

4

Lipids

(Lipids (fixed oils, fats, and waxes) are esters of long-chain fatty acids and alcohols, or of closely related derivatives.) The chief difference between these substances is the type of alcohol; in fixed oils and fats, glycerol combines with the fatty acids; in waxes, the alcohol has a higher molecular weight, e.g., cetyl alcohol.

Fats and fixed oils are obtained from either plants (olive oil, peanut oil) or animals (lard). Their primary function is food (energy) storage. The fixed oils and fats are important products used pharmaceutically, industrially, and nutritionally. Waxes may also be of plant or animal origin. Many drugs contain fixed oils and fats as their principal constituents; the fixed oils and fats are often separated from the crude vegetable drugs (by expression) or the crude animal drugs (by rendering or extraction) and are employed as drugs in the refined state.

Fixed oils and fats differ only as to melting point; those that are liquid at normal temperatures are known as fatty or fixed oils, whereas those that are semisolid or solid at ordinary temperatures are known as fats. Although most vegetable oils are liquid at ordinary temperatures and most animal fats are solid, there are notable exceptions, such as cocoa butter, which is a solid vegetable oil, and cod liver oil, which is a liquid animal fat (see page 292).

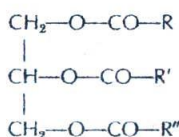
The United States Pharmacopeia includes several tests that determine the

identity, quality, and purity of fixed oils. These tests are based on the chemical constitution of the fatty acids. The **acid value** or **acid number** (the number of milligrams of potassium hydroxide required to neutralize the free fatty acids in 1 g of the substance) indicates the amount of free fatty acids present in the oil; the **saponification value** indicates the number of milligrams of potassium hydroxide required to neutralize the free acids and saponify the esters contained in 1 g of the substance; and the **iodine number** (the number of grams of iodine absorbed, under prescribed conditions, by 100 g of the substance) indicates the degree of unsaturation. Other physical constants, such as melting point, specific gravity, and refractive index, also serve as identity, purity, and quality tests.

Fixed oils and fats of vegetable origin are obtained by expression in hydraulic presses. If the expression is carried out in the cold, the oil is known as a "virgin oil" or a "cold-pressed oil." In contrast, if the expression is carried out in heat, the oil is known as a "hot-pressed oil." Sometimes organic solvents are used for the extraction of oils. Animal fats are separated from other tissues by rendering with steam, with or without pressure. The heat melts the fat, which rises to the top and may be separated by decantation. Oils may be further clarified by filtration and bleached with ozone. Stearins are often removed by chilling and filtration.

Vegetable oils and fats may occur in various parts of the plant but, as a general rule, seeds contain larger quantities of fats and oils than other plant parts. Seeds are the usual source of fixed oils and, as a few examples, the following might be mentioned: cottonseed, linseed, sesame seed, hemp seed, coconut, castor beans, almond, and others. In a few instances, other plant parts yield considerable quantities of fixed oil (pericarp of the olive). In certain fungi (e.g., ergot), fat is the characteristic reserve food material.

Chemically, the fixed oils and fats are glycerides of fatty acids that have the general formula:



If R, R', and R'' are the same fatty acid radical, the compound is called triolein, tripalmitin, tristearin, and so forth. If R, R', and R'' are different fatty acids, a mixed glyceride results. The composition of the glycerides in any fixed oil or fat is influenced by the amounts of various fatty acids that are present during formation. Thus, the composition of fixed oils and fats from any source can vary within certain limits.

Usually, the glycerides of unsaturated fatty acids are liquid, whereas the glycerides of saturated fatty acids of sufficient chain length are solid. The predominance of either type in an oil determines whether the mixture is liquid or solid. Some of the more common fatty acids are:

Caproic	$\text{CH}_3(\text{CH}_2)_4\text{COOH}$
Caprylic	$\text{CH}_3(\text{CH}_2)_6\text{COOH}$
Capric	$\text{CH}_3(\text{CH}_2)_8\text{COOH}$
Lauric	$\text{CH}_3(\text{CH}_2)_{10}\text{COOH}$
Myristic	$\text{CH}_3(\text{CH}_2)_{12}\text{COOH}$
Palmitic	$\text{CH}_3(\text{CH}_2)_{14}\text{COOH}$
Stearic	$\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$
Arachidic	$\text{CH}_3(\text{CH}_2)_{18}\text{COOH}$
Oleic	$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$
Linoleic	$\text{CH}_3(\text{CH}_2)_5\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_5\text{COOH}$

Linolenic	$\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$
Ricinoleic	$\text{CH}_3(\text{CH}_2)_3\text{CHOHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$

BIOSYNTHESIS OF LIPIDS

For many years, the synthesis of fats and fixed oils by living organisms was believed to be effected simply by a reversal of the reactions responsible for their degradation. Specifically, these include the hydrolysis of the glycerol-fatty acid esters by the enzyme lipase and the subsequent removal of 2-carbon units as acetyl-CoA from the fatty acid chain by β -oxidation. Biosynthetic studies indicate that the formation of these lipids utilizes different chemical pathways.

The biosynthesis of the fatty acid moieties is carried out by a series of reactions involving 2 enzyme complexes plus ATP, NADPH_2 , Mn^{++} , and carbon dioxide.

Acetate first reacts with CoA, and the acetyl-CoA thus formed is converted by reaction with carbon dioxide to malonyl-CoA. This, in turn, reacts with an additional molecule of acetyl-CoA to form a 5-carbon intermediate, which undergoes reduction and elimination of carbon dioxide to produce butyryl-CoA. Malonyl-CoA again reacts with this compound to form a 7-carbon intermediate, which is reduced to caproyl-CoA. Repetition of the reaction results in a fatty acid containing an even number of carbon atoms in its chain (Fig. 4-1). Thus, the malonyl portion of malonyl-CoA, a 3-carbon compound, is actually the source of the 2-carbon biosynthetic units of the fatty acids.

Pathways of biosynthesis of unsaturated, branched-chain, odd-numbered, and otherwise modified fatty acids have not been established in detail. There is evidence that the first step in the production of a mono-unsaturated acid is the formation of the acyl-CoA derivative of its saturated analog. This is followed by enzymatic desaturation. Hydroxylation appears to be independent or to follow desaturation. Apparently, hydroxylation is not in-

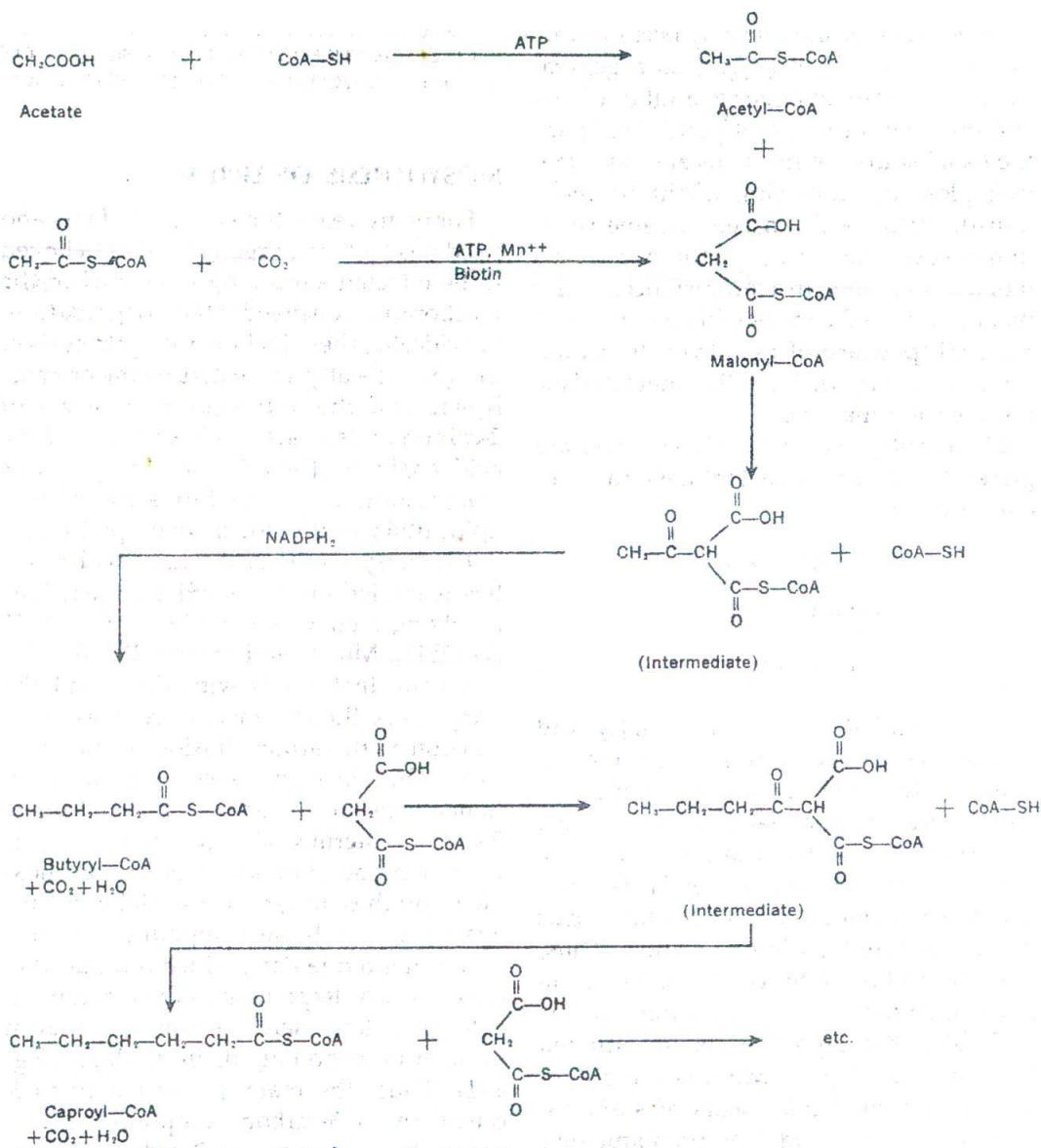


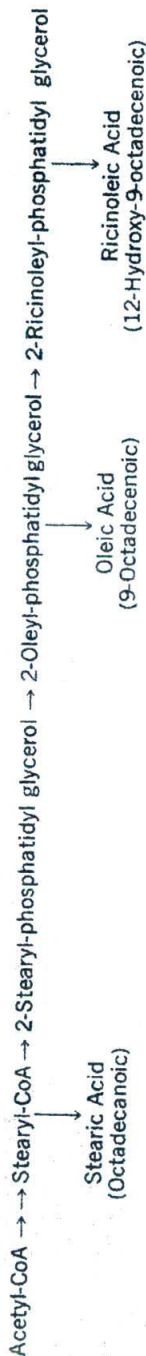
Fig. 4-1. Biosynthesis of fatty acids.

involved as an intermediate step in the desaturation process. Evidence suggests that the saturated acyl group of the acyl-CoA derivative is transferred to the 2-position of phosphatidyl glycerol before the desaturation and additional reactions.

Enzymes present in certain fractions of unripe castor seeds (*Ricinus communis*, Fam. Euphorbiaceae) can hydroxylate oleic

acid to produce ricinoleic acid. The probable sequence for the formation of the latter compound is summarized by the reaction sequence on page 85.

The glycerol moiety utilized in lipid biosynthesis derives mainly from the L-isomer of α -glycerophosphate (L- α -GP). Reactions involved in the formation of a typical triglyceride are summarized in Figure 4-2.



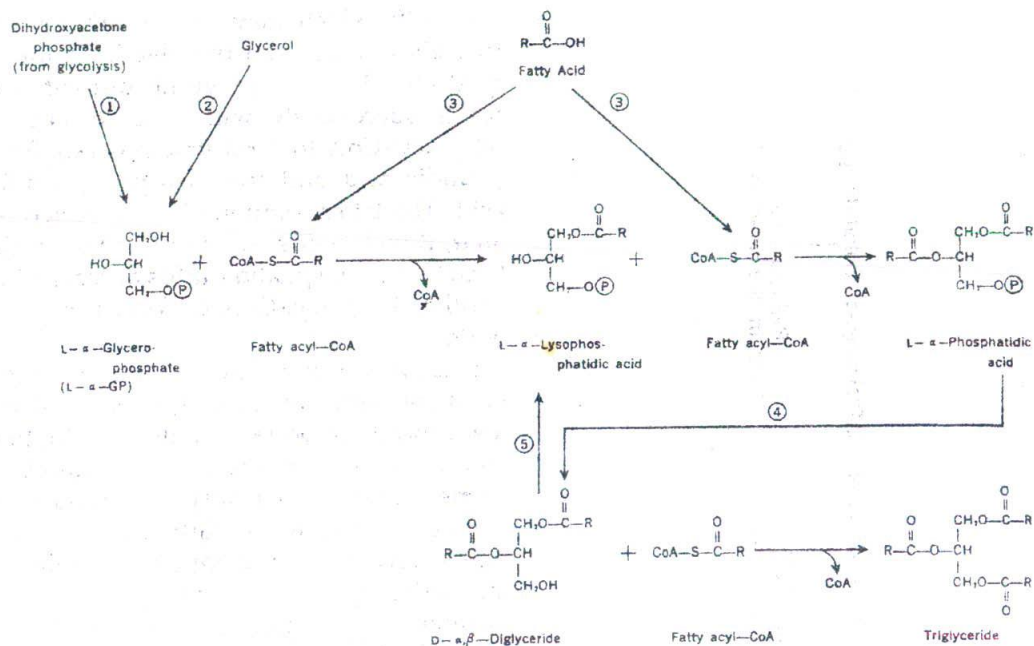
L- α -GP, which may derive either from free glycerol or from the glycolysis intermediate, dihydroxyacetone phosphate, reacts successively with 2 molecules of fatty acyl-CoA to form first L- α -lysophosphatidic acid and then L- α -phosphatidic acid. The latter compound is converted to an α , β -diglyceride, which can either cycle back to the phosphatidic acids or react with another fatty acyl-CoA to form a triglyceride.

Relatively little is known about the biosynthetic pathways leading to other pharmaceutically important lipids. The higher alcohol esters of waxes are probably formed from smaller fatty acid units in a manner analogous to fatty acid biosynthesis. Hydrocarbon compounds of lipids may arise by reduction of squalene or a metabolic equivalent.

Fixed oils are sometimes classified into **drying oils**, **semidrying oils**, and **nondrying oils**. This classification is based on their ability to absorb oxygen from the air. Oxygen saturates the double bonds to form oxides that may polymerize to form hard films. This property of drying oils is of great importance in the paint industry. The double bonds in the unsaturated fatty acids also take up hydrogen under the proper conditions. **Hydrogenation** of the liquid oils produces semisolid fats that are extensively used as cooking fats and shortenings.

Fixed oils may be **hydrogenated** by passing hydrogen, in the presence of nickel or palladium, through the oil heated to 160 to 200°C. The unsaturated glycerides are more or less converted to saturated glycerides, which are solid at room temperature and stable. Many such oils are used for culinary purposes.

Sulfated or sulfonated oils are obtained by reacting sulfuric acid with the oil, keeping the temperature down by chilling. The oil is then washed and neutralized. If the oil contains an olefinic linkage, the acid molecule adds onto the double bond. The compound formed is a sulfate of the fat.



Enzymes and Cofactors Required

1. L- α -GP dehydrogenase + NADH₂
2. Glycerokinase + ATP
3. Acetyl-CoA + ATP
4. Phosphatidic acid phosphatase
5. Diglyceride kinase + ATP

Fig. 4-2. Biosynthesis of a triglyceride.

These materials have surfactant properties that find industrial application.

Fixed oils and fats are employed in pharmaceuticals for their emollient properties. They may also serve, either in their natural form or in emulsions, as vehicles for other medicaments. A few, such as castor oil, have special therapeutic properties; the prostaglandins are other lipid metabolites that have recently attracted considerable attention for their physiologic properties and therapeutic potential. In the arts and in industry, fats and oils are used in the manufacture of soaps (sodium and potassium salts of the fatty acids), as drying oils in the manufacture of paints and varnishes, and as lubricants. Lipids also form an important class of foods; their high caloric value and low osmotic pressure have prompted interest in some plant oils as parenteral nutrients in hyperalimentation

regimens (Intralipid[®], Liposyn[®], Soyacal[®], and Travamulsion[®]).

Sodium morrhuate, the sodium salts of fatty acids obtained from cod liver oil, is used as a sclerosing agent to obliterate varicose veins. Other fatty acids are used as topical antifungal agents, dietary supplements, and agents of pharmaceutical necessity.

The oil-soluble vitamins are lipids by nature and could be included in this chapter according to a strictly chemical classification. However, to achieve uniformity of types of subject matter, they are considered with the water-soluble vitamins in Chapter 11.

Numerous studies are being conducted to screen the fixed oils obtained from the seeds of many plants. Physical properties, pharmacologic activity, and chemical components are being determined in the search

for new therapeutic agents and commercially important lipids. In addition, investigations are being undertaken to ascertain the most advantageous types of antioxidants to prevent or to retard rancidity of fixed oils and fats.

FIXED OILS

Castor Oil

Castor bean or castor oil seed is the ripe seed of *Ricinus communis* Linné (Fam. Euphorbiaceae). *Ricinus* is Latin and means a tick or a bug, referring to the seed's resemblance to some bugs in shape and markings.

The plant is an annual in temperate climates, or a tree, attaining the height of 15 meters, in the tropics. There are many forms of the plant, with variations in the shape of the leaves and the color, size, and markings of the seeds. The fruit is a 3-celled spiny capsule (Fig. 4-3), each cell

containing an ovoid albuminous seed. The plant is indigenous to India. It is extensively cultivated in India, Brazil, other South and Central American countries, the Soviet Union, various parts of Africa, southern Europe, and the southern United States. The seeds have been found in Egyptian tombs. The oil apparently had only technical use until the 18th century, when its medicinal use began.

The seed is anatropous, elliptical-ovoid, somewhat compressed, from 8 to 18 mm in length, and from 4 to 7.5 mm in thickness. Externally, the seed is mottled grayish and brown, but it varies considerably in color. It is smooth, with a prominent whitish caruncle at the somewhat pointed end from which the raphe extends, on the flat or ventral side, to the chalazal end. Its seed coat is thin and brittle and the endosperm is large, white, oily, and bears 2 thin foliaceous cotyledons, one on either side of a central, lenticular cavity, and connected with the short caulicle and radicle,

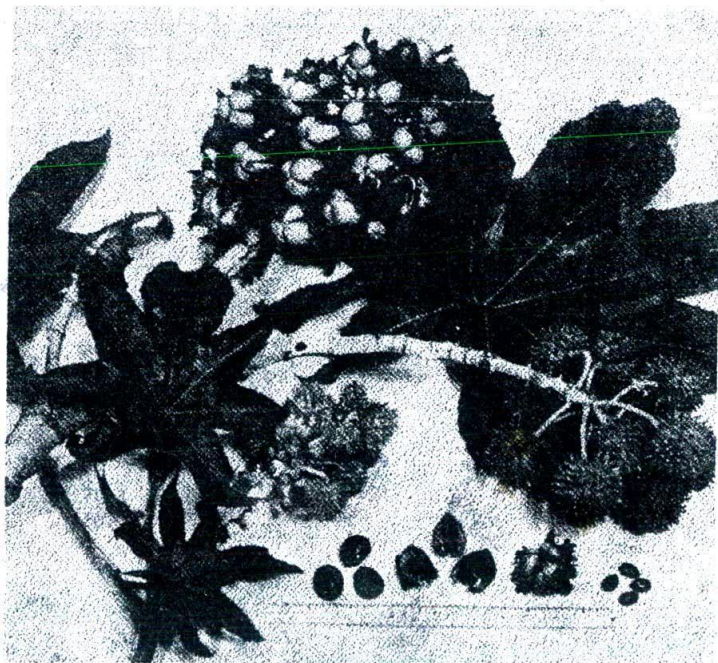


Fig. 4-3. Castor bean (*Ricinus communis*) showing large palmate leaves, immature and mature fruits, and large black seeds (lower center) contrasted with smaller seeds of brown-speckled variety (lower right). (Photo courtesy of Dr. Julia F. Morton, Director, Morton Collectanea, University of Miami.)

the latter directed toward the micropyle (Fig. 4-4).

Castor seeds contain from 45 to 55% of fixed oil; about 20% of protein substances consisting of globulin, albumin, nucleoalbumin, glycoprotein, and ricin (a toxic lectin or hemagglutinin); an alkaloid, ricinine; and several enzymes. The seed coat yields 10% of ash; the kernel yields about 3.5%. Ricin is not removed in the extraction of the castor oil but remains in the oil cake. It is poisonous to cattle but does not affect poultry.

Castor bean pomace contains an allergen that causes allergic reactions in hypersensitive individuals. This powerful allergen is in the nontoxic protein polysaccharide fraction.

Deactivation of toxic substances and removal of the allergenic fraction are problems that must be solved in castor oil production.

Castor oil is the fixed oil obtained from the seed of *Ricinus communis*. It is prepared by passing the seeds through a decorticator, which has rollers with sharp cutting edges that break the testae but do not in-

jure the kernel. The testae are then separated by sieves and compressed air, and the kernels are subjected to pressure. The oil is steamed to destroy albumins, is filtered, and is bleached.

The yield of the "cold-pressed" oil separated by hydraulic pressure is 60% and represents a light-colored, good grade. The remainder of the oil from the seeds is solvent extracted, yielding a darker, lower grade oil.

Castor oil is a pale yellowish or almost colorless, transparent, viscid liquid. It has a faint, mild odor and a bland, characteristic taste.

Castor oil is composed of a mixture of triglycerides, about 75% of which is triricinolein. The remainder consists of diricinoleoglycerides with the third acyl group, representing either oleic, linoleic, dihydroxystearic, or a saturated (palmitic or stearic) acid. Triricinolein is hydrolyzed by lipases in the duodenum to release ricinoleic (12-hydroxy-octadec-9-enoic) acid, which exerts a cathartic effect.

USES AND DOSE. Castor oil is a stimulant cathartic; the usual dose is 15 to 60 ml. The

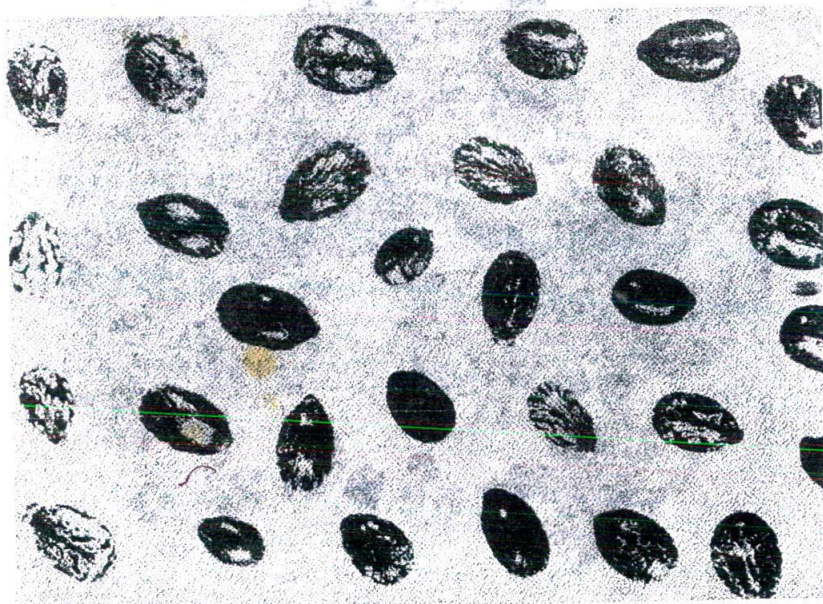


Fig. 4-4. Castor beans.

oil is also used as a plasticizer in flexible collodion. Ricinoleic acid is an ingredient (0.7%) in a vaginal jelly (Aci-Jel[®]) for restoration and maintenance of vaginal acidity. Commercially, castor oil is employed in the manufacture of soaps and as a lubricant for internal combustion engines. Hydrogenated castor oil is used as a stiffening agent in some pharmaceutical formulations.

PROPRIETARY PRODUCTS. Alphamul[®], Emulsoil[®], Neoloid[®], and Purge[®].

Olive Oil

Olive oil is the fixed oil obtained from the ripe fruit of *Olea europaea* Linné (Fam. Oleaceae). Olive oil is sometimes called **sweet oil**. The generic name *Olea* is from the Latin *oliva*, meaning olive or from the Greek *elaion*, meaning oil.

The olive tree is a small evergreen tree that attains a great age but seldom exceeds 10 meters in height. It was apparently a native of Palestine and has been widely cultivated in the Mediterranean countries from remote antiquity. It is now also cultivated in the southwestern United States and many other subtropical localities. There are a large number of cultivated varieties of the olive, the fruits of which vary widely in size, color, and yield of oil.

The fruit is a drupe, usually purple when ripe. The full-grown but green fruit, as well as the ripe fruit, when pickled in brine, is widely used as a condiment. The olive "stone" or endocarp enclosing the seed has been finely comminuted and used as an adulterant of spices and certain powdered drugs.

Olive oil is offered on the market in several grades of purity. **Virgin oil** is obtained by gently pressing the peeled pulp free from the endocarp. First and second grades of edible oil are pressed from crushed pulp, the first grade with less pressure, the second grade from the same pulp with more pressure. Hand-picked olives are used, and the oil is obtained promptly before decomposition produces fatty acids. Finally,

the pulp, mixed with hot water, is pressed again for technical oil; or, the pulp is extracted with carbon disulfide to obtain "sulfur" olive oil of inferior quality. The fallen, decomposed, or refuse olives that are allowed to ferment furnish a low grade "tournant oil," which contains large amounts of free fatty acids.

Olive oil is a pale yellow or light greenish yellow, oily liquid whose odor is slight but characteristic and whose taste is bland to faintly acid. Olive oil is miscible with ether, carbon disulfide, and chloroform and slightly soluble in alcohol. Its specific gravity is 0.910 to 0.915 at 25° C. Upon chilling, olive oil tends to become cloudy, and at 0° C it usually forms a whitish granular mass.

Although the composition of olive oil seems to vary rather widely, 2 major types are recognized based on the relative concentrations of the component acids of the glycerides. The Turkish variety contains about 75% of oleic acid, 10% of palmitic acid, and 9% of linoleic acid, with lesser amounts of stearic, myristic, hexadecenoic, and arachidic acids. The Italian variety contains only about 65% of oleic acid, 15% each of palmitic and linoleic acids, and other minor component acids.

USES. Olive oil is classed as a pharmaceutical aid. It is used as a setting retardant for dental cements and in the preparation of soaps, plasters, and liniments. It is also a demulcent, an emollient, and a laxative. Olive oil is a nutrient and is widely used as a salad oil.

Peanut Oil

Peanut is the ripe fruit or seed of *Arachis hypogaea* Linné (Fam. Leguminosae). The plant is a low annual herb with imparipinnate leaves and yellow papilionaceous flowers. It is native to Brazil but is extensively cultivated in the southern United States, Gambia, Nigeria, and other localities with similar climates. The fruit is not a true nut because the immature pod penetrates the soil and ripens underground. It

contains from 1 to 6 reddish brown seeds. When ripe, the plants with the fruits are raked from the soil into windrows. When dry, the pods are machine separated and sacked for shipment, or the dried plants are threshed to separate and clean the seeds. For human consumption, the fruits are roasted, passed between rollers, and the seeds are separated. The kernels contain about 45% of fixed oil, 20% of protein, and a high content of thiamine; hence, they are highly nutritious and are extensively used as food, both whole and when ground into a paste (**peanut butter**).

Peanut oil is the refined fixed oil obtained from the seed kernels of one or more of the cultivated varieties of *A. hypogaea*. Peanut oil is sometimes referred to as **arachis oil**. It is a colorless or a yellowish liquid with a slightly nutlike odor and a bland taste.

Peanut oil consists of a mixture of glycerides with component acids of the following approximate composition: oleic (50 to 65%); linoleic (18 to 30%); palmitic (8 to 10%); stearic, arachidic, behenic, and lignoceric acids (together, 10 to 12%). It closely resembles olive oil and is used as a pharmaceutical aid. Its principal use is as a food oil. It is nondrying and therefore has no value in paints but does have value as a lubricant. The oil saponifies slowly but yields an excellent, firm, white soap.

USE. Peanut oil is a solvent for intramuscular injections.

Peanut oil cake, the residue following expression of the fixed oil, is a valuable livestock food.

Soybean Oil

Soybean is the ripe seed of *Glycine soja* Siebold et Zaccarini (Fam. Leguminosae), an important food and forage crop. The plant is an annual with trifoliate, hairy leaves, rather inconspicuous, pale blue to violet flowers, and broad pods containing 2 to 5 seeds. The seeds are more or less compressed, spheroidal or ellipsoidal, and vary in color from nearly white to yellow-

green or brownish black. The seeds contain about 35% of carbohydrates, up to 50% of protein substances, up to 20% of fixed oil, and the enzyme, urease.

Soybeans are used medicinally as a food in diabetes and as a general food for humans and livestock.

Soybean oil is the refined, fixed oil obtained from the seeds of the soya plant. The oil is obtained by pressure, and the yield seldom exceeds 10%. It consists of a mixture of glycerides with the following component acids: linoleic (50%); oleic (30%); linolenic (7%); saturated acids, chiefly palmitic and stearic (14%). It is a drying oil with an iodine value between 120 and 141 and is not useful as a cooking oil.

Soybean oil is an ingredient in parenteral nutrients (Intralipid[®], Soyacal[®], and Travamulsion[®]) and is a source of lecithin. **Lecithin** is an ingredient in a number of proprietary products that are useful in controlling deranged lipid and cholesterol metabolisms. Stigmasterol, obtained from the lipid fraction of soybeans, can be used as a precursor for steroidal hormones (see page 174). The oil is used extensively in the manufacture of varnishes, insulators, and other products.

Partially hydrogenated soybean oil is an ingredient in a number of combination products for oral administration (e.g., Controlyte Powder[®], Sustacal Pudding[®], and Travasorb Liquid[®]) that are described as balanced dietary supplements.

Soybean cake, the residue after pressing out the oil, has a high value as a livestock food. It not only contains a large amount of protein and some oil, but the 5% of ash consists largely of potassium and phosphorus.

Soybean meal is the flour sifted from the decorticated, ground seed of *Glycine soja* deprived of fat. It can be used for the detection of urea nitrogen in blood serum by the enzymatic action of the urease in the soybean meal.

Cottonseed Oil

Cottonseed oil is the refined, fixed oil obtained from the seed of cultivated plants

of various varieties of *Gossypium hirsutum* Linné or of other species of *Gossypium* (Fam. Malvaceae). The cottonseed, after ginning off the fibers, is decorticated and cleaned of hulls. The kernels are steamed and pressed at about 1500 lb pressure to yield about 30% of oil. The oil, thus obtained, is turbid and reddish in color. It is refined by filtering, decolorizing, and "winter chilling," which removes the stearin.

Cottonseed oil is a pale yellow, oily liquid. It is odorless and has a bland taste.

The oil consists of a mixture of glycerides with the following component acids: linoleic (45%), oleic (30%), palmitic (20%), myristic (3%), stearic and arachidic (1% of each).

USES. Cottonseed oil is employed pharmaceutically as a solvent for a number of injections. A considerable quantity is hydrogenated and used to make substitutes for lard. A large amount is also used in the manufacture of soap.

Cottonseed cake contains about 0.6% of a toxic principle, gossypol, which occurs in secretory cavities in all parts of the plant. It is present in cold-pressed oil and can be removed by treatment with alkalis.

Sesame Oil

Sesamum seed or sesame seed is the seed of one or more cultivated varieties of *Sesamum indicum* Linné (Fam. Pedaliaceae).

Sesamum is from the Greek *sesamon*, the original name of the plant; *indicum* refers to its habitat, India. The plant is an annual herb attaining a height of about 1 meter. It is native to southern Asia but is cultivated from Africa to the East Indies, in the West Indies, and in the southern United States.

The seeds are small, flattened, oval or ovate, smooth and shiny, and whitish, yellow, or reddish brown. Their taste is sweet and oily. They contain 45 to 55% of fixed oil, 22% of proteins (aleurone), and 4% of mucilage. These seeds are nutritious and form an important food in India. In Europe and America they are used like poppy

seeds on bread and rolls. The fixed oil is obtained by expression.

Sesame oil is the refined, fixed oil obtained from the seed of one or more cultivated varieties of *S. indicum*. It is also referred to as **teel oil or benne oil**. The oil is a pale yellow, oily liquid, almost odorless and bland tasting.

Sesame oil consists of a mixture of glycerides with the following component acids: approximately equal parts of oleic and linoleic (about 43% of each), palmitic (9%), and stearic (4%). The excellent stability of the oil is owing to the phenolic constituent, sesamol, which is produced by hydrolysis of sesamolin, a lignan present in the unaponifiable fraction of the oil.

USES. Sesame oil is classed as a pharmaceutical aid and is used as a solvent for intramuscular injections. It has nutritive, laxative, demulcent, and emollient properties. Sesamolin, contained in the unaponifiable fraction of the oil, is an effective synergist for pyrethrum insecticides.

Almond Oil

Sweet almond and bitter almond consist of the ripe seeds of different varieties of *Prunus amygdalus* Batsch (Fam. Rosaceae). *Prunus* is the classic name of the plum tree; *amygdalus* is from the Greek *amygdolos*, meaning almond tree; *amara* and *dulcis*, the variety designations, are Latin and mean bitter and sweet, respectively.

The tree is native to Asia Minor, Iran, and Syria and is cultivated and naturalized in all tropical and warm-temperate regions. The presence of amygdalin in the bitter almond and its bitter taste distinguish it from sweet almond. Commercial products are obtained mostly from Sicily, southern Italy, southern France, northern Africa, and California. In commerce, the yellowish, more or less porous, fibrous, and brittle endocarp may be present (Fig. 4-5).

Both bitter and sweet almonds are expressed for their fixed oil (45 to 50%). Practical economic considerations favor the use of bitter almonds or sweet almonds of in-



Fig. 4-5. Drupelike fruit of almond (*Prunus amygdalus*); A, whole fruit with distinct suture; B, longitudinal section showing fibrous sarcocarp and thin-shelled endocarp; C, D, E, sections of the seed; c, cotyledons; w, hypocotyl; v, epicotyl or plumule.

ferior quality. Bitter almonds, after maceration to permit hydrolysis of amygdalin, also yield a volatile oil that is used as a flavoring agent. Sweet almonds are extensively used as a food, but bitter almonds are not suitable for this purpose. The seeds of the bitter almond were known to be poisonous in the days of antiquity. The sweet almond is mentioned early in the Old Testament (Genesis 43:11) as one of the fruits Israel commanded his sons to carry from Palestine as a gift to Egypt. Theophrastus makes several references to the almond. Charlemagne (812 A.D.) introduced the tree on the imperial farms, and, in the 14th century, the almond was an important item of Venetian trade.

Almond oil, expressed almond oil, or sweet almond oil is the fixed oil obtained by expression from the kernels of varieties of *P. amygdalus*.

Almond oil consists of a mixture of glycerides with component acids of the following approximate composition: oleic (77%), linoleic (17%), palmitic (5%), myristic (1%).

USES. Expressed almond oil is an emollient and an ingredient in cosmetics.

Persic Oil

Persic oil, apricot kernel oil, or peach kernel oil is the oil expressed from the kernels of varieties of *Prunus armeniaca* Linné (apricot kernel oil) or from the kernels of

varieties of *P. persica* Siebold et Zuccarini (peach kernel oil) (Fam. Rosaceae).

Persic oil is prepared in the same manner as is expressed almond oil. Its characteristics closely resemble those of expressed almond oil, and it is used as a vehicle and pharmaceutical necessity.

Coconut Oil

Coconut oil is the fixed oil obtained by expression or extraction from the seed kernels of the coconut palm, *Cocos nucifera* Linné (Fam. Palmae). This tall, stately tree rises to a height of 30 meters, has a tuft of leaves at the top, and bears 100 or more fruits (coconuts) each year (Fig. 4-6). The oil consists of a mixture of glycerides in which 80 to 85% of the acids are saturated; it is a semisolid at 20° C. Lauric (50%) and myristic (20%) are the major fatty acids. These low-molecular-weight acids give the oil a high saponification value, and coconut oil yields quality soaps and shampoos.

Coconut oil also contains glycerides of caprylic and capric acids (C_8 and C_{10} saturated fatty acids). A lipid fraction containing these medium chain triglycerides (MCT[®]) is used when conventional food fats are not well digested or absorbed. Coconut oil and medium-chain triglycerides are ingredients in a number of combination products for oral administration (e.g., Lonlac Powder[®] and Osmolite Liquid[®]) that



Fig. 4-6. Habit of growth of the fruits of *Cocos nucifera*.

are described as balanced dietary supplements.

Corn Oil

Corn oil is the refined oil obtained from the embryo of *Zea mays* Linné (Fam. Gramineae).

The oil-rich embryos (often called germs) are separated by a flotation process during the preparation of corn starch. After the embryos are washed free of starch and gluten, they are subjected to pressure and heat to express the oil. The **germ oil cake** that remains is ground and sold as cattle feed (**oil cake meal**). The crude oil is clarified by filtering and settling and refined by removing the fatty acids, refrigerating, filtering, and sterilizing. Corn oil is a clear, light yellow, oily liquid that has a faint characteristic odor and taste.

The oil consists of a mixture of glycerides with component acids of the following approximate composition: linoleic (50%), oleic (37%), palmitic (10%), stearic (3%).

Corn oil is used as a solvent for injections; it is also a solvent for irradiated er-

gosterol. It is an edible oil and, as such, is used in salads and in the preparation of food. An emulsion containing 67% of corn oil is used as a high-calorie dietary supplement (Lipomul Oral®). Corn oil is also an ingredient in a number of combination products for oral administration (e.g., Ensure Liquid® and Meritene Liquid®) that are described as balanced dietary supplements. When hydrogenated, the oil becomes semisolid and is used as a shortening for baking.

Safflower Oil

Safflower seed oil is the fixed oil obtained from the seeds of *Carthamus tinctorius* Linné (Fam. Compositae).

The oil consists of a mixture of glycerides whose component acids are largely unsaturated. A typical sample contains linoleic acid (75%), oleic acid (18%), and a mixture of saturated acids totaling about 6%. The claims that ingestion of quantities of polyunsaturated fatty acids in various forms, e.g., margarine, oil-filled capsules, and others, results in a decreased blood cho-

lesterol level are based on insubstantial evidence. Further, there is no indication that a combination of choline, pyridoxine, or other lipotropic substances with unsaturated fatty acids possesses any therapeutic advantage over the substances themselves. Although a number of safflower oil preparations, especially capsules of various sizes, are marketed at present, their use as antilipemics without adequate dietary adjustments is not rational therapy.

An emulsion containing 50% of safflower oil is used orally as a high-calorie dietary supplement (Microlipid®). Safflower oil is an ingredient in Criticare HN Liquid® and High Nitrogen Vivonex Powder®, products that are balanced dietary supplements.

Sunflower Oil

Sunflower oil is the fixed oil obtained from the seeds of cultivated varieties of *Helianthus annuus* Linné (Fam. Compositae).

The oil consists of a mixture of glycerides that are rich in unsaturated acids. The polyunsaturated acid content of sunflower oil is influenced by climate as well as genetics. The linolenic acid content ranges from 44 to 75%, the higher percentages occurring in oils from seeds grown in the cooler or northern temperate regions (e.g., Minnesota and North Dakota for U.S. production). A representative sample of sunflower oil contains 66% linoleic acid and 23% oleic acid. The oil is used as an alternative to corn oil and safflower oil for culinary purposes, and it is an ingredient in a number of specialty dietary supplements marketed under the Travasorb® label (Travasorb Hepatic Powder®, Travasorb Renal Powder®, Travasorb MCT Powder®, Travasorb NH Powder®, and Travasorb STD Powder®).

Ethiodized Oil Injection

Ethiodized oil is an iodine addition product of the ethyl ester of the fatty acids of poppy seed oil. It contains not less than

35.2% and not more than 38.9% of organically combined iodine. It decomposes when exposed to air and sunlight, becoming dark brown in color. Ethiodized oil is packaged in a sterile form.

Ethiodized oil is radiopaque and is used as a diagnostic aid in hysterosalpingography and lymphography.

SPECIALTY PRODUCT. Ethiodol®.

FATS AND RELATED COMPOUNDS

Theobroma Oil

Cacao seeds or cacao beans are the roasted seeds of *Theobroma cacao* Linné (Fam. Sterculiaceae). *Theobroma* is Greek and means "food of the gods"; *cacao* is from the Aztec name of the tree; "chocolate" is from the Nahuatl. It has long been highly esteemed by the Aztecs, the Mexicans, and later by the Europeans, who explored the Americas.

The plant is a tree attaining the height of about 12 meters and is indigenous to Mexico, but widely cultivated in tropical countries. The flowers arise from the older branches or trunk and develop into large, ovoid, fleshy fruits that are 10-furrowed longitudinally, are yellow or reddish, and contain 5 rows of seeds, 10 or 12 in each row (Fig. 4-7). Cacao was known to Columbus and Cortez. Most of the cacao seed on the market is obtained from Ecuador (the Guayaquil variety is especially valuable), Curaçao, Mexico, Trinidad, Central America, Brazil, West Africa (Nigeria and Ghana), Sri Lanka, and the Philippine Islands.

The seeds are separated from the pod and allowed to ferment. During the process, they change from white to dark reddish brown. They are then roasted (not above 140° C) to lose water and develop their characteristic odor and taste. The roasted seeds are passed through a "nibbling" machine to crack the seed coats (**cacao shells**), which are separated from the kernels by winnowing. The broken ker-



Fig. 4-7. Cacao tree (*Theobroma cacao*) showing the peculiar habit of the fruits in developing on the trunk and branches.

nels are called "nibs," and, when ground between hot rollers, they yield a paste containing up to 50% of fat, **cacao butter**. The paste congeals at room temperature to form **bitter chocolate**. **Sweet chocolate** is bitter chocolate to which sugar and vanilla or other flavoring substances have been added. After expressing cacao butter, the marc, which retains some oil, is powdered and is known as **prepared cacao** or **breakfast cocoa**. Some brands of cocoa contain alkali to render it "soluble"; it is, of course, not soluble, but the alkali partially saponifies the fat at the surface of each minute particle, resulting in a smoother and more complete suspension of the cocoa in water or milk.

Cacao seeds or cacao beans are often found on the market as such. The seed is irregularly ellipsoidal or ovoid, somewhat

flattened, and 15 to 30 mm in length. Externally, it is reddish brown to dark brown and the seed coat is thin and shell-like, readily separable from the cotyledons. The latter are fleshy, much folded, and connected with a stout radicle that is situated at the hilum portion of the seed. Their odor is chocolatelike, and the taste is slightly bitter.

The seeds contain 35 to 50% of a fixed oil, about 15% of starch, 15% of proteins, 1 to 4% of theobromine, and 0.07 to 0.36% of caffeine. The red color of the seed is caused by a principle known as cacao-red, which is formed by the action of an enzyme on a glycoside. When the seeds are roasted, the theobromine in the kernel passes into the shell. The shell is a commercial source of this xanthine derivative.

Cocoa is a powder prepared from the roasted, cured kernels of the ripe seed of *Theobroma cacao*. It occurs as a weak reddish to purplish brown to moderate brown powder that has a chocolatelike odor and a taste that is not sweet.

USES. Cocoa is employed in making **cocoa syrup**, which is a flavored vehicle. Cocoa, also known as "breakfast cocoa," is a popular beverage and usually contains more than 22% of "fat" (nonvolatile ether-soluble extractive). **NOTE:** Cocoa containing not more than 12% of nonvolatile ether-soluble extractive is preferred for cocoa syrup; it yields a syrup that has a minimum tendency to separate.

Theobroma oil or **cocoa butter** is the fat obtained from the roasted seed of *T. cacao*. It is a yellowish white solid that has a faint, agreeable odor and a bland, chocolatelike taste. It melts between 30 and 35° C.

Theobroma oil consists of a mixture of glycerides with component acids of the following approximate composition; oleic (37%), stearic (34%), palmitic (26%), linoleic (2%). The relatively sharp melting point of the fat and its comparative brittleness and nongreasiness are owing to its peculiar glyceride structure. Mono-oleo

disaturated glycerides, chiefly oleopalmitostearin, are its major constituents.

Cocoa butter is used pharmaceutically as a suppository base.

Hydrogenated Vegetable Oil

Hydrogenated vegetable oil is refined, bleached, hydrogenated, and deodorized vegetable oil stearins and consists mainly of the triglycerides of stearic and palmitic acids. It is a fine, white powder at room temperature and melts between 61 and 66° C to give a pale yellow, oily liquid. It is used as a tablet lubricant.

Lanolin

Lanolin is the purified, fatlike substance from the wool of the sheep, *Ovis aries* Linné (Fam. Bovidae). It contains between 25 and 30% of water and therefore is commonly called **hydrous wool fat**.

Lanolin is a yellowish white, ointment-like mass that has a slight, characteristic odor. When heated on a steam bath, it separates at first into 2 layers. Continued heating with frequent stirring drives off the water that makes up the lower layer.

The chief constituents are cholesterol and isocholesterol. Lanolin also contains the esters of lanopalmitic, lanoceric, carnaubic, oleic, myristic, and other fatty acids.

USES. Lanolin is used as a water-absorbable ointment base. It is employed for the external administration of remedies locally or by inunction. Lanolin is an ingredient in many skin creams and cosmetics. As such, however, it may act as an allergenic contactant in hypersensitive persons (see page 424).

Anhydrous Lanolin

Anhydrous lanolin is lanolin that contains not more than 0.25% of water. After lanolin has been purified and bleached, it is dehydrated. Anhydrous lanolin is usually referred to as **wool fat**.

USES. Anhydrous lanolin is a water-absorbable ointment base. It is more readily

absorbed through the skin than any other known fat and is therefore valuable as a base for therapeutic agents that are administered by inunction. In addition, it possesses emollient properties.

Lanolin Alcohols

A mixture of aliphatic alcohols, triterpenoid alcohols, and sterols, obtained by the hydrolysis of lanolin, is called **lanolin alcohols**. This product contains not less than 30% cholesterol and is used as an emulsifying agent in ointment formulations.

FATTY ACIDS

A number of fatty acids and their salts and derivatives are employed as agents of pharmaceutical necessity. These acids are usually obtained by hydrolysis of fats or oils. The materials are usually mixtures, and the composition can vary with the source. Some acids are used in topical antifungal preparations; sodium morrhuate is a sclerosing agent, and linoleic and linolenic acids are used as a dietary supplement.

Stearic Acid

Stearic acid of pharmaceutical quality contains not less than 40% of stearic acid and not less than 40% of palmitic acid; the sum of these 2 acids is not less than 90%. **Purified stearic acid** contains not less than 90% stearic acid, and the total content of stearic and palmitic acids is not less than 96%. These materials are hard, white or faintly yellow solids or powders and are practically insoluble in water. Stearic acid is used as an emulsion adjunct and a tablet lubricant.

Calcium stearate and magnesium stearate are used as tablet lubricants, zinc stearate is used in dusting powders, sodium stearate is used as an emulsifying and stiffening agent, and aluminum monostearate is used as a suspending agent. Glycerol monostearate and propylene glycol mon-

ostearate are employed as emulsifying agents; these esters have emollient properties and contribute to the stability of emulsions.

Isopropyl myristate and **isopropyl palmitate** are mixtures consisting of the esters of isopropyl alcohol and saturated high-molecular-weight fatty acids. The respective semisynthetic products contain not less than 90% of the designated esters. These products are used as ingredients in topical emollient creams and ointments. They offer some advantages over vegetable oils, including freedom from oxidation and rancidity and a less oleaginous (greasy) character. In addition, they lack the hypersensitization potential encountered with lanolin.

Oleic Acid

Oleic acid is obtained from edible fats and fixed oils. It is often obtained as a by-product in the production of stearic acid. Oleic acid consists chiefly of *cis*-9-octadecenoic acid and is a colorless to pale yellow, oily liquid. It is practically insoluble in water but is miscible with alcohol. It gradually absorbs oxygen and darkens when exposed to air.

Oleic acid is used as an emulsion adjunct. Ethyl oleate is used as a pharmaceutical vehicle, and oleyl alcohol is employed as an emollient and emulsifying agent. Ethyl oleate, compared with fixed oil vehicles, is less viscous and more rapidly absorbed by body tissues.

Linoleic and Linolenic Acids

Linoleic and linolenic acids are polyunsaturated octadecenoic acids. These fatty acids are essential for human nutrition and have been called vitamin F. A mixture of essential unsaturated fatty acids that contains primarily linoleic and linolenic acids can be obtained from soybean oil and other suitable vegetable oils. This mixture of acids is used as a dietary supplement.

Undecylenic Acid

Undecylenic acid is 10-undecenoic acid. It is prepared by pyrolysis of ricinoleic acid, which is obtained from castor oil. Undecylenic acid has antifungal properties and is an ingredient, often combined with zinc undecylenate or other agents, in ointments and powders for topical application to treat athlete's foot (Decylenes[®], Desenex[®], Merlenate[®], Quinsana Plus[®], and Undoguent[®]). Calcium undecylenate is used in powders for diaper rash and similar skin irritations (Caldesene[®] and Cruex[®]).

Caprylate and propionate salts are also used in topical formulations (e.g., Sopronol[®]) for control of fungal infections. The antifungal activity of glyceryl triacetate (Enzactin[®], Fungacetic[®], and Fungoid[®]), another dermatologic agent, is related to the gradual release of acetic acid; the acid is released in a concentration that is non-irritating.

Sodium Morrhuate

Sodium morrhuate is the sodium salts of the fatty acids of cod liver oil. It is available as a sterile solution and is used as a sclerosing agent to obliterate varicose veins. The usual dose, administered intravenously by special injection, is 1 ml of a 5% solution to a localized area. Sodium morrhuate injection may show a separation of solid material on standing; it should not be used if any such material does not dissolve completely when warmed.

WAXES

Waxes are usually defined as esters resulting from the condensation of high-molecular-weight, straight-chain acids and high-molecular-weight, primary, straight-chain alcohols. Such esters, of course, exist in waxes, but, in reality, waxes are better defined as mixtures of different molecular weight acids and alcohols. In addition, waxes may also contain paraffins.

In plants, waxes are found in connection

with the outer cell walls of epidermal tissue, particularly in fruits and leaves. The function of wax appears to be protection against the penetration or loss of water. Insects also secrete waxes for various purposes. Carnuba wax and bayberry wax are examples of vegetable waxes, and lac wax and beeswax are examples of insect waxes.

Waxes are employed in pharmaceuticals to "harden" ointments and cosmetic creams. They are also used in the preparation of cerates. In industry and the arts, waxes are used for protective coatings.

Synthetic Spermaceti

Spermaceti, a waxy substance obtained from the head of the sperm whale [*Physeter macrocephalus* Linné (Fam. Physeteridae)], was formerly recognized as a quality emollient and a desirable ingredient in cold creams and other cosmetics. However, the sperm whale is an endangered species, and spermaceti is no longer available. Efforts to find a substitute have led to the use of a synthetic spermaceti or of jojoba oil.

Spermaceti consists of a mixture of hexadecyl esters of fatty acids. Hexadecyl dodecanoate (cetyl laurate), hexadecyl tetradecanoate (cetyl myristate), hexadecyl hexadecanoate (cetyl palmitate), and hexadecyl octadecanoate (cetyl stearate) constitute at least 85% of the total esters.

Synthetic spermaceti or cetyl esters wax is a mixture consisting primarily of esters of saturated fatty alcohols (C_{14} to C_{18}) and saturated fatty acids (C_{14} to C_{18}).

Cetyl alcohol is a mixture of solid alcohols consisting chiefly (not less than 90%) of cetyl alcohol or 1-hexadecanol. It is used as an emulsifying aid and as a stiffening agent in pharmaceutical preparations.

Stearyl alcohol is a mixture of solid alcohols consisting chiefly (not less than 90%) of stearyl alcohol or 1-octadecanol. It is used as an alternative to cetyl alcohol, as is cetostearyl alcohol. **Cetostearyl alcohol** contains not less than 40% of stearyl alcohol and not less than 90% of cetyl and stearyl alcohols.

Jojoba Oil

Jojoba oil is a liquid wax expressed from seeds of *Simmondsia chinensis* (Link) Scheider (Fam. Buxaceae). The plant is a bushy shrub native to the arid regions of northern Mexico and to the southwestern United States.

Jojoba seeds contain 45 to 55% of an ester mixture (not triglycerides) that is a liquid at ambient temperatures. The major components identified upon hydrolysis of the mixture are 35% of eicosenoic acid (a C_{20} unsaturated acid), 22% of eicosenol (a C_{20} unsaturated alcohol), and 21% of docosenol (a C_{22} unsaturated alcohol). Hydrogenation of the oil yields a crystalline wax that has the appearance and properties of spermaceti.

Jojoba oil and its hydrogenated derivatives are useful emollients and agents of pharmaceutical necessity.

Beeswax

Yellow wax or beeswax is the purified wax from the honeycomb of the bee, *Apis mellifera* Linné (Fam. Apidae). Wax is secreted in cells on the ventral surface of the last 4 segments of the abdomen of the worker bees. The wax excretes through pores in the chitinous plates and is employed by the young worker bees in the construction of the comb.

The honeycomb, after separation from the honey, is melted in water, then cooled and remelted, and finally strained and allowed to harden in molds.

Beeswax is a solid varying in color from yellow to grayish brown. It has an agreeable, honeylike odor and a faint, characteristic taste. When cold, beeswax is somewhat brittle and exhibits a dull, granular, noncrystalline fracture.

The wax consists principally of alkyl esters of fatty and wax acids (about 72%), chiefly myricyl palmitate; free wax acids (about 14%), especially cerotic acid and its

homologs; hydrocarbons (12%); and other minor constituents, including moisture, pollen, and propolis (bee glue). The latter 2 materials are responsible for most of the color of the wax.

USES. Yellow wax is a stiffening agent and is an ingredient in yellow ointment. It is also used as a base for cerates and plasters. Commercially, it is contained in a number of polishes.

White wax is bleached, purified wax from the honeycomb of the bee, *A. mellifera* Linné (Fam. Apidae). The bleaching process is accomplished by allowing the melted wax to flow slowly over revolving wetted cylinders, upon which it hardens in thin, ribbonlike layers. These layers are removed and exposed to sunlight and air until they are bleached. (The process usually is repeated.) The bleached wax is finally melted and cast into cakes of various shapes. White wax is sometimes referred to as bleached beeswax. A rapid, reliable, and inexpensive method of detecting the presence of certain adulterants of natural beeswax is known as the saponification cloud test.

USES. White wax is employed pharmaceutically in ointments and in cold creams.

Carnauba Wax

Carnauba wax is obtained from the leaves of *Copernicia prunifera* (Mueller) H.E. Moore [*C. cerifera* (Arruda da Camara) Martius] (Fam. Palmae), a palm growing from northern Brazil to Argentina. The wax consists of alkyl esters of wax acids (80%), chiefly myricyl cerotate; free monohydric alcohols (10%); a lactone; resin; and other minor constituents. It is used in the manufacture of candles, wax varnishes, leather and furniture polishes, and in place of beeswax.

PROSTAGLANDINS

Prostaglandins are C_{20} lipid metabolites formed in the body from essential, unsaturated fatty acids of the diet. Prostaglan-

dins apparently occur in nearly all mammalian tissues, but they are present in low concentrations. The major prostaglandins have been grouped into 4 main classes designated as prostaglandins A, B, E, and F. All prostaglandins (PG) have a cyclopentane ring with 2 aliphatic side chains. Subscripts indicate the number of double bonds in the side chains and the stereochemistry of members of each group.

Details of the physiologic roles of prostaglandins remain to be clarified. Attention was initially attracted to these substances in 1930 when it was observed that constituents in human semen could produce contraction and relaxation of the human uterus. A large body of biologic knowledge, especially regarding members of the PGE and PGF series, has been accumulated. Mammalian cells and tissues may respond differently (stimulation or inhibition of a biologic process) to individual prostaglandins; in some instances, this response may be a concentration factor. Prostaglandins appear to act at the level of the cell membrane, and they may modulate the transmission of hormonal or other extracellular stimuli into cyclic AMP for the internal regulation of cellular functions. Actions of this type seem consistent with the pharmacologic effects that have been noted with the prostaglandins. Pharmacologic effects of these compounds involve contraction or, in some cases, relaxation of smooth muscles of the female reproductive system, of the cardiovascular system, of the intestinal tract, and of the bronchi. They also influence gastric secretion and renal function.

Securing a feasible source of the various prostaglandins was a major deterrent to the early exploration of their biologic properties and therapeutic potential. Much of the explosion of knowledge about these compounds during the past decade is a result of several achievements that have resolved the supply problem. Key accomplishments include the development of an enzymatic synthesis that uses prostaglan-

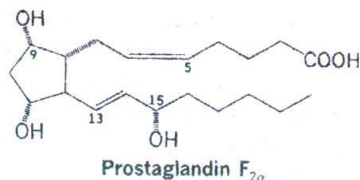
din synthetase from sheep seminal vesicles, the discovery of prostaglandin materials in *Plexaura homomalla* (sea fan or sea whip), which is a coral found in reefs off the Florida coast, and the development of several procedures for total chemical synthesis.

The prostaglandins have diverse pharmacologic effects, and some enthusiasts believe that their therapeutic potential transcends that of the steroids. The use of PGE₂, PGF_{2α}, or 15-methyl PGF_{2α} for termination of second trimester pregnancies and the use of PGE₁ for palliative therapy to maintain temporarily neonates with patent ductus arteriosus and certain congenital heart defects are the only applications that have received FDA approval at this time. However, experimental studies have revealed potential for therapeutic use of various prostaglandins, including to induce labor at term (PGE₂), to prevent premature labor (PGE), to induce menstruation (PGE), to increase fertility in certain conditions (PGE), to manage some types of hypertension (PGA₁ and PGE₂), to control certain cardiac arrhythmias (PGF_{2α}), to correct some defects in red blood cells (PGE), to exert antithrombogenic and thrombolytic activity (PGE₁), to control asthmatic seizures (PGE₁), to inhibit gastric secretions in the treatment of peptic ulcers (PGE), and to treat several other conditions. The multiple effects of the prostaglandins and the diverse response to individual prostaglandins by various body tissues are factors that give above-average chances for undesirable side effects in any therapeutic use of these compounds; this appears to be a problem, but its full significance remains to be evaluated in most situations. Because prostaglandins are formed in situ in most body tissues, the potential for use of prostaglandin synthetase inhibitors is also receiving investigational attention.

Prostaglandin F_{2α}

Prostaglandin F_{2α}, PGF_{2α}, or **dinoprost** is available as the tromethamine salt for use

in terminating second trimester pregnancy. It stimulates contractions of the gravid uterus that are similar to the contractions of the term uterus at labor. Side effects are usually related to the contractile effect of PGF_{2α}; the action may extend to smooth muscle of the gastrointestinal tract, producing vomiting and/or diarrhea, and to smooth muscle of the vascular system, causing elevation in blood pressure.



PGF_{2α} is rapidly inactivated (serum half-life of 10 minutes or less) in the lungs and other body tissues. Two metabolic processes have been identified as participating in the inactivation of this prostaglandin: reduction of the unsaturated bond at position 13 and oxidation of the 15-hydroxyl group to a keto function. A short duration of action is usually considered desirable for oxytocic agents, but it could present a problem in other potential therapeutic applications.

The usual dose of PGF_{2α} is 40 mg by slow injection into the amniotic sac. If the abortion process has not been established or completed within 24 hours, an additional dose of the drug may be administered.

PRESCRIPTION PRODUCT. Prostin F2 alpha®.

15-Methylprostaglandin F_{2α}

15-Methylprostaglandin F_{2α}, 15-methyl PGF_{2α}, or **carboprost** is the 15-methyl analog of PGF_{2α}. The 15-methyl substituent precludes metabolic inactivation via oxidation of the 15-hydroxyl group and permits a substantially different dosage regimen. It is available as the tromethamine salt, it elicits pharmacologic responses similar to those of PGF_{2α}, and it is used in terminating second trimester pregnancy.

The usual initial dose of 15-methyl PGF_{2α}

is 200 μg by deep intramuscular injection; the dosage may be repeated at 1.5 to 3.5 hour intervals, depending on uterine response. The total dose should not exceed 12 mg, and the therapeutic duration should not exceed 2 days.

PRESCRIPTION PRODUCT. Prostin/15 M[®].

Prostaglandin E₂

Prostaglandin E₂, PGE₂, or dinoprostone is another uterine stimulant that has been approved for termination of second trimester pregnancy. PGE₂ differs from PGF_{2 α} only in that the 9-oxygen substituent is a keto group. PGE₂ is available as a vaginal suppository that should be stored at a temperature below -20°C .

A 20-mg suppository is inserted intravaginally every 3 to 5 hours until abortion occurs, but the maximum dose should not exceed 240 mg. The pharmacologic effects of PGE₂ are similar to those of PGF_{2 α} ; a notable exception is the lack of vasoconstriction and resulting hypertension with high doses of PGE₂. Frequently encountered adverse reactions include vomiting, pyrexia, diarrhea, nausea, headache, and chills.

PRESCRIPTION PRODUCT. Prostin E2[®].

Prostaglandin E₁

Prostaglandin E₁, PGE₁, or alprostadil differs from PGE₂ only in the reduction of the unsaturated bond at position 5. PGE₁ produces vasodilation, inhibits platelet aggregation, and stimulates intestinal and uterine smooth muscle. The vasodilation property underlies its use for palliative therapy to maintain temporarily neonates with patent ductus arteriosus and congenital heart defects that restrict the pulmonary or systemic blood flow. The dilated ductus arteriosus facilitates blood oxygenation and body perfusion pending surgical correction of the congenital defects.

PGE₁ is metabolized rapidly (up to 80% on the first pass through the lungs) by oxidation of the 15-hydroxyl group, and the drug is administered by continuous intra-

venous infusion of the lowest dosage that maintains the desired response. The initial infusion rate is usually 0.1 μg per kg of body weight per minute. It is available in 1-ml ampules containing 500 μg of the drug.

PRESCRIPTION PRODUCT. Prostin VR Pediatric[®].

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