THE MODIFICATION OF THE DURATION OF DRUG ACTION

PHARMACEUTICAL CONSIDERATIONS

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Factors Modifying the Rate of Onset of Action of a Drug

If the title of this Symposium is interpreted in its most rigid sense it could be argued that modification of the time of onset of the action of a drug is excluded from consideration. Nevertheless, immediate onset of action is nearly always desirable both in normal dosage forms and in prolonged acting preparations. Occasionally, delayed onset is deliberately arranged, as in one brand of an hypnotic tablet which is claimed to contain an "alarm clock" which acts some 8 hours after ingestion, but in practice the differences between individuals to which Dragstedt[1] has drawn attention are so great that it is doubtful if a preparation of this nature is of value.

Oral preparations. In unmodified oral preparations, speedy onset of action is dependant upon rapid disintegration and it is doubtful, even now, whether its importance is fully appreciated. In various countries the permitted disintegration times of Official tablets differ widely; the British Pharmacopoeia with a few exceptions requires 15 minutes as a maximum, while the United States Pharmacopoeia specifies times varying from 15 minutes to 2 hours or even longer.

The disintegration time found for a particular tablet will vary according to the method employed for its determination which is usually specified by the Pharmacopoeia concerned. The use of a moving disc in the tube holding the tablet, permitted by the British Pharmacopoeia[2] if the tablets do not otherwise comply with the official requirements, and now obligatory in the Unites States Pharmacopoeia[3] usually decreases disintegration time, but with some tablets made with a base which becomes sticky when wet and which stick to the disc, this time is substantially increased.

Although a maximum disintegration time of 15 minutes is the lowest requirement of any Pharmacopoeia, it is possible to prepare tablets which disintegrate more rapidly and this is particularly desirable in preparations given to produce direct relief, such as analgesics and symptomatic anti-asthmatics, and drugs intended to combat conditions such as migraine.

A number of factors influence the disintegration rate of tablets; composition, the disintegrant and the manner in which it is incorporated, the lubricant, the water-content of the granule and compression. The most generally used disintegrant is maize or potato starch, but Berry and Ridout[4] drew the attention of this Conference in 1950 to the value of alginic acid, a claimed advantage being that since it may be wetted and re-dried without loss of swelling and therefore of disintegrating power, it may be used as the granulating agent by adding it to the tablet mix after allowing it to swell in water, so that the granules themselves contain a disintegrant. If they do not it is possible for a tablet to pass the disintegration test of both the British and United States Pharmacopoeias by

disintegrating to granules which pass the 10 mesh wire sieve specified, while the granules themselves may disintegrate only slowly with consequent slow release of the medicament. Tablets prepared by direct compression of a water soluble substance when it occurs in a suitable granular or crystalline form should also contain a disintegrant, for tablets of sodium chloride, sodium bromide or calcium gluconate, for example, dissolve slowly unless disintegration is assisted by a suitable additive.

Hydrophobic lubricants such as magnesium stearate or talc delay disintegration and though often more effective than starch the use of the latter has the advantage that it assists, rather than impedes, disintegration.

The disintegration time of tablets may change on storage; usually to lengthen though occasionally it becomes shorter. This is associated with a change in hardness, and when the disintegration time lessens the tablets sometimes become so soft that they are no longer usable. This change is often associated with the water content of the granules at the time of compression. Granules compressed with a water content in excess of their equilibrium value with normal atmospheric humidity produce tablets which on storage lose moisture and become harder with a corresponding increase in disintegration time, the reverse being also true. While the former condition is the more common, the increasing practice of air-conditioning, when the relative humidity is held below normal, has led to the use of starch to control the moisture content and of glycerol to prevent excessive drying[5]. Compression at the time of manufacture is of importance; excessive compression leading directly to increase in disintegration time.

Parenteral preparations. More immediate onset of action usually follows parenteral injection, particularly by the intravenous route. This may involve no change in the drug itself as with Vitamins B_1 and C, a number of alkaloids and other substances normally administered orally. Slight change in the chemical nature can frequently render suitable for injection drugs which orally are given in an insoluble form, thus the sodium salt of prednisolone hemisuccinate is soluble in water and may be given intravenously, by which route it exerts a spectacularly instantaneous effect when compared with the oral use of prednisolone, the intramuscular injection of a suspension of the steroid or even with the infusion of an equivalent dose of Hydrocortisone Injection, while phenobarbitone as the sodium salt given intravenously acts very rapidly. Physiologically, the simultaneous use of hyaluronidase hastens the absorption of drugs given subcutaneously or intramuscularly.

Prolongation of Drug Action

Oral Preparations

Lazarus and Cooper[6] have summarised the aims which oral sustained release preparations have been designed to accomplish as follows.

"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".

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

"To reduce the number of doses administered".

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

Dragstedt[1] earlier suggested that praiseworthy as objectives such as these may be, they are not necessarily always achieved nor should it be assumed that they constitute encouragement to the extension of such preparations in a random or wide-spread manner. He draws attention to the number of variables involved when a tablet is taken orally, insofar as the time the tablet remains in the stomach and intestine, and the nature of the digestive juices with which it comes in contact, are concerned, and he considers that it would be valueless to attempt to determine the average of such variables which would apply to only a few individuals. He states that no drug should be given in the form of a prolonged action preparation if accuracy of dosage is important, if absorption from the gastrointestinal tract is impaired or erratic or if the total dose administered as a prolonged action preparation is more than two or three times the usual therapeutic dose unless the drug concerned is known to have a wide margin of safety. Campbell and his colleagues[7–10] have studied the "physiological availability" of certain drugs, particularly those where absorption could be measured by their concentration in the blood and urine, as a function of the disintegration time of the tablets containing them and from this stated that simple tablets should have an *in vitro* disintegration time of less than 60 minutes to ensure complete availability of the drug. This is not confirmed by all workers. Tablets of sodium salicylate, the disintegration of which has been delayed by enteric coating, exert satisfactory activity[11], and Lazarus and Cooper[6], quote evidence, mainly obtained with the sulphonamides which can be readily determined in body fluids and tissues, which has shown that prolonged acting preparations do provide physiologically significant blood levels even when the disintegration time of the dosage form is greater than 60 minutes.

Methods which have been used to gain some picture of the release rate of a drug from a prolonged-action preparation *in vivo* when the determination of its concentration in blood is impossible have been mainly confined to following the disintegration of tablets containing a radio-opaque substance by X-rays, though this has limited application in man due to possible damage to the tissues. This method has been used to follow the disintegration rate of barium sulphate capsules *in vivo*[12] the time taken being about double that found by the USP method, and this suggests that the values for the release rate of a drug from a prolonged-action preparation found *in vitro* can be used only with caution when referred to the release rate to be expected in man.

In vitro methods of determining release rates are described by Lazarus and Cooper[6]. The procedures, which differ mainly in detail dependant upon the type of preparation being tested, normally employ simulated

gastric and intestinal juices at 37°, controlled agitation of the eluant and of the preparation being tested and some type of sieve to separate the disintegrated particles from the bulk of the product. In all cases the amount of drug released at varying time intervals is calculated from the assay of either the eluant or the residue remaining undisintegrated.

Pharmaceutical Methods of Prolonging Drug Action in Oral Preparations

(*a*) *Tablets and capsules.* An early attempt to provide a repeat action involved the simultaneous ingestion of two tablets or capsules one of which had received a coating intended to delay availability of the drug for some hours, by which time it was assumed that the effect produced by the normal preparation would have disappeared. This method was quickly simplified by preparing a tablet made up of a core containing one dose coated with a delaying layer covered with a layer containing an initial dose on the outside. This does not provide the continuous slow release of medicament which is desired and is no better, but only more convenient, than taking two tablets at an interval of time. It is also difficult in practice to control the manufacturing process of pan coating so that a uniform thickness of coat is obtained and very variable disintegration times have been reported[13] for commercial batches of enteric coated tablets, even within the same batch.

A considerable advance in obtaining continuous slow release is due to Blythe[14] who, instead of a "repeat action" tablet, suggested the use of a large number of small pellets coated with varying thicknesses of a coat intended to delay the release of the drug, some pellets being left uncoated to provide the initial dose, the mixed pellets being supplied in hard gelatin capsules. These pellets are manufactured by applying the drug to a core, commonly sugar granules, and then coating by the pan coating process, coatings of different thicknesses being distinguished by colour. The lack of uniformity in coating thickness associated with this process is here an advantage, since with the large number of pellets in each capsule it is reasonable to assume that continuous slow and regular release of the drug will be achieved.

Tablets have been prepared either from a mixed granulate, part of which has been treated to retard disintegration or from coated pellets using a wax or fatty base to prevent damage to the protective coating on compression, but scoring or deformity of the coating may occur during tabletting causing variation in the rate of release of the drug[6].

(*b*) *Oral preparations other than tablets and capsules.* Though most work has been carried out on tablets and capsules for prolonged action medication the application of this principle to liquid preparations has not been entirely overlooked. Lang[15] has summarised the methods now in use. A water-insoluble drug may be prepared as a suspension either using material of large particle size, or after adsorption to an ion exchange resin or protein. The drug may also be suspended in a water-in-oil emulsion, or coated with substances insoluble in the gastric juice. Methods of preparation are quoted by Lazarus and Cooper.

Chemical Methods of Prolonging Drug Action in Oral Preparations

The most fully exploited chemical method to obtain slow release in oral preparations involves combination of an acidic or alkaline drug with an ion exchange resin[16,17]. Alkaline drugs combined with cation exchangers of the sulphonic acid type to give a resinate, release the drug as the hydrochloride in both stomach and intestine and since elution is dependent only upon ion concentration[18] which does not vary widely in the digestive juices the release rate is fairly constant.

A more regular rate of elution is obtained if incompletely converted resin, or a mixture of the resinate with the hydrogen form, is used, since this depresses the initial release rate. Acidic drugs combined with an anion exchanger release the drug in the acidic form in the stomach and as the sodium salt in the intestine, but have not yet been widely used.

Other chemical methods which have been employed for obtaining prolonged action in oral preparations involve either change in the chemical nature of the drug itself or the manufacture of derivatives. The barbiturate series is an example of the former and exhibits the common characteristic of such modifications that usually the interval between administration of the drug and the onset of its therapeutic effect corresponds to its duration of action.

Examples of the latter are methylpentynol and mephenesin which, as the carbamates, have a lengthened duration of action.

Physiological Methods of Prolonging Drug Action in Oral Preparations

In certain instances the action of drugs given orally can be prolonged by simultaneous administration of a substance which competes with them for excretion by the renal tubules. Caronamide[19,20], sodium benzoate[21] and probenecid[22,23] have been used for this purpose.

A number of subtances are now under clinical investigation which delay or inhibit drug metabolism. Of these, aminoethyldiphenylpropyl acetate and 2,4-dichloro-6-phenylphenyloxyethyldiethylamine have been claimed greatly to prolong the action of phenytoin and methoin, morphine and pethidine, and amphetamine.

Parenteral preparations. Parenteral preparations having prolonged activity are of particular importance for medicaments which are rapidly eliminated and require frequent administration if a satisfactory level in blood and tissues is to be obtained, and for those drugs which have to be given for a long time or throughout the lifetime of the patient. For this reason they have been largely confined to the field of penicillin and the hormones, in the former case because of the necessity of obtaining rapidly a high concentration of the antibiotic in the blood and maintaining this high level during treatment in the face of rapid deactivation and excretion, and in the latter to enable a chronic condition to be treated for a long time without the necessity of frequent injections.

The methods which have been employed to increase the duration of activity of parenteral preparations may be summarised as follows. 1. Physiological modification of absorption or excretion. 2. Modification

of the solvent. 3. Chemical modification of the drug. 4. Adsorption of the drug. 5. The use of suspensions. 6. Implantation pellets.

This classification is somewhat idealised for it is very common for several of these methods to be employed simultaneously to obtain the desired result.

Physiological modification of absorption or excretion. It is well known that a drug given by the intramuscular or subcutaneous route is less rapidly effective than the same drug given intravenously. Increased duration of action may follow modification of the route of injection, thus heparin given intravenously increases blood coagulation time within about 10 minutes but the effect is transient, usually having disappeared within about 3 hours, while the same preparation given in larger dose intramuscularly produces a less rapid response but a substantially prolonged effect[24]. Absorption can be delayed by adding to the injection a vasoconstrictor such as adrenaline, as in procaine—adrenaline. Attempts have been made to extend this principle to insulin and to penicillin[25], but it is unsuitable for continuous treatment as the number of injections of adrenaline involved may lead to secondary effects. Caronamide and probenecid given by mouth, delay the excretion of certain antibiotics, particularly penicillin, given simultaneously by injection, but it is unlikely that such a method can ever be of general application.

Modification of the solvent. When a drug is soluble both in water and in an oily vehicle, as, for instance, with oestrone in low concentration, the oily solution is significantly more long acting than the aqueous one. For water-soluble drugs, the addition of gelatin, carboxymethylcellulose and polyvinylpyrrolidone to the aqueous injection has been claimed to increase the duration of activity of some[26–28] and to be ineffective with others[29,30] and the use of carboxymethylcellulose and polyvinylpyrrolidone is declining following warnings that they may be carcinogenic in the high concentrations required[31,32] Dextran which is claimed to be non-carcinogenic[32] has been suggested as an alternative.

It is doubtful whether the increase of viscosity of the solution caused by the presence of the colloid is responsible for the delay mechanism, though increased duration of action is shown by procaine penicillin suspensions sufficiently concentrated to have thixotropic properties[33]. It has been suggested that apart from complex formation[34–36] the delay action of polyvinylpyrrolidone may be due to the formation of a micelle into which the medicament is adsorbed or to a slowing of renal excretion without apparent disturbance of the renal function, particularly as it is effective parenterally in association with a drug given orally[26], but at the present time the mechanism is by no means clear.

Addition of beeswax to a suspension of penicillin in oil[37] causes substantial prolongation of action though it has been suggested that the mode of action may be due rather to the production of a mild inflammatory reaction in the tissues than to the increased viscosity of the injection. Beeswax may be replaced by aluminium monostearate in penicillin in oil injections and is effective in prolonging the effect of oil solutions of cyanocobalamin[30].

The action of a water-soluble drug may be prolonged by preparing a water-in-oil emulsion of the aqueous solution, and a heparin preparation of this type has been suggested[38].

Chemical modification of the medicament. Chemical modification is directed to either the production of insolubility or delay in utilisation. The former is well exemplified by penicillin and insulin. The combination of procaine and benzyl penicillin yields procaine benzylpenicillin[39] which is only slightly soluble in water and in oils and which, in suspension in oil, is long acting both *in vitro* and *in vivo*[40]. Numerous other insoluble salts of penicillin have been the subject of investigation and patents. The advantages of such derivatives are three-fold, firstly the insolubility of the product in water confers stability, rendering possible the formulation of aqueous suspensions which retain their activity for a long time; secondly, on injection, the insoluble material forms a depot from which the derivative is slowly leached, and thirdly there is probably some further delay in utilisation while the derivative is broken down in the body to release an active penicillin molecule. Esters of penicillin do not appear to be effective in man[41,42], owing to the absence of a penicillin esterase in human blood which is present in some animal species[43].

Insoluble compounds of insulin were introduced with the intention of modifying the transitory nature of soluble insulin. The relatively insoluble complex of protamine and insulin[44] first produced in 1936 was shortly afterwards superseded by protamine zinc insulin[45] the extreme insolubility of which confers remarkable stability and an increase in the duration of activity.

Other proteins may be similarly employed, the prolonged action being less pronounced when a protein less alkaline than protamine, which has an isoelectric point of about 12, is used.

Delayed action preparations such as isophane or NPH insulin containing relatively little zinc and a reduced amount of protamine have a shorter duration of action than protamine zinc insulin[46] but have the advantage that they may be mixed with unmodified insulin for simultaneous injection when the quick action of the latter is required, whereas with protamine zinc insulin in similar conditions the rapid action of the added unmodified insulin is lost.

Sensitivity may be encountered with these preparations due to the protein content, and more recently insoluble zinc-insulin preparations free from protein have been made[47] by precipitating insulin in the presence of zinc under nearly neutral conditions in the absence of ions having an affinity for zinc, giving either amorphous or crystalline material which may be suspended in an aqueous vehicle for injection; the amorphous material is rapid in onset of action which is prolonged for about 12 hours, while the crystalline material is rather slower in onset and lasts about as long as protamine zinc insulin. The great difference between the particle sizes of the amorphous and crystalline types does not lead to the difference in duration of activity which might be expected, which suggests that the variation between the two types is more fundamental than this.

Chemical modification of the steroid hormones has not been directed towards the production of insolubility since this group is without exception insoluble in water at a therapeutic dosage level, but has been concerned with delaying metabolism to an active molecule. Esterification of one or more of the free hydroxyl groups in the steroid molecule by an organic acid is the method usually adopted and Junkmann and Witzel[48] have listed some 500 steroid esters most of which have been tested pharmacologically for prolongation of activity, the greatest amount of work having

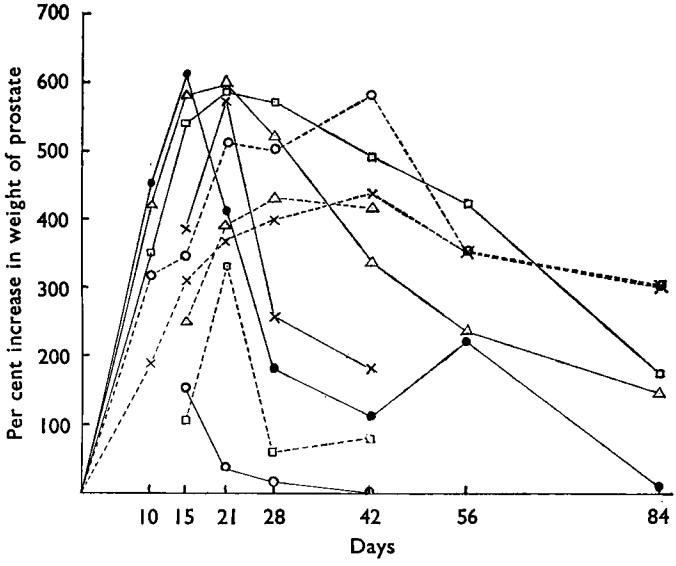

FIG. 1. Percentage increase in prostate weight of castrated rats after a single intramuscular injection of a series of testosterone esters. Figures in parentheses show the number of carbon atoms in the esterifying acid.

○——○ propionate (2)
△——△ oenanthate (7);
○---○ pelargonate (9);
△---△ undecanoate (11);
●——● phenylpropionate for comparison.
×——× caproate (6);
□——□ caprylate (8);
×---× decanoate (10);
□---□ laurate (12);

(After Dekanski and Chapman, unpublished.)

been directed to the esters of the androgens and, in particular, testosterone. Reasonably good agreement has been found in this series between the duration of activity and the rate of saponification of the ester treated with homogenised human or rat liver[49], the lower the rate of hydrolysis, the longer acting the ester, but Junkmann and Witzel point out that similar agreement was not obtained, particularly with testosterone phenylacetate, phenylpropionate and hexahydrobenzoate, when the rate of saponification was determined in alcoholic potassium hydroxide[50].

In general, esterification with a long chain fatty acid produces the greatest prolongation of activity, which increases to a maximum with an optimum chain length of the acid. Figure 1 shows the result of some

unpublished work carried out in our own Laboratories on a series of esters, varying in chain length from C_6 to C_{12} which suggests that C_9 (pelargonate) or C_{10} (decanoate) is the optimum for this series. The initial delay in response characteristic of most long acting preparations is also seen and demonstrates that if a uniform level of activity with rapid onset is to be obtained a mixture of esters such as the propionate, phenylpropionate and decanoate should be used, rather than the long acting decanoate alone. These esters become more soluble in oil with increase in chain length of the esterifying acid, enabling the larger doses required to be given in a small dose-volume.

Adsorption. Adsorption of a drug on to an insoluble carrier has been used as a means of prolonging the activity of toxins and toxoids, and is of considerable importance as one method of delaying the utilisation of the protein hormone, corticotrophin. The carrier is usually the hydroxide or phosphate of either aluminium or zinc, adsorption occurring only when these substances are in a colloidal form.

In 1954, Homan and others[51] showed that both zinc phosphate and zinc hydroxide, precipitated from a solution of corticotrophin, carried with them the corticotrophic activity and produced a suspension of small particle size which was easily injected and from which the active material was slowly released after injection; they considered also that since zinc can inhibit several kinds of protein splitting enzymes[52–54] the simultaneous slow release of zinc compounds present in this preparation would protect the corticotrophin from destruction.

Preparations based on zinc phosphate are clinically effective[55] but may crystallise on storage with release of adsorbed corticotrophin into solution and a consequent decrease in the duration of activity. Suspensions are freshly prepared for clinical use by mixing a solution of corticotrophin containing zinc chloride with a solution of sodium phosphate containing sodium hydroxide before injection. A similar preparation using zinc hydroxide, which is not liable to crystallise, as the carrier, is manufactured ready for use.

Crystal suspensions. Crystal suspensions of steroid hormones are not as long acting as might at first be considered probable. A crystal suspension of testosterone propionate is intermediate in duration of effect between the oil solution and an implantation pellet[56] and while pharmacological work has shown that both duration and response is about doubled when the crystal suspension is compared with the oil solution of this steroid ester[57], the response to the crystal suspension declines rapidly. The duration of action of such crystal suspensions varies directly with the size of the crystals[58], but a limit must be imposed since pain on injection increases with increasing crystal size[59]. Crystal growth occurs with some steroids and while it can be largely prevented in many cases by careful formulation, it is potentiated by continuous fluctuation of temperature which should be avoided during storage. Attempts have been made to overcome these difficulties by dissolving the hormone in a water-soluble solvent, which, on injection, should dissolve in the body fluids leaving a crystalline residue of the steroid *in situ*; propylene glycol solutions have

been used for this purpose, and a more elaborate method consists in dissolving the hormone in benzyl alcohol which is soluble about 1 in 25 in water and emulsifying this solution in water saturated with benzyl alcohol[60]. Some suspensions are still widely used not because of any great prolongation effect but because solubility considerations render this the only way to provide a therapeutic dose in a reasonable dose-volume.

Suspensions prepared from steroids crystallised under non-sterile conditions, when spores may act as centres of crystallisation, are difficult to sterilise by autoclaving unless the particle size is less than 50μ[61], and this finding is of importance since the normal test for sterility would not indicate the presence of viable spores within the crystals.

Implants. The form of prolonged duration medication introduced in 1937[62] originally known as implantation pellets and now officially abbreviated to "implants", consists of a hard tablet which, inserted beneath the skin or into the muscle tissue, slowly dissolves in the body fluids which surround it, liberating continuously a small amount of the medicament into the blood stream.

A medicament in this form must be active in very small dosage, and must be required to exert its activity for long periods, and for these reasons its application has so far been limited to the restricted but important field of hormone therapy where it closely simulates the effect of a functioning gland.

Attempts have been made to prepare implants of water soluble hormones by mixing the drug with insoluble substances such as cholesterol before compression[63] but all implants at present available are prepared from one or other of the steroid hormones, which are just sufficiently soluble in body fluids to enable a therapeutic level to be maintained.

Implants are manufactured either by compression of the pure sterile material, or by melting and casting into shape in a mould. The former method is of universal application, but the latter is restricted to hormones with a melting point below about 200°, since those with a higher melting point discolour or char on melting, and is not satisfactory for the stilboestrol series of synthetic oestrogens which fall to powder after solidification. Little difference has been noted clinically in the effect of implants prepared by either method though it is claimed that the process of fusion leads to a more uniform product than can be obtained by the compression process. Protein matter deposits within the substance of a compressed implant[64] after insertion, and it has been suggested[65] that this is due to the presence of pores in the compressed product which are presumed to be absent in that made by fusion. This deposition may be demonstrated by dissolving the implant, after removal from the body, in an organic solvent, when an insoluble residue remains in the shape of the implant to which the name "ghost" has been applied[64], and it has been claimed[66,67] that this "ghost" formation decreases the rate of absorption. A capsule of connective tissue also forms in the body around implants of either type but this is not deleterious. In spite of the presumed less porous structure of fused implants there is evidence that they tend to be utilised more rapidly than those made by compression[65].

The mobilisation of the hormone is limited by the rate of solubility in the body fluid rather than by the final solubility of the substance. The absorption rate from superficial areas can be expressed mathematically as a hyperbolic curve[65] which reflects the decreasing surface area of the

TABLE I

CORRELATION OF APPROXIMATE AVERAGE DAILY ABSORPTION RATE AND SURFACE AREA IN FUSED IMPLANTS OF DEOXYCORTONE ACETATE

Weight (mg.)	Diameter (mm.)	Length (mm.)	Surface area sq. mm.	Average daily absorption (mg.)	Average absorption mg./sq. mm.
25	2·2	6·0	49	0·30	0·0061
50	4·5	2·8	71	0·45	0·0063
100	4·5	5·5	110	0·70	0·0063
150	4·5	8·3	149	0·90	0·0060
200	4·5	11·0	187	1·10	0·0058
300	7·0	6·6	222	1·30	0·0058

implant during absorption and we have found that if the average daily absorption is related to the original surface area, fair agreement is seen (Tables I and II).

This consideration is of importance in controlling, not only the daily dosage but also the duration of activity. Increased dosage rate can be achieved most accurately by increasing the number of implants inserted at one time, whereas an increase in the weight of material implanted as a single

TABLE II

CORRELATION OF APPROXIMATE AVERAGE DAILY ABSORPTION RATE AND SURFACE AREA IN FUSED IMPLANTS OF TESTOSTERONE

Weight (mg.)	Diameter (mm.)	Length (mm.)	Surface area sq. mm.	Average daily absorption (mg.)	Average absorption mg./sq. mm.
25	2·2	6·0	49	0·40	0·0081
50	4·5	2·8	71	0·70	0·0098
100	4·5	5·5	110	1·10	0·0100
150	4·5	8·3	149	1·35	0·0090
200	4·5	11·0	187	1·50	0·0080
300	7·0	6·6	222	1·70	0·0076
350	7·0	7·7	246	1·80	0·0073

pellet, while it leads to some increase in daily dosage, is of greater importance in determining the time during which the implant continues to exert its therapeutic effect.

Implants are usually prepared from the unmodified hormone if it is stable, as with testosterone, progesterone or oestradiol, or from a normal relatively short acting ester such as deoxycortone acetate if the free steroid decomposes. Use of the long-acting esters is of no advantage since the rate of utilisation is sufficiently limited by the rate of solution.

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DISCUSSION

The following points arose out of the DISCUSSION.

While the emphasis of the meeting was on prolonging the action of drugs, extended action could be a disadvantage, as the drug might be difficult to control, and its actions impossible to terminate. There is often a need for a drug having a rapid but short duration of action. The value of a series of "peak" blood levels of a drug as opposed to "plateau" levels was a question of trial, but blood levels were only one factor. Tissue concentrations of the drug were of more importance, and diffusibility must be taken into account. Frequency of administration should be related to storage in the tissue. Prolonging action by the modification of the metabolic degradation of drugs by chemical methods was suggested, as was also chemically modifying an active compound such that upon *in vivo* attack by enzymes the parent compounds would be liberated. The information that polyvinylpyrrolidone was carcinogenic stemmed from a report of work on the substance in which the processing conditions were far more drastic than would be imposed in the preparation of medicaments incorporating the polymer, and therefore the claim was misleading. The inclusion of excipients in implants or their manufacture by the sintering process would affect the properties of the product. Evidence of the unsatisfactory nature of many enteric-coated tablets was cited. Further consideration should be given to the potentialities of sublingual absorption. Disintegration of the granules as well as of the tablets was essential for reliable absorption of insoluble drugs. Sustained action tablets should not be used for all drugs: there might be adverse effects on the kidney or liver.