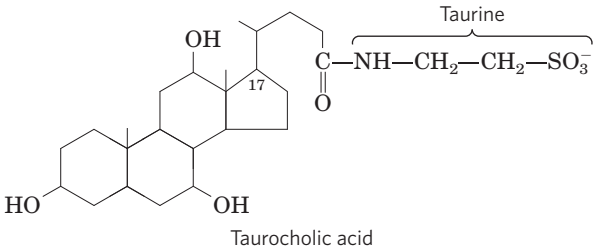
expression. **Bile acids** are polar derivatives of cholesterol that act as detergents in the intestine, emulsifying dietary fats to make them more readily accessible to digestive lipases.



Taurocholic acid
(a bile acid)

We return to cholesterol and other sterols in later chapters, to consider the structural role of cholesterol in biological membranes (Chapter 11), signaling by steroid hormones (Chapter 12), and the remarkable biosynthetic pathway to cholesterol and transport of cholesterol by lipoprotein carriers (Chapter 21).

SUMMARY 10.2 Structural Lipids in Membranes

- The polar lipids, with polar heads and nonpolar tails, are major components of membranes. The most abundant are the glycerophospholipids, which contain fatty acids esterified to two of the hydroxyl groups of glycerol, and a second alcohol, the head group, esterified to the third hydroxyl of glycerol via a phosphodiester bond. Other polar lipids are the sterols.
- Glycerophospholipids differ in the structure of their head group; common glycerophospholipids are phosphatidylethanolamine and phosphatidylcholine. The polar heads of the glycerophospholipids are charged at pH near 7.
- Chloroplast membranes are rich in galactolipids, composed of a diacylglycerol with one or two linked galactose residues, and sulfolipids, diacylglycerols with a linked sulfonated sugar residue and thus a negatively charged head group.
- Some archaea have unique membrane lipids, with long-chain alkyl groups ether-linked to glycerol at both ends and with sugar residues and/or phosphate joined to the glycerol to provide a polar or charged head group. These lipids are stable under the harsh conditions in which these archaea live.
- The sphingolipids contain sphingosine, a long-chain aliphatic amino alcohol, but no glycerol. Sphingomyelin has, in addition to phosphoric acid and choline, two long hydrocarbon chains, one contributed by a fatty acid and the other by sphingosine. Three other classes of sphingolipids are cerebrosides, globosides, and gangliosides, which contain sugar components.
- Sterols have four fused rings and a hydroxyl group. Cholesterol, the major sterol in animals, is both a structural component of membranes and precursor to a wide variety of steroids.

10.3 Lipids as Signals, Cofactors, and Pigments

The two functional classes of lipids considered thus far (storage lipids and structural lipids) are major cellular components; membrane lipids make up 5% to 10% of the dry mass of most cells, and storage lipids more than 80% of the mass of an adipocyte. With some important exceptions, these lipids play a *passive* role in the cell; lipid fuels are stored until oxidized by enzymes, and membrane lipids form impermeable barriers around cells and cellular compartments. Another group of lipids, present in much smaller amounts, have *active* roles in the metabolic traffic as metabolites and messengers. Some serve as potent signals—as hormones, carried in the blood from one tissue to another, or as intracellular messengers generated in response to an extracellular signal (hormone or growth factor). Others function as enzyme cofactors in electron-transfer reactions in chloroplasts and mitochondria, or in the transfer of sugar moieties in a variety of glycosylation reactions. A third group consists of lipids with a system of conjugated double bonds: pigment molecules that absorb visible light. Some of these act as light-capturing pigments in vision and photosynthesis; others produce natural colorations, such as the orange of pumpkins and carrots and the yellow of canary feathers. Finally, a very large group of volatile lipids produced in plants serve as signals that pass through the air, allowing plants to communicate with each other, and to invite animal friends and deter foes. We describe in this section a few representatives of these biologically active lipids. In later chapters, their synthesis and biological roles are considered in more detail.

Phosphatidylinositols and Sphingosine Derivatives Act as Intracellular Signals

Phosphatidylinositol and its phosphorylated derivatives act at several levels to regulate cell structure and metabolism. Phosphatidylinositol 4,5-bisphosphate (Fig. 10–16) in the cytoplasmic (inner) face of plasma membranes serves as a reservoir of messenger molecules that are released inside the cell in response to extracellular signals interacting with specific surface receptors. Extracellular signals such as the hormone vasopressin activate a specific phospholipase C in the membrane, which hydrolyzes phosphatidylinositol 4,5-bisphosphate to release two products that act as intracellular messengers: inositol 1,4,5-trisphosphate (IP_3), which is water-soluble, and diacylglycerol, which remains associated with the plasma membrane. IP_3 triggers release of Ca^{2+} from the endoplasmic reticulum, and the combination of

diacylglycerol and elevated cytosolic Ca^{2+} activates the enzyme protein kinase C. By phosphorylating specific proteins, this enzyme brings about the cell's response to the extracellular signal. This signaling mechanism is described more fully in Chapter 12 (see Fig. 12–10).

Inositol phospholipids also serve as points of nucleation for supramolecular complexes involved in signaling or in exocytosis. Certain signaling proteins bind specifically to phosphatidylinositol 3,4,5-trisphosphate in the plasma membrane, initiating the formation of multienzyme complexes at the membrane's cytosolic surface. Formation of phosphatidylinositol 3,4,5-trisphosphate in response to extracellular signals therefore brings the proteins together in signaling complexes at the surface of the plasma membrane (see Fig. 12–16).

Membrane sphingolipids also can serve as sources of intracellular messengers. Both ceramide and sphingomyelin (Fig. 10–13) are potent regulators of protein kinases, and ceramide or its derivatives are involved in the regulation of cell division, differentiation, migration, and programmed cell death (also called apoptosis; see Chapter 12).

Eicosanoids Carry Messages to Nearby Cells

Eicosanoids are paracrine hormones, substances that act only on cells near the point of hormone synthesis instead of being transported in the blood to act on cells in other tissues or organs. These fatty acid derivatives have a variety of dramatic effects on vertebrate tissues. They are involved in reproductive function; in the inflammation, fever, and pain associated with injury or disease; in the formation of blood clots and the regulation of blood pressure; in gastric acid secretion; and in various other processes important in human health or disease.

All eicosanoids are derived from arachidonic acid (20:4($\Delta^{5,8,11,14}$)) **(Fig. 10–18)**, the 20-carbon polyunsaturated fatty acid from which they take their general name (Greek *eikosi*, "twenty"). There are three classes of eicosanoids: prostaglandins, thromboxanes, and leukotrienes.

Prostaglandins (PG) contain a five-carbon ring originating from the chain of arachidonic acid. Their name derives from the prostate gland, the tissue from which they were first isolated by Bengt Samuelsson and Sune Bergström. Two groups of prostaglandins were originally defined: PGE (*e*ther-soluble) and PGF (*f*osfat (Swedish for phosphate) buffer–soluble). Each group contains numerous subtypes, named PGE_1, PGE_2, PGF_1, and so forth. Prostaglandins have an array of functions. Some stimulate contraction of the smooth muscle of the uterus during menstruation and labor. Others affect blood flow to specific organs, the wake-sleep cycle, and the responsiveness of certain tissues to hormones such as epinephrine and glucagon. Prostaglandins in a third group elevate body temperature (producing fever) and cause inflammation and pain.

The **thromboxanes** have a six-membered ring containing an ether. They are produced by platelets (also called thrombocytes) and act in the formation of blood clots and the reduction of blood flow to the site of a clot. As shown by John Vane, the nonsteroidal antiinflammatory drugs (NSAIDs)—aspirin, ibuprofen, and

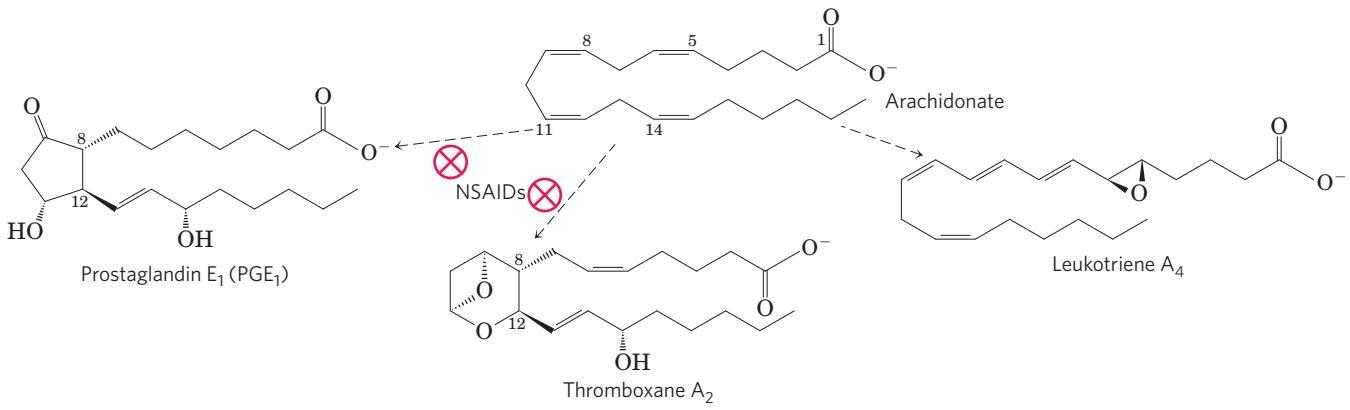


FIGURE 10–18 Arachidonic acid and some eicosanoid derivatives. Arachidonic acid (arachidonate at pH 7) is the precursor of eicosanoids, including the prostaglandins, thromboxanes, and leukotrienes. In prostaglandin E_1, C-8 and C-12 of arachidonate are joined to form the characteristic five-membered ring. In thromboxane A_2, the C-8 and C-12 are joined and an oxygen atom is added to form the six-membered ring. Leukotriene A_4 has a series of three conjugated double bonds. Nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin and ibuprofen block the formation of prostaglandins and thromboxanes from arachidonate by inhibiting the enzyme cyclooxygenase (prostaglandin H_2 synthase).

John Vane, Sune Bergström, and Bengt Samuelsson

meclofenamate, for example—inhibit the enzyme prostaglandin H_2 synthase (also called cyclooxygenase, or COX), which catalyzes an early step in the pathway from arachidonate to prostaglandins and thromboxanes (Fig. 10–18; see also Fig. 21–15).

Leukotrienes, first found in leukocytes, contain three conjugated double bonds. They are powerful biological signals. For example, leukotriene D_4, derived from leukotriene A_4, induces contraction of the smooth muscle lining the airways to the lung. Overproduction of leukotrienes causes asthmatic attacks, and leukotriene synthesis is one target of antiasthmatic drugs such as prednisone. The strong contraction of the smooth muscle of the lungs that occurs during anaphylactic shock is part of the potentially fatal allergic reaction in individuals hypersensitive to bee stings, penicillin, or other agents. ■

Steroid Hormones Carry Messages between Tissues

Steroids are oxidized derivatives of sterols; they have the sterol nucleus but lack the alkyl chain attached to ring D of cholesterol, and they are more polar than cholesterol. Steroid hormones move through the bloodstream (on protein carriers) from their site of production to target tissues, where they enter cells, bind to highly specific receptor proteins in the nucleus, and trigger changes in gene expression and thus metabolism. Because hormones have very high affinity for their receptors, very low concentrations of hormones (nanomolar or less) are sufficient to produce responses in target tissues. The major groups of steroid hormones are the male and female sex hormones and the hormones produced by the adrenal cortex, cortisol and aldosterone **(Fig. 10–19)**. Prednisone and prednisolone are steroid drugs with potent antiinflammatory activities, mediated in part by the inhibition of arachidonate release by phospholipase A_2 and consequent inhibition of the synthesis of leukotrienes, prostaglandins, and thromboxanes. These drugs have a variety of medical applications, including the treatment of asthma and rheumatoid arthritis. ■

Vascular plants contain the steroidlike brassinolide (Fig. 10–19), a potent growth regulator that increases the rate of stem elongation and affects the orientation of cellulose microfibrils in the cell wall during growth.

Vascular Plants Produce Thousands of Volatile Signals

Plants produce literally thousands of different lipophilic compounds, volatile substances that are used to attract pollinators, to repel herbivores, to attract organisms that defend the plant against herbivores, and to communicate with other plants. Jasmonate, for example (see Fig. 12–33), derived from the fatty acid 18:3($\Delta^{9,12,15}$) in membrane lipids, triggers the plant's defenses in response to insect-inflicted damage. The methyl ester of jasmonate gives the characteristic fragrance of jasmine oil, which is

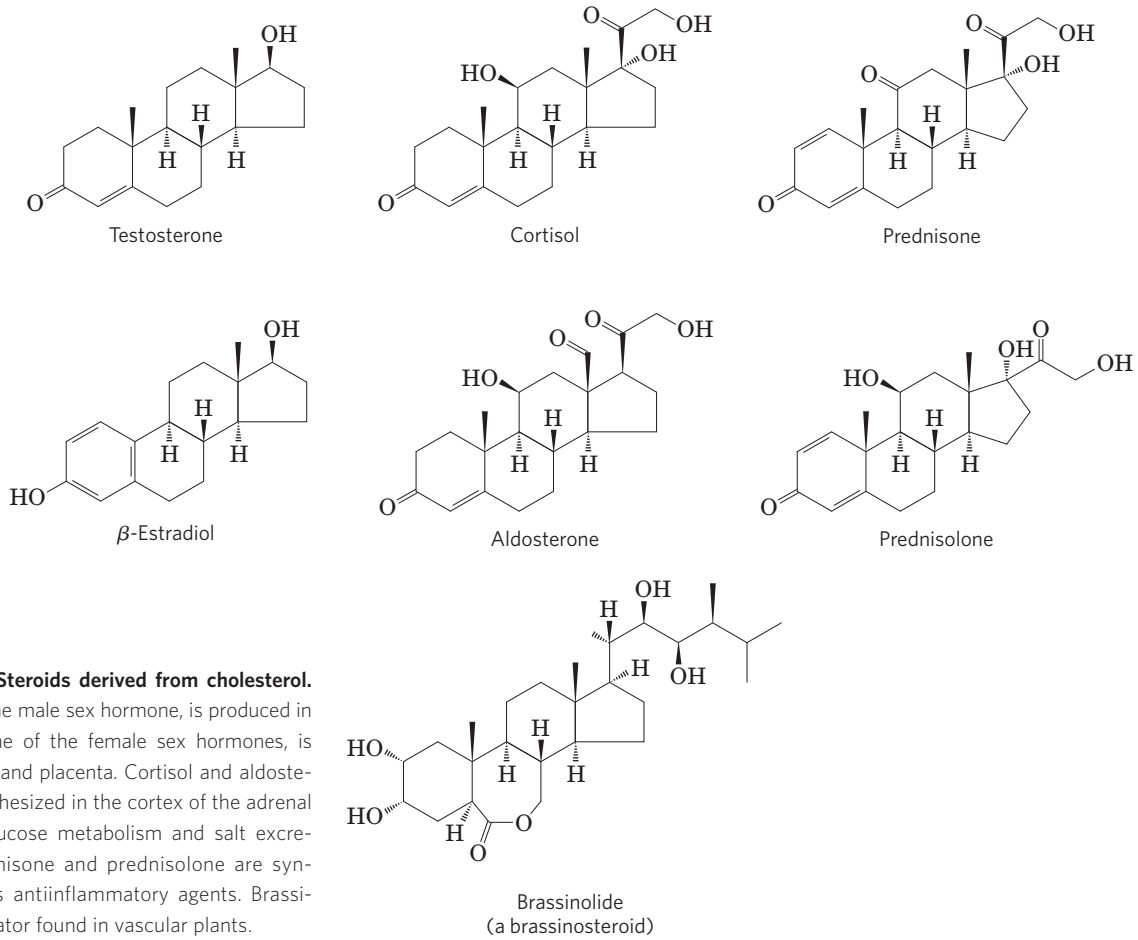
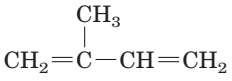


FIGURE 10–19 Steroids derived from cholesterol. Testosterone, the male sex hormone, is produced in the testes. Estradiol, one of the female sex hormones, is produced in the ovaries and placenta. Cortisol and aldosterone are hormones synthesized in the cortex of the adrenal gland; they regulate glucose metabolism and salt excretion, respectively. Prednisone and prednisolone are synthetic steroids used as antiinflammatory agents. Brassinolide is a growth regulator found in vascular plants.

widely used in the perfume industry. Many of the plant volatiles are derived from fatty acids, or from compounds made by the condensation of five-carbon isoprene units; these include geraniol (the characteristic scent of geraniums), β-pinene (pine trees), limonene (limes), menthol, and carvone (see Fig. 1–24a), to name but a few.



Isoprene

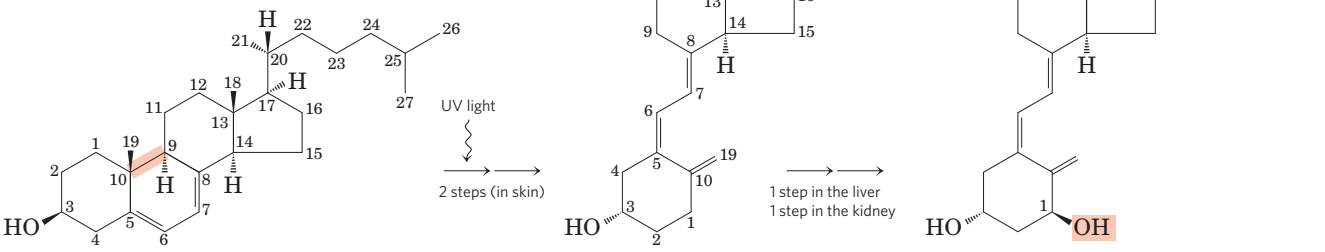
Vitamins A and D Are Hormone Precursors

During the first third of the twentieth century, a major focus of research in physiological chemistry was the identification of **vitamins**, compounds that are essential to the health of humans and other vertebrates but cannot be synthesized by these animals and must therefore be obtained in the diet. Early nutritional studies identified two general classes of such compounds: those soluble in nonpolar organic solvents (fat-soluble vitamins) and those that could be extracted from foods with aqueous solvents (water-soluble vitamins). Eventually the fat-soluble group was resolved into the four vitamin groups A, D, E, and K, all of which are isoprenoid compounds synthesized by the condensation of multiple isoprene units. Two of these (D and A) serve as hormone precursors.

Vitamin D_3, also called **cholecalciferol**, is normally formed in the skin from 7-dehydrocholesterol in a photochemical reaction driven by the UV component of sunlight **(Fig. 10–20a)**. Vitamin D_3 is not itself biologically active, but it is converted by enzymes in the liver and kidney to 1α,25-dihydroxyvitamin D_3 (calcitriol), a hormone that regulates calcium uptake in the intestine and calcium levels in kidney and bone. Deficiency of vitamin D leads to defective bone formation and the disease rickets, for which administration of vitamin D produces a dramatic cure (Fig. 10–20b). Vitamin D_2 (ergocalciferol) is a commercial product formed by UV irradiation of the ergosterol of yeast. Vitamin D_2 is structurally similar to D_3, with slight modification to the side chain attached to the sterol D ring. Both have the same biological effects, and D_2 is commonly added to milk and butter as a dietary supplement. Like steroid hormones, the product of vitamin D metabolism, 1α,25-dihydroxyvitamin D_3, regulates gene expression by interacting with specific nuclear receptor proteins (pp. 1182–1183).

Vitamin A (retinol), in its various forms, functions as a hormone and as the visual pigment of the vertebrate eye **(Fig. 10–21)**. Acting through receptor proteins in the cell nucleus, the vitamin A derivative retinoic acid regulates gene expression in the development of epithelial tissue, including skin. Retinoic acid is the active ingredient in the drug tretinoin (Retin-A), used in the treatment of severe acne and wrinkled skin. Retinal, another vitamin A derivative, is the pigment that initiates the response of rod and cone cells of the retina to light, producing a

(a)



7-Dehydrocholesterol — Cholecalciferol (vitamin D_3) — 1α,25-Dihydroxyvitamin D_3 (calcitriol)

FIGURE 10–20 Vitamin D_3 production and metabolism. **(a)** Cholecalciferol (vitamin D_3) is produced in the skin by UV irradiation of 7-dehydrocholesterol, which breaks the bond shaded light red. In the liver, a hydroxyl group is added at C-25; in the kidney, a second hydroxylation at C-1 produces the active hormone, 1α,25-dihydroxyvitamin D_3. This hormone regulates the metabolism of Ca^{2+} in kidney, intestine, and bone. **(b)** Dietary vitamin D prevents rickets, a disease once common in cold climates where heavy clothing blocks the UV component of sunlight necessary for the production of vitamin D_3 in skin. In this detail from a large mural by John Steuart Curry, *The Social Benefits of Biochemical Research* (1943), the people and animals on the left show the effects of poor nutrition, including the bowed legs of a boy with classical rickets. On the right are the people and animals made healthier with the "social benefits of research," including the use of vitamin D to prevent and treat rickets. This mural is in the Department of Biochemistry at the University of Wisconsin–Madison.

(b)

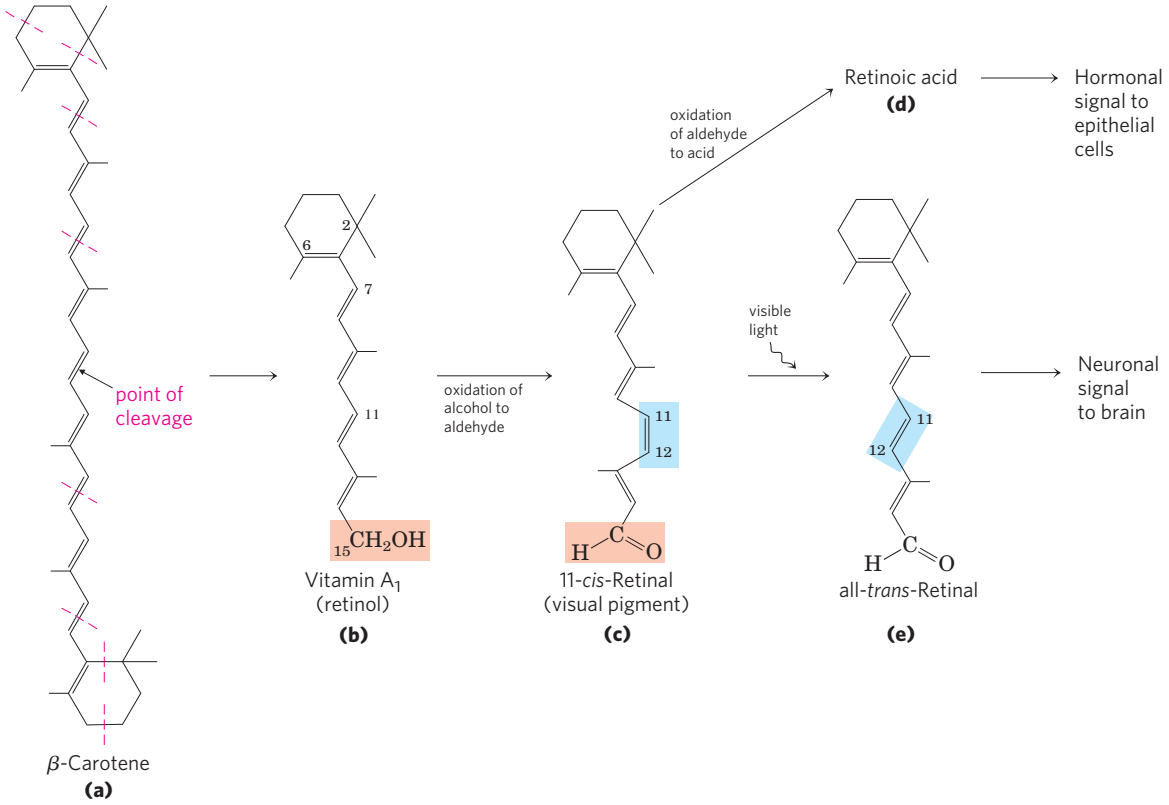


FIGURE 10–21 **Vitamin A_1 and its precursor and derivatives. (a)** β-Carotene is the precursor of vitamin A_1. Isoprene structural units are set off by dashed red lines (see p. 373). Cleavage of β-carotene yields two molecules of vitamin A_1 (retinol) **(b)**. Oxidation at C-15 converts retinol to the aldehyde, retinal **(c)**, and further oxidation produces retinoic acid **(d)**, a hormone that regulates gene expression. Retinal combines with the protein opsin to form rhodopsin (not shown), a visual pigment widespread in nature. In the dark, retinal of rhodopsin is in the 11-*cis* form (c). When a rhodopsin molecule is excited by visible light, the 11-*cis*-retinal undergoes a series of photochemical reactions that convert it to all-*trans*-retinal **(e)**, forcing a change in the shape of the entire rhodopsin molecule. This transformation in the rod cell of the vertebrate retina sends an electrical signal to the brain that is the basis of visual transduction, a topic we address in more detail in Chapter 12.

neuronal signal to the brain. This role of retinal is described in detail in Chapter 12.

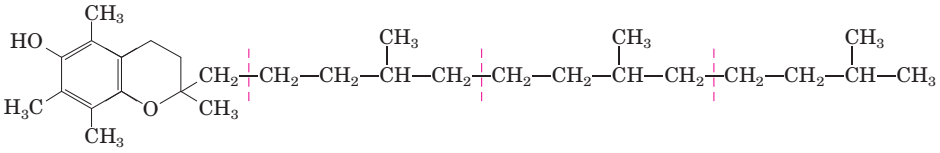
Vitamin A was first isolated from fish liver oils; liver, eggs, whole milk, and butter are also good dietary sources. In vertebrates, β-carotene, the pigment that gives carrots, sweet potatoes, and other yellow vegetables their characteristic color, can be enzymatically converted to vitamin A. Deficiency of vitamin A leads to a variety of symptoms in humans, including dryness of the skin, eyes, and mucous membranes; retarded development and growth; and night blindness, an early symptom commonly used in diagnosing vitamin A deficiency. ■

Vitamins E and K and the Lipid Quinones Are Oxidation-Reduction Cofactors

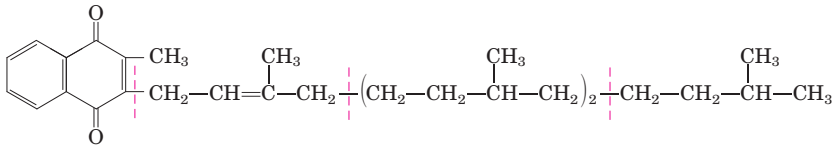
Vitamin E is the collective name for a group of closely related lipids called **tocopherols**, all of which contain a substituted aromatic ring and a long isoprenoid side chain **(Fig. 10–22a)**. Because they are hydrophobic, tocopherols associate with cell membranes, lipid deposits, and lipoproteins in the blood. Tocopherols are biological antioxidants. The aromatic ring reacts with and destroys the most reactive forms of oxygen radicals and other free radicals, protecting unsaturated fatty acids from oxidation and preventing oxidative damage to membrane lipids, which can cause cell fragility. Tocopherols are found in eggs and vegetable oils and are especially abundant in wheat germ. Laboratory animals fed diets depleted of vitamin E develop scaly skin, muscular weakness and wasting, and sterility. Vitamin E deficiency in humans is very rare; the principal symptom is fragile erythrocytes.

The aromatic ring of **vitamin K** (Fig. 10–22b) undergoes a cycle of oxidation and reduction during the formation of active prothrombin, a blood plasma protein essential in blood clotting. Prothrombin is a proteolytic enzyme that splits peptide bonds in the blood protein fibrinogen to convert it to fibrin, the insoluble fibrous protein that holds blood clots together (see Fig. 6–39). Henrik Dam and Edward A. Doisy independently discovered that vitamin K deficiency slows blood clotting, which can be fatal. Vitamin K deficiency is very uncommon in humans, aside from a small percentage of infants who suffer from hemorrhagic disease of the newborn, a potentially fatal disorder. In the United States, newborns are routinely given a 1 mg injection of vitamin K. Vitamin K_1 (phylloquinone) is found in green plant leaves; a related form, vitamin K_2 (menaquinone), is formed by bacteria living in the vertebrate intestine.

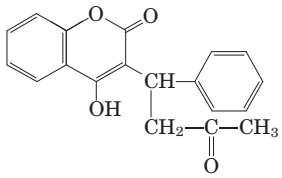
(a) Vitamin E: an antioxidant



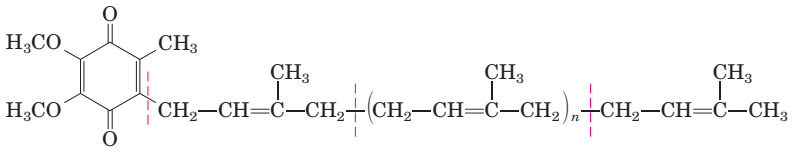
(b) Vitamin K_1: a blood-clotting cofactor (phylloquinone)



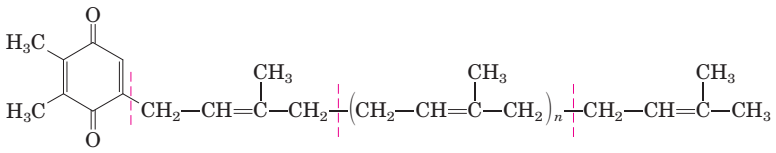
(c) Warfarin: a blood anticoagulant



(d) Ubiquinone: a mitochondrial electron carrier (coenzyme Q) (n = 4 to 8)



(e) Plastoquinone: a chloroplast electron carrier (n = 4 to 8)



(f) Dolichol: a sugar carrier (n = 9 to 22)

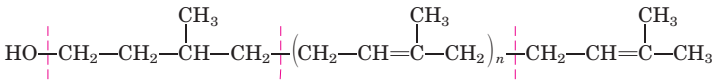


FIGURE 10–22 Some other biologically active isoprenoid compounds or derivatives. Units derived from isoprene are set off by dashed red lines. In most mammalian tissues, ubiquinone (also called coenzyme Q) has 10 isoprene units. Dolichols of animals have 17 to 21 isoprene units (85 to 105 carbon atoms), bacterial dolichols have 11, and those of plants and fungi have 14 to 24.

Henrik Dam, 1895–1976

Edward A. Doisy, 1893–1986

Warfarin (Fig. 10–22c) is a synthetic compound that inhibits the formation of active prothrombin. It is particularly poisonous to rats, causing death by internal bleeding. Ironically, this potent rodenticide is also an invaluable anticoagulant drug for treating humans at risk for excessive blood clotting, such as surgical patients and those with coronary thrombosis. ■

Ubiquinone (also called coenzyme Q) and plastoquinone (Fig. 10–22d, e) are isoprenoids that function as lipophilic electron carriers in the oxidation-reduction reactions that drive ATP synthesis in mitochondria and chloroplasts, respectively. Both ubiquinone and plastoquinone can accept either one or two electrons and either one or two protons (see Fig. 19–3).

Dolichols Activate Sugar Precursors for Biosynthesis

During assembly of the complex carbohydrates of bacterial cell walls, and during the addition of polysaccharide units to certain proteins (glycoproteins) and lipids (glycolipids) in eukaryotes, the sugar units to be added are chemically activated by attachment to isoprenoid alcohols called **dolichols** (Fig. 10–22f). These compounds have strong hydrophobic interactions with membrane lipids, anchoring the attached sugars to the membrane, where they participate in sugar-transfer reactions.