Introduction to the Principles of Drug Design

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Preface

Paul Ehrlich's concept that protozoal diseases could be cured by the administration of synthetic chemicals which selectively reacted with the target tissue of the protozoa rather than that of the host, and Domagk's later expansion of this view to the treatment of bacterial diseases with the introduction of prontosil, set the scene for a major breakthrough in the treatment by drugs of other types of disease, ailments and conditions where the target tissue may be an enzyme, a macromolecular structure such as DNA, RNA, or even a structure of unknown constitution. This approach has been so well developed that, with the expanding knowledge of the biochemical and physiological processes occurring in both the healthy and diseased state, it has become possible to select a target tissue and, from a knowledge of its characteristics, to design drugs with the correct size, shape, hydrophilic–lipophilic ratio, disposition of functional groups to selectively react with it to elicit the required clinical response. This procedure, however, involves considerable ingenuity on the part of the designer. This is despite the fact that he has currently at his command an array of established manipulative procedures enabling him to develop a clinically effective drug by modification of a parent drug lacking the essential requirements (such as selectivity for the target site, chemical stability, resistance to premature metabolism) necessary for evoking an optimal therapeutic response.

This introduction to the principles of drug design is intended for use in undergraduate pharmacy courses in medicinal chemistry and as an aid in similar courses in pharmacology and biochemistry where there is a need to appreciate the rationales behind the design of drugs. Graduates in chemistry just entering the pharmaceutical industry would find that it provides a suitable background for their future work.

The emphasis in this book is on principles, which are appropriately illustrated by groups of drugs in current (or even future) use. It is not our intention to deal comprehensively with all conceivable groups of drugs, or to consider drugs grouped on the basis of particular pharmacological actions. This would require repeated descriptions of a range of design aspects relevant to each group so that design considerations would become subservient to the biologically observable actions. We aim to provide a framework of basic drug design/principles into which current drugs, and more importantly future drugs following on new developments, may be fitted. This approach should provide the newly qualified graduate with an understanding of new developments as they become elaborated in future years.

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HJS. HW

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1.1 INTRODUCTION

To produce a pharmacological or therapeutic effect, a drug must reach its site or sites of action in a concentration sufficient to initiate a response. The concentration achieved, whilst being related to the amount of drug administered, will also depend on the extent and rate at which the drug is absorbed from its site of administration and its distribution by the bloodstream to other parts of the body. The characteristic effect of a drug will disappear when the drug is removed from the body and consequently from its site of action, either in an unchanged form or after metabolism of the drug has taken place giving metabolites which are removed by the process of excretion. Information on how the body handles a drug in terms of absorption, distribution, metabolism and excretion is therefore essential when selecting the dose, route and form of drug administration if a desired therapeutic effect is to be produced with minimal unwanted or toxic effects.

1.2 ABSORPTION

A drug may enter the body either by enteral or by parenteral administration. The enteral route refers to oral, sublingual and rectal administration whilst parenteral includes routes such as intravenous, intramuscular and subcutaneous injections; inhalation; and topical application to the skin and eye. Apart from drugs introduced directly into the systemic circulation by intravenous injection, absorption from the site of administration is essential if a drug is to gain entry to the bloodstream and thus reach its site of action. The process of absorption is consequently of fundamental importance in determining the pharmacological and therapeutic activity of a drug. Delays or losses of drug during absorption may contribute to variability in drug response or may result in a failure of drug therapy.

For the process of absorption to take place, a drug must cross at least one cell membrane and the ease with which it does so will reflect the concentration of drug achieved in the tissues and body fluids. It is therefore necessary to consider briefly the structure of cell membranes and the physico-chemical mechanisms involved in the passage of drugs across these membranes, together with the variety of factors which influence this process. It should be emphasized that as well as drug absorption, the processes of distribution, metabolism and excretion likewise involve the passage of drugs or their breakdown products across cell membranes.

1.2.1 Structure of cell membranes

Living cells are surrounded by membranes whose function is to maintain the integrity of the cell and to regulate the transfer of nutrients, waste products and

regulatory substances to and from the cytoplasm. The membrane is thus semipermeable, measuring approximately 8 nm in total thickness.

Overton suggested that the rate at which various substances enter cells is proportional to the distribution of the substance between lipid and water, the lipid-soluble substance entering the cell more readily. This suggestion was supported by other workers and led to the theory that the cell is surrounded by a thin layer of lipid-like material interdispersed with minute water-filled channels. Membranes are now considered to be composed of bimolecular layers of phospholipid molecules enclosing a central fluid matrix. The cationic heads of the phospholipid molecules are orientated to form an almost continuous polar layer on both the inside and outside of the cell membrane. In contrast, the long hydrophobic chains of the phospholipid molecules extend into the central core of the membrane. Since these chains are in a state of flux in the living cell, the matrix can be considered to consist of a sea of liquid lipid. Globular proteins are embedded in the membrane matrix often extending through all three layers of the membrane. Pores or channels through which water-soluble molecules (such as alcohol and water itself) can pass may be associated with these proteins.

1.2.2 Modes of transfer across cell membranes

The transfer of substances across cell membranes can occur by a number of possible mechanisms. The most important are: (*a*) direct passage through its lipid or aqueous channels down a concentration gradient, often called passive diffusion; and (*b*) carrier-mediated transfer of polar molecules called facilitated diffusion or, in some instances, active transport. Other modes of transfer include pinocytosis, in which invaginations of the cell membrane engulf drops of extracellular fluid enabling solute to be carried through in the resulting vacuoles of water; persorption; filtration or aqueous diffusion; and finally diffusion of ions.

1.2.2.1 *Passive diffusion*

Most drugs are transferred across cell membranes by passive diffusion from a region of higher concentration to one of lower concentration. Passive transfer is described by Fick's first law which states that the rate of diffusion across a membrane (dC/dt) is proportional to the difference in drug concentration either side of the membrane (ΔC), i.e.

$$\frac{dC}{dt} = -k\Delta C = -k(C_1 - C_2), \tag{1.1}$$

where C_1 and C_2 denote the concentrations of drug on each side of the membrane, C_1 being greater than C_2 and k representing the rate constant for diffusion. This is a proportionality constant incorporating the diffusion coefficient of the drug, the surface area of the membrane and the permeability of the membrane to the specific drug. If a large concentration gradient is maintained throughout the absorption phase, then $C_1 \gg C_2$ and consequently the concentration gradient (ΔC) is nearly

equal to C_1. Therefore, Equation 1.1 may be rewritten as

$$\frac{dC}{dt} \simeq -kC_1, \tag{1.2a}$$

which is the familiar form of a first order rate equation.

The concentration gradient can be replaced by the quantity of drug administered (A) and Equation 1.2*a* may then be written as

$$\frac{dA}{dt} = -k_a A, \tag{1.2b}$$

where k_a is the rate constant for absorption and represents the fraction of the amount administered that is absorbed in unit time. Integration of this equation gives

$$A_t = A_0 e^{-tka}, \tag{1.3}$$

where A_0 is the amount of drug administered (dose), A_t is the amount remaining unabsorbed at time t after the commencement of absorption and e is the base of natural logarithms. Assuming no losses of drug occur before or during absorption, the quantity of drug absorbed in time t, (Q_t) is the difference between A_0 and A_t, i.e.

$$Q_t = A_0 - A_t. \tag{1.4}$$

Substituting for A_t in Equation 1.3 gives

$$Q_t = A_0(1 - e^{-tka}). \tag{1.5}$$

In other words, the quantity of drug absorbed rises rapidly initially and then more slowly, approaching exponentially a plateau level. As $t \to \infty$, $Q_\infty \to A_0$ since $e^{-\infty} \to 0$.

Replacing A_0 in Equations 1.3 and 1.5 by fD, where f is the fraction of the dose available to the body and D is the dose administered, gives

$$A_t = fD e^{-tka}, \tag{1.6}$$

$$Q_t = fD(1 - e^{-tka}). \tag{1.7}$$

As already stated, the rate of diffusion of a drug is a function of the surface area over which the transfer occurs, the permeability of the cell membrane and the concentration gradient across the membrane, i.e.

$$\text{rate of diffusion} = \begin{pmatrix}\text{permeability}\\ \text{constant}\end{pmatrix} \times \begin{pmatrix}\text{surface}\\ \text{area}\end{pmatrix} \times \begin{pmatrix}\text{concentration}\\ \text{difference}\end{pmatrix}.$$

Thus a doubling of surface area of the membrane doubles the probability that drug molecules will collide with the membrane and, as a result, the rate of absorption will be increased by a factor of two. Similarly, the greater the concentration gradient, the greater will be the rate of diffusion of a drug across a membrane. However, many drugs pass rapidly through a membrane while others pass slowly. This difference in the ease of passage across a membrane may be expressed in terms of the permeability constant which is a characteristic of both the drug molecule

and the cell membrane, i.e.

$$\begin{pmatrix}\text{permeability}\\ \text{constant}\end{pmatrix} = \frac{(\text{diffusion coefficient}) \times (\text{partition coefficient})}{(\text{membrane thickness})}.$$

The major source of variation in this equation is the partition coefficient of a drug between the lipid membrane and the aqueous environment. Lipid-soluble drugs have high permeability constants and consequently penetrate membranes with ease. In contrast, ionized compounds partition poorly into lipids. Whilst the long hydrocarbon ester chains of the phospholipid membrane promote the solubility of drug molecules incorporating hydrocarbon and aryl groups (van der Waals' and hydrophobic forces are relevant) it must also be realized that natural phosphatidyl esters also possess dipolar characteristics due to C—O and C=O groups. These give rise to bond dipoles due to unequal distribution of electrons. Such features facilitate the lipid solubility of covalent molecules also possessing dipolar characteristics but which are still non-ionic in character. This explains why increased lipid solubility and hence penetration of cell membranes may be effected by incorporating electronegative substituents into neutral molecules. Thus, C—O, C—S and C—halogen groups promote dipole–dipole attraction with cell membrane structures, which aids passive diffusion into the cell.

(a) Lipid solubility As previously stated, cell membranes can be considered to be a double layer of protein–lipid material studded with water-filled pores. It is therefore to be expected that lipid-soluble substances will cross such a membrane by simply dissolving in, and diffusing across, the lipid layers. The ability of a substance to dissolve in lipid can be measured in terms of its partition coefficient between an aqueous and immiscible non-aqueous phase such as *n*-octanol, or chloroform. The influence of a drug's partition coefficient on its ability to pass through biological membranes can be demonstrated by comparing the partition coefficients of a number of different members of a homologous series of lipid-soluble compounds with their ability to cross cell membranes. It is found that the permeability of the membranes to each member of the series is directly proportional to the partition coefficient. The increasing molecular weight as the series is ascended exerts only a negligible effect. This is in contrast to substances that diffuse through aqueous channels, where molecular size is important. In general, the higher the value of the partition coefficient the more rapidly will the drug be transferred across cell membranes (*see* Table 1.1).

(b) Influence of pK_a and pH Many drugs are weak electrolytes and as such are partly dissociated in solution. In general, only the undissociated molecule is soluble in the lipid, the ions are not. For this reason, the dissociation constant of a drug plays a vital part in determining the ability of a drug to cross cell membranes and this in turn is influenced by the pH of the environment. The interrelationship between the dissociation constant, pH of the medium and lipid solubility of a drug often dictates its absorption characteristics and constitutes the pH-partition theory of drug absorption. The dissociation constant is often expressed for both acids and

Table 1.1 Relationship between chloroform/water partition coefficient and the absorption of barbiturates from the rat colon[a]

Barbiturate	*Partition coefficient*	*Percentage absorbed*
Barbitone	0·7	12
Phenobarbitone	4·8	20
Cyclobarbitone	13·9	24
Pentobarbitone	28·0	30
Secobarbitone	50·7	40

[a] Data from Schanker L. S. (1959) Absorption of drugs from the rat colon. *J. Pharmacol. Exp. Ther.* **126**, 283–90.

bases as a pK_a value (the negative logarithm of the acid dissociation constant). The pK_a values of several drugs and their relative strengths as acids or bases are given in Fig. 1.1.

The relationship between pK_a and pH and the extent of ionization is given by the Henderson–Hasselbach equation, i.e.

$$\text{for an acid, } pK_a - pH = \log (f_u/f_i), \tag{1.8}$$

$$\text{for a base, } pK_a - pH = \log (f_i/f_u), \tag{1.9}$$

where f_u and f_i are the fractions of the drug present in the un-ionized and ionized forms, respectively (*see also* Section 3.1.1.1). Thus, a solution of the weak acid aspirin (pK_a 3·5) in the stomach at pH 1 will have more than 99% of the drug in the un-ionized form. Since the un-ionized form of aspirin is lipid soluble, the drug is rapidly absorbed in the stomach. Most weakly acidic drugs are absorbed in the stomach since they exist largely in the un-ionized state at low pH values.

In contrast, poor absorption of basic drugs in the stomach can be explained by Equation 1.9. For example, a solution of codeine (pK_a 8) in the stomach will have only one molecule in a million in the un-ionized form. Indeed, most basic drugs are so highly ionized in the acid fluids of the stomach that absorption is negligible. However, weak bases ($pK_a < 2·5$) such as antipyrine may be absorbed to some extent in the stomach because they are significantly un-ionized even in this strongly acidic environment. Absorption of most weakly basic drugs is rapid in the near neutral fluids of the small intestine (*see* Equation 1.9). Thus, the passage of a weakly acidic drug across a membrane is favoured by its presentation in an acid medium such as stomach fluids, while the transfer of a weakly basic drug is increased if the pH of the solution is increased. Nevertheless, the absorption of all orally administered drugs, weak acids as well as weak bases, probably takes place more rapidly in the proximal intestine than in the stomach. Whilst this may initially appear contrary to the pH-partition theory, the large surface area offered by the small intestine reduces the necessity for a large fraction of the drug to be in its un-ionized state. For example, at pH 7, only 0·1% of aspirin is in the un-ionized form but, despite this fact, aspirin is well absorbed from the small intestine when

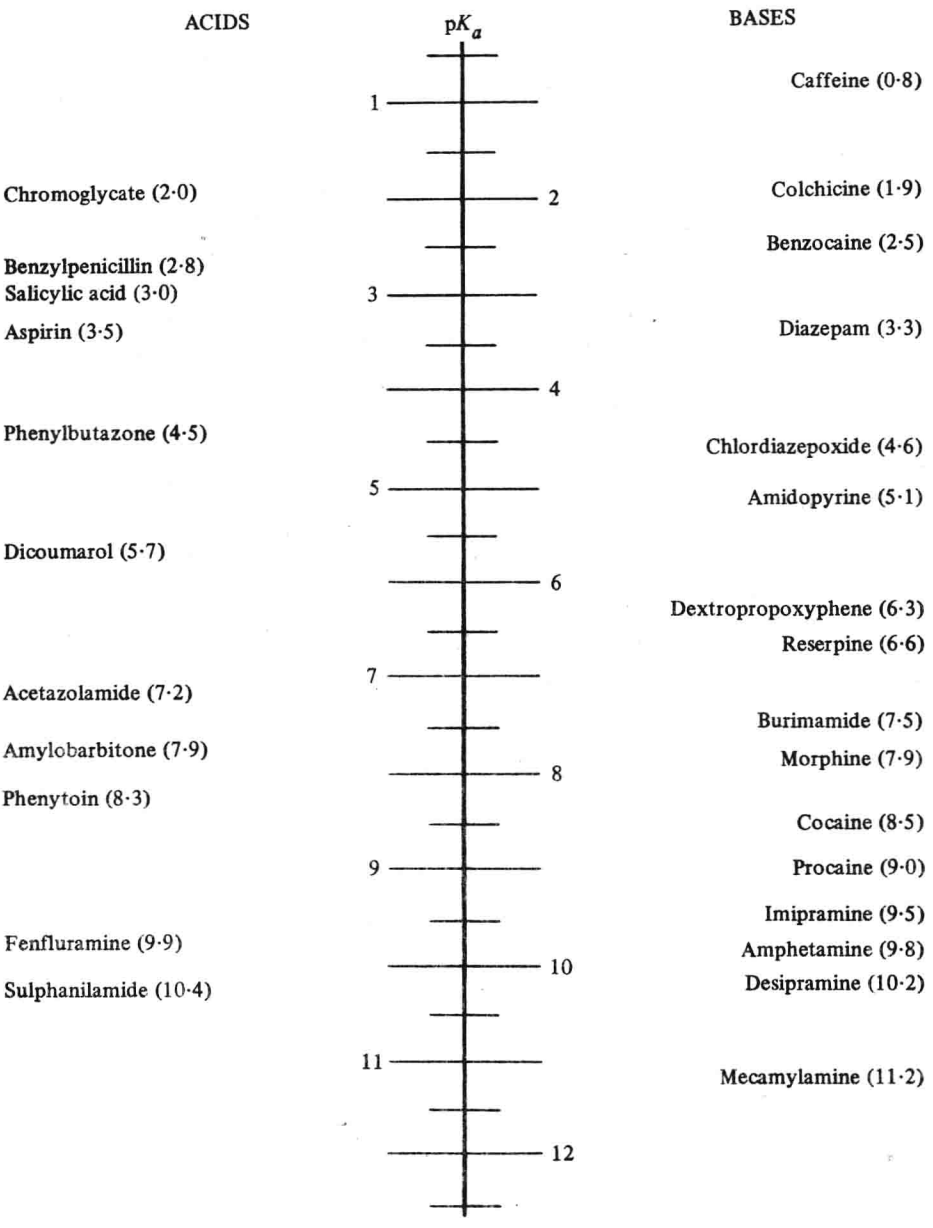

Fig. 1.1 Some pK_a values of acidic and basic drugs.

administered orally to man. Certain strong organic acids and bases, such as sulphonic acid derivatives and quaternary ammonium bases, are ionized over a wide range of pH values and have low lipid solubility. Therefore, their passage across cell membranes is rather poor and this is reflected in their poor absorption from the gastrointestinal tract.

1.2.2.2 *Carrier-aided transfer*

Some substances, though polar and of low lipid solubility, penetrate membranes much faster than anticipated, assuming that only passive diffusion through an inert lipoidal barrier occurs. Here a specialized carrier-mediated transport system is involved.

A carrier can be considered as a membrane component capable of forming a complex with the substance to be transported. The complex moves across the membrane and releases the substrate on the other side. A characteristic of a carrier-aided transport system is that high concentrations of the transported substance saturate the carrier. The effect of this is to limit the amount of substrate that can be transported. This is in contrast to the process of passive diffusion across lipid membranes, or through pores, where the amount conveyed increases proportionately with its concentration.

Of the two types of carrier-aided transport which have been proposed, facilitated diffusion accounts for the transfer of very few drugs and is not further discussed here.

Although few drugs undergo active transport, it is an important mechanism for the transfer of their metabolites. In active transport, the substrate is carried through the membrane against a concentration gradient and expenditure of metabolic energy is involved. The carrier can be saturated and since it has group specificity it can be inhibited competitively by other substrates. Because active transport requires the expenditure of energy, this process will also be affected by metabolic inhibitors such as 2,4-dinitrophenol or reduced temperatures.

Active transport mechanisms occur in the gastrointestinal tract (e.g. amino acids and possibly methyldopa), in the renal tubule and across membranes dividing extracellular from intracellular fluid compartments at the blood–brain and placental barriers.

1.2.2.3 *Pinocytosis*

Pinocytosis is a term which describes the active uptake of substances by a process similar to phagocytosis. Microscopic invaginations of a cell membrane engulf drops of extracellular fluid and solute molecules are carried through in the resulting vacuoles. Although important in the absorption of large molecules such as proteins and nucleic acids, this process is of little importance in the transport of drug molecules across cell membranes, except perhaps in the case of oral vaccines. However, efforts are currently being directed towards incorporating drugs into liposomes, which may then be taken up selectively by cells that are capable of pinocytosis.

1.2.2.4 *Persorption*

It has been recognized recently that particles in the micrometer range (e.g. starch grains) pass through the intestinal wall directly, entering either the lymph or the portal circulation. Entry appears to be via loose junctions around intestinal goblet

cells. The importance of this process for drug absorption from the gastrointestinal tract remains to be evaluated.

1.2.2.5 *Filtration or aqueous diffusion*

Water-soluble substances are able readily to diffuse through the aqueous channels or 'pores' in the cell membrane providing they are not of too large a molecular weight. This is essentially a process of solvent drag, the rate of diffusion being governed by Fick's first law.

1.2.2.6 *Diffusion of ions*

Ions are not soluble in lipids but, like water-soluble non-polar molecules, can diffuse across a membrane down a concentration gradient provided that their molecular weight is not too large. In instances where a cell membrane is polarized, one side being positively charged and the other negatively charged, a positive charged ion (cation) in aqueous solution will be driven across the membrane from the positive to the negative side. The extent to which this process will take place will be dependent on the potential difference across the membrane. Likewise, an anion in contact with the negative face will be driven across the membrane to the positive side. The passage of ions by this latter process does not require a concentration difference of the diffusing ion on the two sides of the membrane.

1.2.3 Routes of administration

Drugs are seldom, if ever, applied directly to their sites of action but are administered at regions remote from these sites. They subsequently have to be absorbed from the point of entry (e.g. stomach or intestine) into the bloodstream. When administering any drug, a route of administration, as well as a suitable dose and dosage form (e.g. tablet, capsule) must be selected in order to ensure that the drug will reach its site of action in a pharmacologically effective concentration and be maintained at this concentration for an adequate period of time. There is often a choice of route by which a drug may be given, so a knowledge of the advantages and disadvantages of the possible routes of administration is particularly important. Possible routes of drug administration are divided into two major classes: enteral, whereby drugs are absorbed from the alimentary canal and parenteral, in which drugs enter the bloodstream directly (intravenous injection) or by some other non-enteral absorptive route (intramuscular or subcutaneous injection).

1.2.3.1 *Enteral*

The enteral route of administration can be subdivided into three classes. Firstly, the oral route, where a drug is swallowed and is subsequently absorbed through the mucous membrane of the small intestine or, to a limited extent, from the stomach. Secondly, sublingual, where a drug is placed under the tongue and absorbed

through the buccal cavity (e.g. glyceryl trinitrate in the treatment of angina pectoris). Thirdly, the rectal route, where a drug is given either in a solid form as a suppository (e g. aminophylline for the relief of bronchial asthma), or in solution as an enema (e.g. paraldehyde for sedation) with absorption taking place through the rectal and colonic mucosa. In each case, passage of drug across the membranes dividing the absorption site from the blood is a prerequisite for absorption and, for this to occur, the drug must be in solution.

(a) Oral route The most common method of drug administration is by swallowing. In such cases, the gastrointestinal tract plays a major role in determining the rate and extent of drug absorption. Oral ingestion is convenient, relatively safe and economical and is the route preferred by patients, providing the drug is presented in a palatable and suitable dosage form. However, this route has a number of disadvantages. The drug may cause irritation of the gastrointestinal mucosa, resulting in nausea and vomiting. It may become mixed with food, destroyed by digestive enzymes or low gastric pH, pass too rapidly down the gastrointestinal tract or interact with other drugs being administered concurrently. The small intestine is the most important site for drug absorption in the gastrointestinal tract. This is largely due to its structure, which offers a far greater epithelial surface area for drug absorption than other parts of the gastrointestinal tract.

Apart from the above, many other factors influence the rate and extent of drug absorption such as the physico-chemical properties of the drug, its concentration at the site of absorption, the surface area for absorption and blood flow to the site of absorption.

The great majority of drugs which are swallowed are weak organic bases or acids and, as previously stated, are absorbed from the gastrointestinal lumen by lipid diffusion of the un-ionized form. Since the fraction of ionized to un-ionized form is pH-dependent, the pH at the absorption site is an important factor in determining the rate and extent of absorption. Thus, absorption will be maximal where ionization is suppressed to the greatest extent. However, absorption is often complicated by other factors. Thus, despite the fact that aspirin is largely in the un-ionized form in the secretions of the stomach, its solubility is low. In fact, it is more soluble at the pH of the intestinal contents although it is then predominantly in its ionized form. This fact, together with the greater absorbing surface area of the small intestine, results in up to two-thirds of an orally administered dose of aspirin being absorbed from the intestine.

For very strong organic bases such as quaternary ammonium compounds, the concentration of un-ionized drug is so low that absorption by diffusion is slow and incomplete at any physiological pH. However, sufficient may be absorbed, possibly by aqueous diffusion, to produce a pharmacological effect (e.g. hexamethonium). In addition, a few drugs with low molecular weight are rapidly absorbed by the process of aqueous diffusion (e.g. ethanol).

Other mechanisms of drug absorption in the gastrointestinal tract include active transport, pinocytosis and co-absorption with lipids. Some drugs that are

chemically related to nutrients are absorbed by the same active transport mechanism (e.g. methyldopa and L-dopa with amino acids; methotrexate with pyrimidines). Drugs with large molecular weights, or which exist in solution in molecular aggregates, are probably taken up by pinocytosis (e.g. the complex of intrinsic factor with vitamin B_{12}). A few drugs with very high lipid solubility are absorbed from the intestinal tract together with long-chain fatty acids and their monoglycerides, cholesterol and fat-soluble vitamins (e.g. digitoxin and griseofulvin).

In theory, weakly acidic drugs should be better absorbed from the stomach than the intestine because a large fraction of the dose would be in an un-ionized, lipid-soluble form. However, the limited time for which the drug is present in the stomach and the limited surface area of the stomach more than balance the influence of the pH in determining the optimal site for absorption. Thus, any factor that promotes gastric emptying increases the rate of absorption of nearly all drugs. Prompt gastric emptying is also important for drugs that are unstable in stomach fluids (e.g. benzylpenicillin). Gastric emptying is promoted by fasting or hunger, alkaline buffer solutions, anxiety, diseases such as hyperthyroidism and some drugs such as the anti-emetic metoclopramide. Generally gastric emptying of liquids is much faster than that of solid food or solid dosage forms.

Slow gastric emptying can seriously delay the onset of effects of drugs such as analgesics or sedatives. Gastric emptying can be retarded by fats and fatty acids in the diet, bulky or viscous foods, mental depression, diseases such as gastroenteritis, pyloric stenosis, gastric ulcer and hypothyroidism, and by many drugs including tricyclic antidepressants (imipramine, amitriptyline), anticholinergics (atropine, propantheline) and the antacid, aluminium hydroxide. Differences in gastric emptying among subjects is a major contributory factor in the variability of the rate of absorption of drugs from conventional dosage forms, although the overall extent or completeness of drug absorption is usually similar.

Motility of the intestine also plays its part in determining the duration of contact of a drug with absorbing surfaces. This is particularly important for drugs that are poorly absorbed from the intestine, where a prolonged intestinal transit time, brought about by atropine-like spasmolytics and morphine-like analgesics, may result in increased absorption. Conversely, a decrease in transit time, such as is produced by laxatives, may decrease absorption.

In general, gastrointestinal absorption is favoured by an empty stomach. Food will not only have the effect of reducing the concentration of drug in the gastrointestinal tract which will limit its rate of absorption (but not amount absorbed) but will also delay gastric emptying. This explains why drugs are frequently recommended to be taken on an empty stomach when a rapid onset of action is desired. Only when a drug is irritating to the gastric mucosa is it reasonable to administer it with or after a meal. In this instance, there may be a significant decrease in the rate of absorption although the total amount absorbed may be expected to be unchanged.

The absorption of a few drugs is promoted if taken after food. For example, the absorption of griseofulvin can be doubled following postprandial administration.

The intestine has an excellent blood supply which ensures that an absorbed drug is rapidly removed as soon as it passes through the intestinal membrane. In this way, the concentration gradient across the membrane is continuously maintained. For highly lipid-soluble drugs, or those that pass freely through the aqueous-filled pores, passage across a membrane may be so rapid that equilibrium is established between the drug in the blood and that at the absorption site by the time the blood is removed from the membrane. In this instance, the rate-limiting step controlling drug absorption is blood flow and not penetration of the intestinal membrane.

The binding of a drug to plasma proteins lowers the concentration of free drug after absorption and this results in the maintenance of a high concentration gradient which aids absorption.

Drug decomposition is an important factor in gastrointestinal absorption. Acid-labile drugs, such as the penicillins, are unstable at the low pH of the gastric contents. Likewise, a number of esteric drugs (e.g. procaine, acetylcholine and succinylcholine) are hydrolysed by gastric acid and are consequently relatively inactive when taken orally. Polypeptide drugs (e.g. insulin, oxytocin, vasopressin) are destroyed by the proteolytic digestive enzymes of the gastrointestinal tract. In addition to decomposition by host enzymes, drugs may be metabolized or undergo chemical changes by enzymes secreted by bacteria which live as commensal organisms in the large intestine. For example, by hydrolysing glucuronide conjugates, they allow the reabsorption of the parent drug molecule which may then be engaged in enterohepatic cycling (*see* pp. 35–6). Succinyl- and phthalylsulphathiazole have to be hydrolysed by bacterial enzymes to yield the active sulphonamide before they are effective as intestinal sterilizers.

The intestinal mucosa contains sulphate-conjugating enzymes which may inactivate certain drugs during absorption (e.g. isoprenaline). Similarly, the pharmacological activity of chlorpromazine may be decreased by sulphate conjugation while other drugs are only partly conjugated during absorption (e.g. oestrogens, methyldopa, L-dopa and salicylamide).

An amino acid decarboxylase present in the gastrointestinal mucosa inactivates part of the administered dose of L-dopa during its absorption. Since this decarboxylation takes place mainly in the gastric mucosa, the absorption of L-dopa is increased if gastric emptying is increased.

Hydrolytic enzymes in the gastrointestinal mucosa inactivate glyceryl trinitrate, and are the reason for this drug being administered by the sublingual route rather than being swallowed. These enzymes also partially inactivate analgesic drugs (e.g. pethidine, methadone, dextropropoxyphene and pentazocine). However, hydrolysis of aspirin and dexamethasone phosphate lead to breakdown products which retain pharmacological activity.

Drugs absorbed from the gastrointestinal tract are immediately carried away from their site of absorption by the portal circulation to the liver, where they may be subjected to rapid metabolism. In some instances almost total destruction of the drug results, while in others an active metabolite may be formed (e.g. propranolol, alprenolol; *see* Chapter 7). Loss of drug from the blood circulation on passage through the liver is termed a presystemic or first-pass effect (*see* p. 27). Oral