INTERNATIONAL STUDENT EDITION

PHARMACOLOGY

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Third Edition

CHURCHILL LIVINGSTONE

PHARMACOLOGY

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PHARMACOLOGY

We dedicate this book to the memory of Professor H. O. Schild. Under his authorship the textbook Applied Pharmacology, the predecessor of the present book, set a standard we have tried to maintain.

For Churchill Livingstone

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Preface

For this third edition, as in the previous two, our approach has been not only to describe what drugs do but to emphasise the mechanisms by which they act – where possible at the cellular and molecular level. Therapeutic agents have a high rate of obsolescence and many are replaced each year; an appreciation of the mechanisms of action of the class of drugs to which a new agent belongs provides a good starting point for understanding and using the new compound intelligently.

In this edition, the clinical aspects of the book have been strengthened by the addition of a clinical pharmacologist as the third author. Furthermore, the therapeutic use of drugs has been given prominence by setting it out in easily identified pink 'clinical boxes'.

All chapters have been updated. As regards new material, we have taken into account not only new agents but also recent extensions of basic knowledge which presage further drug development. There are now new chapters on nitric oxide and on neurodegenerative disease and its treatment and there has been major revision of the sections on cardiovascular pharmacology, drugs acting on 5-HT-receptors, drug interactions, growth factors and cytokines, drug toxicity, and the course of HIV infection and approaches to its treatment. The sections on the general principles of how drugs act and on receptor pharmacology and signal transduction mechanisms have been updated and extended. As before, we have included chapters on measurement in pharmacology and on CNS transmitters as a basis for understanding the actions of drugs on the CNS. In addition, we have emphasised information which sheds new light on the aetiology and treatment of peptic ulcer, cyclo-oxygenases and the action of NSAIDs, and the biology of cancer, since there may well be a change in therapeutic practice in the first of these and rapid progress in new drug development in the latter two.

Inappropriate immune and inflammatory responses are involved in many if not most of the diseases which the clinician will meet, and the development of drugs to control these processes is a major concern of the pharmaceutical industry. Students of both pharmacology and medicine need to be aware of recent progress in these fields and we have therefore updated the sections on inflammation and allergy.

We have again incorporated short sets of key points, set off in red-outlined boxes throughout the text. These are not intended to be comprehensive summaries but rather to highlight pharmacological information which we consider important. We feel that inclusion of these boxes is of value because, with factual knowledge in pharmacology so extensive and expanding so rapidly, students can easily find the information load daunting.

As before, we have put emphasis on the chemical structures of those drugs for which knowledge of structure/activity relationships enhances appreciation of how the drugs act, and we have omitted many chemical structures which do not add to pharmacological understanding in favour of diagrams which do.

Pharmacology is a lively scientific discipline in its own right, with an importance beyond that of providing a basis for the use of drugs in therapy. We have therefore, where appropriate, included brief coverage of the use of drugs as probes for elucidating cellular and physiological functions, even when the compounds have no clinical uses.

It was gratifying to find that many readers found helpful the short summaries of relevant physiological and biochemical processes which we had placed at the beginning of many chapters to form a basis for the subsequent discussion of pharmacological actions; we have therefore retained and updated these. To cater for graduate students and university teachers who apparently found the previous editions

useful, we have included fairly extensive sections on 'References and further reading' at the end of each chapter.

We are grateful to the readers who have written appreciative letters about the book and particularly to those who made constructive comments, which we have done our best to incorporate. Comments on the new edition will be welcome.

London 1995

H. P. Rang
M. M. Dale
J. M. Ritter

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GENERAL PRINCIPLES

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Pharmacology can be defined as the study of the manner in which the function of living systems is affected by chemical agents. It is a rather young science, having first achieved independent recognition at the end of the nineteenth century in Germany. Long before this, of course, medical remedies based on herbs were in widespread use, but there was a surprising reluctance to apply anything resembling scientific principles to therapeutics. Even Robert Boyle, who laid the scientific foundations of chemistry in the middle of the seventeenth century, was content, when dealing with therapeutics (*A Collection of Choice Remedies*, 1692), to describe and recommend a hotchpotch of messes consisting of worms, dung, urine and the moss from a dead man's skull. It may be said, indeed, that therapeutics was scarcely influenced by science until the mid-nineteenth century, at which date Virchow dismissed the subject thus: 'Therapeutics is in an empirical stage cared for by practical doctors and clinicians, and it is by means of a combination with physiology that it must rise to be a science, which today it is not.' At that time, knowledge of the normal and abnormal functioning of the body was simply too incomplete to provide even a rough basis for understanding drug effects; at the same time there was a strong feeling that disease and death were semi-sacred subjects, appropriately dealt with by authoritarian, rather than scientific, doctrines. The history of malaria treatment shows how clinical practice could display an obedience to authority, and ignore what appear to be easily ascertainable facts. Cinchona bark was recognised as a specific and effective treatment, and a sound protocol for its use was laid down by Lind in 1765. In 1804, however, Johnson stated, on the basis of clinical practice in India, that cinchona bark was unsafe until the fever had subsided, and he recommended instead the use of large doses of calomel in the early stages. This advice, though murderous in practice, was generally acted upon for the next 40 years.

DRUGS IN MEDICINE

Repeated attempts were made to construct systems of therapeutics, many of which produced even worse results than pure empiricism. One of these was *allopathy*, espoused by James Gregory (1735–1821). The favoured remedies included blood-letting, emetics and purgatives, and these were used until the dominant symptoms of the disease were suppressed. Many patients died from such treatment, and it was in reaction against it that Hahnemann introduced the practice of *homoeopathy* in the early nineteenth century. The guiding principles of homoeopathy are:

- like cures like
- activity can be enhanced by dilution.

The system rapidly drifted into absurdity: for example, Hahnemann recommended the use of drugs at dilutions of $1:10^{60}$, equivalent to 1 molecule in a sphere the size of the orbit of Neptune.

Many other systems of therapeutics have come and gone, and the variety of dogmatic principles that

they embodied have tended to hinder rather than advance scientific progress.*

Drugs have, for many years, been the most widely used form of therapeutic intervention available to doctors. Reliance on natural products, mainly from plants, predominated until, in the 1920s, synthetic chemicals were first introduced, and the modern pharmaceutical industry began to develop. Natural products are still important in some fields, notably chemotherapy (Ch. 35), but new synthetic chemicals are now the main source of new drugs. The last decade has seen the rapid emergence of biotechnology as a source of new therapeutic agents in the form of antibodies, enzymes and various regulatory proteins, including hormones, growth factors and cytokines. Very recently, the first human trials of gene therapy have begun, in which DNA is introduced into the genome of cells with the aim of correcting specific genetic or pathological defects (see Tolstoshev 1993). This trend will undoubtedly increase (see Weatherall 1991). The dividing line between these approaches and pharmacologically based therapeutics is an arbitrary one. In this book, only passing reference is made to biotechnologically based therapeutics.

Scientific understanding of drug action—the kind of understanding that enables us to predict the pharmacological effects of a novel chemical substance, or to design a chemical that will produce a specified therapeutic effect—is growing rapidly, but is still far from complete. Even so, certain generalisations are possible, and these are discussed in this chapter.

*Therapeutic systems whose basis lies outside the domain of science are, of course, very much alive today, and they are even gaining ground under the general banner of 'alternative' or 'holistic' medicine. Mostly they reject the 'medical model' which attributes disease to an underlying derangement of normal function which can be defined in biochemical or structural terms, detected by objective means, and influenced beneficially by appropriate chemical or physical interventions. They focus instead mainly on subjective malaise, which may be disease-associated or not. Abandoning objectivity in defining and measuring disease goes along with a similar departure from scientific principles in assessing therapeutic efficacy, with the result that principles and practices can gain acceptance without satisfying any of the criteria of validity that would convince a critical scientist, and that are required by law to be satisfied before a new drug can be introduced into therapy. As with electric hand-dryers, public acceptance has little to do with demonstrable efficacy; this is perhaps to be expected in a market economy.

To begin with, we should gratefully acknowledge Paul Ehrlich for insisting early in this century that drug action should be understood in terms of conventional chemical interactions between drugs and tissues, and for dispelling the idea that the remarkable potency and specificity of action of some drugs put them somehow out of reach of chemistry and physics and required the intervention of magical 'vital forces'. Although it is the case that many drugs produce actions in doses and concentrations so small that the dimensions assume an almost astronomical remoteness, low concentrations still involve very large numbers of molecules. Thus one drop of a solution of a drug at only 10^{-10} mol/l still contains about 10^{10} drug molecules, so there is no mystery in the fact that it may produce an obvious pharmacological response. Some bacterial toxins (e.g. diphtheria toxin) act with such precision that a single molecule taken up by a target cell is sufficient to kill it.

THE BINDING OF DRUG MOLECULES TO CELLS

One of the basic tenets of pharmacology is that drug molecules must exert some chemical influence on one or more constituents of cells in order to produce a pharmacological response. In other words, drug molecules must get so close to the molecules of which cells are made that the functioning of the cellular molecules is altered. Of course, the molecules in the organism vastly outnumber the drug molecules and if the drug molecules were merely distributed at random, the chance of interaction with any particular class of cellular molecule would be negligible. Pharmacological effects therefore require, in general, the non-uniform distribution of the drug molecule within the body or tissue, which is the same as saying that drug molecules must be 'bound' to particular constituents of cells and tissues in order to produce an effect. Ehrlich summed it up thus: '*Corpora non agunt nisi fixata*' (in this context, 'A drug will not work unless it is bound').*

*There are actually, if one looks hard enough, several exceptions to Ehrlich's dictum, drugs which act without being bound to any tissue constituent (for example osmotic diuretics, osmotic purgatives, antacids, heavy metal chelating agents). The principle remains true for the great majority, however.

Understanding the nature of these binding sites, and the mechanisms by which the association of a drug molecule with a binding site leads to a physiological response, constitutes the major thrust of pharmacological research. Most drugs produce their effects by binding, in the first instance, to protein molecules. There may be some exceptions to this. For example, the group of non-specific depressant substances, to which many general anaesthetics belong (see Ch. 26), have long been thought to produce their effects by an interaction with membrane lipid rather than with protein, though even this cherished theory is under strong attack from the protein lobby (see Franks & Lieb 1987). Apart from this, the only important exception to proteins as target sites is DNA, on which a number of antitumour and antimicrobial drugs act (Ch. 35), as well as mutagenic and carcinogenic agents (Ch. 43).

Protein targets for drug binding

Four kinds of regulatory proteins are commonly involved as primary drug targets, namely:

- enzymes
- carrier molecules
- ion channels
- receptors.

A few other types of protein (e.g. structural proteins such as tubulin, which specifically binds **colchicine**; Ch. 12) are known to function as drug targets, and it must be remembered that there exist many drugs whose sites of action have not yet been analysed in detail. Furthermore, many drugs are known to bind (in addition to their primary targets) to plasma proteins (see Ch. 4), as well as to cellular constituents, without producing any obvious physiological effect. Nevertheless, the generalisation that most drugs act on one or other of the four types of protein listed above serves as a good starting point.

Further discussion of the mechanisms by which such binding leads to cellular responses is given in Chapter 2.

A note on terminology

The term *receptor* tends to be used loosely, and can cause confusion. Some authors use it to mean *any* target molecule with which a drug molecule has to combine in order to elicit its specific effect, which can include any of the four types listed. Thus, the voltage-sensitive sodium channel of excitable membranes is sometimes referred to as the 'receptor' for local anaesthetics (see Ch. 34), or the enzyme dihydrofolate reductase as the 'receptor' for **methotrexate** (Ch. 36). In each case the drug molecule combines with and incapacitates the protein molecule, thus producing its effect. This is different from the situation where, for example, adrenaline acts on a receptor in the heart (see Ch. 7). In this case, the receptor molecule has no other function but to serve as a recognition site for catecholamines. When adrenaline binds to the receptor, a train of reactions is initiated (see Ch. 2), leading to an increase in force and rate of the heartbeat. The receptor produces an effect only when adrenaline is bound; otherwise it is functionally silent.* This, in general, is true of all hormone and neurotransmitter receptors. In this context, certain substances (*agonists*) can be said to 'activate' the receptors, and others (*antagonists*) may combine at the same site without causing activation. Receptors of this type form a key part of the system of chemical communication that all multicellular organisms use to coordinate the activities of their cells and organs. Without them we would be no better than a bucketful of amoebae. The distinction between agonists and antagonists only exists for receptors with this type of physiological regulatory role; we cannot usefully speak of 'agonists' for the noradrenaline carrier or for the voltage-sensitive sodium channel or for dihydrofolate reductase. In pharmacology it is best to reserve the term 'receptor' for interactions of the regulatory type, where the small molecule (*ligand*) may function either as an agonist or as an antagonist; in practice this limits use of the term to receptors which have a physiological regulatory function, and this usage will be observed in this book.** More details about the molecular nature of receptors, and the ways in which they influence cell function, are given in Chapter 2.

*Actually some receptors, such as the benzodiazepine receptor (Ch. 27) show resting activity, which can be either increased or decreased when a ligand molecule binds.

**We break our own rule in Chapter 15 by referring to the 'LDL receptor', a term in common usage to describe a macromolecule—not strictly a receptor according to our definition—which plays a key role in lipoprotein metabolism.

DRUG SPECIFICITY

For a drug to be in any way useful as either a therapeutic or a scientific tool, it must act selectively on particular cells and tissues. In other words it must show a high degree of *binding-site specificity*. Conversely, proteins that function as drug targets generally show a high degree of *ligand specificity*; they will recognise only ligands of a certain precise type, and ignore closely related molecules.

These principles of binding-site and ligand specificity can be clearly recognised in the actions of a mediator such as angiotensin (Ch. 14). This peptide acts strongly on vascular smooth muscle, and on the kidney tubule, but has very little effect on other kinds of smooth muscle, or on the intestinal epithelium. Other mediators affect a quite different spectrum of cells and tissues, the pattern in each case being determined by the specific pattern of expression of the protein receptors for the various mediators. On the other hand, a small chemical change, such as conversion of one of the amino acids in angiotensin from L- to D-form, or removal of one amino acid from the chain, can inactivate the molecule altogether, since the receptor fails to bind the altered form. The complementary specificity of ligands and binding sites is central to explaining many of the phenomena of pharmacology. One of the most exciting themes at the present time is the increasing understanding of protein structure and its relation to the remarkable powers of molecular recognition that many proteins (and particularly drug targets) possess. It is no exaggeration to say that the ability of proteins to interact in a highly selective way with other molecules—including other proteins—is the basis of living machines. Its relevance to the understanding of drug action will be a recurring theme in this book.

Finally, it must be emphasised that no drug acts with complete specificity. Thus histamine antagonists (Ch. 12), although they can be shown to have a higher affinity for histamine receptors than for other sites, produce many effects, such as sedation and prevention of vomiting, which do not appear to depend on histamine antagonism. In general, the lower the potency of a drug, and the higher the dose needed, the more likely it is that sites of action other than the primary one will assume significance. In clinical terms, this is often associated with the appearance of unwanted side effects, of which no drug is free.

The main thrust of pharmacological research in recent years has been to characterise, in molecular terms, the primary site of action of many different types of drug. The success of this approach has illuminated the mode of action of several important drugs whose actions were until recently not understood at all, only described. **Aspirin** is one example where, thanks to the work on prostaglandins by Vane and his colleagues (see Ch. 11), a multitude of apparently unrelated effects can now be explained in terms of inhibition of a single group of enzymes responsible for converting arachidonic acid to prostanoids. Similarly, the **benzodiazepines**, an important group of minor tranquillisers, are now known to act on specific sites in the brain, thereby potentiating the action of an inhibitory neurotransmitter (gamma-aminobutyric acid; see Ch. 24); the action of **morphine-like analgesics** (Ch. 31) has also been narrowed to specific receptor sites for these drugs, whose actions had been described in exhaustive physiological detail many years previously without any real insight into mechanism having been achieved.

Targets for drug action

- A drug is a chemical that affects physiological function in a *specific way*.
- Most drugs are effective because they bind to particular target proteins, namely:
  —enzymes
  —carriers
  —ion channels
  —receptors.
- Specificity is reciprocal: individual classes of drug bind only to certain targets, and individual targets recognise only certain classes of drug.
- No drugs are completely specific in their actions. In many cases, increasing the dose of a drug will cause it to affect targets other than the principal one, and lead to side effects.

RECEPTOR CLASSIFICATION

Where the action of a drug can be construed in terms of its combination with a special type of receptor, this provides a valuable means for classification and refinement in drug design. For example,

by the mid-1960s, analysis of the numerous actions of histamine (see Ch. 11) showed that some of its effects (the H_1 effects, such as smooth muscle contraction) were strongly antagonised by the competitive histamine antagonists then known. Black and his colleagues, in 1970, suggested that the remaining actions of **histamine**, which included its powerful stimulant effect on gastric secretion, might represent a second class of histamine receptor. They tested this theory by preparing histamine analogues, some of which showed selectivity in stimulating gastric secretion while having only a weak effect on smooth muscle. By seeing which parts of the histamine molecule conferred this type of specificity, they were able to develop selective antagonists. Such antagonists proved to be potent in blocking gastric acid secretion and all of the other effects now classified as H_2 effects. A third type of histamine receptor (H_3) has recently been defined.

This example illustrates the principle of receptor classification based on pharmacological criteria—receptors being classified on the basis of the effects of particular drugs—which continues to be a valuable and widely-used approach. In recent years, however, new experimental approaches have revealed several different criteria on which to base receptor classification. The first of these was the direct measurement of ligand binding to receptors (see p. 13), which allowed many new receptor subclasses to be defined—subclasses only very dimly discernible from studies of drug effects. More recently, molecular cloning has revealed the amino acid sequence of many receptors (see Ch. 2), providing a completely new basis for classification at a much finer level of detail than can be reached through pharmacological analysis. Finally, analysis of the biochemical pathways that are activated in response to receptor activation (see Ch. 2) shows patterns that provide yet another basis for classification. The result of this data explosion has been that receptor classification has suddenly become very much more detailed, with a proliferation of receptor subtypes for all of the main types of ligand; more worryingly, alternative molecular and biochemical classifications began to spring up which were incompatible with the accepted pharmacologically defined receptor classes. Responding to this growing confusion, the International Union of Pharmacological Sciences (IUPHAR) has set up various expert working groups to produce agreed receptor classifications for the major types, taking into account the pharmacological, molecular and biochemical information available. These wise men have a hard task, and the results will be neither perfect nor final, but are essential to ensure a consistent terminology. To the student, this may seem an arcane exercise in taxonomy, generating much detail but little illumination; the tedious lists of drug names, actions and side effects that used to burden the subject are in danger of being replaced by exhaustive tables of receptors, ligands and transduction pathways. In this book, we have tried to avoid detail for its own sake, and include only such information on receptor classification as seems interesting in its own right, or is helpful in explaining the actions of important drugs. A useful summary of known receptor classes is now published annually (*Trends in Pharmacological Sciences, Receptor Supplement*).

QUANTITATIVE ASPECTS OF DRUG–RECEPTOR INTERACTIONS

An excellent account of the quantitative analysis of drug–receptor interactions is available for those seeking more detail than is given here (Kenakin 1987).

The first step in drug action on specific receptors is the formation of a reversible drug–receptor complex, the reactions being governed by the Law of Mass Action. Suppose that a piece of tissue, such as heart muscle or smooth muscle, contains a total number of receptors N_{tot}, for an agonist such as adrenaline. When the tissue is exposed to adrenaline at concentration x_A and allowed to come to equilibrium, a certain number N_A of the receptors will become occupied, and the number of vacant receptors will be reduced to $N_{tot} - N_A$. Normally the number of adrenaline molecules applied to the tissue in solution greatly exceeds N_{tot}, so that the binding reaction does not appreciably reduce x_A. The magnitude of the response produced by the adrenaline will be related (even if we do not know exactly how) to the number of receptors occupied, so it is useful to consider what quantitative relationship is predicted between N_A and x_A. The reaction can be represented by:

$$\underset{\substack{\text{drug}\\(x_A)}}{\text{A}} + \underset{\substack{\text{free receptor}\\(N_{tot}-N_A)}}{\text{R}} \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} \underset{\substack{\text{complex}\\(N_A)}}{\text{AR}}$$

The Law of Mass Action (which states that the

rate of a chemical reaction is proportional to the product of the concentrations of reactants) can be applied to this reaction.

$$\text{Rate of forward reaction} = k_{+1}x_A(N_{tot} - N_A) \quad (1.1)$$

$$\text{Rate of backward reaction} = k_{-1}N_A \quad (1.2)$$

At equilibrium the two rates are equal:

$$k_{+1}x_A(N_{tot} - N_A) = k_{-1}N_A \quad (1.3)$$

The proportion of receptors occupied or 'occupancy', $p_A = N_A/N_{tot}$, which is independent of N_{tot}, is:

$$p_A = \frac{x_A}{x_A + k_{-1}/k_{+1}} \quad (1.4)$$

Defining the equilibrium constant for the binding reaction, $K_A = k_{-1}/k_{+1}$, equation (1.4) can be written:

$$p_A = \frac{x_A}{x_A + K_A} \text{ or } p_A = \frac{x_A/K_A}{x_A/K_A + 1} \quad (1.5)$$

This important result is known as the *Langmuir equation*, after the physical chemist who derived it to describe the adsorption of gases by metal surfaces.*

The equilibrium constant, K_A, is a characteristic of the drug and of the receptor; it has the dimensions of concentration and is numerically equal to the concentration of drug required to occupy 50% of the sites at equilibrium. (Verify from equation (1.5) that when $x_A = K_A$, $P_A = 0.5$.) The higher the *affinity* of the drug for the receptors, the lower will be K_A. Equation (1.5) describes the relationship between occupancy and drug concentration, and generates a characteristic curve known as a *rectangular hyperbola*, as shown in Figure 1.1A. It is common in pharmacological work to use a logarithmic scale of concentration; this converts the hyperbola to a symmetrical sigmoid curve (Fig. 1.1B).

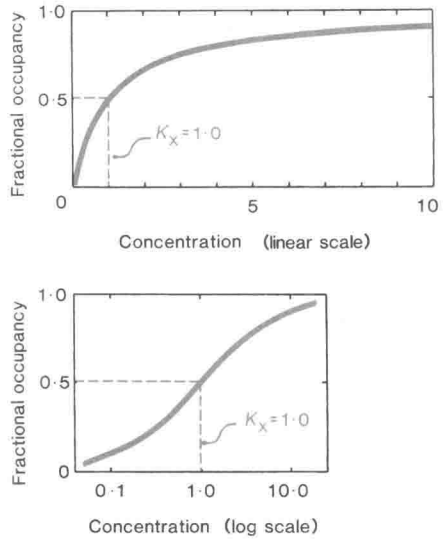

Fig. 1.1 Theoretical relationship between occupancy and ligand concentration, plotted according to equation (1.5). A. Plotted with a linear concentration scale, this curve is a rectangular hyperbola. **B.** Plotted with a logarithmic concentration scale, this is a symmetrical sigmoid curve.

AGONIST CONCENTRATION–EFFECT CURVES

It is now possible to measure directly the binding of drugs to their receptors in tissues (see p. 13) and to show that equation (1.5) is obeyed. Much more often it is a biological response, such as a rise in blood pressure, contraction or relaxation of a strip of smooth muscle in an organ bath, or the activation of an enzyme, that is actually measured and plotted as a *concentration–effect* or *dose–response curve*, as in Figure 1.2. These look similar to the theoretical concentration–occupancy curves in Figure 1.1B, and it is tempting to try to use such experimental curves to measure the affinity of agonist drugs for their receptors by making the assumption that the response produced is directly proportional to occupancy. This is, however, rarely valid, for in general the response is a complex, non-linear function of occupancy. For an integrated physiological response, such as a rise in arterial blood pressure produced by adrenaline, several different processes interact. **Adrenaline** (see Ch. 7) increases cardiac output and constricts some blood vessels while dilating others, and the change in arterial pressure itself evokes a reflex response which modifies the primary response to the drug. It is obviously unrealistic to expect that the final effect will be directly proportional to occupancy in this instance, and the same is true of most drug-induced effects.

A second difficulty in drawing inferences about agonist affinity from concentration–effect curves is

*It should actually have been named after A V Hill, the physiologist who derived it in 1909, but so many equations bear his name that it would be excessive to insist on adding another.