many types of dispersed substances and is an effective stabilizer for oil-in-water emulsions.

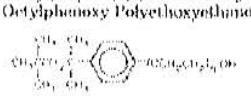
Therapeutically, it is used as a *bulk laxative* in the treatment of *chronic constipation*. Taken with 1 or 2 glasses ful of water, it forms a colloidal solution in the upper alimentary tract; this solution loses water in the colon, forming a gel that increases the bulk and softness of the stool. The gel is bland, demulcent and nonirritating to the gastrointestinal tract. Once a normal stool develops, the dose should be reduced to a level adequate for maintenance of good function. Although it takes up water from the gastrointestinal tract quite readily, methylcellulose tablets have caused fecal impaction and intestinal obstruction when taken with a limited amount of water. It also is used as a topical ophthalmic protectant, in the form of 0.5 to 1% solution serving as artificial tears or a contact-lens solution applied to the conjunctiva, 0.05 to 0.1 mL at a time, 3 or 4 times a day as needed.

Dose—*Usual*, as laxative, 1 to 1.5 g, with water, 2 to 4 times a day.

Dosage Forms Tablets: 500 mg; Ophthalmic Solution: 0.5 and 1%; Syrup: 5.91 g/30 mL.

Octoxynol 9

Polyoxy-1,2-ethanediyl, α-[4-(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy-, Octylphenoxy Polyethoxyethanol NF XII



Polyethylene glycol mono[*p*-(1,1,3,3-tetramethylbutyl)phenyl] ether [9002-93-1]; an anhydrous liquid mixture of mono-*p*-(1,1,3,3-tetramethylbutyl)phenyl ethers of polyethylene glycols in which *n* varies from 5 to 15, and which has an average molecular weight of 647, corresponding to the formula $C_{34}H_{62}O_{11}$.

Preparation—By reacting *p*-(1,1,3,3-tetramethylbutyl)phenol with ethylene oxide at elevated temperature under pressure in the presence of NaOH.

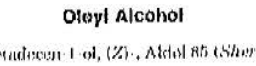
Description—Clear, pale yellow, viscous liquid, having a faint odor and a bitter taste; specific gravity about 1.064; pH (1 in 100 aqueous solution) about 7.

Solubility—Miscible with water, alcohol or acetone; soluble in benzene or toluene; insoluble in solvent hexane.

Uses—A nonionic detergent, emulsifier and dispersing agent. It is an ingredient in *Nitrofurazone Solution*. See *Polyethylene Glycol 400* (page 1313).

Oleyl Alcohol

9-Octadecen-1-ol, (*Z*)-, Alcol 85 (*Sherex*)



(*Z*)-9-Octadecen-1-ol [143-28-2] $C_{18}H_{36}O$ (268.48); a mixture of unsaturated and saturated high-molecular-weight fatty alcohols consisting chiefly of oleyl alcohol.

Preparation—One method reacts ethyl oleate with absolute ethanol and metallic sodium (*Org Syn Coll III*: 673, 1955).

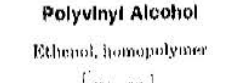
Description—Clear, odorless to light yellow, oily liquid; faint characteristic odor and bland taste; iodine value between 85 and 90; hydroxyl value between 205 and 215.

Solubility—Soluble in alcohol, ether, isopropyl alcohol or light mineral oil; insoluble in water.

Uses—*A pharmaceutic aid* (emulsifying agent or emollient).

Polyvinyl Alcohol

Ethenol, homopolymer



Vinyl alcohol polymer [9002-89-5] $(C_2H_4O)_n$.

Preparation—Polyvinyl acetate is approximately 88% hydrolyzed in a methanol-methyl acetate solution using either mineral acid or alkali as a catalyst.

Description—White to cream-colored powder or granules; odorless.

Solubility—Freely soluble in water; solution effected more rapidly at somewhat elevated temperatures.

Uses—A *suspending agent* and *emulsifier*, either with or without the aid of a surfactant. It commonly is employed as a lubricant and protectant in various ophthalmic preparations, such as decongestants, artificial tears and contact-lens products (see page 1593).

Povidone

2-Pyrrolidinone, 1-ethenyl-, homopolymer; Polyvinylpyrrolidone; PVP

1-Vinyl-2-pyrrolidinone polymer [9003-39-8] $(C_6H_9NO)_n$; a synthetic polymer consisting of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is produced commercially as a series of products having mean molecular weights ranging from about 10,000 to about 700,000. The viscosity of solutions containing 10% or less is essentially the same as that of water; solutions more concentrated than 10% become more viscous, depending upon the concentration and the molecular weight of the polymer used. It contains 12 to 13% of nitrogen.

Preparation—1,4-Butanediol is dehydrogenated thermally with the aid of copper to γ-butyrolactone, which is then reacted with ammonia to form 2-pyrrolidinone. Addition of the latter to acetylene yields vinylpyrrolidinone (monomer) which is polymerized thermally in the presence of hydrogen peroxide and ammonia.

Description—White to creamy white, odorless powder, hygroscopic; pH (1 in 20 solution) 3 to 7.

Solubility—Soluble in water, alcohol or chloroform; insoluble in ether.

Uses—A *dispersing* and *suspending* agent in pharmaceutical preparations.

Propylene Glycol Monostearate

Octadecanoic acid, monoester with 1,2-propanediol

1,2-Propanediol monostearate [1323-39-3]; a mixture of the propylene glycol mono- and diesters of stearic and palmitic acids. It contains not less than 90% of monoesters of saturated fatty acids, chiefly propylene glycol monostearate ($C_{21}H_{42}O_3$) and propylene glycol monopalmitate ($C_{19}H_{38}O_3$).

Preparation—By reacting propylene glycol with stearoyl chloride in a suitable dehydrochlorinating environment.

Description—White, wax-like solid or white, wax-like beads or flakes; slight, agreeable, fatty odor and taste; congeals not lower than 45°; acid value not more than 2; saponification value 155 to 165; hydroxyl value 150 to 170; iodine value not more than 3.

Solubility—Dissolves in organic solvents such as alcohol, mineral or fixed oils, benzene, ether or acetone; insoluble in water but may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent.

Uses—A *surfactant*. It is particularly useful as a dispersing agent for perfume oils or oil-soluble vitamins in water, and in cosmetic preparations.

Silicon Dioxide, Colloidal—page 1325.

Sodium Lauryl Sulfate

Sulfuric acid monododecyl ester sodium salt; Irium; Duponol C (*Dupont*); Gardinol WA (*Proctor & Gamble*)

Sodium monododecyl sulfate [151-21-3]; a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate. The combined content of sodium chloride and sodium sulfate is not more than 8%.

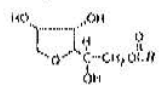
Preparation—The fatty acids of coconut oil, consisting chiefly of lauric acid, are catalytically hydrogenated to form the corresponding alcohols. The latter are then esterified with sulfuric acid (sulfated) and the resulting mixture of alkyl bisulfates (alkylsulfuric acids) is converted into a mixture of sodium salts by reacting with alkali under controlled conditions of pH.

Description—Small, white or light yellow crystals having a slight, characteristic odor.
Solubility—1 g in 10 mL water, forming an opalescent solution.
Incompatibilities—Reacts with *cationic surface-active agents* with loss of activity, even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids, and calcium and magnesium ions.

Uses—An emulsifying, detergent and wetting agent in ointments, tooth powders and other pharmaceutical preparations, and in the metal, paper and pigment industries. See Chapters 19 and 87.

Sorbitan Esters

Spans (*Atlas*)



Sorbitan esters (*monolaurate* [1338-39-2]; *monooleate* [1338-43-8]; *monopalmitate* [26266-57-9]; *monostearate* [1338-41-6]; *trioleate* [26266-58-0]; *tristearate* [26658-19-5]).
Preparation—Sorbitol is dehydrated to form a *hexitan* which is then esterified with the desired fatty acid. See *Polysorbates*, page 1314, which are polyethylene glycol ethers of sorbitan fatty acid esters.

Description—*Monolaurate:* Amber, oily liquid; may become hazy or form a precipitate; viscosity about 4250 cps; HLB no 8.6; acid no 7.0 max; saponification no 158 to 170; hydroxyl no 330 to 358. *Monooleate:* Amber liquid; viscosity about 1000 cps; HLB no 4.3; acid no 8.0 max; saponification no 146 to 160; hydroxyl no 193 to 210. *Monopalmitate:* Tan, granular waxy solid; HLB no 6.7; acid no 4 to 7.5; saponification no 140 to 150; hydroxyl no 275 to 305. *Monostearate:* Cream to tan beads; HLB no 4.7; acid no 5 to 10; saponification no 147 to 157; hydroxyl no 235 to 260. *Trioleate:* Amber, oily liquid; viscosity about 200 cps; HLB no 1.8; acid no 15 max; saponification no 170 to 190; hydroxyl no 65 to 70. *Tristearate:* Tan, waxy beads; HLB no 2.1; acid no 12 to 15; saponification no 176 to 188; hydroxyl no 66 to 80.
Solubility—*Monolaurate:* Soluble in methanol or alcohol; dispersible in distilled water and hard water (200 ppm); insoluble in hard water (20,000 ppm). *Monooleate:* Soluble in most mineral or vegetable oils; slightly soluble in ether; dispersible in water; insoluble in acetone. *Monopalmitate:* Dispersible (50°) in distilled water or hard water (200 ppm); soluble in ethyl acetate; insoluble in cold distilled water or hard water (20,000 ppm). *Monostearate:* Soluble (above melting point) in vegetable oils or mineral oil; insoluble in water, alcohol and propylene glycol. *Trioleate:* Soluble in mineral oil, vegetable oils, alcohol or methanol; insoluble in water. *Tristearate:* Soluble in isopropyl alcohol; insoluble in water.

Uses—Nonionic *surfactants* used as *emulsifying agents* in the preparation of water-in-oil emulsions.

Stearic Acid—page 1312.

Stearyl Alcohol

1-Octadecanol [112-92-5] $C_{18}H_{38}O$ (270.50); contains not less than 90% of stearyl alcohol, the remainder consisting chiefly of cetyl alcohol [$C_{16}H_{34}O$ = 242.44].

Preparation—Through the reducing action of lithium aluminum hydride on ethyl stearate.

Description—White, unctuous flakes or granules having a faint, characteristic odor and a bland taste; melts 55 to 60°.
Solubility—Insoluble in water; soluble in alcohol, chloroform, ether or vegetable oils.

Uses—A surface-active agent used to *stabilize emulsions* and increase their ability to retain large quantities of water. See *Hydrophilic Ointment* (page 1312). *Hydrophilic Petrolatum* (page 1311), and Chapters 19 and 87.

Sterculia Gum—page 786.

Tragacanth

Gum Tragacanth; Hog Gum; Goat's Thorn

The dried gummy exudation from *Astragalus gummifer* Labillardière, or other Asiatic species of *Astragalus* (Fam. *Leguminosae*).
Constituents—60 to 70% bassorin and 30 to 40% soluble gum (*tragacanthin*). The bassorin swells in the presence of water to form a gel and tragacanthin forms a colloidal solution. Bassorin, consisting of complex methoxylated acids, resembles pectin. Tragacanthin yields glucuronic acid and arabinose when hydrolyzed.

Description—Flattened, lamellated, frequently curved fragments or straight or spirally twisted linear pieces 0.5 to 2.5 mm in thickness; white to weak-yellow in color; translucent; horny in texture; odorless; insipid, mucilaginous taste. When powdered, it is white to yellowish white.
Introduced into water, tragacanth absorbs a certain proportion of that liquid, swells very much, and forms a soft adhesive paste, but does not dissolve. If agitated with an excess of water, this paste forms a uniform mixture; but in the course of 1 or 2 days the greater part separates, and is deposited, leaving a portion dissolved in the supernatant fluid. The finest mucilage is obtained from the whole gum or *flake* form. Several days should be allowed for obtaining a uniform mucilage of the maximum gel strength. A common adulterant is *Karaya Gum*, and the USP/NF has introduced tests to detect its presence.
Solubility—Insoluble in alcohol.

Uses—A *suspending agent* in lotions, mixtures and extemporaneous preparations and prescriptions. It is used with emulsifying agents largely to increase consistency and retard creaming. It is sometimes used as a *demulcent* in sore throat, and the jelly-like product formed when the gum is allowed to swell in water serves as a basis for pharmaceutical jellies, eg, *Ephedrine Sulfate Jelly*. It also is used in various confectionery products. In the form of a glycerite, it has been used as a pill excipient.

Tragacanth Mucilage—*Preparation:* Mix glycerin (18 g) with purified water (75 mL) in a tared vessel, heat the mixture to boiling, discontinue the application of heat, add tragacanth (6 g) and benzoic acid (0.2 g) and macerate the mixture during 24 hr, stirring occasionally. Then add enough purified water to make the mixture weigh 100 g, stir actively until of uniform consistency, and strain forcibly through muslin. *Uses:* A suspending agent for insoluble substances in internal mixtures. It is also a *protective* agent.

Xanthan Gum

Keltrol (*Kelco*)

A high-molecular-weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with *Xanthomonas campestris*, then purified by recovery with isopropyl alcohol, dried and milled; contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as sodium, potassium or calcium salt; yields 4.2 to 5% of carbon dioxide.
Preparation—See above and US Pats 3,433,708 and 3,557,016.

Description—White or cream-colored, tasteless powder with a slight organic odor; powder and solutions stable at 25° or less; does not exhibit polymorphism; aqueous solutions are neutral to litmus.
Solubility—1 g in about 3 mL of alcohol; soluble in hot or cold water.

Uses—A hydrophilic colloid to thicken, suspend, emulsify and stabilize water-based systems.

Other Emulsifying and Suspending Agents

Chondrus [Irish Moss; Carrageenan]—The dried sun-bleached plant of *Chondrus crispus* (Linné) Stackhouse (Fam *Gigartinaceae*). *Uses:* Principally, as an emulsifying agent for liquid petrolatum and for cod liver oil. It is also a protective.
Malt—The partially germinated grain of one or more varieties of *Hordeum vulgare* Linné (Fam *Gramineae*) and contains amylolytic enzymes. Yellowish or amber-colored grains, having a characteristic odor and a sweet taste. The evaporated aqueous extract constitutes malt extract.
Malt Extract—The product obtained by extracting malt, the partially and artificially germinated grain of one or more varieties of *Hordeum vulgare* Linné (Fam *Gramineae*). *Uses:* An infrequently used emulsifying agent.

Ointment Bases

Ointments are semisolid preparations for external application to the body. They should be of such composition that they soften, but not necessarily melt, when applied to the skin. Therapeutically, ointments function as protectives and emollients for the skin, but are used primarily as vehicles or bases for the topical application of medicinal substances. Ointments also may be applied to the eye or eyelids.

Ideally, an ointment base should be compatible with the skin, stable, permanent, smooth and pliable, nonirritating, nonsensitizing, inert and readily able to release its incorporated medication. Since there is no single ointment base which possesses all these characteristics, continued research in this field has resulted in the development of numerous new bases. Indeed, ointment bases have become so numerous as to require classification. Although ointment bases may be grouped in several ways, it is generally agreed that they can be classified best according to composition. Hence, the following four classes are recognized herein: oleaginous, emulsifiable, emulsion bases and water-soluble.

For completeness, substances are included that, although not used alone as ointment bases, contribute some pharmaceutical property to one or more of the various bases.

Oleaginous Ointment Bases and Components

The oleaginous ointment bases include fixed oils of vegetable origin, fats obtained from animals and semisolid hydrocarbons obtained from petroleum. The vegetable oils are used chiefly in ointments to lower the melting point or to soften bases. These oils can be used as a base in themselves when a high percentage of powder is incorporated.

The vegetable oils and the animal fats have two marked disadvantages as ointment bases: their water-absorbing capacity is low and they have a tendency to become rancid. Insofar as vegetable oils are concerned, the second disadvantage can be overcome by hydrogenation, a process which converts many fixed oils into white, semisolid fats or into hard, almost brittle, waxes.

The hydrocarbon bases comprise a group of substances with a wide range of melting points so that any desired consistency and melting point may be prepared with representatives of this group. They are stable, bland, chemically inert and will mix with virtually any chemical substance. Oleaginous bases are excellent emollients.

White Ointment

Ointment USP XI; Simple Ointment

White Wax	50 g
White Petrolatum	950 g
To make	1000 g

Melt the white wax in a suitable dish on a water bath, add the white petrolatum, warm until liquefied, then discontinue the heating, and stir the mixture until it begins to congeal. It is permissible to vary the proportion of wax to obtain a suitable consistency of the ointment under different climatic conditions.

Uses—An emollient and vehicle for other ointments.

Yellow Ointment

Yellow Wax	50 g
Petrolatum	950 g
To make	1000 g

Melt the yellow wax in a suitable dish on a steam bath, add the petrolatum, warm until liquefied, then discontinue the heating, and stir the mixture until it begins to congeal. It is permissible to vary the proportion of wax to obtain a suitable consistency of the ointment under different climatic conditions.

Uses—An emollient and vehicle for other ointments. Both white and yellow ointment are known as "simple ointment." White ointment should be used to prepare white ointments and yellow ointments should be used to prepare colored ointments when simple ointment is prescribed.

Cetyl Esters Wax

"Synthetic Spermaceti"

A mixture consisting primarily of esters of saturated fatty alcohols (C_{14} to C_{18}) and saturated fatty acids (C_{14} to C_{18}). It has a saponification value of 109 to 120 and an acid value of not more than 5.

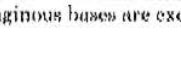
Description—White to off white, somewhat translucent flakes; crystalline structure and pearly luster when cake; faint odor and a bland, mild taste; free from rancidity; specific gravity 0.820 to 0.840 at 50°; iodine value not more than 1; melts 43 to 47°.

Solubility—Insoluble in water; practically insoluble in cold alcohol; soluble in boiling alcohol, ether, chloroform or fixed and volatile oils; slightly soluble in cold solvent hexane.

Uses—A replacement for spermaceti used to give consistency and texture to ointments, eg, *Cold Cream* and *Rose Water Ointment*.

Oleic Acid

(*Z*)-9-Octadecenoic acid; Oleinic Acid; Elaic Acid



Oleic acid [112-80-1] obtained from tallow and other fats, and consists chiefly of (*Z*)-9-octadecenoic acid (282.47). Oleic acid used in preparations for internal administration is derived from edible sources.

It usually contains variable amounts of the other fatty acids present in tallow such as linolenic and stearic acids.

Preparation—Obtained as a by-product in the manufacture of the solid stearic and palmitic acids used in the manufacture of candles, stearates and other products. The crude oleic acid is known as "red oil," the stearic and palmitic acids being separated by cooling.

Description—Colorless to pale yellow, oily liquid; lard-like odor and taste; specific gravity 0.893 to 0.895; congeals at a temperature not above 10°; pure acid solidifies at 4°; at atmospheric pressure it decomposes when heated at 80 to 100°; on exposure to air it gradually absorbs oxygen, darkens and develops a rancid odor.

Solubility—Practically insoluble in water; miscible with alcohol, chloroform, ether, benzene or fixed and volatile oils.

Incompatibilities—Reacts with *alkalies* to form soaps. *Heavy metals* and *calcium salts* form insoluble oleates. *Iodine solutions* are decolorized by formation of the iodine addition compound of the acid. It is oxidized to various derivatives by *nitric acid*, *potassium permanganate* and other agents.

Uses—Classified as an emulsion adjunct, which reacts with alkalis to form soaps that function as emulsifying agents; it is used for this purpose in such preparations as *Benzyl Benzoate Lotion* and *Green Soap*. It also is used to prepare oleate salts of bases.

Olive Oil

Sweet Oil

The fixed oil obtained from the ripe fruit of *Olea europaea* Linné (Fam *Oleaceae*).

Preparation—By crushing recently collected ripe olives in a mill without breaking the putamen, then moderately pressing the pulpy mass. This produces the highest grade oil, known as *virgin oil*, "sublime oil" or "first expressed oil." The mass in the press then is mixed with water and again expressed with greater pressure, an oil of second quality resulting. Any oil remaining in the press cake is finally extracted with carbon disulfide, or the mass is thrown into large cisterns, mixed with water and the oil allowed to separate. This is sometimes called "Pyrene oil," "bagasse oil" or "huile d'enfer." When bought in bulk or from unlabeled containers, cottonseed oil, colza oil, grapeseed oil, sesame oil or other bland oils are not uncommonly found as adulterants. Large quantities of this oil are imported from Italy and other countries bordering the Mediterranean, and it is produced to a limited extent in the Southern US, chiefly in California.

Description—Pale yellow or light greenish yellow, oily liquid; slight, characteristic odor and taste, with a faintly acrid aftertaste; specific gravity 0.910 to 0.915.

Solubility—Slightly soluble in alcohol; miscible with carbon disulfide, chloroform or ether.

Uses—In making cerates, ointments, liniments, and plasters. It is a bland oil, well-suited for *emollient* purposes and for food. It also is used as an emollient laxative; sufficient must be given so that enough escapes digestion to soften the stool.

Dose—The usual dose is **30 mL**.

Paraffin

Paraffin Wax, Hard Paraffin

A purified mixture of solid hydrocarbons obtained from petroleum.

Description—Colorless or white, more or less translucent mass with a crystalline structure; slightly greasy to the touch; odorless and tasteless; congeals 47 to 65°.

Solubility—Freely soluble in chloroform, ether, volatile oils or most warm fixed oils; slightly soluble in dehydrated alcohol; insoluble in water or alcohol.

Uses—Mainly, to increase the consistency of some ointments.

Petrolatum

Yellow Soft Paraffin; Amber Petrolatum; Yellow Petrolatum; Petroleum Jelly; Paraffin Jelly

A purified mixture of semisolid hydrocarbons obtained from petroleum. It may contain a suitable stabilizer.

Preparation—The "residuums," as they are termed technically, which are obtained by the distillation of petroleum, are purified by melting, usually treating with sulfuric acid and then percolating through recently burned bone black or adsorptive clays; this removes the odor and modifies the color. Selective solvents are also sometimes employed to extract impurities.

It has been found that the extent of purification required to produce *Petrolatum* and *Light Mineral Oil* of official quality removes antioxidants that are naturally present, and the purified product subsequently has a tendency to oxidize and develop an offensive odor. This is prevented by the addition of a minute quantity of α-tocopherol, or other suitable antioxidant, as is now permissible.

Description—Unctuous mass of yellowish to light amber color; not more than a slight fluorescence after being melted; transparent in thin layers; free or nearly free from odor and taste; specific gravity 0.815 to 0.880 at 60°; melts between 38 and 60°.

Solubility—Insoluble in water; almost insoluble in cold or hot alcohol or in cold dehydrated alcohol; freely soluble in benzene, carbon disulfide, chloroform or turpentine oil; soluble in ether, solvent hexane or in most fixed and volatile oils, the degree of solubility in these solvents varying with the composition of the petrolatum.

Uses—A base for ointments. It is highly occlusive and therefore a good emollient but it may not release some drugs readily.

White Petrolatum

White Petroleum Jelly; White Soft Paraffin

A purified mixture of semisolid hydrocarbons obtained from petroleum, and wholly or nearly decolorized. It may contain a suitable stabilizer.

Preparation—In the same manner as petrolatum, the purification treatment being continued until the product is practically free from yellow color.

Description—White or faintly yellowish, unctuous mass; transparent in thin layers, even after cooling to 0°; specific gravity 0.815 to 0.880 at 60°; melts 38 to 60°.

Solubility—Similar to that described under *Petrolatum*.

Uses—Similar to yellow petrolatum but often is preferred because of its freedom from color. It is employed as a protective, a base for ointments and cerates and to form the basis for burn dressings. See *Petrolatum Gauze* (page 758).

Spermaceti

A waxy substance obtained from the head of the sperm whale, *Physeter macrocephalus* Linné (Fam *Physeteridae*).

Constituents—A mixture of several constituents of which cetin, or cetyl palmitate [$C_{15}H_{31}COOC_{16}H_{33}$], predominates. When recrystallized from alcohol, *cetin* is obtained, while the mother liquor on evaporation deposits an oil, *cetin elain*, which when saponified yields *cetin elaic acid*, an acid resembling, but distinct from, oleic acid.

Preparation—By pumping the oleaginous material from the head of the sperm whale, separating the liquid portion known as sperm oil and purifying the remaining crude solid, which is this substance.

Description—White, somewhat translucent, slightly unctuous masses; crystalline fracture and pearly luster; faint odor and a bland, mild taste; free from rancidity; specific gravity about 0.94; melts 44 to 52°.

Solubility—Insoluble in water; practically insoluble in cold alcohol; slightly soluble in cold solvent hexane; soluble in boiling alcohol, ether, chloroform or fixed and volatile oils.

Uses—One of the solid fatty substances formerly employed to give consistency and texture to cerates and ointments, as in *Cold Cream* and *Rose Water Ointment*. In the interest of whale conservation, this has been replaced by *cetyl esters wax* (also known as *synthetic spermaceti*).

Dose—*For external use, topically*, as required.

Starch Glycerite

Starch Glycerin

Starch	100 g
Benzoic Acid	2 g
Purified Water	200 mL
Glycerin	700 mL
To make about	1000 g

Rub the starch and the benzoic acid with the purified water in a porcelain dish until a smooth mixture is produced, then add the glycerin, and mix well. Heat the mixture on a sand bath to a temperature between 140 and 144°, with constant but gentle stirring until a translucent, jelly-like mass results, and then strain through muslin.

It should be freshly prepared.

Uses—Although not an oleaginous base, this *emollient* preparation is sometimes used as a substitute for a fatty ointment. It also has been used as a *pill excipient*.

Dose—*For external use, topically*, as required.

White Wax

Bleached Beeswax; White Beeswax; Bleached Wax

The product of bleaching and purifying yellow wax that is obtained from the honeycomb of the bee [*Apis mellifera* Linné (Fam *Apidae*)].

Preparation—The color of yellow wax is discharged by exposing it with an extended surface to the combined influence of air, light and moisture. In one process a stream of melted wax is directed on a revolving cylinder kept constantly wet, upon which it congeals in thin layers which are spread on linen cloths stretched on frames and

exposed to the air and light, care being taken to wet and occasionally turn them. In a few days they are partially bleached; but to remove the color completely it is necessary to repeat the whole process one or more times. When sufficiently bleached, it is melted and cast into small circular cakes.

Description—Yellowish white, nearly tasteless, somewhat translucent solid; faint, characteristic odor; free from rancidity; melts 62 to 65°; specific gravity about 0.95.

Solubility—Insoluble in water; sparingly soluble in cold alcohol; boiling alcohol dissolves the cerotic acid and a portion of the myricin, which are constituents; completely soluble in chloroform, ether or fixed and volatile oils; partly soluble in cold benzene or cold carbon disulfide; completely soluble in these liquids at about 30°.

Uses—A stiffening agent in many preparations such as cerates, pastes and ointments.

Yellow Wax

Beeswax; Yellow Beeswax

The purified wax from the honeycomb of the bee, *Apis mellifera* Linné (Fam *Apidae*).

Constituents—A mixture of three substances: (1) *myricin*, insoluble in boiling alcohol and consisting chiefly of *myricyl palmitate* [$C_{30}H_{61}(C_{16}H_{31}O_2)$] and *myricyl alcohol* [$C_{30}H_{61}OH$]; (2) *cerin* or *cerotic acid* [$C_{26}H_{52}O_2$], formerly called *cerin* when obtained only in an impure state, which is dissolved by boiling alcohol, but crystallizes out on cooling and (3) *cerolein*, which remains dissolved in the cold alcoholic liquid. The latter is probably a mixture of fatty acids.

Preparation—It is a natural secretion of bees. It is obtained on the large scale by first abstracting the honey from the combs by shaving off the ends of the cells, draining and then placing them in centrifuges. The honey is rapidly whirled out, water is added and the wax is cleaned thoroughly and quickly; it then is melted and strained and run into molds to cool and harden.

Description—Yellow to grayish brown solid; agreeable, honeylike odor; faint, characteristic taste; when cold it is somewhat brittle and when broken it presents a dull, granular, noncrystalline fracture; becomes pliable from the heat of the hand; specific gravity about 0.95; melts between 62 and 65°.

Solubility—Insoluble in water; sparingly soluble in cold alcohol; completely soluble in chloroform, ether or fixed and volatile oils; partly soluble in cold benzene or carbon disulfide; completely soluble in these liquids at about 30°.

Uses—A stiffening agent in many pharmaceutical preparations and ingredient of many polishes.

Absorbent Ointment Bases

The term absorbent is used here to denote the water-absorbing or emulsifying properties of these bases and not to describe their action on the skin. These bases, sometimes called *emulsifiable ointment bases*, are generally anhydrous substances which have the property of absorbing (emulsifying) considerable quantities of water and still retaining their ointment-like consistency. Preparations of this type do not contain water as a component of their basic formula, but if water is incorporated, when and as desired, a W/O emulsion results. The following official products fall into this category.

Anhydrous Lanolin

Wool Fat USP XVI; Refined Wool Fat

Lanolin that contains not more than 0.25% of water.

Constituents—Contains the sterols *cholesterol* [$C_{27}H_{45}OH$] and *oxycholesterol*, as well as triterpene and aliphatic alcohols. About 7% of the alcohols are found in the free state, the remainder occurring as esters of the following fatty acids: *carnaubic*, *cerotic*, *lignoceric*, *lanopalmitic*, *myristic* and *palmitic*. Some of these are found free. The emulsifying and emollient actions of lanolin are due to the alcohols that are found in the unsaponifiable fraction when lanolin is treated with alkali. Constituting approximately one-half of this fraction and known as *lanolin alcohols*, the latter is comprised of *cholesterol* (30%), *lanosterol* (25%), *cholestanol* (*dihydrocholesterol*) (3%), *agnosterol* (2%) and various other alcohols (40%).

Preparation—By purifying the fatty matter (*suint*) obtained from the wool of the sheep. This natural wool fat contains about 30% of free fatty acids and fatty acid esters of *cholesterol* and other higher alcohols. The cholesterol compounds are the important constituents and, to secure these in a purified form, many processes have been devised. In one of these the crude wool fat is treated with weak alkali, the saponified fats and emulsions centrifuged to secure the aqueous soap solution, from which, on standing, a layer of partially purified wool fat separates. This product is further purified by treating it with calcium chloride and then dehydrated by fusion with unslaked lime. It is finally extracted with acetone and the solvent subsequently separated by distillation. This differs from lanolin in that the former contains practically no water.

Description—Yellow, tenacious, unctuous mass; slight, characteristic odor, melts between 36 and 42°.

Solubility—Insoluble in water, but mixes without separation with about twice its weight of water; sparingly soluble in cold alcohol; more soluble in hot alcohol; freely soluble in ether or chloroform.

Uses—An ingredient of ointments, especially when an aqueous liquid is to be incorporated. It gives a distinctive quality to the ointment, increasing absorption of active ingredients and maintaining a uniform consistency for the ointment under most climatic conditions. However, it has been omitted from many ointments on the recommendation of dermatologists who have found that many patients are allergic to this animal wax.

Hydrophilic Petrolatum

Cholesterol	30 g
Stearyl Alcohol	30 g
White Wax	80 g
White Petrolatum	860 g
To make	1000 g

Melt the stearyl alcohol, white wax, and white petrolatum together on a steam bath, then add the cholesterol, and stir until it completely dissolves. Remove from the bath, and stir until the mixture congeals.

Uses—A *protective* and *water-absorbable ointment base*. It will absorb a large amount of water from aqueous solutions of medicating substances, forming a W/O type of emulsion. See *Ointments* (page 1602).

Other Absorption Ointment Bases

Hydroxystearin Sulfate [Sulfated Hydrogenated Castor Oil; SHRO] A substance prepared by sulfating hydrogenated castor oil. Pale, yellow-brown, unctuous semisolid mass; faint odor containing about 9% organically bound SO_3. Dispersible in water and glycerin; miscible with propylene glycol, petrolatums or fixed oils. *Uses:* A surface-active agent used in preparing hydrophilic ointment bases and other emulsions.

Emulsion Ointment Bases and Components

Emulsion ointment bases are actually semisolid emulsions. These preparations can be divided into two groups on the basis of emulsion type: emulsion ointment base water-in-oil (W/O) type and emulsion ointment base oil-in-water

(O/W) type. Bases of both types will permit the incorporation of some additional amounts of water without reducing the consistency of the base below that of a soft cream. However, only O/W emulsion ointment bases can be removed readily from the skin and clothing with water. W/O emulsions are better emollients and protectants than are O/W emulsions. W/O emulsions can be diluted with oils.

Cetyl Alcohol

Cetostearyl Alcohol; "Palmityl" Alcohol; Aldol 52 (*Sherex*)

$CH_3(CH_2)_{14}CH_2OH$

1-Hexadecanol [124-29-8] $C_{16}H_{34}O$ (242.44); a mixture of not less than 90% of cetyl alcohol, the remainder chiefly stearyl alcohol.

Preparation—By catalytic hydrogenation of palmitic acid, or saponification of spermaceti, which contains cetyl palmitate.

Description—Unctuous, white flakes, granules, cubes or castings; faint characteristic odor and a bland, mild taste; melts 45 to 50°; not less than 90% distils between 316 and 336°.

Solubility—Insoluble in water; soluble in alcohol, chloroform, ether or vegetable oils.

Uses—Similar to *Stearyl Alcohol* (page 1308). It also imparts a smooth texture to the skin and is used widely in cosmetic creams and lotions.

Cold Cream

Petrolatum Rose Water Ointment USP XVI

Cetyl Esters Wax	125 g
White Wax	120 g
Mineral Oil	560 g
Sodium Borate	5 g
Purified Water	190 mL
To make about	1000 g

Reduce the cetyl esters wax and the white wax to small pieces, melt them on a steam bath with the mineral oil and continue heating until the temperature of the mixture reaches 70°. Dissolve the sodium borate in the purified water, warmed to 70° and gradually add the warm solution to the melted mixture, stirring rapidly and continuously until it has congealed.

If the ointment has been chilled, warm it slightly before attempting to incorporate other ingredients (see USP for allowable variations).

Uses—Useful as an emollient, cleansing cream and ointment base. It resembles *Rose Water Ointment*, differing only in that mineral oil is used in place of almond oil and omitting the fragrance. This change produces an ointment base which is not subject to rancidity like one containing a vegetable oil. This is a W/O emulsion.

Glyceryl Monostearate

Octadecanoic acid, monoester with 1,2,3-propanetriol

Monostearin [31566-31-1]; a mixture chiefly of variable proportions of glyceryl monostearate $[C_3H_5(OH)_2C_{18}H_{35}O_2 = 358.56]$ and glyceryl monopalmitate $[C_3H_5(OH)_2C_{16}H_{31}O_2 = 330.51]$.

Preparation—Among other ways, by reacting glycerin with commercial stearoyl chloride.

Description—White, wax-like solid or occurs in the form of white, wax-like beads, or flakes; slight, agreeable, fatty odor and taste; does not melt below 55°; affected by light.

Solubility—Insoluble in water, but may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent; dissolves in hot organic solvents such as alcohol, mineral or fixed oils, benzene, ether or acetone.

Uses—A thickening and emulsifying agent for ointments. See *Ointments* (page 1602).

Hydrophilic Ointment

Methylparaben	0.25 g
Propylparaben	0.15 g
Sodium Lauryl Sulfate	10 g
Propylene Glycol	120 g
Stearyl Alcohol	250 g
White Petrolatum	250 g
Purified Water	370 g
To make about	1000 g

Melt the stearyl alcohol and the white petrolatum on a steam bath, and warm to about 75°. Add the other ingredients, previously dissolved in the water and warmed to 75°, and stir the mixture until it congeals.

Uses—A *water-removable ointment base* for the so-called "washable" ointments. This is an O/W emulsion.

Lanolin

Hydrous Wool Fat

The purified, fat-like substance from the wool of sheep, *Ovis aries* Linné (Fam *Bovidae*); contains 25 to 30% water.

Description—Yellowish white, ointment-like mass, having a slight, characteristic odor; when heated on a steam bath it separates into an upper oily and a lower water layer; when the water is evaporated a residue of *Lanolin* remains which is transparent when melted.

Solubility—Insoluble in water; soluble in chloroform or ether with separation of its water of hydration.

Uses—Largely as a vehicle for ointments, for which it is admirably adapted, on account of its compatibility with skin lipids. It emulsifies aqueous liquids. Lanolin is a W/O emulsion.

Stearic Acid

Octadecanoic acid; Cetylacetic Acid; Stearophanic Acid

Stearic acid [57-11-4]; a mixture of stearic acid $[C_{18}H_{36}O_2 = 284.48]$ and palmitic acid $[C_{16}H_{32}O_2 = 256.43]$, which together constitute not less than 90.0% of the total content. The content of each is not less than 40.0% of the total.

Purified Stearic Acid USP is a mixture of the same acids which together constitute not less than 96.0% of the total content, and the content of $C_{18}H_{36}O_2$ is not less than 90.0% of the total.

Preparation—From edible fats and oils (see exception below) by boiling them with soda lye, separating the glycerin and decomposing the resulting soap with sulfuric or hydrochloric acid. The stearic acid subsequently is separated from any oleic acid by cold expression. It also is prepared by the hydrogenation and subsequent saponification of *olein*. It may be purified by recrystallization from alcohol.

Description—Hard, white or faintly yellowish somewhat glossy and crystalline solid, or a white or yellowish white powder; an odor and taste suggestive of tallow; melts about 55.5° and should not congeal at a temperature below 54°; the purified acid melts at 69 to 70° and congeals between 68 and 69°; slowly volatilizes between 90 and 100°.

Solubility—Practically insoluble in water; 1 g in about 20 mL of alcohol, 2 mL of chloroform, 3 mL of ether, 25 mL of acetone or 6 mL of carbon tetrachloride; freely soluble in carbon disulfide; also soluble in amyl acetate, benzene or toluene.

Incompatibilities—Insoluble stearates are formed with many *metals*. Ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when *zinc* or *calcium* salts are compounded therein.

Uses—In the preparation of sodium stearate which is the solidifying agent for the official glycerin suppositories, in enteric tablet coating, ointments and for many other commercial products, such as toilet creams, vanishing creams, solidified alcohol, etc. (When labeled solely for external use, it is exempt from the requirement that it be prepared from edible fats and oils.)

Other Emulsion Ointment Base Component

Wool Alcohols BP—Prepared by the saponification of the grease of the wool of sheep and separation of the fraction containing cholesterol and other alcohols. It contains not less than 30% cholesterol. Golden-brown solid, somewhat brittle when cold but becoming plastic when warm, with a faint characteristic odor; has a smooth and shiny fracture; melts not below 58°; acid value not more than 2; saponification value not

more than 12; emulsions made with this material do not darken on the surface or acquire an objectionable odor in hot weather. Insoluble in water; moderately soluble in alcohol; completely soluble in 25 parts of boiling anhydrous alcohol; freely soluble in ether, chloroform or petroleum ether. *Uses:* An emulsifying agent for the preparation of W/O emulsions; as a water absorbable substance in ointment bases; to improve the texture, stability and emollient properties of O/W emulsions. It is known also as *Lanolin Alcohols*.

Water-Soluble Ointment Bases and Components

Included in this section are bases prepared from the higher ethylene glycol polymers (PEG). These polymers are marketed under the trademark of Carbowax. The polymers have a wide range in molecular weight. Those with molecular weights ranging from 200 to 700 are liquids; those above 1000 are wax-like solids. The polymers are water-soluble, nonvolatile and unctuous agents. They do not hydrolyze or deteriorate and will not support mold growth. These properties account for their wide use in washable ointments. Mixtures of PEG are used to give bases of various consistency, such as very soft to hard bases for suppositories.

Glycol Ethers and Derivatives

This special class of ethers is of considerable importance in pharmaceutical technology. Both mono- and polyfunctional compounds are represented in the group. The simplest member is ethylene oxide [CH_2CH_2O], the internal or cyclic ether of the simplest glycol, ethylene glycol [$HOCH_2CH_2OH$]. External mono- and diethers of ethylene glycol [$ROCH_2CH_2OH$ and $ROCH_2CH_2OR'$] are well-known due largely to research done by the Carbide & Carbon.

Preparation—In the presence of NaOH at temperatures of the order of 120° to 135° and under a total pressure of about 4 atmospheres, ethylene oxide reacts with ethylene glycol to form compounds having the general formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, commonly referred to as condensation polymers and termed polyethylene (or polyoxyethylene) glycols. Other glycols besides ethylene glycol function in similar capacity, and the commercial generic term adopted for the entire group is polyalkylene (or polyoxyalkylene) glycols.

Nomenclature—It is to be noted that these condensation polymers are bifunctional; ie, they contain both ether and alcohol linkages. The compound wherein $n = 1$ is the commercially important diethylene glycol [$HOCH_2CH_2OCH_2CH_2OH$], and its internal ether is the familiar dioxane [$CH_2CH_2OCH_2CH_2O$]. The mono- and diethers derived from diethylene glycol have the formulas $ROCH_2CH_2OCH_2CH_2OH$ and $ROCH_2CH_2OCH_2CH_2OR'$. The former commonly are termed "*Carbitols*" and the latter "*Cellosolves*," registered trademarks belonging to Carbide & Carbon Co.

Polyethylene glycols are differentiated in commercial nomenclature by adding a number to the name which represents the average molecular weight. Thus, polyethylene glycol 400 has an average molecular weight of about 400 (measured values for commercial samples range between 380 and 420) corresponding to a value of n for this particular polymer of approximately 8. Polymers have been produced in which the value of n runs into the hundreds. Up to n = approximately 15, the compounds are liquids at room temperature, viscosity and boiling point increasing with increasing molecular weight. Higher polymers are waxy solids and are termed commercially *Carbowaxes* (another Carbide & Carbon trademark).

It should be observed that the presence of the two terminal hydroxyl groups in the polyalkylene glycols makes possible the formation of both ether and ester derivatives, several of which are marketed products.

Uses—Because of their vapor pressure, solubility, solvent power, hygroscopicity, viscosity and lubricating characteristics, the polyalkylene glycols or their derivatives function in many applications as effective replacements for glycerin and water-insoluble oils. They find considerable use as plasticizers, lubricants, conditioners and finishing agents for processing textiles and rubber. They also are important as emulsifying agents and as dispersants for such diverse substances as dyes, oils, resins, insecticides and various types of pharmaceuticals. In addition, they are employed frequently as ingredients in ointment bases and in a variety of cosmetic preparations.

Polyethylene Glycols

Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, Carbowaxes (*Carbide & Carbon*); Alpeg (*ICI*)

$$H[OCH_2CH_2]_nOH$$

Polyethylene glycols [25322-68-3].

Preparation—Ethylene glycol is reacted with ethylene oxide in the presence of NaOH at temperatures in the range of 120° to 135° under pressure of about 4 atm.

Description—*Polyethylene glycols 200, 300, 400* and *600* are clear, viscous liquids at room temperature. *Polyethylene glycols 900, 1000, 1450, 3350, 4500* and *8000* are white, waxy solids. The glycols do not hydrolyze or deteriorate under typical conditions. As their molecular weight increases, their water solubility, vapor pressure, hygroscopicity and solubility in organic solvents decrease; at the same time, freezing or melting range, specific gravity, flash point and viscosity increase. If these compounds ignite, small fires should be extinguished with carbon dioxide or dry-chemical extinguishers and large fires with "alcohol" type foam extinguishers.

Solubility—All members of this class dissolve in water to form clear solutions and are soluble in many organic solvents.

Uses—These possess a wide range of solubilities and compatibilities, which make them useful in pharmaceutical and cosmetic preparations. Their blandness renders them highly acceptable for hair dressings, hand lotions, sun-tan creams, leg lotions, shaving creams and skin creams (eg, a peroxide ointment which is stable may be prepared using these compounds, while oil-type bases inactivate the peroxide). Their use in washable ointments is discussed under *Ointments* (page 1602). They also are used in making suppositories, hormone creams, etc. See *Polyethylene Glycol Ointment* (below) and *Glycol Ethers* (above). The liquid polyethylene glycol 400 and the solid polyethylene glycol 3350, used in the proportion specified (or a permissible variation thereof) in the official Polyethylene Glycol Ointment, provide a water-soluble ointment base used in the formulation of many dermatological preparations. The solid, waxy, water-soluble glycols often are used to increase the viscosity of liquid polyethylene glycols and to stiffen ointment and suppository bases. In addition, they are used to compensate for the melting point-lowering effect of other agents, ie, chloral hydrate, etc, on such bases.

Polyethylene Glycol Ointment USP—*Preparation:* Heat polyethylene glycol 3350 (400 g) and polyethylene glycol 400 (600 g) on a water bath to 65°. Allow to cool, and stir until congealed. If a firmer preparation is desired, replace up to 100 g of polyethylene glycol 400 with an equal amount of polyethylene glycol 3350. If 6 to 25% of an aqueous solution is to be incorporated in this ointment, replace 50 g of polyethylene glycol 3350 by 50 g of stearyl alcohol. *Uses:* A water-soluble ointment base.

Polyoxyl 40 Stearate

Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, octadecanoate; Myrj (*ICI*)

$$RCOO(C_2H_4O)_nH$$

(RCOO is the stearate moiety, n is approximately 40)

Polyethylene glycol monostearate [9004-99-3]; a mixture of monostearate and distearate esters of mixed polyoxyethylene diols and corresponding free glycols, the average polymer length being equivalent to about 40 oxyethylene units. *Polyoxyethylene 50 Stearate* is a similar mixture in which the average polymer length is equivalent to about 50 oxyethylene units.

Preparation—One method consists of heating the corresponding polyethylene glycol with an equimolar portion of stearic acid.

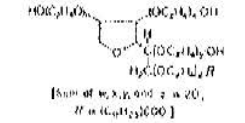
Description—White to light-tan waxy solid; odorless or has a faint fat-like odor; congeals between 37 and 47°.

Solubility—Soluble in water, alcohol, ether or acetone; insoluble in mineral or vegetable oils.

Uses—Contains ester and alcohol functions that impart both lyophilic and hydrophilic characteristics to make it useful as a surfactant and emulsifier. It is an ingredient of some water-soluble ointment and cream bases.

Polysorbates

Sorbitan esters, poly(oxy-1,2-ethanediyl) derivs, Manitans (*Ives-Cameron*); Sorlates (*Abbott*); Tweens (*ICI*)



[Sum of w, x, y, and z = 20, R = $(C_{11}H_{23})COO$]

Sorbitan esters, polyoxyethylene derivatives; fatty acid esters of sorbitol and its anhydrides copolymerized with a varying number of moles of ethylene oxide. The NF recognizes: *Polysorbate 20* (*structure given above*), a laurate ester; *Polysorbate 40*, a palmitate ester; *Polysorbate 60*, a mixture of stearate and palmitate esters; and *Polysorbate 80*, an oleate ester.

Preparation—These important nonionic surfactants (page 268) are prepared starting with sorbitol by (1) elimination of water-forming sorbitan (a cyclic sorbitol anhydride); (2) partial esterification of the sorbitan with a fatty acid such as oleic or stearic acid yielding a hexitan ester known commercially as a *Span* and (3) chemical addition of ethylene oxide yielding a *Tween* (the polyoxyethylene derivative).

Description—*Polysorbate 80*: Lemon- to amber-colored, oily liquid; faint, characteristic odor; warm, somewhat bitter taste; specific gravity 1.07 to 1.09; pH (1:20 aqueous solution) 6 to 8.

Solubility—*Polysorbate 80*: Very soluble in water, producing an odorless and nearly colorless solution; soluble in alcohol, cottonseed oil, corn oil, ethyl acetate, methanol or toluene; insoluble in mineral oil.

Uses—Because of their hydrophilic and lyophilic characteristics, these nonionic surfactants are very useful as emulsifying agents forming O/W emulsions in pharmaceuticals, cosmetics and other types of products. Polysorbate 80 is an ingredient in *Coal Tar Ointment* and *Solution*. See *Glycol Ethers* (page 1313).

Other Water-Soluble Ointment Base Component

Polyethylene Glycol 400 Monostearate USP XVI—An ether, alcohol and ester. Semitransparent, whitish, odorless or nearly odorless mass; melts from 30 to 34°. Freely soluble in carbon tetrachloride, chloroform, ether or petroleum benzin; slightly soluble in alcohol; insoluble in water. *Uses:* A nonionic surface-active agent in the preparation of creams, lotions, ointments and similar pharmaceutical preparations, which are readily soluble in water.

Pharmaceutical Solvents

The remarkable growth of the solvent industry is attested by the more than 300 solvents now being produced on an industrial scale. Chemically, these include a great variety of organic compounds, ranging from hydrocarbons through alcohols, esters, ethers and acids to nitroparaffins. Their main applications are in industry and the synthesis of organic chemicals. Comparatively few, however, are used as solvents in pharmacy, because of their toxicity, volatility, instability and/or flammability. Those commonly used as pharmaceutical solvents are described in this section.

Acetone

2-Propanone; Dimethyl Ketone

CH_3COCH_3

Acetone [67-64-1] C_3H_6O (58.08).

Caution—It is very flammable. Do not use where it may be ignited.

Preparation—Formerly obtained exclusively from the destructive distillation of wood. The distillate, consisting principally of methanol, acetic acid and acetone was neutralized with lime and the acetone was separated from the methyl alcohol by fractional distillation. Additional quantities were obtained by pyrolysis of the calcium acetate formed in the neutralization of the distillate.

It now is obtained largely as a by-product of the butyl alcohol industry. This alcohol is formed in the fermentation of carbohydrates such as corn starch, molasses, etc, by the action of the bacterium *Clostridium acetobutylicum* (Weizmann fermentation) and it is always one of the products formed in the process. It also is obtained by the catalytic oxidation of isopropyl alcohol, which is prepared from propylene resulting from the "cracking" of crude petroleum.

Description—Transparent, colorless, mobile, volatile, flammable liquid with a characteristic odor; specific gravity not more than 0.789; distils between 55.5 and 57°; congeals about −95°; aqueous solution neutral to litmus.

Solubility—Miscible with water, alcohol, ether, chloroform or most volatile oils.

Uses—An *antiseptic* in concentrations above 80%. In combination with alcohol it is used as an antiseptic *cleansing* solution. It is employed as a menstruum in the preparation of oleoresins in place of ether. It is used as a *solvent* for dissolving fatty bodies, resins, pyroxylin, mercurials, etc, and also in the manufacture of many organic compounds such as chloroform, chlorobutanol and ascorbic acid.

Alcohol

Ethanol; Spiritus Vini Rectificatus; S. V. R.; Spirit of Wine; Methylcarbinol

Ethyl alcohol [64-17-5]; contains 92.3 to 93.8%, by weight (94.9 to 96.0%, by volume), at 15.56° (60°F) of C_2H_5OH (46.07).

Preparation—Has been made for centuries by fermentation of certain carbohydrates in the presence of *zymase*, an enzyme present in yeast cells. Usable carbohydrate-containing materials include molasses, sugar cane, fruit juices, corn, barley, wheat, potato, wood and waste sulfite liquors. As yeast is capable of fermenting only D-glucose, D-fructose, D-mannose and D-galactose it is essential that more complex carbohydrates, such as starch, be converted to one or more of these simple sugars before they can be fermented. This is accomplished variously, commonly by enzyme- or acid-catalyzed hydrolysis.

The net reaction that occurs when a hexose, glucose for example, is fermented to alcohol may be represented as

$$C_6H_{12}O_6 \rightarrow 2C_2H_5OH + 2CO_2$$

but the mechanism of the process is very complex. The fermented liquid, containing about 15% of alcohol, is distilled to obtain a distillate containing 94.9% of C_2H_5OH, by volume. To produce *absolute alcohol*, the 95% product is dehydrated by various processes.

It may be produced also by hydration of ethylene, abundant supplies of which are available from natural and coke oven gases, from waste gases of the petroleum industry and other sources. In another synthesis acetylene is hydrated catalytically to acetaldehyde, which then is hydrogenated catalytically to ethyl alcohol.

Description—Transparent, colorless, mobile, volatile liquid; slight but characteristic odor; burning taste; boils at 78° but volatilizes even at a low temperature, and is flammable; when pure, it is neutral towards all indicators; specific gravity at 15.56° (the US Government standard temperature for Alcohol) not above 0.816, indicating not less than 92.3% of C_2H_5OH by weight or 94.9% by volume.

Solubility—Miscible with water, acetone, chloroform, ether or many other organic solvents.

Incompatibilities—This and preparations containing a high percentage of alcohol will precipitate many inorganic salts from an aqueous solution. *Acacia* generally is precipitated from a hydroalcoholic medium when the alcohol content is greater than about 35%.

Strong *oxidizing agents* such as *chlorine, nitric acid, permanganate* or *chromate* in acid solution react, in some cases violently, with it to produce oxidation products.

Alkalies cause a darkening in color due to the small amount of aldehyde usually present in it.

Uses—In pharmacy principally for its solvent powers (page 216). It also is used as the starting point in the manufacture of many important compounds, like ether, chloroform, etc. It also is used as a fuel, chiefly in the denatured form.

It is a CNS depressant. Consequently, it occasionally has been administered intravenously for preoperative and postoperative sedation in patients in whom other measures are ineffective or contraindicated. The dose employed is 1 to 1.5 mL/kg. Its intravenous use is a specialized procedure and should be employed only by one experienced in the technique of such use.

It is used widely and abused by lay persons as a sedative. It has, however, no medically approved use for this purpose. Moreover, alcohol potentiates the CNS effects of numerous sedative and depressant drugs. Hence, it should not be used by patients taking certain prescription drugs or OTC medications (see page 1862).

Externally, it has a number of medical uses. It is a solvent for the toxicodendrol causing *ivy poisoning*, and should be used to wash the skin thoroughly soon after contact. In a concentration of 25% it is employed for bathing the skin for the purpose of *cooling* and *reducing fevers*. In high concentrations it is a *rubefacient* and an ingredient of many liniments. In a concentration of 50% it is used to prevent sweating in *astringent* and *antihidrotic* lotions. It also is employed to cleanse and harden the skin and is helpful in preventing *bedsores* in bedridden patients. In a concentration of 60 to 90% it is germicidal. At optimum concentration (70% by weight) it is a good *antiseptic* for the skin (*local anti-infective*) and also for instruments. It also is used as a *solvent* to cleanse the skin splashed with phenol. High concentrations of it often are injected into nerves and ganglia for the *relief of pain*, accomplishing this by causing nerve degeneration.

Denatured Alcohol

An act of Congress June 7, 1906, authorizes the withdrawal of alcohol from bond without the payment of internal revenue tax, for the purpose of denaturation and use in the arts and industries. This is ethyl alcohol to which have been added such denaturing materials as to render the alcohol unfit for use as an intoxicating beverage. It is divided into two classes, namely, *completely denatured alcohol* and *specially denatured alcohol*, prepared in accordance with approved formulas prescribed in Federal Industrial Alcohol Regulations 3.

Information regarding the use of alcohol and permit requirements may be obtained from the Regional Director, Bureau of Alcohol, Tobacco and Firearms, in any of the following offices: Cincinnati, OH; Philadelphia, PA; Chicago, IL; New York, NY; Atlanta, GA; Dallas, TX and San Francisco, CA. Federal regulation provides that completely and specially denatured alcohols may be purchased by properly qualified persons from duly established denaturing plants or bonded dealers. No permit is required for the purchase and use of completely denatured alcohol unless the purchaser intends to recover the alcohol.

Completely Denatured Alcohol—This term applies to ethyl alcohol to which has been added materials (methyl isobutyl ketone, pyronate, gasoline, acetaldol, kerosene, etc) of such nature that the products may be sold and used within certain limitations without permit and bond.

Specially Denatured Alcohol—This alcohol is intended for use in a greater number of specified arts and industries than completely denatured alcohol and the character of the denaturant or denaturants used is such that specially denatured alcohol may be sold, possessed and used only by those persons or firms that hold basic permits and are covered by bond.

Formulas for products using specially denatured alcohol must be approved prior to use by the Regional Director, Bureau of Alcohol, Tobacco and Firearms in any of the regional offices listed above.

Uses—Approximately 50 specially denatured alcohol formulas containing combinations of more than 90 different denaturants are available to fill the needs of qualified users. Large amounts of specially denaturated alcohols are used as raw materials in the production of acetaldehyde, synthetic rubber, vinegar and ethyl chloride as well as in the manufacture of proprietary solvents and cleaning solutions. Ether and chloroform can be made from suitably denatured alcohols and formulas for the manufacture of Iodine Tincture, Green Soap Tincture and Rubbing Alcohol are set forth in the regulations.

Specially denatured alcohols also are used as solvents for surface coatings, plastics, inks, toilet preparations and external pharmaceuticals. Large quantities are used in the processing of such food and drug products as pectin, vitamins, hormones, antibiotics, alkaloids and blood products. Other uses include supplemental motor fuel, rocket and jet fuel, antifreeze solutions, refrigerants and cutting oils. Few products are manufactured today that do not require the use of alcohol at some stage of production. Specially denatured alcohol may not be used in the manufacture of foods or internal medicines where any of the alcohol remains in the finished product.

Rose Water Ointment

Cold Cream; Galen's Cerate

Cetyl Esters Wax	125 g
White Wax	120 g
Almond Oil	560 g
Sodium Borate	5 g
Stronger Rose Water	25 mL
Purified Water	165 mL
Rose Oil	0.2 mL
To make about	1000 g

Reduce the cetyl esters wax and the white wax to small pieces, melt them on a steam bath, add the almond oil and continue heating until the temperature of the mixture reaches 70°. Dissolve the sodium borate in the purified water and stronger rose water, warmed to 70°, and gradually add the warm solution to the melted mixture, stirring rapidly and continuously until it has cooled to about 45°. Incorporate the rose oil.

It must be free from rancidity. If the ointment has been chilled, warm it slightly before attempting to incorporate other ingredients (see USP for allowable variations).

History—Originated by Galen, the famous Roman physician-pharmacist of the 1st century AD, was known for many centuries by the name of *Unguentum or Ceratum Refrigerans*. It has changed but little in proportions or method of preparation throughout many centuries.

Uses—An *emollient* and *ointment base*. It is a W/O emulsion.

Diluted Alcohol

Diluted Ethanol

A mixture of alcohol and water containing 41.0 to 42.0%, by weight (48.4 to 48.5%, by volume), at 15.56°, of C_2H_5OH (46.07).

Preparation—

Alcohol	500 mL
Purified Water	500 mL

Measure the alcohol and the purified water separately at the same temperature, and mix. If the water and the alcohol and the resulting mixture are measured at 25°, the volume of the mixture will be about 970 mL.

When equal volumes of alcohol and water are mixed together, a rise in temperature and a contraction of about 3% in volume take place. In small operations the contraction generally is disregarded; in larger operations it is very important. If 50 gal of official alcohol are mixed with 50 gal of water, the product will not be 100 gal of diluted alcohol, but only 96½ gal, a contraction of 3½ gal. USP *Proof Spirit* differs from this and is stronger; it contains 50%, by volume, of absolute alcohol at 15.56° (60°F). This corresponds to 42.5% by weight, and has a specific gravity of 0.9341 at the same temperature. If spirits have a specific gravity lower than that of "proof spirit" (0.9341), they are said to be "*above proof*;" if greater, "*below proof*."

It also may be prepared from the following:

Alcohol	408 g
Purified Water	500 g

Rules for Dilution—The following rules are applied when making an alcohol of any required lower percentage from an alcohol of any given higher percentage:

1. By Volume—Designate the volume percentage of the stronger alcohol by *V*, and that of the weaker alcohol by *v*.

Rule—Mix *v* volumes of the stronger alcohol with purified water to make *V* volumes of product. Allow the mixture to stand until full contraction has taken place, and until it has cooled, then make up the deficiency in the *V* volumes by adding more purified water.

Example—An alcohol of 30% by volume is to be made from an alcohol of 94.0% by volume.—Take 30 volumes of the 94.9% alcohol, and add enough purified water to produce 94.9 volumes at room temperature.

II. **By Weight**—Designate the weight-percentage of the stronger alcohol by *W*, and that of the weaker alcohol by *w*.

Rule—Mix *w* parts by weight of the stronger alcohol with purified water to make *W* parts by weight of product.

Example—An alcohol of 50% by weight is to be made from an alcohol of 92.3% by weight.—Take 50 parts by weight of the 92.3% alcohol, and add enough purified water to produce 92.3 parts by weight.

Description—As for *Alcohol*, except its specific gravity is 0.935 to 0.937 at 15.56°, indicating that the strength of C_2H_5OH corresponds to that given in the official definition.

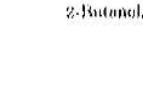
Uses—A menstruum in making tinctures, fluidextracts, extracts, etc. Its properties already have been described fully in connection with the various preparations. Its value consists not only in its *antiseptic* properties, but also in its possessing the *solvent* powers of both water and alcohol. See *Alcohol*.

Nonbeverage Alcohol

This is tax-paid alcohol or distilled spirits used in the manufacture, by approved formula, of such medicines, medicinal preparations, food products, flavors or flavoring extracts as are unfit for beverage purposes. Internal Revenue Service Regulations provide that qualified holders of Special Tax Stamps who use tax paid alcohol or distilled spirits in the types of products listed above, may file a claim for *alcohol tax drawback* or refund of a considerable part of the tax paid.

Amylene Hydrate

2-Butanol, 2-methyl-, Tertiary Amyl Alcohol; Dimethylethylcarbinol



tert-Pentyl alcohol [75-85-4] $C_5H_{12}O$ (88.15).

Preparation—Amylene is mixed with 2 volumes of 60% H_2SO_4, both previously cooled to 0°, for about 1 hr; then neutralized with soda, distilled and the first half of the distillate containing most of the amylene hydrate is treated with anhydrous potassium carbonate and redistilled.

Description—Clear, colorless liquid of camphoraceous odor; solution neutral to litmus; specific gravity 0.809 to 0.807; distils completely between 97 and 103°.

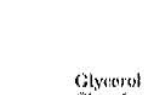
Solubility—1 g in about 8 mL of water; miscible with alcohol, chloroform, ether or glycerin.

Uses—Chiefly, a *pharmaceutic necessity for Tribromoethanol Solution* (RPS-15, page 985). It has been used as a *sedative-hypnotic* in doses of 1 to 4 g administered in glycerin.

Chloroform—page 1320.
Ether—page 1041.
Ethyl Acetate—page 1294.

Glycerin

1,2,3-Propanetriol; Glycerol



Glycerol [56-81-5] $C_3H_8O_3$ (92.09).

Chemically, it is the simplest trihydric alcohol. It is worthy of special note because the two terminal alcohol groups are primary, whereas the middle one is secondary. Thus this becomes the first polyhydric alcohol which can yield both an aldose (*glyceraldehyde*) and a ketose (*dihydroxyacetone*).

Preparation—

1. By saponification of fats and oils in the manufacture of soap.
2. By hydrolysis of fats and oils through pressure and superheated steam.
3. By fermentation of beet sugar molasses in the presence of large amounts of sodium sulfite. Under these conditions a reaction takes place expressed as

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \rightarrow \underset{\text{Glycerin}}{C_3H_5(OH)_3} + \underset{\text{Acetaldehyde}}{CH_3CHO} + CO_2$$

4. Glycerin is now prepared in large quantities from propylene, a petroleum product. This hydrocarbon is chlorinated at about 400° to form allyl chloride, which is converted to allyl alcohol. Treatment of the unsaturated alcohol with hypochlorous acid [HOCl] yields the chlorohydrin derivative. Extraction of HCl with soda lime yields 2,3-epoxypropanol which undergoes hydration to glycerin.

Description—Clear, colorless, syrupy liquid with a sweet taste and not more than a slight, characteristic odor, which is neither harsh nor disagreeable; when exposed to moist air it absorbs water and also such gases as H_2S and SO_2; solutions are neutral; specific gravity not below 1.249 (not less than 95% $C_3H_5(OH)_3$); boils at about 290° under 1 atm, with decomposition, but can be distilled intact in a vacuum.

Solubility—Miscible with water, alcohol methanol; 1 g in about 12 mL of ethyl acetate or about 15 mL of acetone; insoluble in chloroform, ether or fixed and volatile oils.

Incompatibilities—An explosion may occur if it is triturated with strong *oxidizing agents* such as *chromium trioxide, potassium chlorate* or *potassium permanganate*. In dilute solutions the reactions proceed at a slower rate forming several oxidation products. Iron is an occasional contaminant of it and may be the cause of a darkening in color in mixtures containing *phenols, salicylates, tannin*, etc.

With *boric acid or sodium borate*, it forms a complex, generally spoken of as glyceroboric acid, which is a much stronger acid than boric acid.

Uses—One of the most valuable products known to pharmacy by virtue of its *solvent* property. It is useful as a *humectant* in keeping substances moist, owing to its hygroscopicity. Its agreeable taste and high viscosity adapt it for many purposes. Some modern ice collars and ice bags contain it and water hermetically sealed within vulcanized rubber bags. The latter are sterilized by dipping in a germicidal solution and are stored in the refrigerator until needed. It also has some therapeutic uses. In pure anhydrous form, it is used in the eye to reduce corneal edema and to facilitate ophthalmoscopic examination. It is used orally as an evacuant and, in 50 to 75% solution, as a systemic osmotic agent.

Isopropyl Alcohol—page 1167.

Methyl Alcohol

Methanol; Wood Alcohol

CH_3OH

Methanol [67-56-1] CH_4O (32.04).

Caution—It is poisonous.

Preparation—By the catalytic reduction of carbon monoxide or carbon dioxide with hydrogen. A zinc oxide-chromium oxide catalyst is used commonly.

Description—Clear, colorless liquid; characteristic odor; flammable; specific gravity not more than 0.790; distils within a range of 1° between 63.5 and 65.7°.

Solubility—Miscible with water, alcohol, ether, benzene or most other organic solvents.

Uses—*A pharmaceutic aid* (solvent). It is toxic. Ingestion may result in blindness; vapors also may cause toxic reactions.

Methyl Isobutyl Ketone

2-Pentanone, 4-methyl-,

$(CH_3)_2CHCH_2COCH_3$

4-Methyl-2-pentanone [108-10-1]; contains not less than 99% of $C_6H_{12}O$ (100.16).

Description—Transparent, colorless, mobile, volatile liquid; faint, ketonic and camphoraceous odor; distils between 114 and 117°.

Solubility—Slightly soluble in water; miscible with alcohol, ether or benzene.

Uses—*A denaturant* for rubbing alcohol and also *a solvent* for gums, resins, nitrocellulose, etc. It may be irritating to the eyes and mucous membranes, and, in high concentrations, narcotic.

Monoethanolamine

Ethanol, 2-amino-, Ethanolamine; Ethylolamine

$HOCH_2CH_2NH_2$

2-Aminoethanol [141-43-5] C_2H_7NO (61.08).

Preparation—This alkanolamine is prepared conveniently by treating ethylene oxide with ammonia.

Description—Clear, colorless, moderately viscous liquid; distinctly ammoniacal odor; affected by light; specific gravity 1.013 to 1.016; distils between 167 and 173°.

Solubility—Miscible in all proportions with water, acetone, alcohol, glycerin or chloroform; immiscible with ether, solvent hexane or fixed oils; dissolves many essential oils.

Uses—A *solvent* for fats, oils and many other substances, it is a pharmaceutical necessity for *Thimerosal Solution* (page 1173). It combines with fatty acids to form soaps which find application in various types of emulsions such as lotions, creams, etc.

Propylene Glycol

$CH_3CH(OH)CH_2OH$

1,2-Propanediol [57-55-6] $C_3H_8O_2$ (76.10).

Preparation—Propylene is converted successively to its chlorohydrin (with HOCl), epoxide (with Na_2CO_3) and glycol (with water in presence of protons).

Description—Clear, colorless, viscous and practically odorless liquid; slightly acrid taste; specific gravity 1.035 to 1.037; completely distils between 184 and 189°; absorbs moisture from moist air.

Solubility—Miscible with water, alcohol, acetone or chloroform; soluble in ether; dissolves many volatile oils; immiscible with fixed oils.

Uses—A *solvent*, *preservative* and *humectant*. See *Hydrophilic Ointment* (page 1311).

Trolamine

Ethanol, 2,2',2''-nitrilotris-, Triethanolamine

2,2',2''-Nitrilotriethanol [102-71-6] $N(C_2H_4OH)_3$ (149.19); a mixture of alkanolamines consisting largely of triethanolamine, containing some diethanolamine [$NH(C_2H_4OH)_2$ = 105.14] and monoethanolamine [$NH_2C_2H_4OH$ = 61.08].

Preparation—Along with some mono- and diethanolamine, by the action of ammonia on ethylene oxide.

Description—Colorless to pale yellow, viscous, hygroscopic liquid; slight odor of ammonia; aqueous solution is very alkaline; melts about 21°; specific gravity 1.120 to 1.128; a strong base and readily combines even with weak acids to form salts.

Solubility—Miscible with water or alcohol; soluble in chloroform; slightly soluble in ether or benzene.

Uses—In combination with a fatty acid, eg, oleic acid (see *Benzyl Benzoate Lotion*, page 1246), as an *emulsifier*. See *Monoethanolamine*.

Water—page 1300.

Other Pharmaceutical Solvents

Alcohol, Dehydrated, BP, PhI [Dehydrated Ethanol; Absolute Alcohol]—Transparent, colorless, mobile, volatile liquid; characteristic odor; burning taste; specific gravity not more than 0.798 at 15.56°; hygroscopic, flammable and boils about 78°C. Miscible with water, ether or chloroform. *Uses:* A pharmaceutical solvent; also used by injection for relief of pain (see *Alcohol*, page 1314).

Coconut Oil [Cocoanut Oil; Copra Oil]—The fixed oil obtained by expression or extraction from the kernels of the seeds of *Cocos nucifera* Linné (Fam *Palmae*). Pale yellow to colorless liquid between 28 and 30°, semisolid at 20° and a hard, brittle crystalline solid below 15°; odorless and tasteless or has a faint odor and taste characteristic of coconut; it must not be used if it has become rancid; melts about 23°; specific gravity 0.918 to 0.923. Readily soluble in alcohol, ether, chloroform, carbon disulfide or petroleum benzin; insoluble in water.

Petroleum Benzin [Petroleum ether; Purified benzin]—Clear, colorless, volatile liquid; ethereal or faint, petroleum-like odor; neutral reaction; specific gravity 0.634 to 0.660. Practically insoluble in water; miscible with ether, chloroform, benzene or fixed oils. *Caution:* Highly flammable, and its vapor, when mixed with air and ignited, may explode. *Uses:* A solvent for fats, resins, oils and similar substances.

Miscellaneous Pharmaceutical Necessities

The agents listed in this section comprise a heterogeneous group of substances with both pharmaceutical and industrial applications. Pharmaceutically, some of these agents are used as diluents, enteric coatings, excipients, filtering agents and as ingredients in products considered in other chapters. Industrially, some of these agents are used in various chemical processes, in the synthesis of other chemicals and in the manufacture of fertilizers, explosives, etc.

Acetic Acid

Acetic acid; a solution containing 36 to 37%, by weight, of $C_2H_4O_2$ (60.05).

Preparation—By diluting with distilled water an acid of higher concentration, such as the 80% product, or more commonly glacial acetic acid, using 360 mL of the latter for the preparation of each 1000 mL of acetic acid.

Description—Clear, colorless liquid, having a strong characteristic odor and a sharply acid taste; specific gravity about 1.045; congeals about −14°; acid to litmus.

Solubility—Miscible with water, alcohol or glycerin.

Uses—In pharmacy as a *solvent* and *menstruum*, and for making diluted acetic acid. It also is used as a starting point in the manufacture of many other organic compounds, eg, acetates, acetanilid, sulfonamides, etc. It is official primarily as a *pharmaceutic necessity* for the preparation of *Aluminum Subacetate Solution* (RPS-17, page 778).

Diluted Acetic Acid

Dilute Acetic Acid

A solution containing, in each 100 mL, 5.7 to 6.3 g of $C_2H_4O_2$.

Preparation—

Acetic Acid	158 mL
Purified Water, a sufficient quantity, to make	1000 mL

Mix the ingredients.

Note—This acid also may be prepared by diluting 58 mL of glacial acetic acid with sufficient purified water to make 1000 mL.

Description—Essentially the same properties, solubility, purity and identification reactions as *Acetic Acid*, but its specific gravity is about 1.008 and it congeals about −2°.

Uses—*Bactericidal* to many types of microorganisms and occasionally is used in 1% solution for surgical dressings of the skin. A 1% solution is *spermatocidal*. It also is used in vaginal douches for the management of *Trichomonas*, *Candida* and *Hemophilus* infections.

Glacial Acetic Acid

Concentrated Acetic Acid; Crystallizable Acetic Acid; Ethanoic Acid; Vinegar Acid

CH_3COOH

Glacial acetic acid [64-19-7] $C_2H_4O_2$ (60.05).

Preparation—This acid is termed "glacial" because of its solid, glassy appearance when congealed. In one process it is produced by distillation of weaker acids to which has been added a water-entraining substance such as ethylene dichloride. In this method, referred to as "azeotropic distillation," the ethylene dichloride dis-

tils out with the water before the acid distils over, thereby effecting concentration of the latter.

In another process the aqueous acid is mixed with triethanolamine and heated. The acid combines with the triethanolamine to form a triethanolamine acetate. The water is driven off first; then, at a higher temperature, the triethanolamine compound decomposes to yield this acid.

A greater part of the acid now available is made synthetically from acetylene. When acetylene is passed into this acid containing a metallic catalyst such as mercuric oxide, ethylidene diacetate is produced which yields, upon heating, acetic anhydride and acetaldehyde. Hydration of the former and air oxidation of the latter yield this acid.

Description—Clear, colorless liquid; pungent, characteristic odor; when well-diluted with water, it has an acid taste; boils about 118°; congeals at a temperature not lower than 15.6°, corresponding to a minimum of 99.4% of CH_3COOH; specific gravity about 1.05.

Solubility—Miscible with water, alcohol, acetone, ether or glycerin; insoluble in carbon tetrachloride or chloroform.

Uses—A *caustic* and *vesicant* when applied externally and is often sold under various disguises as a *corn solvent*. It is an excellent *solvent* for fixed and volatile oils and many other organic compounds. It is used primarily as an *acidifying agent*.

Almond Oil—RPS-16, page 720.

Aluminum

Aluminum Al (26.98); the free metal in the form of finely divided powder. It may contain oleic acid or stearic acid as a lubricant. It contains not less than 95% of Al, and not more than 5% of *Acid-Insoluble substances*, including any added fatty acid.

Description—Very fine, free-flowing, silvery powder free from gritty or discolored particles.

Solubility—Insoluble in water or alcohol; soluble in hydrochloric and sulfuric acids or in solutions of fixed alkali hydroxides.

Uses—A *protective*. An ingredient in *Aluminum Paste* (RPS-14, page 772).

Aluminum Monostearate

Aluminum, dihydroxy(octadecanoato-*O*)-,

Dihydroxy(stearato)aluminum [7047-84-9]; a compound of aluminum with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of aluminum monostearate and aluminum monopalmitate. It contains the equivalent of 14.5 to 16.5% of Al_2O_3 (101.96).

Preparation—By interaction of a hydroalcoholic solution of potassium stearate with an aqueous solution of potassium alum, the precipitate being purified to remove free stearic acid and some aluminum distearate simultaneously produced.

Description—Fine, white to yellowish white, bulky powder; faint, characteristic odor.

Solubility—Insoluble in water, alcohol or ether.

Uses—A *pharmaceutical necessity* used in the preparation of *Sterile Procaine Penicillin G with Aluminum Stearate Suspension* (see page 1101).

Strong Ammonia Solution

Stronger Ammonia Water; Stronger Ammonium Hydroxide Solution; Spirit of Hartshorn

Ammonia [1336-21-6]; a solution of NH_3 (17.03), containing 27.0 to 31.0% (*w/w*) of NH_3. Upon exposure to air it loses ammonia rapidly.

Caution—Use care in handling it because of the caustic nature of the Solution and the irritating properties of its vapor. Cool the container well before opening, and cover the closure with a cloth or similar material while opening. Do not taste it, and avoid inhalation of its vapor.

Preparation—Ammonia is obtained commercially chiefly by synthesis from its constituent elements, nitrogen and hydrogen, combined under high pressure and at high temperature in the presence of a catalyst.

Description—Colorless, transparent liquid; exceedingly pungent, characteristic odor; even when well-diluted it is strongly alkaline to litmus; specific gravity about 0.90.

Solubility—Miscible with alcohol.

Uses—Only for chemical and pharmaceutical purposes. It is used primarily in making ammonia water by dilution and as a chemical reagent. It is too strong for internal administration. It is an ingredient in *Aromatic Ammonia Spirit* (page 1533).

Bismuth Subnitrate

Basic Bismuth Nitrate; Bismuth Oxynitrate; Spanish White; Bismuth Paint; Bismuthyl Nitrate

Bismuth hydroxide nitrate oxide [1304-85-4] $Bi_5O(OH)_9(NO_3)_4$ (1461.99); a basic salt which, dried at 105° for 2 hr, yields upon ignition not less than 79% of Bi_2O_3 (465.96).

Preparation—A solution of bismuth nitrate is added to boiling water to produce the subnitrate by hydrolysis.

Description—White, slightly hygroscopic powder; suspension in distilled water is faintly acid to litmus (pH about 5).

Solubility—Practically insoluble in water or organic solvents; dissolves readily in an excess of hydrochloric or nitric acid.

Incompatibilities—Slowly hydrolyzed in *water* with liberation of nitric acid; thus, it possesses the incompatibilities of the acid. *Reducing agents* darken it with the production of metallic bismuth.

Uses—A *pharmaceutical necessity* in the preparation of milk of bismuth. It also is used as an *astringent*, *adsorbent* and *protective*; however, its value as a protective is questionable. This agent, like other insoluble bismuth salts, is used topically in lotions and ointments.

Barium Hydroxide Lime

A mixture of barium hydroxide octahydrate and calcium hydroxide. It also may contain potassium hydroxide and may contain an indicator that is inert toward anesthetic gases such as ether, cyclopropane and nitrous oxide, and that changes color when the barium hydroxide lime no longer can absorb carbon dioxide.

Caution—Since it contains a soluble form of barium, it is toxic if swallowed.

Description—White or grayish white granules; may have a color if an indicator has been added.

Uses—A carbon dioxide adsorbent. See *Soda Lime* (page 1325).

Boric Acid

Boric acid (H_3BO_3); Boracic Acid; Orthoboric Acid

Boric acid [10043-35-3] H_3BO_3 (61.83).

Preparation—Lagoons of the volcanic districts of Tuscany formerly furnished the greater part of this acid and borax of commerce. Borax is now found native in California and some of the other western states; calcium and magnesium borates are found there also. It is produced from native borax, or from the other borates, by reacting with hydrochloric or sulfuric acid.

Description—Colorless scales of a somewhat pearly luster, or crystals, but more commonly a white powder slightly unctuous to the touch; odorless and stable in the air; volatilizes with steam.

Solubility—1 g in 18 mL of water, 18 mL of alcohol, 4 mL of glycerin, 4 mL of boiling water or 6 mL of boiling alcohol.

Uses—A buffer, and it is this use that is recognized officially. It is a very weak *germicide* (*local anti-infective*). Its nonirritating properties make its solutions suitable for application to such delicate structures as the cornea of the eye. Aqueous solutions are employed as an eye wash, mouth wash and for irrigation of the bladder. A 2.2% solution is isotonic with lacrimal fluid. Solutions, even if they are made isotonic, will hemolyze red blood cells. It also is employed as a dusting powder, when diluted with some inert material. It can be absorbed through irritated skin, eg, infants with diaper rash.

Although it is not absorbed significantly from intact skin, it is absorbed from damaged skin and fatal poisoning, particularly in infants, has occurred with topical application to burns, denuded areas, granulation tissue and serous cavities. *Serious poisoning can*

result from oral ingestion of as little as 5 g. Symptoms of poisoning are nausea, vomiting, abdominal pain, diarrhea, headache and visual disturbance. Toxic alopecia has been reported from the chronic ingestion of a mouth wash containing it. The kidney may be injured and death may result. Its use as a preservative in beverages and foods is prohibited by national and state legislation. *There is always present the danger of confusing it with dextrose when compounding milk formulas for infants. Fatal accidents have occurred.* For this reason boric acid in bulk is colored, so that it cannot be confused with dextrose.

It is used to prevent discoloration of physostigmine solutions.

Dose—*Topically*, as required.

Calcium Hydroxide

Slaked Lime; Calcium Hydrate

Calcium hydroxide [1305-62-0] $Ca(OH)_2$ (74.09).

Preparation—By reacting freshly prepared calcium oxide with water.

Description—White powder; alkaline, slightly bitter taste; absorbs carbon dioxide from the air forming calcium carbonate; solutions exhibit a strong alkaline reaction.

Solubility—1 g in 630 mL of water or 1300 mL of boiling water; soluble in glycerin or syrup; insoluble in alcohol; the solubility in water is decreased by the presence of fixed alkali hydroxides.

Uses—In the preparation of *Calcium Hydroxide Solution*.

Calcium Hydroxide Topical Solution

Calcium Hydroxide Solution; Lime Water

A solution containing, in each 100 mL, not less than 140 mg of $Ca(OH)_2$ (74.09).

Note—The solubility of calcium hydroxide varies with the temperature at which the solution is stored, being about 170 mg/100 mL at 15°, and less at a higher temperature. The official concentration is based upon a temperature of 25°.

Preparation—

Calcium Hydroxide	3 g
Purified Water	1000 mL

Add the calcium hydroxide to 1000 mL of cool, purified water, and agitate the mixture vigorously and repeatedly during 1 hr. Allow the excess of calcium hydroxide to settle. Dispense only the clear, supernatant liquid.

The undissolved portion of the mixture is not suitable for preparing additional quantities of the solution.

The object of keeping lime water over undissolved calcium hydroxide is to insure a saturated solution.

Description—Clear, colorless liquid; alkaline taste; strong alkaline reaction; absorbs carbon dioxide from the air, a film of calcium carbonate forming on the surface of the liquid; when heated, it becomes turbid, owing to the separation of calcium hydroxide, which is less soluble in hot than in cold water.

Uses—To dilute to be effective as a gastric antacid. It is employed *topically as a protective* in various types of lotions. In some lotion formulations it is used with olive oil or oleic acid to form calcium oleate that functions as an emulsifying agent. The USP classes it as an *astringent*.

Dose—*Topically*, in astringent solutions and lotions as required (see *Calamine Lotion*, page 762).

Calcium Pantothenate, Racemic—page 1022.

Calcium Stearate

Octadecanoic acid, calcium salt

Calcium stearate [1592-23-0]; a compound of calcium with a mixture of solid organic acids obtained from fats and consists chiefly of variable proportions of stearic and palmitic acids [calcium stearate, $C_{36}H_{70}CaO_4$ = 607.03; calcium palmitate, $C_{32}H_{62}CaO_4$ = 550.92]; contains the equivalent of 9 to 10.5% of CaO (calcium oxide).

Preparation—By precipitation from interaction of solutions of calcium chloride and the sodium salts of the mixed fatty acids (stearic and palmitic).

Description—Fine, white to yellowish white, bulky powder; slight, characteristic odor; unctuous and free from grittiness.

Solubility—Insoluble in water, alcohol or ether.

Uses—A *lubricant* in the manufacture of compressed tablets. It also is used as a conditioning agent in food and pharmaceutical products. Its virtually nontoxic nature and unctuous properties makes it ideal for these purposes.

Calcium Sulfate

Sulfuric acid, calcium salt (1:1); Gypsum; Terra Alba

Calcium sulfate (1:1) [7778-18-9] $CaSO_4$ (136.14); *dihydrate* [10101-41-4] (172.17).

Preparation—From natural sources or by precipitation from interaction of solutions of calcium chloride and a soluble sulfate.

Description—Fine, white to slightly yellow-white, odorless powder.

Solubility—Dissolves in diluted HCl; slightly soluble in water.

Uses—A *diluent* in the manufacture of compressed tablets. It is sufficiently inert that few undesirable reactions occur in tablets made with this substance. It also is used for making plaster casts and supports.

Carnauba Wax

Obtained from the leaves of *Copernicia cerifera* Mart (Fam *Palmae*).

Preparation—Consists chiefly of *myricyl cerotate* with smaller quantities of *myricyl alcohol*, *ceryl alcohol* and *cerotic acid*. It is obtained by treating the leaf buds and leaves of *Copernicia cerifera*, the so called *Brazilian Wax Palm*, with hot water.

Description—Light-brown to pale yellow, moderately coarse powder; characteristic bland odor; free from rancidity; specific gravity about 0.99; melts about 84°.

Solubility—Insoluble in water; freely soluble in warm benzene; soluble in warm chloroform or toluene; slightly soluble in boiling alcohol.

Uses—A pharmaceutic aid used as a *polishing agent* in the manufacture of coated tablets.

Microcrystalline Cellulose

Cellulose [9004-34-6]; purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

Preparation—Cellulose is subjected to the hydrolytic action of 2.5 *N* HCl at the boiling temperature of about 105° for 15 min, whereby amorphous cellulosic material is removed and aggregates of crystalline cellulose are formed. These are collected by filtration, washed with water and aqueous ammonia and disintegrated into small fragments, often termed cellulose crystallites, by vigorous mechanical means such as a blender. US Pat 3,141,875.

Description—Fine, white, odorless, crystalline powder; consists of free-flowing, nonfibrous particles.

Solubility—Insoluble in water, dilute acids or most organic solvents, slightly soluble in NaOH solution (1 in 20).

Uses—A tablet diluent and disintegrant. It can be compressed into self-binding tablets which disintegrate rapidly when placed in water.

Microcrystalline Cellulose and Sodium Carboxymethylcellulose—A colloid-forming, attrited mixture of microcrystalline cellulose and sodium carboxymethylcellulose. Tasteless, odorless, white to off-white, coarse to fine powder; pH (dispersion) 6 to 8. Swells in water, producing, when dispersed, a white, opaque dispersion or gel; insoluble in organic solvents or dilute acids. *Uses*: Pharmaceutic aid (suspending agent). *Grades Available* (amounts of sodium carboxymethylcellulose producing viscosities in the concentrations designated): 8.5%, 120 cps in 2.1% solution; 11%, 120 cps in 1.2% solution; 11%, 65 cps in 1.2% solution.

Powdered Cellulose—page 1305.

Cellulose Acetate Phthalate

Cellulose, acetate, 1,2-benzenedicarboxylate

Cellulose acetate phthalate [9004-38-6]; a reaction product of the phthalic anhydride and a partial acetate ester of cellulose. When

dried at 105° for 2 hr, it contains 19 to 23.5% of acetyl (C_2H_3O) groups and 30 to 36.0% of phthalyl (*o*-carboxybenzoyl, $C_8H_5O_3$) groups.

Preparation—Cellulose is esterified by treatment with acetic and phthalic acid anhydrides.

Description—Free-flowing, white powder; may have a slight odor of acetic acid.

Solubility—Insoluble in water or alcohol; soluble in acetone or dioxane.

Uses—An *enteric tablet-coating material*. Coatings of this substance disintegrate due to the hydrolytic effect of the intestinal esterases, even when the intestinal contents are acid. *In vitro* studies indicate that cellulose acetate phthalate will withstand the action of artificial gastric juices for long periods of time, but will disintegrate readily in artificial intestinal juices.

Cherry Juice

The liquid expressed from the fresh ripe fruit of *Prunus cerasus* Linné (Fam *Rosaceae*); contains not less than 1% of malic acid [$C_4H_6O_5$ = 134.09].

Preparation—Coarsely crush washed, stemmed, unpitted, sour cherries in a grinder so as to break the pits but not mash the kernels. Dissolve 0.1% of benzoic acid in the mixture, and allow it to stand at room temperature (possibly for several days) until a small portion of the filtered juice remains clear when mixed with one-half of its volume of alcohol and the resulting solution does not become cloudy within 30 min. Press the juice from the mixture and filter it.

Description—Clear liquid; aromatic, characteristicless odor; sour taste; affected by light; the color of the freshly prepared juice is red to reddish orange; pH 3 to 4; specific gravity 1.045 to 1.075.

Uses—To prepare *Cherry Syrup* (page 1301).

Carbon Tetrachloride

Methane, tetrachloro-, Tetrachloromethane

Carbon tetrachloride [56-23-5] CCl_4 (153.82).

Preparation—One method consists of catalytic chlorination of carbon disulfide.

Description—Clear, colorless liquid; characteristic odor resembling that of chloroform; specific gravity 1.588 to 1.590; boils about 77°.

Solubility—Soluble in about 2000 volumes water; miscible with alcohol, acetone, ether, chloroform or benzene.

Uses—Officially recognized as a *pharmaceutical necessity* (solvent). Formerly it was used as a cheap *anthelmintic* for the treatment of *hookworm* infections but it causes severe injury to the liver if absorbed.

Chloroform

Methane, trichloro-,

Trichloromethane [67-66-3] $CHCl_3$ (119.38); contains 99 to 99.5% of $CHCl_3$, the remainder consisting of alcohol.

Caution—Care should be taken not to vaporize it in the presence of a flame, because of the production of harmful gases (hydrogen chloride and phosgene).

Preparation—Made by the reduction of carbon tetrachloride with water and iron and by the controlled chlorination of methane.

The pure compound readily decomposes on keeping, particularly if exposed to moisture and sunlight, resulting in formation of phosgene (carbonyl chloride [$COCl_2$]) and other products. The presence of a small amount of alcohol greatly retards or prevents this decomposition; hence, the requirement that it contain 0.5 to 1% of alcohol. The alcohol combines with any phosgene forming ethyl carbonate, which is nontoxic.

Description—Clear, colorless, mobile liquid; characteristic, ethereal odor; burning, sweet taste; not flammable but its heated vapors burn with a green flame; affected by light and moisture; specific gravity 1.474 to 1.478, indicating 99 to 99.5% of $CHCl_3$; boils about 61°; not affected by acids, but is decomposed by alkali hydroxide into alkali chloride and sodium formate.

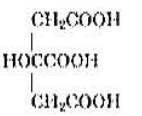
Solubility—Soluble in 210 volumes of water; miscible with alcohol, ether, benzene, solvent hexane, acetone or fixed and volatile oils.

Uses—An obsolete *inhalation anesthetic*. Although it possesses advantages of nonflammability and great potency, it rarely is used due to the serious toxic effects it produces on the heart and liver. Internally, it has been used, in small doses, as a *carminative*. Externally, it is an *irritant* and when used in liniments it may produce blisters.

It is categorized as a pharmaceutic aid. It is used as a *preservative* during the aqueous percolation of vegetable drugs to prevent bacterial decomposition in the process of manufacture. In most instances it is evaporated before the product is finished. It is an excellent solvent for alkaloids and many other organic chemicals and is used in the manufacture of these products and in chemical analyses.

Citric Acid

1,2,3-Propanetricarboxylic acid, 2-hydroxy-,



Citric acid [77-92-9] $C_6H_8O_7$ (192.12); *monohydrate* [5949-29-1] (210.14).

Preparation—Found in many plants. It formerly was obtained solely from the juice of limes and lemons and from pineapple wastes. Since about 1926 the acid has been produced largely by fermentation of sucrose solution, including molasses, by fungi belonging to the *Aspergillus niger* group, theoretically according to the following reaction

$C_{12}H_{22}O_{11}$	$+ 3O_2 \rightarrow$	$2H_3C_6H_5O_7$	$+ 3H_2O$
Sucrose	**Oxygen**	**Citric Acid**	**Water**

but in practice there are deviations from this stoichiometric relationship.

Description—Colorless, translucent crystals, or a white, granular to fine crystalline powder; odorless; strongly acid taste; the hydrous form effloresces in moderately dry air, but is slightly deliquescent in moist air; loses its water of crystallization at about 50°; dilute aqueous solutions are subject to molding (fermentation), oxalic acid being one of the fermentation products.

Solubility—1 g in 0.5 mL of water, 2 mL of alcohol or about 30 mL of ether; freely soluble in methanol.

Uses—In the preparation of *Anticoagulant Citrate Dextrose Solution*, *Anticoagulant Citrate Phosphate Dextrose Solution*, *Citric Acid Syrup* and *effervescent salts*. It also has been used to dissolve urinary bladder calculi, and as a mild astringent.

Cocoa Butter

Cacao Butter; Theobroma Oil; Oil of Theobroma

The fat obtained from the roasted seed of *Theobroma cacao* Linné (Fam *Sterculiaceae*).

Preparation—By grinding the kernels of the "chocolate bean" and expressing the oil in powerful, horizontal hydraulic presses. The yield is about 40%. It also has been prepared by dissolving the oil from the unroasted beans by the use of a volatile solvent.

Constituents—Chemically, it is a mixture of stearin, palmitin, olein, laurin, linolein and traces of other glycerides.

Description—Yellowish, white solid; faint, agreeable odor; bland (if obtained by extraction) or chocolate-like (if obtained by pressing) taste; usually brittle below 25°; specific gravity 0.858 to 0.864 at 100°/25°; refractive index 1.454 to 1.458 at 40°.

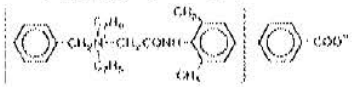
Solubility—Slightly soluble in alcohol; soluble in boiling dehydrated alcohol; freely soluble in ether or chloroform.

Uses—Valuable in pharmacy for making suppositories by virtue of its low fusing point and its property of becoming solid at a temperature just below the melting point. See *Suppositories* (page 1569). In addition to this use, it is an excellent emollient application to the skin when inflamed; it also is used in various skin creams, especially the so-called "*skin foods*." It also is used in massage.

Titanium Dioxide—page 772.

Denatonium Benzoate

Benzenemethanaminium *N*-[2-[(2,6-dimethylphenyl)amino]-2-oxoethyl]-*N,N*-diethyl-, benzoate;



Benzyldiethyl[(2,6-xylylcarbamoyl)methyl]ammonium benzoate [3734-33-6] $C_{28}H_{34}N_2O_3$ (446.59).

Preparation—2-(Diethylamino)-2',6'-xylidide is quaternized by reaction with benzyl chloride. The quaternary chloride is then treated with methanolic potassium hydroxide to form the quaternary base which, after filtering off the KCl, is reacted with benzoic acid. The starting xylidide may be prepared by condensing 2,6-xylidine with chloroacetyl chloride and condensing the resulting chloroacetoxylidide with diethylamine. US Pat 3,080,327.

Description—White, odorless, crystalline powder; an intensely bitter taste; melts about 168°.

Solubility—1 g in 20 mL of water, 2.4 mL of alcohol, 2.9 mL of chloroform or 5000 mL of ether.

Uses—A *denaturant* for ethyl alcohol.

Dextrin

British Gum; Starch Gum; Leiocom

Dextrin [9004-53-9] $(C_6H_{10}O_5)_n$.

Preparation—By the incomplete hydrolysis of starch with dilute acid, or by heating dry starch.

Description—White or yellow, amorphous powder (*white*: practically odorless; *yellow*: characteristic odor); dextrorotatory; $[\alpha]_D^{20}$ generally above 200°; does not reduce Fehling's solution; gives a reddish color with iodine.

Solubility—Soluble in 3 parts of boiling water, forming a gummy solution; less soluble in cold water.

Uses—An *excipient* and *emulsifier*.

Dextrose

Anhydrous Dextrose; Dextrose Monohydrate; Glucose; D(+)-Glucose; α-D(+)-Glucopyranose; Medicinal Glucose; Purified Glucose; Grape Sugar; Bread Sugar; Cerelose; Starch Sugar; Corn Sugar

D-Glucose monohydrate [5996-10-1] $C_6H_{12}O_6.H_2O$ (198.17); *anhydrous* [50-99-7] (180.16). A sugar usually obtained by the hydrolysis of starch. For the structure, see page 382.

Preparation—See *Liquid Glucose* (page 1321).

Description—Colorless crystals or a white, crystalline or granular powder; odorless; sweet taste; specific rotation (anhydrous) +52.5 to +53°; anhydrous dextrose melts at 146°; dextrose slowly reduces alkaline cupric tartrate TS in the cold and rapidly on heating, producing a red precipitate of cuprous oxide (difference from *sucrose*).

Solubility—1 g in 1 mL of water or 100 mL of alcohol; more soluble in boiling water or boiling alcohol.

Uses—See *Dextrose Injection* (page 800). It also is used, instead of lactose, as a supplement to milk for infant feeding.

Dichlorodifluoromethane

Methane, dichlorodifluoro-,

CCl_2F_2

Dichlorodifluoromethane [75-71-8] CCl_2F_2 (120.91).

Preparation—Carbon tetrachloride is reacted with antimony trifluoride in the presence of antimony pentafluoride.

Description—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° about 4383 torr.

Uses—A *propellant* (No 12, see page 1696).

Dichlorotetrafluoroethane

Ethane, 1,2-dichloro-1,1,2,2-tetrafluoro-,

$CClF_2CClF_2$

1,2-Dichlorotetrafluoroethane [76-14-2] $C_2Cl_2F_4$ (170.92).

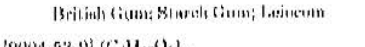
Preparation—By reacting 1,1,2-trichloro-1,2,2-trifluoroethane with antimony trifluorodichloride $[SbF_3Cl_2]$, whereupon one of the 1-chlorine atoms is replaced by fluorine. The starting trichlorofluoroethane may be prepared from hexachloroethane by treatment with SbF_3Cl_2 (Henne Al.: *Org Reactions II*: 65, 1944).

Description—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° about 1620 torr; usually contains 6 to 10% of its isomer, $CFCl_2$–CF_3.

Uses—A *propellant* (No 114 and 114a, see page 1696).

Edetic Acid

Glycine, *N,N'*-1,2-ethanediylbis[*N*-(carboxymethyl)]-,



(Ethylenedinitrilo)tetraacetic acid [60-00-4] $C_{10}H_{16}N_2O_8$ (292.24).

Preparation—Ethylenediamine is condensed with sodium monochloroacetate with the aid of sodium carbonate. An aqueous solution of the reactants is heated to about 90° for 10 hr, then cooled and acidified with HCl whereupon the acid precipitates. US Pat 2,130,505.

Description—White, crystalline powder; melts with decomposition above 220°.

Solubility—Very slightly soluble in water; soluble in solutions of alkali hydroxides.

Uses—A *pharmaceutic aid* (metal complexing agent). The acid, rather than any salt, is the form most potent in removing calcium from solution. It may be added to shed blood to prevent clotting. It also is used in pharmaceutical analysis and the removal or inactivation of unwanted ions in solution. Salts of the acid are known as edetates. See *Edetate Calcium Disodium* (page 824) and *Edetate Disodium* (page 825).

Ethylcellulose

Cellulose ethyl ether [9004-57-3]; an ethyl ether of cellulose containing 44 to 51% of ethoxy groups. The *medium-type* viscosity grade contains less than 46.5% ethoxy groups; the *standard-type* viscosity grade contains 46.5% or more ethoxy groups.

Preparation—By the same general procedure described on page 1306 for *Methylcellulose* except that ethyl chloride or ethyl sulfate is employed as the alkylating agent. The 45 to 50% of ethoxy groups in the official ethylcellulose corresponds to from 2.25 to 2.61 ethoxy groups/$C_6H_{10}O_5$ unit, thus representing from 75 to 87% of the maximum (theoretical) ethoxylation, which is 3 ethoxy groups/$C_6H_{10}O_5$ unit.

Description—Free-flowing, white to light tan powder; forms films that have a refractive index of about 1.47; aqueous suspensions are neutral to litmus.

Solubility—The medium-type is freely soluble in tetrahydrofuran, methyl acetate, chloroform or mixtures of aromatic hydrocarbons with alcohol; the standard-type is freely soluble in alcohol, methanol, toluene, chloroform or ethyl acetate; both types are insoluble in water, glycerin or propylene glycol.

Uses—A *pharmaceutic aid* as a tablet binder and for film-coating tablets and drug particles.

Gelatin—page 1306.

Liquid Glucose

Glucose; Starch Syrup; Corn Syrup

A product obtained by the incomplete hydrolysis of starch. It consists chiefly of dextrose [D(+)-glucose, $C_6H_{12}O_6$ = 180.16] dextrins, maltose and water.

Preparation—Commercially by the action of very weak H_2SO_4 or HCl on starch.

One of the processes for its manufacture is as follows: The starch, usually from corn, is mixed with 5 times its weight of water containing less than 1% of HCl, the mixture is heated to about 45° and then transferred to a suitable reaction vessel into which steam is passed

under pressure until the temperature reaches 120°. The temperature is maintained at this point for about 1 hr, or until tests show complete disappearance of starch. The mass is then heated to volatilize most of the hydrochloric acid, sodium carbonate or calcium carbonate is added to neutralize the remaining traces of acid, the liquid is filtered, then decolorized in charcoal or bone-black filters, as is done in sugar refining and finally concentrated in vacuum to the desired consistency.

When made by the above process, it contains about 30 to 40% of dextrose mixed with about an equal proportion of dextrin, together with small amounts of other carbohydrates, notably maltose. By varying the conditions of hydrolysis, the relative proportions of the sugars also vary.

If the crystallizable dextrose is desired, the conversion temperature is higher and the time of conversion longer. The term "glucose," as customarily used in the chemical or pharmaceutical literature, usually refers to dextrose, the crystallizable product.

The name "grape sugar" sometimes is applied to the solid commercial form of dextrose because the principal sugar of the grape is dextrose, although the fruit has never been used as a source of the commercial supply.

Description—Colorless or yellowish, thick, syrupy liquid; odorless, or nearly so; sweet taste; differs from sucrose in that it readily reduces hot alkaline cupric tartrate TS, producing a red precipitate of cuprous oxide.
Solubility—Miscible with water; sparingly soluble in alcohol.

Uses—As an ingredient of *Cocoa Syrup* (page 1301), as a tablet binder and coating agent, and as a diluent in pilular extracts; it has replaced glycerin in many pharmaceutical preparations. It is sometimes given *per rectum* as a *food* in cases where feeding by stomach is impossible. It should not be used in the place of dextrose for intravenous injection.

Hydrochloric Acid

Chlorhydric Acid; Muriatic Acid; Spirit of Salt

Hydrochloric acid [7647-01-0] HCl (36.46); contains 36.5 to 38.0%, by weight, of HCl.

Preparation—By the interaction of NaCl and H_2SO_4 or by combining chlorine with hydrogen. It is obtained as a by-product in the manufacture of sodium carbonate from NaCl by the Leblanc process in which common salt is decomposed with H_2SO_4. HCl is also a by-product in the electrolytic production of NaOH from NaCl.

Description—Colorless, fuming liquid; pungent odor; fumes and odor disappear when it is diluted with 2 volumes of water; strongly acid to litmus even when highly diluted; specific gravity about 1.18.
Solubility—Miscible with water or alcohol.

Uses—Officially classified as a pharmaceutic aid that is used as an acidifying agent. It is used in preparing *Diluted Hydrochloric Acid* (page 783).

Hypophosphorous Acid

Phosphinic acid

Hypophosphorous acid [6303-21-5] HPH_2O_2 (66.00); contains 30 to 32% by weight, of H_3PO_2.

Preparation—By reacting barium or calcium hypophosphite with sulfuric acid or by treating sodium hypophosphite with an ion-exchange resin.

Description—Colorless or slightly yellow, odorless liquid; solution is acid to litmus even when highly diluted; specific gravity about 1.13.
Solubility—Miscible with water or alcohol.
Incompatibilities—Oxidized on exposure to *air* and by nearly all *oxidizing agents*. *Mercury, silver* and *bismuth salts* are reduced partially to the metallic state as evidenced by a darkening in color. *Ferric compounds* are changed to ferrous.

Uses—An *antioxidant* in pharmaceutical preparations.

Isopropyl Myristate

Tetradecanoic acid, 1-methylethyl ester

$CH_3(CH_2)_{12}COOCH(CH_3)_2$

Isopropyl myristate [110-27-0] $C_{17}H_{34}O_2$ (270.45).

Preparation—By reacting myristoyl chloride with 2-propanol with the aid of a suitable dehydrochlorinating agent.

Description—Liquid of low viscosity; practically colorless and odorless; congeals about 5° and decomposes at 208°; withstands oxidation and does not become rancid readily.
Solubility—Soluble in alcohol, acetone, chloroform, ethyl acetate, toluene, mineral oil, castor oil or cottonseed oil; practically insoluble in water, glycerin or propylene glycol; dissolves many waxes, cholesterol or lanolin.

Uses—*Pharmaceutic aid* used in cosmetics and topical medicinal preparations as an emollient, lubricant and to enhance absorption through the skin.

Kaolin—see page 796.

Lactic Acid

Propanoic acid, 2-hydroxy-, 2-Hydroxypropionic Acid; Propanoloic Acid; Milk Acid

$CH_3CH(OH)COOH$

Lactic acid [50-21-5] $C_3H_6O_3$ (90.08); a mixture of lactic acid and lactic acid lactate ($C_6H_{10}O_5$) equivalent to a total of 85 to 90%, by weight, of $C_3H_6O_3$.

Discovered by Scheele in 1780, it is the acid formed in the souring of milk, hence the name *lactic*, from the Latin name for milk. It results from the decomposition of the lactose (milk sugar) in milk.

Preparation—A solution of glucose or of starch previously hydrolyzed with diluted sulfuric acid is inoculated, after the addition of suitable nitrogen compounds and mineral salts, with *Bacillus lactis*. Calcium carbonate is added to neutralize the lactic acid as soon as it is formed, otherwise the fermentation stops when the amount of acid exceeds 0.5%. When fermentation is complete, as indicated by failure of the liquid to give a test for glucose, the solution is filtered, concentrated and allowed to stand. The calcium lactate that crystallizes is decomposed with dilute sulfuric acid and filtered with charcoal. The lactic acid in the filtrate is extracted with ethyl or isopropyl ether, the ether is distilled off and the aqueous solution of the acid concentrated under reduced pressure.

Description—Colorless or yellowish, nearly odorless, syrupy liquid; acid to litmus; absorbs water on exposure to moist air; when a dilute solution is concentrated to above 60%, lactic acid lactate begins to form; in the official acid the latter amounts to about 12 to 15%; specific gravity about 1.20; decomposes when distilled under normal pressure but may be distilled without decomposition under reduced pressure.
Solubility—Miscible with water, alcohol or ether; insoluble in chloroform.

Uses—In the preparation of *Sodium Lactate Injection* (page 821). It also is used in babies' milk formulas, as an acidulant in food preparations, and in 1 to 2% concentration in some spermatocidal jellies. A 10% solution is used as a bactericidal agent on the skin of neonates. It is corrosive to tissues on prolonged contact. A 16.7% solution in flexible collodion is used to remove warts and small cutaneous tumors.

Lactose

D-Glucose, 4-*O*-β-D-galactopyranosyl-, Milk Sugar

Lactose [63-42-3] $C_{12}H_{22}O_{11}$ (342.30); *monohydrate* [10039-26-6] (360.31); a sugar obtained from milk.

For the structural formula, see page 382.

Preparation—From skim milk, to which is added diluted HCl to precipitate the casein. After removal of the casein by filtration, the reaction of the whey is adjusted to a pH of about 6.2 by addition of lime and the remaining albuminous matter is coagulated by heating; this is filtered out and the liquid set aside to crystallize. Animal charcoal is used to decolorize the solution in a manner similar to that used in purifying sucrose.

Another form of lactose, known as β-lactose, also is available on the market. It differs in that the D-glucose moiety is β instead of α. It is reported that this variety is sweeter and more soluble than ordinary lactose and for that reason is preferable in pharmaceutical manufacturing where lactose is used. Chemically, β-lactose does not appear to differ from ordinary α-lactose. It is manufactured in the same way as α-lactose up to the point of crystallization, then the

solution is heated to a temperature above 93.5°, this being the temperature at which the α form is converted to the β variety. The β form occurs only as an anhydrous sugar whereas the α variety may be obtained either in the anhydrous form or as a monohydrate.

Description—White or creamy white, hard, crystalline masses or powder; odorless; faintly sweet taste; stable in air, but readily absorbs odors; pH (1 in 10 solution) 4.0 to 6.5; specific rotation +54.8 to +55.5°.

Solubility—1 g in 5 ml of water or 2.6 ml of boiling water; very slightly soluble in alcohol; insoluble in chloroform or ether.

Uses—A *diluent* largely used in medicine and pharmacy. It is generally an ingredient of the medium used in penicillin production. It is used extensively as an addition to milk for infant feeding.

Magnesium Chloride

Magnesium chloride hexahydrate [7791-18-6] $MgCl_2.6H_2O$ (203.30); *anhydrous* [7786-30-3] (95.21).

Preparation—By treating magnesite or other suitable magnesium minerals with HCl.

Description—Colorless, odorless, deliquescent flakes or crystals, which lose water when heated to 100° and loose HCl when heated to 110°; pH (1 in 20 solution in carbon dioxide free water) 4.5 to 7.

Solubility—Very soluble in water; freely soluble in alcohol.

Uses—*Electrolyte replenisher; pharmaceutical necessity* for hemodialysis and peritoneal dialysis fluids.

Magnesium Stearate

Octadecanoic acid, magnesium salt

Magnesium stearate [557-04-0]. A compound of magnesium with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. It contains the equivalent of 6.3 to 8.0% of MgO (40.30).

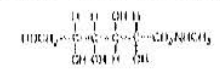
Description—Fine, white, bulky powder; faint, characteristic odor; unctuous, adheres readily to the skin and free from grittiness.

Solubility—Insoluble in water, alcohol or ether.

Uses—A *pharmaceutical necessity (lubricant)* in the manufacture of compressed tablets.

Meglumine

D-Glucitol, 1-deoxy-1-(methylamino)-,



1-Deoxy-1-(methylamino) D-glucitol [6284-40-8] $C_7H_{17}NO_5$ (195.21).

Preparation—By treating glucose with hydrogen and methylamine under pressure and in the presence of Raney nickel.

Description—White to faintly yellowish white, odorless crystals or powder; melts about 130°.

Solubility—Freely soluble in water; sparingly soluble in alcohol.

Uses—In forming salts of certain pharmaceuticals, surface-active agents and dyes. See *Diatrizoate Meglumine Injections* (page 1276), *Iodipamide Meglumine Injection* (page 1276) and *Iothalamate Meglumine Injection* (page 1277).

Light Mineral Oil

Light Liquid Petrolatum NF XII; Light Liquid Paraffin; Light White Mineral Oil

A mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabilizer.

Description—Colorless, transparent, oily liquid, free, or nearly free, from fluorescence; odorless and tasteless when cold, and develops not more than a faint odor of petroleum when heated; specific gravity 0.818 to 0.880; kinematic viscosity not more than 33.5 centistokes at 40°.

Solubility—Insoluble in water or alcohol; miscible with most fixed oils, but not with castor oil; soluble in volatile oils.

Uses—Officially recognized as a *vehicle*. Once it was used widely as a vehicle for nose and throat medications; such uses are now considered dangerous because of the possibility of lipoid pneumonia. It sometimes is used to cleanse dry and inflamed skin areas and to facilitate removal of dermatological preparations from the skin. It should never be used for internal administration because of "leakage." See *Mineral Oil* (page 789).

Nitric Acid

Nitric acid [7697-37-2] HNO_3 (63.01); contains about 70%, by weight, of HNO_3.

Preparation—May be prepared by treatment of sodium nitrate (Chile saltpeter) with sulfuric acid, but usually produced by catalytic oxidation of ammonia.

Description—Highly corrosive fuming liquid; characteristic, highly irritating odor; stains animal tissues yellow; boils about 120°; specific gravity about 1.41.

Solubility—Miscible with water.

Uses—*Pharmaceutic aid* (acidifying agent).

Nitrogen

Nitrogen [7727-37-9] N_2 (28.01); contains not less than 99%, by volume, of N_2.

Preparation—By the fractional distillation of liquified air.

Uses—A diluent for medicinal gases. Pharmaceutically, is employed to replace air in the containers of substances which would be affected adversely by air oxidation. Examples include its use with fixed oils, certain vitamin preparations and a variety of injectable products. It also is used as a propellant.

Persic Oil

Apricot Kernel Oil; Peach Kernel Oil

The oil expressed from the kernels of varieties of *Prunus armeniaca* Linné (Apricot Kernel Oil), or from the kernels of varieties of *Prunus persica* Sieb et Zucc (Peach Kernel Oil) (Fam *Rosaceae*).

Description—Clear, pale straw-colored or colorless, almost odorless, oily liquid with a bland taste; specific gravity 0.910 to 0.923; not turbid at temperatures above 15°.

Solubility—Slightly soluble in alcohol; miscible with ether, chloroform, benzene or solvent hexane.

Uses—A *vehicle*. It also is used in preparing cold creams.

Phenol

Carbolic Acid

C_6H_5OH

Phenol [108-95-2] C_6H_6O (94.11).

Preparation—For many years made only by distilling crude carbolic acid from coal tar and separating and purifying the distillate by repeated crystallizations, it now is prepared synthetically.

A more recent process uses chlorobenzene as the starting point in the manufacture. The chlorobenzene is produced in a vapor phase reaction, with benzene, HCl and oxygen over a copper catalyst, followed by hydrolysis with steam to yield HCl and phenol (which is recovered).

Description—Colorless to light pink, interlaced, or separate, needle-shaped crystals, or a white or light pink, crystalline mass; characteristic odor; when undiluted, it whitens and cauterizes the skin and mucous membranes; when gently heated, phenol melts, forming a highly refractive liquid; liquefied by the addition of 10% of water; vapor is flammable; gradually darkens on exposure to light and air; specific gravity 1.07; boils at 182°; congeals not lower than 39°.

Solubility—1 g in 15 ml of water; very soluble in alcohol, glycerin, chloroform, ether or fixed and volatile oils; sparingly soluble in mineral oil.

Incompatibilities—Produces a liquid or soft mass when triturated with *camphor, menthol, acetanilid, acetophenetidin, aminopyrine, antipyrine, ethyl aminobenzoate, methenamine, phenyl salicylate, resorcinol, terpin hydrate, thymol* and several other substances including some *alkaloids*. It also softens *cocoa butter* in suppository mixtures.

It is soluble in about 15 parts of water; stronger solutions may be

obtained by using as much glycerin as phenol. Only the crystallized form is soluble in fixed oils and liquid petroleum, the liquefied form is not all soluble due to its content of water. *Albumin* and *gelatin* are precipitated by it. *Collodion* is coagulated by the precipitation of pyroxylin. Traces of *iron* in various chemicals such as *alum, borax*, etc, may produce a green color.

Uses—A *caustic, disinfectant, topical anesthetic* and pharmaceutical necessity as a *preservative* for injections, etc. At one time widely used as a germicide and still the standard against which other antiseptics are compared, it has few legitimate uses in modern medicine. Nevertheless, it is still used in several proprietary antiseptic mouthwashes, hemorrhoidal preparations and burn remedies. In full strength, a few drops of the liquefied form may be used to cauterize small wounds, dogs bites, snake bites, etc. It commonly is employed as an *antipruritic*, either in the form of phenolated calamine lotion (1%), phenol ointment (2%) or a simple aqueous solution (0.5 to 1%). It has been used for sclerosing hemorrhoids, but more effective and safer drugs are available. A 5% solution in glycerin is used in simple earache. Crude carbolic acid is an effective, economical agent for disinfecting excrement. It is of some therapeutic value as a *fungicide*, but more effective and less toxic agents are available. If accidentally spilled, it should be removed promptly from the skin by swabbing with alcohol.

Liquefied Phenol [Liquefied Carbolic Acid is phenol maintained in a liquid condition by the presence of 10.0% of water. It contains not less than 89.0%, by weight, of C_6H_6O. *Note—When it is to be mixed with a fixed oil, mineral oil or white petrolatum, use the crystalline Phenol, not Liquefied Phenol. Preparation:* Melt phenol (a convenient quantity) by placing the unstoppered container in a steam bath and applying heat gradually. Transfer the liquid to a tared vessel, weigh, add 1 g of purified water for each 9 g of phenol, and mix thoroughly. *Description:* Colorless liquid, which may develop a red tint upon exposure to air and light; characteristic, somewhat aromatic odor; when undiluted it cauterizes and whitens the skin and mucous membranes; specific gravity about 1.085; when it is subjected to distillation, the boiling temperature does not rise above 182°, which is the boiling temperature of phenol; partially solidifies at about 15°. *Solubility:* Miscible with alcohol, ether or glycerin; a mixture of liquefied phenol and an equal volume of glycerin is miscible with water. *Uses:* A formulation which facilitates the dispensing of concentrated phenol. Its therapeutic uses are described above under *Phenol*. It is a *pharmaceutical necessity for Phenolated Calamine Lotion* (page 762).

Phenyl Salicylate—RPS-15, page 1269.

Phosphoric Acid

Orthophosphoric Acid; Syrupy Phosphoric Acid; Concentrated Phosphoric Acid

Phosphoric acid [7664-38-2] H_3PO_4 (98.00); contains 85 to 88%, by weight, of H_3PO_4.

Preparation—Phosphorus is converted to phosphorus pentoxide [P_2O_5] by exposing it to a current of warm air, then the P_2O_5 is treated with water to form phosphoric acid. The conversion of the phosphorus to the pentoxide takes place while the phosphorus, distilling from the phosphorus manufacturing operation, is in the vapor state.

Description—Colorless, odorless liquid of a syrupy consistency; specific gravity about 1.71.

Solubility—Miscible with water or alcohol, with the evolution of heat.

Uses—To make the diluted acid and as a weak acid in various pharmaceutical preparations. Industrially, it is used in dental cements and in beverages as an acidulant.

Diluted Phosphoric Acid [Dilute Phosphoric Acid] contains, in each 100 mL, 9.5 to 10.5 g of H_3PO_4 (98.00). *Preparation:* Mix phosphoric acid (69 mL) and purified water (qs) to make 1000 mL. *Description:* Clear, colorless, odorless liquid; specific gravity about 1.057. Miscible with water or alcohol. *Uses: A pharmaceutical necessity.* It also has been employed in *lead poisoning* and in other conditions in which it is desired to administer large amounts of phosphate and at the same time produce a mild acidosis. It has been given in the dose of 60 mL a day (5 mL/hour) under carefully controlled conditions.

Potassium Metaphosphate

Metaphosphoric acid (HPO_3), potassium salt

Potassium metaphosphate [7790-53-6] KPO_3 (118.07); a straight-chain polyphosphate, having a high degree of polymerization; contains the equivalent of 59 to 61% of P_2O_5.

Preparation—By thermal dehydration of monopotassium phosphate (KH_2PO_4).

Description—White, odorless powder.

Solubility—Insoluble in water; soluble in dilute solutions of sodium salts.

Uses—*Pharmaceutic aid* (buffering agent).

Monobasic Potassium Phosphate

Phosphoric acid, monopotassium salt; Potassium Biphosphate; Potassium Acid Phosphate; Potassium Dihydrogen Phosphate; Sörensen's Potassium Phosphate

Monopotassium phosphate [7778-77-0] KH_2PO_4 (136.09).

Preparation—H_3PO_4 is reacted with an equimolar quantity of KOH and the solution is evaporated to crystallization.

Description—Colorless crystals or a white, granular or crystalline powder; odorless and stable in air; pH (1 in 100 solution) about 4.5.

Solubility—Freely soluble in water; practically insoluble in alcohol.

Uses—A component of various buffer solutions. Medicinally, it has been used as a urinary acidifier.

Pumice

Pumex

A substance of volcanic origin, consisting chiefly of complex silicates of aluminum, potassium and sodium.

Description—Very light, hard rough, porous, grayish masses or a gritty, grayish powder of several grades of fineness; odorless, tasteless and stable in the air.

Three powders are available:

Pumice Flour or *Superfine Pumice*—Not less than 97% passes through a No 200 standard mesh sieve.

Fine Pumice—Not less than 95% passes through a No 150 standard mesh sieve, and not more than 75% passes through a No 200 standard mesh sieve.

Coarse Pumice—Not less than 95% passes through a No 60 standard mesh sieve, and not more than 5% passes through a No 200 standard mesh sieve.

Solubility—Insoluble in water and is not attacked by acids or alkali hydroxide solutions.

Uses—A *filtering* and *distributing medium* for pharmaceutical preparations. Because of its grittiness the powdered form is used in certain types of soaps and cleaning powders and also as a *dental abrasive*.

Pyroxylin

Cellulose, nitrate; Soluble Guncotton

Pyroxylin [9004-70-0]; a product obtained by the action of a mixture of nitric and sulfuric acids on cotton, and consists chiefly of cellulose tetranitrate $[(C_{12}H_{16}N_4O_{18})_n]$.

Note—The commercially available form is moistened with about 30% of alcohol or other suitable solvent. The alcohol or solvent must be allowed to evaporate to yield the dried substance described in the Pharmacopeia.

Preparation—Schönbein, in 1846, found that nitric acid acts on cotton and produces a soluble compound. It subsequently was proved that this substance belongs to a series of closely related nitrates in which the nitric acid radical replaces the hydroxyl of the cellulose formula. This usually is indicated by taking the double empirical formula for cellulose $C_{12}H_{20}O_{10}$ and indicating replacement of four of the OH groups thus

$$\underset{\text{Cellulose}}{C_{12}H_{20}O_{10}} + 4HNO_3 \rightarrow \underset{\substack{\text{Cellulose}\\ \text{Tetranitrate}}}{C_{12}H_{16}O_6(NO_3)_4} + 4H_2O$$

The compound used in preparing collodion is a varying mixture of the di-, tri-, tetra- and pentanitrates, but is mainly tetranitrate. The hexanitrate is the true explosive guncotton, and is insoluble in ether, alcohol, acetone or water.

Description—Light yellow, matted mass of filaments, resembling raw cotton in appearance, but harsh to the touch; *exceedingly flammable* burning, when unconfined, very rapidly and with a luminous flame; when kept in well-closed bottles and exposed to light, it is decomposed with the evolution of nitrous vapors, leaving a carbonaceous residue.

Solubility—Insoluble in water; dissolves slowly but completely in 25 parts of a mixture of 3 volumes of ether and 1 volume of alcohol; soluble in acetone or glacial acetic acid and precipitated from those solutions by water.

Uses—A *pharmaceutical necessity* for *Collodion* (RPS-16, page 717).

Rosin

Resina; Colophony; Georgia Pine Rosin; Yellow Pine Rosin

A solid resin obtained from *Pinus palustris* Miller, and from other species of *Pinus* Linné (Fam *Pinaceae*).

Constituents—American rosin contains *sylvic acid* [$C_{20}H_{30}O_2$], *α-, β-* and *γ-abietic acids* [$C_{20}H_{30}O_2$], *γ-pinic acid* (from which *α-* and *β*-pinic acids are gradually formed) and *resene*. Some authorities also include *pimaric acid* [$C_{20}H_{30}O_2$] as a constituent. French rosin is called *galipot*.

Description—Sharply angular, translucent, amber-colored fragments, frequently covered with a yellow dust; fracture brittle at ordinary temperatures, shiny and shallow-conchoidal; odor and taste are slightly terebinthinate; easily fusible and burns with a dense, yellowish smoke; specific gravity 1.07 to 1.09.

Solubility—Insoluble in water; soluble in alcohol, ether, benzene, glacial acetic acid, chloroform, carbon disulfide, dilute solutions of sodium hydroxide and potassium hydroxide or some volatile and fixed oils.

Uses—A pharmaceutical necessity for *Zinc-Eugenol Cement* (page 1328). Formerly, and to some extent still, used as a component of plasters, cerates and ointments, to which it adds adhesive qualities.

Purified Siliceous Earth

Purified Kieselguhr; Purified Infusorial Earth; Diatomaceous Earth; Diatomite

A form of silica [SiO_2] [7631-86-9] consisting of the frustules and fragments of diatoms, purified by boiling with acid, washing and calcining.

Occurrence and Preparation—Large deposits of this substance are found in Virginia, Maryland, Nevada, Oregon and California, usually in the form of masses of rocks, hundreds of feet in thickness. Under the microscope it is seen to consist largely of the minute siliceous frustules of diatoms. It must be purified carefully in a manner similar to that directed for *Talc* (page 1327), and thoroughly calcined. The latter treatment destroys the bacteria which are present in large quantities in the native earth.

Description—Very fine, white, light-gray or pale-buff mixture of amorphous powder and lesser amounts of crystalline polymorphs, including quartz and cristobalite; gritty, readily absorbs moisture and retains about four times its weight of water without becoming fluid.

Solubility—Insoluble in water, acids or dilute solutions of alkali hydroxides.

Uses—Introduced into the USP as a distributing and *filtering medium* for aromatic waters; also suitable for filtration of elixirs. Like talc, it does not absorb active constituents.

Colloidal Silicon Dioxide

Silica [7631-86-9] SiO_2 (60.08); a submicroscopic fumed silica prepared by the vapor-phase hydrolysis of a silicon compound.

Description—Light, white, nongritty powder of extremely fine particle size (about 15 nm).

Solubility—Insoluble in water or acids (except hydrofluoric); dissolved by hot solutions of alkali hydroxides.

Uses—A *tablet diluent* and as a *suspending* and *thickening agent* in pharmaceutical preparations.

Soda Lime

A mixture of calcium hydroxide and sodium or potassium hydroxide or both.

It may contain an indicator that is inert toward anesthetic gases such as ether, cyclopropane and nitrous oxide, and that changes color when the soda lime no longer can absorb carbon dioxide.

Description—White or grayish white granules; if an indicator is added, it may have a color; absorbs carbon dioxide and water on exposure to air.

Uses—Neither a therapeutic nor a pharmaceutical agent. It is a *reagent for the absorption of carbon dioxide* in anesthesia machines, oxygen therapy and metabolic tests. Because of the importance of the proper quality for these purposes it has been made official and standardized.

Sodium Borate

Sodium Tetraborate; Sodium Pyroborate; Sodium Biborate

Borax [1303-96-4] $Na_2B_4O_7.10H_2O$ (381.37); anhydrous [1330-43-4] $Na_2B_4O_7$ (201.22).

Preparation—Found in immense quantities in California as a crystalline deposit. The earth, which is strongly impregnated with borax, is lixiviated; the solution is evaporated and crystallized.

Calcium borate, or *cotton balls*, also occurs in the borax deposits of California, and sodium borate is obtained from it by double decomposition with sodium carbonate.

Description—Colorless, transparent crystals, or a white, crystalline powder; odorless; the crystals often are coated with white powder due to efflorescence; solution alkaline to litmus and phenolphthalein; pH about 9.5.

Solubility—1 g in 16 mL of water, 1 mL of glycerin or 1 mL of boiling water; insoluble in alcohol.

Incompatibilities—Precipitates many *metals* as insoluble borates. In aqueous solution it is alkaline and precipitates *aluminum salts* as aluminum hydroxide, *iron salts* as a basic borate and ferric hydroxide and *zinc sulfate* as zinc borate and a basic salt. *Alkaloids* are precipitated from solutions of their salts. Approximately equal weights of *glycerin* and boric acid react to produce a decidedly acid derivative generally called glyceroboric acid. Thus, the addition of glycerin to a mixture containing it overcomes incompatibilities arising from an alkaline reaction.

Uses—As a pharmaceutical necessity, it is used as an alkalizing agent and as a buffer for alkaline solutions. Its alkalizing properties provide the basis for its use in denture adhesives and its buffering action for its use in eyewash formulations.

Sodium Carbonate

Carbonic acid, disodium salt, monohydrate; Monohydrated Sodium Carbonate USP XVII

Disodium carbonate monohydrate [5968-11-6] $Na_2CO_3.H_2O$ (124.00); *anhydrous* [497-19-8] (105.99).

Preparation—The initial process for its manufacture was devised by Leblanc, a French apothecary, in 1784, and consists of two steps: first, the conversion of common salt [NaCl] into sodium sulfate by heating it with sulfuric acid and, second, the decomposition of the sulfate by calcium carbonate (limestone) and charcoal (coal) at a high temperature to yield this salt and calcium sulfide. The carbonate then is leached out with water.

It currently is prepared by the electrolysis of sodium chloride, whereby sodium and chlorine are produced, the former reacting with water to produce sodium hydroxide and this solution treated with carbon dioxide to produce the salt. The process is used most extensively in localities where electric power is very cheap.

The monohydrated form is made by crystallizing a concentrated solution of this salt at a temperature above 35° (95°F), and stirring the liquid so as to produce small crystals. It contains about 15% of water of crystallization.

Soda ash is a term designating a commercial quality of the anhydrous salt. Its annual production is very large, and it has a wide variety of applications, among which are the manufacture of glass, soap and sodium salts; it also is used for washing fabrics.

Washing soda, or *sal soda*, is the salt with 10 molecules of water. It is in the form of colorless crystals which rapidly effloresce in the air.

Description—Colorless crystals or a white, crystalline powder; stable in air under ordinary conditions; when exposed to dry air above 50° it effloresces, and at 100° becomes anhydrous; decomposed by weak acids forming the salt of the acid and liberating carbon dioxide; aqueous solution alkaline to indicators (pH about 11.5).

Solubility—1 g in 3 mL of water or 1.5 mL of boiling water; insoluble in alcohol.

Incompatibilities—*Acids, acid salts* and *acidic preparations* cause its decomposition. Most *metals* are precipitated as carbonates, hydroxides or basic salts. *Alkaloids* are precipitated from solutions of their salts.

Uses—Occasionally, for dermatitides topically as a lotion; it has been used as a mouthwash and a vaginal douche. It is used in the preparation of the sodium salts of many acids. The USP recognizes it as a pharmaceutic aid used as an alkalizing agent.

Sodium Hydroxide

Caustic Soda, Soda Lye

Sodium hydroxide [1310-73-2] NaOH (40.00); includes not more than 3% of Na_2CO_3 (105.99).

Caution—Exercise great care in handling it, as it rapidly destroys tissues.

Preparation—By treating sodium carbonate with milk of lime, or by the electrolysis of a solution of sodium chloride as explained under *Potassium Hydroxide* (page 767). It now is produced largely by the latter process. See also *Sodium Carbonate*, above.

Description—White, or nearly white, fused masses, small pellets, flakes, sticks and other forms; hard and brittle and shows a crystalline fracture; exposed to the air, it rapidly absorbs carbon dioxide and moisture; melts at about 318°; specific gravity 2.13; when dissolved in water or alcohol, or when its solution is treated with an acid, much heat is generated; aqueous solutions, even when highly diluted, are strongly alkaline.

Solubility—1 g in 1 mL of water; freely soluble in alcohol or glycerin.

Incompatibilities—Exposed to air, it absorbs *carbon dioxide* and is converted to sodium carbonate. With *fats* and *fatty acids* it forms soluble soaps; with *resins* it forms insoluble soaps. See *Potassium Hydroxide* (page 767).

Uses—Too alkaline to be of medicinal value but occasionally used in veterinary practice as a caustic. It is used extensively in pharmaceutical processes as an alkalizing agent and is generally preferred to potassium hydroxide because it is less deliquescent, and less expensive; in addition, less of it is required since 40 parts of it are equivalent to 56 parts of KOH. It is a pharmaceutical necessity in the preparation of *Glycerin Suppositories* (page 786).

Sodium Stearate

Octadecanoic acid, sodium salt

Sodium stearate [822-16-2] $C_{18}H_{35}NaO_2$ (306.47) consists chiefly of sodium stearate and sodium palmitate [$C_{16}H_{31}NaO_2$ = 278.41].

Preparation—Stearic acid is reacted with an equimolar portion of NaOH.

Description—Fine, white powder, soapy to the touch; usually has a slight, tallow-like odor; affected by light; solutions are alkaline to phenolphthalein TS.

Solubility—Slowly soluble in cold water and cold alcohol; readily soluble in hot water and hot alcohol.

Uses—Officially, a pharmaceutic aid used as an emulsifying and stiffening agent. It is an ingredient of glycerin suppositories. In dermatological practice it has been used topically in mycosis and other skin diseases.

Starch

Corn Starch; Wheat Starch; Potato Starch

Starch [9005-25-8]; consists of the granules separated from the mature grain of corn [*Zea mays* Linné (Fam *Gramineae*)] or of wheat [*Triticum vestivum* Linné] (Fam *Gramineae*), or from tubers of the potato [*Solanum tuberosum* Linné (Fam *Solanaceae*)].

Preparation—In making starch from corn, the germ is separated mechanically and the cells softened to permit escape of the starch granules. This generally is done by permitting it to become sour and decomposed, stopping the fermentation before the starch is affected. On the small scale, it may be made from wheat flour by making a stiff ball of dough and kneading it while a small stream of water trickles upon it. It is carried off with the water, while the *gluten* remains as a soft, elastic mass; the latter may be purified and used for various purposes to which gluten is applicable. Commercially, its quality largely depends on the purity of the water used in its manufacture. It may be made from potatoes by first grating them, and then washing the soft mass upon a sieve, which separates the cellular substances and permits the starch granules to be carried through. It then must be washed thoroughly by decantation, and the quality of this starch also depends largely on the purity of the water that is used in washing it.

Description—Irregular, angular, white masses or fine powder; odorless; slight, characteristic taste. *Corn starch:* Polygonal, rounded or spheroidal granules up to about 35 μm in diameter which usually have a circular or several-rayed central cleft. *Wheat starch:* Simple lenticular granules 20 to 50 μm in diameter and spherical granules 5 to 10 μm in diameter; striations faintly marked and concentric. *Potato starch:* Simple granules, irregularly ovoid or spherical, 30 to 100 μm in diameter, and subspherical granules 10 to 35 μm in diameter; striations well-marked and concentric.

Solubility—Insoluble in cold water or alcohol; when it is boiled with about 20 times its weight of hot water for a few minutes and then cooled, a translucent, whitish jelly results; aqueous suspension neutral to litmus.

Uses—Has absorbent and demulcent properties. It is used as a dusting powder and in various dermatological preparations; also as a pharmaceutic aid (filler, binder and disintegrant). *Note—Starches obtained from different botanical sources may not have identical properties with respect to their use for specific pharmaceutical purposes, eg, as a tablet-disintegrating agent. Therefore, types should not be interchanged unless performance equivalency has been ascertained.*

Under the title *Pregelatinized Starch* the NF recognizes starch that has been processed chemically or mechanically to rupture all or part of the granules in the presence of water, and subsequently dried. Some types may be modified to render them compressible and flowable.

Storax

Liquid Storax; Styrax; Sweet Gum; Prepared Storax

A balsam obtained from the trunk of *Liquidambar orientalis* Miller, known in commerce as Levant Storax, or of *Liquidambar styraciflua* Linné, known in commerce as American Storax (Fam *Hamamelidaceae*).

Constituents—The following occur in both varieties: *styracin* (*cinnamyl cinnamate*), *styrol* (*phenylethylene*, C_8H_8), *α-* and *β-storesin* (the cinnamic acid ester of an alcohol called *storesinol*), *phenylpropyl cinnamate*, free *cinnamic acid* and *vanillin*. In addition to these, Levant storax contains *ethyl cinnamate*, *benzyl cinnamate*, free *storesinol*, *isocinnamic acid*, *ethylvanillin*, *styrogenin* and *styrocamphene*. This variety yields from 0.5 to 1% of *volatile oil*; from this have been isolated *styrocamphene*, *vanillin*, the cinnamic acid esters of *ethyl*, *phenylpropyl*, *benzyl* and *cinnamyl alcohols*, *naphthalene* and *styrol*.

The American variety contains, in addition to the aforementioned substances common to both varieties, *styrresin* (the cinnamic acid ester of the alcohol *styresinol*, an isomer of storesinol) and *styresinolic acid*. It yields up to 7% of a dextrorotatory volatile oil, the composition of which has not been investigated completely; styrol and traces of vanillin have been isolated from it.

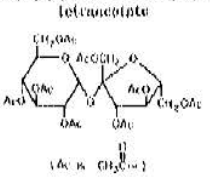
Description—Semiliquid, grayish to grayish brown, sticky, opaque mass, depositing on standing a heavy dark brown layer (Levant storax); or a semisolid, sometimes a solid mass, softened by gently warming (American storax); transparent in thin layers; characteristic odor and taste; more dense than water.

Solubility—Insoluble in water, but soluble, usually incompletely, in an equal weight of warm alcohol; soluble in acetone, carbon disulfide or ether, some insoluble residue usually remaining.

Uses—An *expectorant* but is used chiefly as a local remedy, especially in combination with benzoin; eg, it is an ingredient of *Compound Benzoin Tincture* (page 760). It may be used, like benzoin, to protect fatty substances from rancidity.

Sucrose Octaacetate

α-D-Glucopyranoside, 1,3,4,6-tetra-*O*-acetyl-β-D-fructofuranosyl-, tetraacetate



(Ac is $CH_3C(=O)$–)

Sucrose octanecetate [126-14-7] $C_{72}H_{98}O_{19}$ (678.60).

Preparation—Sucrose is subjected to exhaustive acetylation by reaction with acetic anhydride in the presence of a suitable condensing agent such as pyridine.

Description—White, practically odorless powder; intensely bitter taste; hygroscopic; melts not lower than 78°.

Solubility—1 g in 1100 mL of water, 11 mL of alcohol, 0.3 mL of acetone or 0.6 mL of benzene; very soluble in methanol or chloroform; soluble in ether.

Uses—A *denaturant* for alcohol.

Sulfurated Potash

Thiosulfuric acid, dipotassium salt, mixt. with potassium sulfide ($K_2(S,)$); Liver of Sulfur

Dipotassium thiosulfate mixture with potassium sulfide (K_2S_x) [39365-88-3]; a mixture composed chiefly of potassium polysulfides and potassium thiosulfate. It contains not less than 12.8% of S (sulfur) in combination as sulfide.

Preparation—By thoroughly mixing 1 part of sublimed sulfur with 2 parts of potassium carbonate and gradually heating the mixture in a covered iron crucible until the mass ceases to swell and is melted completely. It then is poured on a stone or glass slab and, when cold, broken into pieces and preserved in tightly closed bottles. When the heat is regulated properly during its production, the reaction is represented approximately by

$$3K_2CO_3 + 8S \rightarrow 2K_2S_3 + K_2S_2O_3 + 3CO_2$$

As this product rapidly deteriorates on exposure to moisture, oxygen and carbon dioxide, it is important that it be prepared recently to produce satisfactory preparations.

Description—Irregular pieces, liver-brown when freshly prepared, changing to a greenish yellow; decomposes upon exposure to air; an odor of hydrogen sulfide and a bitter, acrid, alkaline taste; even weak acids cause the liberation of H_2S from sulfurated potash; 1 in 10 solution light brown in color and alkaline to litmus.

Solubility—1 g in about 2 mL of water, usually leaving a slight residue; alcohol dissolves only the sulfides.

Uses—Extensively in dermatological practice, especially in the official *White Lotion* or *Lotio Alba* (page 762). The equation for the reaction of the potassium trisulfide in preparing the lotion is

$$ZnSO_4 + K_2S_3 \rightarrow ZnS + 2S + K_2SO_4$$

The mixture of insoluble zinc sulfide and sulfur gives the lotion its creamy white appearance.

Talc

Talcum; Purified Talc; French Chalk; Soapstone; Steatite

A native, hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate.

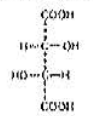
Occurrence and Preparation—The native form, called *soapstone* or *French chalk*, is found in various parts of the world. An excellent quality is obtained from deposits in North Carolina. Deposits of a high grade, conforming to the USP requirements, also are found in Manchuria. The native form usually is accompanied by variable amounts of mineral substances. These are separated from it by mechanical means, such as flotation or elutriation. It then is powdered finely, treated with boiling dilute HCl, washed well and dried.

Description—Very fine, white, or grayish white crystalline powder; unctuous to the touch, adhering readily to the skin, and free from grittiness.

Uses—Officially, as a dusting powder and pharmaceutic aid; in both categories it has many specific uses. Its medicinal use as a dusting powder depends on its desiccant and lubricant effects. When perfumed, and sometimes medicated, it is used extensively for toilet purposes under the name *talcum powder*; for such use it should be in the form of an impalpable powder. When used as a filtration medium for clarifying liquids a coarser powder is preferred to minimize passage through the pores of the filter paper; for this purpose it may be used for all classes of preparations with no danger of adsorption or retention of active principles. It is used as a lubricant in the manufacture of tablets, and as a dusting powder when making handmade suppositories. Although it is used as a lubricant for putting on and removing rubber gloves, it should not be used on surgical gloves because even small amounts deposited in organs or healing wounds may cause granuloma formation.

Tartaric Acid

Butanedioic acid, 2,3-dihydroxy-, Butanedioic acid, 2,3-dihydroxy-, [*R*-(*R**,*R**)]



L-(+)-Tartaric acid [87-69-4] $C_4H_6O_6$ (150.09).

Preparation—From *argol*, the crude cream of tartar (potassium bitartrate) deposited on the sides of wine casks during the fermentation of grapes, by conversion to calcium tartrate which is hydrolyzed to tartaric acid and calcium sulfate.

Description—Large, colorless or translucent crystals, or a white granular to fine crystalline powder; odorless; acid taste; stable in the air; solutions acid to litmus; dextrorotatory.

Solubility—1 g in 0.8 mL of water, 0.5 mL of boiling water, 3 mL of alcohol or 250 mL of ether; freely soluble in methanol.

Uses—Chiefly, as the acid ingredient of preparations in which it is neutralized by a bicarbonate, as in effervescent salts, and the free acid is completely absent or present only in small amounts in the finished product. It also is used as a buffering agent.

Trichloromonofluoromethane

Methane, trichlorofluoro-,

$CFCl_3$

Trichlorofluoromethane [75-69-4] CCl_3F (137.37).

Preparation—Carbon tetrachloride is reacted with antimony trifluoride in the presence of a small quantity of antimony pentachloride. The reaction produces a mixture of CCl_3F and CCl_2F_2 which is readily separable by fractional distillation.

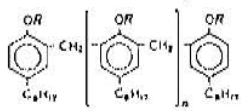
Description—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° is about 796 torr; boils about 24°.

Solubility—Practically insoluble in water; soluble in alcohol, ether or other organic solvents.

Uses—A *propellant* (No 11, see page 1696).

Tyloxapol

Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane; (*Various Mfrs*)



[*R* is $CH_2CH_2O(CH_2CH_2O)_mCH_2CH_2OH$; *m* is 6 to 9; *n* is not more than 5]

p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde [25301-02-4].

Preparation—*p*-(1,1,3,3-Tetramethylbutyl)phenol and formaldehyde are condensed by heating in the presence of an acidic catalyst and the polymeric phenol thus obtained is reacted with ethylene oxide at elevated temperature under pressure in the presence of NaOH. US Pat. 2,454,541.

Description—Amber, viscous liquid; may show a slight turbidity; slight aromatic odor; specific gravity about 1.072; stable at sterilization temperature and in the presence of acids, bases and salts; oxidized by metals; pH (5% aqueous solution) 4 to 7.

Solubility—Slowly but freely soluble in water; soluble in many organic solvents, including acetic acid, benzene, carbon tetrachloride, carbon disulfide, chloroform or toluene.

Uses—A nonionic detergent that depresses both surface tension and interfacial tension. It is a component of Alevaire (*Sterling*) and Enaclene (*Alcon*). It also is used in contact-lens-cleaner formulations.

Zinc-Eugenol Cement

Zinc Compounds and Eugenol Cement NF XI

The Powder

Zinc Acetate	0.5 g
Zinc Stearate	1 g
Zinc Oxide	70 g
Rosin	28.5 g

Powder the rosin and incorporate it with about an equal weight of zinc oxide until thoroughly mixed. Sift the mixture on a sieve of not less than 100-mesh. Regrind the material which does not pass through the sieve with more of the zinc oxide and sift again; repeat the process until all of the material readily passes through the sieve. Thoroughly mix the zinc stearate and zinc acetate with a portion of the zinc oxide and pass through a 100-mesh sieve. Thoroughly mix the two mixtures with the remainder of the zinc oxide.

The Liquid

Eugenol	85 mL
Cottonseed Oil	15 mL

The Cement

To prepare the cement, mix 10 parts of the powder with 1 part of the liquid to a thick paste immediately before use. *Note:* The amount of liquid may be varied to give any desired consistency.

Description—*Powder:* Yellowish white to white in color; *Liquid:* Thin and colorless to weak yellow, having a strong aromatic odor of clove and a pungent, spicy taste; affected by light; specific gravity 1.043 to 1.048; refractive index 1.528 to 1.531 at 20°.

Solubility—*Liquid:* miscible with alcohol, chloroform or ether; only slightly soluble in water.

Uses—In general dental practice as a *dental protective*, ie, as a pulp capping or a *temporary filling*.

Iso-Alcoholic Elixir

Iso-Elixir

Low-Alcoholic Elixir
High-Alcoholic Elixir ..... of each a calculated volume

Mix the ingredients.

Low-Alcoholic Elixir

Compound Orange Spirit	10 mL
Alcohol	100 mL
Glycerin	200 mL
Sucrose	320 g
Purified Water, a sufficient quantity,	
To make	1000 mL

Alcohol Content—8 to 10%.

High-Alcoholic Elixir

Compound Orange Spirit	4 mL
Saccharin	3 g
Glycerin	200 mL
Alcohol, a sufficient quantity,	
To make	1000 mL

Alcohol Content—73 to 78%.

Uses—Intended as a general *vehicle* for various medicaments that require solvents of different alcohol strengths. When it is specified in a prescription, the proportion of its two ingredients to be used is that which will produce a solution of the required alcohol strength.

The alcohol strength of the elixir to be used with a single liquid galenical in a prescription is approximately the same as that of the galenical. When galenicals of different alcohol strengths are used in the same prescription, the elixir to be used is to be of such alcohol strength as to secure the best solution possible. This generally will be found to be the average of the alcohol strengths of the several ingredients.

For nonextractive substances, the lowest alcohol strength of the elixir that will yield a perfect solution should be chosen.

Other Miscellaneous Pharmaceutical Necessities

Bucrylate [Propenoic acid, 2-cyano-, 2-methylpropyl ester; Isobutyl 2-cyanoacrylate [1069-55-2] $C_8H_{11}NO_2$ (153.18); (*Ethicon*)]—*Preparation:* One method reacts isobutyl 2-chloroacrylate with sodium cyanide. *Uses:* Surgical aid (tissue adhesive).

Ceresin [Ozokerite; Earth Wax; Cerosin; Mineral Wax; Fossil Wax]—A hard, white odorless solid resembling spermaceti when purified, occurring naturally in deposits in the Carpathian Mountains, especially in Galicia. It is a mixture of natural complex paraffin hydrocarbons. Melts between 61 and 70°; specific gravity 0.91 to 0.92; stable toward oxidizing agents. Soluble in 30% alcohol, benzene, chloroform, petroleum, benzin or hot oils. *Uses:* Substitute for beeswax; in dentistry, for impression waxes.

Ethylenediamine Hydrate BP, Phl [$H_2NCH_2CH_2NH_2.H_2O$]—Clear, colorless or slightly yellow liquid with an ammoniacal odor and characteristic alkaline taste; solidifies on cooling to a crystalline mass (mp 10°); boils 118 to 119°; specific gravity about 0.96; hygroscopic and absorbs CO_2 from the air; aqueous solutions alkaline to litmus. Miscible with water or alcohol; soluble in 130 parts of chloroform; slightly soluble in benzene and ether. *Uses:* In the manufacture of aminophylline and in the preparation of aminophylline injections.

Ferric Oxide, Red—Contains not less than 99% Fe_2O_3. It is made by heating native ferric oxide or hydroxide at a temperature which will yield a product of the desired color. The color is governed by the temperature and time of heating, the presence and kind of other metals and the particle size of the oxide. A dark-colored oxide is favored by prolonged heating at high temperature and the presence of manganese. A light-colored oxide is favored by the presence of aluminum and by finer particle size. *Uses:* Imparting color to mercadamine and cosmetics.

Ferric Oxide, Yellow—Contains not less than 97.5% Fe_2O_3. It is prepared by heating ferrous hydroxide or ferrous carbonate in air at a low temperature. *Uses:* As for *Red Ferric Oxide* (above).

Honey NF XII [Mel; Clarified Honey; Strained Honey] is the saccharine secretion deposited in the honeycomb by the bee, *Apis mellifera* Linné (Fam *Apidae*). It must be free from foreign substances such as parts of insects, leaves, etc, but may contain pollen grains. *History:* Honey is one of the oldest of food and medicinal products. During the 16th and 17th centuries it was recommended as a cure for almost everything. *Constituents:* *Invert sugar* (62 to 83%), *sucrose* (0 to 8%) and *dextrin* (0.28 to 7%). *Description:* Thick, syrupy liquid of a light yellowish to reddish brown color; translucent when fresh, but frequently becomes opaque and granular through crystallization of dextrose; characteristic odor and a sweet, faintly acrid taste. *Uses:* A sweetening agent and pharmaceutic necessity.

Hydriodic Acid, Diluted—Contains, in each 100 mL, 9.5 to 10.5 g of HI (127.91), and 600 mg (to 1 g of HI) H_3PO_2 (66.00). The latter is added to prevent the formation of free iodine. *Caution: It must not be dispensed or used in the preparation of other products if it contains free iodine.* *Preparation:* On a large scale, by the interaction of iodine and hydrogen sulfide. *Description and Solubility:* Colorless or not more than pale-yellow, odorless liquid; specific gravity about 1.1. Miscible with water or alcohol. *Uses:* In *Hydriodic Acid Syrup* (page 1302). The latter has been used as an expectorant. It also is used in the manufacture of inorganic iodides and disinfectants. The 57% acid also is used for analytical purposes, such as methoxyl determinations.

Lime [Calx; Calcium Oxide; Quicklime; Burnt Lime; Calx Usta; CaO (56.08)]—*Preparation:* By calcining *limestone* (a native calcium carbonate) in kilns with strong heat. *Description and Solubility:* Hard, white or grayish white masses or granules, or a white or grayish white powder; odorless; solution strongly alkaline. 1 g soluble in about 840 mL of water or 1740 mL of boiling water; soluble in glycerin or syrup; insoluble in alcohol. *Uses:* In making mortar, whitewash and various chemicals and products. It is an ingredient in *Sulfurated Lime Solution* (RPS 16, page 1187). In the USP, calcium hydroxide has replaced it, as it is more stable and more readily available of a quality suitable for medicinal use than that usually obtainable. Unless protected from air, it soon becomes unfit for use, due to the action of carbon dioxide and moisture in the air. See *Calcium Hydroxide* (page 1319).

Peach Oil—An oil resembling almond oil obtained from *Persica vulgaris* (Fam *Rosaceae*). See *Persic Oil* (page 1323).

Polacrilin Potassium [Methacrylic acid polymer with divinylbenzene, potassium salt [39394-76-5]; Amberlite IRP-88 (*Rohm & Haas*)]—Prepared by polymerizing methacrylic acid with divinylbenzene and the

resulting resin is neutralized with KOH. Dry, buff-colored, odorless, tasteless, free-flowing powder; stable in light, air and heat; insoluble in water. *Uses: Pharmaceutic aid* (tablet disintegrant).

Poloxalene [Glycols, polymers, polyethylene-polypropylene [9003-11-6]; Bloat Guard (*SmithKline*)]—Polypropylene glycol is reacted with ethylene oxide. *Uses. Pharmaceutic aid* (surfactant).

Raspberry Juice—The liquid expressed from the fresh ripe fruit of *Rubus idaeus* Linné or of *Rubus strigosus* Michaux (Fam *Rosaceae*); contains not less than 1.5% of acids calculated as citric acid. *Preparation:* Express the juice from the washed, well-drained, fresh, ripe red raspberries. Dissolve 0.1% of benzoic acid in the expressed juice and allow it to stand at room temperature (possibly for several days) until a small portion of the filtered juice produces a clear solution when mixed with ½ of its volume of alcohol, the solution remaining clear for not less than 30 min. Strain the juice from the mixture or filter it, if necessary. *Description.* Clear liquid with an aromatic, characteristic odor and a characteristic, sour taste; freshly prepared juice red to reddish orange; affected by light; specific gravity 1.025 to 1.045; pH 2.7 to 3.8; refractive index not less than 1.3445. *Uses* In the preparation of *Raspberry Syrup* (page 1302), a *flavored vehicle.*

Sarsaparilla—The dried root of *Smilax aristolochiaefolia* Miller, known in commerce as Mexican Sarsaparilla; or of *Smilax regelii* Killip et Morton, known in commerce as Honduras Sarsaparilla; or of *Smilax febrifuga* Kunth, known in commerce as an Ecuadorian Sarsaparilla; or of undetermined species of *Smilax* Linné, variously known in commerce as Ecuadorian and Central American Sarsaparilla (Fam *Liliaceae*).—Contains glycosides of the saponin group, *sarsasaponin* (*parillin*) and *smilasaponin* (*smilacin*), which are related structurally to the digitalis glycosides, and possess the steroid nucleus. When hydrolyzed with dilute acids, they split into sugars and the corresponding sapogenin. Sarsasaponin yields *sarsasapogenin* (*parigenin*) plus one rhamnose and two glucose molecules, and smilacin yields *smilagenin* plus sugar molecules. Starch, resin, coloring matter and volatile oils also are present. This drug was first used in Europe in the 16th century as a much-vaunted remedy for syphilis. The origin of the name is in doubt. *Uses.* Being without pharmacological actions, it is not employed in modern therapeutics, although the laity is inclined to attribute certain therapeutic virtues to its use.

Sodium Glutamate [Sodium Acid Glutamate [142-47-2] $HOOCCH(NH_2)CH_2CH_2COONa$]—White or nearly white, crystalline powder. Very soluble in water; sparingly soluble in alcohol. *Uses:* Imparts a meat flavor to foods.

Sodium Thioglycollate [Sodium Mercaptoacetate; $HSCH_2COONa$]—Hygroscopic crystals which discolor on exposure to air or iron. Freely soluble in water; slightly soluble in alcohol. *Uses* Reducing agent in Fluid Thioglycollate Medium for sterility testing.

Suet, Prepared [Mutton Suet]—Internal fat of the abdomen of the sheep, *Ovis aries* (Fam *Bovidae*), purified by melting and straining. White, solid fat with a slight, characteristic odor and taste when fresh; melts between 45° and 50° and congeals between 37° and 40°; must be preserved in a cool place in tight containers. *Uses:* In ointments and cerates.

Urea [Carbamide [57-13-6] $CO(NH_2)_2$(60.06)]—A product of protein metabolism; prepared by hydrolysis of cyanamide or from carbon dioxide by ammonolysis. Colorless to white crystals or white, crystalline powder; almost odorless but may develop a slight odor of ammonia in presence of moisture; melts 132 to 135°. 1 g dissolves in 1.5 mL of water or 10 mL of alcohol; practically insoluble in chloroform or ether. *Uses:* A protein denaturant that promotes hydration of keratin and mild keratolysis in dry and hyperkeratotic skin. It is used in 2 to 20% concentrations in various dry-skin creams.

CHAPTER 69

Pharmacological Aspects of Substance Abuse

Frederick J Goldstein, PhD
Professor of Pharmacology

G Victor Rossi, PhD
Vice President of Academic Affairs and Professor of Pharmacology

Philadelphia College of Pharmacy and Science
Philadelphia, PA 19104

Substance abuse continues to be a major problem within the US and will remain so in the 21st century. Although recent data indicate a decline in the use of certain illicit drugs by high-school seniors (Table I), there has been no change in the percent who drink alcohol. Unfortunately, among the many American adults currently dependent upon alcohol and other psychoactive chemicals are members of the health profession, eg, pharmacists, nurses and physicians.

Substance abuse may originate with the *physician*, the *patient* seeking medical treatment or with the *adolescent* drug experimenter. Physician-generated misuse may result when there is insufficient concern or time to evaluate the patient adequately as a candidate for psychoactive drug therapy. Treatment is all too often directed toward the alleviation of symptoms without a concerted effort to identify possible deep-seated causes and respond to the emotional as well as the medical needs of the patient. Overprescribing of mood-altering drugs involves potential harm not just to the individual but to society at large. While physician-generated drug misuse represents a relatively small percentage of the overall problem, it is especially regrettable that any negative contribution arises from the actions or inactions of health professionals.

Patient-originated abuse encompasses a larger aspect and persists despite significant efforts by the majority of physicians and pharmacists to restrict the dispensing of psychoactive agents. Some patients will visit several physicians, obtain a number of prescriptions for barbiturates, tranquilizers, stimulants and/or narcotics and present each prescription to a different pharmacy. Thus, the patient may accumulate substantial quantities of controlled substances either for personal use or for resale. Attempts to thwart such patterns of drug acquisition have, thus far, been unsuccessful.

Peer pressure, alienation, hedonism, mass-media advertising, affluence and boredom are among the factors most frequently cited as those leading to the misuse of drugs by adolescents. The consumption of alcoholic beverages, cigarette smoking and the liberal use of sedatives, tranquilizers and central nervous system (CNS) stimulants by adults, particularly family members, foster the development of a cavalier attitude toward drugs, and increase the likelihood of drugtaking among adolescents.

Three basic stages of adolescent drug usage have been defined as the initial experimental phase, periodic recreational phase and compulsive (chronic) pattern. That many young people resist involvement with drugs or do not progress to chronic or serious patterns of abuse emphasizes the importance of personality traits in the genesis of drug dependency. Persons of any age who have a low frustration tolerance, cannot cope with the daily pressures of life, require instantaneous gratification or who have unfulfilled dependency needs and serious problems of socialization may come to rely on drug use in order to escape, albeit temporarily, from a psychological environment which is bleak, joyless and/or filled with anxiety.

As stated, many factors are involved in the process by which an individual ultimately selects the pharmacological route of escape from stress. Recent studies indicate that a small percentage of the population may have a genetic predisposition for developing an addiction to at least one drug—alcohol. However, it is quite clear that some potential addicts can resist entering this pathway if they become aware of the toxicological consequences of drug abuse. Many school, religious and community organizations have, in fact, made substantial efforts to present educational programs devoted to acute and chronic toxicities produced by psychoactive substances. Pharmacists should expand their participation in these programs; in this regard, the following information can be of assistance.

Central Nervous System Depressants

Opioids (Narcotics)

Heroin is the opioid most often abused. The preference for heroin is not based on its unique euphoric properties but is largely a matter of economics; heroin is the most potent of the opioids, thus providing maximum profit per kilogram to those engaged in illicit traffic.

Early in the course of heroin use, intravenous injection is followed quickly by a sense of exquisite visceral pleasure which is similar to sexual orgasm (the *rush*), an enveloping feeling of contentment and the receding of internal conflicts. Taken orally, heroin also produces relaxation, euophoria and indifference to pain and stress but not the "rush." In the susceptible individual, the intense desire to recapture this drug experience contributes to the establishment of an emotional or psychic dependency.

With frequently repeated administration, the individual becomes progressively less responsive to the drug; thus,

Table I—National Survey of Lifetime Use[a] of Drugs by High-School Seniors[b]

	1985	1987	Change from 1985
Alcohol	92.2%	92.2%	0.0%
Barbiturates	9.2%	7.4%	−1.8%
Cocaine	17.3%	15.2%	−2.1%
Marijuana	54.2%	50.2%	−4.0%
Methaqualone	6.7%	4.0%	−2.7%

[a] Percent who ever used.
[b] *National Institute on Drug Abuse Notes*, Summer 1988.

everincreasing doses are sought in an attempt to duplicate the characteristic effects. Chronic suppression of central nervous system function results in a dependent state in which the drug must be taken on a regular basis to maintain a reasonable semblance of well-being and equilibrium and to prevent the anguish of the abstinence syndrome. Thus, opioid addicts soon find themselves taking heroin not for the pleasurable effects but primarily to prevent withdrawal.

Tolerance to opioids does not develop uniformly. For example, addicts experience, during chronic use, lessened respiratory depressant, analgesic, sedative, emetic and euphoric effects. Some may show decreased miosis while most suffer chronically from the constipating effects of the drug. Drug tolerance always is relative, never absolute; a dose always exists that is capable of causing death from respiratory paralysis, and overdosage is a common cause of fatalities among opioid addicts. Although death associated with heroin use has been attributed routinely to overdosage, other factors sometimes may be involved.

Quinine frequently is employed by "dealers" to dilute pure heroin because, like the opioid, it is bitter and produces vasodilation simulating the *rush*. Thus, addicts cannot detect adulteration readily and may unknowingly inject themselves with large quantities of quinine, which may produce significant myocardial depression. Codeine, while significantly less potent than heroin, also can produce death from overdosage.

Withdrawal symptoms usually reach maximum intensity 36 to 72 hr after the last dose of heroin and subside gradually within 7 to 10 days. The severity of the abstinence syndrome is determined largely by the degree of acquired physical dependence and the rate of elimination of the drug.

The signs and symptoms of opioid withdrawal include yawning, sneezing, lacrimation, restlessness, anxiety, insomnia, nausea, vomiting, gastrointestinal cramps and diarrhea, sweating, gooseflesh, generalized body aches, fever, tremors, muscle spasms and jerking movements. Excessive perspiration, vomiting and diarrhea combined with diminished food and fluid intake may result in dehydration, acid-base disturbances and ketosis. Occasionally, cardiovascular collapse occurs.

Withdrawal symptoms can be suppressed either by administering the drug of dependence or another narcotic. If an opioid, such as methadone, is given initially in a stabilizing amount and then the dosage reduced gradually, the intensity of the abstinence syndrome may be lessened appreciably.

The opioid addict is subject to risks arising out of indifference to minimal nutritional and hygienic requirements with a consequent high incidence of viral hepatitis, bacterial endocarditis, tetanus, pulmonary infection, pulmonary edema and thrombophlebitis.

The use of nonsterile injection equipment and intravascular introduction of cotton fibers and adulterants, such as lactose and talc, all contribute to the development of local and systemic infectious disorders and pulmonary granulomatosis. Hyperamylasemia often is observed during the acute phase of heroin-induced pulmonary disturbances. Increased serum immunoglobulin levels are encountered commonly in addicts. Although the clinical consequences of this finding are understood incompletely, serological tests for syphilis are false-positive in a significant proportion of such individuals.

Noninfectious complications of opioid addiction include transverse myelitis, rhabdomyolysis with cardiac involvement and myoglobinuria and Horner's syndrome. Quinine contained in *street* heroin preparations produces amblyopia and thrombocytopenia. An aqueous mixture consisting of crushed tablets of pentazocine (Talwin) and tripelennamine (Pyribenzamine), with the street name of "T's and Blues', has been used intravenously by addicts; the effects are reported to be similar to the heroin *rush*.

Toxic reactions can be serious and include tonic-clonic seizures and acute respiratory distress with hypoxia. The latter effects apparently result from deposition of insoluble ingredients of this mixture, eg, talc, in lung tissue thus causing pulmonary granulomas.

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), an extremely toxic by-product of illicit meperidine synthesis, destroys certain types of brain tissue (nigrostriatal) after only a few doses; this produces Parkinson's disease in the abuser which, like the degenerative clinical disease occurring in geriatric patients, is irreversible.

Women who persist in the use of heroin during pregnancy give birth to opioid-dependent offspring. The signs of withdrawal in the newborn appear within several hours to several days and include high-pitched crying, sleeplessness, irritability, tremor, vomiting and diarrhea; the latter may result in severe dehydration. Narcotic-dependent infants are born smaller and exhibit an uncoordinated and ineffectual sucking reflex, which reduces nutritive consumption. Phenobarbital, diazepam, paregoric or chlorpromazine have been used to alleviate narcotic withdrawal in neonates.

The approaches to treatment of the adult addict involve medical as well as psychiatric and social aspects. A basic obstacle in any approach to the treatment of opioid addiction is the characteristic high rate of recidivism.

Methadone maintenance, currently one of the most widely employed techniques in the management of opioid addiction, involves stabilizing the patient on a regular daily oral dose of methadone, preferably in conjunction with supportive psychological or psychiatric counseling. In this context, the maintenance drug does not provide true pharmacological blockade; rather, regular administration results in the development of tolerance to methadone and cross-tolerance to heroin. Thus, the addict will not experience the heroin-induced "rush" and euphoria unless doses substantially higher than usual are injected.

Theoretically, when unburdened by these factors which motivate addiction, methadone may be withdrawn gradually. However, many former narcotic abusers cannot maintain a drug-free state and either reestablish their addiction to heroin or request continued metadone therapy. In contrast, some addicts refuse to enter a methadone maintenance program. The reasons for this decision include

- The claim by some narcotic abusers that methadone is just another type of drug dependence and one which is more difficult to surrender than heroin use—in fact, methadone withdrawal can be more intense and painful than heroin detoxification.
- Methadone significantly impairs human reproductive capacity by decreasing both ejaculate volume and sperm motility (heroin produces a lesser effect upon fertility).
- Family members may be endangered—a number of children have died after ingesting the liquid methadone preparations used by their parents.

An alternative approach, based on the conditioning theory of opioid dependence, employs narcotic antagonists to extinguish drug-seeking behavior by blocking the euphoric effects of heroin. Nalorphine first was suggested for this purpose but its limited duration of action and high incidence of hallucinogenic reactions made its use impractical. Cyclazocine is effective orally and provides blockage for up to 24 hr but, like nalorphine, is an active analgesic and is associated with a variety of disturbing psychotomimetic reactions. Naloxone (*Narcan*), a "pure" opioid antagonist (ie, possesses no agonist properties), produces fewer unpleasant effects but is relatively short-acting.

Naltrexone (*Trexan*), a longer-acting derivative, can block the effects of heroin for approximately 72 hr. The results of clinical trials are disappointing since many addicts

under treatment refuse to take a drug which is devoid of narcotic-like effects.

Clonidine (*Catapres*), an α_2-receptor-agonist, has been used successfully in treating heroin withdrawal reactions; in some cases, it is more efficacious than methadone.

Barbiturates

The clinical use of barbiturates has declined substantially in recent years. The benzodiazepines, while not free of adverse reactions, are safer and have supplanted barbiturates in the treatment of anxiety and insomnia. It is clear that, in general, hypnotics (barbiturates and nonbarbiturates) should not be prescribed for more than a 14 to 28-day period. Beyond this time efficacy decreases (a decline in hypnotic activity may begin after only 7 days of continuous therapy). Pharmacists should monitor these prescriptions very closely, consulting with both the patient and physician in order to insure proper use and prevent dependence problems.

The hazards encountered in the use of barbiturates include occasional unanticipated idiosyncratic or hypersensitivity reactions and accidental overdosage as may occur in young children unaware of the potential danger or in adults during a hypnotic drug-induced semistuporous state of "automatism." For most persons, sleep provides only a temporary respite but, all too frequently, intentional overdosage with easily accessible sleep-inducing drugs provides an avenue of permanent escape from the pressures of reality.

Barbiturates reduce the amount of time spent in the REM (rapid eye movement) phase of sleep. The reduction of REM sleep for a period of several days may cause the individual to become irritable or to evidence disturbances in personality and rationality. When the hypnotic is withdrawn abruptly, there is a rebound increase in the REM phase often associated with nightmares, a feeling of having slept poorly or actual insomnia. "Rebound" REM makes it difficult for the patient to give up the drug and contributes to the development of drug dependency.

The signs and symptoms of barbiturate and alcohol intoxication are strikingly similar. Visual perception, recall, reaction-time coordination and other indexes of psychomotor functioning are affected, the degree of impairment largely depending on the concentration of drug in the brain. Intoxication, either with alcohol or a barbiturate, is characterized by difficulty in thinking, reduction of ego controls, poor judgment, confusion and emotional instability. Neurological impairment and muscular incoordination are major factors in the personal injuries and involvement in vehicular accidents which are common occurrences during the course of intoxication with these drugs. The CNS suppressant effects of alcohol, barbiturates and opiates, such as heroin, are mutually reinforcing; extemporaneous combinations of these depressants may result in unpredictably abrupt and severe incapacitation.

Low doses of barbiturates (as employed for daytime sedation, nighttime sleep induction or the control of epilepsy) are often taken for indefinite periods without eliciting tolerance or physical dependency. These phenomena generally occur only with doses considerably in excess of those customarily employed in medical practice. To illustrate, the usual oral hypnotic dose of pentobarbital sodium or secobarbital sodium is 100 to 200 mg, whereas oral doses of these barbiturates in excess of 400 mg/day (and generally in the range of 600 to 800 mg/day) for approximately 1 month are required to induce clinically significant tolerance and physical dependency. Parenteral (subcutaneous or intravenous) administration of barbiturates may lead to physical dependency at lower dose levels and within a shorter period of time.

The amount of barbiturate that may be consumed by the compulsive abuser varies considerably, but average daily doses of 1 to 1.5 g of short-acting derivatives are not uncommon, and some individuals may use as much as 2.5 g/day over prolonged periods of time.

Withdrawal reactions, which in some cases may be more hazardous than the opioid abstinence syndrome, develop upon abrupt cessation of chronic barbiturate overuse. Mild to moderate withdrawal reactions include anorexia, apprehension, tremulousness, muscular weakness, mental confusion and postural hypotension. A severe barbiturate withdrawal syndrome may involve profound disorientation, delirium and hallucinations and convulsive seizures of an episodic or protracted nature. Most individuals who have ingested eight or more hypnotic doses of a barbiturate per day over an extended period will experience convulsions during withdrawal. In extreme cases the barbiturate abstinence syndrome may terminate in cardiovascular collapse and death. With the longer-acting barbiturates, withdrawal symptoms are slower in onset and less severe than those encountered with the shorter-acting derivatives.

Pharmacological treatment of barbiturate dependency generally is approached by replacement with either pentobarbital or phenobarbital at an initial dose sufficient for stabilization; the dose then is reduced gradually over a period of several days to weeks depending on the individual patient response.

Nonbarbiturate Sedative-Hypnotics

Neurological impairment, psychological and physical dependency, and an abstinence syndrome similar to that associated with barbiturate abuse may result from excessive use of many nonbarbiturate sedative-hypnotic and antianxiety agents, including chloral hydrate, glutethimide, methyprylon, methaqualone, meprobamate, chlordiazepoxide or diazepam.

Methaqualone remains a "street" drug of choice. Although claims have been made that it and other nonbarbiturate hypnotics (eg, chloral hydrate or triclofos) produce little or no effect on REM sleep, other reports challenge this distinction and a final conclusion has not been advanced yet.

Acroparesthesia (tingling and numbness in the extremities) may occur prior to the onset of hypnotic activity, particularly when sleep does not ensue rapidly. This sensation is experienced by many methaqualone abusers and probably contributes to the aphrodisiac effect (similar to the 'Spanish Fly' phenomenon). Increased muscle tone often is evident; it even may be observed while the patient is in a deep coma and may last for several days. Acute toxicity differs from that of the barbiturates in that marked respiratory and cardiovascular depression generally are not seen after large doses of methaqualone.

Psychological dependence and tolerance to methaqualone have been observed, but the results of studies on the development of physical dependence are equivocal. Apparent withdrawal symptoms, such as headache, anorexia, nausea, abdominal cramps and interference with sleep, have been noted in those investigations reporting physical dependency. These relatively minor symptoms may occur during abstinence in the individual who has been taking five hypnotic doses of methaqualone daily for several months.

Severe reactions which may be encountered occasionally during methaqualone withdrawal include convulsions and toxic psychoses. Ingesting alcohol with methaqualone is very dangerous, leading to a serious impairment of judgment and psychomotor coordination. At least one state reports a high death rate from injuries sustained in car accidents where the drivers, passengers and/or pedestrians used this drug combination.

Mandrax, a combination of methaqualone (250 mg) and

diphenhydramine (25 mg), has been abused by addicts in Great Britain, Canada and Australia. The reactions due to overdosage with this drug combination are similar to those of methaqualone but are potentially more severe since diphenhydramine, which possesses central antimuscarinic activity, may produce psychological disturbances, excitation, ataxia and convulsive seizures (diphenhydramine does not influence the absorption or biotransformation of methaqualone).

Meprobamate produces sedation and relaxation comparable to that of the barbiturates, although the clinically effective dose of meprobamate is higher. Cognitive activity may be compromised by chronic oral doses of 800 mg of meprobamate per day, while at daily doses of more than 1600 mg, psychomotor performance may be reduced significantly. Psychic dependence and tolerance occur with prolonged high-dose administration and physical dependence develops after consumption of 3 g or more per day for several weeks. Depending on the dosage and duration of use, meprobamate withdrawal reactions may range from anxiety, insomnia and tremors to hallucinations, convulsions, coma and death.

Chlordiazepoxide, taken in doses of 300 to 600 mg a day for several months, may result in physical dependency resembling that observed with the barbiturates and meprobamate. However, withdrawal symptoms may be delayed for several days after chlordiazepoxide is terminated, due possibly to slow elimination of the drug. Agitation, insomnia, anorexia, depression, psychological disturbances and convulsions are among the reactions which follow the cessation of prolonged administration of high doses of chlordiazepoxide.

Diazepam, the most widely prescribed benzodiazepine derivative, also may induce physical dependence. Patients receiving 15 mg a day for 4 to 6 months, or higher doses (60 to 120 mg) for about 2 months may, upon withdrawal, experience gastric cramps, sweating, agitation, tremors, insomnia, confusion, disorientation, auditory and visual hallucinations, delusions, paranoia and depression.

Serious acute intoxication may occur when benzodiazepines are combined with other depressants, eg, ethanol, narcotics, other sedative-hypnotics, tricyclic antidepressants or antipsychotic agents. Simultaneous ingestion of ethanol and diazepam is particularly dangerous. In addition to the expected additive CNS-depressant effects, in the presence of ethanol, diazepam blood levels are elevated, compared to diazepam taken alone. Some reports suggest the possibility of teratogenicity resulting from administration of meprobamate or certain benzodiazepines during the first trimester; in the interest of caution, the use of these antianxiety agents should be restricted during this critical period of pregnancy.

The medical and pharmaceutical professions bear a grave responsibility in prescribing and dispensing barbiturates, benzodiazepines and pharmacologically related agents. Physicians, pharmacists and nurses often fail to convey adequately to the patient the potential of these drugs for ensnarement in a vicious web of emotional need, often progressing to escalated consumption and, ultimately, the development of a dangerous degree of psychological and physiological dependency. Although only a limited number of drugs were discussed in the above sections, it is important to note that *any* substance causing acute CNS depression is capable of producing psychological and/or physical dependency during chronic use.

The legitimate application of drugs should not be jeopardized by irrational fears arising from situations created by their uncontrolled use. However, it is equally important to recognize that certain drugs, by virtue of their ability to elicit profound changes in mood and feeling, may, in the emotionally predisposed person, lead to a degree of psychic dependency and compulsive use detrimental to the individual and to society.

Alcohol

Although greater publicity usually is accorded to marijuana, hallucinogens and narcotics, alcohol remains the major drug of abuse in the US. Approximately 15% of all US health costs are for the treatment of chronic alcoholism and associated toxicities.

Alcoholic intoxication spans a range of blood-ethanol concentrations from 0.05%, at which level some impairment of judgment occurs, to above 0.40%, associated with profound depression of vital physiological functions. Concentrations in excess of 0.60% usually are fatal.

Although many states regard an individual as being "legally drunk" at levels above 0.10%, controlled studies have demonstrated repeatedly that functional deficits such as impaired adaptation to light, reduced psychomotor performance with prolonged reaction times and generalized deterioration of simulated driving skills are evident at blood-alcohol concentrations well below 0.08%. Thus, individuals with blood-alcohol levels below those required for legal classification as intoxicated may, nevertheless, be dangerous drivers.

Compelling statistics compiled over many years implicate alcohol as a principal contributor to motor vehicle accidents with consequent injuries and fatalities. Public outrage by groups such as *Mothers Against Drunk Drivers* (*MADD*) has been directed recently toward the legislative and judicial systems for their minimal penalization of drunk drivers, particularly the repeat offender. As a result, most states now have passed stricter laws with more severe penalties. All 50 states now require a person to be 21 yr old in order to drink alcohol.

Two-day jail terms for first offenses and quicker suspension of the operator's license now are routine aspects of punishment. However, none of these statutes can restore the lives of innocent children and adults who have been killed by intoxicated drivers. The prevention of alcohol abuse through educational and other methods remains the approach most likely to reduce deaths. Many airline pilots and railroad engineers currently are involved in such programs.

Severe alcoholic intoxication may result in forms of amnesia characterized as "state-dependent learning" or as a "blackout." In the former, an individual can recall what transpired under the influence of alcohol only if again subjected to an intoxicated state. Generally, information acquired while under the effects of alcohol is remembered poorly or not retained in the nondrug condition.

"Blackout" refers to a severe short-term memory deficit; subjects cannot recall what occurred while intoxicated even if they again become inebriated. Assaultive or destructive behavior (eg, suicide, attempted suicide or homicide) associated with drinking frequently takes place during an amnesic state.

Estimates of the number of alcoholics in any society are very imprecise; the number of individuals in the US alone, whose lives are involved inextricably with alcohol, is numbered conservatively in the several millions. The cost in terms of lost productivity, accidents, crimes, self-degradation and the disruption of family, business and social bonds is beyond computation. Chronic abuse leads to debilitating pathological alterations which seriously impair the alcoholic's health and diminish life expectancy; these effects may be summarized as follows:

1. *Mortality*
   The probability of premature death is approximately three times that of the general population, in addition to a greater frequency of fatal accidents and suicides; pathological changes are contributory.
2. *Cardiovascular*
   While several clinical studies show a reduced incidence of heart disease (possibly due to elevation in protective serum high-density lipoproteins) among persons who consume an average of 2 oz or less of alcohol per day, heavy drinkers (more than 2 oz a day) are at greater risk of developing various cardiovascular disorders which include:

a. permanent dilation of peripheral blood vessels around nose and eyes
b. hypertension
c. atherosclerotic heart disease
d. congestive heart failure
e. peripheral vascular disease
f. cerebrovascular disease (eg, stroke)

3. *Neurological*
Observed clinical changes may occur as:
a. cerebellar ataxia (motor incoordination)
b. decreased ability to perform cognitive tasks (eg, verbal and nonverbal tests)
c. polyneuropathy
d. nystagmus
e. Korsakoff psychosis
f. Wernike encephalopathy (may include some or all of above, ie, 3a to 3e)
Cerebral atrophy, documented by computerized axial tomography, can be extensive and has been linked to functional neurological deficits. Of particular interest is a report which suggests the loss of cognitive skills may be related more to consumption of substantial amounts of alcohol per drinking episode than to the frequent use of limited quantities. Partial recovery may occur with total abstinence.

4. *Hepatic*
Degenerative alterations in liver morphology and function appear during chronic alcoholism and develop progressively in the following order (includes sequelae):
a. alcoholic fatty liver (hepatic pain and tenderness)
b. alcoholic hepatitis (nausea, vomiting, anorexia, weight loss, abdominal pain)
c. cirrhosis (jaundice, encephalopathy)
As with alcohol-induced neurological changes, cessation of drinking usually prevents further deterioration.

5. *Gastrointestinal*
Ulcer formation and extensive gastrointestinal bleeding frequently are seen in addition to:
a. esophagitis
b. gastritis
c. intestinal malabsorption (of, for example, fat, folic acid, thiamine, vitamin B_{12})
d. chronic diarrhea
e. steatorrhea

6. *Pancreatic*
Chronic pancreatitis often is observed after approximately 7 yr of heavy alcohol use (usually appears before cirrhosis). Pancreatic failure may produce insulin-dependent diabetes mellitus.

7. *Hematological*
Anemia may be caused by deficiencies of folic acid and/or iron; other disorders are:
a. thrombocytopenia
b. granulocytopenia

8. *Endocrine*
a. diabetes mellitus
b. pseudo-Cushing's syndrome
c. hypogonadism
(1) female: amenorrhea
(2) male: low plasma testosterone levels, impotence, infertility, testicular atrophy

9. *Infection*
a. bacteremia
b. bacterial peritonitis
c. pneumonia
d. tuberculosis

10. *Cancer*
a. esophageal
b. hepatic
c. laryngeal
d. pharyngeal
e. mouth
f. breast (possibly)

Although alcoholic beverages constitute an appreciable source of calories, they provide no vitamins, minerals or proteins. Nutritional deficiencies associated with long-term heavy drinking may constitute major factors in the development of polyneuritis and cirrhosis of the liver. However, evidence suggests that liver damage results from the direct hepatotoxic effect of alcohol and/or its metabolites and that cirrhosis may occur independently of nutritional status.

Alcohol passes readily from the maternal to the fetal circulation, thus frequent consumption of alcohol during pregnancy creates an unnatural intrauterine environment for the developing fetus. Infants born to alcoholic mothers usually are underdeveloped and exhibit a slow growth rate and mental retardation. Current evidence suggests that these effects may be permanent. Cardiovascular aberrations, including systolic murmurs (due to possible ventricular septal defects) and congestive heart failure (resulting from possible atrial septal defects), and craniofacial abnormalities (such as short palpebral fissures and maxillary hypoplasia) have been documented as patterns of malformation in infants born to chronic alcoholic women. This dysmorphic pattern has been classified as the Fetal Alcohol Syndrome (FAS) and is most likely to occur when maternal consumption is equivalent to 90 mL (or more) of absolute alcohol per day.

The chronic ingestion of alcohol results in pharmacodynamic and drug-disposition tolerance. However, the degree of tolerance is not as great as that which occurs with morphine. Physical dependence develops to alcohol, which is similar to that observed with barbiturates and narcotics. The severity of the alcohol-abstinence syndrome can be correlated with the degree of intoxication and its duration. A relatively short period of heavy drinking may be followed by headache, nausea, vomiting, general malaise and slight tremulousness during the "drying-out" period.

Abrupt cessation of alcohol consumption after 1 week or more of intoxication may be associated further with anxiety, insomnia, confusion, tremors and hallucinations. Long periods of intense intoxication may, upon withdrawal, result in delirium tremens, a syndrome characterized by increased autonomic activity (eg, fever, sweating and tachycardia), agitation, disorientation, severe tremors or convulsive seizures and frightening hallucinations, usually of a visual form.

Hereditary predisposition, endocrine abnormalities, psychological defects, susceptible personality structure and sociocultural and economic impacts are among the many factors that have been considered as interacting in the causation of alcohol addiction. Because of the many conflicting hypotheses on the etiology of alcoholism, there is no standard approach to therapy. There is a general agreement, however, that a prerequisite for successful therapy is *total* abstinence from alcohol and, for all practical purposes, this represents the only viable solution for the individual alcoholic.

Efforts to correct the drinking habit almost invariably fail if the patient attempts merely to reduce his consumption of alcohol. Indeed, the failure of the alcoholic to accept the realization that he is incapable of drinking in moderation is regarded as a primary obstacle to the ultimate resolution of the problem.

Some alcoholics stop drinking of their own volition, others are able to discontinue the habit with the aid of professional or peer-group counseling and still others continue to relapse despite repeated and intensive rehabilitative efforts. Therapeutic measures employed, with varying degrees of success, in the long-term management of the alcoholic patient include participation in supportive social organizations for combating alcoholism (eg, Alcoholics Anonymous), psychiatric therapy and the use of neuroleptic or antianxiety agents, although the latter may result in substitution of one form of drug dependence for another. The unpleasant interaction between alcohol and disulfiram may be used both as a deconditioning device and as a deterrent.

Volatile Hydrocarbons

Volatile hydrocarbons (eg, glue, carbon tetrachloride, gasoline, nail polish remover, lighter fluid, paint, lacquer, varnish thinner—even those solvents found in typewriter correction fluid and adhesive tape remover!) are abused most frequently by young individuals between 10 and 15 yr of age. These liquids usually are deposited in a handkerchief, rag or bag which is then placed over the nose and mouth and the vapors inhaled, a process known as "huffing." Initial exhilaration and CNS excitation may occur with blurring of vi-

sion, ringing in the ears, slurred speech and staggering gait. These effects generally last from 30 to 45 min after inhalation. Depending upon the quantity of vapor inhaled, drowsiness, stupor and unconsciousness may result.

Occasionally, volatile hydrocarbon abuse precipitates psychotic behavior, but susceptible individuals are apparently those who manifest personality disturbances antecedent to drug use. Amnesia often follows recovery. In extreme cases of intoxication, death due to respiratory paralysis may occur.

Psychological dependence can develop and, although physical dependency does not, this latter situation probably is attributable primarily to the limited duration of volatile hydrocarbon use, rather than to the pharmacological properties of these chemicals. If volatile hydrocarbons were abused frequently and for a sufficiently long period, physical dependency might be established, as is the case with other potent CNS depressants, eg, barbiturates and narcotics.

Physical signs associated with the use of volatile hydrocarbons include characteristic odors, irritation of mucous membranes and elevated pulse rate. Chronic abuse may produce damage to the kidneys, liver, heart and brain. In glue sniffers with sickle-cell disease, severe anemia has been observed, possibly as a result of bone-marrow depression. Chromosome damage in glue sniffers has been reported but this adverse reaction remains to be established definitely.

The inhalation of butyl nitrites (primarily isobutyl nitrite) produces pharmacological effects similar to amyl nitrite. Butyl nitrites are found in room deodorizers which contain one or more isomers (eg, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl). Euphoria, the most desired immediate effect, often is accompanied by dizziness, fainting, cutaneous flushing, headache and hypotension, all of which are due to significant peripheral vasodilation. Subsequent effects include dermal irritation leading to lesions on the lips, nose, penis and scrotum. Since nitrites may be carcinogenic, chronic inhalation may produce cancer. Many homosexual men have used nitrite inhalants, which may promote Kaposi's sarcoma, commonly found on the nose tips and oral mucosa of such individuals who ultimately contract AIDS.

Aerosol Propellants

More than 2 billion aerosol spray cans are produced each year for such diverse applications as household cleaners, furniture waxes, insecticides, hair sprays, antitussives, paints, antisticking coatings for cookware, deodorizers, disinfectants and cocktail-glass chillers. Many of these aerosols also are widely abused by youthful drug experimenters, primarily teenagers.

The effects which result from "huffing" aerosols generally are similar to those described for volatile hydrocarbons. Reports in the medical literature have described several cases of collapse and death of young persons within a very short time after deliberate inhalation of the contents of various aerosol containers. This phenomenon has been designated "sudden sniffing death" (SSD). The appellation implies a greater degree of specificity, however, than may be warranted. The mechanisms involved in SSD have yet to be elucidated. Autopsy findings have been negative in that no anatomical cause of death has been established. Suffocation, frozen vocal cords and respiratory failure may accompany SSD but do not appear to be the primary factors, since death occurs so rapidly.

Considerable attention has been directed to the fluoroalkane propellant gases (most often Freons) as possible causative agents of SSD. The data provided by some experimental animal studies suggest that the fluoroalkanes are capable of producing direct myocardial depression, bradycardia, atrioventricular block and ventricular dysrhythmias. Other studies conducted with these chemicals, however, have not revealed significant direct cardiotoxicity. Fluoroalkane propellants and volatile hydrocarbon solvents also may have an indirect action on the heart, ie, sensitization of myocardial tissue to the arrhythmogenic effect of the catecholamines. Thus, in individuals exposed to inordinate concentrations of these materials, endogenous epinephrine released during severe stress or physical activity might be expected to produce a markedly deleterious effect on cardiac function. Hypercapnia, as would result from rebreathing the air in a small, closed environment (eg, bag sniffing), may potentiate further the cardiotoxicity of catecholamine, fluoroalkane or volatile hydrocarbon combinations.

Asthmatic patients have been found dead surrounded by one or more bronchodilator aerosol containers, the contents of which have been expended. Investigations into the nature of such fatalities indicate that a severe asthmatic attack itself may be the major cause of death. However, it also has been suggested that fluoroalkane propellants combined with epinephrine or isoproterenol may produce lethal cardiac arrhythmias if the recommended dose of inhalant is exceeded.

Isolated reports have linked the appearance of sarcoid-like lesions in the lungs and premalignant pulmonary lesions to the increased use of aerosol preparations. However, the validity of the presumed association remains to be confirmed.

Deaths related to aerosol propellant abuse have declined during the past few years. This trend apparently is due to elimination of Freons from spray cans in order to prevent environmental damage (eg, destruction of ozone layer in upper atmosphere).

Nitrous Oxide

Inhaling nitrous oxide for nonmedical purposes, ie, to induce a "high," remains a current national problem which is not confined to teenagers. Students at both the college-undergraduate and health-professional level, as well as licensed practitioners, are known to be among the abusers. Supplies of nitrous oxide have been obtained through the theft of large cylinders (eg, as used in hospitals) or the purchase of whipped-cream cartridges which contain approximately 3 L of nitrous oxide.

Acute, uncontrolled exposure can be lethal by promoting unconsciousness in the user who then collapses into a body position which could be suffocating. At least one death has occurred in this manner. Other fatalities are known and the Drug Enforcement Administration estimates that nitrous oxide-related deaths are underreported.

Chronic toxicity develops not only in abusers but also in health professionals who employ nitrous oxide for legitimate purposes. An extensive survey of dentists and dental assistants found that when exposure was "heavy," ie, more than 3000 hr over a 10-yr period (6 hr per week), the number of reported adverse effects was four times greater than those experiencing "light" exposure, ie, less than 3000 hr per 10 yr. The initial signs and symptoms of nerve damage occur as numbness and paresthesias (unusual feelings in limbs described as burning and/or tingling). Later, muscle weakness and gait disturbances may develop. In abusers, this polyneuropathy could become permanent. Other effects of prolonged use which are firmly linked less include headaches, nephrotoxicity, hepatotoxicity, neoplastic disease, spontaneous abortions (higher than normal rate) and teratogenicity.

Marijuana (Marihuana)

Marijuana is obtained from one of man's oldest cultivated plants, *Cannabis sativa*. The biologically active principles of cannabis are concentrated in the resinous exudate of the flower clusters. Traditionally, the female plants have been

harvested for their high resin yield. Chemical analyses have indicated, however, that the cannabinoid content of the resin does not differ significantly between the male and female plants. The potency of preparations derived from cannabis varies enormously depending on their composition and method of formulation. *Hashish*, the unadulterated resin from the flowering tops of cultivated female plants, is a most potent form.

By legal definition (US Federal Statutes), the term *marijuana* embraces all parts, extracts, derivatives or preparations of cannabis, including the pure resin. However, as usually encountered in the Western hemisphere, marijuana comprises a mixture of the leaves, flowering tops and other structural parts of the cannibis plant, generally dried, chopped and incorporated in a form for smoking.

Although Δ^9-tetrahydrocannabinol (THC) appears to be the major active constituent of marijuana, biological activity may be attributable largely to the 11-hydroxy metabolite. Marijuana cigarettes ordinarily obtainable in the US contain about 1 to 2% THC. Based on an average cigarette weight of approximately 500 mg, the amount of available THC ranges from 5 to 10 mg. Stronger products, ie, those with 3 to 5% THC, are currently available in the American "market."

Depending on its potency, a marijuana cigarette will produce moderate to intense psychopharmacological effects which reach a peak within 15 min and persist for 1 to 4 hr. As compared to smoking, marijuana consumed orally is about ⅛ as potent and the onset of activity is delayed but markedly prolonged.

One of the most consistently demonstrable effects of marijuana in humans is elevation of the pulse rate; the rate may rise by 50% or more above the preexposure level and increases may be sustained for several hours. Within limits, the intensity of this response appears to be related to the amount of drug consumed. Blockade by propranolol implicates β-adrenergic receptor activation in the mechanism of THC-induced tachycardia. However, that the increase in heart rate occurs without a simultaneous increase in left ventricular performance suggests the operation of an antivagal mechanism by THC. Smoking marijuana while taking other drugs known to produce tachycardia, eg, nortriptyline, can result in a very substantial elevation of heart rate.

Blood pressure changes are variable; slight elevations and reductions of systolic and diastolic pressure have been noted. Continuous electrocardiographic monitoring of subjects who smoked cigarettes calibrated to contain 20 mg of THC revealed no ECG alterations that could be attributed definitely to marijuana intoxication. In contrast to the increased heart rate observed in humans, THC produces bradycardia in several animal species, eg, the rat, cat or dog.

Reddening of the conjunctiva (conjunctival congestion) is another consistent response to marijuana. That reddening also occurs after oral administration of THC indicates that this is not an artifact produced by irritation from smoke. Despite a belief long associated with marijuana, significant changes in pupillary diameter are not observed. Although marijuana does not elevate the respiratory rate, oral administration may produce airway dilation, probably by direct relaxation of bronchial musculature, for a period of several hours.

Appetite is stimulated in human and subhuman species, but without concurrent alteration of the blood glucose level. Weight gain, which often occurs during prolonged use of marijuana, probably is related more to increased caloric intake than to excessive fluid retention. Disturbances of equilibrium and muscular coordination as well as hyperreflexia during marijuana intoxication have been reported. Other physiological changes noted with marijuana include dryness of the mouth and throat, irritation of the oropharyngeal mucosa, nausea and occasional vomiting, tinnitus and paresthesias.

The marijuana-induced state is characteristically a hypersuggestible state; psychological and perceptual effects are influenced markedly by the mental attitude, mood expectations of the user and the setting and circumstances attending its use. Typically, there is a sense of relaxation, inner contentment, euphoria or even elation; thoughts flow in disconnected fashion in a dream-like state; time and space orientation are impaired; body image is distorted; perception of colors and sounds is altered, usually intensified; laughter comes easily and may be uncontrollable but sometimes mood is subdued or depressed.

The subjective responses to marijuana correlate generally with the onset and duration of tachycardia and conjunctival vascular congestion. EEG changes have been recorded in THC-treated animals, and it has been suggested that the activation of septal areas associated with pleasure and emotion may play a role in certain of the observed psychological alterations.

Short-term memory frequently is impaired and information learned while under the influence of marijuana is recalled effectively only when the individual again is subjected to the drug effect, ie, state-dependent learning. Intense depersonalization, loss of insight, disorganized thinking and speech and grossly distorted perception occur with high doses but true hallucinations rarely are experienced, except at toxic levels. This contrasts with the hallucinogenic drugs (eg, LSD, DMT) which induce organized visual illusions and hallucinations at subtoxic doses.

Performance in psychometric tests is affected variably, depending on the nature of the task, its complexity and the dose of marijuana. Generally, marijuana produces a dose-related psychomotor performance decrement. In tests of driving skills, speedometer errors were increased but braking, signaling or steering responses essentially were unimpaired. There is, however, a significant delay in light adaptation which may seriously impair driving at night. Marijuana prolongs the time needed to regain normal vision after exposure to bright light as, for example, from the headlights of an oncoming automobile. This effect is dose-related and may persist for 2 hr after marijuana use.

That deficiencies in these responses may contribute to automobile accidents is suggested by the finding of measurable blood levels of THC in some motorists involved in traffic violations. In a recent study, subjects with plasma THC levels above 25 to 30 ng/mL failed coordination tests routinely given to drivers to assess the severity of alcohol intoxication. However, the temporal correlation between plasma THC levels and degree of incoordination was not as accurate as with alcohol.

Adverse reactions to marijuana occur relatively infrequently. They have been classified by Weil[1] as follows:

1. Normal population.
   Simple depressive reactions—occur in neophyte users; terminate spontaneously.
   Panic reactions—occur mainly in individuals who have inhibitions regarding use of psychoactive drugs; patient may be anxious, depressed, fearful, withdrawn or agitated but, generally, is panicked due to physiological and/or psychological effects which are misinterpreted as life-threatening.
   Toxic psychoses—serious, temporary disturbances of normal brain activity; patients are disoriented and frequently experience hallucinations.
2. Persons who previously have taken hallucinogenic drugs.
   Precipitation of "flashbacks"—marijuana may induce recurrences of a "trip" which developed originally from previous consumption of a hallucinogenic drug.
   Precipitation of delayed psychotic reactions to hallucinogenic drugs—hallucinogens occasionally produce psychotic reactions several months after use—marijuana may have been the triggering factor but this cannot be established definitely.
3. Persons with a history of psychoses.
   Many individuals who have unpleasant experiences with marijuana are ambulant schizophrenics—in some of these cases marijuana may precipitate true psychotic reactions.

Death in humans resulting directly from marijuana toxicity appears to be a rare phenomenon. Acute-toxicity determinations in animals reveal that extremely large amounts are necessary to cause death and that the median, lethal dose-to-median effective dose ratio (ie, LD50/ED50) for marijuana is many times greater than that obtained with either the barbiturates or alcohol. Children who accidently ate marijuana-containing cookies became intoxicated and presented with varying degrees of effects routinely observed in adults, eg, tachycardia, bilateral conjunctival hyperemia (congestion), ataxia and nystagmus; recovery was uneventful and occurred within 6 hr.

The continued use of marijuana may result in psychological dependence, and tolerance may develop to psychological (characteristic "high" time estimation), physiological (tachycardia) and combined (psychomotor coordination) effects of marijuana. The evidence for psychological tolerance accrues, in part, from the observation that chronic users tend to increase the amount consumed, or resort to a more potent variety in order to experience altered states of consciousness. Clinical laboratory studies provide data to support the other forms of tolerance. The mechanisms involved in tolerance to marijuana may include cellular adaptation, particularly within the CNS, and an increased biotransformation capacity.

Conversely, the phenomenon of "reverse tolerance," or sensitization to marijuana, has been reported. This may be attributable to psychological or metabolic factors, or a combination of both. Experience undoubtedly plays a role in the user's awareness and enjoyment of a marijuana-induced "high," and, with repeated conditioning, less of a stimulus is necessary to trigger the anticipated subjective effects. In addition, long-term smokers appear to be more efficient, inhaling and retaining more smoke per puff than the novice. THC and, possibly, active metabolites of this molecule are eliminated slowly from the body. Some chronic users continue to excrete THC in the urine for 20 to 30 days after terminating all marijuana smoking and/or ingestion. The frequent use of marijuana, therefore, may result in significant *in vivo* accumulation with a consequent reduction in the amount of drug needed to exceed a psychoactive threshold in the brain. Such accumulation has been reported to occur in volunteer subjects who claim having had no prior exposure to marijuana. Approximately 50% of a standardized dose of THC was present in the plasma of naive subjects 56 hr after administration. The factors possibly contributing to this prolonged retention include an enterohepatic recirculation of THC and/or active metabolites, binding to plasma proteins and sequestration in adipose tissue with delayed metabolism. In chronic marijuana smokers the biological half-life of THC was reduced appreciably (ie, $t_{1/2} = 28$ hr), but this period still is sufficiently long to result in accumulation if marijuana is used daily or more frequently.

Physical dependence may occur, since after 1 week of THC administration, a withdrawal syndrome has been observed which consisted of anorexia, nausea, insomnia, sweating, hyperthermia and tremor. The mildness of these responses probably is due to the slow elimination of THC from the body, which allows physiological and psychological systems to adjust to a drug-free state gradually.

Under experimental conditions employing male animals, and in human smokers, marijuana decreased testosterone blood levels, testicular size and weight, spermatogenesis and sexual potency. The inhibition of the release of luteinizing hormone (LH) from the pituitary gland, and the testicular responses to LH stimulation have been cited as possible mechanisms. However, THC also has weak estrogenic activity, as demonstrated by animal studies and clinical examination (including biopsy) of young males who developed gynecomastia during heavy marijuana use. THC inhibits ovulation in rats, rabbits and monkeys. The disruption of menstrual cycles has occurred in women who smoke marijuana on a regular basis.

Studies conducted with laboratory animals have shown that prolonged administration of THC may inhibit growth, impair lactation, promote thyroid hyperplasia and elevate plasma corticosteroid levels. These physiological alterations appear to reflect primarily actions of THC on the pituitary gland. High doses of THC in animals have been reported to induce hyperactivity and convulsive seizures indicative of neurotoxicity. Lacking comparable data in humans the significance of these studies must be interpreted cautiously.

Prolonged marijuana use may lead to serious pulmonary toxicity. *In vitro* tests employing lung explants demonstrated that marijuana smoke can induce premalignant and malignant cellular changes. Chronic exposure of animals to marijuana smoke led to severe bronchiolitis and squamous metaplasia of the tracheal mucosa, and fatal respiratory complications occurred in some cases. Bronchial biopsies in humans who were long-term marijuana smokers also revealed squamous metaplasia. Substantial respiratory impairment, indicated by a significant increase in resistance to airflow (suggestive of obstructive lung disease), and high carboxyhemoglobin levels also have been observed in these individuals. Both abnormalities are comparable to those associated with chronic tobacco smoking. In this regard, smoking one marijuana cigarette increases the concentration of carbon monoxide and tar in the lungs comparable to five or more tobacco cigarettes. Pulmonary toxicity should be considered a probable consequence of chronic marijuana smoking.

The suppression of cellular-mediated immune responsiveness has been demonstrated in young, chronic marijuana smokers, but this effect is transitory. The lymphocytic response observed in marijuana smokers was similar to that of patients in whom impairment of T (thymus-derived) cell immunity is known to occur. Some clinical studies have shown no significant suppression of lymphocyte function. Current clinical data indicate no increase in malignancies and infections among chronic marijuana smokers.

Personality, attitudinal and behavioral changes frequently are associated with chronic marijuana smoking. There characteristically is a reduction in motivation, the desire to be productive, creative or contributive, and the individual may experience acute feelings of insecurity. Although elements of this syndrome are typical of normal adolescent turmoil, compulsive involvement with marijuana may accelerate or project into, intensify and delay emergence from this ambivalent phase of life. Marijuana may foster similar disruptions in older persons but evidence also exists that individuals can continue to function effectively in artistic and other creative areas while indulging in frequent but moderate use of the drug.

The LaGuardia Report (Mayor's Committee on Marijuana, New York City, 1944) stated that "marijuana will not produce a psychosis *de novo* in a well-integrated stable person." Judging from the medical literature published subsequent to this report, primary marijuana psychosis is relatively rare in the US. The precipitation of serious psychological problems appears to occur primarily in persons with preexisting personality or emotional disturbances. The use of marijuana by schizophrenic patients, including those being treated with antipsychotic agents, may result in rapid and serious deterioration of their mental state necessitating rehospitalization in some cases.

Some studies have demonstrated a positive correlation between marijuana dosage and birth defects. However, other investigations have failed to provide evidence that marijuana possesses teratogenic activity. THC administered to

pregnant rats and dogs is transferred rapidly to fetal tissue and results in a higher than expected incidence of abnormal pregnancies and stillborn offspring. Malformations observed include cleft palate, accessory ribs, fused ribs and asynchronous and retarded vertebral ossification. Women who smoke marijuana while pregnant experience a longer period of labor and their newborn weigh less than normal and have altered CNS activity. THC is lipid-soluble and passes into the milk of the lactating female. Thus, marijuana specifically should be avoided by women who are breast-feeding their newborn.

Although primary attention has been directed to the adverse physiological and social effects of marijuana, there are several indications that the tetrahydrocannabinols may possess clinically useful properties. When administered to patients with advanced cancer, oral doses of THC (capsules containing 7 to 10 mg in sesame oil) elicited mild analgesic, antidepressant, tranquilizing and antiemetic effects. However, a rapid development of tolerance, sometimes by the third dose, has limited THC use in these patients. Further, at these doses, and more frequently at a higher (20 mg) dose, disturbing side effects, eg, dizziness, ataxia, blurred vision and excessive sedation, were observed. Although it often stimulates appetite, marijuana is not useful in treatment of anorexia nervosa. In fact, it probably should be contraindicated since persons with this disorder possess some underlying psychological abnormality which can be exacerbated by oral THC administration, ie, some patients receiving this therapy have developed significant dysphoria manifested as paranoia and loss of self-control. Other investigations have demonstrated significant and prolonged reduction of intraocular pressure by marijuana in glaucoma patients. The proposed anti-inflammatory and anticonvulsant activities of THC await further clinical evaluation.

Although much remains to be developed, there is beginning to emerge a reasonably clear picture of the acute pharmacological and toxicological effects of marijuana. While it will take longer to identify chronic toxic effects, the current deficiency of such observations should not, therefore, be misinterpreted.

Cigarettes

Although warnings have been published for 90 yr—"very many chronic, and often fatal, ailments are produced by the use of tobacco" (*Frank Merriwell's Book of Athletic Development*, Street & Smith, 1901)—many Americans are just recognizing the health risk from smoking cigarettes and are abandoning their use in significant numbers.

Cigarette smoking accounts for approximately ⅓ of all cancer deaths in this country and is the leading single cause of such mortality. Lung cancer and cigarette smoking have been linked convincingly by numerous clinical studies. There is a similar, though less frequent, association with pipe and cigar smoking.

Current evidence shows clearly that lung cancer deaths among women has increased substantially over the past 40 yr. This greater mortality is associated with a proportional increase in the number of women who have become cigarette smokers. Further evidence of this correlation is found in data from two states. In Washington, over a 10-yr period, the lung cancer death rate in women increased by more than 100% but the breast cancer death rate did not change significantly. In Utah, where a strong antismoking attitude prevails, the lung cancer death rate among women is less than 50% of that for breast cancer.

All smokers should be encouraged to stop since, after several years of nonsmoking, the risk of developing bronchogenic carcinoma approaches that of nonsmokers. Smokers also have a higher incidence of both periodontal disease and cancer of the oral cavity than nonsmokers. Bladder carcinoma, manifest both before and after the appearance of lung cancer, is another risk, as is cervical cancer. Switching to 'low tar, low nicotine' products may not be an improvement, since clinical studies show that smokers take more frequent and deeper puffs of these cigarettes than of regular ones in order to maintain their usual plasma levels of nicotine.

Bronchitis and respiratory tract disorders, in general, are more prevalent, not only in smokers, but among their family members as well since an exposure to cigarette smoke often is inescapable in the relatively closed atmosphere of a house or apartment.

Cardiovascular disorders occur more frequently, and the risk of death from coronary heart disease is significantly greater in smokers than in nonsmokers. In patients with hypertension, hypercholesterolemia or diabetes the risk of coronary heart disease is increased further by cigarette smoking. Peripheral vascular disease and cerebrovascular insufficiency also are encountered more often in smokers. A common link to these cardiovascular diseases appears to be the damage to blood vessel (eg, coronary artery) walls which occurs more frequently among smokers and which serves to promote formation of atherosclerotic plaques.

Myocardial infarction is a relatively rare complication in premenopausal females; however, cigarette smoking progressively increases the incidence of myocardial infarction to as much as 20-fold among women smoking 35 or more cigarettes per day. Since female hormones may be a factor in the lower rates of cardiovascular disease in women as compared to men, it is pertinent to note that menopause often occurs at an earlier age in women smokers.

Recent data also show an increase in stroke among young and middle-aged women who smoke cigarettes.

Smokers have elevated carboxyhemoglobin (COHb) levels due to inhalation of excess carbon monoxide from the combustion of tobacco. Significant carboxyhemoglobinemia reduces oxygen transport by the circulatory system. Environmental conditions result in the formation of COHb equivalent to approximately 0.5% of total hemoglobin in the nonsmoker. Smoking one pack of cigarettes per day may produce COHb in the range of 6% or more, a level which may result in interference with subtle CNS processes, eg, the judgment used in automobile driving.

Heavy smokers may show COHb levels of up to 20% of total hemoglobin, which places a substantial strain on the cardiovascular system. Such alterations in oxygen transport have led to consideration of possible restrictions on using smokers' blood for transfusions. An additional consequence of high carbon monoxide levels is secondary polycythemia, ie, tissue hypoxia due to prolonged exposure to carbon monoxide results in increased red-cell mass.

Gastrointestinal disturbances associated with smoking include epigastric discomfort, gastritis and, possibly, gastric and duodenal ulceration. An increase in gastric acid regurgitation into the esophagus apparently accounts for cigarette-induced heartburn which frequently is painful in heavy smokers.

Pyloric incompetence and subsequent reflux of duodenal juices may be a contributory factor in the gastritis and gastric ulceration since bile injures the gastric mucosa, particularly in the absence of food in the stomach. In addition, nicotine may cause areas of ischemia in the gastrointestinal tract and may reduce pancreatic buffering secretions, thus peptic ulceration may occur in the presence of even normal rates of gastric acid secretion.

Continued cigarette smoking during antiulcer therapy diminishes the probability of successful treatment.

In regard to influenza, several studies show that smokers contract this disease at a higher rate and experience a great-

er degree of incapacitation (ie, more lost work days than nonsmokers).

Considerable data show that smoking during pregnancy is associated with higher than normal rates of miscarriage, spontaneous abortion, prenatal mortality and premature birth. The newborn of women who smoke during pregnancy are more likely to be underweight, be short in stature and have a smaller head. These effects are dose-related, ie, the incidence increases in proportion to the number of cigarettes smoked per day. Weight, height and head circumference decrements persist 4 to 7 yr after birth.

Smokeless Tobacco—Switching to smokeless tobacco does *not* reduce toxicity. The use of two cans of snuff per week is equivalent to smoking two packs of cigarettes per day. The absorption of nicotine is rapid, peak plasma levels occurring within 5 minutes of application to the oral mucosa and twice as much nicotine is absorbed than from cigarettes. Leukoplakic lesions and cancers occur in the user's mouth, causing premature death in some teenagers and adults (Babe Ruth was a heavy user of smokeless tobacco and died of an oropharyngeal tumor at age 52).

Central Nervous System Stimulants

Amphetamines

The clinical indications for amphetamines include

The management of certain behavioral disturbances in children, eg, attention disorder (hyperkinetic syndrome) associated with minimal brain dysfunction.

The symptomatic control of narcolepsy.

The treatment of exogenous obesity, as short-term (ie, a few weeks) adjuncts in a regimen of weight reduction based on caloric restriction.

Benzphetamine, chlorphentermine, clortermine, diethylpropion, phendimetrazine or phentermine, alternatives to amphetamines in weight-reduction programs, also are subject to misuse and abuse. These compounds are related chemically and pharmacologically to the amphetamines, but possess a somewhat higher anorexiant-to-central stimulant ratio and peripheral sympathomimetic activity.

Misuse encompasses the episodic ingestion of amphetamines to suppress fatigue and prolong wakefulness and alertness, thus enabling the individual to continue mental or physical activity beyond his or her usual limit of endurance. Teachers frequently are witness to the futility of hyperamphetaminization—in the form of the tense, distraught student whose effective functioning is precluded by disorientation and mental short-circuiting or in the form of the exhausted and depressed student whose chemical props have collapsed.

Despite the hazards involved, long-distance truck drivers similarly use amphetamines to dispel monotony and boredom. Although the practice is overtly pernicious, the administration of amphetamines prior to engaging in athletic activity (eg, swimming, running, weight throwing) may improve performance to a degree that could be decisive in competition.

There remains a significant "gray area" of misuse—the prescribing of amphetamines and amphetamine-like drugs for unjustifiable reasons or, at best, in cases where the therapeutic rationale is questionable. To the busy medical practitioner, CNS stimulant and depressant drugs may provide an expedient, if less than ideal, means of helping his patients cope with the pressures and frustrations of everyday life. In the treatment of obesity these drugs provide a questionably effective and often self-deceptive approach to a complex biomedical problem.

Clearly, those engaged in prescribing and dispensing drugs must exorcise skilled judgment in eliminating as candidates for amphetamine therapy those patients so emotionally predisposed as to explore the secondary values of their anorexiants, ie, the mental lift, elan and psychic crutch upon which they increasingly may depend to cope with crises, real or imaginary.

Amphetamine abuse relates primarily to the nonsupervised ingestion or injection of large doses of amphetamine or its many chemical derivatives to experience the drug-induced psychic excitation, euphoria or "high," and the physical maelstrom of restless energy. Methamphetamine (methedrine, "speed") is a favored congener among habitual amphetamine users who generally inject the drug into a vein. This provides an almost instantaneous onset of the euphoric effect (the "flash" or "rush") which is ineffable and ecstatic.

A marked degree of tolerance to the amphetamines can be acquired as, eventually, several grams of drug per day may be consumed. There have been reports of the use of more than 10 g of methamphetamine intravenously over a 24-hr period. Tolerance does not develop uniformly to all the CNS effects. The compulsive user may evidence increased nervousness, anxiety and persistent insomnia as the dose is increased.

In a typical pattern of abuse immense doses of amphetamines are injected every few hours around the clock. These "runs," during which the individual remains awake continuously, generally last 3 to 6 days but may be prolonged to weeks if the user is able to sleep even as little as 1 hr a day. The appetite for food is suppressed and there is a feeling of unbridled energy and a compulsion for constant activity. Intravenous injection of enormous doses of amphetamines elicits a "chemically generated trauma," which appears linked inseparably to the acquired psychological dependence. The intense psychotoxic syndrome ultimately forces an interruption of drug use and the individual lapses into a protracted period of deep sleep (the "crash").

Although it generally is considered that the amphetamines do not induce a physical dependence, abrupt withdrawal is characterized by lethargy and profound depression, both psychic and physical, which reinforces the drive to resume their use.

Massive abuse of amphetamines frequently leads to considerable mental and physical deterioration. Intravenous injection of large doses is extremely disabling, socially and psychologically, and has resulted in psychiatric complications ranging from subtle personality changes to paranoid psychoses. Harm to the individual and to society often arises during psychotoxic episodes. In contrast to the decreased psychological drives of the opiate user, the compulsive user of CNS stimulants has exaggerated drives. Analyzing the personality factors which underlie the preferential abuse of CNS stimulants versus narcotics, it has been postulated that the amphetamine abuser uses the stimulant as one of a variety of compensatory maneuvers to maintain a posture of active confrontation with the environment. In contrast, the heroin abuser reduces anxiety via repression and withdrawal.

The hyperactivity, the compulsivity, the feeling of great muscular strength, the paranoid delusions and the auditory and visual hallucinations may combine to make the amphetamine or cocaine user capable of committing serious antisocial acts. Chronic users of stimulant drugs also are accident-prone, since they are unaware of their fatigue until it overcomes them at an inopportune time.

As in any situation in which hypodermic equipment is shared without proper sterilization, there exists a risk of bloodborne infection, notably viral hepatitis and AIDS. Among amphetamine abusers, evidence has been noted of hepatic damage so common as to suggest the possibility of a direct toxic effect on the liver.

Parenteral administration of large doses of sympathomimetic amines may result in morbidity or mortality due to

intracranial hemorrhage or cardiac arrhythmias secondary to severe hypertension. Necrotizing angiitis was observed in Rhesus monkeys given repeated injections of methamphetamine for a 2-week period, and clinical descriptions of cerebral vasculitis and hemorrhage following the injection of this sympathomimetic amine have been reported. Intravenous injection of amphetamines may result in a syndrome characterized by fever, leukemoid reaction, disseminated intravascular coagulation and rhabdomyolysis. These factors may be responsible for the development of acute renal failure in certain amphetamine abusers.

MDMA (3,4-methylenedioxymethamphetamine), also known as "Ecstasy," is a "designer" drug which, according to its users, increases their awareness and the ability to communicate. In regard to toxicity, a recent study demonstrated that MDMA selectively damaged central (brain) nerve fibers in monkeys after only 4 consecutive days of administration. Since monkeys also are sensitive to MPTP, a known neurotoxin in drug addicts, this preclinical investigation suggests that humans may be at risk following MDMA use.

Cocaine

Cocaine, as extracted by chewing leaves of the coca plant (*Erythroxylon coca*), has dispelled hunger, provided a sense of well-being and enhanced the physical endurance of Andean Indians since before the Conquistadors. Even today, in the Andean regions of South America, chewing coca leaves is regarded as no more deviant a practice than smoking tobacco leaves by persons in other parts of the world.

The subjective effects, toxicity and present-day patterns of cocaine abuse are remarkably similar to those of amphetamine. Until recently, cocaine was very expensive when purchased from illicit sources. However, larger amounts are now being smuggled successfully into the US, leading to reductions of the "street" price. This lower cost, in the presence of a more plentiful supply, has resulted in a greater number of citizens becoming cocaine addicts. When it is unavailable, abusers often resort to amphetamine. Extemporaneous mixtures of cocaine and amphetamine or heroin are common in the contemporary drug scene.

Regardless of the route of administration of cocaine (oral, nasal insufflation, intravenous), there is good correlation between the appearance of certain physical effects (tachycardia, elevated blood pressure) and psychological alterations ("high," pleasantness, anorexia). Free-base cocaine available as "crack," is absorbed rapidly after smoking; peak plasma levels occur within minutes.

Prolonged use may be associated with weight loss, insomnia, anxiety, paranoia, sensations of insects crawling under the skin ("cocaine bugs") and hallucinations (primarily visual—flashes of light or "snow lights"; may also be tactile, olfactory and auditory). Ulceration and perforation of the nasal septum also may occur. In one reported case of chronic cocaine sniffing, the patient presented with a continuous nasal discharge that was not mucus. Instead, it was shown to be cerebrospinal fluid leaking from the CNS area due to extensive cocaine-induced local tissue and nerve (olfactory) damage.

Large doses of cocaine may result in cardiac dysrhythmias, tremors, convulsions and delirium. Deaths have been reported following every route of cocaine administration, including nasal insufflation. Unusual fatalities have occurred in drug dealers who, to avoid detection, swallowed prophylactics filled with cocaine; when several condoms ruptured in the gastrointestinal tract, lethal concentrations of cocaine were absorbed.

Tolerance to cocaine develops very rapidly (tachyphylaxis), particularly when used daily. Although a "line" of cocaine has about 25 mg, some addicts have used 8 to 9 *grams* per day. Treatment consists of abrupt and complete cessation (as opposed to gradual—approximately 7 days—reduction with most CNS depressants).

A withdrawal syndrome, which includes increased appetite, fatigue (abuser may sleep for 24 straight hr) and depression (with increased suicidal tendency) usually occurs in cases of chronic administration. The craving for cocaine during withdrawal is very intense during the first 7 days and appears to be linked to hypersensitive dopamine receptors (compensatory biological adaptation to cocaine-induced dopamine depletion). Bromocriptine (Parlodel), a dopamine receptor agonist, has been employed successfully in treating this aspect of cocaine withdrawal.

Physical dependence, therefore, does occur with chronic cocaine abuse. However, its presence is unnecessary when classifying someone as an addict since addiction is characterized as "a behavioral pattern of compulsive drug abuse" associated with "overwhelming involvement with the use of a drug, the securing of its supply and a high tendency to relapse after withdrawal."[2] In this frame of reference, the chronic user of cocaine or amphetamine is an *addict*.

Psychotomimetics

Psychotomimetics constitute a structurally diverse group of naturally occurring and synthetic molecules. Interest in these compounds resides more in their misuse than in their legitimate medical use. They are of value as research tools in experimental psychiatry and in the exploration of central neurochemical mechanisms, but their therapeutic application remains limited and highly controversial.

At high dosage levels many drugs may disorganize mental function with resulting confusion, delirium, hallucinations and, frequently, memory loss or amnesia. Such drugs include atropine, scopolamine (and related centrally acting anticholinergics), quinine, quinidine, digitalis glycosides, mecamylamine, adrenocorticosteroids, nalorphine, disulfiram, bromides and certain heavy metals. The *toxic psychoses* produced by these drugs are due primarily to generalized metabolic disruption of both neural and extraneural systems rather than to discrete neurophysiological perturbations.

Certain chemicals, however, are uniquely capable of inducing dramatic changes in psychic processes (ie, perception, thought, feeling, mood and behavior) in doses which do not produce generalized metabolic disruption and which do not cause marked disturbances in sensorimotor or autonomic functioning. These compounds generally are classified as *psychotomimetics*, although the extent to which they mimic spontaneously occurring psychotic states is inconsistent and incomplete. Other imaginative designations for such substances include *psychosomimetics, psychotogenics, psychodysleptics, psychedelics, hallucinogenics, mysticomimetics* and *phantasticants*.

On a structural basis, psychotogenic chemicals may be classified into three major groups:

Substituted *indole alkylamines*, eg, dimethyltryptamine, psilocybin or lysergic acid diethylamide.

Substituted *phenyl alkylamines*, eg, mescaline or dimethoxymethylamphetamine.

A structurally *heterogeneous* group, including the glycolate ester, ditran [a mixture of *N*-ethyl-3-piperidyl-(30%) and *N*-ethyl-2-pyrrolidyl-methylcyclopentylphenyl glycolate (70%)] and the piperidine derivative, phencyclidine.

With the exception of lysergic acid diethylamide, the chemical nature and pharmacological properties of the various psychotomimetics will be considered only briefly. The interested reader is referred to several comprehensive reviews on this extensive and complex category of psychoactive agents (refer to the *Bibliography*).

Dimethyltryptamine

Hallucinogenic activity is characteristic of a large series of *N*-alkylated tryptamines. Structurally, the simplest of these is *N,N*-dimethyltryptamine (DMT). This compound occurs naturally in the seeds of *Piptadenia peregrina*. A powder prepared from these seeds, and referred to as *cohaba snuff*, is used by Haitian natives to induce mystical states of consciousness. DMT is not effective when taken orally. Perceptual and mood changes result when the compound is inhaled (snuffed), smoked or introduced parenterally. Its effects are rapid in onset and limited in duration (a few hours), irrespective of the route of administration. Synthetic higher homologs of DMT, ie, diethyltryptamine (DET) and dipropyltryptamine (DPT), produce qualitatively similar psychological effects which are, however, considerably longer-lasting.

Psilocybin and Psilocin

Psilocybin, the phosphate ester of 4-hydroxy-DMT occurs to the extent of about 0.3% in the Mexican mushroom, *Psilocybe mexicana*. Dephosphorylation *in vivo*, by alkaline phosphatase, converts psilocybin to psilocin (4-hydroxy-DMT). The loss of the phosphoric acid radical reduces the polarity of the molecule, enabling more-efficient penetration of the blood-brain barrier, which may account for the relatively greater hallucinogenic potency of psilocin as compared to psilocybin. Although psilocin is less potent than LSD (ie, approximately $1/100$ as active on a milligram basis) and produces a less-persistent psychedelic state, when equivalent doses are administered blind it generally is impossible for subjects acquainted with the LSD phenomenon to differentiate between the two drugs.

Mescaline

One of the first phenyl alkylamine hallucinogens to be identified was mescaline (3,4,5-trimethoxyphenethylamine), isolated originally from "mescal buttons," the flowering heads of the peyote cactus, *Lophophora williamsii*. This plant material long has been used by the Mescalero Apaches of the Southwest American plains in their quasireligious ceremonies of peyotism. Mescaline is not a particularly potent psychotomimetic. The equivalent oral dose of mescaline (usually 5 mg/kg in humans) is approximately 4000 times larger than that of LSD. Following oral administration, mescaline produces a characteristic syndrome of sympathomimetic effects, anxiety, hyperreflexia, static tremors and psychic perturbations including vivid hallucinations, usually of a visual nature. In man, mescaline has a biological half-life of about 6 hr. It is excreted in the urine principally in the form of the unaltered drug and the inert metabolite 3,4,5-trimethoxyphenylacetic acid.

The addition of an alpha-methyl substituent to mescaline produces 3,4,5-trimethoxyamphetamine (TMA), a psychotogen approximately twice as potent as mescaline. Its enhanced potency is due presumably to a decreased susceptibility to oxidative deamination provided by alkylation of the alpha-carbon.

The TMA analogue, 2,5-dimethoxy-4-methylamphetamine (DOM), is a potent psychedelic agent employed extensively by certain drug abusers and designated by them as STP (an acronym derived ostensibly from the terms "serenity, tranquility, peace"). In doses of 5 mg or more, it produces intense and relatively long-lasting emotional changes and perceptual distortions. Cases have been reported of individuals actively hallucinating for several days following a single oral dose.

The consideration of the pharmacology and structure-activity relationships of the numerous synthetic dimethoxyamphetamines, trimethoxyamphetamines and methoxymethylenedioxyamphetamines is beyond the scope of this presentation; this area has been reviewed extensively by Shulgin *et al*[3] and Snyder and Richelson.[4]

Lysergic Acid Diethylamide

The dextrorotatory isomer of lysergic acid diethylamide (LSD), synthesized by Hofmann in 1938, remains the most potent psychotogenic agent either of natural or synthetic origin discovered to date. Although as little as 25 μg of LSD may produce subjective effects, intense depersonalization usually requires doses in the range of 100 to 250 μg. Structurally, LSD is related to the ergot alkaloids, notably ergonovine. This structural resemblance may account for certain pharmacological and toxicological similarities among LSD and the lysergic acid alkaloids of ergot.

Metabolism—Following oral administration, LSD is absorbed rapidly and widely, but not distributed uniformly throughout the body. It is bound strongly to plasma proteins; highest concentrations are found in the liver, kidneys and lungs. Considerably less than 1% of an orally administered dose penetrates into the CNS. Autoradiographic analyses of brain samples obtained from animals injected with ^{14}C-labeled LSD revealed relatively high concentrations in the auditory and visual reflex areas. While the distribution of LSD within the brain would appear to suggest the functional involvement of specific neural areas in the psychotogenic phenomenon, there is an imperfect correlation between drug localization and sites of drug action.

In humans the biological half-life of LSD is approximately 3.5 hours; this corresponds roughly with the duration of the peak psychosensory effects which then subside gradually over an 8- to 12-hr period.

Pharmacological Effects—LSD possesses considerable CNS-stimulant activity. It produces an EEG pattern characteristic of central activation, alertness or arousal and causes insomnia in laboratory animals and humans. LSD counteracts the central depressant effect of barbiturates and is antagonized by such suppressants as chlorpromazine.

LSD produces a sequential, though somewhat overlapping, pattern of physiological and behavioral changes, the intensity and duration of which largely are dose-dependent. Pupillary dilation, tachycardia, tremulousness, hyperthermia and elevated blood glucose and free-fatty-acid levels, indicative of adrenergic activation, frequently are manifest during the early phases of the LSD response. These physiological alterations may be attributed both to primary LSD effects and to nonspecific stress-anxiety reactions.

Controlled studies of individuals under the influence of LSD uniformly reveal a generalized impairment of objective indices of adaptive behavior and psychomotor performance, especially those processes and procedures that require critical judgment and coordination. It is likely that intellectual and motor decrements are due to attenuation of attention and motivation as well as to sensory-cognitive disturbances.

Perceptual alterations constitute the most dramatic effects of LSD; their kaleidoscopic patterns defy a brief description. Illusions and pseudohallucinations, mostly of a visual or tactile nature, are experienced commonly, whereas true hallucinations are relatively infrequent. Synesthesia, the crossover from one sensory modality to another, is an often-encountered LSD phenomenon. Colors may be "heard" and music may become "palpable." Moods and emotions may range from euphoria, elation and ecstasy to dysphoria, depression and despair. The psychological state produced by LSD cannot be generalized with precision. As with other psychotropic drugs, the response depends on many variables, including the dose administered, the personality and expectations of the individual as well as environmental influences.

Mechanisms of Action—The neurophysiological corre-

lates of LSD-induced alterations in behavior are understood incompletely. However, recent data indicate that LSD and other hallucinogens act at postsynaptic serotonin receptor sites ($5HT_2$ subtype). The effect of LSD upon raphe neurons rosembles that of an excess of serotonin at postsynaptic receptor sites.

Experimental and Therapeutic Uses—LSD has been employed extensively to induce experimental psychoses for the primary purpose of studying aberrant mental states under controlled conditions. Despite prodigious efforts, the LSD model has not yielded pertinent clues to the biochemical etiology of schizophrenia.[4]

Several investigators have proposed LSD as an adjunct to conventional psychotherapy and as an aid in treatment of chronic alcoholism. LSD also has been reported to provide long-lasting "euphor-analgesia" in patients with terminal cancer. The feasibility and effectiveness of LSD for these purposes remain unestablished and controversial. LSD has no approved therapeutic uses and currently is an investigational drug subject to rigid state and federal regulations.

Dependence Liability—Marked psychological dependence on LSD is observed rarely as usage tends to be occasional or sporadic rather than frequent or compulsive. A high degree of tolerance to the physiological and behavioral effects of LSD develops after three or four doses taken within a relatively short period of time. This acquired resistance disappears rapidly if drug intake is terminated. There is considerable cross-tolerance among LSD, mescaline and psilocybin, but this phenomenon has not been demonstrated between LSD and either amphetamine or Δ^9-THC. As physical dependence on LSD does not develop, there is no characteristic abstinence syndrome upon abrupt discontinuation.

Toxicity—Despite its extreme psychotogenic potency the acute toxicity of LSD is remarkably low. The medical literature records no verified case of death in man attributable to the direct toxic effects of the drug, although fatal accidents and suicides have occurred during states of LSD intoxication. Homicides committed by persons apparently under the influence of LSD have been reported relatively infrequently. Most of the individuals involved evidenced premorbid psychopathological tendencies and thus the role of LSD in violent and assaultive behavior is equivocal.

LSD-induced feelings of depersonalization and affective, perceptual and cognitive distortions may, on occasion, result in disorientation, confusion and acute panic reactions characterized by anxiety, fear and a sense of helplessness and loss of control. "Bad trips" generally follow the ingestion of high doses of LSD by nontolerant persons. They also are likely to occur in inexperienced users, those with ambivalent attitudes toward the drug experience or in disturbing or threatening surroundings. Reequilibration usually takes place within 24 to 48 hr.

Recurrences of perceptual distortions may be experienced in the postdrug state by a relatively high percentage of LSD users. These "flashbacks," which vary in length from a few seconds to several minutes, may occur up to 5 yr after the drug was last taken. Flashbacks may be spontaneous but often are triggered by periods of emotional stress or anxiety or by other psychotropic drugs, such as marijuana. The mechanism of recurrent hallucinosis is unknown but may reflect a persistent disruption of psychological defense mechanisms with a periodic emergence of repressed fears or conflicts.

Chronic disruptive states associated with anxiety, depression, somatic disturbances and difficulty in functioning, which are relatively resistant to psychotherapy, commonly follow LSD use. Protracted schizophreniform psychotic states with paranoid behavior represent infrequently occurring but tragic psychological consequences of LSD. Most, but possibly not all, such cases involve unstable individuals with prepsychotic or premorbid personality traits. An unfavorable prognosis is indicated by motor retardation, withdrawal, blunt affect, anergy and suicidal ideation during the initial hospitalization period. Treatment varies, but lithium has been proven effective for the alleviation of LSD-induced psychosis.

There are several reports of inflammatory fibrosis occurring in individuals who have consumed LSD. This complication has been recorded previously with other lysergic acid derivatives, notably methysergide. Arteriospasm resulting in obstruction of the internal carotid artery, and the development of peripheral gangrene necessitating partial amputation of the extremities, constitute isolated case reports indicating that LSD shares the vasoconstrictor activity of other ergot alkaloids.

In 1967 investigators first reported chromosome damage in human leukocytes cultured *in vitro* with LSD. Although the clinical significance of this finding was exaggerated grossly in the public news media, the widespread publicity contributed to a significant downturn in the abuse of LSD at that time. The possibility of affecting generations yet unborn apparently struck a chord of moral responsibility in many who were convinced of their personal ability to maintain psychic control but who were unwilling to "pollute the genetic stream."

Genetic studies conducted with LSD have been reviewed critically by Dishotsky *et al.*[5] Although the relationships between LSD and chromosomal damage, leukemogenicity and teratogenicity remain unresolved, certain tentative conclusions appear warranted.

Data supporting a positive relationship between LSD and chromosomal aberrations have been obtained primarily with individuals reported to have taken LSD obtained in the black market. In most instances, the amount of LSD consumed cannot be ascertained or only can be approximated. The reputed LSD samples may contain other drugs or contaminants, either added or incompletely separated during the process of illicit synthesis. The population under study frequently extemporize with barbiturates, amphetamines, opiates, cocaine, marijuana and other psychotogens, in addition to LSD.

Chemically pure LSD administered under controlled conditions has, in several studies, failed to produce detectable damage to chromosomes or has produced transient chromosomal aberrations in peripheral leukocytes, but these defects were no longer evident several months after LSD administration. Transient chromosomal breaks in white blood cells occur spontaneously. They can be increased by certain antibiotics and antineoplastic agents and even by commonly employed drugs such as aspirin and caffeine. Viral infections are associated with an increased rate of chromosomal disruption. Hepatitis, gastrointestinal and upper respiratory viral infections are common among chronic drug abusers. Thus, it appears that chromosomal damage, when found, is related to a history of drug abuse in general and not to LSD specifically.

The pathological significance of chromosomal aberrations in continuously replenished peripheral leukocytes is equivocal. Testicular and bone-marrow biopsies in rhesus monkeys given repeated oral doses of LSD have not revealed significant chromosomal alterations in gametogenic and hemopoietic tissues.

Two cases of acute leukemia developing subsequent to the use of LSD are recorded. Although a causal relationship has not been established it may be premature to dismiss the association as merely coincidental.

Some studies suggest a higher incidence of spontaneous abortion among pregnant women who reportedly took LSD prior to or after conception, and a greater number of congen-

ital anomalies among live infants born to mothers exposed to this drug. However, several complicating factors preclude a definitive correlation of increased reproductive risk with LSD ingestion. Among these are the indeterminate nature of purported LSD samples obtained "on the street," a common history of multiple usage of illicit drugs, a high incidence of infectious diseases (especially viral illnesses) and marginal maternal nutrition. Although the effect of LSD on human pregnancy and fetal malformations remains uncertain, discretion dictates the avoidance of this drug by women of childbearing age.

Phencyclidine

Phencyclidine (PCP, "angel dust"), chemically and pharmacologically similar to ketamine (Ketalar) used to induce "dissociative anesthesia," is probably the most dangerous substance abused in the US. There is no consensus as to the precise pharmacological classification of PCP. The compound may, depending on the dose and other circumstances of use, exhibit stimulant, depressant, analgesic and hallucinogenic properties. In "street" form, PCP often is adulterated and frequently misrepresented as THC, mescaline, LSD, amphetamine, cocaine or many other psychoactive agents.

Although occasionally ingested orally or injected intravenously, PCP most commonly is smoked (after placing it on marijuana or dried parsley leaves in a "joint") or "snorted" (nasal insufflation). By smoking, the experienced user can limit the dose of PCP (self-titration) to a level with which he is comfortable and less likely to overdose than when the drug is taken orally.

While PCP ingestion can produce euphoria, adverse reactions more commonly are observed, particularly in naive users. An excellent classification of PCP effects has been developed by Rappolt *et al*[6] based upon their treatment of more than 250 cases. Tachycardia and elevated blood pressure are consistent findings and appear, in varying degrees, within each of the following categories:

Stage I: 2 to 5 mg PCP (serum concentration, 25 to 90 ng/mL)

Subjects are disoriented, combative and violent. They also experience ataxia, alterations in perception of visual, auditory and tactile sensations, excessive sweating and salivation and analgesia (they may injure themselves unknowingly due to this analgetic property).

Deaths occurr when subjects lose control of motor function yet attempt activities which require significant physical skill, eg, some try to swim but subsequently drown. Other fatalities happen after abusers engage in violent fights or fall asleep in the middle of a street and are crushed by a motor vehicle.

Stage II: 5 to 25 mg PCP (serum concentration, 90 to 300 ng/mL)

The patient presents with coma and does not respond to verbal communication; reactions to painful stimuli will occur, however. Muscle spasms and severe hyperthermia also may be present.

Stage III: Above 25 mg PCP (serum concentrations, above 300 ng/mL)

Deep coma is observed with patients showing no response to extremely painful stimuli. Seizures also are likely and may develop into status epileptics.

Although the data are more difficult to interpret, it appears that a number of deaths solely and directly are related to excessive blood levels of PCP. Cerebral hypoxia due to severe spasm of cerebral blood vessels may be a mechanism of lethality.

Delayed psychological reactions (delirium, psychosis and/or agitation) occurring approximately 1 week after consumption of high doses of PCP have been observed. This may be due to the high, lipid-solubility of the drug resulting in an accumulation in, and slow release from, adipose tissue; the $t_{1/2}$ is approximately 18 hr. On occasion, patients hospitalized for a psychiatric examination have their blood analyzed for PCP levels. In some of these cases, a result showing an absence of PCP may be incorrect. The methods of analysis using high-performance liquid chromatography (HPLC), gas chromatography with flame ionic detection (GC-FID) or radioimmunoassay (RIA) are accurate only down to levels of 100 to 200 ng/mL. However, as presented above, serum PCP concentrations between 25 and 90 ng/mL are sufficient to induce aberrant behavior. A recent study employing a more sensitive assay procedure, a glass capillary-gas chromatography thermionic specific (nitrogen) detector (GC-N) capable of measuring levels as low as 5 pg/mL, reported that of 135 patients admitted for psychiatric evaluation, 78 had PCP levels between 1 and 50 ng/mL. This is a significant observation since it can assist physicians in determining the correct treatment.

A two- to four-fold tolerance develops if PCP is administered chronically to laboratory animals. However, experiments performed to date do not suggest that PCP produces physical dependence comparable to that which develops to the opiates or other CNS depressants.

In normal volunteers, PCP induces a schizophrenic-like state. Thus, as is the situation with marijuana, individuals with psychoses (diagnosed or undiagnosed) particularly are vulnerable to PCP. Schizophrenics experience a deterioration of their condition, possibly culminating in stuporous or excitatory catatonia or paranoia accompanied by auditory hallucinations.

Rhabdomyolysis (skeletal muscle degeneration), myoglobinuria and renal failure have developed after acute, large doses of PCP, whereas chronic use is associated with both psychological and physical dependence, and alterations in memory, speech and vision. These latter changes are suggestive of organic brain damage.

Treatment of Acute Drug Overdosage

A major problem in treating incoherent drug-overdosed patients, ranging from comatose to delirious, is the absence of definitive data regarding the substance(s) responsible for the intoxication. Upon admission to an emergency center it is imperative that staff members consult persons on the scene or the patient's friends in an attempt to obtain as much information as possible about the drug(s), amounts and modes of administration, circumstances leading to the overdosage and pertinent aspects of the patient's medical history, eg, does the patient have diabetes or epilepsy? Due, however, to extensive adulteration of "street" drugs, the information obtained on drug identity and quantity must be evaluated with caution. Symptomatic treatment is advisable until a definitive diagnosis can be established. The following is a limited presentation of options available for treating adverse reactions to psychoactive substances.

Volatile Hydrocarbons—The treatment of acute intoxication with volatile hydrocarbons is similar to that employed for barbiturate overdosage. If the vapors are inhaled, oxygen (or a 95% O_2 and 5% CO_2 gas mixture) may be administered. When volatile hydrocarbons are swallowed, gastric lavage rather than an emetic should be used. The injection of epinephrine or other sympathomimetic amines should be avoided due to the possibility of myocardial sensitization and precipitation of cardiac arrhythmias.

Opioids—Naloxone remains the drug-of-choice in countering narcotic analgetic overdosage. This narcotic antagonist, which possesses little or no agonistic activity, may be administered to the unconscious patient in the absence of a definitive diagnosis of narcotic overdosage. Naloxone will not produce additional CNS-depressant effects in the event that acute poisoning is due to barbiturates or other nonnarcotic depressants.

Psychotomimetics—In cases of adverse psychological reactions to hallucinogens ("bad trips"), patients should be maintained in a supportive and nonthreatening environment. Verbal contact should be established for reality defining and reassurance ("talk-down") that the episode eventually will terminate. If pharmacological intervention appears indicated, the use of diazepam (or a related benzodiazepine derivative) avoids the hazards which may be encountered with a phenothiazine in an unsuspected case of anticholinergic drug intoxication or in an individual with a history of convulsive disorders. When known anticholinergic agents are taken in excessive quantities, physostigmine, which antagonizes both central and peripheral atropine-like effects, is the drug-of-choice.

Phencyclidine—The treatment of PCP overdosage differs from that associated with hallucinogens as intoxicated patients should not be engaged in an extended "talk-down" process. Isolation, with periodic observation, is beneficial as in relieving the symptoms of acute schizophrenic reactions. Diazepam may control severe agitation. Acidification of the urine with ascorbic acid or cranberry juice (avoid ammonium chloride or orange juice) accelerates the excretion of PCP and may reduce the incidence of delayed reactions.

Cocaine—Adverse reactions to cocaine are usually of short duration and may terminate before treatment is initiated. Propranolol may be employed to attenuate the cardiovascular disturbances in cases of moderate cocaine overdosage. Diazepam may suppress the CNS excitation, although the possibility of adding to subsequent cocaine-induced respiratory depression must be considered.

Amphetamines—Disturbances of the sympathetic nervous system observed in amphetamine toxicity should be treated if they threaten the patient. Acidification of the urine (avoid ammonium chloride or orange juice) can shorten the duration of attendant psychoses significantly. In the presence of acute renal failure accompanying shock and rhabdomyolysis associated with amphetamine intoxication, substantial fluid replacement is indicated.

* * * *

Pharmacists can participate in the early management of acute drug poisoning by advising the use of ipecac *syrup* (not the fluidextract) in appropriate situations. If the subject has ingested a potentially harmful quantity of drugs and is conscious, *syrup of ipecac* may be employed in the following oral doses: patient under 1 yr—10 mL; 1 to 12 yr—15 mL; over 12 yr—30 mL. Subsequently, 250 to 500 mL of liquid should be given. Vomiting within 30 min occurs in approximately 90% of patients receiving this regimen. If emesis does not ensue within 30 min, the recommended dose, with additional fluids, may be repeated. Syrup of ipecac is less useful if more than 60 min have elapsed since consumption of the drug overdose. If the patient does not vomit after two doses of the ipecac, the dosage should be recovered by gastric lavage.

References

1. Weil AT: *N Engl J Med* 282: 997, 1970.
2. Jaffe JH. In Gilman AG, Goodman LS *et al*, eds: *The Pharmacological Basis of Therapeutics*, 7th ed, Macmillan, New York, 532, 1985.
3. Shulgin AT *et al*: *Nature* 221: 537, 1969.
4. Snyder SH, Richelson E. In Efron DH, ed: *Psychotomimetic Drugs*, Raven, New York, 43, 1970.
5. Dishotsky NI *et al*: *Science* 172: 431, 1971.
6. Rappolt RT *et al*: *Clin Toxicol* 16: 509, 1980.

Bibliography

Opioids

Cami J *et al*: *Clin Pharmacol Ther* 38: 336, 1985.
Christie DJ *et al*: *Arch Int Med* 143: 1174, 1983.
D'Agostino and Arnett EN: *JAMA* 241: 277, 1979.
Nathenson G *et al*: *J Pediatr* 81: 899, 1972.
Pearson MA *et al*: *Clin Toxicol* 15: 267, 1979.
Singer TP *et al*: *Toxicology* 49: 17, 1988.
Soin JS *et al*: *JAMA* 224: 1717, 1973.

Barbiturates

Kay DC *et al*: *Clin Pharmacol Ther* 13: 221, 1972.
Smith DE, Wesson DR: *JAMA* 213: 294, 1970.
Solomon F *et al*: *N Engl J Med* 300: 803, 1979.

Nonbarbiturate Depressants

Faulkner TP *et al*: *Clin Toxicol* 15: 23, 1979.
Gerald MC, Schwirian PM: *Arch Gen Psychiat* 28: 627, 1973.
Ionescu-Pioggia, M *et al*: *Int Clin Psychopharmacol* 3: 97, 1988.
Schnoll SH, Fishkin R: *J Psychedel Drugs* 5: 79, 1972.

Alcohol

Agarwal BN *et al*: *NY J Med* 73: 1331, 1973.
Becker JT *et al*: *Alcohol: Clin Exper Res* 7: 213, 1983.
Gill JS *et al*: *N Engl J Med* 315: 1041, 1986.
Hammond KB *et al*: *JAMA* 226: 63, 1973.
Harris RE, Wynder EL: *JAMA* 269: 2867, 1988.
Jones KL *et al*: *Lancet* 1: 1267, 1973.
Jones RJ *et al*: *JAMA* 249: 2517, 1983.
Myers RD: *Ann Rev Pharmacol Toxicol* 18: 125, 1978.
Slavney PR, Gran G: *J Clin Psychiatry* 39: 782, 1978.

Volatile Hydrocarbons

Hayden JW *et al*: *Clin Toxicol* 11: 549, 1977.
Haverkos HW, Dougherty J: *Am J Med* 84: 497, 1988.
Sigell LT *et al*: *Am J Psychiatry* 135: 1216, 1978.

Aerosols

Harris WS: *Arch Intern Med* 131: 162, 1973.
Kilen SM, Harris WS: *J Pharmacol Exp Ther* 183: 245, 1973.
Sharp CW, Brehm ML, eds: *NIDA Research Monograph* 15: October, 1977.
Steadman C *et al*: *Med J Aust* 141: 115, 1984.

Marijuana

Dalterio S *et al*: *Pharmacol Biochem Behav* 8: 673, 1978.
Gross H *et al*: *J Clin Psychopharm* 3: 165, 1983.
Hollister LE: *Pharmacol Rev* 38: 1, 1986.
Lemberger L, Rubin A: *Drug Metab Rev* 8: 59, 1978.
Reeve VC *et al*: *Drug Alcohol Depend* 11: 167, 1983.
Tashkin DP *et al*: *Ann Intern Med* 89: 539, 1978.
Treffert DA: *Am J Psychiatry* 135: 1213, 1978.
Weinberg D *et al*: *Pediatrics* 71: 848, 1983.
Wu T-C *et al*: *N Engl J Med* 318: 347, 1988.

Cigarettes

Colditz, GA *et al*: *N Engl J Med* 318: 937, 1988.
Edwards TA: *Br Med J* 1: 637, 1977.
Fielding JE: *N Engl J Med* 298: 337, 1978.
Grimes DS, Goddard J: *Br Med J* 2: 460, 1978.
Jick H *et al*: *Lancet* 1: 1354, 1977.
Kline J *et al*: *N Engl J Med* 297: 793, 1977.
Read NW, Grech P: *Br Med J* 3: 313, 1973.
Slone O *et al*: *N Engl J Med* 298: 1273, 1978.
Stolley PD: *Ibid* 309: 428, 1983.
Trevathan E *et al*: *JAMA* 250: 499, 1983.

Smokeless Tobacco

Benowitz NL *et al*: *Clin Pharmacol Ther* 44: 23, 1988.

Central Nervous System Stimulants

Cohen S: *JAMA* 231: 74, 1975.
Dackis CA, Gold MS: *Lancet* 1: 1151, 1985.
Finkle B, McCloskey KL: *J Forensic Sci* 23: 173, 1978.
Goldstein FJ: *Med Times* 116: 123, 1987.
Resnick RB, Kestenbaum RS: *Science* 195: 696, 1977.
Ricaurte GA *et al*: *JAMA* 260: 51, 1988.
Sawicka EH and Trosser A: *Br Med J* 286: 1476, 1983.
Siegl RK: *Am J Psychiatry* 135: 309, 1978.
Suarez CA *et al*: *JAMA* 238: 1391, 1977.

Psychotomimetics

Brawley P, Duffield JC: *Pharmacol Rev* 24: 31, 1972.
Efron DH, ed: *Psychotomimetic Drugs*, Raven, New York, 1970.
Jacobs BL: *Am Sci* 75: 386, 1987.

Lake CR *et al*: *Am J Psychiatry 138:* 1508, 1981.
Lipton MA *et al*, eds: *Psychopharmacology: A Generation of Progress*, Raven, New York, 1978.
Smythies JR. In *Neurosciences Research Symposium Summaries*, MIT Press, Cambridge, MA, 1971.
Usdin E, Forrest IS, eds: *Psychotherapeutic Drugs*, Dekker, New York, 1976–77.

Phencyclidine

Allen RM, Young SJ: *Am J Psychiatry 135:* 1081, 1978.
Aniline D *et al*: *Biol Psychiatry 15:* 813, 1980.
Burns RS *et al*: *West J Med 125:* 345, 1975.
Burns RS, Lerner SE: *Clin Toxicol 12:* 463, 1978.
Cohen S: *JAMA 238:* 515, 1977.
Cook CE *et al*: *Fed Proc 42:* 2666, 1983.
Hoogwerf B *et al*: *Clin Toxicol 14:* 47, 1979.
James SH, Schnoll SH: *Ibid 9:* 573, 1976.
Peterson RC, Stillman RC, eds: *NIDA Research Monograph 21:* August, 1978.

Treatment of Acute Drug Overdosage

Bledsoe BE *et al*, eds: *Prehospital Emergency Pharmacology*, Prentice-Hall, 1988.
Kline NS *et al*, eds: *Psychotropic Drugs: A Manual for Emergency Management of Overdose*, Medical Economics, Oradell, NJ, 1974.
Veltri JC, Temple AR: *Clin Toxicol 9:* 407, 1976.

CHAPTER 75

Preformulation

Louis J Ravin, PhD
Department of Pharmaceutics
Research & Development
Smith Kline & French Laboratories
King of Prussia, PA 19406

Galen W Radebaugh, PhD
Director of Pharmaceutics
Parke-Davis Pharmaceutical Research Division
Warner-Lambert Co
Morris Plains, NJ 07950

The attention presently being given to multisource pharmaceutical products regarding their equivalency places much emphasis on the formulation of these products. In some instances, the bioavailability of a drug formulation represents a quality parameter of enormous proportion. It is a matter of record that with certain drugs, depending on the formulation, the rate at which the drug substance becomes available can vary significantly from very high to none at all. As a result, the effectiveness of these formulations will range dramatically from that expected to no effect. Unfortunately, most examples are less dramatic and fall somewhere in between. The difference in the bioavailability of these drug products is less readily discernible, but nonetheless real. This has led to a great deal of confusion and information which, though understood by the scientist, is unclear and jumbled to the practitioner. That information which is available also has been interpreted differently by different individuals or groups, depending very often on the motivation, viewpoint and attitude of the interpreter.

Drug products indeed do vary in their bioavailability characteristics and this variation, in most instances, is related directly to formulation considerations. To optimize the performance of drug products, it is necessary to have a complete understanding of the physical-chemical properties of drug substances prior to formulating them into drug products. The development of an optimum formulation is not an easy task, and many factors readily influence formulation properties. Drug substances rarely are administered as chemical entities, but almost always are given in some kind of formulation. These may vary from a simple solution to a very complex drug delivery system. The complexity usually is not intentional, but rather is determined by the properties that are expected from or built into the dosage form and by the resulting composition that is required to achieve these qualities.

The high degree of uniformity, physiological availability and therapeutic quality expected of modern medicinal products usually are the results of considerable effort and expertise on the part of the formulating pharmacist. These qualities are attained by careful selection and control of the quality of the various ingredients employed, appropriate manufacturing according to well-defined processes and, most importantly, adequate consideration of the many variables that may influence the composition, stability and utility of the product. In dealing with the formulation of new products it has become necessary to apply the best research methods and tools in order to develop, produce and control the potent, stable and effective dosage forms which make up our modern medical armamentarium.

The pharmaceutical formulator has need for specialized areas of science in order to acquire scientific information about the drug substance which is necessary to develop an optimum dosage form. The pharmaceutical industry is in an era in which one can no longer rely on past experience to formulate. A thorough understanding of the physical and chemical properties as well as the pharmacokinetic and biopharmaceutical behavior of each drug substance being developed is necessary. In short, as much information as possible must be acquired about the drug substance very early in its development. This requires an interdisciplinary approach at the preformulation stage of development. Fig 75-1 schematically indicates that the development of any drug product requires a multidisciplinary approach, involving basic science, during the preformulation stage followed by applied science during the development stage.

This chapter will discuss the physical-chemical evaluation that takes place during the preformulation stage of development. In addition, consideration will be given to some specialized formulation ingredients that may require discretion in their selection.

Preformulation may be described as a stage of development during which the physical pharmacist characterizes the physical-chemical properties of the drug substance in question which are considered important in the formulation of a stable, effective and safe dosage form. Such parameters as crystal size and shape, pH-solubility profile, pH-stability profile, polymorphism, partitioning effect, drug permeability and dissolution behavior are evaluated. During this evaluation possible interactions with various inert ingredients intended for use in the final dosage form also are considered. The data obtained from this evaluation are integrated with data obtained from the preliminary pharmacologic and biochemical studies and provide the formulating pharmacist with information that permits selection of the optimum dosage form containing the most desirable inert ingredients for use in its development.

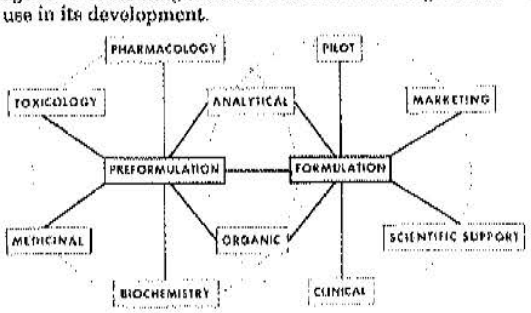


Fig 75-1. The wheels of product development.

Preformulation work usually is initiated after a compound has shown sufficient activity to merit further testing in humans. When this decision is made, the various disciplines begin to generate data essential for properly evaluating the performance of the drug substance. A stability-indicating analytical assay is very important. Since this often takes considerable time, it sometimes is necessary to rely on thin-layer chromatographic procedures to determine if a drug molecule is degrading. Accelerated testing procedures are used to promote breakdown of the compound being tested. Attempts are made to isolate and characterize the breakdown products in order to identify the mechanism of breakdown. This information provides a lead to the development pharmacist in his efforts to formulate the product.

During a preformulation study it is necessary to maintain some degree of flexibility. Problem areas must be identified early. For example, selection of a suitable salt form of the drug may be critical. Toxicity studies usually are scheduled early. Consequently, if the salt form under consideration has some deficiencies, they should be pointed out so that alternate salts may be prepared and evaluated prior to beginning toxicity studies.

When preformulation studies are initiated, the chemical usually is in short supply; 25 g of chemical is an ample supply, but many preliminary evaluations have been done with less. The initial supply usually originates as excess from batches prepared by the medicinal chemists. They usually have preliminary data such as melting point, solubility, spectral data and structure of the compound. The direction taken for the evaluation is determined by the structure and the intended dosage forms to be developed (eg, one would not waste time determining the stability of a solution of a compound if there was no interest in a liquid dosage form). Many areas must be evaluated critically for each compound, and it is essential that problem areas be identified early, otherwise delays could occur if a problem surfaced during the development phase for the compound. Some consequences of poor preformulation work are

Possible use of unsatisfactory salt form.
Poor stability of the active ingredient.
Testing compound of marginal activity.
Increased development costs.
Increased development time.

When preformulation studies are completed, the data are compiled and transferred to the development pharmacist, who, in turn, uses this information to plan his development work on the finished dosage forms.

Physical Properties

Description

Since the pure drug entity is in short supply at the outset of most preliminary evaluations, it is extremely important to note the general appearance, color and odor of the compound. These characteristics provide a basis for comparison with future lots. During the preparation of scale-up lots the chemist usually refines or alters the original chemical synthetic route. This sometimes results in a change in some of the physical properties. When this takes place, comparisons can be made with earlier lots and decisions made regarding solvents for recrystallization.

Taste usually warrants some consideration, especially if the drug is intended for oral use in pediatric dosage forms. In such cases consideration should be given to the preparation of alternate salt forms or possible evaluation of excipients that mask the undesirable taste.

Microscopic Examination

Each lot of drug substance, regardless of size, is examined microscopically and a photomicrograph taken. The microscopic examination gives a gross indication of particle size and characteristic crystal properties. These photomicrographs are useful in determining the consistency of particle size and crystal habit from batch to batch, especially during the early periods of chemical synthesis; if a synthetic step is changed, they also give an indication of any effect the change may have on crystal habit. One must keep in mind that the photomicrograph only gives a qualitative indication of particle size distribution; it always is necessary to do a particle-size analysis for a more accurate picture of the distribution of particles in any particular batch of drug substance.

Particle Size

The uses of pharmaceutical products in a finely divided form are diverse. From knowledge of their particle size, such drugs as griseofulvin, nitrofurantoin, spironolactone, procaine penicillin and phenobarbital have been formulated so as to optimize activity. Other drugs, formulated in suspension or emulsion systems, in inhalation aerosols or in oral dosage forms, may contain finely divided material as an essential component. One of the basic physical properties common to all these finely divided substances is the particle-size distribution, ie, the frequency of occurrence of particles of every size. What is of practical interest usually is not the characteristics of single particles but rather the mean characteristics of a large number of particles. It must be emphasized, however, that knowledge of size characteristics is of no value unless adequate correlation has been established with functional properties of specific interest in the drug formulation. Many investigations demonstrating the significance of particle size are reported in the literature. It has been shown that dissolution rate, absorption rate, content uniformity, color, taste, texture and stability depend to varying degrees on particle size and distribution. In preformulation work it is important that the significance of particle size in relation to formulation be established early. Preliminary physical observations sometimes can detect subtle differences in color. If this can be attributed to differences in particle-size distribution, it is important to define this distribution and recommend that more attention be given to particle size in preparing future batches of drug substance. This effect also is evident when preparing suspensions of poorly soluble materials. One may observe batch-to-batch differences in the color of a suspension which can be related to differences in particle size. Sometimes, when small particles tend to agglomerate, a subtle change in color or texture may be evident.

Sedimentation and flocculation rates in suspensions are in part governed by particle size. In concentrated deflocculated suspensions the larger particles exhibit hindered settling and the smaller particles settle more rapidly. In flocculated suspensions the particles are linked together into flocs which settle according to the size of the floc and porosity of the aggregated mass. Flocculated suspensions are preferred since they have less tendency to cake and are more rapidly dispersible. Thus, it is apparent that the ultimate height, H_u, of sediment as a suspension settles depends on particle size. The ratio H_u/H_o, or the degree of suspendibility as affected by particle size, is valuable information for the formulator in order to prepare a satisfactory dosage form.

The rate of dissolution of small particles usually is faster than that of larger ones because rate of dissolution depends on the specific surface area in contact with the liquid medium. This usually is described by the modified Noyes-Whitney equation for dissolution rate dA/dt

$$\frac{dA}{dt} = KS(C_s - C) \qquad (1)$$

where A is the amount of drug in solution, K is the intrinsic dissolution rate constant, S is the surface area, C_s is the

concentration of a saturated solution of the drug and C is the drug concentration at time t. The surface area of an object, regardless of shape, varies inversely with its diameter and confirms the above effect of particle size on dissolution rate. Solubility also has been observed to depend on particle size. Dittert, *et al*,[1] reported data for an experimental drug, 4-acetamidophenyl 2,2,2-trichloroethyl carbonate, which demonstrated that the dissolution rate and, in turn, bioavailability were affected by particle size. Although the ultimate amount of drug in solution may not be significant with respect to the dose administered, the formulator should be aware of this potential. With poorly soluble drugs it is extremely important to take these factors into account during the design of the dosage form.

Flow properties of drugs can be influenced by particle size, and particle size reduction to extremely small sizes (less than 10 μm) may be inadvisable for some drug substances. Entrapped air adsorbed on the surface of the particles and/or surface electrical charges sometimes impart undesirable properties to the drug. For example, adsorbed air at the drug-particle surface may prevent wetting of the drug by surrounding fluid, and electrically induced agglomeration of fine particles may decrease exposure of the drug surface to surrounding dissolution medium. Such effects act as dissolution rate-limiting steps since they minimize maximum drug surface-liquid contact.

Crystal growth is also a function of particle size. Finer particles tend to dissolve and subsequently recrystallize and adhere to larger particles. This phenomenon is referred to as *Ostwald ripening*. Protective colloid systems can be used to suppress this nucleation. Preformulators can generate information concerning the effectiveness of different colloids that is extremely important to the formulator when he is given the task of preparing a suspension dosage form.

Particle-size reduction may be deleterious for some drug substances. Increasing surface area by milling or other methods may lead to rapid degradation of a compound. Drug substances also may undergo polymorphic transformation during the milling process. The preformulator must always be cognizant of these potential problems, and whenever the decision is made to reduce particle size, the conditions must be controlled and the stability profile evaluated. If a problem does arise, it is the responsibility of the preformulator to note it and attempt to resolve it prior to turning the drug substance over to the formulating pharmacist.

Gastrointestinal absorption of a poorly soluble drug may be affected by the particle-size distribution. If the dissolution rate of the drug is less than the diffusion rate to the site of absorption and the absorption rate itself, then the particle size of the drug is of great importance. Smaller particles should increase dissolution rate and, thus, bring about more rapid gastrointestinal absorption. One of the first observations of this phenomenon was made with sulfadiazine. Blood-level determinations showed that the drug in suspension containing particles 1 to 3 μm in size was absorbed more rapidly and more efficiently than from a suspension containing particles 7 times larger. Maximum blood levels were about 40% higher and occurred 2 hours earlier. Increased bioavailability with particle-size reduction also has been observed with griseofulvin. The extent of absorption of an oral dose increased 2.5 times when the surface area was increased approximately sixfold. Micronized griseofulvin permits a 50% decrease in dosage to obtain a satisfactory clinical response.

On the other hand, it was found that with nitrofurantoin there was an optimal average particle size that minimized side effects without affecting therapeutic response. In fact, a commercial product containing large particles is available. For chloramphenicol, particle size has virtually no effect on total absorption but it significantly affects the rate of appearance of peak blood levels of the drug. After administration of 50-μm particles, as well as 200-μm particles, peak levels occurred in 1 hour; with 400-μm particles peak levels occurred in 2 hours; with 800-μm particles peak levels occurred in 3 hours. All four preparations had the same physiological availability, which implies that the absorption of chloramphenicol occurs uniformly over a major portion of the intestinal tract.

Reduction of particle size also may create adverse responses. For example, fine particles of the prodrug trichloroethyl carbonate were more toxic in mice than regular and coarse particles.[2] Increasing the surface area for water-soluble drugs, and possibly for weakly basic drugs, appears to be of little value. Absorption of weak bases usually is rate-limited by stomach emptying time rather than by dissolution. As previously mentioned, particle size is of importance only when the absorption process is rate-limited by the dissolution rate in gastrointestinal fluids.

The previous discussion considered the effect of particle size of the drug substance and its relationship to formulation. The particle size of the inert ingredients merits some attention. When one is concerned with particle size, all ingredients used in preparing the dosage form should be evaluated and some recommendation regarding their control should be made prior to full-scale development of a dosage form. It is recommended highly that particle size and its distribution be determined, optimized, monitored and controlled when applicable, particularly during early preformulation studies when the decision is made with regard to a suitable dosage form. The more common methods of determining particle size of powders used in the pharmaceutical industry include sieving, microscopy, sedimentation and stream scanning.

Sieving or Screening—Sieving or screening is probably one of the oldest methods of sizing particles and still is used commonly to determine the size distribution of powders in the size range of 325 mesh (44 μm) and greater. These data serve usually as a rough guideline in evaluating raw materials with regard to the need for milling. The basic disadvantages of screen analysis are the large sample size required and the tendency for blinding of the screens due to static charge or mechanical clogging. The advantages include simplicity, low cost and little skill requirement of the operator.

Microscopy—Microscopy is the most universally accepted and direct method of determining particle-size distribution of powders in the subsieve range, but this method is tedious and time-consuming. The preparation of the slide for counting particles is important because the sample must represent the particle-size distribution of the bulk sample. Extreme care must be taken in obtaining a truly representative sample from the bulk chemical. The cone and quartering technique usually gives a satisfactory sample. The sample should be properly suspended, dispersed and mixed thoroughly in a liquid which has a different refractive index from the particles being counted. A representative sample is mounted on a slide having a calibrated grid. For counting, random fields are selected on the slide and the particles are sized and counted. Between 500 and 1000 particles should be counted to make statistical treatment of the data meaningful.

Sedimentation—Sedimentation techniques utilize the dependence of velocity of fall of particles on their size. Application is made of the Stokes equation (see page 295) which describes a relationship between the rate at which a particle settles in a fluid medium to the size of that particle. Although the equation is based on spherical-shaped particles, it is used widely to determine the weight-size distribution of irregularly shaped particles. Data obtained by this procedure are usually reliable; however, the result may not agree with those obtained by other methods because of the limitations of the shape factor.

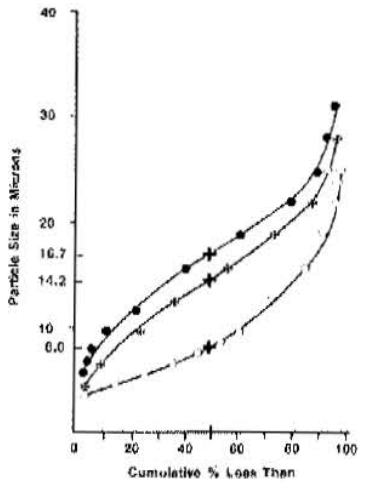


Fig 75-2. Particle size distribution of NBS glass beads (Standard Reference Material No 1003) expressed in terms of O = number of particles; ● = weight of particles; ⊘ = surface area of particles.

The *Andreasen Pipette Method* is used most commonly for sedimentation studies. Exact volumes are withdrawn at prescribed times and at a specified liquid depth. The liquid is evaporated and the residue of powder is weighed. The data are used in the Stokes equation and a weight-size distribution is calculated. Precautions must be observed with this method. Proper dispersion, consistent sampling, temperature control of the suspending medium and concentration should be achieved in order to obtain consistent results.

Stream Scanning—Stream scanning is a technique in which a fluid suspension passes through a sensing zone where the individual particles are electronically sized, counted and tabulated. The great advantage of this technique is that data can be generated in relatively short periods of time with reasonable accuracy. Literally thousands of particles can be counted in seconds and used in determining the size-distribution curve. The data are in a number of particles per class interval and can be expressed mathematically as the arithmetic mean diameter and graphed accordingly. Fig 75-2 illustrates a plot of typical data obtained for NBS Standard Reference Material No 1003.

The *Coulter Counter* and the *HIAC Counter* are used widely in the field of particle-size analysis in the pharmaceutical industry. They can be used to follow crystal growth in suspensions very effectively. Figure 75-3 shows the change in particle size with time for an aqueous suspension of Form I of an experimental drug. It appears that the growth of the particles decreases significantly after 6 hours. The photomicrograph shown in Fig 75-4 depicts the significant increase in particle size after 6 hours. Further treatment of the data as shown in Fig 75-5 enables one to establish rates of growth for suspended particles. Simply reading off the intercepts at the 1%, 2% or 3% oversize and plotting this increase in diameter with time enables one to calculate the rate of growth of particles in a suspension. This is shown in Fig 75-6.

Light Scattering—Light-scattering methods are generally fast, inexpensive and induce minimal artifacts. In general, such methods operate by measuring light diffraction from suspended particles without forming an image of the particles onto a detector. A typical unit is the laser diffraction particle sizer (*Malvern*). In it, a liquid dispersion of particles flows through a beam of laser light. Light scattered by the particles and the unscattered remainder are

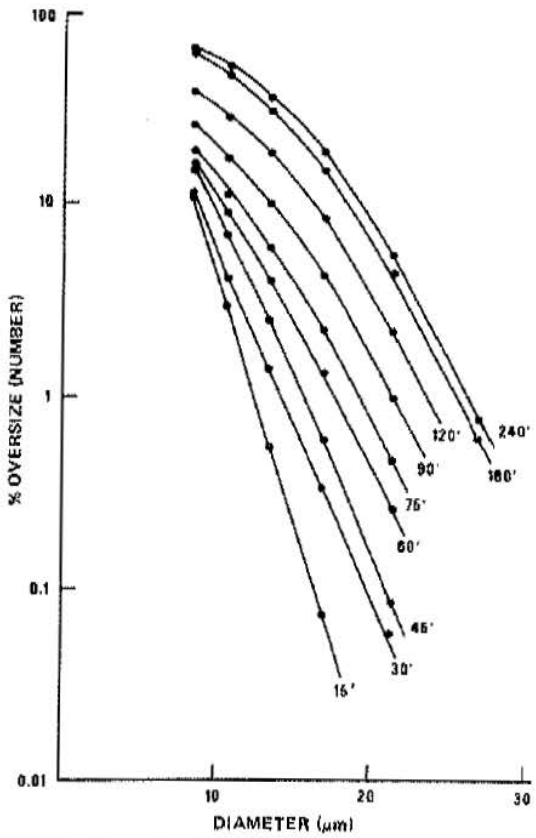


Fig 75-3. Change in particle size with time for an aqueous suspension of Form I of an experimental drug.

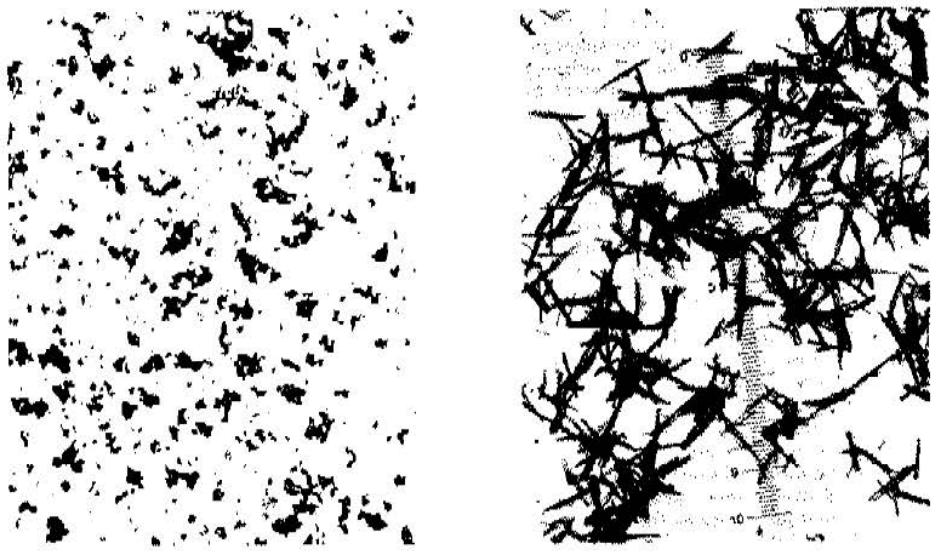
incident onto a receiver lens that forms a diffraction pattern of the scattered light. The scattered light and unscattered light then are gathered on detectors so the total light power is monitored as it allows the sample volume concentration to be determined. Each particle scatters light at a favored scattering angle that is related to its diameter. The detector provides an electronic output that makes it possible for a computer to deduce the volume-size distribution that gives rise to the observed scattering characteristics. Results may also be transformed to the equivalent surface or number distribution. Refer to Chapters 19 and 30.

Partitioning Effect

If an excess of liquid or solid is added to a mixture of two immiscible liquids, it will distribute itself between the two phases so that each becomes saturated. If the substance is added to the immiscible solvents in an amount insufficient to saturate the solutions, it still will distribute between the two layers in a definite concentration ratio. If C_1 and C_2 are the equilibrium concentrations of the substance in Solvent 1 and Solvent 2, the equilibrium expression becomes

$$\frac{C_1}{C_2} = k \qquad (2)$$

The equilibrium constant k is known as the distribution ratio or partition coefficient. Biologically, in order for a pharmacological response to occur, it is necessary that the drug molecule cross a biological membrane. The membrane, consisting of protein and lipid material, acts as a



FORM I

INITIAL SUSPENSION

FORM I

SUSPENSION AFTER 6 HOURS.

Fig 75-4. Photomicrographs showing change in crystal size for a suspension of Form I of an experimental drug.

lipophilic barrier to most drugs. The resistance of this barrier to drug transfer is related to the lipophilic nature of the molecule involved. (See Chapter 35.)

Understanding the partitioning effect and the dissociation constant enables one to estimate the site of absorption of a new chemical entity. If one assumes the stomach to have a pH range of 1.0 to 3.0 and the small intestines to have a pH range from 5 to 8, in most cases acidic drugs (pK_a 3) will be absorbed more rapidly in the stomach while more basic drugs (pK_a 8) will be absorbed more rapidly in the intestinal tract. There are exceptions, however. Some compounds have low partition coefficients and/or are ionized highly over the entire physiological pH range, but still show good bioavailability.

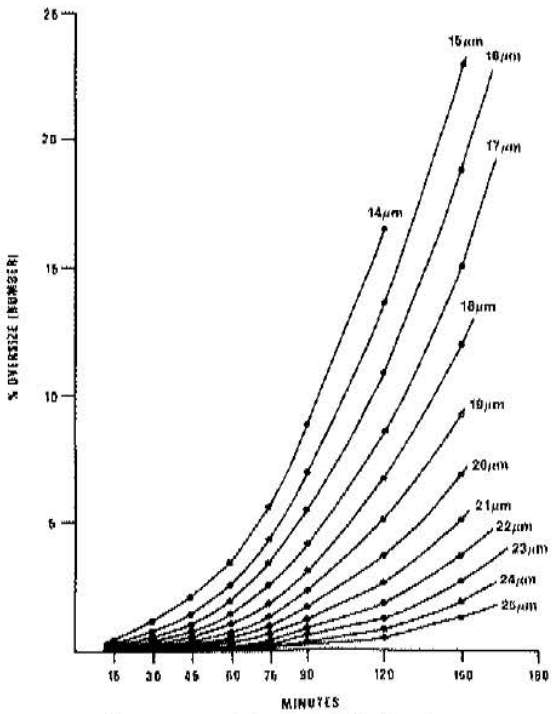


Fig 75-5. Change in cumulative count with time for an aqueous suspension of Form I of an experimental drug.

Polymorphism

A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different

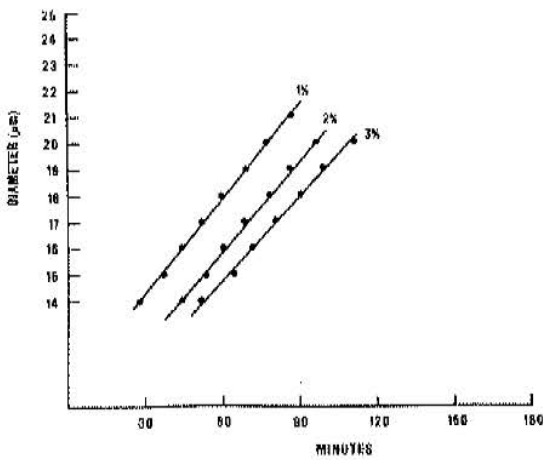


Fig 75-6. Rate of growth of Form I of experimental drug in aqueous suspension.

arrangements of the molecules of the compound in the solid state. The molecule itself may be of different shape in the two polymorphs, but that is not necessary and, indeed, certain changes in shape involve formation of different molecules and, hence, do not constitute polymorphism. Geometric isomers or tautomers, even though interconvertible and reversibly so, cannot be called polymorphs although they may behave in a confusingly similar manner.

A safe criterion for classification of a system as polymorphic is the following: two polymorphs will be different in crystal structure but identical in the liquid or vapor states. Dynamic isomers will melt at different temperatures, as do polymorphs, but will give melts of different composition. In time, each of these melts changes to an equilibrium mixture of the two isomers with temperature-dependent compositions. Some reported cases of polymorphism are undoubtedly dynamic isomerism, since the two behave quite similarly.

Polymorphism is the ability of any element or compound to crystallize as more than one distinct crystalline species, eg, carbon as a cubic diamond or hexagonal graphite. Different polymorphs of a given compound are, in general, as different in structure and properties as the crystals of two different compounds. Solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapor pressure, stability, etc all vary with the polymorphic form. In general, it should be possible to obtain different crystalline forms of a drug substance exhibiting polymorphism and, thus, modify the performance properties for that compound. To do so requires a knowledge of the behavior of polymorphs. There are numerous reviews on the subject of polymorphism. In addition, numerous indications of the importance of polymorphism in pharmaceuticals are reported in the literature. Extensive studies of polymorphism have been conducted on steroids, barbiturates, antihistamines and sulfonamides. Preformulation usually includes rigorous studies to determine the presence of polymorphs in new drug substances being prepared for preliminary investigation in test animals. Some of the parameters routinely investigated are the number of polymorphs that exist, relative degree of stability of the various polymorphs, presence of a glassy state, stabilization of metastable forms, temperature stability ranges for each polymorph, solubilities, method of preparation of each form, effect of micronization or tableting and interaction with formulation ingredients.

The initial task of the preformulator is to determine whether or not the drug substance being evaluated exists in more than one crystalline form. The following procedures are usually followed to cause crystallization of a metastable form:[2]

1. Melt completely a small amount of the compound on a slide and observe the solidification between crossed polars. If, after spontaneous freezing, a transformation occurs spontaneously or can be induced by seeding or scratching, the compound probably exists in at least two polymorphic forms. It is essential to prevent nucleation of the stable form by inducing supercooling. Supercooling can be induced by using a small sample size, holding the melt for approximately 30 sec about 10° above the melting point; carefully setting aside the compound without physical shock before observing it and rapid cooling of the compound.
2. Heat a sample of the compound on a hot stage and observe whether a solid-solid transformation occurs during heating.
3. Sublime a small amount of the compound and attempt to induce a transformation between the sublimate and the original sample by mixing the two in a drop of saturated solution of one of them. If the two are polymorphs, the more stable one will be more insoluble and will grow at the expense of the more soluble metastable form. This process will continue until the metastable form is transformed completely to the stable form. If the samples are not polymorphs, one may dissolve but the other will not grow. If the two are identical forms, nothing will occur.
4. Maintain an excess of the compound in a small amount of solvent held near the melting point of the compound. Isolate the suspended solid. Care should be taken to maintain the temperature during this step. Test the isolated material with an original sample using the procedure outlined in 3, above.
5. Recrystallize the compound from solution by shock-cooling, and observe a portion of the precipitated material suspended in a drop of the mother liquor. The drop then may be seeded with the original compound to check for solution-phase transformation. If the precipitate is a different polymorph, a solution-phase transformation should take place.

Once it has been established that polymorphism occurs, there are procedures which enable the preformulator to prepare the various forms in larger quantities for further evaluation and suitability for incorporation into dosage forms.

Once a compound has been shown to exist in more than one crystalline form, a number of techniques are available to identify the different polymorphic phases present. Each of these techniques could be successful in identifying the phase, but a combination of methods provides a means for isolation and identification of each crystalline modification. In order to confirm the presence of more than one crystalline form of a compound, it is advisable to identify the modifications present by more than one method. Using only one method for confirming the presence of polymorphs sometimes may be misleading.

Microscopy—Optical crystallography is used in the identification of polymorphs. Crystals exist in isotropic and anisotropic forms. When isotropic crystals are examined, the velocity of light is the same in all directions, while anisotropic crystals have two or three different light velocities or refractive indices. This method requires the services of a trained crystallographer.

Hot-Stage Methods—The polarizing microscope, fitted with a hot or cold stage, is very useful for investigating polymorphs. An experienced microscopist can tell quickly whether polymorphs exist; the degree of stability of the metastable forms; transition temperatures and melting points; rates of transition under various thermal and physical conditions and whether to pursue polymorphism as a route to an improved dosage form.

X-Ray Powder Diffraction—Crystalline materials in powder form give characteristic X-ray diffraction patterns made up of peaks in certain positions and varying intensities. Each powder pattern of the crystal lattice is characteristic for a given polymorph. This method has the advantage over other identification techniques in that the sample is examined as presented. Some care should be exercised in reducing and maintaining particle-size control. A very small sample size is needed and the method is nondestructive. This method has been used by several investigators in identifying polymorphs in pharmaceuticals.

Infrared Spectroscopy—This procedure is useful in identification of polymorphs. Solid samples must be used since polymorphs of a compound have identical spectra in solution. The technique can be used for both qualitative and quantitative identification.

Thermal Methods—Differential scanning calorimetry and differential thermal analysis have been used extensively to identify polymorphs. In both methods, the heat loss or gain resulting from physical or chemical transitions occurring in a sample is recorded as a function of temperature as the substance is heated at a uniform rate. Enthalpic changes, both endothermic and exothermic, are caused by phase transitions. For example, fusion, sublimation, solid-solid transition and water loss generally produce endothermic effects while crystallization produces exothermic effects. Thermal analysis enables one to calculate the thermodynamic parameters for the systems being evaluated. Heats of fusion can be obtained and the rate of conversion of polymorphs determined.

Dilatometry—Dilatometry measures the change in volume caused by thermal or chemical effects. Ravin and Higuchi[4] used dilatometry to follow the melting behavior of theobroma oil by measuring the specific volume of both rapidly and slowly cooled theobroma oil as a function of increasing temperature. The presence of the metastable form was shown by a contraction in the temperature range of 20° to 24°. This is illustrated in Fig 75-7. Dilatometry is extremely accurate; however, it is very tedious and time-consuming. It is not used widely.

Proton magnetic resonance, nuclear magnetic resonance and electron microscopy sometimes are used to study polymorphism.

Polymorphs can be classified into one of two types: (1) *enantiotropic*—one polymorphic form can be changed reversibly into another one by varying the temperature or pressure, eg, sulfur and (2) *monotropic*—one polymorphic form is unstable at all temperatures and pressures, eg, glyceryl stearates. At a specified temperature and pressure, only one polymorphic form will be thermodynamically stable. However, other metastable forms may exist under the

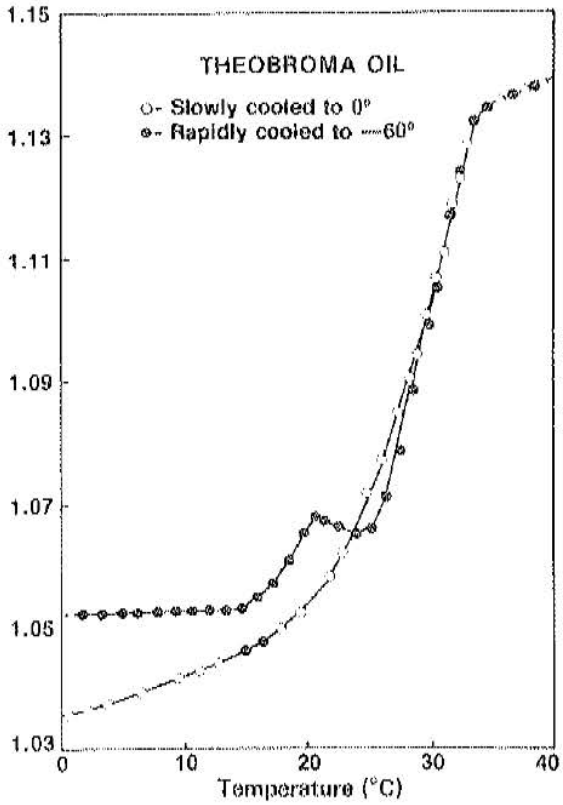


Fig 75-7. Dilatometric curves: theobroma oil, slowly and rapidly cooled.

same conditions. These metastable forms will convert to the stable lattice structures with time. The first indication of the significance of a polymorphic transformation in a pharmaceutical system was noted with novobiocin. The amorphous form of novobiocin was found to be well-absorbed; however, when formulated into a suspension, a reversion of the metastable form to the more stable crystalline form occurred resulting in poor absorption.

After it has been determined that a drug substance does exist in more than one crystalline form, the conditions under which each can be produced should be established. In this manner, proper crystallizing conditions can be maintained from batch to batch to ensure a uniform and acceptable raw material. Recrystallization solvent, rate of crystallization and other factors may cause one crystal form to dominate. During the preliminary investigation to establish these conditions, it is necessary to monitor the forms prepared. For example, during the preliminary work with an indole derivative, differential scanning calorimetry, X-ray analysis and infrared analysis were used to establish that polymorphs were present and that they could be prepared satisfactorily. Figs 75-8, 75-9, and 75-10 show the respective data for this conclusion. When polymorphs are shown to be present, experiments should be designed to determine whether or not the properties differ sufficiently to alter their pharmaceutic or biologic behavior.

Dissolution tests can be used initially to show differences in apparent equilibrium solubilities provided a discriminating solvent system is used. Fig 75-11 illustrates dissolution data for two polymorphs of an indole derivative which had similar dissolution in the medium used; however, when a more discriminating dissolution medium was used, it was

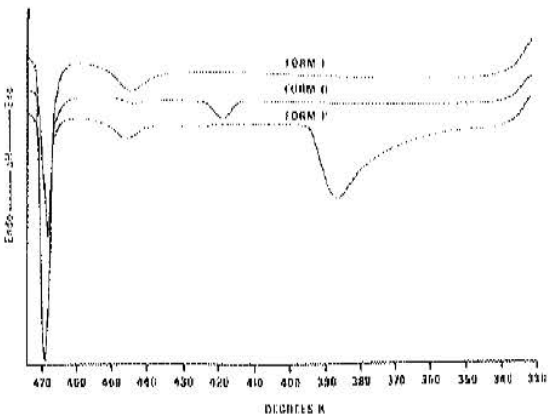


Fig 75-8. Thermograms for Forms I, I' and II of SK&F 30097.

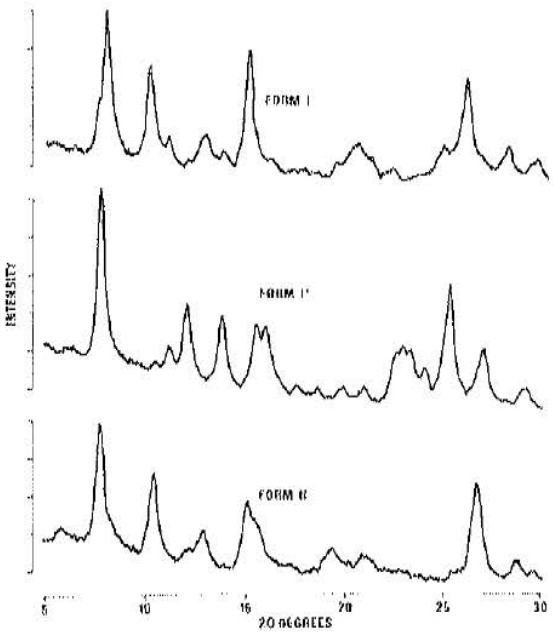


Fig 75-9. X-Ray diffractograms for Forms I, I' and II of SK&F 30097.

possible to show differences in their dissolution characteristics. This is illustrated in Fig 75-12. From the data presented for the indole derivative, it was concluded that there would be no appreciable difference in the availability of the two forms if they were to be administered orally in a solid dosage form. Subsequent testing in animals confirmed this. The Nernst equation relates the rate of concentration increase to the solubility of a dissolving solid and is commonly written as

$$\frac{dc}{dt} = \frac{AD}{Vh}(C_s - C_t) \tag{3}$$

where A is the area of the dissolving interface of the solid, D is the diffusion coefficient of the solute in the solvent, V is the volume of the solvent, h is the thickness of the diffusion layer and C_s and C_t are concentration of the solute at saturation and at time t, respectively. The equation reduces to

$$\frac{dc}{dt} = \frac{AD}{Vh}C_s \tag{4}$$

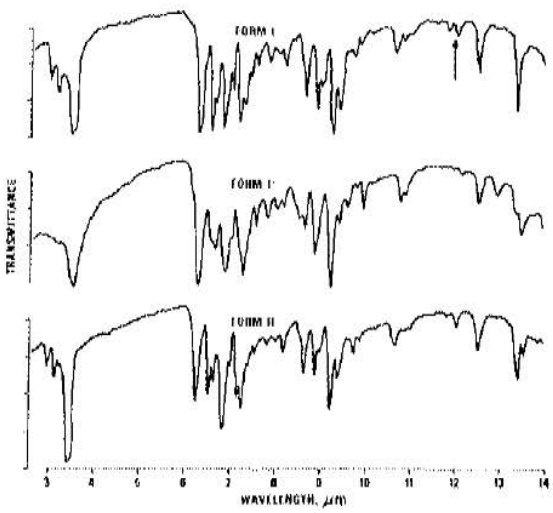


Fig 75-10. Infrared spectra of Forms I, I' and II of SK&F 30097.

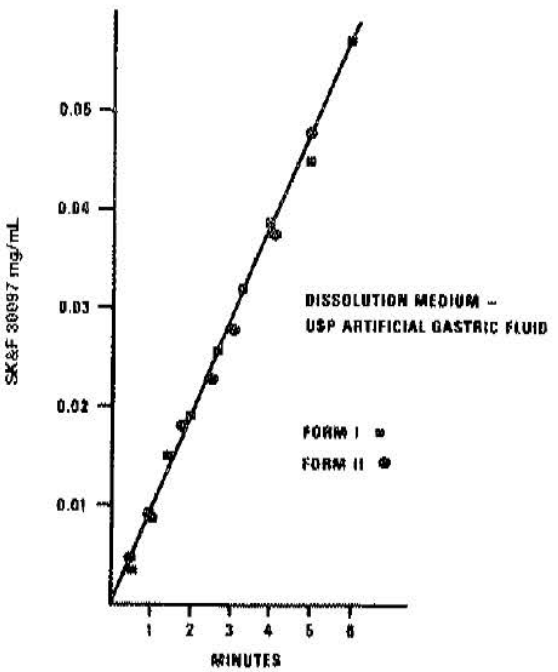


Fig 75-11. Dissolution behavior of Forms I and II of SK&F 30097 in artificial gastric fluid.

for the experimental conditions where $C_s > C_f$. Since D is a property of the solute molecule and the solvent, it is independent of the solid-state form. The experimental conditions can be selected such that A, V and h can be maintained constant in measuring the dissolution rates of different polymorphic forms. The dissolution rate then is directly proportional to C_s, the saturation solubility, and the differences in the solubilities, can be related to their free energies.

The solubility and dissolution behavior of several polymorphs of chloramphenicol palmitate have been determined. Figs 75-13 and 75-14 illustrate the data obtained at several temperatures. It is apparent from the dissolution behavior that the maximum values obtained were good ap-

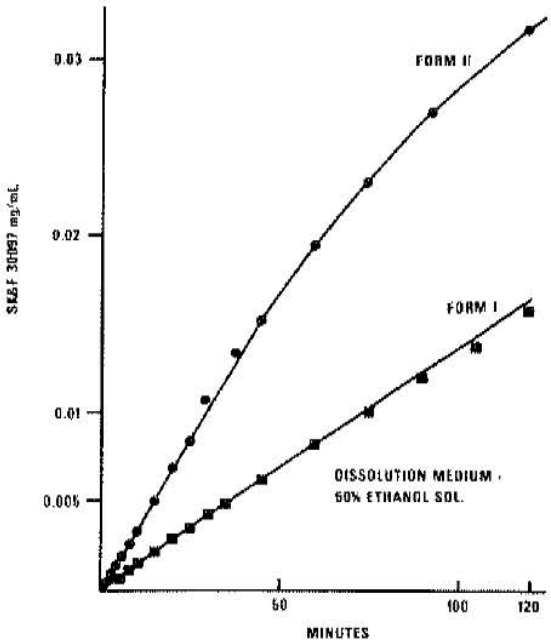


Fig 75-12. Dissolution behavior of Forms I and II of SK&F 30097 in 50% ethanol solution.

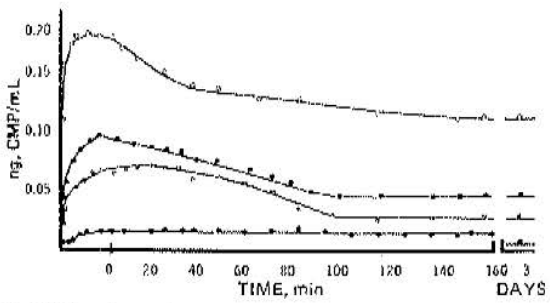


Fig 75-13. Dissolution curves for Polymorph C of chloramphenicol palmitate in 35% *t*-butyl alcohol and water at 30, 20, 15 and 0°. Key: 30°, O—O; 20°, ■—■; 15°, Δ—Δ; 0°, ●---●.

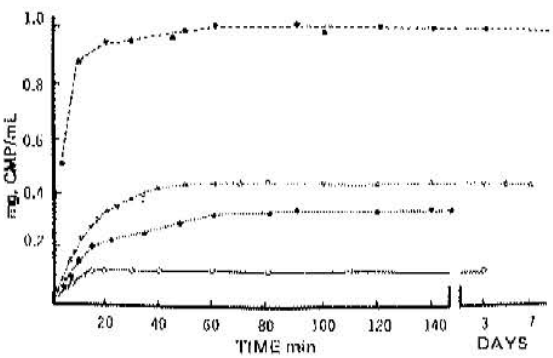


Fig 75-14. Dissolution curves for Polymorphs A and B of chloramphenicol palmitate in 35% *t*-butyl alcohol and water at 30 and 38°. Key: Polymorph A, 30°, O---O; Polymorph B, 30°, Δ. . .Δ; Polymorph A, 38°, ♦- - -♦; Polymorph B, 36° ●- - -●.

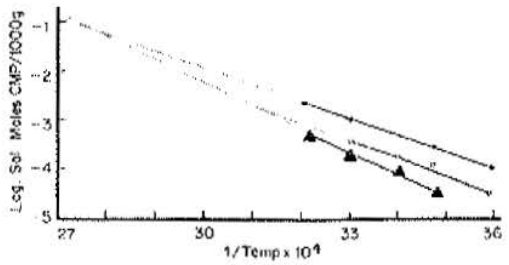


Fig 75-15. The van't Hoff type plot for Polymorphs A, B, and C of chloramphenicol palmitate. Key: Polymorphs A ▲; B ●—●; and C O—O.

Table I—Thermodynamic Values Calculated for Polymorphs *A*, *B* and *C* of Chloramphenicol Palmitate[5]

Polymorph	Transition Temp. (°C) to Form A	Heat of Solution, kcal/mole	ΔG_T, cal/mole[a]	ΔS_{303} esu	ΔS_{trans} esu[a]
A	....	21.8	....	....	....
B	88	15.4	−774	−18	−17
C	50	17.2	−465	−13	−14

[a] Calculated for the conversion to Polymorph *A*.

proximations of the solubility of the various forms. Therefore, obtaining data at several temperatures would enable one to calculate the thermodynamic quantities involved in the transition from the metastable to the stable form. A plot of the solubility data as a function of temperature in a typical van't Hoff fashion is shown in Fig 75-15. The straight-line relationship enables one to calculate the heats of solution for the various forms and also, by extrapolation, to approximate the transition temperatures for the various forms. These values are shown in Table I.[5]

At constant temperature and pressure, the free-energy differences between the polymorphs can be calculated by

$$\Delta G_t = RT \ln \frac{C_s \text{ Polymorph A}}{C_s \text{ Polymorph B}} \qquad (5)$$

This equation relates the solubility, C_s, of the polymorphic forms at a particular temperature, T, to the free energy differences, ΔG_t. Table I also contains the free-energy differences calculated for the polymorphs. The enthalpy changes also can be determined for the various transitions by subtracting the heat of solution derived for the stable form from that of the metastable form. Also, at any particular temperature, T, the entropy for the transition of polymorphs can be evaluated by the following relationship

$$\Delta S_t = \frac{\Delta H_{B \to A} - \Delta G_t}{T} \qquad (6)$$

The values computed for the transitions also are included in Table I. At the transition temperature, ΔG_t is equal to zero and the entropy can be calculated, neglecting the free-energy term in Eq 6.

The thermodynamic relationships discussed are based on the assumption that Henry's Law is obeyed. Knowledge of these thermodynamic relationships enables the preformulator to select more rationally the more energetic polymorphic form of the drug being investigated for further pharmacological studies and also to have a preliminary assessment of its probable stability.

When a preformulation group inadequately investigates polymorphic drug forms, problems may develop during the development stage. Crystal growth in suspensions resulting in poor uniformity, poor appearance, poor bioavailability, transformation occurring during milling or granulation resulting in changes in the physical and biological characteristics, inadequate pharmacological response and poor chemical stability are typical problems that may become evident.

Solubility

In dealing with new drug substances, it is extremely important to know something about their solubility characteristics, especially in aqueous systems since they must possess some limited aqueous solubility to elicit a therapeutic response. When a drug substance has an aqueous solubility less than 1 mg/mL in the physiologic pH range (1–7), a potential bioavailability problem may exist and preformulation studies should be initiated to alleviate the problem. Equilibrium solubility of the drug substance should be determined in a solvent or solvent system which does not have any toxic effects on the test animal. This is done by placing an excess of drug in a vial with the solvent. The vial is agitated at constant temperature and the amount of drug determined periodically by analysis of the supernatant fluid. Equilibrium is not achieved until at least two successive samples have the same result. Experience with solubility determinations would indicate that equilibrium is usually attained by agitating overnight (approximately 24 hours). Solubility determinations can be conducted at several temperatures since the resultant drug products ultimately will be subjected to a wide variation in temperature.

If the solubility of the drug substance is less than the required concentration necessary for the recommended dose, steps must be taken to improve its solubility. The approach taken usually will depend on the chemical nature of the drug substance and the type of drug product desired. If the drug substance is acidic or basic, its solubility can be influenced by pH. Through the application of the Law of Mass Action, the solubility of weakly acidic and basic drug substances can be predicted as a function of pH with a considerable degree of accuracy, using the following equations for the weakly acidic and basic drugs.

Weak Acid $\qquad$ *Weak Base*

$$S_t = K_s\left(1 + \frac{K_a}{[H^+]}\right) \qquad S_t = K_s\left(1 + \frac{[H^+]}{K_a}\right) \qquad (7)$$

There are many drug substances for which pH adjustment does not provide an appropriate means for effecting solution. Very weakly acidic or basic drugs may require a pH that could fall outside the accepted tolerable physiological range or may cause stability problems with formulation ingredients. For example, an experimental indole had an equilibrium solubility at pH 1.2 of approximately 50 mg/mL. However, when the pH of this system was increased to approximately 2.0, the solubility decreased to less than 0.1 mg/mL. In cases like this one, or with nonelectrolytes, it is necessary to use some other means of achieving better solubility.

Cosolvent systems have been used quite effectively to achieve solubility for poorly soluble drug substances under investigation. Propylene glycol, glycerin, sorbitol and polyethylene glycols have enjoyed a wide range of success in this area. They have been very useful and generally acceptable for improving solubility. Additional solvents such as glyceryl formal, glycofurol, ethyl carbonate, ethyl lactate and dimethylacetamide have been cited in a review article by Spiegel and Noseworthy;[6] however, it must be emphasized that with the possible exception of dimethylacetamide all of these solvents have not been used in oral products and their

acceptability may be doubtful. The number of vehicles readily available to improve solubility is rather limited, yet the frequency of their use is rather high. Solubilizing a new drug substance can improve its availability. For example, when a triazinoindole was administered in a 0.02% solution it showed an equivalent response in antiviral activity to a 2.5% suspension. Information generated early in the preformulation stage can result in a refinement of the dosage regimen and allow for a more accurate estimation of the effective dose.

Cosolvents usually serve a twofold purpose in many pharmaceutical liquid products. They not only effect solution of the drug substance but also improve the solubility of flavoring constituents added to the product. Ideally, in determining the appropriate ratio of cosolvents to achieve the concentration one must achieve, it is recommended to effect solution at the concentration desired and then place the solution at 5° and allow it to equilibrate. If precipitation occurs under these conditions, it may be necessary to alter the cosolvent ratio.

The use of surfactants of various types—nonionic, cationic or anionic—as solubilizing agents for medicinal substances is widespread (see Chapter 19 for illustrations of specific uses). The effect of Triton WR-1339 in solubilizing several steroids is shown in Fig 75-16.[7] The effect of an anionic, a cationic and a nonionic surfactant on the solubility of an antianginal compound being considered for clinical trials is shown in Fig 75-17. From such data investigators may be guided in the selection of solubilizing agents for use in preparations to be studied in humans, but it must be emphasized that the acceptability of a particular solubilizing agent depends also on other factors that determine its suitability for the intended use. For example, surfactants are known to interact with some preservatives and thereby decrease preservative action, for which reason the preformulator should always recommend some type of biological test to demonstrate that the activity of the drug substance being studied is not reduced when it is solubilized by a surfactant.

Complexation phenomena sometimes can be used to impart better solubility characteristics. However, the degree of association and the extent to which solubility can be increased generally is not adequate for use in pharmaceutical products. In addition, many complexing agents have physiological activity. The most noteworthy example of the utility of complexation to enhance solubility is the PVP-iodine complex. Hydrotropy sometimes can be used to enhance solubility. High concentrations of urea, salicylates and xanthines have been used successfully on several occasions. Again, the concept is available but the increase in solubility normally observed is not adequate for use in pharmaceutical products.

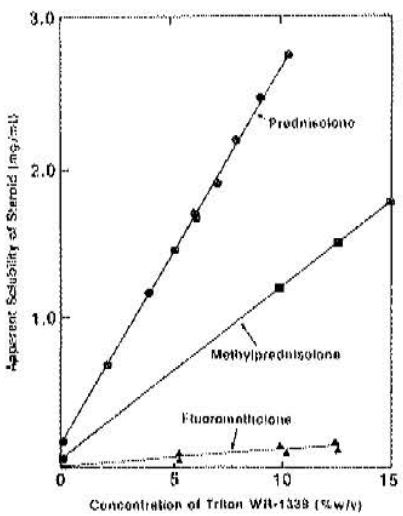


Fig 75-16. The effect of varying concentrations of Triton WR-1339 in water on the solubility of some anti-inflammatory steroids.[7]

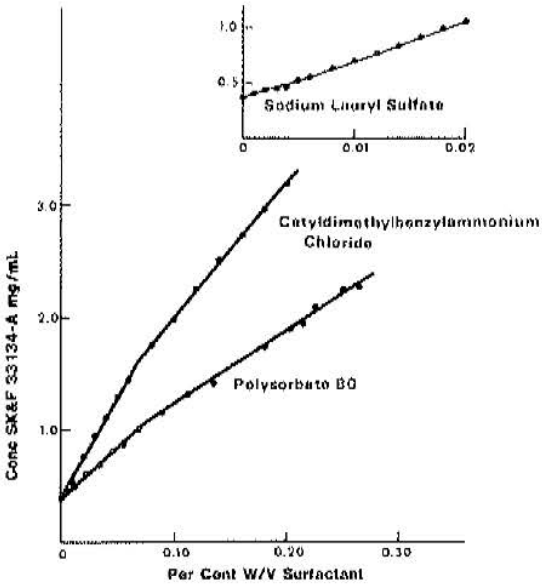


Fig 75-17. Effect of surfactant concentration on the solubility of SK&F 33134-A.

Salt Formation

Salt-forming agents often are chosen empirically by the pharmaceutical chemist primarily on the basis of the cost of raw materials, ease of recrystallization and percentage yield. Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound in dosage forms. Furthermore, even when many salts of the basic compound have been prepared, there are no effective screening techniques which make the selection process of the salt an easier task for the pharmacist. The fundamental considerations which may have some influence on salt selection are physical and chemical stability, hygroscopicity, flowability and solubility.

The number of salt forms available to the chemist is large. Table II lists the cations and anions present in FDA-approved commercially marketed salts of pharmaceutical agents.[8] The monoprotic hydrochlorides have been the most frequent choice of the available anionic salt-forming radicals, while sodium has been the most predominant cation. During preformulation evaluation it is extremely important to establish that the particular salt form in question will have properties that will result in a minimum of problems during the development of the dosage forms. Since toxicity studies usually are initiated soon after a compound has been designated for further studies in man, it is important that the salt form selected has been given a critical evaluation to determine whether or not its properties are suitable.

Since physical and chemical stability are vital to any pharmaceutical product, it is imperative that the preformulator evaluate both parameters. A systematic determination of the thermal stability, solution stability (at several pH's) and

Table II—FDA-Approved Commercially Marketed Salts

Anion	Percent[a]	Anion	Percent[a]
Acetate	1.26	Iodide	2.02
Benzenesulfonate	0.25	Isethionate[i]	0.88
Benzoate	0.51	Lactate	0.76
Bicarbonate	0.13	Lactobionate	0.13
Bitartrate	0.63	Malate	0.13
Bromide	4.68	Maleate	3.03
Calcium edetate	0.25	Mandelate	0.38
Camsylate[b]	0.25	Mesylate	2.02
Carbonate	0.38	Methylbromide	0.76
Chloride	4.17	Methylnitrate	0.38
Citrate	3.03	Methylsulfate	0.88
Dihydrochloride	0.51	Mucate	0.13
Edetate	0.25	Napsylate	0.25
Edisylate[c]	0.38	Nitrate	0.64
Estolate[d]	0.13	Pamoate (Embonate)	1.01
Esylate[e]	0.13	Pantothenate	0.25
Fumarate	0.25	Phosphate/diphosphate	3.16
Gluceptate[f]	0.13	Polygalacturonate	0.13
Gluconate	0.51	Salicylate	0.88
Glutamate	0.25	Stearate	0.25
Glycollylarsanilate[g]	0.13	Subacetate	0.38
Hexylresorcinate	0.13	Succinate	0.38
Hydrabamine[h]	0.25	Sulfate	7.46
Hydrobromide	1.90	Tannate	0.38
Hydrochloride	42.98	Tartrate	3.64
Hydroxynaphthoate	0.25	Teoclate[j]	0.13
		Trithiodide	0.13

Cation	Percent[a]	Cation	Percent[a]
Organic:		Metallic:	
Benzathine[k]	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine[l]	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

[a] Percent is based on total number of anionic or cationic salts in use through 1974. [b] Camphorsulfonate. [c] 1,2-Ethanedisulfonate. [d] Lauryl sulfate. [e] Ethanesulfonate. [f] Glucoheptonate. [g] *p*-Glycollamidophenylarsonate. [h] *N,N'*-Didehydroabietylethylenediamine. [i] 2-Hydroxyethanesulfonate. [j] 8-Chlorotheophyllinate. [k] *N,N'*-Dibenzylethylenediamine. [l] *N*-Methylglucamine.

light-sensitivity of the drug substance provides essential input toward the selection of the most suitable derivative. Studies usually are initiated early to identify problems. Samples of the salts in question usually are placed under exaggerated conditions of heat and light in the presence and absence of moisture and subsequently analyzed to determine the amount of breakdown. In many instances stability-indicating analytical methods may not be available. In these cases it is necessary to resort to thin-layer chromatography to establish a qualitative assessment of stability. At the same time, samples are placed under high-humidity conditions and weighed periodically to determine the degree of hygroscopicity of the compounds. Compounds that have a tendency to adsorb or absorb moisture may present flowability problems during encapsulation.

Solubility characteristics also are evaluated. When a particular salt form has very good solubility (greater than 10%) it sometimes is difficult to prepare a suitable granulation using an aqueous granulating fluid, especially for high doses. Granulations prepared by these methods will not dry satisfactorily or the granulation will not flow uniformly from the hopper, resulting in a large weight variation during the compression stage. A critical evaluation of this type with different salt forms has been proven quite effective in enabling the preformulator to make the selection of the salt form of choice for further development.

Compressibility and Compactibility

Tablets remain a preferred dosage form, and information obtained during preformulation studies on the ability of powdered drugs to be compressed and compacted can be a valuable aid to formulators. Compressibility and compactibility relate directly to tableting performance. Compressibility can be defined as the ability of a powder to decrease in volume under pressure, while compactibility can be defined as the ability of a powder to be compressed into a tablet of a certain strength or hardness. Even though powdered drugs usually are formulated with excipients to modify compression and compaction properties, the properties of the powdered drug alone may be the primary determinant of its ability to be manufactured into a tablet. Significant differences in compression and compaction behavior often can be observed in different lots of the same drug. For example, changes in crystallization or milling procedures may produce differences in behavior.

Compression and compaction most often are evaluated by measuring the tensile strength and hardness of compacts. Tensile strength commonly is measured by diametral compression of round tablets, where the analysis of strength accounts for the dimensions of the tablet.[9] Transverse compression of square compacts between platens narrower than the compact is reported to provide more reproducible results on a wider variety of powders.

Hardness can be defined as the resistance of a solid to local permanent deformation. Deformation hardness tests usually are measured by static impression or dynamic methods. The static method involves the formation of a permanent indentation on a solid surface by a gradual and regularly increasing stress load. Hardness is determined by the load and size of the indentation and is expressed as force per unit area. In dynamic tests, the solid surface is exposed to an abrupt impact such as a swinging pendulum or an indenter allowed to fall under gravity onto the surface. Hardness then is determined from the rebound height of the pendulum or the volume of the resulting indentation.

Heistand has used adaptations of a compression test and a hardness test to obtain measurements that are used to formulate three dimensionless parameters or indices.[10] The indices are used to characterize the relative tableting performance of individual components or mixtures. The *Strain Index* is the ratio of dynamic indentation hardness to reduced Young's modulus. The *Bonding Index* is the ratio of tensile strength to indentation hardness. The *Brittle Fracture Index* is obtained by comparing the tensile strengths of square compacts with and without a hole at their center. The indices themselves do not measure intrinsic properties of a chemical compound, but rather the traits that influence the tableting performance of a specific lot of chemical. It is necessary to know the magnitude of all three indices to predict the variety of tableting properties that may be incurred. Such information can act as a guide in selecting excipients to overcome problem properties of a drug ingredient.

Chemical Properties

The evaluation of the physical and chemical stability of a new drug substance is an important function of the preformulation group. The initial work should be designed to identify those factors that may result in an alteration of the drug substance under study. The physical pharmacist initially can anticipate the possible type of breakdown that a compound will be subjected to by examination of the chemical structure of the compound. For example, esters and amides are sensitive to hydrolytic degradation while acri-

dances and catecholamines are sensitive to oxidative degradation. With this preliminary knowledge one may more effectively design studies to identify the problems early. At this point the primary concern is not the pathway or mechanism of degradation. A stability-indicating method of analysis usually is not available early in the preformulation phase. Techniques such as thin-layer chromatography, diffuse reflectance and thermal analysis can be used to provide data to assess preliminary stability. Sometimes, the preliminary evaluation is complicated by the presence of impurities. It is essential that the drug under study be pure before any stability tests are undertaken. The presence of impurities can lead to erroneous conclusions in the preformulation evaluation.

Drug Substance Stability—It is extremely important to determine the stability of the bulk chemical as early as possible. One hardly would expect to prepare stable dosage forms with a chemical substance that was not stable in the pure state. Samples of the chemical are subjected usually to various conditions of light, heat and moisture in the presence and absence of oxygen. The chemical is placed in sealed vials with and without moisture and stored at various elevated temperatures which may vary to some degree from laboratory to laboratory. Light-sensitivity is measured by exposing the surface of the compound to light. Sunlamps are sometimes used to exaggerate light conditions. Hygroscopicity is evaluated by placing the chemical in open petri dishes at relative humidities from 30 to 100%. The samples are monitored regularly for physical changes, moisture pick-up and chemical degradation.

Most drug substances are either stable at all conditions, stable under special conditions of handling, unstable with special handling or completely unstable. When drug substances are found to have some stability problems, it may be important to define the pathway of degradation and initiate studies to stabilize the compound with appropriate additives.

At this point, it may be advisable to consider some of the more prominent reactions accounting for instability of new drug substances. Obviously, some compounds will not undergo any appreciable decomposition if kept dry and away from air in a sealed container. It must always be assumed that the new drug substance is in some kind of formulation environment that may lead to instability problems.

Hydrolytic Degradation—Hydrolysis is probably the degradative process encountered most frequently in the formulation of new drugs. It is safe to assume that most new drugs will be exposed to water at some stage during processing or during storage; hence, hydrolysis may occur unless the conditions are optimum. Hydrolysis occurs with esters, amides, salts of weak acids and strong bases and thioesters, among others. A few drug compounds that undergo hydrolytic degradation are procaine, penicillin, aspirin and chlorothiazide.

From a kinetic standpoint, hydrolysis reactions are second-order reactions because the rate is proportional to the concentration of two reactants. However, in aqueous solutions, since water is usually present in excess and at relatively constant concentration, the reactions are treated experimentally as monomolecular or first-order reactions. This simplification permits calculations of the extent of decomposition under precise experimental conditions by less-complicated means. Extrapolation of the exaggerated rates to room temperature makes it possible to establish more expeditiously shelf-life stability of potential new drug products.

The rate of hydrolysis can be affected by temperature and by hydrogen or hydroxyl ion concentration when the hydrolytic process is dependent on pH. Fig 75-18 shows the pseudo-first-order behavior as a function of pH for carbuterol in aqueous solution at constant ionic strength at 85°. The

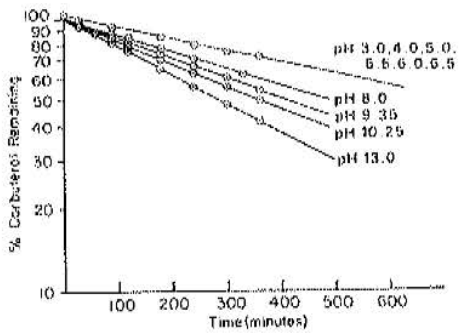


Fig 75-18. Effect of pH on carbuterol degradation at 85° (μ = 0.5).

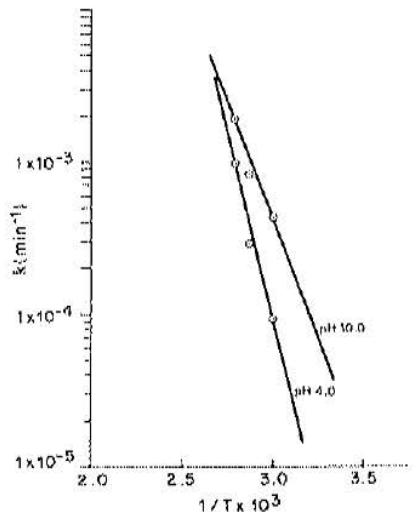


Fig 75-19. Typical Arrhenius-type plot depicting the temperature dependency of carbuterol hydrolysis at pH 4.0 and 10.0.

effect of temperature is illustrated in Fig 75-19 for carbuterol at pH 4.0 and 10.0 respectively.[11] For solids, the amount of moisture present is minimal. When considering a drug substance that undergoes hydrolytic degradation, studies are designed to establish the conditions of pH and buffer concentration where minimum decomposition occurs. There sometimes is a wide range of pH adjustment that a drug substance can tolerate. For example, idoxuridine was shown to have maximum stability over a pH range from 2.0 to 6.0. Fig 75-20 shows the pH-stability profile.[12] Another drug substance, carbuterol, hydrolyzed by an intramolecular process showed maximum stability over a wide pH range. Even though these compounds exhibited a wide range of pH for optimum stability in aqueous solution, they could not be formulated and provide products with satisfactory shelf lives without special cosolvent systems and/or special storage conditions. Cefazolin was shown to have a narrow pH range for maximum stability as indicated in Fig 75-21.[13] Buffering aqueous solutions to provide a pH for optimum stability can lead to stability problems. Stability sometimes is affected by buffer concentration; for example, carbuterol stability was shown to be affected by phosphate buffer concentration.

Another manner in which the physical pharmacist can overcome an instability due to hydrolysis is to recommend the preparation of an insoluble salt form or to prepare a solid

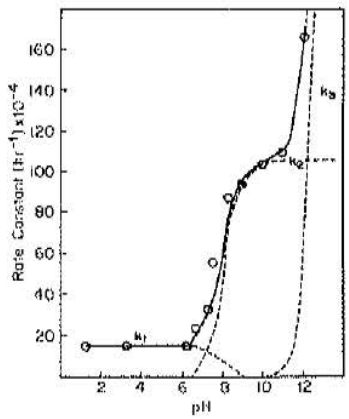


Fig 75-20. Plot showing pH-rate profile for hydrolysis of idoxuridine at 60°. Circles represent experimental results. Solid line corresponds to theoretical pH-rate profile. Broken line designates contribution of k_1, k_2 and k_3 at any pH value.

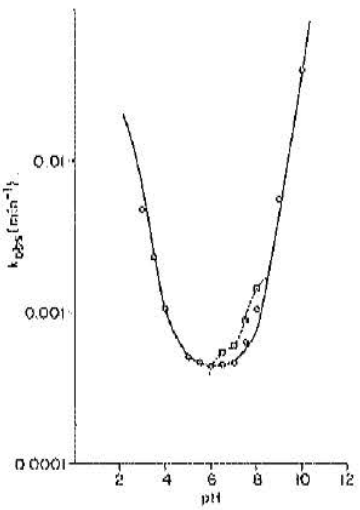


Fig 75-21. pH-Rate profile of cefazolin degradation in aqueous solution at 60° (μ = 0.6). Solid line: theoretical profile; circles: experimental profile; squares: rates uncorrected for buffer effect.

dosage form. Insoluble chlorothiazide is stable in neutral aqueous suspensions, but solutions of the sodium salt at relatively high pH decompose rapidly. Frequently, the replacement of water by some other solvent, such as alcohol or the polyhydroxy solvents, reduces the hydrolytic rate of degradation for some systems. Acetylsalicylic acid suspensions containing high concentrations of sorbitol improved stability. Ampicillin also was shown to be more stable when the concentration of alcohol was increased. The formation of molecular complexes with aromatic esters greatly reduces the hydrolytic rate of degradation.

It also has been shown that stability of some compounds may vary depending on whether or not they exist in the micellar or nonmicellar state. For example, a difference in the chemical stability of penicillin exists in the micellar state from that in the monomeric state.

Oxidation—Oxidative degradation is as important as hydrolysis in the preliminary stability evaluation of new-drug substances. Studies should be initiated to establish the oxidative route, then steps should be taken to determine what additives can minimize the degradation. Oxidative degradation is common with many drug compounds. Ascorbic acid, epinephrine, vitamin A, chlorpromazine, isoproterenol, morphine, resorcinol and unsaturated fats and oils are subject to oxidative degradation. The oxidation reaction depends on several factors, including temperature, oxygen concentration in the liquid, impurities present and the concentration of the oxidizable component. The temperature effect in solutions is usually minimal; however, in the dry state it is more pronounced since other factors such as moisture dictate its stability behavior.

Initially, it is important to establish that oxidation is taking place. Solutions of the drug substance in question are exposed to various exaggerated conditions of light and oxygen tension in amber and flint-glass containers. Samples are analyzed for degradation. When it has been established that the oxidative route is the principal pathway for degradation, appropriate additives are used to determine what effect they might have on the stability. Sometimes pH is critical, since a great number of oxidation-reduction processes depend on the concentration of hydrogen or hydroxyl ions. Light usually accelerates degradation, thus the storage of products in dark containers does much to preserve stability. Photochemical changes many times involve the formation of other reactive compounds or free radicals which function to propagate the decomposition, once started. Auto-oxidation may occur in the absence of light when susceptible materials, such as fats and oils, are stored in the presence of air. The auto-oxidation of phenolic compounds is of special significance since compounds such as epinephrine and isoproterenol degrade in this manner. Heavy metal ions, eg, cupric and ferric, accelerate the oxidation of ascorbic acid and the phenothiazines. Frequently, only trace quantities of these ions, occurring as impurities, may be sufficient to cause an increased rate of decomposition. This can be a consistent problem since many of the so-called inert ingredients may have heavy metal contaminants.

The oxygen concentration in solution is a factor in many cases and often depends upon the temperature of storage or the solvent employed. Oxygen is more soluble in water at lower temperatures so that oxygen-dependent reactions can sometimes proceed more rapidly at the lower temperatures. Ascorbic acid is more stable in 90% propylene glycol or in Syrup USP than in water, presumably because of the lower oxygen concentration in these vehicles. Oxidative degradation is an extremely complex process since the overall rate is dependent upon several factors. Preparations sensitive to oxidation are sometimes stabilized by effectively removing the oxygen and by the addition of suitable additives. Nitrogen flushing has been used successfully for this purpose. A wide variety of reducing agents and compounds to sequester metals and inhibit chain reactions has been employed for stabilization, but relatively few are acceptable for parenteral products. Often, it is necessary to combine ingredients and adjust pH to maximize stability. Detailed kinetic studies have been reported for the oxidative decomposition of prednisolone.

The physical pharmacist has a difficult task with oxidative degradation. Initially, experiments must be designed that will encompass many variables. Preparing samples at several concentrations containing antioxidants plus sequestering agents at several pH levels and placing them in flint or amber containers with and without nitrogen is a common procedure. The subsequent evaluation of these limited data is critical. Light-sensitivity studies with several formulations of prochlorperazine resulted in the selection of a stable formula. In a study with idoxuridine it was shown that placing the aqueous solution in an amber container was sufficient to protect the product from oxidative degradation.

Drug Substance–Excipient Interaction—Drug substance–excipient studies are designed to determine a list of excipients that can be used routinely in the final dosage forms. Lactose, sucrose, calcium sulfate, dicalcium phosphate, starch and magnesium stearate are some of the substances routinely tested in combinations. Some basic observations with the drug substance and/or its salt form sometimes can dictate what excipients can be used. For example, one would not consider using sucrose or lactose if the drug substance being considered is a primary amine. This system has the potential for interaction to form a colored compound readily detected by a color change.

Various means have been used for detecting potential interactions and incompatibilities. Diffuse reflectance techniques have been used to detect interactions. This has been done by comparing the spectra obtained initially with those obtained after storage at exaggerated conditions. A shift in absorption has been interpreted as an interaction. Thin-layer chromatography also has been used. When excipients are present it is usually advisable to set a mixture of the excipients at the same conditions as the excipient-drug mixtures. This will give a comparison of the chromatograms of both systems. If any new degradation products are present, the source may be determined more easily.

Mixtures containing at least two levels of drug concentration with excipients are sealed in vials containing 5% water. These vials are stored under exaggerated conditions of light and heat for various time periods. The resultant samples are observed physically and analyzed by an appropriate technique to get a qualitative determination. At this point in the stability evaluation, which is a preliminary screening process, it is not necessary to know exactly how much has degraded. It is an all-or-none effect. The search is for the excipients that have no effect on the stability of the active ingredient.

When solution interactions are being investigated and no incompatibilities are evident, it is wise to recommend an *in vivo* experiment to evaluate availability. On occasion, interaction may occur in solution that is not detectable with routine procedures. For example, clindamycin was found to interact with cyclamates, which interfere with the absorption of the drug.

Other Changes—Optically active substances may lose their optical activity; eg, through racemization. If the enantiomorphic compounds possess different degrees of physiologic action, such changes may result in reduced therapeutic effects. Epinephrine has been shown to undergo racemization under various acidic and basic conditions. Although the potential for this to become evident during a preformulation evaluation is rare, one should always be aware of this possibility. Polymerization is also a remote possibility. Darkening of glucose solution is attributed to polymerization of the breakdown product, 5-(hydroxymethyl)furfural. Isomerization, which is the process involving the change of one structure into another having the same empirical formula but with different properties in one or more respects, also can occur; again, the occurrence is rare. Deamination and decarboxylation can occur sometimes. This type of change would be detected easily since the resultant degradation products would have completely different properties.

Permeability

A preformulation evaluation should include studies to assess the passage of drug molecules across biological membranes. These membranes act as lipid barriers to most drugs and permit the absorption of lipid-soluble substances by passive diffusion. Lipid-insoluble substances can cross the barrier only with considerable difficulty. The pH-partition theory explains the interrelationship of the dissociation constant, lipid solubility, pH at the absorption site and the absorption characteristics of drugs across membranes. The theory has evolved following a series of investigations in laboratory animals and man and is the basis of much of the current understanding of absorption of drugs.

Data obtained from basic physical-chemical studies described earlier may give the preformulation scientist an indication of possible absorption difficulties. Experimental techniques are available that can be used to give a more accurate assessment of absorption problems. An *in vitro* system that has been used extensively consists of an aqueous/organic solvent/aqueous system which has the advantage of being simple, allows for accurate pH control, membrane thickness and other variables. It can be described mathematically in precise terms. However, the interpretation and correlation of data are limited when applied to biologic systems.

Another *in vitro* procedure, the everted sac technique, is a simple and reproducible method for determining the absorption characteristics of drugs. Isolated segments of rat small intestines are everted and filled with a solution of the drug being evaluated, and the passage of drug through the membrane is determined. This technique has been used to measure the permeability of a number of drug substances.[14] It also can evaluate both passive and active transport of drugs. The fact that the preparation has been removed from the animal and its normal blood supply is a distinct disadvantage.

The *in situ* technique developed by Doluisio, *et al*,[15] for the study of membrane permeability appears to overcome the disadvantages of the everted sac technique. Since the intestine is not removed from its blood supply, the results would be expected to be similar to those obtained in intact animals. A disadvantage of the technique is that the procedure does not account for the loss of fluid from the solution by absorption in the intestine. Nonabsorbable markers, such as phenol red, can be added to the drug solution to solve this problem.

The techniques described can give the preformulation scientist an indication of possible absorption problems or suggest that little or no difficulty will be observed in the passage of a particular drug product through the biological membranes. This information, along with eventual studies in man, serves to establish possible *in vitro/in vivo* correlation for dissolution and bioavailability. These data are important in establishing quality-control specifications for the products which will ensure consistent biological performance from subsequent lots.

Proteins and Peptides

Proteins and peptides produced by the commercialization of biotechnology are presenting preformulation scientists with new challenges. In general, protein and peptide drugs are more expensive to produce, more potent and more difficult to analyze than nonprotein and nonpeptide drugs. They frequently are formulated as parenterals instead of oral dosage forms because they are unable to be absorbed from the GI tract, unstable in GI fluids or subject to rapid first-pass metabolism. Degradation of proteins and peptides occurs not only by covalent bond reaction but also by denaturation. The prediction of shelf-life by the Arrhenius equation is usually not applicable.

Degradation by reaction of the covalent bond can be characterized by the following major reactions: hydrolysis, transpeptidation, racemization, oxidation, diketopiperazine formation, disulfide exchange and photodecomposition. Hydrolysis can occur at the peptide linkage (R-NH-CO-R), but it is more stable than the ester linkage (R-O-CO-R)

unless cleavage is assisted by a neighboring group. Hence, peptides such as oxytocin and captopril are stable enough for liquid parenteral formulations. Transpeptidation occurs when amino acid residues cyclize back onto the peptide chain and the cyclic intermediate undergoes hydrolysis. Racemization can occur in acidic or alkaline medium, and if proline or glycine occur in the *N*-terminal position, diketopiperazine formation is facilitated. Cysteine, methionine and tryptophan are susceptible to oxidation, and since disulfide exchange is concentration-dependent, oligomers are formed frequently as a result of the creation of disulfide bonds between peptide chains. Photodecomposition of tryptophan residues may lead to discoloration and photoproducts of increased molecular weight.

Degradation via denaturation occurs when the conformational structure of a protein or peptide is altered. Potential factors that can denature a molecule include ionic strength, surface-active agents or processing conditions that subject the molecule to shear or adsorption. Identification of the preferred conformation, and mechanisms by which it can be altered, is critical in formulating the molecule as a stable drug. Hydrogen bonds act to stabilize conformational structure and the presence of water promotes hydrogen bonding. Hence, agents that disrupt the water-protein interaction such as salts and molecules with ionic side chains can promote conformational instability.

Several methods can be used to study denaturation of proteins. These include thermal analysis, determination of critical micelle concentration, determination of cloud-point, light scattering and fluorescence spectrometry. Thermal analysis with a scanning microcalorimeter is used to measure energies of transition in solution and is useful for determining the effect of stabilizing excipients on proteins in solution. Measurement of the critical micelle concentration also can be used as a tool to study the ability of an excipient to stabilize or disrupt the hydrophobic interactions which promote micellerization. Cloud-point measurements (the temperature, when cooled, at which a solution becomes cloudy) also have been suggested as a tool to study the effects of solvents or excipients on denaturation. Fluorescence spectrometry can be used to measure thermal denaturation by using a fluorescent probe whose fluorescence increases when a protein is denatured.

Proteins and peptides can be stabilized in many ways, usually employing empirical, rather than theoretical, procedures. For parenteral formulations, excipients are added to enhance stability. Serum albumin, itself a relatively stable protein, is used commonly as a stabilizer for peptides and proteins. It may inhibit surface adsorption and act as a cryoprotectant during lyophilization. Amino acids, such as glutamic or aspartic acid, may chelate metals such as zinc, which may cause aggregation; however, metal ions, such as calcium, are essential to the stability of certain amylases and proteases. Phospholipids and fatty acids also are potential stabilizers. Even though surfactants have a high denaturing effect, they also may inhibit the effects of other denaturants.

Proteins, as opposed to nonprotein drugs, may find a dilute aqueous medium unfavorable. Therefore, one should attempt to create an environment similar to the natural habitat of the specific protein. This environment would be rich in proteins and carbohydrates, low in oxygen and have a high degree of immobilized water. However, as methodologies for studying denaturation and degradation become more defined, the number of excipients needed to stabilize a formulation can be limited selectively.

Formulation Ingredients

Although preliminary screening of commonly used excipients with new-drug substances has become routine in preformulation studies, there are occasions when problems arise because of the interaction with additives such as preservatives, stabilizers, dyes and, possibly, flavors. A discussion of some problems that have risen is in order to make formulators aware that they should be concerned about the potential for interaction whenever another ingredient is added to a formulation.

Preservatives—Each time a liquid or semisolid pharmaceutical dosage form is prepared, it is necessary to include a preservative in the formulation. Such preservatives as sodium benzoate, sorbic acid and the methyl and propyl esters of *p*-hydroxybenzoic acid (parabens) have been used in these systems for many years. There have been reports that the parabens have been inactivated when used in the presence of various surface-active agents and vegetable gums. This loss of activity might be due to the formation of complexes between the preservative and the surfactant. A dialysis technique has been used to demonstrate an interaction between polysorbate 80 and the parabens. This observation becomes critical if the level of preservative added is borderline with respect to the preservative-activity threshold. The desired preservative effect may not be achieved unless an excess of the preservative is added to compensate for that which is complexed. It also has been shown that molecular complexes form when the parabens are mixed with polyethylene glycol, methylcellulose, polyvinylpyrrolidone or gelatin. The degree of binding was less than that observed with polysorbate 80. Sorbic acid also interacts with polysorbates but does not interact with polyethylene glycols. The quaternary ammonium compounds also are bound by polysorbate 80 to reduce their preservative activity. Benzyl alcohol also was shown to be adsorbed by certain types of rubber stoppers. Subsequent work has shown that butyl rubber does not interact with benzyl alcohol.

Antioxidants—During the preformulation evaluation of compounds that are sensitive to oxidation often it is commonplace to test several levels of antioxidant concentrations added to aqueous systems in order to determine the relative effectiveness of the antioxidants. Sodium bisulfite and ascorbic acid are two antioxidants that are used widely in pharmaceutical systems. Sodium bisulfite yields a colorless water-soluble salt when it is oxidized. It will add to double bonds, react with aldehydes and certain ketones and contributes in bisulfite cleavage reactions. Many of the reactions with bisulfite are irreversible, and the resulting sulfonic acids frequently are biologically inactive. Epinephrine has been shown to interact with bisulfite to form a bisulfite addition product. Other sympathomimetic drugs, principally the *ortho*- or *para*-hydroxybenzyl alcohol derivatives, also react with bisulfite in a similar manner. The *meta*-hydroxy alcohol does not react. Sometimes these interactions are reversible as in the case with the adrenocorticosteroid molecules.

Ascorbic acid, on the other hand, is less reactive. However, when mixed with compounds having a primary amine nucleus, there is the tendency for interaction to form a highly colored Schiff base. One must be aware of this possibility when selecting a suitable antioxidant.

Suspending Agents—Occasionally, it will be necessary to consider the use of a suspending agent to prepare some preliminary suspension preparations for stability evaluation prior to starting toxicity testing. The physical pharmacist should be aware of the potential for these additives to react with the drug substance being evaluated. Anionic water-soluble compounds, such as sodium carboxymethylcellulose, alginic acid, carrageenin and other hydrocolloids, although generally considered inert, frequently interact with drug compounds in solution. Carboxymethylcellulose and carrageenin form complexes, or possibly salts, with many medicinal agents including procaine, chlorpromazine, benadryl,

quinine, chlorpheniramine, neomycin and kanamycin. In some instances the formation of the complex imparted better stability to the system. When this problem is suspected, it is important to conduct appropriate tests to insure that an interaction does not take place in the system being evaluated.

Dyes—Although preformulation tests usually are conducted long before any consideration of coloring the intended dosage forms, they should not be overlooked. Dyes are chemical in nature and contain reactive sites capable of causing incompatibilities. Several studies have demonstrated that certified dyes do react with drug substances. Sugars, such as dextrose, lactose and sucrose, were found to increase the rate of fading of FD&C Blue #2. Insoluble complexes also were formed when quaternary ammonium compounds were formulated with FD&C Blue #1.

Summary

The preformulation evaluation of new-drug substances has become an integral part of the development process. A thorough understanding of the physical-chemical properties of the new-drug substance under study provides the development pharmacist with data that are essential in designing stable and efficacious dosage forms. Many of the problems discussed and the solutions offered in this chapter resulted from application of scientific training of present-day pharmaceutical scientists. Their diverse skills, creative aptitudes and initiative provide the pharmaceutical industry with the essential ingredients to develop drug products that help maintain the health-care process at its highest level of excellence.

References

1. Dittert LW, *et al: J Pharm Sci 57:* 1146, 1968.
2. Dittert LW, *et al: J Pharm Sci 57:* 1269, 1968.
3. Halebian H, McCrone W: *J Pharm Sci 58:* 911, 1969.
4. Ravin LJ, Higuchi T: *J APhA, Sci Ed 46:* 732, 1957.
5. Aguiar AJ, Zelmer JE: *J Pharm Sci 58:* 983, 1969.
6. Spiegel AJ, Noseworthy MM: *J Pharm Sci 52:* 917, 1963.
7. Guttman DE, *et al: J Pharm Sci 50:* 305, 1961.
8. Berge SM, *et al: J Pharm Sci 66:* 1, 1977.
9. Fell J, Newton J: *J Pharm Sci 59:* 688, 1970.
10. Hiestand H, Smith D: *Powder Tech 38:* 145, 1984.
11. Ravin LJ, *et al: J Pharm Sci 67:* 1523, 1978.
12. Ravin LJ, *et al: J Pharm Sci 53:* 1064, 1964.
13. Rattie ES, Guttman DE, Ravin LJ: *Arzneim-Forsch 28:* 944, 1978.
14. Kaplan SA, Cotler S: *J Pharm Sci 61:* 1361, 1972.
15. Dehuisio JT, Billups NF, Dittert LW, Sugita ET, Swintosky JV: *J Pharm Sci 58:* 1196, 1969.

Bibliography

Carstensen JT: *Pharmaceutics of Solids and Solid Dosage Forms*, Wiley, New York, 1977.
Greene DS: *Modern Pharmaceutics*, Marcel Dekker, New York, Chap 6, 1979.
Poole JW: *FMC Problem Solver and Reference Manual*, FMC Corp, Philadelphia, Section 5, 1982.
Fiese EF, Hagen TA: *The Theory and Practice of Industrial Pharmacy*, Lea & Febiger, Philadelphia, 1986, Chap 8.
Leuenberger H, Rohera BD, *Pharm Res 3:* 12, 1986.
Wang YJ, Hanson MA, *J Parenteral Sci Technol 42* (2S): S3, 1988.

CHAPTER 76

Bioavailability and Bioequivalency Testing

Anthony R DiSanto, PhD

Vice President, Drug Delivery Research and Development
The Upjohn Company
Kalamazoo, MI 49001

Pharmacy is a profession that requires the use of a number of scientific disciplines as well as the individual professional experience of its practitioners. Compounding of medications has become a small part of the pharmacist's practice, now replaced largely by his major role and responsibility for safeguarding drug-product quality through proper selection of multisource drug products. One need not become embroiled in the controversy of brand-name vs generic products, for this is not the issue. The problem is one of discriminate selection of a drug product available from different manufacturers—often of substitution of one product for another, whether it involves a brand-to-generic, generic-to-brand or generic-to-generic change.

For the pharmacist to accept such responsibility, he must be reasonably knowledgeable in biopharmaceutics, with particular emphasis on drug bioavailability and bioequivalence. Variable clinical response to the same dosage form of a drug product supplied by two or more drug manufacturers is well-recognized. In this chapter only bioavailability problems will be discussed. Chemical equivalence, lot-to-lot uniformity of physicochemical characteristics and stability equivalence are but a few of the other factors that are important, as they too can affect a patient's ultimate clinical response to a drug.

One must not be led to a feeling of overconfidence in the simplicity of product selection solely because the FDA promulgated bioavailability regulations. Even for the limited number of multisource drug products that require some type of bioequivalence testing, it should be recognized that the testing is only on one lot of the product. Similarly, where only *in vitro* assessment is required, data provided are limited to one to three lots. There is a misconception that once a product is marketed that the FDA continues to test each lot. This is not the case as very few drug products are followed up at the FDA laboratories. The question of *continued* assurance of bioequivalence and chemical equivalence must, therefore, be posed by the pharmacist. This is where the challenge lies, and the pharmacist has to call on both his technical training and experience to make appropriate drug-product selection decisions.

Bioavailability

In any discussion of bioavailability and bioequivalency testing, it is perhaps best to start with the basic concepts and factors that can affect the bioavailability of a drug and consider how these can affect bioequivalency and the clinical outcome of drug treatment. At the outset, the terms used in this chapter require careful definition since, as in any area, some terms have been used in many different contexts by different authors.

Bioavailability is an absolute term that indicates measurement of both the true rate and total amount (extent) of drug that reaches the general circulation from an administered dosage form.

Equivalence is more a relative term that compares one drug product with another or with a set of established standards. Equivalence may be defined in several ways:

1. *Chemical equivalence* indicates that two or more dosage forms contain the labeled quantities (plus or minus specified range limits) of the drug.
2. *Clinical equivalence* occurs when the same drug from two or more dosage forms gives identical *in vivo* effects as measured by a pharmacological response or by control of a symptom or disease.
3. *Therapeutic equivalence* implies that one structurally different chemical can yield the same clinical result as another chemical.
4. *Bioequivalence* indicates that a drug in two or more similar dosage forms reaches the general circulation at the same *relative* rate and the same *relative* extent, ie, that the plasma (blood or serum) level profiles of the drug obtained using the two dosage forms are, within reason, "superimposable."

Dosage Forms—In the dose titration of any patient the objective is, in conceptual terms, to attain and maintain a blood level which exceeds the minimum effective level required for response, but which does not exceed the minimum toxic (side-effect) level. This is shown graphically in Fig 76-1. There are three major absorption factors which can affect the general shape of this blood-level curve and thus drug response.

1. The dose of the drug administered, ie, the blood levels will rise and fall in proportion to the dose administered.
2. The same as the first but brought about by a different process, is the amount of drug absorbed from a given dosage form. The effect of having only one-half of the drug absorbed from a dosage form is equivalent to lowering the dose (Fig 76-2).
3. The rate of absorption of the drug. If absorption from the dosage form is more rapid than the rate of absorption which gave the profile in Fig 76-1, toxic (side-effect) levels can be exceeded. If absorption from the dosage form is sufficiently slow, minimum effective levels may never be attained (Fig 76-3).

A combination of these last two factors is also possible (Fig 76-4) and is probably the most likely result in real life.

In any of these instances, the time course and extent of clinical response to the drug has been altered.

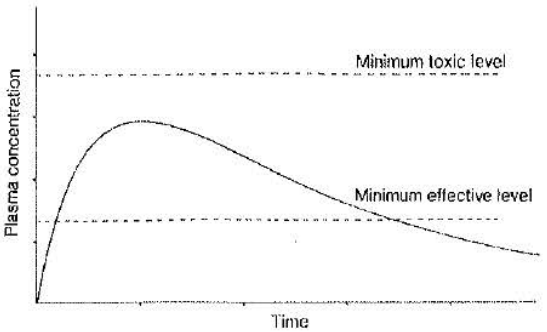


Fig 76-1. Typical plasma-level curve of a drug with effective and toxic (side-effect) levels defined.

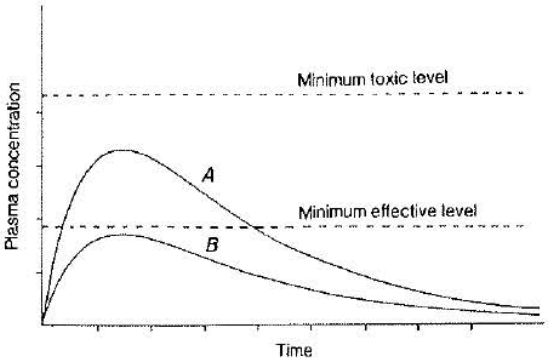


Fig 76-2. Effect of the extent of drug absorption from a dosage form on drug-plasma levels and efficacy. The extent of absorption from Dosage Form *B* is 50% of that from Dosage Form *A*.

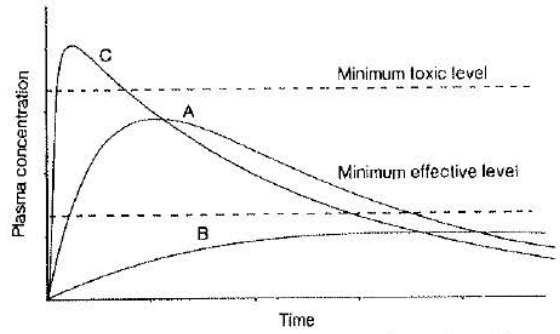


Fig 76-3. Effect of the rate of drug absorption from a dosage form on the plasma-level profile and efficacy. The rates of absorption from Dosage Forms *B* and *C* are $\frac{1}{10}$ and 10 times those from Dosage Form *A*.

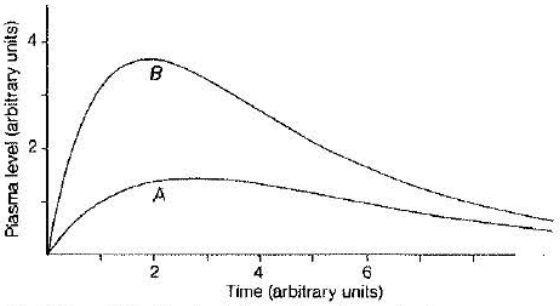


Fig 76-4. Computer simulation of the plasma-level curves for two dosage forms of the same drug assuming that the rate and extent of drug absorption for Dosage Form *A* were 50% and 50%, respectively, of those for Dosage Form *B*.

Both factors, extent and rate of drug absorption, can be affected by the dosage form in which the drug is contained. The effect may be intentional, as in sustained-release medication, or unintentional, as brought about by a change in the composition and/or method of manufacture of the dosage form.

It is important to remember that in most dosage forms the only ingredient regulated by law is the active drug. The choice of the other materials (adjuvants) used to prepare a satisfactory dosage form is up to the individual manufacturer. It is through these changes, in composition and manufacturing technique, that unintended changes in bioavailability and bioequivalency may occur. A description of the formulation of dosage forms and the factors which must be considered by the formulating pharmacist is given in Chapter 75.

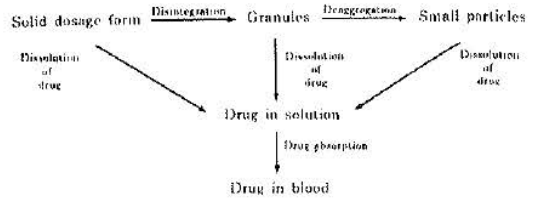


Fig 76-5. Sequence of events involved in the dissolution and absorption of a drug from a solid oral dosage form.

Dissolution Rate—For a drug to be absorbed, it must first go into solution. In Fig 76-5, the steps in the dissolution and absorption of a tablet or capsule dosage form are outlined. Similar profiles could be developed for any solid or semisolid dosage form, ie, oral suspensions, parenteral suspensions or suppositories. The theory and mechanics of drug-dissolution rate are described in detail in Chapter 31. Suffice it to say that the physical characteristics of the drug and the composition of the tablet (dosage form) can have an effect on the rates of disintegration, deaggregation and dissolution of the drug. As such, these can affect the rate of absorption and resultant blood levels of the drug.

Properties of the Drug—The physical characteristics of the drug which can alter bioavailability are discussed in Chapters 35 and 75 and consist of: the polymorphic crystal form, choice of the salt form, particle size, use of the hydrated or anhydrous form, wettability and solubility of the drug. Chapter 75 also discusses several other properties which can affect drug-product quality adversely. Many of these factors should be discovered during the chemical testing of the drug product prior to the sale of the dosage form and should not, therefore, affect, unknowingly, the bioavailability of the drug product.

Properties of the Dosage Form—The various components of the solid or semisolid dosage form, other than the active ingredient, are discussed in Chapter 89. Only an overview, for tablet dosage forms, will he given here. In addition to the active ingredient, a tablet product usually will contain:

Binders are used to provide a free-flowing powder from the mix of tablet ingredients so that the material will flow when used on a tablet machine. The binder also provides a cohesiveness to the tablet. Too little binder will give flow problems and tablets which do not maintain their integrity; too mueh may affect adversely the release (dissolution rate) of the drug from the tablet.

Fillers are used to give the powder bulk so that an acceptable-size tablet is produced. Most commercial tablets weigh from 100 to 500 mg so it is obvious that for many potent drugs the filler comprises a large portion of the tablet. The binding of drug to the filler may occur and affect bioavailability.

Disintegrants are used to cause the tablets to disintegrate when exposed to an aqueous environment. Too much will produce tablets which may disintegrate in the bottle due to atmospheric moisture; too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the drug from the dosage form.

Lubricants are used to enhance the flow of the powder to the tablet machine and to prevent sticking of the tablet in the die of the tablet machine after the tablet is compressed. Lubricants are usually hydrophobic materials such as stearic acid, magnesium or calcium stearate. Too little lubricant will not permit satisfactory tablets to be made; too much may produce a tablet with a water-impervious hydrophobic coat, which can inhibit the disintegration of the tablet and dissolution of the drug.

The integrity of the manufacturer is not a true physical ingredient of the tablet, but it can have an effect on the clinical performance of the dosage form. Many of the problems which arise here are related to, and detectable by, the physical and chemical quality controls the manufacturer applies to his product (see Chapter 82). For example, with low-dose potent drugs the determination that all the active ingredient is present, on the average, in the dosage form must be complemented by

the determination that each tablet contains the specified dose. It is quite possible with potent drugs that the assay of combined tablets (10 to 20) may be within compendial limits while the drug contents of individual tablets may far exceed these limits in both positive and negative directions. Such variations in dose, and thus bioavailability, are detectable and controllable by a chemical assay of the tablets. However, these assays and other determinations may not always be done by manufacturers with low integrity. This defect may be out of ignorance of the law or intentional disregard for it. The existence of laws and federal regulations does not mean that everyone, at any given point in time, is complying with such laws and regulations.

Bioequivalency Testing

The awareness of the potential for clinical differences between otherwise chemically equivalent drug products has been brought about by a multiplicity of factors which include, among others, better methods for clinical efficacy evaluation, development of techniques to measure microgram or nanogram quantities of drugs in biological fluids, improvements in the technology of dosage-form formulation and physical testing, awareness of a significant number of reported clinical inequivalencies in the literature, increased costs of classical clinical evaluation, the objective, quantitative nature of bioavailability tests and the increase in the number of chemically equivalent products on the market due to patent expirations on the wonder drugs of the 1950s and 1960s.

The increase in the number of similar products from multiple sources frequently has placed people involved in the delivery of health care in the position of having to select one from among several apparently equivalent products. As with any decision, the more pertinent the data available, the more comfortable one is in arriving at the final decision. The need to make these choices, in light of the potential for *in vivo* inequivalency among products, has increased the demand for quantitative data on the clinical equivalence of similar drug products. Bioequivalency testing represents one alternative solution to clinical testing for efficacy.

Requirements for bioequivalency data on drug products should not be applied indiscriminately. For example, with single-supplier drugs, for which clinical efficacy has been established, bioequivalency testing is moot. However, bioavailability data on three lots would be an excellent measure of reproduceable bioavailability. This assures the quality of the innovator and should serve as a guide for permissable variability in the multisource product. In this context the *raison d'etre* for bioequivalency testing should not be forgotten, ie, it has been developed to substitute for the clinical evaluation of drug products. Bioequivalency data cannot be required if bioanalytical methodology is not available. However, in a number of cases pharmacodynamic data may provide a more sensitive, objective evaluation of a product's clinical equivalency than will clinical testing.

Pharmacokinetic evaluation of bioavailability data is not necessary to show bioequivalence of two drug products. Pharmacokinetics has its major utility in the prediction or projection of dosage regimens and/or in providing a better understanding of observed drug reactions or interactions which result from the accumulation of drug in some specific site, tissue or "compartment" of the body. The basis of all statements that two drug products are bioequivalent must be that the responses observed (blood, serum or plasma level, urinary excretion or pharmacologic response) for one drug product essentially are superimposable on the responses observed for the second drug product.

The phrase "essentially are superimposable" must be consistent with the clinical realities of the situation. The easy, but relatively rare, decisions in the evaluation of the bioequivalence of two drug products are those where the two products are exactly superimposable (definitely bioequivalent) and those where the two products differ in their bioequivalency parameters by 50% or more (definitely *bioinequivalent*). The demonstration of absolute differences of 10% or less in the bioavailability of two dosage forms is an assignment which frequently is not possible with today's analytical tools and clinical facilities. In the area of 10 to 20% or even 30% differences between two dosage forms in bioequivalency parameters, clinical judgment must be applied to evaluate the significance of these differences. The effect of a possible 10 to 30% change in dose on the patient's response must be considered carefully before one decides that an apparent or possible 20% difference in bioavailability is acceptable *or* unacceptable. It should be noted that the usual bioavailability difference allowed by the FDA is ±20%. There is no absolute reason why this value was picked.

Even with dosage forms whose bioavailabilities have been established (within 10 to 20%), there is a potential for undesirable, unexpected clinical response when changing the medication for a well-stabilized patient from one drug supplier to another.

It is important to realize that a 10 to 20% bioavailability difference observed in normal, healthy volunteers cannot be any less in a patient where factors affecting drug absorption already may be compromised. These relatively small bioavailability differences observed in healthy volunteers could be doubled or tripled depending on the disease, the state of the disease, the age of the patient, whether the patient is bedridden, has achlorhydria, has hypermotility or hypomobility, etc. Variables associated with the patient in general are unreconcilable and their individual cumulative effect on bioavailability is unknown. When one compounds this patient variability with a drug product that is less than optimally absorbed, the outcome cannot be predicted. The patient for whom the drug is prescribed is the critical factor not to be overlooked in product selection.

Evaluation of Bioequivalency Data

The following sections will highlight some of the tests that should be considered when evaluating the data from bioequivalency studies. The topics discussed will be directed specifically toward blood- or plasma-level evaluations. With minor modifications, the approaches outlined can be used for urinary excretion measurements or for suitable, quantitative pharmacological response measurements.

General Study Design—Bioavailability studies usually are conducted in normal, healthy adults under standardized conditions. Usually, single doses of the test and reference product will be evaluated. However, in selected cases, multiple-dose regimens must be used, eg, acid-labile drugs. The goal of the studies is to evaluate the performance of the dosage forms under standardized conditions. The assumption that any change in conditions or subject health will affect both dosage forms in a similar fashion is not valid and separate tests should be performed.

The protocol should define the acceptable age and weight range for the subjects to be used. It should define the clinical parameters which will be used to characterize a normal, healthy adult; eg, physical examination observations, clinical chemistry and hematological evaluations. The subjects should have been drug-free for at least 2 weeks prior to testing to eliminate possible drug-induced influences on liver enzyme systems. Normally, the subjects will fast overnight prior to dosing and will not eat until a standard meal is provided 2 to 4 hr postdosing. The dosage forms should be given to subjects in a randomized manner, using a suitable crossover design, so that possible daily variations are distributed equally between all dosage forms tested. The protocol should define sample-collection times and techniques to collect the biological fluid. The method of storage of the samples also should be defined.

Bioavailability Assessment and Data Evaluation—Several parameters are used to provide a general evaluation of the overall rate and extent of absorption of a drug. An analysis of all characteristics is required before one can implicate any one factor or parameter as indicating bioequivalence or a lack of bioequivalence.

The blood (or serum or plasma) concentration-time curve is the focal point of bioavailability assessment and is obtained when serial blood samples taken after drug administration are analyzed for drug concentration. The concentrations are plotted on graph paper on the ordinate (or y) axis and the times after drug administration that the samples were obtained on the abscissa (or x) axis.

A drug product is administered orally at time zero, and the blood drug concentration at this time clearly should be zero. As the product passes through the gastrointestinal system (stomach, intestine) it must go through the sequence of events depicted in Fig 76-5. As the drug is absorbed, increasing concentrations of the drug are observed in successive samples until the maximum concentration is achieved. This point of maximum concentration is called the peak of the concentration-time curve. If a simple one-compartment model describes the pharmacokinetics of the drug tested, the peak concentration represents approximately the point in time when absorption and elimination of the drug have equalized.

The section of the curve to the left of the peak represents the absorption phase (usually absorption and distribution), during which the rate of absorption exceeds the rate of elimination. The section of the curve to the right of the peak is called the elimination phase, during which the rate of elimination exceeds the rate of absorption. It should be understood that elimination begins as soon as the drug appears in the blood stream and continues until all of the drug has been eliminated. Elimination is classically the log-linear portion of the curve. Absorption continues too for some period of time into the elimination phase.

One must recognize that elimination of the drug includes all processes of elimination, urinary excretion as well as metabolism, of the drug by various tissues and organs. The "efficiency" of metabolism and urinary excretion will determine the shape of the elimination phase of the curve.

Bioavailability studies are performed in healthy, adult volunteers under rigid conditions of fasting and activity because the objective is to obtain *quantitative* information on the influence of pharmaceutical formulation variables on the drug-product's absorption. Drug blood-level profiles, therefore, allow quantification of the *rate* and *extent* of drug absorption and are critical in establishing the *efficiency* of the drug product in delivering the drug to the systemic circulation.

Arguments that bioavailability testing should be done in a "disease-state population" are not tenable if the object of the study is to assess drug formulations. If, on the other hand, the purpose is to determine the effect of "disease" on the efficiency of absorption from the drug product(s), then one must use the disease-state population. The reasoning is obvious. In order to assure that any differences observed in the drug blood-level profiles are attributable to formulation factors, one must hold all other variables constant, ie, food, activity, state of disease, etc.

One need not be limited to drug blood-level profiles, but in a similar manner many obtain cumulative urinary drug amount-time profiles. Drug *concentration* is determined in the urine at specified time intervals and the *amount* excreted per interval determined by multiplying the concentration by the volume of urine obtained in that interval. The amounts per interval then are cumulated and ultimately the maximum amount excreted in the urine is obtained. This value is analogous to the area under the blood concentration-time curve. A typical cumulative urinary drug amount-time profile for several nitrofurantoin products is presented in Fig 76-6.

In assessing the bioequivalency of drug products one must quantitate the *rate* and *extent* of absorption. The factors of the rate and extent of absorption can be determined by evaluating three parameters of a blood level concentration-time profile. Three parameters describing a blood level curve are considered important in evaluating the bioequivalency of two or more formulations of the same drug; these are the peak height concentration, the time of the peak concentration and the area under the blood (serum or plasma) concentration-time curve.

Peak Height Concentration—The height of the peak of the blood level-time curve obviously represents the highest drug concentration achieved after oral administration. It is reported as an amount per volume measurement, eg, micrograms/mL or units/mL or grams/100 mL, etc. The importance of this parameter is illustrated in Fig 76-7 where the blood concentration-time curves of two different formulations of a drug are represented. A line has been drawn across the curve at 4 μg/mL. Suppose the drug is an analgesic and 4 μg/mL is the minimum effective concentration (*MEC*) of the drug in blood. If, then, the blood concentration curves in Fig 76-7 represent the blood levels obtained after administration of equal doses of two formulations of the drug and it is known that analgesia would not be produced unless the minimum effective concentration was achieved or exceeded, it becomes clear that Formulation *A* should produce pain relief while Formulation *B*, even though it seemed well-absorbed, would not produce the desired pharmacological effect and would be ineffective in producing analgesia.

On the other hand, if the two curves represent blood con-

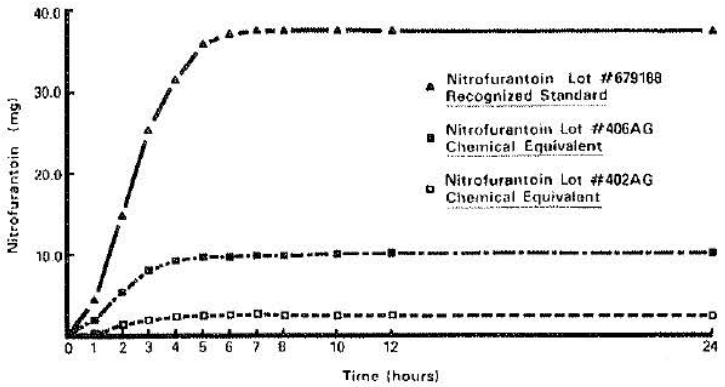


Fig 76-6. Average cumulative amounts of nitrofurantoin excreted from three lots of two commercially available products after a single oral dose of 100 mg of nitrofurantoin.

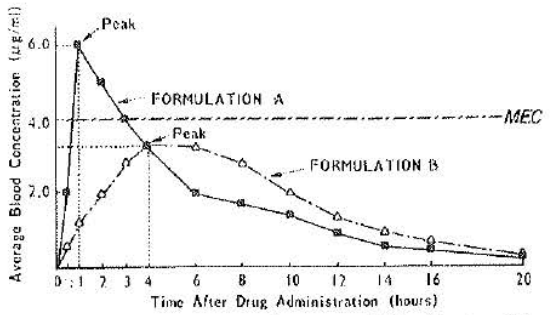


Fig 76-7. Blood concentration-time curves obtained for two different formulations of the same drug demonstrating relationship of the profiles to the minimum effective concentration (*MEC*).

centrations following equal doses of two different formulations of the same cardiac glycoside, and 4 μg/mL now represents the minimum toxic concentration (*MTC*) and 2 μg/mL represents the *MEC* (Fig 76-8), Formulation *A*, although effective, may also be toxic, while Formulation *B* produces concentrations well above the *MEC* but never achieves toxic levels.

Time of Peak Concentration—The second parameter of importance is the measurement of the length of time necessary to achieve the maximum concentration after drug administration. This time is called the time of peak blood concentration. In Fig 76-7, for Formulation *A* the time necessary to achieve peak blood concentration is 1 hr; for Formulation *B* it is 4 hr. This parameter is related closely to the rate of absorption of the drug from a formulation and may be used as a simple measure of rate of absorption.

To illustrate its importance, suppose the two curves in Fig 76-8 now represent two formulations of an analgesic and that in this case the minimum effective concentration is 2 μg/mL. Formulation *A* will achieve the *MEC* in 30 min; Formulation *B* does not achieve that concentration until 2 hr. Obviously, Formulation *A* would then produce analgesia much more rapidly than Formulation *B* and would probably be preferable as an analgesic agent. On the other hand, if one were more interested in the duration of the analgesic effect than on the time of onset, Formulation *B* would present more sustained activity, maintaining serum concentrations above the *MEC* for a longer time (8 hr) than Formulation *A* (5½ hr).

Area Under the Concentration-Time Curve—The third, and sometimes the most important parameter for evaluation, is the area under the serum, blood or plasma concentration-time curve (AUC). This area is reported in amount/volume × time (eg, μg/mL × hours or grams/100 mL × hours, etc) and can be considered representative of the amount of drug absorbed following administration of a single dose of the drug.

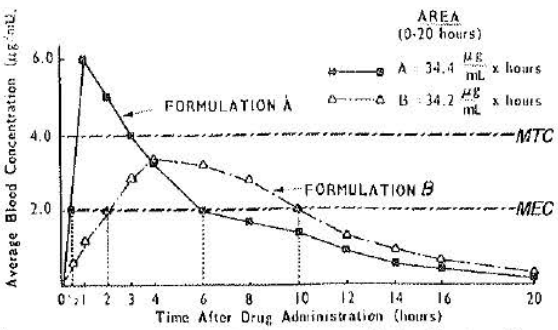


Fig 76-8. Blood concentration-time curves obtained for two different formulations of same the drug demonstrating relationship of the profiles to the minimum toxic concentration (*MTC*) and the minimum effective concentration (*MEC*).

Returning to Fig 76-8, the curves, although much different in shape, have approximately the same areas (A = 34.4 μg/mL × hours; B = 34.2 μg/mL × hours) and both formulations can be considered to deliver the same amount of drug to the systemic circulation. Thus, one can see that AUC does not represent the only criterion on which bioequivalency can be judged. All the results, as a composite, must be used in reaching a decision as to biocquivalency; no one parameter serves this purpose.

Statistical Sense and Nonsense—When statistical evaluations are employed in bioequivalency testing one must be careful not to assume, from a statement that "no statistically significant differences were detected," that two drug products are, therefore, bioequivalent. The basis of most tests for statistically significant differences is that the two products are assumed to be the same until proven otherwise. Therefore, if the data presented are highly variable (large standard deviation, ie, wide range of values), it would be possible to show that there was no statistically significant difference between an AUC of 100 units (%) versus an AUC of 40 units (%). In this case the statistical test does not indicate that the AUCs are truly similar; it simply means that the data were too variable from patient to patient for the statistics to be able to detect a 60-unit (%) difference in areas, even if it existed.

There are two types of errors associated with any statistical test. These are:

1. **Alpha (α) Error**—This is the error with which most people are familiar and is the error associated with the statement, "The data have been analyzed statistically." α error is the probability (defined by the p value) by saying the two treatments are different when in fact they are the same. It should be noted that while highly significant p values reduce the alpha error, they provide no indication of the possibility that the two treatments being called the same when in fact they are different.
2. **Beta (β) Error**—This is the error associated with the possibility of calling two treatments the same when in fact they are different. As the maximum percent difference between means which can be detected with an α error of $p \leq 0.05$ is reduced, the β error also is reduced. This increase in statistical sensitivity (reduced α and β error) is obtained by reducing the variability of the data. Variability usually is reduced by increasing the number of data points (subjects) in a bioavailability study. It is implicit that the analytical methodology is specific, sensitive and precise.

The objective of statistical testing for bioavailability evaluation should be to minimize both the α and β error. Since both errors are related mathematically to the variability of the data collected, the solution is relatively simple. Sufficient data should be gathered so that the general statistical test (α error test) would detect, if it existed, a predetermined percent difference (20% for example) between the two dosage forms. If, for example, the two treatments are found statistically not to be ($p \leq 0.05$) different significantly, the results indicate that there is only 1 chance in 20 that the treatments are claimed to be different when in fact they are the same.

If there were 18 subjects in the above example and a 20% difference would have been significantly different statistically, there would be a β error of 4 chances in 20 that a 25% difference between means was not detected. That is, that treatments which differed by more than 25% were claimed to be the same when in fact they were different. The level of statistical sensitivity which one feels is adequate (20% as a rule of thumb) must be reevaluated for each drug product tested based on the clinical performance of the drug.

Statistical analysis also can go to the other extreme. For example, tests might show that an AUC of 100 units (100%) was statistically significantly different from an AUC of 90

units (90%). If the clinical impression of the drug being evaluated was that a 20% difference in dose (plasma levels) would not be clinically significant, in this example it must be concluded that the statistical test is too sensitive and the difference observed, even if real, is not significant clinically. Therefore, the drug products are bioequivalent in spite of the statistical findings.

Statistics should be used, in bioavailability testing, as a tool to determine if sufficient subjects have been included to minimize the effect of patient-to-patient variability in the data analysis. The results of statistical testing should not be used *as the decision* but to help *make the decision*. One must apply some statistical sense in order to avoid statistical nonsense.

A Common Pitfall: Cross-Study Comparisons—Perhaps the single most-common error made in interpreting bioavailability data is that of *cross-study comparison*. This occurs when the blood concentration-time curve of a drug product in one study is compared with the blood concentration-time curve of that drug product in another study. There are three reasons why such cross-study comparisons are dangerous and can lead to false conclusions. The following examples used to illustrate the three points are taken from actual bioavailability data.

Different Subject Population—In Fig 76-9, a research lot of potassium phenoxymethyl penicillin was compared with the appropriate reference standard for that product. The research-lot drug was found to be bioequivalent, with average peak-serum concentrations differing by 8% and the area differing by only 9%. In another study conducted with a full-manufacture lot of the test product, the same lot of the reference standard potassium phenoxymethyl penicillin was used. The results of this study are shown in Fig 76-10. Again, the two products were found to be bioequivalent as the peak and area parameters differed by less than 5%. In these two studies, identical test conditions were used and the same analytical procedure and laboratory was employed. However, if one compares the serum levels for the reference standard lot found in Fig 76-9, with the levels for the same lot of tablets in the study in Fig 76-10, sizable differences in blood levels are found as shown in Fig 76-11.

The average peak serum levels for this lot of tablets were found to be 8.5 units/mL and 12.5 units/mL in the two respective studies, a difference of approximately 31%. Likewise, the average AUC was found to differ by approximately 21%. Such differences are the sole result of cross-study

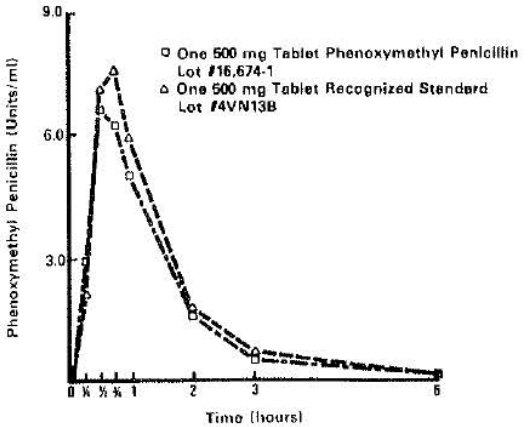


Fig 76-9. Average serum concentration of phenoxymethyl penicillin following oral administration of 500 mg given as one tablet of Recognized Standard (△), or of Test Product, Research Lot (□).

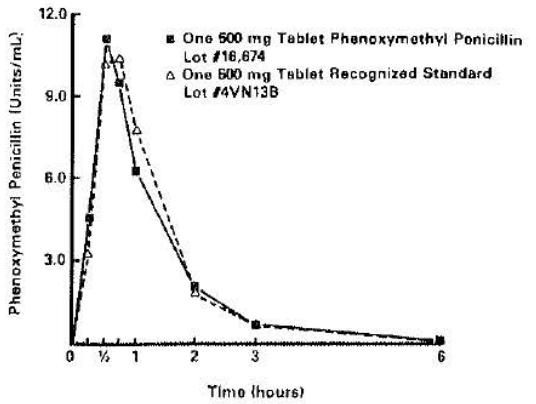


Fig 76-10. Average serum concentration of phenoxymethyl penicillin following oral administration of 500 mg given as one tablet of Recognized Standard (△), or of Test Product, Full Mfg Lot (■).

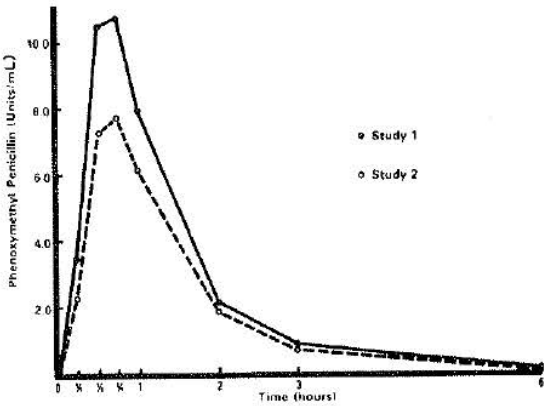


Fig 76-11. Average serum concentration of phenoxymethyl penicillin following a single oral 500-mg dose of Recognized Standard, in two different subject populations.

comparisons and are not due to differences in actual bioavailability.

The same lot of reference standard tablets was used in both studies. Hence, the difference must be due to the experimental variables which occur normally from study to study. The major difference between the two studies was the subject population involved. In the first study, healthy, adult, male, prison volunteers were used, whereas in the second study, there were 17 females and 7 males in a hospital clinic, also described as normal, healthy volunteers. An appreciable difference in sex distribution was obvious when comparing these studies. Adjustments for body weight and surface area alone did not correct for the apparent discrepancies in peak concentration or blood level AUC. It is difficult to determine the exact factors which caused the observed differences. This example should serve as a note of caution in comparing absolute bioavailability values of peak concentration and area under the curve from different studies.

Different Study Conditions—Parameters such as the food or fluid intake of the subject before, during and after drug administration can have dramatic effects on the absorption of certain drugs. Fig 76-12 shows the results of a three-way crossover test where the subjects were fasted 12 hr overnight and 2 hr after drug administration of an uncoated

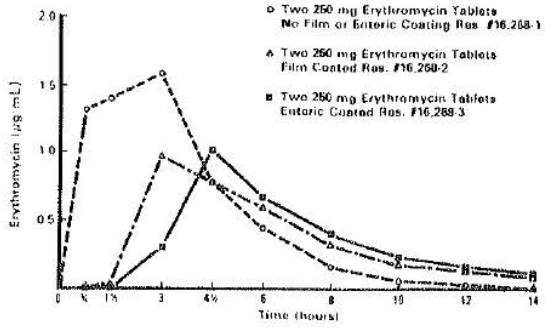


Fig 76-12. Average serum erythromycin concentration administered in 500-mg doses as three different tablet dosage forms. The results were obtained from 21 healthy adult subjects following an overnight fast of 12 hr before and 2 hr after drug administration.

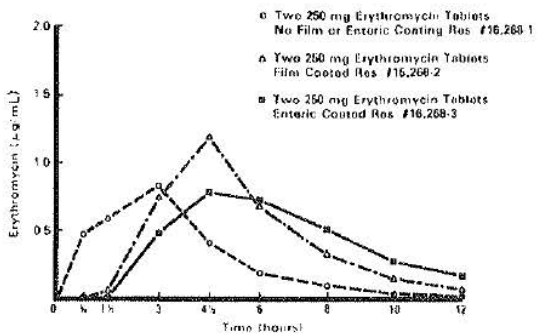


Fig 76-13. Average serum erythromycin concentration administered in 500-mg doses as three different tablet dosage forms. The results were obtained from 12 healthy adult subjects with only a 2-hr fast before drug administration.

tablet, a film-coated tablet or an enteric-coated tablet of erythromycin.

The results of this study suggest that the unprotected tablet is superior to both the film-coated and enteric-coated tablets in terms of blood-level performance. These results

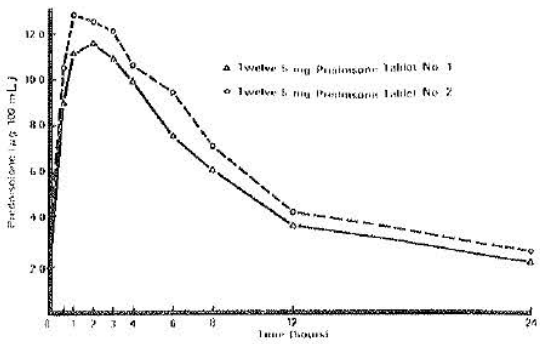


Fig 76-15. Average plasma prednisolone levels following 60 mg of prednisone administered to 24 normal adults as a single oral dose of twelve 5-mg prednisone tablets from two different manufacturers. Plasma levels were determined by a competitive protein-binding assay.

also suggest that neither film-coating nor enteric-coating is necessary for optimal blood-level performance. Figure 76-13 shows results with the same tablets when the study conditions were changed to only a 2-hr preadministration fast with a 2-hr postadministration fast. In this case, the blood levels of the uncoated tablet were depressed markedly while the film-coated and enteric-coated tablets showed relatively little difference in blood levels.

From this second study, it might be concluded that film-coating appears to impart the same degree of acid stability as an enteric coating. This might be acceptable if only one dose of the antibiotic was required. However, Fig 76-14 shows the results of a multiple-dose study in which the enteric-coated tablet and the film-coated tablet were administered 4 times a day, immediately after meals. The results show that the film coating does not impart the degree of acid stability as does the enteric coating when the tablets are administered immediately after food in a typical clinical situation.

Different Assay Methodology—Depending on the drug under study, there may be more than one assay method available. For example, some steroids can be assayed by a radioimmunoassay, competitive protein-binding, gas-liquid

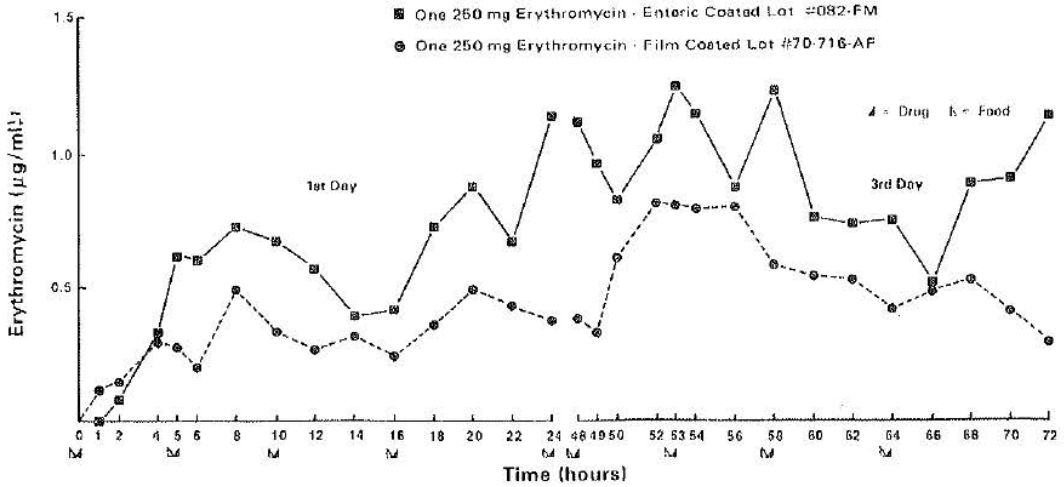


Fig 76-14. Average serum erythromycin concentration-time profiles administered in two different tablet dosage forms. The results were obtained from 24 healthy adult subjects following administration of 250 mg 4 times a day, with meals and at bedtime.

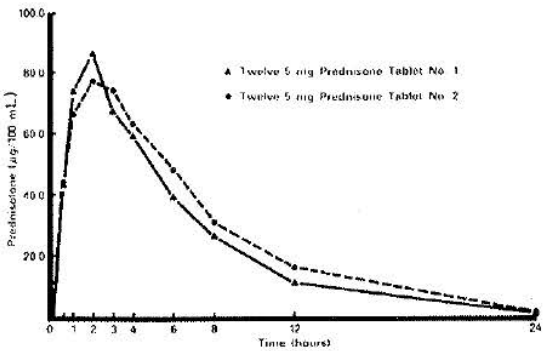


Fig 76-16. Average plasma prednisolone levels following 60 mg of prednisone administered to 24 normal adults as a single oral dose of 12 5-mg prednisone tablets from two different manufacturers. Plasma levels were determined by a radioimmunoassay procedure.

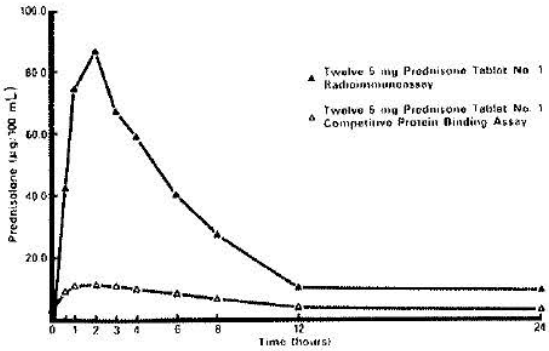


Fig 76-17. Average plasma prednisolone profiles administered as a single 60-mg dose to 24 normal adults. Plasma levels were determined by both a competitive protein binding assay and a radioimmunoassay.

chromatograph or, indirectly, by a 17-hydroxycorticosteroid assay.

Figures 76-15 and 76-16 show the results of a comparison of prednisone tablets using a competitive protein-binding method and a radioimmunoassay, respectively. The serum concentration-time curves resulting from each method lead to the same conclusion, that the products are bioequivalent. However, Fig 76-17 shows a comparison of the absolute values obtained by the two assay methods with the same product.

Obviously, the wrong conclusion would have been reached if one product had been assayed by one method and the other product by the other method and the results had been compared. Even in cases where only one assay method is employed, there are numerous modifications with respect to technique among laboratories which could make direct comparisons hazardous.

The backbone of any bioavailability study involving plasma (or urine) levels of drug, in addition to good study design and subject controls, is the analytical methodology used to determine the levels of a drug. In most cases one *probably* can assume that the precision and reliability of the method employed in a given study have been established to a sufficient degree to make the results of the study internally consistent. As demonstrated, major problems arise when, without careful evaluation of the analytical methodology employed, one attempts to compare the data of studies from different laboratories. Even with similar analytical methodology performed by the same laboratory, it would be unreasonable to expect agreement, using the same dosage form, of closer than 20 to 25% for plasma levels, AUCs, etc, from one study to the next.

Under the *best* conditions, cross-study comparisons are relatively insensitive, and at worst they can be misleading. Cross-study comparisons certainly cannot be used to make decisions or estimations of differences in drug products with the generally acceptable sensitivity of difference detection of 20% or less.

With insufficient data on the correlation of plasma levels with clinical response, it is difficult to decide if it is the peak plasma level or the total body load of a drug that is important. Changes in the rate of absorption require changes in the dose given (body load) for maintenance of similar peak plasma levels. Decisions as to which is more important, body load or peak level, are made with difficulty and tend to reduce the objective quantitation sought in bioavailability testing.

Bibliography

Chodos DJ, DiSanto AR: *Basics of Bioavailability*, The Upjohn Co, Kalamazoo, 1973.
Dittert LW, DiSanto AR: *J APhA NS13*:(8): 000 1973.
DiSanto AR *et al*: *Int J Clin Pharmacol 13*: 220–227, 1976.

CHAPTER 79

Tonicity, Osmoticity, Osmolality and Osmolarity

Frederick P Siegel, PhD

Professor of Pharmaceutics
College of Pharmacy, University of Illinois
Chicago, IL 60612

It generally is accepted that osmotic effects have a major place in the maintenance of homeostasis (the state of equilibrium in the living body with respect to various functions and to the chemical composition of the fluids and tissues, eg, temperature, heart rate, blood pressure, water content or blood sugar). To a great extent these effects occur within or between cells and tissues where they cannot be measured. One of the most troublesome problems in clinical medicine is the maintenance of adequate body fluids and proper balance between extracellular and intracellular fluid volumes in seriously ill patients. It should be kept in mind, however, that fluid and electrolyte abnormalities are not diseases, but are the manifestations of disease.

The physiological mechanisms which control water intake and output appear to respond primarily to serum osmoticity. Renal regulation of output is influenced by variation in rate of release of pituitary antidiuretic hormone (ADH) and other factors in response to changes in serum osmoticity. Osmotic changes also serve as a stimulus to moderate thirst. This mechanism is sufficiently sensitive to limit variations in osmoticity in the normal individual to less than about 1%. Body fluid continually oscillates within this narrow range. An increase of plasma osmoticity of 1% will stimulate ADH release, result in reduction of urine flow and, at the same time, stimulate thirst that results in increased water intake. Both the increased renal reabsorption of water (without solute) stimulated by circulating ADH and the increased water intake tend to lower serum osmoticity.

The transfer of water through the cell membrane occurs so rapidly that any lack of osmotic equilibrium between the two fluid compartments in any given tissue usually is corrected within a few seconds and, at most, within a minute or so. However, this rapid transfer of water does not mean that complete equilibration occurs between the extracellular and intracellular compartments throughout the entire body within this same short period of time. The reason is that fluid usually enters the body through the gut and then must be transported by the circulatory system to all tissues before complete equilibration can occur. In the normal person it may require 30 to 60 min to achieve reasonably good equilibration throughout the body after drinking water. Osmoticity is the property that largely determines the physiologic acceptability of a variety of solutions used for therapeutic and nutritional purposes.

Pharmaceutical and therapeutic consideration of osmotic effects has been, to a great extent, directed toward the side effects of ophthalmic and parenteral medicinals due to abnormal osmoticity, and to either formulating to avoid the side effects or finding methods of administration to minimize them. More recently this consideration has been extended to total (central) parenteral nutrition, to enteral hyperalimentation ("tube" feeding) and to concentrated-fluid infant formulas.[1] Also, in recent years, the importance of osmometry of serum and urine in the diagnosis of many pathological conditions has been recognized.

There are a number of examples of the direct therapeutic effect of osmotic action, such as the intravenous use of mannitol as a diuretic which is filtered at the glomeruli and thus increases the osmotic pressure of tubular urine. Water must then be reabsorbed against a higher osmotic gradient than otherwise, so reabsorption is slower and diuresis is observed. The same fundamental principle applies to the intravenous administration of 30% urea used to affect intracranial pressure in the control of cerebral edema. Peritoneal dialysis fluids tend to be somewhat hyperosmotic to withdraw water and nitrogenous metabolites. Two to five percent sodium chloride solutions or dispersions in an oleaginous base (Muro, *Bausch & Lomb*) and a 40% glucose ointment are used topically for corneal edema. Ophthalgan (*Ayerst*) is ophthalmic glycerin employed for its osmotic effect to clear edematous cornea to facilitate an ophthalmoscopic or gonioscopic examination. Glycerin solutions in 50 to 75% concentrations [Glyrol (*IO Lab*), Osmoglyn (*Alcon*)] and isosorbide solution [Ismotic (*Alcon*)] are oral osmotic agents for reducing intraocular pressure. The osmotic principle also applies to plasma extenders such as polyvinylpyrrolidone and to saline laxatives such as magnesium sulfate, magnesium citrate solution, magnesium hydroxide (via gastric neutralization), sodium sulfate, sodium phosphate and sodium biphosphate oral solution and enema (*Fleet*).

An interesting osmotic laxative which is a nonelectrolyte is a lactulose solution. Lactulose is a nonabsorbable disaccharide which is colon-specific, wherein colonic bacteria degrade some of the disaccharide to lactic and other simple organic acids. These, *in toto*, lead to an osmotic effect and laxation. An extension of this therapy is illustrated by Cephulic (*Merrell-Dow*) solution, which uses the acidification of the colon via lactulose degradation to serve as a trap for ammonia migrating from the blood to the colon. The conversion of ammonia of blood to the ammonium ion in the colon ultimately is coupled with the osmotic effect and laxation, thus expelling undesirable levels of blood ammonia. This product is employed to prevent and treat frontal systemic encephalopathy.

Osmotic laxation is known with the oral or rectal use of glycerin and sorbitol. Epsom salt has been used in baths and compresses to reduce edema associated with sprains. A relatively new approach is the indirect application of the osmotic effect in therapy via osmotic pump drug delivery systems.[2]

If a solution is placed in contact with a membrane that is permeable to molecules of the solvent, but not to molecules of the solute, the movement of solvent through the membrane is called osmosis. Such a membrane is often called *semipermeable*. As the several types of membranes of the body vary in their permeability, it is well to note that they are *selectively* permeable. Most normal living-cell membranes maintain various solute concentration gradients. A selectively permeable membrane may be defined either as one that does not permit free, unhampered diffusion of all