Pharmacology

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Preface

This book is intended primarily for preclinical medical students and science students studying pharmacology, but clinicians who wish to brush up their basic science and scientists in other disciplines who want to get an overall grasp of pharmacology may find it useful.

It is the successor to '*Applied Pharmacology*' by H O Schild and has developed out of it. Both authors were students under Heinz Schild and in writing the present book we have had very much in mind his approach to pharmacology. However, because of the developments in the subject and in the biological sciences in general, we felt it apposite not just to update his text but to rewrite it. We have reduced somewhat the element of clinical pharmacology in view of the fact that this material is best dealt with when students have had some experience of clinical medicine and because there are now many excellent textbooks on clinical pharmacology. Consequently we have abandoned the title '*Applied Pharmacology*' in favour of '*Pharmacology*', the subject being defined as 'the study of the effects of chemical substances on living tissue'. Inherent in this definition is the fact that pharmacology is not synonymous with clinical pharmacology; it provides the clinician with the agents used in therapeutics and with the understanding of how they work, but it is concerned not only with drugs used in treatment but also with drugs used as investigatory tools. With this definition in mind we have concentrated on pharmacodynamics and pharmacokinetics, and in the context of the former we have stressed *mechanisms* of action, believing that if an individual understands more of *how* a drug works he or she will use it more intelligently in the clinic or laboratory. In addition to dealing with drugs as such, we have placed emphasis on 'mediators', since understanding the body's method of controlling its own functions is a route not only to the understanding of how exogenous chemical substances affect it but also to the rational development of new drugs. Descriptions of peripheral neurotransmitters such as acetylcholine and noradrenaline, of hormones such as hydrocortisone, and of inflammatory mediators such as histamine, have always formed part of pharmacology textbooks and it is well known that investigation of the actions and structure/activity relationships of these substances has led to the development of valuable drugs for the clinician. We have carried this approach a little further, with an eye on future developments. Thus, in the sections on the central nervous system we have included discussions of various CNS neurotransmitters and neuromodulators (GABA, glutamate, neuropeptides, etc), and their possible significance in some clinical disorders, even though useful drugs that are known to act by affecting the metabolism or actions of these mediators have yet to emerge. Similarly we have included brief descriptions of inflammatory mediators such as platelet activating factor and interleukin-I and their possible role in conditions such as asthma and rheumatoid arthritis. Drugs used in inflammation and as immunosuppressives form an important part of the therapeutic armamentarium and an appreciation of how they act and how new drugs in this area are likely to be developed requires some knowledge of what happens in inflammation. Since pathology and immunology generally come later in the medical course than pharmacology, and since pharmacology students generally do not study these subjects at all, we have included a brief outline of the main events in the inflammatory and immune responses.

While making it clear that any mistakes in the book are our own, we would like to acknowledge help and advice from the following people: Dr J G Blackman, Dr D G Haylett, Isobel Heyman, Dr D M James, Dr I F James, Prof. J Mandelstam, Dr R Pitt-Rivers and Dr G Robinson. In particular we wish to acknowledge the invaluable help of Janet Martin, who drew all the diagrams and Marie-Claire Stuart, Annabel Giles and Joyce Mancini who prepared the text.

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SECTION ONE

General principles

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Mechanisms of drug action

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 (1692), who laid the scientific foundations of chemistry in the middle of the seventeenth century, was content when dealing with therapeutics, 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 the knowledge of the normal and abnormal functioning of the body were 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 recognized 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 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.

SYSTEMS OF 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**, which was espoused by James Gregory (1735–1821). The favourite remedies were 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 (a) that like cures like, and (b) that 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 one molecule in a sphere the size of the orbit of Neptune. Many other systems of therapeutics have come and gone, but the variety of dogmatic principles that they embodied has tended to hinder rather than advance scientific progress. Scientific understanding of drug action—the kind of understanding that enables us to predict what pharmacological effects a novel chemical substance is likely to produce, or to design a chemical that will produce a specified therapeutic effect—is still extremely patchy. To get to the root of how the intrusion of a particular chemical substance affects the functioning of any given cell or organ obviously requires a detailed knowledge of the normal biochemical and physiological machinery, and it must be remembered that physiology only began to be studied intensively about 100 years ago, and biochemistry only about 50 years ago. Even so, from the plethora of experimental data on drug action amassed in the last 50 years or so, certain generalizations emerge, and these are discussed in this chapter.

To begin with we should gratefully acknowledge Paul Ehrlich (1913) for insisting 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} M 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 approach the molecules of which cells are made sufficiently closely 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 an interaction with any particular class of cellular molecule would be negligible. Pharmacological effects therefore require, in general, the non-uniform distribution of the drug molecules 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'). A consideration of the different types of drug binding leads us to a useful general classification of drug action which is valid, even though for most drugs we have little or no information about the molecular details of the binding process.

To get an appreciation of the range of possibilities in the binding of drug molecules, let us consider examples at two extremes, namely **ethanol** and **histamine** (an endogenous amine released locally from damaged tissues) which are about as different as two drugs can be, in four general respects:

1. *Potency*. Most effects of histamine are produced in concentrations ranging from about 10^{-8} to 10^{-5} M, whereas ethanol is effective at concentrations ranging from about 10^{-2} to 10^{-1} M in body fluids. The legal limit for driving a car (80 mg/100 ml blood) corresponds to about 18 mM ethanol. On a molar basis, the difference in potency between ethanol and histamine is thus about five or six orders of magnitude. The high potency of histamine is by no means exceptional in pharmacology: drugs which act at concentrations of about 10^{-9} M are quite common and there are reliable reports of effects produced at 10^{-11}–10^{-12} M (for example, the action of serotonin on mollusc hearts, and the action of peptides such as angiotensin on vascular smooth muscle).

2. *Biological specificity*. Histamine has a number of pharmacological actions, but it may produce opposite effects on apparently similar tissues, and it is without observable effects on many more. Thus it causes a powerful contraction of bronchial smooth muscle, but a relaxation of vascular smooth muscle, stimulating gastric secretion, but not salivary secretion. In contrast ethanol produces a more or less similar inhibitory effect on most cells and tissues. The physiological effects of alcohol may be highly complex but at a cellular level its actions are rather uniform, whereas those of histamine are highly selective, in the sense that its actions are confined to a few specific cell types.

3. *Chemical specificity*. Changes in the chemical