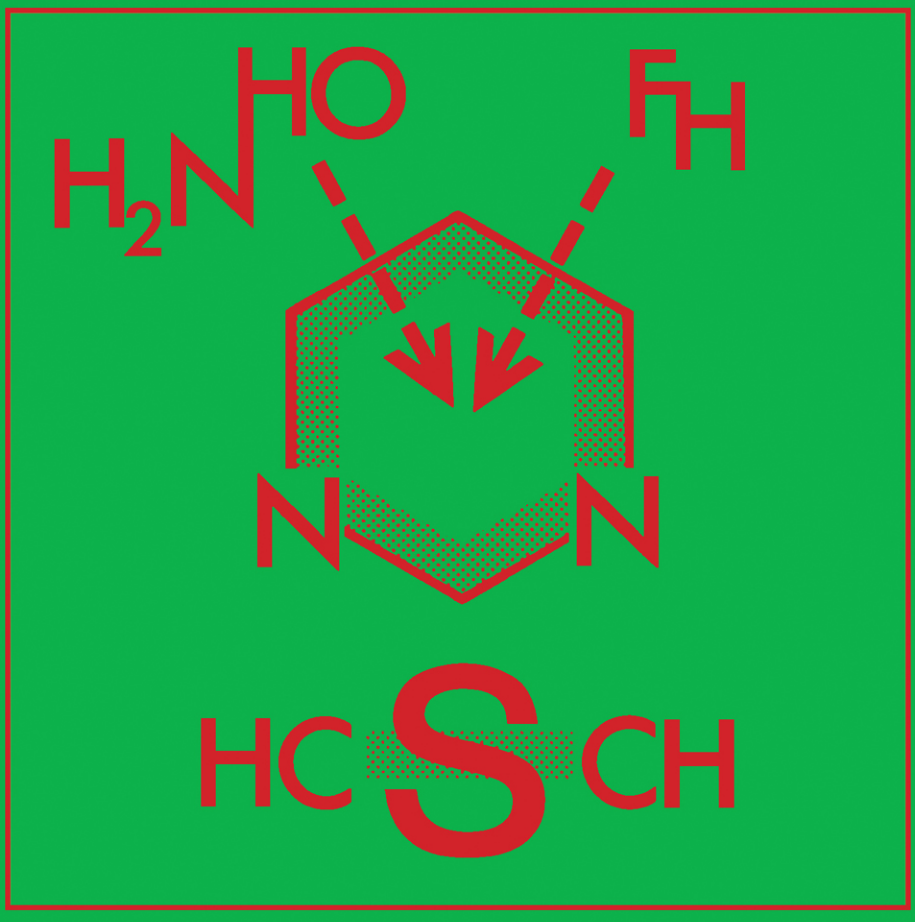
Introduction to the Principles of

Drug Design

John Smith Hywel Williams



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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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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