The Nature of Receptor Groups and Models of Receptors

A *receptor group* is that portion of the receptor molecule with which an agonist acts and which is vital to the function of the receptor. Studies of receptor group composition and configuration are too complex for the purposes of this text; consequently, only a brief sketch will be made here to orient the reader to the nature of the approach.

From the chemical configuration and reactivity of agonists and antagonists, certain deductions can be made about the structure of a receptor group. For example, all highly active agonists of muscarinic receptors are cations at physiological pH. This suggests that the receptor group contains an anionic group and that the force of attraction is electrostatic, at least in part, which agrees with thermodynamic data. That van der Waals forces (especially Heitler-London fluctuation forces) may also make an important contribution to binding is suggested by the requirement for *N*-methyl groups and by the low but definite activity of the nonionizable quaternary carbon analog of acetylcholine, 3,3-dimethylbutyl acetate. This establishes a requirement for an auxiliary structure close to the anionic site. Studies of the contribution to activity of ester and carbonyl oxygen among analogs of acetylcholine, intramolecular distances and the stereospecificity of various isomers and conformers have indicated a partial cationic (proton donor) site between 2.5 and 4 Å and a region of high electronic density (electron donor) between 5 and 7 Å from the anionic site. This is similar to the way in which the active site of acetylcholinesterase was mapped (see page 427, and Figs 25-44, 45 and 46).

The structure–activity relationships among competitive inhibitors also must be consistent with any model of a receptor. However, binding sites additional to the receptor group can be involved, and results are frequently more difficult to interpret than those with agonists. Nevertheless, studies with antagonists have made a substantial contribution to receptor group analysis. There is considerable interest in antagonists that combine irreversibly with the receptor, since such drugs offer a way of marking (affinity labeling) the receptor for isolation and for identification of the receptor group.

Since receptors for autonomic agonists are embedded in the cell membrane, they have been difficult to isolate without inactivation. Several laboratories have succeeded in isolating proteins, the chemical properties of which are consistent with those expected of various receptors. Receptors for steroid hormones have been easier to isolate, and some have been characterized relatively well. Further details of drug-receptor interactions and the nature of receptors can be found in the works on receptors and molecular pharmacology.

Up- and Down-Regulation—In many receptor-effector systems, if there is a paucity of agonist, the system will respond by increasing the responsiveness, number of receptors on the effector membrane or number of coupling proteins or enzymes in the effector system. This is known as *up-regulation*. In adrenergic systems, sympathetic denervation has been shown to increase the number of post-synaptic β-adrenoreceptors at some junctions and the availability of nucleotide-binding protein units and/or adenylate cyclase molecules at others. Hyperthyroid activity also increases the number of β-adrenoreceptors in heart muscle, which explains the excessive heart rate. Denervation of skeletal muscle causes a great multiplication of what is normally a minor type of nicotinic receptor, and the new receptors spread across the entire myocyte membrane. Prolonged blockade of receptors by antagonists also may cause up-regulation. The abrupt discontinuation of treatment, such that drug levels fall faster than re-regulation, may be followed by excessive activity, eg, in pernicious tachycardia and angina pectoris from abrupt withdrawal of propranolol.

Excessive agonism will lead to a decrease in the number of receptors or in stimulus-response coupling. This is one cause of tachyphylaxis or tolerance, such as occurs to the bronchodilator effects of β-adrenoreceptor agonists. Abrupt withdrawal may result in poor residual function or in rebound effects, depending upon the type of effect caused by the agonist. Excessive agonism also may cause desensitization by agonist-induced changes in receptor conformation to inactive, slowly reconformable states.

Mechanism of Drug Action

Any metabolic or physiological function provides a potential mechanism of action of a drug. The term *mechanism of action* has been employed in a number of ways. In the past it was often the habit to confuse the site, or locus of action, with the mechanism of action. For example, the mechanism of the hypotensive action of tetraethylammonium ion originally was described as that of ganglionic blockade, which did nothing more than identify the anatomical structure upon which the drug acted. In a general sense, this was a partial elucidation of the mechanism of action, if mechanism is used in the mechanical sense of the entire linkage between the input and output of a machine. However, there has been a gradual narrowing of the definition of mechanism of action to be restricted to only the first event in the action–effect sequence, that is, only to the alteration of receptor function by the drug. In this sense, the mechanism of action of tetraethylammonium is defined more appropriately as that of competition with acetylcholine for nicotine cholinergic receptors on the postsynaptic ganglion cell membrane, even though the alteration in receptor function is not defined. The ultimate mechanism of action is known for only a few drugs.

It is customary to speak of a drug as a stimulant or a depressant, of the action as being excitatory or inhibitory, etc. Such terms describe only the effect and not the action, and they have no bearing upon whether the drug augments receptor function or diminishes it. In biological systems, positive and negative modulation and feedback occur at every level, the organ as well as the subcellular. Thus, an agonist to a negative modulator may be able to bring about the same effect as an antagonist to a positive modulator. It is possible for an antagonist or inhibitor to elicit an excitatory effect. An example is the convulsant action of strychnine, which results from its antagonism of glycine, an important mediator of postsynaptic inhibition in the central nervous system. Conversely, it is possible for an agonist to elicit an inhibitory effect. An example is the reflex bradycardia that results from the stimulant action of veratrum alkaloids on chemoreceptors in the left ventricle.

Because of the central role *enzymes play* in cellular function, it is not surprising that thoughts about the mechanism of action of drugs has focused largely upon enzymes. Agonist drugs conceivably could serve as substrates, cofactors or activators. At the present time, no drug is known definitely to exert its action as a substrate or as a cofactor, exclusive of vitamins and known nutrients. However, at least three classes of drugs are known and several are suspected to work through the activation of enzymes.

The most notable example of enzyme activation is that of epinephrine and similar β-adrenoreceptor agonists, which activate adenyl cyclase to increase the production of 3′,5′-cyclic adenylic acid (cyclic AMP; cAMP). The metabolic and cardiac effects of catecholamines are attributable, in part, to the increment in cAMP. One modulator of adenyl cyclase is the β-adrenergic receptor. The β-adrenoreceptor is coupled to adenylate cyclase through a regulatory protein that binds GDP and GTP (G-protein). When GDP is present, the agonist-receptor complex is associated with the regulatory protein. GTP causes transfer of the regulatory protein to adenylate cyclase and dissociation of the β-adrenoreceptor. Glucagon also owes its hyperglycemic action to activation of hepatic adenylate cyclase. A number of other agonists also activate adenylate cyclase. There is, thus, the interesting phenomenon of one enzyme, adenyl cyclase, being activated by numerous chemically unrelated drugs. Since β-adrenergic-blocking agents do not antagonize glucagon, it is obvious that glucagon works upon a different receptor than does epinephrine.

Thus, cAMP activates protein kinases that increase the activity of phosphorylase, actomyosin, the sequestration of calcium by the sarcoplasmic reticulum and calcium channels. Therefore, a brief activation of the β-adrenoreceptor sets in motion a cascade of events that greatly amplify the signal. Kinases also participate in down-regulation and desensitization.

Other important enzymes coupled to receptors are guanylate cyclase and phospholipases A and C, which are involved with membrane fluidity and calcium channels, respectively.

Many drugs are inhibitors of enzymes. When the drug is a *competitive inhibitor* of a natural endogenous substrate of the enzyme, it is called an *antimetabolite* (see also page 431). Examples of antimetabolites are sulfonamides, which compete with para-aminobenzoic acid and, thus, interfere with its incorporation into dihydrofolic acid and methotrexate, which competes with folic acid for dihydrofolate reductase and, thus, interferes with the formation of folinic acid. It might seem that anticholinesterases are also antimetabolites, although they are never placed into that classification. The reason is that the products of cholinesterase–acetylcholine interaction do not subserve important metabolic functions, as do folic and folinic acids, so that the organism is not deprived of an important metabolite by the action of the cholinesterase inhibitors.

Some drugs are competitive inhibitors of enzyme systems whose natural function appears not to produce useful metabolites but to rid the body of foreign substances. Inhibitors of the hepatic microsomes and probenecid fall into this category; the hepatic microsomes do perform a few biotransformations on endogenous substrates, but the renal tubular anion transport system does not appear to be required to eliminate any important endogenous substances.

Since neither the hepatic microsomes nor the tubular anion transport system seems to be involved in response systems, inhibitors of these enzyme systems are antagonists without corresponding agonists. Indeed, even natural endogenous substrates of enzymes are rarely considered to be agonists.

Noncompetitive enzyme inhibitors among drugs also are known. Examples are cyanide, fluoride, disulfiram and cardiac glycosides. When enzyme inhibition brings about a positive response—eg, the cholinergic effects of the anticholinesterases or the effects of diazoxide consequent to inhibition of phosphodiesterase—the drug appears to be an agonist. Yet, there can be no competitive antagonist to such an inhibitor, since the competitor to the drug is more substrate, to which the effect of the drug is actually attributable.

Acetylcholine increases the permeability of the subsynaptic membrane to cations and the heart muscle membrane to potassium. The mechanism is thought generally to involve a change in conformation of a protein constituent of the potassium channel, so that pore size or permeability constant is affected. The muscarinic receptor is coupled to the potassium channel through a G-protein. Other autonomic agonists also are known to alter the permeability to ions, in part through activation of adenyl cyclase, guanyl cyclase, phospholipase-c or other enzymes. Many drugs and toxins act through *alterations in the structural and physical properties of membranes*. To the extent that some of such substances may disperse themselves generally throughout the lipid phase of the membrane rather than to combine with special chemical entities, no definite receptors for such drugs can be said to exist.

The mechanism of action of certain drugs, especially autonomic drugs, often is stated to be *mimicry* of a natural neurohumor or hormone. Thus, methacholine mimics acetylcholine as an agonist. This does not define the mechanism of action, unless the mechanism of action of the natural substance is known.

Mimicry usually occurs because of a structural similarity between the natural substance and the mimetic drug. Mimicry in agonist functions is easy to demonstrate, but the site of action may not always be mimicry of the natural agonist at its receptor but rather at an allosteric site on a receptor or at its storage site to *release* the natural agonist.

Examples of mimetics that act by release of the natural mediator are indirectly acting sympathomimetics such as *d*-amphetamine, mephentermine, ephedrine (in part), tyramine and others, which are now known to act by displacing norepinephrine from storage sites within the adrenergic neuron. Many of such indirectly acting sympathomimetics lack a direct action on the adrenergic receptor, although some, like ephedrine, act both upon the receptor and the storage complex. Another mimetic by a release mechanism is carbachol, which promotes the presynaptic discharge of acetylcholine.

In these examples, there is a close structural similarity between the mimetic and the released mediator. In the case of many releasers of histamine (such as tubocurarine, polymyxin or morphine), no close chemical relationship exists between the releaser and the released. In such instances, release has been explained by activation of receptors on the mast-cell membrane which promote exocytosis of the histamine-containing granules, by an influx of calcium and activation of microtubules, all of which may be involved in moving the granules out of the mast cell.

Structural similarity also may aid mimicry by promoting chemical combination with an enzyme of destruction or some other means of disposition. For example, metaraminol, amphetamine, etc *inhibit membrane transport* into the neuron and, hence, inhibit the neuronal recapture of released norepinephrine. Consequently, the extraneuronal concentration of norepinephrine in the nearby region of the receptors does not drop as rapidly as in the absence of the mimetic, and the action of the mediator is sustained.

Some inhibitors of the enzymes of the destruction of mediators are structurally similar enough to the mediator to have some agonist action. This is true of neostigmine, which has a direct stimulant action on nicotinic receptors in addition to its anticholinesterase action. In contrast, the anticholinesterase, physostigmine, has some antagonist actions on cholinergic receptors and also an effect to interfere with acetylcholine synthesis.

The above multiple actions come about because all the structures that interact with a small molecule mediator (the receptor, synthesizing enzyme, destructive enzyme, storage molecule, membrane transport carrier) must have some common structural features and affinities. A drug that re-

acts with one of these molecules has a distinct probability of interacting with another.

The recognition of the critical role of *ions* in the function of membranes, the excitability of cells and the activity of many enzymes has generated a renewed interest in ions in the mechanism of action of certain drugs. The inorganic ions, some of which are used as drugs, lend themselves automatically to a discussion of ionic mechanisms. The repair of electrolyte deficiencies by replacement therapy warrants no further comment here. Some nonphysiological ions act as imperfect impersonators of physiological ions; lithium partly substitutes for sodium, bromide for chloride and thiocyanate for iodide, and each may owe its pharmacological action, in part, to a sluggish mobility through membrane channels, through which their sister ions normally pass readily when traffic is not impeded by "slowly moving vehicles." Iodide has an effect to increase the penetrance of drugs into caseous and necrotic areas, to aid in the resolution of gummatous lesions, to reduce the viscosity of mucous secretions and other odd effects; it is thought to do so by increasing the hydration of collagen and mucoproteins by a poorly understood mechanism. The transition elements and heavy metals have in common the ability to form complexes with a variety of physiologically active substances, particularly the active centers of many enzymes. *Chelation* and other types of *complexation* are the mechanisms of action of several drugs used to treat heavy-metal intoxication, diseases that involve abnormal body burdens or plasma levels of heavy metals and hypercalcemia. Chelates and chelation are discussed in more detail in Chapter 14.

There is much interest in the effects of drugs on ion movements. Cardiac glycosides are known to inhibit an ATPase involved in the membrane transport of sodium and several other substances, which indirectly causes an increase in intracellular calcium content. In part, the mechanisms of action of local anesthetics, quinidine and various other drugs also are speculated to involve calcium movements. In the past decade there has appeared a whole new class of drugs, the calcium channel blockers.

Concomitant with the development of molecular biology was the appreciation that drugs act through *nuclear* and *extranuclear genetic mechanisms*. Nitrogen mustards have long been known to interfere with the replication of DNA. Streptomycin, kanamycin, neomycin and gentamicin cause misreading by the ribosomes of the code incorporated into messenger RNA; tetracyclines, erythromycin and chloramphenicol inhibit the synthesis of protein at the ribosomes; and chloroquine, novobiocin and colchicine inhibit DNA polymerase. Other drugs induce the production of enzymes; aldosterone appears to act by inducing the synthesis of the enzyme, membrane ATPase, necessary to sodium transport. In general, steroid hormones combine with a cytosolic receptor, the complex of which is processed and translocated to the chromatin, where gene expression is altered. Many drugs induce one or more of the hepatic and extrahepatic cytochrome P-450 enzymes.

A number of drugs have simple mechanisms that do not involve an action at the cellular level. Examples are bulk and saline cathartics, osmotic diuretics and cholestyramine. Although such drugs usually do not generate much excitement among pharmacologists, they do serve as a reminder of the many avenues through which a mechanism of action may be expressed. Throughout the various chapters of Part 6, specific mechanisms of action may be mentioned.

Absorption, Distribution and Excretion

No matter by which route a drug is administered it must pass through several to many biological membranes during the processes of absorption, distribution, biotransformation and elimination. Since membranes are traversed in all of these events, the subject of this section will begin with a brief description of biological membranes and membrane processes and the relationship of the physiochemical properties of a drug molecule to penetrance and transport.

Structure and Properties of Membranes

The concept that a membrane surrounds each cell arose shortly after the cellular nature of tissue was discovered. The biological and physiochemical properties of cells seemed in accord with this view. In the past, from time to time, the actual existence of the membrane has been questioned by brilliant men, and ingenious explanations have been advanced to explain cellular integrity and the osmotic and electrophysiological properties of cells. Microchemical, x-ray diffraction, electron microscopic, nuclear magnetic resonance, electron spin resonance and other investigations have proved both the existence and nature of the plasma, mitochondrial, nuclear and other cell membranes. The description of the plasma membrane that follows is much oversimplified, but it will suffice to provide a background for an understanding of penetrance into and through membranes.

Structure and Composition—The cell membrane has been described as a "mayonnaise sandwich," in which a bimolecular layer of lipid material is entrained between two parallel monomolecular layers of protein. However, the protein does not make continuous layers, like the bread in a sandwich, but rather is sporadically scattered over the surfaces, like icebergs; ie, much of the protein is below the surface. In Fig 35-8 the lipid layers are represented as a somewhat orderly, closely packed lamellar array of phospholipid molecules associated tail-to-tail, each "tail" being an alkyl chain or steroid group and the "heads" being polar groups, including the glycerate moieties, with their polar ether and carbonyl oxygens and phosphate with attached polar groups. In reality, the lamellar portion is probably not

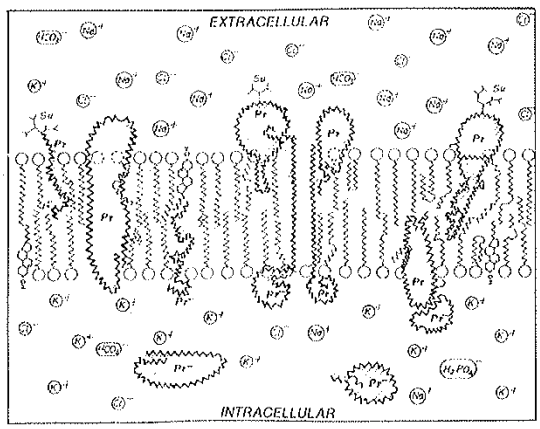

Fig 35-8. Simplified cross section of a cell membrane (components are not to scale). The lipid interior of the lamellar portion of the membrane consists of various phospholipids, fatty acids, cholesterol and other steroids. Ions are indicated in order to illustrate differences in size relative to the channel. *Pr:* protein; *Su:* sugar.

so orderly, since its composition is quite complex. Chains of fatty acids of different degrees of saturation and cholesterol cannot array themselves in simple parallel arrangements. Furthermore, the polar heads will assume a number of orientations depending upon the substances and groups involved. Moreover, the lamellar portion is penetrated by large globular proteins, the interior of which, like the lipid layers, has a high hydrophobicity, and some fibrous proteins.

The plasma membrane appears to be asymmetrical. The lipid composition varies from cell type to cell type and perhaps from site to site on the same membrane. There are, for example, differences between the membrane of the endoplasmic reticulum and the plasma membrane, even though the membranes are coextensive. Where membranes are double, the inner and outer layers may differ considerably; the inner and outer membranes of mitochondria have been shown to have strikingly different compositions and properties. Some authorities have expressed doubt as to the existence of the protein layers in biological membranes, although the evidence is preponderantly in favor of at least an outer glycoprotein coat. Sugar moieties also are attached to the outer proteins; these sugar moieties are important to cellular and immunological recognition and adhesion and have other functions as well.

The cell membrane appears to be perforated by water-filled pores of various sizes, varying from about 4 to 10 Å, the majority of which are about 7 Å. Probably all major ion channels are through the large globular proteins that traverse the membrane. Through these pores pass inorganic ions and small organic molecules. Since sodium ions are more hydrated than potassium and chloride ions, they are larger and do not pass as freely through the pores as potassium and chloride. The vascular endothelium appears to have pores at least as large as 40 Å, but these seem to be interstitial passages rather than transmembrane pores. Lipid molecules small enough to pass through the pores may do so, but they have a higher probability of entering into the lipid layer, from where they will equilibrate chemically with the interior of the cell. From work on monolayers, some researchers contend that it is not necessary to postulate pores to explain the permeability to water and small water-soluble molecules.

Stratum Corneum—Although the stratum corneum is not a membrane in the same sense as a cell membrane, it offers a barrier to diffusion, which is of significance in the topical application of drugs. The stratum corneum consists of several layers of dead keratinized cutaneous epithelial cells enmeshed in a matrix of keratin fibers and bound together with cementing desmosomes and penetrating tonofibrils of keratin. Varying amounts of lipids and fatty acids from dying cells, sebum and sweat are contained among the dead squamous cells. Immediately beneath the layer of dead cells and above the viable epidermal epithelial cells is a layer of keratohyaline granules and various water-soluble substances, such as alpha-amino acids, purines, monosaccharides and urea.

Both the upper and lower layers of the stratum corneum are involved in the cutaneous barrier to penetration. The barrier to penetration from the surface is in the upper layers for water-soluble substances and the lower layers for lipid-soluble substances, and the barrier to the outward movement of water is in the lowest layer.

Membrane Potentials—Across the cell membrane there exists an electrical potential, always negative on the inside and positive on the outside. If a cell did not have special-membrane electrolyte-transport processes, its membrane potential would be mainly the result of the Donnan equilibrium (see Chapter 14) consequent to the semipermeability of the membrane. Such potentials generally lie between 2 and 5 mv.

A cell with a membrane across which diffusible electrolyte distribution is purely passive would be expected to have a high internal concentration of sodium, such as is true for the erythrocytes of some species. However, the interior of most cells is high in potassium and low in sodium, as depicted in Fig 35-8. This unequal distribution of cations attests to special electrolyte-transport processes and to differential permeabilities of diffusible ions, so that the membrane potential is higher than that which would result from a purely passive Donnan distribution. In nerve tissue or skeletal and cardiac muscle, the membrane potential ranges upwards to about 90 mv. The electrical gradient is on the order of 50,000 v/cm, because of the extreme thinness of the membrane. Obviously, such an intense potential gradient will influence strongly the transmembrane passages of charged drug molecules.

Diffusion and Transport

Transport is the movement of a drug from one place to another within the body. The drug may diffuse freely in uncombined form with a kinetic energy appropriate to its thermal environment, or it may move in combination with extracellular or cellular constituents, sometimes in connection with energy-yielding processes that allow the molecule or complex to overcome barriers to simple diffusion.

Simple Nonionic Diffusion and Passive Transport—Molecules in solution move in a purely random fashion, provided they are not charged and moving in an electrical gradient. Such random movement is called *diffusion;* if the molecule is uncharged, it is called *nonionic diffusion.*

In a population of drug molecules, the probability that during unit time any drug molecule will move across a boundary is directly proportional to the number of molecules adjoining that boundary and, therefore, to the drug concentration. Except at dilutions so extreme that only a few molecules are present, the actual rate of movement (molecules/unit time) is directly proportional to the probability and, therefore, to the concentration. Once molecules have passed through the boundary to the opposite side, their random motion may cause some to return and others to continue to move further away from the boundary. The rate of return is likewise proportional to the concentration on the opposite side of the boundary. It follows that, although molecules are moving in both directions, there will he a net movement from the region of higher to that of lower concentration, and the net transfer will be proportional to the concentration differential. If the boundary is a membrane, which has both substance and dimension, the rate of movement is also directly proportional to the permeability and inversely proportional to the thickness. These factors combine into Fick's Law of Diffusion,

$$\frac{dQ}{dt} = \frac{\overline{D}A(C_1 - C_2)}{x} \qquad (5)$$

where Q is the net quantity of drug transferred across the membrane, t is time, C_1 is the concentration on one side and C_2 on the other, x is the thickness of the membrane, A is the area and $\overline{D}$ is the diffusion coefficient, related to permeability. The equation is more nearly correct if chemical activities are used instead of concentrations. Since a biological membrane is patchy, with pores of different sizes and probably with varying thickness and composition, both $\overline{D}$ and x probably vary from spot to spot. Nevertheless, some mean values can be assumed.

It is customary to combine the membrane factors into a single constant, called a permeability constant or coefficient, P, so that $P = \overline{D}/x$, A in Eq 5 having unit value. The rate of net transport (diffusion) across the membrane then becomes

$$\frac{dQ}{dt} = P(C_1 - C_2) \quad (6)$$

As diffusion continues, C_1 approaches C_2, and the net rate, dQ/dt, approaches zero in exponential fashion characteristic of a first-order process. Equilibrium is defined as that state in which $C_1 = C_2$. The equilibrium is, of course, dynamic, with equal numbers of molecules being transported in each direction during unit time. If water is also moving through the membrane, it may either facilitate the movement of drug or impede it, according to the relative directions of movement of water and drug; this effect of water movement is called *solvent drag*.

Ionic or Electrochemical Diffusion—If a drug is ionized, the transport properties are modified. The probability of penetrating the membrane is still a function of concentration, but it is also a function of the potential difference or electrical gradient across the membrane. A cationic drug molecule will be repelled from the positive charge on the outside of the membrane, and only those molecules with a high kinetic energy will pass through the ion barrier. If the cation is polyvalent, it may not penetrate at all.

Once inside the membrane, a cation simultaneously will be attracted to the negative charge on the intracellular surface of the membrane and repelled by the outer surface; it is said to be moving along the *electrical gradient*. If it also is moving from a higher towards a lower concentration, it is said to be moving along its *electrochemical gradient*, which is the sum of the influences of the electrical field and the concentration differential across the membrane.

Once inside the cell, cations will tend to be kept inside by the attractive negative charge on the interior of the cell, and the intracellular concentration of drug will increase until, by sheer numbers of accumulated drug particles, the outward diffusion or mass escape rate equals the inward transport rate, and electrochemical equilibrium is said to have occurred. At electrochemical equilibrium at body temperature (37°C), ionized drug molecules will be distributed according to the Nernst equation,

$$\pm\log\frac{C_o}{C_i} = \frac{ZE}{61} \quad (7)$$

where C_o is the molar extracellular and C_i the intracellular concentration, Z is the number of charges per molecule and E is the membrane potential in millivolts. Log C_o/C_i is positive when the molecule is negatively charged and negative when the molecule is positively charged.

Facilitated Diffusion—Sometimes a substance moves more rapidly through a biological membrane than can be accounted for by the process of simple diffusion. This accelerated movement is termed *facilitated diffusion*. It is thought to be due to the presence of a special molecule within the membrane, called a *carrier*, with which the transported substance combines. There is considered to be a greater permeability to the carrier–drug complex than to the drug alone, so that the transport rate is enhanced. After the complex traverses the membrane, it dissociates. The carrier must either return to the original side of the membrane to be reused or constantly be produced on one side and eliminated on the other in order for the carrier process to be continuous. Many characteristics of facilitated diffusion, formerly attributed to ion carriers, can be explained by ion exchange. Although facilitated diffusion resembles active transport, below, in its dependence upon a continuous source of energy, it differs in that facilitated diffusion will only transport a molecule along its electrochemical gradient.

Active Transport—Active transport may be defined as energy-dependent movement of a substance through a biological membrane against an electrochemical gradient. It is characterized by the following:

1. The substance is transported from a region of lower to one of higher electrochemical activity.
2. Metabolic poisons interfere with transport.
3. The transport rate approaches an asymptote (ie, saturates) as concentration increases.
4. The transport system usually shows a requirement for specific chemical structures.
5. Closely related chemicals are competitive for the transport system.

Many drugs are secreted from the renal tubules into urine, from liver cells into bile or from the cerebrospinal fluid into blood by active transport, but the role of active transport of drugs in the distribution into most body compartments and tissues is less well known. Active transport is required for the penetrance of a number of sympathomimetics into neural tissue and for the movement of several anticancer drugs across cell membranes.

Pinocytosis and Exocytosis—Many, perhaps all, cells are capable of a type of phagocytosis called *pinocytosis*. The cell membrane has been observed to invaginate into a saccular structure containing extracellular materials and then pinch off the saccule at the membrane, so that the saccule remains as a vesicle or vacuole within the interior of the cell. Since metabolic activity is required and since an extracellular substance may be transported against an electrochemical gradient, pinocytosis shows some of the same characteristics as active transport. However, pinocytosis is relatively slow and inefficient compared to most active transport, except in gastrointestinal absorption, in which pinocytosis is of considerable importance.

It is not known to what extent pinocytosis contributes to the transport of most drugs, but many macromolecules and even larger particles can be absorbed by the gut. Pinocytosis probably explains the oral efficacy of the Sabin polio vaccine. Some drugs themselves affect pinocytosis; eg, adrenal glucocorticoids markedly inhibit the process in macrophages and other cells involved in inflammation.

Exocytosis is more or less the reverse of pinocytosis. Granules, vacuoles or other organelles within the cell move to the cell membrane, fuse with it and extrude their contents into the interstitial space.

Physicochemical Factors in Penetrance

Drugs and other substances may traverse the membrane primarily either through the pores or by dissociation into the membrane lipids and subsequent diffusion from the membrane into the cytosol or other fluid on the far side of the membrane. The physicochemical prerequisites are different according to which route is taken. To pass through the pores, the "diameter" of the molecule must be smaller than the pore, but the molecule can be longer than the pore diameter. The probability that a long, thin molecule will be oriented properly is low, unless there is also bulk flow and the transmembrane passage of large molecules is slow.

Water-soluble molecules with low lipid solubility usually are thought to pass through the membrane mainly via the pores and, to a small extent, by pinocytosis, but recent work with lipid monolayers suggests that small water-soluble molecules also may be able to pass readily through the lipid, and the necessity of postulating the existence of pores has been questioned. Nevertheless, experimental data on penetrance overwhelmingly favor the concept of passage of water-soluble lipid-insoluble substances through pores. If there is a membrane carrier or active transport system, a low solubility of the drug in membrane lipids is no impediment to penetration, since the drug-carrier complex is assumed to have an appropriate solubility and energy from an active transport system enables the drug to penetrate the energy barrier "imposed by the lipids." Actually, the lipids are not an important energy barrier; rather, the barrier is the force

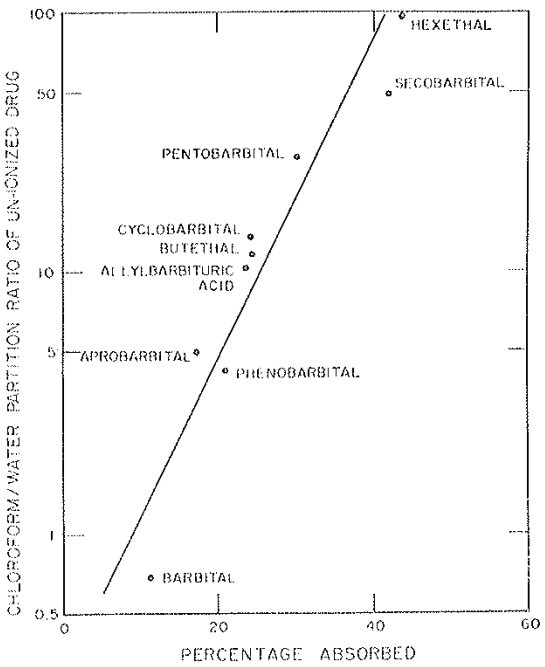

Fig 35-9. The relationship of absorption of the un-ionized forms of drugs from the colon of the rat to the chloroform:water partition coefficient (courtesy, Schanker[6]).

of attraction of the solvent water for its dipolar to polar solute, so that it is difficult for the solute to leave the water and enter the lipid.

Drugs with a high solubility in the membrane lipids, of course, pass easily through the membrane. Even when their dimensions are small enough to permit passage through pores, lipid-soluble drugs primarily pass through the membrane lipids, not only because chemical partition favors the lipid phase but also because the surface area occupied by pores is only a small fraction of the total membrane area.

Lipid Solubility and Partition Coefficients—As early as 1902, Overton investigated the importance of lipid solubility to the penetrance and absorption of drugs. Eventually, it was recognized that more important than lipid solubility was the lipid–water distribution coefficient; ie, a high lipid solubility does not favor penetrance unless the water solubility is low enough so that the drug is not entrained in the aqueous phase.

In Fig 35-9 is illustrated the relationship between the chloroform–water partition coefficient and the colonic absorption of barbiturates. Chloroform probably is not the optimal lipid solvent for such a study, and natural lipids from nerve or other tissues have been shown to be superior in the few instances in which they have been employed. Nevertheless, the correlation shown in the figure is a convincing one.

When the water solubility of a substance is so low that a significant concentration in water or extracellular fluid cannot be achieved, absorption may be negligible in spite of a favorable partition coefficient. Hence, mineral oil, petrolatum, etc are virtually unabsorbed. The optimal partition coefficient for permeation of the skin appears to be lower than that for the permeation of the cell membrane, perhaps being as low as one.

Dipolarity, Polarity and Nonionic Diffusion—The partition coefficient of a drug depends upon the polarity and the size of the molecule. Drugs with a high dipole moment, even though un-ionized, have a low lipid solubility and, hence, poor penetrance. An example of a highly dipolar substance with a low partition coefficient, which does not penetrate into cells, is sulfisoxazole. Sulfadiazine is somewhat less dipolar, has a chloroform–water partition coefficient ten times that of sulfisoxazole and readily penetrates cells. Ionization not only diminishes lipid solubility greatly but also may impede passage through charged membranes (see *Ionic Diffusion*, page 709).

It is often stated that ionized molecules do not penetrate membranes, except for ions of small diameter. This is not necessarily true, because of the presence of membrane carriers for some ions, which effectively may shield or neutralize the charge (ion-pair formation). The renal tubular transport systems, which transport such obligate ions as tetraethylammonium, probably form ion-pairs. Furthermore, if an ionized molecule has a large nonpolar moiety such that an appreciable lipid solubility is imparted to the molecule in spite of the charge, the drug may penetrate, although usually at a slow rate. For example, various morphinan derivatives are absorbed passively from the stomach even though they

Table I—Rates of Entry of Drugs in CSF and the Degrees of Ionization of Drugs at pH 7.4[7]

Drug	% binding to plasma protein	pK_a[a]	% un-ionized at pH 7.4	Permeability constant (P min^{-1}) ± S.E.
		Drugs mainly ionized at pH 7.4		
5-Sulfosalicylic acid	22	(strong)	0	<0.0001
N-Methylnicotinamide	<10	(strong)	0	0.0005 ± 0.00006
5-Nitrosalicylic acid	42	2.3	0.001	0.001 ± 0.0001
Salicylic acid	40	3.0	0.004	0.006 ± 0.0004
Mecamylamine	20	11.2	0.016	0.021 ± 0.0016
Quinine	76	8.4	9.09	0.078 ± 0.0061
		Drugs mainly un-ionized at pH 7.4		
Barbital	<2	7.5	55.7	0.026 ± 0.0022
Thiopental	75	7.6	61.3	0.50 ± 0.051
Pentobarbital	40	8.1	83.4	0.17 ± 0.014
Aminopyrine	20	5.0	99.6	0.25 ± 0.020
Aniline	15	4.6	99.8	0.40 ± 0.042
Sulfaguanidine	6	>10.0[b]	>99.8	0.003 ± 0.0002
Antipyrine	8	1.4	>99.9	0.12 ± 0.013
N-Acetyl-4-aminoantipyrine	<3	0.5	>99.9	0.012 ± 0.0010

[a] The dissociation constant of both acids and bases is expressed as a pK_a—a negative logarithm of the acidic dissociation constant.

[b] Sulfaguanidine has a very weakly acidic group (pK_a > 10) and two very weakly basic groups (pK_a 2.75 and 0.5). Consequently, the compound is almost completely undissociated at pH 7.4.

are ionized completely at the pH of gastric fluid. Nevertheless, when a drug is a weak acid or base, the un-ionized form, with a favorable partition coefficient, passes through a biological membrane so much more readily than the ionized form that, for all practical purposes, only the un-ionized form is said to pass through the membrane. This has become known as the *principle of nonionic diffusion.*

This principle is the reason that only the concentrations of the un-ionized form of the barbiturates are plotted in Fig 35-9.

For the purpose of further illustrating the principle, Table I is provided. In the table, the permeability constants for penetrance into the cerebral spinal fluid of rats are higher for un-ionized drugs than for ionized ones. The apparent exceptions—barbital, sulfaguanidine and acetylaminoantipyrine—may be explained by the dipolarity of the un-ionized molecules. With barbital, the two lipophilic ethyl groups are too small to compensate for the considerable dipolarity of the un-ionized barbituric acid ring; also it may be seen that barbital is appreciably ionized, which contributes to the relatively small permeability constant. Sulfaguanidine and acetylaminoantipyrine are both very polar molecules. Mecamylamine also might be considered an exception, since it shows a modest permeability even though strongly ionized; there is no dipolarity in mecamylamine except in the amino group.

Absorption of Drugs

Absorption is the process of movement of a drug from the site of application into the extracellular compartment of the body. Inasmuch as there is a great similarity among the various membranes that a drug may pass through in order to gain access to the extracellular fluid, it might be expected that the particular site of application (or *route*) would make little difference to the successful absorption of the drug. In actual fact, it makes a great deal of difference; many factors, other than the structure and composition of the membrane, determine the ease with which a drug is absorbed. These factors are discussed in the following sections, along with an account of the ways that drug formulations may be manipulated to alter the ability of a drug to be absorbed readily.

Routes of Administration

Drugs may be administered by many different routes. The various routes include oral, rectal, sublingual or buccal, parenteral, inhalation and topical. The choice of a route depends upon both convenience and necessity.

Oral Route—This is obviously the most convenient route for access to the systemic circulation, providing that various factors do not militate against this route. Oral administration does not always give rise to sufficiently high plasma concentrations to be effective; some drugs are absorbed unpredictably or erratically; patients occasionally have an absorption malfunction. Drugs may not be given by mouth to patients with gastrointestinal intolerance, or who are in preparation for anesthesia or who have had gastrointestinal surgery. Oral administration also is precluded in coma.

Rectal Route—Drugs that ordinarily are administered by the oral route usually can be administered by injection or by the alternative *lower enteral* route, through the anal portal into the rectum or lower intestine. With regard to the latter, *rectal suppositories* or *retention enemas* formerly were used quite frequently, but their popularity has abated somewhat, owing to improvements in parenteral preparations. Nevertheless, they continue to be valid and, sometimes, very important ways of administering a drug, especially in pediatrics and geriatrics. In Fig 35-10 the availability of a drug by retention enema may be compared with that by the intravenous and oral route and rectal suppository administration. It is apparent that the retention enema may be a very satisfactory means of administration but that rectal suppositories may be inadequate where rapid absorption and high plasma levels are required. The illustration is not intended to lead the reader to the conclusion that a retention enema always will give more prompt and higher blood levels than the oral route, for converse findings for the same drug have been reported,[21] but, rather, to show that the retention enema may offer a useful substitute for the oral route.

Sublingual or Buccal Route—Even though an adequate plasma concentration eventually may be achievable by the oral route, it may rise much too slowly for use in some situations where a rapid response is desired. In such situations parenteral therapy usually is indicated. However, the patients with angina pectoris may get quite prompt relief from an acute attack by the *sublingual* or *buccal* administration of nitroglycerin, so that parenteral administration may be avoided. When only small amounts of drugs are required to gain access to the blood, the buccal route may be very satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route.

Parenteral Routes—These routes, by definition, include any route other than the oral-gastrointestinal (enteral) tract, but in common medical usage the term excludes topical administration and includes only various hypodermic routes. Parenteral administration includes the intravenous, intramuscular and subcutaneous routes. Parenteral routes may be employed whenever enteral routes are contraindicated (see above) or inadequate.

The *intravenous* route may be preferred on occasion, even when a drug may be well-absorbed by the oral route. There is no delay imposed by absorption before the administered drug reaches the circulation, and blood levels rise virtually

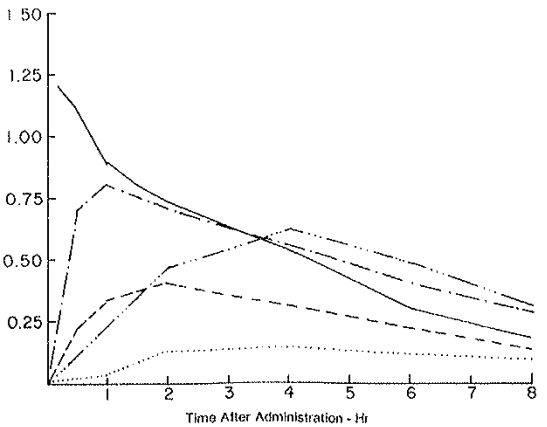

Fig 35-10. Blood concentration in mg/100 mL of theophylline (ordinates) following administration to humans of aminophylline in the amounts and by the routes indicated. Doses: per 70 kg. Theophylline-ethylenediamine by various routes: —— *intravenous, 0.5 g;* – • – • – *retention enema, 0.5 g;* — ··· — ··· — *oral tablets-Pl., 0.5 g;* - - - *oral tablets-Pl., 0.3 g;* ···· *rectal suppository, 0.5 g* (courtesy, Truitt, *et al*,[20] adapted).

as rapidly as the time necessary to empty the syringe or infusion bottle. Consequently, the intravenous route is the preferred route when an emergency calls for an immediate response.

In addition to the rapid rise in plasma concentration of drug, another advantage of intravenous administration is the greater predictability of the peak plasma concentration, which, with some drugs, can be calculated with a fair degree of precision. Smaller doses generally are required by the intravenous than by other routes, but this usually affords no advantage, inasmuch as the sterile injectable dosage form costs more than enteric preparations and the requirements for medical or paramedical supervision of administration also may add to the cost and inconvenience.

Because of the rapidity with which drug enters the circulation, dangerous side effects to the drug may occur which are often not extant by other routes. The principal untoward effect is a depression of cardiovascular function, which is often called *drug shock*. Consequently, some drugs must be given quite slowly to avoid vasculotoxic concentrations of drug in the plasma. Acute, serious, allergic responses also are more likely to occur by the intravenous route than by other routes.

Many drugs are too irritant to be given by the oral, intramuscular or subcutaneous route and must, of necessity, be given intravenously. However, such drugs also may cause damage to the veins (phlebitis) or, if extravasated, cause necrosis (slough) around the injection site. Consequently, such irritant drugs may be diluted in isotonic solutions of saline, dextrose or other media and given by slow infusion, providing that the slower rate of delivery does not negate the purpose of the administration in emergency situations.

Absorption by the *intramuscular* route is relatively fast and this parenteral route may be used where an immediate effect is not required but a prompt effect is desirable. Intramuscular deposition also may be made of certain repository preparations, rapid absorption not being desired. Absorption from an intramuscular depot is more predictable and uniform than from a subcutaneous site.

Irritation around the injection site is a frequent accompaniment of intramuscular injection, depending upon the drug and other ingredients. Because of the dangers of accidental intravenous injection, medical supervision generally is required. Sterilization is necessary.

In *subcutaneous* administration the drug is injected into the alveolar connective tissue just below the skin. Absorption is slower than by the intramuscular route but, nevertheless, may be prompt with many drugs. Often, however, absorption by this route may be no faster than by the oral route. Therefore, when a fairly prompt response is desired with some drugs, the subcutaneous route may not offer much advantage over the oral route, unless for some reason the drug cannot be given orally.

The slower rate of absorption by the subcutaneous route is usually the reason why the route is chosen, and the drugs given by this route are usually those in which it is desired to spread the action out over a number of hours, in order to avoid either too intense a response, too short a response or frequent injections. Examples of drugs given by this route are insulin and sodium heparin, neither of which is absorbed orally and both of which should be absorbed slowly over many hours. In the treatment of asthma, epinephrine usually is given subcutaneously to avoid the dangers of rapid absorption and consequent dangerous cardiovascular effects. Many repository preparations, including tablets or pellets, are given subcutaneously. As with other parenteral routes, irritation may occur. Sterile preparations also are required. However, medical supervision is not required always and self-administration by this route is customary with certain drugs, such as insulin.

Intradermal injection, in which the drug is injected into, rather than below the dermis, is rarely employed, except in certain diagnostic and test procedures, such as screening for allergic or local irritant responses.

Occasionally, even by the intravenous route, it is not possible, practical or safe to achieve plasma concentrations high enough so that an adequate amount of drug penetrates into special compartments, such as the cerebrospinal fluid, or various cavities, such as the pleural cavity. The brain is especially difficult to penetrate with water-soluble drugs. The name *blood-brain barrier* is applied to the impediment to penetration. When drugs do penetrate, the choroid plexus often secretes them back into the blood very rapidly, so that adequate levels of drugs in the cerebrospinal fluid may be difficult to achieve. Consequently, *intrathecal** or *intraventricular* administration may be indicated.

Body cavities such as the pleural cavity normally are wetted by a small amount of effusate which is in diffusion equilibrium with the blood and, hence, is accessible to drugs. However, infections and inflammations may cause the cavity to fill with serofibrinous exudate which is too large to be in rapid diffusion equilibrium with the blood. *Intracavitary* administration, thus, may be required. It is extremely important that sterile and nonirritating preparations be used for intrathecal or intracavitary administration.

Inhalation Route—Inhalation may be employed for delivering gaseous or volatile substances into the systemic circulation, as with most general anesthetics. Absorption is virtually as rapid as the drug can be delivered into the alveoli of the lungs, since the alveolar and vascular epithelial membranes are quite permeable, blood flow is abundant and there is a very large surface for absorption.

Aerosols of nonvolatile substances also may be administered by inhalation, but the route is used infrequently for delivery into the systemic circulation because of various factors which contribute to erratic or difficult-to-achieve blood levels. Whether or not an aerosol reaches and is retained in pulmonary alveoli depends critically upon particle size. Particles greater than 1 μm in diameter tend to settle in the bronchioles and bronchi, whereas particles less than 0.5 μm fail to settle and mainly are exhaled. Aerosols are employed mostly when the purpose of administration is an action of the drug upon the respiratory tract itself. An example of a drug commonly given as an aerosol is isoproterenol, which is employed to relax the bronchioles during an asthma attack.

Topical Route—Topical administration is employed to deliver a drug at, or immediately beneath, the point of application. Although occasionally enough drug is absorbed into the systemic circulation to cause systemic effects, absorption is too erratic for the topical route to be used routinely for systemic therapy. However, various transdermal preparations of nitroglycerin and clonidine are employed quite successfully for systemic use. Some work with aprotic solvent vehicles such as dimethyl sulfoxide (DMSO) also has generated interest in topical administration for systemic effects. A large number of topical medicaments are applied to the skin, although topical drugs are also applied to the eye, nose and throat, ear, vagina, etc.

In man, percutaneous absorption probably occurs mainly from the surface. Absorption through the hair follicles occurs, but the follicles in man occupy too small a portion of the total integument to be of primary importance. Absorption through sweat and sebaceous glands generally appears to be minor. When the medicament is rubbed on vigorously,

* Intrathecal administration denotes administration into the cerebrospinal fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles, which is the most common mode of intrathecal administration.

the amount of the preparation that is forced into the hair follicles and glands is increased. Rubbing also forces some material through the stratum corneum without molecular dispersion and diffusion through the barrier. Rather large particles of substances such as sulfur have been demonstrated to pass intact through the stratum corneum. When the skin is diseased or abraded, the cutaneous barrier may be disrupted or defective, so that percutaneous absorption may be increased. Since much of a drug that is absorbed through the epidermis diffuses into the circulation without reaching a high concentration in some portions of the dermis, systemic administration may be preferred in lieu of, or in addition to, topical administration.

Factors That Affect Absorption

In addition to the physicochemical properties of drug molecules and biological membranes, various factors affect the rate of absorption and determine, in part, the choice of route of administration.

Concentration—It is self-evident that the concentration, or, more exactly, the thermodynamic activity, of a drug in a drug preparation will have an important bearing upon the rate of absorption, since the rate of diffusion of a drug away from the site of administration is directly proportional to the concentration. Thus, a 2% solution of lidocaine will induce local anesthesia more rapidly than a 0.2% solution. However, drugs administered in solid form are not absorbed necessarily at the maximal rate (see *Physical State of Formulation and Dissolution Rate*, below).

After oral administration the concentration of drugs in the gut is a function of the dose, but the relationship is not necessarily linear. Drugs with a low aqueous solubility (eg, digitoxin) quickly saturate the gastrointestinal fluids, so that the rate of absorption tends to reach a limit as the dose is increased. The peptizing and solubilizing effects of bile and other constituents of the gastrointestinal contents assist in increasing the rate of absorption but are in themselves somewhat erratic. Furthermore, many drugs affect the rates of gastric, biliary and small intestinal secretion, which causes further deviations from a linear relationship between concentration and dose.

Drugs that are administered subcutaneously or intramuscularly also may not show always a direct linear relationship between the rate of absorption and the concentration of drug in the applied solution, because osmotic effects may cause dilution or concentration of the drug, if the movement of water or electrolytes is different from that of the drug. Whenever possible, drugs for hypodermic injection are prepared as isotonic solutions. Some drugs affect the local blood flow and capillary permeability, so that at the site of injection there may be a complex relationship of concentration achieved to the concentration administered.

Physical State of Formulation and Dissolution Rate—The rate of absorption of a drug may be affected greatly by the rate at which the drug is made available to the biological fluid at the site of administration. The intrinsic physicochemical properties, such as solubility and the thermodynamics of dissolution, are only some of the factors which affect the rate of dissolution of a drug from a solid form. Other factors include not only the unavoidable interactions among the various ingredients in a given formulation but also deliberate interventions to facilitate dispersion (eg, comminution, Chapter 75 and dissolution, Chapter 31) or retard it (eg, coatings, Chapter 90 and slow-release formulations, Chapter 91). There are also factors that affect the rate of delivery from liquid forms. For example, a drug in a highly viscous vehicle is absorbed more slowly from the vehicle than a drug in a vehicle of low viscosity; in oil-in-water emulsions, the rate depends upon the partition coefficient. These manipulations are the subject of biopharmaceutics (see Chapter 91).

Area of Absorbing Surface—The area of absorbing surface is an important determinant of the rate of absorption. To the extent that the therapist must work with the absorbing surfaces available in the body, the absorbing surface is not subject to manipulation. However, the extent to which the existing surfaces may be used is subject to variation. In those rare instances in which percutaneous absorption is intended for systemic administration, the entire skin surface is available.

Subsequent to subcutaneous or intramuscular injections, the site of application may be massaged in order to spread the injected fluid from a compact mass to a well-dispersed deposit. Alternatively, the dose may be divided into multiple small injections, although this recourse is generally undesirable.

The different areas for absorption afforded by the various routes account, in part, for differences in the rates of absorption by those routes. The large alveolar surface of the lungs allows for extremely rapid absorption of gases, vapors and properly aerosolized solutions; with some drugs the rate of absorption may be nearly as fast as intravenous injection. In the gut the small intestine is the site of the fastest, and hence most, absorption because of the small lumen and highly developed villi and microvilli; the stomach has a relatively small surface area, so that even most weak acids are absorbed predominately in the small intestine despite a pH partition factor that should favor absorption from the stomach (see *The pH Partition Principle*, page 716).

Vascularity and Blood Flow—Although the thermal velocity of a freely diffusible average drug molecule is on the order of meters per second, in solution the rate at which it will diffuse away from a reference point will be much slower. Collisions with water and/or other molecules, which cause a random motion, and the forces of attraction between the drug and water or other molecules slow the net mean velocity.

The time taken to traverse a given distance is a function of the square of the distance; on the average it would take about 0.01 sec for a net outward movement of 1 μm, 1 sec for 10 μm, 100 sec for 100 μm, etc. In a highly vascular tissue, such as skeletal muscle, in which there may be more than 1000 capillaries/sq mm of cross section, a drug molecule would not have to travel more than a few microns, hence, less than a second on the average, to reach a capillary from a point of extravascular injection.

Once the drug reaches the blood, diffusion is not important to transport and the rate of blood flow determines the movement. The velocity of blood flow in a capillary is about 1 mm/sec, which is 100 times faster than the mean net velocity of drug molecules 1 mm away from their injection site. The velocity of blood flow is even faster in the larger vessels. Less than a minute is required to distribute drug molecules from the capillaries at the injection site to the rest of the body.

From the above discussion it follows that absorption is most rapid in the vascular tissues. Drugs are absorbed more rapidly from intramuscular sites than from less vascular subcutaneous sites, etc. Despite the small absorbing surface for buccal or sublingual absorption, the high vascularity of the buccal, gingival and sublingual surfaces favors an unexpectedly high rate of absorption. Because of hyperemia, absorption will be faster from inflamed than from normal areas, unless the presence of edema lengthens the mean distance between capillaries and, thus, negates the effects of hypermia on absorption.

Vasoconstriction may have a profound effect upon the rate of absorption. When a local effect of a drug is desired,

as in local anesthesia, absorption away from the infiltered site may be impeded greatly by vasoconstrictors included in the preparation. Unwanted vasoconstriction sometimes may cause serious problems. For example, in World War II many wounded soldiers were given subcutaneous morphine without evident effect. As a result, injections were sometimes repeated more than once. When the patient was removed to the field hospital, toxic effects would occur suddenly. The explanation is that cold-induced vasoconstriction occurred in the field; when the patient was warmed in the hospital, vasodilation would result and the victim would be flooded with drug. Shock also contributes to the effect, since during shock the blood flow is diminished and there also may be a superimposed vasoconstriction; repair of the shock condition then facilitates absorption.

Extravascularly injected molecules too large to pass through the capillary endothelium will, of necessity, enter the systemic circulation through the lymph. Thus, the lymph flow may be important to the absorption of a few drugs.

Movement—A number of factors combine so that movement at the site of injection increases the rate of absorption. In the intestine, segmental movements and peristalsis aid in dividing and dispersing the drug mass. The continual mixing of the chyme helps keep the concentration maximal at the mucosal surface. The pressures developed during segmentation and peristalsis also may favor a small amount of filtration. Movement at the site of hypodermic injection also favors absorption, since it tends to force the injected material through the tissue, increasing the surface area of drug mass and decreasing the mean distance to the capillaries. Movement also increases the flow of blood and lymph. The selection of a site for intramuscular injection may be determined by the amount of expected movement, according to whether the preparation is intended as a fast-acting or a repository preparation.

Gastric Motility and Emptying—The motility of the stomach is more important to the rate at which an orally administered drug is passed on to the small intestine than it is to the rate of absorption from the stomach itself, since for various reasons noted above, absorption from the stomach is usually of minor importance.

The average emptying time of the unloaded stomach is about 40 min and the half-time is around 10 min, though it varies according to its contents, reflex and psychological factors, as well as the action of certain autonomic drugs or disease. The effect of food to delay absorption is due, in part, to its action to prolong emptying time. The emptying time causes a delay in the absorption of drug, which may be unfavorable or favorable according to what is desired. In the case of therapy with antacids, gastric emptying is a nuisance, since it removes the antacid from the stomach where it is needed.

Solubility and Binding—The dissolution of drugs of low solubility is generally a slow process. Indeed, low solubility is the result of a low rate of departure of drug molecules from the undispersed phase. Furthermore, since the concentration around the drug mass is low, the concentration gradient from the site of deposition to the plasma is small and the rate of diffusion is low, accordingly.

When it is desired that a drug have a prolonged action but not a high plasma concentration, a derivative of low solubility is often sought. The "insoluble" estolates and other esters of several steroids have durations of action of weeks because of the slow rates of absorption from the sites of injection. Insoluble salts or complexes of acidic or basic drugs also are employed as repository preparations; for example, the procaine salt of penicillin G has a low solubility and is used in a slow release form of the antibiotic.

The solubility of certain macromolecules is dependent critically on the ionization of substituent groups. When they are amphiprotic, they are least soluble at their isoelectric pH. Insulin is normally soluble at the pH of the extracellular fluid, but by combining insulin with the right proportion of a basic protein, such as protamine, the isoelectric pH can be made to be approximately 7.4 and the complex can be used as a low-solubility prolonged-action drug. For more details, see Chapter 91.

Some drugs may bind with natural substances at or near the site of application. The strongly ionized mucopolysaccharides in connective tissue, ground substance and mucous secretions of the gut are retardants to the absorption of a number of drugs, especially large cationic or polycationic molecules. In the gut, the binding is the least at low pH, which should favor absorption of large cations from the stomach; however, absorption from the stomach is slow (see above), so that the absorption of large cations occurs mainly in the upper duodenum where the pH is still relatively low. Pharmacologically inactive quaternary ammonium compounds sometimes are included in an oral preparation of a quaternary ammonium drug for the purpose of saturating the binding sites of mucin and other mucopolysaccharides and, thereby, enhancing the absorption of drug.

In addition to mucopolysaccharides in mucous secretions, food in the gastrointestinal track binds many drugs and slows absorption. Antacids, especially aluminum hydroxide plus other basic aluminum compounds and magnesium trisilicate, bind amine and ammonium drugs and interfere with absorption.

Donnan Effect—The presence of a charged macromolecule on one side of a semipermeable membrane (impermeable to the macromolecule) will alter the concentration of permeant ionized particles according to the Donnan equilibrium (page 716). Accordingly, drug molecules of the same charge as the macromolecule will be constrained to the opposite side of the membrane. The presence of appropriately charged macromolecules not only will influence the distribution of drug ions in accordance with the Donnan equation but also increase the rate of transfer of the drug across the membrane, because of mutual ionic repulsion. This effect is sometimes used to facilitate the absorption of ionizable drugs from the gastrointestinal tract. The Donnan effect also operates to retard the absorption of drug ions of opposite charge; however, the mutual electrostatic attraction of a macromolecule and drug ion generally results in actual binding, which is more important than the Donnan effect.

Vehicles and Absorption Adjuvants—Drugs that are to be applied topically to the skin and mucous membranes often are dissolved in vehicles that are thought to enhance penetrance. For a long time it was thought that oleaginous vehicles promoted the absorption of lipid-soluble drugs. However, the role and effect of the vehicle has proven to be quite complex. In the skin at least five factors are involved:

1. The effect of the vehicle to alter the hydration of the keratin in the barrier layer.
2. The effect of the vehicle to promote or prevent the collection of sweat at the surface of the skin.
3. The partition coefficient of the drug in a vehicle-water system.
4. The permeability of the skin to the undissolved drug.
5. The permeability of the skin to the vehicle.

The effect of the vehicle to aid in the access of the drug to the hair follicles and sebaceous glands also may be involved, although in man the follicles and glands are probably ordinarily of minor importance to absorption.

A layer of oleaginous material over the skin prevents the evaporation of water, so that the stratum corneum may become macerated and more permeable to drugs. In dermatology it is sometimes the practice to wrap the site of application with plastic wrap or some other waterproof material for the purpose of increasing the maceration of the stratum

corneum. However, the layer of perspiration that forms under an occlusive vehicle may become a barrier to the movement of lipid-soluble drugs from the vehicle to the skin, but it may facilitate the movement of water-soluble drugs. Conversely, polyethylene glycol vehicles remove the perspiration and dehydrate the barrier, which decreases the permeability to drugs; such vehicles remove the aqueous medium through which water-soluble drugs may pass down into the stratum corneum but at the same time facilitate the transfer of lipid-soluble drugs from the vehicle to the skin.

Even in the absence of a vehicle, it is not clear what physicochemical properties of a drug favor cutaneous penetration, high lipid-solubility being a prerequisite, according to some authorities, and an ether–water partition coefficient of approximately one, according to others. Yet, the penetration of ethanol and dibromomethane are nearly equal, and other such enigmas exist. It is not surprising, then, that the effects of vehicles are not altogether predictable.

A general statement might be made that if a drug is quite soluble in a poorly absorbed vehicle, the vehicle will retard the movement of the drug into the skin. For example, salicylic acid is 100 times as permeant when absorbed from water than from polyethylene glycol and pentanol is 5 times as permeant from water as from olive oil. Yet, ethanol penetrates 5 times faster from olive oil than from either water or ethanol, all of which denies the trustworthiness of generalizations about vehicles.

Since the 1960s, there has been much interest in certain highly dielectric aprotic solvents, especially dimethyl sulfoxide (DMSO). Such substances generally prove to be excellent solvents for both water- and lipid-soluble compounds and for some compounds not soluble in either water or lipid solvents. The extraordinary solvent properties probably are due to a high polarizability and van der Waals bonding capacity, a high degree of polarization (dipole moment) and a lack of association through hydrogen bonding. As a vehicle, DMSO greatly facilitates the permeation of the skin and other biological membranes by numerous drugs, including such large molecules as insulin. The mechanism is understood poorly. Such vehicles have a potential for many important uses, but they are at present only experimental, pending further investigations on toxicity.

From time to time, a claim is made that a new ingredient of a tablet or elixir enhances the absorption of a drug, and a comparison of plasma levels of the old and new preparations seems to support the claim. Upon further investigation, however, it may be revealed that the new so-called absorption adjuvant is replacing an ingredient that previously bound the drug or delayed its absorption; thus, the new "adjuvant" is not an adjuvant but rather it is only a nondeterrent.

Other Factors—A number of other less-well-defined factors affect the absorption of drugs, some of which may operate, in part, through factors already cited above. Disease or injury has a considerable effect upon absorption. For example, debridement of the stratum corneum increases the permeability to topical agents, meningitis increases the permeability of the blood–brain barrier, biliary insufficiency decreases the absorption of lipid-soluble substances from the intestine and acid–base disturbances can affect the absorption of weak acids or bases. Certain drugs, such as ouabain, that affect active transport processes may interfere with the absorption of certain other drugs. The condition of the *ground substance*, or "intracellular cement," probably bears on the absorption of certain types of molecules. Hyaluronidase, which depolymerizes the mucopolysaccharide ground substance, can be demonstrated to facilitate the absorption of some, but not all, drugs from subcutaneous sites.

Drug Disposition

The term *drug disposition* is used here to include all processes which tend to lower the plasma concentration of drug, as opposed to drug absorption, which elevates the plasma level. Consequently, the distribution of drugs to the various tissues will be considered under *Disposition*. Some authors use the term disposition synonymously with elimination, that is, to include only those processes which decrease the amount of drug in the body. In the present context, disposition comprises three categories of processes: distribution, biotransformation and excretion.

Distribution, Biotransformation and Excretion

The term *distribution* is self-explanatory. It denotes the partitioning of a drug among the numerous locations where a drug may be contained within the body. *Biotransformations* are the alterations in the chemical structure of a drug that are imposed upon it by the life processes. *Excretion* is, in a sense, the converse of absorption, namely, the transportation of the drug, or its products, out of the body. The term applies whether or not special organs of excretion are involved.

Distribution

The body may be considered to comprise a number of *compartments:* enteric (gastrointestinal), plasma, interstitial, cerebrospinal fluid, bile, glandular secretions, urine, storage vesicles, cytoplasm or intracellular space, etc. Some of these "compartments," such as urine and secretions, are open-ended, but since their contents relate to those in the closed compartments, they also must be included.

At first thought, it may seem that if a drug were distributed passively (ie, by simple diffusion) and the plasma concentration could be maintained at a steady level, the concentration of a drug in the water in all compartments ought to become equal. It is true that some substances, such as ethanol and antipyrine, are distributed nearly equally throughout the body water, but they are more the exception than the rule. Such substances are mainly small, uncharged, nondissociable, highly water-soluble molecules.

The condition of small size and high water solubility allows for passage through the pores without the necessity of carrier or active transport. Small size also places a limit on van der Waals binding energy and configurational complementariness, so that binding to proteins in plasma, or cells, is slight. The presence of a charge on a drug molecule makes for unequal distribution across charged membranes, in accordance with the Donnan distribution (see below). Dissociability causes unequal distribution when there is a pH differential between compartments, as discussed under *The pH Partition Principle* (see below). Thus, even if a drug is distributed passively, its distribution may be uneven throughout the body. When active transport into, or a rapid metabolic destruction occurs within, some compartments, uneven distribution is also inevitable.

The pH Partition Principle—An important consequence of nonionic diffusion is that a difference in pH between two compartments will have an important influence upon the partitioning of a weakly acidic or basic drug between those compartments. The partition is such that the un-ionized form of the drug has the same concentration in both compartments, since it is the form that is freely diffusible; the ionized form in each compartment will have the

concentration that is determined by the pH in that compartment, the pK and the concentration of the un-ionized form. The governing effect of pH and pK on the partition is known as the *pH partition principle.*

To illustrate the principle, consider the partition of salicylic acid between the gastric juice and the interior of a gastric mucosal cell. Assume the pH of the gastric juice to be 1.0, which it occasionally becomes. The pK_a of salicylic acid is 3.0 (Martin[10] provides one source of pK values of drugs). With the Henderson–Hasselbach equation (see page 242) it may be calculated that the drug is only 1% ionized at pH 1.0.* The intracellular pH of most cells is about 7.0. Assuming the pH of the mucosal cell to be the same, it may be calculated that salicylic acid will be 99.99% ionized within the cells. Since the concentration of the un-ionized form is theoretically the same in both gastric juice and mucosal cells, it follows that the total concentration of the drug (ionized + un-ionized) within the mucosal cell will be 10,000 times greater than in gastric juice. This is illustrated in Fig 35-11. Such a relatively high intracellular concentration can have important osmotic and toxicologic consequences.

Had the drug been a weak base instead of an acid, the high concentration would have been in the gastric juice. In the small intestine, where the pH may range from 7.5 to 8.1, the partition of a weak acid or base will be the reverse of that in the stomach, but the concentration differential will be less, because the pH differential from lumen to mucosal cells, etc, will be less. The reversal of partition as the drug moves from the stomach to the small intestine accounts for the phenomenon that some drugs may be absorbed from one gastrointestinal segment and returned to another. The weak base, atropine, is absorbed from the small intestine, but, because of pH partition, it is "secreted" into the gastric juice.

The pH partition of drugs has never been demonstrated to be as marked as that illustrated in Fig 35-11 and in the text. Not only do many drug ions probably pass through the pores of the membrane to a significant extent, but also some may pass through the lipid phase, as explained above for the morphinans and mecamylamine. Furthermore, ion-pair formation in carrier transport also bypasses nonionic diffusion. All processes that tend toward an equal distribution of drugs across membranes, and among compartments, will cause further deviations from theoretical predictions of pH partition.

Electrochemical and Donnan Distribution—A drug ion may be distributed passively across a membrane in accordance with the membrane potential, the charge on the drug ion and the Donnan effect. The relationship of the membrane potential to the passive distribution of ions is expressed quantitatively by the Nernst equation (Eq 7, page 709) and already has been discussed. Barring active transport, pH partition and binding, the drug will be said to be distributed according to the electrical gradient or to its "equilibrium" potential. If the membrane potential is 90 mv, the concentration of a univalent cation will be 30 times as high within the cell as without; if the drug cation is divalent, the ratio will be 890. The distribution of anions would be just the reverse. If the membrane potential is but 9 mv, the ratio for a univalent cation will be only 1.4 and for a divalent cation only 2.0. It, thus, can be seen how important membrane potential may be to the distribution of ionized drugs.

It was pointed out under *Membrane Potentials*, page 707, that large potentials derive from active transport of ions but that small potentials may result from Donnan distribution. Donnan membrane theory is discussed in Chapter 14. According to the theory, the ratio of the intracellular/extracellular concentration of a permeant univalent anion is equal to the ratio of extracellular/intracellular concentration of a permeant univalent cation. A more general mathematical expression that includes ions of any valence is

$$\left(\frac{A_i}{A_e}\right)^{1/Z_a} = \left(\frac{C_e}{C_i}\right)^{1/Z_c} = r \qquad (8)$$

where A_i is the intracellular and A_e the extracellular concentration of anion, Z_c is the valence of cation, Z_a is the valence of anion, C_i is the intracellular and C_e the extracellular concentration of cation and r is the Donnan factor. The value of r depends upon the average molecular weight and valence of the macromolecules (mostly protein) within the cell and the intracellular and extracellular volumes. Since the macromolecules within the cell are charged negatively, the cation concentration will be higher within the cell, that is, $C_i > C_e$. Since a Donnan distribution results in a membrane potential, the distribution of drug ion also will be in keeping with the membrane potential.

The Donnan distribution also applies to the distribution of a charged drug between the plasma and interstitial compartment, because of the presence of anionic proteins in the plasma. Eq 8 applies by changing the subscript i to p, for plasma, and e to i, for interstitial. The Donnan factor, r, for plasma–interstitial space partition is about 1.05:1.

Binding and Storage—Drugs frequently are bound to plasma proteins (especially albumin), interstitial substances, intracellular constituents and bone and cartilage. If binding is extensive and firm, it will have a considerable impact upon the distribution, excretion and sojourn of the drug in the body. Obviously, a drug that is bound to a protein or any other macromolecule will not pass through the membrane in the bound form; only the unbound form can negotiate among the various compartments.

The partition among compartments is determined by the binding capacity and binding constant in each compartment. As long as the binding capacity exceeds the quantity of drug in the compartment, the following equation generally applies:

* The relationship of ionization and partition to pH and pK has been formulated in several different ways, but the student may calculate the concentrations from simple mass law equations. More sophisticated calculations and reviews of this subject are available.[6,11-16]

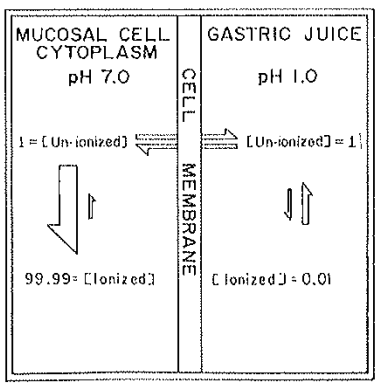

Fig 35-11. Hypothetical partition of salicylic acid between gastric juice and the cytoplasm of a gastric mucosal cell. It is assumed that the ionized form cannot pass through the cell membrane. The intragastric concentration of salicylic acid is arranged arbitrarily to provide unit concentration of the un-ionized form. *Bracketed values:* concentration; *arrows:* relative size depicts the direction in which dissociation-association is favored at equilibrium.

$$\log D_b = \log K + a \log D_f \quad (9)$$

where D_b is the concentration of bound drug, D_f is the concentration of free drug and a and K are constants characteristic of the drug and binding macromolecule. The equation is that of a Freundlich isotherm. As the binding capacity is approached, the relationship no longer holds. For a nondissociable drug at equilibrium, D_f will be the same in all communicating compartments, so that it would be possible to calculate the partition if K and a are known for each compartment. Except for plasma, the values of K and a are generally unknown, hut the percent bound is often known. From the percent bound, the partition also can be calculated, as in Fig 35-12. However, the logarithmic relationships shown in Eq 9 serve as a reminder that the percent bound changes with the concentration, so that the partition will vary with the dose. If the drug is a weak acid or base, the unionized free form negotiates among the compartments, but the ionized form is often the more firmly bound, and calculations must take into account the dissociation constant and the different K's and a's of the ionized and un-ionized forms.

It is misbelieved commonly that binding in the plasma interferes with the activity of a drug and the intracellular binding in a responsive cell increases activity or toxicity. Both binding in plasma and in the tissues decreases the concentration of free drug, but this is easily remedied by adjusting the dose to give a sufficient concentration for pharmacological activity. The distribution and activity of the free form is not affected by binding. The principal effect of binding is to increase the initial dose requirement for the drug and create a reservoir of drug from which the drug may be withdrawn as the free form is excreted or metabolized. However, if the binding is extremely firm and release is slow, the rate of release may not be enough to sustain the free form at a sufficient level for pharmacological activity; in such instances the bound drug cannot be considered a reserve.

The effect of binding upon the sojourn of a drug may be considerable. For example, quinacrine, which may he concentrated in the liver to as much as several thousand times the concentration in plasma, may remain in the body for months. Some iodine-containing radiopaque diagnostic agents are bound strongly to plasma protein and may remain in the plasma for as long as 2 yr. In pathological conditions, such as nephrosis, diahetes or cirrhosis, in which plasma protein levels may be decreased, the plasma protein hinding, loading dose and duration of action all may be decreased.

If a drug is hound to a functional macromolecule, binding may relate to pharmacological activity and toxicity, providing that the binding is at a critical center of the macromolecule. The binding by nucleic acids of certain antimalarials, such as quinacrine, undoubtedly contributes to the parasiticidal actions as well as to toxicity.

Most drugs are bound to proteins by relatively weak forces, such as van der Waals (London, Keesom or Debye) forces, or hydrogen or ionic bonds. Consequently, binding constants generally are small and binding is usually readily reversible. The larger the molecule, the greater the van der Waals bonding, so that large drug molecules are more likely to be bound strongly than are small ones.

Just as shape and the nature of functional groups is important to drug–receptor combination, so they also are to binding. Drugs of similar shape and/or chemical affinities may bind at the same sites on a binding protein and hence compete with one another. For example, phenylbutazone displaces warfarin from human plasma albumin, which may cause an increase in the anticoagulant effect of warfarin. Some drugs also may displace protein-bound endogenous constituents. For example, sulfisoxazole displaces bilirubin from plasma proteins; in infants with kernicterus the freed bilirubin floods the central nervous system and causes sometimes fatal toxicity.

Depending on the lipid–water coefficient, a drug may be taken up into fatty tissue. The ratio of concentration in fat, to that in the plasma, will not be the same as dictated by the partition coefficient because of the content of water and nonlipids in adipose tissue, and because electrolytes and other solutes alter the dielectric constant and hence solubilities from those of pure water. Lipoproteins, and even nonpolar substituents on plasma proteins, also take up lipid-soluble molecules, so that solubility in plasma can be considerably higher than that in water. The relatively high solubility of ether in plasma makes plasma a pool for ether, the filling of which delays the onset of anesthesia. However, ether and other volatile anesthetics are taken up gradually into the adipose tissue, which acts as a store of the anesthetic. The longer the anesthetic is administered, the greater the store and the longer it takes for anesthesia to terminate when inhalation has been discontinued.

Another notable substance that is taken up readily into fat is thiopental. Even though there is a high solubility of this barbiturate in fat, the low rate of blood flow in fat limits the rate of uptake. Because the blood flow in the brain is very high, thiopental rapidly enters brain tissue. However, it soon equilibrates with the other tissues, and the brain concentration falls as that in the other tissues (eg, muscle or liver) increases. Gradually, however, the fat accumulates the drug at the expense of other compartments. The gradual entry of thiopental into fat at the expense of plasma, muscle or liver is illustrated in Fig 35-13.

Nonequilibrium and Redistribution—Thus far, the distribution of drugs has been discussed mainly as though equilibrium or steady state conditions exist after a drug is absorbed and distributed. However, since most drugs are administered at intervals and the body content of drug rises and falls with absorption and destruction-excretion, neither

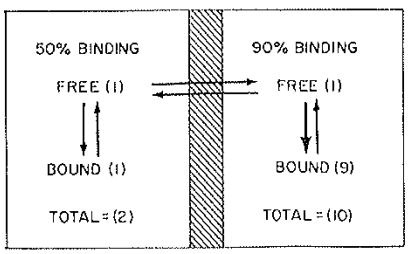

Fig 35-12. Distribution of a drug between two compartments in which the degrees of binding to protein differ. The percent of binding is indicated. Only the unbound drug can pass through the membrane. *Bracketed values:* concentration (courtesy, Schanker[12]).

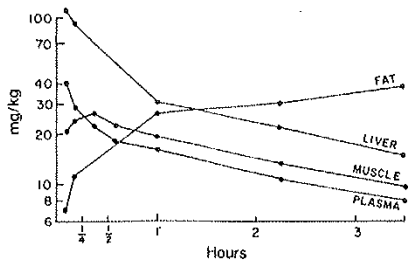

Fig 35-13. Predisposition of thiopental for fat. 25 mg/kg was given to a dog. After a brief sojourn in the moro vascular tissues, thiopental gradually transfers to fat, where the lipid-soluble drug dissolves in fat droplets (courtesy, Brodie and Hogben[13]).

a true equilibrium among the body compartments nor a steady state exists.

The term equilibrium is used misleadingly to describe the conditions that exist when the plasma concentration and the concentration in a tissue are equal, as exemplified at the point of intersection of the curves for plasma and muscle or plasma and fat in Fig 35-13. But such "equilibrium" with fat occurs much later than "equilibrium" with muscle, so that no true equilibrium really exists among all the compartments. Furthermore, the crossover point for plasma and any one tissue is not necessarily an equilibrium point, because the rates of ingress and egress from the tissue are not necessarily equal when the internal and external concentrations are equal, since there are numerous factors that make for unequal distribution (pH partition, Donnan effect, electrochemical distribution, active transport, binding, etc).

A study of Fig 35-13 shows that the distribution of thiopental continually changed during the 3.5 hr of observation. At the end of the period, the content in fat was still increasing while that in each of the other compartments was decreasing. This time-dependent shift in partition is called *redistribution*. Eventually, the content in fat would have reached a peak, which would represent as nearly a true equilibrium point as could be achieved in the dynamic situation where metabolic destruction and a slight amount of excretion of the drug was taking place. Once the concentration in the fat had reached its peak, its content would have declined in parallel with that in the other tissues and the partition among the compartments would have remained essentially constant. Redistribution, then, takes place only until the concentration in the slowest filling compartment reaches its peak, so long as the kinetics of elimination are constant.

An index of distribution known as the *volume of distribution* (amount of drug in the body divided by plasma concentration) is of considerable usefulness in pharmacokinetics but is of limited value in defining the way in which a drug is partitioned in the body. Volume of distribution is discussed on page 727.

The word *space* is often used synonymously with volume of distribution. It is employed especially when the distributed substance has a volume of distribution that is essentially identical to a physical real space or body compartment. *N*-acetyl-4-aminoantipyrine is distributed evenly throughout the total body water and is not bound to proteins or other tissue constituents. Thus, the acetylaminoantipyrine space, or volume of distribution, coincides with that of total body water. Inulin, sucrose, sulfate and a number of other substances essentially are confined to extracellular water, so that an inulin space, for example, measures the extracellular fluid volume. Evans blue is confined to the plasma, so that the Evans blue space is the plasma volume. Such space measurements with standard space indicators are a necessary part of studies on the distribution of drugs, since it is desirable to compare the volume of distribution to a drug to the physiological spaces.

Biotransformations

Most drugs are acted upon by enzymes in the body and converted to metabolic derivatives called metabolites. The process of conversion is called *biotransformation*. Metabolites are usually more polar and less lipid-soluble than the parent drug because of the introduction of oxygen into the molecule, hydrolysis to yield more highly polar groups or conjugation with a highly polar substance. As a consequence, metabolites often show less penetrance into tissues and less renal tubular resorption than the parent drug, in accordance with the principle of the low penetrance of polar and high penetrance of lipid-soluble substances. For similar reasons, metabolites are usually less active than the parent drug, often inactive; even if they are appreciably active, they generally are excreted more rapidly. Therefore, the usual net effect of biotransformation may be said to be one of *inactivation* or *detoxication*.

There are, however, numerous examples in which biotransformation does not result in inactivation. Table III (page 742) lists a number of drugs that generate active metabolites; in a few instances activity derives entirely from the metabolite.

There are also examples in which the parent drug has no activity of its own but is converted to an active metabolite: parathion, malathion and certain other anticholinesterases require metabolic activation; inactive chloroguanide is converted to an active triazine derivative; phenylbutazone is hydroxylated to the antirheumatic hydroxyphenylbutazone; inactive pentavalent arsenicals are reduced to their active trivalent metabolites and there are other examples of an activating biotransformation.

When a delayed or prolonged response to a drug is desired or an unpleasant taste or local reaction is to be avoided, it is a common pharmaceutical practice to prepare an inactive or nonoffending precursor, such that the active form may be generated in the body. This practice has been termed *drug latentiation*. Chloramphenicol palmitate, dichloralphenazone and the estolates of various steroid hormones are examples of deliberately latentiated drugs. Because inactive metabolites do not always result from biotransformation, the term detoxication should not be used as a synonym for biotransformation. See Chapter 25.

Biotransformations take place principally in the liver, although the kidney, skeletal muscle, intestine or even plasma may be important sites of the enzymatic attack of some drugs. Since plasma lacks the enzymes and structures required for electron transport, biotransformations in plasma are mostly hydrolytic.

Endoplasmic Reticulum and Microsomal System—Biotransformations in the liver mainly occur in *smooth endoplasmic reticulum*. The endoplasmic reticulum is a tubular system which courses through the interior of the cell but also appears to communicate with the interstitial space, and its membrane is continuous with the cell membrane. Some of the reticulum is lined with ribonucleoprotein particles, called ribosomes, which are engaged in protein synthesis; this is the *rough* endoplasmic reticulum. Although the smooth endoplasmic reticulum lacks such a granular appearance, it is invested heavily with numerous enzymes which biotransform many drugs and some endogenous substances.

When a broken-cell homogenate of the liver is prepared, the reticulum becomes fragmented and the fragments form vesicular structures called *microsomes*. Although the microsomes are artifacts, it is the practice to refer to the *microsomal drug metabolizing system* rather than to the smooth endoplasmic reticulum.

The microsomal system is peculiar in that both oxidations and reductions usually require the reducing cofactor, reduced nicotinamide adenine dinucleotide phosphate (NADPH). This is because microsomal oxidations proceed by way of the introduction of oxygen rather than by dehydrogenation and NADPH is essential to reduce one of the atoms of oxygen. The drug first binds to an oxidized cytochrome P-450. The drug–cytochrome complex then is reduced by NADPH-cytochrome reductase; the reduced complex then combines with oxygen, after which the metabolite is released and oxidized cytochrome P-450 is regenerated. Cytochrome P-450 is a generic term that includes at least 30 and perhaps as many as 100 separate enzymes.[17]

Some of the enzymes of the microsomal system are quite easily *induced;* that is, a substrate of the enzyme may increase considerably the activity of that enzyme by increasing

the biosynthesis of that enzyme. An increase in the amount of smooth endoplasmic reticulum sometimes also occurs concomitantly with enzyme induction.

Treatment of an experimental subject with phenobarbital greatly will increase the rate of metabolism of phenobarbital, which necessitates larger and more frequent doses of the drug in order to maintain a constant sedative effect. Moreover, phenobarbital may induce an increased metabolism of some other, but not all, barbiturates as well as some unrelated drugs, such as strychnine and warfarin. Oddly, warfarin does not induce its own biotransformation readily. At the present time, both self-induction and cross-induction appear capricious and unpredictable.

Induction may create therapeutic problems. For example, the use of phenobarbital during treatment with warfarin increases the dose requirement for warfarin. If the physician is unaware of this interaction and fails to increase the dose, the patient may suffer a thrombotic episode. If the dose of warfarin has been increased and the phenobarbital is then discontinued, the rate of metabolism of warfarin may drop to its previous level, so that the patient is overdosed, with hemorrhagic consequences. Some drugs inhibit rather than induce the microsomal system, which reduces the dose requirement and may lead to toxicity. Cimetidine is an example of a drug that inhibits the hepatic metabolism of a number of other drugs.

The activity of the microsomal system is affected by many factors other than the presence of drugs. Age, sex, nutritional states, pathological conditions, body temperature and genetic factors are among the influences that have been identified. Age, particularly, has received considerable attention. Infants have a poorly developed microsomal system, which accounts for the low dose requirement for morphine and also explains the high toxicity of chloramphenicol in infants.

The activity and selectivity of the microsomal system varies greatly from species to species, so that care must be exercised in extrapolating experimental findings in laboratory animals to man.

Types of Biotransformations—Biotransformations may be *degradative*, wherein the drug molecule is diminished to a smaller structure, or *synthetic*, wherein one or more atoms or groups may be added to the molecule. Very few drugs are degraded completely. However, it is more useful to categorize biotransformations with respect to "metabolic" (nonconjugative) biotransformations and conjugative biotransformations. The former is called phase I and the latter phase II. In phase I, pharmacodynamic activity may be lost; however, active and chemically reactive intermediates also may be generated. The polarity of the molecule may or may not be increased sufficiently to increase excretion markedly. In phase II, metabolites from phase I may be conjugated and sometimes the original drug may be conjugated, thus bypassing phase I. Phase II generates metaholites of high polarity which are excreted readily.

Biotransformations may be placed into five categories: (1) oxidation, (2) reduction, (3) hydrolysis, (4) conjugation and (5) miscellaneous. Oxidation, reduction and hydrolysis comprise phase I. Conjugation comprises phase II. Most of the miscellaneous biotransformations belong in phase I.

Oxidation—Oxidation is more common than any other type of biotransformation. Oxidations that occur primarily in the liver microsomal system include side-chain hydroxylation, aromatic hydroxylation, deamination (which is oxidative and results in the intermediate formation of RCHO), *N*-, *O*-, and *S*-dealkylation (which probably involves hydroxylation of the alkyl group followed by oxidation to the aldehyde) and sulfoxide formation. *N*-Demethylation involves a different system from *N*-dealkylation of higher radicals.

Oxidations that occur elsewhere, other than the microsomes, are generally dehydrogenations followed by the addition of oxygen or water. Examples are the oxidation of alcohols by alcohol dehydrogenase, the oxidation of aldehyde by aldehyde dehydrogenase and the deamination of monoamines by monoamine oxidase and diamines by diamine oxidase. The oxidation of purines, like caffeine and theophylline, is also extramicrosomal.

Reduction—Reductions are relatively uncommon. They mainly occur in liver microsomes, but they occasionally take place in other tissues. Examples are the reduction of nitro and nitroso groups (as in chloramphenicol, nitroglycerin and organic nitrites), of the azo group (as in prontosil) and of certain aldehydes to the corresponding alcohols (as with the deaminated serotonin metabolite, 5-hydroxytryptophal, to 5-hydroxytryptophol).

Hydrolysis—Hydrolysis is a common biotransformation among esters and amides. Esterases are located in many structures besides the microsomes. For example, cholinesterases are found in plasma, erythrocytes, liver, nerve terminals, junctional interstices and postjunctional structures, and procaine esterases are found in plasma. Various phosphatases and sulfatases also are distributed widely in tissues and plasma, although few drugs are appropriate substrates. The hydrolytic deamidation of meperidine occurs primarily in the hepatic microsomes.

Conjugation—A large number of drugs, or their metabolites, are conjugated. Conjugation is the biosynthetic process of combining a chemical compound with a highly polar and water-soluble natural substance to yield a water-soluble, usually inactive, product. Conjugations generally involve either esterification, amidation, mixed anhydride formation, hemiacetal formation or etherization.

Glucuronic acid is the most frequent partner to the drug in conjugation. Actually, the drug reacts with uridine diphosphoglucuronic acid rather than with simple glucuronic acid. The drug or drug metabolite combines at the number 1 carbon (aldehyde end) and not at the carboxyl end of glucuronic acid. The hydroxyl group of an alcohol or a phenol attacks the number 1 carbon of the pyran ring to replace uridine diphosphate. The product is a hemiacetal-like derivative. Since the product is not an ester, the term *glucuronide* is appropriate. Rarely, thiols and amines may form analogous glucuronides.

Carboxyl compounds form esters, appropriately called *glucuronates*, in replacing the uridine diphosphate. *Sulfuric acid* is also a frequent conjugant, especially with phenols and to a lesser extent with simple alcohols. The sulfurated product is called an *ethereal sulfate*. Occasionally sulfuric acid conjugates with aromatic amines to form *sulfamates*. *Phosphoric acid* also conjugates with phenols and aromatic amines. The conjugation of benzoic acid with glycine to yield hippuric acid is a classical example of an *amidation* conjugative process. Cysteine may take the place of glycine, through the intermediation of glutathione, to yield mercapturic acids with certain aromatic acids.

Amidations with amino acids are less frequent than *acetylation*, partly because few drugs are carboxylic compounds. Aromatic amines and occasionally aliphatic amines or heterocyclic nitrogen frequently are acetylated. Acetyl-CoA is the biological reagent rather than acetic acid itself. Unlike most other conjugates, the acetylate (amide) is usually less water-soluble than the parent compound. The acetylation of the para-amino group of the sulfonamides is a prime example of this type of conjugation.

Although most conjugations occur in the liver, the microsomal system is not involved. Some conjugations occur in the kidney or in other tissues.

Miscellaneous—Many amines, especially derivatives of β-phenylethylamine and heterocyclic compounds, are methylated in the body. The products are usually biologically active, sometimes more so than the parent compound. *N-Methylation* may occur in the cell sap of the liver and elsewhere, especially in chromaffin tissue in the case of phenylethylamines.

Phenolic compounds may be *O*-methylated. *O-Methylation* is the principal route of biotransformation of catecholamines such as epinephrine and norepinephrine, the methyl group being introduced on the *meta*-hydroxy substituent. Both *N*- and *O*-methylation require *S*-methyladenosyl cysteine.

Desulfuration, in which oxygen may replace sulfur, takes place in the liver. Thiopental is converted in part to pentobarbital by desulfuration, and parathion is transformed to paraoxon.

Dehalogenation of certain insecticides and various halogenated hydrocarbons may take place, principally in the liver but not in the microsomes.

Excretion

Some drugs are not biotransformed in the body. Others may be biotransformed, but their products still remain to be eliminated. It follows that excretion is involved in the elimination of all drugs and/or their metabolites. Although the kidney is the most important organ of excretion, some substances are excreted in bile, sweat, saliva, gastric juice or from the lungs.

Renal Excretion—The excretory unit of the kidney is called the *nephron* (Fig 35-14). There are several million nephrons in the human kidney. The nephron is essentially

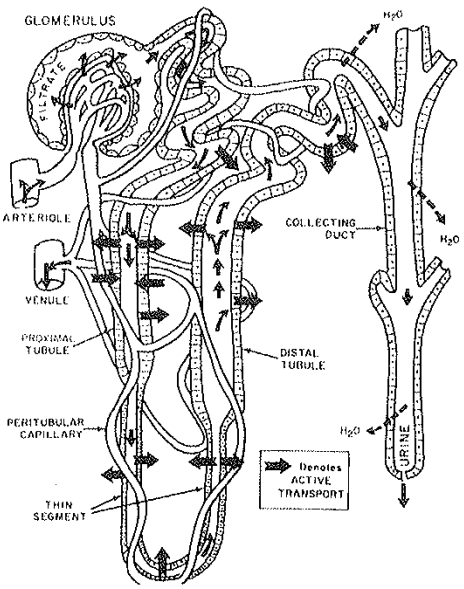

Fig 35-14. Diagram of a mammalian nephron. Note how the lower loops of the postglomerular capillaries course downward and double back along with the tubule. This allows countercurrent distribution to maintain hyperosmolar urine within the thin segment.

a filter funnel, called *Bowman's capsule*, with a long stem, called a *renal tubule*. It also is recognized now that the collecting duct is functionally a part of the nephron. The *blood vessels* that invest the capsule and the tubule are also an essential part of the nephron.

Bowman's capsule is packed with a tuft of branching interconnected capillaries (*glomerular tuft*), which provide a large surface area of capillary endothelium ("filter paper") through which fluid and small molecules may filter into the capsule and begin passage down the tubule. The glomerular tuft, together with Bowman's capsule, constitute the *glomerulus*. The glomerular capillary endothelium and the supporting layer of Bowman's capsule have channels ranging upward to 40 Å. Consequently, all unbound crystalloid solutes in plasma, and even a little albumin, pass into the glomerular filtrate.

The postglomerular vessels, which lie close to the tubules, are critically important to renal function in that substances resorbed from the filtrate by the tubule are returned to the blood along these vessels. The tubule is not straight but rather first makes a number of convolutions (called a *proximal convoluted tubule*), then courses down and back up a long loop (called the *loop of Henle*), makes more convolutions (the *distal convoluted tubule*) and finally joins the collecting duct. The loop of Henle is divided into a *proximal (descending) tubule*, a thin segment and a *distal (ascending) tubule*.

As the glomerular filtrate passes through the proximal tubule, some solute may be resorbed (*tubular resorption*) through the tubular epithelium and returned to the blood. Resorption occurs in part by passive diffusion and in part by active transport, especially with sodium and glucose. Chloride follows sodium obligatorily.

In the proximal region, the tubule is quite permeable to water, so that resorbed solutes are accompanied by enough water to keep the resorbate isotonic. Consequently, although the filtrate becomes diminished in volume by approximately 80% in the proximal tubule, it is not concentrated.

Some *acidification* occurs in the proximal tubule as the result of carbonic anhydrase activity in the tubule cells and the diffusion of hydronium ions into the lumen. In the lumen the hydronium ion reacts with bicarbonate ion, which is converted to resorbable nonionic CO_2.

There is also active transport of organic cations and anions into the lumen (*tubular secretion*), each by a separate system. These active transport systems are extremely important in the excretion of a number of drugs; for example, penicillin G is secreted rapidly by the anion transport system and tetraethylammonium ion by the cation transport system. Probenecid is an inhibitor of anion secretion and, hence, decreases the rate of loss of penicillin from the body.

As the filtrate travels through the thin segment it becomes concentrated, especially at the bottom, as a result of active resorption and a countercurrent distribution effect enabled by the recurrent and parallel arrangement of the ascending segment, the parallel orientation of the collecting duct and the similar recurrent geometry of the associated capillaries.

In the thick segment of the ascending loop of Henle, both sodium and chloride are transported actively.

In the distal tubule, sodium resorption occurs partly in *exchange* for potassium (*potassium secretion*) and for hydronium ions. Adrenal mineralocorticoids promote distal tubular sodium resorption and potassium and hydronium secretion. *Ammonia secretion* also occurs, so that the urine either may be acidified or alkalinized, according to acid–base and electrolyte requirements.

Water is resorbed selectively from the distal end of the distal convoluted tubule and the collecting ducts; water resorption is under the control of the antidiuretic hormone.

Drugs also may be resorbed in the distal tubule; the pH of the urine there is extremely important in determining the rate of resorption, in accordance with the principle of nonionic diffusion and pH partition. The pH of the tubular fluid also affects the tubular secretion of drugs.

As an example of the importance of urine pH, in humans the secondary amine, mecamylamine, is excreted more than four times faster when the urine pH is less than 5.5 than when it is above 7.5; Fig 35-15 illustrates the effect of urine pH on the excretion of this amine. The effect of urine pH on the excretion of a weak acid, sulfaethidole (for the structure, see page 1109, RPS-15), is shown in Fig 35-16.

The urine pH and, hence, drug excretion may fluctuate widely according to the diet, exercise, drugs, time of day and other factors. Obviously, the excretion of weak acids and bases can be controlled partly with acidifying or alkalinizing salts, such as ammonium chloride or sodium bicarbonate, respectively. Comparative studies on potency and efficacy

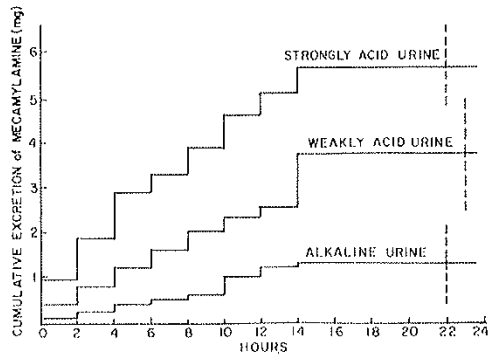

Fig 35-15. The effect of urinary pH on the mean cumulative excretion in man of mecamylamine during the first day after oral administration of 10 mg. *Vertical broken lines:* standard deviation (courtesy, Milne, *et al*[18]).

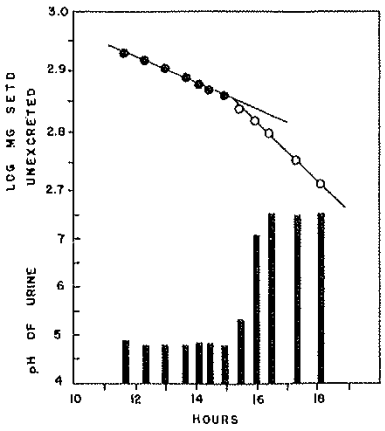

Fig 35-16. The effect of urinary pH on the excretion of sulfaethidole in a human subject after oral administration of 2 g. *Bars* (lower half): urinary pH; *circles* (open and closed, top): log of the amount of drug remaining in the body; *negative slopes* (of lines defined by the circles): a function of the rate constant of excretion. Note the abrupt increase in rate when the urinary pH is changed from acidic to neutral or slightly alkaline (courtesy, Kostenbauder, *et al*[19]).

in man have demonstrated the importance of controlling urinary pH. Urine pH is important only when the drug in question is a weak acid or base of which a significant fraction is excreted. The plasma levels will change inversely to the excretory rate. For example, it has been shown clinically with quinidine that alkalinization of the urine not only decreases the urine concentration but also increases the plasma concentration and toxicity.

The collecting duct also resorbs sodium and water, secretes potassium, acidifies and concentrates the urine. Antidiuretic hormone (ADH) controls the permeability to water of both the collecting duct and the distal tubule.

Renal clearance and the kinetics of renal elimination are discussed in Chapter 36 (page 730).

Biliary Excretion and Fecal Elimination—Many drugs are secreted into the bile and, thence, pass into the intestine. A drug that is passed into the intestine via the bile may be reabsorbed and not lost from the body. This cycle of biliary secretion and intestinal resorption is called *enterohepatic circulation*. Examples of drugs enterohepatically circulated are morphine and the penicillins. The biliary secretory systems greatly resemble those of the kidney tubules. The enterohepatic system may provide a considerable reservoir for a drug.

If a drug is not absorbed completely from the intestine, the unabsorbed fraction will be eliminated in the feces. An unabsorbable drug that is secreted into the bile will likewise be eliminated in the feces. Such fecal elimination is called *fecal excretion*. Only rarely are drugs secreted into the intestine through the succus entericus (intestinal secretions), although a number of amines are secreted into gastric juice.

Alveolar Excretion—The large alveolar area and high blood flow make the lungs ideal for the excretion of appropriate substances. Only volatile liquids or gases are eliminated from the lungs. Gaseous and volatile anesthetics essentially are eliminated completely by this route. Only a small amount of ethanol is eliminated by the lungs, but the concentration in the alveolar air is related so constantly to the blood alcohol concentration that the analysis of expired air is acceptable for legal purposes. The high aqueous solubility and relatively low vapor pressure of ethanol at body temperature account for the retention of most of the substance in the blood. Carbon dioxide from those drugs that are partly degraded also is excreted in the lungs.

Pharmacokinetics

Pharmacokinetics is the science that treats of the rate of absorption, extent of absorption, rates of distribution among body compartments, rate of elimination and related phenomena. Because of its importance, two chapters, *Basic Pharmacokinetics* (page 725) and *Clinical Pharmacokinetics* (page 746), have been devoted to the subject.

Drug Interaction and Combination

Frequently a patient may receive more than one drug concurrently. Case records show that surgical patients commonly receive more than ten, and sometimes as many as 30, drugs and the patient is often under the influence of several drugs at once, sometimes unnecessarily. Multiple-drug administration also is common for patients hospitalized for infections and other disorders. Furthermore, a patient may be suffering from more than one unrelated disorder which demands simultaneous treatment with two or more drugs. In such instances, interactions are unsolicited and often unexpected.

In addition to the administration of drugs concurrently for their independent and unrelated effects, drugs are sometimes administered concurrently deliberately to make use of expected interactions.

Types of Interaction and Reasons for Combination Therapy

A drug may affect the response to another drug in a quantitative way. On the one hand, the intensity of either the therapeutic effect, or side effect, may be augmented or suppressed. On the other hand, a qualitatively different effect may be brought out. The mechanisms of such interactions are many and not always are understood. A drug may not necessarily affect either the quality or initial intensity or effect of another drug, but may cause significant to profound changes in the duration of action. The nature of this type of interaction generally is understood fairly well, although it may not yet have been ascertained for any particular drug combination. The deliberate use of combined interacting drugs is most valid when the mechanism of the interaction is understood and the combined effects are both quantifiable and predictable. The rationales of drug combination and the principles involved are discussed below.

Combinations to Increase Intensity of Response or Efficacy—Sometimes the basis for the action of one drug to increase the intensity of response to another is well understood, but often the reason for a positive interaction is obscure. A terminology has arisen that frequently is not only enlightening as to mechanisms and principles but also which is somewhat confusing.

Drugs that elicit the same quality of effect and are mutually interactive are called *homergic*, regardless of whether there is anything in common between the separate response systems. Thus, the looseness of the term admits a pressor response consequent to an increase in cardiac output to be

homergic with one resulting from arteriolar constriction, even though there is not one common responsive element, the blood pressure itself being but a passive indicator. However, homergic drugs usually have in common at least part of a response system. Thus, both norepinephrine and pitressin stimulate some of the same vascular smooth muscle, even though they do not excite the same receptors.

Two homergic drugs can be agonists of the same receptor, so that the entire response system is common to both. Such drugs are called *homodynamic*. As discussed under *Drug Receptors and Receptor Theory* (page 702), homodynamic drugs will generate dose–intensity of effect curves with parallel slopes, but not necessarily with identical maxima or efficacies, if one of the drugs is a partial agonist.

From mass-law kinetics and dose–effect data of the separate drugs, it is possible to predict the combined effects of two agonists to the same receptor. If both drugs are full agonists, theory predicts that an *EDx* of Drug *A* added to an *EDy* of Drug *B* should elicit the same effect as that of an *EDy* of Drug *A* added to an *EDx* of Drug *B*. An example is shown in Fig 35-17. Dose–percent data with homodynamic drugs can be treated in the same way.[21]

Drugs whose combined effects fit the above conditions are called *additive*. If the response to the combination exceeds the expected value for additivity, the drugs are considered to be *supra-additive*. Purely homodynamic drugs do not show supra-additivity; however, if one drug in the pair has an additional action to affect the concentration or penetrance of the other or to prime the response system in some way, two agonists to the same receptor may exhibit supra-additivity. Two homergic drugs are *infra-additive* if their combined effect is less than expected from additivity. As with supra-additivity, infra-additivity must involve an action elsewhere than on a common receptor.

Two drugs are said to be *summative* if a dose of drug that elicits response x added to a dose of another drug that elicits response y gives the combined response $x + y$. Very little significance usually can be attached to summation. Unless the dose–intensity curve of each drug is linear, rather than log-linear, summation cannot be predicted from the two curves. When summation does occur with the usual clinical doses of two drugs, it almost never occurs over the entire dose range; indeed, if the dose of each of the two drugs is greater than an ED50, summation is theoretically impossible unless it is possible to increase the maximal response. At best, summation is an infrequent clinical finding limited to one or two doses.

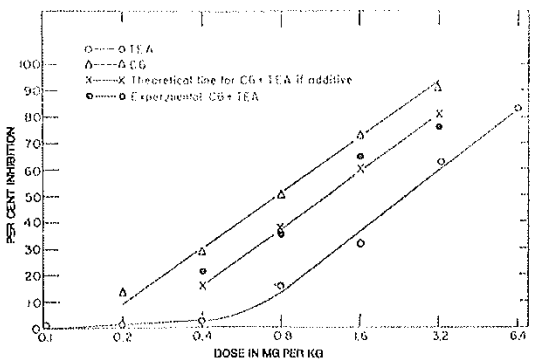

Fig 35-17. Additive inhibitory effects of tetraethylammonium (TEA) and hexamethonium (C6) on the superior cervical ganglion of the cat. The theoretical line for additivity was calculated on the basis that an increment of TEA added to an EDx of C6 should have the same effect as if it were added to an EDx of TEA. When TEA and C6 were administered together, an equal amount of each was given. The dose is the sum of the doses of the two components (courtesy, Harvey[20]).

Two drugs are said to be *heterergic* if the drugs do not cause responses of the same quality. When heterergy is positive, ie, the response to one drug is enhanced by the other, *synergism* is said to occur. The word often has been used to describe any positive interaction, but it should be used only to describe a positive interaction between heterergic drugs. The term *potentiation* has been used synonymously with synergism, but misuse of the term has led to the recommendation that the term be dropped. Synergism is often the result of an effect to interfere with the elimination of a drug and, thus, to increase the concentration; synergism also may result from an effect on penetrance or on the responsivity of the effector system. Examples of a synergistic effect, in which responsivity is enhanced, are the action of adrenalcorticoids to enhance the vasoconstrictor response to epinephrine and the increase of epinephrine-induced hyperglycemia consequent to impairment by theophylline of the enzymatic destruction of the cAMP which mediates the response.

In clinical practice two homodynamic drugs rarely are coadministered for the purpose of increasing the response, since a sufficient dose of either drug should be able to achieve the same effect as a combination of the two. Most clinical combinations with positively interacting drugs are with heterergic drugs.

Combinations to Decrease Individual Doses and Toxicity—When homodynamic drugs are coadministered, it is usually for the purpose of decreasing toxicity. If the toxicities of two homodynamic drug are infra-additive, the toxicity of combined partial doses of the two drugs often will be less than with full doses of either drug. This principle is valid for trisulfapyrimidines mixture (see page 1181).

Combinations to Attack a Disease Complex at Different Points—With many diseases, more than one organ or tissue may be affected or events at more than one locus may bear upon the ultimate perturbation. For example, in duodenal ulcer, psychic factors appear to increase activity in the vagus nerve, which modulates gastric secretion, so that it is rational to explore the effects of sedatives, ganglionic blocking drugs, antimuscarinic drugs and antacids, singly and in combination. In heart failure the decrement in renal plasma flow and changes in aldosterone levels promote the retention of salt and water, so that diuretics and digitalis usually are employed concomitantly. Pain, anxiety and agitation or depression are frequent accompaniments of various pathologic processes, so that it is to be expected that analgesics, tranquilizers, sedatives or antidepressives frequently will be given at the same time, along with other drugs intended to correct the specific pathology.

Combinations to Antagonize Untoward Actions—The side effects of a number of drugs can be prevented, or suppressed, by other drugs. An antagonist may compete with the drug at the receptor that initiates the side effect, depress the side-effector system at a point other than the receptor, or stimulate an opposing system.

Antagonism at the receptor is *competitive antagonism* if the antagonist attaches at the same receptor group as the agonist (see page 703). Antagonism at a different receptor group, or inhibition elsewhere in the response system, is *noncompetitive antagonism*. Both competitive and noncompetitive antagonism are classified as *pharmacological antagonism*. The stimulation of an opposing system is *physiological antagonism*.

Examples of pharmacological antagonism are the use of atropine to suppress the muscarinic effects of excess acetylcholine consequent to the use of neostigmine and the use of antihistaminics to prevent the effects of histamine liberated by tubocurarine. Examples of physiological antagonism are

the use of amphetamine to correct partially the sedation caused by anticonvulsant doses of phenobarbital and the administration of ephedrine to correct hypotension resulting from spinal anesthesia.

Combinations That Affect Elimination—Only a few drugs presently are used purposefully to elevate or prolong plasma levels by interfering with elimination, although continued interest in such drugs probably will increase the number.

Probenecid, which already has been mentioned to antagonize the renal secretion of penicillin, was introduced originally for this purpose. However, because penicillin G is inexpensive and available in repository forms, as well as oral forms (obviating the need for injection), it is less imperative to retard the excretion of penicillin. The low nonallergenic toxicity of penicillin permits very large doses to be given without concern for the high plasma concentrations that result, which also means that there is little necessity for increasing the biological half-life of the drug. Consequently, probenecid is not used routinely today in combination with penicillin.

The use of vasoconstrictors to increase the sojourn of local anesthetics at the site of infiltration continues, but few other clinical examples of the deliberate use of one drug to interfere with either the distribution or elimination of another can be cited. Nevertheless, the subject of the effect of one drug on the elimination of another has become immensely active. Innumerable drugs affect the fate of others and the therapist must be aware of such interactions.

Drugs that induce cytochrome P-450s enhance the elimination of drugs that are metabolized by the liver microsomes. There would be very little point ordinarily to solicit combinations that would shorten the duration of action or lower plasma levels, unless it were to reduce an overdosage. However, since such combinations are used unwittingly or unavoidably, this type of interaction is of great clinical importance.

Combinations to Alter Absorption—In the section on *Vehicles and Absorption Adjuvants* (page 714) it was mentioned that certain substances facilitate the absorption of others. The use of such absorption adjuvants generally is included under the subject of formulation rather than under drug combination. Although drugs which increase blood flow, motility, etc have an effect to increase the rate of absorption, the use of such drugs so far has not proved to be very practical. When it is desired to slow the absorption of drugs, various physical or physicochemical means prove to be more effective and less troublesome than drug combinations.

Fixed Combinations of Drugs

Concomitant treatment with two or more drugs frequently is unnecessary, and it, generally, immeasurably complicates therapy and the evaluation of response and toxicity. Nevertheless, it is often warranted, even essential and cannot be condemned categorically. However, with fixed-dose or fixed-ratio combinations, in which the drugs are together in the same preparation, there are certain disadvantages, except for a few rare instances like trisulfapyrimidines.

The disadvantages are as follows: patients differ in their responsivity or sensitivity to drugs and adjustments in dosage or dose-interval may be necessary. If adjustment of only one component of the mixture is required, it is undesirable that the schedule of the second component be adjusted obligatorily, as it is in a fixed combination. According to which way the dose is adjusted, either toxicity or loss of the therapeutic effect may result. Furthermore, when adverse effects to either component occur, both drugs must be discontinued. The fixed combination denies the physician flexible control of therapy. Especially when one component in a mixture is superfluous yet potentially toxic, as is often the case, the promotion of fixed combinations is reprehensible. However, the separate administration of drugs used in combination often complicates treatment for the patient, who, in an outpatient situation and sometimes in the hospital, may not take all of his medication or who may take it at inappropriate intervals. The resulting consequences may be worse than those of fixed combinations in certain instances. Consequently, a summary dismissal of fixed combinations is unwarranted. Rather, the fundamentals of pharmacokinetics and clinical experience must be brought together with biopharmaceutics to analyze present combinations and to predict possible new allowable combinations.

Dangers in Multiple-Drug Therapy

Some objections to fixed-dose combinations were stated above. Also the unanticipated effects of drug combinations have been touched upon, particularly with respect to effects upon elimination. But it should be made clear that more is at stake than simply the biological half-life of a drug. On page 717 an example was given of the grave clinical consequences of the effect of phenobarbital to enhance the biotransformation of warfarin. Other examples of dangerous interactions, such as the effect of several antidepressants greatly to synergize catecholamines, may be cited. Even some antibiotics antagonize each other and increase mortality.

In addition to the obvious pitfalls posed by the interactions themselves, the use of multiple-drug therapy fosters careless diagnosis and a false sense of security in the number of drugs employed. Multiple-drug therapy should never be employed without a convincing indication that each drug is beneficial beyond the possible detriments or without proof that a therapeutically equivocal combination is definitely harmless. Finally, the expense to the patient warrants consideration.

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CHAPTER 36

Basic Pharmacokinetics

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Pharmacokinetics is the discipline which is concerned with the rates of movement of a drug or its metabolites into the body, among its many compartments, out of the body and also which attempts to evaluate the rates of biotransformations of the drug and its metabolites. As in chemistry, it involves primarily following the rate of change in concentration in the appropriate compartment(s), most often in the extracellular fluid (plasma) and/or urine. However, pharmacokinetics is by no means limited to observations of concentration; rates of movement of a drug can be followed by isotopes or other means. The application of pharmacokinetics to drug formulation and treatment regimens also is within the scope of this title. The applications to treatment regimens and other clinical uses of pharmacokinetics are treated in Chapter 37, *Principles of Clinical Pharmacokinetics.*

Orders of Processes

The order of any process is determined by the probability that the appropriate unit events will occur in a given population within a given time. Processes may be zero-order, first-order, second-order, etc, depending upon the number of variables that determine the probability. In pharmacokinetics, only zero-order and first-order processes are important, the latter being of overwhelming significance; consequently, only the kinetics of these two processes will be treated in this chapter.

First-Order Processes

When activity is random within a population of a single species, the probability that a given event will occur is directly proportional to the size of the population. For example, the probability that some atom in a population of radionuclides will disintegrate in any instant is directly proportional to the number of radionuclide atoms in the population. Similarly, the number of molecules of drug that diffuse across a given boundary (eg, the vascular endothelium) per unit time will be proportional directly to the number of molecules near the boundary, which, in turn, is proportional to the concentration. This is the basis of Fick's Law of Diffusion (page 208). Any process in which the rate of change in a population is directly proportional to the population is known as a *first-order* process. In such a process, the time-dependent change in concentration is defined by the equation

$$C = C_0 e^{-kt} \qquad \text{[units of wt} \cdot \text{vol}^{-1} \text{ or molar, etc]} \qquad (1)$$

where C is the concentration at time t, C_0 is the initial concentration (time zero), t is time, e is the natural (Naperian) log base and k is a proportionality constant known as the rate constant. (For a derivation of Eq 1, see page 247.) In a diffusion process, the magnitude of k is determined by the temperature, mobility, permeability and other factors. The numerical value of k also will depend upon the time units (min vs hr, etc) chosen.

Eq 1 predicts that as t approaches infinity, C approaches zero, which would be true for irreversible processes like radioactive decay, diffusion into infinite space, some exentropic SN_1 chemical decompositions and certain enzymatic reactions. However, in a confining space, diffusion and many chemical reactions reach an equilibrium state in which C approaches a finite asymptote as t approaches infinity. Figure 36-1 illustrates a simple situation in which the asymptote is necessarily finite. To satisfy the conditions of this

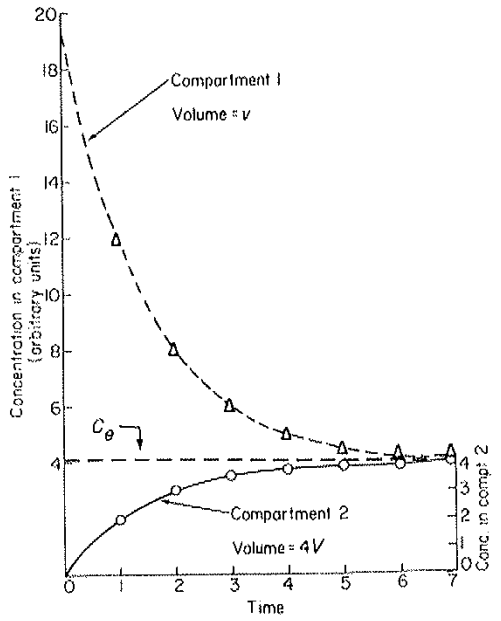

Fig 36-1. Idealized diffusion kinetics of a hypothetical drug that equilibrates between two compartments. Transfer is from compartment 1 into compartment 2. The equilibrium concentration is ⅕ of that initially in compartment 1, because the final volume of distribution is 5 times that of compartment 1.

closed system, $(C_0 - C_e)$ must be substituted for C_0 in Eq 1, C_e being the equilibrium concentration.

In Eq 1, the algebraic sign of k is usually negative, which indicates a diminishing concentration with time. However, in Fig 36-1 the concentration in compartment 2 rises logarithmically with time; nevertheless, k is negative, since the rate diminishes exponentially with time. The equation for the logarithmically rising concentration in compartment 2 will take the form of Eq 5 (page 727), in which C_e would be used in lieu of C_p^∞.

Eq 1 can be written in the log form,

$$\log C = \log C_0 - 0.434kt \qquad \text{[no units]} \tag{2}$$

The coefficient 0.434 results from the conversion of the natural log base, e, to log base 10 (0.434 = 1/2.303). The equation determines that a plot of log C against t will be rectilinear (bottom of Fig 36-1) with a slope of $-0.434k$ and an ordinate-intercept of C_0. For pharmacokinetics, this is a useful type of plot, because, in the straight-line form, back extrapolation to estimate C_0 is easier and more accurate than from a curve, and k can also be determined graphically.

Rate Constants and Half-Life—Since first-order processes are characterized by exponential or logarithmic kinetics, it follows that a constant fraction of the present or instantaneous population (eg, concentration) changes per unit time, that fraction being equal to $0.434k$; k has the units of t^{-1}. Another way of expressing the rate of change is that of half-time (or especially *half-life*, if the population is decreasing), with the notation $t_{1/2}$. The half-time is the time that it takes the population to decrease (or increase) by 50% of the total possible change. By setting C equal to $\frac{1}{2}C_0$ in either Eqs 1 or 2 and solving for t (which is $t_{1/2}$ under these constraints),

$$t_{1/2} = \frac{0.693}{k} \qquad \text{[units of time]} \tag{3}$$

Zero-Order Processes

When an enzyme or transport system is saturated, the activity cannot be increased further by increases in the concentration of substrate. Consequently, the rate remains constant so long as the concentration of substrate is in excess of the saturating concentration. In this situation, the rate is independent of the concentration. The kinetics are described as being of *zero-order*, and it is customary to speak of the process as being a zero-order process. The equation describing zero-order kinetics is

$$C = C_0 - kt \qquad \text{[conc vol}^{-1}\text{]} \tag{4}$$

where k has the units of amount/unit time. A plot of C against t on Cartesian coordinates will yield a straight line; a plot of log C against t will yield a curved line. As the process continues, the concentration eventually will fall to subsaturation levels, and the kinetics will change, usually to first-order kinetics, so that it is more appropriate to speak of the initial kinetics and not the process as being zero-order.

Pharmacokinetic Models

The plasma, cerebrospinal fluid, interstitial space, glandular or renal tubular lumina, gall bladder, etc and each cell are all compartments which a drug may or may not enter or leave with different rate constants. In addition, binding to protein or other sequestration also is governed by characteristic rate processes. Consequently, it might be expected that the kinetics of absorption, distribution and elimination would be very complex and perhaps beyond analysis and mathematical description. Fortunately, the rates of distribution among the various tissues and myriad cells generally are not dispersed greatly, and most such processes are first-order. Thus, the kinetics behave as though the drug were being distributed among one, two or, at the most, a few compartments, and they are amenable to mathematical modeling. Like the volume of distribution (page 727), a pharmacokinetic compartment is fictive or virtual and may be difficult to define in precise anatomical terms. Therefore, a compartment is defined mainly by its pharmacokinetic parameters.

Open One-Compartment Model

In this model, the body is assumed to behave as though it were a single compartment, that is, as though there were no barriers to movement of a drug within the total body space and as though the final equilibrium distribution is attained instantaneously. In practice, the model adequately describes the pharmacokinetic behavior of a drug if the final equilibrium distribution is attained rapidly in comparison to the rates of absorption and elimination. The term *open* indicates that input and output (from any and all routes of administration and elimination, respectively) are unidirectional and that the one compartment (ie, body) is not within a confined space and hence does not come into chemical equilibrium with its external environment. In simple diagram, such an open one-compartment model is depicted in Fig 36-2. In the diagram, the compartment represents the entire body (excluding the lumina of the gastrointestinal tract, urinary tract, pulmonary alveoli, etc, which communicate with the open environment). The term, V_d is the *volume of distribution* (see page 727). However, V_d is not necessarily that of the body or even total body water; as noted on page 728, the volume of distribution, V_d, is a fictive one considered to be equal to fD/C_p (where f is the fraction absorbed, D is the dose and C_p is the plasma concentration) in which it hypothetically is assumed that the concentration is the same throughout the volume and is equal to the plasma concentration. In reality, concentration is not homogeneous throughout, but this cannot be determined from C_p alone (which simply averages all inputs and outputs); as long as distribution equilibrium is achieved rapidly, the kinetics as perceived through blood or urine concentrations are the same whether distribution is homogeneous or heterogeneous.

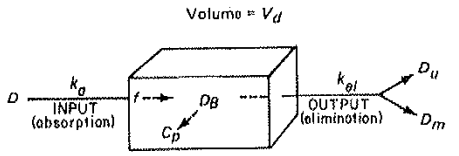

Fig 36-2. The open one-compartment pharmacokinetic model. An amount of drug, D_B, is absorbed from the administered dose, D, with a rate constant of k_a into a compartment with volume V_d and is distributed instantaneously to reach a plasma concentration C_p. V_d is obtained by dividing D_B by C_p. D_B = dose D times f, the fraction absorbed. Drug is eliminated from the compartment with a rate constant k_{el}. D_u is the amount excreted into urine, feces, expired air, sweat, milk, etc; D_m is the amount of drug metabolized.

In order to derive formulae to describe time-related changes in C_p, it is convenient to consider absorption and elimination separately, as though each were occurring in the absence of the other, then to add them algebraically to determine the total integral kinetics.

Absorption—If a drug is administered intravenously in a single, rapid injection, absorption is bypassed. The time for such injections is usually so short compared to other pharmacokinetic processes that it is customary to consider the peak plasma concentration and equilibrium distribution to occur instantaneously in one-compartment systems. This is depicted in panel A of Fig 36-3. In the model for the figure, there is no elimination and C_p remains constant once injection is accomplished. With constant intravenous infusion (panel B), C_p rises rectilinearly so long as infusion continues at a constant rate. With other routes of administration, absorption usually manifests first-order kinetics, since most drugs are absorbed by simple diffusion. Thus, the drug disappears exponentially from the site of administration (as from compartment 1 in Fig 36-1). The equation for the concentration of a drug in the plasma after a single extravascular dose of a drug, assuming no elimination takes place, is

$$C_p = C_p^{\infty} - C_p^{\infty} e^{-k_a t} \qquad \text{[units: wt} \cdot \text{vol}^{-1}\text{, etc]} \qquad (5)$$

where C_p is the concentration at time t, C_p^{∞} is the final concentration at "infinite" time and k_a is the absorption rate constant (units: time^{-1}). Absorption is characterized by a half-time equal to $0.693/k_a$. Bimolecular absorption processes, such as facilitated diffusion or active transport, also often show first-order kinetics, especially at drug concentrations well below those at which the carrier system will become saturated. At saturation, the kinetics become zero-order. Even the rate of dissolution of a drug approximates a first-order process, provided that the drug is soluble readily and diffuses rapidly. If the solubility and diffusibility are low, it will approximate a zero-order process so long as there is saturation around the solid phase. Some sustained-release dosage forms are designed to release drugs at a constant rate (zero-order) over long periods of time.

Absorption by the oral route rarely conforms to simple first-order kinetics. A drug is absorbed at different rates from the stomach and the three segments of the intestine, partly simultaneously and partly sequentially. Absorption from the stomach usually is quite slow compared to that from the small intestine, and it is sometimes so slow that a significant amount of drug appears in the blood only after the stomach contents are emptied. Thus, there may be a *lag* between the time of drug administration and the appearance of drug in the blood. That is, the curve describing the time-dependent rise in C_p does not pass through the origin. An example of lag in the absorption of pentobarbital is shown in Fig 36-4. Enteric-coated or other delayed-release dosage forms also cause lag. The mathematical formulation of lag

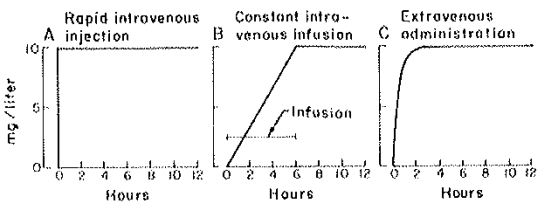

Fig 36-3. Time-concentration curves for injection (A), infusion (B) and extravenous (C) administration of drug in the one-compartment model. The volume of the compartment is 100 L (V_d = 100 L); the amount of drug administered in each instance is 1000 mg. Drug elimination has been set to zero, so that the time-concentration curve for each model of administration can be examined without the complication of simultaneous elimination (courtesy, Bigger,[1] adapted).

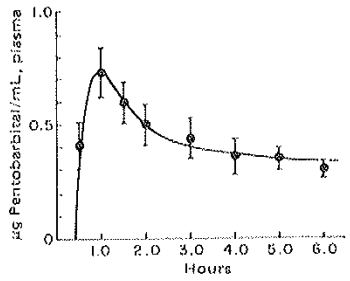

Fig 36-4. The time course of pentobarbital in the blood of a fasting human subject following the oral administration of 50 mg. The figure shows a lag-time of about 20 min, approximately the emptying time of the fasting stomach (courtesy, Dittert[2]).

will be deferred to the next section in connection with Eq 28. Factors affecting absorption are enumerated on page 713. Some changes in gastrointestinal conditions during the course of absorption are part of diurnal rhythms or are caused by the drug itself, which make it impossible to establish a steady basal state for description; others may result from emotionality, ingestion of foodstuffs, water, other drugs, etc, and can be controlled adequately for scientific purposes but may vary greatly in practical circumstances. Absorption by other routes is also subject to variability. Some drugs that are completely absorbed in normal patients may not be absorbed in persons with abnormal gastrointestinal function, as the result of genetic, pathological or surgical factors. Many drugs are not absorbed completely even when gastrointestinal function is optimal. Absorption can be limited by the physical state of the drug and by other substances in the dosage form. The amount of drug absorbed into the body (D_B) is related to the dose as follows:

$$D_B = fD \qquad \text{[units: wt]} \qquad (6)$$

where D_B is the amount absorbed (drug in the body), f is the fraction absorbed and D is the dose administered. The property of a drug to be absorbed from its dosage form is known as *bioavailability*, and f is the bioavailability factor. The bioavailability factor often is determined by comparison of the area under the concentration curve (AUC) of a given dose of drug given orally with that of the same dose given intravenously (see page 736).

Distribution—In the open one-compartment model, the body is treated as though it were a single compartment in which the absorbed drug is mixed instantaneously and homogeneously. Clearly, the assumption of instantaneous equilibrium establishes only an ideal mathematical boundary condition to facilitate pharmacokinetic calculations. At best, no drug could be equilibrated in less than one circulation time, and no drug has been shown to distribute so rapidly. However, for practical purposes, a distribution time of a few minutes is negligible compared to absorption and elimination times. Only water-soluble drugs of small molecular size which are confined completely to the extracellular space equilibrate rapidly enough to meet the requirements of the ideal one-compartment model, but, for clinical purposes, the one-compartment model is adequate to describe the pharmacokinetics of a large number of drugs.

Volume of Distribution and Distribution Coefficient—The hypothetical volume within which a drug is distributed is known as the *volume of distribution*, V_d. It may be calculated by dividing the amount of drug in the body, D_B, by the plasma concentration, C_p, where C_p is the concentration in plasma. It is important to note that C_p is usually the total concentration of unbound plus bound drug. Under real conditions, D_B and C_p vary with time, and computation

must be made in such a way as to eliminate the time variable. One such way is to extrapolate C_p to zero time (eg, see Figs 36-6 and 36-8), in which case

$$V_d = f\,D/C_p^0 \qquad (7)$$

where D is the dose administered, f is the bioavailability factor (fraction that reaches the systemic circulation) and C_p^0 is the plasma concentration at zero time, determined by extrapolation. When the drug is given intravenously, $D_B = D$.

Of course, V_d will vary with body weight, so that it needs to be normalized in a way that allows comparisons among individuals of different body weights. Such a normalized V_d is the *distribution coefficient*,* Δ', calculated by the equation

$$\Delta' = V_d/BW \qquad (8)$$

where BW is body weight. Units are usually mL/g or L/kg, and care must be taken to employ the appropriate units of weight, concentration and volume in Eqs 7 and 8. The notation Δ' is a more serviceable parameter than V_d and is the form of V_d usually found in tables of pharmacokinetic data, usually under the heading, "Volume of Distribution," rather then Δ'.

Although V_d and Δ' are derived as though the concentration was equal to C_p throughout the volume, concentration is, in fact, almost never homogeneous, and consequently V_d and Δ' are only imaginary (fictive, virtual) volumes. Factors that make for nonhomogeneous distribution are: binding to proteins, dissolution into body lipids, pH partition, active transport, electrochemical and Donnan distributions, etc. Even if C_p (free) rather than C_p (total) is used to calculate V_d, V_d would not represent a real space, because of these manifold factors that cause uneven distribution. Consequently, the principal utility of V_d or Δ' is not so much in permitting an estimation of where the drug is distributed but rather as a measure of the reservoir from which a drug is being delivered and/or cleared (see page 729 and Table II, page 731). However, with appropriate considerations, V_d or Δ' also may indicate the general ability of a drug to penetrate membranes, dissolve in fat or bind extensively to extravascular macromolecules.

Highly polar, poorly penetrant drugs tend to be confined mostly to the extracellular space; if these drugs are little bound to plasma proteins, they will have Δ's of about 0.3 mL/g, less if there is significant binding to plasma proteins. The lower limit to Δ' is about 0.04 mL/g, which approximately is equal to the plasma volume. Drugs that are distributed throughout body water and are not bound or concentrated have Δ's of approximately 0.7 mL/g, the Δ' of body water. Lipid-soluble drugs that are bound negligibly to plasma protein have Δ's that range usually from about 0.7 to 3–4 mL/g, depending upon water-lipid distribution coefficients. Some drugs that bind strongly to chromatin have Δ's that approach 1000 mL/g. However, many drugs combine penetrance, lipid solubility and protein binding in such proportions to make it difficult to interpret the meaning of Δ' without ancillary information.

Since, by definition, V_d varies reciprocally with C_p, it is essential to recognize that binding to plasma proteins, by increasing C_p, will decrease V_d. Despite this, plasma protein binding has no *real* effect on extravascular distribution. Since it is only the free form that moves among the spaces and tissues, it follows that alterations in plasma protein binding alone will not alter the extravascular (indeed, extraplasma) distribution. Only the calculated, fictive quantity, Δ', is affected. For example, nafcillin has a Δ' of 0.29 mL/g and is 90% bound to plasma proteins. If there was no protein binding, Δ' would equal 2.9 mL/g, a volume sufficiently larger than that of water, to suggest considerable extravascular binding. However, it is not the masking of the degree of extravascular distribution that is the source of difficulty when there is significant binding to plasma proteins, but rather because the extent of protein binding is not always constant. Both the quantity and binding properties (affinity and capacity) of human plasma proteins can vary in health, disease and the presence of other drugs (see pages 195 and 716). If the degree of binding of nafcillin to plasma proteins was to change to 50% as the result of hypoalbuminuria, Δ' would become nearly 0.48 mL/g. The Δ' of ampicillin, which is bound only to the extent of 18%, would not be affected so greatly. A further complication of binding to plasma proteins is occasioned when the degree of binding, and hence the magnitude of Δ', is dose-dependent. There are a number of known examples in which Δ' varies with the dose.

Elimination—Once a drug is absorbed, it is transported by the blood to the tissues, among which it is distributed, metabolized and/or excreted; all of these processes lower the plasma concentration of the drug. Each separate process ordinarily has first-order kinetics, and the overall change in plasma concentration is described by the linear combination (or algebraic addition) of the separate equations. In the one-compartment model, the kinetics of distribution are ignored, since distribution occurs so rapidly that distribution occurs before any practical blood-sampling or repetitive dosing occurs. Thus, after intravascular administration the plasma concentration, C_p, will fall exponentially according to Eq 1. Such an exponential elimination of theophylline, given intravenously, is shown in Fig 36-5. According to Eq 2, if the data of Fig 36-5 are plotted semilogarithmically, as in Fig 36-6, a straight line should result. Several derived data can be obtained from such a plot. Extrapolation to zero time (ie, the y intercept) gives C_p^0, the theoretical plasma concentration at time zero. It is a theoretical concentration, because neither injection nor distribution actually is instantaneous. Nevertheless, C_p^0 is a very practical figure. For example, from it may be derived the volume of distribution, V_d, simply by dividing the dose, D, by C_p^0 (see page 727). In the figure, C_p^0 = 0.0115 mg/mL, so that V_d is 43.5 L, or about 89% of the volume of total body water in a 70-kg adult. The plasma half-time, $t_{1/2}$, can be determined directly from the graph or from the elimination rate constant, k_{el}, by means of Eq 3. (Conversely, k_{el} could be derived from $t_{1/2}$, determined visually from a graph.) When determining k_{el} from the slope, it must be kept in mind that the log of the concentration must be used rather than the antilog that is

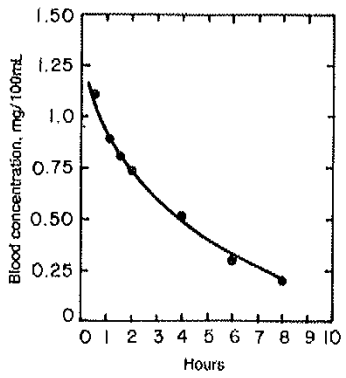

Fig 36-5. Elimination curve of average blood levels of theophylline in 11 human subjects after intravenous administration of 0.5 g aminophylline per 70 kg to each (courtesy, data, Truitt, *et al* [3]).

* Δ' is not to be confused with water-lipid distribution coefficients.

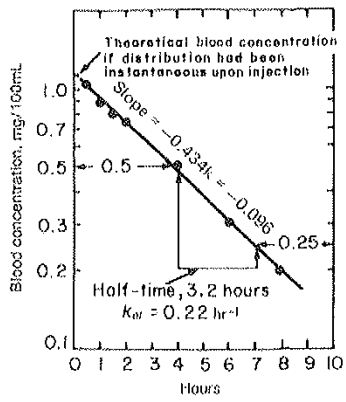

Fig 36-6. Semilog plot of the elimination curve in Fig 36-5. Note the log scale of the ordinate.

plotted on the log-scaled ordinate in the figure. In natural logarithms, the slope $(\ln C_{p1} - \ln C_{p2})/(t_2 - t_1)$ is equal to k_{el}; in decilogarithms, the slope $(\log C_{p1} - \log C_{p2})/(t_2 - t_1)$ is equal to $0.434k_{el}$. From the figure, k_{el} is found to be 0.22 hr^{-1}. However, this is an *instantaneous* rate and is not the same as the fraction that disappears over a finite interval, eg, 1 hr. Nevertheless, it is sometimes convenient to use k_{el} for calculation of the amount of drug lost per unit time, eg, for the calculation of maintenance doses during chronic drug therapy. If the time interval under consideration is very short (at least $\frac{1}{7}t$) as compared to the half-life of the drug, k_{el} may be considered to be an indication of the percentage of the drug lost during the time interval. For example, if the half-life of a drug is 6.93 hr, k_{el} would equal 0.1 hr^{-1}, and approximately 10% of the drug would be lost in 1 hr. Thus, if 100 mg of drug were present at the beginning of the hour, 10 mg would be lost by the end of the hour. (The exact amount of drug lost is determined by use of Eq 2 and is found to be 9.51 mg in 1 hr, a difference of about 5% from the approximated value.) If such an approximation was used in the example given in Fig 36-6 (1 hr is a little less than $\frac{1}{3}$ of the half-life) and the amount of drug present is 100 mg, the figures comparable to the illustration above would be 22 versus 19.7 mg, respectively, almost a 12% difference.

Within the group of 11 subjects in the above study, there were considerable differences in k_{el} or $t_{1/2}$ among the members. One cannot overemphasize the caveat not to take too literally the average half-life data found in various tables or other literature but rather to assume a probability that the half-life in a given patient may depart considerably from that average value. The half-lives of some drugs vary over a wide range even in normal individuals. The half-life of amitriptyline, a drug with a complex metabolic and excretory elimination, varies nearly tenfold; even the half-life of penicillin, a drug with a simple excretory elimination, varies twofold. In persons with hepatic or renal failure, the published mean half-life data may not even be in a range applicable to such persons.

The half-life also may vary widely from species to species; for example, in man, the half-life of sulfaethidole is about 8 hr, whereas in cattle it is less than 2 hr. Half-lives also vary considerably even among congeneric drugs, as may be seen with the sulfonamides shown in Table I.

The biological half-life must not be confused with the time for the response to decline by 50%, since dose, the requirement for a threshold concentration, latency of response and other factors may cause a nonparallelism between blood concentration and intensity of response. In fact, because the relationship between effect and plasma concentration is usually logarithmic, effect tends to decline in a linear, not loglinear, fashion.

Table I—The Approximate Biologic Half-Life in Man of Several Sulfonamides[4]

Drug	$t_{1/2}$ (hr)
Sulfamethylthiadiazole	2
Sulfaethidole	8
Sulfisoxazole	8
Sulfamethoxypyridazine	34

In Fig 36-2, the rate constant for elimination is designated k_{el}, without reference to the mode or route of elimination. However, k_{el} may be a compound constant equal to the sum of the rate constants that define the various simultaneous (ie, parallel) contributory processes, such as biotransformation, renal excretion, biliary secretion, etc. Thus, the compound or overall constant is $K = k_1 + k_2 + k_3 \ldots k_n$, where k_1, $k_2 \ldots k_n$ are the rate constants of the separate contributory processes. Consider the case in which a drug simultaneously is biotransformed and excreted unchanged in the urine. The initial concentration, C_p^0, therefore will be diminished by both $C_p^0 e^{-k_m t}$ and $C_p^0 e^{-k_u t}$, where m designates metabolism and u renal excretion. (In some notations, k_u is designated k_r, k_{10}, k_3 or k_e.) Therefore, Eq 2 adapted for the two processes becomes

$$\log C_p = \log C_p^0 - 0.434k_m t - 0.434k_u t$$
$$= \log C_p^0 - 0.434(k_m + k_u)t \qquad \text{[no units]} \quad (9)$$

Thus, $k_m + k_u$ combine to make a single constant, which is the overall elimination rate constant. In order to identify it as a compound, or overall, constant, it is sometimes designated as K, rather than k_{el}.

Clearance and Routes of Elimination—The half-life of a drug is a useful pharmacokinetic parameter. Since half-life is expressed in units of time, it is an easily understood, concise indication of the rate of disappearance or accumulation of a drug. Further, it is used to estimate the time necessary to attain a new steady state whenever a steady state is altered by a change in the factors determining dose regimen, namely, drug dose, bioavailability, the dose interval, rate of elimination and volume of distribution (see page 740). However, the elimination half-life of a drug is a complex function of drug distribution, biotransformation and elimination. A more direct expression of the rate of drug elimination is drug clearance.

Clearance is the rate of removal of a drug or other substance from the body, expressed as the *in vivo* volume equivalent of the substance being removed per unit time. In order to illustrate the concept, assume that drug D is being eliminated from the body at a rate of 0.1% per minute. The absolute amount of drug that was eliminated would therefore be equal to 0.1% D_B per minute. Since D_B is distributed as though it were in a volume V_d (volume of distribution, page 740), one can calculate the fictive volume equivalent of the amount of drug lost per minute, which in this instance would be 0.1% V_d/min. Since the relative rate of loss, 0.1%/min or 0.001/min is, in fact, k_{el}, it may be seen that

$$Cl_t = k_{el} \times V_d \qquad \text{[vol/unit time]} \quad (10)$$

where Cl_t is total body clearance. It may be expressed in units of mL/min, L/hr or mL/kg/min; the reader must be alert to the units in which given clearance data are expressed. It must be emphasized that clearance is a hypothetical or fictive quantity, since the body rarely clears a drug completely from a specific volume of body fluid. Only when elimination is flow-limited is the blood that passes through the eliminating organs(s) totally cleared, so that the effluent blood is essentially devoid of drug; in such an in-

stance the clearance approximates the rate of blood flow. If the concentration in the effluent blood were to be only 0.5 of the affluent blood, the clearance would be said to be 0.5 that of the blood flow.

Although clearance is the dV/dt equivalent of dD_B/dt, or the volume equivalent of the drug lost per unit time, the hypothetical volume cannot be regarded as also having been eliminated. Just as the depleted effluent blood from the eliminating organ is returned to the systemic circulation to mix with all the blood and as drug is redistributed and re-equilibrated among the vascular and extravascular components of V_d, the fictive volume that is "cleared" remains a part of V_d, so that the only change that is effected is one in concentration, of which C_p is the index. Since V_d and k_{el} are both constant, it follows that Cl_t is also constant.

The concept of clearance can be applied to the whole body or to specific organs. The former application is a convenient way to indicate overall drug elimination; the latter application is used to indicate the contribution of a specific organ to drug disappearance.

Total Systemic (Whole Body) Clearance—Total body clearance is the sum of all the separate clearances that contribute to drug elimination, ie, $Cl_{tot} = Cl_{metab} + Cl_{renal}$, etc. It is essential that k_{el} be expressed in the same time units as are used in clearance (usually min). In Eq 10, dividing by 60 converts k_{el} in hr^{-1} to min^{-1}, so that clearance can be expressed in mL/min. Whole-body clearance in a one-compartment system is also equal to dose divided by the area under the curve:

$$Cl_{tot} = D/AUC_0 \qquad [mL \cdot min^{-1}] \qquad (11)$$

where AUC_0 is the area under the curve (AUC), discussed on page 736. The determination of Cl_{tot} in the two-compartment system is discussed on page 739.

Renal Excretion and Clearance—The principles of renal excretion and clearance have been used for approximately 50 years as tools for studying renal physiology and pathology and hence were adapted early to pharmacokinetics. Consequently, renal clearance of drugs is a classic illustration of the general subject of clearance. As discussed in Chapter 35, all drugs are filtered in the glomerulus and some also are secreted into the urine by renal tubular cells; there is also resorption of drugs from the tubular luminal fluid back into the blood as the fluid passes along the tubule. Glomerular filtration is the passage through the glomerular vascular endothelium of the plasma fluid and all solutes therein small enough to pass through the pores; that is, it is the filtration of water and all micromolecular solutes. Thus, it is independent of the presence of drug and is a function of the filtration pressure (which relates to blood pressure) and the mean transit time across the glomerular capillaries. The rate of filtration is known as the *glomerular filtration rate, GFR*, and it has the units of vol/min (usually mL/min). In turn, the transit time is determined by the rate of flow of blood through the glomeruli; this rate of blood flow is known as the *renal plasma flow, RPF*. Since only a fraction of the plasma is filtered during passage through the glomerulus, it is useful to designate this fraction as the filtration fraction, *FF*, where $FF = GFR/RPF$. The average renal *plasma* (not blood) flow in the adult human male is approximately 600–700 mL/min, and the *GFR* is approximately 100–125 mL/min (of which 99% of the water is resorbed and returned to the blood); thus, the filtration fraction is approximately 0.2.

Under basal conditions, the *GFR* is roughly constant in time. Therefore, the only major variable that determines the rate of filtration of free drug is the concentration of drug in the plasma. Thus,

$$F = C_{pf} \cdot GFR \qquad [\text{units: } mL \cdot min^{-1}] \qquad (12)$$

where F is the filtration rate of the drug, usually in units of mg/min, and C_{pf} is the amount of *free* drug in the plasma. If the drug is unbound, $C_{pf} = C_p$. If the drug is bound to plasma protein, then

$$F = [C_p(1 - p)] \cdot GFR \qquad [mL \cdot min^{-1}] \qquad (13)$$

where p is the fraction bound to plasma protein.

The *GFR* may be determined by the steady-state rate of excretion of any nonbound chemical substance that is not secreted subsequently and/or resorbed by the renal tubules, so that the amount of substance which appears in the urine is all of that which was filtered and no more. Two such substances are *creatinine* and *inulin*. With creatinine, the endogenous plasma levels are nearly constant, and thus creatinine lends itself readily to the determination of *GFR*. Either inulin or creatinine may be given by constant intravenous infusion; usually, creatinine is used. However, it is not customary to express the *GFR* of creatinine or of drugs as F, in terms of mg/min, but rather in terms of *clearance*. As discussed above, clearance is a hypothetical volume of plasma which, if completely cleared of its content of drug in unit time, would be equivalent to the amount of drug that disappears in unit time. In the instance of filtration, it is easy to visualize clearance as that volume filtered/min, since the filtered volume actually is separated physically from the blood. Thus, the *creatinine clearance*, or *GFR*, is equal to the total amount of creatinine found in the urine (equal to urine concentration times urine volume) divided by the plasma concentration.

The general concept of clearance can be applied to the kidney according to the equation

$$Cl_{ren} = \frac{\bar{C}_u V}{\bar{C}_p t} \qquad [mL \cdot min^{-1}] \qquad (14)$$

where Cl_{ren} is renal clearance, $\bar{C}_u$ is concentration in mg/mL of drug in urine collected during time t, V is urine volume in mL generated in time t (min) and $\bar{C}_p$ is the mean concentration (during the collection interval, t) of drug in the plasma in mg/mL; the units are thus mL/min. Urine is collected from the bladder by catheter or by voiding. At the beginning of the collection interval (time from last voiding) both $\bar{C}_p$ and $\bar{C}_u$ are higher than at the end. Consequently, $\bar{C}_p$ must be calculated; $\bar{C}_u$ is automatically the mean of the instantaneous collecting duct concentrations. Equation 14 is valid whether the drug is "cleared" by filtration or by tubular secretion and whether or not tubular resorption occurs. If the drug is protein-bound, the formula becomes

$$Cl_{ren(corr)} = \frac{\bar{C}_u V}{\bar{C}_p t(1 - p)} \qquad [mL/min] \qquad (15)$$

where $Cl_{ren(corr)}$ is the corrected renal clearance.

The ratio between Cl_{ren} and Cl_{creat}, Cl_{ren}/Cl_{creat} (or Cl_{ren}/Cl_{inulin}), is known as the *clearance ratio*. If the drug is protein-bound and the *corrected clearance* is used, the ratio $Cl_{ren(corr)}/Cl_{creat}$ is known as the *excretion ratio*.

If an unbound drug is filtered only and not resorbed, the excretion ratio will be 1 and the clearance about 125 mL/min; if the drug subsequently is resorbed, the excretion ratio will be less than 1 and the clearance will lie between 125 and 1 mL/min, the values depending upon the degree of resorption. A clearance of 1 mL/min suggests distribution and elimination like those of water. If there is tubular secretion (plus obligatory filtration), the excretion ratio may exceed 1, and the clearance could be as high as 600–700 mL/min, depending upon the extent of tubular secretion and resorption. *Para*-aminohippuric acid (PAHA) is not bound to plasma protein, is not tubularly resorbed and is secreted so fast by the renal tubules that the plasma passing through the kidney is 90% cleared of PAHA. Thus Cl_{PAHA} is

equal to 0.90 *RPF*. This is called the *effective renal plasma flow, ERPF*. The excretion ratio of PAHA is about 5 to 6.

Eq 14 can be rearranged so that

$$\frac{\bar{C}_u}{t} = \frac{\bar{C}_p Cl_{ren}}{v} \qquad [\text{wt} \cdot \text{vol}^{-1} \cdot \text{min}^{-1}] \qquad (16)$$

Thus, it may be seen that the concentration of drug in newly formed urine is directly proportional to the plasma concentration. Since the plasma concentration falls exponentially during the collection interval, t, it follows that the instantaneous urine concentration in the collecting ducts, likewise, must fall exponentially and hence the rate of fall can be expressed by a first-order rate constant, k_u. This constant relates to renal clearance as follows:

$$k_u = \frac{Cl_{ren}}{V_d} \qquad [\text{min}^{-1}] \qquad (17)$$

The excretory rate constant may be simple, as with a drug like creatinine, or compound, as with a drug that is secreted tubularly and/or resorbed.

The overall renal elimination constant, k_r, is defined by

$$k_r = k_g + k_{ts} - k_{tr} \qquad [\text{min}^{-1}] \qquad (18)$$

where k_g is the constant for glomerular filtration, k_{ts} for tubular secretion and k_{tr} for tubular resorption. Although k_r might be thought to be the same as k_u on page 729, in practice it is not, because clearance data are obtained from time-averaged concentrations and cannot provide instantaneous rates. However, creatinine-derived k_r is close to the instantaneous k_u at the midpoint of the collection period.

By combining Eqs 3 and 17 and assuming that there is no other route of elimination,

$$t_{1/2} = 0.693 \frac{V_d}{Cl_{ren}} \qquad [\text{time}] \qquad (19)$$

The units of time must be the same for both $t_{1/2}$ and Cl_{ren}. The equation enables the calculation of some thought-provoking information about the biological half-lives of nonmetabolized drugs of different excretion profiles and volumes of distribution. Approximate hypothetical half-lives of drugs of different volumes of distribution and renal clearance are shown in Table II. The drugs are assumed to be eliminated only by renal excretion. A volume of distribution of 50 L is that of total body water, 15 L is that of extracellular water and 50,000 L is that of a drug strongly bound in the tissues. Because of biotransformations, few drugs have half-lives longer than 1 yr. However, a few radioopaque iodine-containing diagnostic agents are so tightly bound that their half-lives exceed 1 yr. At the other extreme, a half-life of 15 min by renal elimination is uncommon, because few drugs that are totally cleared have volumes of distribution as small as that of extracellular water. However, the half-life of penicillin G is about 30 min.

Although data from collected urine cannot provide instantaneous rates, it does allow the calculation of the plasma half-life. The instantaneous excretion rate, dD_u/dt (where D_u is the amount of drug in urine), is directly proportional to the body burden, D_B, such that

$$dD_u/dt = k_u D_B \qquad [\text{wt} \cdot \text{min}^{-1}] \qquad (20)$$

But, D_B is falling exponentially with a rate constant k, so that $D_B = D_B^0 e^{-kt}$; therefore, $dA/dt = k_u D_B^0 e^{-kt}$. It follows that the slope of a plot of the log of the excretion rate versus time will have a slope of $-0.434k$, analogous to Eq 2 (adapted to total content rather than concentration). The y intercept of such a plot is $\log k_{el} = D_B^0$, where D_B^0 is the amount of drug in the body at zero time. However, data on excretion rates require renal catheterization and are subject to considerable error. An alternative, usually more accurate, method of estimating k from urine concentration is to employ the cumulative amount excreted. In this method,

$$D_u = \frac{D_B k_u}{k}(1 - e^{-kt}) \qquad [\text{wt}] \qquad (21)$$

Since k_u/k expresses the proportion of D_B being transferred to the urine, $D_B^0 k_u/k$ represents the total amount of drug excreted, or D_u^∞, where ∞ designates infinite time. Eq 21 in log form, with the above substitution and transposition, becomes

$$\log (D_u^\infty - D_u) = \log D_B^0 \frac{k_u}{k} - 0.434kt$$
$$= \log D_u^\infty - 0.434kt \qquad [\text{no units}] \qquad (22)$$

The slope of the plot against time is also $-0.434k$ and $(D^\infty - D_u)$ is the amount of drug that remains in the body. The equation applies if the drug is administered intravascularly. This is known as the sigma minus method (sigma for the integral D_u^∞ and minus for the $-D_u$). Urine needs to be collected for only 3 or 4 half-lives in order for the semilog plot to yield a reliable slope and $t_{1/2}$. The method is useful especially when plasma concentrations are low.

Hepatic Clearance—The concept of hepatic clearance is like that of renal clearance, and hepatic clearance is likewise a hypothetical volume of blood per min imagined to be totally cleared of drug during passage through the liver. Unlike renal clearance, the input is both portal venous and hepatic arterial blood and the output is both hepatic venous blood and bile, rather than arterial blood and urine, respectively. Portal venous blood and bile cannot be sampled readily, so that the concepts involved in hepatic clearance serve better to provide a model for understanding the role of the liver in pharmacokinetics than a clinical methodology for its direct measurement.

Although the mathematical treatment of hepatic clearance has been developed for steady-state conditions, rather than for exponentially falling drug concentrations in the inputs and outputs to the liver, the subject is appropriate at this place, in conjunction with other clearances.

The *hepatic clearance*, Cl_H, can be defined by the equation

$$Cl_H = HBF\left(\frac{C_{ap} - C_v}{C_{ap}}\right) = HBF \cdot E \qquad [\text{mL} \cdot \text{min}^{-1}] \qquad (23)$$

Table II—Hypothetical Half-Lives of Drugs of Differing Volumes of Distribution and Clearances

Drug No.	Distribution	V_d, L	Renal Disposition	Clearance, mL/min	Half-Life
1	Total body water	50	Filtered and resorbed with water	1	24 days
2	Total body water	50	Filtered, no resorption	125	4.67 hr
3	Total body water	50	Tubular secretion, total clearance	700	50 min
4	Extracellular water	15	Tubular secretion, total clearance	700	15 min
5	Strongly bound in tissues	50,000	Filtered and resorbed with water	1	66 yr
6	Strongly bound in tissues	50,000	Tubular secretion, total clearance	700	35 days

where HBF is the total hepatic blood flow, C_{ap} the hypothetical mean of mixed hepatic arterial and portal venous concentrations and C_v is the hepatic venous concentration. The ratio, $(C_{ap} = C_v)/C_{ap}$, is the *extraction ratio*, E. Unlike glomerular filtration, there is an upper limit to the absolute quantity of drug that can be cleared and hence to the extraction ratio. Extraction is flow-limited only so long as the biotransforming enzyme system is not approaching saturation. The maximal clearance in the presence of normal blood flow has been called the *total intrinsic clearance*, Cl_{intr}. The extraction ratio expressed in terms of Cl_{intr} is

$$E = \frac{Cl_{intr}}{HBF + Cl_{intr}} \qquad [\text{no units}] \tag{24}$$

which may be substituted into Eq 23, to yield

$$Cl_H = HBF\left(\frac{Cl_{intr}}{HBF + Cl_{intr}}\right) = HBF \cdot E \qquad [\text{mL} \cdot \text{min}^{-1}] \tag{25}$$

The intrinsic clearance becomes

$$Cl_{intr} = \frac{HBF \cdot E}{1 - E} \qquad [\text{mL} \cdot \text{min}^{-1}] \tag{26}$$

Cl_{intr} is thus somewhat analogous to V_{max}/K_m in enzyme kinetics.

Eqs 23 through 26 emphasize that hepatic clearance and extraction are functions both of hepatic blood flow and the capacity of hepatic enzymes to biotransform (or secrete into bile) the drug that is delivered. In order to appreciate the relative dependencies on Cl_{intr} and HBF, various assumed values may be substituted into the equations. What will be found is that the larger the Cl_{intr}, the more Cl_H tends to be flow-limited (ie, dependent upon the rate of delivery of blood), whereas when Cl_{intr} is small, Cl_H is metabolism-limited. At constant blood flow with a drug in which elimination is predominately hepatic, when intrinsic clearance and hence extraction ratios are small, a significant change in intrinsic clearance will be accompanied by a significant change in $t_{1/2}$; when intrinsic clearance is high, a significant change may be accompanied by a small, often insignificant, change in $t_{1/2}$ but a significant decrease in bioavailability. In the latter instance, $t_{1/2}$ is determined mostly by the fraction of the cardiac output that passes through the liver. Figures illustrating these features, an excellent discussion of hepatic clearance and various models of hepatic elimination are available,[b] as well as a treatment of the effect of binding of drug to plasma protein. Binding to plasma protein limits clearance when intrinsic clearance is low but not when it is high.

Although the determination of Cl_{intr} is too involved for routine investigative purposes, it may be estimated according to the equation

$$Cl_{intr} = \frac{\left(1 - \frac{D_{un}}{fD}\right)D}{AUC_0} \qquad [\text{mL} \cdot \text{min}^{-1}] \tag{27}$$

where D_{un} is the total quantity of drug excreted unchanged, f is the fraction absorbed, D is the dose administered and AUC_0 is the total area under the blood concentration-time curve after intravenous administration. The meaning of AUC will be discussed later (page 737).

Some drugs may be used to illustrate some of the points emphasized by the model. For example, at blood concentrations of ethanol above 0.02–0.04%, the hepatic alcohol dehydrogenase system is saturated, and hence hepatic blood flow will have little effect on Cl_H of ethanol above the concentration indicated. This implies that liver disease or injury will not much affect the rate that ethanol is cleared from the blood, a fact of some forensic importance. The hepatic biotransformations of pentobarbital and phenytoin are relatively slow, ie, Cl_{intr} are low; consequently, the induction of hepatic cytochrome P450 will increase Cl_H, almost in proportion to the degree of induction, and the $t_{1/2}$ will be shortened accordingly. The hepatic biotransformation of lidocaine is extremely rapid, ie, the Cl_{intr} is very high, so that Cl_H is limited by hepatic blood flow. This means that by the oral route, in which all of the absorbed drug obligatorily passes through the liver, only very small amounts will survive the pass through the liver into the systemic circulation. This nearly total clearance as the drug passes through the liver into the rest of the body is known as the *first-pass effect*. The clinical significance of the first-pass effect is discussed in Chapter 37. The flow-limitation in the hepatic metabolism of lidocaine also means that in congestive heart failure or shock, in which hepatic blood flow is diminished, the rate of biotransformation will decrease and $t_{1/2}$ will increase.

Biliary secretion contributes to hepatic clearance and hence is included in the above pharmacokinetic considerations. However, drugs that are excreted intact or in a form from which the drug can be sequestered in the intestines and subsequently resorbed (enterohepatic recirculation) may have complex pharmacokinetics if the rate of biliary secretion is an appreciable fraction of the hepatic clearance and if the enterohepatic reservoir is large.

Other Routes and Clearances—The kidney and liver are usually the major organs in the elimination of drugs, and all other routes combined often contribute negligibly. However, with the volatile anesthetics, pulmonary clearance is the major route, and pulmonary clearance becomes dominant; pulmonary clearance of gases is flow-limited. With some drugs, mammary secretion is appreciable, and the presence of drug in milk may present hazards to nursing children; however, pharmacokinetics in the mother usually is not affected by lactation. Salivary secretion is too small to affect systemic pharmacokinetics, but the concentration of drug in saliva usually parallels that in plasma, so that, with some drugs, it is possible to follow systemic pharmacokinetics by sampling saliva.

Absorption Plus Elimination—The kinetics of absorption and disposition must now be put together to define the time-related curve which describes the plasma concentration of a drug administered *extra*vascularly. The curve is determined by the algebraic sum of all processes involved in absorption, distribution and elimination. Since disposition (distribution plus elimination) begins as soon as the drug enters the blood stream, the plasma concentration reflects all these processes from the outset.

The time course of the plasma concentration of a drug in a one-compartment body can be obtained by combining algebraically Eqs 1 and 5, with appropriate rate constants, and substituting fD/V_d for C_p^∞. When the equations for absorption and elimination are thus combined

$$C_p = \frac{fDk_a}{V_d(k_a + k_{el})}(e^{-k_{el}t} - e^{-k_a t}) \qquad [\text{wt} \cdot \text{vol}^{-1}] \tag{28}$$

where f is the fraction absorbed, D is the dose, etc.

This equation simplifies to

$$C_p = C_p^0 e^{-k_{el}t} - C_p^0 e^{-k_a t} \qquad [\text{wt} \cdot \text{vol}^{-1}] \tag{29}$$

where C_p^0 and the C_p^∞ of Eq 5 are the same, since they both represent all of dose, D, distributed in V_d. If there is a lag, the t-factor in the exponents of e should be $t - t_1$, where t_1 is the lag time. Figure 36-7 shows a plot of the plasma concentration for each of absorption and elimination separately and when the two are combined.

In Fig 36-7 the parameters of absorption and elimination were assumed, in order to construct the figure. In practice, drug concentration-time data are obtained empirically, and the parameters are obtained from a semilog plot of the data,

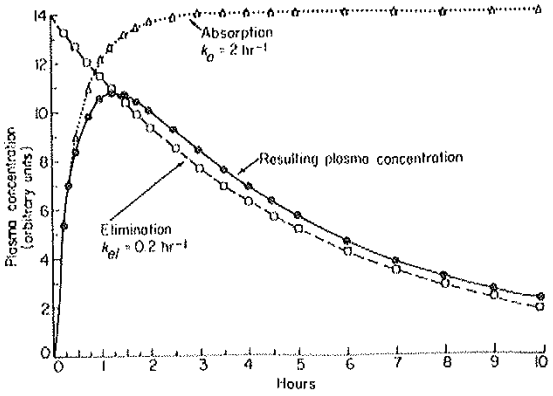

Fig 36-7. Time course of the plasma concentration of a hypothetical drug with simple first-order absorption and elimination kinetics. The rate constants are shown in the figure. The half-time for elimination is 3.47 hr.

as in Fig 36-8. The rising phase of the plot is not log-linear, since that which is added by absorption is diminished by elimination. Only after absorption is complete does the plot become log-linear, since now there is no opposing process at work against the mono-exponential decline in concentration. The time at which absorption essentially is complete is called the *absorption time* and is detected as that time at which the plot becomes log-linear. However, prior to the absorption time, the concentration at the site of deposition becomes equal to that in plasma. This is called the *equilibrium time*. It is also the *peak-time* for plasma concentration. Because of the interplay of physicochemical and active transport factors that affect the distribution of a drug, true chemical equilibrium is not reached necessarily at the pharmacokinetic equilibrium point. The log-linear line described by the elimination phase, when back-extrapolated to the y-axis, yields a theoretical C_p^0, just as with intravascular injection, and $V_{d(extrap)}$ can be calculated accordingly. Furthermore, the slope of the log-linear elimination segment of the semilog plot is equal to $-0.434k_{el}$, as with intravascular injection. The absorption rate constant, k_a, also can be obtained from the plot, if the empirical curve is subtracted from the back-extrapolated elimination line. This is done by subtracting the real values for C_p (C_1, C_2, etc) at various times during the absorption phase from the extrapolated values for C_p, designated C', on the back-extrapolated elimination line. It must be remembered that the antilog and not the log of C must be used if *log C* is plotted in Cartesian coordinates. This method of dissecting a compound function into its separate components is known as the *method of residuals*, or *back-feathering*. The back-feathered *absorption* line is the dashed line; its slope is negative, as though it were being seen from the site of administration.

The *peak concentration*, *time of peak concentration* and *duration of action* are affected by various factors, some of which are discussed below.

Peak Concentration—That the peak concentration should vary with the dose is self-evident; according to Eq 28, it is directly proportional to the dose (assuming that absorption and elimination are first-order processes). Figure 36-9 shows how peak concentration varies directly with dose. Note that the time of peak concentration is the same for all doses; this independence of peak time from dose is approximately true in all multicompartment systems. Departures from the generalization occur especially when the rate of absorption or elimination is different at high from those at low concentration; ie, when it is dose-dependent (see page 744).

Time of Peak Concentration—The time of peak concentration must not be confused with the time of peak effect. Effect often lags behind plasma concentration, sometimes because the tissue concentration at the point of action has not yet reached its peak and sometimes because a response may have a considerable latency. The latency of effect of reserpine or phenytoin (in its anticonvulsant effect) is measured in hours to days. Occasionally, the time of peak effect may precede the time of peak concentration because of a reflex or other compensatory process which limits effect before the concentration becomes maximal. This is often true with oral administration of ethanol or ephedrine. Both the peak concentration and time of peak concentration are considerably affected by the rate constants for absorption and elimination. In Fig 36-10, the effect of differences in absorption rate is shown indicating that the higher the absorption rate, the higher the peak concentration and the earlier the time of peak concentration. Figure 36-11 shows the effect of differences in rate of elimination depicting that the higher the elimination rate, the lower the peak concentration but the earlier the time of peak concentration. The two effects of absorption rate and elimination rate can be

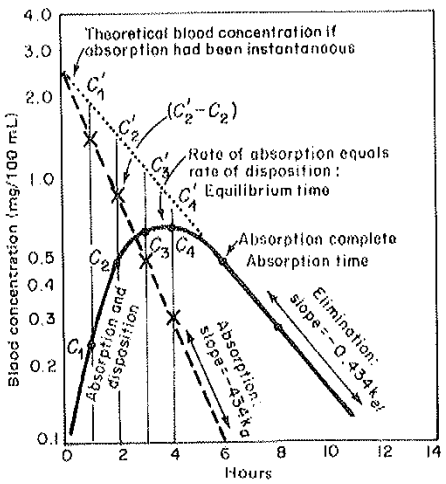

Fig 36-8. Kinetics of absorption and disposition of theophylline in the human subject after oral administration of 0.5 g of aminophylline per 70 kg. Blood concentration is plotted on a log scale (courtesy, data, Truitt, *et al*[3]).

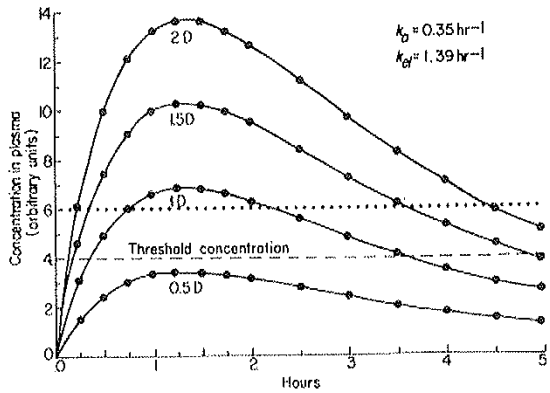

Fig 36-9. The effect of the size of the dose of a drug on the peak concentration, time of peak concentration and duration of action. The data are calculated from a one-compartment model.

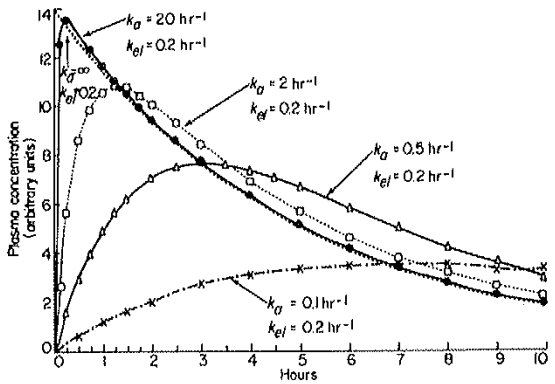

Fig 36-10. The effect of differences in the rate of absorption of drugs on the peak concentration, time of peak concentration and sojourn in the body. The rate of elimination is the same for all curves. The dotted line ($k_a = \infty$) is approximately what the concentration curve would be, had the drug been given intravenously. The data were calculated from a one-compartment model.

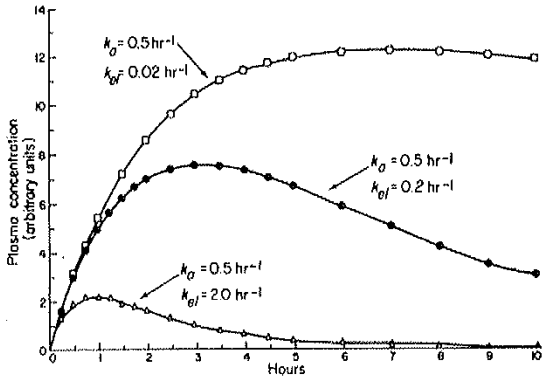

Fig 36-11. The effect of differences in the rate of elimination of drugs on the peak concentration, time of peak concentration and sojourn in the body. The rate of absorption is the same for all curves. The data were calculated from a one-compartment model.

treated as a single phenomenon if the ratio of k_a/k_{el} is considered rather than the separate rate constants (Fig 36-12).

The effects illustrated in Figs 36-10 to 36-12 have certain clinical implications:

1. *Differences in the rate of absorption are of more significance for slowly than for rapidly absorbed drugs.* In Fig 36-10, the peak blood levels are achieved when $k_a = 2\ hr^{-1}$ ($t_{1/2} = 0.35$ hr) is only 13% lower than when $k_a = 20\ hr^{-1}$ ($t_{1/2} = 0.035$ hr), but the difference in the level when $k_a = 0.1\ hr^{-1}$ ($t_{1/2} = 6.93$ hr) is 49% lower than that when $k_a = 0.5\ hr^{-1}$ ($t_{1/2} = 1.39$ hr), even though in the latter the rate difference was less than in the former comparison. It is thus apparent that differences in the release rates among different products of the same drug, or that differences in gastrointestinal motility, blood flow, etc, may be important, depending upon k_a/k_{el}. This point has a special relevance to sustained-release and depot formulations. With a number of drugs, especially among the anorectic drugs, the dose with a sustained-release form often is approximately the same as that of a rapid-release form; thus, the former has a long duration in the body but yields low blood levels when used in a single dose. Except with the initial dose, the differences are of lesser importance in a multiple-dose regimen. Small differences in the rate of absorption of rapidly absorbed drugs are usually of minor significance.

2. *When the rate of absorption is rapid relative to that of elimination, differences in the rate of elimination do not greatly affect the peak concentration consequent to a single dose* (compare top two curves of Fig 36-12). Thus, in such instances, the peak concentration is relatively insensitive to normal variations in the rate of elimination. Consequently, with such a drug, the size of the initial dose in a multiple-dose regimen often may not need to be diminished in the presence of renal or hepatic impairment; however, subsequent doses require adjustment.

3. *A change in the time of peak concentration or of peak effect is usually an indication of a change in one of or both k_a and k_{el}.*

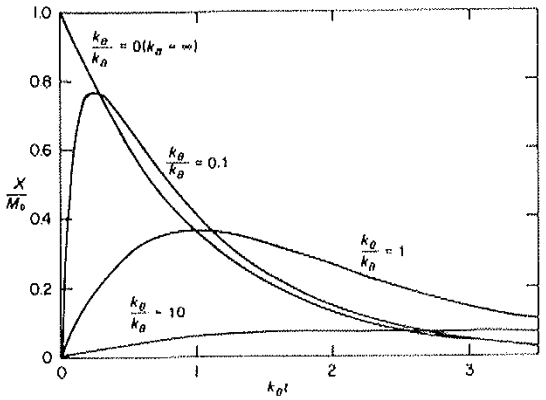

Fig 36-12. The effect of differences in the ratio, k_{el}/k_a (k_e/k_a in diagram), on the peak concentration, time of peak concentration and sojourn in the body. The ordinate, X/M_0, actually represent the fraction of a dose that is in the body, but they are directly proportional to concentration and thus serve to represent concentration. The abscissa can be converted to time by dividing by k_e, the elimination rate constant (courtesy, Goldstein, *et al* [6]).

Duration of Action—The duration of action of a drug is related to its pharmacokinetics in a rather complicated way. It is usually shorter than the sojourn of the drug in the body, because a threshold, or minimal effective, concentration must be reached before the effect occurs (see Fig 36-9), and the effect usually ceases when the plasma concentration falls below the threshold level. In a one-compartment system, duration of action tends to be proportional to log-dose. In a two-compartment system, it tends to be proportional to log-dose only when the site of action is in the central compartment and the effective concentrations (minimum to maximum) are entirely within the concentrations found during the elimination phase. In Fig 36-9, the duration of action is 3.25 hr with dose D, 4.6 hr with $1.5D$ and 5.4 hr with $2D$; were the threshold at 6 (dotted line), instead of 4 (dashed line), the respective durations would have been 1.5, 3.25 and 4.25 hr. Although the example in which the threshold is 6 provides that the duration of action would be disproportionately prolonged as the dose is increased, the contrary is seen when the threshold is 4. Consequently, *increasing the dosage is usually not a feasible way of increasing the duration of action* and toxic concentrations are often reached more predictably than duration is prolonged.

With a few drugs, there is no mathematically definable relationship between duration of action and persistence of the plasma concentration. With reserpine, for example, the effect outlasts the sojourn of the drug, because of the depletion of a slowly replaceable biological mediator.*

Multiple-Dose Administration—This refers to the administration of a succession of doses at intervals such that the drug does not leave the body completely in each interval between doses. The usual procedure in a multiple-dose regimen is to administer a drug repetitively with a constant dose interval, designated τ, with both dose and τ chosen so as to maintain the plasma concentration in the therapeutic

* Careful studies show that trace amounts of reserpine in the body outlast the effect and the duration of action may be related to these trace amounts. These residual amounts, however, are much smaller than are required to initiate the catecholamine-depleting action.

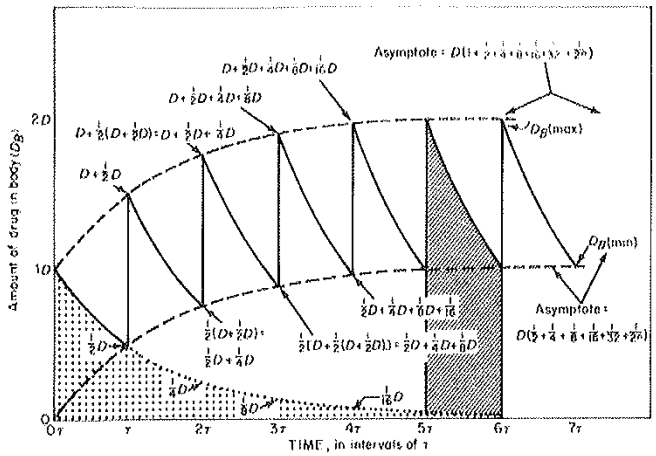

Fig 36-13. The accumulation of drug in the body during a regime of multiple dosing. Dose, D, is administered intravenously at intervals, τ, equal to the half-life, $t_{1/2}$. Thus, after each dose, the amount in the body, D_B, has decreased to half the previous peak amount at the time each dose is administered. When the cumulated amount in the body after injection reaches $2D$, the body content will fluctuate from $2D$ to $1D$ during each dose interval thereafter. Approximately 5 half-lives are required before this leveling off (plateau) of the body content occurs. The stippled area is the area under the elimination curve of a single injection, if no second dose had been given. The cross-hatched area is the area under the curve during a single-dose interval. The two areas are equal.

range. Some features of such repetitive dosing may be seen from the construction reproduced in Fig 36-13.

Accumulation and Plateau Principle—If the novice reader will make his own construction, it will aid greatly his understanding of the subject. In the construction, the amount of drug in the body, D_B, is plotted against time. Dose, D, is given repetitively, intravenously, at intervals such that $\tau = t_{1/2}$, in order to facilitate the construction. The first dose is given at $\tau = 0$; since it is given intravenously, the amount in the body rises to $D_B = 1$ essentially instantaneously. Immediately, D_B falls exponentially with the first-order kinetics of Eq 1, except that whole-body content, rather than C_p, is plotted. Since $\tau = t_{1/2}$, at τ, $D_B = {}^1/_2D$; when the next dose, D, is added, it brings the body content up to $D + {}^1/_2D$. During each dose interval, D_B falls exponentially to one-half the previous postinjection peak. As D_B rises after each administration, the rate (*not* the rate constant) of elimination rises proportionately, until eventually the amount eliminated during τ essentially equals the amount injected. The maximum and minimum values of D_B, $D_{B(max)}$ and $D_{B(min)}$, during τ, approach respective asymptotes, shown on the graph. As $t \rightarrow \infty$, $D_{B(max)} \rightarrow 2D$ and $D_{B(min)} \rightarrow D$. Thus, although D_B fluctuates between $D_{B(max)}$ and $D_{B(min)}$, once the asymptotes are approximated closely, D_B can be thought of as having reached a qualified *steady-state* condition, and the pharmacokinetics are sometimes called steady-state pharmacokinetics. Also, D_b is said to have reached a *plateau*. It is important to note that the rate at which the plateau is reached is at exactly the same rate at which drug is eliminated from the body after a single dose. Thus, the exponentially falling line for the elimination of D given at $\tau = 0$ (had no further doses been given) is the mirror image of the line connecting the sequential $D_{B(max)}$s. The principle that *when the rate of absorption is fast compared to the rate of elimination* ($k_a > 5k_{el}$) *the rate at which the multiple-dose steady state is approached is determined only by* k_{el}, and is known as the *plateau principle*. This is the fundamental feature of one-compartment multiple-dose kinetics. It obtains irrespective of the value of τ. However, the plateau concentrations do depend upon τ (see below).

In Fig 36-13, the drug was administered intravenously, so that no time-dependent absorption had to be considered. When absorption is involved, the $C_{p(max)}$ is not as high as with intravascular administration, but is blunted and occurs with a latency after administration that is determined by k_a/k_{el}, just as in single-dose administration. The appearance of the C_p-time curve with multiple-dose administration is shown in Fig 36-14. The value of C_p at any time during multiple-dose administration can be calculated according to Eq 30.

$$C_p = \frac{fk_a}{V_d(k_{el} - k_a)}\left[\left(D^*e^{-nk_{el}t} + D \cdot \frac{1 - e^{-nk_{el}\tau}}{1 - e^{-k_{el}\tau}}\right) - \left(D^*e^{-nk_{el}\tau} + D \cdot \frac{1 - e^{-nk_{el}\tau}}{1 - e^{-k_{el}\tau}}\right)\right] \quad [\text{wt} \cdot \text{vol}^{-1}] \quad (30)$$

where n is the nth dose, τ is the dose-interval, t is the time since the last dose, D is the maintenance dose, D^* is the initial or loading dose (see below) and f is the fraction absorbed (bioavailability factor). With this equation, C_p, rather than D_B, is calculated; however, it will be recalled that

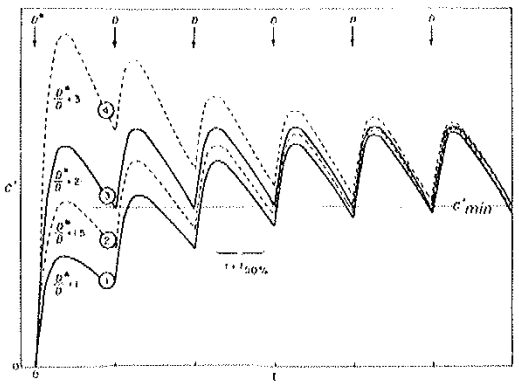

Fig 36-14. Time course of the plasma concentration of a drug administered according to a multiple-dose schedule. C' (ordinate); concentration; t (abscissa): time; D^*: initial dose; D: maintenance dose; τ: dose-interval (equal to $t_{1/2}$ in this illustration); C'_{min}: minimum concentration after each dose (same as $C_{p(min)}$ in text) (courtesy, Krüger-Thiemer[7]).

$C_p^0 = D/V_d$, and similarly, $C_p = D_B/V_d$, so that the equation easily is modified to calculate either C_p or D_B and the same principles apply in either form.

It is important to know how many half-lives must transpire before the plateau is approached closely enough to be considered complete for practical purposes. The value of $D_{B(min)}$ is approximately 93% complete at 4τ and 97% at 5τ; $D_{B(max)}$ is 97% at 4τ and 98.5% at 5τ. Thus, it may be stated that, for practical purposes, the plateau state is reached in approximately 5 half-lives, provided $k_a > 5k_{el}$. This is another form of the *plateau principle. The principle applies whenever the steady state conditions are perturbed;* that is, *5 half-times will be required to reach a new plateau,* whether the plasma concentration is rising or falling to a new plateau (see Fig 36-14).

Maximum and Minimum Concentrations—During multiple dosing, $C_{p(max)}$ and $C_{p(min)}$ are described by Eqs 31 and 32:

$$C_{p(max)n} = \frac{C_p^0\,(1 - e^{-nk_{el}\tau_a})}{1 - e^{-k_{el}\tau}} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (31)$$

$$C_{p(min)n} = \frac{C_p^0\,(1 - e^{-nk_{el}\tau})}{1 - e^{-k_{el}\tau}} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (32)$$

where n is the nth dose, C_p^0 is the concentration that would have occurred from instantaneous absorption and distribution (obtained by extrapolation of the elimination curve to zero time) and t_a is the absorption time. The term C_p^0 may be replaced by fD/V_d^{ss}. During the plateau state, $1 - e^{nk_{el}\tau}$ becomes $e^{-k_{el}\tau}$, and $C_{p(max)}$ and $C_{p(min)}$ are designated C_{max}^{ss} and C_{min}^{ss}, respectively. The equation is valid only when $k_a > 5k_{el}$. It can be seen that $C_{p(max)}$ is determined by both k_a and k_{el} (k_a shows itself only indirectly, in t_a) and $C_{p(min)}$ by k_{el}. The greatest difference between $C_{p(max)}$ and $C_{p(min)}$ occurs when the drug is given intravenously; when $\tau = t_{1/2}$, after intravenous injection, $C_{p(max)}/C_{p(min)}$ theoretically is equal to 2. With extravascular administration, the ratio is always less than that with intravenous administration, the ratio being determined by k_a/k_{el}. As k_a/k_{el} decreases, $C_{p(max)}/C_{p(min)}$ decreases.

Average Concentration and Body Content—The average concentration during the plateau state is described by Eq 33.

$$C_{p(ave)} = \frac{fD}{V_d k_{el}\tau} = \frac{1.44\,t_{1/2}fD}{V_d\tau} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (33)$$

The coefficient 1.44 is the reciprocal of 0.693 in Eq 3. The term $C_{p(ave)}$ is a time-averaged concentration and therefore is really a mean concentration. Since $C_p = D_B/V_d$, it follows that

$$D_{B(ave)} = \frac{fD}{k_{el}\tau} = \frac{1.44\,t_{1/2}fD}{\tau} \qquad [\text{wt}] \qquad (34)$$

It is self-evident that the plasma concentration, or amount of drug in the body, is directly proportional to the fraction of drug absorbed (f, bioavailability factor). The appearance of f in these equations and Eq 30, however, serves as a reminder that a change from one drug product to another with a different bioavailability, f', will be accompanied by changes in $C_{p(ave)}$ and $D_{B(ave)}$, as well as in the maxima and minima. The equations also reemphasize that a change in $t_{1/2}$ (or k_{el}) will affect $C_{p(ave)}$ and $D_{B(ave)}$, all other factors being held constant. Since k_{el} and f (and sometimes V_d in relation to weight) vary from patient to patient, the dosage of certain drugs always needs to be ascertained with laboratory assistance and acumen. The effects of changes in τ are discussed below.

Importance of Dose-Interval—The ratio $C_{p(max)}/C_{p(min)}$ depends on the dose-interval, τ. If the interval is increased and the dose is unchanged, $C_{p(max)}$, $C_{p(min)}$ and $C_{p(ave)}$ all decrease, but $C_{p(max)}/C_{p(min)}$ is increased. If τ is decreased, then $C_{p(max)}$, $C_{p(min)}$ and $C_{p(ave)}$ increase, but $C_{p(max)}/C_{p(min)}$ is decreased. This is shown in Fig 36-15. To avoid a change in $C_{p(ave)}$ consequent to a change in τ, the dose may be changed appropriately, in accordance with Eqs 32 and 33. Nevertheless, the wider fluctuations between $C_{p(max)}$ and $C_{p(min)}$, when τ is lengthened, cannot be avoided simply by adjusting the dose (see Fig 36-16, broken lines). If $C_{p(min)}$, rather than $C_{p(ave)}$, is held constant, the fluctuations become even larger (Fig 36-16, solid lines), and the hazard of the

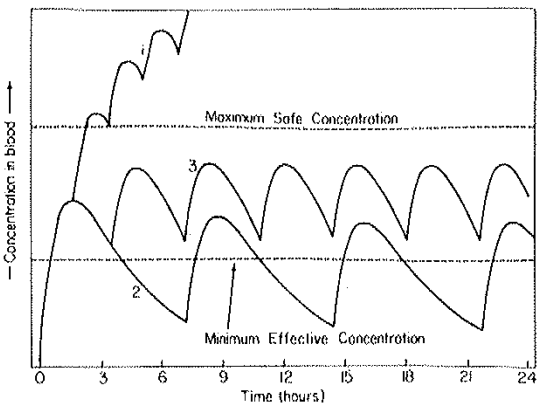

Fig 36-15. The effect of the dose interval on the time course of the plasma concentration of a drug administered in a multiple-dose regimen. $D^* = 4$, $D = 3$ and $k_a/k_{el} = 3$. The dose interval is 1.7 hr in Curve 1, 7.7 hr in Curve 2 and 3.8 hr in Curve 3 (courtesy, Notari[8]).

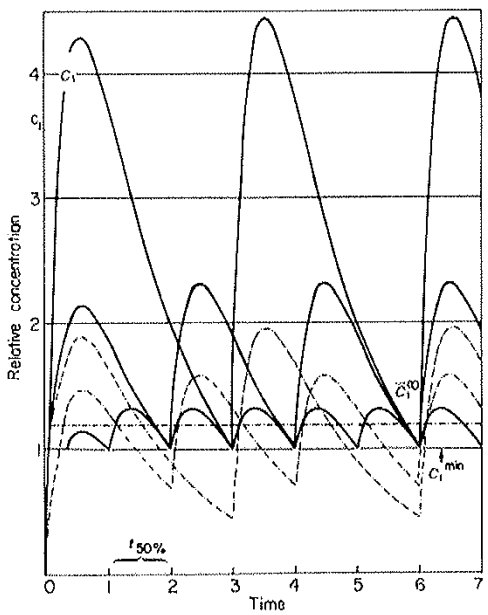

Fig 36-16. Fluctuations in the plasma concentration of a drug when the dose interval is changed but the dose is altered to maintain the same minimal (solid lines) or average (broken lines) concentration during maintenance. C_1^{min} is the minimal concentration (corresponding to $C_{p(min)}$ in the text) and $\bar{C}_1^{ss}$ is the average concentration during maintenance (corresponding to $C_{p(ave)}$ in the text). Time is in multiples of the half-life (courtesy, Krüger-Thiemer,[7] adapted).

concentration reaching the toxic range is increased. Conversely, *the greater the number of divided doses, the smaller the fluctuations in plasma concentration*. For drugs with a narrow therapeutic range, it is usually inadvisable to dose at intervals longer than $t_{1/2}$. With digitoxin, τ is much smaller than $t_{1/2}$, and the fluctuations in plasma concentration are consequently less than 10%. However, for drugs with a high therapeutic index and which do not require a steady plasma concentration for an adequate therapeutic action, dose intervals much larger than $t_{1/2}$ may be used conveniently. Penicillin G is such a drug; it is more convenient to give large doses at 4-hr intervals, or longer, than at 30- to 60-min intervals ($t_{1/2}$ = 30 to 60 min).

Cumulation Ratio and Persistence Factor—From the above, it is evident that the drug cumulated in the body during the repetitive administration approaches different amounts (asymptotes) in the plateau state according to the magnitude of τ in relation to $t_{1/2}$ (or k_{el}). The dose-interval must be a convenient interval that not only is easy for the patient or medical and paramedical personnel to keep track of but also one which does not subject the patient to an annoying or difficult number of doses per day. Furthermore, $t_{1/2}$ varies from patient to patient. Consequently, it is rare when $\tau = t_{1/2}$, although it is sometimes close enough that the difference is inconsequential. Therefore, it is important to be able to estimate the extent of cumulation with any dose interval in any patient. This can be done with information derived from a single dose, by means of the *accumulation factor*, r_a.

$$r_a = \frac{1}{1 - e^{-k_{el}\tau}} \qquad \text{[no units]} \tag{35}$$

The component factor, $e^{-k_{el}\tau}$, is the *persistence factor*, r, which is the fraction by which C_p or D_B falls during the dose interval. When the plateau, or steady state, is reached the cumulated plasma concentration or body content will be larger than that from the first dose by a factor known as the *cumulation ratio* (or *drug amount ratio*), R_c.

$$R_c = \frac{1}{k_{el}\tau} = \frac{1.44\, t_{1/2}}{\tau} = \frac{\bar{C}_t^{ss}}{\bar{C}_0^{\infty}} \left(\text{or} \frac{\bar{D}_{Bt}^{ss}}{\bar{D}_{B0}^{\infty}} \right) \qquad \text{[no units]} \tag{36}$$

where $\bar{C}_t^{ss}$ is the mean concentration during one dosage interval during the steady state and $\bar{C}_0^{\infty}$ is the mean concentration from $t = 0$ to $t = \infty$ after a single dose; $\bar{D}_{Bt}^{ss}$ and $\bar{D}_{B0}^{\infty}$ are the corresponding respective body contents. Since both $\bar{C}_0^{\infty}$ and $\bar{C}_t^{ss}$ can be estimated from the AUC, it is appropriate to discuss this further.

Area under Curve (AUC)—The area under the monoexponentially falling, single-dose plasma concentration-time curve is the integral of the differential form of Eq 1, from $t = 0$ to $t = \infty$:

$$AUC^{0\text{-}\infty} = \bar{C}^{0\text{-}\infty} = \int_0^{\infty} C\,dt$$

$$= \int_0^{\infty} C_p^0 e^{-k_{el}t}\,dt = \frac{C_p^0}{k_{el}} \qquad \text{[wt} \cdot \text{vol]}^{-1} \cdot \text{time]} \tag{37}$$

Although the units are concentration times time, the value is equal to the time-averaged concentration and hence is called the *average concentration* $\bar{C}_0^{\infty}$, although it is more appropriately a *log-mean* concentration. If the amount of drug in the body is used, instead of plasma concentration, the AUC is equal to the *time-averaged body content*. The average body content could, of course, be calculated from $\bar{C}_0^{\infty}$ by multiplying by V_d.

Even when two or more exponential processes act additively on the plasma concentration (or body content), as in absorption plus elimination, the $AUC^{0\text{-}\infty}$ equals $\bar{C}_p^{\infty}$ (or $\bar{D}_B^{\infty}$). The interested student may verify this by integrating any of Eqs 28–30. In the two-compartment system (see below), $AUC^{0\text{-}\infty}$ for a plasma concentration-time curve correctly equals $\bar{C}_p^{\infty}$; however, $\bar{D}_B^{\infty}$ cannot be calculated from $\bar{C}_p^{\infty}$, because the plasma concentration differs from the average body concentration.

Since $AUC^{0\text{-}\infty} = C_p^0/k_{el}$ in the one-compartment system, it is obvious that AUC does not provide any new information that otherwise cannot be obtained, as by back-extrapolation or regression analysis. Nevertheless, AUC frequently is used in lieu of C_p^0/k_{el}. For example, in the determination of the bioavailability factor, f, the $AUC^{0\text{-}\infty}$, after *extra*vascular administration ($AUC_{ev}^{0\text{-}\infty}$), divided by the AUC after *intra*vascular administration ($AUC_{iv}^{0\text{-}\infty}$) is equal to f.

The term $AUC^{0\text{-}\infty}$ is not the only AUC that may be used in pharmacokinetics. The AUC during different time intervals, under supposedly steady-state conditions, could be employed to detect time- or concentration-related changes in clearance (eg, see Eqs 11 and 27). During the plateau, or steady state, the AUC during one dose interval (AUC^{ss}) is of special interest. To evaluate $AUC^{0\text{-}\infty}$ requires many samples taken over a long period of time, which is an inconvenience to the subject or patient. The value of AUC^{ss} can provide the same derived information with fewer samples and less time. This is because $AUC^{ss} = AUC^{0\text{-}\infty}$. Thus, in Fig 36-13, the stippled area, which is $AUC^{0\text{-}\infty}$, would be equal to the cross-hatched area, AUC^{ss}, except for the negligible stippled area that remains after 5τ. At $t = \infty$, the two areas would be essentially identical. In this comparison of AUCs, the identical areas do not mean that $\bar{C}_p^{\infty}$ is identical to $\bar{C}_p^{ss}$, but it does enable AUC^{ss} to be used to calculate values of single-dose parameters and *vice versa*.

Constant Infusion and Sustained Release—A constant infusion or sustained release of a drug may be regarded as a series of minidoses given at infinitely short dose intervals. When infusion is intravascular, the plasma concentration will rise in logarithmic fashion with the same time course and cumulation factor as with multiple dosing, ie, with a rate constant of k_{el}. Thus, the plateau principle applies equally to constant infusion and multiple dosing. After discontinuation of infusion, the plasma concentration falls exponentially with a rate constant k_{el}, in accordance with Eq 1. These principles are illustrated in Fig 36-17.

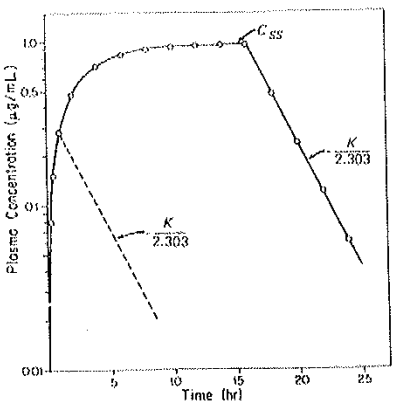

Fig 36-17. Semilogarithmic plot of plasma concentration during and after cessation of a constant intravenous infusion of a drug in a one-compartment system. Whether infusion is stopped prior to the attainment of a plateau or after, the plasma concentration will fall log-linearly with a slope of $-0.434k_{el}$. In the figure, K is k_{el} and $1/2.303 = 0.434$. C_{ss} is the steady-state concentration, C_p^{ss} (courtesy, Gibaldi and Perrier[9]).

The steady-state plasma concentration, C_p^{ss}, is equal to the infusion rate divided by the whole body clearance:

$$C_p^{ss} = \frac{R^0}{Cl_{tot}} = \frac{R^0}{V_d k_{el}} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (38)$$

where R^0 is the infusion rate. The term V_d must be expressed in the same volume units as R^0; Cl_{tot} and R^0 must be in the same time units as k_{el}.

With sustained-release dosage forms, in which the release is approximately constant for long periods of time, the pharmacokinetics are like those of constant infusion.

Loading and Maintenance—In Fig 36-13, $D_{B(max)} \rightarrow 2D$; consequently, had $2D$ been given for the first dose and D thereafter, the plateau condition would have been reached immediately. This illustrates the *principle of loading*. The same effect of loading is shown by curve 3 in Fig 36-14; in both these figures, $\tau = t_{1/2}$. The initial dose is called the *loading dose*, D^*, and each subsequent dose is called the *maintenance dose*, D. Since it takes about 5 half-lives to reach the plateau state, it is very important to use a loading dose with drugs that have long half-lives or in situations in which it is desirable that the optimal therapeutic concentration be reached rapidly.

The loading dose, D^*, should approximate the amount of drug in the body which will be contained during maintenance (ie, the plateau state). The most direct way to calculate D^* is with the equation

$$D^* = \frac{V_d \cdot C_{p(max)}^{ss}}{f} \qquad [\text{wt}] \qquad (39)$$

assuming that V_d^{ss} and $C_{p(max)}^{ss}$ are both known. A first dose so calculated achieves a $C_{p(max)}$ that is equal to that at the steady state only for *intra*vascular administration. After *extra*vascular administration $C_{p(max)}$ is less than that after *intra*vascular administration and hence the loading dose is proportionately smaller. With some intravascularly administered drugs, the loading dose is calculated deliberately to be less than that calculated by Eq 39. Among reasons for choosing a lower dose than that calculated by Eq 39 is that the effects of the first of a series of doses often elicits greater responses than do subsequent doses, because reflex, hormonal and other counter-regulatory effects have not had enough time to come into full play. This practice applies even to some *extra*vascularly administered drugs, such as prazosin. Consequently, C_p^{ss}, or even $C_{p(min)}^{ss}$, may be used *in lieu* of $C_{p(max)}^{ss}$. It must be remembered that with such underloading the steady state is not achieved fully with the loading dose. With drugs which have a very low and erratic therapeutic index and potentially fatal toxicity, the loading dose may be divided into smaller doses, to be given at various intervals before the first maintenance dose; this permits monitoring of both C_p and clinical effects during loading and allows an assessment of whether the intended maintenance dose is correct. Fractional loading also is used when a drug with a low therapeutic index has a significant distribution phase, such that toxic plasma concentrations occur before distribution equilibrium occurs. With some drugs, an appropriate V_d^{ss} is not known, thus making Eq 39 inapplicable. With such drugs, D^* can be calculated from traditional, empirical maintenance doses by means of the equation

$$D^* = \frac{D}{(1 - e^{-k_a \tau})(1 - e^{-k_{el} \tau})} \qquad [\text{wt}] \qquad (40)$$

The equation correctly applies only when $k_a > 3k_{el}$. Also, D^* can be calculated according to

$$D^* = fD/R_c = 1.44 f D t_{1/2}/\tau \qquad [\text{wt}] \qquad (41)$$

where R_c is the cumulation ratio (see Eq 36).

The time course of the plasma concentration after different loading doses is shown in Fig 36-14. When $D^* = 2D$, the plateau maintenance concentration is approximated closely when $\tau = t_{1/2}$ but is smaller than 2 when $\tau < t_{1/2}$ and greater when $\tau > t_{1/2}$.

In Fig 36-14, it should be noted that if the loading dose is not optimal, either too low or too high, the plateau state is approached with the same time course as when no loading dose is given.

When a constant intravenous infusion is used, the principle of loading also applies, because the plateau principle applies; loading may be accomplished with one or more rapid intravenous doses, called boluses or slugs, or by an initial period of rapid infusion to bring the plasma concentration to the maintenance level. The loading dose can be calculated from Eq 39 or the infusion rate and half-time, as

$$D_0^* = \frac{R_0 t_{1/2}}{0.434 \log 2} \qquad [\text{wt}] \qquad (42)$$

Open Two-Compartment Model

The one-compartment model adequately describes the pharmacokinetics of many drugs. However, with an even larger number of drugs, after intravenous administration, the decline in plasma concentration is not monoexponential but rather manifests two or more monoexponential components which are discernible in the semilogarithmic plot of C_p versus time. The most common is a decline which manifests two components; the open two-compartment model most adequately describes such pharmacokinetics. Other models having more compartments or other complexities will be mentioned later briefly.

Description of the Model—In the open two-compartment model, the body is considered to comprise two compartments in dynamic equilibrium, as depicted in Fig 36-18. The compartment into which the drug is directly absorbed and from which the drug is eliminated is called compartment 1, or the *central compartment*. The blood is a part of this compartment, is the transporting and distributing medium and is the medium actually sampled for chemical and pharmacokinetic analysis; consequently, compartment 1 is some-

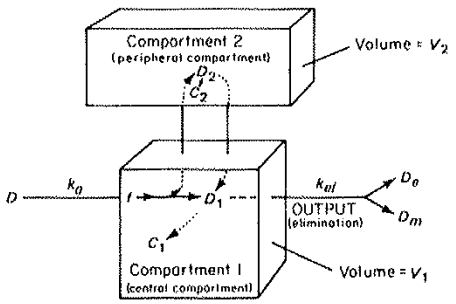

Fig 36-18. Diagram of open two-compartment pharmacokinetic model. An amount of drug, fD, is absorbed from the administered dose, D, with a first-order rate constant of k_a into compartment 1 of volume V_1. Some of the absorbed drug enters compartment 2 with a first-order rate constant of k_{12} and is returned into compartment 1 with a first-order rate constant of k_{21}. D_1 is the amount of drug in compartment 1 and D_2 in compartment 2; C_1 and C_2 are the respective concentrations in compartments 1 and 2 ($C_1 = C_p$). Drug is eliminated from compartment 1 with a first-order rate constant, k_{el}, which, however, is obscured by the lag in transfer of drug from compartment 2 to compartment 1. D_e is the amount excreted into urine, feces, expired air, sweat, milk, etc; D_m is the amount of drug metabolized. The relative volumes of V_1 and V_2 may vary greatly, V_1 sometimes being the larger and other times the smaller.

times misleadingly called the blood or plasma compartment, even though the erythrocytes or plasma proteins may sometimes behave kinetically as though they were part of compartment 2. In the simple two-compartment model, compartment 2 is closed and communicates with the environment only through the central compartment, being, as it were, peripheral to the events of absorption and elimination; consequently, it is called the *peripheral compartment*. Sometimes, it also is called the tissue compartment, which is misleading, since usually some tissues, or certain cell types within otherwise peripheral tissues, may be kinetically in compartment 1. It is important to reiterate that the compartments are fictive and are defined by the kinetic behavior of the drug within the body and not necessarily by identifiable anatomical entities. To avoid confusion and to enable a simple numerical designation of model components and distribution rate constants by number, the terms compartment 1 and compartment 2 will be used hereafter.

The movement of drug between compartments is defined by characteristic first-order rate constants. The subscript indicates the direction of movement; thus k_{12} (subscript one-two, not twelve) indicates movement from compartment 1 to compartment 2 and k_{21} the reverse direction. The constants k_a and k_{el} are entirely analogous to the like-designated respective absorption and elimination rate constants of the one-compartment model. However, k_{el} is not observed directly from the decline in plasma concentrations, since both the characteristic overall rate of the elimination processes and the rates of diffusion into, and recruitment from, compartment 2 combine to control the rate of decline in plasma concentration (see below). Once an infinitesimal amount of drug is absorbed, all processes occur simultaneously, ie, in parallel. Nevertheless, since the various processes have different time constants, one process will run its course to a practical end earlier than another, and events may be thought of as occurring sequentially, with overlap, in the order; absorption, distribution and elimination. So long as $k_a > (k_{12} + k_{21})/k_{21} > k_{el}$, the terminal phase will be a steady decline in concentration (see Fig 36-19), during which the distribution ratio, C_1/C_2, will be constant.

Absorption—Absorption does not differ from that in the open one-compartment model and does not require further description. However, the determination of absorption characteristics from the log plasma concentration-time curves is complicated by the distribution phase, and the method of residuals (page 733) entails the resolution of three, rather than two, components (see below).

Distribution and Elimination—After the intravascular administration of a drug which obeys two-compartment kinetics, the plasma concentration falls in a complex two-process fashion, but in an arithmetic plot the two components may not always be evident to the eye. When concentration-time data are plotted semilogarithmically, however, the separate processes of distribution and elimination are identified easily by the method of residuals (back-feathering, page 733 and Fig 36-8), if the rate of distribution exceeds significantly that of elimination. In Fig 36-19, such a resolution has been made for the drug pralidoxime. In the figure, it may be seen that after 2 hr the curve assumes a log-linear character. The assumption is made that the distribution phase essentially is complete and a pseudoequilibrium has been reached between the two compartments. Therefore, the late log-linear segment of the line, with the slope -0.434β, represents the elimination phase. If this line is subtracted from the nonlog-linear portion of curve, the distribution phase is the residual line. In order to do this, the log-linear segment is back-extrapolated. From this extrapolated line are obtained the antilogs to be subtracted from the temporally corresponding antilogs on the unresolved, original curve. The respective differences, or residuals,

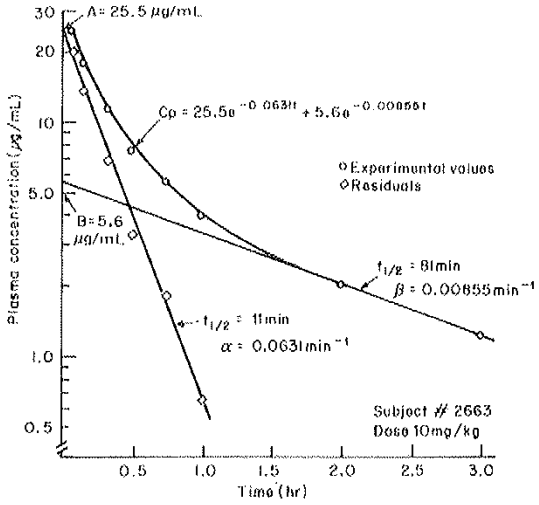

Fig 36-19. Resolution of the plasma concentration curve for pralidoxime into its distribution and elimination components after intravenous administration. Note that plasma concentration is plotted on a logarithmic scale. The time constant for the elimination phase is determined from the slope, -0.434β; it is a hybrid constant and β is not the same as k_{el} (see text). Likewise, the time constant for distribution, α, is obtained from the slope, -0.434α, of the distribution line; α is also a hybrid constant (courtesy, Gibaldi and Perrier[9]).

then are plotted semilogarithmically to reveal the log-linear line that represents distribution only. From the log-linear properties of the separate, but algebraically additive, lines representing the two processes of distribution and elimination, it may be inferred that the equation for the original compound curve was

$$C_1 = Ae^{-\alpha t} + Be^{-\beta t} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (43)$$

where C_1 is the concentration of drug in compartment 1 (the central compartment), α and β are first-order rate constants for the distribution and elimination phases, respectively and A and B are fictive plasma concentrations to be discussed on page 740. The constant β describes the late rate of disappearance of drug from compartment 1 but is not the same as k_{el} (see below). It is the rate constant from which the biological half-life is calculated in a two-compartment system ($t_{1/2} = 0.693/\beta$).

Hybrid and Prime Kinetic Parameters—In Fig 36-19, the slope of the late, slower elimination line is -0.434β, where β is a first-order time constant for elimination. However, β is determined not only by the rate capacities of the irreversible elimination processes but also by the rates at which drug is transferred out of and back into compartment 1. Therefore, β is a compound, or hybrid, rate constant. It is equal to the fraction of drug in the central compartment, sometimes designated as f^*, in the postdistributive (elimination) phase times the elimination constant, k_{el}, for the central compartment. Thus

$$\beta = f^* k_{el} \qquad [\text{time}^{-1}] \qquad (44)$$

Alpha, α, is a hybrid constant that combines k_{21}, k_{el} and β:

$$\alpha = \frac{k_{21} k_{el}}{\beta} \qquad [\text{time}^{-1}] \qquad (45)$$

Interestingly, the equation for α does not include k_{12}, although f^* does depend upon $(k_{12} + k_{21})/k_{21}$. The sum of α and β can be expressed entirely in terms of prime constants:

$$\alpha + \beta = k_{12} + k_{21} + k_{el} \qquad [\text{time}^{-1}] \tag{46}$$

However, these prime constants cannot be determined directly and must be derived from the hybrid constants that are obtainable from graphical or regression analysis. The formulae are

$$k_{el} = \frac{A + B}{\frac{A}{\alpha} + \frac{B}{\beta}} \qquad [\text{time}^{-1}] \tag{47}$$

$$k_{12} = \frac{AB\,(\beta - \alpha)^2}{(A + B)(A\beta + B\alpha)} \qquad [\text{time}^{-1}], \tag{48}$$

and

$$k_{21} = \frac{A\beta + B\alpha}{A + B} \qquad [\text{time}^{-1}] \tag{49}$$

where A and B are the zero-time intercepts of the residual distribution line and the postdistributive (elimination) line, respectively. Each represents a fictive concentration that describes a limit when the other variable is set to zero (ie, the other process is nonexistent).

The volume of compartment 1 (central compartment) can be obtained from C_p^0 (ie, $V_1 = fD/C_p^0$). From the fictive concentration, B, the apparent volume of distribution during the postdistributive phase can be calculated, since $A + B = C_p^0$. From $A - B$ may be obtained the value of compartment 2. (Volumes of distribution are discussed below.) C_p^0 can be determined more accurately by summing the two log-linear extrapolates than from extrapolation of the unresolved curve. The coefficients A and B are also hybrid, since the value of B depends upon all of k_{21}, k_{12} and k_{el}.

Volumes of Distribution—The volume of distribution, V_d, of a drug is a useful pharmacokinetic parameter that relates C_p to D_B (see page 727). Even though it is fictive, it provides not only some insight into distribution but also importantly relates to the rate of clearance of drug from plasma, and changes in pathological conditions reveal changes in the physiological-biochemical conditions. By means of the distribution coefficient, Δ', data from one patient may be applied to others of different body weights (see page 728).

In the open two-compartment system, the determination of V_d is complicated by the slow attainment of distribution "equilibrium" (ie, steady state) between two compartments, and the volume of distribution is changing continually during the distribution phase. It is especially important to know V_d during the postdistribution phase (in which case V_d only applies during postdistribution times) or to estimate V_d by methods that cancel the distributive factors.

Theoretically, the most accurate method for estimating V_d is known as the *steady-state* method, of which there are three variations. In this, the ideal procedure is to give a continuous intravenous infusion until the steady state (ie, plateau) is reached. During the steady state, the amount of drug in the peripheral compartment (compartment 2) is constant. Under these conditions

$$V_d^{ss} = \frac{k_{12} + k_{21}}{k_{21}} \cdot V_1 \qquad [\text{vol}] \tag{50}$$

Note that V_d^{ss} is independent of k_{el} and β. There are, however, several disadvantages to this approach, the principal ones being that for most drugs the steady state is reached only after prolonged infusion, since 5 or more half-lives often will require days of infusion, and that V_1, k_{12}, k_{21} and β need to be determined. This can be done by discontinuing infusion and resolving the curve of the declining plasma concentration into its component parts. Fortunately, the same information can be obtained from the mean plasma concentration during one dose-interval at steady state, C^{ss}. In this,

$$V_d^{ss} = \frac{fD(k_{12} + k_{21})}{C^{ss}k_{21}k_{el}\tau} \qquad [\text{vol}] \tag{51}$$

where k_{el} is the rate of elimination from the central compartment. Provided that elimination occurs only from the central compartment, Eqs 50 and 51 are valid for any n-compartment model. This method has the same disadvantage as the infusion method in that dosing must be continued to the steady state, which, however, with repetitive dosing is more comfortable and less expensive than continuous infusion. An advantage is that extravascular routes may be employed and that only one dose-interval need be sampled, thus making the determination of V_d^{ss} applicable to drugs with long half-lives.

The value of V_d^{ss} also can be determined from areas under the curve (AUC) during and after constant intravenous infusion

$$V_d^{ss} = \frac{D_\Sigma \cdot AUC_{t(ss)}}{C^{ss} \cdot AUC^{0\text{-}\infty}} \qquad [\text{vol}] \tag{52}$$

where $t(ss)$ is the time to reach steady state, D_Σ is the cumulated dose at $t(ss)$, $AUC_{t(ss)}$ is the area under the plasma concentration-time curve from $t = 0$ to $t = t(ss)$ and $AUC^{0\text{-}\infty}$ is the total area under the curve from $t = 0$ to $t = \infty$, providing that the infusion is stopped at the achievement of steady state or that the AUC, during any overrun into the plateau state, is eliminated from the determination of $AUC^{0\text{-}\infty}$. The method has the advantage that the determination of k_{12}, k_{21}, k_{el} or V_1 is not necessary.

A second method of determining V_d is that in which V_d is calculated from V_1, k_{el} and β:

$$V_{d(\beta)} = \frac{V_1 k_{el}}{\beta} \qquad [\text{vol}] \tag{53}$$

The designation $V_{d(\beta)}$ indicates the method of calculation. The rationale for the method is the valid assumption that plasma and tissue concentrations decline in parallel during the postdistributive phase, so that the distribution ratio, which will be equal to Δ', is constant after the distributive phase has come to completion. The method has been shown to yield the same values for V_d as one based on area:

$$V_{d(area)} = \frac{fD}{AUC^{0\text{-}\infty}} = \frac{fD}{(A/\alpha + B/\beta)\beta} = V_{d(\beta)} \qquad [\text{vol}] \tag{54}$$

The method is independent of the route of administration, so long as the fraction absorbed, f, is used.

On page 739, on which the parameters derived from curves such as that in Fig 36-19 were discussed, it was pointed out that the zero-time extrapolates A and B were fictive concentrations from which apparent volumes of distribution could be obtained. The extrapolate β gives a volume known as $V_{d(extrap)}$:

$$V_{d(extrap)} = \frac{D}{B} \qquad [\text{vol}] \tag{55}$$

The method does not take into account the effect of process k_{21} to limit the size of the peripheral compartment and hence tends to overestimate D_B, except at zero time. However, it has the advantage of rapid determination.

The value of $V_{d(area)}$ is the most correct approximation of V_d to apply to the postdistribution phase and $V_{d(ss)}$ is correct for constant infusion at steady state but otherwise underestimates D_B. By magnitude, these three volumes of distribution rank as follows: $V_d^{area} > V_d^{ss} > V_1$.

Clearance—The definition and concept of clearance can be found on page 729. The definition of clearance applies

whether the elimination occurs in a one- or multi-compartment system, hence clearance is model-independent. However, mathematical identities of clearance do depend on the model. In the open two-compartment model, β and $V_{d(area)}$ are applicable in the calculation of total body clearance:

$$Cl_{tot} = \beta V_{d(area)} \qquad [\text{usually mL} \cdot \text{min}^{-1}] \qquad (56)$$

Since it is customary to express clearance in units of mL/min, β must be expressed in min and $V_{d(area)}$ in mL. An analogous formula is based on the condition of the model that elimination occurs only from the central compartment, so that the applicable volume and elimination-rate constant are used:

$$Cl_{tot} = k_{el} V_1 \qquad [\text{mL} \cdot \text{min}^{-1}] \qquad (57)$$

Cl_{tot} also can be expressed in terms of α, A, β, B and D:

$$Cl_{tot} = \frac{D}{A/\alpha + B/\beta} \qquad [\text{mL} \cdot \text{min}^{-1}] \qquad (58)$$

Absorption Plus Distribution and Elimination—After extravascular administration in a two-compartment system, there are three first-order processes occurring simultaneously: absorption, distribution and elimination. These processes all add algebraically, as follows

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} - C_p^0 e^{-k_a t} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (59)$$

They can be resolved by various methods, of which the easiest is the method of residuals already illustrated in Figs 36-8 and 36-19. However, in a two-compartment system, the first residual line is a compound line (absorption + distribution) and must be resolved further into its two component lines. Figure 36-20 is an example of the method of residuals applied to two-compartment data. The first step is the subtraction of the late postdistribution (elimination) line (with slope -0.434β) from the curve, which leaves a two-component residual curve. This residual curve has a late, postabsorptive log-linear segment of slope -0.434α. If the absorption segment of the curve of residuals is subtracted from the extrapolated α-line, a log-linear second residual line with a slope of $-0.434k_a$ will be generated. The extrapolated intercepts A and B have the meanings previously discussed. The zero-time intercept of the absorption residual line is equal to C_p^0 and hence, theoretically equals $A + B$. Kinetic parameters other than α, A, β and B are calculated by means of Eqs 44 and 45. The absorption parameters for other routes of absorption can be determined similarly, except with certain sustained-release dosage forms, which release approximately at a steady rate over long periods of time.

In the example illustrated by Fig 36-20, only two or three points each could be used for establishing the log-linear segments of the residual distribution and absorption lines, which, therefore, may be in considerable error. This indicates the importance of taking frequent enough samples, especially during the absorption and distribution phases, to provide reliable kinetic data.

Multiple-Dose Administration—Equations 30–34, which describe various aspects of the fluctuating plasma concentrations in the one-compartment system, are complex. It may be appreciated that the additional complexities conferred by two compartments renders the analogous equations intricate and difficult to follow for the nonspecialist. However, one-compartment equations modified in minor ways apply to two-compartment systems with reasonable accuracy, when the distribution phase after one dose is approximately complete before the next dose is administered. Under these conditions, β may be substituted for k_{el} and $V_{d(area)}$ for V_d, to adapt one-compartment equations to two-compartment systems for rough approximations of the

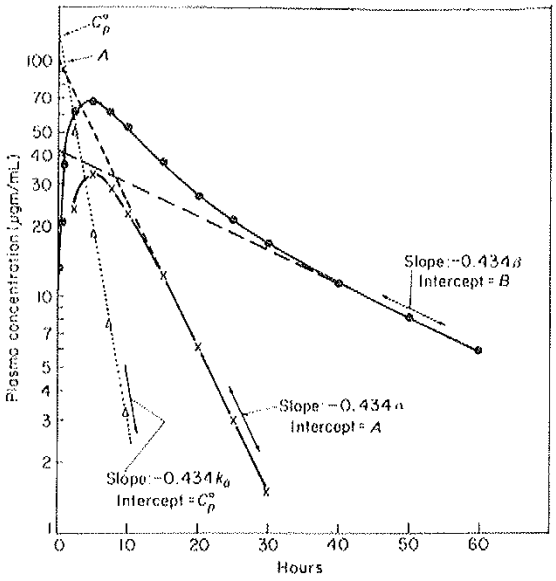

Fig 36-20. Resolution of absorption, distribution and elimination components of a concentration-time curve of a drug with two-compartment kinetics. The solid curve is a semilogarithmic plot of plasma concentrations. The method of residuals was used to resolve the component lines. The postdistribution, or elimination, line of slope -0.434β (— —) was subtracted from the concentration-time curve. The difference, or residual line (X—X) retained the absorption and distribution components. The log-linear segment of this line represents the postabsorption ("distribution") line, of slope -0.434α. A second residual line representing the absorption phase was obtained by subtracting the absorptive segment (first four points) of the first residual curve (X—X) from the extrapolated α line of slope -0.434α (- - - -) to give the residual absorption line of slope $-0.434k_a$ (· · · · ·). The zero-time intercepts of the extrapolated lines defined by k_a (· · · · ·), α (- - - -) and β (— —) are C_p^0, A and B, respectively (courtesy, data, Gibaldi and Perrier[9]).

two-compartment parameters and plasma concentrations. Thus,

$$C^{ss} = \frac{fD}{\beta V_{d(area)}^T} \qquad [\text{wt} \cdot \text{vol}^{-1}] \qquad (60)$$

Adaptation of one-compartment equations for accumulation ratios and loading dose also usually gives values that satisfactorily approximate those calculated with more rigorous equations. The respective adapted equations are

$$R_c = \frac{1}{1 - e^{-\beta i}} \qquad [\text{no units}] \qquad (61)$$

and

$$D_0^* = R_c D \qquad [\text{wt}] \qquad (62)$$

where R_c, D_0^*, and D are the accumulation ratio, optimal loading dose and maintenance dose, respectively. In some instances, eg, when a rapid response to lidocaine is desired, a loading dose calculated with Eq 61 will be too low to provide adequate antidysrhythmic effects of the drug during the distribution phase. In this case, a loading dose can be approximated by use of the formula

$$D^* = V_1 C_p \qquad [\text{wt}] \qquad (63)$$

where D^* is the loading dose, V_1 is the volume of the central

compartment and C_p is the target (immediate central compartment) plasma concentration.

The rate at which the steady state is attained depends almost entirely on β. The plateau principle essentially applies, and approximately 5 half-lives, based on β, are required to reach the *steady state*. Essentially all precepts emanating from the one-compartment plateau principle are applicable if two-compartment β is used in place of one-compartment k_{el}.

Nonconformities and Miscellany

Fallibility of Assumptions—General pharmacokinetic concepts are applicable to many drugs without significant modification. Implicit in these concepts are certain assumptions which, however, do not apply to all drugs or drug recipients. Some of the basic assumptions are (1) the pharmacological effect is elicited by the drug administered (and which is being assayed in the blood), (2) the pharmacokinetic parameters remain constant with both time and dose and (3) the peak effect occurs when the concentration is at its peak at the site of action, binding and sequestration follow first-order kinetics and, in short, the models chosen for kinetic analysis are correct. When these assumptions are not valid, significant clinical consequences accrue, and theoretical and/or empirical modification of the models may be necessary. Therefore, it is worthwhile to examine some departures from the more common or commonly assumed behavior and some miscellaneous pharmacokinetic considerations not stressed elsewhere in this chapter.

Active Metabolites and Latentiation—Some drugs are biotransformed to a metabolite that has a pharmacological action like that of the parent drug. With these, the pharmacokinetics of each of parent drug and its metabolite may or may not be simple and easy to define, but the combined pharmacodynamic (and sometimes pharmacokinetic) action may rise and fall in a complex way because of the different time courses, distributions and routes of elimination of the two active molecules. For example, the anticonvulsant trimethadione (TMO) is un-ionized at body pH, is little excreted and has a V_d of about 600 mL/kg and a half-life of about 4 hr, whereas its anticonvulsant metabolite, dimethadione, is a weak acid, is excreted and excretion is affected by urine pH, has a V_d of 400 mL/kg and has a half-life of about 10 days. It is obvious that a study of the pharmacokinetics of TMO alone would be of little value in predicting a therapeutic regimen and precautions.

Two or more active metabolites may increase the complexity greatly. There are a few drugs in which it is only the metabolite, not the parent drug, that is active; with these, the relationship of pharmacokinetics to pharmacodynamics is simpler, provided that it is the metabolite that is followed. It is sometimes deliberately the practice to prepare a drug that is inactive with the intention that the drug be converted to an active metabolite once it is in the tissues. This practice is known as *latentiation*. Latentiation may be used when it is desired to slow down the rate of delivery of drug to the tissues, a kind of systemic sustained release, as it were, or when the active metabolite is locally toxic at the site of administration. Some drugs which generate active metabolites are shown in Table III. Not shown are drugs whose metabolites have no therapeutic activity but which have toxic or other pharmacodynamic activity.

The amount of a metabolite of a drug in the body at any one time depends upon both the rate of transformation of the drug to metabolite and the rate of disposition of the metabolite. The body content of metabolite will continue to rise so long as the content of precursor is high enough that the rate of biotransformation to metabolite exceeds the rate of elimination of the metabolite. When the concentration of drug or precursor falls to a level below which there is no longer a net gain in content of metabolite, the metabolite concentration will fall.

Table III—Some Drugs with Pharmacologically Active Metabolites

Parent Drug	Active Metabolite(s)
Acetohexamide	Hydroxyhexamide
Allopurinol	Alloxanthine
Aldophosphoramide	Phosphoramide mustard
Amitriptyline	Nortriptyline
Chloral Hydrate	Trichloroethanol
Chlordiazepoxide	Desmethylchlordiazepoxide, Demoxepam
Codeine	Morphine
Dacarbazine	5-Aminoamidazole-4-carboxamide
Diazepam	Desmethyldiazepam
Digitoxin	Digoxin
Flurazepam	Desalkylflurazepam
Fluorouracil	Fluorodeoxyuridine phosphate
Glutethimide	4-Hydroxyglutethimide
Imipramine	Desipramine
Lidocaine	Glycinexylidide
Meperidine	Normeperidine
Mephobarbital	Phenobarbital
Methyldopa	α-Methylepinephrine, α-methylnorepinephrine
Methamphetamine	Amphetamine
Phenacetin	Acetaminophen
Phenylbutazone	Oxyphenbutazone
Prednisone	Prednisolone
Primidone	Phenobarbital
Propoxyphene	Norpropoxyphene
Procainamide	*N*-Acetylprocainamide
Propranolol	4-Hydroxypropranolol
Spironolactone	Canrenone, Canrenoate
Sulfasalazine	Sulfapyridine
Tamoxiphen	4-Hydroxytamoxiphen
Trimethadione (TMO)	Dimethadione (DMO)

The kinetics of the fall in concentration depends upon which rate is faster, the elimination of drug precursor or the elimination of metabolite. If that of the drug is faster, the content of metabolite will rise above that of the drug, and the drug will soon disappear. This eventually leaves the content of cumulated metabolite to decline according to the kinetics of its own disposition.

In Fig 36-21, drug B illustrates the rate-limiting effect of the disposition of a metabolite. When the rate constant for the elimination of the drug or precursor is slower than that of the metabolite, as with drug A in Fig 36-21, the content of metabolite never reaches that of the drug and it eventually declines according to the kinetics of biotransformation of the drug. That is, the content of metabolite is mainly that which is being produced moment-to-moment. The figure is adapted from a plot of data from a computer analysis of a multivariable model.

The kinetics of the generation and elimination of a metabolite relative to those of its drug precursor are important when the metabolite is either toxic or therapeutically active. In the latter instance the kinetics are the kinetics of latentiation. Where the metabolite is toxic, a pattern such as in A would be less likely to generate toxic concentrations as in B.

When the disposition of the drug precursor involves more than one process, or when there is more than one metabolite, the kinetics necessarily are more complex than in the illustrations presented above.

Other Pharmacokinetic Models—Apparent kinetic nonconformities may result when the system does not obey the simple open one- or two-compartment models. In the two-compartment model discussed in this chapter, elimination took place from the central compartment; however,

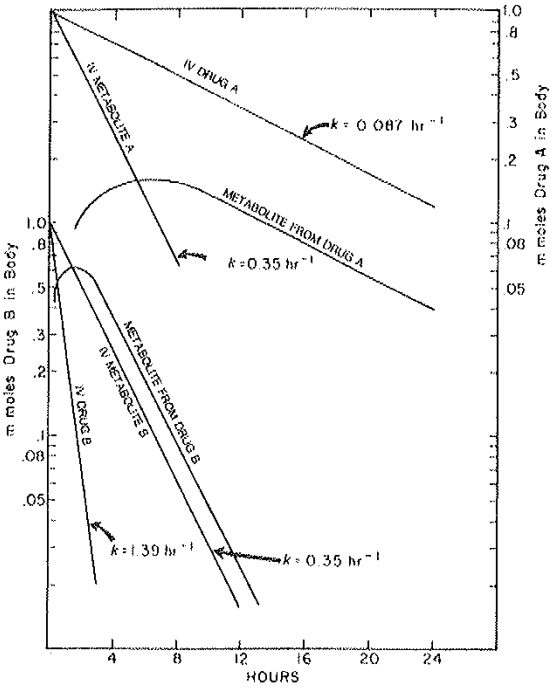

Fig 36-21. Computer plot of the relationship of the amount of drug metabolite in the body to the amount of drug in the body at different relative rates of disposition of drug and metabolite. With Drug A, the metabolite is eliminated at a much faster rate than the parent drug. Curve "IV Metabolite A": the blood concentration when the metabolite is given intravenously; curve "Metabolite from Drug A": the concentration of metabolite actually biotransformed from Drug A. With Drug B the metabolite is eliminated at a much slower rate than the parent drug (courtesy, combined replot of two figures, Martin[10]).

other two-compartment models in which elimination takes place partly or entirely in the peripheral compartment are more appropriate with some drugs. Even absorption into a peripheral compartment appears to occur with some drugs. In addition to alternate two-compartment models, three- or multi-compartment models are required occasionally to account for the pharmacokinetic behavior of certain drugs. In the common *three-compartment* model, the central compartment communicates with two peripheral compartments (which are not interconnected), one called the *shallow compartment* and the other the *deep compartment*. Distribution into the shallow compartment is faster than into the deep compartment.

Many drugs that are described as having one- or two-compartment kinetics actually have more complicated kinetics. There is no drug that displays true one-compartment kinetics, since distribution is never instantaneous. With any drug, sampling within the first minute to one-half hour will show one or more distribution phases.

Nonlinearities—Nonlinearity is a term applied to all nonconformities in which a semilogarithmic plot of plasma concentration-time data cannot be resolved completely into log-linear components, ie, into first-order processes. There may be various causes, such as capacity-limited elimination (ie, saturation of elimination system), capacity-limited absorption or transport, changes in protein binding, changes in pH at the site of absorption, changes in blood flow to the site of absorption and/or elimination, low or erratic dissolution or release rates from dosage forms, low solubility of the drug, drug-induced or other change in body temperature, etc. Some apparent nonlinearities are the result of fitting straight lines to nonlinear data under the assumption that deviations are experimental error.

Protein Binding—The binding of a drug to protein or other macromolecules can affect the pharmacokinetics of a drug, the magnitude of the effect depending on the fraction of the drug that is bound, the fraction of the binding sites that are occupied by the drug and the rates of association and dissociation. If only a small fraction of drug is bound, the kinetic consequences may be minor or negligible, even if binding is very tight. The effect of the binding of a large fraction of drug depends somewhat on whether the drug is bound tightly or loosely; if the rate of dissociation is quite rapid in comparison to the rate of delivery to sites of distribution and elimination or in comparison to the intrinsic rate of elimination, the kinetic consequences also may be minor. The greatest consequences accrue to binding with high capacity and slow dissociation.

It cannot be overemphasized that in the analysis of plasma, the total concentration of drug (ie, both free and bound drug) usually is determined. However, it is only the free drug that can move across cell membranes, and equilibrium or steady-state conditions are established only through the movement of free drug. Therefore, total drug concentrations are defective indicators of a true kinetic situation unless a correction is made for the extent of protein binding. Without such corrections, errors can be serious. Binding to plasma protein has a profound effect not only on V_d but also on apparent renal filtration fraction and clearance, as may be seen in Eqs 13 and 15. If the plasma concentration was not corrected for binding, Cl_{ren} would be in error by a factor of $1/(1 - p)$, where p is the fraction bound; however, when excretion occurs mainly by active tubular transport, protein binding often has a negligible effect on renal clearance. Similarly, when intrinsic hepatic clearance is low, protein binding greatly affects the clearance, the effect being to decrease clearance.

The binding of a drug to plasma proteins retards the rate of distribution and delays the attainment of equilibrium or steady-state conditions. It is as though the transport of some molecules of the drug across a membrane has to wait until these molecules dissociate and are free to diffuse.

When the amount of a drug bound to plasma proteins does not approach saturation, ie, the binding capacity of the proteins, the fraction of drug bound approximately is constant over a therapeutic dose range. However, when the amount exceeds about 50% of the saturation value, the percent of drug bound may vary considerably with dose, which will give rise to dose-dependent kinetics (see below). Under the condition of near-saturation, changes in the protein content of the blood also will make large differences in the percent bound and hence in the various pharmacokinetic parameters. Certain pathological conditions, such as uremia, some congestive heart failure, starvation, etc, may be accompanied by hypoproteinemia and albumin with altered binding properties and hence abnormal pharmacokinetics.

Time-Dependent Kinetics—A drug with low to intermediate intrinsic clearance, and which induces an increase in the activity of its own biotransforming enzyme system, will decrease $t_{1/2}$ and increase clearance and, if its kinetics show two-compartment kinetics, its V_d. Since such an induction requires time, usually several dose-intervals of repetitive dosing, the kinetics vary with time and are called time-dependent. Allosteric (or feedback) inhibition by accumulated metabolites of a drug, or an effect of a drug to impair its route or elimination, also will cause time-dependent (and dose-dependent) changes in the kinetics. Drugs that cause the depletion of some slowly repleteable intermediary factor, such as the depletion of norepinephrine by reserpine or the irreversible inhibition of acetylcholinesterase by isoflur-

ophate, will manifest time-dependent effects on body function which do not correlate with the drug pharmacokinetics. With some drugs, especially central nervous system depressants, the drug effect recruits time-dependent homeostatic counteradjustments that tend to terminate the effect prematurely and to increase the dose requirement for effect (ie, causes tolerance), so that the pharmacokinetics lose their predictability with time. Similarly, drug-induced changes in the receptor properties of the response system will tend to produce a time-dependent dissociation of the pharmacokinetics from the pharmacodynamics.

Dose-Dependent Kinetics—With some drugs, the pharmacokinetics differ more with high, than with low doses. Such changes may be due to: saturation of a biotransforming enzyme or excretory transport system, toxic impairment of the organ of excretion at high doses, differences in intercompartment permeability and V_d at high and low doses, drug-induced changes in blood flow and hence in distribution and clearance, saturation of protein binding sites or the recruitment of new binding sites at high doses, etc. In those instances in which the elimination route is saturated (also called capacity-limited), it is evident that the half-life will increase, as can be seen in Fig 36-22. The cause of the dose-dependent increase in $t_{1/2}$ at the higher doses is the saturation of the enzyme systems that form salicyluric acid and carboxybenzoxyglucuronide. It is usual to speak of the kinetics during the saturation phase as being zero-order, but they are not truly zero-order. The saturated system manifests zero-order kinetics, but alternative routes of elimination, such as through salicyl glucuronide and glomerular filtration and renal tubular secretion, still manifest first-order kinetics, so that elimination is a mixture of zero- and first-order processes. In any event, since elimination is no longer completely a first-order process in the saturation phase, there is no overall elimination rate constant and hence no constant half-life. During repetitive dosing with the large doses, the new $\bar{C}^{ss}$ will be determined by both the zero-order and first-order elimination processes, as well as the dose, but the time required to reach the new plateau will be determined only by the remaining first-order processes; since the first-order overall elimination constant, K, has been diminished, the time-to-plateau will be increased accordingly. Kinetic behavior of this type is mathematically analogous to the familiar Michaelis-Menten expression for enzyme kinetics, and dose-dependent kinetics are sometimes called *Michaelis-Menten* kinetics. They also are called *saturation*, or *capacity-limited*, kinetics.

Examples of important drugs which show dose-dependent kinetics are aspirin, phenylbutazone, probenecid, levodopa, phenytoin and dicumarol. Ethanol obeys essentially zero-order elimination kinetics at blood concentrations above 0.02–0.04%, which is a fact of considerable importance in court cases involving ethanol. The clinical significance of dose-dependent kinetics will be discussed further in Chapter 37.

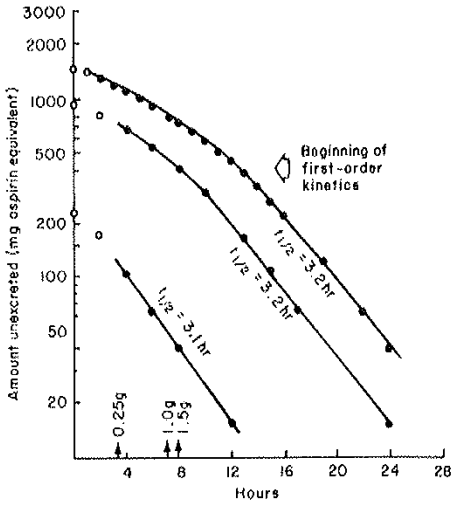

Fig 36-22. Dose-dependent elimination of salicylate in a normal 22-year-old male. Doses taken were 0.25, 1.0 and 1.5 g aspirin, respectively. Vertical arrows on the time axis indicate the time necessary to eliminate 50% of the dose. Stated half-times ($t_{1/2}$) are for straight-line portion of curves where elimination rate is first-order. However, during the early hours after the larger doses, the slope at any time (tangent to the curve) is flatter, hence $t_{1/2}$ is longer, than during the first-order phase (courtesy, Gibaldi and Perrier,[9] modified from Levy[11]).

Chirality—Chiral drugs often are given as racemic mixtures, and the pharmacokinetics and pharmacodynamics of the drugs are studied as if the drug were one entity. It is now becoming clear that this approach may be in error because evidence is accumulating which shows that the pharmacokinetics (as well as pharmacodynamics) of individual enantiomers are not the same and that failure to differentiate among them will give misleading kinetic data for the active form of the molecule. Details of the importance of chirality in pharmacokinetics have been summarized.[12]

Kinetics in the Evaluation of Drugs and Drug Products

The utility of pharmacokinetics in devising appropriate dosage regimens is obvious. Kinetic studies also are important to the study of the influence of inhibitors of elimination, eg, probenecid on the excretion of penicillin, and the effect of one drug on the disposition of another.

Plasma or tissue concentrations and their kinetics are not only valid but essential in comparing the bioavailability of drug products in which the excipients, adjuvants, etc, may vary but the active ingredients are the same. Such data are critical to a proper appraisal of the practice of prescribing drugs by proprietary names.

Kinetics also are employed to compare different drugs, but the meaning of such comparisons is often obscure, and claims of therapeutic superiority based on kinetics must be accepted cautiously. The kinetics of disposition are important to a comparison of drugs in a class in which toxic effects are frequent; it is often desirable to use a drug with a short biological half-life, so that a toxic episode may be terminated quickly upon discontinuation of medication. Furthermore, it is valid to compare the fluctuations in plasma concentration among drugs consequent to multiple-dose administration, provided, of course, that for the class of drugs in question, the extent of fluctuation has an important bearing on efficacy or toxicity.

A comparison of peak or mean blood levels achieved by equal doses of different drugs is not entirely meaningless. It is true that the dose of a drug may be adjusted to compensate for a difference in potency from some reference drug, but it is often difficult for the physician to alter the dose except in multiples of the unit dose provided by the manufacturer. Partly because of the inertia of precedence and habit and partly because it is easier for the physician to memorize

doses as a group, closely related drugs whose potencies differ only moderately may all be available in the same dose. Thus, tetracyclines are available as "250's" or "500's," even though they are not equipotent, sulfonamides as 1 g, etc. It is therefore valid for the physician to choose the drug whose unit dose yields a blood level closest to the optimum. Unfortunately, many physicians do not have the prerequisite knowledge for such a choice and hence may be susceptible to misleading promotional arguments about the superiority of one product over another. Some of these points will be elaborated in the following chapter on *Clinical Pharmacokinetics*.

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Supplementary Reading

Note: Refs 6–9 are textbooks or monographs on general pharmacokinetics. Ref 5 is a monograph on hepatic clearance.

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CHAPTER 37

Clinical Pharmacokinetics

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In Chapter 36 the basic principles of pharmacokinetics were presented. Clinical pharmacokinetics is the discipline in which basic pharmacokinetic principles are applied to the development of rational dosage regimens. In this chapter the concepts of pharmacokinetics are placed into perspective with the development of individualized drug dosage regimens. The clinical significance of the processes of drug absorption, distribution, elimination and influence of disease states on these processes are emphasized. Examples will be given of the ways pharmacokinetic principles can be applied in the calculation and adjustment of dosage regimens designed to fit the pharmacokinetic and pharmacodynamic properties of drugs and specific disease states that alter drug disposition. The principles of therapeutic drug monitoring and the rational use of this clinical science in the management of patients also are discussed.

An individualized dosage regimen for a patient involves a decision about the dose or amount of drug to be administered, interval between doses, route of administration and patient factors that may change during the course of drug administration. The latter implies that there is a plan for monitoring the therapeutic and adverse effects of the drug. Decisions about drug dose, dosage intervals and route of administration are based on the clinical knowledge of the disease being treated, efficacy of the drug in treating the disease and absorption, distribution and elimination of the drug.

Absorption

Drugs are administered by a variety of routes including intravenous, intramuscular, inhalation, oral, rectal, vaginal and topical application to the skin. The choice of the route depends on the many patient- and drug-related factors discussed in Chapter 35. In practical terms, the important considerations in this choice include the systemic availability of a particular dosage form, rate and extent of drug absorption and patient convenience.

Oral Route—This route is chosen most frequently because of ease of administration and patient acceptance. However, the number of variables involved in the absorption of drugs from the stomach and small intestine make the oral route of administration quite complex.

Plasma concentration-time curves will reflect some of these complexities. One of these is the relative rates of absorption of different preparations of the same drug (Fig 37-1[1]), in which preparation *A* represents a simple, rapidly absorbed preparation of a drug; *B* is a more slowly absorbed derivative of the same base. The bioavailabilities of *A* and *B* are identical and *C* is the same compound as *B*, but in a dosage form that is only 50% as bioavailable as *B*. *A* is absorbed rapidly (ie, k_a for *A* is greater than for *B* or *C*) and the peak level is in the therapeutic plasma concentration range.

The advantage of such a preparation is that a pharmacodynamic response can be expected to occur quickly, provided the response is related to plasma concentration. To appreciate the clinical relevance of the situation, consider *A* to be quinidine sulfate, an antiarrhythmic drug. For quinidine sulfate, the absorption rate constant, k_a, is large in relation to the elimination rate constant, k_{el}, and the peak concentration usually occurs in 1 to 2 hr. The rapid absorption is important in clinical situations in which some degree of urgency exists.

It may be desirable, in the initiation of therapy of ominous ventricular premature contractions, to use a preparation with the characteristics of quinidine sulfate. The half-life of quinidine is 4 to 6 hr, so that frequent doses (every 4 hr) are necessary to maintain effective blood concentrations of the drug. The short half-life can be an advantage, since steady-state concentrations of quinidine are achieved within 24 hr (plateau principle). Therefore, one can decide within a day whether quinidine will be useful in suppressing the ventricular premature contractions. However, the fact that a dose must be administered every 4 to 6 hr to maintain therapeutic plasma concentrations is somewhat of a disadvantage in that it is inconvenient and may result in noncompliance.

B, with its slower rate of absorption, reaches a lower peak concentration at a considerably later time even though given in the same dose. There are clinical consequences of this. For example, if *B* was the sustained-release form of quinidine gluconate, it would be less desirable than quinidine sulfate for the initiation of drug therapy, where a rapid therapeutic response is needed. Because of its prolonged

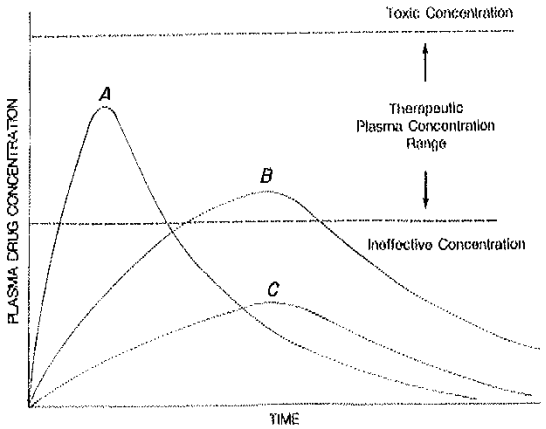

Fig 37-1. Plasma drug concentration-time curves of three preparations of the same drug. *A* is rapidly and completely absorbed. *B* is not absorbed as rapidly as *A* but is 100% available. *C* has the same time-to-peak concentration as *B* but is only 50% as available (Courtesy, adaptation, Benet[1]).

absorption, this preparation commonly is administered every 8 to 12 hr. This is so because the slower rate of absorption enables the dose to be increased commensurate with a longer dose-interval without peak concentrations that rise into the toxic range.

When treating a patient in which a rapid (but not immediate) effect is required (as with asymptomatic ventricular premature contractions), it is advisable to use a dosage form to initiate therapy that is rapidly and completely absorbed. Once the drug is shown to be effective in a particular patient, the dosage form can be changed to one with characteristics similar to *B*, so that less-frequent dosing is required and patient compliance is improved.

The preparation represented by *C in the same dose* as *A* or *B* is probably not an acceptable way to administer this drug. The total amount of drug *C* that is absorbed is only half of that of *B* (area-under-the-plasma concentrations-time curve, AUC, for *C* is half of the AUC for *B*). Thus, it would require twice the dose to attain blood levels equivalent to *A* or *B*.

The treatment of asthma with theophylline is an example in which a rapidly absorbed dosage form is used to initiate therapy and a prolonged-release dosage form is used for maintenance therapy. When a patient has an acute asthma attack or worsening bronchitis that requires bronchodilator therapy, it is advisable to use the theophylline-ethylenediamine complex (aminophylline). This dosage form can be administered either intravenously or orally; the former should be used to initiate treatment in the acute asthmatic patient who requires prompt therapy, so that neither a delay in achieving therapeutic plasma concentrations nor bioavailability are factors in the initial therapeutic response.

Following the administration of a loading dose (see under *Distribution*, page 749), the drug should be given by continuous intravenous infusion until the acute symptoms have subsided, which may take 24 to 72 hr. In the patient with less-severe symptoms, aminophylline can be administered orally four times a day. Once the patient's condition has improved and an effective dose of theophylline has been established, then it may be possible to switch the patient to a prolonged-release formulation for maintenance therapy.

The absorption and bioavailability of Theodur and Sustaire, two sustained-release theophylline preparations, permit 12-hr dosing intervals; Slo-Phyllin Gyrocaps should be given every 8 hr. The total daily dose of theophylline that was required during intravenous aminophylline administration is divided into smaller oral doses given at intervals appropriate for the characteristic of the preparation or dosage form used.

It is important to keep in mind that the absorption and plasma-time curve characteristics for these preparations usually have been established in healthy volunteers or asthmatic patients without other illnesses. Patients who eliminate theophylline rapidly (ie, smokers) may have increased dosage requirements, and the dosage interval may have to be shortened to avoid recurrent asthmatic symptoms between doses.

Prolonged-release dosage forms have the additional advantage that fluctuations in blood levels of the drug will be less than with rapidly absorbed dosage forms. There is evidence for some drugs that the reduction in rapidly changing blood levels may improve efficacy and decrease adverse effects. For example, the dose of fentanyl or ketamine required to maintain anesthesia was reduced by nearly 50% when the drugs were given by continuous infusion rather than by intermittent bolus.[2]

This reduced dose also resulted in more rapid recovery with less-prolonged sedation. These findings suggest that a reduction of fluctuation in the plasma concentrations will reduce total dosage requirement. If such a reduction in plasma concentration fluctuation also applies to oral prolonged-release dosage forms, it would provide a distinct advantage for their use.

The bioavailability of a particular drug product, by any route of administration, can be determined by comparison of the AUC of a drug given by the route of interest with that of the same dose given intravenously (see Chapter 35). In the case of an orally administered drug, it is the ratio of the AUC after an oral dose to the AUC after an intravenous dose. The decreased bioavailability of an oral dose may be due to poor gastrointestinal absorption of the drug because it does not go completely into solution, as it may be degraded in the gastrointestinal lumen, or it does not pass across the intestinal mucosa. Furthermore, in order to reach the general circulation, drugs taken orally must pass through the wall of the gastrointestinal tract and then to the liver via the portal vein. Thus, drug metabolism may occur in the gut wall or in the liver and severely limit the delivery of parent drug to the general circulation.

If the extraction of the drug by the liver is efficient, oral administration results in low bioavailability and sometimes limited pharmacological effect. This is commonly referred to as *first-pass metabolism*. Table I lists some of the drugs known to exhibit first-pass metabolism. Because their extraction is high and their rate of metabolism great, the rate-limiting step in the clearance of drugs in Table I is liver blood flow. The metabolism of these drugs can be referred to as *flow-limited*. The clinical significance of changes in liver blood flow on drug bioavailability will be discussed under *Drug Therapy in Hepatic Disease*.

Different dosage forms of the same drug may have different systemic bioavailabilities. The ratio of the AUC for one dosage form to that of another dosage form is termed the *relative bioavailability*. A drug usually has the highest bioavailability if administered orally as an aqueous solution; finely comminuted drugs in suspension follow closely. However, as a drug is packed into hard gelatin capsules or compacted into tablets, its bioavailability decreases. Furthermore, a drug in one dosage form made by one manufacturer may have a different bioavailability from that of another manufacturer.

With drugs for which bioavailability varies significantly from product to product, if one product initially has been efficacious, it is advisable to continue with that product. If for economical or other reasons the product must be changed to that manufactured by a different company, it is wise to observe the patient carefully for a possible change in clinical response indicative of a change in bioavailability. Products designed for prolonged-release sometimes have a low bioavailability. However, this may not be a problem during maintenance therapy so long as therapeutic serum concentrations are achieved consistently.

The presence of food in the stomach or intestine can have a profound influence on the rate and extent (bioavailability) of drug absorption. Initial absorption studies for a new drug, performed in healthy volunteers, commonly include fasting and nonfasting conditions. Therefore, in general, and for controlled diets, the effect that food may have on

Table I—Drugs that Exhibit First-Pass Metabolism

Acetylsalicylic acid	Metoprolol
Alprenolol	Morphine
Amitriptyline	Nitroglycerin
Desipramine	Nortriptyline
Dopamine	Pentazocine
Imipramine	Prazosin
Isoproterenol	Propoxyphene
Lidocaine	Propranolol
Meperidine	Salicylamide

drug absorption may be known when a drug is introduced into the market. Unfortunately, food-drug interactions are not consistent, and the presence of food may enhance or diminish the absorption of drugs. The most common type of interaction occurs when a food constituent binds the drug and the food-drug complex cannot pass through the gut wall. For example, complexation of tetracycline antibiotics may occur when these drugs are administered with dairy products or with antacids containing aluminum, calcium or magnesium.

The presence of a large meal in the stomach will delay gastric emptying. If a drug that is absorbed in the intestine is ingested with a large meal, the delay in gastric emptying may result in a delay in absorption of the drug. However, the presence of food in the stomach also has been shown to *increase* absorption of some drugs. For example, the bioavailabilities of the β-adrenergic blocking drugs, propranolol and metoprolol, are enhanced by the presence of food.[3] Therefore, because of the difficulty in predicting the absorption pattern of a drug in the presence of food, it is usually advisable to administer drugs when the stomach is empty or 30 min prior to meals; an exception is with drugs which cause gastrointestinal irritation and nausea. These drugs must be given with food to prevent these side effects. It is recommended that such drugs *always* be taken with food to compensate for the differences in absorption that might occur if they were given one time with food and another time without food.

Water taken concomitantly with certain drugs may increase bioavailability. The administration of aspirin, erythromycin stearate, amoxicillin or theophylline with 250 mL of water results in greater bioavailability than if the same drugs are ingested with only 25 mL of water.[4] It is probable that the increased amount of water enhances the amount of drug absorbed by improving drug dissolution as well as by hastening gastric emptying.

Diseases that affect the structure and function of the gastrointestinal tract also are capable of altering the absorption of drugs after oral administration. However, no consistent pattern develops; rather, there appears to be a complex relationship between the effect of the disease on stomach and intestinal functions and the absorption of the drug in question. For example, diseases, such as diabetes mellitus or chronic renal failure, which delay gastric emptying, will markedly delay the absorption and onset of effect of drugs that must reach the small intestine before they are absorbed. This has been a problem with the use of phenytoin in patients with chronic renal failure. Celiac disease and Crohn's disease, which alter the intestinal epithelium, have been studied in detail.[5] In these diseases, absorption of some drugs is affected greatly, but there is no consistent pattern of altered drug absorption.

When a drug is to be administered orally to a patient with altered gastrointestinal motility, diseases of the stomach and small or large intestine, previous stomach or intestinal surgery or gastrointestinal infection, there is a considerable probability that drug-absorption characteristics in these patients will differ from those in healthy volunteers. This may result in a change in the time of peak blood level or the extent of absorption. It is advisable to observe such patients closely for clinical effect during initial drug administration and during chronic dosing in order to assess the influence of alterations in absorption and correct dosing regimens accordingly. Monitoring drug blood concentrations may be beneficial in adjusting dose.

Nonoral Routes—Drugs are administered by a variety of nonoral routes including subcutaneous, intramuscular, intravenous, inhalation, percutaneous, buccal, sublingual, rectal, vaginal, intra-arterial and intrathecal. In the cases of inhalation, topical application to the skin or mucous membranes, rectal, vaginal, intra-arterial or intrathecal administration, the route often is chosen to ensure that drugs reach a specific site with a minimum of systemic absorption. The rationale is that the maximum concentration of drug will be at the site of action so that side effects will be lessened. Nevertheless, if large doses are administered by these routes, enough drug may reach the general circulation to produce side effects. Therefore, the dose and preparation should be such that limited quantities of drug reach the systemic circulation.

The beta-adrenergic agonists, metaproterenol and albuterol, when administered by inhalation, produce bronchodilatation at doses that avoid serious systemic side effects. Similarly, the corticosteroid, beclomethasone, also can be administered by this route for the management of chronic asthma. Low doses of beclomethasone by inhalation are without the serious systemic side effects of oral steroids. However, as the dose is increased beyond two inhalations 4 times a day, for an average daily dose of 400 μg, there is a greater incidence of side effects, including adrenal suppression.

The *topical* administration of drugs rapidly is becoming an important route of drug administration of systemic drugs. Previously used only for the application of drugs for local effects in diseases of the skin, it now is being explored as a means of administering drugs for their systemic effects.

Nitroglycerin commonly is applied to the skin in the form of an ointment or transdermal patches; it is absorbed rapidly and provides sustained blood levels. Sublingual nitroglycerin also is employed to produce therapeutic blood levels; it produces a maximal effect on anginal pain within 3 to 5 min but lasts only 20 to 60 min. In contrast, nitroglycerin ointment provides peak blood concentrations in about 1 hr and the effect on anginal pain may last for several hours. The sublingual tablets should be used to suppress acute angina attacks, whereas nitroglycerin ointment or transdermal patches may be useful to prevent recurrence of episodes of angina for prolonged periods, such as during the night. Whether or not the continuous administration of nitrates by this route will result in the development of tolerance is not clear at this time. Transdermal patches containing clonidine or estrogen are available for the treatment of hypertension or estrogen-replacement therapy, respectively.

Close *intra-arterial* administration of drugs is used to get drugs directly to a target site or organ in high concentration. After it has passed through the target region it is distributed in the entire blood volume, which reduces the systemic levels of the drug and the consequent side effects. One example is the use of cytotoxic drugs for the treatment of primary or metastatic tumors of the liver. The infusion of drugs into the hepatic artery exposes the tumor to higher drug concentrations than can be tolerated with intravenous administration. If the drug is extracted efficiently by the liver, the exposure of sensitive tissues such as bone marrow and gastrointestinal epithelium to the drug will be decreased. For example, after hepatic artery infusion of floxuridine (FUDR), hepatic vein concentrations are 2 to 6 times higher than comparable drug concentrations following intravenous infusion, yet systemic blood concentrations are 75% less.[6] Thus, the therapeutic index of FUDR in the treatment of liver cancer is increased considerably by hepatic arterial infusion. This type of selective drug administration may be beneficial with other drugs that have low therapeutic indices.

Intrathecal injection is used to deliver drugs to the spinal cord or brain in sufficient concentration to produce an effect but at the same time to reduce the incidence or severity of systemic side effects. The intrathecal administration of the cancer chemotherapeutic agent, methotrexate, frequently is employed in the management of leukemic involvement of

the central nervous system. The epidural administration of morphine, which produces long-lasting (6 to 30 hr) analgesia with minimal side effects, is proving to be of benefit in the management of chronic pain.

Distribution

Once a drug is absorbed into the general circulation, it distributes into various tissues and body fluids. The nature and extent of this distribution depends on several factors such as the extent of drug binding to plasma or tissue proteins, blood flow to selected areas of the body, lipid-solubility of the drug and, consequently, its ability to permeate membranes. In clinical practice, concern about drug distribution often arises regarding the penetration of an antibiotic into the central nervous system, into abscesses at any location, into bone for the treatment of osteomyelitis and into specific body fluids such as synovial fluid.

In most cases, the distribution of a drug within the body is determined by the nature of the drug. However, distribution occasionally is altered by the disease process for which it is being used. For example, in healthy individuals, the concentration of penicillin in the nervous system is much less than in serum. However, in patients with inflamed meninges, as in bacterial meningitis, large daily parenteral doses of penicillin can result in bactericidal concentrations in the cerebrospinal fluid. Thus, pneumococcal and meningococcal meningitis can be treated effectively with intravenous penicillin. Increased penetration into the brain in these diseases occurs because the inflamed meninges are more permeable to the penicillin. Also, active transport of penicillin out of the cerebrospinal fluid back into plasma may be impaired in meningitis, thus causing an increase in penicillin concentration in the brain.

In Chapter 36 the term *volume of distribution* (V_d) was introduced. Despite the fact that the V_d of a drug is a very important pharmacokinetic term, it is important to recall that knowing the V_d of a drug does not indicate necessarily how or where a drug is distributed within the body. The abstract nature of the V_d is illustrated with a drug such as the tricyclic antidepressant, amitriptyline. The V_d for amitriptyline is 20 L/kg, which represents a total V_d of 1400 L in a 70-kg man. This large V_d indicates that the amount of drug in the plasma is small in relation to the amount in extravascular compartments and implies that tissue concentrations of the drug probably are very large. Since the volume of total body water in a 70-kg man is less than 70 L, a V_d of 1400 L also illustrates that V_d does not represent a real volume. Drugs with a large V_d usually are distributed extensively to tissues where they commonly are bound to tissue constituents such as DNA or other macromolecules, or dissolved in lipids, whereas drugs that are bound extensively to *plasma* proteins will have smaller V_ds.

One situation in which knowledge of the size of the V_d is useful clinically is in the management of the patient with a severe drug overdose. If a drug such as amitriptyline has a large V_d, it is likely that after an overdose neither hemodialysis nor hemoperfusion will be an effective way of lowering the total body concentration of the drug. Dialysis may lower the plasma drug concentration temporarily, but there will be redistribution from tissues into plasma soon after the dialysis is stopped.

Knowledge of the V_d also is important in determining the loading dose of a drug. This is the dose of a drug administered initially to bring the plasma concentration to a level anticipated during maintenance. An example will illustrate how the V_d is used to determine the loading dose of theophylline. The V_d of theophylline is approximately 0.5 L/kg, and a commonly desired plasma concentration is 10 μg/mL (10 mg/L). Equation 7 (page 728) shows that

$$V_d = \frac{fD}{C_p}$$

where f is the bioavailability factor or the fraction of drug administered that reaches the systemic circulation, D is the dose of drug administered and C is the plasma concentration desired. Since the f for theophylline is 0.96 it can be considered to be 1. Thus

$$0.5 \text{ L/kg} = \frac{1 \cdot D}{10 \text{ mg/L}}$$

and

$$D = 5 \text{ mg/kg} = 350 \text{ mg/70 kg}$$

This dose, administered as a 30-min intravenous infusion, an oral solution or as an uncoated, rapidly dissolving tablet, will result in a peak plasma theophylline concentration of approximately 10 mg/L in patients who have not received theophylline recently.

The V_d usually is considered to be a constant parameter of a drug, so that the loading dose is independent of subsequent changes in drug elimination produced by disease. For example, the loading dose of gentamicin in a patient with severe renal failure usually will not be different from that in a patient with normal renal function. Therefore, therapy can be started with the conventional loading dose without knowing the actual status of renal function.

The severity of renal failure as measured by creatinine clearance (see below) nevertheless will have to be determined prior to calculation of the maintenance dose. There are some clinical situations, however, in which the V_ds of various drugs may be altered so that the loading dose may have to be altered appropriately. The V_d of a drug may be affected by a variety of factors such as protein binding, disease states, body habitus and age. As a rule, the effect of changes in protein binding on the V_d are important only for drugs which are bound 90% or greater to plasma proteins.

Propranolol provides an example in which in patients with chronic liver disease the V_d is increased significantly because plasma protein binding is decreased. This occurs because a greater fraction of unbound drug has access to tissue. The V_d of digoxin in patients with severe congestive heart failure usually is decreased from that in patients with normal cardiac output. Consequently, the loading dose of digoxin is reduced in these patients. Severe dehydration and sepsis result in contraction of the extracellular space and a consequent decrease in the V_d of drugs that largely are confined to this physiological space.

The degree of obesity also may affect the V_d of some drugs. The relative V_d (Δ'; V_d/kg) of water-soluble, lipid-insoluble drugs varies inversely with percent body fat; the Δ' of lipid-soluble, water-insoluble drugs varies directly with body fat. Even in extremely obese patients the increase in body weight may not be accompanied by an increase in the V_d for water-soluble drugs, such as aminoglycoside antibiotics, which will not distribute into fat tissue.

Calculation of the loading dose of these antibiotics in obese patients illustrates this problem. If actual body weight, rather than the ideal body weight or lean body mass, is used to calculate a loading dose of an aminoglycoside antibiotic, elevated peak concentrations may occur in obese patients. Nevertheless, an excessive loading dose is preferable to the risk of possible subtherapeutic concentrations from a miscalculated adjusted dose in a seriously ill patient.

Calculation of maintenance dosing should be made using ideal body weight to avoid consistently elevated peak plasma concentrations. In the first year of life, infants are known to have a larger extracellular space per unit of body weight than adults so that the Δ' of some drugs is also greater. This has been shown to be true for ampicillin, ticarcillin and amika-

cin. Changes in the V_d occur frequently in elderly patients as the result of changes in lean body mass. A linear increase in the Δ' with increasing age has been demonstrated to occur with diazepam.[7]

It should be kept in mind that the V_d for a particular drug in an individual patient may change during therapy. An example might occur when a severely dehydrated patient is treated with intravenous fluids. Unfortunately, there are no accurate means by which the V_d of a particular drug can be determined in an individual patient without first administering the drug in question. Therefore, in situations where one suspects that the V_d may be altered, it is important to monitor blood concentrations of drug, or clinical response, to ensure that therapeutic, and neither toxic nor inadequate, plasma concentrations are being achieved. This particularly is true during initial cumulative drug administration or when a loading dose is being given.

Protein Binding—Pharmacological effect is related closely to the free concentration of drug at its site of action. However, all drugs are bound to some extent to plasma and/or tissue proteins, and the free-drug concentration often may represent only a fraction of the amount of drug in the body. For most drugs the total-drug concentration is measured in plasma and related to an observed therapeutic effect. Thus, recommended therapeutic concentrations commonly are expressed as the total drug concentration in plasma, simply because total-drug concentration is much easier to assay than free-drug concentration. If something occurs that perturbs the protein binding of drug, then either more or less may be free in plasma (and thus free at the site of action) and "standard" therapeutic drug concentration guidelines no longer apply. This situation is made more complex because changes in protein binding may alter elimination as well as distribution. There is definitely a need to understand the therapeutic consequences of alterations in drug-protein binding in order to individualize drug therapy.

The major factors that affect drug-protein binding include the types of proteins available for binding, the binding affinities and capacities and the presence of competing substances, such as endogenous substances and other drugs. Albumin is the major protein in serum, and drug binding to albumin, consequently, has been studied in detail. Drug binding to alpha$_1$-acid glycoprotein and lipoprotein also has been shown to be of clinical significance for certain drugs. There are little data on the ability of other plasma proteins to bind most drugs.

For the purpose of discussing protein binding, drugs can be classified as either acidic or basic (Table II). Acidic drugs commonly bind to plasma albumin, and concomitantly administered acidic drugs may displace one another from their binding sites. Basic drugs may bind to either albumin or alpha$_1$-acid glycoprotein. If a drug is displaced from its binding protein by another drug or by a disease process, the concentration of free drug in plasma (and at the receptor site) will increase temporarily, an effect which then may increase temporarily the pharmacologic response.

Table II—Drugs More Than 90% Bound To Plasma Proteins

Basic drugs	Acidic drugs
Alfentanil	Acetylsalicylic acid
Amitriptyline	Cloxacillin
Chlorpromazine	Naproxyn
Desipramine	Penicillin
Diazepam	Phenylbutazone
Flurazepam	Phenytoin
Imipramine	Probenecid
Lidocaine	Sulfinpyrazone
Lorazepam	Tolbutamide
Nifedipine	Warfarin
Nortriptyline	
Propranolol	
Quinidine	
Verapamil	

The clinical impact of displacement depends on the total amount of drug in the body that is bound, the extent of displacement, whether the drug is also tissue-bound, the V_d and whether the drug is a high-clearance or low-clearance drug. High-clearance drugs are those with an extraction ratio (see below) of close to 1, so that the extraction usually is insensitive to the extent of protein binding. A low-clearance drug, on the other hand, has a lower extraction ratio, and the clearance of the drug may be very sensitive to protein binding.

Warfarin is an example of a low-clearance drug for which the clearance has been shown to vary with the fraction of unbound drug. Thus, after warfarin has been displaced from protein binding sites, $C_{p(free)}$ increases and clearance increases. The increased metabolism will result in the elimination of excess $C_{p(free)}$ and restore the original free-drug levels. Nevertheless, the initial release of bound drug may cause a temporary depletion of clotting factors and consequent bleeding.

The effects of protein displacement are usually of clinical significance only when binding exceeds 85 to 90%. Consider a drug which is 98% bound to plasma proteins. A displacement of 2% potentially will increase free-drug concentration by 100%. However, this does not mean necessarily that free-drug concentration in plasma actually will increase by 100%, because free drug usually distributes quickly into tissues. After redistribution, the actual increase in free-drug concentration in plasma depends on the V_d. If the V_d is large, the increase in plasma concentration may be minimal; if the V_d is small, the concentration at the receptor site may rise significantly and elicit an increase in intensity of drug action. To make matters more complex, a decrease in protein binding also can increase directly the V_d by decreasing the total concentration in plasma, from which the V_d is calculated.

Diseases can alter drug-protein binding by decreasing the amount of protein available for binding and by inhibiting drug binding. Table III lists some conditions that increase or decrease plasma proteins.

Hypoalbuminemia and elevated alpha$_1$-acid glycoprotein have been shown to have the most dramatic effect on drug-protein binding. A normal concentration of serum albumin is 4 g/dL, and a concentration of 2 g/dL would be considered

Table III—Conditions Capable of Altering Plasma Proteins

	Albumin	Alpha$_1$-Acid Glycoprotein
Decreased plasma protein	Burns	Nephrotic syndrome
	Chronic liver disease	
	Cystic fibrosis	
	Protein-losing enteropathy	
	Nephrotic syndrome	
	Pregnancy	
	Chronic renal failure	
	Trauma	
Increased plasma protein	Hypothyroidism	Celiac disease
		Crohn's disease
		Myocardial infarction
		Renal failure
		Rheumatoid arthritis
		Trauma

severe hypoalbuminemia. The effect of hypoalbuminemia on drug-protein binding has the greatest impact if 90% or greater of the drug is bound, if the number of binding sites on albumin are limited or if the drug has a low V_d. It has been shown that a change in plasma albumin concentration from 3.5 down to 2.3 g/dL causes the protein binding of phenytoin to change from 90% to 80.8%.[8] The reduced binding results in an inversely proportional increase in total plasma clearance, so that in steady-state the unbound-drug concentration remains unchanged. Thus, it is probably unnecessary to alter the total daily dose. However, the decrease in total plasma drug concentration poses a potential problem for the interpretation of routine plasma concentrations. This problem is discussed in further detail under *Drug Therapy in Renal Disease*.

Diseases also can affect the affinity of drugs for albumin. The best-known example occurs in chronic renal failure, in which accumulated endogenous compounds, which are not significantly removed by dialysis, displace acidic drugs from albumin binding sites. In disorders or situations in which free fatty acid levels are increased, acidic drugs are displaced from albumin binding sites. Quantitatively, when the free fatty acid/albumin ratio exceeds 3.5, the binding of acidic drugs usually is reduced significantly.[9]

Elimination

The elimination of drugs from the body usually occurs either by excretion into the urine or by biotransformation to metabolites that are eliminated in the urine or feces. The mechanisms whereby the kidneys and liver eliminate drugs and the pharmacokinetic principles behind these processes were presented in Chapters 35 and 36, respectively. In this section, emphasis will be placed on the practical application of these principles toward the development of individualized dosage regimens.

When drugs are approved by the FDA, their elimination has been studied in detail, usually only in healthy volunteers. Nevertheless, there is often enough information available to make rational decisions about the individualization of drug doses in patients who might have impaired elimination. The most important information is whether the drug is eliminated unchanged in the urine or biotransformed in the liver. With a drug for which the major route of elimination is renal, it is necessary to know if excretion is by tubular secretion, glomerular filtration or by a combination of secretion and filtration. With a drug of which the elimination is principally by the liver it is necessary to know if the biotransformation is primarily by a Phase I (oxidation) reaction or a Phase II (conjugation) reaction, if the metabolite(s) is/are pharmacologically active and if the drug exhibits first-pass metabolism. With the knowledge of these facts about each drug, one can determine if it is necessary to adjust the dosage regimen in a patient with kidney or liver impairment.

As indicated in Chapter 36, drug clearance is a more direct expression of elimination than is half-life. This is mentioned here only to remind the reader to be cautious about equating impaired renal or hepatic function with a change in drug half-life. If a decrease in the renal elimination of a drug is accompanied by an increase in half-life, it is necessary to know this to adjust the dosage regimen. However, the elimination half-life of a drug is a complex function of elimination and the V_d, and it is possible to have a change in the V_d in patients with renal or hepatic impairment such that there is no alteration in half-life. Furthermore, it is possible to have a drug with a high total body clearance yet a long half-life. This seeming contradiction occurs when drugs with a very high clearance also have a large V_d.

One class of drugs that displays this contradiction is the tricyclic antidepressants; the members have rapid clearances of about 1500 mL/min as the result of hepatic metabolism, but their plasma elimination half-life may be as long as 20 hr. Because of their large V_d (1000 to 2000 L) and rapid redistribution between tissues and plasma, drug cleared from the plasma almost completely is replaced by drug from the peripheral compartment. As already mentioned, this is important to remember when deciding about the use of extracorporeal (hemodialysis or hemoperfusion) systems to remove drugs from the body of an overdosed patient.

For a drug with a half-life of 20 hr it might appear that an extracorporeal system would enhance drug elimination. However, clearance of the tricyclic antidepressants by dialysis is small compared to normal hepatic clearance. If the drug also has a large V_d, redistribution likely would keep the plasma levels elevated and hemodialysis or hemoperfusion would have to be continued for an unusually long time to enhance significantly the removal of drug from the body.

Renal Excretion—Unchanged drug or drug metabolites can be eliminated from the body by way of the kidneys, as mentioned above. Drug excretion by this route takes place either as a result of filtration through the glomerulus, by tubular secretion or both. A knowledge of how a drug is excreted can be useful in predicting the effect that renal disease will have on its elimination. Drugs that are excreted by tubular secretion generally can be divided into organic acids, such as penicillin and probenecid, and organic bases such as cimetidine.

As indicated in Chapter 35, the organic acids and bases are secreted by separate transport systems. Among the organic acids there is competition in transport such that the coadministration of two such drugs can result in decreased elimination and elevated blood concentrations of each.

Sometimes this competition can be used to advantage, as in the administration of probenecid in combination with penicillin in the treatment of gonorrhea. The result is that the clearance of penicillin is reduced and the plasma penicillin concentrations remain high for a prolonged period of time; the combination is more effective than penicillin alone. Since the therapeutic index of penicillin is high, such interactions are useful. However, if probenecid is administered with the cytotoxic drug, methotrexate, the secretion of the latter drug is impaired and significant toxicity may occur. When tubular secretion is high, plasma protein binding usually does not affect active secretion by the proximal tubule.

Most drugs are excreted by the kidney via filtration across the glomerular membrane. Glomerular filtration is a passive, nonsaturable process. Because of the small size of the pores of the glomerular membrane, only free drug in plasma can be filtered; consequently, drugs that are bound to plasma proteins are filtered poorly. Displacement from proteins actually can increase the amount of drug filtered in the glomerulus and hence eliminated in the urine.

The glomerular clearance of drugs is directly proportional to the glomerular filtration rate (GFR). It follows that a decrease in GFR will result in a proportional decrease in the rate of glomerular elimination of a drug. Thus, measurement of the GFR can be very helpful in the individualization of dosage regimens in patients with impaired renal function. The GFR generally is estimated by measuring the clearance of either inulin or creatinine. Inulin must be infused intravenously, whereas creatinine, a product of muscle metabolism, is released *in vivo* at a relatively constant rate, thus obviating the need for constant intravenous infusion. Urinary creatinine excretion usually exceeds the amount filtered by about 10% because of a small amount of renal tubular secretion of creatinine. However, because determination of GFR by creatinine clearance is inexpensive and easy to do and, because the difference between inulin and

creatinine clearance is not significant *clinically*, creatinine clearance commonly is used to estimate GFR. It is very important to realize that the creatinine clearance is an accurate estimate of GFR only if renal function is stable. If renal function is decreasing, serum creatinine concentrations will be increasing, and it may take several days to reach a new steady-state. Until a new steady state is reached, the GFR cannot be estimated accurately from serum creatinine concentrations, and serum creatinine should not be used to calculate an individualized dose of a drug. Although creatinine clearance only measures the GFR, it frequently is used in the determination of the dosage regimens of drugs that are eliminated both by filtration and by tubular secretion. Unfortunately, there is no simple test to measure tubular secretion. Therefore, dosage adjustment based on creatinine clearance may not be appropriate for patients receiving drugs that are secreted actively by the renal tubules.[10]

The effect of changes in urine pH and urine flow on drug excretion already have been discussed in Chapter 35. In routine drug therapy, these parameters are not considered to be of great importance. However, the alkalinization of urine to pH 8 by the administration of sodium bicarbonate is used routinely to treat overdoses of phenobarbital and salicylates, since ionization of these weak acids reduces their reabsorption and increases their elimination.

Drug Therapy In Renal Disease—Drug administration to patients with impaired renal function is complicated by their associated medical problems, by the number of drugs they receive and by the alterations in drug disposition and elimination that occur. In renal disease, the protein binding of acidic or neutral, but not basic, drugs in plasma usually is altered. Some of the reasons to explain changes in protein binding include:

1. Hypoalbuminemia that occurs as a result of protein loss in the urine.
2. Competition for protein binding sites with small acidic molecules that accumulate in uremia.
3. Changes in the conformation of albumin that results in decreased affinity for binding sites.
4. Accumulation of drug metabolites that might displace parent drug from proteins.

Whichever the cause for changes in binding, the clinical importance of changes in plasma binding and/or protein concentration is that care must be used to interpret plasma drug concentrations.

Measured plasma drug concentrations usually are reported as total drug, ie, bound plus free drug. For example, therapeutic plasma concentrations of phenytoin in persons with normal plasma protein content are 10 to 20 mg/L, of which only 1 to 2 mg/L represents free drug. In patients with renal failure, the *free* phenytoin concentration is unchanged, whereas the *total* drug concentration falls to 5 to 10 mg/L, because of changes in protein concentration. The clinician might, therefore, be mislead into thinking that an increase in dose was necessary to increase the plasma concentration. In fact, because the free phenytoin levels are unchanged in patients with renal disease a dosage adjustment is not warranted. The renal elimination of metabolites can also be affected by impaired renal function.

The uremic state has been shown to have an effect on the biotransformation of many drugs. However, the effects of uremia on drug metabolism often are inconsistent and not predictable, and the clinical significance of such effects usually are not known. The clinical importance of the reduced elimination of drug metabolites is better understood. Table III in Chapter 36 lists active drug *metabolites*, many which are eliminated by the kidneys.

Procainamide is acetylated in the liver to *N*-acetylprocainamide, which has cardiac effects similar to those of the parent drug. This metabolite is eliminated by the kidneys, and its plasma concentration is increased in patients with impaired renal function. Patients with renal failure who are treated with procainamide should be observed closely for signs of clinical procainamide toxicity, and plasma concentrations of both procainamide and *N*-acetylprocainamide should be monitored.

Dosage adjustment of drugs in patients with renal impairment should be based on a knowledge of the pharmacokinetic parameters of the drug and, when indicated, on monitoring of plasma drug concentration. The aim of individualizing dosing regimens in patients with impaired elimination (renal or hepatic) is to maintain an average plasma concentration ($C_{p(ave)}$) similar to that of patients with normal elimination and, thus, to avoid unnecessary toxicity or loss of efficacy.

In Eq 32 in Chapter 36 it can be seen that $C_{p(ave)}$ is a direct function of dose (D) and bioavailability (f) and an inverse function of the dosing interval (τ) and clearance ($V_d \cdot k_{el}$). In the patient with impaired elimination or decreased clearance, $C_{p(ave)}$ will increase until a new plateau is reached (plateau principle). If clearance is impaired markedly or if the therapeutic index of the drug is small, toxicity may occur.

It is apparent from the same equation that either an appropriate decrease in dose or increase in the dosing interval will offset a decrease in elimination, and a $C_{p(ave)}$ can be attained that is similar to that in a nonimpaired patient.

In the patient with renal impairment, individualization of drug therapy requires knowledge of the degree of impairment and its effect on drug elimination in order to choose a proper dose or dosing interval to achieve a desired $C_{p(ave)}$. As discussed above, the endogenous creatinine clearance is usually the most practical index of GFR and it is used widely (with the limitations indicated) to determine the degree of renal impairment in a patient with renal disease.

The translation of the degree of impairment into a dosage regimen is not simple. In the literature there are a variety of nomograms and equations available to aid in calculating dosage regimens in patients with renal impairment. Each has its proponents and opponents and each is based on a set of assumptions that provide limitations to its use. None take into account all of the complexities discussed above. Therefore, a nomogram or an equation used to determine a dose of a drug to be given to a patient with renal impairment must be used only as a guideline and, when possible, should be used along with monitoring of plasma drug concentration, when indicated, and careful clinical observation to ensure optimal therapy.

Drug clearance in patients with renal insufficiency (Cl_{ri}) can be estimated from the relationship of the creatinine clearance in the renal-impaired patient, the creatinine clearance of normal persons and the clearance of drug by renal and nonrenal clearance mechanisms according to the equation

$$Cl_{ri} = Cl_{renal} \times \frac{Cl_{creat\ impaired}}{Cl_{creat\ normal}} + Cl_{nonrenal} \qquad (1)$$

where Cl_{renal} is the normal renal clearance, $Cl_{creat\ impaired}$ is the creatinine clearance in the patient, $Cl_{creat\ normal}$ is the creatinine clearance in normal persons and $Cl_{nonrenal}$ is the nonrenal clearance. The renal and nonrenal clearances may not be available; therefore, to determine a proper dosage regimen, one must rely on the pharmacokinetic information that is available in the literature; the elimination rate constants, k_{el}, in normal patients and in patients with complete anuria frequently are available. The values for these constants for many drugs have been listed in Table IV. Dettli[11] has derived a nomogram in which these elimination rate constants and the creatinine clearance can be used to determine an individualized dosage regimen for patients with

Table IV—Drug Elimination Rate Constants in Normal and Anephric Patients

Drug	Normal k_{el} (hr^{-1})	Anephric k_{el} (hr^{-1})
Alpha-methyldopa	0.17	0.03
Amikacin	0.40	0.04
Amoxicillin	0.70	0.10
Amphotericin B	0.04	0.02
Ampicillin	0.70	0.10
Carbenicillin	0.60	0.05
Cefazolin	0.40	0.04
Cephacetrile	0.70	0.03
Cephalexin	1.00	0.03
Cephalothin	1.40	0.04
Cephaloridine	0.50	0.03
Chloramphenicol	0.30	0.20
Chlorpropamide	0.02	0.008
Chlortetracycline	0.10	0.10
Clindamycin	0.47	0.10
Cloxacillin	1.40	0.35
Colistimethate	0.20	0.04
Digitoxin	0.004	0.003
Digoxin	0.017	0.006
Doxycycline	0.03	0.03
Erythromycin	0.50	0.14
Ethambutol	0.58	0.09
Fluorocytosine	0.24	0.01
Gentamicin	0.30	0.01
Isoniazid		
(fast acetylators)	0.60	0.20
(slow acetylators)	0.20	0.08
Kanamycin	0.40	0.01
Lidocaine	0.40	0.36
Lincomycin	0.15	0.06
Methicillin	1.40	0.17
Minocycline	0.05	0.03
Nafcillin	1.20	0.48
Oxacillin	1.40	0.35
Oxytetracycline	0.08	0.02
Penicillin G	1.40	0.05
Polymyxin B	0.16	0.02
Procainamide	0.22	0.01
Propranolol	0.20	0.16
Quinidine	0.07	0.06
Rifampin	0.25	0.25
Streptomycin	0.27	0.01
Sulfadiazine	0.08	0.03
Sulfamethoxazole	0.70	0.70
Tetracycline	0.08	0.01
Ticarcillin	0.60	0.06
Tobramycin	0.36	0.01
Trimethoprim	0.60	0.02
Vancomycin	0.12	0.003

decreased renal function. This nomogram is reproduced in Fig 37-2.

An example of how this nomogram can be applied is as follows. The ratio $k_{el(anephric)}/k_{el(normal)}$ is the fraction of the usual dose of a drug to be administered when there is anuria. When this ratio is entered on the left ordinate of the nomogram in Fig 37-2 and connected by a line to the upper-right-hand corner, the dose fraction is described for a range of creatinine clearances from 0 to 100 mL/min (100 mL/min is that of a normal 70-kg person). A line then is drawn vertically from the patient's creatinine clearance on the abscissa to the dose fraction line. From this point of intersection, a second line is drawn horizontally to the left ordinate of the nomogram. The point of intersection on the left ordinate is the dose fraction for that particular drug corresponding to the compromised creatinine clearance.

Insofar as the maintenance dose is concerned, the dosage regimen in the patient in renal failure can be modified by

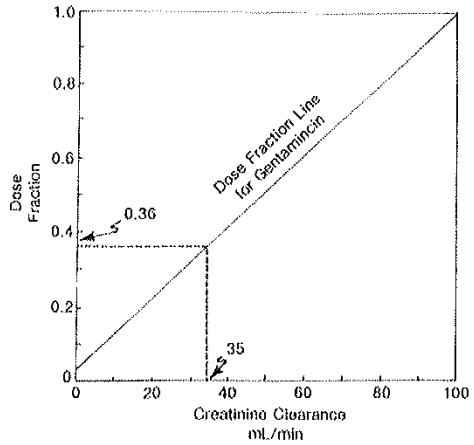

Fig 37-2. Nomogram used to determine the fraction of a dose that should be administered to a patient with a particular creatinine clearance. An example is given for a patient with a creatinine clearance of 35 mL/min and a ratio of $k_{el(anephric)}/k_{el(normal)}$ of 0.03. The dose fraction in this case is determined to be 0.36. This dose fraction then is used to adjust the dose or dosage interval for a patient with that degree of renal impairment (courtesy, adaptation, Dettli[11]).

adjusting either the dose or the dosage interval according to the calculated dose fraction. The maintenance dose can be adjusted by multiplying the normal dose by the dose fraction

$$D_{ri} = D \cdot \text{Dose Fraction} \quad (2)$$

where D_{ri} is the dose in renal insufficiency, D is the usual dose in normal persons and dose fraction is the value determined from the nomogram as described above. The dosage interval, τ, can be adjusted by dividing by the dose fraction

$$\tau_{ri} = \tau/\text{Dose Fraction} \quad (3)$$

where τ_{ri} is the dosage interval in renal insufficiency. An example of an adjustment in a gentamicin dosage regimen for a patient with an impaired creatinine clearance of 35 mL/min is as follows: the usual gentamicin dosage regimen in a patient with normal renal function is a loading dose of 80 mg followed by 80 mg every 8 hr. From Table IV it can be seen that

$$k_{el(anephric)}/k_{el(normal)} = 0.01/0.30 = 0.03$$

When 0.03 is entered on the left ordinate of the nomogram and a line is extended to the upper-right-hand corner, the dose-fraction line for gentamicin is described. From a creatinine clearance of 35 mL/min on the abscissa a line is drawn vertically to the gentamicin dose-fraction line. From this point of intersection a corresponding point on the left ordinate of the nomogram is a dose fraction of 0.36. The dosage interval then can be adjusted as

$$\tau_{ri} = \tau/\text{Dose Fraction}$$
$$= 8 \text{ hr}/0.36$$
$$= 22.2 \text{ hr}$$

Thus, in a patient with such an impaired renal function, a once-a-day dose of 80 mg is likely to maintain therapeutic plasma concentrations. The maintenance dose for gentamicin in this patient also could be adjusted using Eq 2 as follows

$$D_{ri} = D\cdot\text{Dose Fraction}$$
$$= 80\text{ mg}\cdot 0.36$$
$$= 28.8\text{ mg}$$

Thus, 29 mg administered every 8 hr would provide therapeutic plasma concentrations in this patient. The decision to adjust the dose or the dosage interval also should be individualized. Fluctuations in plasma concentration of gentamicin will be less if the dosage interval is lengthened to 24 hr. However, there may be a therapeutic reason to have peak plasma concentrations occur 3 times a day rather than only once. As mentioned above this, or any other nomogram or calculation for dosage adjustment, is only an approximation. Once the dosage adjustment has been made, careful clinical observation and, when indicated, monitoring of plasma concentrations is warranted. Since the loading dose depends primarily on the V_d, a change only in k_{el} does not necessitate a change in the loading dose.

Drug Therapy in Hepatic Disease—The biotransformation of drugs is discussed extensively in Chapter 35. Although many organs are involved in drug biotransformation, the liver is the most important. One might therefore assume that all patients with liver disease would demonstrate a predictable decline in drug elimination by the liver. This is not the case. There are several factors that complicate the management of drug therapy in patients with liver disease.

There are no routinely performed laboratory tests that predict the effect of liver disease on drug metabolism. Unlike the correlation between creatinine clearance and renal clearance of drugs, there is not a good correlation between the commonly available tests of liver function and drug clearance by the liver. In fact, the elimination rates of many biotransformed drugs are unaffected by liver disease.

Drug elimination by the liver may be affected by several factors including liver blood flow, protein binding and volume of distribution, in addition to drug-metabolizing capacity.

Liver disease is not a single well-defined entity but comprises a number of various structural and functional alterations. These include inflammation and necrosis, which generally alter only liver cell function and hence drug-metabolizing activity; cirrhosis, which may impair both liver cell function and liver blood flow; cholestasis, which may impair both biotransformation and biliary elimination and neoplasia, which may both impair cell function and decrease blood flow.

The discussion of biotransformation in Chapter 35 indicates that the process of hepatic elimination of drugs is complex, involving many different types of chemical reactions. While this is true, for practical purposes it is most important to know whether a drug is metabolized by an oxidation (Phase I) or conjugation (Phase II) reaction. The specific type of chemical reaction is of less clinical importance. Many drugs are biotransformed first by an oxidation reaction and the resulting metabolite then is conjugated to facilitate urinary excretion. In these cases it is the oxidation reaction that probably is most important.

The clinical significance of knowing the general reactions involved in the metabolism of drugs is related to administration of such drugs in the patient with hepatic impairment. It generally is accepted that liver disorders which affect hepatocyte cell function will impair drug oxidation long before drug conjugation is altered. A specific example occurs within the benzodiazepine class of drugs. On the one hand, chlordiazepoxide and diazepam are metabolized initially by oxidation reactions that have been demonstrated to be impaired in patients with alcoholic cirrhosis.[7,12]

Accordingly, the elimination of these drugs is decreased, and elevated blood levels may result during chronic therapy. On the other hand, oxazepam and lorazepam undergo only conjugation with glucuronic acid prior to being eliminated in the urine. Glucuronidation does not appear to be affected in clinically stable alcoholic cirrhosis, and the elimination of these drugs is no different than in healthy volunteers.[13,14] From a pharmacokinetic point of view, oxazepam and lorazepam are more rational choices than diazepam or chlordiazepoxide for use in patients with alcoholic cirrhosis.

Most studies of drug elimination in patients with liver disease have been performed in patients with either acute viral hepatitis or alcoholic liver disease. One should be careful about extrapolating these data to patients with other types of liver disease, such as chronic forms of hepatitis, neoplasias of the liver or cholestasis. Furthermore, one must not extrapolate studies of the metabolism of one drug in patients with liver disease to another drug, even though the metabolic reactions appear to be similar. There is a multiplicity of subpopulations of cytochrome P-450 enzymes. One drug may be metabolized by one of these subpopulations, while another drug is metabolized by another enzyme. For this reason, there is often poor correlation between the oxidations of two drugs.

Hepatic disease also can produce changes in serum proteins and in liver blood flow which can influence the elimination of drugs. Because the liver is the site of synthesis of serum proteins, patients with severe chronic liver disease frequently have decreased protein binding of drugs. In addition, there may be decreased protein binding as a result of qualitative changes in serum proteins. Liver blood flow is dominated by the portal venous system that drains the mesenteric veins. Thus, all drugs absorbed from the oral route pass through the liver via the portal vein. In certain types of liver disease, most commonly alcoholic cirrhosis, there is shunting of the portal circulation away from functioning hepatocytes. This leads to increased pressures within the portal system and shunting of drugs away from the drug-metabolizing enzymes.

One method of classifying drugs by the characteristics of hepatic elimination is to divide them into those with a high hepatic extraction ratio and those with a low hepatic extraction ratio. As described in the explanation of Eq 23 of Chapter 36, the hepatic extraction ratio is defined as

$$E = \frac{C_{ap} - C_v}{C_{ap}}$$

where C_{ap} is the hypothetical mean of mixed hepatic arterial and portal venous drug concentrations, and C_v is the hepatic venous drug concentration. The hepatic clearance, Cl_H, of a drug is determined by its extraction ratio as

$$Cl_H = HBF\cdot E$$

where HBF is total hepatic blood flow. The classification of drugs according to their hepatic extraction ratios is shown in Table V. Hepatic blood flow is usually the rate-limiting factor in the hepatic clearance of drugs with high extraction

Table V—Classification of Drugs According to Their Hepatic Extraction Ratios

Drugs with an Extraction Radio Greater than 0.5	
Lidocaine	Nortriptyline
Propranolol	Morphine
Pethedine	Labetalol
Pentazocine	Verapamil
Propoxyphene	Metoprolol
Drugs with an Extraction Ratio Less than 0.5	
Binding-Sensitive	*Binding-Insensitive*
Phenytoin	Theophylline
Diazepam	Acetaminophen
Tolbutamide	Hexobarbital
Warfarin	Chloramphenicol
Chlorpromazine	
Digitoxin	
Quinidine	

ratios, and the metabolism of such drugs are considered to be *flow-limited* metabolism. These drugs demonstrate first-pass metabolism in that after oral administration a major portion of the drug does not reach the systemic circulation. Their bioavailability is low and their metabolism is sensitive to anything that alters hepatic blood flow. Thus, for example, the elimination of lidocaine can be decreased substantially in patients with congestive heart failure, which usually causes a reduction in hepatic blood flow. In patients with cirrhosis and portal hypertension, the shunting of blood away from functioning hepatocytes has the greatest impact on drugs with a high hepatic extraction ratio. In patients with portal hypertension, the bioavailability of drugs with a high extraction ratio may be increased significantly, so that toxic blood levels may result. At the present time there is no routine laboratory test that will predict this effect in an individual patient. Rather, it is advisable to start with a low dose of drug and increase the dose slowly to achieve the desired response.

The rate of metabolism for drugs with a low extraction ratio is dependent on the concentration of drug at the hepatic enzyme site, which is proportional to the free concentration of drug in plasma. Consequently, drugs in this class can be divided further into those in which hepatic elimination is either sensitive or insensitive to protein binding. Drugs with a hepatic elimination distinctly sensitive to protein binding are generally 80 to 99+% bound, whereas drugs with a hepatic elimination clearly insensitive to protein binding are less than 30% bound. Conditions that affect plasma protein binding can have a significant effect on the hepatic clearance of a binding-sensitive drug but usually not a binding-insensitive drug.

Although much is known about the hepatic metabolism of drugs and the factors that can affect their hepatic elimination, the use of drugs in patients with potential altered hepatic clearance is still empirical in that there are no specific guidelines relating the severity of hepatic disease and drug elimination. To a great extent this is due to the multiplicity of drug-metabolizing enzymes, and it is unlikely that a single or simple battery of laboratory tests will suffice to predict the hepatic elimination of all drugs. Applying the known facts about liver disease along with the knowledge of drug elimination by the liver usually will permit a rational use of drugs in patients with disorders of the liver.

Therapeutic Drug Monitoring

Rational drug therapy requires individualization of the dosage regimen for a particular patient. In many instances this can be done by *monitoring the clinical response* to drug therapy. For example, if a patient with hypertension is not responding to therapy and there is no reason to suspect poor compliance, it may be appropriate to increase the dose until the patient's blood pressure is under control. Whenever a drug is administered, well-defined therapeutic end-points should be a preferred part of the management plan.

Observation of the clinical response or monitoring a reliable laboratory test may be easy with certain classes of drugs such as antihypertensives, oral hypoglycemics, oral anticoagulants, analgesics or drugs used to lower serum uric acid or serum lipids. For other drugs, the definition of a therapeutic end-point may not be clear or the onset of toxicity may occur at dosages only slightly above therapeutic concentrations. For some of these drugs one should monitor the serum drug concentration and thus determine if the dose administered to an individual patient is achieving therapeutic concentrations.

The following are several criteria and typical examples that should be considered before measured drug serum concentrations are of clinical value.

The drug must have a reversible action. An example of drugs with irreversible action would be the alkylating agents which exert a lasting effect after a single dose. At the present time there seems to be little need for routinely monitoring the plasma concentration of these drugs.

The development of tolerance at the receptor site should not occur. A therapeutic concentration range for morphine is not rational, since the dose requirements may increase with use.

The pharmacokinetic properties of the drug are taken into account in the blood sampling schedule. If sampling is performed in a maintenance regimen, steady state should have been achieved prior to sampling. Steady state may occur 4 to 5 half-lives after the initiation of therapy if a loading dose is not administered. Changes in drug half-life produced by disease must be taken into account. Qualitative differences in the metabolism or excretion of drugs also are known to occur in patients with hepatic and/or renal disease. For example, patients with impaired renal function may experience prolonged respiratory depression when treated with morphine, due, in part, to the accumulation of an active metabolite, morphine-6-glucuronide. For drugs with a short half-life, peak (1 or 2 hr after oral dosing) and trough (predosing) determinations are advisable. The distribution phase should be complete before drug concentrations are measured. Slow-release formulations of drugs have different absorption characteristics and different plasma concentration versus time profiles that must be taken into account when interpreting a single plasma concentration. The chronic administration of some drugs (ie barbiturates) results in the induction of hepatic drug-metabolizing enzymes. A decrease in the steady-state plasma concentration of that drug, or others metabolized by the induced hepatic enzymes, may occur unless the dose of that drug is increased.

The presence of active metabolites should be taken into consideration. The serum concentrations of the *N*-acetylprocainamide metabolite of procainamide should be considered when assessing antiarrhythmic activity after administering procainamide. This is particularly true in patients with renal failure who may eliminate the metabolite slowly. Active metabolites also are responsible for toxicity (ie acetaminophen). Most assays for the measurement of plasma drug concentrations do not account for active toxic metabolites that are present at very low plasma concentrations.

The analytical method must be sensitive enough to measure accurately the expected serum concentrations and selective enough to be certain that interfering substances will not influence the results. Most clinical drug assays do not distinguish between enantiomers if a racemic mixture of drug is administered. It is important to consider this when interpreting the plasma concentration of a drug if one enantiomer is more active or there is stereoselective disposition. The (*S*)-warfarin enantiomer is about five times more potent in man than the (*R*)-enantiomer; the *S*-(+)-enantiomer of disopyramide is bound more avidly to plasma proteins than its corresponding *R*-(−)-enantiomer. Some drugs (ie phenytoin) may be adsorbed by plastics in intravenous tubing, syringes and blood-collection tubes. When analytical results do not fit the clinical situation, consideration should be given to adsorption as a potential problem.

The data must be evaluated in the context of sound clinical judgment. Treat the patient, not the serum drug concentration. An example is the patient who is taking digoxin and develops a low plasma potassium. Hypokalemia makes the myocardium more sensitive to the rhythm disorders produced by digoxin. Thus, the patient with a normal serum digoxin concentration may experience drug-induced cardiotoxicity if hypokalemia also is present.

Table VI—Therapeutic Ranges for Drugs

Amikacin	Trough	4–8	mg/L
	Peak	20–30	mg/L
Carbamazepine		4–8	mg/L
Digoxin		0.8–2	μg/L
Disopyramide		2–5	mg/L
Ethosuximide		40–100	mg/L
Gentamicin	Trough	0.5–2	mg/L
	Peak	5–10	mg/L
Lidocaine		1.2–5	mg/L
Phenobarbital		15–40	mg/L
Phenytoin		10–20	mg/L
Primidone (see phenobarbital)		5–12	mg/L
Procainamide		4–10	mg/L
N-Acetylprocainamide		10–30	mg/L[a]
Quinidine		1.5–4.5	mg/L
Theophylline		10–20	mg/L
Tobramycin	Trough	0.5–2	mg/L
	Peak	4–10	mg/L
Valproic Acid		50–100	mg/L

[a] Total of procainamide and *N*-acetylprocainamide.

Table VII—Pharmacokinetic Parameters of Commonly Monitored Drugs

Drug	Volume of distribution (L/kg)	Protein binding (%)	Oral availability (%)	Route of elimination	Half-Life		Dose adjustment required	
					Normal	Anephric	Renal failure	Liver failure
Amikacin	0.25	<5	Parenteral only	Renal	3 hr	2–4 days	Yes	No
Carbamazepine	0.8–1.4	75	70	Hepatic—epoxide metabolite is active	10–26 hr	—	No	No
Digoxin	5.1–7.4	20–40	50–93	Renal	33–51 hr	3.6 days	Yes	No
Disopyramide	0.5	50–80	80–85	Renal and Hepatic	6–10	45	Yes	No
Ethosuximide	0.62	Negligible	100	Hepatic	60 hr adults 30 hr children	—	No	No
Gentamicin	0.25	<5	Parenteral only	Renal	2 hr	2–3 days	Yes	No
Lidocaine	1.6	60	Parenteral only	Hepatic—metabolites are active	1.5 hr	—	No	Yes
Phenobarbital	1.0	46	80–100	Hepatic primarily	3–4 days	—	No	Yes
Phenytoin	0.6	90	90	Hepatic	10–30 hr concentration dependent	—	No	Only in severe cases
Primidone	0.6	14	100	Hepatic—phenobarbital and phenyl-ethylmalonyl-amide (PEMA) are active metabolites	3–12 hr 29–36 hr metabolites	—	No	No
Procainamide	2.2	15	75–95	Renal and Hepatic *N*-acetylprocainamide is active	2.5–4.5 hr	10–15 hr	Yes	No
Quinidine	0.5	60–80	70–95	Hepatic—metabolite active	6 hr	—	No	No
Theophylline	0.3–0.6	55	Complete	Hepatic	3–9 hr	—	No	Yes
Tobramycin	0.25	<5	Parenteral only	Renal	2 hr	2–4 days	Yes	No
Valproic acid	0.2	90	70–100	Hepatic	10–15 hr	—	No	Yes, use with caution

Therapeutic drug monitoring requires as much clinical skill as does titration of an oral anticoagulant dose by monitoring the prothrombin time. A basic assumption in this principle is that free drug at the *active site* is in equilibrium with total drug in plasma or serum. This has been shown probably to be true for many drugs. Furthermore, for these drugs, optimum therapeutic effects and minimal toxicity is observed when the serum drug concentration lies within an empirically determined therapeutic plasma concentration range. However, there is overlap between the therapeutic and subtherapeutic serum drug concentrations. Therefore, therapeutic drug monitoring should be considered as an aid to, not a substitute for, careful clinical observation in the management of drug therapy.

The purpose of this section is to provide some guidelines to follow for therapeutic drug monitoring and some of the salient features of the drugs being monitored. Table VI contains a list of drugs commonly monitored and the serum concentrations thought to represent the therapeutic range.

Interpretation of plasma drug concentrations clearly requires a broad knowledge of clinical pharmacokinetics. Recently, several sources of pharmacokinetic data have become available.

An appendix of pharmacokinetic data, developed by Benet and Sheiner,[15] is available. Included are excellent compilations of availability, urinary excretion, protein binding, clearance, volume of distribution, half-life and therapeutic and toxic concentrations for most of the currently used drugs. Data are accompanied by references so that the original work can be documented.

The newsletter, *Perspectives in Clinical Pharmacy*,[16] provides timely discussions of popular topics in clinical pharmacokinetics.

Another useful reference is by Gerson.[17] Included are chapters on the major drug classes with detailed discussions of the commonly used drugs.

The pharmacokinetics of abused substances are covered by Barnett and Chiang.[18]

Table VII provides important pharmacokinetic information for commonly monitored drugs. A sound knowledge of the clinical pharmacokinetics of each drug, a critical use of plasma drug concentrations as described above and a thorough clinical evaluation of the patient will provide the data required for the development of rational drug therapy.

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CHAPTER 38

Topical Drugs

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A large number of chemical agents may be applied to the skin and mucous membranes for their local effects. Many of these, such as antibiotics, antiseptics, corticosteroids, antineoplastics and local anesthetics, belong to distinct pharmacologic classes treated elsewhere in this text, and will not be discussed in this chapter. The remainder comprise a heterogeneous group of agents which, by exclusion, are mostly nonselective in action.

Those locally acting agents that have limited chemical and pharmacologic activity generally have a *physical* basis of action. Included in this group are protectives, adsorbents, demulcents, emollients and cleansing agents. The relative inertness of many of these substances renders them of value as vehicles and excipients. Consequently, many in this group are also pharmaceutical necessities and may be treated in Chapter 66.

Those locally acting agents that have general *chemical* reactivity include most astringents, irritants, rubefacients, vesicants, sclerosing agents, caustics, escharotics, many keratolytic (desquamating) agents and a miscellaneous group of dermatologics including hypopigmenting and antipruritic agents.

Although the skin and mucous membranes differ considerably in structure and function, they are similar in penetrability (to chemical agents) and in their response to certain physical and pharmacologic stimuli. Thus, many of the agents found in this chapter may be applied to both types of surfaces. Nevertheless, it is obvious that many agents, for which there is either contraindication or no rationale for their application to the mucous membranes, may be applied only to the skin.

In its broadest pharmacologic sense a protective is any agent that isolates the exposed surface (skin or mucous membrane) from harmful or annoying stimuli. In common practice only those substances that protect by mechanical or other physical means are considered to be protectives, although the surface action of adsorbents and demulcents cannot be divorced from their chemical properties. Protectives such as demulcents and emollients customarily are placed in separate categories; that practice is followed here.

The abridged category of protectives mainly comprises the dusting powders, adsorbents, mechanical protective agents and plasters.

Protectives and Adsorbents

Dusting Powders

Certain relatively indifferent (inert and insoluble) substances are used to cover and protect epithelial surfaces, ulcers and wounds. Usually these substances are subdivided very finely. They generally absorb moisture and, therefore, also act as cutaneous desiccants. The absorption of skin moisture decreases friction and also discourages certain bacterial growth.

The water-absorbent powders should not be administered to wet, raw surfaces because of the formation of cakes and adherent crusts. Starch and other carbohydrate powders not only may become doughy but they also may ferment. Consequently, such powders often contain an antiseptic. Most impalpable powders are absorptive, to some extent. Whether absorption of substances, other than water, contributes to the protection of the skin is uncertain; however, absorption of fatty acids and other constituents of perspiration, along with cutaneous drying, contributes to a deodorant action of the powders. It generally is held that the adsorptive capacity is important to the gastrointestinal protective action of chemically inert powders taken internally.

The chemically inert dusting powders are not entirely biologically inert, despite the name. When entrained in pores or wounds or left upon parietal surfaces, certain of the dusting powders, eg, talc, may cause irritation, granulomas, fibrosis or adhesions. Even without direct irritation or obstruction of the perspiration, dust can be troublesome.

Several of the dusting powders are incorporated into ointments, creams and lotions.

Bentonite—page 1305.
Boric Acid—page 1318.
Calcium Carbonate, Precipitated—page 776.
Talc—page 1327.
Titanium Dioxide—page 772.
Zinc Oxide—page 762.

Zinc Stearate

Octadecanoic acid, zinc salt

Zinc stearate [557-05-1]. A compound of zinc with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of zinc stearate and zinc palmitate. It contains the equivalent of 12.5–14.0% of ZnO(81.38).

Preparation—An aqueous solution of zinc sulfate is added to a sodium stearate solution, and the precipitate is washed with water until free of sulfate and dried.

Description—Fine, white, bulky powder, free from grittiness with a faint characteristic color; neutral to moistened litmus paper.

Solubility—Insoluble in water, alcohol or ether but is soluble in benzene.

Uses—In *water-repellent* ointments and as a *dusting powder* in dermatologic practice for its desiccating, astringent and *protective* effects. It has been removed from baby dusting powders, owing to accidental, fatal inhalations.

Mechanical and Chemical Protectives

Several materials may be administered to the skin to form an adherent, continuous coat which either may be flexible or semirigid, depending upon the substances and the manner in which they are applied. Such materials may serve three purposes: (1) to provide occlusive protection from the external environment, (2) to provide mechanical support and (3) to serve as vehicles for various medicaments.

The two principal classes of mechanical protectives are the collodions and plasters. Neither is used to much extent today. This is because there is increasing recognition of the beneficial effects of air in maintaining a normally balanced cutaneous bacterial flora of low pathogenicity. Also, the mechanical protectives may of themselves be somewhat irritating because of interference with normal water transport through the skin caused by certain oleaginous and resinous ingredients, especially in plasters. It also is recognized that rubber in adhesive plaster may induce eczema. The cerates may be employed similarly to the plasters. Bandages, dressings and casts also afford mechanical protection and support (see Chapter 105 for additional information). A brief discussion of plasters is included in Chapter 87.

A number of insoluble and relatively inert powders remain essentially unchanged chemically in the gastrointestinal tract. If the particles possess surface properties that favor their clinging to the gastrointestinal mucosa, and especially if they split up into tabular shapes, they offer mechanical protection against abrasion and may even offer slight protection against toxins and chemical irritants. Many such protectives also are adsorbents (charcoal, bismuth compounds, kaolin) or astringents (zinc and bismuth compounds). They are discussed under those categories.

Aluminum Hydroxide Gel—page 775.

Collodion

Contains not less than 5.0%, by weight, of pyroxylin.

Pyroxylin	40 g
Ether	750 mL
Alcohol	250 mL
To make about	1000 mL

Add the alcohol and the ether to the pyroxylin contained in a suitable container, and stopper the container well. Shake the mixture occasionally until the pyroxylin is dissolved.

Description—Clear, or slightly opalescent, viscous liquid; colorless, or slightly yellowish and has the odor of ether; specific gravity between 0.765 and 0.775.

Alcohol Content—22 to 26% of C_2H_5OH.

Uses—Chiefly to seal small wounds, for the preparation of medicated collodions and to protect nonaffected areas of the skin from topically applied irritants, corrosives, etc.

Caution—Collodion is highly flammable.

Flexible Collodion [Collodium Flexile]—See *RPS 16*, page 717. See also *Salicylic Acid Collodion* (page 768).

Absorbable Gelatin Film

Gelfilm (*Upjohn*)

A sterile, nonantigenic, water-insoluble, gelatin film obtained from a specially prepared gelatin-formaldehyde solution by drying on plates at constant temperature and humidity with subsequent sterilization by dry heat at 146° to 149°C for 12 hr.

Description—Light amber, transparent, pliable film that becomes rubbery when moistened.

Solubility—Insoluble in water; it assumes a rubbery consistency after being in water for a few minutes.

Uses—Both as a *mechanical protective* and as a *temporary supportive structure* and *replacement matrix* in *surgical repair of defects in membranes*, such as the dura mater and the pleura. When emplaced between damaged or operated structures, it prevents adhesions. When moistened, the film becomes pliable and plastic, so that it can be fitted to the appropriate surface. Absorption requires 1 to 6 months. It is also a component of stomadhesive, to be placed around an ostomy.

Dose—Applied in the form of sheets, previously soaked in isotonic sodium chloride solution and cut to the desired shape.

Dosage Forms—Film: 100 × 125 mm; Ophthalmic Film: 25 × 50 mm.

Zinc Gelatin

Zinc Gelatin Boot; Unna's Boot; Unna's Paste

Zinc Oxide	100 g
Gelatin	150 g
Glycerin	400 g
Purified Water	350 g
To make about	1000 g

Gradually add the gelatin to the cold purified water, with constant stirring, allow the mixture to stand for 10 min, and then heat on a steam bath until the gelatin dissolves. Add the zinc oxide, which previously has been rubbed to a smooth paste with the glycerin, and stir carefully until a smooth jelly result.

Uses—Melted and applied in the molten state between layers of bandage to act as a *protective* and to support varicosities and similar lesions of the lower limbs. After a period of about 2 weeks the dressing is removed by soaking with warm water.

Dose—*External*, as an occlusive boot.

Dosage Forms—Impregnated Gauze, in 10-yd lengths in following widths: 2¼, 2½, 3 and 4 in; impregnated with white or pink paste (the latter colored with a small amount of ferric oxide).

Kaolin—page 796.

Lanolin—page 1312.

Lanolin, Anhydrous—page 1311.

Mineral Oil—page 788.

Mineral Oil Emulsion—page 788.

Mineral Oil, Light—page 788.

Olive Oil—page 1309.

Peanut Oil—page 1303.

Petrolatum—page 788.

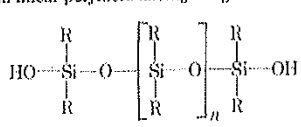
Other Mechanical and Chemical Protectives

Petrolatum Gauze [Petrolated Gauze]—Absorbent gauze saturated with white petrolatum. The weight of the petrolatum is 70–80% of the weight of the Gauze. It is sterile. Prepared by adding, under aseptic conditions, molten, sterile, white petrolatum to dry, sterile, absorbent gauze, previously cut to size, in the ratio of 60 g of petrolatum to each 20 g of gauze. *Uses:* A *protective* dressing; also as packing material for postoperative plugs, packs, rolls and tampons, and as a wick, drain or wrap-around for tubing. It is claimed that there is no danger of tissue maceration and that no growth of granulation tissue through it occurs.

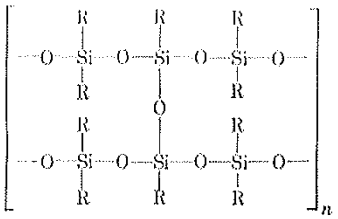
Dimethicone [Poly(dimethylsiloxane; poly[oxy(dimethylsilylene)] [9006-65-9] $(C_2H_6OSi)_n$]—A water-repellent silicone oil consisting essentially of dimethyl siloxane polymers of the 200 series of fluids (see *Silicones*, below). It is a water-white, viscous, oil-like liquid; immiscible with water or alcohol; miscible with chloroform or ether. *Uses:* Has skin-adherent and water-repellent properties. It is both a protective and an emollient, for which its FDA classification is Category 1. Applied to the skin, it forms a *protective* film that provides a barrier to ordinary soap and water and water-soluble irritants. The film may last several hours if the skin is exposed mainly to aqueous media. The film provides a less-effective barrier to synthetic detergents and lipid-soluble materials, such as organic solvents. It should not be applied except in contact dermatoses and dermatoses aggravated by substances that can be repelled by the silicone. It is useful in preventing irritation from ammonia produced by the urine of infants, but it may exacerbate preexisting irritation. The occlusive protection by the silicone is detrimental to inflamed, traumatized, abraded or excoriated skin and to lesions requiring free drainage. However, applied adjacent to such lesions, it offers protection against irritating discharges and maceration. It practically is harmless, and does not sensitize skin but it does cause temporary irritation to the eyes. It may be incorporated into ointments, creams and gels. *Dose:* Apply uniformly with rubbing 3 or 4 times for the first day or two, then twice daily. *Dosage Forms:* Aerosol, Cream and Ointment: 20 and 30%. All concentrations from 1 to 30% are approved.

Silicones (*Polyorganosiloxanes*)—These are organosilicon polymers containing chains of alternating oxygen and silicon atoms with substituent organic groups, frequently methyl or phenyl, attached to each silicon atom.

Preparation: These polymers may be prepared synthetically by condensing alkylated or arylated *silanols*. Disubstituted *silanediols* $[R_2Si(OH)_2]$ form linear polymers having the general formula:



Cross-linked polymers result from condensation of mixtures of substituted silanediols and monosubstituted *silanetriols* [$RSi(OH)_3$], represented by the following partial formula where R is a hydrocarbon radical:



One method of preparation involves interaction of silicon tetrachloride with appropriate Grignard reagents to yield alkylated or arylated dichlorosilanes. After hydrolysis to the corresponding substituted silanols, dehydration procedures are used to effect condensation polymerization. The overall reaction, as it involves a disubstituted silanediol, may be represented as:

$$SiCl_4 \xrightarrow{RMgX} R_2SiCl_2 \xrightarrow{HOH} R_2Si(OH)_2 \xrightarrow{-HOH} HO[Si(R)_2O]_nH$$

Silicon tetrachloride	Disubstituted dichlorosilane	Disubstituted silanediol	Silicone linear polymer

Properties: Silicones with a wide range of properties may be produced by varying the substituent R and the degree of cross-linking. Physically, silicones vary from mobile liquids through viscous liquids and semisolids to solids. Viscosities range from 0.65 to 1,000,000 centistokes. In general, they display high- and low-temperature stability. They are odorless, tasteless, relatively inert chemically and physiologically, water-repellent and possess antifoam characteristics. Unmodified silicones are generally insoluble in water; because of this the liquids often are termed *silicone oils;* however, a water-soluble sodium salt of a simple silicone, chemically *sodium methyl siliconate* [$CH_3Si(OH)_2ONa$], has been marketed.

Uses: Preparations containing silicones have various dermatological uses (see *Dimethicone*) and are used as ingredients of bases for ointments and liniments. In the form of inhalation sprays, silicone preparations have been employed in the treatment of pulmonary edema involving frothing of fluid in the upper respiratory tract. They also are used orally as antiflatulent or gastric defoaming agents (see *Simethicone*, page 799). A silicone *bouncing putty* has found acceptance for use as a physical agent in treating conditions requiring finger exercise. The water-repellent properties of the silicones have found considerable use in a great variety of applications where complete drainage of aqueous fluids from surfaces is desirable.

Silicones virtually are nonirritating; consequently, silicone rubbers are used in various indwelling catheters, tubes, etc, and in some types of prostheses. Liquid silicones are used also to fill in hypoplastic body areas for cosmetic purposes, although they tend to relocate because of flow under gravity and motion.

In addition to uses involving antifoaming, water-repellent and nonirritating characteristics, silicones also are employed to prevent sticking of one object to another and then are referred to commonly as release agents. Examples of such employment include release of rubber and plastics from molds, food from metal, ice from the wings of aircraft and capsules and tablets from molds and dyes in which they are fabricated.

Silicone rubbers are used to encapsulate steroid hormones and other drugs intended for chronic use, in order to retard absorption and effect a repository action lasting in some instances for as long as 1 yr. Continuing developments in this field offer interesting possibilities.

Zinc Carbonate [CO_3Zn(125.38)]—White rhombohedroids. Soluble 10 ppm in water at 15°; soluble in dilute acids, alkalies or solutions of ammonium salts. *Uses:* Both for its lubricity and as a drying agent. As a skin protectant it falls into FDA Category I. It is included in commercial topical burn and sunburn products and extemporary protectants. *Dose:* 0.2 to 2%.

Demulcents

Demulcents are protective agents that are employed primarily to alleviate irritation (*demulcere*—to smooth down), particularly of mucous membranes or abraded tissues. They also often are applied to the skin. They generally are applied to the surface in viscid sticky preparations that cover the area readily. The local action of chemical, mechanical or bacterial irritants, thereby, is diminished, and pain, reflexes, spasm or catarrh are attenuated. They also prevent drying of the affected surface. The demulcents may be applied to the skin in the form of lotions, cataplasms or wet dressing, to the gastrointestinal tract in the form of demulcent liquors or enemas and to the throat in the form of pastilles, lozenges or gargles. Demulcents also are included in artificial tears and in wetting agents for contact lenses. When demulcents are applied as solid material (as in lozenges or powders), the liquid is provided by secreted or exuded fluids. Demulcents frequently are medicated. In such instances the demulcent may be an adjuvant, a corrective or a pharmaceutical necessity. Many of the demulcents are also laxatives (page 783) and are used as such, or they are used with laxatives or antacids for their demulcent and lubricating action.

A variety of chemical substances possess demulcent properties. Among these are the alginates, mucilages, gums, dextrins, starches, certain sugars and polymeric polyhydric glycols. Mucus, in itself, is a natural demulcent. Certain silicates that form silicic acid on exposure to air or gastric juice and glycerin, although it is of low molecular weight and has relatively low binding power, frequently are placed among the demulcents. Also the colloidal hydrous oxides, hydroxides and basic salts of several metals are claimed to be demulcent, but acceptable clinical proof of the claim has not been provided.

The hydrophilic colloidal properties of most of the demulcents make them valuable emulsifiers and suspending agents in water-soluble ointments and suspensions. They also retard the absorption of many injections and, thus, may be employed in sundry depot preparations. Many of the demulcents mask the flavor of medicaments by means of at least three physical phenomena: (1) they apparently coat the taste receptors and render them less sensitive, (2) they incorporate many organic solutes into micelles and, thereby, diminish the free concentration of such solutes and (3) they coat the surfaces of many particles in suspension. Because of the adhesiveness of the demulcents, they are employed widely as binding agents in tablets, lozenges and similar dosage forms. Consequently, certain demulcents will be discussed in Chapter 66.

Acacia—page 1304.

Benzoin

Gum Benjamin; Benzoe

The balsamic resin obtained from *Styrax benzoin* Dryander or *Styrax parallelonеurus* Perkins, known in commerce as Sumatra Benzoin, or from *Styrax tonkinensis* (Pierre) Craib ex Hartwich, or other species of the Section *Anthostyrax* of the genus *Styrax*, known in commerce as Siam Benzoin (Fam *Styraceae*).

Sumatra benzoin yields not less than 75.0% of alcohol-soluble extractive, and Siam benzoin yields not less than 90.0% of alcohol-soluble extractive.

Constituents—Siam benzoin contains about 68% of crystalline *coniferyl benzoate* [$C_{17}H_{16}O_4$]; up to 10% of an amorphous form of this compound is also present. Some *coniferyl alcohol* (*m-methoxy-p-hydroxycinnamyl alcohol*, mp 73–74°) occurs in the free state as well. Other compounds that have been isolated are *benzoic acid* 11.7%, *d-siaresinolic acid* 6%, *cinnamyl benzoate* 2.3% and *vanillin* 0.3%.

Sumatra benzoin has been reported to contain benzoic and cinnamic acid esters of the alcohol *benzoresinol* and probably also of coniferyl alcohol, free *benzoic* and *cinnamic acids*, *styrene*, 2 to 3% of *cinnamyl cinnamate* (also called *styracin*), 1% of *phenylpropyl cinnamate*, 1% of *vanillin*, a trace of *benzaldehyde*, a little *benzyl cinnamate* and the alcohol *d-sumaresinol* [$C_{30}H_{48}O_4$].

Description—*Sumatra Benzoin:* Blocks or lumps of varying size made up of compacted tears, with a reddish brown, reddish gray or grayish brown resinous mass. *Siam Benzoin:* Compressed pebble-like tears of varying size and shape. Both varieties are yellowish to rusty

brown externally and milky white on fracture; hard and brittle at ordinary temperatures but softened by heat; aromatic and balsamic odor; aromatic and slightly acrid taste.

Uses—A *protective* application for irritations of the skin. When mixed with glycerin and water, the tincture may be applied locally for *cutaneous ulcers, bedsores, cracked nipples* and *fissures* of the lips and anus. For throat and bronchial inflammation, the tincture may be administered on sugar. The tincture and compound tincture sometimes are used in boiling water as steam inhalants for their *expectorant* and *soothing action* in acute laryngitis and croup. In combination with zinc oxide, it is used in baby ointments.

Dose—*Topical*, as a 10% tincture or compound tincture (below).

Compound Benzoin Tincture [Balsamum Equitis Sancti Victoris, Balsamum Commendatoris, Balsamum Catholicum, Balsamum Traumaticum, Balsamum Vulnerarium, Balsamum Persicum, Balsamum Suecium, Balsamum Friari, Balsamum Vervaini, Guttae Nader, Guttae Jesuitarium, Tinctura Balsamica, Balsam of the Holy Victorious Knight, Commander's Balsam, Friar's Balsam, Turlington's Drops, Persian Balsam, Swedish Balsam, Vervain Balsam, Turlington's Balsam of Life, Balsam de Maltha, Ward's Balsam, Jerusalem Balsam, Saint Victor's Balsam, Wade's Drops, Wound Elixir and Balsamic Tincture]—*Preparation:* With benzoin (in moderately coarse powder, 100 g), aloe (in moderately coarse powder, 20 g), storax (80 g) and tolu balsam (40 g), prepare a tincture (1000 mL) by Process M (page 1543), using alcohol as the menstruum. *Alcohol Content:* 74 to 80% of C_2H_5OH. *Uses:* Especially valuable in acute *laryngitis*, also in croup, when added to hot water and the vapor inhaled. By adding a teaspoonful of the tincture to boiling water in an inhaler, and inhaling the vapor, very effective results may be obtained. See Chapter 104. Also administered, on sugar, for throat and bronchial inflammation and as a local application, when mixed with glycerin and water, for *ulcers, bedsores, cracked nipples* and *fissures* of the lips and anus. *Dose: Topical*, as required; *inhalation*, 1% in very hot water.

Carbomer Methylcellulose—page 1306.
Gelatin—page 1306.
Glycerin—page 931.
Glycerin Suppositories—page 785.
Glycyrrhiza—page 1295.
Hydroxypropyl Cellulose—page 1306.
Hydroxypropyl Methylcellulose—page 1306.
Hydroxyethyl Cellulose—page 1306.

Hydroxypropyl Methylcellulose Ophthalmic Solution

A sterile solution of hydroxypropyl methylcellulose, of a grade containing 19.0–30.0% methoxy and 4.0–12.0% hydroxypropoxy groups; may contain antimicrobial, buffering and stabilizing agents.

Uses—A wetting solution for contact lenses. Its demulcent action decreases the irritant effect of the lens on the cornea. It also imparts viscous properties to the wetting solution, which assists the lens in staying in place. The demulcent effect also finds application in ophthalmic decongestants. "Artificial tear" formulations containing this drug may be used when lacrimation is inadequate. A 2.5% solution is used in gonioscopes.

Dose—*Topical, to the conjunctiva*, **1 drop** of 0.3 to 1% solution 3 or 4 times a day.

Dosage Forms—0.3, 0.5 and 1% solutions.

Methylcellulose—page 1306.

Methylcellulose Ophthalmic Solution

A sterile solution of methylcellulose; may contain antimicrobial, buffering and stabilizing agents.

Uses—For the same purposes, and in the same manner, as *Hydroxypropyl Methylcellulose Ophthalmic Solution*, above.

Dosage Forms—0.25, 0.5 and 1%.

Pectin—page 796.
Polyvinyl Alcohol—page 1307.

Polyvinyl Alcohol Ophthalmic Solution

VasoClear A (*Cooper Vision*)

A sterile solution of polyvinyl alcohol, which may contain antimicrobial, buffering and stabilizing agents and other demulcent substances.

[9002-89-5] (Polyvinyl alcohol).

Preparation—By partial hydrolysis (*ca* 90%) of polyvinyl acetate.

Description—A white powder which is a linear polymer, $-(CH_2-CHOH)_n-$, where the value of n is between 500 and 5000; pH (1 in 25 aqueous solution) between 5.0 and 8.0.

Solubility—Soluble in water; insoluble in organic solvents.

Uses—A wetting solution for contact lenses. The polyvinyl alcohol has a demulcent action that helps protect the eye from irritation by the contact lens. It is also used in "artificial tears" employed when there is insufficient lacrimation. It is applied to the conjunctiva, **1 or 2 drops**, 3 or 4 times a day or as needed.

Dosage Forms—1, 1.4, 2, 3, and 4% solutions.

Emollients

Emollients are bland, fatty or oleaginous substances which may be applied locally, particularly to the skin, and also to mucous membranes or abraded tissues. Water-soluble irritants, air and airborne bacteria are excluded by an emollient layer. The skin also is rendered softer (*emollier*—to soften) and more pliable through penetration of the emollient into the surface layers, through the slight congestion induced by rubbing and massage upon application and especially through mechanical interference with both sensible and insensible water loss.

Emollients have certain disadvantages. It now is recognized that retention of perspiration below the emollient and exclusion of air render conditions favorable to the growth of anaerobic bacteria. Furthermore, the rubbing during application aids in the spreading of cutaneous bacteria. Consequently, the use of emollients to cover burns and abrasions is diminishing. The liquid emollients may be used for mild catharsis (page 783) and for protection against gastrointestinal corrosives; however, castor oil is hydrolyzed in the gut to the irritating ricinoleic acid and, hence, is employed as an emollient only externally. Orally administered liquid emollients may be aspirated into the trachea and lungs, especially in infants and in the debilitated, and, thus, induce "oil aspiration pneumonia." This condition also may be induced by emollient nose drops.

The chief use of emollient substances is to provide vehicles for lipid-soluble drugs (as in ointments and liniments), hence, many of them are described among the pharmaceutical necessities (Chapter 66). It is widely, but incorrectly, held that such vehicles facilitate the transport through the skin of their active ingredients. On the contrary, when the oil:water partition coefficient is greater than 1.0, the penetration is retarded and the emollient vehicle prolongs the action of the active ingredient. Emollient substances also are employed commonly in both cleansing and antiphlogistic creams and lotions. Compound ointment bases, creams and other medicated applications are treated elsewhere in this book (Chapter 86). Only the simple emollients and important compounded ointments that are used frequently for their emollient actions are listed below.

Castor Oil—page 785.
Castor Oil, Sulfated—page 1311.
Cocoa Butter—page 1611.
Coconut Oil—page 1317.
Cold Cream—page 1312.
Corn Oil—page 1303.

Cottonseed Oil—page 1303.
Ointment, Hydrophilic—page 1312.
Rose Water Ointment—page 1315.
Sesame Oil—page 1303.
Theobroma Oil—page 1320.
White Ointment—page 1309.
Yellow Ointment—page 1309.

Other Emollients

Myristyl Alcohol [Tetradecyl Alcohol |112-72-1] $CH_3(CH_2)_{12}CH_2OH$ (214.38)]—White crystalline alcohol; specific gravity 0.824; melts at 30°. Insoluble in water; soluble in ether; slightly soluble in alcohol. Obtained by reduction of fatty acid esters. *Use:* Emollient in cold creams.

Shark Liver Oil—The oil extracted from the livers of the *soupfin shark, Galeorhinus zyopterus* or *Hypoprion brevirostris*, both of which are rich in vitamins A and D. *Uses:* An emollient and protectant, the FDA classification of which is Category I. It is used in burn and sunburn ointments. *Dose:* Usually 3%.

Astringents and Antiperspirants

Astringents are locally applied protein precipitants which have such a low cell penetrability that the action essentially is limited to the cell surface and the interstitial spaces. The permeability of the cell membrane is reduced, but the cells remain viable. The astringent action is accompanied by contraction and wrinkling of the tissue and by blanching. The cement substance of the capillary endothelium and the basement membrane is hardened, so that pathological transcapillary movement of plasma protein is inhibited and local edema, inflammation and exudation, thereby, are reduced. Mucus or other secretions also may be reduced, so that the affected area becomes drier.

Astringents are used therapeutically to arrest hemorrhage by congulating the blood (*styptic* action, page 816) and to check diarrhea, reduce inflammation of mucous membranes, promote healing, toughen the skin or decrease sweating. The *antiperspirant* effect is the result both of the closure of the sweat ducts by protein precipitation to form a plug and peritubular irritation that promotes an increase in inward pressure on the tubule. Astringents also possess some *deodorant* properties by virtue of interaction with odorous fatty acids liberated or produced by action of bacteria on lipids in sweat, and by an action suppressing bacterial growth, partly because of a decrease in pH.

Many astringents are irritants or caustics in moderate to high concentrations. Consequently, strict attention must be paid to the appropriate concentration. Most astringents are also antiseptics, hence, many of them are discussed in Chapter 62.

The principal astringents are (1) the salts of the cations aluminum, zinc, manganese, iron or bismuth, (2) certain other salts that contain these metals (such as permanganates) and (3) tannins, or related polyphenolic compounds. Acids, alcohols, phenols and other substances that precipitate proteins may be astringent in the appropriate amount or concentration; however, such substances generally are not employed for their astringent effects, because they readily penetrate cells and promote tissue damage. Strongly hypertonic solutions dry the affected tissues and, thus often, but wrongly, are called astringents, unless protein precipitation also occurs.

Alcohol—page 1314.

Alum

Sulfuric acid, aluminum potassium salt (2:1:1), dodecahydrate; Sulfuric acid, aluminum ammonium salt (2:1:1), dodecahydrate; Alumen; Alumen Purificatum; Purified Alum

Aluminum ammonium sulfate (1:1:2) dodecahydrate [7784-26-1]; anhydrous [7784-25-0] (237.14); or aluminum potassium sulfate (1:1:2) dodecahydrate [7784-24-9]; anhydrous [10043-67-1] (258.19).

The label of the container must indicate whether the salt is ammonium alum $[AlNH_4(SO_4)_2.12H_2O = 453.32]$ or potassium alum $[AlK(SO_4)_2.12H_2O = 474.38]$.

Preparation—Prepared from the mineral *bauxite* (a hydrated aluminum oxide) and sulfuric acid, with the addition of ammonium or potassium sulfate for the respective alums. Ammonium alum is prevalent on the market because of its lower cost.

Description—Large, colorless crystals, crystalline fragments or a white powder; odorless and has a sweetish, strongly astringent taste; solutions are acid to litmus.

Solubility—1 g ammonium alum is soluble in 7 mL water, and 1 g potassium alum is soluble in 7.5 mL water; both are soluble in about 0.3 mL boiling water, but they are insoluble in alcohol; alum is freely but slowly soluble in glycerin.

Incompatibilities—When alum is dispensed in powders with *phenol, salicylates* or *tannic acid*, gray or green colors may be developed due to traces of iron in the alum. A partial liberation of its water of crystallization permits it to act as an acid toward *sodium bicarbonate*, thus liberating carbon dioxide. Ammonia is liberated simultaneously from ammonium alum. *Alkali hydroxides and carbonates, borax* or *lime water* precipitate aluminum hydroxide from solutions of alum. The alums possess the incompatibilities of the water-soluble sulfates.

Uses—A powerful *astringent* in acidic solutions. It is slightly antiseptic, probably due to bacteriostasis through liberation of acid on hydrolysis. It sometimes is used as a local *styptic*, and frequently is employed in making astringent lotions and douches. It is used especially by athletes to toughen the skin. As an astringent it is used in concentrations of 0.5 to 5%. Some vulvovaginal cleansing and deodorant preparations contain alum.

Styptic pencils are made by fusing potassium alum, usually with the addition of some potassium nitrate, and pouring into suitable molds.

Caution—Do not confuse *styptic* pencils with *caustic* pencils (page 767); the latter contain *silver nitrate*.

Dose—*Topical*, as a **0.5 to 5%** solution.

Aluminum Acetate Topical Solution

Acetic acid, aluminum salt; Liquor Burowii; Burow's Solution

$Al(OCOCH_3)_3$

Yields, from each 100 mL, 1.20–1.45 g of aluminum oxide $[Al_2O_3 = 101.96]$, and 4.24 to 5.12 g of acetic acid $[C_2H_4O_2 = 60.05]$, corresponding to 4.8 to 5.8 g of aluminum acetate [139-12-8] $C_6H_9AlO_6$ (204.12). It may be stabilized by the addition of not more than 0.6% of boric acid.

Caution—This solution should not be confused with Aluminum Subacetate Topical Solution which is a stronger preparation.

Note—Dispense only clear Aluminum Acetate Solution.

Description—Clear, colorless liquid having a faint acetous odor, and a sweetish, astringent taste; specific gravity about 1.022; pH 3.6 to 4.4.

Uses—As an astringent dressing or as an astringent mouth wash and gargle. Aluminum acetate is included in preparations to treat athlete's foot, dermatidides, diaper rash, dry skin, poison ivy poisoning and inflammation of the external ear.

Dose—*Topical*, to the skin, as a wet dressing containing a **1:10** to **1:40 dilution** of the solution.

Aluminum Chloride

[7784-13-6] $AlCl_3.6H_2O$ (241.43); *anhydrous* [7446-70-0] (133.34).

Preparation—By heating aluminum in chlorine gas, then dissolving the product in water and crystallizing, or by dissolving freshly precipitated aluminum hydroxide in hydrochloric acid and concentrating to permit crystallization.

Description—White or yellowish white, crystalline powder; deliquescent; sweet, astringent taste; solutions are acid to litmus.

Solubility—1 g in about 0.9 mL water or 4 mL alcohol; soluble in glycerin.

Uses—Extensively employed on the skin as an astringent and anhidrotic; it is included in some proprietary preparations formu-

lated for this purpose. It is used especially in the treatment of soggy athlete's foot, to promote drying and, hence, to enhance the efficacy of specific antifungal drugs. For ordinary antiperspirant use the basic salt *aluminum chlorohydroxide*, $Al_2Cl(OH)_n$, is preferable as it is less irritating and causes less deterioration of clothing than does this drug. It may have a special use in the treatment of *hyperhidrosis of the palms, soles or axillae*, for which a 20% solution in absolute ethanol is used. In the presence of water, it hydrolyzes to aluminum chlorohydroxide and hydrochloric acid, which can cause irritation, especially in fissures, discomfort and also deterioration of clothing. Concentrations below 15% cause a low incidence of irritation. Consequently, it is essential that the area to be treated is completely dry before application. To protect bedclothes, the treated area is sometimes covered with plastic wrap, but such occlusion of the axillae may result in boils or furuncles. It should not be applied to the axillae immediately after shaving or used where the skin is irritated or broken. Concentrations above 15% are used as caustics.

Dose—*Topical*, to the skin, as 6.25 to 30% solution. The 20% alcoholic solution may be applied on 2 successive days and twice a week thereafter, except that it may be applied twice a day for athlete's foot.

Aluminum Chlorohydrates

The hydrate of aluminum chloride hydroxide [1327-41-9] $Al_2Cl(OH)_5$.

Uses—Mainly employed in antiperspirant products, for which they have been rated safe and effective in concentrations of 25% (as anhydride) or less. Since solutions or suspensions are less acidic than those of aluminum chloride, they cause a lower incidence of irritation to the skin.

Dose—*Topical*, to the axilla, as a 2.5 to 25% cake, ointment, solution or suspension.

Aluminum Sulfate

Sulfuric acid, aluminum salt (3:2), hydrate; Cake Alum; Patent Alum; Pearl Alum; Pickle Alum; "Papermaker's Alum"

Aluminum sulfate (2:3) hydrate [17927-65-0] $Al_2(SO_4)_3.xH_2O$; anhydrous [10043-01-3] (342.14).

Preparation—By reacting freshly precipitated aluminum hydroxide with an appropriate quantity of sulfuric acid. The resulting solution is evaporated and allowed to crystallize.

Description—White crystalline powder, shining plates or crystalline fragments; stable in air; odorless and has a sweet, mildly astringent taste; aqueous solution (1 in 20) is acid and has a pH not less than 2.9.

Solubility—1 g in about 1 mL water; insoluble in alcohol.

Uses—A powerful *astringent*, acting much like alum. It is used widely as a *local antiperspirant* and is the effective ingredient in some commercial antiperspirant products. Solutions usually are buffered with sodium aluminum lactate to make them less irritating. It is used for water purification in the "alum flocculation" process. It is a *pharmaceutical necessity* for *Aluminum Subacetate Solution*.

Dose—*Topical*, to the skin, as an 8% solution.

Bismuth Subcarbonate—page 799.

Bismuth Subnitrate—page 775.

Calamine

Iron oxide (Fe_2O_3), mixt. with zinc oxide; Prepared Calamine; Lapis Calaminaria; Artificial Calamine

Calamine [8011-96-9]; contains, after ignition, not less than 98.0% ZnO (81.38).

Preparation—By thoroughly mixing zinc oxide with sufficient ferric oxide (usually 0.5 to 1%) to obtain a product of the desired color.

It originally was obtained by roasting a native zinc carbonate, then known as *calamine*, hence, the name. This name also is applied by mineralogists to a native form of zinc silicate, which is not suitable for making medicinal calamine.

Description—Pink powder, all of which passes through a No 100 standard mesh sieve. It is odorless and almost tasteless.

Solubility—Insoluble in water; dissolves almost completely in mineral acids.

Uses—Similar to those of zinc oxide, being employed chiefly as an *astringent* and in *protective* and soothing ointments and lotions for *sunburn, ivy poisoning*, etc. It often is prescribed by dermatologists to give opacity and a flesh-like color to lotions or ointments.

Dose—*Topical*, to the skin, in various concentrations in lotions and ointments.

Calamine Lotion [Lotio Calaminae]—*Preparation:* Dilute bentonite magma (250 mL) with an equal volume of calcium hydroxide solution. Mix calamine (80 g) and zinc oxide (80 g) intimately with glycerin (20 mL) and about 100 mL of the diluted magma, triturating until a smooth, uniform paste is formed. Gradually incorporate the remainder of the diluted magma. Finally add calcium hydroxide solution (qs) to make 1000 mL, and shake well. If a more viscous consistency in the Lotion is desired, the quantity of bentonite magma may be increased to not more than 400 mL. *Note: Shake thoroughly before dispensing.*

Phenolated Calamine Lotion [Lotio Calaminae Composita; Compound Calamine Lotion]—*Preparation:* Mix liquefied phenol (10 mL) and calamine lotion (990 mL) to make 1000 mL. Commercial preparations also contain 8.4% isopropyl alcohol and have various other modifications. See *Calamine*. *Note: Shake thoroughly before dispensing.*

Glutaral—page 1165.

Potassium Permanganate—page 1173.

Resorcinol—RPS-16, page 1107.

Silver Nitrate—page 766.

White Lotion

Lotio Alba; Lotio Sulfurata

Zinc Sulfate	40 g
Sulfurated Potash	40 g
Purified Water, a sufficient quantity, To make	1000 mL

Dissolve zinc sulfate and sulfurated potash separately, each in 450 mL purified water, and filter each solution. Add slowly the sulfurated potash solution to the zinc sulfate solution with constant stirring. Then add the required amount of purified water, and mix.

Note—Prepare freshly and shake thoroughly before dispensing. For further discussion see *Sulfurated Potash* (page 1327).

Uses—An *astringent*, *protective* and mild antimicrobial preparation. The astringency is attributable to the zinc ion. The thiosulfates and polysulfides in it exert antibacterial and antifungal actions (see *Sodium Thiosulfate*, RPS-16, page 1176). White lotion is used in the treatment of acne vulgaris.

Dose—*Topical*, to the skin, as required.

Zinc Oxide

Flowers of Zinc; Zinc White; Pompholyx; Nihil Album; Lana Philosophica

Zinc oxide [1314-13-2] ZnO (81.38).

Preparation—By heating zinc carbonate at a low red heat until the carbon dioxide and water are expelled.

Description—Very fine, odorless, amorphous, white or yellowish white powder, free from gritty particles; gradually absorbs carbon dioxide from the air; when strongly heated it assumes a yellow color which disappears on cooling; its suspension in water is practically neutral.

Solubility—Insoluble in water or alcohol; soluble in dilute acids, solutions of the alkali hydroxides or ammonium carbonate solution.

Incompatibilities—Reacts slowly with fatty acids in *oils* and *fats* to produce lumpy masses of zinc oleate, stearate, etc. *Vanishing creams* tend to dry out and crumble. Whenever permissible, it is advisable to levigate it to a smooth paste with a little mineral oil before incorporation into an ointment.

Uses—Has a mild *astringent*, *protective* and *antiseptic* action. In the form of its various official ointments and pastes it is employed widely in the treatment of dry skin and such skin disorders and infections as *acne vulgaris, prickly heat, insect stings and bites, ivy poisoning, diaper rash, dandruff, seborrhea, eczema, impetigo, ringworm, psoriasis, varicose ulcers* and *pruritus*. It is contained in some sunscreens. It is included in some vulvovaginal deodorant preparations and in preparations for the treatment of hemorrhoids.

It also is used in dental cements and temporary fillings. It is the essential ingredient in *Calamine* (page 762).

Dose—*Topical*, as a 5 to 25% cream, lotion, ointment, paste, baby powder or rectal suppository.

Dosage Forms—Ointment: 20%; Paste: 25%. In numerous combinations: 2 to 15%.

Zinc Pyrithione—page 1173.

Zinc Sulfate—page 1170.

Zinc Undecylenate—page 1237.

Other Astringents and Antiperspirants

Aluminum Zirconium Chlorhydrate—*Uses:* Mainly in antiperspirant products. Because of the propensity of the zirconium to elicit allergic reactions and sarcoid-like granulomas, the compound is not included in aerosols, because of possible pulmonary complications if inhaled. *Dose:* To the axilla, in a concentration not to exceed 20% (as anhydride).

Tannic Acid [Gallotannic Acid; Tannin; Digallic Acid] [1401-55-4]—A tannin usually obtained from nutgalls, the excrescences produced on the young twigs of *Quercus infectoria* Olivier and allied species of *Quercus* Linné (Fam *Fagaceae*). Yellowish white to light brown amorphous powder, glistening scales or spongy masses; usually odorless with a strong astringent taste; gradually darkens on exposure to air and light. 1 g dissolves in about 0.35 mL water or 1 mL warm glycerin; very soluble in alcohol; practically insoluble in chloroform or ether. *Incompatibilities:* Solutions gradually darken on exposure to air and light through oxidation of phenolic groups to quinoid structures. It is incompatible with most enzymes, gums, salts of many metals and many other substances.

Uses: On an open sore or denuded surface, it forms a film of protein tannate that acts as a mechanical protective which excludes external irritants and infectives and, thus, provides some relief from pain. However, it is not antibacterial and not only does not inhibit the growth of bacteria entrained beneath the film but actually may create favorable conditions for the growth of certain anaerobes. For this reason, and also the fact that it is absorbed sufficiently from large denuded areas to cause liver damage, it is no longer used in the treatment of burns and should not be used on any large lesion. Nevertheless, it is incorporated in 8 to 10% concentration in several products to treat ivy or oak poisoning. As a 7% gel it is used on cold sores, fever blisters and cankers. It is included in 2.16% concentration in a hemorrhoidal preparation and in 4% concentration in a keratolytic product for removing corns, calluses and warts, these concentrations probably being too low to contribute significantly to the supposed efficacies. In 25% solution it is used to reduce inflammation and harden skin around ingrown toenails, thus increasing comfort and making nail-cutting easier.

Its content in tea accounts for the use of strong tea as an internal antidote, presumably for the dual purpose of precipitating toxic alkaloids and hardening the surface of the gastrointestinal mucosa and its mucous layer.

Zinc Caprylate [Zinc octanoate [557-09-5] $C_{16}H_{30}O_4Zn$ (351.79)]—Lustrous scales. Sparingly soluble in boiling water; moderately soluble in boiling alcohol. *Uses:* In the treatment of athlete's foot. The astringency of the zinc decreases inflammation and wetness. The caprylate has a weak antifungal action. *Dose:* As a 5% ointment.

Zinc Chloride [Zinc chloride [7646-85-7] $ZnCl_2$ (136.29)]—Prepared by reacting metallic zinc or zinc oxide with hydrochloric acid and evaporating the solution to dryness. White, or nearly white, odorless, crystalline powder, or as porcelain-like masses, or in moulded pencils; very deliquescent; aqueous solution (1 in 10) is acid to litmus. 1 g dissolves in 0.5 mL water, about 1.5 mL alcohol or about 2 mL glycerin; solution in water or alcohol is usually slightly turbid, but the turbidity disappears on addition of a small quantity of HCl. *Incompatibilities:* Soluble zinc salts are precipitated as zinc hydroxide by alkali hydroxides, including ammonium hydroxide; the precipitate is soluble in an excess of either the fixed or the ammonium hydroxide. *Carbonates, phosphates, oxalates, arsenates,* and *tannin* cause precipitation. The precipitation with sodium borate can be prevented by addition of an amount of glycerin equal in weight to the sodium borate. In weak aqueous solutions, it has a tendency to form the insoluble basic salt by hydrolysis and about one-half its weight of ammonium chloride has been used for the purpose of stabilization. It is very *deliquescent*. It has the incompatibilities of chlorides, being precipitated by *silver* and *lead salts*. *Uses:* In high concentrations it is caustic and has been used as a caustic agent to treat corns, calluses and warts. In the low concentrations in which it is marketed it is astringent and mildly antibacterial and probably does not contribute to keratolysis. Although it is used in mouthwashes, the contact time is too short, and only an astringent and not an antibacterial action results. *Dose: Topical*, to the teeth, as a 10% solution; to skin and mucous membranes for astringency and antimicrobial actions, as a 0.1 to 2% solution.

Zinc Ricinoleate [Zinc [*R*-(*Z*)]-12-hydroxy-9-octadecenoate $(C_{18}H_{33}O_3)_2Zn$ (660.24)]—Only as a deodorant for ostomies.

Zirconium Oxide [Zirconium Dioxide; Zirconic Anhydride, Zirconia; [1314-23-4] ZrO_2 (123.22)]—White powder or crystals. Insoluble in water; soluble in acids. *Uses:* Has weak astringent and adsorptive activity, for which it is employed in topical preparations for treating rhus dermatitis (ivy and oak poisoning). However, it is not only poorly effective for this purpose but it also can cause allergic reactions that may give rise to sarcoid-like granulomas. Consequently, its use should be condemned. Zirconium salts also are subject to the same criticisms.

Irritants, Rubefacients and Vesicants

The *irritants* are drugs that act locally on the skin and mucous membranes to induce hyperemia, inflammation and, when the action is severe, vesication. Agents that induce only hyperemia are known as *rubefacients*. Rubefaction is accompanied by a feeling of comfort, warmth and, sometimes, itching and hyperesthesia. Appropriately low concentrations of directly applied or inhaled vapors of volatile aromatic irritants, such as camphor or menthol, induce a sensation of coolness rather than warmth. When the irritation is more severe, plasma escapes from the damaged capillaries and forms blisters (vesicles). Agents that induce blisters are known as *vesicants*. Most rubefacients also are vesicants in higher concentrations. Certain irritants may be relatively selective for various tissues or cell types, so that hypersecretion of the surface, seborrheic abscesses, paresthesia or other effects may be noted in the absence of appreciable hyperemia.

Irritants have been used empirically for many centuries, probably even prehistorically. They may be employed for counterirritation, the mechanism of which is poorly understood. A moderate to severe pain may be obscured by a milder pain arising from areas of irritation appropriately placed to induce reflex stimulation of certain organs or systems, especially respiratory. Sensory and visible effects of irritation sometimes give the patient assurance that he is receiving effective medication. Taken internally, many irritants exert either an emetic or laxative action. Irritant laxatives are listed on page 783. A few irritants, especially cantharides, on absorption into the blood stream, irritate the urogenital tract and, consequently, have been dangerously employed as *aphrodisiacs*. Certain irritants also possess a healing action on wounds, possibly the result of local stimulation. Many condiments are irritants. In high concentrations, many irritants are corrosive.

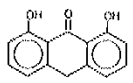
Alcohol—page 1314.

Alcohol, Rubbing—page 1164.

Ammonia Spirit, Aromatic—RPS-17, page 15.

Anthralin

1,8,9-Anthracenetriol; Dithranol; Dioxyanthranol; Cignolin; Anthra-Derm (*Dermik*); Lasan (*Stiefel*)



1,8-Dihydroxyanthranol [480-22-8] $C_{14}H_{10}O_3$ (226.23).

Preparation—Anthraquinone is sulfonated to the 1,8-disulfonic acid, which is isolated from the reaction mixture and then heated with a calcium hydroxide-calcium chloride mixture to form 1,8-dihydroxy-9,10-anthraquinone, which is reduced with tin and HCl to anthralin.

Description—Yellowish brown, crystalline powder; odorless and tasteless; melts between 175° and 181°.

Solubility—Insoluble in water; slightly soluble in alcohol; soluble in chloroform; slightly soluble in ether.

Uses—Although long considered to be an irritant, its principal therapeutic action is the reduction of epidermal DNA synthesis and mitotic activity. It is used in the treatment of *psoriasis, alopecia areata, eczema* and other *chronic dermatoses*. It usually is used in

combination with ultraviolet light and a daily coal tar "bath." To avoid harmful irritation, medicaments containing it should not be used on the face, scalp, genitalia or intertriginous skin areas; they should not be applied to blistered, raw or oozing areas of the skin, and should be kept from the eyes, since they may cause severe conjunctivitis, keratitis or corneal opacity. Renal irritation, casts and albuminuria may result when the drug is absorbed systemically. The hands should be washed immediately after applying medication. A reversible slight discoloration of the skin may occur.

Dose—*Topical*, to the skin, as a 0.1 to 1% cream or ointment, once a day with cream and once or twice a day with ointment. The concentration should be low initially and increased only as necessary.

Dosage Forms—Cream: 0.1, 0.2, 0.25, 0.4, 0.5 and 1%; Ointment: 0.1, 0.25, 0.4, 0.5, 1 and 2%.

Benzoin Tincture, Compound—page 760.

Coal Tar

Pix Carbonis; Prepared Coal Tar BP; Pix Lithanthracis; Gas Tar

The tar obtained as a by-product during the destructive distillation of bituminous coal.

Description—Nearly black, viscous liquid, heavier than water, with a characteristic naphthalene-like odor and a sharp burning taste; on ignition it burns with a reddish, luminous and very sooty flame, leaving not more than 2% of residue.

Solubility—Only slightly soluble in water, to which it imparts its characteristic odor and taste and a faintly alkaline reaction; partially dissolved by alcohol, acetone, methanol, solvent hexane, carbon disulfide, chloroform or ether; to the extent of about 95% by benzene, and entirely by nitrobenzene with the exception of a small amount of suspended matter.

Uses—A *local irritant* used in the treatment of *chronic skin diseases*. Like anthralin, its primary action is to decrease the epidermal synthesis of DNA and, hence, to suppress hyperplasia. Occasionally, it may cause rash, burning sensation or other manifestations of excessive irritation or sensitization. Since photosensitization may occur, the treated area should be protected from sunlight. It should be kept away from the eyes and from raw, weeping or blistered surfaces. Temporary discoloration of the skin may occur.

Dose—*Topical*, to the skin: *cleansing bar*, 2% once or twice a day; *cream*, 1.6 to 5%, 2 or 3 times a day; *gel*, 5 to 7.5% once or twice a day; *lotion*, 2 to 5%, 2 to 4 times a day; *ointment*, 1 to 5%, 2 or 3 times a day; *paste*, 5% once or twice a day; *shampoo*, 0.5 to 10% twice a week; *solution*, 2.5 to 20% straight or diluted 1:3 with water 1 to 3 times a day; *suspension*, 7.5 to 33.3% diluted in lukewarm water at intervals directed by the physician.

Dosage Forms—Cleansing Bar: 2%; Cream: 1.6 and 5%; Gel: 5 and 7.5%; Lotion: 2 and 5%; Ointment: 1 and 5%; Paste: 5%; Shampoo: 0.5, 1, 2, 3, 4.3, 5, 9 and 10%; Topical Solution: 2.5, 5 and 20%; Topical Suspension: 7.5, 30 and 33.3%.

Green Soap—RPS-17, page 786.

Green Soap Tincture—RPS-17, page 766.

Methyl Salicylate—page 1295.

Resorcinol—RPS-16, page 1107.

Resorcinol Ointment, Compound—RPS-16, page 1107.

Resorcinol Monoacetate—RPS-16, page 1107.

Storax—page 1326.

Tolu Balsam—page 1299.

Turpentine Oil, Rectified—RPS-16, page 808.

Other Irritants, Rubefacients and Vesicants

Camphor [Bicyclo [2.2.1] heptane-2-one, 1,7,7-trimethyl-, 2-Camphanone; 2-Bornanone [76-22-2] $C_{10}H_{16}O$ (152.24); Gum Camphor; Laurel Camphor]—A ketone obtained from *Cinnamomum camphora* (Linné) Nees et Ebermaier (Fam *Lauraceae*) (Natural Camphor) or produced synthetically (Synthetic Camphor). *Preparation:* Natural crude camphor may be obtained by steam distilling chips of the camphor tree; the crude camphor so obtained is purified, usually by sublimation. One method of producing synthetic camphor starts with *pinene* [$C_{10}H_{16}$], a hydrocarbon obtained from turpentine oil. The pinene is saturated with hydrogen chloride at 0° forming bornyl chloride [$C_{10}H_{17}Cl$]. On heating the bornyl chloride with sodium acetate and glacial acetic acid, it is converted into isobornyl acetate, which is subsequently hydrolyzed to isobornyl alcohol [$C_{10}H_{17}OH$] and oxidized with chromic acid to camphor. Synthetic camphor resembles natural camphor in most of its properties except that it is a racemic mixture and, therefore, lacks optical activity. When camphor is mixed in approximately molecular proportions with chloral hydrate, menthol, phenol or thymol, liquefaction ensues; such mixtures are known as *eutectic mixtures* (see page 176).

Description: Colorless or white crystals, granules or crystalline masses; or as colorless to white, translucent, tough masses; a penetrating, characteristic odor, a pungent, aromatic taste and is readily pulverizable in the presence of a little alcohol, ether or chloroform; specific gravity about 0.99; melts between 174° and 179° and slowly volatilizes at ordinary temperature and in steam. *Solubility:* 1 g in about 800 mL water, 1 mL alcohol, about 0.5 mL chloroform or 1 mL ether; freely soluble in carbon disulfide, solvent hexane or fixed and volatile oils. *Incompatibilities:* Forms a liquid or a soft mass when rubbed with *chloral hydrate, hydroquinone, menthol, phenol, phenyl salicylate, resorcinol, salicylic acid, thymol* or other substances. It is precipitated from its alcoholic solution by the addition of water. It is precipitated from camphor water by the addition of soluble salts.

Uses: Locally, weakly *analgesic*, mildly *analgesic* (*antipruritic*) and *rubefacient* when rubbed on the skin. The spirit is applied locally to allay itching caused by insect stings. It also is used as a counterirritant in humans for *inflamed joints, sprains* and *rheumatic* and other *inflammatory* conditions such as colds in the throat and chest. Although the patient may feel improved, the inflammation is not affected. However, reflexly induced local vasoconstriction may mediate a mild nasopharyngeal decongestant effect. When taken internally in small amounts it produces a feeling of warmth and comfort in the gastrointestinal tract, and, therefore, formerly was much used as a *carminative*. Systemically, it is a reflexly active *circulatory* and *respiratory stimulant*. However, its use as a stimulant is obsolete. It also possesses a slight *expectorant* action and is included in some cough-suppressant mixtures. Concentrations above 11% are not safe. Toxicity consists of nausea and vomiting, headache, feeling of warmth, confusion, delirium, convulsions, coma or respiratory arrest. Camphor is a pharmaceutical necessity for *Flexible Collodion* and *Camphorated Opium Tincture*. *Dose: Topical*, to the skin, rectum or throat, as a 0.1 to 3% lotion, cream, spray or ointment, or 10% tincture (spirit), no more than 3 to 4 times a day. For topical analgesia, concentrations of 0.1 to 3% are used; for counterirritation, 3 to 11%.

Cantharidin [(3aα,4β,7β,7aα-Hexahydro-3a,7a-dimethyl-4,7-epoxyisobenzofuran-1,3-dione[56-25-7] $C_{10}H_{12}O_4$ (196.21)]—The active principle of *Cantharides*. White platelets soluble 1 g in 40 mL acetone, 65 mL chloroform, 560 mL ether or 150 mL ethyl acetate; soluble in oils. *Uses:* Produces intradermal vesiculation. It is used to remove warts, particularly the periungual type. It is applied under an occlusive bandage. The vesicle eventually breaks, becomes encrusted and falls off in 1 to 2 weeks. *Dose:* Topical, to the wart, as a 0.7% solution.

Capsicum—The dried ripe fruit of *Capsicum frutescens* Linné, *Solonaceae*, which contains less than 1% of capsaicin [(*E*)-*N*-[4-Hydroxy-3-methoxyphenyl)methyl]-8-methyl-6-nonaneamide[404-86-4] $C_{18}H_{27}NO_3$ (305.40), which is the active ingredient. *Uses:* Its active ingredients are mildly irritant, causing erythemia and a feeling of warmth without vesication. Its preparations are used as counterirritants. *Dose:* The equivalent of 0.025 to 0.25% of capsicum applied to the skin no more than 3 or 4 times a day.

Ichthammol [Ammonium Ichthosulfonate; Sulfonated Bitumen; Ictiol; Ichthymall (*Mallinckrodt*), Ichthyol (*Stiefel*) [8029-68-3]]—It is obtained by the destructive distillation of certain bituminous schists, sulfonating the distillate and neutralizing the product with ammonia.

It yields not less than 2.5% of NH_3 (ammonia) and not less than 10% of total sulfur.

Constituents: It belongs to a class of preparations containing, as essential constituents, salts or compounds of a mixture of acids designated by the group name *sulfoichthyolic acid*, formed by sulfonation of the oil obtained in the destructive distillation of certain bituminous shales. Sulfoichthyolic acid is characterized by a high sulfur content, the sulfur existing largely in the form of sulfonates, sulfones and sulfides. *Description* and *Solubility:* Reddish brown to brownish black, viscous fluid, with a strong, characteristic, empyreumatic odor. Miscible with water, glycerin fixed oils or fats; partially soluble in alcohol or ether. *Incompatibilities:* Becomes granular in the presence of *acids* or under the influence of *heat*. In solution, it is precipitated by acids and *acid salts* as a dark, sticky mass; *alkalies* liberate ammonia; many *metallic salts* cause precipitation. *Uses:* A mildly astringent irritant and local antibacterial agent with moderate emollient and demulcent properties. It is used alone or in combination with other antiseptics for the treatment of skin disorders such as *insect stings and bites, erysipelas, psoria-*

sis and *lupus erythematosus* and to produce healing in *chronic inflammations*. It also is used to treat *inflammation* and *boils* in the external ear canal. Medical opinion is divided as to whether this agent is useful. In higher concentrations, irritation is frequent and rashes may develop. It should be kept away from the eyes and other sensitive surfaces. It has been reported to cause hyperepithelialization, an action that would be counterproductive in the treatment of psoriasis. *Dose: Topical*, to the skin as a 10 or 20% ointment or external ear canal as a 10% ointment.

Juniper Tar [Cade Oil]—The empyreumatic volatile oil obtained from the woody portions of *Juniperus oxycedrus* Linné (Fam *Pinaceae*). Dark brown, clear, thick liquid, having a tarry odor and a faintly aromatic, bitter taste. Very slightly soluble in water; 1 volume dissolves in 9 volumes of alcohol; dissolves in 3 volumes of ether, leaving a slight, flocculent residue; miscible with chloroform. *Uses:* A mildly irritant oil that is employed as a topical antipruritic in several chronic dermatologic disorders, such as *psoriasis, atopic dermatitis, pruritus, eczema* and *seborrhea*. Since it is irritant to the conjunctiva and also may cause chemosis of the cornea, care should be taken to keep it out of the eyes. Systemic absorption may result in renal damage. *Dose: Topical*, as 1 to 5% ointment applied once a day; it also is used as a 4% shampoo or 34% bath.

Menthol [Cyclohexanol, 5-methyl-2-(1-methylethyl)-, *p*-Menthan-3-ol; Peppermint Camphor [1490-04-6] $C_{10}H_{20}O$ (156.27)]—An alcohol obtained from diverse mint oils or prepared synthetically. It may be levorotatory [(−)-Menthol] from natural or synthetic sources, or racemic [(±)-Menthol].

Preparation: It owes its odor chiefly to menthol, which is obtained from it by fractional distillation and allowing the proper fraction to crystallize, or by chromatographic processes. Among numerous methods of synthesis of an optically inactive menthol, the most popular involves the catalytic hydrogenation of thymol (obtained from natural sources or synthesized from *m*-cresol or cresylic acid). The difficulty in the synthesis of (−)-menthol arises from the fact that menthol contains three asymmetric carbon atoms, and there are thus eight stereoisomers, designated as (−)- and (+)-menthol, (−)- and (+)-isomenthol, (−)- and (+)-neomenthol, and (−)- and (+)-neoisomenthol. To obtain a product meeting USP requirements, it is necessary to separate (−)-menthol from its stereoisomers, for which purpose fractional crystallization, distillation under reduced pressure or esterification may be used. The other stereoisomers differ from the official (−)-menthol in physical properties and possibly to some extent in pharmacologic action.

Description: Colorless, hexagonal, usually needle-like crystals, or fused masses, or a crystalline powder, with a pleasant, peppermint-like odor; (−)-menthol melts between 41° and 44°; (±)-menthol congeals at 27° to 28°. *Solubility:* Very soluble in alcohol, chloroform or ether; freely soluble in glacial acetic acid, mineral oil or in fixed and volatile oils; slightly soluble in water. *Identification:* When mixed with about an equal weight of camphor, chloral hydrate, phenol or thymol, it forms a "eutectic" mixture liquefying at room temperature. *Incompatibilities:* Produces a liquid or soft mass when triturated with *camphor, phenol, chloral hydrate, resorcinol, thymol* or numerous other substances. *Labeling:* The label on the container indicates whether it is levorotatory or racemic.

Uses: In low concentrations, selectively stimulates the sensory nerve endings for cold and, hence, causes a sensation of coolness. Some local analgesic effects also accompany this effect. Higher concentrations not only stimulate sensory endings for heat and other pain, but also may cause some irritation. Consequently, there may first be a sensation of coolness, then a slight prickly and burning sensation. The local analgesia and sensation of coolness are employed in the treatment of insect bites and stings, itching (antipruretic effect), minor burns and sunburn, hemorrhoids, toothache, cankers, cold sores and sore throat. The local analgesic effect also is the probable basis of the antitussive use, although the value of the drug as an antitussive remains unproved. Care must be taken to avoid the inhalation of irritant concentrations. The contribution of a placebo effect to some of these effects cannot be discounted. It is incorporated into irritant products used to treat acne vulgaris, dandruff, seborrhea, calluses, corns, warts and athlete's foot and in vaginal preparations to lessen the sense of irritation. Whatever effects the rubbing of menthol-containing ointment on the chest possess to relieve pulmonary congestion in colds and allergy are attributable to counterirritation and placebo effects. It also is contained in counterirritants for the treatment of muscle aches. *Dose: Topical*, to the skin, as a 0.1 to 2% lotion or ointment; to the throat, as a 0.08 to 0.12% lozenge. *Inhalation*, 15 mL of 1% liquid or 10 mL of 2% ointment per quart of water, to be dispensed by steam inhalation.

Peruvian Balsam [Peru Balsam; Balsam of Peru; Indian Balsam; Black Balsam]—Obtained from *Myroxylon pereirae* (Royle) Klotzsch (Fam *Leguminosae*). Contains from 60 to 64% of a volatile oil termed *cinnamein* and from 20 to 28% of *resin*. Cinnamein is a mixture of compounds, among which the following have been identified: the esters *benzyl benzoate, benzyl cinnamate, cinnamyl cinnamate* (*styracin*) and the alcohol *peruviol* (considered by some to be identical with the sesquiterpene alcohol *nerolidol*, $C_{15}H_{26}O$) as ester, free *cinnamic acid;* about 0.05% of *vanillin;* and a trace of *coumarin*. The resin consists of benzoic and cinnamic acid. *Description* and *Solubility:* Dark brown, viscid liquid; transparent and appears reddish brown in thin layers; agreeable odor resembling vanilla, a bitter, acrid taste, with a persistent after-taste and free from stringiness or stickiness. It does not harden on exposure to air; specific gravity 1.150 to 1.170. Nearly insoluble in water, but soluble in alcohol, chloroform or glacial acetic acid, with not more than an opalescence; partly soluble in ether or solvent hexane. *Uses: A local irritant and vulnerary*. It once was used as a dressing to promote growth of epithelial cells in the treatment of *indolent ulcers, wounds* and certain *skin diseases*, eg, scabies. It presently is an ingredient in suppositories used in the treatment of hemorrhoids and anal pruritus. Allergic reactions to it occassionally occur. Ointments containing both this and sulfur present a problem in compounding, since the resinous part of the balsam tends to separate. This difficulty may be overcome by mixing the balsam with an equal amount of castor oil, prior to incorporating it into the base; or alternatively, by mixing it with solid petroxolin [An ointment vehicle (oxygenated petroleum) consisting of liquid paraffin, oleic acid and ammoniated alcohol]. *Dose: Topical, rectal*, 1.8 to 30 mg in suppositories.

Pine Tar [Pix Pini; Pix Liquida; Tar]—The product obtained by the destructive distillation of the wood of *Pinus palustris* Miller, or of other species of *Pinus* Linné (Fam *Pinaceae*). Usually obtained as a by-product in the manufacture of charcoal or acetic acid from wood. It is a complex mixture of phenolic bodies for the most part insoluble in water. Among these are *cresol, phlorol, guaiacol, pyrocatechol, caerulignol* and *pyrogallol* ethers. Traces of *phenol* and *cresols* also are present as well as hydrocarbons of the paraffin and benzene series. *Description* and *Solubility:* Very viscid, blackish brown liquid; translucent in thin layers, but becomes granular and opaque with age; has an empyreumatic, terebinthinate odor, a sharp, empyreumatic taste and is more dense than water; solution is acid to litmus. Miscible with alcohol, ether, chloroform, glacial acetic acid or with fixed and volatile oils; slightly soluble in water, the solution being pale yellowish to yellowish brown. *Uses:* Externally as a mild *irritant* and *local antibacterial* agent in chronic *skin diseases*, especially eczema and psoriasis. Its volatile constituents are claimed to be *expectorant* but their efficacy is unproven; its inhalations were formerly used for this purpose. *Dose: Topical*, as a 1.8 to 30% shampoo.

Sclerosing Agents

A number of irritant drugs are of sufficient activity to damage cells but are not so potent as to destroy large numbers of cells at the site of application. Such agents promote fibrosis and are used to strengthen supporting structures, close inguinal rings, etc. The intimal surface of blood vessels may break down under attack by such agents and thus initiate thrombosis, which may be an undesirable side effect. This action is the basis of the use of sclerosing agents in the reduction of varicose veins and hemorrhoids. Sclerosing agents generally are regarded as obsolete. They can be harmful when improperly used and sometimes even when used with caution.

Sclerosing Agents

Morrhuate Sodium Injection—A sterile solution of the sodium salts of the fatty acids of cod liver oil. It contains 50 mg of sodium morrhuate/mL. A suitable antimicrobial agent, not to exceed 0.5%, and ethyl or benzyl alcohol, not to exceed 3%, may be added. *Note: It may show a separation of solid matter on standing. Do not use the material if such solid does not dissolve completely upon warming.* Prepared by heating cod liver oil with alcoholic sodium hydroxide until completely saponified. After dilution with water the alcohol is removed by distillation. Dilute H_2SO_4 is then added to the aqueous solution, and the liberated organic acids are separated or preferably extracted with a suitable immiscible solvent such as ether. Just-sufficient aqueous NaOH then is added to neutralize the acids. About 20 mg of benzyl alcohol/mL of the Injection usually is added to lessen the pain of injection. *Uses:* Formerly, widely used as a *sclerosing* and *fibrosing agent* for obliterating *varicose veins*. Irritants of this type once were employed for closure of hernial rings, fibrosing of uncomplicated hemorrhoids, removal of condylomata acuminata and in other conditions where the ultimate objective was production of fibrous tissue. *Dose: Intravenous*, by special injection, 0.5 to 5 mL of a 5% injection to a localized area; *usual*, 1 mL. *Dosage Forms:* 5 and 30 mL.

Sodium Tetradecyl Sulfate [7-Ethyl-2-methyl-4-undecanol hydrogen sulfate sodium salt [139-88-8] $C_{14}H_{29}NaO_4S$ (316.43); STS; Sotradecol Sodium (*Elkins-Sinn*)]—One method of preparation reacts the corresponding alcohol with $ClSO_3H$ and neutralizes the resulting hydrogen sulfate ester with Na_2CO_3. Occurs as a white, waxy, odorless solid. Soluble in water, alcohol or ether. *Uses:* A *sclerosing agent* similar in action to sodium morrhuate. It formerly was used widely as a buffered solution in the *obliteration of varicose veins and internal hemorrhoids.* For such purposes, the solution is injected directly into the vein. Injection outside of the vein may cause sloughing. For this reason, the substance is not used to close inguinal rings. The principal untoward effect is pain immediately upon injection, although brief; mild anaphylactoid and idiosyncratic responses rarely occur. Because the substance is an anionic surface-active agent, it also is used as a wetting agent to promote spreading of certain topical antiseptics. *Dose:* By injection directly into the target vein, as a 1 or 3% solution, depending on the size of the vein. The volume then to be injected at any one site varies from 0.2 to 2.0 mL, depending on the concentration and the number of previous injections at the site, the larger volumes being given only after several previous injections. No more than 10 mL of the 3% solution or 6 mL of the 5% solution should be given at any one time. The interval between injections varies from 5 to 7 days. *Dosage Form:* Injection: 1 and 3% in 2-mL ampuls.

Caustics and Escharotics

Any topical agent that causes destruction of tissues at the site of application is a *caustic* (or corrosive).

Caustics may be used to induce desquamation of cornified epithelium ("keratolytic" action) and, therefore, are used to destroy warts, condylomata, keratoses, certain moles and hyperplastic tissues.

If the agent also precipitates the proteins of the cell and the inflammation exudate, there is formed a scab (or eschar), which later is organized into a scar; such an agent is an *escharotic* (or cauterizant). Most, but not all, caustics are also escharotic. Furthermore, certain caustics, especially the alkalies, redissolve precipitated proteins, partly by hydrolysis, so that no scab or only a soft scab forms; such agents penetrate deeply and generally are unsuitable for therapeutic use. Escharotics sometimes are employed to seal cutaneous and aphthous ulcers, wounds, etc. Since most escharotics are bactericidal, it formerly was thought that chemical cauterization effected sterilization; however, sterilization is not achieved always, especially by those agents which remain bound to the protein precipitate. The growth of certain bacteria even may be favored by the chemically induced necrosis and by the protection of the scab.

Acetic Acid, Glacial—page 1317.
Alum—page 761.
Aluminum Chloride—page 761.
Phenol—page 1323.

Podophyllum

Mandrake; May Apple

The dried rhizome and roots of *Podophyllum peltatum* Linné (Fam *Berberidaceae*); it yields not less than 5% of podophyllum resin.

Constituents—From 3 to 6% of resin along with up to 1% of quercetin and podophyllotoxin and peltatin glucosides. At least 16 different compounds have been isolated and characterized. The aglycone *podophyllotoxin* [$C_{22}H_{22}O_8$] is the lactone of 1-hydroxy-2-(hydroxymethyl)-6,7-methylenedioxy-4-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid. Hydrolytic rupture of the lactone ring yields *podophyllic acid* [$C_{22}H_{24}O_9$], the 2,3-*trans* form of which is *podophyllinic acid* while the 2,3-*cis* form is *picropodophyllinic acid.*

Although podophyllotoxin has been demonstrated to possess marked caustic, cathartic and toxic properties, it is believed that not it, but an amorphous *resin*, called *podophylloresin*, is the chief cathartic principle of the drug. However, podophyllotoxin is safer and ultimately probably will replace the crude preparations.

Uses and Dose—See *Podophyllum Resin.*

Podophyllum Resin

Uses—Supersedes podophyllum (above). Certain glycosides and polynuclear lactones in the resin interact with tubulin and, thus, interfere with cell cycling and intracellular dynamics such as to cause the eventual death of affected cells. Applied topically, it is corrosive in the region of contact. It mainly is used in the treatment of *condyloma accuminatum* but also of *juvenile papilloma of the larynx, multiple superficial epitheliomatoses* (basal cell and squamous cell carcinomas), *precancerous keratoses* (seborrheic, actinic and radiation keratoses), *verrucae fibroids* and *calluses.* Some pain usually occurs at the site of application; if it is excessive, the drug should be removed with ethanol or isopropyl alcohol. Resin on adjacent normal tissues also should be removed. Pain may be avoided somewhat by treating only a small area of surface at any one time. *It especially is irritating to the eyes and mucous membranes.* Treatment of large surfaces also may result in excessive absorption and systemic effects, such as nausea and vomiting, tachycardia, shallow respiration, leukopenia, thrombocytopenia, renal damage, paralytic ileus, lethargy, stupor, psychotic confusional states and peripheral neuropathy, including flaccid paralysis. Systemic absorption is enhanced by occlusion. The drug is contraindicated in pregnancy and lactation.

Dose—*Topical, adults* and *children*, to the *skin*, *condyloma accuminata*, as a 25% solution, the resin to remain in place for 6 hr; application may be repeated weekly for up to 4 weeks, if necessary; *superficial epitheliomatoses* and *precancerous keratoses*, as a 25% solution once a day, to be continued until several days after a slough has occurred; *to laryngeal lesions, juvenile laryngeal papilloma*, as a 12.5% solution to the papilloma, initially once a day, but progressively longer intervals may be elected as the lesions shrink (medical authorities hold that short intervals are more effective); the 12.5% solution is to be extemporized by diluting the 25% solution in 95% ethanol.

Dosage Form—Topical Solution: 25%.

Salicylic Acid—page 768.
Silver Nitrate—page 766.

Silver Nitrate

Nitric acid silver(1+) salt; Argenti Nitras

Silver(1+) nitrate [7761-88-8] $AgNO_3$ (169.87).

Preparation—By the action of nitric acid on metallic silver.

Description—Colorless or white crystals; on exposure to light in the presence of organic matter, it becomes gray or grayish black; pH of solutions about 5.5.

Solubility—1 g in 0.4 mL water, 30 mL alcohol, about 250 mL acetone, slightly more than 0.1 mL boiling water or about 6.5 mL of boiling alcohol; slightly soluble in ether.

Incompatibilities—Easily reduced to metallic silver by most *reducing agents*, including *ferrous salts, arsenites, hypophosphites, tartrates, sugars, tannins, volatile oils* and other *organic substances.* In neutral or alkaline solutions, precipitated by *chlorides, bromides, iodides, borax, hydroxides, carbonates, phosphates, sulfates, arsenites* and *arsenates. Potassium permanganate, tannic acid* and *soluble citrates and sulfates* may cause a precipitate if sufficiently concentrated. In acid solution, only the *chloride, bromide* and *iodide* are insoluble. *Ammonia water* dissolves many of the insoluble silver salts through formation of the silver diammine complex, $Ag(NH_3)_2^+$.

Uses—Silver ions combine with proteins and cause denaturation and precipitation. As a result, silver ions have astringent, caustic, bactericidal and antiviral properties. In low concentrations, silver-denatured protein is confined to the interstitial spaces and the surface of denuded, weeping areas, so that only astringent and antimicrobial effects occur; with higher concentrations, cell membranes are disrupted, so that caustic effects result. The corroded site will become covered with a scab of silver protein precipitate.

It is used mainly in podiatry as a caustic to *destroy excessive granulation tissue*, such as *corns, calluses, granuloma pyogenicum* and *plantar warts*, to *reduce neurovascular helomas, remove papillomas* and *cauterize small nerve endings* and *blood vessels.* As an astringent, it is used to treat *impetigo vulgaris* and *pruritis* as well as *indolent ulcers, wounds* and *fissures.* It also is used as a *styptic*, especially in dentistry.

As an antiseptic, it mainly is employed prophylactically against *ophthalmia neonatorum.* It formerly was applied regularly to

burned surfaces because of its high efficacy against both staphylococci and pseudomonas. However, the precipitation of AgCl at the site of application and in dressing depletes plasma choride and can cause serious electrolyte disturbances; consequently, the drug seldom is used in burn therapy today. Refer to RPS-17, page 1165, for a discussion of its prior uses as an antiseptic.

Excessive corrosion at the target site and corrosion from inadvertent application or leakage away from the intended site can occur. Dental cones or pieces of toughened silver nitrate that are accidentally ingested can cause death. Elemental silver from the bioreduction of silver ion may reside permanently at the site of application and cause a bluish-to-black discoloration called argyria. Locally injected sodium thiosulfate sometimes can remove the silver. Nitrate ion absorbed from large, denuded surfaces can cause methemoglobinemia. Only concentrations 0.5% or below should be applied to raw wounds, fresh cuts or broken skin.

Dose—*Topical, antiseptic*, to the *conjunctiva*, **0.1 mL** of a **1%** solution; to the *burned skin* or *open lesion* (neither advised), **0.1** to **0.5%** solution as a wet dressing. *Astringent*, to the *affected skin*, as a **10%** solution for *impetigo vulgaris* and as a **10** or **25%** solution for *pruritis*. *Caustic*, to the *lesion* only, as a **10%** solution or ointment for *helomas* and to *cauterize small nerve endings* and *blood vessels*, as a **25** or **50%** solution for *plantar warts* and as a **50%** solution for *granulation tissue, granuloma pyogenica* and *papillomatous growths*.

Dosage Forms—Ointment: 10%; Topical Solution: 10, 25 and 50%. For *Toughened Silver Nitrate*, see RPS-17, page 784.

Other Caustics and Escharotics

Dichloroacetic Acid [Dichloroacetic acid $C_2H_2Cl_2O_2$ (128.95)]—Pungent liquid miscible with water, alcohol or ether. *Uses:* See *Trichloroacetic Acid*.

Nitric Acid—Contains 67–71% HNO_3. A fuming liquid, very caustic, with a characteristic, highly irritating odor; boils at 120°; specific gravity about 1.41. Miscible with water. *Uses:* As a cauterizing agent for the immediate sterilization of dangerously infected wounds, such as the bite from a rabid animal; it does not penetrate too deeply and forms a firm eschar.

Podophyllotoxin—[(5*R*,5a*R*,9*R*)-5,5a,6,8,8a,9-Hexahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6-one [518-28-5] $C_{22}H_{22}O_8$ (414.41)]—Found in the rhizomes of several species of plants, principally *Podophyllum peltatum* L. *Berberidaceae, P emodi* and *Juniperus virginiana* L., *Coniferae*. For the synthesis see *JACS 103:* 6208, 1981. Occurs as hydrated crystals; melts about 115° (dec) and about 184° after drying; a number of polymorphic forms exist. Very slightly soluble in water; soluble in alcohol, chloroform or acetone. *Uses:* Actions, uses and adverse effects are those of *Podophyllum Resin* (page 766), except that the therapeutic index is greater. It is several times more potent. It is an investigational drug. *Dose: Topical*, to the *skin, adults* and *children*, as a 0.5 to 1% solution twice a day for 3 days.

Potassium Hydroxide [Potassium hydroxide; Caustic Potash; Lye; Potash Lye [1310-58-3] contains not less than 85.0% of total alkali, calculated as KOH (56.11), including not more than 3.5% of K_2CO_3 (138.21)] *Caution—Exercise great care in handling, as it rapidly destroys tissues. Do not handle it with bare hands.* Prepared by electrolysis of a solution of potassium chloride in a diaphragm cell that does not allow liberated chlorine to react with it. It is prepared in the form of sticks, pellets, flakes or fused masses. Sticks or pellets are made by evaporating a solution of it to a fluid of oily consistency and then pouring the hot liquid into suitable molds in which it solidifies. *Description* and *Solubility:* White, or nearly white, fused masses, small pellets, flakes, sticks, and other forms; hard and brittle and shows a crystalline fracture; exposed to air it rapidly absorbs carbon dioxide and moisture, and deliquesces; melts at about 360–380°; when dissolved in water or alcohol, or when its solution is treated with an acid, much heat is generated; solutions, even when highly diluted, are strongly alkaline. 1 g dissolves in 1 mL water, 3 mL alcohol or 2.5 mL glycerin at 25°; very soluble in boiling alcohol. *Incompatibilities:* Bases react with *acids* to form salts, liberate alkaloids from aqueous solutions of *alkaloidal salts*, and promote various hydrolysis reactions such as the decomposition of *chloral hydrate* into chloroform and a formate or the breakdown of *salol* into phenol and a salicylate. Only the alkali hydroxides are appreciably soluble in water. Nearly all common *metals* will be precipitated as hydroxides when solutions of their salts are added to solutions of the alkali hydroxides. Certain hydroxides, however, notably those of aluminum, zinc, arsenic or lead, will dissolve in excess of sodium or potassium hydroxide. *Uses:* A *caustic*, principally in veterinary practice. The end of a stick of potassium hydroxide may be inserted into a section of rubber tubing, or wrapped several times with tin foil, to avoid cauterizing the fingers of the operator. It is used also as a *pharmaceutical necessity* in several pharmacopeial preparations.

Trichloroacetic Acid [Acetic acid, trichloro-, Trichloroacetic acid [76-03-9] $C_2HCl_3O_2$ (163.39)]—Usually made by oxidizing chloral hydrate with fuming nitric acid. Colorless, deliquescent crystals having a slight, characteristic odor; melts at about 58° and boils at 196°–197°. *Solubility:* 1 g in about 0.1 mL water; soluble in alcohol or ether. *Uses:* Precipitates proteins and used as a *caustic* on the skin or mucous membranes to destroy local lesions and for treatment of various dermatologic diseases. Its chief use is to destroy ordinary warts and juvenile flat warts. It is employed extensively as a precipitant of protein in the chemical analysis of body fluids and tissue extracts, as well as a decalcifier and fixative in microscopy. *Caution—Trichloroacetic Acid is highly corrosive to the skin. Dose: Topical*, to the skin, as a 15 to 100% *w/v* solution, carefully applied with a cotton-tipped applicator or glass rod. Concentrations above 50% are not recommended.

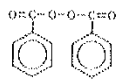
Zinc Chloride—page 763.

Keratolytics (Desquamating Agents)

The epidermis consists of layers of flat cells, called *stratified squamous epithelial cells*. They are bound together by desmosomes and penetrating tonofibrils, both of which largely consist of keratin. The outer layer of the epidermis, the cornified epithelium or stratum corneum, is made up of the collapsed ghosts of the squamous cells and, as such, is principally a tight network of keratin and lipoprotein. Certain fungi, especially the dermatophytes, utilize keratin and, therefore, reside in the stratum corneum in those places where the degree of hydration and the pH are sufficiently high. One way such mycoses may be suppressed is that of removal of the stratum corneum, a process that is called *desquamation*. Certain chemical substances, especially among phenols and sulfhydryl compounds, loosen the keratin and, thus, facilitate desquamation. These substances are called *keratolytics*. Aqueous maceration of the stratum corneum also favors desquamation. In addition to the treatment of epidermophytosis, keratolytics are used to thin hyperkeratotic areas. Most keratolytics are irritant. Irritants also can cause desquamation by causing damage to and swelling of the basal cells.

Benzoyl Peroxide

(Various Mfrs)



[94-36-0] $C_{14}H_{10}O_4$ (242.23); contains 65–82% of benzoyl peroxide; also contains about 26% of water for the purpose of reducing flammability and shock sensitivity.

Preparation—Benzoyl chloride is reacted with a cold solution of sodium peroxide.

Description—White, granular powder, having a characteristic odor; melts about 104°; *may explode with heat*.

Solubility—Sparingly soluble in water or alcohol; soluble in acetone, chloroform or ether.

Caution (For the drug entity—not the dosage forms)—It may explode at temperatures higher than 60° or cause fires in the presence of reducing substances. Store it in the original container, treated to reduce static charges. Do not transfer it to metal or glass containers fitted with friction tops. Do not return unused material to its original container, but destroy it by treatment with NaOH solution (1 in 10) until addition of a crystal of KI results in no release of free iodine.

Uses—Possesses mild antibacterial properties, especially against anaerobic bacteria. It is also mildly irritant, and it exerts moderate keratolytic and antiseborrheic actions. Its principal use is in the treatment of mild *acne vulgaris* (in which it is comedolytic) and *acne rosaceae*, but it also is used in the treatment of decubital and stasis ulcers.

It causes stinging or burning sensations for a brief time after application; with continued use these effects mostly disappear. After 1 or 2 weeks of use there may be a sudden excess dryness of the

skin and peeling. The drug must be kept away from the eyes, and from inflamed, denuded or highly sensitive skin, such as the circumoral areas, neck and skin of children. It should not be used in conjunction with harsh abrasive skin cleansers. It can cause contact dermatitis. It can bleach hair and fabrics.

Dose—*Topical*, to the *skin*, *adults* and *children 12 yr or older*, as a 5 or 10% cleansing bar 2 or 3 times a day, 5 to 10% cream or gel 1 or 2 times a day, 5 to 20% lotion 1 to 4 times a day, 5 or 10% cleansing lotion 1 or 2 times a day, 5% facial mask once a day, 10% soap 1 or 2 times a day or 10% stick 1 to 3 times a day. The 20% lotion is used only for the treatment of decubital and stasis ulcers.

Dosage Forms—Cleansing Bar: 5 and 10%; Cream: 5, 7 and 10%; Gel: 2.5, 5 and 10%; Lotion: 5, 5.5, 10 and 20%; Cleansing Lotion: 5 and 10%; Facial Mask: 5%; Stick: 10%.

Fluorouracil—page 1151.

Resorcinol—RPS-16, page 1107.

Resorcinol Ointment, Compound—RPS-16, page 1107.

Salicylic Acid

Benzoic acid, 2-hydroxy-, *o*-Hydroxybenzoic Acid

Salicylic acid [69-72-7] $C_7H_6O_3$ (138.12).

Preparation—Mostly by the Kolbe-Schmidt process in which CO_2 is reacted with sodium phenolate under pressure at about 130° to form sodium salicylate, followed by treatment with mineral acid.

Description—White, fine, needle-like crystals or as a fluffy, white, crystalline powder; the synthetic acid is white and odorless; sweetish, afterward acrid, taste; stable in the air; melts between 158° and 161°.

Solubility—1 g in 460 mL water, 3 mL alcohol, 45 mL chloroform, 3 mL ether, 135 mL benzene or about 15 mL boiling water.

Uses—Used *externally* on the skin, where it exerts a slight *antiseptic* action and considerable *keratolytic* action. The latter property makes it a beneficial agent in the local treatment of certain forms of *eczematoid dermatitis*. It also is included in products for the treatment of *psoriasis*, for which the FDA classification is Category 1. Tissue cells swell, soften and ultimately desquamate. Salicylic Acid Plaster often is used for this purpose. The drug is especially useful in the treatment of *tinea pedis* (athlete's foot) and *tinea capitis* (ringworm of the scalp), since the fungus grows and thrives in the stratum corneum. Keratolysis both removes the infected horny layer and aids in penetration by antifungal drugs. It is combined with benzoic acid in an ointment long known as Whitfield's Ointment. It also is combined commonly with zinc oxide, sulfur or sulfur and coal tar. It is incorporated into mixtures for the treatment of acne, dandruff and seborrhea, insect bites and stings and into soaps and vaginal douches, but efficacy remains to be established. In high concentrations it is *caustic* and may be used to remove *corns*, *calluses*, *warts* and other growths.

Collodions or solutions of 17% or higher and other forms above 25% concentration should not be employed if the patient has diabetes mellitus, peripheral vascular disease or inflammation or infection at the intended site of application. Continuous application of the drug to the skin can cause dermatitis. Systemic toxicity resulting from application to large areas of the skin has been reported. It is not employed internally as an analgesic because of its local irritating effect on the gastrointestinal tract.

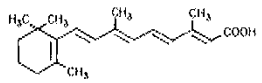
Dose—*Topical*, to the *skin*, *keratolytic*, as a 16.7 or 17% collodion once a day, 2.5 to 10% cream under occlusion once every 3 to 5 days, 2% foam once or twice a day, 5 or 6% gel under occlusion once a day, 1.8% lotion once or twice a day, 3 to 10% ointment once a day, 2 or 4% shampoo once or twice a week, 3.5% soap once a day or 17% solution once a day; *antipsoriatic*, as a 5 or 6% gel under occlusion or 3 to 10% ointment once a day; *antiseborrheic*, as a 1.8% lotion, 3 to 10% ointment or 2 or 4% shampoo once a day; *antiacne*, as a 2% foam once or twice a day, 5 or 6% gel under occlusion once a day, 3 to 6% ointment once a day or 3.5% soap once a day; *caustic*, as a 25% cream once every 3 to 5 days, 25 to 60% ointment under occlusion every 3 to 5 days, or 40% plaster once a day.

Dosage Forms—Flexible Collodion: 16.7 and 17%; Cream: 2.5, 10 and 25%; Gel: 5 and 6%; Lotion: 1.8%; Ointment: 25, 40 and 60% (3 to 10% ointments must be extemporized); Plaster: 40%; Shampoo: 2 and 4%; Soap: 3.5%; Topical Solution: 17%.

Sulfur, Precipitated—page 1247.

Tretinoin

Retinoic acid; Retin-A (*Ortho*)



all *trans*-Retinoic acid [302-79-4] $C_{20}H_{28}O_2$ (300.44).

Preparation—By oxidation of vitamin A aldehyde which may be obtained by oxidation of vitamin A. *Biochem J 90:* 569, 1964.

Description—Yellow to light-orange crystals or crystalline powder with the odor of ensilage; should be stored in cold and protected from light and air; melts between 176 and 181°.

Solubility—Insoluble in water; slightly soluble in alcohol; slightly soluble in chloroform; 1 g in 10 mL boiling benzene.

Uses—It is retinoic acid, or so-called *vitamin A acid*, which is formed when the aldehyde group of retinene (retinal) is oxidized to a carboxyl group. It is not known whether retinoic acid has a physiologic function, but some authorities consider it to be the form of vitamin A that acts in the skin. This view is supported by the fact that retinol and retinal have very little action on the skin but large systemic doses of vitamin A evoke prominent dermatologic changes.

Topically, it causes inflammation, thickening of the epidermis (acanthosis) and local intercellular edema, which leads to some separation of the epidermal cells. Follicular epithelial cells become less adhesive, the stratum corneum loosens and exfoliation may occur. High concentrations can cause vesiculation. These actions are used in the treatment of *acne vulgaris*. The loosened horny layer makes it easier for the comedo to rise up and discharge, and the inflammatory response mobilizes white cells which attack the bacteria in the follicle. In the early stages of treatment, the sudden surfacing of obscured preexisting comedones makes it appear that the acne has been exacerbated, but the new comedones do not coalesce into cysts or nodules and scarring does not occur. The exaggerated stage may last for as long as 6 weeks, after which improvement comes rapidly. Shortly after discontinuation of treatment, relapses readily occur. Deep cystic nodular acne (acne conglobata) or severe cases usually are not improved by the drug.

Various hyperkeratotic conditions are reported to respond to it, responses being sometimes exceptionally dramatic. *Solar* and *follicular keratosis*, *lamellar ichthyosis*, *keratosis palmaris* and *plantaris* and other hyperplastic dermatoses have been treated successfully with the drug. It also has been used in the treatment of some skin cancers. Recent reports indicate that it may somewhat rejuvenate sun-aged skin.

It is an antioxidant and free-radical scavenger. There is some evidence not only that topical applications may provide some protection from actinic and other radiation effects on the skin, including cancer, but that internally it may be protective against carcinogenesis from radiation and carcinogens. Systemically, it does not cause the toxic effects of large doses of vitamin A.

In concentrations of 0.05 to 0.1%, it causes a transient feeling of warmth or mild stinging, and erythema follows. Peeling of the skin may occur. Irritation and peeling are marked more when the concentration exceeds 0.1%. When peeling, crusting or blistering occurs, medication should be withheld until the skin recovers, or the concentration should be reduced. The drug should not be applied around the eyes, nose or angles of the mouth, because the mucosae are much more sensitive than the skin to the irritant effects. It also may cause severe irritation on eczematous skin. It should not be applied along with, or closely following, other irritants or keratolytic drugs. Exposure to sunlight should be avoided if possible. Both hypo- and hyperpigmentation have been reported, but the conditions appear to be reversible and temporary.

Dose—*Topical*, *usual*, to the skin, 0.01 to 0.1% once a day at bedtime.

Dosage Forms—Cream: 0.05 and 0.1%; Gel: 0.01 and 0.025%; Topical Solution: 0.05%.

Trichloroacetic Acid—page 767.

Urea—page 931.

Cleansing Preparations

The skin may be cleansed with detergents, solvents or abrasives, singly or in combination. Among the detergents, the soaps have enjoyed the greatest official status, more through custom than through special merit. The nonsoap detergents became important, not only as household hand cleansers, but also in dermatologic and surgical practice as well. However, because many nonsoap detergents do not decompose in sewage disposal plants, there has been a return to real soap. Some of the antiseptic "soaps" still contain synthetic detergents. Soap interferes with the action of many antiseptics, which is one reason synthetic detergents often are used in antiseptic cleansing preparations. However, synthetic detergents also interact with some antiseptics. Anionic nonsoap skin detergents rarely sensitize the skin and, thus, are prescribed when the user is allergic to soap.

Ordinary soaps tend to be alkaline, with pH ranging from 9.5 to 10.5. Superfatted soaps have a pH in the lower end of the range. Synthetic detergents usually have a pH of 7.5 or less. Neutral toilet bars contain synthetic detergents.

Shampoos are liquid soaps or detergents used to clean the hair and scalp. Both soaps and shampoos often are used as vehicles for dermatologic agents.

Many bar soaps contain either triclosan or triclocarban as antiseptics in concentrations which suppress bacterial production of body odors but which effectively are not antiseptic. A number of soaps and shampoos contain keratolytic and antiacne ingredients. Abrasive soaps contain particles of alumina, polyethylene or sodium tetraborate decahydrate.

It commonly, but erroneously, is believed that soap has an antiseptic action. The promotion of either soap or synthetic detergents alone for the control of acne is unwarranted; antiseptic substances must be added to the cleansing material or be used separately. Quantitative studies of the cutaneous flora before and after cleansing with soap or with other anionic detergents show a negligible antiseptic effect. However, the removal of loose epidermis lessens the likelihood that cutaneous bacteria will be transferred from the skin to other structures. Certain cationic detergents employed in dermatology are antiseptic. Detergents are treated under *Surface-Active Agents* (page 267).

The choice of organic solvents to cleanse the skin depends largely upon the nature of the material to be removed. In medical practice ethanol and isopropyl alcohol are the most frequently employed organic solvents. Cleansing creams act both as solvents and as detergents. Other soapless cleansers variously contain petrolatum, vegetable oils, lanolin, high-molecular-weight alcohols, various carbohydrate derivatives, oatmeal and other ingredients.

Alcohol—page 1314.
Alcohol, Rubbing—page 1164.
Benzalkonium Chloride—page 1164.
Green Soap—RPS-17, page 786.
Hexachlorophene Cleansing Emulsion—page 1166.
Isopropyl Rubbing Alcohol—page 1167.
Sodium Lauryl Sulfate—page 1307.

Miscellaneous Dermatologics

Gargles, nasal washes, douches, enemata, etc generally contain as basic ingredients substances described under other categories in this chapter. These preparations are described under *Aqueous Solutions*, page 1521.

Antiphlogistics include alcohol and several creams and lotions that cool the skin by evaporation. Many antiphlogistic preparations also contain an astringent and a local anesthetic or camphor or menthol.

Commonly employed *antipruritics* also depend largely upon local anesthetics and the soothing effect of cooling, although emollients or demulcents may be included, especially depending upon the etiology of the pruritus. The antipruritic properties of phenol preparations largely derive from superficial local anesthesia.

Vulnerary and *epithelizing* properties are attributed to numerous irritants and to several dyes; however, few reliable data exist to support most claims to vulnerary action.

Sunscreens contain aromatic compounds, like aminobenzoic acid, which efficiently absorb the harmful ultraviolet (UV) rays from the incident sunlight and transmit mainly the less harmful wavelengths, or titanium dioxide, which reflects sunlight from the surface of application. UV light in the spectral range of 290–320 nm causes suntan and sunburn; therefore, a sunscreen to prevent tan or burn should have a high molar absorptivity in this range. However, *photosensitization* (ie, the photoactivation of chemicals to make them toxic or allergenic) may occur with wavelengths as high as 500 nm; consequently, to protect recipients of certain drugs (tetracyclines, sulfonamides, erythromycin, promazine, chlorpromazine, promethazine, psoralens), sunscreens with a broader absorption spectrum are required. An adequate broad spectrum is usually achieved with combinations of sunscreens (eg, dioxybenzone and oxybenzone).

Melanizers are substances that promote the pigmentation of the skin. Most melanizers produce their effect by sensitizing the skin to UV light,* so that the effect is principally the same as if the subject had been exposed for a long time to the sun.

Skin bleaches, or *demelanizers*, mostly contain hydroquinone derivatives.

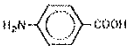
Hair bleaches generally contain peroxides.

There is a large variety of *depilatories* on the market. Many of them are sulfhydryl compounds, especially thioglycollates, which reduce the disulfide bonds of keratin, thus softening the hair to the point where it can be separated easily from the epidermis. Some of the same compounds are used in lower concentrations in hairwaving preparations. There is one drug, minoxidil, an antihypertensive drug, which can *increase hair growth* and *treat baldness*. Diazoxide probably will prove to have similar activity.

Antiperspirants have been included among the astringents.

Aminobenzoic Acid

Benzoic acid, 4-amino-, PABA



p-Aminobenzoic acid [150-13-0] $C_7H_7NO_2$ (137.14).

Preparation—*p*-Nitrotoluene is oxidized with permanganate to *p*-nitrobenzoic acid, and the nitro group is then reduced to amino with iron and hydrochloric acid.

Description—White or slightly yellow, odorless crystals or crystalline powder; melts between 186° and 189°; discolors on exposure to air or light.

* This action is termed a *photodynamic action*. The term has been used loosely to include all instances of enhanced sensitivity to light, but in strict definition it is confined to photosensitization in which the participation of oxygen is required. In the photodynamic process, light of wavelengths too long to be ordinarily effective may be used, so that the activating spectrum may be shifted toward longer wavelengths.

Solubility—Slightly soluble in water or chloroform; freely soluble in alcohol or solutions of alkali hydroxides and carbonates; sparingly soluble in ether.

Uses—A *sunscreen*. It absorbs UV light of wavelengths in the region of 260 to 313 nm; its molar absorptivity at 288.5 nm is 18,300. However, it does not absorb throughout the near UV range, so that drug-related photosensitivity and phototoxicity may not be prevented by it, but in combination with benzophenone it does protect against some drug-induced phototoxicities. Nevertheless, in the 260–313 nm range, it has the highest protection index of current sunscreen agents.

For animal species that do not use preformed folic acid, which contains the *p*-aminobenzoyl moiety, it is a B-vitamin. However, man does not use it, and its promotion in vitamin preparations preys on the ignorance of the consumer. It or its potassium salt is promoted as an agent that softens or regresses fibrotic tissue in Peyronie's disease, scleroderma, dermatomyositis, morphea and pemphigus. The claims for the antifibrotic actions are substantiated poorly, and the actions and uses are not mentioned in major works on pharmacology and therapeutics.

Topically, it is rarely allergenic to recipients but phototoxicity and photoallergenicity occur. Systemic side effects include nausea, anorexia, fever and rash.

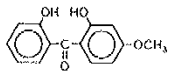
Dose—*Topical*, as a sunscreen, 4 to 15% in solutions, lotions, creams and lipsticks. *Oral, adults*, 12 g a day in 4 to 6 divided doses; *children*, 1 g/10 lb a day in divided doses, to be diluted and taken with food.

Dosage Forms—Capsules: 500 mg; Cream: 4% (may also contain sodium PABA); Gel: 5%; Lotion: 5%; Powder: 2, 100 and 453 g; Solution: 5%; Stick: 5% (may contain red petrolatum); Tablets: 30, 100 and 500 mg.

Cetyl Alcohol—page 1312.

Dioxybenzone

Methanone, (2-hydroxy-4-methoxyphenyl)(2-hydroxyphenyl)-, Spectra-Sorb UV 24 (*American Cyanamid*); Solaquin (*Elder*)



2,2′-Dihydroxy-4-methoxybenzophenone [131-53-3] $C_{14}H_{12}O_4$ (244.25).

Preparation—By a Friedel-Crafts reaction in which *o*-methoxybenzoyl chloride is added gradually to a mixture of 1,3-dimethoxybenzene, chlorobenzene and aluminum chloride. The reaction conditions are such that both methoxy groups ortho to the carbonyl bridge in the initial condensation product are demethylated. US Pat 2,853,521.

Description—Off-white to yellow powder; congeals not lower than 68°.

Solubility—Practically insoluble in water; freely soluble in alcohol or toluene.

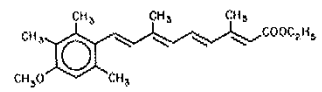
Uses—A *sunscreen* of intermediate molar absorptivity (11,950 at 282 nm), but it absorbs throughout the UV spectrum and, hence, affords protection not only against sunburn but also against the photodynamic, photosensitizing and phototoxic effects of drugs. At present, it is marketed in combination with the closely related *Oxybenzone* (page 771).

Dose—*Topical*, as a 3% lotion.

Dosage Forms—Dioxybenzone and Oxybenzone Cream: 3% of each ingredient.

Etretinate

2,4,6,8-Nonanetetraenoic acid, 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-, ethyl ester (*all-E*); Tegison (*Roche*)



[54350-48-0] $C_{23}H_{30}O_3$ (354.49).

Preparation—One scheme involves the Wittig condensation of diphenyl 2,3,6-trimethyl-4-methoxybenzylphosphonium chloride and 8-oxo-3,7-dimethyl-2,4,6-octane-trienoic acid (*all-trans*) in the presence of butylene oxide; *Experientia 34:* 1113, 1978.

Description—Crystalline solid melting about 104°.

Uses—Although not a topical drug, it is a retinoid closely related to tretinoin and is used only for its dermatologic actions; consequently, it is included in this chapter. It is used in the treatment of recalcitrant *psoriasis*, especially the severe pustular erythrodermic type. It decreases scaling, erythema and the thickness of lesions and causes epithelial and dermal cells to redifferentiate to normal cells. Sometimes, dramatic improvement occurs within 2 weeks and complete clearing in 1.5 to 4.5 mo. However, relapses are frequent once treatment is discontinued and sometimes even during chronic maintenance. It can be used alone or in low-dose combination with PUVA therapy. The mechanism of action is unknown, but it is undoubtedly like that of vitamin A. Activity resides in the acid metabolite.

Adverse effects occur in more than 75% of recipients. They include chapped lips, peeling of the palms, soles and fingertips, dryness of the mucous membranes, sore tongue, cheilitis, rhinorrhea, nosebleed, gingival bleeding, loss of hair, nail abnormalities, dry and irritated cornea, sclera and conjunctiva (50%), epidermal fragility, easy sunburning and other effects. Occasionally, pseudotumor cerebri, metastatic calcification of ligaments and tendons, and liver dysfunction or necrosis occur. In children and adolescents there may be premature closure of the epiphyses. Plasma cholesterol and triglycerides rise and high-density lipoprotein decreases. The drug is also teratogenic. Adverse effects are less with the low doses used with PUVA.

Absorption after oral administration is incomplete. It is increased by whole milk and other lipid-containing foods. There is a rapid metabolism during which it is deesterified to the acid metabolite. A much slower degradation and conjugation follows, the metabolites being secreted into bile and urine. Nearly all of the circulating drug is bound to plasma lipoproteins, but the active metabolite is bound to albumin. Ultimately, it is taken up into fat, where it may be found even as long as 2 yr after the last dose. The apparent elimination half-life is about 120 days. This persistence of drug in the body militates against the use of the drug in fertile women of child-bearing age, since the incidence of congenital defects is high even when conception occurs months after the drug is discontinued. The drug also is excreted into milk; effects in the nursing infant are not known.

Dose—*Oral, adult, initially* 0.25 to 1.5 mg/kg a day in divided doses, the dose depending upon the type and seriousness of the disorder; with erythrodermic psoriasis, the initial dose is 0.25 mg/kg a day, increased weekly with increments of 0.25 mg/kg a day until a response occurs; *maintenance*, 0.5 to 0.75 mg/kg a day. Maintenance usually is not begun until after 8 to 16 weeks of treatment. The above doses are higher than those used concurrently with PUVA treatment.

Dosage Form—Capsules: 10 and 25 mg.

Hydrogen Peroxide Solution—page 1171.

Hydroquinone

1,4-Benzenediol; *p*-Dihydroxybenzene; Hydroquinol; Quinol; Eldoquin and Eldopaque (*Elder*)

Hydroquinone [123-31-9] $C_6H_6O_2$ (110.11).

Preparation—Various processes are employed. One involves reacting a sulfuric acid solution of aniline with manganese dioxide and reducing the resulting *p*-benzoquinone with sodium bisulfite.

Description—Fine, white needles; darkens on exposure to air; melts between 172 and 174°.

Solubility—1 g in about 17 mL water, 4 mL alcohol, 51 mL chloroform or 16.5 mL ether.

Uses—A *hypopigmenting* agent employed percutaneously to lighten localized areas of hyperpigmented skin, such as skin blem-

ishes, lentigo, melasma, chloasma, freckles, etc. Its action is temporary, so that it is necessary to repeat the application at frequent intervals. It is a mild irritant, and erythema or rash may develop, which requires discontinuation of the drug. It should not be used near the eyes or in open cuts. It is contraindicated in the presence of sunburn, miliaria or irritated skin. It is not to be used in children.

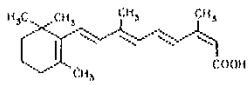
Dose—*Topical*, to the skin, *adults* and *children over 12 yr* as a 2 to 4% cream, gel, lotion or ointment to the affected area once or twice a day.

Dosage Forms—Cream: 2 and 4%; Gel: 4%; Lotion: 2%; Ointment: 2 and 4%.

Hydroxyurea—page 1158.

Isotretinoin

13-*cis*-Retinoic Acid; Accutane (*Roche*)



3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-*cis*-4-*trans*-6-*trans*-8-*trans*-nonatetraenoic acid [4759-48-2] $C_{20}H_{28}O_2$ (300.44). Differs from tretinoin (vitamin A) only in the configuration of the unsaturation at the α and β carbon atoms, which is *cis* rather than *trans*.

Uses—Although not a topical drug, it is a dermatologic agent and, hence, is described here. Its primary action is to decrease the production of sebum, which lends itself to the treatment of severe *nodular* and *cystic acne* (acne conglobata). The size of the sebaceous gland is decreased and there is a change in the morphology and secretory capacity of the cells (dedifferentiation). Complete clearing of lesions is seen in about 90% of cases. A single course of treatment usually brings about long-lasting, sometimes permanent, remissions.

It also appears to diminish hyperkeratosis and has been reported to be effective in *rosacea*, gram-negative *folliculitis*, *lamellar ichthyosis*, *Darier's disease*, *pityriasis rubra pilaris* and *keratocanthoma*.

Adverse effects include facial dermatitis, fragile skin, thinning and drying of the hair, reversible cheilitis and dry skin, mouth, eyes and conjunctivitis in 25 to 80% of recipients. Peeling of the palms and soles and sensitivity to sunburn occur in about 5% of users. Urethral inflammation also occurs frequently. Joint pains and exacerbation of rheumatoid arthritis also has been reported to occur in about 16% of patients. Sedimentation rate, serum triglyceride concentration and serum levels of alanine and aspartate transaminases transiently occur in about 25% of users. In spite of the relatively high incidence of side effects, treatment rarely has to be discontinued.

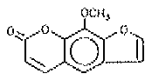
After oral administration, peak blood concentrations occur within 1 to 4 hr. The compound is oxidized to 4-hydroxy-13-*cis*-retinoic acid, which is then glucuronidated and is secreted into the bile. The elimination half-life is 11 to 39 (mean 20) hr. Isotretinoin should not be given during pregnancy or nursing.

Dose—*Oral*, *adult*, for *acne*, 1 to 2 mg/kg a day in 2 divided doses for 15 to 20 weeks. If the cyst count has not been reduced by more than 70%, a second course of treatment may be given after a wait of 2 months. Persons over 70 kg or who have severe chest and back involvement usually require doses at the high end of the range. For *severe rosacea* or gram-negative *folliculitis*, 0.25 to 0.5 mg/kg twice a day. For *hyperkeratoses*, up to 4 mg/kg.

Dosage Forms—Capsules: 10, 20 and 40 mg.

Methoxsalen

7*H*-Furo [3,2-*g*][1]benzopyran-7-one, 9-methoxy-, Ammoidin; 9-Methoxypsoralen; Xanthotoxin; Oxsoralen (*Elder*)



[298-81-7] $C_{12}H_8O_4$ (216.19).

Preparation—Occurs naturally in *Psorales coryfolia*, *Ammi majus*, *Ruta chalepensis* and various other plants. It may be synthesized by methods described in *JACS 79:* 3491, 1957, and in US Pat 2,889,337.

Description—White to cream-colored, odorless, fluffy, needle-like crystals; melts between 143° and 148°.

Solubility—Practically insoluble in cold water, sparingly soluble in boiling water; freely soluble in chloroform; soluble in boiling alcohol, acetone or acetic acid; soluble in aqueous alkalies with ring cleavage; reconstitution occurs on neutralization.

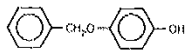
Uses—A psoralen melanizer. It increases the photodynamic pigmentation of skin; it does not induce pigmentation in the absence of UV light or melanocytes. It is used in the treatment of *vitiligo* and to *desensitize to sunlight*. Severe sunburning can occur with topical application; it is customary to protect the surrounding skin with a sunscreen. It also is used in PUVA treatment of *psoriasis*, *mycosis fungoides* and *cutaneous T-cell lymphoma;* in these, irradiation activates it to cross-link DNA. It may have value in the PUVA treatment of *alopecia areata*, *inflammatory dermatoses*, *eczema* and *lichen planus*. After oral administration gastrointestinal upset and central nervous system toxicities, such as vertigo and excitement, also occur. Consequently, the drug should be used orally only under medical supervision. It is additive with other photosensitizing drugs and the furocumarin pigments in carrots, celery, figs, limes, mustard, parsley and parsnips. It inhibits the metabolism of caffeine.

Dose—*Topical*, as a 1% lotion (see the package literature for details of application and use). *Oral*, *adults* and *children over 12 yr*, for *vitiligo*, 30 to 40 mg once a day 2 to 4 hr before exposure to ultraviolet light or at longer than 48-hr intervals 2 or 3 times a week; for *psoriasis*, *mycosis fungoides* or *cutaneous T-cell lymphoma*, 0.6 mg/kg 2 or 3 hr before UVA exposure (see the package literature for details).

Dosage Forms—Capsules: 10 mg; Lotion: 1%.

Monobenzone

Phenol, 4-(phenylmethoxy)-, Monobenzyl Ether of Hydroquinone; Benoquin (*Elder*)



p-(Benzyloxy)phenol [103-16-2] $C_{13}H_{12}O_2$ (200.24).

Preparation—Prepared in various ways. One method involves condensing sodium *p*-nitrophenolate with benzyl chloride to produce benzyl *p*-nitrophenyl ether followed by (1) reduction of nitro to amino, (2) diazotization of amino and (3) hydrolytic decomposition of the diazonium compound to the corresponding phenol.

Description—White, odorless, crystalline powder possessing very little taste; melts between 117° and 120°.

Solubility—1 g in >10,000 mL water, 14.5 mL alcohol, 29 mL chloroform or 14 mL ether.

Uses—A *depigmenting agent* or *demelanizer*. It acts by interfering with the formation of melanin, which is the principal cutaneous pigment. It is recommended only for the final depigmentation in *vitiligo*. It is not recommended for treatment of lentigo, severe freckling and other types of hyperpigmentation. It is not effective against pigmented moles or malignant melanoma. Its pigment-decreasing action is somewhat erratic. Irritation of varying degrees occurs in a considerable number of patients.

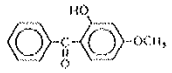
Dose—*Topical*, *adults* and *children over 12 yr*, to the skin, as a 20% cream 2 or 3 times a day.

Dosage Forms—Cream: 20%.

Minoxidil—page 837.

Oxybenzone

Methanone, (2-hydroxy-4-methoxyphenyl)phenyl-, (*Various Mfrs*)



2-Hydroxy-4-methoxybenzophenone [131-57-7] $C_{14}H_{12}O_3$ (228.25).

Preparation—Benzoic acid is condensed with resorcinol monomethyl ether by heating in the presence of $ZnCl_2$ or polyphosphoric acid (103% H_3PO_4 equivalent), and PCl_3. US Pat 3,073,866.

Description—White to off-white powder; congeals not lower than 62°.

Solubility—Practically insoluble in water; freely soluble in alcohol or toluene.

Uses—A *sunscreen* with a high molar absorptivity (20,381 at 290 nm), and it absorbs in both the long and short UV spectrum 270–350 nm. Therefore, it serves not only to prevent sunburn but also to protect against the photodynamic, photosensitizing and phototoxic effects of various drugs. Contact with the eyes should be avoided. At present, it is marketed only in combination with other sunscreens.

Dose—*Topical*, as a 3 to 5% cream, 0.5% lipstick and 2 or 3% lotion in combination with other sunscreens.

Ringer's Irrigation—RPS-16, page 762.
Sodium Bicarbonate—page 777.

Sodium Fluoride

Sodium fluoride [7681-49-4] NaF (41.99).

Preparation—By interaction of 40% HF with an equivalent quantity of NaOH or Na_2CO_3.

Description—White, odorless powder.

Solubility—1 g in 25 mL water; insoluble in alcohol.

Uses—A *dental caries prophylactic*. Fluoridation of municipal water supplies is considered a safe and practical public health measure, a concentration of about 1 ppm of fluoride in the water supply resulting in a 50 to 65% reduction in the incidence of dental caries in permanent teeth. Ingested fluoride is effective only while teeth are being formed. The fluoride is incorporated into tooth salts as fluoroapatite. Excessive intake during development of teeth may cause mottling; hence, mottling of newly erupted teeth is an indication to reduce fluoride intake. Where drinking water contains less than 0.7 ppm of fluoride, dietary supplements for children with unerupted teeth may provide some future protection.

Topical application results in changes only in the outer layers of enamel or exposed dentin. In children, repeated application of a 2% solution of the drug to cleaned teeth results in a 16 to 49% reduction of dental caries; adult teeth are protected to a lesser extent by topical application. Topical application also is used to *densensitize* teeth.

Orally administered, it produces new bone formation in some patients with osteoporosis, especially when calcium and vitamin D (and estrogens in women) are administered concomitantly to facilitate mineralization of the new bone. However, the bone may become brittle.

It removes calcium from tissues and also poisons certain enzymes. Large oral doses may cause nausea and vomiting, which usually can be prevented by taking the substance with food. Pastes, rinses, solutions and gels for topical applications should not be swallowed.

Dose (as sodium fluoride)—*Topical*, to the teeth, as a 0.02 to 2% solution, 1.1 or 2.71% gel or 0.22 to 2.3% toothpaste. *Oral*, 1.5 to 3 **ppm** (equivalent to 0.7 to 1.3 ppm of fluoride ion) in drinking water; as a supplement, when the drinking water contains less than 0.3 ppm of fluoride ion, **0.55 mg** a day for infants from 2 wk to 2 yr of age, **1.1 mg** once a day for children from 2 to 3 yr and **2.2 mg** for those from 3 to 13 yr, and when the drinking water contains 0.3 to 0.7 ppm of fluoride ion, **550 μg** once a day for children 2 to 3 yr and **1.1 mg** for those 3 to 13 yr. The fluoride ion equivalents of 550 μg, 1.1 mg, and 2.2 mg of the drug are 250 μg, 500 μg, and 1 mg, respectively. For *osteoporosis*, up to **60 mg** a day. *Caution: It is poisonous.*

Dosage Forms—Drops: 0.275, 0.55 and 1.1 mg/drop; Gel: 1.1 and 2.71%; Rinse: 0.02, 0.05, 0.2 and 0.44%; Solution: 1.1, 3.3, 5.5, and 20 mg/mL; Chewable Tablets: 0.55, 1.1 and 2.2 mg. Sodium Fluoride and Orthophosphoric Acid: Gel: 1.23% fluoride ion and 1% phosphoric acid.

Sodium Monofluorophosphate

Phosphorofluoridic acid, sodium salt

$FPO(ONa)_2$

Disodium phosphorofluoridate [10163-15-2] (143.95).

Preparation—Substantially pure drug is produced by fusing a mixture of sodium metaphosphate and sodium fluoride, in stoichiometric proportion, in a closed vessel from which moist air is excluded.

Description—White to slightly gray, odorless powder.

Solubility—Freely soluble in water.

Uses—Like *Sodium Fluoride*, above, it promotes the replacement of the hydroxyapatite by fluoroapatite in the tooth salts and, hence, is used as a *dental prophylactic* against dental caries. It has the advantage over sodium fluoride in that the teeth do not require special preparation before application, it is effective when included in dentifrices and in dentifrices there is no hazard with respect to local toxicity to the gingivae or systemic intoxication from ingestion.

Dose—*Topical*, to the teeth, in dentifrice containing 0.76%.

Stannous Fluoride

Tin Difluoride; Fluoristan

Tin fluoride (SnF_2) [7783-47-3] (156.69); contains not less than 71.2% Sn^{2+} (stannous tin), and about 24% F^- (fluoride).

Preparation—Stannous oxide is dissolved in 40% HF and the solution is evaporated out of contact with air.

Description—White, crystalline powder with a bitter, salty taste; melts at about 213°.

Solubility—Freely soluble in water; practically insoluble in alcohol, ether or chloroform.

Uses—Alters the composition and crystalline structure of the hydroxyapatite-like salts that make up the bulk of enamel and dentin, so that the tooth material is more resistant to acidic erosion and dental caries (decay). The substance is applied only topically, so that the tooth substance is only affected in the superficial layers, and it must be applied periodically. It is most effective when applied to the tooth surface after the teeth have been cleaned thoroughly by a dentist. However, there is good evidence that even when incorporated into tooth pastes the drug has a retardant effect on the development of dental caries.

Dose—*Topical*, to the teeth, generally as 0.4% gel or 0.1% rinse.

Dosage Forms—Capsules (for solution): 0.4, 0.65 and 0.8 g; Concentrate: 30%; Gel: 0.4%.

Titanium Dioxide

Titanic Anhydride

Titanium oxide (TiO_2) [13463-67-7] TiO_2 (79.88).

Preparation—By adding ammonia or an alkali carbonate to a solution of titanyl sulfate ($TiOSO_4$). Titanic acid [$Ti(OH)_4$ or $TiO(OH)_2$] is precipitated and, after filtration and washing, is dried and ignited.

Description—White, amorphous, tasteless, odorless, infusible powder; density about 4; suspension in water (1 in 10) neutral to litmus.

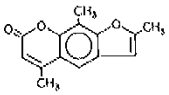
Solubility—Insoluble in water, HCl, HNO_3 or dilute H_2SO_4.

Uses—Its powder has a very high reflectance at visible and UV wavelengths, and, hence, it serves as an excellent white pigment. In ointments or lotions it reflects a very high proportion of incident sunlight, hence, protecting the skin from sunburn and serving as a *sunblock*. It also is used in cosmetics and as a dusting powder. Topically, it is devoid of toxicity.

Dose—*Topical*, as 2 to 25% cream, lotion or ointment as required.

Trioxsalen

7*H*-Furo[3,2-*g*][1]benzopyran-7-one, 2,5,9-trimethyl-, 6-Hydroxy-β,2,7-trimethyl-5-benzofuranacrylic Acid δ-Lactone; Trisoralen (*Elder*)



[3902-71-4] $C_{14}H_{12}O_3$ (228.25).

Caution: Avoid contact with the skin.

Preparation—2-Methylresorcinol is cyclized with ethyl acetoacetate with the aid of sulfuric acid to 7-hydroxy-4,8-dimethylcoumarin (I). Treatment with allyl bromide in the presence of potassium carbonate transforms I into the 7-allyloxy compound which, on reacting with acetic anhydride in the presence of *N,N*-diethylaniline and anhydrous sodium acetate, rearranges and esterifies to give the 7-acetoxy-6-allyl compound (II). Bromination of II followed by reaction with sodium methoxide yields trioxsalen. US Pat 3,201,421.

Description—White to off-white, odorless, tasteless crystalline solid; stable in light, air and heat; melts at about 230°.

Solubility—1 g in 1150 mL alcohol, 84 mL chloroform or 43 mL methylenedichloride; practically insoluble in water.

Uses—Although not a topical drug, it closely relates to other drugs in this section. It facilitates the action of near UV light to induce melanin (skin pigment) formation. It is used to cause repigmentation in idiopathic *vitiligo* and to enhance pigmentation to *increase tolerance to sunlight* or for *cosmetic purposes*. The increased tolerance to sunlight does not occur until enhanced pigmentation has occurred, and the user must be cautioned that severe sunburning with less than normal exposure can occur early during the course of treatment. The increase in dermal pigment occurs gradually over a period of several days of repeated exposure. Care must be taken to protect the eyes and lips during treatment. The manufacturer's recommended schedule of exposure should be used except at high altitudes, where exposure times should be appropriately reduced.

It is contraindicated in persons with photosensitizing diseases, such as infectious leukoderma, porphyria or lupus erythematosus and when photosensitizing drugs are being given. The drug sometimes may cause gastric irritation and emesis. Children under 12 should not take it.

Dose—*Oral, adults* and *children over 12 yr*, **5 to 10 mg** 2 hr before exposure to sunlight. For the treatment of vitiligo the exposure should be repeated once a day for 4 days, and subsequent exposures should be determined according to the results of the initial 4 days. For the enhancement of pigmentation, treatment should not exceed 2 weeks, and the total accumulated dose in any one treatment course should not exceed 140 mg. Persons who show side effects of the drug should take only 5 mg; the duration of use will be necessarily prolonged over that in persons taking the usual dose of 10 mg.

Dosage Forms—Tablets: 5 mg.

Urea—page 931.

Other Miscellaneous Topical Drugs

Allantoin 2,5-Dioxo-4-imidazolidinylurea [97-59-6]; $C_4H_6N_4O_3$ (158.12)]—Prepared by oxidation of uric acid. Colorless crystals melting at 238°. 1 g dissolves in 190 mL water or 500 mL alcohol; nearly insoluble in ether. *Uses:* In World War I it was noticed that maggot-infested wounds seemed to heal better than uninfested wounds, an effect attributed to this drug produced by maggots. It is used topically as a vulnerary to stimulate tissue repair in suppurating wounds, resistant ulcers, acne, seborrhea, cold sores, hemorrhoids and various dermatologic infections and psoriasis. It frequently is combined with astringents, keratolytics, coal tar, antiseptics and antifungal drugs. The silver salt has been used in the topical treatment of extensive burns. *Dose: Topical*, 0.2 to 2% in creams, lotions or shampoos and 0.3 to 0.5% in ointments for hemorrhoids.

Cinoxate [2-Ethoxyethyl *p*-methoxycinnamate [104-28-9]; $C_{14}H_{18}O_4$ (250.29)]—A viscous liquid that may have a slightly yellow tinge; boils at about 185°. Practically insoluble in water; miscible with alcohols. *Uses:* A *sunscreen* that absorbs UV light at 270 to 328 nm and has a relatively high molar absorptivity (19,400 at 306 nm) but not absorbing well throughout the entire offending range of UV light. Consequently, it is used principally in preparations intended to promote tanning rather than to protect against photosensitivity and phototoxicity. *Dose: Topical*, 1.75 to 4% in creams, gels or lotions.

Dextranomer [Dextran 2,3-dihydroxypropyl-2-hydroxy-1,3-propanediyl ether [56087-11-7] Dextran polymer; Debrisan (*Pharmacia*)]—Small, dry beads of a three-dimensional dextran polymer; highly hygroscopic. 1 g absorbs about 4 g water. *Uses:* For drying, cleansing and debridement of exudative *venous stasis ulcers, infected wounds* and *burns*; it is not useful for cleansing nonexudative wounds or lesions. The beads not only absorb water but also proteins, including fibrin/fibrinogen degradation products and, thus, prevent encrustation. The beads are poured into the cleansed wound, which is circumscribed with petroleum jelly, and a compress is taped in place to retain the material. Changes may be made up to 3 or 4 times a day, as needed. The beads must be removed before skin grafting is attempted. Care must be taken to prevent cross-contamination from patient to patient. On the floor the beads are slippery and, thus, hazardous.

Digalloyl Trioleate [[17048-39-4; 27436-80-2] $C_{68}H_{106}O_{12}$ (1115.59)]—*Uses:* A sunscreen with an absorption band at 270 to 320 nm. It is used topically as a 3.5% cream or 2.5% lipstick.

Dihydroxyacetone [1,3-Dihydroxydimethyl ketone [96-26-4] $C_3H_6O_3$ (90.08)]—The ketone resulting from oxidation of the secondary alcohol group of glycerin. A crystalline powder; fairly hygroscopic; characteristic odor and sweet taste. The normal form is the dimer, slowly soluble in 1 part water or 15 parts alcohol; the monomer formed in solution is very soluble in water, alcohol or ether. *Uses:* Interacts with keratin in the stratum corneum to form a dark pigment that simulates the appearance of a suntan. It is incorporated in several sunscreen preparations. Since the sunscreen component is usually present in a concentration lower than optimal, such preparations may not provide protection to photosensitive persons.

Ethyl Dihydroxypropylaminobenzoate [Ethyl 4-[bis(hydroxypropyl)]aminobenzoate [58882-17-0] $C_{15}H_{23}NO_4$ (281.35); Amerscreen (*Amerchol*)]—*Uses:* A sunscreen with a limited absorption spectrum (280 to 330 nm) characteristic of *p*-aminobenzoates but a relatively high molar absorptivity. It is used mainly in suntan products. *Dose: Topical*, in concentrations of 1 to 5%.

Ethylhexyl Methoxycinnamate [2-Ethylhexyl *p*-methoxycinnamate [5466-77-3] $C_{18}H_{26}O_3$ (290.40)]—*Uses:* A sunscreen with a narrow absorption band of 290 to 320 nm and a moderate molar absorptivity. *Dose: Topical*, in 2 to 7.5% concentration in creams, lotions and oils.

Glyceryl *p*-Aminobenzoate [1,2,3-Propanetriol 1-(4-aminobenzoate) [136-44-7] $C_{10}H_{13}NO_4$ (211.21)]—Prepared by esterification of aminobenzoic acid with glycerin. A waxy semisolid or syrup. Insoluble in water, oils or fats; soluble in ethanol, isopropanol or propylene glycol. *Uses:* A sunscreen that absorbs UV light at 264 to 315 nm and which has a relatively high molar absorptivity (17,197 at 295 nm) but a limited spectrum, therefore used primarily to promote tanning rather than to protect sensitive persons. *Dose: Topical*, 2 to 3% in lotions.

Homosalate [3,3,5-Trimethylcyclohexyl salicylate; homomenthyl salicylate [118-56-9] $C_{16}H_{22}O_3$ (262.36); ing of Coppertone (*Plough*); Filtrosol "A" (*Norda*); Heliophan (*Greeff*)]—*Uses:* A liquid with relatively low molar absorptivity (6,720 at 310 nm) and limited absorption in the near ultraviolet range (290 to 315 nm), so that it is used mainly to promote tanning. Photosensitive persons may not be protected from burns and phototoxicity. *Dose: Topical*, 4 to 10% in creams, lotions or oils.

Methyl Anthranilate [Methyl 2-aminobenzoate [134-20-3] $C_8H_9NO_2$ (151.16)]—A constituent of several essential oils; also obtained by esterifying anthranilic acid with methyl alcohol. A crystalline substance; melts at 25°. Slightly soluble in water; freely soluble in alcohol or ether. *Uses:* A sunscreen, with the lowest molar absorptivity of all sunscreens (941 at 315 nm); also, it does not absorb throughout the near UV range (absorption band, 290 to 320 nm) and, therefore, is used in combination with other sunscreens or light-protectives. It also is used as a perfume in ointments and cosmetics. *Dose: Topical*, to the skin, 5% in creams, lotions or ointments.

Octyl salicylate—*Uses:* A sunscreen with an absorption band at 280 to 320 nm and a moderate absorptivity. It is used primarily in conjunction with other sunscreens in suntan products.

Padimate A [Pentyl *p*-(dimethylamino)benzoate [14779-78-3] $C_{14}H_{21}NO_2$ (235.33); (*Various Mfrs*)]—A mixture of pentyl, isopentyl and 2-methylbutyl esters of *p*-aminobenzoic acid. Yellow liquid with a faint, aromatic odor. Practically insoluble in water or glycerin; soluble in alcohol, chloroform, isopropyl alcohol or mineral oil. *Uses:* A sunscreen of moderate molar absorptivity but relatively narrow UV absorption spectrum (290 to 315 nm) characteristic of other aminobenzoic acid derivatives. *Dose: Topical*, to the skin, as a 1.4 to 8% cream, foam, lotion or stick.

Padimate O [2-Ethylhexyl 4-(dimethylamino)benzoate [21245-02-3] $C_{17}H_{27}NO_2$ (277.41); (*Various Mfrs*)]—A light-yellow mobile liquid with a faint, aromatic odor. Practically insoluble in water, alcohol or mineral oil. *Uses:* See *Padimate A*.

Red Petrolatum—*Uses:* Owing to its opacity, it is used in sunblock creams, ointments and sticks. Concentrations range from 30 to 100%.

CHAPTER 66

Pharmaceutical Necessities

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This chapter describes substances that are of little or no therapeutic value, but which are useful in the manufacture and compounding of various pharmaceutical preparations. Hence, they are referred to as pharmaceutical necessities. The substances described include antioxidants and preservatives; coloring, flavoring and diluting agents; emulsifying and suspending agents; ointment bases; pharmaceutical solvents and miscellaneous agents. For a more detailed review of the uses of these agents, the interested reader is referred to the various chapters in Part 8 of this book.

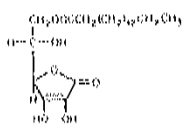
Antioxidants and Preservatives

An antioxidant is a substance capable of inhibiting oxidation and that may be added for this purpose to pharmaceutical products subject to deterioration by oxidative processes as, for example, the development of rancidity in oils and fats or the inactivation of some medicinals in the environment of their dosage forms. A preservative is, in the common pharmaceutical sense, a substance that prevents or inhibits microbial growth and may be added to pharmaceutical preparations for this purpose to avoid consequent spoilage of the preparations by microorganisms. Both antioxidants and preservatives have many applications in making medicinal products.

Alcohol—page 1314.

Ascorbyl Palmitate

L-Ascorbic acid, 6-hexadecanoate; Ascorbic Acid Palmitate (ester)



L-Ascorbic acid 6-palmitate [137-66-6] $C_{22}H_{38}O_7$ (414.54).

Preparation—By condensing palmitoyl chloride with ascorbic acid in the presence of a suitable dehydrochlorinating agent such as pyridine.

Description—White to yellowish white powder having a characteristic odor; melts 107° and 117°.

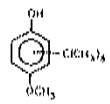
Solubility—1 g in >1000 mL of water, 125 mL of alcohol, >1000 mL of chloroform or >1000 mL of ether.

Uses—An *antioxidant* used in foods and pharmaceuticals. It also is used to prevent rancidity, to prevent the browning of cut apples, in meat curing and in the preservation of canned or frozen foods.

Benzoic Acid—page 1235.
Benzalkonium Chloride—page 1104.
Benzethonium Chloride—page 1170.
Benzyl Alcohol—page 1056.

Butylated Hydroxyanisole

Phenol, (1,1-dimethylethyl)-4-methoxy-, Tenox BHA (*Eastman*)



tert-Butyl-4-methoxyphenol [25013-16-5] $C_{11}H_{16}O_2$ (180.25).

Preparation—By an addition interaction of *p*-methoxyphenol and 2-methylpropene. US Pat 2,428,745.

Description—White or slightly yellow, waxy solid having a faint, characteristic odor.

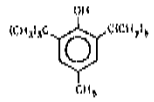
Solubility—Insoluble in water; 1 g in 4 mL of alcohol, 2 mL of chloroform or 1.2 mL of ether.

Uses—An *antioxidant* in cosmetics and pharmaceuticals containing fats and oils.

Butylparaben—page 1170.

Butylated Hydroxytoluene

Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-, Butylated Hydroxytoluene Crystalline (*Diamond-Shamrock*); Tenox BHT (*Eastman*)



2,6-Di-*tert*-butyl-*p*-cresol [128-37-0] $C_{15}H_{24}O$ (220.35).

Preparation—By an addition interaction of *p*-cresol and 2-methylpropene. US Pat 2,428,745.

Description—White, tasteless crystals with a mild odor; stable in light and air; melts at 70°.

Solubility—Insoluble in water; 1 g in 4 mL of alcohol, 1.1 mL of chloroform or 1.1 mL of ether.

Uses—An *antioxidant* employed to retard oxidative degradation of oils and fats in various cosmetics and pharmaceuticals.

Cetylpyridinium Chloride—page 1171.

Chlorobutanol

2-Propanol, 1,1,1-trichloro-2-methyl-, Chlorbutol; Chlorbutanol; Acetone chloroform; Chloretone (*Parke-Davis*)

$(CCl_3)C(CH_3)_2OH$

1,1,1-Trichloro-2-methyl-2-propanol [57-15-8] $C_4H_7Cl_3O$ (177.46); *hemihydrate* [6001-64-5] (186.46).

Preparation—Chloroform undergoes chemical addition to acetone under the catalytic influence of powdered potassium hydroxide.

Description—Colorless to white crystals, of a characteristic, somewhat camphoraceous odor and taste; anhydrous melts about 95°; hydrous melts about 76°; boils with some decomposition 165 and 168°.

Solubility—1 g in 125 mL of water, 1 mL of alcohol or about 10 mL of glycerin; freely soluble in chloroform, ether or volatile oils.

Incompatibilities—The anhydrous form must be used in order to prepare a clear solution in liquid petrolatum. It is decomposed by *alkalies; ephedrine* is sufficiently alkaline to cause its breakdown with the formation of ephedrine hydrochloride which will separate from a liquid petrolatum solution. It is only slightly soluble in water, hence alcohol must be used to dissolve the required amount in certain vehicles. A soft mass is produced by trituration with *antipyrine, menthol, phenol* and other substances.

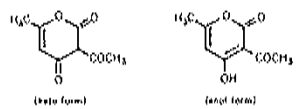
Uses—Topically, as a solution in clove oil as a *dental analgesic*. It has *local anesthetic* potency to a mild degree and has been employed as an anesthetic dusting powder (1 to 5%) or ointment (10%). It has antibacterial and germicidal properties. It is used chiefly as a *preservative* in solutions of epinephrine, posterior pituitary, etc. When administered orally, it has much the same therapeutic use as chloral hydrate. Hence, it has been employed as a sedative and hypnotic. It has been taken orally to allay vomiting due to gastritis.

Dose—*Topical*, as a 25% solution in clove oil.

Other Dose Information—The oral dose is 300 mg to 1 g, given in tablets or capsules.

Dehydroacetic Acid

Keto form: 2*H*-Pyran-2,4(3*H*)-dione, 3-acetyl-6-methyl-,



Enol form: 3-Acetyl-4-hydroxy-6-methyl-2H-pyran-2-one [520-45-6 (Keto)], [771-03-9 (enol)] $C_8H_8O_4$ (168.15).

Preparation—By fractional distillation of a mixture of ethyl acetoacetate and sodium bicarbonate, maintaining almost total reflux conditions, allowing only ethanol to be removed. The residue is distilled under vacuum. *Org Syn Coll Vol III:* 231, 1955.

Description—White to creamy-white crystalline powder melting about 110° with sublimation.

Solubility—One g dissolves in 25 g of acetone, 18 g of benzene, 5 g of methanol or 3 g of ethanol.

Uses—Preservative.

Ethylenediamine

1,2-Ethanediamine

$H_2NCH_2CH_2NH_2$

Ethylenediamine [107-15-3] $C_2H_8N_2$ (60.10).

Caution—Use care in handling because of its caustic nature and the irritating properties of its vapor.

Note—It is strongly alkaline and may readily absorb carbon dioxide from the air to form a nonvolatile carbonate. Protect it against undue exposure to the atmosphere.

Preparation—By reacting ethylene dichloride with ammonia, then adding NaOH and distilling.

Description—Clear, colorless or only slightly yellow liquid, having an ammonia-like odor and strong alkaline reaction; miscible with water and alcohol; anhydrous boils 116 to 117° and solidifies at about 8°; volatile with steam; a strong base and readily combines with acids to form salts with the evolution of much heat.

Uses—A *pharmaceutical necessity for Aminophylline Injection*. It is irritating to skin and mucous membranes. It also may cause sensitization characterized by asthma and allergic dermatitis.

Ethylparaben—page 1171.
Ethyl Vanillin—page 1204.
Glycerin—page 1027.
Hypophosphorus Acid—page 1322.
Methylparaben—page 1172.

Monothioglycerol

1,2-Propanediol, 3-mercapto-,

$HSCH_2CH(OH)CH_2OH$

3-Mercapto-1,2-propanediol [96-27-5] $C_3H_8O_2S$ (108.15).

Preparation—An ethanolic solution of 3-chloro-1,2-propanediol is heated with potassium bisulfide.

Description—Colorless or pale yellow, viscous liquid having a slight sulfidic odor; hygroscopic; specific gravity 1.241 to 1.250; pH (1 in 10 solution) 3.5 to 7.

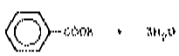
Solubility—Freely soluble in water; miscible with alcohol; insoluble in ether.

Uses—A pharmaceutic aid stated to be used as a preservative. It has been used in 1:5000 solution to stimulate healing of wounds, and as a 1:1000 jelly in atrophic rhinitis.

Phenol—page 1323.
Phenylethyl Alcohol—page 1297.
Phenylmercuric Nitrate—page 1172.

Potassium Benzoate

Benzoic acid, potassium salt



[582-25-2] $C_7H_5KO_2$ (160.21) (anhydrous).

Description—Crystalline powder.

Solubility—Soluble in water or alcohol.

Uses—Preservative.

Potassium Metabisulfite

Dipotassium pyrosulfite

[16731-55-8] $K_2S_2O_5$ (222.31).

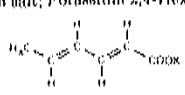
Description—White crystals or crystalline powder with an odor of SO_2. Oxidizes in air to the sulfate. May ignite on powdering in a mortar if too much heat develops.

Solubility—Freely soluble in water; insoluble in alcohol.

Uses—Antioxidant.

Potassium Sorbate

2,4-Hexadienoic acid, (*E,E*)-, potassium salt; 2,4-Hexadienoic acid, potassium salt; Potassium 2,4-Hexadienoate



Potassium (*E,E*)-sorbate; potassium sorbate [590-00-1] [24634-61-5] $C_6H_7KO_2$ (150.22).

Preparation—Sorbic Acid is reacted with an equimolar portion of KOH. The resulting potassium sorbate may be crystallized from aqueous ethanol. US Pat 3,173,948.

Description—White crystals or powder with a characteristic odor; melts about 270° with decomposition.

Solubility—1 g in 4.5 mL of water, 35 mL of alcohol, >1000 mL of chloroform or >1000 mL of ether.

Uses—A water-soluble salt of sorbic acid used in pharmaceuticals to *inhibit the growth of molds and yeasts*. Its toxicity is low, but it may irritate the skin.

Propylparaben—page 1173.
Sassafras Oil—page 1300.
Sodium Benzoate—page 1173.

Sodium Disulfite

Sulfurous acid, monosodium salt; Sodium Hydrogen Sulfite; Sodium Acid Sulfite; Leucogen

Monosodium sulfite [7631-90-5] $NaHSO_3$ and sodium metabisulfite ($Na_2S_2O_5$) in varying proportions; yields 58.5–67.4% of SO_2.

Description—White or yellowish white crystals or granular powder having the odor of sulfur dioxide; unstable in air.
Solubility—1 g in 4 mL of water; slightly soluble in alcohol.

Uses—An *antioxidant* and *stabilizing agent*. Epinephrine hydrochloride solutions may be stabilized by the addition of small quantities of the salt. It also is used to help solubilize kidney stones. It is useful for removing permanganate stains and for solubilizing certain dyes and other chemicals (see *Menadione Sodium Bisulfite*, RPS-17, page 1011).

Sodium Metabisulfite

Disulfurous acid, disodium salt

Disodium pyrosulfite [7681-57-4] $Na_2S_2O_5$ (190.10).
Preparation—Formed when sodium bisulfite undergoes thermal dehydration. It also may be prepared by passing sulfur dioxide over sodium carbonate.

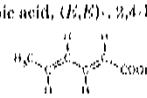
Description—White crystals or white to yellowish crystalline powder having an odor of sulfur dioxide; on exposure to air and moisture, it is slowly oxidized to sulfate.
Solubility—1 g in 2 mL of water; slightly soluble in alcohol; freely soluble in glycerin.

Uses—A *reducing agent*. It is used in easily oxidized pharmaceuticals, such as epinephrine hydrochloride and phenylephrine hydrochloride injections, to retard oxidation.

Sodium Propionate—page 1236.

Sorbic Acid

2,4-Hexadienoic acid, (*E*,*E*)-, 2,4-Hexadienoic acid



(*E*,*E*)-Sorbic acid; Sorbic acid [22500-92-4] [110-44-1] $C_6H_8O_2$ (112.13).
Preparation—By various processes. Refer to US Pat 2,921,090.

Description Free-flowing, white, crystalline powder, having a characteristic odor; melts about 133°.
Solubility 1 g in 1000 mL of water, 10 mL of alcohol, 16 mL of chloroform, 30 mL of ether or 19 mL of propylene glycol.

Uses—A *mold and yeast inhibitor*. It also is used as a fungistatic agent for foods, especially cheeses.

Sulfur Dioxide

Sulfur dioxide [7446-09-5] SO_2 (64.06).
Preparation—By burning sulfur or sulfides and by reacting a bisulfite or a sulfite with a strong acid.

Description—Colorless, nonflammable gas, with a strong, suffocating, odor characteristic of burning sulfur; 1 L weighs 2.927 g at 760 mm and 0°; readily liquefies under pressure forming a colorless liquid with a density of approximately 1.5 g/mL and a boiling point of −10°.
Solubility—1 volume of water dissolves approximately 36 volumes of it at 760 mm and 20°; 1 volume of alcohol dissolves approximately 114 volumes under the same conditions; soluble in ether or chloroform.
Note—It is used mostly in the form of a gas in pharmaceutical applications, and is described herein for such purposes. However, it is usually packaged under pressure, hence the USP specifications (Water, Nonvolatile residue and *Sulfuric acid), are designed for the testing of its liquid form.*

Uses—The gas in the presence of moisture forms sulfurous acid which is a *bleaching agent*, *fungicide* and *bactericide*. For this reason fruits often are exposed to the gas before drying to prevent darkening and the growth of molds and bacteria. The gas is also an *antioxidant* and a pharmaceutical necessity for *Injections*. It may be intensely irritating to the eyes and respiratory tract.

Thimerosal—page 1173.

Other Antioxidants and Preservatives

Anoxomer [1,4-Benzenediol, 2-(1,1-dimethylethyl)-, polymer with diethenyl benzene, 4-(1,1-dimethylethyl)phenol, 4-methoxyphenol, 4,4′-(1-methylethylidene)bis[phenol] and 4-methylphenol {80837-57-2} $(C_{10}H_{14}O_2)_n(C_{10}H_{10})_x(C_{10}H_{14}O)_m(C_7H_8O_2)_s(C_{16}H_{16}O_2)_t(C_7H_8O)_r$. *Uses:* Antioxidant and food additive.
Maleic Acid BP [*cis*-Butenedioic acid $C_4H_4O_4$ (116.07); Toxilic acid] —*Preparation:* Benzene vapor is oxidized by passage over heated vanadium pentoxide. Odorless, white, crystalline powder having a strongly acid taste; melts about 136°. Soluble in 1.5 parts of water, 2 parts of alcohol or 12 parts of ether. *Uses:* In the preparation of ergometrine maleate injection or as a rancidity retardant in fats and oils (1:10,000).
Propyl Gallate BP [Propyl 3,4,5-Trihydroxybenzoate]—White to creamy-white crystalline powder; odorless; slightly bitter taste. Soluble in 1000 parts of water or 3 parts of alcohol. *Uses:* A preservative.

Coloring, Flavoring and Diluting Agents

The use of properly colored and flavored medicinal substances, although offering no particular therapeutic advantage, is of considerable importance psychologically. A water-clear medicine is not particularly acceptable to most patients, and, in general, is thought to be inert. Many very active medicinal substances are quite unpalatable, and the patient may fail to take the medicine simply because the taste or appearance is objectionable. Disagreeable medication can be made both pleasing to the taste and attractive by careful selection of the appropriate coloring, flavoring and diluting agents. Therefore, judicious use of these substances is important in securing patient cooperation in taking or using the prescribed medication and continued compliance with the prescriber's intent.

Coloring Agents or Colorants

Coloring agents may be defined as compounds employed in pharmacy solely for the purpose of imparting color. They may be classified in various ways, eg, inorganic or organic. For the purpose of this discussion two subdivisions are used: *Natural Coloring Principles* and *Synthetic Coloring Principles*. The members of these groups are used as colors for pharmaceutical preparations, cosmetics, foods and as bacteriological stains and diagnostic agents.

Natural Coloring Principles

Natural coloring principles are obtained from mineral, plant and animal sources. They are used primarily for artistic purposes, as symbolic adornments of natives, as colors for foods, drugs and cosmetics and for other psychological effects.

Mineral colors frequently are termed *pigments* and are

used to color lotions, cosmetics and other preparations, usually for external application. Examples are *Red Ferric Oxide* (page 1328) and *Yellow Ferric Oxide* (page 1328), titanium dioxide (page 772) and carbon black.

The term pigment also is applied generically to plant colors by phytochemists. Many plants contain coloring principles that may be extracted and used as colorants, eg, chlorophyll. Anattenes are obtained from annatto seeds and give yellow to orange water-soluble dyes. Natural beta-carotene is a yellow color extracted from carrots and used to color margarine. Alizarin is a reddish-yellow dye obtained from the madder plant. The indigo plant is the source of a blue pigment called indigo. Flavones, such as riboflavin, rutin, hesperidin and quercetin, are yellow pigments. Saffron is a glycoside that gives a yellow color to drugs and foods. Cudbear and red saunders are two other dyes obtained from plants. Most plant colors now have been characterized and synthesized, however, and those with the desirable qualities of stability, fastness and pleasing hue are available commercially as synthetic products.

Animals have been a source of coloring principles from the earliest periods of recorded history. For example, *Tyrian purple*, once a sign of royalty, was prepared by air oxidation of a colorless secretion obtained from the glands of a snail (*Murex brandaris*). This dye now is known to be 6,6'-dibromoindigo, and has been synthesized, but cheaper dyes of the same color are available. Cochineal from the insect *Coccus cacti* contains the bright-red coloring principle *carminic acid*, a derivative of anthraquinone. This dye is no longer used in foods and pharmaceuticals due to *Salmonella* contamination.

Synthetic Coloring Principles

Synthetic coloring principles date from 1856 when W H Perkin accidentally discovered *mauveine*, also known as a *Perkin's purple*, while engaged in unsuccessful attempts to synthesize quinine. He obtained the dye by oxidizing aniline containing *o*- and *p*-toluidines as impurities. Other discoveries of this kind followed soon after, and a major industry grew up in the field of coal-tar chemistry.

The earliest colors were prepared from aniline and for many years all coal-tar dyes were called aniline colors, irrespective of their origin. The coal-tar dyes include more than a dozen well-defined groups among which are *nitroso-dyes, nitro-dyes, azo-dyes, oxazines, thiazines, pyrazolones, xanthenes, indigoids, anthraquinones, acridines, rosanilines, phthaleins, quinolines* and others. These in turn are classified, according to their method of use, as *acid dyes* and *basic dyes*, or *direct dyes* and *mordant dyes*.

Certain structural elements in organic molecules, called chromophore groups, give color to the molecules, eg, azo (—N=N—), nitroso (—N=O), nitro (—NO_2), azoxy (—N=N—O—), carbonyl (>C=O) and ethylene (>C=C<). Other such elements augment the chromophore groups, eg, methoxy, hydroxy and amino groups.

Stability—Most dyes are relatively unstable chemicals due to their unsaturated structures. They are subject to fading due to light, metals, heat, microorganisms, oxidizing and reducing agents plus strong acids and bases. In tablets, fading may appear as spotting and specking.

Uses—Most synthetic coloring principles are used in coloring fabrics and for various artistic purposes. They also find application as indicators, bacteriological stains, diagnostic aids, reagents in microscopy, etc.

Many coal-tar dyes originally were used in foodstuffs and beverages without careful selection or discrimination between those that were harmless and those that were toxic and without any supervision as to purity or freedom from poisonous constituents derived from their manufacture.

After the passage of the Food and Drugs Act in 1906, the US Department of Agriculture established regulations by which a few colors came to be known as *permitted colors*. Certain of these colors may be used in foods, drugs and cosmetics, but only after certification by the FDA that they meet certain specifications. From this list of permitted colors may be produced, by skillful blending and mixing, other colors that may be used in foods, beverages and pharmaceutical preparations. Blends of certified dyes must be recertified.

The word "permitted" is used in a restricted sense. It does not carry with it the right to use colors for purposes of deception, even though they are "permitted" colors, for all food laws have clauses prohibiting the coloring of foods and beverages in a manner so as to conceal inferiority or to give a false appearance of value.

The certified colors are classified into three groups: FD&C dyes which legally may be used in foods, drugs and cosmetics, D&C dyes which legally may be used in drugs and cosmetics and External D&C dyes which legally may be used only in externally applied drugs and cosmetics. There are specific limits for the pure dye, sulfated ash, other extractives, soluble and insoluble matter, uncombined intermediates, oxides, chlorides and sulfates. As the use status of these colors is subject to change, the latest regulations of the FDA should be consulted to determine how they may be used—especially since several FD&C dyes formerly widely used have been found to be carcinogenic even when "pure" and, therefore, have been banned from use.

The Coal-Tar Color Regulations specify that the term "externally applied drugs and cosmetics" means drugs and cosmetics which are applied only to external parts of the body and not to the lips or any body surface covered by mucous membrane. No certified dye, regardless of its category, legally may be used in any article which is to be applied to the area of the eye.

Lakes are calcium or aluminum salts of certified dyes extended on a substrate of alumina. They are insoluble in water and organic solvents, hence are used to color powders, pharmaceuticals, foods, hard candies and food packaging.

The application of dyes to pharmaceutical preparations is an art that can be acquired only after an understanding of the characteristics of dyes and knowledge of the composition of the products to be colored has been obtained. Specific rules for the choice or application of dyes to pharmaceutical preparations are difficult to formulate. Each preparation may present unique problems.

Preparations which may be colored include most liquid pharmaceuticals, powders, ointments and emulsions. Some general hints may be offered in connection with solutions and powders, but desired results usually can be obtained only by a series of trials. In general, an inexperienced operator tends to use a much higher concentration of the dye than is necessary, resulting in a dull color. The amount of dye present in any pharmaceutical preparation should be of a concentration high enough to give the desired color and low enough to prevent toxic reactions and permanent staining of fabrics and tissues.

Liquids (Solutions)—The dye concentration in liquid preparations and solutions usually should come within a range of 0.0005% (1 in 200,000) and 0.001% (1 in 100,000), depending upon the depth of color wanted and the thickness of column to be viewed in the container. With some dyes, concentrations as low as 0.0001% (1 in 1,000,000) may have a distinct tinting effect. Dyes are used most conveniently in the form of stock solutions.

Powders—White powders usually require the incorporation of 0.1% (1 in 1000) of a dye to impart a pastel color. The dyes may be incorporated into the powder by dry-blending in a ball mill or, on a small scale, with a mortar and pestle.

The dye is incorporated by trituration and geometric dilution. Powders also may be colored evenly by adding a solution of the dye in alcohol or some other volatile solvent having only a slight solvent action on the powder being colored. When this procedure is employed, the solution is added in portions, with thorough mixing after each addition, after which the solvent is allowed to evaporate from the mixture.

Many of the syrups and elixirs used as flavoring and diluting agents are colored. When such agents are used no further coloring matter is necessary. The use of colored flavoring agents is discussed in a subsequent section. However, when it is desired to add color to an otherwise colorless mixture, one of the agents described in the first section may be used.

Incompatibilities—FD&C dyes are mainly anionic (sodium salts), hence are incompatible with cationic substances. Since the concentrations of these substances are generally very low, no precipitate is evident. Polyvalent ions such as calcium, magnesium and aluminum also may form insoluble compounds with dyes. A pH change may cause the color to change. Acids may release the insoluble acid form of the dye.

Caramel

Burnt Sugar Coloring

A concentrated solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed and a uniform dark brown mass results, a small amount of alkali, alkaline carbonate or a trace of mineral acid being added while heating.

Description—Thick, dark brown liquid with the characteristic odor of burnt sugar, and a pleasant, bitter taste; specific gravity not less than 1.30; 1 part dissolved in 1000 parts of water yields a clear solution having a distinct yellowish orange color which is not changed and no precipitate is formed after exposure to sunlight for 6 hr; when spread in a thin layer on a glass plate, it appears homogeneous, reddish brown and transparent.

Solubility—Miscible with water in all proportions and with dilute alcohol up to 55% by volume; immiscible with ether, chloroform, acetone, benzene, solvent hexane or turpentine oil.

Uses—To produce a brown color in elixirs, syrups and other preparations.

Flavoring Agents

Flavor

The word flavor refers to a mixed sensation of taste, touch, smell, sight and sound, all of which combine to produce an infinite number of gradations in the perception of a substance. The four primary tastes—*sweet*, *bitter*, *sour* and *saline*—appear to be the result partly of physicochemical and partly of psychological action. Taste buds (Fig 66-1), located mainly on the tongue, contain very sensitive nerve endings that react, in the presence of moisture, with the flavors in the mouth and as a result of physicochemical activity electrical impulses are produced and transmitted via the seventh, ninth and tenth cranial nerves to the areas of the brain which are devoted to the perception of taste. Some of the taste buds are specialized in their function, giving rise to areas on the tongue which are sensitive to only one type of taste. The brain, however, usually perceives taste as a composite sensation, and accordingly the components of any flavor are not readily discernible. Children have more taste buds than adults, hence are more sensitive to tastes.

Taste partly depends on the ions which are produced in the mouth, but psychologists have demonstrated that sight (color) and sound also play a definite role when certain reflexes become conditioned through custom and association of sense perceptions. Thus, in the classic experiments of Pavlov demonstrating "conditioned reflexes," the ringing of a bell or the showing of a circle of light caused the gastric juices of a dog to flow although no food was placed before it, and much of the enjoyment derived from eating celery is due to its crunchy crispness as the fibrovascular bundles are crushed. The effect of color is just as pronounced; oleomargarine is unpalatable to most people when it is uncolored, but once the dye has been incorporated gourmets frequently cannot distinguish it from butter. Color and taste must coincide, eg, cherry flavor is associated with a red color.

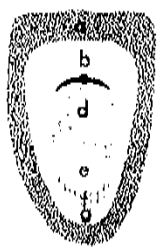


Fig 66-1. Upper Surface of the tongue. a: Taste receptors for all tastes; b: sweet, salty and sour; c: salty and sour; d: sour only; e: no taste sensation; f: sweet and sour and g: bitter, sweet and sour (adapted from Crocker EC: *Flavor*, McGraw-Hill, New York, 22, 1945).

A person suffering from a head cold finds his food much less palatable than usual because his sense of smell is impaired, and, if the nostrils are held closed, raw onions taste sweet and it is much easier to ingest castor oil and other nauseating medicines. The volatility of a substance is an important factor that is influenced by the warmth and moisture of the mouth since the more volatile a compound, the more pronounced its odor. The sense of smell detects very minute amounts of material and is usually much more sensitive in detecting the presence of volatile chemicals, but the tongue is able to detect infinitesimal amounts of some vapors if it is protruded from the mouth so that solution of the gases in the saliva may take place. In this manner traces of sulfur dioxide can be detected in the air since it dissolves in the saliva and creates a sour taste.

Flavors described as hot are those that exert a mild counterirritant effect on the mucosa of the mouth, those that are astringent and pucker the mouth contain tannins and acids that produce this effect by reacting with the lining of the mouth and wines possess a bouquet due to the odor of the volatile constituents. Indian turnip (Jack-in-the-pulpit) owes its flavor largely to the stinging sensation caused by the minute acicular crystals of calcium oxalate which penetrate the mucous membrane.

Other physiological and physical factors that also may affect taste are coarseness or grittiness due to small particles, eg, ion-exchange resins. Antidiarrheal preparations have a chalky taste. Menthol imparts a cool taste because it affects the coldness receptors. Mannitol gives a cool sensation when it dissolves because its negative of heat of solution will cause the temperature to drop. For this reason, mannitol often is used as the base for chewable tablets.

There is a definite threshold of taste for every substance, which varies somewhat with the individual and with the environment. The experienced chef tastes his delicacies at the temperature at which they will be served since heat and cold alter the flavor of many preparations. Thus, lemon

loses its sour taste entirely at an elevated temperature and other flavors become almost nonvolatile, tasteless and odorless when cooled sufficiently. In addition to the influence of temperature, the sensitivity of each individual must be considered. For example, it has been determined by experiment that the amount of sugar that can just be detected by the average individual is about 7 mg. However, this amount cannot be tasted by some and it is definitely sweet to others.

People are more sensitive to odor than to taste. There are about 10,000 to 30,000 identifiable scents, of which the average person can identify about 4000. Women are more sensitive to odors than men. Additional insights can be obtained by reading Cagan RH, Kare MR: *Biochemistry of Taste and Olfaction*, Academic, 1981, and Beidler LM (ed): *Handbook of Sensory Physiology*, vol IV, pts 1 and 2, Springer-Verlag, 1971.

Preservation of Flavors—Most monographs of official products contain specific directions for storage. Proper methods of storage are essential to prevent deterioration which in many instances results in destruction of odor and taste. Under adverse conditions undesirable changes occur due to one or a combination of the following: enzymatic activity, oxidation, change in moisture content, absorption of odors, activity of microorganisms and effects of heat and light. In certain products some of the changes wrought by these factors are desirable, as when esters are formed due to the activity of enzymes and when blending and mellowing results from the interchange of the radicals of esters (*transesterification*).

One method for protecting readily oxidizable substances, such as lemon oil, from deteriorating, and thus preserving their original delicate flavor, is to microencapsulate them by spray-drying. The capsules containing the flavors then are enclosed in various packaged products (eg, powdered gelatins) or tablets which are flavored deliciously when the capsule is disintegrated by mixing and warming with water or saliva.

Correlation of Chemical Structure with Flavor and Odor—The compounds employed as flavors in vehicles vary considerably in their chemical structure, ranging from simple esters (methyl salicylate), alcohols (glycerin) and aldehydes (vanillin) to carbohydrates (honey) and the complex volatile oils (anise oil). Synthetic flavors of almost any desired type are now available. These frequently possess the delicate flavor and aroma of the natural products and also the desirable characteristics of stability, reproducibility and comparatively low cost. Synthetic products such as cinnamaldehyde and benzaldehyde, first officially recognized when several of the essential oils became scarce during World War II, have been used widely.

There is a close relationship between chemical structure and taste. Solubility, the degree of ionization and the type of ions produced in the saliva definitely influence the sensation interpreted by the brain.

Sour taste is caused by hydrogen ions and it is proportional to the hydrogen-ion concentration and the lipid solubility of the compound. It is characteristic of acids, tannins, alum, phenols and lactones. Saltiness is due to simultaneous presence of anions and cations, eg, KBr, NH_4Cl and sodium salicylate. High-molecular-weight salts may have a bitter taste. Sweet taste is due to polyhydroxy compounds, polyhalogenated aliphatic compounds and α-amino acids. Amino and amide groups, especially if the positive effect is balanced by the proximity of a negative group, may produce a sweet taste. Sweetness increases with the number of hydroxy groups, possibly due to increase in solubility. Imides such as saccharin and sulfamates such as cyclamates are intensely sweet. Cyclamates have been removed from the market because they reportedly cause bladder tumors in rats. Free bases such as alkaloids and amides such as amphetamines give bitter tastes. Polyhydroxy compounds with a molecular weight greater than 300, halogenated substances and aliphatic thio compounds also may have bitter tastes. Unsaturation frequently bestowe a sharp, biting odor and taste upon compounds.

No precise relationship between chemical structure and odor has been found. There are no primary odors, and odors blend into each other. Polymerization reduces or destroys odor; high valency gives odor and unsaturation enhances odor. A tertiary carbon atom often will give a camphoraceous odor, esters and lactones have a fruity odor and ketones have a pleasant odor. Strong odors often are accompanied by volatility and chemical reactivity.

Selection of Flavors

The proper selection of flavors for disguising nauseating medicines aids in their ingestion. Occasionally, sensitive patients have become nauseated sufficiently to vomit at the thought of having to take disagreeable medication, and it is particularly difficult to persuade children to continue to use and retain distasteful preparations. There is a need to know the allergies and idiosyncrasies of the patient; thus, it is foolish to use a chocolate-flavored vehicle for the patient who dislikes the flavor or who is allergic to it, notwithstanding the fact that this flavor is generally acceptable.

Flavoring Methodology

Each flavoring problem is unique and requires an individual solution. The problem of flavoring is further complicated because flavor and taste depend on individual preferences. In solving flavoring problems the following techniques have been used:

1. *Blending*—Fruit flavors blend with sour taste; bitter tastes can be blended with salty, sweet and sour tastes; salt reduces sourness and increases sweetness; chemicals such as vanillin, monosodium glutamate and benzaldehyde are used for blending.
2. *Overshadow*—Addition of a flavor whose intensity is longer and stronger than the obvious taste, eg, methyl salicylate, glycyrrhiza and oleoresins.
3. *Physical*—Formation of insoluble compounds of the offending drug, eg, sulfonamides; emulsification of oils; effervescence, eg, magnesium citrate solution; high viscosity of fluids to limit contact of drug with the tongue, and mechanical procedures such as coating tablets, are physical methods to reduce flavoring problems.
4. *Chemical*—Adsorption of the drug on a substrate, or formation of a complex of the drug with ion-exchange resins or complexing agents.
5. *Physiological*—The taste buds may be anesthetized by menthol or mint flavors.

Flavors, as used by the pharmacist in compounding prescriptions, may be divided into four main categories according to the type of taste which is to be masked, as follows:

1. *Salty Taste*—Cinnamon syrup has been found to be the best vehicle for ammonium chloride, and other salty drugs such as sodium salicylate and ferric ammonium citrate. In a study of the comparative efficiency of flavoring agents for disguising salty taste, the following additional vehicles were arranged in descending order of usefulness: orange syrup, citric acid syrup, cherry syrup, cocoa syrup, wild cherry syrup, raspberry syrup, glycyrrhiza elixir, aromatic elixir and glycyrrhiza syrup. The last-named is particularly useful as a vehicle for the salines by virtue of its colloidal properties and the sweetness of both glycyrrhizin and sucrose.
2. *Bitter Taste*—Cocoa syrup was found to be the best vehicle for disguising the bitter taste of quinine bisulfate, followed, in descending order of usefulness, by raspberry syrup, cocoa syrup, cherry syrup, cinnamon syrup, compound sarsaparilla syrup, citric acid syrup, licorice syrup, aromatic elixir, orange syrup and wild cherry syrup.
3. *Acrid or Sour Taste*—Raspberry syrup and other fruit syrups are especially efficient in masking the taste of sour substances such as hydrochloric acid. Acacia syrup and other mucilaginous vehicles are best for disguising the acrid taste of substances, such as capsicum, since they tend to form a colloidal protective coating over the taste buds of the tongue. Tragacanth, unlike acacia, may be used in an alcoholic vehicle.

4. *Oily Taste*—Castor oil may be made palatable by emulsifying with an equal volume of aromatic rhubarb syrup or with compound sarsaparilla syrup. Cod liver oil is disguised effectively by adding wintergreen oil or peppermint oil. Lemon, orange and anise or combinations of these are also useful. It is better to mix most of the flavor with the oil before emulsifying it, and then the small remaining quantity can be added after the primary emulsion is formed.

Those flavors that are most pleasing to the majority of people are associated with some stimulant of a physical or physiological nature. This may be a central nervous stimulant such as caffeine, which is the reason so many enjoy tea and coffee as a beverage, or it may be a counterirritant such as one of the spices that produce a "biting" sensation or an agent which "tickles" the throat such as soda water. Sherry owes its sharp flavor to its acetaldehyde content, and some of the volatile oils contain terpenes that are stimulating to the mucous surfaces.

Selection of Vehicles

Too few pharmacists realize the unique opportunity they have in acquainting physicians with a knowledge of how to increase both the palatability and efficacy of their prescribed medicines through the judicious selection of vehicles. Because of the training a pharmacist receives, his knowledge of the characteristics of various pharmaceuticals and therapeutic agents and his technique and skill in preparing elegant preparations are well-developed, so that he is qualified admirably to advise concerning the proper use of vehicles.

A large selection of flavors is available as well as a choice of colors, so that one may prescribe a basic drug for a prolonged period, but by changing the vehicle from time to time, the taste and appearance are so altered that the patient does not tire of the prescription or show other psychological reactions to it.

The statement of the late Dr Bernard Fantus that "the best solvent is the best vehicle" helps to explain the proper use of a flavoring vehicle. For example, a substance that is soluble in alcohol, eg, phenobarbital, will not leave an alcoholic vehicle readily to dissolve in the aqueous saliva.

Waters—These are the simplest of the vehicles and are available with several flavors. They contain no sucrose, a fact to be considered at times, since sucrose under certain circumstances may be undesirable. They are likewise nonalcoholic, another fact which frequently influences vehicle selection.

Elixirs—These have added sweetness that waters lack, and they usually contain alcohol, which imparts an added sharpness to the flavor of certain preparations, making the latter more pleasing to the taste. Elixirs are suitable for alcohol-soluble drugs.

Syrups—These vehicles, like elixirs, offer a wide selection of flavors and colors from which to choose. Their specific value, however, lies particularly in the fact that they are intensely sweet and contain little or no alcohol, a combination which makes them of singular value as masking agents for water-soluble drugs.

Vehicles consisting of a solution of pleasantly flavored volatile oils in syrup or glycerin (1:500) have been employed successfully in producing uniform and stable preparations. These vehicles are prepared by adding 2 mL of the volatile oil, diluted with 6 mL of alcohol, to 500 mL of glycerin or syrup, which has been warmed gently. The solution is added a little at a time with continuous shaking, and then sufficient glycerin or syrup is added to make 1000 mL, and mixed well.

Alcohol solutions of volatile oils are sometimes used as "stock solutions" for flavoring pharmaceuticals.

A listing of substances, most of them official, used as flavors, flavored vehicles or as sweeteners, is given in Table I. Additional information on flavoring ingredients may be obtained in Furia TE, Bellanca A: *Fenaroli's Handbook of Flavor Ingredients*, Chemical Rubber, Cleveland, 1971.

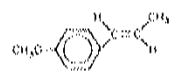
Table I—Flavoring Agents

Acacia syrup	Honey
Anethole	Iso-Alcoholic elixir
Anise oil	Lavender oil
Aromatic elixir	Lemon oil
Benzaldehyde	Lemon tincture
Benzaldehyde elixir, compound	Mannitol
Caraway	Methyl salicylate
Caraway oil	Nutmeg oil
Cardamom oil	Orange, bitter, elixir
Cardamom seed	Orange, bitter, oil
Cardamom spirit, compound	Orange flower oil
Cardamom tincture, compound	Orange flower water
Cherry juice	Orange oil
Cherry syrup	Orange peel, bitter
Cinnamon	Orange peel, sweet, tincture
Cinnamon oil	Orange spirit, compound
Cinnamon water	Orange syrup
Citric acid	Peppermint
Citric acid syrup	Peppermint oil
Clove oil	Peppermint spirit
Cocoa	Peppermint water
Cocoa syrup	Phenylethyl alcohol
Coriander oil	Raspberry juice
Dextrose	Raspberry syrup
Eriodictyon	Rosemary oil
Eriodictyon fluidextract	Rose oil
Eriodictyon syrup, aromatic	Rose water
Ethyl acetate	Rose water, stronger
Ethyl vanillin	Saccharin
Fennel oil	Saccharin calcium
Ginger	Saccharin sodium
Ginger fluidextract	Sarsaparilla syrup, compound
Ginger oleoresin	Sorbitol solution
Glucose	Spearmint
Glycerin	Spearmint oil
Glycyrrhiza	Sucrose
Glycyrrhiza elixir	Syrup
Glycyrrhiza extract	Thyme oil
Glycyrrhiza extract, pure	Tolu balsam
Glycyrrhiza fluidextract	Tolu balsam syrup
Glycyrrhiza syrup	Vanilla
	Vanilla tincture
	Vanillin
	Wild cherry syrup

Acacia Syrup—see page 1301.

Anethole

Benzene, 1-methoxy-4-(1-propenyl)-, (*E*)-, Anethol; Anise Camphor



(*E*)-*p*-Proponylanisole [4180-23-8] $C_{10}H_{12}O$ (148.20); obtained from anise oil and other sources, or prepared synthetically.

Preparation—It is the principal constituent of anise and fennel oil and usually is obtained from these sources by fractionating and chilling the proper fraction whereby it crystallizes out.

Description—Colorless or faintly yellow liquid at or above 23°; aromatic odor of anise and a sweet taste; affected by light; specific gravity 0.983 to 0.988; distills completely 231 to 237° and congeals at not less than 20°; its alcohol solution is neutral to litmus.

Solubility—Very slightly soluble in water; freely soluble in alcohol; miscible with chloroform or ether; yields a clear solution with 2 volumes of alcohol.

Uses—A *flavoring agent*. Its uses are similar to those of anise oil. It sometimes is sold as *Synthetic* or *Artificial Anise Oil* for flavoring and is a licorice-like flavor used in *Diphenhydramine Hydrochloride Elixir*.

Anise Oil

Aniseed Oil; Star Anise Oil

The volatile oil distilled with steam from the dried, ripe fruit of *Pimpinella anisum* Linné (Fam *Umbelliferae*) or from the dried, ripe fruit of *Illicium verum* Hooker filius (Fam *Magnoliaceae*).

Note—If solid material has separated, carefully warm the oil until it is completely liquefied, and mix it before using.

Constituents—The official oil varies somewhat in composition, depending upon whether it was obtained from *Pimpinella anisum* or the star anise, *Illicium verum*. *Anethole* is the chief constituent of both oils, occurring to the extent of 80 to 90%. *Methyl chavicol*, an isomer of anethole, and *anisic ketone* [$C_{10}H_{12}O_2$] are also found in both oils, as are small amounts of many other constituents.

Description—Colorless or pale yellow, strongly refractive liquid, having the characteristic odor and taste of anise; specific gravity 0.978 to 0.988; congeals not below 15°.

Solubility—Soluble in 3 volumes of 90% alcohol.

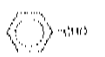
Uses—Extensively as a *flavoring agent*, particularly for licorice candies. It has been given as a *carminative* in a dose of about 0.1 mL.

Aromatic Elixir—page 1302.

Aromatic Elixir, Red—RPS-15, page 1240.

Benzaldehyde

Artificial Essential Almond Oil



Benzaldehyde [100-52-7] C_7H_6O (106.12).

Preparation—By the interaction of benzal chloride with lime in the presence of water. Benzal chloride is obtained by treating boiling toluene with chlorine.

Description—Colorless, strongly refractive liquid, having an odor resembling that of bitter almond oil, and a burning aromatic taste; affected by light; specific gravity 1.041 to 1.046; boils about 180°, solidifies about −56.5° and on exposure to air it gradually oxidizes to benzoic acid.

Solubility—Dissolves in about 350 volumes of water; miscible with alcohol, ether, chloroform or fixed and volatile oils.

Uses—In place of bitter almond oil for *flavoring* purposes; it is much safer than the latter because it contains no hydrocyanic acid. It also is used extensively in *perfumery* and in the manufacture of dyestuffs and many other organic compounds, such as aniline, acetanilid or mandelic acid.

Compound Benzaldehyde Elixir—*Preparation:* Dissolve benzaldehyde (0.5 mL) and vanillin (1 g) in alcohol (50 mL); add syrup (600 mL), orange flower water (150 mL) and sufficient purified water, in several portions, shaking the mixture thoroughly after each addition, to make the product measure 1000 mL; then filter, if necessary, until the product is clear. *Alcohol Content:* 3 to 5%. *Uses:* A useful vehicle for administering bromides and other salts, especially when a low alcoholic content is desired.

Camphor Water—RPS-13, page 436.

Caraway

Carum; Caraway Seed; Caraway Fruit; Kümmel

The dried ripe fruit of *Carum carvi* Linné (Fam *Umbelliferae*).

Constituents—About 5% of *volatile oil*, with a little *fixed oil* and other constituents.

Uses—A *flavor*. It also has been used empirically as a *carminative* and *stimulant*.

Caraway Oil [Oleum Carvi]—A volatile oil distilled from the dried, ripe fruit of *Carum carvi* Linné (Fam *Umbelliferae*); yields not less than 50% (*v/v*) of $C_{10}H_{14}O$ (carvone). The chief odoriferous component of the oil is the ketone *d-carvone* [$C_{10}H_{14}O$], which is the optical isomer of the levorotatory variety occurring in spearmint oil. The remainder of the oil consists mainly of the terpene *d-limonene* [$C_{10}H_{16}$]. Colorless or pale yellow liquid, with the characteristic odor and taste of caraway; specific gravity 0.900 to 0.910. *Uses:* In making caraway water and as a flavor and *carminative* in other pharmaceutical preparations.

Cardamom Seed

Cardamom Fruit; Cardamom; Ceylon or Malabar Cardamom

The dried ripe seed of *Elettaria cardamomum* (Linné) Maton (Fam. *Zingiberaceae*).

It should be removed recently from the capsule.

Constituents—A *volatile oil*, the yield of which is 1.3% from Malabar Ceylon Seeds and 2.6% from Mysore-Ceylon Seeds. *Fixed oil* is present to the extent of 10%, also starch, mucilage, etc.

Uses—A *flavor*. For many years it was employed empirically as a *carminative*.

Cardamom Oil—The volatile oil distilled from the seed of *Elettaria cardamomum* (Linné) Maton (Fam *Zingiberaceae*). Varieties of the oil contain *d-α-terpineol* [$C_{10}H_{17}OH$] both free and as the acetate, 5 to 10% *cineol* [$C_{10}H_{18}O$] and *limonene* [$C_{10}H_{16}$]. The Ceylon Oil, however, contains the alcohol *4-terpineol* (*4-carbamenthenol*) [$C_{10}H_{17}OH$], the terpenes *terpinene* and *sabinene*, and *acetic* and *formic acids*, probably combined as esters. Colorless or very pale yellow liquid possessing the aromatic, penetrating and somewhat camphoraceous odor of cardamom, and a persistently pungent, strongly aromatic taste; affected by light. Specific gravity 0.917 to 0.947; miscible with alcohol; dissolves in 5 volumes of 70% alcohol. *Uses:* A *flavor*.

Cardamom Tincture, Compound—page 1302.

Cherry Juice—page 1320.

Cherry Syrup—page 1301.

Cinnamon

Saigon Cinnamon; True Cinnamon; Saigon Cassia

The dried bark of *Cinnamomum loureirii* Nees (Fam. *Lauraceae*).

It contains, in each 100 g, not less than 2.5 mL of volatile oil.

Uses—A *flavoring agent*. Formerly, it was used as a carminative.

Cinnamon Oil [Cassia Oil; Oil of Chinese Cinnamon]—The volatile oil distilled with steam from the leaves and twigs of *Cinnamomum cassia* (Nees) Nees ex Blume (Fam *Lauraceae*), rectified by distillation; contains not less than 80%, by volume, of the total aldehydes of cinnamon oil. Cinnamaldehyde is the chief constituent. Yellowish or brownish liquid, becoming darker and thicker on aging or exposure to the air, and having the characteristic odor and taste of cassia cinnamon; specific gravity 1.045 to 1.063. Soluble in an equal volume of alcohol, 2 volumes of 70% alcohol or an equal volume of glacial acetic acid. *Uses:* A *flavor*. It formerly was used in a dose of 0.1 mL for flatulent colic.

Cocoa

Cacao USP XVI; Prepared Cocoa; Powdered Cocoa; Cocoa Powder; Medium-Fat Cocoa

A powder prepared from the roasted, cured kernels of the ripe seed of *Theobroma cacao* Linné (Fam *Sterculiaceae*).

It yields 10 to 22% of nonvolatile, ether-soluble extractive.

Preparation—The cocoa bean is dark as the result of a fermentation and roasting process which it undergoes. *Plain chocolate* consists of shelled cocoa beans (*cocoa nibs*) ground to a smooth paste which forms a hard cake when it cools because of the high fat content (50 to 58%).

It is the food prepared by pulverizing the residue remaining after part of the fat has been removed by expression from plain chocolate. It may be flavored by the addition of ground spice, ground vanilla bean, vanillin, ethylvanillin, coumarin, salt and other flavors as long as they do not imitate the flavor of chocolate, milk or butter. Three types are recognized depending on fat content: *breakfast cocoa* or *high fat cocoa* (22% minimum), *cocoa* or *medium-fat cocoa* (10 to 22%) and *low-fat cocoa* (less than 10%).

Sweet chocolate is plain chocolate plus added sugar and flavor (usually vanilla).

Milk chocolate is a mixture of sweet chocolate and milk powder or other dairy product. Chocolate and the products described above contain the purines theobromine and caffeine, and considerable quantities of fat (cocoa butter or theobroma oil), as well as protein and starch. These factors are lowered in sweet chocolate because of the large amount of added sugar (more than 50% of the final product).

Description—Weak reddish to purplish brown to moderate brown powder having a chocolate-like odor and taste, free from sweetness.

Uses—A food and pharmaceutically as a flavor in tablets, syrups, pill and tablet coatings, troches, etc.

Cocoa Syrup—page 1301.

Coriander—page 1290.

Coriander Oil

The volatile oil distilled with steam from the dried ripe fruit of *Coriandrum sativum* Linné (Fam *Umbelliferae*).

Constituents—The alcohol *d-linaloöl* (formerly termed *"coriandrol"*) is the chief constituent of this oil, occurring in amounts varying from 60 to 80%. Other constituents include *l-borneol, geraniol, pinenes, terpinenes* and *p-cymene*.

Description—Colorless or pale yellow liquid, having the characteristic odor and taste of coriander; specific gravity 0.863 to 0.875.

Solubility—Soluble in 3 volumes of 70% alcohol.

Uses—A flavoring agent. It formerly was employed in a dose of 0.1 mL as a *carminative*.

Denatonium Benzoate—page 1321.

Eriodictyon

Consumptives' Weed; Mountain Balm; Yerba Santa

The dried leaf of *Eriodictyon californicum* (Hooker et Arnott) Torrey (Fam *Hydrophyllaceae*).

Constituents—A bitter *resin, volatile oil, eriodictyonone* [$C_{16}H_{14}O_6$, also called *homoeriodictyol*], *fixed oil, tannin, gum*, etc.

Uses—A pharmaceutical necessity. It is used in the preparation of *Eriodictyon Fluidextract*.

Eriodictyon Fluidextract [Yerba Santa Fluidextract]—*Preparation:* Using Eriodictyon (in moderately course powder, 1000 g), prepare the fluidextract by Process A (page 1543), using a mixture of 4 volumes of alcohol and 1 volume of water as the menstruum. Macerate the drug during 48 hr, then percolate at a moderate rate and reserve the first 800 mL of percolate. *Alcohol Content:* 57 to 62%. *Uses:* A peculiar, aromatic *flavor* used in syrups and elixirs, especially for masking the taste of bitter drugs like quinine. Because of its resinous character it requires an alkali to render it soluble in aqueous mixtures.

Eriodictyon Syrup, Aromatic—page 1301.

Ethyl Acetate

Acetic acid, ethyl ester; Acetic Ether

$CH_3COOC_2H_5$

Ethyl acetate [141-78-6] $C_4H_8O_2$ (88.11).

Preparation—By slow distillation of a mixture of alcohol and acetic acid in the presence of sulfuric acid.

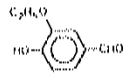
Description—Transparent, colorless liquid with a fragrant and refreshing, slightly acetous odor, and a peculiar acetous, burning taste; specific gravity 0.894 to 0.898; distils 76 to 77.5°.

Solubility—1 mL in about 10 mL of water; miscible with alcohol, acetone, ether, chloroform or fixed and volatile oils.

Uses—Chiefly as a *flavoring agent*. It is used industrially in artificial fruit essence, as a *solvent* for nitrocellulose varnishes and lacquers and as a solvent in organic chemistry.

Ethyl Vanillin

Benzaldehyde, 3-ethoxy-4-hydroxy-, Bourbonal; Ethovan; Vanillal; Vanirome



3-Ethoxy-4-hydroxybenzaldehyde [121-32-4] $C_9H_{10}O_3$ (166.18).

Preparation—By reacting *o*-ethoxyphenol with formaldehyde and *p*-nitrosodimethylaniline in the presence of aluminum and water.

Description—Fine, white or slightly yellowish crystals; odor and taste similar to vanillin; affected by light; solutions are acid to litmus; melts about 77°.

Solubility—1 g in about 100 mL of water at 50°; freely soluble in alcohol, chloroform, ether or solutions of fixed alkali hydroxides.

Uses—A *flavor*, like vanillin, but stronger.

Eucalyptus Oil

The volatile oil distilled with steam from the fresh leaf of *Eucalyptus globulus* Labillardière or of some other species of *Eucalyptus* L'Heritier (Fam *Myrtaceae*). It contains not less than 70% of $C_{10}H_{18}O$ (eucalyptol).

Constituents—The most important constituent is *eucalyptol (cineol)*. Other compounds include *d-α-pinene, globulol, pinocarveol, pinocarvone* and several aldehydes.

Description—Colorless or pale yellow liquid, having a characteristic, aromatic, somewhat camphoraceous odor, and a pungent, spicy, cooling taste; specific gravity 0.905 to 0.925 at 25°.

Solubility—Soluble in 5 volumes of 70% alcohol.

Uses—A *flavoring agent* and an *expectorant* in chronic bronchitis. It also has *bacteriostatic* properties. This oil may be toxic.

Fennel Oil

The volatile oil distilled with steam from the dried ripe fruit of *Foeniculum vulgare* Miller (Fam *Umbelliferae*).

Note—If solid material has separated, carefully warm the oil until it is completely liquefied, and mix it before using.

Constituents—*Anethole* [$C_{10}H_{12}O$] is the chief constituent, occurring to the extent of 50 to 60%. Some of the other constituents are *d*-pinene, phellandrene, dipentene, fenchone, methylchavicol, anisaldehyde and anisic acid.

Description—Colorless or pale yellow liquid, having the characteristic odor and taste of fennel; specific gravity 0.953 to 0.973; congealing temperature is not below 3°.

Solubility—Soluble in 8 volumes of 80% alcohol or in 1 volume of 90% alcohol.

Uses—A flavoring agent. It formerly was employed in a dose of 0.1 mL as a *carminative*.

Glycyrrhiza

Licorice Root; Liquorice Root; Sweetwood; Italian Juice Root; Spanish Juice Root

The dried rhizome and roots of *Glycyrrhiza glabra* Linné, known in commerce as Spanish Licorice, or of *Glycyrrhiza glabra* Linné var *glandulifera* Waldstein et Kitaibel, known in commerce as Russian Licorice, or of other varieties of *Glycyrrhiza glabra* Linné, yielding a yellow and sweet wood (Fam. *Leguminosae*).

Constituents—This well-known root contains 5 to 7% of the sweet principle *glycyrrhizin*, or *glycyrrhizic acid* which is 50 times as sweet as cane sugar. There also is present an oleoresinous substance to which its slight acridity is due. If alcohol or an alkali is used as a menstruum for the root and the preparation not treated to deprive it of acridity, it will have a disagreeable aftertaste. For this reason boiling water is used for its extraction in both the extract and the fluidextract.

Description—The USP/NF provides descriptions of *Unground Spanish and Russian Glycyrrhizas, Histology* and *Powdered Glycyrrhiza*.

Uses—Valuable in pharmacy chiefly for its *sweet flavor*. It is one of the most efficient substances known for masking the taste of bitter substances, like quinine. Acids precipitate the glycyrrhizin and should not be added to mixtures in which glycyrrhiza is intended to mask disagreeable taste. Most of the imported licorice is used

by tobacco manufacturers to flavor tobacco. It also is used in making candy.

Pure Glycyrrhiza Extract [Pure Licorice Root Extract]—*Preparation:* Moisten 1000 g of glycyrrhiza, in granular powder, with boiling water, transfer it to a percolator, and percolate with boiling water until the glycyrrhiza is exhausted. Add enough diluted ammonia solution to the percolate to impart a distinctly ammoniacal odor, then boil the liquid under normal atmospheric pressure until it is reduced to a volume of about 1500 mL. Filter the liquid, and immediately evaporate the filtrate until the residue has a pilular consistency. Pure extract of glycyrrhiza differs from the commercial extract in that it is almost completely soluble in aqueous mixtures. The large amount of filler used in the commercial extract to give it firmness renders it unfit to use as a substitute for the pure extract. *Description:* Black, pilular mass having a characteristic, sweet taste. *Uses:* A *flavoring agent*. One of the ingredients in *Aromatic Cascara Sagrada Fluidextract*.

Glycyrrhiza Fluidextract [Licorice Root Fluidextract; Liquid Extract of Liquorice]—*Preparation:* To 1000 g of coarsely ground glycyrrhiza add about 3000 mL of boiling water, mix, and allow to macerate in a suitable, covered percolator for 2 hr. Then allow the percolation to proceed at a rate of 1 to 3 mL/min, gradually adding boiling water until the glycyrrhiza is exhausted. Add enough diluted ammonia solution to the percolate to impart a distinctly ammoniacal odor, then boil the liquid actively under normal atmospheric pressure until it is reduced to a volume of about 1500 mL. Filter the liquid, evaporate the filtrate on a steam bath until the residue measures 750 mL, cool, gradually add 250 mL of alcohol and enough water to make the product measure 1000 mL, and mix. *Alcohol Content:* 20 to 24%, by volume. *Uses:* A pleasant *flavor* for use in syrups and elixirs to be employed as vehicles and correctives.

Glycyrrhiza Elixir—page 1302.
Glycyrrhiza Syrup—page 1302.
Honey—page 1302.
Hydriodic Acid Syrup—page 1302.
Iso-Alcoholic Elixir—page 1328.

Lavender Oil

Lavender Flowers Oil

The volatile oil distilled with steam from the fresh flowering tops of *Lavandula officinalis* Chaix ex Villars (*Lavandula vera* DeCandolle) (Fam *Labiatae*) or produced synthetically. It contains not less than 35% of esters calculated as $C_{12}H_{20}O_2$ (linalyl acetate).

Constituents—It is a product of considerable importance in perfumery. *Linalyl acetate* is the chief constituent. *Cineol* appears to be a normal constituent of English oils. Other constituents include *amyl alcohol*, *d-borneol* (small amount); *geraniol*, *lavandulal* ($C_{10}H_{16}O$); *linalool*; *nerol*; *acetic*, *butyric*, *valeric*, and *caprylic acids* (as esters); traces of *d-pinene*, *limonene* (in English oils only) and the sesquiterpene *caryophyllene*; *ethyl n-amyl ketone*; an aldehyde (probably *valeric aldehyde*) and *coumarin*.

Description—Colorless or yellow liquid, having the characteristic odor and taste of lavender flowers; specific gravity 0.875 to 0.888.
Solubility—1 volume dissolves in 4 volumes of 70% alcohol.

Uses—Primarily as a *perfume*. It formerly was used in doses of 0.1 mL as a *carminative*.

Lemon Oil

The volatile oil obtained by expression, without the aid of heat, from the fresh peel of the fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*), with or without the previous separation of the pulp and the peel. The total aldehyde content, calculated as citral ($C_{10}H_{16}O$), is 2.2–3.8% for California-type oil, and 3.0–5.5% for Italian-type oil.

Note—Do not use oil that has a terebinthine odor.

Constituents—From the standpoint of odor and flavor, the most noteworthy constituent is the aldehyde *citral*, which is present to the extent of about 4%. About 90% of *d-limonene* is present; small amounts of *l-α-pinene*, *β-pinene*, *camphene*, *β-phellandrene* and γ-terpinene also occur. About 2% of a solid, nonvolatile substance called *citroptene*, *limettin* or *lemon-camphor*, which is dissolved out of the peel, also is present. In addition, there are traces of several other compounds: *α-terpineol*; the *acetates of linalool* and *geranial*; *citronellal*, *octyl* and *nonyl aldehydes*; the sesquiterpenes *bisabolene* and *cadinene* and the ketone *methylheptenone*.

When fresh, the oil has the fragrant odor of lemons. Because of the instability of the terpenes present, the oil readily undergoes deterioration by oxidation, acquiring a terebinthinate odor.

Description—Pale yellow to deep yellow or greenish yellow liquid, with the characteristic odor and taste of the outer part of fresh lemon peel; specific gravity 0.849 to 0.855.
Solubility—Soluble in 3 volumes of alcohol; miscible in all proportions with dehydrated alcohol, carbon disulfide or glacial acetic acid.

Uses—A *flavor* in pharmaceutical preparations and in certain candies and foods.

Methyl Salicylate

Benzoic acid, 2-hydroxy-, methyl ester; Gaultheria Oil; Wintergreen Oil; Betula Oil; Sweet Birch Oil; Teaberry Oil; Artificial Wintergreen Oil; Synthetic Wintergreen Oil

Methyl salicylate [119-36-8] $C_6H_4(OH)COOCH_3$ (152.15); produced synthetically or obtained by maceration and subsequent distillation with steam from the leaves of *Gaultheria procumbens* Linné (Fam *Ericaceae*) or from the bark of *Betula lenta* Linné (Fam *Betulaceae*).

Note—It must be labeled to indicate whether it was made synthetically or distilled from either of the plants mentioned above.

Preparation—Found naturally in gaultheria and betula oils and in many other plants but the commercial product is usually synthetic, made by esterifying salicylic acid with methyl alcohol in the presence of sulfuric acid and distilling.

Description—Colorless, yellowish or reddish liquid, having the characteristic odor and taste of wintergreen; specific gravity (synthetic), 1.180 to 1.185, (from gaultheria or betula), 1.176 to 1.182; boils between 219 to 224° with some decomposition.
Solubility—Slightly soluble in water; soluble in alcohol or glacial acetic acid.

Uses—A pharmaceutical necessity and *counterirritant* (local analgesic). As a pharmaceutical necessity, it is used to flavor the official *Aromatic Cascara Sagrada Fluidextract*, and it is equal in every respect to wintergreen oil or sweet birch oil. As a counterirritant, it is applied to the skin in the form of a liniment, ointment or cream; care should be exercised since salicylate is absorbed through the skin.

Caution—Because it smells like wintergreen candy, it is ingested frequently by children and has caused many fatalities. *Keep out of the reach of children.*

Dose—*Topical*, in lotions and solutions in 10 to 25% concentration.

Monosodium Glutamate

Glutamic acid, monosodium salt, monohydrate

[142-47-2] $C_5H_8NNaO_4 \cdot H_2O$ (187.13)
Preparation—From the fermentation of beet sugar or molasses or by hydrolysis of vegetable proteins.

Description—White, crystalline powder. The pentahydrate effloresces in air to form the monohydrate.
Solubility—Very soluble in water; sparingly soluble in alcohol.

Uses—Flavoring agent and perfume.

Nutmeg Oil

Myristica Oil NF XIII; East Indian Nutmeg Oil; West Indian Nutmeg Oil

The volatile oil distilled with steam from the dried kernels of the ripe seeds of *Myristica fragrans* Houttuyn (Fam *Myristicaceae*).

Constituents—It contains about 80% of *d-pinene* and *d-camphene*, 8% of *dipentene*, about 6% of the alcohols *d-borneol*, *geraniol*, *d-linalool* and *terpineol*, 4% of *myristicin*, 0.6% of *safrol*, 0.3% of *myristic acid* free and as esters, 0.2% of *eugenol* and *isoeugenol* and traces of the alcohol *terpineol-4*, a citral-like aldehyde and several acids, all present as esters.

Description—Colorless or pale yellow liquid having the characteristic odor and taste of nutmeg; specific gravity (East Indian Oil) 0.880 to 0.910, (West Indian Oil) 0.854 to 0.880.

Solubility—Soluble in an equal amount of alcohol; 1 volume of East Indian Oil in 3 volumes of 90% alcohol; 1 volume of West Indian Oil in 4 volumes of 90% alcohol.

Uses—Primarily as a *flavoring agent*. It is used for this purpose in *Aromatic Ammonia Spirit* (page 1533). The oil also is employed as a *flavor* in foods, certain alcoholic beverages, dentifrices and tobacco; to some extent, it also is used in perfumery. It *formerly* was used as a *carminative* and *local stimulant* to the gastrointestinal tract in a dose of 0.03 mL. In overdoses, it acts as a narcotic poison. *This oil is very difficult to keep and even if slightly terebinthinate is unfit for flavoring purposes.*

Orange Oil

Sweet Orange Oil

The volatile oil obtained by expression from the fresh peel of the ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*). The total aldehyde content, calculated as decanal ($C_{10}H_{20}O$), is 1.2 to 2.5%.

Note—Do not use oil that has a terebinthine odor.

Constituents—Consists of *d-limonene* to the extent of at least 90%; in the remaining 5 to 10% are the odorous constituents, among which, in samples of American origin, are *n-decylic aldehyde, citral, d-linalool, n-nonyl alcohol* and traces of *esters* of *formic, acetic, caprylic* and *capric* acids.

In addition to most of these compounds, Italian-produced oil contains *d-terpineol, terpinolene, α-terpinene* and *methyl anthranilate*.

Kept under the usual conditions it is very prone to decompose, and rapidly acquires a terebinthine odor.

Description—Intensely yellow orange or deep orange liquid, which possesses the characteristic odor and taste of the outer part of fresh sweet orange peel; specific gravity 0.842 to 0.846.

Solubility—Miscible with dehydrated alcohol and with carbon disulfide; dissolves in an equal volume of glacial acetic acid.

Uses—A *flavoring agent* in elixirs and other preparations.

Orange Flower Oil

Neroli Oil

The volatile oil distilled from the fresh flowers of *Citrus aurantium* Linné (Fam *Rutaceae*).

Constituents—*β-Ocimene, l-α-pinene, l-camphene, dipentene, l-linalool, geraniol, farnesal, d-terpineol, phenylethyl alcohol, nerol, nerolidol, decylic aldehyde, jasmone, methyl anthranilate, indole, acetic esters of the alcohols* present and traces of *esters of benzoic, phenylacetic* and *palmitic acids*.

Description—Pale yellow, slightly fluorescent liquid, which becomes reddish brown on exposure to light and air; distinctive, fragrant odor, similar to that of orange blossoms, and an aromatic, at first sweet, then somewhat bitter, taste; may become turbid or solid at low temperatures; specific gravity 0.863 to 0.880; neutral to litmus paper; an alcoholic solution has a *violet fluorescence*.

Uses—A *flavor* and *perfume*. Several less valuable varieties of the oil are known commercially. These are designated as *Bigarade* (from the fresh flowers of bitter orange, the ordinary neroli oil), *Portugal* (from the fresh flowers of sweet orange) and *Petit-grain* (from the leaves and young shoots of the bitter orange). The finest variety is known as *Petale*.

Orange Flower Water—page 1300.

Sweet Orange Peel Tincture

Preparation—From sweet orange peel, which is the outer rind of the nonartificially colored, fresh, ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*), by Process M (page 1543). Macerate 500 g of the sweet orange peel (*Note—Exclude the inner, white portion of the rind*) in 900 mL of alcohol, and complete the preparation with alcohol to make the product measure 1000 mL. Use talc as the filtering medium.

The white portion of the rind must not be used, as the proportion of oil, which is only in the yellow rind, is reduced, and the bitter principle *hesperidin* is introduced.

Alcohol Content—62 to 72%.

Uses—A *flavor*, used in syrups, elixirs and emulsions. This tincture was introduced to provide a delicate orange flavor direct from the fruit instead of depending upon orange oil which so frequently is terebinthinate and unfit for use. The tincture keeps well.

Compound Orange Spirit

Contains, in each 100 mL, 25 to 30 mL of the mixed oils.

Orange Oil	200 mL
Lemon Oil	50 mL
Coriander Oil	20 mL
Anise Oil	5 mL
Alcohol, a sufficient quantity,	
To make	1000 mL

Mix the oils with sufficient alcohol to make the product measure 1000 mL.

Alcohol Content—65 to 75%.

Uses—A *flavor* for elixirs. An alcoholic solution of this kind permits the uniform introduction of small proportions of oils and also preserves orange and lemon oils from rapid oxidation. These two oils should be bought in small quantities by the pharmacist, since the spirit is made most satisfactorily from oils taken from bottles not previously opened. This will insure that delicacy of flavor which should always be characteristic of elixirs.

Orange Syrup

Syrup of Orange Peel

Contains, in each 100 mL, 450 to 550 mg of citric acid ($C_6H_8O_7$).

Sweet Orange Peel Tincture	50 mL
Citric Acid (anhydrous)	5 g
Talc	15 g
Sucrose	820 g
Purified Water, a sufficient quantity,	
To make	1000 mL

Triturate the talc with the tincture and citric acid, and gradually add 400 mL of purified water. Then filter, returning the first portions of the filtrate until it becomes clear, and wash the mortar and filter with enough purified water to make the filtrate measure 450 mL. Dissolve the sucrose in this filtrate by agitation, without heating, and add enough purified water to make the product measure 1000 mL. Mix and strain.

Note—Do not use syrup that has a terebinthine odor or taste or shows other indications of deterioration.

Alcohol Content—2 to 5%.

Uses—A pleasant, acidic vehicle.

Peppermint

American Mint; Lamb Mint; Brandy Mint

Consists of the dried leaf and flowering top of *Mentha piperita* Linné (Fam *Labiatae*).

Uses—The source of green color for *Peppermint Spirit* (page 798). The odor of fresh peppermint is due to the presence of about 2% of a volatile oil, much of which is lost on drying the leaves in air. It is cultivated widely both in the US and France. It formerly was used as a carminative.

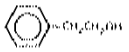
Peppermint Oil—The volatile oil distilled with steam from the fresh overground parts of the flowering plant of *Mentha piperita* Linné (Fam *Labiatae*), rectified by distillation and neither partially nor wholly dementhol ized. It yields not less than 5% of esters, calculated as menthyl acetate [$C_{12}H_{22}O_2$], and not less than 50% of total menthol [$C_{10}H_{20}O$], free and as esters. *Constituents:* This is one of the most important of the group of volatile oils. The chief constituent is *Menthol* (page 765) which occurs in the levorotatory form; its ester, *menthyl acetate*, is present in a much smaller amount. Other compounds which are present include the ketone *menthone, piperitone, α-pinene, l-limonene, phellandrene, cadinene, menthyl isovalerate, isovaleric aldehyde, acetaldehyde, menthofuran, cineol*, an unidentified *lactone* [$C_{10}H_{18}O_2$] and probably *amyl acetate*. Colorless or pale yellow liquid, having a strong,

penetrating odor of peppermint and a pungent taste, followed by a sensation of cold when air is drawn into the mouth; specific gravity 0.896 to 0.908; 1 volume dissolves in 3 volumes of 70% alcohol. *Uses:* A *flavoring agent, carminative, antiseptic* and *local anesthetic*. It also is used extensively as a *flavor* in candy, chewing gum, etc.

Peppermint Spirit—page 798.
Peppermint Water—page 1300.

Phenylethyl Alcohol

Benzeneethanol; 2-Phenylethanol



Phenethyl alcohol [60-12-8] $C_8H_{10}O$ (122.17); occurs in a number of essential oils such as those of rose, neroli, hyacinth, carnation and others.

Description—Colorless liquid with a rose-like odor and a sharp, burning taste; solidifies at −27°; specific gravity 1.017 to 1.020.

Solubility—1 g in 60 mL of water; ≥1 mL of alcohol, chloroform or ether; very soluble in fixed oils, glycerin or propylene glycol; slightly soluble in mineral oil.

Uses—Introduced for use as an antibacterial agent in ophthalmic solutions, but it is of limited effectiveness.

It is used in *flavors*, as a *soap perfume* and in the preparation of synthetic oils of rose and similar flower oils. It is also a valuable perfume fixative.

Pine Needle Oil

Dwarf Pine Oil

The volatile oil distilled with steam from the fresh leaf of *Pinus mugo* Turra and its variety *pumilio* (Haenke) Zenari (Fam *Pinaceae*); contains 3 to 10%, by weight, of esters calculated as $C_{12}H_{20}O_2$ (bornyl acetate).

Constituents—It contains the terpenes *l-α-pinene, β-pinene, l-phellandrene, l-limonene, dipentene*, and possibly *sylvestrene*, the ester *bornyl acetate* and several unidentified terpene and sesquiterpene alcohols.

Description—Colorless to yellowish liquid, having a pleasant, aromatic odor and a bitter, pungent taste; specific gravity 0.853 to 0.871 at 25°.

Solubility—Dissolves in 4.5 to 10 volumes of 90% alcohol, often with turbidity.

Uses—Chiefly as a *perfume* and *flavoring agent*. It also is employed as an inhalant in bronchitis.

Raspberry Syrup—page 1302.

Rose Oil

Otto of Rose; Attar of Rose

The volatile oil distilled with steam from the fresh flowers of *Rosa gallica* Linné, *Rosa damascena* Miller, *Rosa alba* Linné, *Rosa centifolia* Linné and varieties of these species (Fam *Rosaceae*).

Constituents—From the quantitative standpoint the chief components are the alcohols *geraniol* [$C_{10}H_{18}O$] and *l-citronellol* [$C_{10}H_{20}O$]. The sesquiterpene alcohols *farnesol* and *nerol* occur to the extent of 1% and 5 to 10%, respectively. Together, the four alcohols constitute 70 to 75% of the oil. *Phenylethyl alcohol*, which comprises 1% of the oil, is an important odoriferous constituent. Other compounds present are *linalool, eugenol, nonyl aldehyde*, traces of *citral* and two solid hydrocarbons of the paraffin series.

Description—A colorless or yellow liquid, which has the characteristic odor and taste of rose; at 25°, a viscous liquid; on gradual cooling it changes to a translucent, crystalline mass, which may be liquefied easily by warming; specific gravity 0.848 to 0.863 at 30° compared with water at 15°; 1 mL mixes with 1 mL of chloroform without turbidity; on the addition of 20 mL of 90% alcohol to this solution, the resulting liquid is neutral or acid to moistened litmus paper and deposits a crystalline residue within 5 min on standing at 20°.

Uses—Principally as a *perfume*. It is recognized officially for its use as an ingredient in *Rose Water Ointment* and cosmetics.

Stronger Rose Water

Triple Rose Water

A saturated solution of the odoriferous principles of the flowers of *Rosa centifolia* Linné (Fam *Rosaceae*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

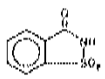
Note—When diluted with an equal volume of purified water, it may be supplied when *Rose Water* is required.

Description—Nearly colorless and clear liquid which possesses the pleasant odor and taste of fresh rose blossoms; must be free from empyreuma, mustiness and fungal growths.

Uses—An ingredient in *Rose Water Ointment*. It sometimes is prepared extemporaneously from concentrates or from rose oil, but such water is not official and rarely compares favorably with the fresh distillate from rose petals.

Saccharin

1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide; Gluside; *o*-Benzosulfimide
Saxin (*Burroughs Wellcome*); Sweeta (*Squibb*)



1,2-Benzisothiazolin-3-one 1,1-dioxide [81-07-2] $C_7H_5NO_3S$ (183.18).

Preparation—Toluene is reacted with chlorosulfonic acid to form *o*-toluenesulfonyl chloride, which is converted to the sulfonamide with ammonia. The methyl group then is oxidized with dichromate yielding *o*-sulfamoylbenzoic acid which, when heated, forms the cyclic imide.

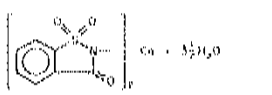
Description—White crystals or a white crystalline powder; odorless or has a faint aromatic odor; in dilute solution it is intensely sweet; solutions are acid to litmus; melts between 226 to 230°.

Solubility—1 g in 290 mL of water, 31 mL of alcohol or 25 mL of boiling water; slightly soluble in chloroform or ether; readily dissolved by dilute solution of ammonia, solutions of alkali hydroxides or solutions of alkali carbonates with the evolution of CO_2.

Uses—A sweetening agent in *Aromatic Cascara Sagrada Fluidextract* and highly alcoholic preparations. It is an intensely sweet substance. A 60-mg portion is equivalent in sweetening power to approximately 30 g of sucrose. It is used as a *sweetening agent* in vehicles, canned foods, beverages and in diets for diabetics to replace the sucrose. The relative sweetening power of saccharin is increased by dilution.

Saccharin Calcium

1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide, calcium salt, hydrate (2:7)
Calcium *o*-Benzosulfimide



1,2-Benzisothiazolin-3-one 1,1-dioxide calcium salt hydrate (2:7) [6381-91-5] $C_{14}H_8CaN_2O_6S_2.3\frac{1}{2}H_2O$ (467.48); *anhydrous* [6485-34-3] (404.43).

Preparation—Saccharin is reacted with a semimolar quantity of calcium hydroxide in aqueous medium and the resulting solution is concentrated to crystallization.

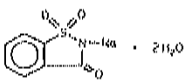
Description—White crystals or a white, crystalline powder; odorless or has a faint aromatic odor; and an intensely sweet taste even in dilute solutions; in dilute solution it is about 300 times as sweet as sucrose.

Solubility—1 g in 2.6 mL of water or 4.7 mL of alcohol.

Uses and Dose—See *Saccharin*.

Saccharin Sodium

1,2-Benzisothiazol-3(2H)-one, 1,1-dioxide, sodium salt, dihydrate; Soluble Saccharin, Soluble Glusidе; Sodium o-Benzosulfimide



1,2-Benzisothiazolin-3-one 1,1-dioxide sodium salt dihydrate [6155-57-3] $C_7H_4NNaO_3S.2H_2O$ (241.19); *anhydrous* [128-44-9] (205.16).

Preparation—Saccharin is dissolved in an equimolar quantity of aqueous sodium hydroxide and the solution is concentrated to crystallization.

Description—White crystals or a white crystalline powder; odorless or has a faint aromatic odor and an intensely sweet taste even in dilute solutions; in dilute solution it is about 300 times as sweet as sucrose; when in powdered form it usually contains about ¼ the theoretical amount of water of hydration due to efflorescence.

Solubility—1 g in 1.5 mL of water or 50 mL of alcohol.

Uses—Same as *Saccharin* but has the advantage of being more soluble in neutral aqueous solutions.

Application—15 to 60 mg as necessary.

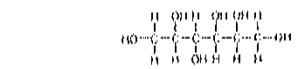
Dosage Form—Tablets: 15, 30 and 60 mg.

Sarsaparilla Syrup, Compound—RPS-13, page 445.

Shorry Wine—page RPS-15, page 1240.

Sorbitol

Sionin; Sorbit; D-Sorbitol; D-Glucitol Sorbo (*Atlas*)



D-Glucitol [50-70-4] $C_6H_{14}O_6$ (182.17); it may contain small amounts of other polyhydric alcohols.

Preparation—Commercially by reduction (hydrogenation) of certain sugars, such as glucose.

Description—White, hygroscopic powder, granules or flakes, having a sweet taste; the usual form melts about 96°.

Solubility—1 g in about 0.45 mL of water; slightly soluble in alcohol, methanol or acetic acid.

Uses—An *osmotic diuretic* given intravenously in 50% (*w/v*) solution to diminish edema, lower cerebrospinal pressure or reduce intraocular pressure in glaucoma. It also is used as a laxative, sweetener, humectant, plasticizer and, in 70% (*w/w*) solution, as a vehicle.

Dose—50 to 100 mL of a 50% solution; *laxative, oral*, 30 to 50 g.

Sorbitol Solution is a water solution containing, in each 100 g, 69–71 g of total solids consisting essentially of D-sorbitol and a small amount of mannitol and other isomeric polyhydric alcohols. The content of D-sorbitol [$C_6H_8(OH)_6$] in each 100 g is not less than 64 g. *Description:* Clear, colorless, syrupy liquid, having a sweet taste and no characteristic odor; neutral to litmus; specific gravity not less than 1.285; refractive index at 20° 1.455 to 1.465. *Uses:* It is not to be injected. It has been used as a replacement for propylene glycol and glycerin.

Spearmint

Spearmint Leaves; Spearmint Herb; Mint

The dried leaf and flowering top of *Mentha spicata* Linné (*Mentha viridis* Linné) (Common Spearmint) or of *Mentha cardiaca* Gerard ex Baker (Scotch Spearmint) (Fam *Lahiatae*).

Fresh spearmint is used in preparing mint sauce and also the well-known mint julep. The volatile oil is the only constituent of importance in this plant; the yield is from ½ to 1%.

Uses—A flavoring agent.

Spearmint Oil is the volatile oil distilled with steam from the fresh over-ground parts of the flowering plant of *Mentha spicata* or of *Mentha cardiaca;* contains not less than 55%, by volume, of $C_{10}H_{14}O$ (carvone = 150.22). The chief odoriferous constituent is the ketone *l-carvone*. American oil also contains *dihydrocarveol acetate* [$CH_3COOC_{10}H_{17}$], *l-limonene* [$C_{10}H_{16}$], a small amount of *phellandrene* [$C_{10}H_{16}$] and traces of *esters of valeric* and *caproic acids*. Colorless, yellow or greenish yellow liquid, having the characteristic odor and taste of spearmint; specific gravity 0.917 to 0.934; soluble in 1 volume of 80% alcohol, but upon further dilution may become turbid. *Uses:* Primarily as a flavoring agent. It also has been used as a *carminative* in doses of 0.1 mL.

Sucrose

α-D-Glucopyranoside, β-D-fructofuranosyl-, Sugar; Cane Sugar; Beet Sugar

Sucrose [57-50-1] $C_{12}H_{22}O_{11}$ (342.30); a sugar obtained from *Saccharum officinarum* Linné (Fam *Gramineae*), *Beta vulgaris* Linné (Fam *Chenopodiaceae*), and other sources. It contains no added substances.

For the structural formula, see page 382.

Preparation—Commercially from the sugar cane, beet root and sorghum. Originally, sugar cane was the only source, but at present the root of *Beta vulgaris* is used largely in Europe, and to an increasing degree in this country, for making sucrose.

The sugar cane is crushed and the juice amounting to about 80% is expressed with roller mills. The juice after "defecation" with lime and removal of excess of lime by carbonic acid gas, is run into vacuum pans for concentration and the saccharine juice is evaporated in this until it begins to crystallize. After the crystallization is complete, the warm mixture of crystals and syrup is run into centrifuges, in which the crystals of raw sugar are drained and dried. The syrup resulting as a by-product from raw sugar is known as *molasses*. Raw beet sugar is made by a similar process, but is more troublesome to purify than that made from sugar cane.

The refined sugar from either raw cane or beet sugar is prepared by dissolving the raw sugar in water, clarifying, filtering and, finally, decolorizing the solution by passing it through bone-black filters. The water-white solution finally is evaporated under reduced pressure to the crystallizing point and then forced to crystallize in small granules which are collected and drained in a centrifuge.

Description—Colorless or white crystals, crystalline masses or blocks, or a white, crystalline powder; odorless; sweet taste; stable in air; solutions neutral to litmus; melts with decomposition from 160 to 185°; specific gravity of about 1.57; specific rotation at 20° not less than +65.9°; unlike the other official sugars (dextrose, fructose and lactose), it does not reduce Fehling's solution even in hot solutions; also differs from these sugars in that it is darkened and charred by sulfuric acid in the cold; fermentable and, in dilute aqueous solutions, it ferments into alcohol and eventually acetic acid.

Sucrose is hydrolyzed by dilute mineral acids, slowly in the cold, and rapidly on heating into one molecule each of dextrose or levulose. This process is known technically as "inversion" and the product is referred to as "invert sugar;" the term inversion being derived from the change, through the hydrolysis, in the optical rotation from dextro of the sucrose to levo of the hydrolyzed product. The enzyme *invertase* also hydrolyzes sucrose.

Solubility—1 g in 0.5 mL of water, 170 mL of alcohol or in slightly more than 0.2 mL of boiling water; insoluble in chloroform or ether.

Uses—Principally as a pharmaceutical necessity for making syrups and lozenges. It gives viscosity and consistency to fluids.

Intravenous administration of hypertonic solutions has been employed chiefly to initiate *osmotic diuresis*. Such a procedure is not completely safe and renal tubular damage may result, particularly in patients with existing renal pathology. Safer and more effective diuretics are available.

Compressible Sugar

Sucrose that may contain some starch, malto-dextrin or invert sugar; contains 95.0 to 98.0% of sucrose.

Description—White, crystalline, odorless powder; sweet taste; stable in air.

Solubility—The sucrose portion is very soluble in water.

Uses—A *pharmaceutic aid* as a *tableting excipient* and *sweetening agent*. See also *Sucrose*.

Confectioner's Sugar

Sucrose ground together with corn starch to a fine powder; contains 95.0 to 97.0% of sucrose.

Description—Fine, white, odorless powder; sweet taste; stable in air; specific rotation not less than +62.6°.

Solubility—The sucrose portion is soluble in cold water; this is entirely soluble in boiling water.

Uses—A *pharmaceutic aid* as a *tableting excipient* and *sweetening agent*. See also *Sucrose*.

Syrup—page 1302.

Tolu Balsam

Tolu

A balsam obtained from *Myroxylon balsamum* (Linné) Harms (Fam *Leguminosae*).

Constituents—Up to 30% *resin*, about 7% *volatile oil*, 12 to 15% free *cinnamic acid*, 2 to 8% benzoic acid and 0.05% *vanillin*. The volatile oil is composed chiefly of *benzyl benzoate* and *benzyl cinnamate*, *ethyl benzoate*, *ethyl cinnamate*, a terpene called *tolene* (possibly identical with *phellandrene*) and the sesquiterpene alcohol *farnesol* also have been reported to be present.

Description—Brown or yellowish brown, plastic solid; transparent in thin layers and brittle when old, dried or exposed to cold temperatures; pleasant, aromatic odor resembling that of vanilla and a mild, aromatic taste.

Solubility—Nearly insoluble in water or in solvent hexane; soluble in alcohol, chloroform or ether, sometimes with slight residue or turbidity.

Uses—A *vehicle*, *flavoring agent* and stimulating *expectorant* as a syrup. It is also an ingredient of *Compound Benzoin Tincture* (page 760).

Tolu Balsam Syrup [Syrup of Tolu; Tolu Syrup]—*Preparation:* Add tolu balsam tincture (50 mL, all at once) to magnesium carbonate (10 g) and sucrose (60 g) in a mortar, and mix intimately. Gradually add purified water (430 mL) with trituration, and filter. Dissolve the remainder of sucrose (760 g) in the clear filtrate with gentle heating, strain the syrup while warm and add purified water (qs) through the strainer to make the product measure 1000 mL. Mix thoroughly. *Note:* May be made also in the following manner: Place the remaining sucrose (760 g) in a suitable percolator, the neck of which nearly is filled with loosely packed cotton, moistened after packing with a few drops of water. Pour the filtrate, obtained as directed in the formula above, upon the sucrose, and regulate the outflow to a steady drip of percolate. When all of the liquid has run through, return portions of the percolate, if necessary, to dissolve all of the sucrose. Then pass enough purified water through the cotton to make the product measure 1000 mL. Mix thoroughly. *Alcohol Content:* 3 to 5%. *Uses:* Chiefly for its agreeable *flavor* in cough syrups. *Dose:* 10 mL.

Tolu Balsam Tincture [Tolu Tincture]—*Preparation:* With tolu balsam (200 g), prepare a tincture by Process M (page 1543), using alcohol as the menstruum. *Alcohol Content:* 77 to 83%. *Uses:* A balsamic preparation employed as an addition to expectorant mixtures; also used in the preparation of *Tolu Balsam Syrup*. *Dose:* 2 mL.

Vanilla

Vanilla Bean

The cured, full-grown, unripe fruit of *Vanilla planifolia* Andrews, often known in commerce as Mexican or Bourbon Vanilla, or of *Vanilla tahitensis* J W Moore, known in commerce as Tahiti Vanilla (Fam *Orchidaceae*); yields not less than 12% of anhydrous extractive soluble in diluted alcohol.

Constituents—Contains a trace of a volatile oil, fixed oil, 4% resin, sugar, *vanillic acid* and about 2.5% *vanillin* (see below). The highest grade of vanilla comes from Madagascar; considerable quantities of the drug also are produced in Mexico.

Uses—A flavor.

Note—Do not use if it has become brittle.

Vanilla Tincture [Extract of Vanilla]—*Preparation:* Add water (200 mL) to comminuted vanilla (cut into small pieces, 100 g) in a suitable covered container, and macerate during 12 hr, preferably in a warm place. Add alcohol (200 mL) to the mixture of vanilla and water, mix well and macerate about 3 days. Transfer the mixture to a percolator containing sucrose (in coarse granules, 200 g), and drain; then pack the drug firmly, and percolate slowly, using diluted alcohol (qs) as the menstruum. If the percolator is packed with an evenly distributed mixture of the comminuted vanilla, sucrose and clean, dry sand, the increased surface area permits more efficient percolation. This tincture is unusual in that it is the only official one in which sucrose is specified as an ingredient. *Alcohol Content:* 38 to 42%. *Uses:* A *flavoring agent*. See *Flavors*, page 1290.

Vanillin

Benzaldehyde, 4-hydroxy-3-methoxy-.

4-Hydroxy-3-methoxybenzaldehyde [121-33-5] $C_8H_8O_3$ (152.15).

Preparation—From vanilla, which contains 2 to 3%. It also is found in many other substances, including tissues of certain plants, crude beet sugar, asparagus and even asafetida. Commercially, it is made synthetically. While chemically identical with the product obtained from the "vanilla bean," "flavoring preparations" made from it never equal in flavor the preparation in which vanilla alone is used because vanilla contains other odorous products. It is synthesized by oxidation processes from either coniferin or eugenol, by treating guaiacol with chloroform in the presence of an alkali, and by other methods.

Description—Fine, white to slightly yellow crystals, usually needle-like having an odor and taste suggestive of vanilla; affected by light; solutions are acid to litmus; melts from 81 to 83°.

Solubility—1 g in about 100 mL of water, about 20 mL of glycerin or 20 mL of water at 80°; freely soluble in alcohol, chloroform, ether or solutions of the fixed alkali hydroxides.

Incompatibilities—Combines with *glycerin*, forming a compound which is almost insoluble in alcohol. It is decomposed by *alkalies* and is oxidized slowly by the *air*.

Uses—Only as a *flavor*. Solutions of it sometimes are sold as a synthetic substitute for vanilla for flavoring foods but it is inferior in flavor to the real vanilla extract.

Water—page 1300.

Water, Purified—page 1301.

Wild Cherry Syrup—page 1302.

Other Flavoring Agents

Anise NF IX [Anise Seed; European Aniseed; Sweet Cumin]—The dried ripe fruit of *Pimpinella anisum* Linné. It contains about 1.75% of volatile oil. *Uses:* A flavor and carminative.

Ceylon Cinnamon—The dried inner bark of the shoots of coppiced trees of *Cinnamomum zeylanicum* Nees (Fam *Lauraceae*); contains, in each 100 g, not less than 0.5 mL volatile oil. *Uses:* A *carminative* and *flavor*.

Clove—The dried flower-bud of *Eugenia caryophyllus* (Sprengel) Bullock et Harrison (Fam *Myrtaceae*). It contains, in each 100 g, not less than 16 mL of clove oil. *Uses:* An *aromatic* in doses of 0.25 g and as a condiment in foods.

Coriander—The dried ripe fruit of *Coriandrum sativum* Linné (Fam *Umbelliferae*); yields not less than 0.25 mL volatile coriander oil/100 g. *Uses:* Seldom used alone, but sometimes is combined with other agents, chiefly as a *flavor*. It also is used as a condiment and flavor in cooking.

Eucalyptol [Cineol; Cajeputol; $C_{10}H_{18}O$ (154.25)]—Obtained from eucalyptus oil and from other sources. Colorless liquid, having a characteristic, aromatic, distinctly camphoraceous odor and a pungent, cooling, spicy taste. 1 volume is soluble in 5 volumes of 60% alcohol; miscible with alcohol, chloroform, ether, glacial acetic acid or fixed or volatile oils; insoluble in water. *Uses:* Primarily as a *flavoring agent*. Locally it is employed for its *antiseptic* effect in inflammations of the nose and throat and in certain skin diseases. It sometimes is used by inhalation in bronchitis.

Fennel [Fennel Seed]—The dried ripe fruit of cultivated varieties of *Foeniculum vulgare* Miller (Fam *Umbelliferae*); contains 4 to 6% of an oxygenated volatile oil and 10% of a fixed oil. *Uses:* A *flavor* and *carminative*.

Ginger NF [Zingiber]—The dried rhizome of *Zingiber officinale* Roscoe (Fam *Zingiberaceae*), known in commerce as Jamaica Ginger, African Ginger and Cochin Ginger. The outer cortical layers often are removed either partially or completely. *Constituents:* A pungent substance, *gingerol*; volatile oil (Jamaica Ginger, about 1%; African Ginger, 2 to 3%), containing the terpenes *d*-*camphene* and *β*-*phellandrene* and the sesquiterpene *zingiberene*; *citral cineol* and *borneol*. *Uses:* A *flavoring agent*. It formerly was employed in a dose of 600 mg as an intestinal stimulant and carminative in colic and in diarrhea.

Ginger Oleoresin—Yields 18 to 35 mL of volatile ginger oil/100 g of oleoresin. *Preparation:* Extract the oleoresin from ginger, in moderately coarse powder, by percolation, using either acetone, alcohol or ether as the menstruum.

Glycyrrhiza Extract [Licorice Root Extract; Licorice]—An extract prepared from the rhizome and roots of species of *Glycyrrhiza* Tournefort ex Linné (Fam *Leguminosae*). *Description:* Brown powder or in flattened, cylindrical rolls or in masses; the rolls or masses have a glossy

black color externally, and a brittle, sharp, smooth, conchoidal fracture; the extract has a characteristic and sweet taste which is not more than very slightly acrid. *Uses:* A *flavoring agent*.

Lavendor [Lavandula]—The flowers of *Lavandula spica* (*Lavandula officinalis* or *Lavandula vera*); contains a volatile oil with the principal constituent *l*-linalyl acetate. *Uses:* A *perfume*.

Lemon Peel USP XV, BP [Fresh Lemon Peel]—The outer yellow rind of the fresh ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*); contains a volatile oil and hesperidin. *Uses:* A *flavor*.

Lemon Tincture USP XVIII [Lemon Peel Tincture]—*Preparation:* From lemon peel, which is the outer yellow rind of the fresh, ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*), by *Process M* (page 1543), 500 g of the peel being macerated in 900 mL alcohol and the preparation being completed with alcohol to make the product measure 1000 mL. Use talc as the filtering medium. The white portion of the rind must not be used, as the proportion of oil, which is found only in the yellow rind, is reduced and the bitter principle, hesperidin, introduced. *Alcohol Content:* 62 to 72%. *Uses:* A flavor, its fineness of flavor being assured as it comes from the fresh fruit, and being an alcoholic solution it is more stable than the oil.

Myrcia Oil [Bay Oil; Oil of Bay]—The volatile oil distilled from leaves of *Pimenta racemosa* (Miller) J W Moore (Fam *Myrtaceae*); contains the phenolic compounds eugenol and chavicol. *Uses:* In the preparation of bay rum as a *perfume*.

Orange Oil, Bitter—The volatile oil obtained by expression from the fresh peel of the fruit of *Citrus aurantium* Linné (Fam *Rutaceae*); contains primarily *d*-limonene. Pale yellow liquid with a characteristic aromatic odor of the Seville orange; if it has a terebinthinate odor, it should not be dispensed; refractive index 1.4725 to 1.4755 at 20°. It differs little from *Orange Oil* (page 1296) except for the botanical source. Miscible with anhydrous alcohol and with about 4 volumes alcohol. *Uses:* A *flavor*.

Orange Peel, Bitter [Bitter Orange; Curacao Orange Peel; Bigarade Orange]—The dried rind of the unripe but fully grown fruit of *Citrus aurantium* Linné (Fam *Rutaceae*). *Constituents:* The inner part of the peel from the bitter orange contains a volatile oil and the glycoside *hesperidin* ($C_{28}H_{34}O_{15}$). This, upon hydrolysis in the presence of H_2SO_4, yields *hesperetin* ($C_{16}H_{14}O_6$), *rhamnose* ($C_6H_{12}O_5$), and D-glucose ($C_6H_{12}O_6$). *Uses:* A *flavoring agent*. It has been used as a bitter.

Orange Peel, Sweet USP XV—The fresh, outer rind of the nonartificially colored, ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*); the white, inner portion of the rind is to be excluded. Contains a volatile oil but no hesperidin, since the glycoside occurs in the white portion of the rind. *Uses:* A *flavor*.

Orris [Orris Root; Iris; Florentine Orris]—The peeled and dried rhizome of *Iris germanica* Linné, including its variety *florentina* Dykes (*Iris florentina* Linné), or of *Iris pallida* Lamarck (Fam *Iridaceae*); contains about 0.1 to 0.2% of a volatile oil (orris butter), myristic acid and the ketone irone; irone provides the fragrant odor of orris. *Uses:* A *perfume*.

Pimenta Oil [Pimento Oil; Allspice Oil]—The volatile oil distilled from the fruit of *Pimenta officinalis* Lindley (Fam *Myrtaceae*). *Uses:* A *carminative* and *stimulant* and also as a *condiment* in foods.

Rosemary Oil—The volatile oil distilled with steam from the fresh flowering tops of *Rosmarinus officinalis* Linné (Fam *Labiatae*); yields not less than 1.5% of esters calculated as bornyl acetate ($C_{12}H_{20}O_2$), and not less than 8% of total borneol ($C_{10}H_{18}O$), free and as esters. *Constituents:* The amount of esters, calculated as bornyl acetate, and of total borneol, respectively, varies somewhat with its geographic source. Cineol is present to the extent of about 19–25%, depending on the source. The terpenes *d*- and *l*-α-*pinene*, *dipentene* and *camphene*, and the ketone *camphor* also occur in this oil. *Description:* Colorless or pale yellow liquid, having the characteristic odor of rosemary, and a warm, camphoraceous taste; specific gravity 0.894 to 0.912. Soluble in 1 volume of 90% alcohol, by volume, but upon further dilution may become turbid. *Uses:* A *flavor* and *perfume*, chiefly, in rubefacient liniments such as *Camphor and Soap Liniment*.

Sassafras—The dried bark of the root of *Sassafras albidum* (Nuttall) Nees (Fam *Lauraceae*). *Uses:* Principally because of its high content of volatile oil which serves to disguise the taste of disagreeable substances. An infusion (*sassafras tea*) formerly was used extensively as a home remedy, particularly in the southern states.

Sassafras Oil—The volatile oil distilled with steam from *Sassafras*. *Uses:* A *flavor* by confectioners, particularly in hard candies. Either the oil or safrol is used as a *preservative* in mucilage and library paste, being far superior to methyl salicylate for this purpose. Since the oil is *antiseptic*, it sometimes is employed in conjunction with other agents for local application in diseases of the nose and throat; safrol also is used in this way.

Wild Cherry [Wild Black Cherry Bark]—The carefully dried stem bark of *Prunus serotina* Ehrhart (Fam *Rosaceae*), free of borke and preferably having been collected in autumn. *Constituents:* A glucoside of *d-mandelonitrile* ($C_6H_5CHOH.CN$) known as *prunasin* (page 385), the enzyme *emulsin*, tannin, a bitter principle, starch, resin, etc. In the BP and the English literature this drug has been termed "Virginian Prune"—a literal but incorrect translation of the older botanical name, *Prunus virginiana*. *Uses:* A *flavoring agent*, especially in cough preparations. It is an ingredient in *Wild Cherry Syrup*. As with bitter almond, contact with water, in the presence of emulsin, results in the production of benzaldehyde and HCN. All preparations of wild cherry should be made without heat in order to avoid destruction of the enzyme which is responsible for the production of the free active principles.

Diluting Agents

Diluting agents (vehicles or carriers) are indifferent substances which are used as solvents for active medicinals. They are of primary importance for diluting and flavoring drugs which are intended for oral administration, but a few such agents are designed specifically for diluting parenteral injections. The latter group is considered separately.

The expert selection of diluting agents has been an important factor in popularizing the "specialties" of manufacturing pharmacists. Since a large selection of diluting agents is available in a choice of colors and flavors, the prescriber has an opportunity to make his own prescriptions more acceptable to the patient. The best diluting agent is usually the best solvent for the drug. Water-soluble substances, for example, should be flavored and diluted with an aqueous agent and alcohol-soluble drugs with an alcoholic vehicle. Thus, the diluting agents presented herein are divided into three groups on the basis of their physical properties: aqueous, hydroalcoholic and alcoholic.

Aqueous Diluting Agents

Aqueous diluting agents include aromatic waters, syrups and mucilages. Aromatic waters are used as diluting agents for water-soluble substances and salts, but cannot mask the taste of very disagreeable drugs. Some of the more common flavored aqueous agents and the official forms of water are listed below.

Orange Flower Water

Stronger Orange Flower Water; Triple Orange Flower Water

A saturated solution of the odoriferous principles of the flowers of *Citrus aurantium* Linné (Fam. *Rutaceae*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

Description—Should be nearly colorless, clear or only faintly opalescent; the odor should be that of the orange blossoms; it must be free from empyreuma, mustiness and fungoid growths.

Uses—A *vehicle flavor* and *perfume* in syrups, elixirs and solutions.

Peppermint Water

A clear, saturated solution of peppermint oil in purified water, prepared by one of the processes described under *Aromatic Waters* (page 1522).

Uses—A *carminative* and *flavored vehicle*.

Dose—15 mL.

Tolu Balsam Syrup—page 1209.

Water

Water [7732-18-5] H_2O (18.02).

Drinking water, which is subject to EPA regulations with respect to drinking water, and which is delivered by the municipal or other local public system or drawn from a private well or reservoir, is the starting material for all forms of water covered by Pharmacopeial monographs.

Drinking water may be used in the preparation of USP drug substances (eg, in the extraction of certain vegetable drugs and in the manufacture of a few preparations used externally) but not in the preparation of dosage forms, or in the preparation of reagents or test solutions. It is no longer the subject of a separate monograph (in the USP), inasmuch as the cited standards vary from one community to another and generally are beyond the control of private parties or corporations.

Purified Water

Water obtained by distillation, ion-exchange treatment, reverse osmosis or any other suitable process; contains no added substance.

Caution—*Do not use this in preparations intended for parenteral administration. For such purposes, use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection,* page 1304.

Preparation—From water complying with EPA regulations with respect to drinking water. A former official process for water, when prepared by distillation, is given below. The pharmacist who is preparing sterile solutions, and must have freshly distilled water of exceptionally high grade, not only free from all bacterial or other microscopic growths but also free from the products of metabolic processes resulting from the growth of such organisms in the water, advantageously may follow this plan. The metabolic products commonly are spoken of as pyrogens and usually consist of complex organic compounds which cause febrile reactions if present in the solvent for parenteral medicinal substances.

Distillation Process

Water	1000 Vol
To make	750 Vol

Distil the water from a suitable apparatus provided with a block-tin or glass condenser. Collect the first 100 volumes and reject this portion. Then collect 750 volumes and keep the distilled water in glass-stoppered bottles, which have been rinsed with steam or very hot distilled water immediately before being filled. The first 100 volumes are discarded to eliminate foreign volatile substances found in ordinary water and only 750 volumes are collected, since the residue in the still contains concentrated dissolved solids.

Description—Colorless, clear liquid, without odor or taste.

Uses—A *pharmaceutic aid* (vehicle and solvent). It must be used in compounding dosage forms for internal (oral) administration as well as sterile pharmaceuticals applied externally, such as collyria and dermatological preparations, but these must be sterilized before use.

Whenever water is called for in official tests and assays, this must be used.

Syrups Used as Diluting Agents

Syrups are useful as diluting agents for water-soluble drugs and act both as solvents and flavoring agents. The flavored syrups usually consist of simple syrup (85% sucrose in water) containing appropriate flavoring substances. *Glycyrrhiza Syrup* is an excellent vehicle for saline substances because of its colloidal properties, sweet flavor and lingering taste of licorice. *Acacia Syrup* is valuable in disguising the taste of urea. Fruit syrups are especially effective for masking sour tastes. *Aromatic Eriodictyon Syrup* is the diluting agent of choice for masking the bitter taste of alkaloids. *Cocoa Syrup* and *Cherry Syrup* are good general flavoring agents.

Acacia Syrup

Acacia, granular or powdered	100 g
Sodium Benzoate	1 g
Vanilla Tincture	5 mL
Sucrose	800 g
Purified Water, a sufficient quantity,	
To make	1000 mL

Mix the acacia, sodium benzoate and sucrose; then add 425 mL of purified water, and mix well. Heat the mixture on a steam bath until solution is completed. When cool, remove the scum, add the vanilla tincture and sufficient purified water to make the product measure 1000 mL, and strain, if necessary.

Uses—A *flavored vehicle* and *demulcent*.

Cherry Syrup

Syrupus Cerasi

Cherry Juice	475 mL
Sucrose	800 g
Alcohol	20 mL
Purified Water, a sufficient quantity,	
To make	1000 mL

Dissolve the sucrose in cherry juice by heating on a steam bath, cool and remove the foam and floating solids. Add the alcohol and sufficient purified water to make 1000 mL, and mix.

Alcohol Content—1 to 2%.

Uses—A pleasantly *flavored vehicle* which is particularly useful in masking the taste of saline and sour drugs.

Cocoa Syrup

Cacao Syrup; Chocolate-flavored Syrup; Chocolate Syrup

Cocoa	180 g
Sucrose	600 g
Liquid Glucose	180 g
Glycerin	50 mL
Sodium Chloride	2 g
Vanillin	0.2 g
Sodium Benzoate	1 g
Purified Water, a sufficient quantity,	
To make	1000 mL

Mix the sucrose and the cocoa, and to this mixture gradually add a solution of the liquid glucose, glycerin, sodium chloride, vanillin and sodium benzoate in 325 mL of hot purified water. Bring the entire mixture to a boil, and maintain at boiling temperature for 3 min. Allow to cool to room temperature and add sufficient purified water to make the product measure 1000 mL.

Note—Cocoa containing not more than 12% nonvolatile, ether-soluble extractive ("fat") yields a syrup having a minimum tendency to separate. "Breakfast cocoa" contains over 22% "fat."

Uses—A pleasantly *flavored vehicle*.

Aromatic Eriodictyon Syrup

Aromatic Yerba Santa Syrup; Syrupus Corrigens

Eriodictyon Fluidextract	32 mL
Potassium Hydroxide Solution (1 in 20)	25 mL
Compound Cardamom Tincture	65 mL
Lemon Oil	0.5 mL
Clove Oil	1 mL
Alcohol	32 mL
Sucrose	800 g
Magnesium Carbonate	5 g
Purified Water, a sufficient quantity,	
To make	1000 mL

Dissolve the oils in the alcohol, add the fluidextract and the tincture, then the potassium hydroxide solution and 325 mL of purified water. Add the magnesium carbonate, shake the mixture, allow it to stand overnight, filter and add sufficient purified water through the filter to make the liquid measure 500 mL. Pour this filtrate upon the sucrose contained in a bottle, dissolve by placing the bottle in hot water and agitating the contents frequently. Cool the solution and add sufficient purified water to make the product measure 1000 mL.

Alcohol Content—6 to 8%.

Incompatibilities—Alkaline in reaction due to the potassium hydroxide used in its manufacture. *Acids* are neutralized with usually a

concurrent precipitation of the resins of the syrup. The tannin which it contains introduces the incompatibilities of that substance.

Uses—A pleasantly *flavored vehicle*, especially adapted to the administration of bitter substances like quinine.

Syrup

Simple Syrup

Sucrose	850 g
Purified Water, a sufficient quantity,	
To make	1000 mL

May be prepared by using boiling water or, preferably, without heat, by the following process:

Place the sucrose in a suitable percolator the neck of which is nearly filled with loosely packed cotton moistened, after packing, with a few drops of water. Pour carefully about 400 mL of purified water upon the sucrose, and regulate the outflow to a steady drip of percolate. Return the percolate, if necessary, until all of the sucrose has dissolved. Then wash the inside of the percolator and the cotton with sufficient purified water to bring the volume of the percolate to 1000 mL, and mix.

Specific Gravity—Not less than 1.30.

Uses—A *sweet vehicle*, sweetening agent and as the basis for many flavored and medicated syrups.

Other Syrups Used As Diluting Agents

Citric Acid Syrup USP XVIII [Syrup of Lemon]—*Preparation:* Dissolve citric acid (hydrous, 10 g) in purified water (10 mL), and mix the solution with syrup (950 mL). Add lemon tincture (10 mL), and enough syrup to make the product measure 1000 mL, and mix. *Note: Do not dispense it if it has a terebinthine odor or taste or shows other indications of deterioration. Alcohol Content:* Less than 1%. *Incompatibilities:* Reactions characteristic of the acid which it contains; hence, it is not a suitable vehicle for alkaline ingredients such as phenobarbital sodium from which it precipitates phenobarbital. *Uses:* Solely as a *pleasant vehicle*, the formula making it possible to prepare extemporaneously and quickly a syrup having the flavor of lemon.

Glycyrrhiza Syrup USP XVIII [Licorice Syrup]—*Preparation:* Add fennel oil (0.05 mL) and anise oil (0.5 mL) to glycyrrhiza fluidextract (250 mL) and agitate until mixed. Then add syrup (qs) to make the product measure 1000 mL, and mix. *Alcohol Content:* 5 to 6%. *Incompatibilities:* The characteristic flavor is destroyed by acids due to a precipitation of the glycyrrhizin. *Uses:* A *flavored vehicle*, especially adapted to the administration of bitter or nauseous substances.

Hydriodic Acid Syrup—Contains, in each 100 mL 1.3 to 1.5 g HI (127.91). *Preparation:* Mix diluted hydriodic acid (140 mL) with purified water (550 mL), and dissolve dextrose (450 g) in this mixture by agitation. Add purified water (qs) to make the product measure 1000 mL, and filter. *Caution: It must not be dispensed if it contains free iodine, as evidenced by a red coloration. Description:* Transparent, colorless, or not more than pale straw-colored, syrupy liquid; odorless and has a sweet, acidulous taste; specific gravity about 1.18; hydriodic acid is decomposed easily in simple aqueous solution (unless protected by hypophosphorous acid) free iodine being liberated, and if taken internally, when in this condition, it is irritating to the alimentary tract. The dextrose used in this syrup should be of the highest grade obtainable. *Incompatibilities:* The reactions of the *acids* (page 1523) as well as those of the water-soluble iodide salts. Oxidizing agents liberate iodine; alkaloids may be precipitated. *Uses:* Traditionally as a *vehicle for expectorant* drugs. Its therapeutic properties are those of the iodides. *Dose: Usual*, 5 mL.

Raspberry Syrup USP XVIII—*Preparation:* Dissolve sucrose (800 g) in raspberry juice (475 mL) by heating on a steam bath, cool and remove the foam and floating solids. Add alcohol (20 mL) and purified water (qs) to make 1000 mL, and mix. *Alcohol Content:* 1 to 2%. *Incompatibilities:* Raspberry juice is prepared to contain not less than 1.6% citric acid; the syrup, therefore, has reactions characteristic of this acid, notably its incompatibility with alkaline substances. *Uses:* A pleasantly *flavored vehicle* used to disguise the salty or sour taste of saline medicaments.

Wild Cherry Syrup USP XVIII—*Preparation:* Pack wild cherry (in coarse powder, 150 g), previously moistened with water (100 mL), in a cylindrical percolator, and add water (qs) to leave a layer of it above the powder. Macerate for 1 hr, then proceed with rapid percolation, using added water, until 400 mL of percolate is collected. Filter the percolate, if necessary, add sucrose (675 g) and dissolve it by agitation, then add glycerin (150 mL), alcohol (20 mL) and water (qs) to make the product measure 1000 mL. Strain if necessary. *It may be made also in the following manner:* The sucrose may be dissolved by placing it in a second percolator as directed for preparing *Syrup*, and allowing the percolate from the wild cherry to flow through it and into a graduated vessel containing the glycerin and alcohol until the total volume measures 1000 mL. *Note:* Heat is avoided, lest the enzyme emulsin be inactivated. If this should happen, the preparation would contain no free HCN, upon which its action as a sedative for coughs mainly depends. For a discussion of the chemistry involved, see *Wild Cherry* (page 1300). *Alcohol Content:* 1 to 2%. *Uses:* Chiefly as a *flavored vehicle* for cough syrups.

Mucilages Used as Diluting Agents

Mucilages are also suitable as diluting agents for water-soluble substances, and are especially useful in stabilizing suspensions and emulsions.

The following mucilage used for this purpose is described under *Emulsifying and Suspending Agents*, page 1304.

Acacia Mucilage—page 1304.

Hydroalcoholic Diluting Agents

Hydroalcoholic diluting agents are suitable for drugs soluble in either water or diluted alcohol. The most important agents in this group are the elixirs. These solutions contain approximately 25% alcohol. *Medicated* elixirs which have therapeutic activity in their own right are not included in this section. Listed below are the common, nonmedicated elixirs which are used purely as diluting agents or solvents for drugs.

Aromatic Elixir

Simple Elixir

Orange Oil	2.4 mL
Lemon Oil	0.6 mL
Coriander Oil	0.24 mL
Anise Oil	0.06 mL
Syrup	375 mL
Talc	30 g
Alcohol,	
Purified Water, each, a sufficient quantity,	
To make	1000 mL

Dissolve the oils in alcohol to make 200 mL. To this solution add the syrup in several portions, agitating vigorously after each addition, and afterwards add, in the same manner, the required quantity of purified water. Mix the talc with the liquid, and filter through a filter wetted with diluted alcohol, returning the filtrate until a clear liquid is obtained.

Alcohol Content—21 to 23%.

Uses—A pleasantly *flavored vehicle*, employed in the preparation of many other elixirs. The chief objection to its extensive use is the high alcohol content (about 22%) which at times may counteract the effect of other medicines.

Cardamom Spirit, Compound—RPS-15, page 1236.

Other Hydroalcoholic Diluting Agents

Glycyrrhiza Elixir [Elixir Adjuvans; Licorice Elixir]—*Preparation:* Mix glycyrrhiza fluidextract (125 mL) and aromatic elixir (875 mL) and filter. *Alcohol Content:* 24 to 25%. *Uses:* A *flavored vehicle.*

Flavored Alcoholic Solutions

Flavored alcoholic solutions, of high alcoholic concentration, are useful as flavors to be added in small quantities to syrups or elixirs. The alcohol content of these solutions is approximately 50%. There are two types of flavored alcoholic solutions: tinctures and spirits. Only nonmedicated tinctures and spirits are used as flavoring agents.

Compound Cardamom Tincture

Cardamom Seed, in moderately coarse powder	20 g
Cinnamon, in fine powder	25 g
Caraway, in moderately coarse powder	12 g
To make	1000 mL

Prepare a tincture by Process M (page 1543), macerating the mixed powders in 750 mL of a mixture of 50 mL of glycerin and 950 mL of diluted alcohol and completing the preparation by using first the remainder of the mixture of alcohol and glycerin prepared as directed above, and then diluted alcohol.

Note—Compound cardamom tincture may be colored with one or more colors (page 1288).

Alcohol Content—43 to 47%.

Uses—A useful vehicle because of its pleasant *flavor* and color.

Lemon Tincture—page 1300.

Myrcia Spirit, Compound—RPS-13, page 452.

Orange Spirit, Compound—page 1296.

Orange Peel, Sweet, Tincture—page 1296.

Peppermint Spirit—page 798.

Diluting Agents for Injections

Injections are liquid preparations, usually solutions or suspensions of drugs, intended to be injected through the skin into the body. Diluting agents used for these preparations may be aqueous or nonaqueous and must meet the requirements for sterility and also of the pyrogen test. Aqueous diluting agents include such preparations as *Sterile Water for Injection* and various sterile, aqueous solutions of electrolytes and/or dextrose. Nonaqueous diluting agents are generally fatty oils of vegetable origin, fatty esters and polyols such as propylene glycol and polyethylene glycol. These agents are used to dissolve or dilute oil-soluble substances and to suspend water-soluble substances when it is desired to decrease the rate of absorption and, hence, prolong the duration of action of the drug substances. Preparations of this type are given intramuscularly. See *Parenteral Preparations*, page 1545.

Corn Oil

Maize Oil

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

Preparation—Expressed from the Indian corn embryos or germs separated from the grain in starch manufacture.

Description—Clear, light yellow, oily liquid with a faint characteristic odor and taste; specific gravity 0.914 to 0.921.

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

Uses—Main official use is as a *solvent* and *vehicle for injections*. It is used as an edible oil substitute for solid fats in the management of hypercholesterolemia. Other uses include making soaps and for burning. It is a semidrying oil and therefore unsuitable for lubricating or mixing paint.

Cottonseed Oil

Cotton Seed Oil; Cotton Oil

The refined fixed oil obtained from the seed of cultivated plants of various varieties of *Gossypium hirsutum* Linné or of other species of *Gossypium* (Fam *Malvaceae*).

Preparation—Cotton seeds contain about 15% oil. The testae of the seeds are first separated, and the kernels are subjected to high pressure in hydraulic presses. The crude oil thus has a bright red to blackish red color. It requires purification before it is suitable for medicinal or food purposes.

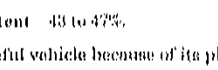
Description—Pale yellow, oily liquid with a bland taste; odorless or nearly so; particles of solid fat may separate below 10°; solidifies at about 0° to −5°; specific gravity 0.915 to 0.921.

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

Uses—Official as a *solvent* and *vehicle for injections*. It is sometimes taken orally as a mild cathartic in the dose of 30 mL or more. Taken internally, digestible oils retard gastric secretion and motility and increase the caloric intake. It also is used in the manufacture of soaps, oleomargarine, lard substitutes, glycerin, lubricants and cosmetics.

Ethyl Oleate

(*Z*)-9-Octadecenoic acid, ethyl ester



Ethyl oleate [111-62-6] $C_{20}H_{38}O_2$ (310.52).

Preparation—Among other ways, by reacting ethanol with oleoyl chloride in the presence of a suitable dehydrochlorinating agent.

Description—Mobile, practically colorless liquid, having an agreeable taste; specific gravity 0.868 to 0.874; acid value not greater than 0.5; iodine value 75 to 85; sterilized by heating at 150° for 1 hr; properties similar to those of almond and arachis oils, but is less viscous and more rapidly absorbed by the tissues; boils about 207°.

Solubility—Does not dissolve in water; miscible with vegetable oils, mineral oil, alcohol or most organic solvents.

Uses—A *vehicle* for certain intramuscular injectable preparations.

Peanut Oil

Arachis Oil; Groundnut Oil; Nut Oil; Earth-Nut Oil

The refined fixed oil obtained from the seed kernels of one or more of the cultivated varieties of *Arachis hypogaea* Linné (Fam *Leguminosae*).

Description—Colorless or pale yellow, oily liquid, with a characteristic nutty odor and a bland taste; specific gravity 0.912 to 0.920.

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

Uses—A *solvent* in preparing oil solutions for injection (page 1549). It also is used for making liniments, ointments, plasters and soaps, as a substitute for olive oil.

Sesame Oil

Teel Oil; Benne Oil; Gingili Oil

The refined fixed oil obtained from the seed of one or more cultivated varieties of *Sesamum indicum* Linné (Fam *Pedaliaceae*).

Description—Pale yellow, almost odorless, oily liquid with a bland taste; specific gravity 0.916 to 0.921.

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

Uses—A *solvent* and *vehicle* in official injections. It is used much like olive oil both medicinally and for food. It does not readily turn rancid. It also is used in the manufacture of cosmetics, iodized oil, liniments, ointments and oleomargarine.

Water for Injection

Water purified by distillation or by reverse osmosis. It contains no added substance.

Caution—It is intended for use as a solvent for the preparation of parenteral solutions. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render it sterile and thereafter protect it from microbial contamination.

Description—Clear, colorless, odorless liquid.

Uses—*Pharmaceutic aid* (vehicle and solvent).

Bacteriostatic Water for Injection

Sterile water for injection containing one or more suitable antimicrobial agents.

Note—Use it with due regard for the compatibility of the antimicrobial agent or agents it contains with the particular medicinal substance that is to be dissolved or diluted.

Uses—*Sterile vehicle* for parenteral preparations.

Sterile Water for Injection

Water for Parenterals

Water for injection sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Description—Clear, colorless, odorless, liquid.

Uses—For the preparation of *all aqueous parenteral solutions*, including those used in *animal assays*. See page 1547 for a detailed discussion.

Sterile Water for Irrigation

Water for injection that has been sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Description—Clear, colorless, odorless liquid.

Uses—An *irrigating solution*.

Emulsifying and Suspending Agents

An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid that is immiscible with the first liquid. Emulsions are formed and stabilized with the help of emulsifying agents, which are surfactants and/or viscosity-producing agents. A suspension is defined as a preparation containing finely divided insoluble material suspended in a liquid medium. The presence of a suspending agent is required to overcome agglomeration of the dispersed particles and to increase the viscosity of the medium so that the particles settle more slowly. Emulsifying and suspending agents are used extensively in the formulation of elegant pharmaceutical preparations for oral, parenteral and external use. For the theoretical and practical aspects of emulsions the interested reader is referred to pages 300 and 1605. More detailed information on the use of suspending agents is given on page 1538.

Acacia

Gum Arabic

The dried gummy exudate from the stems and branches of *Acacia senegal* (Linné) Willdenow or of other related African species of *Acacia* (Fam *Leguminosae*).

Constituents—Principally calcium, magnesium and potassium salts of the polysaccharide *arabic acid*, which on acid hydrolysis yields L-arabinose, L-rhamnose, D-galactose and an aldobionic acid containing D-glucuronic acid and D-galactose.

Description—*Acacia:* Spheroidal tears up to 32 mm in diameter or angular fragments of white to yellowish white color; translucent or somewhat opaque; very brittle; almost odorless; produces a mucilaginous sensation on the tongue. *Flake Acacia:* White to yellowish white, thin flakes. *Powdered Acacia:* White to yellowish white, angular microscopic fragments. *Granular Acacia:* White to pale yellowish white, fine granules. *Spray-dried Acacia:* White to off-white compacted microscopic fragments or whole spheres.

Solubility—Insoluble in alcohol, but almost completely soluble in twice its weight of water at room temperature; the resulting solution flows readily and is acid to litmus.

Incompatibilities—*Alcohol or alcoholic solutions* precipitate acacia as a stringy mass when the alcohol amounts to more than about 35% of the total volume. Solution is effected by dilution with water. The mucilage is destroyed through precipitation of the acacia by *heavy metals*. *Borax* also causes a precipitation which is prevented by glycerin. It contains calcium and, therefore, possesses the incompatibilities of this ion.

It contains a *peroxidase* which acts as an oxidizing agent and produces colored derivatives of *aminopyrine, antipyrine, cresol, guaiacol, phenol, tannin, thymol, vanillin* and other substances. Among the alkaloids affected are *atropine, apomorphine, cocaine, homatropine, hyoscyamine, morphine, physostigmine* and *scopolamine*. A partial destruction of the alkaloid occurs in the reaction. Heating the solution of acacia for a few minutes at 100° destroys the peroxidase and the color reactions are avoided.

Uses—Extensively as a *suspending agent* for insoluble substances in water (page 1538), in the preparation of emulsions (pages 298 and 1534) and for making pills and troches (page 1664).

It is used for its *demulcent* action in inflammations of the throat or stomach.

Its solutions should not be used as a substitute for serum protein in the treatment of *shock* and as a *diuretic* in hypoproteinemic edema, since it produces serious syndromes that may result in death.

Acacia Mucilage [Mucilage of Gum Arabic]. *Preparation:* Place acacia (in small fragments, 350 g) in a graduated bottle having a wide mouth and a capacity not greatly exceeding 1000 mL, wash the drug with cold purified water, allow it to drain and add enough warm purified water, in which benzoic acid (2 g) has been dissolved, to make the product measure 1000 mL. After stoppering, lay the bottle on its side, rotate it occasionally, and when the acacia has dissolved strain the mucilage. *It also may be prepared as follows:* dissolve benzoic acid (2 g) in purified water (400 mL) with the aid of heat, and add the solution to powdered or granular acacia (350 g), in a mortar, triturating until the acacia is dissolved. Then add sufficient purified water to make the product measure 1000 mL, and strain if necessary. This second method is primarily for extemporaneous preparation. *Uses:* A *demulcent* and a *suspending agent*. It also has been employed as an *excipient* in making pills and troches, and as an *emulsifying agent* for cod liver oil and other substances. *Caution—It must be free from mold or any other indication of decomposition.*

Agar

Agar-Agar; Vegetable Gelatin; Gelose; Chinese or Japanese Gelatin

The dried, hydrophilic, colloidal substance extracted from *Gelidium cartilagineum* (Linné) Gaillon (Fam *Gelidiaceae*), *Gracilaria confervoides* (Linné) Greville (Fam *Sphaerococcaceae*) and related red algae (Class *Rhodophyceae*).

Constituents—Chiefly of the calcium salt of a galactan mono-(acid sulfate).

Description—Usually in bundles of thin, membranous, agglutinated strips or in cut, flaked, or granulated forms; may be weak yellowish orange, yellowish gray to pale yellow or colorless; tough when damp, brittle when dry; odorless or with a slight odor; produces a mucilaginous sensation on the tongue. Also supplied as a white to yellowish white or pale-yellow powder.

Solubility—Insoluble in cold water; soluble in boiling water.

Incompatibilities—Like other gums, it is dehydrated and precipitated from solution by *alcohol*. *Tannic acid* causes precipitation; *electrolytes* cause partial dehydration and decrease in viscosity of sols.

Uses—A relatively ineffective bulk-producing laxative used in a variety of proprietary cathartics. In mineral oil emulsions it acts as a stabilizer. The usual dose is 4 to 16 g once or twice a day.

It also is used in culture media for bacteriological work and in the manufacture of ice cream, confectionaries, etc.

Alginic Acid

Alginic acid [9005-32-7] (average equivalent weight 200); a hydrophilic colloidal carbohydrate extracted with dilute alkali from various species of brown seaweeds (*Phaeophyceae*).

Preparation—Precipitates when an aqueous solution of *Sodium Alginate* is treated with mineral acid.

Description—White to yellowish white, fibrous powder; odorless or practically odorless, and tasteless; pH (3 in 100 dispersion in water) 1.5 to 3.5; pK_a (0.1*N* NaCl, 20°) 3.42.

Solubility—Insoluble in water or organic solvents; soluble in alkaline solutions.

Uses—A *pharmaceutic aid* (tablet binder and emulsifying agent). It is used as a sizing agent in the paper and textile industries.

Sodium Alginate

Alginic acid, sodium salt; Algin; Manucol; Norgine; Kelgin (*Kelco*)

Sodium alginate [9005-38-3] (average equivalent weight 220); the purified carbohydrate product extracted from brown seaweeds by the use of dilute alkali. It consists chiefly of the sodium salt of alginic acid, a polyuronic acid composed of beta-D-mannuronic acid residues linked so that the carboxyl group of each unit is free while the aldehyde group is shielded by a glycosidic linkage.

Description—Nearly odorless and tasteless, coarse or fine powder, yellowish white in color.

Solubility—Dissolves in water, forming a viscous, colloidal solution; insoluble in alcohol or in hydroalcoholic solutions in which the alcohol content is greater than about 30% by weight; insoluble in chloroform, ether or acids, when the pH of the solution becomes lower than about 3.

Uses—A *thickening* and *emulsifying agent*. This property makes it useful in a variety of areas. For example, it is used to impart smoothness and body to ice cream and to prevent formation of ice particles.

Bentonite

Wilkinite; Soap Clay; Mineral Soap

Bentonite [1302-78-9]; a native, colloidal, hydrated aluminum silicate.

Occurrence—Bentonite is found in the Midwest of the US and Canada. Originally called *Taylorite* after its discoverer in Wyoming, its name was changed to bentonite after its discovery in the Fort Benton formation of the Upper Cretaceous of Wyoming.

Description—Very fine, odorless powder with a slightly earthy taste, free from grit; the powder is nearly white, but may be a pale buff or cream-colored.

The US Geological Survey has defined bentonite as "a transported stratified clay formed by the alteration of volcanic ash shortly after deposition." Chemically, it is $Al_2O_3.4SiO_2.H_2O$ plus other minerals as impurities. It consists of colloidal crystalline plates, of less than microscopic dimensions in thickness, and of colloidal dimensions in breadth. This fact accounts for the extreme swelling that occurs when it is placed in water, since the water penetrates between an infinite number of plates. A good specimen swells 12 to 14 times its volume.

Solubility—Insoluble in water or acids, but it has the property of absorbing large quantities of water, swelling to approximately 12 times its original volume, and forming highly viscous thixotropic suspensions or *gels*. This property makes it highly useful in pharmacy. Its gel-forming property is augmented by the addition of small amounts of alkaline substances, such as magnesium oxide. It does not swell in organic solvents.

Incompatibilities—*Acids* and *acid salts* decrease its water-absorbing power and thus cause a breakdown of the magma. Suspensions are most stable at a pH above 7.

Uses—A *protective colloid* for the *stabilization of suspensions*. It also has been used as an emulsifier for oil and as a base for plasters, ointments and similar preparations.

Bentonite Magma—*Preparation:* Sprinkle bentonite (50 g), in portions, on hot purified water (800 g), allowing each portion to become thoroughly wetted without stirring. Allow it to stand with occasional stirring for 24 hr. Stir until a uniform magma is obtained, add purified water to make 1000 g, and mix. The magma may be prepared also by mechanical means such as by use of a blender, as follows: Place purified water (about 500 g) in the blender, and while the machine is running, add bentonite (50 g). Add purified water to make up to about 1000 g or up to the operating capacity of the blender. Blend the mixture for 5 to 10 min, add purified water to make 1000 g, and mix. *Uses:* A *suspending agent* for insoluble medicaments.

Carbomer

Carboxypolymethylene

A synthetic high-molecular-weight cross-linked polymer of acrylic acid; contains 56 to 68% of carboxylic acid (—COOH) groups. The viscosity of a neutralized preparation (2.5 g/500 mL water) is 30,000 to 40,000 centipoises.

Description—White, fluffy powder with a slight characteristic odor; hygroscopic; pH (1 in 100 dispersion) about 3; specific gravity about 1.41.

Solubility (neutralized with alkali hydroxides or amines)—Dissolves in water, alcohol and glycerin.

Uses—A *thickening, suspending, dispersing* and *emulsifying agent* for pharmaceuticals, cosmetics, waxes, paints and other industrial products.

Carrageenan

Carrageenan [9000-07-1].

Preparation—The hydrocolloid extracted with water or aqueous alkali from certain red seaweeds of the class *Rhodophyceae*, and separated from the solution by precipitation with alcohol (methanol, ethanol or isopropanol) or by drum-roll drying or freezing.

Constituents—It is a variable mixture of potassium, sodium, calcium, magnesium and ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers, the hexoses being alternately linked α-1,3 and β-1,4 in the polymer. The three main types of copolymers present are *kappa-carrageenan*, *iota-carrageenan* and *lambda-carrageenan*, which differ in the composition and manner of linkage of monomeric units and the degree of sulfation (the ester sulfate content for carrageenans varies from 18 to 40%). *Kappa-carrageenan* and *iota-carrageenan* are the gelling fractions; *lambda-carrageenan* is the nongelling fraction. The gelling fractions may be separated from the nongelling fraction by addition of potassium chloride to an aqueous solution of carrageenan. Carrageenan separated by drum-roll drying may contain mono- and diglycerides or up to 5% of polysorbate 80 used as roll-stripping agents.

Description—Yellow-brown to white, coarse to fine powder; odorless; tasteless, producing a mucilaginous sensation on the tongue.

Solubility—All carrageenans hydrate rapidly in cold water, but only *lambda-carrageenan* and sodium carrageenans dissolve completely. Gelling carrageenans require heating to about 80° for complete solution where potassium and calcium ions are present.

Uses—In the pharmaceutical and food industries as an emulsifying, suspending and gelling agent.

Carboxymethylcellulose Sodium

Carbose D; Carboxymethocel S; CMC; Cellulose Gum (*Hercules*)

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]; contains 6.5–9.5% of sodium (Na), calculated on the dried basis. It is available in several viscosity types: low, medium, high and extra high.

Description—White to cream-colored powder or granules; the powder is hygroscopic; pH (1 in 100 aqueous solution) about 7.5.

Solubility—Easily dispersed in water to form colloidal solutions; insoluble in alcohol, ether or most other organic solvents.

Uses—*Pharmaceutic aid* (suspending agent, tablet excipient or viscosity-increasing agent). In tablet form it is used as a hydrophilic colloid laxative.

Dose—*Usual, adult, laxative*, 1.5 g 3 or 4 times a day.

Dosage Form: Tablets: 500 mg.

Powdered Cellulose

Cellulose [9004-34-6] $(C_6H_{10}O_5)_n$; purified, mechanically disintegrated cellulose prepared by processing alpha cellulose obtained as a pulp from fibrous plant materials.

Description—White, odorless substance, consisting of fibrous particles, which may be compressed into self-binding tablets which disintegrate rapidly in water; exists in various grades, exhibiting degrees of fineness ranging from a free-flowing dense powder to a coarse, fluffy, nonflowing material; pH (supernatant liquid of a 10 g/90 mL aqueous suspension after 1 hr) 5 to 7.5.

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

Uses—*Pharmaceutic aid* (tablet diluent, adsorbent or suspending agent).

Cetyl Alcohol—page 1312.

Cholesterol

Cholest-5-en-3-ol, (3β)-, Cholesterin

Cholest-5-en-3β-ol [57-88-5] $C_{27}H_{46}O$ (386.66).

For the structural formula, see page 389.

A steroid alcohol widely distributed in the animal organism. In addition to cholesterol and its esters, several closely related steroid alcohols occur in the yolk of eggs, the brain, milk, fish oils, wool fat

(16 to 20%), etc. These closely resemble it in properties. One of the methods of commercial production involves extraction of it from the unsaponifiable matter in the spinal cord of cattle, using petroleum benzin. Wool fat also is used as a source.

Description White or faintly yellow, almost odorless pearly leaflets or granules; usually acquires a yellow to pale tan color on prolonged exposure to light or to elevated temperatures; melts 147 to 150°.

Solubility—Insoluble in water; 1 g slowly dissolves in 100 mL of alcohol or about 50 mL of dehydrated alcohol; soluble in acetone, hot alcohol, chloroform, dioxane, ether, ethyl acetate, solvent hexane or vegetable oils.

Uses—To enhance incorporation and emulsification of medicinal products in oils or fats. It is a *pharmaceutical necessity* for *Hydrophilic Petrolatum*, in which it enhances water-absorbing capacity. See Chapter 19.

Dioctyl Sodium Sulfosuccinate (Docusate Sodium)—page 789.

Gelatin

White Gelatin

A product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissues and bones of animals. Gelatin derived from an acid-treated precursor is known as Type A and exhibits an isoelectric point between pH 7 and 9, while gelatin derived from an alkali-treated precursor is known as Type B and exhibits an isoelectric point between pH 4.7 and 5.2.

Gelatin for use in the manufacture of capsules in which to dispense medicines, or for the coating of tablets, may be colored with a certified color, may contain not more than 0.15% of sulfur dioxide, may contain a suitable concentration of sodium lauryl sulfate and suitable antimicrobial agents, and may have any suitable gel strength that is designated by Bloom Gelometer number.

Regarding the special gelatin for use in the preparation of emulsions, see *Emulsions* (page 1534).

Description—Sheets, flakes or shreds, or a coarse to fine powder; faintly yellow or amber in color, the color varying in depth according to the particle size; slight, characteristic bouillon-like odor; stable in air when dry, but is subject to microbial decomposition when moist or in solution.

Solubility—Insoluble in cold water, but swells and softens when immersed in it, gradually absorbing from 5 to 10 times its own weight of water; soluble in hot water, acetic acid or hot mixtures of glycerin and water; insoluble in alcohol, chloroform, ether or fixed and volatile oils.

Uses—In pharmacy, to coat pills and form capsules, and as a vehicle for suppositories. It also is recommended as an emulsifying agent. See under *Emulsions* in Chapters 19 and 83, also *Suppositories* (page 1609), and *Absorbable Gelatin Sponge* (page 816). It also has been used as an adjuvant protein food in malnutrition.

Glyceryl Monostearate—page 1312.

Hydroxyethyl Cellulose

Cellulose, 2-hydroxyethyl ether; Cellosize (*Union Carbide*); Natrosol (*Hercules*)

Cellulose hydroxyethyl ether [9004-62-0].

Preparation—Cellulose is treated with NaOH and then reacted with ethylene oxide.

Description—White, odorless, tasteless, free-flowing powder; softens at about 137°; refractive index (2% solution) about 1.336; pH about 7; solutions are nonionic.

Solubility—Dissolves readily in cold or hot water to give clear, smooth, viscous solutions; partially soluble in acetic acid; insoluble in most organic solvents.

Uses—Resembles carboxymethylcellulose sodium in that it is a cellulose ether, but differs in being nonionic and, hence, its solutions are unaffected by cations. It is used pharmaceutically as a thickener, protective colloid, binder, stabilizer and suspending agent in emulsions, jellies and ointments, lotions, ophthalmic solutions, suppositories and tablets.

Hydroxypropyl Cellulose

Cellulose, 2-hydroxypropyl ether; Klucel (*Hercules*)

Cellulose hydroxypropyl ether [9004-64-2].

Preparation—After treating with NaOH, cellulose is reacted with propylene oxide at elevated temperature and pressure.

Description—Off-white, odorless, tasteless powder; softens at 130°; burns out completely about 475° in N_2 or O_2; refractive index (2% solution) about 1.337; pH (aqueous solution) 5 to 8.5; solutions are nonionic.

Solubility—Soluble in water below 40° (insoluble above 45°); soluble in many polar organic solvents.

Uses—A broad combination of properties useful in a variety of industries. It is used pharmaceutically as a binder, granulation agent and film-coater in the manufacture of tablets; an alcohol-soluble thickener and suspending agent for elixirs and lotions and a stabilizer for emulsions.

Hydroxypropyl Methylcellulose

Cellulose, 2-hydroxypropyl methyl ether

Cellulose hydroxypropyl methyl ether [9004-65-3], available in grades containing 16.5 to 30.0% of methoxy and 4.0 to 32.0% of hydroxypropoxy groups, and thus in viscosity and thermal gelation temperatures of solutions of specified concentration.

Preparation—The appropriate grade of methylcellulose (see below) is treated with NaOH and reacted with propylene oxide at elevated temperature and pressure and for a reaction time sufficient to produce the desired degree of attachment of methyl and hydroxypropyl groups by ether linkages to the anhydroglucose rings of cellulose.

Description—White to slightly off-white, fibrous or granular, free-flowing powder.

Solubility—Swells in water and produces a clear to opalescent, viscous colloidal mixture; undergoes reversible transformation from sol to gel on heating and cooling, respectively. Insoluble in anhydrous alcohol, ether or chloroform.

Uses—A protective colloid that is useful as a dispersing and thickening agent, and in ophthalmic solutions to provide the demulcent action and viscous properties essential for contact-lens use and in "artificial-tear" formulations. See *Hydroxypropyl Methylcellulose Ophthalmic Solution* (page 760).

Lanolin, Anhydrous—page 1311.

Methylcellulose

Cellulose, methyl ether; Methocel (Dow); Cellothyl (*Warner Chilcott*); Hydrolose (*Upjohn*); Synecelose (*Blue Line*)

Cellulose methyl ether [9004-67-5]; a methyl ether of cellulose containing 27.5 to 31.5% of methoxy groups.

Preparation—By the reaction of methyl chloride or of dimethyl sulfate on cellulose dissolved in sodium hydroxide. The cellulose methyl ether so formed is coagulated by adding methanol or other suitable agent and centrifuged. Since cellulose has 3 hydroxyl groups/glucose residue, several methylcelluloses can be made varying, among other properties, in solubility and viscosity. Types useful for pharmaceutical application contain from 1 to 2 methoxy radicals/glucose residue.

Description—White, fibrous powder or granules; aqueous suspensions neutral to litmus; stable to alkalies and dilute acids.

Solubility—Insoluble in ether, alcohol or chloroform; soluble in glacial acetic acid and in a mixture of equal parts of alcohol and chloroform; swells in water, producing a clear to opalescent, viscous colloidal solution; insoluble in hot water and saturated salt solutions; salts of mineral acids and particularly of polybasic acids, phenols and tannins coagulate its solutions, but this can be prevented by the addition of alcohol or of glycol diacetate.

Uses—A synthetic substitute for natural gums that has both pharmaceutic and therapeutic applications. Pharmaceutically, it is used as a *dispersing, thickening, emulsifying, sizing* and *coating agent*. It is an ingredient of many nose drops, eye preparations, burn medications, cosmetics, tooth pastes, liquid dentifrices, hair fixatives, creams and lotions. It functions as a protective colloid for

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

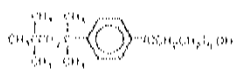
Therapeutically, it is used as a *bulk laxative* in the treatment of *chronic constipation*. Taken with 1 or 2 glasses ful of water, it forms a colloidal solution in the upper alimentary tract; this solution loses water in the colon, forming a gel that increases the bulk and softness of the stool. The 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.

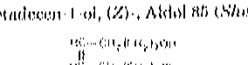
Description—Clear, pale yellow, viscous liquid, having a faint odor and a bitter taste; specific gravity about 1.064; pH (1 in 100 aqueous solution) about 7.

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*)-, Alchol 85 (*Shercx*)



(*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).

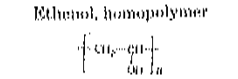
Description—Clear, colorless to light yellow, oily liquid; faint characteristic odor and bland taste; iodine value between 85 and 90; hydroxyl value between 205 and 215.

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.

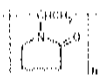
Description—White to cream-colored powder or granules; odorless.

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 (*Procter & 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.

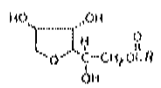
Solubility—1 g in 10 mL water, forming an opalescent solution.

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 145 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* (Linn6) 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.

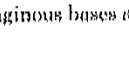
Description—White to off-white, somewhat translucent flakes; crystalline structure and pearly luster when caked; faint odor and a bland, mild taste; free from rancidity; specific gravity 0.820 to 0.840 at 50°; iodine value not more than 1; melts 43 to 47°.

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 0.889 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* [$C_{26}H_{53}O_2$], 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*, *lanoceric*, *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; SHCO] A substance prepared by sulfating hydrogenated castor oil. Pale, yellow-brown, unctuous semisolid mass; faint odor containing about 9% organically bound SO_4. 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 62 (*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% distills 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 66 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.

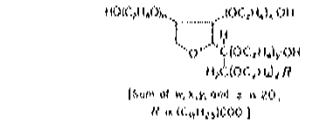
Description—White to light-tan waxy solid; odorless or has a faint fat-like odor; congeals between 37 and 47°.

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 = $(C_{17}H_{33})COO$]

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 1852).

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 *anhidrotic* 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 49.5%, 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 96⅛ gal, a contraction of 3⅞ 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 94.9% 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.

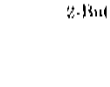
Uses—A menstruum in making tinctures, fluidextracts, extracts, etc. Its properties already have been described fully in connection with the various preparations. Its value consists not only in its *antiseptic* properties, but also in its possessing the *solvent* powers of both water and alcohol. See *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 0.803 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.

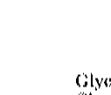
Chloroform—page 1320.

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 [Coconut 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, acetamilid, 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	168 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 1191).

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—You 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 gritti ness.

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 (but 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 4.2% solution; 11%, 65 cps in 4.2% solution.

Powdered Cellulose—page 1305.

Cellulose Acetate Phthalate

Cellulose, acetate, 1,2-benzenedicarboxylate

Cellulose acetate phthalate [9004-38-0]; 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 1925 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°.

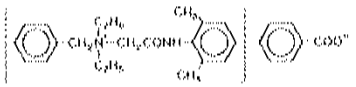
Solubility—Slightly soluble in alcohol; soluble in boiling dehydrated alcohol; freely soluble in ether or chloroform.

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 1609). 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; Leiocum

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; $[\alpha]_D^{25}$ 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 4883 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).

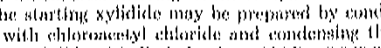
Preparation—By reacting 1,1,2-trichloro-1,2,2-trifluoroethane with antimony trifluorodichloride [SbF_3Cl_2], whereupon one of the 1-chlorine atoms is replaced by fluorine. The starting trichlorofluoroethane may be prepared from hexachloroethane by treatment with SbF_3Cl_2 (Henne AL: *Org Reactions II*: 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 correspond 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 1300.

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 790.

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 50%, 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

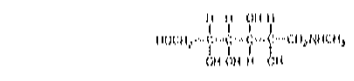
Magnesium stearate [557-04-0]. A compound of magnesium with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. It contains the equivalent of 6.8 to 8.0% of MgO (40.30).

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 1.065; 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 these 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 1.8 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 785).

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 aycosis 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 aestivum* 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 30 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, *styaresin* (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.

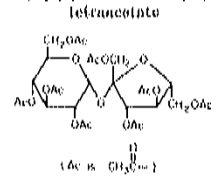
Description—Semiliquid, grayish to grayish brown, sticky, opaque mass, depositing on standing a heavy dark brown layer (Levant storax); or a semisolid, sometimes a solid mass, softened by gently warming (American storax); transparent in thin layers; characteristic odor and taste; more dense than water.

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_3CO—)

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 ($K_2(S_x)$); 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.

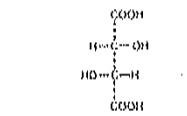
Occurrence and Preparation—The native form, called *soapstone* or *French chalk*, is found in various parts of the world. An excellent quality is obtained from deposits in North Carolina. Deposits of a high grade, conforming to the USP requirements, also are found in Manchuria. The native form usually 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; dextrarotatory.

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.

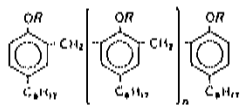
Description—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° is about 796 torr; boils about 24°.

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 $CH_2CH_2O(CH_2CH_2O)_nCH_2CH_2OH$; m is 0 to 6; 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 Enuclene (*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 78°; 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, Ph1 [$H_2NCH_2CH_2NH_2.H_2O$]—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 mercuhumine 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* (0.26 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 HPH_2O_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

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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. artherosclerotic 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, anoroxia, 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 ⅓ 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 exercise 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 resembles 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.

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^2-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.

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CHAPTER 75

Preformulation

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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.

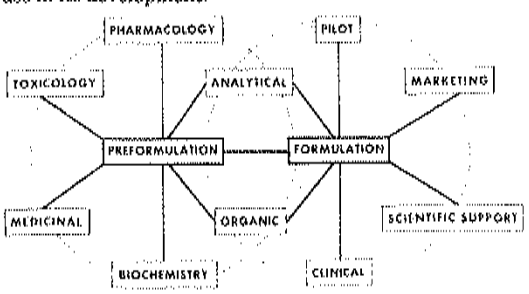


Fig 75-1. The wheels of product development.

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.

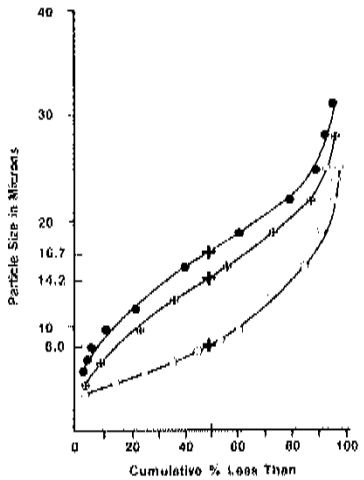


Fig 75-2. Particle size distribution of NBS glass beads (Standard Reference Material No 1003) expressed in terms of ○ = number of particles; ● = weight of particles; ⊗ = surface area of particles.

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

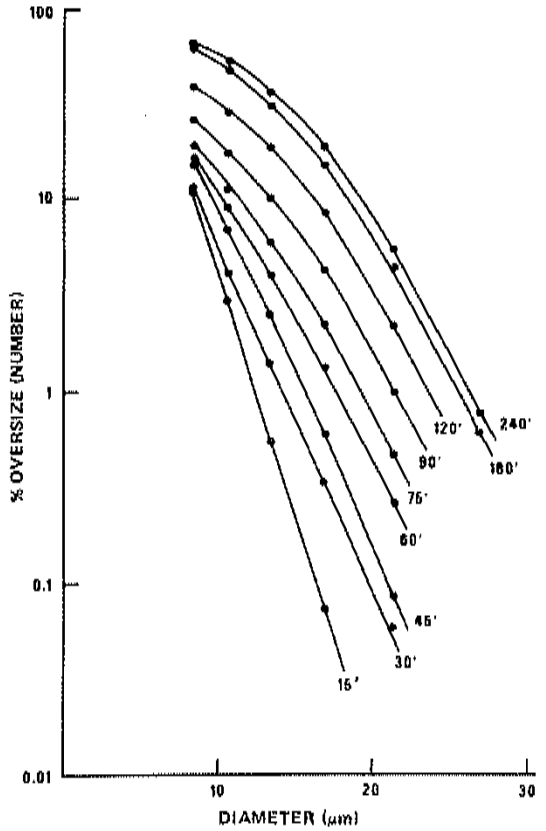


Fig 75-3. Change in particle size with time for an aqueous suspension of Form I of an experimental drug.

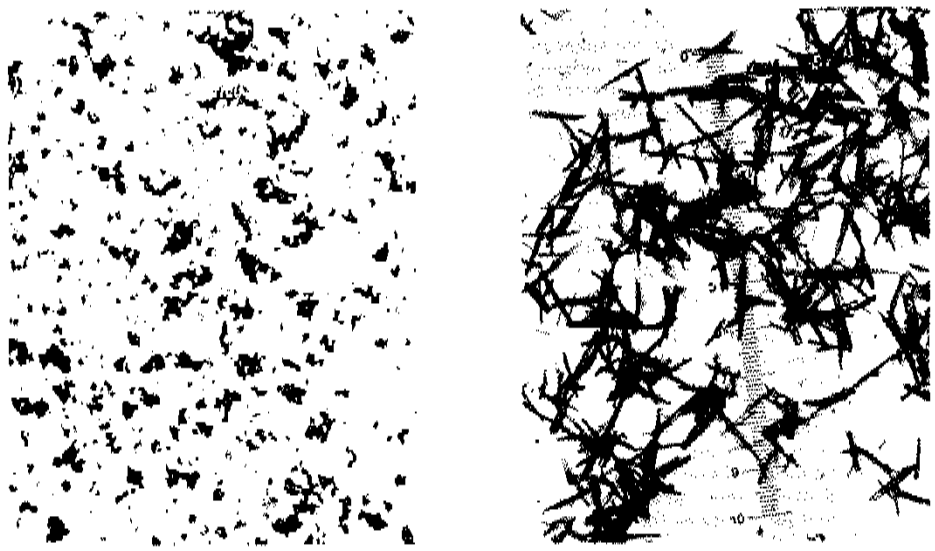
incident onto a receiver lens that forms a diffraction pattern of the scattered light. The scattered light and unscattered light then are gathered on detectors so the total light power is monitored as it allows the sample volume concentration to be determined. Each particle scatters light at a favored 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.

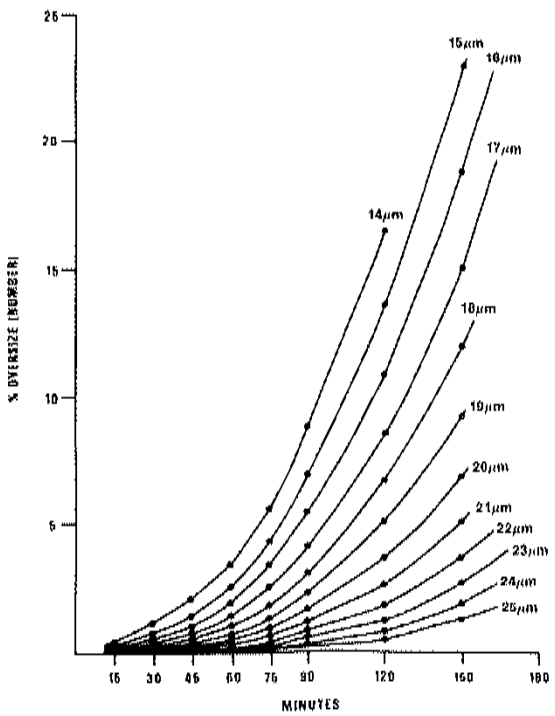


Fig 75-5. Change in cumulative count with time for an aqueous suspension of Form I of an experimental drug.

Polymorphism

A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different

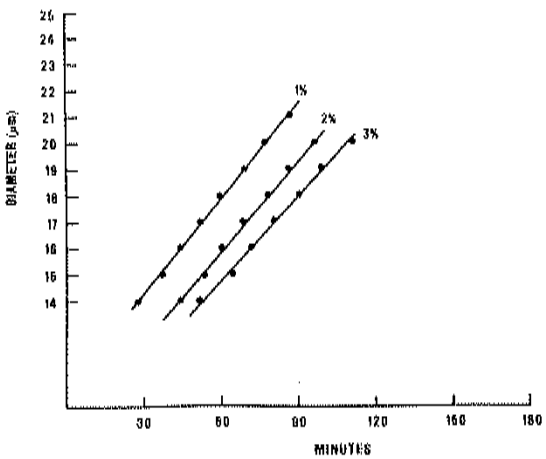


Fig 75-6. Rate of growth of Form I of experimental drug in aqueous suspension.

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:[3]

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

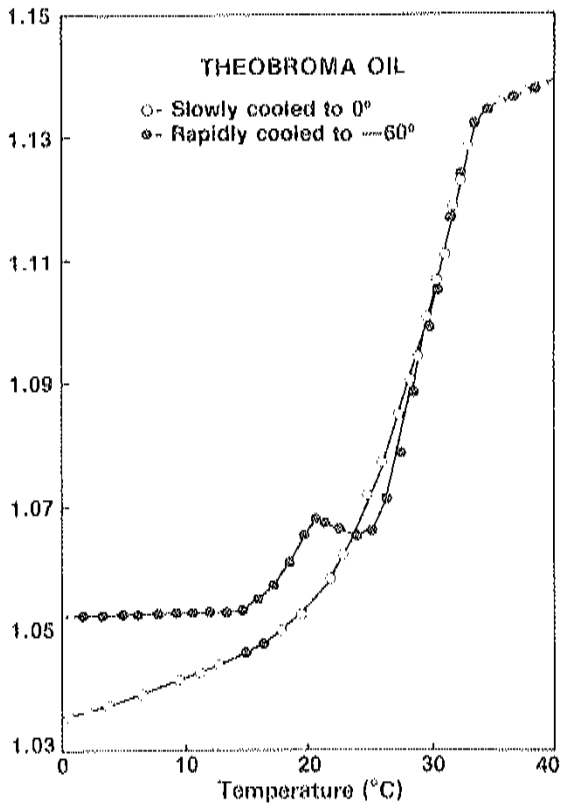


Fig 75-7. Dilatometric curves: theobroma oil, slowly and rapidly cooled.

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

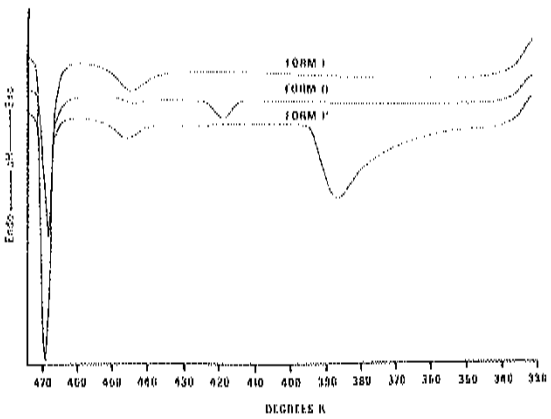


Fig 75-8. Thermograms for Forms I, I' and II of SK&F 30097.

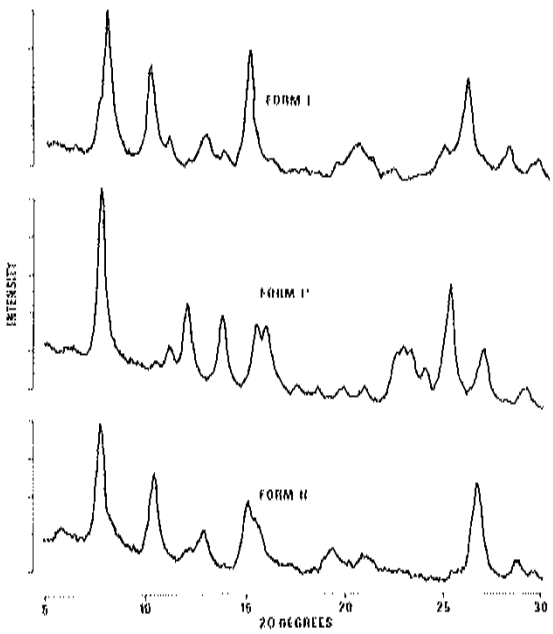


Fig 75-9. X-Ray diffractograms for Forms I, I' and II of SK&F 30097.

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

$$\frac{dc}{dt} = \frac{AD}{Vh}C_s \tag{4}$$

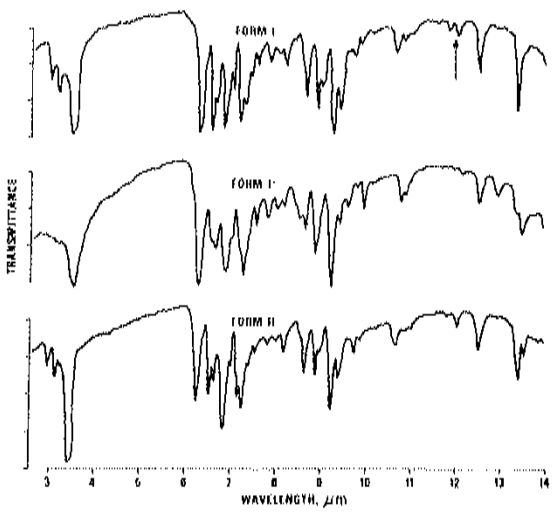


Fig 75-10. Infrared spectra of Forms I, I' and II of SK&F 30097.

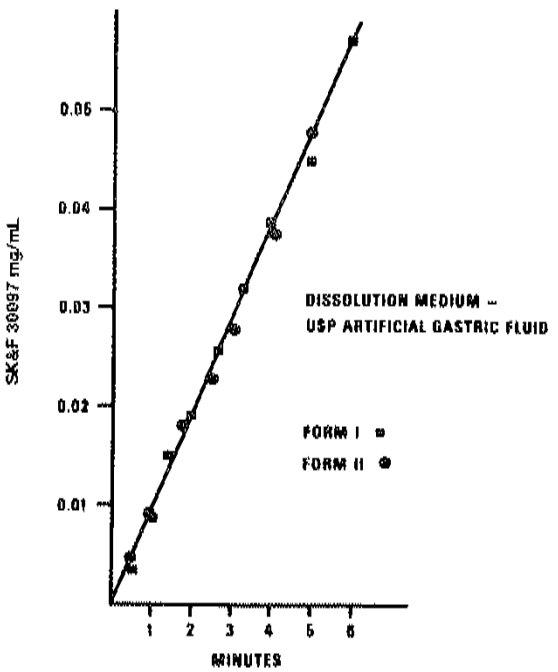


Fig 75-11. Dissolution behavior of Forms I and II of SK&F 30097 in artificial gastric fluid.

for the experimental conditions where $C_s > C_t$. 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-

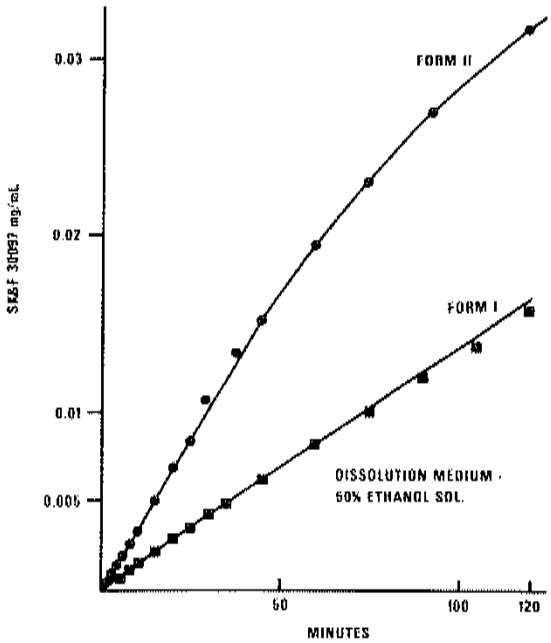


Fig 75-12. Dissolution behavior of Forms I and II of SK&F 30097 in 50% ethanol solution.

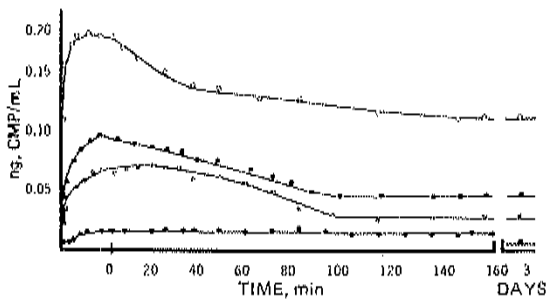


Fig 75-13. Dissolution curves for Polymorph C of chloramphenicol palmitate in 35% *t*-butyl alcohol and water at 30, 20, 15 and 6°. Key: 30°, O—O; 20°, ■—■; 15°, Δ—Δ; 6°, ●···●.

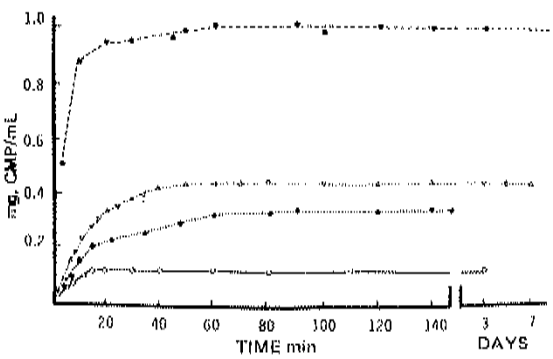


Fig 75-14. Dissolution curves for Polymorphs A and B of chloramphenicol palmitate in 35% *t*-butyl alcohol and water at 30 and 38°. Key: Polymorph A, 30°, O—O; Polymorph B, 30°, Δ. . .Δ; Polymorph A, 38°, ♦- - -♦; Polymorph B, 38° ●- - -●.

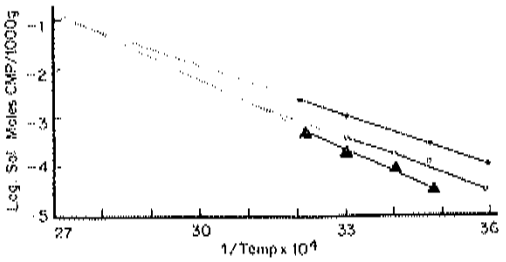


Fig 75-15. The van't Hoff type plot for Polymorphs A, B, and C of chloramphenicol palmitate. Key: Polymorphs A ▲; B ●—●; and C O—O.

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	16.4	−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	*Weak Base*	
$S_t = K_s\left(1 + \frac{K_a}{[H^+]}\right)$	$S_t = K_s\left(1 + \frac{[H^+]}{K_a}\right)$	(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.

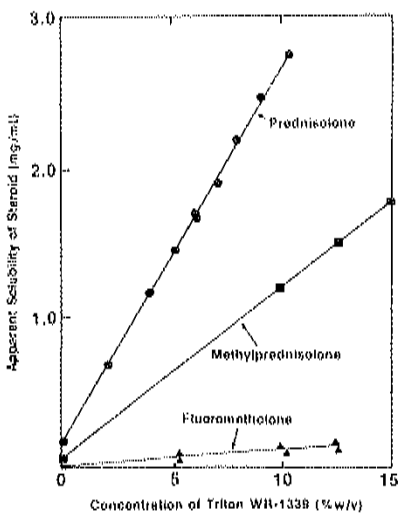


Fig 75-16. The effect of varying concentrations of Triton WR-1339 in water on the solubility of some anti-inflammatory steroids.[7]

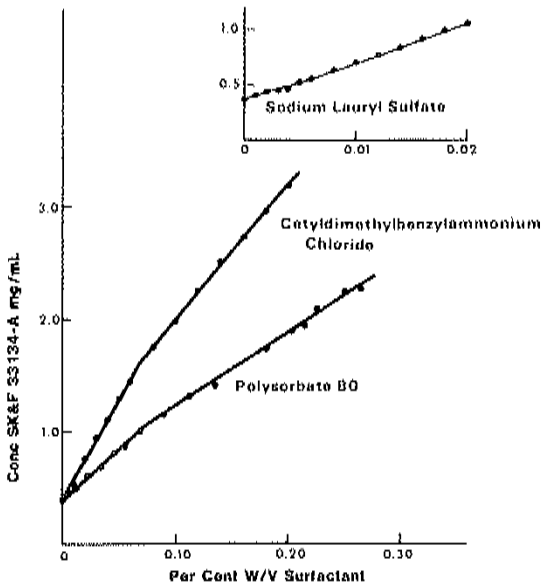


Fig 75-17. Effect of surfactant concentration on the solubility of SK&F 33134-A.

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[f]	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]	0.18	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	0.88
Hydrochloride	42.98	Tartrate	3.64
Hydroxynaphthoate	0.25	Teoclate[i]	0.13
		Triethiodide	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.

Hiestand 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-

danes 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

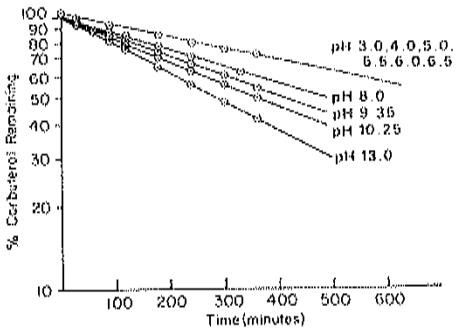


Fig 75-18. Effect of pH on carbuterol degradation at 85° (μ = 0.5).

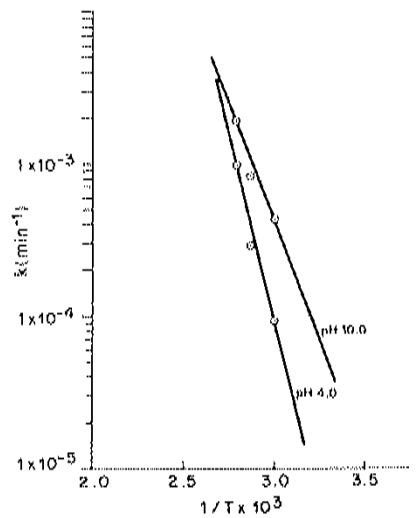


Fig 75-19. Typical Arrhenius-type plot depicting the temperature dependency of carbuterol hydrolysis at pH 4.0 and 10.0.

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

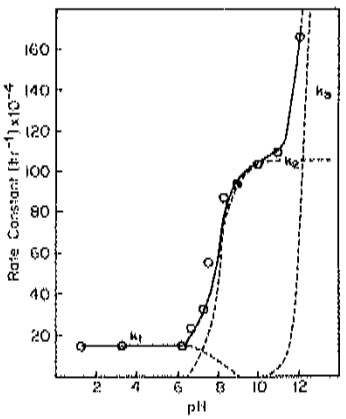


Fig 75-20. Plot showing pH-rate profile for hydrolysis of idoxuridine at 60°. Circles represent experimental results. Solid line corresponds to theoretical pH-rate profile. Broken line designates contribution of k_1, k_2 and k_3 at any pH value.

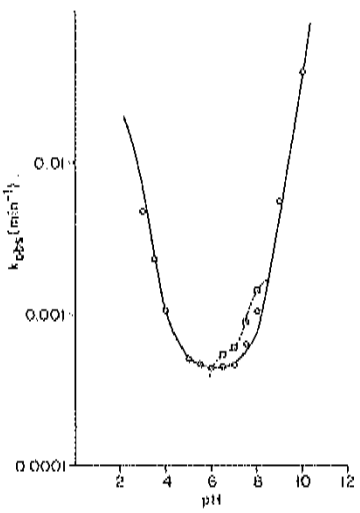


Fig 75-21. pH-Rate profile of cefazolin degradation in aqueous solution at 60° (μ = 0.5). Solid line: theoretical profile; circles: experimental profile; squares: rates uncorrected for buffer effect.

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.

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CHAPTER 76

Bioavailability and Bioequivalency Testing

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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.

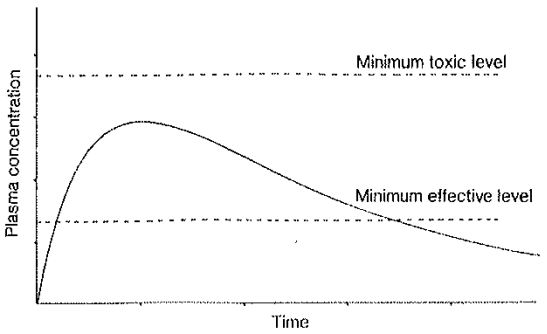

Fig 76-1. Typical plasma-level curve of a drug with effective and toxic (side-effect) levels defined.

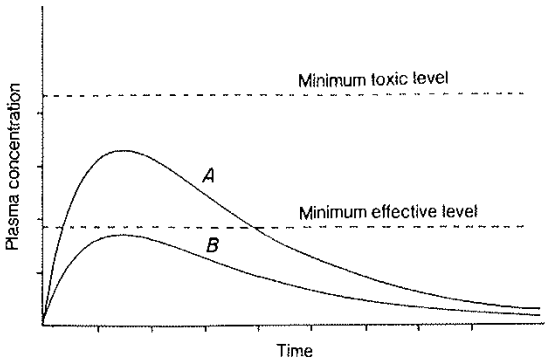

Fig 76-2. Effect of the extent of drug absorption from a dosage form on drug-plasma levels and efficacy. The extent of absorption from Dosage Form *B* is 50% of that from Dosage Form *A*.

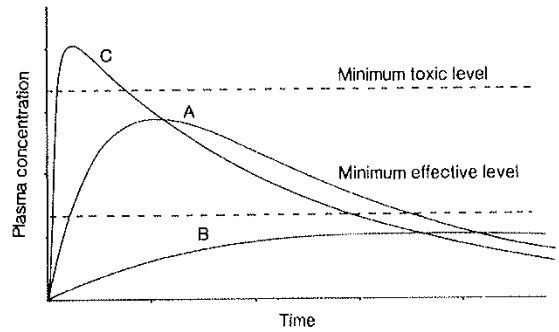

Fig 76-3. Effect of the rate of drug absorption from a dosage form on the plasma-level profile and efficacy. The rates of absorption from Dosage Forms *B* and *C* are 1/10 and 10 times those from Dosage Form *A*.

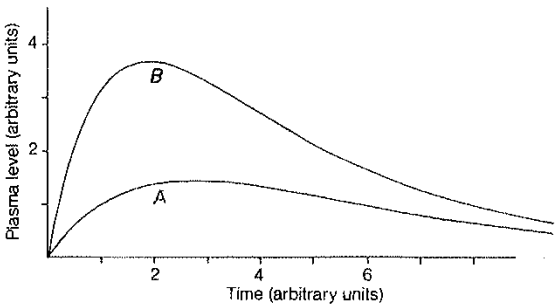

Fig 76-4. Computer simulation of the plasma-level curves for two dosage forms of the same drug assuming that the rate and extent of drug absorption for Dosage Form *A* were 50% and 50%, respectively, of those for Dosage Form *B*.

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.

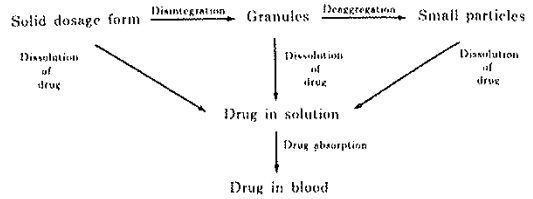

Fig 76-5. Sequence of events involved in the dissolution and absorption of a drug from a solid oral dosage form.

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 multiscore 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-

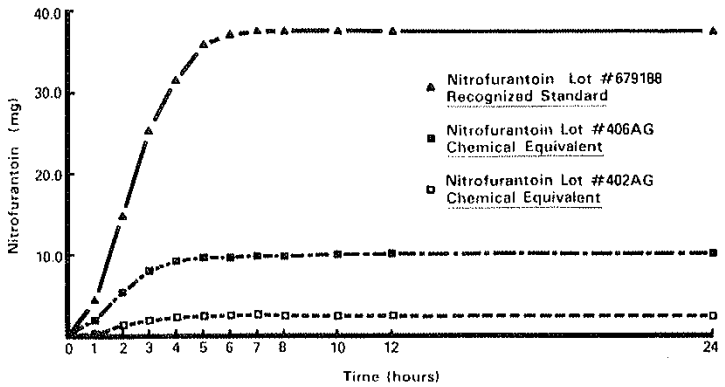

Fig 76-6. Average cumulative amounts of nitrofurantoin excreted from three lots of two commercially available products after a single oral dose of 100 mg of nitrofurantoin.

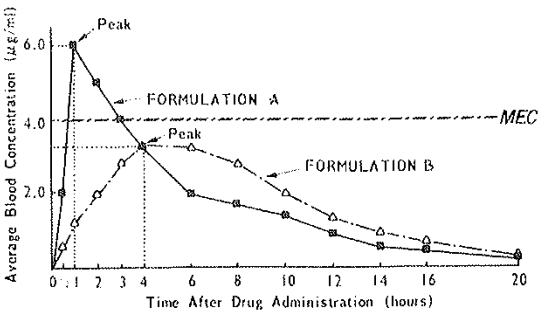

Fig 76-7. Blood concentration-time curves obtained for two different formulations of the same drug demonstrating relationship of the profiles to the minimum effective concentration (*MEC*).

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.

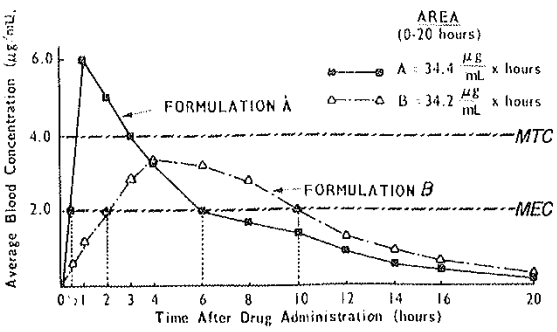

Fig 76-8. Blood concentration-time curves obtained for two different formulations of same the drug demonstrating relationship of the profiles to the minimum toxic concentration (*MTC*) and the minimum effective concentration (*MEC*).

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 bioequivalency; 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