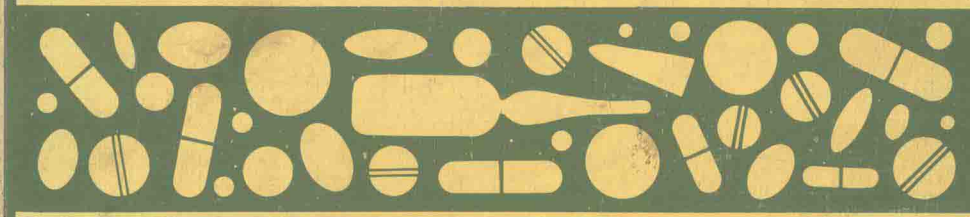
Clinical Pharmacology



D. R. LAURENCE
P. N. BENNETT

FIFTH EDITION

Illustrations by Peter Kneebone

CLINICAL PHARMACOLOGY

D. R. LAURENCE, M.D., F.R.C.P.
Professor of Pharmacology and Therapeutics, Departments of Pharmacology and Clinical Pharmacology, School of Medicine, University College London

and

P. N. BENNETT, M.D., M.R.C.P.
Consultant Physician, Royal United Hospital, Bath and Senior Lecturer in Clinical Pharmacology, University of Bath

FIFTH EDITION

With some illustrations by Peter Kneebone

CHURCHILL LIVINGSTONE
EDINBURGH LONDON AND NEW YORK 1980

CHURCHILL LIVINGSTONE
Medical Division of the Longman Group Limited

Distributed in the United States of America by
Churchill Livingstone Inc., 19 West 44th Street, New York,
N.Y. 10036, and by associated companies,
branches and representatives throughout
the world.

First Edition 1960
Second Edition 1962
Third Edition 1966
Fourth Edition 1973
Translated into Italian
Fifth Edition 1980

ISBN 0 443 01846 4

British Library Cataloguing in Publication Data
Laurence, Desmond Roger
Clinical pharmacology. — 5th ed.
1. Drugs 2. Pharmacology
I. Title II. Bennett, P N
615'.1 RM300 79–42943

Printed in Great Britain at The Pitman Press, Bath

PREFACE

*"For your own satisfaction and for mine, please read this preface."**

This book is about the scientific basis and practice of drug therapy. It is particularly intended for **medical students** in their clinical years, but it contains many more facts and details than a student either needs or should attempt to learn.

The general aspects of the *how* and *why* of drugs are for the student. The practical details are to help him when he begins to prescribe on his own responsibility **after graduating**, and the book is offered as a guide to this.

Thus the **student** should read selectively, and we hope it will not be too difficult for him to do so. We would particularly suggest that the student should read Chs. 1 to 9 and those parts of other chapters covering general background, principles or mechanisms of action. Unfortunately we have been unable to contrive everywhere clearly to separate these sections from the more detailed facts required for such guidance in practical prescribing as we have attempted.

In addition we hope that the book may be of use to some **more experienced doctors** in reminding them of general progress and practice in fields with which, perhaps, they are no longer primarily concerned, but which have not lost interest or all importance for them.

Justification. We believe that doctors who understand something of how drugs get into the body, of how they produce their effects, of their fate and of how evidence of therapeutic effect is assessed, will choose drugs more skilfully and use them more successfully than those who do not. They will less often expose patients to the risks of useless therapy and they will also avoid more of the hazards of adverse effects due to interaction with disease or with other drugs. They will be less likely to mistake the ill-effects of drugs for natural disease and more likely to recognise antagonism or synergism when it unexpectedly arises either from prescribed or from self-medication.

This book represents an attempt to provide pharmacological knowledge that is both interesting and useful to the physician.

Most books of moderate size confine themselves either to discussing the pharmacology of drugs without giving enough information for them to be selected and used effectively, or else they confine themselves to practical therapeutics and ignore the pharmacological background. It is too much to expect the now heavily burdened student to consult and in-

* St. Francis of Sales: preface to *Introduction to the Devout Life* (1609).

tegrate two works, one not always clearly related to clinical practice and the other often as arbitrary and as empirical as a cookery book. *This book is offered as a reasonably brief solution to the problem of combining practical clinical utility with some account of pharmacology.*

It might be thought that the existence of big multi-author books in which each chapter is written by a specialist would make futile a smaller book such as this, for in the available space it is not possible to give a lot of detail. But we believe it is useful to have a book of a size that is manageable other than as a work of reference—that can be compassed by an individual coming to the subject either for the first time or to refresh his general knowledge—and that may help him to use the larger discursive sources more profitably.

How much practical technical detail to include has been difficult to decide. In general, more such detail is provided for therapeutic practices that are complex or potentially dangerous as well as urgent, where there may be no time for consultation with colleagues or search in libraries (e.g. salicylate poisoning) and less, or even none, on therapy that is generally conducted only by specialists or that can wait on such consultation, e.g. anticancer drugs; i.v. oxytocin.

Use of the book. Students are, or should be, concerned to *understand*, to develop a rational, critical attitude to drug therapy and they should therefore chiefly concern themselves with how drugs act and interact in disease and with how evidence of therapeutic effect is obtained and evaluated. They should not allow this to be impeded by attempts to memorise lists of alternative drugs and minor differences between them, or arbitrary practical details, such as dosage or solution strength, which should never be required of them in examinations; the only way to fix these in the mind is by actual prescribing.

The decision to try to include sufficient practical details to enable some drugs to be correctly used has inevitably made substantial parts of the book tedious. In addition, it has been thought necessary to mention numerous drugs of doubtful merit, and what have been aptly called "metooers", in order to enable drugs to be recognized and a choice to be made from amongst the huge number of drugs and preparations of drugs thrust at the clinician by a vigorous pharmaceutical industry.

We hope that students will readily see which sections of the book they can, and indeed should, neglect in their general reading, and that are for use when the responsibility of choice and administration becomes theirs.

Repetition. Readers may notice occasional repetition; this is often deliberate.

The "authority" of a textbook. If a book is to be a useful guide to treatment it must offer clear conclusions and advice. If it is to be of reasonable size alternative courses of action will often have to be omitted, even though they may be satisfactory. What is recommended should be based on sound evidence where this exists, and on an assessment of the opinions of the experienced where it does not. Exceptions to all advice

will occur,* and part of the clinician's skill lies in knowing when to depart from an accepted course. Nor can a textbook take account of all possible modifying factors, e.g. personality, intercurrent disease, metabolic differences.

The status of a textbook as a practical guide has been expressed in a legal judgement where an accusation of negligent treatment made against a doctor was supported by showing that he had not followed the orthodox treatment as stated in various textbooks. The Judge said that textbook writers were writing of a subject in general and not of a particular patient. A doctor was entitled to use his common sense, his experience, and his judgement as far as they fitted into a particular case. "It would be a sorry day for the medical profession if it were to be said that no doctor ought to depart one tittle from that which he saw written in a textbook."† Statements in textbooks were no substitute for the judgement of the physician in charge of the case. "*His Lordship could not follow slavishly the views expressed in textbooks. . .*".† Indeed any sensible author would be horrified at the thought that he was credited with less than the usual human fallibility.

The **guide to further reading** at the end of each chapter is comprised of references to original papers and editorials from a small number of English language journals that are likely to be available in even the most modest hospital library. This is done to enable anyone, anywhere, to gain access to the original literature and to informed opinion on any topic, and also to provide interest and sometimes amusement. We do not attempt to document all the statements we make, which would be impossible without greatly enlarging this, already too long, book.

The titles of articles are included in the particular hope that students will run their eye over the list and find something that attracts them sufficiently to cause them to want to read original work. There is no substitute for contact with original minds or the excitement of following these minds through their efforts at discovery.

The **general references** at the end of the book are to specialist books and journals that cover the whole field.

Reasons for using non-proprietary drug names instead of the sometimes more familiar proprietary names are given in Ch. 7. The index includes an inevitably incomplete range of proprietary names.

It is assumed that the reader will possess a formulary and so the text has not been encumbered with exhaustive lists of preparations

* Control of therapeutic claims is properly exercised by government regulating authority (in the U.K., the Committee on Safety of Medicines), but limitation of the doctor's freedom to prescribe what he has reason to believe best for his patient should be resisted. The solution to bad doctoring is education, not the imposition of limitations on skilled doctors.

† *Lancet* (1960) **1.** 593.

although it is hoped that enough have been mentioned to cover much routine prescribing, and many drugs have been included solely for identification.

D. R. L.
London and Bath, 1980 P. N. B.

ACKNOWLEDGEMENTS

It is not possible for two individuals to cover the whole field of drug therapy from their own knowledge and experience, and we are deeply grateful to all those who have with such good grace given us their time and energy to supply valuable facts and opinions, they principally include:

Dr. B. G. Adams
Dr. E. S. K. Assem
Dr. D. P. Brenton
Dr. G. H. Dewar
Mr. P. E. Glodowski
Dr. D. G. Haylett
Dr. A. Herxheimer
Dr. A. Hollman
Professor E. R. Huehns
Professor D. H. Jenkinson
Miss Rita Jones
Professor N. D. W. Lionel
Dr. A. E. M. McLean
Dr. M. C. Mitcheson
Professor Sir William Paton
Dr. Rosalind Pitt-Rivers
Dr. B. N. C. Prichard
Dr. T. W. E. Robinson
Professor E. J. Ross
Dr. R. L. Souhami
Dr. S. G. Spiro
Dr. E. Joan Stokes
Dr. G. I. M. Swyer
Professor M. K. Sykes
Professor O. M. Wrong

Much of any merit this book may have is due to the generosity of those named above in putting their knowledge and practical experience of the use of drugs at our disposal. Responsibility for any errors rests with us.

In addition, permission to quote directly from the writings of some authorities has been generously granted and we thank the authors and their publishers who have given it.

Peter Kneebone's illustrations speak for themselves.

D. R. L.
P. N. B.

CONTENTS

Notes (1) Tablet size in mg is given in brackets after the drug name.

(2) Manufacturers' *data sheets*, updated annually, are, or should be a source of comprehensive information on prescribing and adverse reactions.

Chapter 1

DRUG THERAPY

> Poisons in small doses are the best medicines; and useful medicines in too large doses are poisonous (William Withering, 1789).

Topics: criteria: benefits and risks: drug-induced disease: adverse reactions, attribution, detection: responsibility for adverse reactions, no fault liability: the practolol accident: hazards of life on drugs: reasons for taking a drug history: the therapeutic situation, placebos, tonics: prescribing and drug consumption: repeat prescriptions: patient compliance: self-medication.

Before treating any patient with drugs* the doctor should have made up his mind on six points:

1. Whether he should interfere with the patient at all and if so—
2. What alteration in the patient's condition he hopes to achieve.
3. That the drug he intends to use is capable of bringing this about.
4. That he can administer the drug in such a way that the right concentration will be attained in the right place at the right time and for the right duration.
5. What other effects the drug may have and whether these may be harmful.
6. Whether the likelihood of benefit, and its importance, outweighs the likelihood of damage, and its importance, i.e. to consider ***benefit versus risk***, or ***efficacy in relation to safety***.

It is obvious that drug therapy involves a great deal more than matching the name of the drug to the name of a disease; it requires knowledge, judgement, skill and wisdom. A book can provide knowledge and can contribute to the formation of judgement, but it can do little to impart skill and wisdom which are the products of experience and innate and acquired capacities.

Everybody knows that drugs can do good.

Medically this good may sometimes seem trivial, as in the avoidance of a sleepless night in a noisy hotel or of social embarrassment from a profusely running nose due to seasonal pollen allergy (hay-fever). Such benefits however, are not necessarily trivial to the recipient, concerned to be at his best in urgent matters, whether of business, of pleasure or of passion.

* A World Health Organisation Scientific Group has defined a drug as "any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient". *Wld. Hlth. Org. techn. Rep. Ser.* (1966). No. 341, p. 7.

A *drug* is a single chemical substance that forms the active ingredient of a *medicine*, which latter may contain many other substances to deliver the drug in a stable form, acceptable and convenient to the patient. The terms will be used more or less interchangeably in this book. To use the word 'drug' intending only a harmful, dangerous or addictive substance is to abuse a respectable and useful word.

Or the good may be literally life-saving, as in serious acute infections (pneumonia, septicaemia) or in the prevention of life-destroying disability from severe asthma, from epilepsy or from blindness due to glaucoma.

Everybody knows that drugs can also do harm.

This harm may be relatively trivial as in hangover from a hypnotic or sleepiness from an H_1-receptor antihistamine used for hay-fever (though these effects may be a cause of serious road accidents).

The harm may also be life-destroying as in the rare sudden death following an injection of penicillin, rightly regarded as one of the safest of antibiotics, or the slower death or disability that occasionally attends the use of drugs that are effective in asthma and rheumatoid arthritis (adrenocortical steroids, penicillamine).

There are risks in taking medicines just as there are risks in food and transport. There are also risks in not taking medicines when they are needed, just as there are risks in not taking food or in not using transport when they are needed.

Efficacy and safety do not lie solely in the chemical nature of the drug. Doctors must choose which drugs to use and must apply them correctly in relation, not only to properties of the drug, but also to those of the patient and his disease. Then patients must use the prescribed medicine correctly.

Drugs are used in three principal ways:

1. **Curative**, as **primary** therapy (as in bacterial and parasitic infections), or as **auxiliary** therapy (as with anaesthetics, and ergometrine and oxytocin in obstetrics).
2. **Suppressive** of diseases or symptoms, used continuously or intermittently to maintain health without attaining cure as in hypertension, diabetes, epilepsy, asthma or to control symptoms such as pain and cough, whilst awaiting recovery from the causative disease.
3. **Preventive** (prophylactic), as when a non-immune person enters a malarial area or contraception.

Benefits and risks

Benefits of drugs are manifest to doctor and patient and also, it might be thought, obvious to even the most unimaginative healthy person who finds himself dismayed by some aspects of modern technology.

Modern technological medicine has been criticised with some justice for waiting for disease to occur and then trying to cure it rather than seeking to prevent it from occurring in the first place. It has also been criticised for failure, as judged by population health statistics.

It is pointed out, for example, that it is improved living conditions, rather than medical treatment that have played the major role in the enormous decline in the death rate from infectious diseases over the past 100 years. It is true that the biggest changes in some important areas of health result from social and economic development rather than from the

application of technical medicine; that "prevention is better than cure" is a familiar saying because it is true.

But people still frequently fall sick and will continue to do so, although the pattern of disease in the community changes, infectious disease in the young giving place to degenerative disease in the old. We must look at population statistics; but we must also, in a humane society, look to the individual sufferer.

It is good to prevent tuberculosis; but those who are unfortunate enough to contract the disease will be grateful for drugs.

It is good to prevent cancer, and ways of doing so for some cancers, e.g. stopping smoking, are known, though seldom adopted; but those who fall sick will be grateful for drugs, surgery and radiation, whether these cure or whether they only ease the passage through the last phase of life.

It is better to prevent some heart disease, by moderate and sensible living, including moderation in eating, though such measures are all too little adopted; but those who fall sick will be grateful for drugs.

It would be better, if we only knew how, to prevent rheumatoid arthritis, epilepsy, pernicious anaemia, many cancers and diabetes, but we do not know how and sufferers are grateful for drugs. In any case we all have eventually to die of something, and the likelihood that the mode of death for most of us, even after practising all the excesses of advice on how to live a healthy life, will be free from pain, anxiety, cough, diarrhoea, paralysis, etc. (the list is endless) seems so small that it can be disregarded. Drugs already provide immeasurable solace in these situations, but better drugs are needed and their development should be encouraged.

Doctors know the sick are thankful for drugs just as a dedicated pedestrian struck down by a passing car is thankful for a motor ambulance to take him to hospital.

Benefits of drugs in individual diseases are discussed throughout this book and will not be further expanded here. But a general discussion of risk is appropriate.

In general, the public want the benefits of drugs but does not fully grasp that risks are inherent in drugs. The public needs to be educated by those who best can do this, the medical, pharmacological and pharmaceutical professions, as to what drugs can and cannot do and as to what can and cannot reasonably be expected of drugs. A group of lawyers advising government in the U.K. has written "public expectation that drugs on the market will be safe is raised by advertising and by the promotional material with which the pharmaceutical industry supply the medical profession". The lawyers went on to state that drugs are not essentially different from other manufactured products insofar as responsibility of producers for safety was concerned. If a group of sensible lawyers can believe this, it is clear that the professions have a substantial task of education.

Whenever a drug is given a risk is taken; it is often so small that

second thoughts are hardly necessary, but sometimes it is substantial. The doctor must weigh up the likelihood of gain for the patient against the likelihood of loss. There are often insufficient data for a rational decision to be reached, but a decision must still be made and this is one of the greatest difficulties of clinical practice. Its effect on the attitudes of doctors is often not appreciated by those who have never been in this situation. The patient's protection lies in the doctor's knowledge of the drug, his knowledge of the disease, and his experience of both, together with his knowledge of the patient. For instance, in typhoid fever the risk of inducing aplastic anæmia with chloramphenicol is far less than the risk of the patient dying from untreated disease. In less dangerous infections the decision is less easy, and should chloramphenicol be used without mishap in, say, bronchitis, it may leave the patient so sensitised that a second or third course may prove fatal. It is impossible to be sure of the magnitude of such a risk in any individual case.

In some diseases in which drugs will ultimately be needed they may not benefit the patient in the early stages. For example, victims of early Parkinsonism or hypertension may be but little inconvenienced by the disease, and the premature use of drugs, whilst perhaps reducing Parkinsonian symptoms and blood pressure respectively, can exact such a price in side-effects that the patient may prefer his untreated state. It is worth remembering that a feeling of languor which may be merely a slight inconvenience to a manual worker, may disable a man who lives by his intellect.

The most shameful act in therapeutics, apart from killing the patient, is to cause disease in a patient who is but little disabled or who is suffering from a self-limiting disorder. Such **iatrogenic* disease**, induced by misguided treatment, is far from rare.

If the doctor is temperamentally an extremist, he will do less harm by therapeutic nihilism than by optimistically overwhelming his patients with well-intentioned polypharmacy. The latter course is the easier to follow because it gives more immediate satisfaction to the patient, his family and indeed to the doctor himself. All are able to feel cosily that it is clear that the doctor is doing all he can, which usually means a great deal more than is wise. Habitual polypharmacy is sure to blur the outline of rational thought which should precede the use of any drug, and both doctor and patient will be the worse for this.

If in doubt whether or not to give a drug to a person who will get better without it, don't.

In 1917, Sollmann felt able to write "Pharmacology comprises some broad conceptions and generalisations, and some detailed conclusions, of such great and practical importance that every student and practitioner should be absolutely familiar with them. It comprises also a large mass of minute details, which would constitute too great a tax on human

* *Iatrogenic* means "physician-caused", i.e. disease consequent on following medical advice.

memory, but which cannot safely be neglected."*

If the last sentence was true when it was written, it is many times more true now. The selection of useful drugs from the multitude, not only offered to, but thrust upon the doctor by skilful and sometimes misleading advertising, is a matter of great importance. The doctor's aim must be not merely to give the patient what will do him good, but to give him *only* what will do him good, or at least more good than harm.

There are three major *grades of risk*, *unacceptable*, *acceptable* and *negligible*. In the presence of serious disease and with sufficient information on both the disease and the drug, then decisions in the first two categories, though they may be painful, present relatively obvious problems. But where the disease risk is remote (e.g. mild hypertension) or where drugs are to be used to increase comfort or to suppress symptoms that are, in fact, bearable, or for convenience rather than need, then the issues of risk acceptance are less obvious.

Risks should not be considered without reference to benefits any more than benefits should be considered without reference to risks.

"Risks are among the facts of life. In whatever we do and in whatever we refrain from doing, we are accepting risk. Some risks are obvious, some are unsuspected and some we conceal from ourselves. But risks are universally accepted, whether willingly or unwillingly, whether consciously or not".†

There are two broad *categories* of risk:

First are those that we accept by *deliberate choice*, even if we do not exactly know their magnitude, or we know but wish they were smaller, or, especially where the risk is remote though the consequences may be grave, we do not even think about the matter. Such risks include transport, and sports, both of which are subject to potent physical laws such as gravity and momentum, and surgery to rectify disorder that could either be tolerated or treated in other ways, e.g. hernia, much cosmetic surgery.

Second are those risks that are *imposed* on us in the sense that they cannot be significantly altered by individual action. Risks such as those of food additives (preservatives, colouring), air pollution and some environmental radioactivity are imposed by man. But there are also risks imposed by nature such as skin cancer due to excess ultraviolet radiation in sunny climes, as well as some radioactivity.

The motives for accepting risk are various and numerous and include the general attitude of individuals to life, to work and to pleasure. There are those who enthusiastically engage in or support caving or mountaineering or hang-gliding and there are those who feel that these risks are unacceptable and, not content with themselves abstaining from such recreations, campaign to have them stopped or controlled.

* Sollman, T. A. (1917). *Manual of Pharmacology*. Philadelphia: Saunders.
† Pochin, E. E. (1975) *Brit. Med. Bull.*, **31**, 184.

It seems an obvious truth that unnecessary risks should be avoided, but there is disagreement on what risks are truly unnecessary and, on looking closely at the matter, it is plain that many people habitually take risks in their daily life that it would be a misuse of words to describe as necessary. This is not a problem that will be resolved either simply or by further study, for there are genuine differences of opinion on absolute evaluation of risk, and differences between individuals on the evaluation of risk in relation to benefit to themselves.

It is also the case that some risks, though known to exist, are, in practice, ignored other than by conforming to ordinary prudent conduct, e.g. the employment of competent electricians and gas fitters in the home, looking before crossing the road, not accepting a lift in a friend's car if he is drunk. In the case of public transport the acceptance of monopoly is not generally felt to pose serious safety issues since the risks are so remote in even a relatively inefficient organisation. In the case of air travel in the U.K. there are about two fatalities per million flights, and in the U.S.A. and Australia one fatality per million flights; the worldwide figure is 3–4 fatalities per million flights*. There can be few passengers who seek out the figures for individual air lines and take them into account before making a booking. The reason for this is that the risks of flying by any reasonably reputable airline are so small as to be ignored by ordinary people, i.e. *the risks are negligible in the sense that they do not influence behaviour*. Also, it only needs one or two big plane crashes to alter the safety ranking of the airlines.

In general it has been suggested that, in medical cases, concern ceases when risks fall below about 1 in 100,000 so that then the procedure becomes regarded as "safe"*. In such cases, when disaster occurs, it can be difficult indeed for the individual to accept that he "deliberately" took a risk; he feels "it should not have happened to him" and in his distress he may seek to lay blame on others where there is no fault or negligence, only misfortune.

The benefits of chemicals used to colour food verge on or even attain negligibility; yet our society, on somewhat weak evidence, considers the risks are also neglibible since it permits their use. A widely used food colour, tartrazine, is known to cause an allergy (asthma) in man. It is unnecessary, but it continues to be used.

The benefits of oral contraceptives and of penicillin are undoubted and the risks are equally undoubted and have been measured, and their use continues and expands because the benefits outweigh the risks.

In no countries are the risks of heroin dependence acceptable, but in all countries the risks of tobacco are acceptable or, at least, accepted. Deaths from uncontrolled tobacco dependence far exceed those of therapeutic agents and of road transport.

The risks of drugs have become a major topic of public and medical

* Ash, P. J. N. *et al.* (1976). *Community Health*, **8**, 29.

concern over the last twenty years, and this concern, often amounting to alarm, has accelerated since the thalidomide disaster of 1960–61 which provided an exceptionally dramatic demonstration of the worst that drugs can do.

There is general agreement that drugs prescribed for disease are themselves the cause of a serious amount of disease (adverse reactions), of death, of permanent disability, of recoverable illness and of minor inconvenience. Adverse ractions are considered in general here and in detail throughout the book and in Chapter 9 where an attempt is made to bring order into this multifarious area.

The amount of drug-induced disease in the community: adverse reactions to drugs

Since drugs are intended to relieve suffering it may be felt peculiarly offensive that they can also cause disease. Therefore it is important to know how much disease they do cause and why they cause it, so that preventive measures can be taken wherever possible.

It is not enough to measure the rate of adverse reactions to drugs, their nature and their severity, though accurate data on these are obviously useful. It is necessary to take, or to try to take, into account which effects are avoidable (by skilled choice and use) and which unavoidable (inherent in drug or patient). Also, different adverse effects can matter to a different degree to different people. In addition, prescribing patterns can vary greatly from one region of a country to another and there are substantial differences between countries.

Since there can be no hope of eliminating all adverse effects of drugs it is necessary to evaluate patterns of adverse reaction against each other. One drug may frequently cause minor ill-effects but be safe as far as life is concerned, though patients do not like it and may take it irregularly, to their own detriment. Another drug may be pleasant to take so that patients take it consistently, with benefit, but it may rarely kill someone. It is not obvious which drug is to be preferred.

Some patients, e.g. those with a past history of allergy or previous reactions to drugs, are up to 4 times more likely to have another drug reaction so that the incidence does not fall evenly on the population taking a drug.

It is also useful to discover the causes of adverse reactions, where these are unknown, for such knowledge can be used to render what are at present unavoidable reactions avoidable.

Avoidable adverse effects will be reduced by more skilful prescribing and this means that doctors, amongst all the other claims on their time, must find time better to understand drugs, as well as to understand their patients and their diseases.

Estimates of the incidence and severity of adverse reactions to drugs are various, for reliable data are hard to get.

But difficulties start with the definition of an adverse reaction (ob-