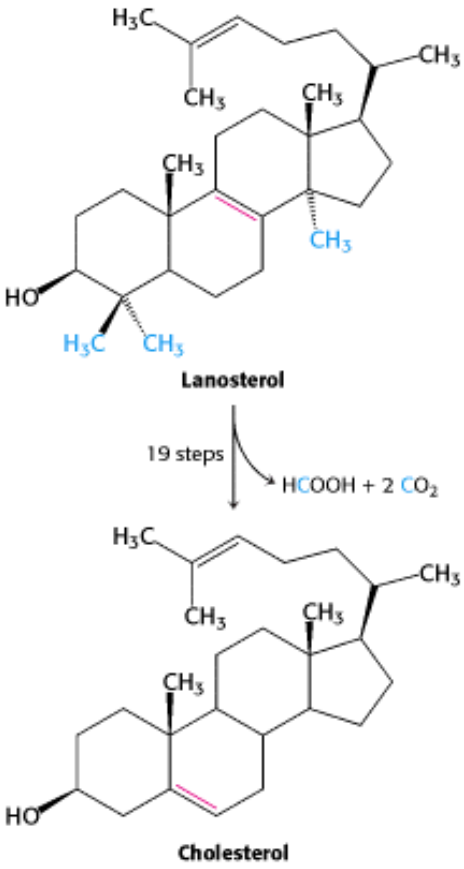



**Figure 26.13. Cholesterol Formation.** Lanosterol is converted into cholesterol in a complex process.

## 26.3. The Complex Regulation of Cholesterol Biosynthesis Takes Place at Several Levels

Cholesterol can be obtained from the diet or it can be synthesized de novo. An adult on a low-cholesterol diet typically synthesizes about 800 mg of cholesterol per day. The liver is the major site of cholesterol synthesis in mammals, although the intestine also forms significant amounts. The rate of cholesterol formation by these organs is highly responsive to the cellular level of cholesterol. *This feedback regulation is mediated primarily by changes in the amount and activity of 3-hydroxy-3-methylglutaryl CoA reductase* (Figure 26.14). As discussed in Section 26.2.1, this enzyme catalyzes the formation of mevalonate, the committed step in cholesterol biosynthesis. HMG CoA reductase is controlled in multiple ways:

**1.** The rate of *synthesis of reductase mRNA* is controlled by the *sterol regulatory element binding protein (SREBP)*. This transcription factor binds to a short DNA sequence called the *sterol regulatory element (SRE)* on the 5′ side of the reductase gene. In its inactive state, the SREBP is anchored to the endoplasmic reticulum or nuclear membrane. When cholesterol levels fall, the amino-terminal domain is released from its association with the membrane by two specific proteolytic cleavages. The released protein migrates to the nucleus and binds the SRE of the HMG-CoA reductase gene, as well as several other genes in the cholesterol biosynthetic pathway, to enhance transcription. When cholesterol levels rise, the proteolytic release of the SREBP is blocked, and the SREBP in the nucleus is rapidly degraded. These two events halt the transcription of the genes of the cholesterol biosynthetic pathways.

**2.** The rate of *translation of reductase mRNA* is inhibited by nonsterol metabolites derived from mevalonate as well as by dietary cholesterol.

**3.** The *degradation of the reductase* is stringently controlled. The enzyme is bipartite: its cytosolic domain carries out catalysis and *its membrane domain senses signals that lead to its degradation.* The membrane domain may undergo a change in its oligomerization state *in response to increasing concentrations of sterols such as cholesterol,* making the enzyme more susceptible to proteolysis. Homologous sterol-sensing regions are present in the protease that activates SREBP. The reductase may be further degraded by ubiquitination and targeting to the 26S proteasome under some conditions. A combination of these three regulatory devices can regulate the amount of enzyme over a 200-fold range.

**4.** *Phosphorylation decreases the activity of the reductase.* This enzyme, like acetyl CoA carboxylase (which catalyzes the committed step in fatty acid synthesis, Section 22.5), is switched off by an AMP-activated protein kinase. Thus, cholesterol synthesis ceases when the ATP level is low.

As we will see shortly, all four regulatory mechanisms are modulated by receptors that sense the presence of cholesterol in the blood.

## 26.3.1. Lipoproteins Transport Cholesterol and Triacylglycerols Throughout the Organism

Cholesterol and triacylglycerols are transported in body fluids in the form of *lipoprotein particles.* Each particle consists of a core of hydrophobic lipids surrounded by a shell of more polar lipids and apoproteins. The protein components of these macromolecular aggregates have two roles: *they solubilize hydrophobic lipids and contain cell-targeting signals.* Lipoprotein particles are classified according to increasing density (Table 26.1): *chylomicrons, chylomicron remnants, very low density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL),* and *high-density lipoproteins (HDL).* Ten principal apoproteins have been isolated and characterized. They are synthesized and secreted by the liver and the intestine.

Triacylglycerols, cholesterol, and other lipids obtained from the diet are carried away from the intestine in the form of large *chylomicrons* (180– 500 nm in diameter; Section 22.1.2). These particles have a very low density ($d$<0.94 g cm$^{-3}$) because triacylglycerols constitute ~99% of their content. Apolipoprotein B-48 (apo B-48), a large protein (240 kd), forms an amphipathic spherical shell around the fat globule; the external face of this shell is hydrophilic. The triacylglycerols in chylomicrons are released through hydrolysis by *lipoprotein lipases.* These enzymes are located on the lining of blood vessels in muscle and other tissues that use fatty acids as fuels and in the synthesis of fat. The liver then takes up the cholesterol-rich residues, known as *chylomicron remnants.*

The liver is a major site of triacylglycerol and cholesterol synthesis (Figure 26.15). Triacylglycerols and cholesterol in excess of the liver's own needs are exported into the blood in the form of very low density lipoproteins ($d$<1.006 g cm$^{-3}$). These particles are stabilized by two lipoproteins—apo B-100 and apo E (34 kd). Apo B-100, one of the largest proteins known (513 kd), is a longer version of apo B-48. Both apo B proteins are encoded by the same gene and produced from the same initial RNA transcript. In the intestine, RNA editing (Section 28.3.2) modifies the transcript to generate the mRNA for apo B-48, the truncated form. Triacylglycerols in very low density lipoproteins, as in chylomicrons, are hydrolyzed by lipases on capillary surfaces. The resulting remnants, which are rich in cholesteryl esters, are called *intermediate-density lipoproteins*(1.006 < $d$ < 1.019 g cm$^{-3}$). These particles have two fates. Half of them are taken up by the liver for processing, and half are converted into low-density lipoprotein (1.019 < $d$ < 1.063 g cm$^{-3}$) by the removal of more triacylglycerol.

*Low-density lipoprotein is the major carrier of cholesterol in blood.* This lipoprotein particle has a diameter of 22 nm and a mass of about 3 million daltons (Figure 26.16). It contains a core of some 1500 esterified cholesterol molecules; the most common fatty acyl chain in these esters is linoleate, a polyunsaturated fatty acid. A shell of phospholipids and unesterified cholesterols surrounds this highly hydrophobic core. The shell also contains a single copy of apo B-100, which is recognized by target cells. *The role of LDL is to transport cholesterol to peripheral tissues and regulate de novo cholesterol synthesis at these sites,* as described in Section 26.3.3. A different purpose is served by *high-density lipoprotein* (1.063 < $d$ < 1.21 g cm$^{-3}$), which picks up cholesterol released into the plasma from dying cells and from membranes undergoing turnover. An acyltransferase in HDL esterifies these cholesterols, which are then either rapidly

shuttled to VLDL or LDL by a specific transfer protein or returned by HDL to the liver.

## 26.3.2. The Blood Levels of Certain Lipoproteins Can Serve Diagnostic Purposes


High serum levels of cholesterol cause disease and death by contributing to the formation of atherosclerotic plaques in arteries throughout the body. This excess cholesterol is present in the form of the low density lipoprotein particle, so-called "bad cholesterol."The ratio of cholesterol in the form of high density lipoprotein, sometimes referred to as "good cholesterol," to that in the form of LDL can be used to evaluate susceptibility to the development of heart disease. For a healthy person, the LDL/HDL ratio is 3.5.

*High-density lipoprotein* functions as a shuttle that moves cholesterol throughout the body. HDL binds and esterifies cholesterol released from the peripheral tissues and then transfers cholesteryl esters to the liver or to tissues that use cholesterol to synthesize steroid hormones. A specific receptor mediates the docking of the HDL to these tissues. The exact nature of the protective effect of HDL levels is not known; however, a possible mechanism is discussed in Section 26.3.5.

## 26.3.3. Low-Density Lipoproteins Play a Central Role in Cholesterol Metabolism

Cholesterol metabolism must be precisely regulated to prevent atherosclerosis. The mode of control in the liver, the primary site of cholesterol synthesis, has already been discussed: dietary cholesterol reduces the activity and amount of 3-hydroxy-3-methylglutaryl CoA reductase, the enzyme catalyzing the committed step. The results of studies by Michael Brown and Joseph Goldstein are sources of insight into the control of cholesterol metabolism in nonhepatic cells. In general, cells outside the liver and intestine obtain cholesterol from the plasma rather than synthesizing it de novo. Specifically, *their primary source of cholesterol is the low-density lipoprotein.* The process of LDL uptake, called *receptor-mediated endocytosis,* serves as a paradigm for the uptake of many molecules.

The steps in the receptor-mediated endocytosis of LDL are as follows (see Figure 12.40).

**1.** Apolipoprotein B-100 on the surface of an LDL particle binds to a specific receptor protein on the plasma membrane of nonhepatic cells. The receptors for LDL are localized in specialized regions called *coated pits,* which contain a specialized protein called *clathrin.*

**2.** The receptor-LDL complex is internalized by *endocytosis,* that is, the plasma membrane in the vicinity of the complex invaginates and then fuses to form an endocytic vesicle (Figure 26.17).

**3.** These vesicles, containing LDL, subsequently fuse with *lysosomes,* acidic vesicles that carry a wide array of degradative enzymes. The protein component of the LDL is hydrolyzed to free amino acids. The cholesteryl esters in the LDL are hydrolyzed by a lysosomal acid lipase. The LDL receptor itself usually returns unscathed to the plasma membrane. The round-trip time for a receptor is about 10 minutes; in its lifetime of about a day, it may bring many LDL particles into the cell.

**4.** *The released unesterified cholesterol can then be used for membrane biosynthesis.* Alternatively, it can be *reesterified for storage inside the cell.* In fact, free cholesterol activates *acyl CoA:cholesterol acyltransferase (ACAT),* the enzyme catalyzing this reaction. Reesterified cholesterol contains mainly oleate and palmitoleate, which are monounsaturated fatty acids, in contrast with the cholesterol esters in LDL, which are rich in linoleate, a polyunsaturated fatty acid (see Table 24.1). It is imperative that the cholesterol be reesterified. High concentrations of unesterified cholesterol disrupt the integrity of cell membranes.

The synthesis of LDL receptor is itself subject to feedback regulation. The results of studies of cultured fibroblasts show that, *when cholesterol is abundant inside the cell, new LDL receptors are not synthesized, and so the uptake of additional cholesterol from plasma LDL is blocked.* The gene for the LDL receptor, like that for the reductase, is regulated by SREBP, which binds to a sterol regulatory element that controls the rate of mRNA synthesis.

## 26.3.4. The LDL Receptor Is a Transmembrane Protein Having Five Different Functional Regions

The amino acid sequence of the human LDL receptor reveals the mosaic structure of this 115-kd protein, which is composed of six different types of domain (Figure 26.18). The amino-terminal region of the mature receptor consists of a cysteine-rich sequence of about 40 residues that is repeated, with some variation, seven times to form the LDL-binding domain (Figure 26.19). A set of conserved acidic side chains in this domain bind calcium ion; this metal ion lies at the center of each domain and, along with disulfide bonds formed from the conserved cysteine residues, stabilizes the three-dimensional structure. Protonation of these glutamate and aspartate side chains of the receptor in lysosomes leads to the release of calcium and hence to structural disruption and the release of LDL from its receptor. A second region of the LDL receptor includes two types of recognizable domains, three domains homologous to epidermal growth factor and six repeats that are similar to the blades of the transducin β subunit (Section 15.2.2). The six repeats form a propeller-like structure that packs against one of the EGF-like domains (Figure 26.20). An aspartate residue forms hydrogen bonds that hold each blade to the rest of the structure. These interactions, too, would most likely be disrupted at the low pH in the lysosome.

The third region contains a single domain that is very rich in serine and threonine residues and contains *O*-linked sugars. These oligosaccharides may function as struts to keep the receptor extended from the membrane so that the LDL-binding domain is accessible to LDL. The fourth region contains the fifth type of domain, which consists of 22 hydrophobic residues that span the plasma membrane. The final region contains the sixth type of domain; it consists of 50 residues and emerges on the cytosolic side of the membrane, where it controls the interaction of the receptor with coated pits and participates in endocytosis. The gene for the LDL receptor consists of 18 exons, which correspond closely to the structural units of the protein. *The LDL receptor is a striking example of a mosaic protein encoded by a gene that was assembled by exon shuffling.*

## 26.3.5. The Absence of the LDL Receptor Leads to Hypercholesteremia and Atherosclerosis

The results of Brown and Goldstein's pioneering studies of *familial hypercholesterolemia* revealed the physiologic importance of the LDL receptor. The total concentration of cholesterol and LDL in the plasma is markedly elevated in this genetic disorder, which results from a mutation at a single autosomal locus. The cholesterol level in the plasma of homozygotes is typically 680 mg $dl^{-1}$, compared with 300 mg $dl^{-1}$ in heterozygotes (clinical assay results are often expressed in milligrams per deciliter, which is equal to milligrams per 100 milliliters). A value of < 200 mg $dl^{-1}$ is regarded as desirable, but many people have higher levels. *In familial hypercholesterolemia, cholesterol is deposited in various tissues because of the high concentration of LDL cholesterol in the plasma.* Nodules of cholesterol called *xanthomas* are prominent in skin and tendons. Of particular concern is the oxidation of the excess blood LDL to form oxidized LDL (oxLDL). The oxLDL is taken up by immune-system cells called macrophages, which become engorged to form foam cells. These foam cells become trapped in the walls of the blood vessels and contribute to the formation of atherosclerotic plaques that cause arterial narrowing and lead to heart attacks (Figure 26.21). In fact, *most homozygotes die of coronary artery disease in childhood.* The disease in heterozygotes (1 in 500 people) has a milder and more variable clinical course. A serum esterase that degrades oxidized lipids is found in association with HDL. Possibly, the HDL-associated protein destroys the oxLDL, accounting for HDL's ability to protect against coronary disease.

*The molecular defect in most cases of familial hypercholesterolemia is an absence or deficiency of functional receptors for LDL.* Receptor mutations that disrupt each of the stages in the endocytotic pathway have been identified. Homozygotes have almost no functional receptors for LDL, whereas heterozygotes have about half the normal number. Consequently, the entry of LDL into liver and other cells is impaired, leading to an increased plasma level of LDL. Furthermore, less IDL enters liver cells because IDL entry, too, is mediated by the LDL receptor. Consequently, IDL stays in the blood longer in familial hypercholesterolemia, and more of it is converted into LDL than in normal people. All deleterious consequences of an absence or deficiency of the LDL receptor can be attributed to the ensuing elevated level of LDL cholesterol in the blood.

## 26.3.6. The Clinical Management of Cholesterol Levels Can Be Understood at a Biochemical Level

Homozygous familial hypercholesterolemia can be treated only by a liver transplant. A more generally applicable therapy is available for heterozygotes and others with high levels of cholesterol. *The goal is to reduce the amount of cholesterol in the blood by stimulating the single normal gene to produce more than the customary number of LDL receptors.* We have already observed that the production of LDL receptors is controlled by the cell's need for cholesterol. Therefore, in essence, the strategy is to deprive the cell of ready sources of cholesterol. When cholesterol is required, the amount of mRNA for the LDL receptor rises and more receptor is found on the cell surface. This state can be induced by a two-pronged approach. First, the intestinal reabsorption of bile salts is inhibited. Bile salts are cholesterol derivatives that promote the absorption of dietary cholesterol and dietary fats (Section 22.1.1). Second, de novo synthesis of cholesterol is blocked.

The reabsorption of bile is impeded by oral administration of positively charged polymers, such as cholestyramine, that bind negatively charged bile salts and are not themselves absorbed. Cholesterol synthesis can be effectively blocked by a class of compounds called *statins* (e.g., lovastatin, which is also called mevacor; Figure 26.22). These compounds are potent competitive inhibitors ($K_i$ < 1 nM) of HMG-CoA reductase, the essential control point in the biosynthetic pathway. Plasma cholesterol levels decrease by 50% in many patients given both lovastatin and inhibitors of bile-salt reabsorption. Lovastatin and other inhibitors of HMG-CoA reductase are widely used to lower the plasma cholesterol level in people who have atherosclerosis, which is the leading cause of death in industrialized societies.


**Figure 26.14. HMG-CoA Reductase.** The structure of a portion of the tetrameric enzyme is shown.

### Table 26.1. Properties of plasma lipoproteins

| Lipoproteins | Major core lipids | Apoproteins | Mechanism of lipid delivery |
|---|---|---|---|
| Chylomicron | Dietary triacylglycerols | B-48, C, E | Hydrolysis by lipoprotein lipase |
| Chylomicron remnant | Dietary cholesterol esters | B-48, E | Receptor-mediated endocytosis by liver |
| Very low density lipoprotein (VLDL) | Endogenous triacylglycerols | B-100, C, E | Hydrolysis by lipoprotein lipase |

| | | | |
|---|---|---|---|
| Intermediate-density lipoprotein (IDL) | Endogenous cholesterol esters | B-100, E | Receptor-mediated endocytosis by liver and conversion into LDL |
| Low-density lipoprotein (LDL) | Endogenous cholesterol esters | B-100 | Receptor-mediated endocytosis by liver and other tissues |
| High-density lipoprotein (HDL) | Endogenous cholesterol esters | A | Transfer of cholesterol esters to IDL and LDL |

*Source:* After M. S. Brown and J. L. Goldstein, *The Pharmacological Basis of Therapeutics.* 7th ed., A. G. Gilman, L. S. Goodman, T. W. Rall, and F. Murad, Eds. (Macmillan, 1985), p. 828.


**Figure 26.15. Site of Cholesterol Synthesis.** Electron micrograph of a part of a liver cell actively engaged in the synthesis and secretion of very low density lipoprotein (VLDL). The arrow points to a vesicle that is releasing its content of VLDL particles. [Courtesy of Dr. George Palade.]

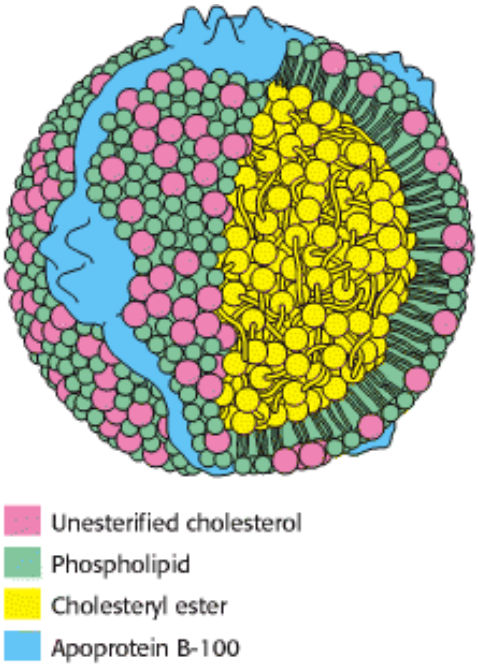



**Figure 26.16. Schematic Model of Low-Density Lipoprotein.** The LDL particle is approximately 22 nm (220 Å) in diameter.

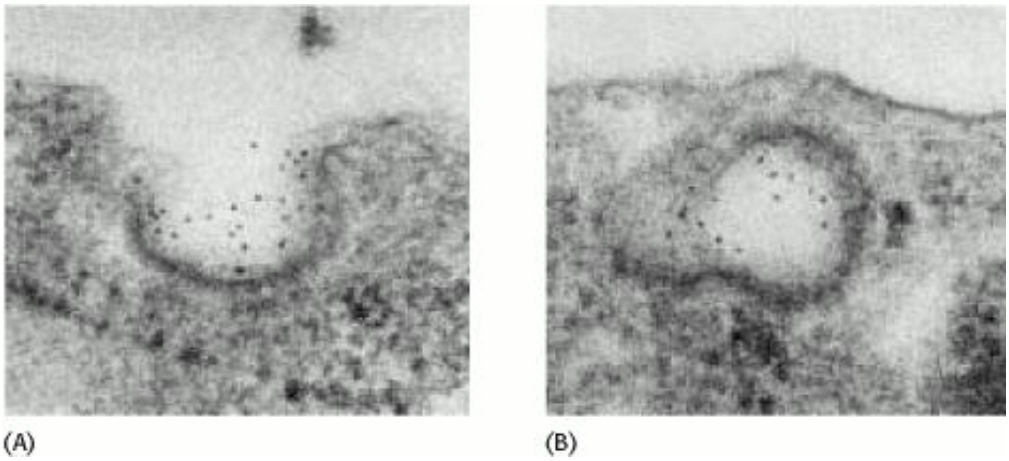



**Figure 26.17. Endocytosis of LDL Bound to Its Receptor.** (A) Electron micrograph showing LDL (conjugated to ferritin for visualization, dark spots) bound to a coated-pit region on the surface of a cultured human fibroblast cell. (B) Micrograph showing this region invaginating and fusing to form an endocytic vesicle [From R. G. W. Anderson, M. S. Brown, and J. L. Goldstein. *Cell* 10 (1977): 351.]

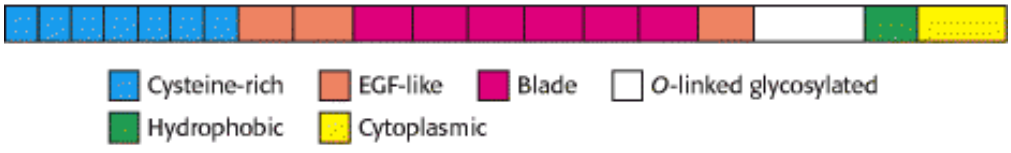



**Figure 26.18. LDL Receptor Domains.** A schematic representation of the amino acid sequence of the LDL receptor showing six types of domain.

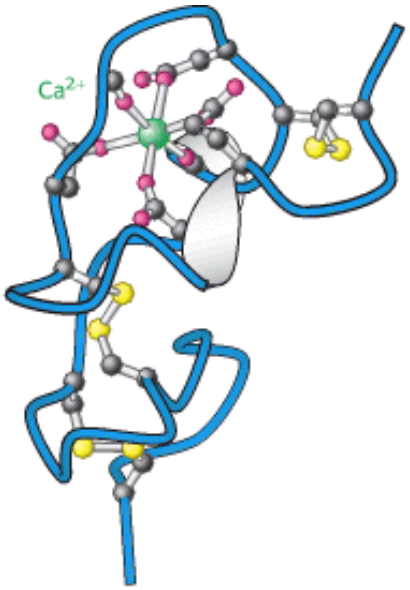



**Figure 26.19. Structure of Cysteine-Rich Domain.** This calcium-binding cysteine-rich domain is repeated seven times at the amino terminus of the LDL receptor.

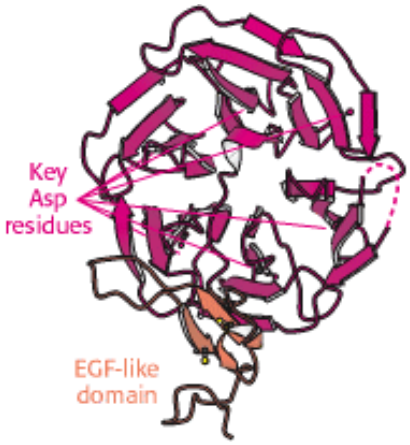



**Figure 26.20. Structure of Propeller Domain.** The six-bladed propeller domain and an adjacent EGF-like domain of the LDL receptor.

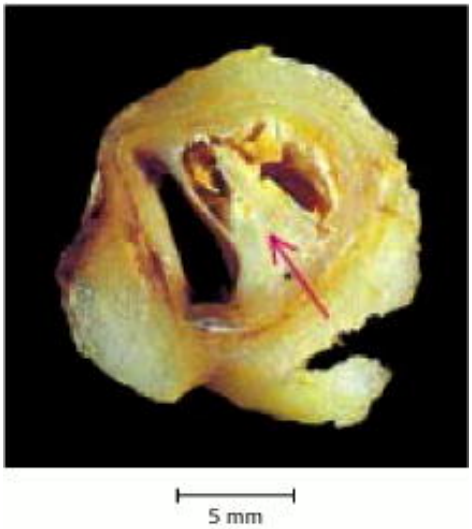



**Figure 26.21. An Atherosclerotic Plaque.** A plaque (marked by an arrow) blocks most of the lumen of this blood vessel. The plaque is rich in cholesterol. [Courtesy of Dr. Jeffrey Sklar.]

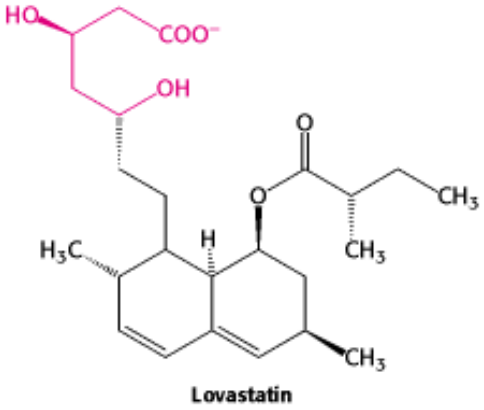



**Figure 26.22. Lovastatin, a Competitive Inhibitor of HMG-CoA Reductase.** The part of the structure that resembles the 3-hydroxy-3-methylglutaryl moiety is shown in red.

## 26.4. Important Derivatives of Cholesterol Include Bile Salts and Steroid Hormones

Cholesterol is a precursor for other important steroid molecules: the bile salts, steroid hormones, and vitamin D.

### *Bile Salts.*

As polar derivatives of cholesterol, *bile salts* are highly effective *detergents* because they contain both polar and nonpolar regions. Bile salts are synthesized in the liver, stored and concentrated in the gall bladder, and then released into the small intestine. Bile salts, the major constituent of bile, *solubilize dietary lipids* (Section 22.1.1). Solubilization increases in the effective surface area of lipids with two consequences: more surface area is exposed to the digestive action of lipases and lipids are more readily absorbed by the intestine. Bile salts are also the major breakdown products of cholesterol.

Cholesterol is converted into trihydroxycoprostanoate and then into *cholyl CoA*, the activated intermediate in the synthesis of most bile salts (Figure 26.23). The activated carboxyl carbon of cholyl CoA then reacts with the amino group of glycine to form *glycocholate* or it reacts with the amino group of taurine ($H_2NCH_2CH_2SO_3^-$), derived from cysteine, to form *taurocholate. Glycocholate is the major bile salt.*

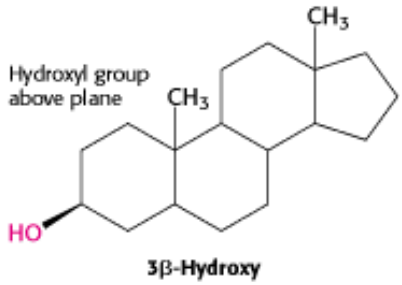
### *Steroid Hormones.*

Cholesterol is the precursor of the five major classes of *steroid hormones:* progestagens, glucocorticoids, mineralocorticoids, androgens, and estrogens (Figure 26.24). These hormones are powerful signal molecules that regulate a host of organismal functions. *Progesterone,* a *progestagen,* prepares the lining of the uterus for implantation of an ovum. Progesterone is also essential for the maintenance of pregnancy. *Androgens* of male secondary sex characteristics, whereas *estrogens* (such as *estrone*) are required for the development of female secondary sex characteristics. Estrogens, along with progesterone, also participate in the ovarian cycle. *Glucocorticoids* (such as *cortisol*) promote gluconeogenesis and the formation of glycogen, enhance the degradation of fat and protein, and inhibit the inflammatory response. They enable animals to respond to stress—indeed, the absence of glucocorticoids can be fatal. *Mineralocorticoids* (primarily *aldosterone*) act on the distal tubules of the kidney to increase the reabsorption of $Na^+$ and the excretion of $K^+$ and $H^+$, which leads to an increase in blood volume and blood pressure. The major sites of synthesis of these classes of hormones are the corpus luteum, for progestagens; the ovaries, for estrogens; the testes, for androgens; and the adrenal cortex, for glucocorticoids and mineralocorticoids.

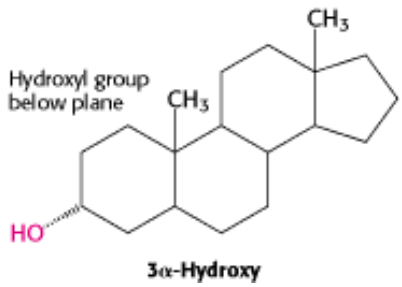
Steroid hormones bind to and activate receptor molecules that serve as transcription factors to regulate gene expression (Section 31.3.1). These small, relatively similar molecules are able to have greatly differing effects because the slight structural differences among them allow interactions with specific receptor molecules.

## 26.4.1. The Nomenclature of Steroid Hormones

Carbon atoms in steroids are numbered as shown for cholesterol in (Figure 26.25). The rings in steroids are denoted by the letters A, B, C, and D. Cholesterol contains two angular methyl groups: the C-19 methyl group is attached to C-10, and the C-18 methyl group is attached to C-13. The C-18 and C-19 methyl groups of cholesterol lie *above* the plane containing the four rings. A substituent that is above the plane is termed β *oriented,* whereas a substituent that is below the plane is α *oriented.*

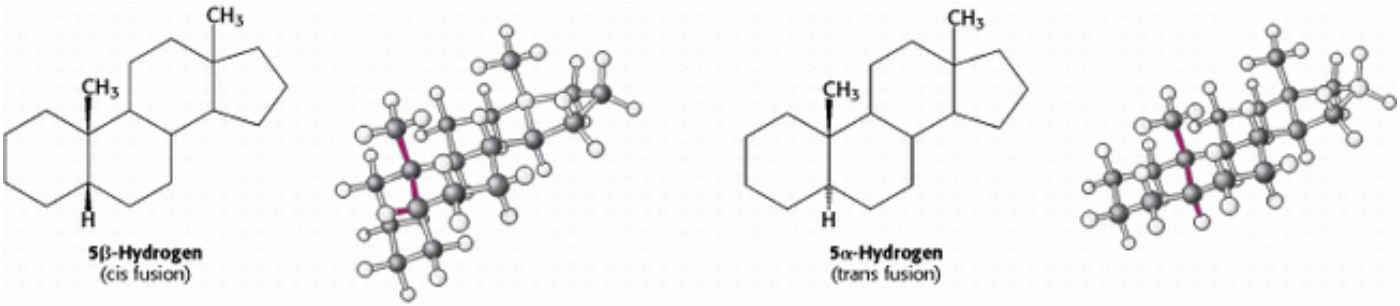


**3β-Hydroxy**



**3α-Hydroxy**

If a hydrogen atom is attached to C-5, it can be either α or β oriented. The A and B steroid rings are fused in a *trans* conformation if the C-5 hydrogen is < *oriented,* and *cis* if it is < *oriented.* The absence of a Greek letter for the C-5 hydrogen atom on the steroid nucleus implies a trans fusion. The C-5 hydrogen atom is α oriented in all steroid hormones that contain a hydrogen atom in that position. In contrast, bile salts have a β-oriented hydrogen atom at C-5. Thus, *a cis fusion is characteristic of the bile salts, whereas a trans fusion is characteristic of all steroid hormones that possess a hydrogen atom at C-5.* A trans fusion yields a nearly planar structure, whereas a cis fusion gives a buckled structure.




## 26.4.2. Steroids Are Hydroxylated by Cytochrome P450 Monooxygenases That Utilize NADPH and $O_2$

Hydroxylation reactions play a very important role in the synthesis of cholesterol from squalene and in the conversion of cholesterol into steroid hormones and bile salts. All these hydroxylations require *NADPH and* $O_2$. The oxygen atom of the incorporated hydroxyl group comes from $O_2$ rather than from $H_2O$. While one oxygen atom of the $O_2$ molecule goes into the substrate, the other is reduced to water. The enzymes catalyzing these reactions are called *monooxygenases* (or *mixed-function oxygenases*). Recall that a monooxygenase also participates in the hydroxylation of aromatic amino acids (Section 23.5.7).

$$RH + O_2 + NADPH + H^+ \longrightarrow ROH + H_2O + NADP^+$$

*Hydroxylation requires the activation of oxygen.* In the synthesis of steroid hormones and bile salts, activation is accomplished by a cytochrome P450, a family of cytochromes that absorb light maximally at 450 nm when complexed in vitro with exogenous carbon monoxide. These membraneanchored proteins (~50 kd) contain a heme prosthetic group. Because the hydroxylation reactions promoted by P450 enzymes are oxidation reactions, it is at first glance surprising that they also consume the reductant NADPH. NADPH transfers its high-potential electrons to a flavoprotein, which transfers them, one at a time, to *adrenodoxin*, a nonheme iron protein. Adrenodoxin transfers one electron to reduce the ferric ($Fe^{3+}$) form of P450 to the ferrous ($Fe^{2+}$) form (Figure 26.26). Without the addition of this electron, P450 will not bind oxygen. Recall that only the ferrous form of hemoglobin binds oxygen (Section 10.2.1). The binding of $O_2$ to the heme is followed by the acceptance of a second electron from adrenodoxin. The acceptance of this second electron leads to cleavage of the O–O bond. One of the oxygen atoms is then protonated and released as water. The remaining oxygen atom forms a highly reactive ferryl ($Fe{=}O$) intermediate. This intermediate abstracts a hydrogen atom from the substrate RH to form $R^{\bullet}$. This transient free radical captures the OH group from the iron atom to form ROH, the hydroxylated product, returning the iron atom to the ferric state.

## 26.4.3. The Cytochrome P450 System Is Widespread and Performs a Protective Function

The cytochrome P450 system, which in mammals is located primarily in the endoplasmic reticulum of the liver and small intestine, is also important in the *detoxification of foreign substances* (xenobiotic compounds) by oxidative metabolism. For example, the hydroxylation of phenobarbital, a barbiturate, *increases its solubility* and *facilitates its excretion.* Likewise, polycyclic aromatic hydrocarbons are hydroxylated by P450, providing sites for conjugation with highly polar units (e.g., glucuronate or sulfate), which markedly increase the solubility of the modified aromatic molecule. One of the most relevant functions of the cytochrome P450 system to human beings is its role in drug metabolism. Drugs such as caffeine and ibuprofen are oxidatively metabolized by these monooxygenases. Indeed, the duration of action of many medications depends on their rate of inactivation by the P450 system. Despite its general protective role in the removal of foreign chemicals, the action of the P450 system is not always beneficial. *Some of the most powerful carcinogens are generated from harmless compounds by the P450 system in vivo* in the process of *metabolic activation.* In plants, the cytochrome P450 system plays a role in the synthesis of toxic compounds as well as