Cholesterol Synthesis,Transport, & Excretion

By

Dr.Qutaiba A. Qasim

(Ph.D in Clinical Biochemistry)

BIOMEDICAL IMPORTANCE

-Cholesterol is present in tissues and in plasma either as free cholesterol or as a storage form, combined with a long-chain fatty acid as cholesteryl ester. In plasma, both forms are transported in lipoproteins .

-Cholesterol is an amphipathic lipid and as such is an **essential structural component of membranes** and of the outer layer of plasma **lipoproteins**. It is synthesized in many tissues from acetyl-CoA and is **the precursor of all other steroids in the body such as corticosteroids, sex hormones, bile acids, and vitamin D.**

BIOMEDICAL IMPORTANCE

It is eliminated from the body either unchanged or after conversion to bile acids in the process known as **reverse cholesterol transport.**

It is a major constituent of **gallstones. However,**

its chief role in pathologic processes is as a factor in the genesis of **atherosclerosis of vital arteries, causing cerebrovascular,** coronary, and peripheral vascular disease.

CHOLESTEROL IS DERIVED ABOUT EQUALLY FROM THE DIET & FROM BIOSYNTHESIS

-A little more than half the cholesterol of the body arises by synthesis (about 700 mg/d), and the remainder is provided by the average diet.

-The liver and intestine account for approximately 10% each of total synthesis in humans. Virtually all tissues containing nucleated cells are capable of cholesterol synthesis, which occurs in the endoplasmic reticulum and the cytosol.

Acetyl-CoA Is the Source of All Carbon Atoms in Cholesterol

The biosynthesis of cholesterol may be divided into five steps:

(1) Synthesis of mevalonate occurs from acetyl-CoA (Figure 26–1).

(2)Isoprenoid units are formed from mevalonate by loss of CO2 (Figure 26–2).

(3) Six isoprenoid units condense to form squalene.

(4) Squalene cyclizes to give rise to the parent steroid, lanosterol.

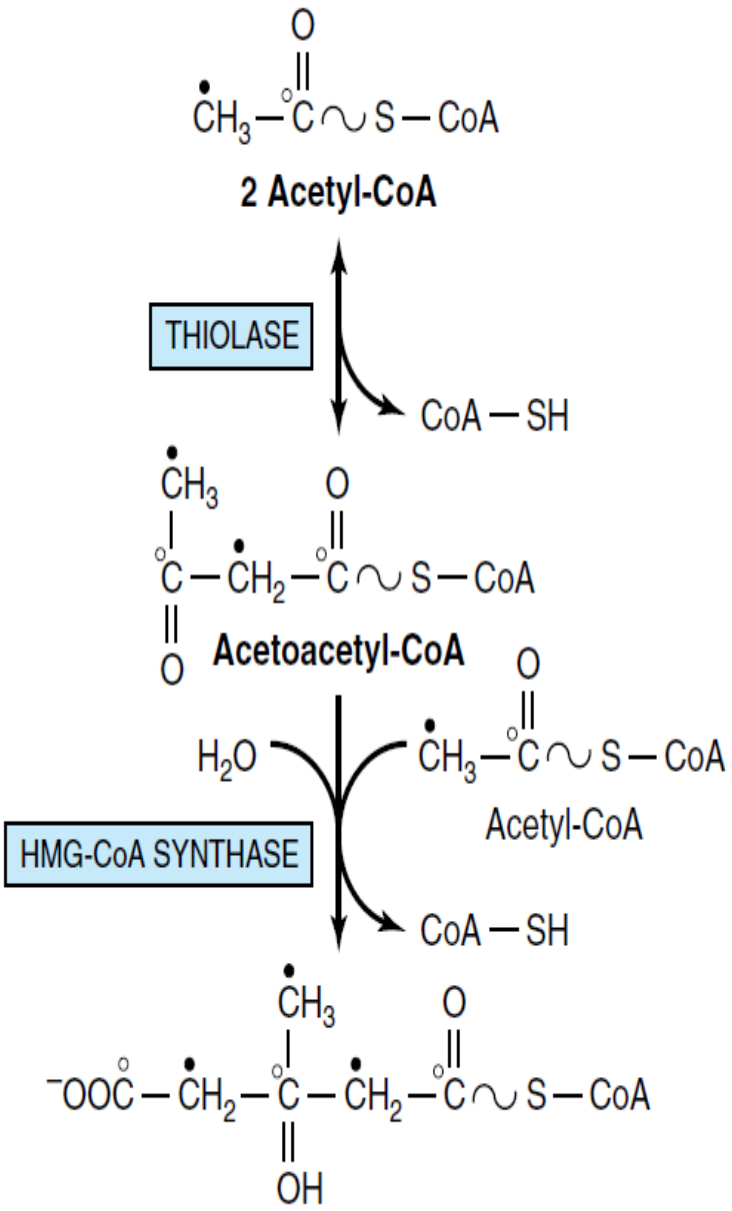
(5) Cholesterol is formed from lanosterol (Figure 26-3)

Step 1—Biosynthesis of Mevalonate

-HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) is formed by the reactions used in mitochondria to synthesize ketone bodies . However, since cholesterol synthesis is extramitochondrial, the two pathways are distinct.

Initially, two molecules of acetyl-CoA condense to form acetoacetyl-CoA catalyzed by cytosolic **thiolase.** Acetoacetyl-CoA condenses with a further molecule of acetyl-CoA catalyzed by **HMG-CoA synthase to form** HMG-CoA, which is reduced to **mevalonate by** NADPH catalyzed by **HMG-CoA reductase.**

This is the principal regulatory step in the pathway of cholesterol synthesis and is the site of action of the most effective class of cholesterol-lowering drugs, the HMG-CoA reductase inhibitors (statins) (Figure 26–1).



Farnesyl Diphosphate Gives to Dolichol & Ubiquinone

The polyisoprenoids **dolichol** (Fi Chapter 47) and **ubiquinone** (Figure from farnesyl diphosphate by the furt to 16 (dolichol) or 3–7 (ubiquii diphosphate residues, respectively. S proteins in the cell membrane are pr nesyl or geranylgeranyl (20 carbon) prenylation is believed to facilitate proteins into lipoid membranes anc volved in protein-protein interactior associated protein trafficking.

CHOLESTEROL SYNTHESIS I CONTROLLED BY REGULATI OF HMG-CoA REDUCTASE

Regulation of cholesterol synthesis i

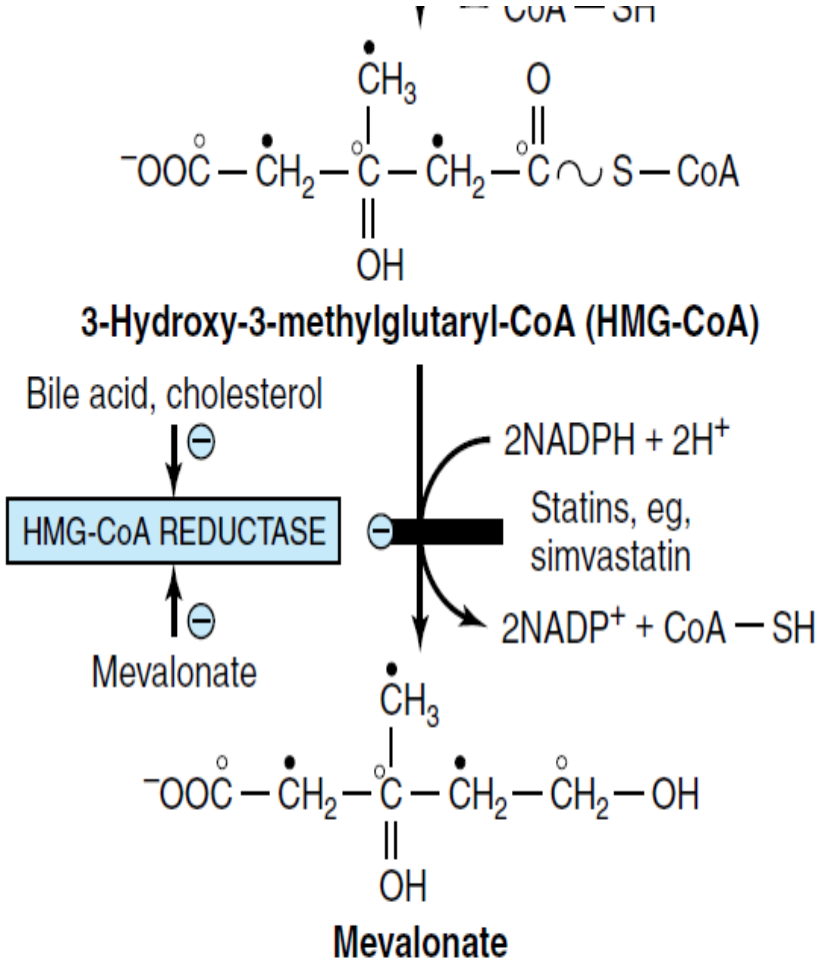


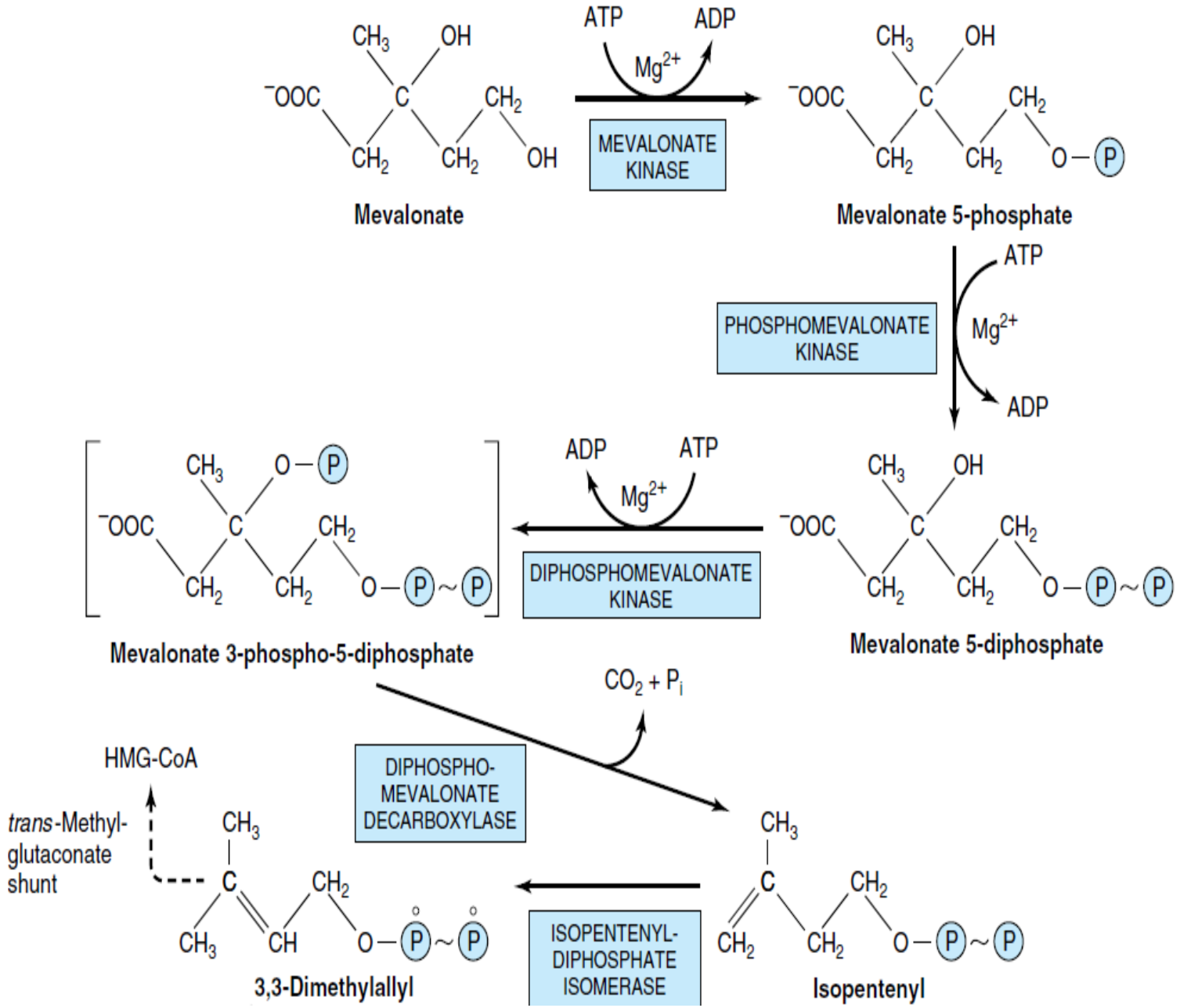
Figure 26–1. Biosynthesis of mevalonate. HMG-CoA reductase is inhibited by atorvastatin, pravastatin, and simvastatin. The open and solid circles indicate the fate of each of the carbons in the acetyl moiety of acetyl-CoA.

CHOLESTEROL SYNTHESIS I CONTROLLED BY REGULATI OF HMG-CoA REDUCTASE

Regulation of cholesterol synthesis i beginning of the pathway, at the HM step. The reduced synthesis of chol animals is accompanied by a decreas the enzyme. However, it is only hepa inhibited by dietary cholesterol. HM in liver is inhibited by mevalonate, th uct of the pathway, and by cholester uct. Cholesterol (or a metabolite, eg, represses transcription of the HM gene and is also believed to influence **urnal variation** occurs in both ch and reductase activity. In addition to regulating the rate of protein synthes tivity is also modulated more rapid tional modification (Figure 26–4).

Step 2—Formation of Isoprenoid Units

Mevalonate is phosphorylated sequentially by ATP by three kinases, and after decarboxylation (Figure 26–2) the active isoprenoid unit, **isopentenyl diphosphate, is** formed.


ATP
ADP
Mg2+
MEVALONATE KINASE
Mevalonate
Mevalonate 5-phosphate
PHOSPHOMEVALONATE KINASE
ATP
Mg2+
ADP
ADP
ATP
Mg2+
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
Isopentenyl

Step 3—Six Isoprenoid Units Form Squalene

Isopentenyl diphosphate is isomerized by a shift of the double bond to form **dimethylallyl diphosphate, then** condensed with another molecule of isopentenyl diphosphate to form the ten-carbon intermediate **geranyl diphosphate (Figure 26–2). A further condensation** with isopentenyl diphosphate forms **farnesyl diphosphate. Two molecules of farnesyl diphosphate** condense at the diphosphate end to form **squalene. Initially,** inorganic pyrophosphate is eliminated, forming presqualene diphosphate, which is then reduced by NADPH with elimination of a further inorganic pyrophosphate molecule.

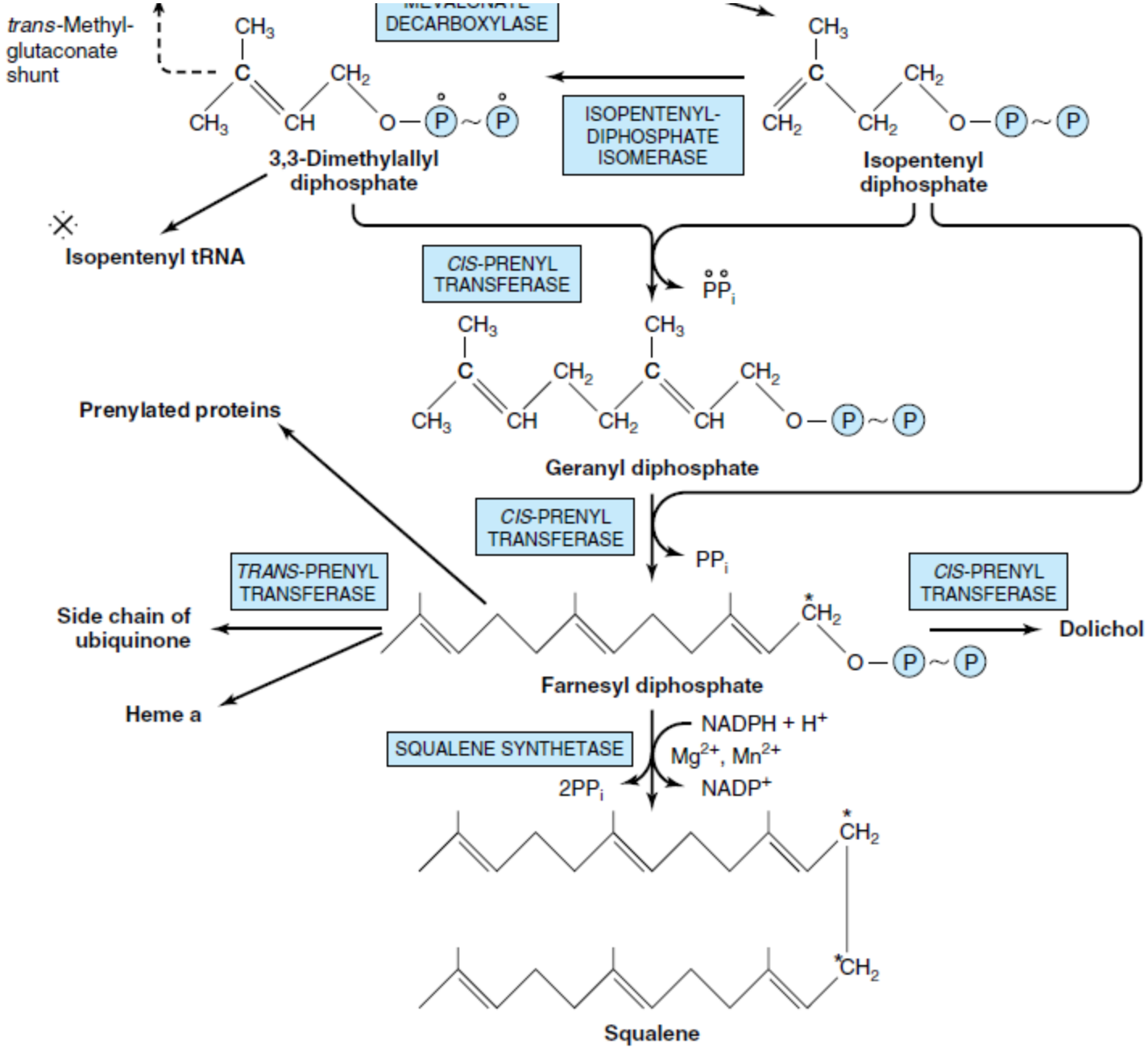
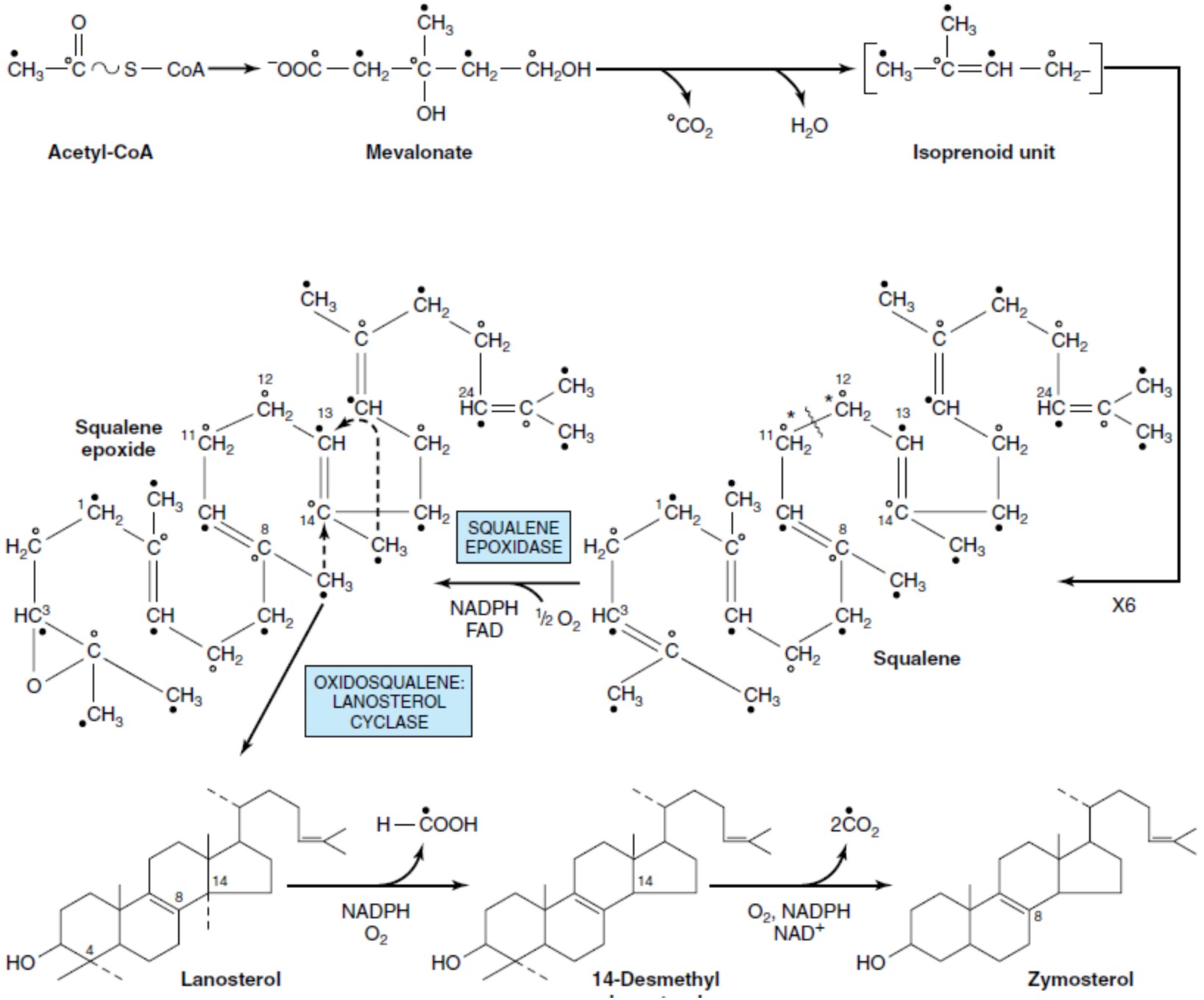


Figure 26–2. Biosynthesis of squalene, ubiquinone, dolichol, and other polyisoprene derivatives. (HMG,

Step 4—Formation of Lanosterol

Squalene can fold into a structure that closely resembles the steroid nucleus (Figure 26–3). Before ring closure occurs, squalene is converted to squalene 2,3-epoxide by a mixed function oxidase in the endoplasmic reticulum, **squalene epoxidase.**

The methyl group on C14 is transferred to C13 and that on C8 to C14 as cyclization occurs, catalyzed by **oxidosqualene:lanosterol cyclase.**


Acetyl-CoA
Mevalonate
Isoprenoid unit
X6
Squalene
Squalene epoxide
SQUALENE EPOXIDASE
NADPH
FAD
½ O2
OXIDOSQUALENE: LANOSTEROL CYCLASE
Lanosterol
NADPH
O2
14-Desmethyl
O2, NADPH
NAD+
Zymosterol

Step 5—Formation of Cholesterol

The formation of cholesterol from **lanosterol takes place in the** membranes of the endoplasmic reticulum and involves changes in the steroid nucleus and side chain (Figure 26–3). The methyl groups on C14 and C4 are removed to form 14-desmethyl lanosterol and then zymosterol.

The double bond at C8–C9 is subsequently moved to C5–C6 in two steps, forming **desmosterol. Finally, the** double bond of the side chain is reduced, producing cholesterol.

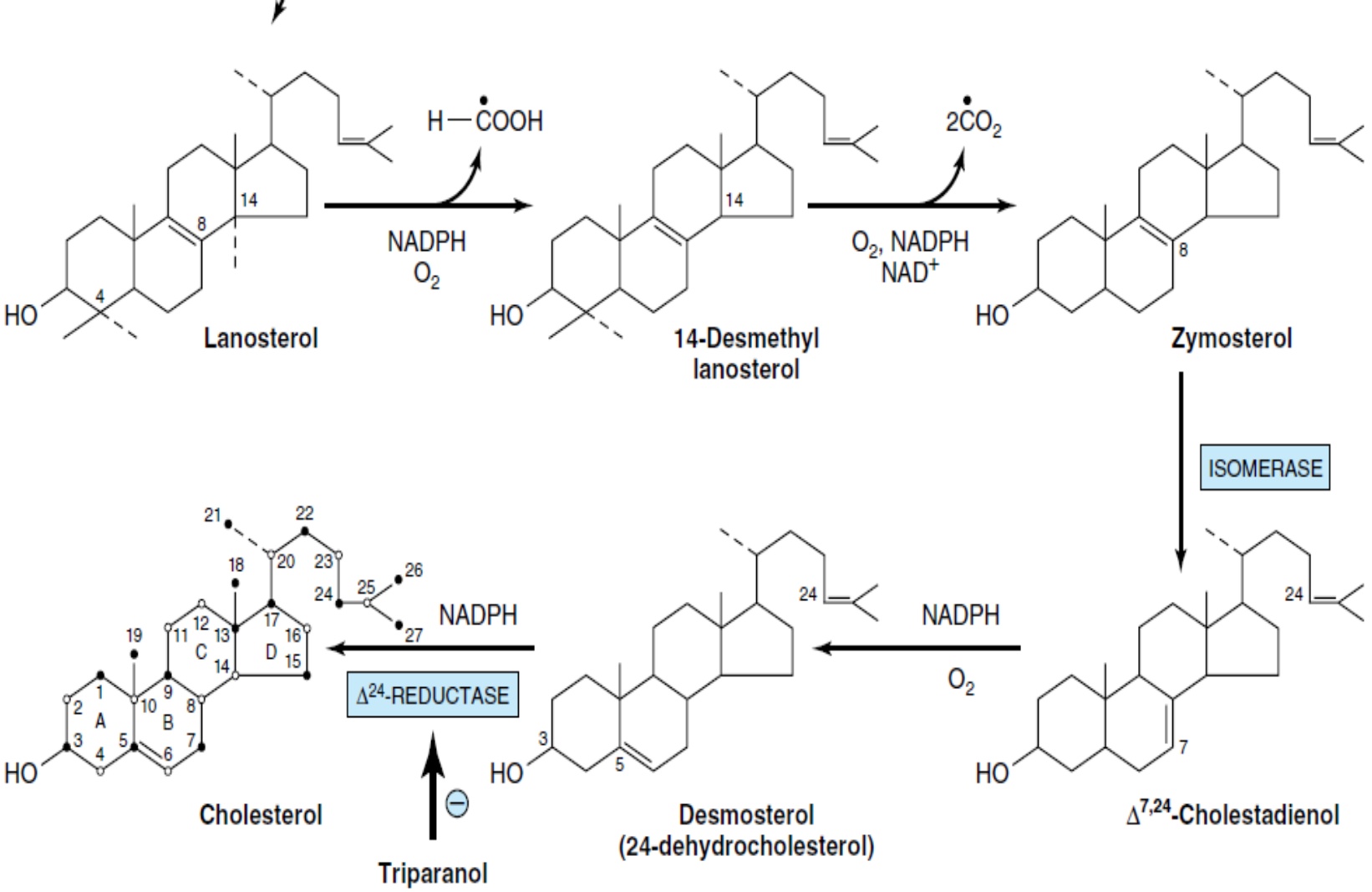


Figure 26–3. Biosynthesis of cholesterol. The numbered positions are those of the steroid nucleus and the open and solid circles indicate the fate of each of the carbons in the acetyl moiety of acetyl-CoA. Asterisks: Refer to labeling of squalene in Figure 26–2.

CHOLESTEROL SYNTHESIS IS CONTROLLED BY REGULATION OF HMG-CoA REDUCTASE

1-The reduced synthesis of cholesterol in starving animals is accompanied by a decrease in the activity of the enzyme. However, it is only hepatic synthesis that is inhibited by dietary cholesterol.

2-HMG-CoA reductase in liver is inhibited by mevalonate, the immediate product of the pathway, and by cholesterol, the main product. Cholesterol represses transcription of the HMG-CoA reductase gene and is also believed to influence translation.

3-A **diurnal variation occurs in both cholesterol synthesis**

and reductase activity.

4-Insulin or thyroid hormone increases HMG-CoA reductase activity, whereas glucagon or glucocorticoids decrease it.

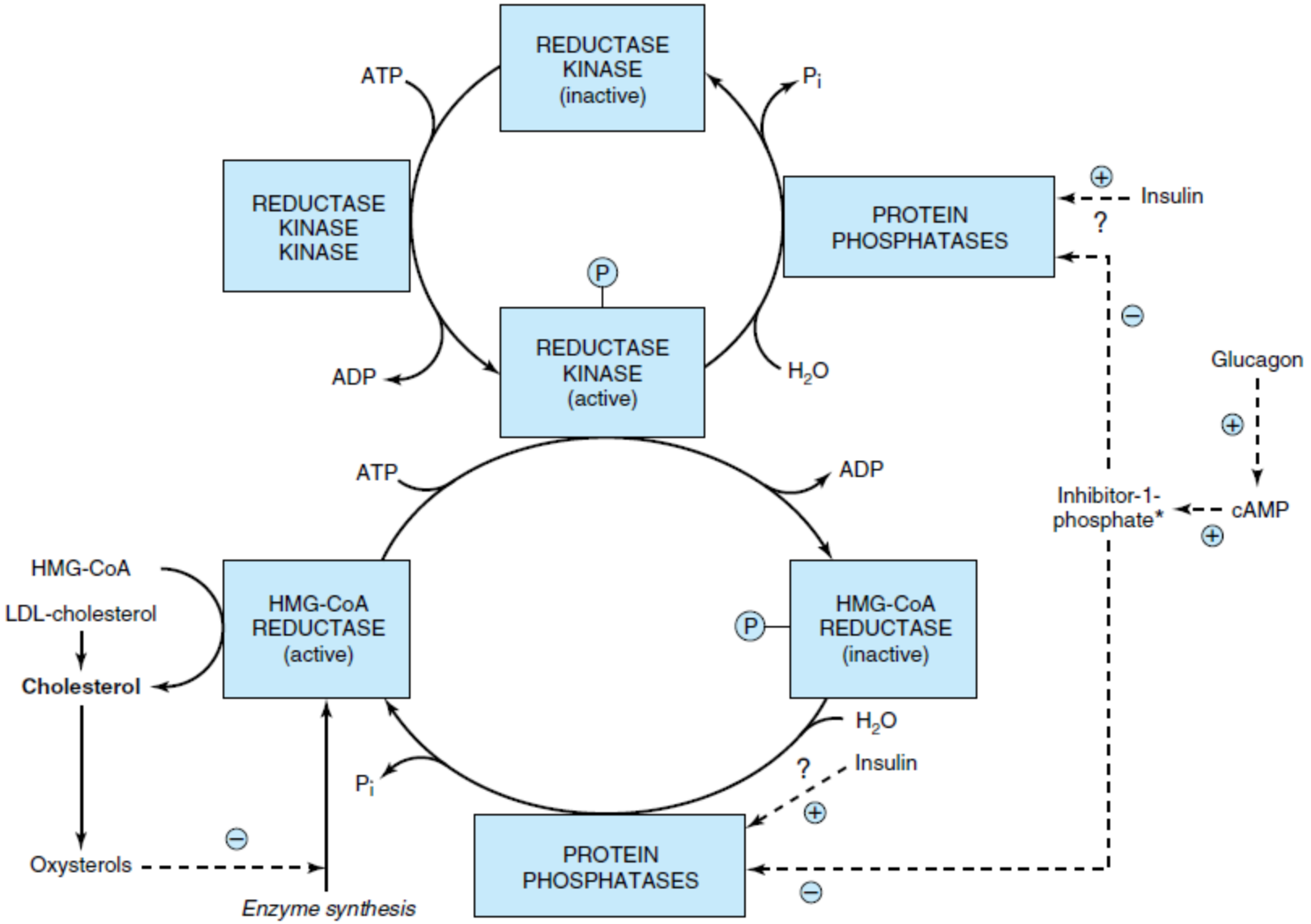


Figure 26–4. Possible mechanisms in the regulation of cholesterol synthesis by HMG-CoA reductase. Insulin has a dominant role compared with glucagon. Asterisk: See Figure 18–6.

MANY FACTORS INFLUENCE THE CHOLESTEROL BALANCE IN TISSUES

-Cell cholesterol increase is due to uptake of cholesterol-containing lipoproteins by receptors, eg, the LDL receptor or the scavenger receptor; uptake of free cholesterol from cholesterol-rich lipoproteins to the cell

-Decrease is due to efflux of cholesterol from the membrane to HDL, promoted by **LCAT (lecithin:cholesterol** acyltransferase)

The LDL Receptor Is Highly Regulated

-After binding, LDL is taken up intact by endocytosis. The apoprotein and cholesteryl ester are then hydrolyzed in the lysosomes, and cholesterol is translocated into the cell. The receptors are recycled to the cell surface. This influx of cholesterol inhibits in a coordinated manner HMG-CoA synthase, HMG-CoA reductase, and, therefore, cholesterol synthesis; stimulates ACAT activity; and down-regulates synthesis of the LDL receptor.

-Thus, the number of LDL receptors on the cell surface is regulated by the cholesterol requirement for membranes, steroid hormones, or bile acid synthesis (Figure

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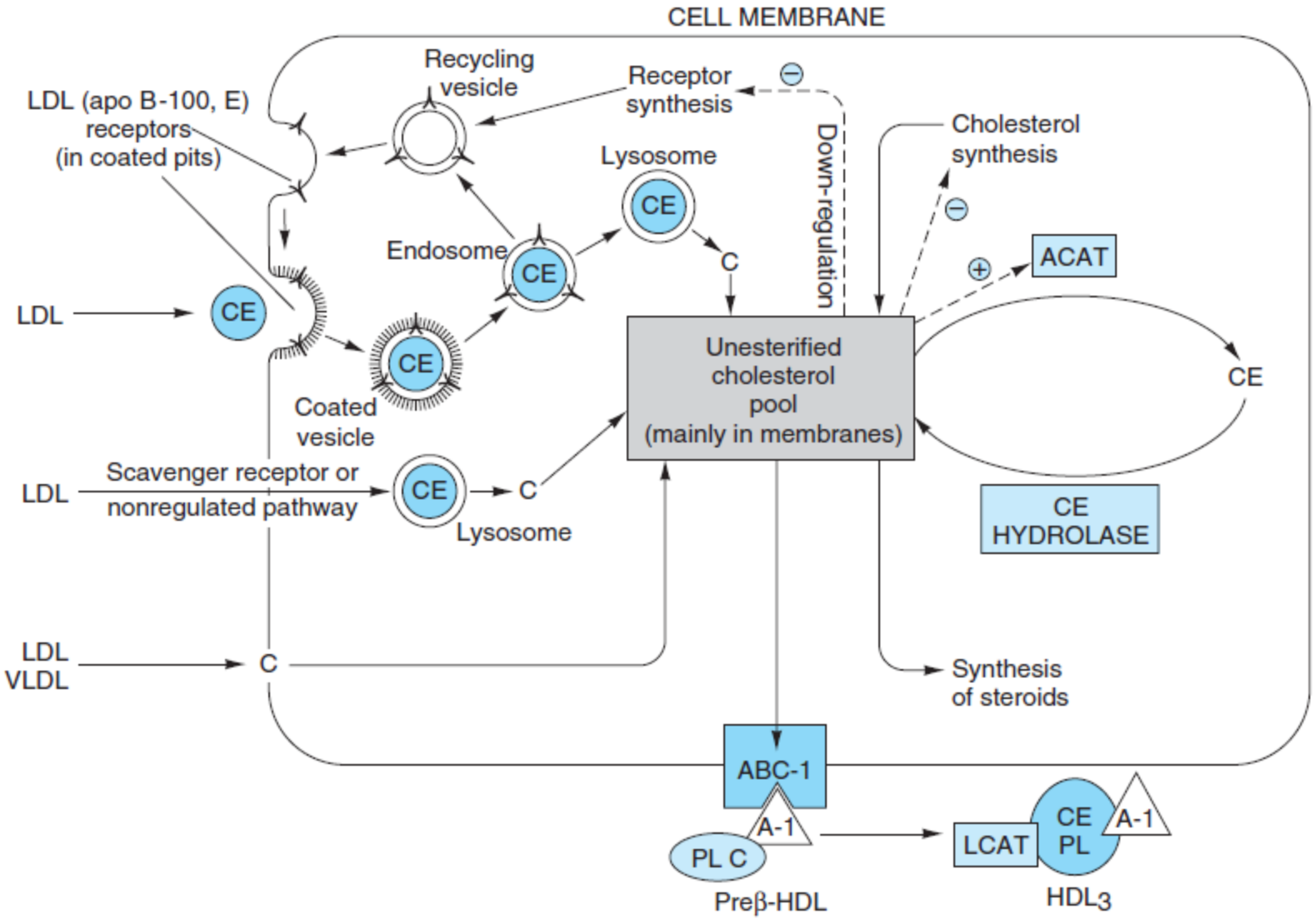

Figure 26–5. Factors affecting cholesterol balance at the cellular level. Reverse cholesterol transport may be initiated by preβ HDL binding to the ABC-1 transporter protein via apo A-I. Cholesterol is then moved out of the cell via the transporter, lipidating the HDL, and the larger particles then dissociate from the ABC-1 molecule. (C, cholesterol; CE, cholesteryl ester; PL, phospholipid; ACAT, acyl-CoA:cholesterol acyltransferase; LCAT

CHOLESTEROL IS TRANSPORTED BETWEEN TISSUES IN PLASMA LIPOPROTEINS (Figure 26–6)

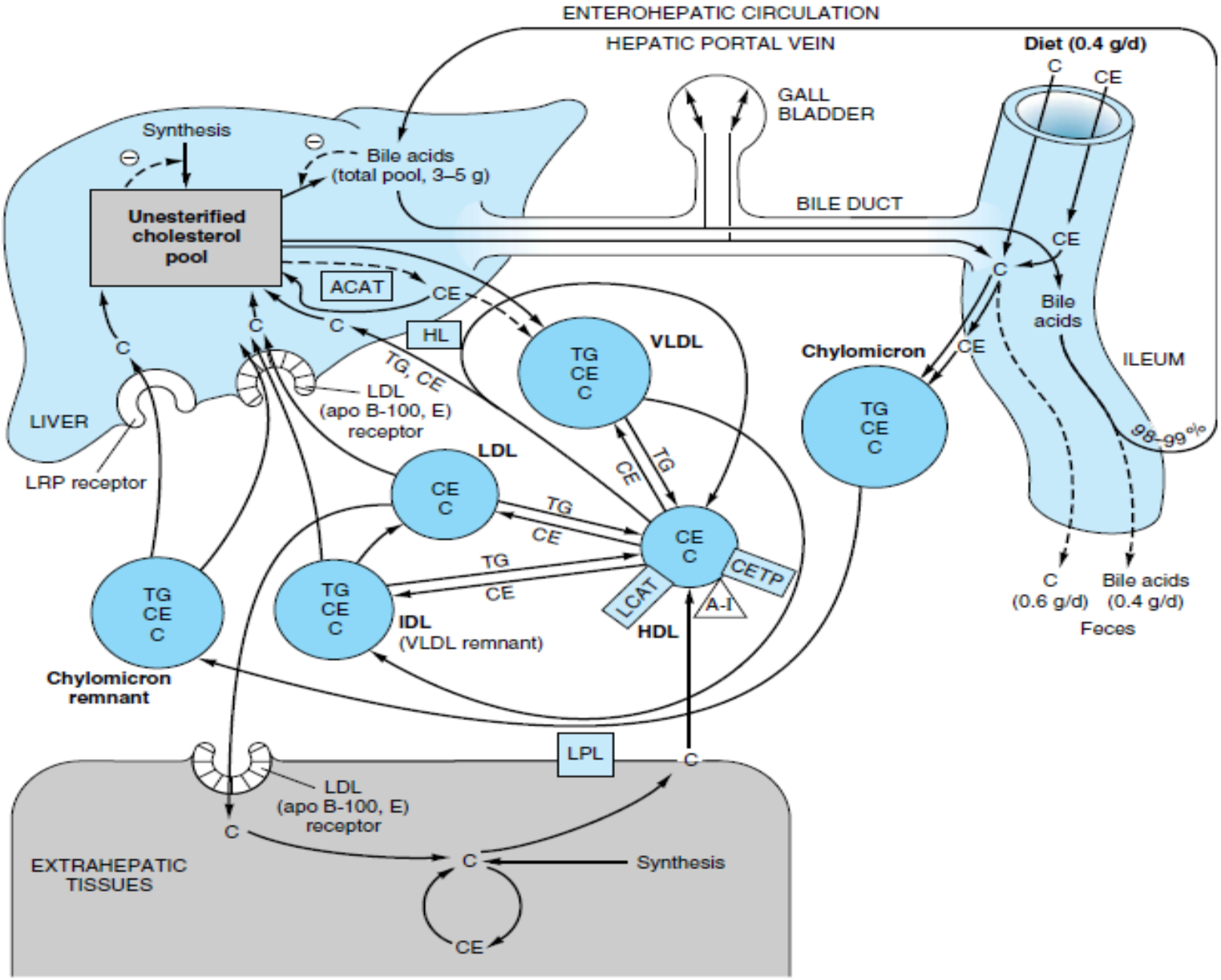

Figure 26–6. Transport of cholesterol between the tissues in humans. (C, unesterified cholesterol; CE, cholesteryl ester; TG, triacylglycerol; VLDL, very low density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACAT, acyl-CoA:cholesterol acyltransferase; LCAT, lecithin:cholesterol acyltransferase; A-I, apolipoprotein A-I; CETP, cholesteryl ester transfer protein; LPL, lipopro-

CHOLESTEROL IS EXCRETED FROM THE BODY IN THE BILE AS CHOLESTEROL OR BILE ACIDS (SALTS)

About 1 g of cholesterol is eliminated from the body per day. Approximately half is excreted in the feces after conversion to bile acids. The remainder is excreted as cholesterol. **Coprostanol is the principal sterol in the** feces; it is formed from cholesterol by the bacteria in the lower intestine.

Bile Acids Are Formed From Cholesterol

-The **primary bile acids are synthesized in the liver from** cholesterol. These are **cholic acid (found in the largest** amount) and **chenodeoxycholic acid (Figure 26–7).**

-The 7α-hydroxylation of cholesterol is the first and principal regulatory step in the biosynthesis of bile acids catalyzed by**7-hydroxylase, a microsomal enzyme.** A typical monooxygenase, it requires oxygen, NADPH, and cytochrome P450. Subsequent hydroxylation steps are also catalyzed by monooxygenases.

Bile Acids Are Formed From Cholesterol

-The pathway of bile acid biosynthesis divides early into one subpathway leading to **cholyl-CoA, characterized by an extra α-OH** group on position 12, and another pathway leading to **chenodeoxycholyl-CoA (Figure 26–7).**

-A second pathway in mitochondria involving the 27-hydroxylation of cholesterol by **sterol 27-hydroxylase .**

-**The primary bile acids (Figure 26–7**) enter the bile as glycine or taurine conjugates. Conjugation takes place in peroxisomes. In humans, the ratio of the glycine to the taurine conjugates is normally 3:1. In the alkaline bile, the bile acids and their conju-gates are assumed to be in a salt form—hence the term "bile salts."

-**A portion of the primary bile acids in the intestine** is subjected to further changes by the activity of the intestinal bacteria. These include deconjugation and 7α- dehydroxylation, which produce the **secondary bile acids, deoxycholic acid and lithocholic acid.**

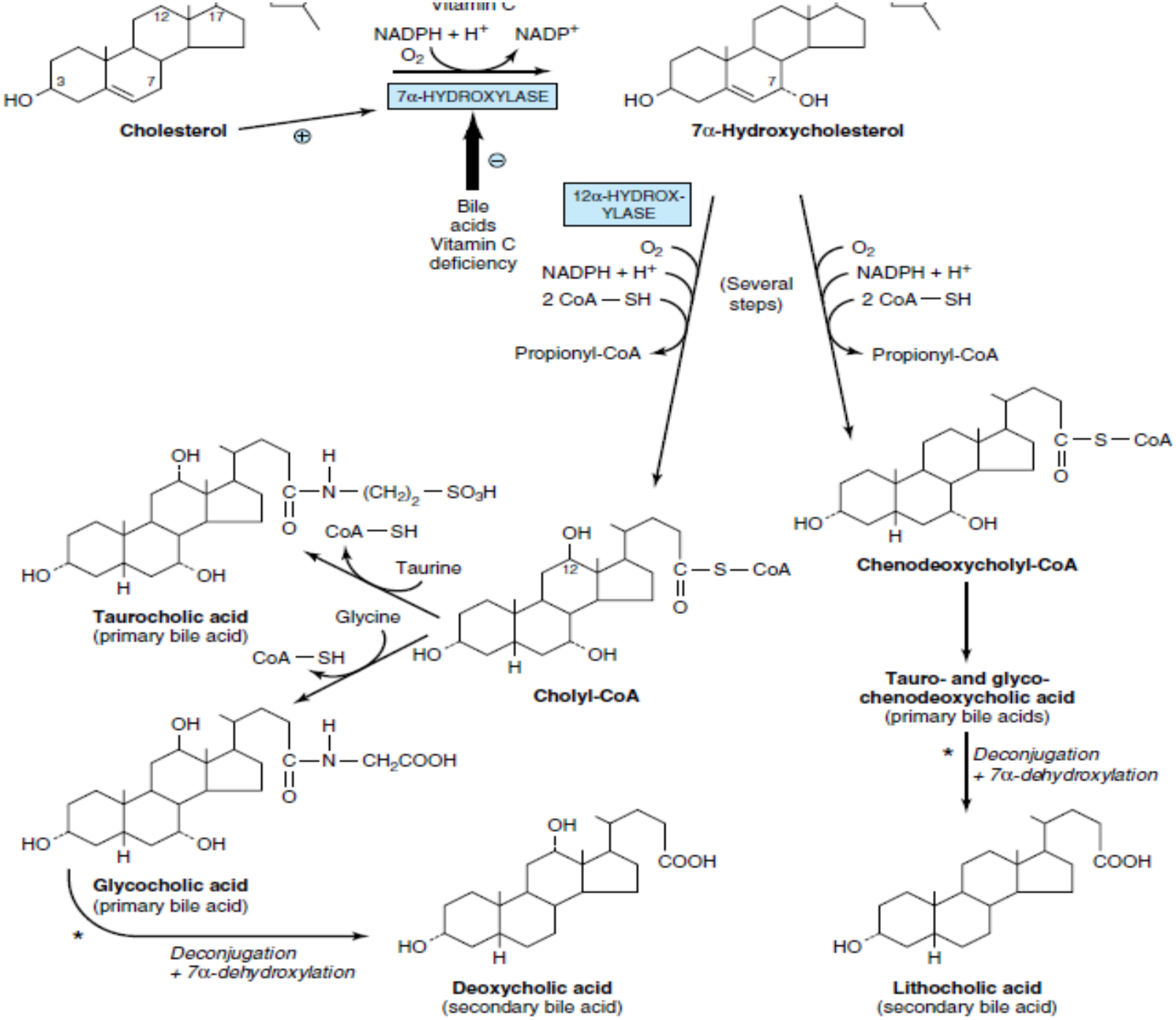

Figure 26–7. Biosynthesis and degradation of bile acids. A second pathway in mitochondria involves hydroxylation of cholesterol by sterol 27-hydroxylase. Asterisk: Catalyzed by microbial enzymes.

Most Bile Acids Return to the Liver in the Enterohepatic Circulation

-98–99% are returned to the liver via the portal circulation. This is known as the **enterohepatic circulation (Figure 26–6).**

-Only a small fraction of the bile salts escapes absorption and is therefore eliminated in the feces. Nonetheless, this represents a major pathway for the elimination of cholesterol.

-Each day the small pool of bile acids (about 3–5 g) is cycled through the intestine six to ten times and an amount of bile acid equivalent to that lost in the feces is synthesized from cholesterol, so that a pool of bile acids of constant size is maintained. This is accomplished by a system of feedback controls.

Bile Acid Synthesis Is Regulated at the 7-α-Hydroxylase Step

-The principal rate-limiting step. The activity of the enzyme is feedback-regulated via the nuclear bile acid-binding receptor **farnesoid X receptor (FXR).**

When the size of the bile acid pool in the enterohepatic circulation increases, FXR is activated and transcription of the cholesterol 7α-hydroxylase gene is suppressed. Chenodeoxycholic acid is particularly important in activating FXR.

-Cholesterol 7α-hydroxylase activity is also enhanced by

cholesterol of endogenous and dietary origin and regulated by insulin, glucagon, glucocorticoids, and thyroid

hormone.