REVIEW ARTICLE

ORAL PROLONGED ACTION MEDICAMENTS: THEIR PHARMACEUTICAL CONTROL AND THERAPEUTIC ASPECTS

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THE successful introduction of oral prolonged action substances has stimulated interest in the physical and chemical means of extending the therapeutic activity of a drug administered by this route. Only in the past few years have clinical reports on such formulations appeared in the medical literature. Concomitantly, questions have been raised concerning *in vitro* and *in vivo* measurements of the release rate of the active ingredient in preparations of this kind. The technique used for measuring the release of active substance from sugar or enteric coated tablets does not necessarily apply to these new forms, and modifications may be necessary. A critical review of sustained action medication, with particular emphasis on the measurement of pharmacological and therapeutic effects, appears appropriate at this time.

Various expressions have been used to describe oral sustained release preparations. Extended action, sustained release, sustained action, oral repository, timed disintegration, timed release, oral depot therapy, prolonged action, prolonged release, controlled release and protracted release are examples of terms in current usage. At a recent meeting of representatives of the major pharmaceutical manufacturing firms in the United States, various suggestions were made for a definitive term other than timed release[1]. In this review article, the terms prolonged action and sustained release will be used interchangeably.

Several definitions have been offered in the literature for prolonged action medication. Lang[2] used the designation "prolonged action" for formulations in which adequate measures provide a longer duration of therapeutic effect of the drug substance than is usually achieved with classical preparations. Theoretically, there would be an equilibrium in the body between the continuous administration and the inactivation and elimination of the active substance within the therepeutically optimal range of concentration. Abrahams and Linnell[3] have stated that ideally an orally administered drug should be in such form that a single dose would be continuously absorbed over an extended period of time thereby maintaining a uniform optimal level in the tissues and avoiding unnecessarily high peak concentrations as well as wasteful depressions. Blythe[4] describes oral sustained release preparations as those which "provide a sustained therapeutic effect by first releasing a therapeutic dose, then gradually and continually releasing medication over a prolonged period."

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He emphasises that sustained release is not to be confused with individual doses, usually two or three, released at widely spaced intervals. Micciche[5] has referred to oral-prolonged action medications as those which have a pre-established and controlled delayed release. This definition implies that the release pattern of the dosage form has been carefully determined and is consistently reproducible. Ettore[6] likewise defines an oral-prolonged action dosage form as one which permits a controlled release of the active drug, in regard to time, but adds the proviso that the relationships between absorption, elimination or metabolism of the drug should have already been studied.

Blythe's definition is based upon a pharmaceutical dosage form while the others are more general. If we are to be guided by these definitions, it is apparent that, before a suitable release pattern can be established, the fate of the drug in the body must be thoroughly understood. In spite of the long history of the use of drugs by absorption from the gastro-intestinal tract, the evolution of basic physiological understanding of the processes involved has been surprisingly slow. This situation may have been due to the experimental difficulties involved in such studies or, more probably, to the absence of a concerted attack on the problem. It is conceivable that the present rather excited interest in prolonged action medication may stimulate the initiation of the basic physiological researches.

Absorption of Drugs

Brodie and Hogben[7] in their review of the factors which affect drug action stated that "the duration of action of a drug will be determined to a considerable degree by localisation in various tissue depots, by metabolic transformation and by the interplay of the actions of absorption and excretion." After oral administration, a systemic drug must be absorbed to be effective. Brodie and associates have postulated the existence of a lipoid barrier between blood and the gastric and intestinal lumens. The lipid-soluble non-ionised forms of organic electrolytes are thought to passively diffuse through the barrier which is restrictive to the ionised lipid-insoluble form. Accordingly the distribution, and hence, from our immediate viewpoint, the absorption of many drugs is related to the dissociation constant of the substances. The acidic dissociation constant, Ka, is frequently expressed as the negative logarithm, pKa. A low value for the pKa of an acidic drug is indicative of a strong acid and a high value is characteristic of a weak acid. The reverse is obviously true for bases. The larger the pKa, the stronger the base. The mathematical factors mentioned in such dissociations and their relationship to pH and biological activity have been elaborated by Albert[8]. Since the dissociation constant is an equilibrium constant, the electrolyte will be 50 per cent dissociated when the pH of the solution containing the electrolyte is equal to the pKa. At one pH unit above or below the pKa value, the substance is only 10 per cent dissociated. Schanker[9,10] studied the absorption of a number of organic acids and bases from the rat stomach and intestine. These

substances differed in physical properties, chemical structure and pharmacological activity, yet their absorption could be predicted from their pKa and lipid solubility characteristics.

Hogben[11] demonstrated that the human stomach can similarly absorb most acidic drugs and weakly basic substances. Acidic drugs with a pKa of 3 or greater were found to be rapidly absorbed from the small intestine of the rat. Basic drugs were rapidly absorbed if their pKa's were less than 8. The rate of absorption of the more acidic and basic drugs was related to their degree of ionisation and lipid solubility of their non-ionised forms.

Other physiological factors of possible significance on the absorption of drugs have been reviewed by Best and Taylor[12] who particularly emphasised the role of stomach emptying time and water and salt concentration of the gastrointestinal tract contents. Levine[13] has emphasised the possible influence of mucin complex formation upon the absorption of certain drugs. In his study of intestinal absorption in man, Borgström[14] sampled the gastrointestinal contents at different levels of the tract. He fed six normal human subjects a 500 g. test meal consisting of corn oil, glucose, lactose and milk proteins, with polyethylene glycol as an indicator of the test meal, and radio-iodinated human serum albumin as the indicator of the food protein.

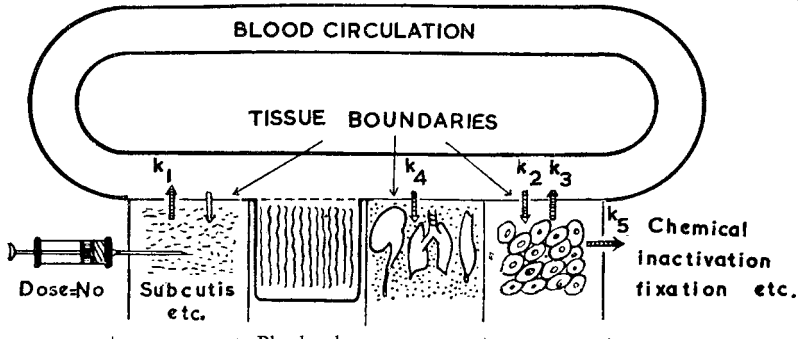
They found that the pH of the stomach contents decreased from four to five units in the first hour to about two units in the fourth hour when the stomach began to empty; the stomach secretions diluted the test meal about three to five times; during the 4-hour sampling period, a maximum amount of food was delivered to the duodenum in the second hour with smaller portions in the other hours; and the intestinal contents showed a constant pH in the duodenum of about 6·0 which gradually increased to 8·0 at the distal end. These investigators also found that the intestinal enzymes in the pancreatic secretion, lipase, trypsin, chymotrypsin and amylase are maintained in appreciable quantities over the length of the small intestine. The secretion of pancreatic juice began 10 to 20 minutes after the ingestion of the test meal and continued to flow as long as there was food in the stomach.

Prolonged Action Parenterals

Before venturing into the subject of prolonging the action of drugs administered orally, it is worthwhile to dwell upon some of the methods employed to prolong the action of drugs administered parenterally. Durel[15] used a 25 per cent injectable solution of polyvinylpyrrolidone as solvent for different water-soluble drugs for the purpose of prolonging their duration of activity in the organism. He reported laboratory and clinical studies which indicated that this solution increased the duration of action of insulin, adrenal cortical hormone, posterior pituitary, penicillin, anaesthetics, hypnotics, sodium salicylate and antihistamines. The mechanism of action of polyvinylpyrrolidone was explained on the basis of two of its properties: the ability of the macromolecule to combine with drugs which are then slowly released after injection and the slowing of

renal excretion without apparently disturbing the renal function. This latter property of retarding renal excretion of polyvinylpyrrolidone may account for its delaying action when the salicylate is given orally and the polyvinylpyrrolidone solution is injected intravenously. But others have been critical of these interpretations.

Substances such as probenecid[16], which inhibit renal tubular excretion, have been employed to prolong the action of drugs excreted in this particular way, like penicillin and aminosalicylic acid. The use of renal inhibitors to achieve this effect has not been received as well as the other techniques. The early investigators, Hagedorn[17] and Scott and Fisher[18] who studied the prolongation of therapeutic activity of insulin by coupling



Local	Drug depot	Blood and equivalent blood volume	Kidneys etc., elimination	Tissues	Tissue inactivation
Symbol ..	D	B	K	T	I
Amount ..	x	y	u	z	w
Volume ..	V_1	V_2	—	V_3	—
Conc. ..	x/V_1	y/V_2	—	z/V_3	—
Perm. coeff.	k'_1	—	k'_4	k'_3	—
Velocity \ out	$k_1=k'_1/V_1$	—	$k_4=k'_4/V_2$	$k_3=k'_3/V_3$	k_5 y
Const. / in	neglected	—	not existing	$k_2=k'_2/V_2$	—
Name of process	Resorption	—	Elimination	Tissue take-up and output	Inactivation

FIG. 1. Scheme of the concept of drug distribution, after Teorell, *Arch. int. Pharmacodyn.*, 1937, **57**, 205. Instead of injection, the drug depot can be administered by other routes.

the zinc salt of insulin with protamine assumed that a decrease in absorption can result in a more desirable distribution in the tissues. A single implantation of six 125 mg. pellets of desoxycorticosterone acetate has been employed to maintain a patient suffering from Addison's disease for an interval of approximately 34 weeks. An injection of about 3 mg. a day of desoxycorticosterone acetate in oil will maintain an Addisonian patient only for one day, while one injection of about 60 mg. of the microcrystalline trimethylacetate derivative of desoxycorticosterone in aqueous suspension vehicle has been demonstrated to maintain a patient for at least 4 weeks[19].

Desoxycorticosterone acetate in the form of implantation pellets is apparently slowly released from its intramuscular implant site, hence accounting for its longer action. When injected as a solution in oil,

desoxycorticosterone acetate probably enters the blood stream more rapidly and is metabolised quickly. The longer and constant therapeutic effect of the trimethylacetate derivative in suspension form may be attributed to the fact that the substance "behaves like a miniature pellet in that a small fraction of the total dose is absorbed daily"[20] and perhaps to its reduced solubility compared to the acetate.

Kinetics of Absorption

The assumption that a decrease in absorption can give a more suitable distribution in the tissues agrees with Teorell's[21] theoretical calculations published in 1937. He studied the kinetics of the distribution of a drug administered extravascularly and derived mathematical formulae which describe the concentration of a drug in the depot, the blood, the tissues, as well as the amount eliminated and inactivated as a function of time. Teorell, considering all extravascular sites including gastrointestinal or drug depots, presented the following "equation" to describe the distribution of a drug after administration:

$$\text{drug depot} \xrightarrow{k_1} \text{blood or equiv. blood volume} \underset{k_3}{\overset{k_2}{\rightleftharpoons}} \text{tissues} \xrightarrow{k_5} \text{tissue inactivation}$$

$$\text{blood or equiv. blood volume} \xrightarrow{k_4} \text{elimination (kidney)}$$

k_1, k_2 . . . k_5 represent the velocity constants which are measures of diffusion or inactivation (and "equivalent blood volume" represents the "lymph and other intercellular liquid and also those tissues which practically instantaneously come into equilibrium with the blood plasma in regard to the particular substance exchanged"). The "equation" actually summarises the schematic diagram (Fig. 1) used by Teorell in illustrating drug distribution graphically.

Using his mathematical formulae, Teorell obtained curves by assigning arbitrary values to the terms in his equations and making the numerical calculations.

It is seen in Figure 2 that a drug which is rapidly absorbed and is subject to elimination by the kidney or to tissue inactivation reaches an early maximum concentration in the blood after administration and then decreases exponentially. The maximum in the tissues occurs at a much later time than the blood peak. Tissue inactivation and elimination decrease the concentration of the drug in the tissues and the blood, whereas in their absence the blood and tissue levels soon reach equilibrium.

Figure 3 demonstrates the effect which different absorption rates have upon the blood and tissue time curves as is evident in curve $k_1 = 0{\cdot}001$ in graphs "B" and "C" of the figure. When the absorption is slow, the concentration magnitude is decreased, *but the duration is prolonged.* Teorell's basic premise is that a change in the absorption properties of a drug will affect the concentration levels and duration in the blood and tissues. He stated that "the maximum drug amount circulating in the blood is directly proportional to the dose given and approximately

directly proportional to the depot resorption intensity and inversely proportional to the elimination intensity."

Swintosky's[22] graphical data for the kinetics of absorption, distribution and excretion of sulphaethylthiadiazole in one individual appear to follow the theoretical curves developed more than 21 years ago by Teorell. In addition, an absorption rate curve is included, a kinetic factor not mentioned by Teorell.

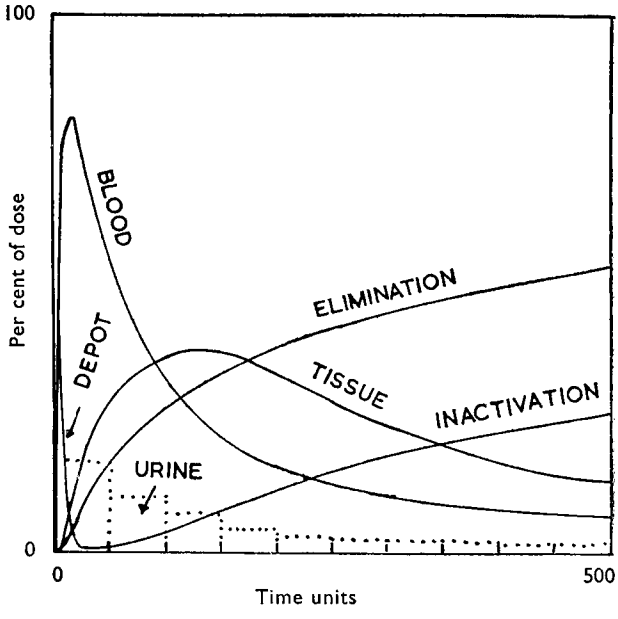


FIG. 2. Typical case of extravascular (i.e. orally or subcutaneously) administration in the presence of both elimination and tissue inactivation. Dotted bars indicate output in urine samples taken at equidistant intervals ($k_1 = 0{\cdot}2$; $k_2 = 0{\cdot}01$; $k_3 = 0{\cdot}005$, i.e. the ratio blood volume/tissue volume is 1 : 2; $k_4 = 0{\cdot}005$; $k_5 = 0{\cdot}002$).

After Teorell, *Arch. int. Pharmacodyn*, 1937, **57**, 205.

Dominguez and Pomerene[23] developed equations for calculating the instantaneous rate of absorption of an inert substance in diffusion equilibrium using creatinine, a substance which is not metabolised in the body. They stated that their method can be extended to more complicated problems in absorption.

The effects of an intravenous drip injection or continuous intravenous injection on blood and tissue concentration was also investigated by Teorell, again on the basis of theoretical mathematical principles[24]. When so administered, the rate of entry into the blood and tissue is constant and independent of time. Even though kidney elimination and tissue inactivation were considered appreciable, the tissue and blood level curves reached and maintained a maximum when the amount of drug entering the blood stream was constant and continuous.

Teorell's equation for extravascularly administered drugs does not show the effects, on the blood and tissue levels, of the absorption of small but continuous additional amounts of a drug substance after the absorption of the initial dose. Nelson[25] has shown that the quantity of drug administered orally which is needed to maintain the therapeutic level can be estimated mathematically. He derived an equation to estimate the

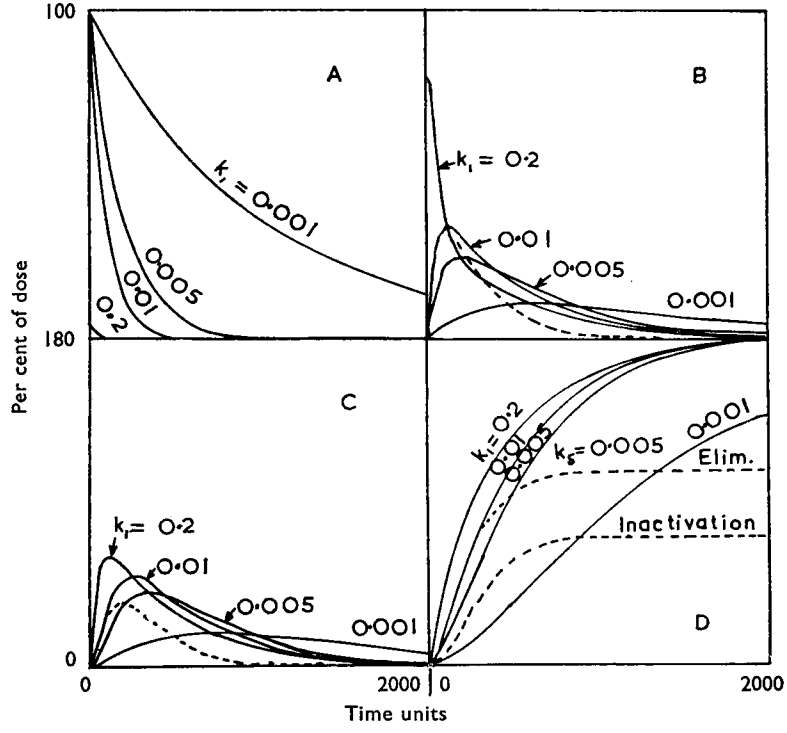


FIG. 3. Extravascular administration at different degrees of drug resorptivity. The figure shows the marked influence that a change in resorptivity (from the depot to the blood) has upon the cumulation curves in blood or the tissues. A, Depot. B, Blood. C, Tissues. D, Elimination (inactivation). k_1 = 0·2, 0·01, 0·005 or 0·001; k_2 = 0·01; k_3 = 0·01, i.e. blood volume/tissue volume is 1 : 1; k_4 = 0·005; k_5 = zero or 0·005.

After Teorell, *Arch. int. Pharmacodyn.*, 1937, **57**, 205.

amount of drug needed to maintain, for a given number of hours, the therapeutic level established by the initial dose contained in the prolonged action preparation. The therapeutic half-life of the drug in the body ($t_{1/2}$) must be known in order to calculate the amount of substance which has to be released from the dosage form. The equation is said to hold for drugs which are eliminated by a first order process:

$A = 0{\cdot}693\ bh/t_{1/2}$ where A = amount of drug required to maintain the level a given number of hours; h = number of hours; b = initial dose required for therapeutic effect.

Nelson states that the cumulative amount of drug released for absorption from a prolonged action preparation when plotted against the time should yield a straight line. A similar statement is made by Blythe[26]. The release of the substance must be constant and continuous if this criterion is to be met.

Boxer, Jelinek, Tompsett, DuBois and Edison[7] studied the effect of repeated intramuscular injections of the same quantities of streptomycin on the blood level in dogs. They concluded that for substances whose rate of decrease in the blood stream is proportional to their concentration,

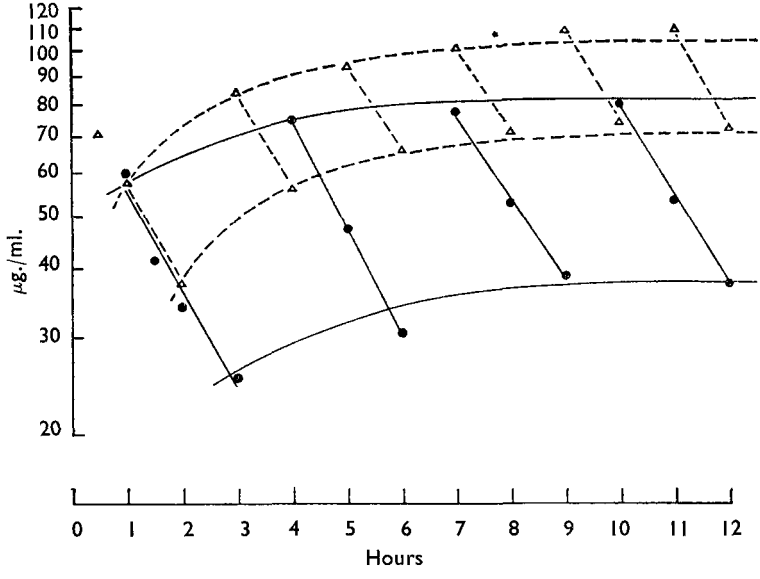


FIG. 4. Streptomycin concentration in the plasma of dogs after repeated intramuscular injections.

●—●20,500 μg./kg. every three hours.
△- -△ „ „ two „

After Boxer and colleagues, *J. Pharmacol.*, 1948, **92**, 226.

repeated injections of the same dose will raise the plasma concentration to a certain maximum level depending upon the time interval between injections. When the time interval between injections was decreased from 3 hours to 2 hours, the amount of drug injected over the entire period was increased by 50 per cent. The maximum concentration rise 1 hour after the injection was only 27 per cent after a steady state was established. However, the minimum concentration was raised 88 per cent and the spread between the maximum and minimum concentration was considerably reduced.

The confining lines in Figure 4 represent the concentration predicted from equations developed by the authors. It is seen that the experimental values confirm the predictions. Furthermore, when the injection intervals decrease, the range between the maximum and minimum values

also decreases. It is apparent that at the steady state of drug blood level concentration the range approaches zero.

Swintosky and associates[28] have shown that a peak blood level concentration for sulphaethylthiadiazole can be maintained for 10 to 12 hours by controlling the dosage administered. The oral administration to four adults of booster doses of 0·22 g. hourly for 8 hours after an initial dose of 2·0 g. resulted in the maintenance of a steady state blood concentration of 10 to 14 mg. per cent. The blood levels began to decrease 12 hours after the initial dose. This experiment illustrates the validity of the principle of providing prolonged therapeutic action by the single administration of an oral formulation, designed to release for immediate absorption a quantity of drug calculated to establish a therapeutic blood level. *The level is then maintained by the release of small booster doses at regular intervals. The work of Teorell, Boxer and Swintosky indicates that a prolonged therapeutic drug level in the blood and tissues may be attained if the substance enters the blood stream at a continuous and constant rate. The amount absorbed per time unit would determine the concentration level.*

The foregoing presentation has attempted to emphasize some of the biological factors which should be considered when formulating a sustained release product together with some of the recent findings concerning the physiology of the gastrointestinal tract. A few of the characteristics and constants of the particular drug, which should be known when formulating for prolonged action, are the minimum therapeutic blood or tissue level, the absorptive rates at various sites in the gastrointestinal tract, the pKa of the substance, tissue inactivation and kidney elimination rate. Many of these values will be average values because of individual variation of drug activity. Since inactivation, biotransformation and elimination rates are frequently unknown or unattainable by currently available analytical techniques, the term biological half-life has been used as a measure of the rate of inactivation of a drug substance. Nelson, as previously mentioned, used the biological half-life quantity in an equation he derived for estimating the quantity of drug necessary to maintain a therapeutic blood or tissue level over an extended period.

The biological half-life is a convenient quantity in chemotherapy since three interdependent factors are usually involved: the drug, the host, and the parasite. The effectiveness of the drug will depend upon the dosage schedule and here one must determine whether total dosage, duration of treatment or the interval between doses is responsible for better therapeutic effect[29]. The rate of inactivation or elimination expressed as the drug's half-life permits calculation of a dosage schedule in the absence of knowledge of the exact mechanism of degradation or biotransformation of the substance. It should be recognised, however, that the expression "half-life" as used here is inexact and bears no relation to the same term as it is applied in nuclear physics.

The standard performance indices representing the kinetic expressions K_b, $(t_{1/2})$ and V_b can be used to interpret blood concentration data[30,31]. These data may then be used to establish time dose relationships for the

drug if there is good correlation of drug tissue concentration and therapeutic efficacy. For drugs which show a first order elimination rate, the biological velocity constant for drug elimination rate, K_b, the biological half-life, $(t_{1/2})_b$, and the distribution volume in the blood, V_b, are readily determined. According to Swintosky the standard performance indices "may be of value in the design of oral sustained release dosage forms because any change in drug release will necessarily influence absorption, excretion and tissue concentrations of the drug."

Objectives and Methods of Obtaining Prolonged Action Dosage Forms

Some drugs such as sulfaphenazol[32], isopropamide[33], and sulphamethoxypyridazine[34] have an intrinsic long duration of activity when administered orally due to their physical and chemical properties and not because of special physical and chemical treatment. However, the major contributions in the development of sustained release preparations have been in methods of controlling the amount of drug available for absorption from the gastrointestinal tract.

Oral sustained action preparations have been designed to accomplish the following objectives.

To provide rapid onset of activity by immediate release of an amount of the active ingredient sufficient to raise the level of the drug in the body to a therapeutic optimum.

To maintain a steady therapeutic drug concentration. As the drug is inactivated or excreted, small additional amounts of active material are released to maintain an even level.

To eliminate deficiency in concentration due to divided or improperly spaced doses.

To reduce by more efficient use the total amount of drug needed.

To reduce the number of doses administered.

To lessen the hazard of defaulting from prescribed treatment by reducing the frequency of dosage.

An incidental advantage of prolonged action over multidose therapy in hospitals has been pointed out by Gooby[35]. This is that a significant amount of time spent in administering drugs is saved when one long acting daily dose replaced three or four single doses.

The methods used by pharmaceutical manufacturers to obtain sustained activity of solid formulations may be generalised.

By coating the active drug with gastro-resistant and slowly entero-soluble substances.

By the use of ion exchange resins to bind active drugs.

By the formation of chemical addition compounds or complexes.

By impregnating or embedding the drug in a base which gradually releases the active principle.

Gastro-resistant and Entero-soluble Coatings

The use of coating on tablets or capsules to delay absorption or to provide a gastro-resistant but entero-soluble film has been employed for

decades. Details of such coating materials have been adequately described by Thompson and Lee[36], Cooper and Gunsel[37], Remington[38] and others.

In general, these coatings depend upon two different mechanisms for their dissolution or penetration. One type resists the acid contents of the stomach but dissolves in the neutral or alkaline medium of the intestine. Shellac and cellulose acetate phthalate are frequently used examples. Historically, this type of coating was used in most so-called enteric tablets. The enteric coated tablet or capsule is designed to resist dissolution in the stomach, to prevent destruction, degradation or dilution of the active ingredient by the gastric secretions enabling the drug to reach the intestine in concentrated form, and, to eliminate gastric irritation or nausea which may be caused by the drug[39]. This approach requires caution since a distinction must be made between the relative, and shifting pH of the intestinal contents and that of intestinal secretions. Not infrequently, the intestinal contents are actually acid rather than alkaline, especially in the upper part.

The other type of coating yields to the chemical and enzymatic contents of the intestinal tract. In some instances, a combination of both coating principles is employed with the object of obtaining prolonged action. In 1938, Crane and Wruble[40] investigated enteric coatings by means of one thousand radiographic studies. They concluded that approximately 15 per cent of the tablets and capsules remained in the stomach for 9 to 10 hours. On the basis of their results and those of other investigators, it is apparent that the ideal timed coating should not be impervious to gastric juice for an unlimited time, but should release its medication at definite intervals after ingestion regardless of the location of the coated material in the alimentary canal. In addition, the coating should not dissolve upon brief contact with intestinal fluid. The delayed action tablet which was an extension of the enteric coating principle, represented the initial approach in controlling the release of a drug in the gastro-intestinal tract. The coating attempted to delay the release of the active ingredient, usually for 4 to 6 hours after ingestion of the tablet or capsule. It was assumed that the drug in the uncoated tablet or capsule which was taken simultaneously with the delayed form would be inactivated or eliminated within 4 hours. This delayed action principle was incorporated into the repeat action tablets so that the patient need only take one tablet to obtain the effect of two single doses at one administration.

Repeat Action Preparations

Repeat action cannot be as easily achieved with a hard gelatin type capsule. Though the capsule can be given an enteric coating, the application of an active drug to the capsule by means of a coating presents an insurmountable manufacturing problem particularly if the dose requires a considerable quantity of the drug substance.

In the repeat action tablet, the two doses are separated by a delaying coat. The initial therapeutic dose and the barrier coat are usually applied to the core, which forms the second dose, by the pan coating process.

It seems to be difficult under general conditions of quantity manufacturing to obtain uniformity of coating thickness or in some instances integrity of coating. Kanig[41] tested seventeen different commercial brands of enteric coated preparations for disintegration time. In each instance, the coating of tablets from the same container disintegrated in varying lengths of time, ranging from 15 minutes to 4 hours.

The release which is obtained by administering two individual doses at separate intervals, a single dose and a delayed single dose at the same time, or a repeat action tablet, results in an initial high concentration of the drug in the body which falls off rapidly. This is followed by another high concentration peak when the second dose is made available. Aside from convenience to the patient, the repeat action tablet has no therapeutic advantage over individually administered single doses. The time interval between ingestion and release of the core of the repeat action tablet depends on the type of delaying coat used. Once this coating is penetrated there is little further delay in the release of the drug.

A tablet of the repeat action type is thus limited as far as continuous release of the active substance is concerned. It is conceivable that a tablet could be manufactured containing many concentric barrier coatings, each designed to release at intervals. Although the difficulties involved in obtaining uniform coatings are multiplied, this approach is being used by at least one manufacturer[42]. Also, by using small drug pellets coated to release at different intervals, the principle of repeat action has been extended to what could be described as a multiple repeat action formulation.

Coated Pellets or Granules

The coated pellet concept originated as a variation of the repeat action tablet. Blythe[4] states: "We theorised that there would be less physiological impedance to the passage of these pellets through the pylorus. If a single tablet fails to disintegrate, one loses the complete benefit of the entire dose; however, if a few of the myriad of small pellets fail to disintegrate at the desired site, this failure will not noticeably alter the effect of the particular dose they contain." In the manufacture of these pellets, the drug is applied to sugar granules or other nuclei. Some of these granules are left uncoated. Others are given varying thicknesses of coating material which serve to delay the release of the drug from the nuclei. The uncoated and coated granules are then blended and placed into a hard gelatin capsule.

Examination of the contents of a typical capsule containing sustained release medication under low power magnification reveals three differently coloured groups of pellets. The colours help the manufacturer to distinguish the pellets with different coating thicknesses and disintegration times. Examination of these coated pellets shows an occasional twin and some variation in the diameter of the spheres. Some of the pellets have rough surfaces, but the more heavily coated ones are smoother in appearance. In the pan coating procedure, it is difficult to control abrasion of

the pellets, to eliminate clustering of the spheres with the eventual formation of odd-shaped pieces and to obtain, in one batch, uniformly coated pellets having the same disintegration time. Some manufacturers have compressed coated pellets into a tablet using a soft fatty or wax-like matrix to cushion the pellets from the trauma of compression. Scoring or deformity of the protective coating may occur during the tableting operation causing variations in the rate of release of the drug.

Other Coatings

In the patent granted to Hermelin[43] a method for manufacturing an oral sustained release dosage form is described. The drug and excipients are mixed thoroughly and a retarding mixture consisting of pharmaceutical glaze, stearic acid and castor oil is intermixed. The mass is dried, comminuted and wetted with an additional quantity of the retarding material. This mass is then dried and comminuted into discrete granules. The granules are compressed into cores and coated with the retarding mixture. Additional active drug is then applied and the tablets are then given a sugar coating.

Another method for obtaining prolonged action by means of the coating procedure employs a retarding agent in a portion of the tablet granulation. The granulations without and with varying amounts of tablet disintegration retarding material are differently coloured. When the granulations are mixed and compressed, the resultant tablet is speckled in appearance.

Use of Ion Exchange Resins

Chaudhry and Saunders[44] studied the release rate of ephedrine and dexamphetamine from a sulphonated, cross-linked polystyrene resin to determine whether ion exchange resins could be used as a means of obtaining oral sustained release of drugs. Earlier, Saunders and Srivastava[45,46] had noted the slow release of alkaloids from ion exchange resins to which the alkaloids were bound. The mechanism of the bonding is very complex. The studies of Chaudhry and Saunders revealed that the release curve could be straightened when the resin is only partly converted to the alkaloidal form or when a mixture of the alkaloid and the hydrogen forms are employed. This results in a reduction of the initial release rate and an increase in the later rate.

Abrahams and Linnell[3] stated that the release of a drug from the resin is dependent solely upon the availability of ions. Since the total concentration of ions in the digestive fluids varies within narrow limits, the rate of interchange of ions and hence the release of the drug would be fairly constant. The equations for the combination of acidic and basic drugs with basic and acidic ion exchange resins, respectively, and for the reactions in the stomach and in the intestine were summarised by the investigators as follows:

Formulation

Acidic ion exchange resin + basic drug $\rightleftharpoons$ drug resinate.
Basic ion exchange resin + acidic drug $\rightleftharpoons$ resin salt.

In the Stomach

Drug resinate + HCl ⇌ acidic resin + drug HCl.
Resin salt + HCl ⇌ resin chloride + acidic drug.

In the Intestine

Drug resinate + NaCl ⇌ sodium resinate + drug HCl.
Resin salt + NaCl ⇌ resin chloride + sodium salt of the drug.

The resin salt and the drug resinate are insoluble in the stomach and intestinal fluids according to Abrahams and Linnell. The reactions are controlled by the "normal laws governing velocity of chemical reactions and are unaffected by enzyme action, peristalsis or other physiological processes." They claim that a drug which has been physically treated with retarding tablet material to prolong its action such as coated granules or enteric coated may not be absorbed uniformly since the disintegration of the protective material depends on individual physiological factors.

An ion exchange resin may have effects other than those intended. Field and co-workers[47] in a study on the retention of sodium by cation exchange resins during restriction of dietary sodium in the dog noted that more sodium ion was free in solution in the terminal ileum than was bound by the resin. This was attributed to hydrogen ions, produced by bacterial fermentation in the colon which were exchanged by the resin for sodium and potassium ions. The sodium ions were then available for absorption in the colon and were not excreted with the resin. Since the resin had a greater affinity for potassium than sodium, the use of the resin could result in potassium depletion if given in sufficient quantity.

Chemical Complexing

Another approach to prolonged action employed commercially is the use of a colloid complex. Tannates of alkaloids, such as codeine, atropine and morphine, and of amphetamine and antihistamines have been prepared. The pentadigalloyl ester-like compound of glucose ($C_{76}H_{52}O_{46}$), the tannic acid official in the U.S. National Formulary X[48], is the preferred form. Cavallitto and Jewell[49] found a 5 to 1 ratio of drug to tannic acid in the tannate provides the most desirable therapeutic compositions because these appear to be the least soluble. Since electrolytes and a low pH increase the rate of release of an amine from its tannate salt, they demonstrated that the addition of pectic or polygalacturonic acids to oral compositions of amine tannates retard the release. The solubility of the tannates increases at low pH and decreases in neutral or slightly alkaline media. This approach to prolonged action is limited since not all drugs form tannates suitable for therapeutic use. Furthermore, the release rate may vary in different individuals since the release is pH dependent.

Prolonged Action by Embedment of Drug

The method of achieving prolonged action by embedding the active drug into a base from which it is gradually leached out enables the manufacturer to control precisely the amount and distribution of the release delaying components.

The preparation of a sustained release tablet representative of this group has been described by Cooper[50]. The active principle is dispersed in a mixture of high melting fats and high molecular weight waxes. Ingredients common to pH dependent enteric coatings such as shellac or cellulose acetate phthalate are not employed. The mixture is ground into uniform particles and compressed to form the core of the tablet. Additional drug for immediate release is contained in the granulation which is compression coated onto the core. The ratio between the amounts of the active drug in the core and in the coating is critical and different for each drug.

The disintegration of the coating in the stomach which occurs within ten minutes after swallowing the tablet, provides the initial therapeutic dose. Additional quantities of active principle are gradually released into the gastrointestinal tract by erosion and leaching. The method of manufacture provides a precision of drug content which is impossible to obtain by pan coating techniques. Another manufacturer utilises an insoluble resin in which the active substance is dispersed. Here, too, the drug is released by the leaching action of the digestive fluids.

Liquid Preparations

Sustained release liquid preparations have been available as suspensions of the drug in an emulsified vehicle or as suspensions of microscopic particles of coated drug. The required large therapeutic doses of sulphonamides can be more readily incorporated in a liquid preparation than a tablet. In addition, their relative water insolubility permits the use of an aqueous vehicle. Sulphonamide tablets generally contain 0·5 g. of active substance, yet 1·0 g. can be suspended in 5 ml. or one teaspoonful of a liquid vehicle.

The emulsified vehicle is an oil-in-water emulsion containing 50 per cent vegetable oils with emulsifiers[51]. The edible vegetable oils are apparently limited in their ability to retard the absorption of all sulphonamides. Sulphisoxazole is readily absorbed in the gastrointestinal tract and showed no difference in blood levels when suspended in an aqueous or lipid emulsion vehicle. The acetylated sulphisoxazole, however, showed higher blood levels from the emulsion than from the aqueous vehicle[52]. Sulphadiazine in a fat emulsion vehicle has been shown to reach a maximum blood level in 8 hours while the peak was reached in 4 hours from an aqueous suspension[53].

Robinson and Svedres[54] described several processes for the preparation of a suspension of minute drug particles coated with disintegration retarding material. In one, the finely powdered drug is suspended in a chloroform solution of a hydrogenated castor oil and spray dried. In another, a suspension of the drug in a melted wax mixture is spray crystallised. In the third procedure, the drug is dispersed in a melt of a glyceryl ester of a fatty acid, which is then congealed and ground to fine particles. The coated particles obtained by any one of the three procedures may then be dispensed in suitable suspension vehicles.

The various methods just described for preparing sustained release dosage forms are suitable for drugs which are usually well absorbed from

the gastrointestinal tract. Drugs having a cumulative action with undesirable side effects[5] and substances which are not well absorbed in the lower intestinal tract should not be prepared in a prolonged action form[4]. Medicaments which must be orally administered in large quantities are not generally prepared in a sustained release form.

The prolonged action oral formulations are still in a state of evolution. Combinations and slight variations of the above as well as new techniques for providing long duration of effect will probably be developed in the future.

In Vitro Test Methods

The laboratory test methods for the measurement of the release of the drug from its formulation are designed to correlate the *in vitro* release of the drug and its release *in vivo*. Significance of *in vitro* results is dependent upon mimicking the *in vivo* environment. In view of our present limited knowledge of the varying conditions in the human gastrointestinal tract, both in the healthy and in the ill, *in vivo* results can be only approximately simulated.

The *in vitro* methods described in the literature for determining release patterns of drugs with long duration of action achieved by mechanical assistance vary with the type and form of product. The methods differ for coated pellets in capsules, tablets, liquid preparations and ion exchange resins.

Many of the methods proposed for the *in vitro* measurement of release rate are modifications of the U.S.P. XV[55] method for enteric coated tablets or capsules.

The conditions common to most *in vitro* release tests are:

The use of simulated gastric and intestinal fluids at 37°, the use of a device for agitating the eluant and product at a fixed speed, and the use of a screen for separating disintegrated particles from the bulk of the product.

The procedures differ in degree rather than in basic principles. The time intervals, the composition of the fluids, the agitator and the mesh size of the screen are the usual variants in the methods. Assay for drug content is performed on the medium after elution, in some procedures, while in others the residue is assayed.

In 1955, Micciche[5] determined the release rate of coated granules. The granules were immersed for four hours in simulated gastric fluid followed by six hours immersion in simulated intestinal fluid. Micciche did not state his reasons why the granules should resist disintegration in gastric fluid for 4 hours and he did not report the details of his method.

Cooper[50] described in detail a method for determining the release rate for tripelennamine in a prolonged action tablet. These tablets are placed in the basket of the Stoll-Gershberg apparatus which is the one employed in the U.S.P. XV tablet disintegration test. The basket is fitted with a No. 40, instead of the No. 10 mesh screen. The smaller mesh is used to prevent the particles which are eroded from the tablets in the disintegration apparatus from slipping through the screen into the fluid when the bath

is changed. These particles continue to release the drug, and if removed before they have disintegrated into finer particles, may present a false picture of the disintegration pattern. The apparatus is filled with simulated gastric fluid. After one hour, the basket is removed from the beaker and the eluant is replaced with an equal volume of fresh simulated gastric fluid. At the end of the second hour simulated intestinal fluid is placed into the beaker. The process is repeated with fresh simulated intestinal fluid for an additional 9 hours. Each portion of eluant removed from the apparatus is separately assayed.

In the opinion of Blythe[4] different *in vitro* tests should be developed for each type of sustained action preparation, particularly when the release of the active substance is dependent upon different principles. Accordingly, he and his colleagues use different *in vitro* methods for capsules, tablets and liquid sustained release preparations. They modified the U.S.P. XV tablet disintegration basket to hold more tubes for testing the release of sustained release sulphaethidole tablets. The simulated gastric fluid was used for $1\frac{1}{2}$ hours and simulated intestinal fluid for an additional $2\frac{1}{2}$ hours. The fluids were maintained at 37°. The residue on the 10 mesh screen was determined at $\frac{1}{2}$, $1\frac{1}{2}$, 2, 3, and 4 hour periods.

When determining the release of a sustained liquid preparation, samples are placed into separate bottles containing a special medium buffered at 6·4 and maintained at pH 6·4. One bottle is used for each time interval and determinations are made at $\frac{1}{4}$, 1, 3, and 6 hours. These modifications of the usual method for tablets are necessary to obtain correlation of *in vivo* and *in vitro* data.

An *in vitro* test method for sustained release capsules of dexamphetamine sulphate was discussed in detail by Souder and Ellenbogen[56]. The method is applicable to other coated granules in capsules. The pooled contents of a number of capsules are mixed in a cylindrical column fitted with baffles and from which they randomly enter a rotating set of seven chutes attached to the bottom of the column. From the chutes they are deposited into receiving containers, from which they are transferred to 90 ml. bottles, one for each time interval, and 60 ml. of simulated gastric fluid is added. The bottles are rotated end over end in a water bath maintained at 37°. A bottle is withdrawn at $\frac{1}{2}$ and another at $1\frac{1}{2}$ hours for analysis. The contents are filtered through a 40 mesh screen, washed with water and the residue on the screen is assayed for drug content. The remaining bottles are also withdrawn from the bath after $1\frac{1}{2}$ hours. The contents of each are filtered on a 40 mesh screen and the residues are transferred to bottles containing simulated intestinal fluid at 37°. The bottles are rotated for the remaining test period and are removed at 2, $4\frac{1}{2}$ and 7 hours from the starting time, filtered, washed, and the residue assayed. The amount of drug released for any time interval is calculated from the difference between the original pellet assay and the particular sample.

Souder and Ellenbogen state that the procedure of assaying the undisintegrated pellets rather than the solution or suspension of the disintegrated portion can be used for soluble and insoluble drugs. Furthermore the method eliminates interference by the test fluid in the assay procedure

and "better sampling control is achieved, since it becomes unnecessary to obtain accurate amounts of material which may be in suspension." The 40 mesh screen was selected because the 16–25 mesh pellets were considered to have disintegrated when they passed through the screen. The authors vary the fluid medium, speed of rotation, temperature of operation, ratio of sample weight to liquid volume and test intervals from preparation to preparation to correlate the laboratory procedure and the *in vivo* release.

Campbell and Theivagt[57] have stated that the *in vitro* test should be run under conditions that approximate to *in vivo* conditions of motion, pH and temperature. They used the Stoll-Gershberg apparatus, but modified the basket to contain a single tube fitted with a 30 mesh screen. The basket containing the sample is lowered into 200 ml. of simulated gastric fluid U.S.P. XV and set in motion for one hour. The fluid is then removed for analysis of drug content. It is replaced by fluid containing one-half the quantity of simulated gastric fluid present in the previous test and sufficient simulated intestinal fluid to make 200 ml. of eluant. Varying the pH of the eluants at hourly intervals was recommended by Dr. Wiley of the Food and Drug Administration in his method which will be described next. This procedure is repeated for seven additional hours. The pH of the eluant solution used in the second hour is 2·4 which jumps to pH 6·6 in the third hour and gradually rises from 7·1 in the fourth hour to 7·5 in the eighth hour. The pH values of the solution are in agreement with Borgström's[14] findings relative to the pH changes in different regions in the gastrointestinal tract. The authors do not explain their preference for a single tube in place of the six tube basket used in the U.S.P. XV tablet disintegration test. Sustained release capsules of dexamphetamine and prolonged action tablets of tripelennamine were found to release 79 per cent of the active substance in 8 hours when tested by this method. But, 98 per cent of Hexocyclium was released from a gradual release tablet when tested by this procedure. Extrapolation of the release values obtained for dexamphetamine and tripelennamine indicate that approximately 95 per cent of the active ingredients would be released in 12 hours.

In the above methods the test intervals are limited to 8 hours probably because of the length of the work-day. Since *in vivo* release is not so limited, any proposed method should include provision for extrapolating data to a 10 or 12 hour period. From a regulatory view-point, manufacturers should be required to show sustained release of a 12-hour period if so labelled.

Under the aegis of the Food and Drug Administration, the Contact Section, representing the major pharmaceutical manufacturing firms in the United States, was requested to develop a single *in vitro* method for sustained release preparations. In view of the variety of the physical forms—coated pellets in capsules, tablets, liquid suspensions and ion exchange resins—and the different pharmacological response of each drug, it is difficult to envisage one *in vitro* method for all sustained action products. The U.S.P. XV recognises uncoated, sugar coated and enteric coated tablets and has three slightly different tests for each. The U.S.P. XV method for uncoated tablets uses water at 37° as the eluant unless

otherwise specified in the individual monograph. For plain coated and enteric coated tablets, an allowance is made for any soluble external coating. The Second Supplement to the U.S.P. XV[58] states that the plain coated tablets should be placed into the tubes of the basket followed by a slotted and perforated cylindrical disk and then eluted with simulated gastric fluid for 30 minutes. If not disintegrated, simulated intestinal fluid is then substituted. The method for enteric coated tablets employs simulated gastric fluid for 60 minutes at the end of which time the disks are added to the tubes and the disintegration time apparatus is set in motion in simulated intestinal fluid. Therefore it should not appear unreasonable to have different *in vitro* release methods for such widely different physical forms. The test which most closely reproduces the pattern of the *in vivo* results for a particular drug should be adapted for quality control purposes. With the objective of setting up standards, Dr. Frank Wiley and associates[59] at the F.D.A. developed an *in vitro* test to measure the release of an active substance from its formulation. In addition he suggested tolerances for different types of preparations.

The treatment vessel is a stoppered cylindrical tube with a coarse porosity fritted glass filter above the bottom outlet. The tube has a side arm outlet for the return of the eluting fluid to a reservoir. The fluid is circulated at a definite rate from the reservoir through the treatment vessel by means of a pump. The whole apparatus is immersed in a water bath maintained at 37°. When testing capsules, the contents of a counted number of capsules are mixed with silicon carbide, placed on the filter and covered with glass wool. For tablets the filter is covered with a layer of glass wool. One hundred ml. of simulated gastric fluid is used for the first hour. Fifty ml. of the solution is removed each hour for analysis nd replaced with 50 ml. of simulated intestinal fluid adjusted to a pH of 7·9 $\pm$ 0·1. The process is repeated for the maximum period indicated on the label.

The method was studied by various manufacturers. The apparatus was considered complex and required constant attention by the operator, thus making it unsuitable for routine control work. The filter plate sometimes became plugged with insoluble matter in the intestinal fluid causing loosening or bursting of the hoses and so altering the flow rate. Results with some tablets varied with the way they were packed with the glass wool. The concensus of opinion was that a better procedure should be investigated. It was generally agreed that the following conditions should be included in a universal *in vitro* test for prolonged action preparations. The eluting fluids should be at 37°; some type of motion should be used, not with the intention of simulating gastrointestinal motility, but to demonstrate that the motion does not cause an unpredictable release pattern; there should be exposure to a solution of varying pH; the apparatus should be available to most laboratories and be easy to use. The Contact Section is studying several proposed methods with the hope of establishing a suitable procedure or procedures for the *in vitro* testing of the prolonged action products.

The tolerances set by Wiley for the sustained action capsules or tablets depend upon whether the products are the equivalent of two or three single

doses. The limits for release, for preparations with the equivalent of two single doses, are not less than 40 per cent or more than 60 per cent release in the first hour with the remainder to be released "after the first hour and before the expiration of the maximum time stated on the label." Tablets or capsules containing the equivalent of three single doses are required to release not less than 25 or more than 40 per cent in the first hour; an additional 24 to 40 per cent should be released between the first and fourth hour and the remainder after the fourth but before the maximum expiration time claimed on the label.

The first set of tolerances for products which contain the equivalent of two single doses does not distinguish between sustained action and repeat action tablets. Sustained action preparations are generally based on the premise that after the initial therapeutic level of drug action is attained small booster doses are released to maintain the therapeutic level of the drug in the tissues. Sustained release tablets or capsules which release 40 to 60 per cent of the drug in the first hour and the balance in an hour and a half or two hours would meet the tolerance but could not be considered prolonged action preparations. Repeat action tablets meeting this requirement would not meet the clinical requirement that the second dose be released three or four hours after ingestion.

The second proposed set of tolerances is also too limiting for many timed release preparations. Some drugs which are intended to release small quantities over a protracted period would fail to meet the requirement of releasing a stated percentage of the total drug content.

Three factors are involved when setting specifications for the release pattern. These are, the minimum quantity periodically required for the therapeutic response; the maximum quantity which may be released without adverse or untoward effects on the patient; and, the total amount released in a given period. The three factors are mutually dependent, but the percentages will vary for each particular drug. The specifications for the minimum periodic release as well as the overall release pattern should be dependent upon the manufacturer's claims because the release pattern developed for each drug varies with the pharmacology of the drug. For example, preparations are designed for: an initial rapid release in the first hour and then gradual release in the subsequent hours; release of distinct doses at periodic intervals, and gradual release of active substance for 8–12 hours.

The release pattern of a drug from a cation exchange resin was determined by Chaudhry and Saunders[44] utilising three techniques. In the closed tube method, the weighed resin granules were placed into separate tubes containing eluting solution, one tube for each time interval. The tubes were rotated end over end in a bath maintained at 25°. The second procedure, which the authors termed the replacement closed tube method and which they preferred, differes from the first only in so far that the solution in the tube is removed by filtration at each time interval and fresh eluant is added to the residual resin granules. The third or infinite bath method required about 75 litres of eluant and approximately one week to run. In this method a continuous stream of solution was passed

at a controlled rate over a bed of resin granules, one particle thick, placed on a sintered glass filter in a closed cell. The filtrate containing the eluted alkaloid was removed from the system at the termination of the test, the granules were washed free of eluant and analysed for alkaloidal content. Complete extraction of the alkaloid was obtained only when fresh solution was brought in contact with the resin as in the infinite bath or the replacement closed tube method. Reabsorption of the extracted alkaloid by the hydrogen form of the resin was prevented by removal of the solution containing the alkaloid. No difference in release rate was found when 0·1 N hydrochloric acid sodium chloride and 0·1 N sodium bicarbonate solution were used as eluants. The resin granules were shown to release approximately 80 per cent of ephedrine in a six-hour period.

The release rate of amphetamine from coated pellets was determined by Royal[60] of the American Medical Association Laboratories who employed the U.S.P. XV tablet disintegration apparatus modified by the addition of a 40 mesh copper wire gauze screen over the 10 mesh stainless steel screen. Plastic discs were used in the tubes to retain the pellets.

Clinical Studies

The published clinical investigations of oral prolonged action medications generally indicate that the authors sought to determine the duration of action of the drug as well as the incidence and degree of side effects. Some investigators have also attempted to measure the time required for onset of action. Since the pharmacological action and dose of the unmodified drug were usually known, the problem confronting the clinician was the approximation of the quantity of the drug to be incorporated into the long acting form to provide a prolonged therapeutic effect. A large dose, as with amphetamine, caused overstimulation in most of the patients, while an insufficient dose had little or no effect[61].

The experimental design of the clinical trials varied with the investigator and with the drug. Very few of the trials were completely objective. Mann[62] employed the capacigraph which measures the volume change produced by the blood pulse wave in a finger. He demonstrated that the prolonged acting tablet form of nitroglycerin had an average duration of 340 minutes which was considered to be twenty times as long as the effect with the sublingual tablet. But the onset of action was delayed; ten or more minutes elapsed before its initial effect was produced. This delay in onset may be objectionable since glyceryl trinitrate is prescribed sublingually primarily because rapid onset of action is desired in relieving anginal attack. The capacigraph should be of value in objective studies of other peripheral vasodilators.

In Vivo Studies

The measurement of drug blood level concentrations whenever such assays are feasible provides a means of estimating the time of onset and the duration of effect. Blood level values of prolonged acting drugs are significant only when the therapeutically effective minimum and maximum blood level concentrations have been established.

Farquhar[63] measured blood levels produced in six children by a sustained action liquid suspension of sulphaethylthiadiazole as part of his clinical study on 512 pediatric patients whom he treated with the sulphonamide in the form of the tablet, the liquid and the suspension. He showed that therapeutic blood concentrations (8 to 15 mg. per cent) were obtained when the plain drug was given every 6 hours and similar values were obtained when the suspension was given every 12 hours. The rest of this study was less objective. The remission of clinical symptoms of infection was the basis on which the forms of the drug were evaluated. For the advanced and severe infections, penicillin in combination with the sulphonamide was necessary for effective treatment.

The histamine wheal test has been tried by Green[64] as an objective means of evaluating a sustained release antihistamine drug, but because of many uncontrollable factors its value is limited. He also made serial X-ray observations of sustained-release capsules in which radiopaque barium sulphate was incorporated. His data (obtained from three subjects) showed that the capsules released their contents over a period of 7 hours or more. The use of a highly insoluble radiopaque substance for determining the release of a drug has been questioned by Cass and Frederik[65]. They considered that a soluble drug might be leached from its coating or protective barrier, particularly if the coating were pitted or otherwise imperfect.

Feinblatt and Ferguson[66] also used barium sulphate as the radiopaque agent in their *in vivo* X-ray study of the disintegration of variously coated granules. The capsules were given to subjects who had no gastrointestinal distress and no contributory physical findings. The capsules contained barium sulphate granules designed to disintegrate immediately, 2, 4, and 6 hours after ingestion of the capsule. They noted that the contents of the capsules were dispersed and scattered in the gastrointestinal tract and that the *in vivo* disintegration time demonstrated by the X-ray plates was longer than that indicated by the *in vitro* modified U.S.P. XIV technique[67]. Though the *in vitro* disintegration time was 2, 4, and 6 hours, the *in vivo* was approximately 2 to 4 hours, 4 to 6 hours and 6 to 10 hours, respectively.

The editor[68] of the *New England Journal of Medicine*, in commenting on the investigation by Feinblatt and Ferguson, made several suggestions in connection with *in vivo* disintegration studies such as filming the subjects every 15 minutes during the first hour to show the dispersal of the material in the upper small bowel, the use of non-fasting subjects, coffee breaks for the patients in the study, and radioactive tracers to provide additional knowledge on gastrointestinal absorption. A re-investigation of the physiology of the gastrointestinal tract related to drug absorption and action was recommended.

Feinblatt and Ferguson[69] in their second study on timed disintegration capsules, apparently acting upon the editor's suggestion, observed the capsules 2, 4, 8 and 16 minutes after administration on an empty stomach. Again, barium sulphate was the radiopaque substance. The granules were distributed throughout the initial segment of the small intestine

16 minutes after administration. They also made observations on pentaerythritol tetranitrate blood concentrations and its effectiveness in the control of pain on 40 patients with anginal symptoms. Though the granules were dispersed in 16 minutes, there was no increase in the existing nitrate blood level until 1½ hours after administration of the capsule. Approximately the same time interval was required for the relief of pain. When the capsules were taken regularly every 12 hours, this time lag was not seen.

The drug apparently lends itself to chronic medication and may not be suitable for relief in an acute attack. The blood studies which were taken at the third, sixth, and ninth hours showed a high nitrate blood level according to the authors. The pain was also substantially controlled. Feinblatt and Ferguson wisely cautioned that the results of their studies should not be extended to other drugs in sustained release form, but should be confined to pentaerythritol tetranitrate. They stressed the fact that the amounts used were small and that the drug was a water-soluble non-metabolite. They urged the investigation of each type of medication in order to increase the available knowledge of the sustained-type formulation.

In order to simulate conditions existing in the gastrointestinal tract when a very soluble drug is administered in prolonged-action form, Simon[70] used water soluble sodium iodomethane sulphonate as the radiopaque medium. He took serial abdominal X-rays at hourly intervals to follow the course and the disintegration pattern of the prolonged-action tablets in which the opacifying agent was incorporated. The sodium iodomethane sulphonate was substituted for triplennamine hydrochloride in the prolonged-action tablet. After 2 hours, the tablets were in the stomach and small bowel. After 8 hours, remnants were seen in the region of the colon, while after 10 hours no trace of the tablets was seen, indicating complete dissolution of the tablets.

Investigators have designed various clinical experiments to evaluate the oral prolonged-action dosage forms in the absence of objective criteria such as blood level studies, X-ray tracings and the measurement of physical changes. Antihistamine drugs, for example, do not lend themselves to blood level studies because their duration in the blood is fleeting. X-ray studies of prolonged-action products are limited in man in view of the current knowledge of possible tissue damage due to radiation exposure.

Anorexigenic Agents

The sustained-release amphetamine preparations have been evaluated as anorexigenic agents in the management of obesity. Gelvin and associates[61,71] considered subjective impressions of appetite suppression to be inadequate and unreliable. Weight reduction was the main criterion in their studies. They also compared the incidence of side effects of the unmodified dexamphetamine with the sustained-release form. The subjects were out-patients at the obesity clinic of a municipal hospital. Objectivity of the study was enhanced by having each patient serve as her own control while taking the sustained-release form, placebo, and the

unmodified dexamphetamine sulphate capsules. The three forms were prepared in such a manner that the subjects did not know which preparation was administered or when a change was made. Though dietary instructions were not strictly adhered to, this lack of cooperation was considered an advantage. Since all the subjects received the same diet, the rate of weight loss was significantly different when the anorexigenic agent was used than when the placebo was taken. On this basis, the investigators reasonably assumed that the dexamphetamine caused less deviation from the diet since no change in blood pressure, pulse rate, blood count or other vital functions could be demonstrated in thirty-eight patients. The average blood pressure readings, as well as the range of these values, were recorded. Gelvin and associates stated that there was "no increase in the incidence of undesirable side effects caused by maintaining the sustained drug effect throughout the day." However, they did not conclude that the gradual release form diminished the number of side effects.

Garrett[72] reported a preliminary clinical study employing amphetamine tannate for the treatment of obesity. Many of the 699 patients were receiving dexamphetamine phosphate and were transferred to the tannate by their physician without their knowledge. The evaluation was based on the patients' subjective interpretations of effectiveness in terms of appetite control and elevation of mood. Sixty-four per cent of the patients were considered to have a good response, while 9·5 per cent had side effects.

In a communication to Abrahams and Linnell[3], Kekwick advised them of his determination of the rate of *in vivo* absorption of creatinine from its resinates. Creatinine was employed because methods of assaying it in blood and urine are reliable and accurate, its pharmacology in man is understood and it may be safely administered in large doses. A high blood level of creatinine was maintained for more than 10 hours when the substance was given orally in the form of its resinate. Its absorption was also delayed. Pure creatinine reached a peak in two hours and fell rapidly to normal in eight hours. The *in vitro* release rate of the creatinine resinate corresponded to the *in vivo* rate. Abrahams and Linnell stated it was reasonable to assume that the *in vivo* results of these drug resinates would correspond to the release pattern obtained with the creatinine resin complex since the *in vitro* release rate of the drug resinates of ephedrine, dexamphetamine, hyoscine and amylobarbitone correspond with the *in vitro* release rate of creatinine resin complex.

Unlike Gelvin and colleagues, Abrahams and Linnell considered the lack of strict adherence to the diet to be partly responsible for the variable weight loss among fifty-three obese patients treated with dexamphetamine sulphate as the resinate complex with or without phenobarbitone. The average weight loss was six pounds in four weeks. Controls apparently were not used in the study. The average duration of inhibition of appetite was claimed to be 12 hours. The subjects who were sensitive to the pure drug as evidenced by dizziness and headache apparently were tolerant of the resinate. The method of obtaining this subjective information from the patient was not described.

To cancel the nonspecific factors of suggestion inherent in a subjective response such as appetite suppression, Freed and associates[73] used the multiple dosage level method to evaluate the effect of a 1 to 3 resin complex mixture of *laevo*-amphetamine and dexamphetamine phosphate. The lowest dosage level served as a control in a manner similar to a placebo. The therapeutic effectiveness of the higher dosage levels were evaluated by comparing them with the lowest dosage administered. A placebo medication was also included in the study. Since they found that the placebo gave a satisfactory clinical response in about 30 per cent of their patients, these investigators assumed that a positive therapeutic result can be claimed only when the drug produced a satisfactory response in 60 per cent or more of the patients. The resin complex was given to persons who were already on an amphetamine therapy for suppression of appetite to produce a loss in weight, and who had previously failed to make satisfactory progress over a period of 4 to 6 weeks. To eliminate the psychological factor of suggestion, the capsules were given as casually as possible and no promise was made to the patient about the results to be expected. The authors claim that the side reactions with the amphetamine resin complex were less disturbing than with the regular tablet therapy. There was a greater appetite suppression and loss of weight after administration of one 20 mg. amphetamine resin capsule than with a dose of 3—10 mg. amphetamine tablets in the uncombined form.

Antihistamine Drugs

Green[64] remarked in a clinical study on sustained-release capsules of chlorprophenpyridamine that satisfactory methods of objectively evaluating antihistamine drugs in practice are lacking and he therefore relied on the patients' comments of effectiveness of the sustained-release form. He admitted that this procedure was subject to many shortcomings and sounded "unscientific." He thought that the clinical patients who commented favourably were influenced by the fact that the preparation required less frequent administration. Rogers[74] was of the opinion that "a better psychological effect" may have been created by informing his patients of the kind of medication being administered. The patients suffering with severe allergic symptoms received one or more anti-allergen extracts and stock catarrhal vaccines suitable for their sensitivities, in addition to the sustained-release capsules of chlorprophenpyridamine. The results were of a subjective nature since they were based on the patient's report of his response to the drug.

In Mulligan's study[75], the patients were also informed of the evaluation of the conventional tablet and the sustained-release capsules of chlorprophenpyridamine. The subjects were asked to record and estimate their degree of allergic discomfort and any side effects which were experienced while on the medication for one week. After one week, the form of medication was switched. The patients preferred the convenience of reduced doses. The incidence of drowsiness was essentially the same for the conventional tablets and the capsules. The degree of drowsiness with the sustained-release capsules was claimed to be less. The extent to

which the patients' judgments were influenced by knowing the details of the study cannot be assessed.

Miller[76] investigated the duration of effect, the time required for onset of therapeutic effect, and the number of sustained action antihistamine (methylaminophenylthenylpiperidine tartrate) tablets required to control allergic symptoms. The patients were asked to record their observations daily. The incidence of side effects was reported to be low. It is of interest to note that three instances of agranulocytosis occurring within a two-month period have been reported with the drug[77]. These records emphasise the necessity of testing a new drug for possible side effects on a large population, particularly with potentially hematotoxic drugs.

Spielman[42] compared a sustained action, three layer tablet designed to release a discrete dose of isothipendyl hydrochloride at different time intervals with the unmodified antihistamine tablet. The patients reported a duration of action of approximately 12 hours for the coated tablet. Placebos were not employed and no statement was made by the investigator whether the patients were favourably influenced by knowing the nature of the study. Modell[78] and Lasagna and Von Felsinger[79] have stated that inaccurate conclusions can be drawn from a clinical study if the subjects are aware of the nature of the study.

Kile[80] reported the use of two antihistamine drugs, prophenpyridamine and pyrilamine, and a mucous membrane decongestant, phenylephrine, in the form of their tannates for the treatment of various dermatoses and allergic hypersensitivities. A therapeutic advantage was claimed for approximately 78 per cent of his patients. He did not elaborate on the method of measuring the varying responses of his patients in terms of symptomatic relief nor were placebos or the unmodified forms of the drugs employed in the study.

Antitussive Drugs

Cass and Frederik[65] considered a statistical evaluation the best approach to achieve a measure of objectivity in a clinical study of antitussive drugs. A comparison was made over three weeks between a placebo and a dihydrocodeinone resin complex at two dose levels in a double blind study with 67 patients suffering from chronic cough as the result of tuberculosis or chronic respiratory infection. Analysis of the results showed the response to correspond with strengths of preparations used, and proved the slow intestinal release of drug from the resin complex. In a comparison in 60 patients between a suspension of dihydrocodeinone and phenyltoloxamine as a resin complex and the citrates of these drugs in solution, each presentation being given for three days, the ion exchange resin form of dihydrocodeinone and phenyltoloxamine was shown to produce as effective antitussive action for approximately 12 hours.

The effectiveness of a combination of dihydrocodeinone and phenyltoloxamine in the form of their resin complexes as a cough suppressant was investigated by Chan and Hays[81]. The patients treated had coughs

of duration from one day to several years. The investigators found the use of the resin complexes gave results superior to those usually obtained when the drugs were given in the same amount in the uncombined form. Their conclusions on the effectiveness of the drugs were apparently based on the opinions of their patients.

Townsend[82] also evaluated the complex as an antitussive agent. The combination resin complex was measured against the aqueous solution of the active drugs in comparable concentrations. A total 24-hour period was considered. A 4 + response was assigned to the resinate if the cough was suppressed for more than 10 hours, while the same response was assigned to the aqueous solution of the drug without the resin when the cough was suppressed for 4 hours. These values were applied because the aqueous solution produced a more rapid control of the cough. The resin combination was shown to be the more effective in prolonging the antitussive action than the aqueous solution of the agents. The dosage requirements varied and adjustments in dosage had to be made individually. Townsend reported that the parents of the patients invariably chose the resinate combination since the resinate maintained adequate antitussive effects over a prolonged period.

Tranquillising Drugs

Morrison[83] and Blake[84] discussed the evaluation of sustained release capsules of prochlorperazine with intrinsically long-acting isopropamide in patients with gastrointestinal disturbance and psychoneurological symptoms. Morrison used the history of each patient's response to previous medication as the baseline for rating the effectiveness of the drug combination. Evaluation of therapy was based on the degree of symptomatic relief reported by the patients and objective findings observed during periodic examination. The clinician stated that "part of the patient acceptance was due, undoubtedly, to the convenience of having to take this combination of drugs only twice a day."

In Blake's study, twenty-eight out of fifty-six patients who had previously taken other medication for the relief of their symptoms served as a control group. The capsules were taken twice a day, morning and night, and the average duration of therapy was 8 weeks. The objective findings were based on physical examination and subjectively on the degree of symptomatic relief. The acceptance of the drug combination by the patient was based on the lack of side effects other than dryness of the mouth and the convenience of taking the drug twice a day. Blake claims that a significant increase in good to excellent results was observed in the control group.

Jacoby and co-workers[85] described a clinical study on the use of sustained release capsules of prochlorperazine and chlorpromazine by fifty-two psychiatric in-patients and twenty-eight out-patients. Administration of the sustained release drugs in doses equivalent to the doses found necessary to maintain the patients on the unmodified form of the drugs yielded comparable psychotherapeutic results. The evaluations were subjective since they were based on consultations with the patients

or their relatives and on periodic examination by a psychiatrist. The incidence of extrapyramidal symptoms was not reduced by the sustained release form, but less drowsiness was claimed.

Beck[86], Grahn[87] and Gagnier[88] have investigated sustained release capsules of reserpine in hypertensive patients. Beck and Grahn evaluated the response to the drug when the patient's blood pressure became stabilised on the maintenance dose. Beck claimed that most of the patients could be maintained on about half the dosage required with the unmodified reserpine and Grahn stated that undesirable side effects were reduced or eliminated by lowering the dose of the sustained release material. Neither investigator compared the single dose tablet with the sustained release form. Ayd[89] has stated that the side effects of reserpine, in the single dose tablet, disappear when the dosage is reduced. Gagnier, however, used the conventional reserpine tablet in his study. Eighteen out of nineteen patients showed a good or fair response to the sustained release form while sixteen out of nineteen showed a similar response on the conventional or unmodified form. In view of the paucity of observations, the conclusion that the sustained release form "is superior to the multidose form for the treatment of most hypertensive patients" is hardly justifiable. This author concludes that reserpine in any form is 85 per cent effective.

Miscellaneous Drugs

McClellan[90], Sablosky[91], and others[92,93] have reported on sulphaethylthiadiazole in the form of a sustained release tablet or in suspension. McClellan found that the sulphonamide required 1·1 more days than penicillin or a combination of penicillin and a pediatric suspension of tetracycline to produce a remission of moderately severe bacterial infections in children. This difference was not considered to be of medical significance. Sablosky reported that the overall efficacy of the sustained release tablets and liquid suspension used in his study for the treatment of bacterial infections in adults and children are not "to be construed as exclusively due to the action of the sustained release form of sulphaethylthiadiazole."

Vasodilators in sustained action form have been studied by Samuels[94] and Fuller and Kassel[95]. Samuels made oscillometric readings, taken at ankle level on patients with arteriosclerosis obliterans, in a study on the the effectiveness of a sustained action tablet of pentaerythritol. The ability to walk a number of city blocks was another criterion. A minimum of 3 months' treatment was required before improved results could be shown. Fuller and Kassel treated patients with angina pectoris with an uncoated sustained-action tablet of triethanolamine trinitrate biphosphate. Two and a half hours elapsed before the tablet provided its vasodilatory effect. It was claimed to last from 6 to 12 hours, depending on the degree of exertion, severity of angina, and "the rate of absorption as related to meals."

Neostigmine bromide and pyridostigmine bromide in prolonged action form were evaluated on myasthenia gravis patients by Schwab and

associates[96]. Some patients found no advantage of the prolonged form over the usual; others experienced symptoms characteristic of overdosage, while other patients used the ordinary tablet during the day and the slow release form at night. The dosage had to be individually adjusted.

Quinalbarbitone in sustained release capsules was compared by Shoemaker[97] with the untreated drug in patients complaining of insomnia. All forty-two of the patients in this study failed to respond to a placebo which was administered as part of the screening procedure. Half of the group was given the sustained release capsules and the other half received the conventional capsules. After one week, the medications were switched without the knowledge of the patient. The prolonged acting capsules had a duration of 6 to 8 hours, while 26 per cent reported sound sleep with the unmodified drug.

Thompson[98] evaluated sustained release capsules containing coated pellets of atropine sulphate, scopolamine hydrobromide and hyoscyamine sulphate which was claimed by the manufacturer to be equivalent to four doses of 0·6 ml. of Tincture of Belladonna B.P. given at 4-hour intervals. The effect of the drugs was determined by measuring the hourly change in salivary flow following citric acid stimulation of the salivary glands. The capsules were given to sixteen male in-patients with no debilitating disease, dehydration or lesions of the salivary glands. The subjects received four capsules in the morning and their response was compared with their salivary index obtained the previous day when no drug was given. Ten additional patients received the equivalent dose (2·4 ml.) of Tincture of Belladonna and the results were compared. Thompson observed a depression in salivary secretion for 7 hours without any serious side effects. He also noted that one capsule released "more belladonna alkaloid than that contained in the stated equivalent of official tincture; if this is confirmed the dosage will need to be reviewed."

Codeine with methyl *ortho*tolyl-quinazolone as resin complexes were found by Cass and Frederik[99] to suppress pain to a satisfactory degree for a period of about 12 hours. Several codeine preparations were simultaneously evaluated in this double blind study. The results were based on the patients' replies to questions relative to the degree of pain relief. Values were assigned to these responses and the values were then statistically evaluated.

Dragstedt[100] has questioned the use of prolonged type vasodilators in angina pectoris. Substances like nitroglycerin are used primarily for their rapid therapeutic effect when administered sublingually. However, the oral administration of these agents for preventing anginal pain is not too well founded. He cites a study which demonstrated that the oral administration of 2 mg. capsules of glyceryl trinitrate was no more effective than a placebo in controlling the pain.

Availability of Drugs

According to Dragstedt, drugs for which "precision of dosage" is very important should not be given in a sustained type preparation. Digitalis glycosides belong to this category. Furthermore, in his opinion, drugs

which normally are erratically absorbed, such as some of the ganglionic blocking agents used in the treatment of hypertension, should not be administered in a prolonged type form. The gastrointestinal absorption of the drug may be even more irregular when administered in this manner.

These two statements on drugs requiring precise dosage and those which are incompletely absorbed were drawn as corollaries by Dragstedt from the work of Campbell and associates[101,102] of the Food and Drug Laboratories of Canada. They studied the "physiological availability" of drugs in various forms as a basis for establishing standards for disintegration tests. "Physiological availability" was defined as the amount of drug absorbed from an oral dosage form as measured by the concentration of the drug in the blood and urine. Using riboflavin[103] and sodium *p*-aminosalicylate[104] tablets, they showed that when the *in vitro* disintegration time was more than 60 minutes, the substances were not completely available. Their procedure for determining the disintegration time was a modification of the U.S.P. XV technique. They inserted a plastic disc into each tube of the disintegration basket to provide a rubbing action which shortened the disintegration time of the tablets. The use of plastic discs is now official in the second supplement to the U.S.P. XV.

Endicott and Kirchmeyer[105] have demonstrated "effective absorption over an 8-hour period" by means of drug blood level studies after the administration of erythromycin tablets with a disintegration time greater than 60 minutes. Enteric coated sodium salicylate tablets with a delayed disintegration time have been shown by Wruble[106] to be physiologically available. Other investigators, as has been mentioned in this review, have demonstrated that the prolonged action preparations provide physiologically significant blood levels for an extended time interval even though the disintegration time of the drug forms was greater than 60 minutes. Many of these studies were made using the sulphonamide drugs. The sulphonamides can be readily determined in the tissues after administration because their dosage is relatively high, the nature of the distribution of the sulphonamide in the body, and the possession of an arylamino group or chemical moieties capable of being transferred into an arylamino group. This group can be easily diazotised and coupled to form an azo dye which can then be assayed. Other substances, especially those administered in small quantities often are not readily detectable in the blood or urine.

Marshall[29] points out that not all drugs can be easily detected in the body. No satisfactory chemical methods have been devised for determining penicillin concentrations in plasma and body fluids. Many reports have appeared giving concentrations in plasma, urine and body fluids but what is being determined is the bacteriostatic activity of penicillin after its administration. Fleming and co-workers[107] have referred to the "antibacterial activity of serum" instead of penicillin concentration. The concentration of a drug in the blood does not necessarily represent the concentration of the drug at the focus of infection. This is important since most bacteria are not in the blood stream, but in the tissues. Actually it is the presence of penicillin in the extracellular fluid and not

in the tissues themselves which is important in treating bacterial infections with this antibiotic, since the bacteria are in the extracellular fluid in infections with the exception of those in the macrophages and leucocytes. Thus blood level measurements for penicillin, while indicating availability, would not assure clinical effectiveness.

The physiology of the gastrointestinal tract has to be considered in a discussion of "physiological availability." Drugs given on an empty stomach or with a quantity of fluid may pass the pylorus and reach the duodenum quickly. Arrival at the duodenum would be delayed if the drug were taken after a meal. If absorption does not occur through the stomach wall, the drug entering a full stomach will not be completely available for absorption within 60 minutes, which is the limit for tablet disintegration suggested by Campbell.

Gruber and associates[108] have shown that the physical posture of the patient will also influence the rate of passage out of the stomach. These workers described techniques other than blood and urine studies which correlate *in vitro* and *in vivo* evaluations of enteric coatings. A saliva iodide test[109] was employed to indicate absorption of compression enteric coated potassium iodide tablets. X-ray examinations were used to determine the disintegration of the tablets as well as to approximate the location of the tablets in the upper gastrointestinal tract. Tablets, tied to strings, were swallowed and inspected at intervals by pulling out the string. A tablet attached to a 20-inch string restricted the tablet to the stomach, while a tablet attached to a 30-inch string could pass into the intestine. The *in vivo* findings and the *in vitro* disintegration studies could be directly correlated.

In a study on erythromycin tablets, Gruber[110] and others, used the string technique together with X-rays and measured serum concentration in blood samples taken every 2, 4, 6, and 8 hours. Therapeutic blood level concentrations were shown to be present within 2 to 9 hours after oral administration of the compression enteric coated 250 mg. erythromycin tablet. *In vitro*, the tablets failed to disintegrate after 1 hour in simulated gastric juice, but disintegrated 20 minutes later in artificial intestinal juice. This study demonstrated the "similarity of results obtained with *in vitro* and *in vivo* test methods."

Conclusions

The development and extensive use of sustained release oral medication has created new opportunities for creative accomplishment on the part of research pharmacists and may also serve to stimulate physiological studies of the mechanism of drug absorption. The significance of physico-chemical factors in the formulation and therapeutic effectiveness of drugs has been known for some time to biochemists, pharmacologists, and research pharmacists concerned with a deeper appreciation of the mechanisms involved in the absorption, utilisation and excretion of drugs. The concept of sustained release therapy applied to the parenteral route of administration in the form of implantation pellets, crystalline suspensions and retardant vehicles has been an accepted part of the armamentarium of

drug treatment for almost two decades. It is somewhat strange, therefore, to observe the vehemence of the attack upon the concept of oral sustained release medications in certain quarters.

The intensity of the objectors appears to be inversely proportional to their knowledge of the inherent problems associated with biological systems. *In vitro* release rates have been under attack as inadequate, by themselves, for preparations of this type. Some critics argue for blood or blood plasma concentrations, others for urinary excretion curves, and the real long-haired biochemists want nothing less than tissue concentrations. Among the critics are a few who are so handy with slide rules that they demand differential equations expressing the inter-relations between all three factors.

But, these attitudes are stimulating, and if not diluted too far, will provide useful information of a basic nature. The strange part is that similar extreme refinement in testing techniques are rarely applied to drugs which are not administered in a sustained release form, but just slide down the oesophagus on their way to unknown blood concentrations or urinary excretion rates. Also concerned are the professional sceptics in the clinical family who on the one hand write critical attacks on all new drugs and drug concepts and with the other write prescriptions for the same drugs to take care of the realities of therapeutics.

The crux of the matter lies in a rather smug attack on the general principle of clinical investigation as a scientific tool, although most scientific labourers in medicine and the allied sciences concede that the ultimate test of a drug's effectiveness is in man. Some now indulge in the machine-age idea that it is inadvisable to trust the observations of either the patient or the physician. The fact that many clinical trials are poorly planned and reach erroneous conclusions is no indictment of the technique in all fields of science. The methodology and design of such experiments and, therefore, the validity of the conclusions is constantly improving.

In the case of sustained action preparations, the problem of the clinician is actually simplified. The pharmacology, toxicology and clinical effectiveness of the drug have generally been evaluated for some time. All that is new is duration. An observant patient or physician may even detect some subtle differences—smoothness of drug effect, diminution or elimination of an annoying side effect, or equal effect with lower total dosage.

There is no doubt that the use of prolonged action dosage forms will be expanded and further developed in terms of improved laboratory testing techniques and more critical clinical evaluation. These developments will serve to clarify the value of the prolonged-type preparations in therapy.

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