Edited by T. B. Binns

Absorption and Distribution of Drugs

Based on an AMAPI Symposium

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Based on a symposium held by the Association of Medical Advisers in the Pharmaceutical Industry

Edited by

T. B. BINNS, M.R.C.P., M.R.C.P.Ed., D.C.H.

Glaxo Laboratories, Greenford, Middlesex
Department of Medicine, West London Hospital

Foreword by

SIR CHARLES DODDS, M.V.O., M.D., F.R.S.

Courtauld Professor of Biochemistry, University of London
President, Royal College of Physicians, London

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PREFACE

THIS book is based on a symposium entitled Factors Affecting the Absorption and Distribution of Drugs held in 1963 at the Royal Society of Medicine, London, by the Association of Medical Advisers in the Pharmaceutical Industry.

I originally suggested this title because I had periodically experienced difficulty in finding out what happened to drugs after their administration. Manufacturers were not always providing the necessary information, if indeed they were collecting it. On the other hand there had appeared, scattered in the literature, a number of papers indicating that the absorption and distribution of drugs were governed by physico-chemical and pharmaceutical principles that could usefully be applied both by manufacturers and clinicians. It seemed that no recent attempt had been made to bring together the available information and that the A.M.A.P.I. was in an unusually strong position to do this, since so many medical and para-medical disciplines were involved.

The book does not claim to be an exact replica of the proceedings. Many of the papers are the same, but some authors asked if they could extend their presentations in the printed version. In particular I encouraged Dr. Brodie to give considerably more detail than the time available at the symposium permitted. He has responded most generously by contributing two uniquely comprehensive reviews of his own and other work on this fundamental subject. These now occupy about one third of the book. I am extremely grateful to him for making the journey to attend the symposium and for all the trouble he has taken in a very busy year.

I also wish to thank the other participants for their ready co-operation; Dr. C. D. Falconer and Dr. J. H. Fryer, respectively Chairman and Treasurer of A.M.A.P.I. at the time of the symposium, for assistance with the administrative arrangements; the Royal Society of Medicine for help and hospitality and the publishers, E. & S. Livingstone Ltd., for their courtesy and efficiency.

More colleagues and their secretaries have helped than I can mention by name but I am especially grateful to Mr. R. W. Calcutt and Mr. L. Borden for redrawing many of the diagrams and formulae, Mrs. Doreen Blake for the index and to my secretary, Mrs. M. E. Hartley, for her willing and valuable assistance.

T. B. BINNS.

FOREWORD

It is now just seven months since the symposium on Factors Affecting the Absorption and Distribution of Drugs was held. This has been a period of intense activity by various official bodies concerned with therapeutic agents. The Government, through the Ministry of Health, has set up a powerful body under the chairmanship of Sir Derrick Dunlop and his organization will go into action on the 1st January, 1964. There can be little doubt that the papers presented at the symposium of the Association of Medical Advisers in the Pharmaceutical Industry will be carefully studied by Sir Derrick and his colleagues, and they will undoubtedly find material of great interest to help them in their deliberations. When one reads these papers again one can see that many of the questions that will occur to other official bodies will also find an answer in the proceedings of this symposium, and it is gratifying to realize that the stimulus for this work came from the Industry in the first instance. The book also demonstrates the readiness of Academic Medicine and the Pharmaceutical Industry to co-operate, at least at the scientific level, and the value to both sides of close collaboration. The whole future of drug research now depends upon it.

E. C. Dodds.

London, W.1.

SESSIONAL CHAIRMEN

SIR CHARLES DODDS, M.V.O., M.D., F.R.S.

Courtauld Professor of Biochemistry, University of London,
Middlesex Hospital Medical School, London, W.1.
President, Royal College of Physicians, London.

M. D. MILNE, M.D., B.Sc., F.R.C.P.

Professor of Medicine, University of London,
Westminster Hospital Medical School, London, S.W.1.

G. M. WILSON, M.D., B.Sc., F.R.C.P.

Professor of Pharmacology and Therapeutics,
University of Sheffield.

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ALIMENTARY ABSORPTION OF DRUGS; PHYSIOLOGICAL CONSIDERATIONS

D. H. SMYTH, M.D., Ph.D.
Professor of Physiology, University of Sheffield.

ABSTRACT

A brief survey is made of the physiological factors that may influence absorption of drugs from the intestine. These are: (1) part of the alimentary tract involved, (2) alimentary motility, (3) intestinal blood flow, (4) effect of digestive secretions, (5) intestinal concentration of drug, (6) other intestinal contents, (7) structure of the intestine, (8) cellular mechanisms in the epithelial cell.

The possible ways in which these may influence absorption of drugs are discussed very briefly, and some suggestions are made which might be of use in considering the particular chemical form in which therapeutic agents are administered. Reference is made also to the relation between absorption *in vivo* and *in vitro*, and the interpretation of experiments for determination of absorption capacity.

THE physiological function of the alimentary tract is the digestion and absorption of nutrient materials. Although we know that mechanisms other than diffusion are concerned in the absorption of at least some representatives of the six groups of nutrients, *i.e.* proteins, fats, carbohydrates, vitamins, salts and water, we know little of the details of these mechanisms even in healthy animals. In the present context we face two additional complications, *i.e.* the absorption of substances usually foreign to the alimentary tract, and furthermore the possibility of this being associated with pathological conditions in the body. The task assigned to me is briefly to discuss the physiological factors that may be involved in drug absorption. This leaves little opportunity for detail, and I therefore propose to draw your attention to some of these factors in the barest outline only, and hope that other papers will fill in details.

SITE OF ABSORPTION

Drugs may be introduced into either end of the alimentary tract and may be absorbed from various parts of it, so that the whole length from mouth to rectum must be considered. A drug

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given orally may be retained in the mouth and absorbed there, or it may be swallowed and absorbed from the stomach or intestine. In general, the higher up it is absorbed the more rapid will be its action, which is presumably desirable in most, although not necessarily in all, cases. Also, the nearer the mouth, the more concentrated is the drug likely to be presented to the absorbing epithelial cells, for in passing down the alimentary tract it becomes progressively diluted with intestinal secretions and intestinal contents. Other advantages of high alimentary absorption are (1) that the substance to be absorbed is less exposed to the possible destructive action of the intestinal secretions, and (2) direct entry into the systemic circulation might enable a higher systemic concentration of drug to be achieved by avoiding preliminary passage through the liver.

Mouth

It follows then that there are considerable advantages to be gained from oral absorption. This method requires some co-operation by the subject, and for this reason might be unsuitable in infants and a small number of other cases. It is however noteworthy that Barrie, Cottom & Wilson (1962) claimed successful oral absorption of respiratory stimulants in newly-born infants. Few quantitative studies have been made on oral absorption. Walton (1944) reviewed the position at that time, and listed a number of drugs which were either effective or ineffective when given by sublingual administration. As lipophilic substances penetrated more easily, he concluded that the important factor in determining the efficacy of oral absorption was the fat-water distribution of the drug.

Stomach

In the stomach the special condition of a high hydrogen ion concentration can be important in influencing absorption by affecting the degree of dissociation, as shown by Schanker, Shore, Brodie & Hogben (1957). I do not wish to go into further details of gastric absorption at present. The older work was reviewed by Karel (1948), and recent studies on absorption have chiefly concerned the intestine.

Intestine

Even within the limits of the intestine there is considerable variation in capacity for absorption. Contrary to views sometimes

held, there is no definite gradient of absorptive capacity down the intestine. There are variations with different regions, with different animals and with different substances, and each species, molecular, ionic and animal, must be considered separately. This is made clear from the data collected by Wilson (1962) for absorption of various substances from different parts of the alimentary tract. The complexity is well shown by fluid absorption in the rat, and Barry, Matthews & Smyth (1961) have shown that glucose-dependent fluid transfer is greater in the jejunum, while glucose-independent fluid transfer is greater in the lower ileum. Definite information about absorption from the human colon is scarce, and in the case of substances given by rectum the actual site of absorption has not often been determined. Matts (1960) has shown that fluid injected into the human rectum may go a surprisingly long distance into the colon within a few minutes, and it would be unwise to assume that only the lower end of the colon is involved in absorption of substances introduced rectally, or even to exclude the possibility that retrograde movement might occur as far as the ileum.

Alimentary Motility

The effect of motility will depend on the part of the alimentary tract from which absorption takes place. If a drug is absorbed from the stomach, but not the intestine, increased rate of gastric emptying may reduce absorption, whereas faster gastric emptying could accelerate absorption of drugs from the intestine. Intestinal motility changes could also produce varying effects. Excessive peristaltic activity could remove the substance before absorption had occurred. On the other hand Cummins & Almy (1953) found that absorption of glucose and methionine were increased in the hyperactive gut, possibly due to better contact of gut contents with absorbing epithelium, or possibly due to increased blood flow.

Decreased intestinal motility could be important in increasing the time available for absorption. If a drug is administered in a series of doses, and if it, or the disease being treated, reduced intestinal motility, a much higher concentration than that intended might well be built up or a more prolonged effect might be produced. Motility of the intestine can produce changes in intraluminal pressure, and Groisser & Farrar (1962) have recently considered the effects of intraluminal pressure on absorption in the human subject. The effect of intestinal motility is obviously more relevant to drug absorption than to absorption of nutrients, as in the former case there is more likelihood of alteration in

intestinal motility, either due to the disease present or to the effect of the drug.

Under the heading of motility the movements of the villi must also be considered. Although the pumping action of the villi popularized by Verzar & McDougall (1936) is still given prominence in many accounts of absorption, it is not based on very firm experimental evidence. The more critical experiments of Wells & Johnson (1934) are often overlooked, in which no evidence was found to support the pumping theory, and the functions of the villi would appear to be restricted to enlargement of the general absorbing surface and possibly to some local mixing effects.

Intestinal Blood Flow

Very little work has been done on the effect of intestinal blood supply on absorption, but presumably it could have an important effect. Not only is the total rate of blood flow important but also its pathway through the intestinal mucosa, a subject on which not much information is available. The idea that splanchnic blood flow is increased during digestion and absorption is a very old one, and has been demonstrated quantitively in the dog (Herrick, Essex, Mann & Baldes, 1934), in man (Brandt, Castleman, Ruskin, Greenwald & Kelly, 1955) and in the rat (Reininger & Sapirstein, 1957), so that there is some physiological basis for the familiar direction in the prescription 'post cibum'. It would seem however that the increased splanchnic blood flow is not a redistribution of blood in favour of the intestine, but that the intestine shares with other organs the effects of increased cardiac output. In man it is interesting that the increased splanchnic blood flow occurs with a protein meal but not with a carbohydrate one. Richards, Wolf & Wolff (1942) have claimed that anxiety, fear and other emotional states cause changes in gastro-intestinal blood flow, a matter that could have some relevance to drug absorption.

Effects of Digestive Secretions

Secretions of the alimentary tract may modify absorption in various ways. In the first place digestive secretions affect pH, which, as already mentioned, could modify absorption. A very different kind of effect is illustrated by absorption of cyanocobalamin, which depends on the presence of intrinsic factor secreted by the gastric mucosa (see Cooper & Castle, 1960). A third way in which alimentary secretions can modify absorption is exemplified by the action of bile on fats, where changes in the physical

form of the substance may favour absorption. A fourth method is by the hydrolytic action of the digestive enzymes. These may act on substances to make them more suitable for absorption, e.g. their action on proteins, or on the other hand they may destroy the substance that is intended for absorption. Examples of this are insulin and oxytocin, and their fate is likely to be shared by other peptides. Whether the destructive action of peptidases could be avoided is an obvious matter for investigation. The attempts of Laskowski, Haessler, Miech, Peanasky & Laskowski (1958) to increase insulin absorption by using a trypsin inhibitor are interesting in this respect. Here it should be remembered that it is not only digestion in the lumen of the intestine that has to be reckoned with, but also intracellular digestion in the epithelial cell. The secretion of mucus could also be important in modifying the accessibility of the drug to the absorbing epithelial surface.

Intestinal Concentration of Drug

This must be an important factor in rate of absorption, and therapeutically attempts might be made to achieve optimum concentration, or to maintain prolonged concentration. (Concentration refers to the form in which the substance is absorbed, which may not necessarily be the same as the form administered.) Substances can be divided into two groups, according to the effect of concentration on absorption; those whose rate-limiting process follows diffusion kinetics, and those which show saturation kinetics. In the former the rate of absorption is proportional to the concentration in the intestine, and presumably for maximum effects the higher the concentration the better. With saturation kinetics increase in rate of absorption falls off with increasing concentration. This was first shown by Cori (1925) for glucose, and has since been shown for other sugars and for many amino acids. In such cases there may be little value in increasing the concentration beyond a maximum level. Whether that level is ever likely to be reached by oral administration must be experimentally determined in each case. The usual concept of saturation kinetics is the attachment of the substance being absorbed to some kind of carrier, in a manner analogous to attachment of an enzyme to its substrate. If this analogy is pursued further, the possibility of 'substrate inhibition' must be envisaged, which would mean that increased concentration of a substance in the intestine might actually reduce the rate of absorption. In these circumstances maintenance of prolonged concentration might be more important than maintenance of high concentration.

Intestinal Contents

The absorption of a particular substance may be affected not only by its own concentration in the lumen of the intestine, but by the concentration of other substances there. Hydrogen ion concentration is not only responsible for extent of dissociation, and activity of digestive enzymes, but in addition may cause destruction of some substances or render others insoluble. Simple chemical reactions between different luminal constituents can produce various effects, e.g. phytic acid may render either calcium or iron insoluble, or the presence of calcium may remove phytic acid and hence prevent it removing iron. A very different type of effect theoretically possible is competition between different substances for the same entry mechanism, e.g. methionine and glycine (Wiseman, 1953), but whether these would ever be present in concentrations sufficient to cause serious competition must be doubtful. Some substances may accelerate the absorption of others, e.g. Comar, Wasserman & Nold (1956) found that absorption of calcium was increased when other constituents of milk were present, and as mentioned later glucose may stimulate water absorption.

Structure of the Intestine

Let us now look at the structure of the intestine in relation to absorption. As the experimental techniques for study of absorption involve both *in vivo* and *in vitro* methods, I should like to have both of these in mind in looking at the wall of the gut. This is shown in a highly diagrammatic form in Figure 1, and consists of (1) a mucous membrane or mucosa, (2) a submucosa, (3) a muscularis externa and (4) a serosal layer. Of these we are most concerned with the mucous membrane, although the other layers should not be ignored. The mucosa consists of the following three layers: (a) The lining epithelium, which is a single layer of columnar cells and goblet cells. Of these only the columnar cells are concerned with absorption. (b) The supporting lamina propria. The most superficial layer of this is the basement membrane on which the epithelium rests. Below this is loose connective tissue containing collagen and reticular fibres, lymphoid tissue, tissue fluid and blood and lymph vessels. Of these only the blood capillaries are shown on the diagram. (c) The muscularis mucosae. The submucous coat consists of loose connective tissue connecting the mucosa to the muscularis externa. In this connective tissue run the larger blood vessels, whose branches penetrate into the lamina

propria of the mucous membrane, and the nerve fibres constituting Meissner's plexus. The muscularis externa consists of two layers of muscle—longitudinal and circular, with Auerbach's plexus lying between them. As no nervous effects on absorption have yet been demonstrated with certainty the nerve fibres (both Meissner's and Auerbach's) have been omitted from the diagram. The serosal layer is formed of the peritoneal coat, which at one side leaves the

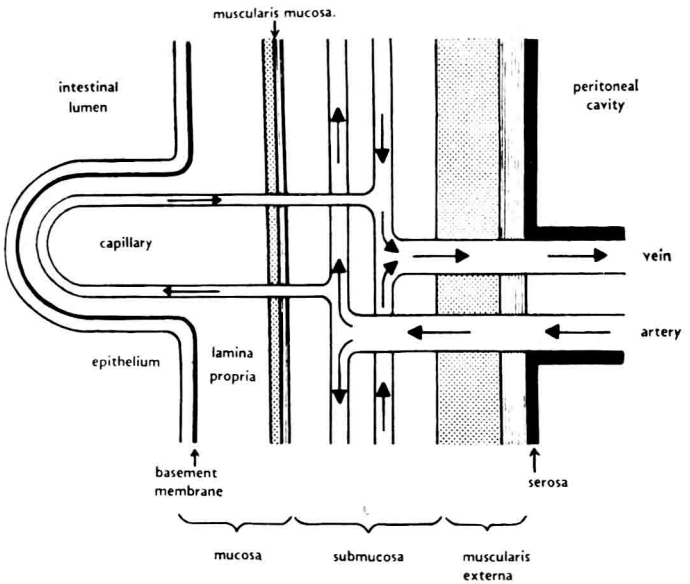

Fig. 1. Diagrammatic representation of the intestine under physiological conditions in relation to absorption. The diagram shows the epithelial layer separating the intestinal lumen from the fluid in the lamina propria. Substances absorbed must first pass into the lamina propria and then through the capillary wall into the blood stream. The lacteals have been omitted to avoid complicating the diagram. (*Drawing by P. Price.*)

gut wall to form the mesentery containing the blood and lymph vessels and nerves. (In order to keep the diagram as simple as possible, lymph vessels have been omitted entirely.)

When substances are absorbed they first leave the intestinal lumen and enter the epithelial cells. After transfer across the cells, a process which may involve various stages, they leave the other side of the cell and enter the fluid of the lamina propria, and from this they enter the blood capillaries or lymph capillaries to be

carried away from the intestine. *In vitro* the conditions are rather different and this is illustrated in Figure 2. The structure of the gut wall is of course the same, but there is no flow of blood through the vessels. These are torn off at the mesenteric border, and the peritoneal surface of the gut is bathed in a fluid we call the serosal fluid. The fundamental absorptive activity of the epithelium remains the same, and just as *in vivo*, the absorbed

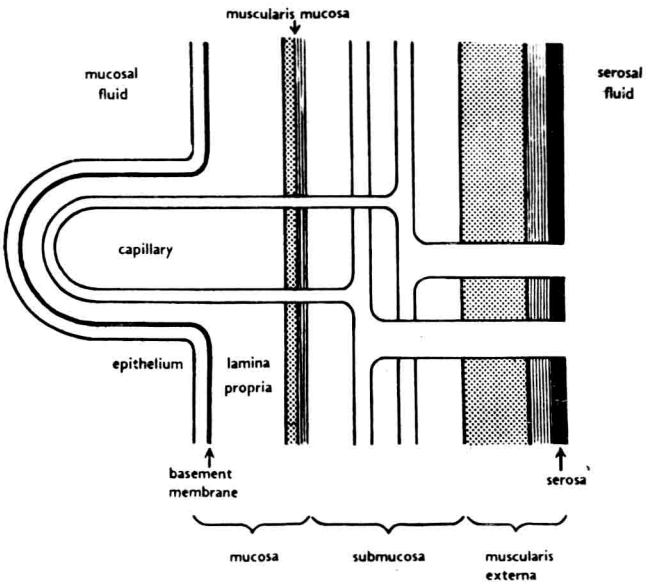

Fig. 2. Diagrammatic representation of the intestine *in vitro* in relation to absorption. The epithelium now separates the mucosal fluid from the fluid of the lamina propria. The mesenteric vessels are torn off at the serosal surface of the gut and this surface is in contact with the serosal fluid. The substances which penetrate into the lamina propria must reach the serosal fluid either by passage through the other layers of the gut wall, or by passing along the lumen of the blood vessels. (*Drawing by P. Price.*)

substances enter the epithelial cells from the luminal fluid, and after transfer across the cells enter the fluid of the lamina propria. As there is no flow of blood through the capillaries, the absorbed substances must get through the rest of the intestinal wall into the fluid bathing the serosal surface. In doing so they probably use two routes. One is the obvious one of diffusion through the various layers of the intestinal wall. The other is the more physio-

logical one, i.e. the capillaries, and fluid transferred may escape from the torn ends of these to enter the serosal fluid. This is suggested by the fact that the first fluid to emerge from the gut wall is blood stained. This picture of intestinal transfer *in vitro* must be clearly understood, because it can influence our interpretation of *in vitro* experiments, which are very extensively used in absorption studies.

When we come to study the absorption process in any particular case, we can approach this in various ways. We can think of it in terms of a two-compartment system separated by a complex membrane. With absorption *in vivo* the two compartments are the fluid in the lumen of the intestine and the plasma or lymph. With absorption *in vitro* the two compartments are the fluid in contact with the epithelial cells (usually called the mucosal fluid) and the fluid bathing the serosal surface of the cells, the serosal fluid. The two-compartment approach is undoubtedly a useful one, and in particular it gives information about such matters as whether the substance absorbed is moved against a concentration gradient, or, if electrical studies are made, against the electrochemical potential. For studies *in vivo* the two-compartment approach is almost the only one possible. *In vitro* the position is rather different, and the two-compartment approach, although very useful, can lead to errors in interpretation of the results. This is more likely to happen if too much emphasis is laid on the serosal fluid, and particularly if changes in this are taken as a measure of the transfer capacity of the intestine. This will be obvious when we discuss the more complex multi-compartment approach.

The two-compartment concept is not adequate to explain the transfer of any substance in detail and we must think about the various stages in the absorption process. These stages are (1) movement from the lumen of the intestine into the epithelial cell, (2) movement across the cell, (3) movement out of the cell into the fluid of the lamina propria, (4) movement from this into the capillaries *in vivo* or serosal fluid *in vitro*. The need for this approach can be shown by considering some fallacies in interpretation of results. The substances (fluid and solutes) that emerge from the epithelial cell pass into the fluid of the lamina propria. *In vitro* they first accumulate here, then find their way into the serosal fluid. Everything that emerges from the epithelial cell however does not enter the serosal fluid, but a considerable amount remains in the gut wall, i.e. between the basement membrane of the epithelial cell, and the peritoneal layer of the gut. This subepithelial reservoir is quite large, and in everted sacs may be