DISPENSING OF MEDICATION

Formerly Husa's Pharmaceutical Dispensing

A Manual on the Formulation of Pharmaceutical Products,
the Dispensing of Prescriptions, and
The Professional Practice of Pharmacy

EDITOR

ERIC W. MARTIN PhC, BSc, MS, PhD,

Adjunct Professor of Biomedical Communication, Columbia University College of Pharmaceutical Sciences; Director of Medical Communication, Lederle Laboratories, Division of American Cyanamid Company. Formerly Editor, *Journal of the American Pharmaceutical Association*, Executive Editor, Pfizer's *Spectrum*, Editor-in-Chief, *Remington's Pharmaceutical Sciences;* Author of *Techniques of Medication, Hazards of Medication*, and some 80 other biomedical publications; licensed pharmacist in Canada and the United States; Founder and first President, Drug Information Association; President, American Medical Writers Association, 1970–1971; Fellow AAAS, American Medical Writers Association, and International Academy of Law and Science, etc.

SEVENTH EDITION

MACK PUBLISHING COMPANY

1971

Library of Congress Catalog Card Number: 70-165831
Printed in the United States of America

CHAPTER 27

Prolonged-Action Medications

Chapter preparation by
Edward Stempel, EdD
Professor and Chairman
Department of Pharmacy
Brooklyn College of Pharmacy
Long Island University
Brooklyn, New York 11216

Significant advances have been made over the years in learning how to develop forms of medication which will effectively provide the patient with a prescribed dose for a specific period of time.[1]

When drugs were administered almost exclusively by the oral route, it was recognized that certain drugs varied considerably as to the duration of their effects. Parenteral administration emphasized this characteristic by eliminating the variable due to gastrointestinal absorption, and such administration served to focus attention upon the fate of the drug within the body. In addition, parenteral administration provided insight into the physical and chemical factors determining the duration of the drug's sojourn and the concurrent duration of action.[2]

Although the interval of drug levels and subsequent decline in these levels do vary, drugs may be classified broadly according to rapidity of action as: (1) instantaneous, (2) immediate, (3) delayed, (4) prolonged (5) immediate and prolonged, and (6) immediate combined with delayed and prolonged-action. "Instantaneous" connotes release within a moment, "immediate" connotes release within an hour, "delayed" indicates a delay of release of drug for several hours after administration, and "prolonged" indicates a slow and steady release of drug during an extended period of several hours, days, or months.

Products that release a therapeutically-active constituent over a period of time have become popular and are known as prolonged-action products. Most commercially available preparations having prolonged action provide a combination of immediate and prolonged action and are usually designated as *prolonged-action, sustained-release, sustained-action, continuous-action, timed-disintegration,* or *timed-release* medication; however, these designations are also applicable but not usually used commercially to describe prolonged-acting products having a combination of delayed and prolonged action.

Although "prolonged-action medication" is synonymously used with "sustained-action medication" in discussions and in this chapter to connote a combination of immediate and prolonged

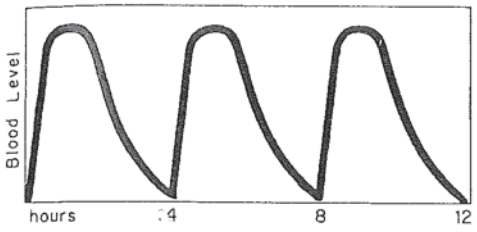


Fig 27-1—The "peak" and "valley" effects which are inevitable with divided doses.

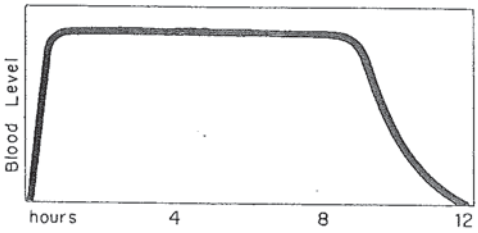


Fig 27-2—The effect of orally-administered prolonged-action medication.

action, Nelson[3] and Parrott[3a] have provided a more finite explanation of these types of medication. They indicate that a sustained-release or sustained-action product provides an initial sufficient amount of drug to cause a rapid onset of desired therapeutic response, and an additional amount of drug that maintains the response at the initial level for a desired number of hours beyond the activity resulting from a conventional dose; the initial desired therapeutic response is maintained because the rate of release of the desired therapeutic concentration is equal to the rate at which the drug is eliminated or inactivated. They indicate that a prolonged-action product also provides an initial sufficient amount of drug to cause a quick therapeutic response, but the product then provides for replacement of the disappearing drug at a rate that is not equal to elimination or inactivation; the drug is replaced at a rate which increases the duration of therapeutic activity compared with conventional single-dose medication. Nelson[3] and Parrott[3a] furthermore state that most preparations that provide a therapeutic response during an extended period are prolonged-action products because of the difficulty of formulating dosage forms wherein drug release is equal to drug elimination or inactivation.

Advantages

There are several reasons[4–7] for attempting to prolong the action of a drug, the most important of which is to maintain the therapeutic effect for a longer period than can be obtained after the administration of conventional single-dose medication. Other reasons are: (1) to reduce the number and frequency of doses administered, (2) to eliminate dips in drug concentration which are inevitable with divided doses (Fig 27-1) and thus maintain an even level of drug concentration in the body (Fig 27-2), (3) to reduce the total amount of drug needed to obtain the desired therapeutic response, (4) to eliminate the inconvenience of night-time administration of drugs, (5) to lessen the possibility of the patient's defaulting from treatment by forgetting to take his medication, (6) to reduce the incidence and intensity of undesirable side effects caused by excessively high peak blood levels of drug that may result from the administration of conventional dosage forms, and (7) to reduce or prevent the irritation of the gastrointestinal tract caused by some orally-administered drugs released in high concentration.

Contraindications or Disadvantages

Dragstedt[8] has pointed out that certain drugs should not be administered in a prolonged-acting dosage form: (1) drugs whose precision of dosage is important (like the anticoagulants and digitalis glycosides), (2) drugs whose absorption from the gastrointestinal tract is impaired or erratic, and (3) drugs with a total dose more than two or three times the usual therapeutic dose unless such drugs are known to have substantially wide margins of safety between their therapeutic and toxic ranges.

Campbell and Morrison[6] have pointed

out that prolonged-action preparations are contraindicated for drugs having an inherently long biologic half-life (such as long-acting sulfonamides). Furthermore, they point out that it is inadvisable for the physician to prescribe prolonged-action preparations unless they possess clear advantages over conventional products; *eg*, sustained-release riboflavin preparations appear unwarranted and unnecessary.

Sometimes, the prolonged effects of sustained-action nitrites may obscure the warning signs of pain, as in angina pectoris, and overexertion with fatal results may ensue.[9]

Levy[7] has indicated the following disadvantages of prolonged-release medication: (1) it is comparatively more costly than medication in a conventional dosage form, (2) it does not permit prompt termination of chemotherapy when this is desired or required, (3) it is limited usually to a single available unit dose or multiples thereof and more accurate adjustment is rarely feasible because prolonged-release dosage forms should not be broken or reduced to small particles by grinding, and (4) it is designed on the basis of an average elimination rate to provide the ideal of maintaining a desired therapeutic effect, and is therefore dependent on continuous replacement of drug eliminated; however, the rates of drug elimination are unequal and vary widely and thus there is the possibility of drug accumulation on the one hand because of too slow an elimination and underdosage on the other hand because of too rapid an elimination.

Drug Availability

In order to have clinical effectiveness, the administered drug must be capable of being available in the body for absorption by the patient, *ie*, the drug must be capable of solution before it can be absorbed.

However, the word "available" is now used by many to indicate physiologic or biologic availability: the degree to which the drug is absorbed by either passive absorption, active transport, or specialized transport. Passive absorption involves simple diffusion across body membranes; with active transport, certain membranes possess components, known as "carriers," which facilitate transport across the membranes.[9a] Specialized transport involves pinocytosis or phagocytosis, and, at present, only some fats are known to be absorbed by this process.[9b]

In passive absorption, Nelson states that the rate at which the drug leaves the absorption site and enters the circulation is directly dependent on the concentration of the drug at the absorption site. As absorption proceeds, the rate becomes progressively slower. When absorption studies indicate that absorption rate is independent of concentration at the absorption site, this observation is taken to be indicative of a transport process in absorption.[10]

For a more detailed discussion of drug availability, see Chapter 3 on *Bioavailability*, page 63.

Drug Distribution

A simplified scheme for drug distribution was provided by Teorell[11] and simplified by Wagner.[12] See Fig 27-3 for Wagner's scheme. According to Wagner,[13] the drug in the depot may enter the blood and return to the depot. (The depot may be the gastrointestinal tract.) Any drug in the blood is in equilibrium with drug in tissues, organs, and other fluids of distribution and the drug is constantly being excreted in the urine unchanged or as metabolites.

Drug Blood Level

Many administered drugs are not uniformly distributed throughout the body and sometimes do not even appear in the blood stream. Even if the drug appears

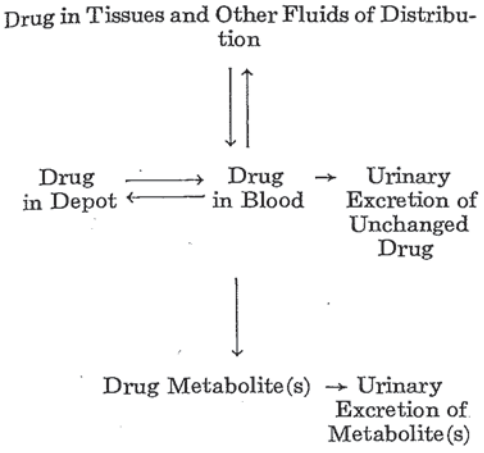


Fig 27-3—Simplified scheme for drug distribution.[12]

in the blood, its concentration in the blood may not parallel the physiological action; the concentration in the blood may closely or only remotely reflect the concentration in the tissues at its site of action.[14] Generally, drug concentration in the target body tissue rather than in the blood stream should be emphasized; nevertheless, an insight into drug concentration in the body is usually reflected by measuring its concentration in the blood. Therefore, the usual aim in therapeutics is to maintain a certain constant concentration of the drug in the blood stream. This concentration is referred to as *blood level* or *drug blood level*.

Urinary Excretion Rate

Campbell, Nelson, and Chapman[15] have pointed out that the evaluation of the release of drugs requires recognition of the fundamental relationship that exists between (1) concentration of drug in the blood or other fluids of distribution, and (2) excretion rate of the drug. It has been established both by experimental and theoretical considerations that, for several drugs and certain other exogenous substances, urinary excretion rate is directly proportional to concentration in the blood. Therefore, instead of drug absorption studies to measure drug blood level at various times after drug administration, Nelson and Schaldemose[16] state that urinary excretion data are frequently capable of supplying quantitative information on the absorption of drugs, without the inconvenience of blood sampling, even though such urinary excretion data are less direct.

Other Indices of Absorption

Whatever measurements are chosen as the index of pharmacological action or absorption, no valid comparison and evaluation of drugs can be made without them.[17] Besides either drug blood level or urinary excretion data, the index may result from a measurement of: the relative concentration of the drug in cerebrospinal fluid; the blood-sugar level; the electrolytes excreted in the urine; or, as with antibiotics, the antibacterial activity of the serum or urine.[17] Also, see pages 1032–1038 for clinical, nutritional, toxicity, radioactive, and roentgenographic studies.

Methods of Prolonging Absorption

Hollister and Levy[17a] indicated that the relative elimination rate of salicylate decreases with increasing dose, and theorized that high doses administered in rapidly-absorbed form have their own "sustaining" effect relative to the elimination rate of lower doses.[17a] Nevertheless, it is not usually desirable to produce a prolonged blood level by giving massive doses. Not only is there a limit to the quantity of a drug that can be safely introduced into the body in massive dosage at one time, but it is generally an ineffective as well as dangerous method for the production of prolonged action.[18] Some methods for prolonging drug action are: slowing inactivation, slowing excretion or elimination, slowing

absorption, or utilizing frequent dosage. The last method is not very desirable.

Slowing Inactivation and Slowing Excretion

Although inactivation and excretion can be mistakenly considered synonymous because excreted drugs are inactivated or out of the sphere of action, slow inactivation is specifically considered to be the action of specific nonexcretory mechanisms.

Inactivation of a drug may be slowed by inhibiting the enzymes that inactivate the drug.[19] For example, the activity of acetylcholine is inhibited by cholinesterase; therefore, by using an anticholinesterase like neostigmine that combines with cholinesterase, the hydrolysis of acetylcholine is slowed and its activity is prolonged.

Drug excretion or elimination from the body by way of the urine may be rapid or slow, and such elimination depends on glomerular filtration, secretion by the tubules, and tubular reabsorption. Drugs which are to a considerable extent reabsorbed by tubular cells have a prolonged stay in the body, *eg*, sulfamerazine.[20]

While it is often possible to govern the rate and amount of drug absorption, it is only rarely possible to govern the rate of drug excretion. The method used to slow drug excretion consists of the reversible inhibition of renal excretion.[21] Carinamide (caronamide or 4′-carboxyphenylmethanesulfonanilide) given with penicillin to dogs caused an increase in penicillin plasma concentration and a slowing of penicillin excretion by the kidneys[22] by blocking a particular excretory mechanism in each kidney. More recently, probenecid (Benemid) has been used to prolong and maintain the therapeutic effect of penicillin by slowing renal tubular excretion of penicillin with no apparent evidence of kidney damage. Probenecid interferes with the renal tubular excretion of *p*-aminosalicylic acid as well as *p*-aminobenzoic acid by inhibiting their conjugation with glycine. Recently, literature indicates that probenecid also decreases the urinary excretion of *p*-aminohippuric acid, phenolsulfonphthalein, pantothenic acid, 17-ketosteroids, and sodium iodomethamate.[22a] Therefore, probenecid is useful as an adjuvant to intensive therapy with some compounds by increasing and prolonging the drug plasma concentration. However, the practical problem of conveniently maintaining an effective concentration of the interfering drug itself has severely restricted the method of slowing excretion of another drug by the reversible inhibition of renal excretion.[23]

Slowing Absorption

The rate and the extent of absorption (per cent of the dose absorbed) are very important factors in influencing blood and tissue levels with respect to time after administration and, therefore, in influencing the intensity of biological action.[24]

Nelson[25] and Dominguez[26] have authored excellent reviews on the kinetics of absorption, distribution, and excretion. Wagner has pointed out that the rate of intravenous injection may be controlled; by all other routes of administration, a drug enters the blood stream at an unknown rate. Under certain circumstances, however, this rate can be determined. Dominguez, Nelson, Swintosky *et al*, and others have separately shown that many orally-administered drugs exhibit a steady state of diffusion during absorption, first-order* metabolic conversion, or first-order urinary excretion of unchanged drug and metabolite(s).[24] If these fundamental premises are fulfilled by a specific drug, then a calculation can be made of the instantaneous rate of absorption at different times after oral administration by at least three

* If the rate of a chemical reaction is independent of the concentration of the reactants, the reaction is referred to as a *zero-order reaction*. Other reactions may proceed at a rate dependent on the concentration of one of the reactants remaining at one time; the rate varies, in these cases, as the first power or exponent of reactant concentration, and these reactions are referred to as *first-order reactions*.

known methods as described in Wagner's excellent reviews of Biopharmaceutics.[24]

It is relevant to point out that methods of slowing absorption are applicable to fairly-rapidly-eliminated drugs such as insulin, corticotropin, heparin, penicillin, etc. Furthermore, no useful measure is served in slowing the absorption of such slowly-eliminated drugs as thyroxin, digitalis glycosides, cyanacobalamin, etc.[27]

The principle common to the factors providing prolonged action by slowing absorption is to decrease the rate of solution of the active ingredient in the circulating body fluids. Among the many factors involved in a slowing of the rate of absorption are: route of administration, vasoconstriction, immiscibility, dissolution rate, relative insolubility or decreased solubility, ionization, particle size and surface area, polymorphism, surface tension of the dissolution medium, viscosity and nature of the vehicle, esterification, polymerization, slowing disintegration and dissolution rate, leaching action, adsorption, ion exchange, and complexation.

Route of Administration

Wilson[28] states that intensity and duration of action of a drug depend on its concentration on the cells on which it acts, and this is determined by its rate of absorption, distribution, and excretion. Nevertheless, the choice of the route of administration usually influences the rate of absorption.

Parenteral Route—In using injectables, the intravenous route is employed when rapid action is essential during emergencies. Intramuscular administration of water-soluble drugs provides less rapid action, while the rate of absorption after subcutaneous administration is slower and more even. Nevertheless, Ballard,[28a] citing other sources, indicates that (1) there is not significant difference in the absorption rate of radioactive-labeled lente insulin from either intramuscular or subcutaneous sites, and (2) no markedly different results were found after either intramuscular or subcutaneous administration of the antimalarial cycloquanil pamoate.

Drugs in a solid pellet form may be implanted under the skin and slowly absorbed over a period of weeks or months.[29] Miller[30] has described pellets as small, rod- or ovoid-shaped, sterile bodies (3.2 × 8 mm) in a compressed form. These are intended for subcutaneous implantation in body tissue (*eg*, the thigh) to serve as a depot for providing slow release of drug over an extended period of time. The sterile pellets are either inserted under the skin of the thigh with a special injector (Kearns Pellet Incisor) or by means of an incision.

The NND[31] stated that a pellet containing 120 mg of desoxycorticosterone acetate is slowly absorbed and provides an effect approximately equivalent to that of daily injections of 0.5 mg. Such 120 mg pellets are effective for 9 to 15 months. Goodman and Gilman,[32] quoting other sources, stated in 1941 that the subcutaneous implantation of crystalline pellets of desoxycorticosterone has proved to be an effective and convenient method for controlling Addison's disease in patients. In 1958, these same authors[33] pointed out that the desoxycorticosterone compound can maintain the life of the Addisonian patient, but the patient is very susceptible to stress. Therefore, cortisone or hydrocortisone should be added to the therapeutic regimen.

In order to maintain a constant level of riboflavin in the tissues, Bromberg *et al*[34] implanted riboflavin pellets in patients. The method was particularly advantageous in patients who could not be trusted to take medication regularly. Pellets containing 50 mg of riboflavin fused with 50 mg of cholesterol maintained a high riboflavin level in man and animals for 45 days.

Parenteral absorption has been reviewed by Wagner.[35] The absorption of implanted solid drug has been reviewed by Ballard and Nelson.[36] The latter investigators[36] indicated that absorption of implanted medication is affected by such

factors as the site of implantation, body movements, and diluents; furthermore, little quantitative information is available concerning the magnitude of the effect. Subsequently, Ballard[37] showed the quantitative relationship that may exist between drug-pellet-absorption rate and the degree of animal physical activity. There was significantly greater absorption of procaine penicillin G pellets in more active animals (rodents).

Crumbling of the pellets may result in increased absorption and overdosage,[31] with possible hazard to the patient. Furthermore, the administration of pellets offers difficulties in administration and sometimes causes local disorders even when properly administered; therefore, they are rarely used.[38]

Oral Route—The oral route of administration is the most convenient as well as the most common method of administering drugs. With the exception of the sublingual route of administration (*eg*, nitroglycerin, isoprenaline, etc), drugs are usually absorbed slowly when administered by the oral route. If a drug is permitted to remain in the mouth, considerable absorption may occur through the mucous membrane. However, if a drug is swallowed rapidly, absorption may commence as soon as it reaches the stomach.[39]

Although absorbability from the mouth and stomach is primarily a property of the specific drug, the dosage form also influences absorption. For example, solutions are usually absorbed faster than either powdered medication or compressed tablets because solid medications can only be absorbed after they have undergone deaggregation and dissolution.

Absorption from the stomach varies with the amount of food in the stomach, the solvent vehicle (if any), the form of the drug,[40] and the volume and constituents of gastric juice.

It has been well established that the volume and constituents of gastric juice contained within the stomach at any time are not constant. These variations do influence the disintegration time of tablets. Usually, a tablet which disintegrates at a slower rate cannot be expected to make its medication as readily available for absorption.

Abbott *et al*,[41] have stated that mucoid material present in gastric juice may, under certain conditions (*ie*, swallowing a tablet dry without water), coat a tablet to render it more resistant to disintegration and prolong its disintegration time. These investigators[42] also pointed out that a similar phenomenon may occur if a tablet is ingested in the early morning on an empty stomach which contains a large proportion of mucous. A high mucoid content of gastric juice may increase disintegration time to 16 or more times the usual tablet-disintegration time.[43]

For a more detailed discussion of the factors and mechanisms affecting gastrointestinal absorption, the reviews by Wagner[44] should be read.

Rectal Route—Enesco *et al*,[45] in studying the comparative absorption of six drugs in 63 normal individuals, found that each of the following five drugs, in separate aqueous solutions, is absorbed more quickly rectally than orally: sodium salicylate, chloral hydrate, methylene blue, atropine sulfate, and morphine sulfate.

Cacchillo and Hassler,[46] in studying the absorption of acetylsalicylic acid from the oral route as well as from various suppository bases administered rectally, measured drug concentration in the blood two hours after administration of the dosage form. These investigators[46] found that there was no significant difference between the absorption of acetylsalicylic acid from tablets given orally and the absorption from a Carbowax base given rectally; however, there was significantly greater absorption from the oral tablets and the Carbowax-type rectal suppositories than from either theobroma oil or glycerinated gelatin rectal suppositories. On the other hand, Peterson *et al*,[47] using sodium iodide labeled with radio-iodine to compare the rate of

absorption from rectal suppositories administered to rats, showed that absorption from a glycerogelatin base was better than from a Carbowax base, and absorption from the latter was better than from a theobroma oil base. However, Peterson *et al*,[47] as well as Cacchillo and Hassler[46] have emphasized that (1) no set rule exists concerning the relative ease of absorption of drugs by the rectum, and (2) individual studies must be undertaken to determine for each drug the base that is best suited for absorption. See pages 840–844.

Most medicinal agents administered in suppository form by the rectal route in a theobroma oil base for systemic action are usually considered to be most slowly absorbed and to provide a therapeutic action over a long period of time. Tice[48] states that theobroma oil may retard the absorption of certain medicinals. Medicinals which are oil-soluble are not readily released because the medicament has a greater affinity for the suppository oil phase than the aqueous fluids bathing the body cavity. Even water-soluble drugs in a theobroma oil base are not released readily because of the barrier action of theobroma oil.

Gradnick[49] has likewise pointed out the importance of the media used in the preparation of suppositories. Fatty media give slow absorption, whereas water-soluble media liberate their medication more easily.

Contrary to Cacchillo and Hassler,[46] Peterson *et al*,[47] Tice,[48] and Gradnick,[49] it has been indicated by Hassler and Sperandio[50] that the onset of hypnotic action of pentobarbital sodium, secobarbital sodium, and amobarbital sodium in albino rats was faster and the duration shorter in theobroma oil than in polyethylene glycol polymer suppositories. Wagner[51] stated that Samelius and Anstrom observed that the rectal absorption of hexobarbital sodium in the rabbit was better from theobroma oil than from a Carbowax base.

Riegelman and Crowell[52] pointed out in 1958 that a number of different *in vivo* rectal absorption studies have been conducted to evaluate separately or concomitantly, at different time intervals, the level of drug in the blood, urine, and the tissues, as well as the specific physiological response. However, unlike the direct radiological approach, such studies have provided much meaningful data by an indirect approach to the absorption problem. Such indirect *in vivo* studies are based on the assumption that the rate of rectal absorption bears a constant and direct relationship to the amount of drug in a certain body fluid (or organ) or to the blood level required to elicit a pharmacological response. Furthermore, unless there is a direct proved relationship between the rate of absorption at the rectal site and the drug concentration in the organ or the blood, it is difficult to draw general conclusions.[53]

Riegelman and Crowell[54] used a direct radiological method for detecting the events taking place at the site of absorption, and indicated that the diffusion of the drug within the vehicle affected or limited the rate of the absorption process. These investigators[55] also indicated the possibility that the rate of solution and the rate of diffusion from the solid-liquid interface is the controlling factor for absorption. Using radio-tagged iodoform and radio-tagged 2,4,6-triiodophenol, at more than one pH at which each drug is undissociated, these investigators showed that a solution of either drug in a solid oleaginous vehicle resulted in a very prolonged absorption time[54] compared with a solution of either drug in a solid or liquid polyethylene glycol vehicle.[55]

Wagner's[56] article on biopharmaceutics provides a more extended review of rectal absorption.

Vasoconstriction

The incorporation of a vasoconstrictor in a solution of a drug that is to be injected subcutaneously tends to slow absorption or release over a prolonged period of time. This technique is used in the combination of epinephrine with local

anesthetics.[29] Specifically, since the anesthetic effect of procaine hydrochloride is not maintained, it is usually administered as a vasoconstrictor, to slow the rate of absorption of procaine.[57] The preparation usually used is the official procaine hydrochloride injection,[58] containing 1% procaine hydrochloride and 1:100,000 epinephrine per 30 ml.

Immiscibility

If prolonged action of a drug is desired, the slowing effect of an oil may be of value and is independent of the viscosity which the oil contributes to the final product. See *Viscosity and Nature of the Vehicle*, page 1014. Oils are immiscible with the moisture of the tissues; this immiscibility prevents direct contact with the cells and thus provides a slower release and greater duration of action.[59]

A water-in-oil emulsion dosage form can be used in prolonged-acting injected products. The internal phase consists of aqueous globules containing medication, and the external phase of the emulsion can be a water-immiscible liquid other than an oil, *eg*, liquid petrolatum, which is slowly broken down in the body (compared with vegetable or animal oils) to slowly release the aqueous medicated globules.[60]

Lazarus and Lachman[60a] cited Hilleman who indicated that diphtheria toxoid adsorbed onto alum showed higher antitoxoid titers than plain toxoid but the immunity was not as sustained as with a toxoid in a mineral-oil emulsion. However, since 1966, mineral oil as an adjuvant in parenterals has been limited to experimental or clinical trials in man.

US Patent 3,149,036, was granted to Woodhour and Stim (assigned to Merck)[60b] for a vegetable oil emulsion adjuvant called Adjuvant 65. It consists of 5% Arlacel A, 43% peanut oil, 2% aluminum monostearate, and 50% of an aqueous phase.[60c]

At the 1966 International Conference on Vaccines against Viral and Rickettsial Diseases of Man, it was reported that clinical and laboratory studies indicated that the recently developed Adjuvant 65 boosts the power of influenza vaccine to produce much higher levels of immunity than those produced with vaccines now in use and the immunity last four to five times longer. Th antigen is bound in the water-in-oil emulsion which provides a repository for its slow release and its wide distribution to the antibody-producing centers of the body, thereby causing the body-immune mechanisms to produce more antibody for a longer period of time.[60d]

Certain drugs, *eg*, chlortrianisene and dibenamine, are very lipid-soluble and are partitioned and deposited in the adipose tissue after administration. Drug deposition in the fatty tissue establishes an equilibrium with other tissues, and the depot gradually releases the drug to provide a prolonged effect.[60e]

Dissolution Rate

Solution rate is usually designated "dissolution" or, more specifically, "dissolution rate." "Solubility" differs in meaning from "dissolution." Solubility refers to an equilibrium condition while dissolution involves a kinetic situation. As indicated in a subsequent portion of this chapter, solubility refers to the maximum amount of material that can be dissolved in a given volume of solvent at constant temperature in any time interval to allow the attainment of saturation. High solubility is not necessarily associated with high dissolution rate although solubility is one of the several factors affecting dissolution rate.[60f]

The dissolution of a substance in a nonreacting solvent may be described by the Noyes-Whitney Law:

$$dc/dt = KS(C_s - C)$$

where dc/dt is the rate of dissolution, S is the surface area of the dissolving solid, K is the dissolution-rate constant (which includes several factors such as the intensity of agitation of the solvent and the diffusion coefficient of the dissolving drug), C is the concentration of drug in the dissolution medium at time t, and

C_s is the con
diffusion layer
terial (equival
a saturated so
rate of diffu
through the d
of the solutio
The aforesa
dissolution ra
to surface are
ticle size will
lution. Where
desired, large
slower dissolu
absorption. P
will be discuss
Morozowicl
there is slow
soluble salts:
amine and et
the median le
its relation t
(mg/cm²/hr)
both the LT_5
dose of drug)
(slower) *in vi*

Relative Ins Solubility

"Insoluble'
tive or absolu
insoluble drug
drugs must d
absorbed; the
or decreased s
duration of a
Solubility
amount of ma
in a given vo
temperature i
the attainme
sorption of d
and ultimate
fluid at absor
sequence sinc
prevent the a
tions.
Solubility
are related o
bility affects
et al[60h] showe
rates of som

C_s is the concentration of drug in the diffusion layer surrounding the solid material (equivalent to the concentration of a saturated solution and governed by the rate of diffusion of solute molecules through the diffusion layer into the body of the solution).[60f]

The aforesaid equation indicates that dissolution rate is directly proportional to surface area; therefore, a smaller particle size will result in more rapid dissolution. Where long-acting formulation is desired, larger particles will result in slower dissolution and subsequent slower absorption. Particle size and surface area will be discussed again on page 1012.

Morozowich *et al*[60g] have shown that there is slow absorption of some slowly-soluble salts: using salts of benzphetamine and etryptamine, and measuring the median lethal time (LT_{50}) in mice and its relation to *in vitro* dissolution rate (mg/cm²/hr) and solubility (mg/ml), both the LT_{50} and LD_{50} (median lethal dose of drug) increased with a decreased (slower) *in vitro* dissolution rate.

Relative Insolubility or Decreased Solubility

"Insoluble" may connote either relative or absolute insolubility. Absolutely-insoluble drugs are not absorbed because drugs must dissolve before they can be absorbed; therefore, relative insolubility or decreased solubility is desired if a long duration of action is desired.

Solubility refers to the maximum amount of material that can be dissolved in a given volume of solvent at constant temperature in any time interval to allow the attainment of saturation. The absorption of drugs is a dynamic process, and ultimate solubility of a drug in the fluid at absorption sites is of limited consequence since absorption and dispersion prevent the attainment of saturated solutions.

Solubility of a drug and absorption are related only to the extent that solubility affects solution rate. (Hamlin *et al*[60h] showed that the initial dissolution rates of some investigated compounds representing many different classes, in given media, were directly proportional to their respective solubilities in those media.) In other words, solubility usually affects solution rate, and solution rate usually affects absorption rate. Therefore, relatively-insoluble drugs may be considered to have a slow rate of absorption.[61]

The stomach is an important site for the absorption of drugs administered orally. Nelson[62] has likewise indicated that one of the factors influencing absorption is the solubility or (relative) insolubility of the drug in the gastric contents. For example, a moderately-soluble (or USP slightly-soluble) medicament like acetylsalicylic acid is readily or rapidly absorbed compared with any poorly-soluble (or USP practically-insoluble) medicament such as bishydroxycoumarin.

Leonards[33] showed that a neutral aspirin solution was absorbed faster than aspirin in a suspension. In another study, Leonards[44] determined the blood plasma concentration of salicylate at 10, 20, 30, 45, and 60 minutes following the oral ingestion of 0.64 Gm of aspirin in various pharmaceutical preparations. The blood plasma concentration of salicylate in 55 normal human subjects was used as an index of the rate of gastrointestinal absorption. The results showed that the absorption rate of aspirin decreased in the following order: sodium acetylsalicylate in 120 ml of water, a commercially-available effervescent preparation containing aspirin (Alka-Seltzer) in 120 ml of water, aspirin powder dissolved in water previously heated to 70–80°C and cooled to 30–40°C prior to ingestion, buffered aspirin tablets followed by 60 to 120 ml of water, and Bayer aspirin tablets. See Fig 27-4. Therefore, the investigator concluded that the rate of gastrointestinal absorption is markedly influenced by solubility.

When suspensions are injected either intramuscularly or subcutaneously, the suspended material (deposited in the tissues) is described as a depot site that

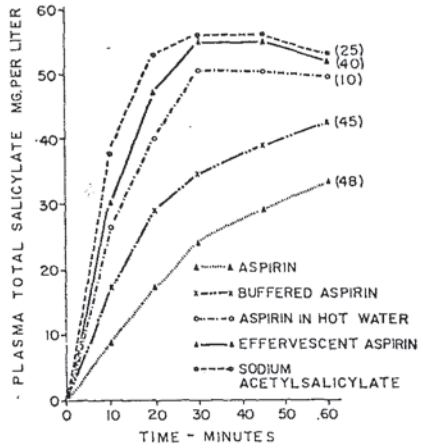


Fig 27-4—Plasma total salicylate concentrations following the oral ingestion of various preparations of aspirin. The total dose was equivalent to 640 mg of aspirin in all cases. Figures in parentheses represent the number of human subjects studied in each group.[64]

ensures prolonged release of medication.[65] A suspension having a high solid-liquid ratio may be unusually effective in further slowing drug absorption; the slowed absorption may arise from the compact deposits readily formed within the tissue by the very thick suspension.[66]

The simplest formulation of a prolonged-acting suspension is the combination of a water-soluble substance in a nonaqueous vehicle. The first successful method for prolonging penicillin blood levels was the development of the Romansky formula. This contained sodium penicillin G in a vehicle of vegetable oil and beeswax. However, the product induced local irritation, pain, and the formation of sterile abscesses at the injection site.[67] Prolonged blood levels may also be achieved by the preparation of less water-soluble substances, which, upon injection, will constitute a reservoir from which the drug will be released slowly.[67] If the vehicle is oleaginous rather than aqueous, an even greater duration of action can usually be expected.

Because of the rapid excretion of aqueous solutions of water-soluble potassium penicillin G or sodium penicillin G, intramuscular injections must be given repeatedly at intervals of 3–12 hours to maintain therapeutic blood levels.[68] However, the preparation of less water-soluble, small particulate crystalline procaine penicillin G (having a solubility of about 0.7%) can be used when it seems desirable to prolong a given effective penicillin level.[69] By utilizing 300,000 units of an intramuscular aqueous suspension of procaine penicillin G, detectable concentrations of penicillin may be found in the blood for at least 8–12 hours in most subjects.[69] Nevertheless, prolonged blood levels are usually obtained at the expense of concentration; that is, lower blood levels are obtained over a longer period of time. With an even less water-soluble derivative such as benzathine penicillin G, penicillin remains in the blood at significantly lower levels for even longer periods of time.[69] By administering 300,000 units of an intramuscular aqueous suspension of benzathine penicillin G, assayable blood levels of penicillin are available for 5–7 days.[70]

Ionization

In a review article by Schanker,[71] it was indicated that the distribution of drugs between plasma and gastric juice has supplied strong evidence that drugs cross the gastric epithelium in their nonionized form, and the ionized form penetrates very slowly, if at all. Furthermore, the epithelial lining of the intestine, like that of the stomach, allows the ready penetration of undissociated drug molecules but impedes the passage of ionized moieties. In experiments with rats, a relation between the degree of ionization and the rate of absorption was revealed: the weaker acids and bases were readily absorbed; stronger, highly ionized acids and bases were more slowly absorbed; and the completely ionized quaternary ammonium compound and sulfonic acids were hardly absorbed.

Particle Size and Surface Area

Particle size and particle-size distribution are important factors in the absorption of drugs since solution rate is di-

rectly related to surface exposed to the solvent. Higuchi[72] has stated that both (1) the absolute particle size, and (2) the particle size and particle-size distribution of a drug sample as it relates to surface area may be important in the rate of dissolution of a drug. When the particle size is greater than about 10 μ, the rate of dissolution is directly proportional to the surface area.[72] Hence, when the particle size is of such a dimensional nature, surface area, not particle size *per se*, is a factor controlling dissolution rate; however, when particles below 10 μ are considered, the particle size, and not the surface area, may be more important.[72]

Finely divided particles dissolve at a faster rate and have higher solubilities than similar macro particles.[73] Hasegawa and Nagai have pointed out a mathematical approach to the tendency for small particles to dissolve faster than larger particles.[73]

Schroeter[74] has indicated that the Noyes-Whitney Law of solution rate concerns itself with the rate at which solids dissolve in solutions when the surface area of exposed solid changes slightly. Nelson[75] states that the reduced form of the Law describes the *in vivo* solution of drugs, and the equation has the form

$$da/dt = KSC_s$$

where da/dt is the dissolution rate, K is a constant whose value depends upon agitation and other factors, S is the surface area, and C_s is the concentration of drug in a layer of fluid adjacent to the dissolving drug. The equation shows that dissolution rate is directly proportional to surface area.

Although there are exceptions, large particles are generally more slowly absorbed than small particles.[76] Riegelman and Crowell,[55] in studying the effect of particle size on rectal absorption, observed that the absorption rate of large particles is less than that of small particles. Simond *et al*,[77] showed that the size of Theelin crystals in an aqueous suspension is very important in determining the duration of estrogenic effect; greater duration of action was obtained when most of the crystals were large. Nelson[78] has indicated that finely powdered tetracycline is absorbed much more readily than a pellet of limited surface area, and the difference has been attributed to the increased surface area obtained when particle size is reduced. Maier and Gasche showed that the duration of action of crystal suspensions (of steroid hormones) varies directly with the size of the crystals; however, Joel has pointed out that a limit must be imposed (on crystal size) since pain on injection increases with increasing particle size.[79] On the other hand, Buckwalter and Dickison[76] have pointed out that there are exceptions to the generality that large particles are more slowly absorbed than small particles. They have shown that particle size and the nature of the vehicle are interdependent; for example, small particles of procaine penicillin G in oil-aluminum stearate systems are absorbed slower than large particles in either oil or oil-beeswax systems.[80]

On the basis of particle size alone, which determines the initial surface presented to dissolution media, differences in blood levels should be expected in accordance with the studies that showed that sulfonamides in the form of a micronized powder provided higher blood levels than the (larger) microcrystals.[81] Glazko *et al*[82] likewise indicated that larger particles produce lower levels. They stated that the hydrolysis rate and subsequent absorption rate of chloramphenicol esters appears to be dependent upon the physical size and total surface area of ester particles of chloramphenicol. However, because of the difficulties in obtaining suspensions of uniform particle size, no quantitative study of this relationship has been made.[83] Nevertheless, these investigators showed that finely divided preparations of water-insoluble esters are readily hydrolyzed and absorbed, while suspensions of larger crystals, which have a smaller surface area per Gm, are hydrolyzed more slowly and consequently produce lower levels.[83]

Because larger particles are usually more slowly absorbed than small particles and large particles usually produce lower blood levels than small particles, it may be stated that large particles produce prolonged blood levels at the expense of concentration.

Polymorphism

A polymorph is a substance crystallizable in several distinct forms, and polymorphism of a drug is its occurrence in various crystal forms. Aguiar *et al*[84] have shown that the absorption of chloramphenicol from chloramphenicol palmitate depends on the hydrolysis rate of the ester which is governed by the rate of solution which is dependent, among other things, on the polymorphic form.

US Patent 2,920,014 was issued to two Danish inventors primarily on an insulin crystal having the shape of a sharp-edged rhombohedron. The application for the patent stated that the effect of the insulin crystals in suspension was distinctly protracted as evidenced at about 8 hours after the injection by blood-sugar values which were only about one-half the magnitude of the value before injection. It is believed that something unexpected results from the special form of the insulin crystal developed by the inventors.[84a]

Surface Tension of the Dissolution Medium

Drugs must be in solution to be absorbed, accordingly, conditions such as low surface tension that facilitate or speed dissolution rate will speed absorption time while conditions such as high surface tension that slow dissolution rate will slow absorption time. For some drugs, therefore, a high surface tension of the dissolution medium will extend absorption time.

Finholt and Solvang[84b] showed that the surface tension of the dissolution medium may have an appreciable effect on the dissolution kinetics of a hydrophobic drug. Under the conditions of their investigation, a hydrophobic drug like phenacetin has an increased (faster) dissolution rate with decreasing particle size when the dissolution medium has a low surface tension and it has a decreased (slower) dissolution rate when the dissolution medium has a high surface tension.

Viscosity and Nature of the Vehicle

The administration of a suspension has been mentioned as a method of prolonging drug action by slowing absorption. While relative insolubility results in such an effect, the viscosity of the vehicle has a similar effect regardless of whether the drug is in solution or suspension.

Gelatin is used as a vehicle for subcutaneous[85] or intramuscular[86] injection when slow absorption of a drug is desired.[85] A vehicle consisting of a gelatin solution with some dextrose is used for such drugs as heparin and adrenocorticotrophic hormone (ACTH). Gelatin is also used in preparing a parenteral gel[86] for intramuscular use that contains cyanocobalamin. The injection of the aforementioned drugs in gelatin solution provides more prolonged effects than when administered in water solution.[87]

Dollerup and Holten[88] have reported that carboxymethylcellulose in a concentration of 1.25% has prolonged the anticoagulant effect of a heparin preparation having a concentration of 100 mg/ml.

Polyvinylpyrrolidone and polyvinyl alcohol have also been used individually as thickening agents to prolong the action of intramuscular injections.[89]

Oleaginous solutions of drugs usually have a longer therapeutic effectiveness than the corresponding aqueous solution. Even oleaginous suspensions of drugs usually have an increased duration of action. For example, crystalline procaine penicillin G suspended in vegetable oil provides detectable blood levels of penicillin for 12 or 24 hours. By increasing the viscosity by the addition of 2% aluminum monostearate, an adequate therapeutic blood level of penicillin may be maintained for 2–4 days.[70]

Coles *et al*[89a] reported that an increase in the content of aluminum monostearate from 0.5 to 2% in a dispersion of

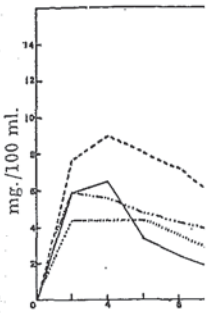


Fig 27-5—Blood level subjects after oral adı pensions and oil-in- acetyl sulfisoxazole —, lipid emulsio Gm; ..., aqueous s zole, 2 Gm; – – –, lipi zole, 4 Gm; · · · —, a sulfisoxazole, 4 Gm.

Clostridium welcl aluminum moı gels resulted in a toxin level in gui tive of the metho gel or the tempe months after inje with the most s still as high as t with a simple al sorbed vaccine. F ity of the vaccir correlation with ment and the pr toxin levels.

Kristensen anc ported prolongat aluminum mono sions. Investigati revealed, among arations of B_{12} ta leased vitamin B depot over a mu than did B_{12} tanr

Oral suspensi water emulsion a vide more prolon suspensions. Fe Patent 2,867,565 the administrati amides in an em

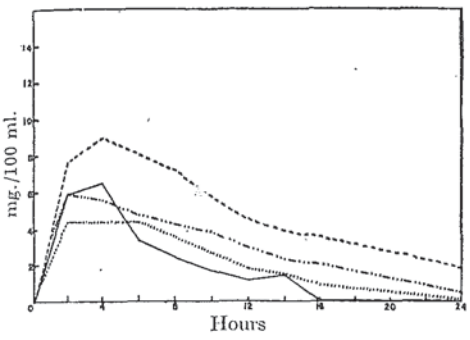


Fig 27-5—Blood levels of sulfisoxazole in human subjects after oral administration of aqueous suspensions and oil-in-water (lipid) emulsions of acetyl sulfisoxazole at doses of 2 and 4 Gm. ——, lipid emulsion acetyl sulfisoxazole, 2 Gm; . . ., aqueous suspension acetyl sulfisoxazole, 2 Gm; – – –, lipid emulsion acetyl sulfisoxazole, 4 Gm; · · · —, aqueous suspension acetyl sulfisoxazole, 4 Gm.[92]

Clostridium welchii Type D toxoid in aluminum monostearate-hydrocarbon gels resulted in an increase in the antitoxin level in guinea pig serum irrespective of the method of preparation of the gel or the temperature of gelation. Six months after injection, the residual titre with the most successful vaccines was still as high as the peak titre obtained with a simple aluminum hydroxide adsorbed vaccine. Furthermore, the viscosity of the vaccines did show a positive correlation with the degree of enhancement and the prolongation of the antitoxin levels.

Kristensen and Hansen[89b] likewise reported prolongation of action due to 2% aluminum monostearate in oil suspensions. Investigations with rabbits clearly revealed, among other things, that preparations of B_{12} tannate in that vehicle released vitamin B_{12} from an intramuscular depot over a much longer period of time than did B_{12} tannate in an oil suspension.

Oral suspensions having an oil-in-water emulsion as the vehicle may provide more prolonged effects than aqueous suspensions. Feinstone[90] obtained US Patent 2,867,565 on the discovery that the administration of absorbable sulfonamides in an emulsion of edible fat with water, in which the oil-drug ratio is less than 20:1, enhances the therapeutic activity of the drug compared with its action in aqueous suspension or in unemulsified oil. Absorption of the drug is markedly facilitated from the emulsion as shown by an almost doubled blood concentration, and an effective blood concentration is maintained for up to six times as long as when equal amounts of the drug are administered in aqueous suspension.

A marketed concentrated suspension of acetyl sulfisoxazole (available as Lipo Gantrisin Acetyl and containing 20% Gantrisin Acetyl in a palatable and readily digestible vegetable oil-in-water emulsion) provides high blood levels over long periods of time. This form of the drug is administered in approximately double the concentration but only one-half as frequently as the aqueous forms.[91] Svenson *et al*[92] found that the dose of 4 Gm of acetyl sulfisoxazole in the oil-in-water emulsion induced a higher peak level than the corresponding aqueous suspension, and the level was maintained better during a 24-hour observation period (compared with a similar study with 2 Gm of the drug). See Fig 27-5.

On the other hand, Buckwalter and Dickison[76] have stated that viscosity *per se* does not appear to influence absorption entirely since some rather viscous products are absorbed faster than less viscous products. Specifically, these investigators pointed out that relatively large particles tend to slow, to some extent, absorption in either oil or oil-beeswax vehicles. However, large particles appear to accelerate absorption in oil-aluminum monostearate suspensions.[93]

Even though viscosity measurements were not made and it is assumed that aqueous suspensions are usually less viscous than either oil suspensions or solutions, the investigation of Richards *et al*[94] likewise indicates that viscosity *per se* does not influence absorption. These investigators[94] concluded that aqueous suspensions of estrone are more lasting in estrogenic action than either oil suspen-

sions or oil solutions. Simond *et al*[95] confirmed the conclusion of Richards *et al*[94] with estrone in aqueous suspension and oil solution, but did not investigate oil suspensions of estrone.

Esterification

Slow absorption may be obtained by the use of esters that provide a therapeutic effect only after slow hydrolysis.

A chemical advance that has proved valuable in the use of the estrogens was the finding that esters of this group of compounds have a much more prolonged action. Esterification increases their potency and duration of action by prolonging metabolism in the body in addition to delaying or slowing absorption at the site of injection.[96] Consequently, the benzoic acid esters of estrone and estradiol are employed when a long sustained action is desired.[97]

Other drugs have also been esterified to prolong their action. The chloramphenicol ester, chloramphenicol palmitate, is relatively insoluble in water and commercially available in suspension (Chloromycetin Palmitate Suspension). The chloramphenicol is split from the ester by the gastrointestinal enzymes and absorbed from the upper intestine. The blood levels of the antibiotic rise more slowly but persist longer when the ester rather than the drug itself is administered.[98] The sedative alcohol methylpentynol (Dormison) can be prolonged in action by converting it into its carbamate (Oblivon-C).[99] Similarly, the carbamate of the spasmolytic drug mephenesin has a more prolonged action than the unesterified drug and is commercially available (Tolseram).[99]

Polymerization

Schueler and Keasling[100] synthesized and studied (pharmacologically) a group of polymeric quaternary ammonium salts, and they found that such polymers had very long durations of action. Whether the mechanism of the increase in duration of effect is due to the increased time required for excretion of large polymeric substances of because the larger molecules are bound more securely to receptors, the polymerization of moieties may be a useful way to increase the duration of action of drugs.[101]

Slowing Disintegration and Dissolution Rate

Many factors are theoretically involved in controlling the absorption of orally-administered tablets. Some of these include: disintegration time; particle size; aggregation between particles and other tablet components such as disintegrators, binders, excipients, etc (a function of tablet-compression force); dissolution time; gastric pH (which affects the ratio of ionized to nonionized drug); and the presence of interfering factors such as gastric mucus, food, adsorbents, and diluents.[101a]

Levy[102] has pointed out that the important prerequisite for rapid drug absorption is fast dissolution of the solid medicament. Slowing disintegration of tablet medication interferes with absorption rate only by its effect upon the dissolution rate. Therefore, slowing disintegration may cause slowed dissolution, and such dissolution may affect absorption.

The first quantitative study of the dissolution process was made by Noyes and Whitney in 1897.[102a] Hixson and Crowell, using a form of the Noyes-Whitney equation, derived an equation for the dissolution of a single particle having a surface area changing with time.[102b] Nelson[102c] has reduced the equation to that previously described in the section on *Particle Size and Surface Area*, page 1012 Niebergall and Goyan[102d] developed an automatic recording apparatus to follow the dissolution process of a drug. Schroeter and Wagner[102e] have automated the dissolution studies of solid dosage forms by using a timer-controlled sampling and dilution system which removes filtered samples from the dissolution medium, makes reproducible dilutions, and records the spectrophotometric absorbence of the diluted sample as a

function of time. McClintock, *et al*[102f] have developed a new nuclear *in vitro* continuous dissolution-rate-measuring method for use in determining dissolution-release-rates of radioactive-labeled materials from solid dosage forms.

In order to establish a meaningful dissolution test which can rank products in accordance with their physiological availability, consideration must be given to the pH of the dissolution medium, surface activity, reaction with mucus components, the presence or absence of bile salts, etc. Furthermore, in order to establish *any* rational *in vitro* test procedures, it is necessary to have a prior knowledge of the physiological availability from clinically acceptable as well as unacceptable products (in order to correlate *in vitro* procedures with *in vivo* data as described on page 1032).[102g]

Disintegration rate may have little or no influence upon dissolution rate. Levy[102] compared the disintegration times and dissolution or initial absorption rates of various acetylsalicylic acid tablets, and he found that the faster-absorbed products actually had longer disintegration times.

Schroeter *et al*[102h] have determined the dissolution rates and disintegration times of 76 lots of tablets containing different drugs: in some cases, there was a quantitative relationship between $t_{50\%}$ (time for 50% of the drug to dissolve) and disintegration time; in other cases, there was no relationship. Middleton *et al*[102i] found, with sugar-coated tablets, that there was a close relationship between disintegration time and the time for 50% of the drug to dissolve.

Levy[102] indicated that the lack of a direct relationship between disintegration and dissolution does not apply to enteric-coated tablets where disintegration can be the determining factor. The previous sentence is also applicable to such specially processed orally-administered dosage forms which are discussed subsequently.

Ideally, with orally-administered prolonged-action medication, the purpose is to produce a dosage form which permits smooth and sustained release of the contained medicament during 8 to 12 or even 24 hours. However, the ideal has been difficult to attain because of the nature and functioning of the gastrointestinal tract and the great variability in such factors as the time required to empty the stomach.[103]

The objective of sustained-drug action has been stated by Blythe[104] and is similarly expressed by Swintosky[105] in different words: "to provide an initial amount of readily available drug so that it becomes effective rapidly, and a maintenance portion which upon continuous release is absorbed in the alimentary tract at a rate which compensates for the loss of drug activity through excretion and metabolism." Swintosky[106] shows the calculations involved in computing the rate at which the maintenance portion must be absorbed to maintain a uniform drug level for a predetermined number of hours as well as those calculations involved in computing what proportion of the dose should be in the quick-release and maintenance portions of the sustained-action dosage unit.

The rate at which the maintenance portion must be absorbed for a predetermined number of hours may be computed from a knowledge of biologic half-life and the rate constant for drug elimination.

Biologic half-life provides information for the determination of the rate constant of drug elimination. Each drug has its own biologic half-life, which can be defined as the time it takes to eliminate one-half of the substance after it is administered. This elimination may be accomplished by metabolism or excretion of the substance unchanged.

Swintosky[106] defines biologic half-life as the time required for the body to dissipate one-half the drug activity after the drug has been absorbed and has attained "diffusion equilibrium." For example, Swintosky[108] points out that, if a drug is given intravenously and time is allowed for its distribution to accessible tissues, the time thereafter required for a certain

drug activity to drop to one-half this activity is the biologic half-life. It has also been mentioned that half-lives vary with experimental conditions. Therefore, a description must be made of the conditions under which half-lives have been determined.[107]

In practical studies, half-life $t_{1/2}$ is determined graphically by plotting drug concentration in the blood or a tissue against time.[106] Figure 27-6 shows that the descending line with the sharpest slope represents the "concentration versus time" data for belladonna alkaloids and $t_{1/2}$ equals about 1 to 1.5 hours; the other line represents sulfaethylthiadiazole (also known as sulfaethidole or SETD) and $t_{1/2}$ equals about 8 hours.[109]

For a system that follows first-order kinetics, the rate constant for drug elimination k may be determined by dividing 0.693 by the biologic half-life $t_{1/2}$ Thus, if a drug has a $t_{1/2}$ of 4.6 hours, it will have a k of 0.15 reciprocal hours (which, by suitable mathematical steps, will result in 15%/hr.[105] Both $t_{1/2}$ and k may be independent of the dose and the dosage form administered.

If it is established, for example, that 0.333 Gm of drug provides a peak response and the elimination rate is 15% per hour, then 15% of the drug must be provided in the maintenance portion per hour; that is, 0.333 Gm × 0.15 = 0.05 Gm per hour. If the dosage unit is to act h hours, then the total drug in the dosage unit may be determined from the relationship.

$$W_t = W_o + W_o kh$$

where W_t is the total weight of drug in the dosage unit, W_o is the weight of the quick-release portion, k is the elimination constant, h is the time in hours during which sustained action may be required. and $W_o\ kh$ is the weight of the maintenance portion. Thus, if W_o = 0.333 Gm, k = 15% per hour, and h = 10, then

$$W_t = 0.333\text{ Gm} + (0.333\text{ Gm} \times 0.15 \times 10),$$

and W_t = 0.833 Gm.

The aforementioned calculations provide the product-development pharmacist with an estimate of the amounts to be used for the dosage unit. However, *in vitro* release tests as well as *in vivo* evaluation studies (both mentioned at the end of this chapter) serve thereafter as further experimental guides to determine the release specifications of the final therapeutically-efficient dosage form.[110]

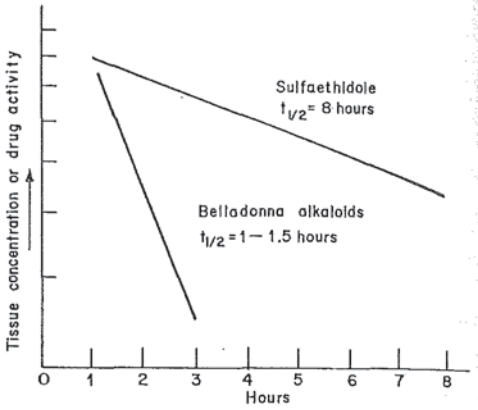


Fig 27-6—Graph illustrating relative differences in disappearance of drug, or drug activity, from the human body following a single dose.[109]

Because some pharmaceutical companies (such as Smith, Kline & French) market specific dosage forms or have US patents for "sustained-action" or "sustained-release" preparations while other companies market or have US patents for "prolonged-action" or "prolonged-release" preparations, neither "sustained" or "prolonged" can be used in subsequent headings to describe the dosage forms if it is remembered that Nelson and Parrott, cited on page 1003, have differentiated these terms in a finite fashion. Therefore, the term "long-acting" is used in the headings to describe preparations having a therapeutic effect during a period of many hours (even though Massengill, Wyeth, and perhaps others use the term "long-acting" as part of product names). On subsequent pages, "sustained" or "prolonged" are used synonymously when describing the products under the headings "long-acting" (in spite of the finite differentiation by

Nelson and Parrott). However, it should be realized that some or all products marketed with the designation "sustained-action" or "sustained-release" may be long acting because the rate of release is equal to the rate of elimination or inactivation.

Long-Acting Capsules—In US Patent 312,041 of February 10, 1885, Upjohn described the preparation of pills by placing starters or nuclei (granules previously prepared with the aid of granulated sugar, talcum, and water) in a revolving pan, setting the pan in motion, moistening the rolling starters, adding the powdered medicinal ingredient or ingredients, and alternately moistening and adding powder until suitable-sized pills were obtained. This technique of using starters was subsequently used in patents for long-acting capsules and other long-acting dosage forms.

Australian Patent 109,438 of January 11, 1940 was granted to Israel Lipowski for a process for producing coatings on medicinal substances reduced to the form of small bodies. Many bodies were coated in groups with varying number and/or varying-material membranes and the resulting groups (each consisting of approximately the same number of bodies) were mixed together for subsequent administration to be absorbed during various specified periods of time. This patent and Upjohn's are considered the forerunners for long-acting capsules and other long-acting dosage forms having granules with varying numbers and/or varying materials of coatings.

In 1952, Smith, Kline & French Laboratories introduced the *Spansule* capsular dosage form containing the active ingredient distributed among many tiny pellets with varying disintegration times. Such capsules release the medication gradually and uniformly over an extended period of time. Blythe[111] states that *Spansule* medication evolved as a solution to the problem of coated tablets remaining in the stomach for a wide variation of a few to 12 hours before entering the duodenum. Furthermore, he states that complete benefit of the entire dose is lost if the tablet fails to disintegrate. However, if a few of the myriad of small pellets in a *Spansule* fail to disintegrate at the desired site, such failure will not noticeably alter the effect of the over-all dose.

Blythe obtained US Patent 2,738,303 (for the *Spansule* capsular dosage form) on March 13, 1956 with an application dated July 18, 1952. The patent provides for a sympathomimetic agent or combination that is continuously released over a long period through the use of a capsule containing a combination of a large number of uncoated and coated pellets. The coated pellets have coatings of various thicknesses of a material that is slowly digestible or dispersible in the gastrointestinal tract. The pellets of the selected medicament can be prepared readily by placing small sugar pellets or nonpareil seeds of 12- or 40-mesh size in a rotating coating pan and coating the pellets or seeds with medication in powdered form. Before the addition of the powdered medicament, the sugar pellets are wetted in the conventional manner using a coating solution such as syrup or gelatin solution. After the medicated pellets have been formed, a number of them are provided with an ingestible coating, like a wax-fat coating, which is capable of slowly disintegrating in the gastrointestinal tract. The most common method of providing the coating is to place the ingestible coating in solution and spray it over the pellets during the rotating operation of the coating pan that holds the pellets. A minimum of 50 coated pellets, containing the selected medicament in an amount of about 200 to 400% by weight of uncoated pellets, are mixed with uncoated pellets to provide a uniform mixture for filling capsules for sustained (or prolonged) action. The uncoated pellets release an initial dose immediately, while the coated pellets release medicament gradually over an extended period of time.

Lazarus and Cooper[112] indicated that the release of the active substance from a *Spansule* is independent of the pH and is

primarily controlled by moisture vapor permeability of the lipid film (on the coated granules or pellets). The rate of moisture permeability is determined by the drug, the composition of the coated material, and the thickness of the coating. They also indicated that the coating should be free of pitting, imperfections, or flaws. Otherwise, the release rate may be altered by premature rupturing of the coating. Furthermore, the pellets should be of uniform size to avoid stratification of pellets of different sizes in the encapsulation process, and it should be ascertained that the pellets prepared by different methods are uniformly distributed.

Heimlich of Smith, Kline & French described, in US Patent 3,119,742 of January 28, 1964, another method for preparing long-acting capsular preparations having coated and uncoated pellets and his procedure varied from the Blythe method (of coating innocuous cores with medicament, dividing the coated cores into groups, applying coatings to different groups to provide different times of release, combining the groups, and encapsulating). The Heimlich method consists of preparing spherical pellets by spraying the medicament with an adhesive, adding more medicament, drying to form spherical pellets which are then coated with either various thicknesses or different coats (to provide different times of release), and encapsulating. This method of not using innocuous cores as starters permits the incorporation of larger doses of drugs in long-acting capsular dosage forms.

Because Lantz and Robinson of Smith, Kline & French claim that the Blythe method of preparing sustained-release pellets entails, among other things, complicated manufacturing techniques, they developed a method for which they received US Patent 3,146,167 on August 25, 1964. The method consists of (1) forming a molten slurry of solid medicament randomly dispersed throughout a lipid material (which is capable of solidification at room temperature, is resistant to gastrointestinal disintegration but slowly disintegrates therein), (2) atomizing the molten slurry through a pressure nozzle to form particles of medicament containing lipid material, and (3) passing said particles through air having a temperature lower than the solidification temperature of the lipid material until the particles congeal as spherical pellets, of 250 μ to 2000 μ in diameter, having solid medicament randomly dispersed throughout the lipid material.

The Upjohn Company has introduced a delayed long-acting *Medule* capsular preparation that consists of coated pellets of uniform size (so that no stratification occurs during the encapsulation process). The coat consists of a styrene-maleic acid copolymer which is pH sensitive and prevents dissolution in the stomach. The copolymer is mentioned in at least two US Patents. Among other things, US Patent 2,897,121 of July 28, 1959, obtained by Wagner, compares drug concentrations in the plasma following oral administration to normal subjects of 40 mg of prednisolone in compressed tablets with the concentration following the same dosage in styrene-maleic acid coated pilules. The comparative study indicates that the coated pilules resulted in a sustained elevation of 17-hydroxy steroid plasma levels over a prolonged period. On March 12, 1963, Enz and King received US Patent 3,081,233 for enteric-coated pilules measuring not more than 0.1 inch in diameter and consisting of a medicinal agent and a coating of a single enteric styrene-maleic acid film-forming material.

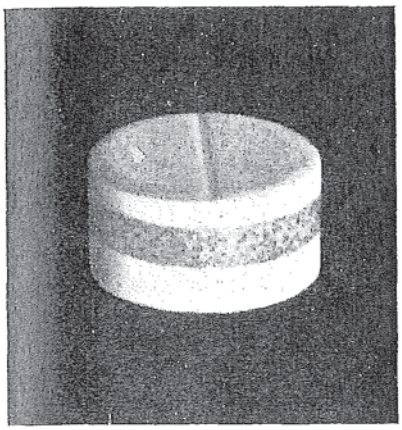
Other pharmaceutical companies provide capsular preparations similar to the aforementioned two long-acting capsule-type preparations. Other patents for long-acting capsular (as well as some other) dosage forms have been reviewed by Stempel.[1]

Some of the commercially available long-acting encapsulated products are listed by Nelson.[113]

Long-Acting Single-Layer Tablets—Such tablets may be prepared by

Fig 27-7—A mu

(1) combini
and uncoat
combining
granules ha
ing thickne
rates of rele
medication
terial, gran
method), an
powdered m
release tabl
the powder
release table
ules, and
medicated
release tabl
the medica
release com
ulation and
compressing
uent that f
around the
constituent
Patents des
have been
With lo
either from
which has b
tion, or (2)
or fatty ba
protective
ing or defor
during tab



Stokes

Fig 27-7—A multilayer tablet.[114a]

(1) combining and compressing coated and uncoated medicated granules; (2) combining and compressing medicated granules having different coatings, varying thicknesses of coatings, or different rates of release; (3) dispersing powdered medication throughout slow-release material, granulating (by wet-granulation method), and compressing; (4) dispersing powdered medication throughout a slow-release tablet composition by slugging the powdered medication and the slow-release tablet composition, forming granules, and compressing; (5) dispersing medicated granules throughout a slow-release tablet composition by combining the medicated granules with the slow-release composition in the form of a granulation and then compressing; and (6) compressing materials having a constituent that forms a gel sheath or barrier around the tablets upon hydration of the constituent in the aqueous body fluids. Patents describing some of these methods have been reviewed by Stempel.[1]

With long-acting tablets prepared either from (1) a mixed granulate, part of which has been coated to slow disintegration, or (2) coated pellets using a wax or fatty base to prevent damage to the protective coating on compression, scoring or deformity of the coating may occur during tablet compression and cause variation in the rate of release of the drug after oral administration.

It should also be realized by both the prescriber and the pharmacist that it is questionable whether tablets intended for long action should be triturated to a fine state of subdivision for inclusion in capsular (or other dosage-form) preparations such as the following prescription that contains two long-acting tablets (Metamine Sustained, Leeming; and Nitroglyn, Key Corp); such trituration possibly defeats the purpose of the intended dosage form by destroying the physical mechanism of long action with the possibility of overdosage.

Thiamin Chloride	20 mg
Niacin	25 mg
Metamine Sustained	1/2 mg
Peritrate	5 mg
Nitroglyn	gr 1/150
Papaverine Hydrochloride	gr 1/10
Dtd number 200	
Signa: One capsule t i d p c	

Obviously, after checking the dosage of each ingredient in each long-acting tablet, the pharmacist found that the dose was correct.

Long-Acting Liquids—Most of the work in producing orally-administered long-acting dosage forms has been in the development of encapsulated or tableted products; however, orally-administered long-acting liquid preparations are also useful.

Smith, Kline & French, besides providing capsules and tablets for sustained action based on slowed disintegration, markets a liquid preparation in which very fine microscopic particles of a drug are dispersed throughout slightly larger microscopic particles of a slowly disintegrating matrix. The resulting microscopic pellets are suspended in a viscous aqueous vehicle. The powdered drug marketed in such form is sulfaethylthiadiazole, which is rapidly excreted by the kidneys (when compared with other clinically-available sulfonamides), and is commercially available in the sustained-action liquid preparation known as Sul-Spansion.

At least two US patents for liquid sustained-action preparations have been assigned to Smith, Kline & French.

Robinson and Svedres obtained US Patent 2,805,977, on September 10, 1957, for a sustained-release oral pharmaceutical preparation and for use of such a preparation in combination with an aqueous vehicle to provide a liquid dosage form. The liquid product of the invention consists of a large number of finely-divided sustained-release particles in combination with an aqueous vehicle. These sustained-release particles, having a size not larger than 100 mesh and not smaller than 0.5 μ, consist of finely-powdered medicament dispersed in a time-delay material which is resistant to disintegration in the gastrointestinal tract and will slowly disintegrate therein. The time-delay material may be selected from the group consisting of (1) a wax, (2) a fatty alcohol having 14 to 31 carbon atoms, (3) a glyceryl ester of a fatty acid having 10 to 22 carbon atoms, (4) a cellulose ether, and (5) a cellulose ester. The specific gravity of the sustained-release particles (at 20°C referred to water at 4°C) should be within the range of about 1 to about 2 and have a density of about 100 to about 150% of that of the aqueous vehicle at 20°C. The aqueous vehicle may contain, in addition to water, a surface-active agent which decreases the surface tension of the water to less than 50 dynes per centimeter and will not adversely affect the time-delay material. A thickening agent may be added to the vehicle to maintain dispersion of the sustained-release particles for a greater period of time. It is also preferable to include from about 0.001 to about 1% by weight of a deflocculating agent.

Grass and Robinson obtained US Patent 2,875,130, on February 24, 1959, for a novel method of preparing a sustained-release pharmaceutical powder and the powder prepared by the method. The process consists of reducing a solid medicament to a particle size of a maximum about 10 μ and mixing the formed particles in about 5 to about 35% by weight of liquefied lipid material which is water insoluble and has a melting point above about 85°C. The mixture is then solidified to form a primary powder having particles with a maximum particle size in the range of from about 5 to 25 μ. The formed primary powder is then mixed (while maintaining a temperature of about 80° to 85°C) with a melt containing about 25 to about 85% lipid material which is substantially water insoluble, resistant to disintegration in the gastrointestinal tract (and will slowly disintegrate therein), and has a melting point which is a minimum of about 5° lower than the melting point of the first-mentioned lipid material. The powder-lipid mixture is mixed with water to form an emulsion between about 80° to 85°C, the emulsion is cooled below about 80°C to precipitate sustained-release pharmaceutical particles with a melting point higher than about 80°C, and the particles are collected by filtration and dried. Such resultant particles can be added to cereal or other solid foods, suspended in a liquid food such as milk or orange juice, or used to form an aqueous liquid suspension that will remain substantially uniform over an extended period of time. The aqueous liquid suspension is prepared with the aid of a suitable nontoxic anionic, cationic, or nonionic surface-active agent in an amount from about 0.25 to 1% by weight of the finished product.

Other pharmaceutical companies have described the use of either ion-exchange resins or tannates in liquid long-acting preparations; however, Jack[114] states that it is doubtful if a large enough particle size would be acceptable in a liquid preparation in order to allow reasonable prolongation of release. The use of either tannates or ion-exchange resins is discussed subsequently (under Adsorption and Ion Exchange).

Long-Acting Multilayer Tablets— Another method for preparing prolonged release tablets is to combine quickly disintegrating and slowly disintegrating portions so that the quickly disintegrat-

ing portion is either of two or more visible layers. See Fig 27-7.

Multilayer tablets can be prepared by two basic methods. The older method consists of filling the die of the rotary press with different granulations in successive layers, one on top of the other, and pressing all the layers together with a single compression. The newer method, called the individual-compression method, consists of filling the die with the first granulation and pressing it to form the first layer, then filling the second granulation into the die containing the compressed first layer, and then pressing to form a finished two-layer tablet; a three-layer tablet could result by using an additional hopper, feed frame, and compression.

Hermelin, Swintosky, and perhaps others have obtained US patents for the preparation of multilayer tablets.

Hermelin obtained US Patent 2,809,917, on October 15, 1957, for a method of making a multilayer tablet having a layer containing an immediate-release medicated preparation and another layer containing a delayed-release preparation which has a slow but continuous solubility in the gastrointestinal tract. The method consists of intimately mixing a powdered drug and an enteric water-insoluble excipient to produce a pasty mass; drying; breaking up the mass by the use of light crushing to form smaller granular particles; and repeating the mixing, drying, and breaking-up process for 3 to 15 times to produce a delayed- and slow-release medicated granulation. The aforementioned granulation is introduced into a tablet die cavity and compressed to form a single solid layer, then the immediate-release medicated granulation is introduced on top of the previously compressed layer and compressed to form a second solid layer that adheres firmly to the first.

Swintosky obtained US Patent 2,951,-792, on September 6, 1960, for a pharmaceutical tablet that provides a combination of an immediate-release dosage to achieve a therapeutic level and a sustained-release dosage to maintain a therapeutic level of the medicament over an extended period of time. Such a tablet lends itself to mass production through the use of tabletting machinery, and said production is markedly less expensive than the production of encapsulated pellets by Blythe's method (previously discussed). The tablet is a substantially flat-faced tablet having two or three layers. A single or pair of immediate-release layers contain a medicament dispersed in a conventional filler such as milk sugar, terra alba, talc, or stearic acid. Such layers quickly dissolve or disintegrate in the fluid of the gastrointestinal tract and rapidly provide a therapeutic blood level of the medicament. A sustained-release layer providing substantially uniform release for a period in excess of four hours is contiguous with the one or two immediate-release layers. Such a sustained-release layer contains the same medicament as the other layer or layers, and the medicament is dispersed within granules of a solid, ingestible, lipid, time-delay material selected from a group consisting of (1) fatty alcohols having from 12 to 31 carbon atoms, (2) glyceryl esters formed from fatty acids having from 10 to 22 carbon atoms, and (3) esters having from 24 to 62 carbon atoms and formed from fatty acids having from 12 to 31 carbon atoms and from fatty alcohols having from 12 to 31 carbon atoms. The total surface area of the sustained-release layer (including the face or faces abutting the immediate-release layer or layers) is in the range of from 2.5 to 25 times the side surface area of the sustained-release layer. The sustained-release layer made in accordance with these dimensional limitations provides a substantially constant and uniform release of medicament as compared to a composition having the form of a ball. (With a ball-shaped form there is an ever-decreasing release of medicament per unit of time as the surface area wears away.)

Warner-Chilcott markets a double-layer tablet containing 20 mg of Peri-

trate in one layer with another 60 mg in a specially prepared wax-base layer which gradually releases the ingredient during a 12-hour period. Wyeth markets a double-layer tablet, Pen Vee L-A, consisting of a layer of penicillin V that is rapidly released and absorbed and a layer of penicillin V that is slowly released and absorbed. However, the poor absorption of penicillin beyond the duodenum indicates that penicillin should be rapidly soluble to permit absorption in the stomach and proximal intestine; therefore, forms of penicillin that are insoluble in the stomach and proximal intestine should not be administered orally, and the penicillins must never be administered in a long-acting or delayed-release dosage form.[114b]

Long-Acting Core Tablets—Tablets having long action may also be prepared by combining quickly-soluble medicament around a core that releases its medication at a later interval, slowly, or both.

With "delayed-action" medication, the drug is usually released several hours after administration. However, long-acting core tablets that release medication immediately and at a later interval are mistakenly referred to as "delayed-action" tablets. Such long-acting core tablets are sometimes correctly designated *prolonged-action* tablets, *repeat-action* tablets, or *laminated* tablets.

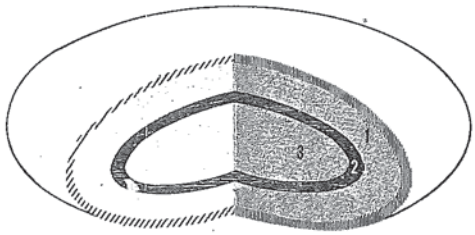
A conventional method for making long-acting core tablets consists of preparing a core containing active ingredient or ingredients and then coating the core with a substance, like a glyceryl ester of a higher fatty acid, which will not be affected by stomach juices but will be dissolved by intestinal fluids; to this coated core is then applied, by means of pan-coating, another layer of active ingredient. After the protective coat has had time to disintegrate, the active material in the inner core is released and the patient receives the second or subsequent dose of medication.

With such long-acting core tablets, the patient receives an initial dose that may be followed by a short period of no drug release; the sudden release of drug after such a latent period may be undesirable in the treatment of certain chronic diseases because the patient may be deprived of therapy at a time when it is required. On the other hand, the possibility exists that the concomitant effect of a second or subsequent dose with the initial dose may lead to a larger undesirable initial dose than was intended.[115]

Hermelin obtained one of the US patents (US Patent 2,736,682 on February 28, 1956) for a method of preparing a prolonged-action core tablet which produces an initial rapid release and a subsequent slow release. The outer envelope of the core contains a drug that is coated or encased in the usual readily-soluble sugar coating that dissolves in the stomach juices and releases the drug quickly. Separating the outer envelope from the inner core is a coating or envelope that resists gastrointestinal fluids for a predetermined period of time. The inner core is prepared by compressing granules consisting of drug, confectioners' glaze, stearic acid, and castor oil; and these granules release drug slowly over a period of time.

Schering's *Repetabs* consist of an outer layer of medication available for immediate release and rapid action, a laminated timed barrier that is not enteric coated (yet defers release of the inner core ingredients for 4 to 6 hours regardless of exposure to acid or alkaline secretions), and an inner core containing another full therapeutic dose. The construction of the Schering *Repetab* has been advertised as in Fig 27-8. Schering has pictured (Fig 27-9) the release of medication from the core before the first therapeutic peak fades, and the establishment of the second therapeutic peak concurrent with or overlapping the end of the first therapeutic peak.[116] However, Cooper[117] has pointed out that the repeat-action tablet provides an amount of medication in the blood in excess of immediate needs shortly after administration, and the levels of the drug drop off sharply after ingestion

Fig 27-8—R
by Schering
for immed
barrier (no
inner core f
to acid or
contains a
providing p
tion.



Schering

Fig 27-8—Repetab construction as advertised by Schering. (1) outer layer contains full dosage for immediate release; (2) laminated timed barrier (not enteric coating) defers release of inner core for 4 to 6 hours regardless of exposure to acid or alkaline secretions; (3) inner core contains a second full therapeutic dose, thus providing prolonged, sustained level of medication.

as the drug is metabolized. Cooper's statement regarding the sharp drop-off of drug blood level is also applicable to the inner core. The result is that therapeutic peaks rise sharply and then fade rapidly in two separate nonoverlapping stages; therefore, Cooper[117] contends that such tablets have no therapeutic advantage over tablets taken at regular intervals. Nevertheless, such long-acting core tablets do provide medication through the sleeping hours.

An innovation in laminated-tablet medication provides prolonged action and relief of symptoms. McDermott obtained US Patent 2,921,001, on January 21, 1960, for a novel core tablet or pill having a taste-indicating signal layer. Such dosage forms (Fig 27-10) consist of (1) an external layer of tasteless therapeutic material that is released in the mouth to provide prompt therapeutic action, (2) a middle signal layer having a signal material (like lemon flavor) to serve to signal for swallowing the tablet after the therapeutic material in the external layer has been released, and (3) a core of therapeutic material absorbable in the gastrointestinal tract to prolong the relief provided initially by the outer layer. Examples indicated in the patent are commercially available from Winthrop as Isuprel-Franol Tablets and Dilcoron Tablets. Since patents usually try to include all possible aspects of a novel idea, the McDermott patent includes the possibility of (1) a signal layer at the exterior, (2) a combination of taste signal and medication in an outermost layer or in an inner layer, and (3) an enteric layer between the signal layer and the core so that the presence of such enteric layer results in the release of medication from the core at a definite point in the gastrointestinal tract.

Instead of disintegration of the central core, which connotes separation of fragmentation, Ciba has adopted a core based on a mixture of fats and solid high-molecular-weight waxes in which the medicament is dispersed so that *erosion*, rather than disintegration, occurs. Such prolonged-release medication is designated by Ciba as a *Lontab*. Cooper[118] states that the outer coating of the *Lontab* disperses immediately, and there is then a slow attack of the core as the surface waxes and fats slowly erode. Then, as the waxes and fats are washed away, more medicament is brought to the surface and absorbed. A personal communication from Cooper[119] indicates that slow *erosion* may be characterized by (1) a core that retains its geometric shape while it loses surface area slowly and regularly by uniform shrinkage, (2) some penetration of the core by gastro-intestinal fluids with resultant dissolution of

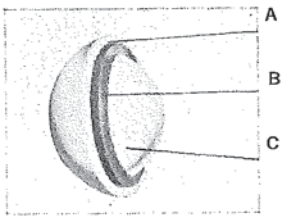


Fig 27-10—Novel core tablet having taste-indicating signal layer. (A) Outer layer containing sugar coating and medicament for prompt therapeutic action. (B) Middle taste-indicating signal layer. (C) Inner core that contains medicament to prolong relief provided initially by outer layer.

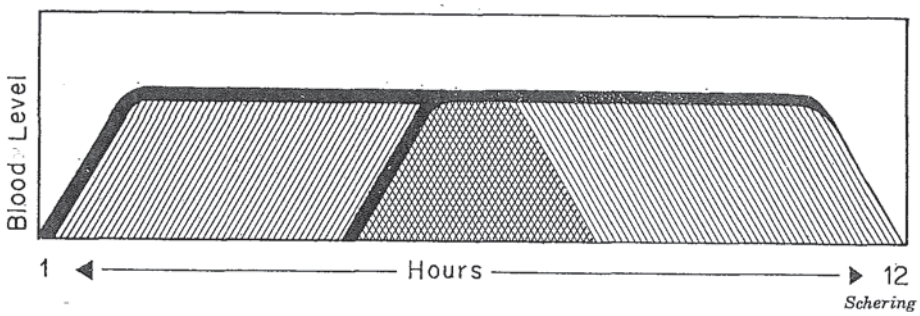


Fig 27-9—Diagram showing blood levels resulting from the release of medication from the outer layer and the inner core of a repeat-action (core) tablet at various times after ingestion.

some of the drug, (3) a core that becomes smaller without actually breaking up, and (4) a core that is not devoid of medication until it is completely disintegrated.

Another long-acting nondisintegrating core-type tablet is marketed by Robins and designated *Extentabs*. These *Extentabs* consist of an outer-colored coating or shell, a fairly thick coating underneath containing one equivalent of the active component, and a central core containing two additional equivalents of the active component. The outer-colored coating and the coating underneath dissolve rapidly when the tablet reaches the stomach. The core, which is processed to resist solution until it reaches the small intestine, contains a vehicle having a homogeneous substance that is slowly soluble in the small intestine. There, the core slowly releases the active component by the process of solution. One can think of slow solution of the vehicle of the core as being similar to the gradual solution of a piece of hard candy held in the mouth even though the time required for completion of solution of the tablet core is many times greater than that of a piece of hard candy.[120]

Leaching Action

Instead of drug release from tablets due to either disintegration or erosion, Abbott markets a long-acting dosage form from which the medicament is leached. "Leaching" connotes penetration of liquid into a tablet to dissolve active ingredient while permitting the tablet to remain substantially intact.

An early US patent that provides for leaching action from tablet medication is US Patent 2,476,182 that was granted to Consolazio on January 16, 1945. His patent was obtained for surrounding granules with water-insoluble, nontoxic, permeable, membranous films. Leaching occurs (1) when fluid dialyzes into the cellular compartments and the enclosed medicament dialyses out into the surrounding fluid, or (2) when the cells become engorged with fluid and the sacs burst to liberate the medicament. When the tablet is completely leached of its active ingredient, the cellular stroma of the impregnating film remains and is eliminated from the system.

The term *Gradumet*, connoting gradual-release medicament, has been applied by Abbott to their tablet-shaped dosage form consisting of physiologically inert plastic containing hundreds of interstitial passages impregnated with the medicinal agent. From these passages, the medicinal agent is leached at a continuous even rate during 8 to 12 hours. More descriptive material concerning this dosage form is found in US Patent 2,987,445 of June 6, 1961 and US Patent 3,087,860 of April 30, 1963.

Leeming also markets a dosage form consisting of the drug intimately mixed with a physiologically inert substance which provides a tablet matrix from which the drug is gradually leached by

the digestive juices during an 8-hr period.[121]

Nysco Laboratories Inc [121a] (Queens, NY) claim that the only type of timed-release process that can be relied upon to provide consistent results without toxicity at all times is one whose release rate is independent of pH, enzymatic activity, and agitation. Their Nyscaps (capsules) contain pellets or microdialysis cells which also release medication by diffusion rather than by disintegration. The process of preparing the pellets includes: (1) converting the active ingredients to pelletized form by coating the active ingredient, either in solution form or powder form, with the aid of an adhesive onto a sugar core; or converting a powdered active ingredient into a pelletized form without the use of an inner starting core; and (2) coating the aforementioned pellet with a solution of material which forms the dialyzing membrane.

After ingestion, there is penetration of fluid into the microdialysis cells to form a saturated solution. This is followed by outward diffusion of drug at a maximum rate because there is the greatest difference between the concentration within the cell and the concentration outside of the cell. As the release process continues and the excess undissolved solid replenishes the diffused saturated solution, the concentration of drug within the cell decreases and the rate of release decreases. At a specific time, the formulated dialysis membrane permits the imbibition of water with swelling with a concomitant increase in permeability of the drug. The two effects of the decreased concentration of drug within the cell and the increased permeability of the membrane offset each other so that the rate of release can be maintained at a desirable level. Thus, the formulation consists of a dialyzing membrane having a predictable and reproducible control permeability and a predictable and reproducible rate of increase of permeability with time.

USV Pharmaceutical Corporation also uses controlled-diffusion microdialysis cells in their Nitrospan (nitroglycerin) and Cerespan (papaverine hydrochloride) capsular products.

Adsorption

Adsorption is defined as the concentration of a substance upon the surface of some liquid or solid called the *adsorbent.*[122] The mechanism of adsorption is obscure; however, Langmuir has suggested that the adsorbent enters into a loose chemical combination with the material adsorbed.[123]

When a protein, colloid, or other adsorptive substance adsorbs medicinal agent, the absorption of the medicinal agent is slowed. Use has been made of the retaining action of protein to prolong the effect of insulin. For example, protamine or salmine and globin in conjunction with insulin provide slow and even insulin effects for many hours.[124] Some authorities may desire to credit the prolonged effect of insulin preparations to a low order of drug solubility. However, the prolonged effect of certain insulin solutions such as the official globin zinc insulin injection[125] is certainly not due to a low order of drug solubility, nor is the prolonged action of *clear protamine zinc insulin*[126] (unlike protamine zinc insulin suspension[127]) due to a low order of drug solubility. Therefore, it might be considered to credit such prolongation of action to the phenomenon of adsorption.

Use has been made of the retaining action of an adsorptive substance to prolong the effect of corticotropin. Corticotropin-zinc hydroxide (official as sterile corticotropin zinc hydroxide suspension[128]) contains purified corticotropin adsorbed on zinc hydroxide, and parenteral administration of the product results in a prolonged therapeutic effect.

The prolongation of the time of therapeutic efficacy of a drug can also result from the oral administration of a relatively insoluble form of the drug or drug combination with an adsorptive substance. Kennon and Higuchi[129] have mentioned Foxalin, a digitoxin-sodium carboxymethylcellulose ionic combina-

tion, which affords uniform sustained release.

Adsorption with the use of ion-exchange resins is discussed under the following heading.

Ion Exchange

Ions are atoms, singly or in groups, that carry an electrical charge. Ion exchange refers to the ability of certain insoluble substances to extract one species of charged atom out of solution and exchange it for another.[130] Stated in another manner, the process of ion exchange is one of double decomposition in which the material or chemical used is able to provide the type of ion required in place of one which is adsorbed from solution.[131] Any material or chemical which has the property of providing such ionic exchange is known as an ion exchanger.[132] Ion exchangers used to replace anions with other anions are anionic exchangers, and ion exchangers used to replace cations with other cations are cationic exchangers. The materials or chemicals used as ion exchangers include minerals, certain types of organic polymers and copolymers, water-insoluble acids and bases, and relatively insoluble organic compounds.[132]

The *Durabond* principle of Neisler is based on the physicochemical laws of ionic bonding and ion exchange to provide prolonged action of a therapeutic agent through the medium of marketed tablets and liquids. The release of medication from such tablets and liquids is independent of the emptying time of the stomach, the motility of the intestinal tract, and the varying pH of the stomach and intestinal tract.

Cavalitto *et al*,[133] have indicated that organic amines can be converted (with the use of tannic acid) to pentamine gallotannates (of limited aqueous solubility) which, in the presence of aqueous solutions of electrolytes, provide a gradual *in vitro* release of soluble therapeutic amine. Since stomach acid could lead to very rapid release of amine from its tannate, the use of an intimate combination with a polymeric polyanionic agent, such as polygalacturonic acid, could protect the tannate from too rapid solution in stomach acid.[133] Such combinations of suitable proportions of amine tannates and polygalacturonic acid provide a gradual rate of release and absorption of the amine drug over a wide range of pH, and products containing such combinations are referred to by the trade name of *Durabond* by Neisler Laboratories, Inc.[133]

A great variety of resins act as ion exchangers and are known as ion-exchange resins. These resins can be grouped into four general categories: strongly basic anion-exchange resins, weakly basic anion-exchange resins, strongly acidic cation-exchange resins, and weakly acidic cation-exchange resins.[134]

Lazarus and Cooper[135] cite Abrahams and Linell who have provided the following equations for the combinations of acidic and basic drugs with basic and acidic ion-exchange resins, respectively:

Formulation for oral administration—

Acidic ion(cationic)exchange resin + basic drug $\rightleftharpoons$ drug resinate

Basic ion(anionic)exchange resin + acidic drug $\rightleftharpoons$ resin salt

In the stomach—

Drug resinate + hydrochloric acid $\rightleftharpoons$ acidic resin + drug HCl

Resin salt + hydrochloric acid $\rightleftharpoons$ resin chloride + acidic drug

In the intestine—

Drug resinate + NaCl $\rightleftharpoons$ sodium resinate + drug HCl

Resin salt + NaCl $\rightleftharpoons$ resin chloride + sodium salt of the drug

When the chemical combination of the drug with the appropriate ion-exchange resin is acted upon by the ions in the digestive juices of the gastrointestinal tract, exchange and the even liberation of the drug occurs over an extended period of time.[136]

Cation-Exchange Resins—The most common cationic exchangers contain

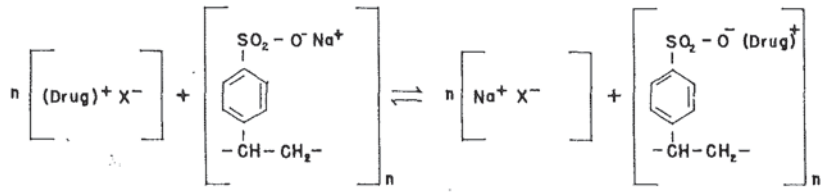


Fig 27-11—Schematic representation of formation of drug resinate.[137]

either carboxyl or sulfonic acid groups distributed throughout the resin particles. The "form" of the resin is named after the exchangeable ion contained in it;[136] for example, the ephedrine form exchanges ephedrine.

The drug resinates are products of a double displacement reaction involving (1) a drug in the form of a cation, and (2) a synthetic acidic cation-exchange resin. This reaction is schematically illustrated in Fig 27-11.[137]

Chaudhry and Saunders,[138] in investigations concerning ephedrine, have found that the ephedrine form of the carboxylic acid (cation-exchange) resin releases ephedrine very rapidly in acid solution, whereas the sulfonic acid (cation-exchange) resin provides a more moderate release in acid solution. Townsend[139] has likewise stated that carboxylic acid cation exchangers, though possessing a higher binding capacity, liberate the drugs more quickly and at a less constant rate than the complexes made with the sulfonic acid cation exchangers. Smith *et al*,[140] in developing a liquid antihistaminic preparation with sustained-release properties, also found that the use of a carboxylic acid (cation-exchange) resin (adsorbate) showed a very rapid release of methapyrilene; and, if a slower and more prolonged release of the drug was desired, the sulfonic acid (cation-exchange) resin appeared to be the carrier of choice. The more rapid removal of drug from a carboxylic acid (cation-exchange) resin and the slower removal of drug from the sulfonic acid (cation-exchange) resin was also shown by Nash and Crabtree.[141]

Hays[142] has stated that Strasenburgh has been marketing a number of preparations since November 1955 based upon ingredients forming complexes with ion-exchange resins. This company has been marketing drugs in tablet and liquid dosage forms based on a sustained-release principle which they have termed *Strasionic*. The principle is based on the fact that the formation of complexes utilizing either organic acids or bases as well as certain ion-exchange resins proceeds at a finite reaction rate and dissociates at a finite rate. If the proper ion-exchange resin is chosen, the rate of dissociation can be controlled to produce a uniform rate of release which is dependent upon the concentration of available ions.

Hays obtained US Patent 3,035,979, on May 22, 1962, for a pharmaceutical composition containing a resin-narcotic compound and a resin-antihistaminic compound in orally-administered unit-dosage forms which can be administered to a patient at prolonged intervals. Dihydrocodeine resin adsorption compound or dihydrocodeinone resin adsorption compound was much more effective singly than the corresponding free drugs administered singly to maintain the cough suppression effect in dogs over a prolonged period of time, and the mixture of either resin-narcotic compound with the dialkylamino ethoxy antihistamine resin was even better. The sulfonic acid cation-exchange resins (previously mentioned) were found to be very suit-

able to react with codeine, dihydrocodeine, morpholinoethyl morphine, or dihydrocodeinone (hydrocodone) to give compounds which hydrolyze slowly and maintain their antitussive effect over a prolonged period.

Complexation

Gennaro[142a] has defined complex compounds as primarily those molecules in which most of the bonding structure can be described by the classic theories of valency between atoms but one or more of the bonds are somewhat anomalous and, therefore, complex. Accordingly, the process of preparing such compounds is referred to as complexation. However, Gennaro[142a] indicates that many compounds which are presently referred to as complexes have been thoroughly studied and their structures sufficiently elucidated to no longer classify them as complex.

A drug contained in a complex is usually pharmacologically ineffective, and must dissociate at some stage in the body before it can exert its usual pharmacologic effect.[142b]

Ion-exchange phenomena may not correctly be included as part of complexation; however, Gennaro states that perhaps there is some rationale for the inclusion of ion exchange because it involves both absorption and adsorption.[142c] Nevertheless, ion-exchange phenomena have been considered separately in previous paragraphs.

Protein Binding—Drugs may be complexed or bound to proteins, and binding by proteins can markedly influence the biological action of such medicinal agents. Levy[142d] has stated that many drugs are partially bound to plasma proteins and exist in the blood in part as free drug and in part as a drug-protein complex. Only the free drug can diffuse to other tissues; the protein-bound portion does not pass across blood-vessel walls in the healthy individual.[142d] The greater the degree of protein binding, the smaller the amount of (unbound) drug which is available to extravascular sites.[142d] Therefore, blood-level data of drugs susceptible to protein binding (like the penicillins) should be accepted with reservation because the high blood levels of the combination of bound and unbound drug actually results in low drug concentration (of unbound drug) in extravascular sites and concomitant low therapeutic effectiveness. Stated in another fashion, such drug-blood-level data are not indicative of therapeutic effectiveness.

The bound drug may provide a reservoir which is converted into the active free form as needed to maintain a constant blood level over extended periods of time, *eg*, suramin strongly binds with plasma or tissue proteins, and the complex acts as a reservoir to release the drug slowly and permit it to exert its antitrypanosomal activity over a period of months following a single dose.[142e] Mepacrine and phenylbutazone also bind with plasma or tissue proteins.[142f]

The tetracyclines form complexes with divalent and trivalent cations (which apparently serve as a connecting bridge between the drug and protein molecules), and are absorbed much less readily than uncomplexed tetracyclines.[142g]

Other Examples—Graham and Baker have indicated that many hydrocolloids are polyanionic, can enter into strong interactions with cationic drugs such as many of the antihistamines, and can probably form highly insoluble complexes with prolongation of therapeutic activity.[142h] Likewise, either zinc or tannic acid insoluble complexes have been used to provide various degrees of increased duration of release, *eg*, zinc insulin and pitressin tannate.[142i] With vitamin B_{12}, neither zinc alone nor tannic acid alone has any marked influence on the retardation of the absorption of the vitamin. However, the reaction product of vitamin B_{12}, tannic acid, and zinc provides a triple complex derivative of greatly enhanced insolubility with retardation of absorption when injected in animals or humans.[142i]

Drug complexation with nonabsorb-

able macromolecules, like polyvinylpyrrolidone, can also be a useful method of retarding or slowing drug absorption.[142j]

Obviously, the above examples of slow absorption could be classified under insolubility; however, the cause of the insolubility is complexation and, therefore, such examples fit into either category.

Evaluation of Prolonged-Action Pharmaceuticals

Blythe[111] stated that formulation work involving oral sustained-release preparations requires that the following determinations be made: the minimal effective therapeutic dose of the drug, the maximum amount that can be given without producing undesirable side effects, the optimal dose, the time required for the drug to produce its peak effect, and the interval of time that any given dose will be effective. These determinations, as well as others, are also applicable to all marketed drug products. Furthermore, before any pharmaceutical is marketed and distributed, the safety and reliability of the product are assured by physical, chemical, pharmacologic and/or clinical evaluations.

Since 1956, the literature has revealed the quality controls or evaluation procedures for prolonged-action pharmaceuticals. (Lest the reader forget, this sentence will serve as a reminder that, as previously indicated on page 1002, the words "prolonged" and "sustained" are used herein interchangeably.) Articles or chapters by Campbell,[143] Lazarus and Cooper,[144] Levy,[145] Myers,[146] Nelson,[147] Parrott,[148] Rosen,[149] and others have covered such evaluation procedures.

Nairn's review article[149a] has indicated the following suggested criteria for the evaluation of prolonged-action medication: (1) a suitable portion of the drug in the prolonged-action dosage form should be absorbed just as rapidly as it is absorbed from the conventional, regular-release, solid or liquid dosage form; (2) the drug in the prolonged-action dosage form should be just as available to the body as it is from a conventional, regular-release, solid or liquid dosage form; (3) high peak concentrations of drug in the plasma should not be observed when the prolonged-action dosage form is administered as compared to the same amount of drug in the conventional, regular-release, solid or liquid dosage form; (4) prolongation of action of the drug in the prolonged-action dosage form should be evident when compared with the same amount of drug in the conventional, regular-release, solid or liquid dosage form; and (5) the prolonged-release dosage form should provide constancy of release.

Section 502(a) of the Food, Drug, and Cosmetic Act defines a drug as misbranded if its labeling is false or misleading; therefore, prolonged-action drugs are misbranded unless they provide the duration of therapeutic effect that is represented in the labeling. Furthermore, any dosage form that contains a quantity of active ingredients which is not recognized as safe for administration as a single dose is considered a new drug within the meaning of section 201(p) of the aforesaid FD&C Act because there is the possibility of unsafe overdosage if such products improperly release active ingredients at one time or over too short a time interval.[146]

The FDA announced, on July 14, 1964, the seizure of a number of products on charges of false claims because the products were labeled as providing up to 12 hours of continuous relief and contained too little active ingredients to be effective over a 12-hr period.[146a]

On September 6, 1967, the *Federal Register* indicated the (unsuccessful) proposal of a regulation to insure that timed-release dosage forms of drugs shall release the active ingredients at a safe and desired rate. Following is the proposal of August 28, 1967, which was signed by the US Deputy Commissioner of Food and Drugs and appeared in the aforementioned *Federal Register:*

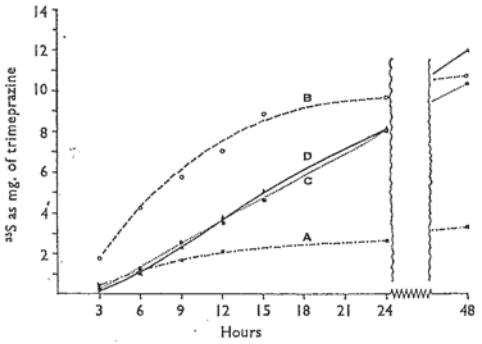


Fig 27-16—Cumulative average ^{35}S urinary excretion of adult human subjects after oral administration of labelled trimeprazine. A: 5 mg once daily to 4 subjects; B: 15 mg once daily to 4 subjects; C: 5 mg 3 times a day every 4 hours (total of 15 mg) to 5 subjects; D: 15-mg sustained-release capsules to 5 subjects. The drug was administered at 0 hour in the once-a-day regimens and at 0, 4, and 8 hours in the 3-divided-doses regimen.[167]

within the compressed timing of a development project. In such cases, it is necessary to decide whether effort is best spent in developing conventional biochemical methodology, pushing the human dose to the limit, or in perhaps synthesizing a radioactively-labeled compound resulting in greater immediate expense but less elapsed time and effort."

When using radioactive-tracer techniques, it must be emphasized that data therefrom must be correlated with clinical response since the persistence of the isotopic atom may occur without regard to any changes in the chemical structure of the molecule in which it has been incorporated.[159a]

Summary Regarding Evaluation Procedures

Campbell and Morrison[168] aptly summarized the status of evaluation of prolonged-action pharmaceuticals by stating in 1962, "Although there are a number of satisfactory products of this type on the market, much more work needs to be done both by industry and by regulatory bodies before the physician can be assured of consistently reliable results from these preparations."

References

1. Stempel E: *Drug Cos Ind* **98**:44 (Jan); 36 (Feb) 1966.

2. Dragstedt CA: *JAMA* **168**:1652, 1958.

3. Nelson E: Chapter 38 of *Remington's Practice of Pharmacy*, 12th Ed. Easton, Pa, Mack Publishing Co, 1961, p 498.

3a. Parrott EL: Chapter 3 of *Prescription Pharmacy*, edited by Sprowls JB Jr. Philadelphia, JB Lippincott Co, 1963, p 139.

4. Wilson A: *J Pharm Pharmacol* 11 Suppl, 46T (Dec) 1959.

5. Cooper J: *Drug Cos Ind* **81**:312, 1957.

6. Campbell JA, Morrison AB: *JAMA* **181**:102, 1962.

7. Levy G: *JAPhA* **NS4**:16, 1964.

8. Dragstedt CA: *JAMA* **168**:1654, 1958.

9. Parrott EL: Chapter 3 of *Prescription Pharmacy*, edited by Sprowls JB Jr. Philadelphia, JB Lippincott Co, 1963, p 148.

9a. Doluisio JT, Swintosky JV: Biopharmaceutics. *Remington's Pharmaceutical Sciences*, 13th Ed. Easton, Pa, Mack Publishing Co, 1965, p 380.

9b. Lowenthal W, Borzelleca JF: *J Pharm Sci* **54**:1793, 1965.

10. Nelson E: Chapter 38 of *Remington's Practice of Pharmacy*, 12th Ed. Easton, Pa, Mack Publishing Co, 1961, p 495.

11. Teorell, T: *Arch Intern Pharmacodyn* **57**:205–226, 1937.

12. Wagner JG: *J Pharm Sci* **50**:360, 1961; *University of Wisconsin School of Pharmacy Bulletin*, Spring 1962, p 4.

13. Wagner JG: *University of Wisconsin School of Pharmacy Bulletin*, Spring 1962, pp 3–4.

14. Drill VA: *Pharmacology in Medicine*. New York, McGraw-Hill Book Co, Inc, 1954, p. 1/11.

15. Campbell JA, Nelson E, Chapman DG: *Can Med Assoc J* **81**:15–20, (July 1) 1959.

16. Nelson E, Schaldemose I: *JAPhA, Sci Ed* **48**:489, 1959.

17. Wilson A: *J Pharm Pharmacol* 11 Suppl, 44T (Dec) 1959.

17a. Hollister L, Levy G: *J Pharm Sci* **54**:1129, 1965.

18. Clark AJ: *Applied Pharmacology*, 7th Ed. Philadelphia, Blakiston Co, 1940, pp 26–27.

19. Wilson A: *J Pharm Pharmacol* 11 Suppl, 50T (Dec) 1959.

20. Drill VA: *Pharmacology in Medicine*. New York, McGraw-Hill Book Co, Inc, 1954, 1–12.

21. Marsh DF: *Outline of Fundamental Pharmacology*. Springfield, Ill, Charles C Thomas, 1951, p 124.

22. Jenkins GL, *et al: The Chemistry of Organic Medicinal Products*, 4th Ed. New York, John Wiley & Sons, 1957, p 292.

22a. Package Insert of Tablets Colbenemid (Benemid & Colchicine). West Point, Pa Merck Sharp & Dohme, April 1968.

23. Wilson A: *J Pharm Pharmacol.* 11 Suppl, 51T (Dec) 1959.

24. Wagner JG: *J Pharm Sci* **50**:362, 1961. *Drug Intell:* **2:** 38–42, 1968.

25. Nelson E: *J Pharm Sci* **50**:181, 1961.

26. Dominguez R: *Medical Physics II*. Chicago, Yearbook Publishers, Inc, 1950, pp 476–489.

27. Wilson A: *J Pharm Pharmacol.* 11 Suppl, 48T (Dec) 1959.

28. Wilson A: *J Pharm Pharmacol.* 11 Suppl, 47T (Dec) 1959.

28a. Ballard BE: *J Pharm Sci* **57**:363, 375, 1968.

29. Goodman L, Gilman A: *The Pharmacological Basis of Therapeutics*. New York, Macmillan Co, 1941, p 8.

30. Miller RH: Chapter 5 of *Husa's Pharmaceutical Dispensing*, 5th Ed. Easton, Pa, Mack Publishing Co, 1959, p 67.

31. *New and Nonofficial Drugs*. Philadelphia, JB Lippincott Co, 1963, p 655.

32. Goodman L, Gilman A: *The Pharmacological Basis of Therapeutics*. New York, Macmillan Co, 1941, p 1239.

33. Goodman L, Gilman A: *The Pharmacological Basis of Therapeutics*. New York, Macmillan Co, 1958, pp 1672–1673.

34. Brzezinski A, Bromberg YM, Sulman FG: *JAPhA, Sci Ed* **46**:110, 1957; citing Bromberg, YM, Brzezinski A, Sulman FG: *Proc Exptl Biol Med* **64**:354, 1947.

35. Wagner JG: *J Pharm Sci* **50**:383–384, 1961.

36. Ballard BE, Nelson E: *J Pharm Sci* **51**:915–924, 1962.

37. Ballard BE: *J Pharm Sci* **55**:515, 1966.

38. Simond A, *et al: JAPhA, Sci Ed* **39:** 52, 1950.

39. Clark AJ: *Applied Pharmacology*, 7th Ed. Philadelphia, Blakiston Co, 1940, p 21.

40. Davison FR: *Synopsis of Materia Medica, Toxicology, and Pharmacology*, 3rd Ed. St. Louis, CV Mosby Co, 1944, p 24.

41. Abbott DD, *et al: JAPhA, Sci Ed* **48:** 19, 1959.

42. Abbott DD, *et al: JAPhA, Sci Ed* **48:** 20, 1959.

43. Abbott DD, *et al: JAPhA, Sci Ed* **48:** 21, 1959.

44. Wagner JG: *J Pharm Sci* **50**:369–378, 1961; *Drug Intel.* Biopharmaceutics, *Drug Intell.* **2**:30–34, 80–85, 112–117, 144–151, 181–186, 244–248, 294–301, 1968; **3**:21–27, 108–112, 170–175, 128–203, 224–229, 278–285, 324–330, 357–363, 1969; 4:17–23, 32–37, 77–82, 92–96, 132–137, 1970.

45. Enesco J, *et al: Bull Acad Med Roumanie* 4:1–9, 1939; cited by *Chem Abstr* **33:** 8308, 1939.

46. Cacchillo AF, Hassler WH: *JAPhA, Sci Ed* **43**:683–684, 1954.

47. Peterson CF, Lee CO, Christian JE: *JAPhA, Sci Ed* **42**:731–734, 1953.

48. Tice LF: *Pharm Intern* **8**:16 (Sept) 1954.

49. *Drug Cos Ind* **79**:103, 1956.

50. Hassler WH, Sperandio GJ: *JAPhA, Prac Ed* **14**:54, 1953.

51. Wagner JG: *J Pharm Sci* **50**:379, 1961; citing Samelius U, Astrom A: *Acta Pharmacol Toxicol* **14**:240, 1958.

52. Riegelman S, Crowell WA: *JAPhA, Sci Ed* **47**:115, 1958.

53. Riegelman S, Crowell WA: *JAPhA, Sci Ed* **47**:127–128, 1958.

54. Riegelman S, Crowell WA: *JAPhA, Sci Ed* **47**:127, 130, 1958.

55. Riegelman S, Crowell WA: *JAPhA, Sci Ed* **47**:130, 1958.

56. Wagner JG: *J Pharm Sci* **50**:359–387, 1961; *Drug Intell.*

57. Jenkins GL, *et al: The Chemistry of Organic Medicinal Products*, 4th Ed. New York, John Wiley & Sons, 1957, p 205.

58. *USP XVII*, pp 519–520, 1965; *USP XVIII*, pp 544.

59. Marsh DF: *Outline of Fundamental Pharmacology*. Springfield, Ill, Charles C Thomas, 1951, p 117.

60. *Drug & Cos Ind* **93**:385, 1963; citing US Pat 3,096,249.

60a. Lazarus J, Lachman L: *Bull Paren Drug Ass* **21**:185, 1967; citing Hilleman MR: *Amer Rev Resp Dis* **90**:683, 1964.

60b. *The New York Times*, Sept 19, 1964, p 31L.

60c. Lazarus J, Lachman L: *Bull Paren Drug Ass* **21**:187, 189, 1967; citing US Pat 3,149,036 of Sept 1964.

60d. *Drug Cos Ind*, (Dec) 1966, p 168.

60e. Parrott EL: *Pharmaceutical Technology*. Minneapolis, Burgess Publishing Co, 1970, p 100.

60f. Levy G: Chapter 2 of *Prescription Pharmacy*, edited by JB Sprowls Jr. Philadelphia, JB Lippincott Co, 1963, p 60.

60g. Morozowich T, *et al: J Pharm Sci* **51**:993, 1962.

60h. Hamlin WE, *et al: J Pharm Sci* **54:** 1651, 1965.

61. Nelson E: *JAPha, Sci Ed* **47**:299, 1958.

62. Nelson E: *J Pharm Pharmacol* 11 Suppl, 49T (Dec) 1959.

63. Truitt EB Jr, Morgan AM: *J Pharm*

Sci **53**:133–134, 1964; citing Leonards JR: *Proc Soc Exptl Biol Med* **110**:304, 1962.

64. Leonards JR: *Clin Pharmacol Exptl Therap* **4**:476–479, 1963.

65. Jenkins GL, *et al: Scoville's The Art of Compounding*, 9th Ed. New York, Blakiston Division, McGraw-Hill Book Co, Inc, 1957, p 299.

66. Ober SS, *et al: JAPhA, Sci Ed* **47**:667, 1958.

67. Barr M: *Mid-Atlantic Apoth.* (Jan) 1957, p 12.

68. *New and Nonofficial Remedies.* Philadelphia, JB Lippincott Co, 1957, p 131.

69. *New and Nonofficial Remedies.* Philadelphia, JB Lippincott Co, 1957, p 129.

70. Barr M: *Mid-Atlantic Apoth.* (Jan) 1957, p 13.

71. Schanker LS: *Ann Rev Pharm* **1**:30, 32, 1961.

72. Wagner JG: *J Pharm Sci* **50**:366, 1961; citing Higuchi WI, Seminar at Upjohn Co, Nov 26, 1959.

73. Wagner JG: *J Pharm Sci* **50**:366, 1961.

74. Schroeter LC: Presentation at St John's University Pharmacy Congress, April 25, 1962.

75. Nelson E: Chapter 38 of *Remington's Practice of Pharmacy*, 12 Ed. Easton, Pa, Mack Publishing Co, 1961, p 497.

76. Buckwalter FH, Dickison HL: *JAPhA, Sci Ed* **47**:661, 1958.

77. Simond A, *et al: JAPhA, Sci Ed* **39**: 53, 1950.

78. Nelson E: Chapter 41 of *Remington's Pharmaceutical Sciences*, 13th Ed. Easton, Pa, Mack Publishing Co, 1965, p 614; citing Nelson E: *JAPhA, Sci Ed* **48**:96, 1959.

79. Edkins RP: *J Pharm Pharmacol* 11 Suppl, 62T (Dec) 1959; citing Maier and Gasche, *Schweiz med Wschr* **76**: 1192, 1946 and Joel *J Clin Endocrinol* **8**:97, 1948.

80. Buckwalter FH, Dickison HL: *JAPhA, Sci Ed* **47**:663, 1958.

81. Nelson E: *JAPhA, Sci Ed* **48**:97, 1959.

82. Glazko AJ, *et al: Antibiot Chemother* **8**: 516, 1958.

83. Glazko AJ, *et al: Antibiot Chemother* **8**: 526, 1958.

84. Aguiar AJ, *et al: J Pharm Sci* **56**:847, 1967.

84a. Cifelli T Jr: *Drug Cos Ind* **86**:356–357, 1960.

84b. Finholt P, Solvang S: *J Pharm Sci* **57**:1325, 1968.

85. Osol A, Farrar GE Jr: *The Dispensatory of the United States of America*, 24th Ed. Philadelphia, JB Lippincott Co, 1947, p 496.

86. *JAPhA, Prac Ed* **18**:181, 1957.

87. *Gelatin*, Gelatin Research Society of America, Inc, New York, 1954, p 22.

88. *American Druggist* **136**: No 6, 49, 1957.

89. *Modern Medicine* **27**: No 6, 236, 1959.

89a. Coles CLJ, *et al: J Pharm Pharmacol* **17**: Suppl, 87S and 90S, 1965.

89b. Kristensen K, Hansen T: *J Pharm Sci* **55**:613, 1966.

90. *Drug Cos Ind* **84**:650, 1959.

91. *New and Nonofficial Drugs.* Philadelphia, JB Lippincott Co, 1964, pp 122–123.

92. Svenson SE, *et al: Antibiot Med* **2**: 150, 1956.

93. Buckwalter FH, Dickison HL, *JAPhA, Sci Ed* **47**:662, 1958.

94. Richards RK, *et al: Proc Soc Exptl Biol Med* **48**:403, 1941.

95. Simond A, *et al: JAPhA, Sci Ed* **39**: 52, 1950.

96. *New and Nonofficial Drugs.* Philadelphia, JB Lippincott Co, 1963, p 689.

97. Goodman L, Gilman A: *The Pharmacological Basis of Therapeutics.* New York, Macmillan Co, 1941, p 1195.

98. Barr M: *Mid-Atlantic Apoth* p 11 (March) 1957.

99. *Modern Medicine* **27**: No 6, 231, 1959.

100. Schueler FW, Keasling HH: *JAPhA, Sci Ed* **45**:792, 1956.

101. Schueler FW, Keasling HH: *JAPhA, Sci Ed* **45**:795, 1956.

101a. Truitt EB, Morgan AM: *J Pharm Sci* **53**:130, 1964.

102. Levy G: *J Pharm Sci* **50**:392, 1961.

102a. Niebergall PJ, Goyan JE: *J Pharm Sci* **52**:30, 1963; citing Noyes AA, Whitney WR: *J Am Chem Soc* **19**:930, 1897.

102b. Niebergall PJ, Goyan JE: *J Pharm Sci* **52**:30, 1963; citing Hixson AW, Crowell JH: *Ind Eng Chem* **23**:923, 1931.

102c. Hamlin WE, Nelson E, Ballard BE, Wagner JG: *J Pharm Sci* **51**:435, 1962; citing Nelson E: *JAPhA, Sci Ed* **46**:607, 1957.

102d. Niebergall PJ, Goyan JE: *J Pharm Sci* **52**:29, 1963.

102e. Schroeter LC, Wagner JG: *J Pharm Sci* **51**:957, 1962.

102f. McClintock WJ, *et al: J Pharm Sci* **54**:1782, 1965.

102g. Riegelman S: *Drug Inf Bull* **3**:67, 1969.

102h. Finholt P, *et al: Medd Norsk Farm Selskap* **28**:19, 1966; citing Schroeter LC, *et al: J Pharm Sci* **51**:865, 1962.

102i. Finholt P, *et al: Medd Norsk Farm. Selskap* **28**:19, 1966; citing Middleton EJ, *et al: J Pharm Sci* **53**:1378, 1964.

103. Martin EW, Ed: *Remington's Pharmaceutical Sciences*, 13th Ed Easton, Pa, Mack Publishing Co, 1965, p 613.

104. Blythe RH: *Drug Stand* **26**:1, 1958.

105. Swintosky JV: *Drug Cos Ind* **87**:552, 1960.

106. Sintosky JV: *Drug Cos Ind* **87**:550, 552, 1960.

107. Swintosky JV: *Drug Cos Ind* **87**:548, 1960.
108. Swintosky JV: *Drug Cos Ind* **87**:550, 1960.
109. Swintosky JV: *Drug Cos Ind* **87**:465, 553, 1960.
110. Swintosky JV: *Drug Cos Ind* **87**:552, 553, 1960.
111. Blythe RH: *Drug Stand* **26**:2, 1958.
112. Lazarus J, Cooper J: *J Pharm Sci* **50**: 722, 1961.
113. Nelson E: Chapter 41 of *Remington's Pharmaceutical Sciences*, 13th Ed. Easton, Pa, Mack Publishing Co, 1965, p 618.
114. Jack D: *Pharm J* June 30, 1962, p 584.
114a. *Drug Cos Ind* **90**:204, 1962.
114b. Gibaldi M: *Continuing Education for Pharmacists, Biopharmaceutics of Antibiotics*, sponsored by the Schools of Pharmacy of State U of NY at Buffalo and St John's U held at St John's U on Nov 15, 1967.
115. Cooper J, Windheuser JJ: US Pat 2,887,438 of April 19, 1959.
116. *Rapid and Prolonged Action Repetabs*. Bloomfield, NJ, Schering Corp, 1954, p 4.
117. Cooper J: *Drug Cos Ind* **81**:313, 1957.
118. Cooper J: *Drug Cos Ind* **81**:400, 1957.
119. Personal communication from Cooper, J., Director of Research, Ciba Pharmaceutical Co, Summit, NJ, March 12, 1964.
120. Personal communication from Jackson EL: AH Robins Co, Dept of Scientific Development, Richmond, Va, Jan 30, 1959.
121. Personal communication from Eckman JW (Aug 25, 1958), and Cain RA (Dec 26, 1961), Thos Leeming & Co, Inc, Parsippany, NJ.
121a. Nysco Laboratories Inc, 34–24 Vernon Blvd, Long Island City, Queens, NY
122. Lyman RA: *American Pharmacy*. Philadelphia, JB Lippincott Co, 1945, p 147.
123. Hawk PB, Bergeim O: *Practical Physiological Chemistry*, 11th Ed. Philadelphia, Blakiston Co, 1937, p 7.
124. Marsh DF: *Outline of Fundamental Pharmacology*. Springfield, Ill, Charles C Thomas, 1951, p 117.
125. *USP XVI*, pp 347–349; *NF XII*, p 176.
126. Osol A, Farrar GE Jr: *The Dispensatory of the United States of America*, 24th Ed. Philadelphia, JB Lippincott Co, 1947, p 570; citing Bailey CC, Marble A: *JAMA* **118**:683–690, 1942.
127. *USP XVIII*, 335–336.
128. *USP XVIII*, 147–148.
129. Kennon L, Higuchi T: *JAPhA, Sci Ed* **45**:157, 1956.
130. *Fortune*, (July) 1951, p 107.
131. Wallwork SC: *Physical Chemistry for Students of Pharmacy and Biology*. New York, Longmans, Green and Co, 1956, p 253.
132. *Amber-Hi-Lites*. Philadelphia, Rohm & Haas Co, (Jan) 1960, p 1.
133. Cavalitto CL, *et al: J Pharm Sci* **52**: 259, 1963.
134. *Amber-Hi-Lites*. Philadelphia, Rohm & Haas Co, (Jan) 1960, p 2.
135. Lazarus J, Cooper J: *J Pharm Pharmacol* **11**:269–270, 1959; citing Abrahams and Linell, *Lancet* **2**:1317, 1957.
136. *Drug Cos Ind* **58**:225, 1958.
137. Becker BA, Swift JG: *Toxicol Appl Pharmacol* **1**:No 1, 42, 1959.
138. Chaudhry NC, Saunders L: *J Pharm Pharmacol* **8**:975, 1956.
139. Townsend EH Jr: *New Eng J Med* **258**:64, 1958.
140. Smith HA, *et al: JAPhA, Sci Ed* **49**: 95, 1960.
141. Nash JE, Crabtree RE: *J Pharm Sci* **50**:137, 1961.
142. *Drug Cos Ind* **82**:511, 1958.
142a. Gennaro AR: Chapter 15 of *Remington's Pharmaceutical Sciences*, 13th Ed. Easton, Pa, Mack Publishing Co, 1965, p 212.
142b. Levy G: Chapter 2 of *Sprowl's Prescription Pharmacy*. Philadelphia, JB Lippincott Co, 1963, p 64.
142c. Gennaro AR: Chapter 15 of *Remington's Pharmaceutical Sciences*, 13th Ed. Easton, Pa, Mack Publishing Co, 1965, pp 212, 217.
142d. Levy G: Chapter 2 of *Sprowls' Prescription Pharmacy*. Philadelphia, JB Lippincott Co, 1963, p 51.
142e. Martin A: *Physical Pharmacy*. Philadelphia, Lea & Febiger, 1960, p 425; citing Goldstein A: *Pharmacol Revs* **1**:102, 1949.
142f. Parrott EL: *Pharmaceutical Technology*. Minneapolis, Burgess Publishing Co, 1970, p 100.
142g. Levy G: Chapter 2 of *Sprowls' Prescription Pharmacy*. Philadelphia, JB Lippincott Co, 1963, p 66; citing Kunin CM, *et al: Clin Pharmacol Ther* **2**:51, 1961 and Kohn KW: *Nature* **191**:1156, 1961.
142h. Graham HD, Baker YM: *J Pharm Sci* **52**:964, 1963.
142i. Thompson RE, *Bull Paren Drug Ass* **14**:8, 1960.
142j. Levy G: Chapter 2 of *Sprowls' Prescription Pharmacy*. Philadelphia, JB Lippincott Co, 1963, p 65.
143. Campbell JA: *Drug Cos Ind* **87**:621, 1960.
144. Lazarus J, Cooper J: *J Pharm Pharmacol* **11**:257, 1959; *J Pharm Sci* **50**:715, 1961.
145. Levy G: Chapter 2 of *Prescription Pharmacy*, edited by Sprowls JB Jr. Philadelphia, JB Lippincott Co, 1963.
146. Myers EL, *Drug & Cos Ind* **87**:622, 1960.

146a. *The New York Times*, July 15, 1964, p 37.
147. Nelson E: Chapter 38 of *Remington's Practice of Pharmacy*, 12th Ed. Easton, Pa, Mack Publishing Co, 1961.
148. Parrot EL: Chapter 3 of *Prescription Pharmacy*, edited by Sprowls JB Jr. Philadelphia, JB Lippincott Co, 1963.
149. Rosen E: Presentation at St. John's University Pharmacy Congress, April 25, 1962.
149a. Nairn JG: *Bul Ontario Col Pharm* **18**:104, 1969.
149b. Personal communication of Nov 25, 1969 from Demus TA, Director of Consumer Services Staff, Office of Assistant Commissioner for Education and Information, US Department of HEW.
150. Myers EL: *Drug Cos Ind* **87**:711, 1960.
151. Myers EL: *Drug Cos Ind* **87**:623, 1960.
151a. Nairn JG: *Bul Ontario Col Pharm* **18**:97, 1969.
152. Lazarus J, Cooper J: *J Pharm Pharmacol* **11**:272–277, 1959.
153. Myers EL: *Drug Cos Ind* **87**:623 etc, 1960.
154. Lazarus J, Cooper J: *J Pharm Sci* **50**: 723–725, 1961.
155. Wagner JR: *Drug Stand* **27**:185, 1959.
156. Wiegand RG, Taylor JD: *Drug Standards*, **27**:165, 1959.
156a. *NF XIII*, pp 882–883.
156b. King RE: Chapter 39 of *Remington's Pharmaceutical Sciences*, 13th Ed. Easton, Pa, Mack Publishing Co, 1965, p 562.
156c. Brownell W, Riegelman S, Mader WJ: *Report of Ad Hoc Committee on Drug Dissolution Methodology*, available from Academy of Pharmaceutical Sciences, 2215 Constitution Ave, NW, Washington, DC 20037.
156d. *NF XIII*, pp 802–803.
156e. Nairn JG: *Bul Ontario Col Pharm* **18**:101, 1969.
157. Lazarus J, Cooper J: *J Pharm Sci* **50**: 725, 1961.
157a. Nairn JG: *Bul Ontario Col Pharm* **18**:102, 1969; citing Bercher PR, *et al: Cur Therap Res* **9**:379, 1967.
157b. Barr WH: *Drug Information Bul* **3**: 37, 1969; citing Murray WJ, *et al: Clin. Pharmacol & Therap* **5**:21, 1964.
157c. Nairn JG: *Bul Ontario Col Pharm* **18**:102, 1969.
157d. Nairn JG: *Bul Ontario Col Pharm* **18**:103, 1969.
157e. Silson JE: *Drug Cos Ind* **96**:714, 1965.
158. Lazarus J, Cooper J: *J Pharm Pharmacol* **11**:277, 1959.
159. Wagner JG, *et al: J Pharmacol Exptl Therap* **129**:105, 1960.
159a. Silson JE: *Drug Cos Ind* **96**:718, 1965.
160. Campbell JA, *et al: Can Med Ass J* **81**:15, July 1, 1959.
161. Campbell JA: *Drug Cos Ind* **87**:705, 1960.
162. Campbell JA: *Drug Cos Ind* **87**:704, 1960.
163. Campbell JA: *Drug Cos Ind* **87**:705–706, 1960.
164. Shenoy KG, *et al: Toxicol Appl Pharmacol* **2**:No 1, 100–110, 1960.
165. Chapman DG, *et al: Can Med Ass J* **81**:470–477, 1959.
165a. Campbell JA, Morrison AB: *Practitioner* **183**:762, 1959.
166. Christian JE: *J Pharm Sci* **50**:1–13, 1961.
167. Rosen E, Swintosky JV: *J Pharm Pharmacol Supp* **12**:237T-244T, 1960.
168. Campbell JA, Morrison AB: *JAMA* **181**:104, 1962.