

**DRUG DISPOSITION
AND PHARMACOKINETICS**
WITH A CONSIDERATION
OF PHARMACOLOGICAL AND
CLINICAL RELATIONSHIPS
STEPHEN H CURRY

Third edition

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Drug disposition and pharmacokinetics

**with a consideration of pharmacological
and clinical relationships**

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Preface to First Edition

There are two sides to the pharmacological coin. One side, which could be entitled 'the effect of the drug on the body', has been considered in a large number of textbooks of pharmacodynamics. The other side, 'the effect of the body on the drug', or the disposition and fate of foreign compounds, has received much less attention and this book represents an attempt to at least partially rectify this situation.

The processes involved in the disposition and fate of drugs in the body are largely physicochemical, but their study is generally thought of as a major component of 'biochemical' pharmacology, alongside pharmacodynamic phenomena involving enzymes and intermediary metabolites. Disposition and fate are sometimes termed 'pharmacokinetics' but this word is best reserved for mathematical studies of the effect of the body on the drug. The subject matter of this text ranges from an introductory chapter concerned with the chemistry of drug molecules to the relationship between drug effects in the clinic and drug concentrations in plasma. The former field of study is the essential basis of the subject, and the latter field of study is likely to be the logical end-point of any investigation in this particular section of applied pharmacology. It is hoped that, as the result of the adoption of this catholic approach to the subject matter, the book will be useful to all groups, both students and post-graduates, scientific and clinical, concerned with the rational investigation and application of drugs.

Where possible, the examples used in this book have been drawn from studies of human pharmacology. Animal studies are however of great relevance in certain cases, and occasionally they are the only source of quotable data. In general, in the field covered by this text, animal studies are most relevant to man when the phenomena under study are wholly physicochemical, and least relevant when energy-requiring processes are involved. Examples have been used as extensively as possible, and the generosity of the various authors and publishers who have given permission for their publications to be extensively quoted is gratefully acknowledged. Individual recognition is given in each figure legend or table. A certain amount of the data is original, and for this I am grateful to

various groups of The London Hospital Medical College students, who, in the course of their studies for MB, BS, and BSc degrees, have engaged in projects which generated quotable data on glutethimide, riboflavin and diazepam.

Particular consideration has been given to pharmacokinetic aspects of multiple dosing, and this has been made possible by the availability of suitable experimental data for nordiazepam, a drug only recently made freely available in the United Kingdom. The quotation of the data, from the research data of Boehringer Ingelheim, Limited, was very kindly authorized by Dr Patrick Knowlson, Medical Director. It is notable that data relating the drug concentrations in plasma following single doses and during long-term treatment is apparently only available at present for the newest drugs. In relation to this area of study, I am also indebted to Mr Ashley Hyams of The London Hospital Medical College computer department, for the solution of the equation in appendix II, and for obtaining the figures listed in table A.1.

Finally, I owe a very special debt of gratitude to my wife, Susan, and to Mrs Carol Brown who together executed the awesome task of preparing the typescript willingly and efficiently.

S.H.C.

February 1974

Preface to Third Edition

The major advances since the preparation of the second edition of *Drug Disposition and Pharmacokinetics* have been in understanding some of the specific biological factors affecting pharmacokinetic processes, in attitudes towards practical use of pharmacokinetic knowledge, and in regard to drug toxicity. Accordingly, the book is now in 15 chapters. Chapter 1 has been extended by inclusion of a brief mathematical section. Chapters 2–4 are little changed, but Chapter 5 of the second edition is now subdivided into four chapters, concerned with general factors, age, genetics and disease, reflecting the explosion of investigative activity in these areas in recent years. Chapter 10 of the second edition has been divided into three chapters, concerned with quantitative pharmacological relationships in general, monitoring, and toxicity. The biochemical role in adverse reactions is increasingly obvious, and hence a separate chapter on toxicity. The other two of these three chapters reflect something which took the scientific world all too long to appreciate. In the 1960s most scientific investigators said that drug responses *must* relate to pharmacokinetics, while others, mainly clinical investigators, were doubtful. Many years passed before it was realized that the two groups were not speaking the same language. The scientists were concerned with detailed studies of time-course of effect, in a longitudinal sense. The doubters were concerned with inter-patient variation in sensitivity, which obviously takes many forms and depends on many factors. Reflecting this, Chapter 13 is a scientific approach to time-course. Chapter 14 is concerned with the relatively sloppy approach of the occasional sample in the clinic. The two applications are, regrettably, worlds apart.

I am again grateful to those who have given assistance, by means of advice, and permission for quotation of work. Dr Robin Whelpton, who played the major part in preparing the protein binding chapter which first appeared in the second edition, has again been a most helpful and valuable advisor.

S.H.C.

April 1980

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1 Chemical Introduction: drug sources, drug classification and chemical properties of drugs

Drugs are chemical in nature. They exert their effects by reacting chemically† with a variety of endogenous materials in the body. These effects are assessed as physiological, biochemical or behavioural changes.

There are two major groups of chemicals studied and used as drugs. Firstly, there is a group of pharmacologically interesting endogenous substances, typified by acetylcholine, histamine and noradrenaline. These substances lead to changes when the amount in the body or in an *in vitro* preparation is increased by dosage. Secondly, there are the non-endogenous, or 'foreign' chemicals which are mostly products of the laboratories of the pharmaceutical industry.

Drug sources

It is of interest to consider the major sources of modern drugs. Table 1.1 demonstrates some of the changes that have taken place in the United Kingdom over the past 20 years. The data in this table were obtained from a study of the entries in the British Pharmacopoeia in the years 1953–73. The British Pharmacopoeia is a chemical reference handbook published every 5 years. It contains a monograph for every established drug and each monograph includes a definition of the drug in question, together with a series of standards and purity tests. In the preparation of table 1.1, the entries were classified into one of ten types. The numbers in each classification were then assessed as a percentage of the total number of entries considered. The table shows the steady increase in the relative significance of synthetic organic chemicals. Also shown is the steady decline in the relative significance of botanical materials, chiefly leaves and barks, and of inorganic chemicals. The absolute significance, as opposed to the relative significance, of some of these materials has of course remained more or less

†In this book, 'reacting chemically' indicates either physicochemically or organochemically. The exact balance of the two, even assuming their differentiation is justified, depends on a variety of factors in any particular case. Similarly, 'physical' and 'chemical' properties are both chemical, but referable to physicochemical or organochemical processes.

Table 1.1 Proportions of the entries in five editions of the British Pharmacopoeia (1953–73) classified into ten groups, differentiated according to source

<i>Type of entry</i>	<i>1953</i>	<i>1958</i>	<i>1963</i>	<i>1968</i>	<i>1973</i>
1 Botanical source—natural product	18.3	12.9	9.6	7.6	7.3
2 Botanical source—purified constituent of natural product	7.1	7.0	6.5	5.4	5.3
3 Zoological source—natural product (including blood products)	3.1	3.2	2.8	1.9	1.8
4 Zoological source—purified constituent of natural product (including natural and semisynthetic steroids)	3.4	4.3	5.6	6.6	6.4
5 Vaccines and other immunological products	4.3	4.0	4.4	4.3	4.1
6 Organic chemicals	35.7	45.3	51.7	54.5	55.4
7 Inorganic chemicals	21.4	15.6	11.7	9.7	9.4
8 Antibiotics (antimicrobial drugs of natural origin)	1.6	3.8	3.7	4.8	5.1
9 Vitamins	1.9	1.6	1.6	1.4	1.3
10 Analytical reagents	3.1	2.7	2.3	1.9	1.8
Approximate number of entries considered	900	1100	1350	1750	1810

constant. This can be deduced by consideration of the relative significance of each type, shown as the percentage in the main part of the table, and the total number of entries in each edition, shown in the bottom line of the table.

Primitive therapeutics relied heavily on a variety of mixtures prepared from botanical and inorganic materials. The botanical materials included some extremely powerful plant extracts, with actions for example on the brain, heart and gastrointestinal tract, and also some quite innocuous potions. The inorganic materials were generally alkalis, which did little more than partially neutralize gastric acidity. Inevitably, the relative importance of these materials has declined, but it should be recognised that about a dozen important drugs are still obtained, as purified chemical constituents, from botanical sources and that alkalis still have a very definite value in certain conditions. Amongst the botanical drugs, morphine is still obtained from opium, cocaine is still obtained from coca leaves, and atropine is still obtained from belladonna. Although the pure compounds can be prepared synthetically in the laboratory, the most economical source is still the botanical material.

Similar considerations apply with some of the drugs of zoological origin. For instance, while the consumption of raw liver (an obviously zoological material) was once of great importance in the treatment of anaemia, modern treatment relies on cyanocobalamin, a complex chemical which occurs in raw liver, and on hydroxycobalamin, a semisynthetic analogue. Another zoological example is insulin, which is obtained from the pancreatic glands of sheep and cattle, and

extensively purified and modified to form several versions of the carefully controlled modern drug (see Chapter 2).

Most other naturally occurring drugs, including antibiotics (antimicrobial drugs of biological origin) and vitamins, are generally nowadays, of known chemical structure, and although their synthesis in the laboratory is in most cases a chemical possibility, it is often more convenient and economical to extract them from natural sources. In the case of one of the antibiotics, penicillin, the basic nucleus is of natural origin, but the modern drugs are semisynthetic modifications of the natural product.

With only minor exceptions, drugs are chemicals with known structures. Some of them are simple, some complex. Some of them are purely synthetic, some are obtained from crude natural products and purified before use. Most are organic chemicals, a few are inorganic chemicals. With all drugs, the emphasis is nowadays on a pure active constituent, with carefully controlled properties, rather than on a mysterious concoction of unknown potency and constitution.

Drug classification

A rigid system for the classification of drugs will never be devised. Increasingly, it is found that drugs possess actions which would permit their categorization in several groups in any one particular classification system. This is shown most strikingly by the use of lignocaine for both local and cardiac effects. Additionally, with constant changes in drug usage, it is not uncommon to find drugs of several different types in use for the same purpose. The number of examples within each type is of course very large. However, drugs are commonly grouped according to one of two major systems. These are on the basis of action or effect, and on the basis of chemistry. It is not possible to include all drugs in either of these groupings, and so a hybrid classification is necessary if all possibilities are to be considered. Table 1.2 shows an abbreviated pharmacological listing. The interpretation of this is quite straightforward, and it is presented as a general aid to the reader of later chapters of this book. Most of the examples quoted in later chapters are mentioned. Not so straightforward is the chemical listing shown in table 1.3. It will be immediately noticed that while all of the groups of drugs in table 1.3 are represented in table 1.2, all of the types in table 1.2 are not represented in table 1.3, as a great many drugs are of chemical types of which there is only a single example, and table 1.2 is only concerned with those chemical groups of drugs which are commonly known by their chemical names.

Two other chemical groups commonly mentioned in pharmacology, and not mentioned in either table 1.2 or table 1.3 are alkaloids and glycosides. Alkaloids are complex nitrogenous bases found in plants. An example is morphine. Glycosides are complex organic molecules containing sugar residues, also found

Table 1.2 Abbreviated listing of drug groups categorized on the basis of pharmacological use or clinical effect, with examples or cross-references to the chemical types in table 1.3

General anaesthetics

- I Gases—e.g. nitrous oxide
- II Volatile liquids—e.g. halothane
- III Intravenous anaesthetics, including some barbiturates

Hypnotics, including some barbiturates and some benzodiazepines

Sedatives, including certain barbiturates, benzodiazepines and phenothiazines

Tranquillizers

- I Major, including certain phenothiazines and butyrophenones
- II Minor, including certain benzodiazepines

Antidepressants

- I Dibenzazepines—e.g. imipramine
- II Monoamine oxidase inhibitors—e.g. tranylcypromine
- III Lithium

C.N.S. stimulants

- I Amphetamines—e.g. amphetamine itself
- II Hallucinogens—e.g. lysergic acid diethylamide
- III Xanthines—e.g. caffeine

Analgesics

- I Narcotics—e.g. morphine and pethidine
- II Mild analgesics, including salicylates

Miscellaneous centrally acting drugs, including respiratory stimulants (analeptics), anticonvulsants, certain muscle relaxants, drugs for Parkinson's disease, antiemetics, emetics and antitussives

Local anaesthetics—e.g. lignocaine

Drugs acting at synapses and nerve endings

- I Acetylcholine and analogues (parasympathomimetic agents)
- II Anticholinesterase drugs—e.g. physostigmine
- III Inhibitors of acetylcholine at parasympathomimetic nerve endings—e.g. atropine
- IV Drugs acting at ganglia—e.g. nicotine
- V Drugs acting at adrenergic nerve endings, including catecholamines and imidazoles
- VI Neuromuscular blocking drugs—e.g. succinylcholine

Drugs acting on the respiratory system

- I Bronchodilators—e.g. isoprenaline
- II Drugs affecting allergic responses—e.g. disodium cromoglycate

Autocoids and their antagonists

- I Histamine and 5-hydroxytryptamine
- II Antihistamines—e.g. promethazine

Cardiovascular drugs

- I Digitalis and digoxin
- II Antiarrhythmic drugs—e.g. quinidine
- III Antihypertensive drugs, including guanidines
- IV Vasodilators—e.g. glyceryl trinitrate
- V Anticoagulants, including coumarins

Diuretics, including thiazides

Locally acting drugs, including gastric antacids and cathartics

Drugs used in the chemotherapy of parasitic diseases, including arsenicals

Drugs used in the chemotherapy of microbial diseases, including penicillins and sulphonamides

Antimitotic drugs—e.g. mustine hydrochloride

Hormones, hormone analogues and hormone antagonists, including steroids, sulphonylureas and biguanides

Table 1.3 Some groups of drugs classified on chemical structure rather than on pharmacological properties or uses

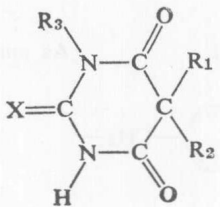
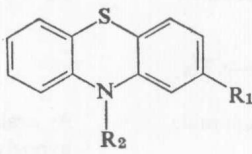
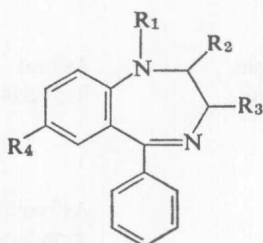
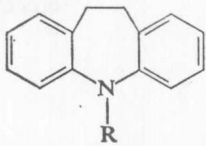
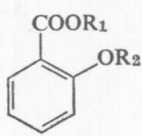
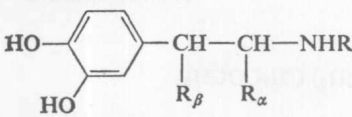
Group	Parent structure	Chemical example	Uses and examples
Barbiturates		Phenobarbitone $R_1 = C_2H_5$ $R_2 = C_6H_5$ $R_3 = H$ $X = O$	As hypnotics and sedatives (pentobarbitone) As anticonvulsants (phenobarbitone) As general anaesthetics (thiopentone)
Phenothiazines		Chlorpromazine $R_1 = Cl$ $R_2 = (CH_2)_3N(CH_3)_2$	As antihistamines (promethazine) In psychiatry as major tranquillizers (chlorpromazine)
Benzodiazepines		Diazepam $R_1 = CH_3$ $R_2 = O$ $R_3 = H_2$ $R_4 = Cl$	As hypnotics and sedatives (diazepam, nitrazepam, chlordiazepoxide)
Dibenzazepines		Imipramine $R = (CH_2)_3N(CH_3)_2$	As antidepressants
Salicylates		Acetylsalicylic acid (aspirin) $R_1 = H$ $R_2 = CO \cdot CH_3$	As mild analgesics
Catecholamines		Adrenaline $R = CH_3$ $R_\alpha = H$ $R_\beta = OH$	Sympathomimetic amines

Table 1.3 continued

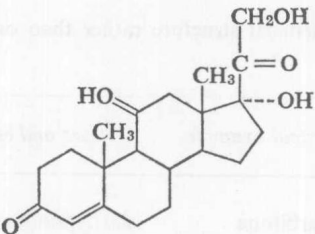
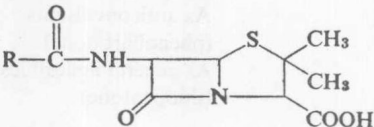

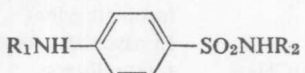

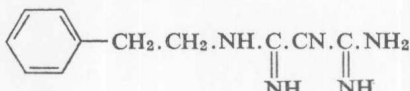
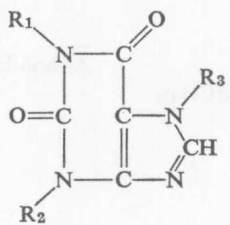
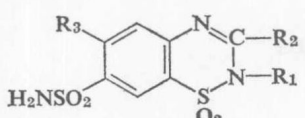
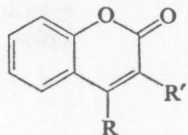
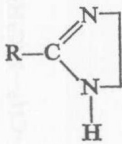
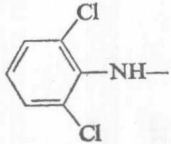
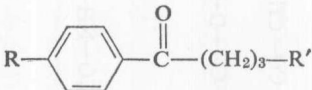
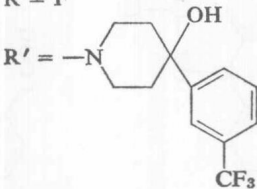
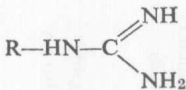
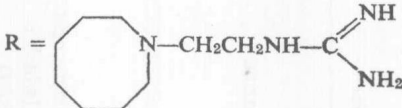
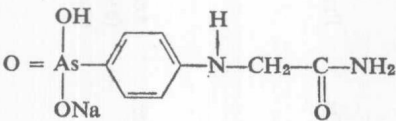
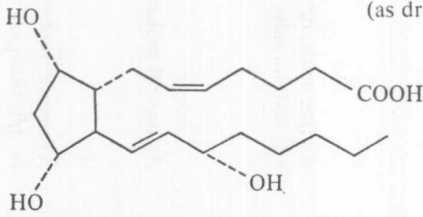
Group	Parent structure	Chemical example	Uses and examples
Steroids		Hydrocortisone (as drawn)	In inflammatory conditions
Penicillins		Penicillin G $R = $ 	As antimicrobial drugs
Sulphonamides		Sulphacetamide $R_1 = H$ $R_2 = CO-CH_3$	As antimicrobial drugs
Sulphonylureas		Chlorpropamide $R = Cl$	As oral hypoglycaemics
Biguanides		Phenformin (as drawn)	As oral hypoglycaemics
Xanthines		Caffeine $R_1 = CH_3$ $R_2 = CH_3$ $R_3 = CH_3$	As respiratory stimulants, diuretics and bronchodilators
Thiadiazines		Chlorthiazide $R_1 = H$ $R_2 = H$ $R_3 = Cl$	As diuretics
Coumarins		Warfarin $R = OH$ $R' = CH(C_6H_5)CH_2COCH_3$	As anticoagulants

Table 1.3 continued

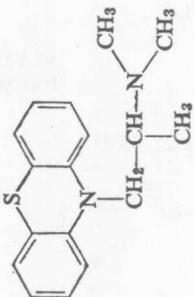
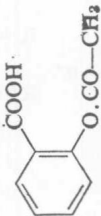
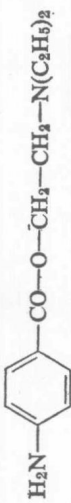
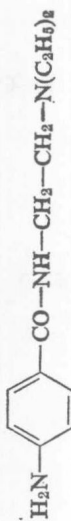
Group	Parent structure	Chemical example	Uses and examples
Imidazolines		Clonidine $R = $ 	As adrenergic antagonists
Butyrophenones		Triperidol $R = F$ $R' = $ 	In psychiatry, as major tranquillizers
Guanidines		Guanethidine $R = $ 	As antihypertensive drugs
Arsenicals	$R-As=O$	Tryparsamide 	As antiprotozoal drugs
Prostaglandins		PGF ₂ (as drawn)	As uterine stimulants and in other procedures

in plants. An example is digoxin. Additionally, it should not be forgotten that some drugs are proteins, peptides or polysaccharides, and there are occasions when amino acids are administered in pharmacological procedures.

Chemical types and chemical properties

Having established that drugs are chemical in nature, and having provided a basis for their classification and categorization, we can now consider their chemical properties as they affect drug distribution and drug action. Table 1.4 gives details of some of the major chemical reactive groups, with names and

Table 1.4 Some important functional groups found in drug molecules

Description of compound type	Functional group	Presentation	Name	Specific example	Formula
Weak bases— e.g. amines	—NRR'	As free bases, or as salts, e.g. hydrochloride	Promethazine		
Weak acids— e.g. carboxylic acids	—COOH	As free acids, or as salts, e.g. sodium salts	Acetylsalicylic acid (aspirin) (which is also an ester)		
Esters	—CO—O—	As neutral molecules	Procaine (which is also an amine)		
Amides	—CO—NH—	As neutral molecules (at physiological pH)	Procaine amide (which is also an amine)		
Sulphonamides	—SO2—NH—	As neutral molecules (at physiological pH)	Sulphanilamide (which is also an amine)	