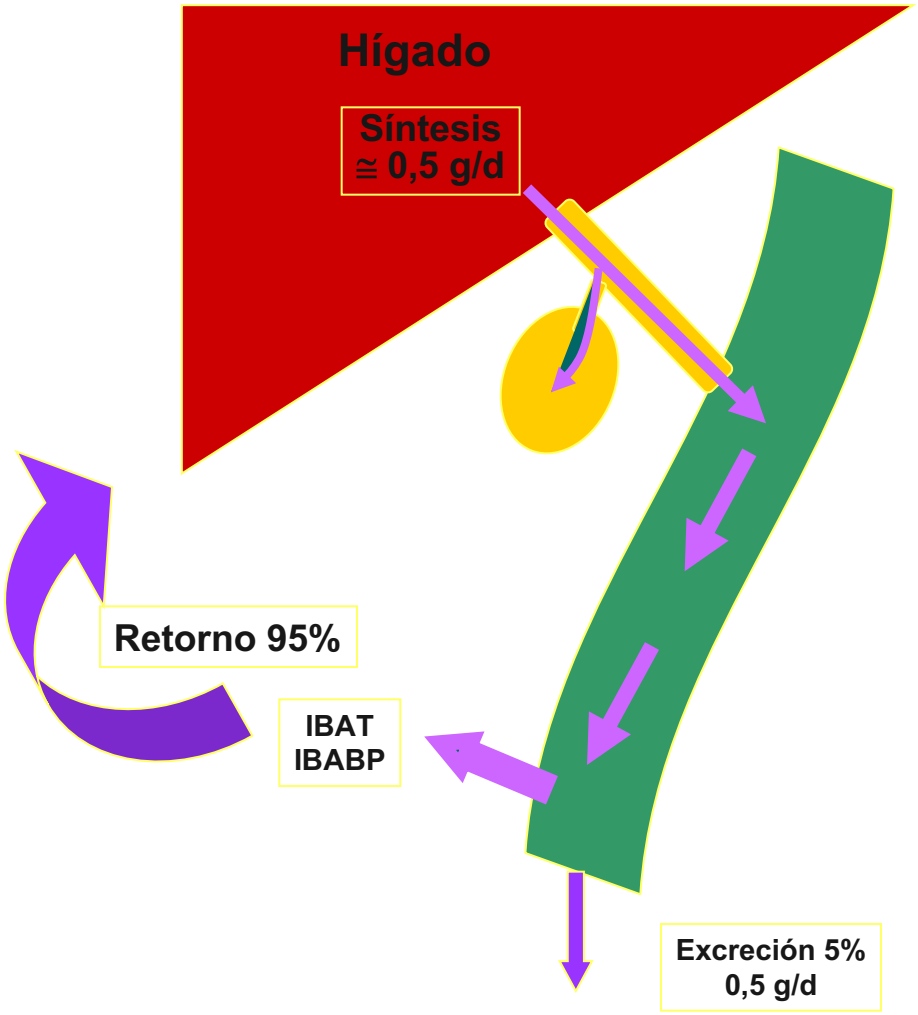
La conjugación de ácidos biliares con glicina o taurina reduce su pKa.

Circulación enterohepática de las sales biliares



- Se elimina 1 g/día.
- Ácidos biliares absorbidos en íleon (3 a 5 g)
- 98-99% retornan al hígado, 1-2% se elimina

Sales biliares: circulacion enterohepatica



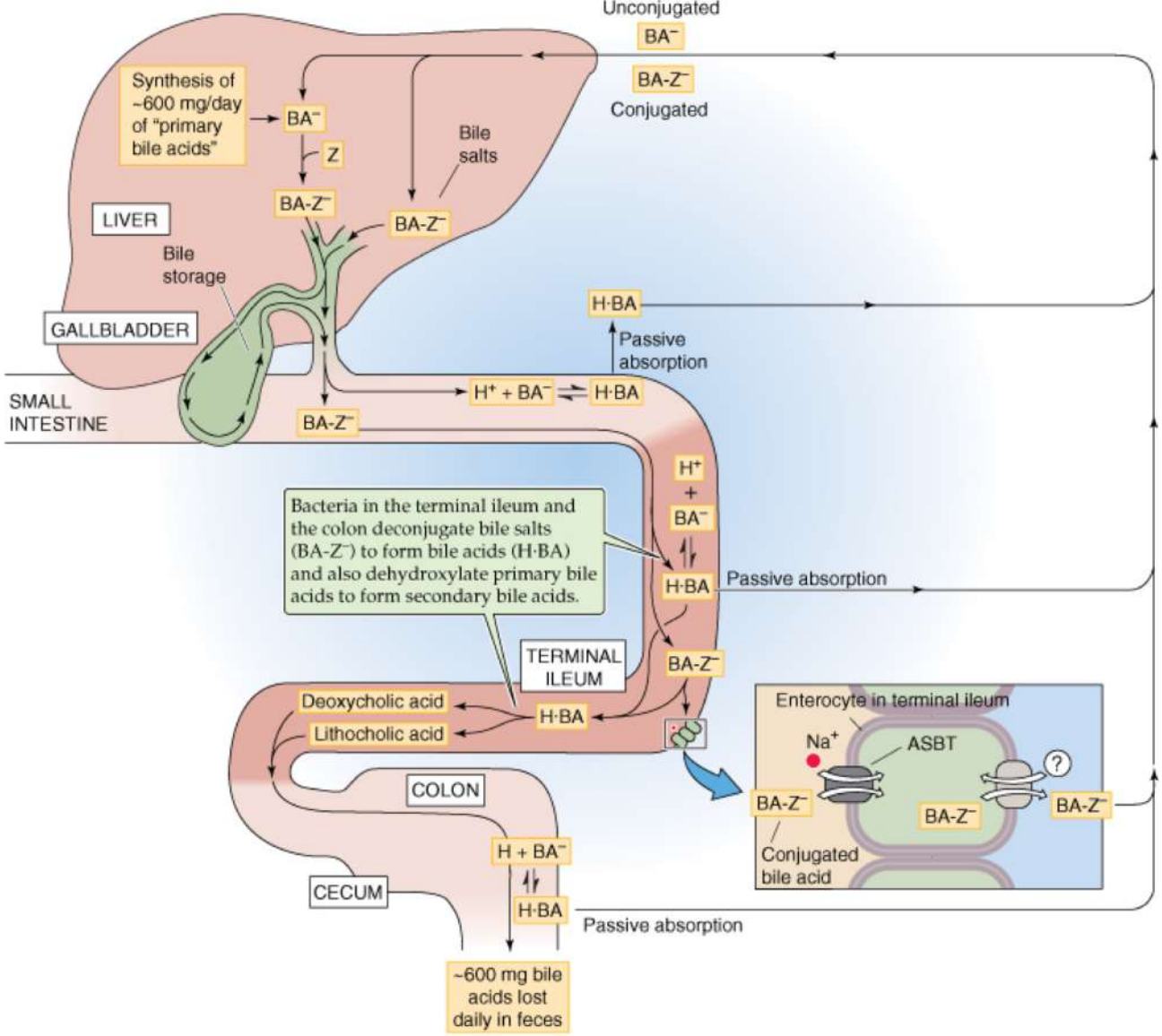


FIGURE 17-29

Enterohepatic circulation of bile salts.