An Introduction to Human Pharmacology

J.D.P. Graham

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OXFORD

OXFORD UNIVERSITY PRESS

NEW YORK TORONTO

Oxford University Press, Walton Street, Oxford OX2 6DP
OXFORD LONDON GLASGOW NEW YORK
TORONTO MELBOURNE WELLINGTON CAPE TOWN
IBADAN NAIROBI DAR ES SALAAM LUSAKA
KUALA LUMPUR SINGAPORE JAKARTA HONG KONG TOKYO
DELHI BOMBAY CALCUTTA MADRAS KARACHI

British Library Cataloguing in Publication Data

Graham, James David Provins
An introduction to human pharamcology.—
(Oxford medical publications).
1. Drugs—Physiological effect
I. Title II. Series
615'.7 RM300 78–40750

ISBN 0–19–263333–3

First published 1979
Reprinted (with corrections) 1979

Printed in Great Britain
by J. W. Arrowsmith Ltd., Bristol

OXFORD MEDICAL PUBLICATIONS

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Preface

The enthusiasm of junior medical students to practise clinical medicine is unbounded; it is the cause of much impatience at the delays and frustration endured before achieving this goal. Nevertheless, it is essential that the would-be clinician has sound knowledge of the properties and the potential for good and bad of the drugs which he will use so freely. The number, complexity, and potency of these is now such that there is a danger that they will on occasion be applied therapeutically without adequate understanding of the hazards. Accordingly the art of therapeutics becomes daily more dependent on the science of clinical pharmacology; but that infant science is the offspring of the basic science of pharmacology as applied to man. An orderly progression from general physiology to pharmacology, to clinical pharmacology and therapeutics is the road to success. In this text, which is in part based on a former one called *Pharmacology for medical students* but in the greater part is new, I have attempted to classify the drugs currently used by their actions and to emphasize the effects on man. They are grouped in so far as possible by similarities in mode of action. Adverse effects are given weight but therapeutic application only sufficient mention to enable the student to associate the drug group with its principal use. It is for this reason, in an attempt to forge a necessary link between basic science and the practice of clinical medicine that a few diseases are illustrated. The most difficult task was to outline the minimal requirement for proper understanding of drugs without fatiguing the beginner or confusing him with detail; this is attempted by selection and is entirely of my choice. I would emphasize that this brief text is an introduction to the subject. I can only hope that it may encourage some to go further and not discourage too many from mastering this key subject.

September 1978 J.D.P.G.

Acknowledgements

I gladly acknowledge my indebtedness to many colleages in the University Hospital of Wales and the Welsh National School of Medicine who have helped me in a variety of ways, and hasten to add that they are in no way responsible for error in this text. I particularly thank those past and present colleagues who provided the data on which several figures and the photographs of illustrative cases are based, and Mrs C. Barrett of the Department of Medical Illustration who fashioned a number of the text figures from rough diagrams. I thank Dr. W. A. Parker and the Clarendon Press for Figs. 1.10 and 1.13; Professor Weidmann of Berne and the New York Academy of Sciences for Fig. 5.11; The Editorial Board of *Journal of Physiology* for Fig. 6.1; and Professor B. B. Brodie of the Laboratory of Chemical Pharmacology, Bethesda, Md. for the data of which Table 1.3 is compiled; to my colleagues Professor J. D. Lever of the Department of Anatomy, University College, Cardiff, Dr. T. L. B. Spriggs of the Department of Pharmacology, Welsh National School of Medicine, and Professor F. Loo of the Department of Anatomy, Szeged, Hungary, for Plates 2 and 3, the former by permission of the Editorial Board of *Acta Histochemica*: several of these figures are transferred from a former text of mine. I thank my secretaries for their patience in sorting out the manuscripts.

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Basic principles

INTRODUCTION

DEFINITIONS

The professional aim of a medical practitioner is to diagnose his patients' ills and to advise the best means to relieve or perhaps to cure them. There are many forms of treatment, spiritual and physical, surgical and medical, by diet, exercise, change of occupation, and drugs. The most important and easiest to apply is by giving appropriate drugs. A drug has therefore been defined, in the medical context, as 'any substance or mixture of substances administered to man destined for use in the diagnosis, treatment, investigation or prevention of disease, or for the modification of physiological function'. Pharmaceutical chemistry is concerned with the chemical structure of drugs, pharmacognosy with the source and characteristics of crude drugs, and pharmacy with the preparation of drugs in forms suitable for medicinal administration. Pharmacology in its broadest sense is concerned with the study of the actions of drugs. The overall effects therefore have to be analysed. This is done by conducting researches on the effect of the drug on isolated systems of the body, on tissues or organs or biochemical mechanisms. It involves repeated tests on fragments of the living body and must therefore be carried out largely on animals, although some use may be made of portions of human tissue recovered at operation. Only when knowledge from such work is available is it possible to check in man the actions which might be useful. Much of the data in this book, therefore, are based on tests done on lower animals. In the profession of medicine, drugs are of interest in so far as they are used in therapeutics, which is the science and art of healing. Obviously, no person who is ignorant of the actions of drugs should recommend them for the treatment of patients. It is necessary, therefore, for students of medicine and ancillary professions to acquire a knowledge of the pharmacology of the drugs which they are likely to use. It is the object of this text to describe the actions of such drugs as are currently in therapeutic use, as far as possible in terms of their effects upon the human organism in health and disease. It must be selective. New medicaments are produced frequently; it is therefore necessary to have an understanding of the ways in which families or groups of drugs act, and what they may reasonably be expected to do or not to do. Since most drugs are given to diseased persons in the hope of restoring normality it is also necessary to have a considerable knowledge of the effects of disease on physiological mechanisms.

Increasingly during the last decade an understanding of the mode of action of drugs has been acquired, largely from the study of biochemical pharmacology or the effects of drugs on the processes of cellular chemistry. This work is seldom undertaken with human tissue. In extrapolating from 'mouse to man' it is necessary to display caution, since species differences can lead to wrong conclusions, particularly in the realm of adverse reactions or toxicology. Nevertheless there are closer resemblances between man and the other mammals than there are differences, and most of the fundamentals which it is proposed to consider in this introductory book are valid qualitatively from one to the other. Difficult areas are those of psychopharmacology where interpretation of drug action on the behaviour of laboratory animals is used as a tentative base for hopeful therapeutic action in mentally disturbed people, and in dermatology where models of human disease are not reproducible in small animals.

THE NAMES OF DRUGS

Most beginners experience some difficulty in assimilating the vocabulary of pharmacology, in particular the names of drugs. Each drug has a chemical name with a few exceptions where the chemical structure is not known or the drug is a mixture of variable matters. If the substance is in therapeutic use the manufacturing company will have given it a euphonious trade (or **proprietary**) name under which it is advertised. This is a registered brand name; the intention, which has largely succeeded, is that this name being easier to remember than the **official** or non-proprietary (approved) name will be used by the prescribing doctor, in which case the pharmacist is required by law to dispense that brand of the drug and none other. An example of a difficult non-proprietary name is chlordiazepoxide; the brand name is *Librium*. There are advantages in using official names (B.P., B.N.F., etc.) or approved names, not that a reputable firm produces drugs other than of B.P. or higher standard, but bulk purchase may ease the financial burden of stocking many brands of the same drug, or allow a flexibility in dispensing a prescription. Some much used drugs have a dozen brand names in one country and appear under 20–23 names in different countries.

ORIGINS AND SOURCES OF DRUGS

Drugs come from many sources. Animal, vegetable, and mineral substances as well as artificially prepared compounds, have been pressed into service as remedial agents. Long before there was any science of experimental pharmacology, or before there was any real knowledge of the causes of disease, a large amount of information accrued by trial and error of the remedial and toxic properties of plants. The most important contemporary source of drugs is by manufacture. A vast international industry is now devoted to this practice. Compounds of many chemical classes and varying complexity of structure, displaying many pharmacological properties, are available as a result. The difficulty which assails the therapist is to select from the array those which are best suited to the immediate purpose. To do so rationally requires some capacity to arrange them in classes or groups and to relate their structure to their properties. The difficulty for the manufacturer is to produce an active and useful drug which does not have adverse properties; often in circumstances of intense competition and soaring costs. Despite these limitations there are more drugs on offer than seems rational or easily to be understood by the physician.

It required a knowledge of chemistry to decide which constituent was responsible for the curative actions of a plant and to determine the nature of this, the **active principle**. Most of this knowledge has been acquired during the last century. The chemical composition of the active principles of many of the important medicinal plants are now known, and it has become possible with advancing knowledge to use them in place of crude drugs. Many are alkaloids—basic substances of organic structure, bitter in taste, and pharmacologically very active, e.g. atropine from *Atropa belladonna*, which antagonizes many of the effects of acetylcholine. Others are glycosides, which contain a carbohydrate as part of the molecule, e.g. digoxin from *Digitalis lanata*, a specific in heat failure. Additionally, one may extract lipids, e.g. castor oil from *Ricinus communis*, a purgative; volatile oils (aromatic; essential), e.g. oil of peppermint from the flowers of *Mentha piperita*, a flavouring agent; carbohydrates such as starches or, for example, the gum from *Acacia senegal*; and tannins, e.g. witch hazel from *Hamamelis virginiana*, an astringent.

A few metallic salts are used as remedies, e.g. compounds of iron, given for anaemia, or magnesium sulphate, a purgative. The properties of several hormones elaborated by the animal body have been determined and the abnormalities associated with them which may give rise to disease. Preparations derived from the carcasses of food-animals are used therapeutically. Some take the form of prepared endocrine gland, e.g. thyroid tablets. The hormonal principle having been firstly isolated and synthesized, it may be preferred for its purity and precise dosage, e.g. thyroxine sodium. Some useful materials are extractible from blood, e.g. gamma globulin, or from tissues, e.g. heparin, an anticoagulant. Such substances may be given to restore to normal a state of deficiency (replacement therapy), e.g. insulin to a diabetic patient, or to increase temporarily the concentration of a hormone for a particular purpose, e.g. corticosteroid in the treatment of asthma.

Pharmacokinetics

Pharmacokinetics is the term used to encompass a knowledge of the absorption, distribution, and fate of a drug. Much of the work has, in the past, been carried out on small laboratory animals, but it is now realized that man differs to a varying extent in respect of the kinetics of his drug handling and that patients vary from one to another, apart from the effect of their disease. It is a major, but not the whole, task of **clinical pharmacology** to fill in these gaps in knowledge.

Biological variation

No two persons are precisely alike in size, shape, biochemical mechanisms, or other measurable variables. If a large sample of persons is collected and one variable which is easily determined with accuracy is recorded the data may be divided into subgroups which contain all those individuals with the same measurement; for example, if the height in mm of 10 000 persons was recorded, the data could be grouped by differences of 5 mm from the lowest to the highest. The **distribution** of the grouped measurements would take the form of a **'normal' distribution or** 'bell-shaped curve' (see Fig. 1.1a). The majority of the sample would be distributed around the mean with a range of twice the standard deviation (s.d.) of that mean. The generality of this relation applies to biological variables including the responses to drugs. It applies to all those factors which determine the kinetics of drug-taking, such as the degree and rate of absorption, transport and binding, metabolic degradation, and clearance. No two persons will handle a fixed dose of a given drug in a precisely similar way. It is a part of the art of therapeutics to recognize this inescapable fact and to adjust one's dosing so as to accommodate those persons who lie on the extremes of the distribution. As to therapeutic efficacy, if those on one side of the curve represent the patients who fail to respond to a drug, those on the other will represent those in whom the given dose was in excess of the minimum effective dose. An added complication, and one which is being increasingly revealed by studies in human drug kinetics is the existence, in any large sample, of sub-populations which differ in a material and relevant respect from one another in relation to the

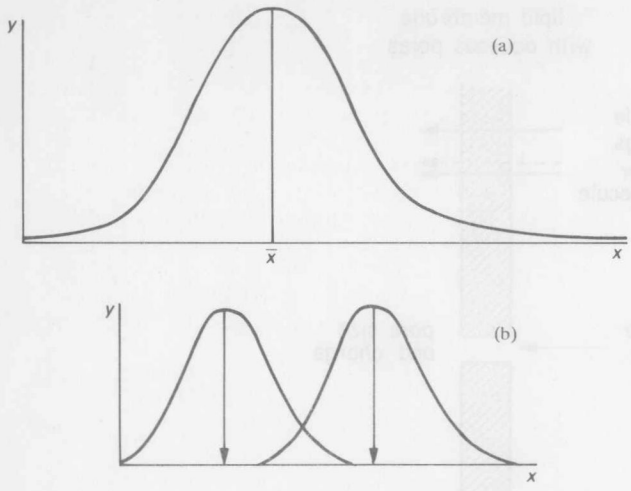


Fig. 1.1. (a). A 'normal' distribution curve of a biological variable. The horizontal axis x is the variable, the vertical y is the probability density which has a maximum value at $\bar{x}$, the mean value around which the measures are symmetrically disposed.

(b). There are two populations within the one sample, with differing $\bar{x}$ but in this case equal y and symmetrical distributions. In the case of drug metabolism these populations are often of differing y values and the lesser one may have a skew distribution. There may be a greater or lesser overlap.

drug. An example of this **bimodal distribution** (see Fig. 1.1b) is that of persons who can taste phenyl carbamide or not, a test much used by field workers to reveal genetically determined relationships in populations. Of more immediate relevance to human pharmacology is the existence of persons who are well- or ill-endowed with acetylating enzymes in their liver. If a drug is metabolized by acetylation before clearance the fate of that drug differs in its time-scale in these two groups of persons and the slow acetylator may as a result become intoxicated (see the tuberculostatic drug isonicotinyl hydrazide, INH, p. 212). There probably are bimodal distributions of many other factors relevant to the kinetics of drugs, of which we are not as yet fully cognizant.

PHARMACOGENETICS

Genetically determined abnormalities of biotransformation (inborn errors of metabolism) may grossly diminish the capacity of a patient to deal with a drug, for example there is a rare condition called Criggler–Najjar syndrome wherein the patient is deficient in the glucuronide synthesis. Such persons have difficulty in excreting salicylates. There are a wide variety of abnormalities, some of the more severe being (1) the precipitation of acute porphyrinuria by barbiturates; (2) a deficiency in glucose 6-phosphatase (von Gierke's disease), which inhibits the hyperglycaemic action of adrenaline or glucagon; (3) a deficiency in galactose 6-phosphate (GL6P)-dehydrogenase which renders the antimalarial drug primaquine haemolytic (as this deficiency is found in male negroes it reduces the efficacy of antimalarial measures); (4) a deficiency in acetylase which results in the patient's failure to acetylate isonicotinyl hydrazide, an important antitubercular drug; clearance is delayed in 'slow inactivators' and toxic levels may be attained; and (5) a deficiency in serum cholinesterase, as a result of which any ester of choline is potentiated.

With reference to the last item, succinylcholine is a muscle relaxant much used by anaesthetists; it is metabolized by de-esterification and if the cholinesterase is inhibited as a result of previous exposure to a long lasting synthetic anticholinesterase (e.g. malathion), or is congenitally deficient, the dose–time relation is grossly and dangerously distorted. The cholinesterase activity of blood can be readily determined in the laboratory by its action on the ester dibucaine and is reported as a 'dibucaine number', normally 80, but in some deficient groups it is 60 and in others it is as low as 20, or even absent.

An important aspect of genetically determined variations in metabolism is the replacement of strains of staphylococcus and other bacteria which were formerly fully susceptible to chemotherapeutic agents by resistent strains of bacteria, many of which arise *de novo* by mutation.

DOSE PRESCRIBED
↓
DOSE INGESTED
↓
DOSE ABSORBED – metabolism
– elimination
↓
CONCENTRATION AT SITE OF ACTION
↓
DOSE-RELATED RESPONSE

ABSORPTION OF DRUGS

ABSORPTION ACROSS MEMBRANES

We may think of a cell membrane as a lipid–protein structure with pores which are filled with water; the pores vary in size, in electrical charge across them and across the more solid part of the membrane. There are specialized uptake and transport mechanisms which can work against a concentration gradient. The factors which determine the rate of transport of drugs across membranes are as illustrated in Figs. 1.2, 1.3.

The principle factors are the oil–water partition (lipid or water solubility), the ionization charges on organic electrolytes, particle size, and the existence of 'pumps'. Passive diffusion goes with a concentration gradient, active diffusion goes against it. The response of a drug is related to the concentration which reaches the site of action. If the drug is applied in solution to some easily penetrable tissue such as a strip of muscle in a glass vessel, the degree of response will be directly related to

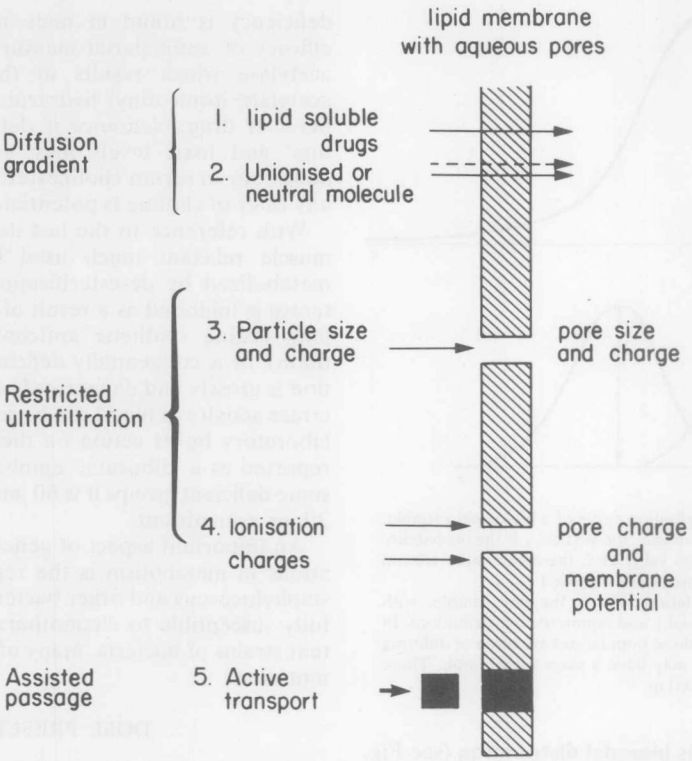


Fig. 1.2. A diagrammatic summary of the factors which affect absorption of drugs. (1) Lipid soluble drugs are readily absorbed; (2) neutral substances, such as alcohol or sugar also absorb readily; (3) micronization of particles of a drug increases absorption; (4) water-soluble weak acids, e.g. aspirin, do not ionize in acid gastric juice and absorb readily from the stomach; (5) iron salts have an active transport system. Similar factors act in reverse for the excretion of drugs.

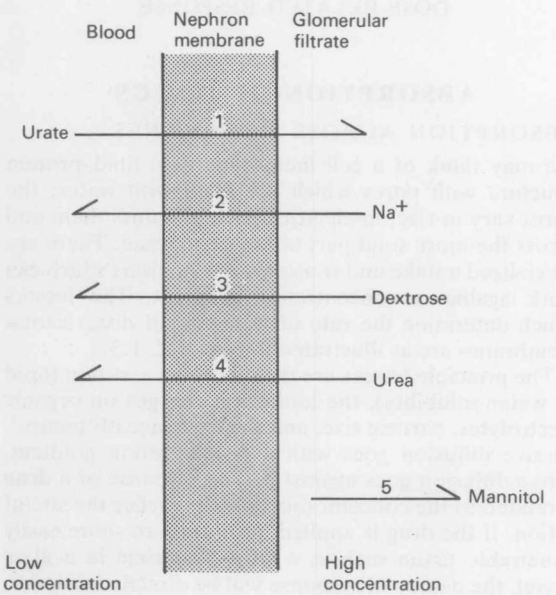


Fig. 1.3. An example of a semi-permeable membrane system displaying several types of passage across it: (1) filtration, e.g. urate; (2) active transport, e.g. the Na^+ pump; (3) facilitated diffusion, e.g. dextrose; (4) passive diffusion, e.g. urea; and (5) failure to pass, e.g. mannitol. Drugs may effect the mechanism of active transport, for example frusemide, a diuretic, inhibits the Na^+ pump.

the molar concentration of the drug but, if the system is more complex, as in an intact animal, and the affinity of the drug for its site of action is not great, many factors will modify the effective concentration achieved. The route of administration affects the quantitative aspects of a drug, for example benzylpenicillin when taken by mouth will be destroyed to a great extent, but when given by injection high levels in the blood can be achieved with much less drug.

Once a drug is absorbed its concentration falls as it comes into equilibrium with the volume of the fluid compartment in which it is distributed, for example ethanol, which equilibrates with 45 l of body water is diluted more than sodium bromide which remains extracellular (15 l); if a drug is strongly bound to plasma protein, e.g. warfarin, the dilution is only in 3 l. If equal weights of the drug are given as is customary in clinical partice, this dilution factor, and the molecular weight, in determining molar concentration, are important.

ROUTES OF ADMINISTRATION

Oral

The majority of drugs are administered for therapeutic purposes by mouth (orally), but a drug can only affect a tissue when it reaches the cells of which the tissue is composed. If it is a local irritant, the drug may be evacuated by vomiting (emetic), or diarrhoea (purgative). Some drugs are so poorly absorbed as to be of little value when given orally. This may be because their chemical nature is such that they are destroyed by the processes of digestion, e.g. insulin; or by bacterial activity in the intestine, e.g. benzylpenicillin; or very poorly absorbed because of physio-chemical properties which make it difficult for the molecule to penetrate the polarized membrane of the mucosal cell, e.g. hexamethonium. Most water-soluble drugs given orally are absorbed more easily if they remain un-ionized, e.g. weak acids in the gastric juice and weak bases in the intestinal fluids. Absorption from the acid medium of the stomach may therefore differ markedly from the absorption from the alkaline medium of the small intestine. Substances such as dextrose and alcohol, which are un-ionized, are absorbed readily from both; iron or calcium are absorbed with difficulty, and as a result of specialized acceptance and transfer systems. If a drug is absorbed from the small intestine, it will pass via the hepatic portal blood to the liver; there it may be so catabolized that this route of administration is ineffective. The difficulty may, on occasion, be overcome by applying the drug in pellet form under the tongue (**sublingual**). Absorption through this highly vascular mucosa is speedy and the venous drainage avoids the liver. **Rectal** administration also bypasses the liver.

Apart from special transport mechanisms, which commonly affect nutrients but not drug molecules, the rate and degree of absorption will be related to the concentration gradient across the absorbing surface which in the intestine is about 200 m^2 in area, and such factors as the relative solubility of the drug in oil and water. Since the semi-permeable cell membrane contains a fatty layer, lipid solubility is a valuable attribute in a drug which is to be absorbed from the alimentary canal. The concentration of active drug available for absorption and the duration of action of the drug may be greatly modified by pharmaceutical processing. It is possible to combine an active drug with a resin or other 'carrier' from which it is only slowly released, or to prepare the drug in a vehicle which offers varying degrees of resistance to the contents of the stomach or intestine and thus delay the release of a drug ('slow release' formulation). It is also possible to increase the absorbability of a compound and thus its efficacy by preparing it in very fine particles, e.g. digoxin.

Parenteral

The other main route is the parenteral one, i.e. by injection, thus avoiding the necessity for absorption across mucosal barriers. Drugs given in this way have to be prepared in a sterile, stable, non-irritating, form and dissolved in water which is free from pyrogens. Drugs so injected are usually speedily and completely absorbed, but there are exceptions. Some are deliberately prepared in **depot form** so that absorption may be delayed and the effect prolonged, e.g. protamine zinc insulin. A compressed tablet of the drug may be inserted under the skin, e.g. implants of testosterone. Other drugs may have added to them a complementary drug which modifies absorption, e.g. adrenaline is added to solutions of the local anaesthetic lignocaine hydrochloride in order to constrict the blood vessels in the area of injection and thus reduce the rate of absorption. If a patient is suffering from peripheral circulatory failure as a consequence of severe trauma, poisoning, or disease, a drug so injected may not be readily absorbed. Hyaluronidase greatly facilitates the spread of injected solutions and thus increases the area for absorption. If a drug is to be injected **subcutaneously** (s.c.) or hypodermically, such factors will affect the concentration attained in the blood. Similar considerations apply to injection of drugs **intramuscularly** (i.m.). Here absorption may be speedier, more complete, and the presence of the drug may be less irritating. The ultimate sophistication is to inject the solution of the drug **intravenously** (i.v.) when it is totally absorbed, diluted in the blood, and rapidly distributed. There is a danger that a temporarily high concentration of the drug will affect a vital organ, e.g. the heart or the brain. To the therapist this route is often justified where speed of effect is desired or a valuable drug is too irritant to inject into the tissues. Rarely a drug may be injected into the cerebrospinal fluid, i.e. **intrathecally**.

The proportion of an absorbed drug which reaches the target organ is related to the blood supply to that organ, but if the drug acts on a specialized receptor

system which is limited in its localization the organ affected may not be that which receives most blood in unit time. Rarely the qualitative nature of the response to a drug is dependent on the route by which it is administered, e.g. magnesium sulphate (Epsom salts) when administered by mouth is not absorbed, holds water by its osmotic power according to concentration, and acts as a saline purgative; if a solution is injected i.v. the magnesium ion depresses cerebral function. Excretion of the salt by the kidney then increases the volume of urine passed—a diuretic action.

Inhalation

Gaseous and volatile drugs, or those administered as a fine spray (aerosol), may be inhaled and absorbed from the respiratory tract or the alveolar surfaces. The same volume of blood passes through the lungs per unit time as circulates in all the rest of the body. This ensures a very speedy distribution and keeps the concentration gradient steep. Equilibrium is speedly reached and the degree of effect can be related to the concentration of drug administered.

The transport of dissolved substances across the alveolus depends on their lipid solubility, for example anaesthetic agents such as diethyl ether rapidly penetrate the lung membrane. Gases are also lipid soluble. The rate of uptake is thus dependent on the partition between the gas–air mixture in the alveolus and the water of the blood (the Ostwald coefficient), rather than any property of the membrane.

Topical application

Many drugs are applied directly to the proposed site of action. If this is a delicate one, e.g. the conjunctival sac or auditory meatus, care has to be taken to present the drug in a non-irritating solvent ('eye drops' and 'ear drops'). Drugs applied topically may be absorbed across mucosal surfaces, or they may remain localized. Ointments, sprays, and paints are applied to the skin. The medicament is not absorbed if the skin is intact but may readily absorb if it is broken or inflamed. There are sprays which may be applied to the nose or throat, and pessaries and suppositaries which may be inserted into the vagina or rectum respectively. A great advantage of topical application of a medicament is that it may be used in a concentration much higher than that attainable by other means.

THE EFFECTS OF DISEASE

Disease states may modify the absorption of drugs (delayed or hastened gastric emptying, malabsorption syndrome, Crohn's disease, chronic diarrhoea, colitis; pulmonary disease for anaesthetics); the metabolic degradation of drugs (hepatitis); or the clearance of drugs (renal failure). Cardiac failure impairs both absorption and clearance (slow circulation, engorgement, oedema, renal failure) and if the patient is treated with a K^+-losing diuretic the toxicity of digoxin and of curarine is increased. The majority of patients who exhibit cardiac failure are put on both types of drug. Pulmonary disease may impair the absorption of anaesthetic gases and hypercapnia is synergistic with all central depressants. The asthmatic is sensitive to broncho-constrictors (nonspecific β-blockers, cholinergic drugs, histamine releasers). Myasthenia gravis is a special condition wherein the patient is at hazard from many drugs which have (normally) a weak muscle paralysing action, e.g. some of the antimalarials. Hyperthyroidism causes a dangerous sensitivity to sympathomimetic drugs, while myxoedema impairs drug metabolism.

DISTRIBUTION

After absorption drugs are distributed like nutrients by the blood stream. A variable and frequently large amount may be bound firmly to the proteins of the blood and tissues and thus rendered temporarily inactive (Fig. 1.4(1)). Such drugs are confined to the plasma, which has a volume of 3 l. The distribution may be general, e.g. ethyl alcohol is found as a solution in all the body water if due time is allowed to achieve equilibrium (Fig. 1.4(3)). The volume thus available in an adult man is about 45 l. A number of important exceptions to this generalized distribution occur. Some drugs cannot pass particular membranous barriers, e.g. that between the blood and the central nervous system (the blood–brain barrier). Lipid soluble drugs traverse the cerebral capillary wall and the processes of the astrocyte cells quite readily, e.g. thiopentone sodium. Water soluble molecules and ions penetrate this barrier much less readily and some fail to do so. Drugs may also be excreted into the cerebrospical fluid (c.s.f.) and from there penetrate locally into the brain. Use is made of this route in experimental work but not with man.

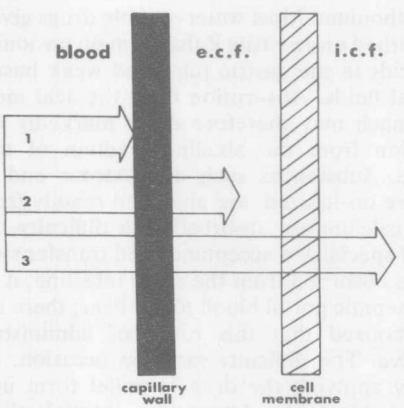


Fig. 1.4. Differential distribution of drugs. After absorption, 1 is bound to protein, 2 and 3 are water soluble and may either penetrate fully (3) or be confined to the extracellular fluid (e.c.f.) (2). Lipid soluble material (also 3) readily penetrates to the intracellular fluid space (i.c.f.). Notable barriers are the placenta, the blood–brain barrier, the eye, the intestinal mucosa, secreting glands, and the kidney.

Two routes to the CNS

blood → cerebral neuron

blood → c.s.f. → cerebral neuron

Other drugs, e.g. bromide, may not pass the semi-permeable membrane of cells in general (Fig. 1.4(2)). They are confined to the extra-cellular water compartment, some 15 l of fluid. There are also special barriers such as the placenta, the secreting cells for milk, tears, saliva, sweat, gastric, pancreatic and intestinal juice, bile, and joint fluids. Drugs may appear in some of these secretions and not in others. Barriers of peculiar significance for the treatment of infection are the zones of inflammation which surround an abscess or the exudate which may fill a cavity, e.g. a pleural effusion. Many drugs penetrate such regions poorly. There are thus ample opportunities for differential distribution. An important example is that of thiopentone sodium, a barbiturate drug which is injected i.v. as part of the technique of general anaesthesia. This drug must readily pass the blood–brain barrier since it quickly affects the brain and abolishes consciousness. It has, however, a short duration of action, due largely to the fact that it is readily dissolved in fat and is therefore rapidly withdrawn from the blood and stored in adipose tissue. Some drugs are actively concentrated in a tissue, e.g. iodine and perchlorate in the thyroid gland. The distribution of a drug to an organ is a function of the delivery of blood to unit volume of the organ in unit time. This varies enormously in health between organs, e.g. pulmonary and coronary circulations; or in time, e.g. skeletal muscle before and during exercise; and is much affected by disease, e.g. atherosclerosis, infarct, neoplasm, etc. Blood flow carries the drug to the tissue:

	l/min	% of body wt	l/1%/min
Liver	1·55	3·5	0·400
Muscle	0·80	48·0	0·016

thus many active drugs are distributed in an unequal manner and the concentration of a drug may be higher in one organ than another. Blood flow greatly affects the distribution of a single dose, but not the 'steady state'. The organ with the highest concentration of the drug is not necessarily the organ with the function most affected by it. An example of the extreme localization of a drug is seen with the antifungal antibiotic griseofulvin found in keratin in the skin and nails.

METABOLISM OF DRUGS

The rate of metabolic degradation of a drug may be the crucial factor in determining its effective concentration. As soon as a drug is absorbed, the concentration of free drug is depleted by fixation to cells or to plasma, by chemical modification, metabolic or otherwise, and by excretion. It is usual for the potency of the drug to be reduced by these means, a result known as **detoxification**, or **biotransformation**. An inactive precursor may be activated e.g. imipramine to desmethylimipramine (DMI); or modified but remain active, e.g. heroin to morphine; or become more active, e.g. codeine to morphine; or be inactivated, e.g. cyanide to thiocyanate. Much of this activity takes place in the endothelial reticulum of the liver cell. Frequently one drug undergoes modification by several means and gives rise to a number of metabolites. Some drugs, such as ethyl alcohol, are metabolized at a steady rate no matter what the concentration, some readily saturate the system, but it is usual for the rate of degradation to decrease as the free concentration falls.

An enzyme-catalysed biotransformation

enzyme precursor = active enzyme + substrate (consumed)
+cofactor ↓
complex → metabolite (utilized or cleared)

Perhaps the most important system involved in the biotransformation or drugs is that found in the smooth endothelium of the liver cell. This is the **microsomal oxidative mechanism** which involves the transfer of one atom of 'active oxygen' to the drug molecule and the formation of one molecule of water. The essential factors are the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), oxygen, and a specialized haemoprotein called cytochrome P450, which is oxidized and then reduced by NADPH-cytochrome P reductase, thus acting as a transfer system. This system handles lipid soluble drugs e.g. amphetamines and steroids. A number of important transformations are carried out in this way e.g. deamination of monoamines, *N*- and *O*-dealkylations, *N*-oxidation, sulphoxidation, and hydroxylation of carbon chains and ring compounds. This involves many drugs and some of these may inhibit enzyme action or induce formation of enzyme (Table 1.1). Some examples of *microsomal transformation* are given overleaf:

Table 1.1. *Enzyme induction and inhibition: sleeping time of mice (min) injected i.p. with pentobarbitone sodium 45 mg/kg.*

	Sample size	mean ± S.E.
Controls	130	42·66 ± 7·07
Iproniazid 50 mg/kg (1 h)	131	74·35 ± 11·66
Phenobarbitone 50 mg/kg (7 days)	119	9·57 ± 1·43

$C < 1 \quad p \ll 0{\cdot}001$

$C > P \quad p \ll 0{\cdot}001$

Two groups of mice were injected daily for 7 days with saline and one group with phenobarbitone sodium 50 mg/kg. On the 8th day one of the saline-injected groups was given iproniazid (INH) 50 mg/kg 1 h before, and all groups were given pentobarbitone sodium 45 mg/kg ip at zero time. The time was measured from the loss of the righting reflex until it was regained ('sleeping time'). These are examples of enzyme-related *drug interaction*. They apply to patients who may be on regular medication with INH or with barbiturate, and to whom another drug is given.

Deamination: amphetamine to phenylacetone
N-dealkylation: demethylation of imipramine
O-dealkylation: paracetamol from phenacetin
O-oxidation: trimethylamine oxide
S-oxidation: chlorpromazine sulphoxide
Epoxidation: organo-chlorine insecticides
Hydroxylation (aromatic): phenobarbitone in the ring
(aliphatic): pentobarbitone alcohol.

There are also important *non-microsomal pathways*; these include those of *non-synthetic transformation*:

Oxidation: ethyl alcohol to aldehyde; monoamine oxidase (MAO) on tyramine
β-hydroxylation: amphetamine to norephedrine
Reduction: chloral hydrate to trichlorethanol
Hydrolysis: procaine to *p*-aminobenzoic acid and diethylamino-ethanol
Decarboxylation: dihydroxyphenylalanine to dopamine

and *synthetic transformation*:

Acetylation: sulphonamide to acetylsulphonamide
Alkylation: noradrenaline, etc. to normetanephrine by catechol *O*-methyl transferase
Conjugation: phenols as ethereal sulphates, by sulphatase in the intestinal wall and liver. This usually produces an inactive soluble product
Glucuronides: trichloroethenol as urochloralic acid, in liver and kidney
Glycine conjugation: *p*-aminosalicylic acid
Glutamine conjugation

Table 1.2 lists the natural metabolic pathways which are utilized for drug metabolism. Water soluble drugs are handled by oxidases, peroxidases, and dehydrogenases.

Table 1.2. *The relation between natural metabolic pathways and the detoxification of drugs*

Natural substrate	Transformation	Competing drug
Acetylcholine	Hydrolysis	Aspirin
Noradrenaline	Methylation	Quinidine
Bilirubin	Glycuronide	Chloramphenicol
Bile acid	Glycine	Salicylic acid
Choline	Acetylation	Sulphonamide
Cortisone	Reduction	Prednisolone
Steroid	Sulphate	Chloroamphenicol
Steroid	Oxidation (microsomal)	Phenobarbitone
Xanthine	Oxidation (non-microsomal)	Ethanol

Extramural metabolism occurs by activity of the flora of the gut – bacteria, protozoa, and fungi. Perhaps the most important aspect of this metabolism is the splitting off of glycuronide from a drug which has been conjugated in the liver and excreted in bile. This process encourages reabsorption and contributes to enterohepatic circulation of the drug. In the majority of cases drugs are at a low concentration which in no way saturates the enzyme responsible. As a result the reaction procedes as a **first order reaction** i.e. the rate is linearly proportional to the concentration of substrate (see Fig. 1.5).

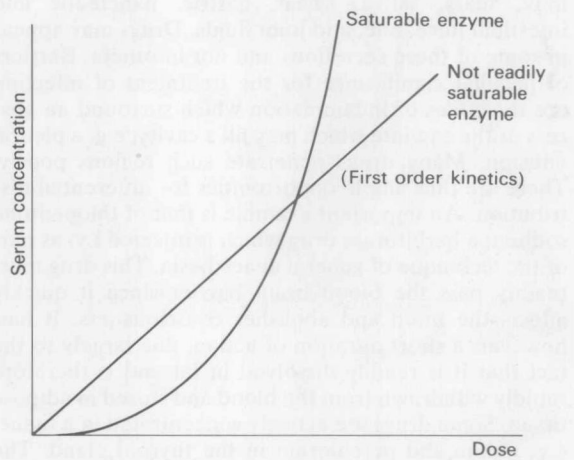
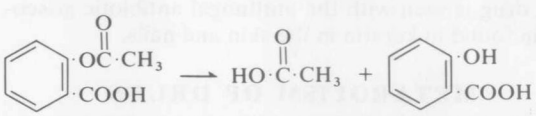


Fig. 1.5. As the dose increases the serum level will rise in a linear fashion if the mechanism of metabolic degradation is not a bottleneck, but if the enzyme is saturable the rise in non-linear and may be catastrophically steep. If the drug is metabolized by first order kinetics (as most are) a linear relation exists between daily dose and serum concentration and the amount of the drug metabolized. With saturation kinetics the relation rapidly forms a plateau and there is no linearity with the concentration.

$CH_3 \cdot CH_2OH \rightarrow CH_3 \cdot CHO \rightarrow CH_3 \cdot COOH$
Ethanol — Acetaldehyde — Acetic acid
Non-microsomal oxidation

$CCl_3 \cdot CH(OH)_2 \rightarrow CCl_3 \cdot CH_2OH$ *Reduction*
Chloral hydrate — Trichlorethanol



Aspirin — Acetic acid — Salicylic acid
Hydrolysis

THE EFFECTS OF DISEASE

If a patient is suffering from reduced liver function e.g. infective hepatitis, or cirrhosis, great care must be taken to reduce the amount of drug prescribed since it may not be metabolized at a normal rate. If a patient is

in a severe state of shock with low blood pressure, low cardiac output, and probable reduction in oxygenation and in body temperature (hypothermia), the hepatic detoxifying capacity is much reduced and poisoning by drugs is compounded.

EXCRETION

Clearance rates

Drug molecules, intact or as metabolites, by themselves or conjugated, are removed from the body by the physiological channels of excretion—bile, faeces, urine, or gas. The effectiveness of this process may be spoken of as the clearance and an acceptable measure of it is the time taken to reduce by half the initial concentration of the drug in the blood. Successful clearance depends on the maintenance of active physiological mechanisms of transport (the heart, vessels, blood, and circulation) and of excretion (kidney and bowel function, lungs and respiration, sweating), and is related to the physicochemical properties of the drug molecule, in particular solubility in water, and to the degree and firmness of binding to protein. For most drugs the phase of elimination proceeds such that the log of concentration versus time is linear (see Fig. 1.6). If the drug is almost entirely eliminated by metabolism the enzyme involved may be deficient or there may be another drug substrate present. In that case the enzyme may be saturable within therapeutic concentrations and the relation is no longer linear. If a drug is highly bound to tissue protein the concentration in plasma will be low. An idea of it may be gained by calculating the apparent volume of distribution. Marked differences in the time for half clearance occur, e.g. for benzyl penicillin in man it is an hour, for salicylate half a day, for digitoxin a week.

RENAL CLEARANCE

The main route of excretion is in urine and clearance by this means is related to the initial concentration of the drug in the blood. Provided that there is no reabsorption, nor active secretory mechanism and given an adequate and steady formation of urine, the higher the concentration of the drug, the greater the amount cleared in unit time. A constant percentage of the remaining amount is cleared each hour. As the concentration in blood falls, the rate of clearance diminishes though the total amount which has been excreted rises. About 1 per cent per minute will be cleared by glomerular filtration and if there is no reabsorption the majority of it will be gone in four hours. It follows that the physician must increase the initial concentration (dose) by ten times in order to double the duration of effect of a drug which is thus cleared. This can seldom be achieved without toxicity, hence the need to give repeated doses of most drugs when used therapeutically. If the drug is not reabsorbed by the renal tubule after filtration and the rate of formation of urine is increased, the rate of clearance will also be increased.

The pH of the urine will affect ionization of weak acids or bases. Un-ionized drug is reabsorbed; ionized drug is cleared. This is the basis of the diuretic treatment of acute poisoning. If a drug is actively secreted by the renal tubules into the urine, e.g. penicillin, it may

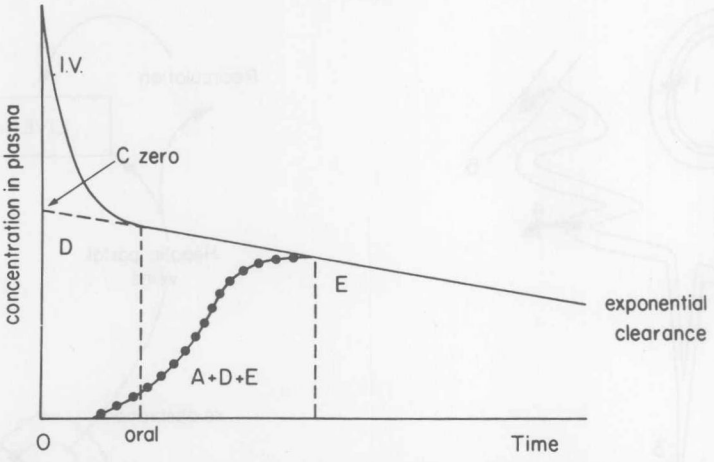


Fig. 1.6. The time course of the decline in plasma level of a drug administered i.v. or orally. The former gives instant high concentration, rapid distribution (D) and thereafter in most cases an exponential elimination (E) i.e. the log concentration in plasma versus time gives a linear relation from which a half time for clearance ($Ct/2$) may be calculated. If the slope is carried back to zero time the theoretical value C_0 indicates the concentration which would have existed at zero time if instant distribution had occurred. After oral administration absorption (A) is slow, distribution (D) and some elimination (E) go on contemporaneously but after due time elimination proceeds as before. The verticals indicate the time taken to stabilize the drug level.

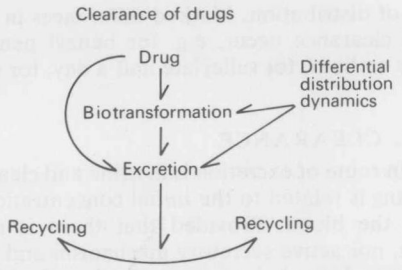


Fig. 1.7. A drug may be excreted (in the bile, urine, etc.) directly after or subsequent to transformation (conjugation etc.). At the same time it is being distributed at varying rates into and again out of depots (muscle, fat, etc.) and subjected to the initial excretory cycle. This may be complicated by reabsorption and recycling.

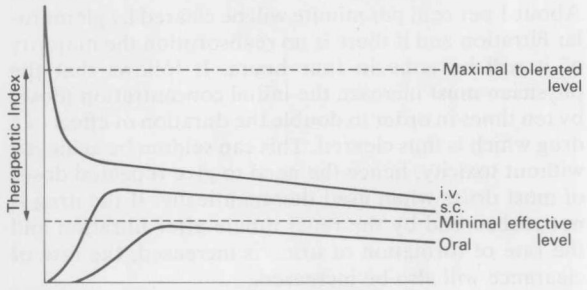


Fig. 1.8. The effect of the route of administration on peak levels of a drug in the plasma; on possible dose-related adverse effects, and on the maintenance of an effective concentration. Intravenously the drug may prove toxic before it is distributed; orally it may not reach an effective level. The higher the plasma concentration the more speedily it may be eliminated by the kidney. Note the Therapeutic Index or margin of safety.

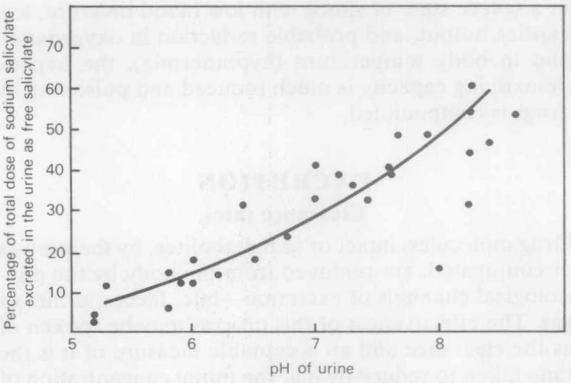


Fig. 1.10. An example of increased excretion of a drug (salicylate) caused by modifying the pH of the urine by giving sodium bicarbonate by mouth. Alkaline diuresis is successful in clearing a drug from the body. (Data from Parker, W. A. (1948) *Quart. J. Med.* **17**, 229.)

be possible to reduce this loss by giving an otherwise inactive substance which competes with it for the route of excretion. Probenecid is such a substance. These are examples of drug interaction by interference with the rate of clearance.

GFR and biliary and tubular excretion minus tubular and GIT reabsorption = clearance

The importance of bile as a route of clearance is now fully recognized. Once excreted the drug is cleared in faeces, but some drugs are reabsorbed to a significant extent through the **entero-hepatic circularion** (see Fig. 1.11). The effect is to prolong the existence of the drug

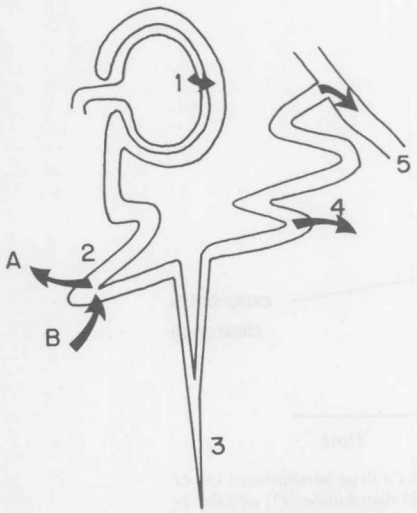


Fig. 1.9. 1. The glomerulus—the site of filtration. 2. The proximal tubule. (A) Passive reabsorption of lipid soluble drugs in un-ionized form. (B) Active secretion of organic acids and bases. 3. The loop of Henlé—the pH of urine determines degree of ionization. 4. The distal tubule–passive reabsorption as at 2A. 5. The collecting tubule—ionized and lipid-insoluble drug excreted into urine.

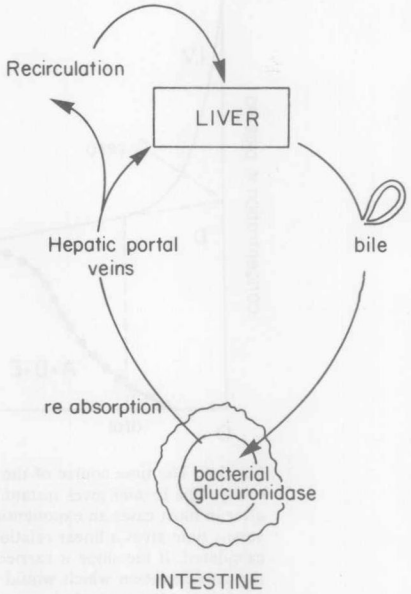


Fig. 1.11. The entero-hepatic circulation of a drug which is excreted in bile.

in the body. Examples are digitoxin and ampicillin. Use may be made of these facts in treating biliary tract infection; on the other hand failure of biliary function (e.g. hepatitis, cirrhosis) inevitably means a grave reduction in the capacity to clear drugs of this type. Other routes of clearance are the lungs and expired air for gaseous or volatile substances such as general anaesthetics; the faeces for substances which are excreted from the large bowel; and, in minimal amounts, sweat, milk, or desquamating skin.

EFFECTS OF DISEASE

Renal failure obviously reduces the capacity for clearance of drugs in the urine. Glomerular filtration ceases during severe hypotension (systolic pressure approximately 10 kPa). Concentration of drugs in the urine is helpful in the treatment of infections of the urinary tract. Some drugs, if used over prolonged periods, cause nephrotoxicity, e.g. phenacetin.

CUMULATION AND THE STEADY STATE

If less of a drug is excreted than is absorbed over a given period of time the concentration in the body will rise. This occurs more easily with slowly than with rapidly cleared drugs. If it is other than a temporary process, the drug may reach a toxic concentration, e.g. with digoxin. If there is no urgency and in order to avoid cumulation the dosage should be adjusted to give a steady and slow rise in blood level (see Fig. 1.12). If therapeutic considerations demand, it may be desirable to give a large initial dose (loading dose) to establish an effective level quickly, and continue with a lesser or maintenance dose which equals the daily excretion at that desired blood level (see Fig. 1.13). This technique

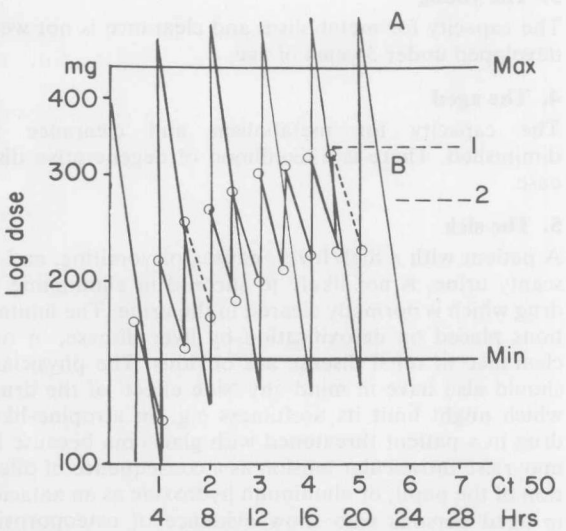


Fig. 1.12. The effect of the time interval between doses on plasma levels and total dosage required. For drug X, assume immediate and total absorption, half-life $Ct/2$ or $Ct_{50} = 4$ h, plasma volume remains constant, and plasma concentration is proportional to dose given.

(A) Dose given as 400 mg 4-hourly—total 2·4 g/day. Note the wide range of plasma levels, above maximal tolerated and below minimal effective level. Steady state achieved (1) after 4–5 doses at intervals of twice the $Ct/2$.

(B) Half the dose given as 100 mg 2-hourly. The range of levels is less extreme, but slower to achieve minimum effective level. No toxic level is reached. Steady state achieved (2) at similar time to A, but at a lower level.

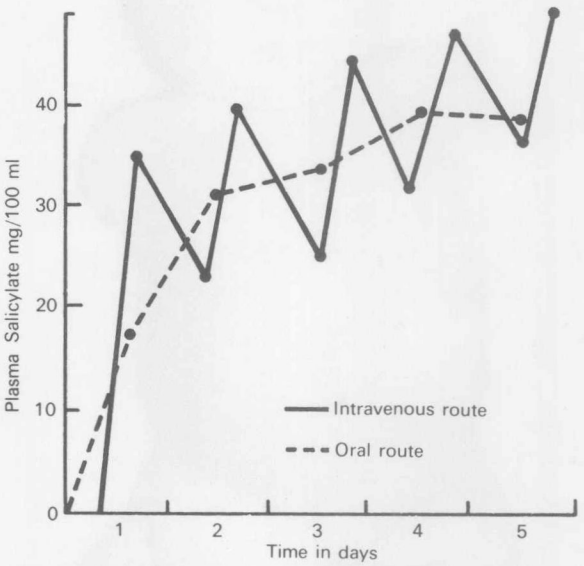


Fig. 1.13. The effect of the route of administration on the concentration of a drug; an example of cumulation. 10 g of sodium salicylate was given to patients each day in intravenous infusion, or in divided doses by mouth. At the end of the first day the plasma level of salicylate was 18 mg per 100 ml after oral administration, whereas the intravenous route produced double that concentration in less time. Thereafter repeated doses caused a rise in concentration, which represents a daily gain of the excess of the intake over the output. If the toxic level is 35 mg per 100 ml, this was attained immediately by the intravenous route, but might not be attained for 3 to 4 days by oral administration. Excretion more nearly kept pace with absorption when the latter was spread over the day.

is commonly practised in therapy with digitalis. The higher the level desired the greater this initial amount will be. There are special **'slow release' preparations** available which are designed to ensure a continuous absorption of a drug at a reasonable steady rate over a long period of time. These may be oral preparations which contain sub-units of the single dosage unit, in particles which dissolve at different times, or in which the active drug is bonded to a resin which only slowly releases it; or absorbed to a plastic artifact which may be inserted into the uterus or rectum. Such a pharmaceutical form is a depot preparation. It may vary from an oily solution for injection s.c., a suspension of particles which are slow to dissolve or a solid implant in tablet or bolus form.