Molecular foundations of drug–receptor interaction

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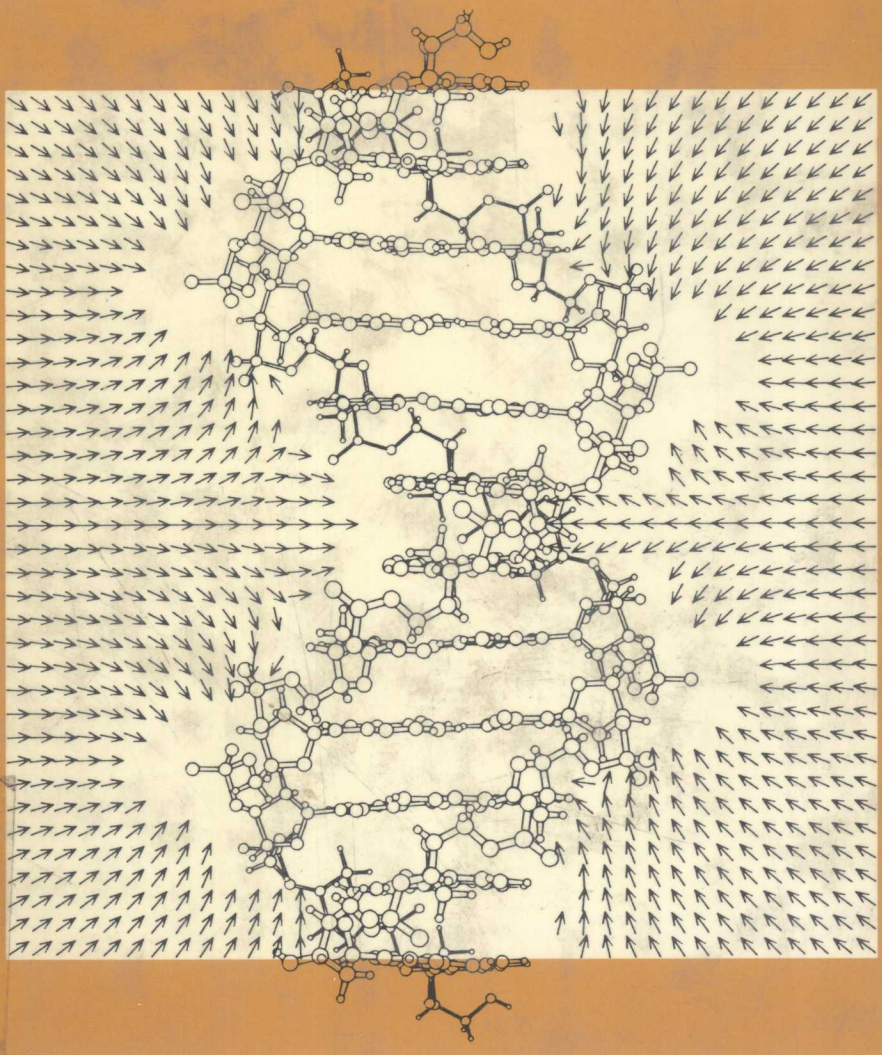

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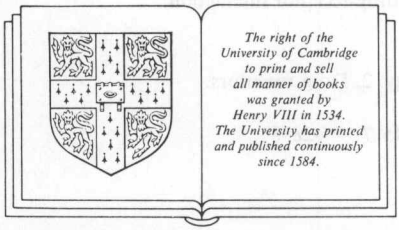

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PREFACE

In the beginning, before *Molecular Foundations* was formed, a meeting with the Biological Sciences Editor of Cambridge University Press was held to discuss possible approaches to the subject. The editor explained that she did not require either another standard text on molecular pharmacology or a catalogue of facts and chemical formulae compiled into a massive scientific 'Bible'.

'We are in the computer age now and it is time there was a book dealing with molecular pharmacology to reflect this', she finally stated.

The principal objective of this book, therefore, has been to draw together those strands of research, carried out since 1970, that widen our understanding of the molecular details of drug–receptor interaction. Hopefully, the book is more substantial than an introduction, but it is not an exhaustive treatment of the subject. Only what I consider to be primary material is surveyed here; much detailed background literature has not been handled. Technical items can be found by returning to the original papers cited in the references. Part of this material has been used in Part 2 of the Natural Sciences Tripos (Pharmacology) and so could be useful as an advanced undergraduate textbook. However, most of the book is of more specialist interest and should appeal to research scientists working in the wider field of biomolecular interactions.

One of the major difficulties in writing a book to the brief that it must be modern and up to date, lies in the limitation that the research one has to consider is of necessity novel, speculative and largely untested. The writer has to run the risk, if he includes contemporary material, of drawing attention to work which may, at a later date, prove to be unreliable. Nevertheless, research is a restless occupation and there is much to be said for propagating the stimulus of new ideas to provoke further thought, so that out of the melting pot of controversy these ideas can be refined to stand the test of time.

The main thrust of this book is to shift the emphasis away from phenomenological experiments of pharmacology to molecular theory, that is, to move to the place where we can ask questions that are too difficult, or impossible, to answer by conventional experiments. At this level of questioning we can only construct hypotheses based on molecular theory and provide computational simulations to test our ideas. For example, we cannot measure the molecular electrostatic potential in the cleft of a drug binding site but, given the atomic charges obtained from a quantum chemistry calculation, we can compute the potential and make some deductions from those computations about drug action and specificity. How could we test our prediction of the value of the potential? In this brave new world of computational chemistry there are many pitfalls to trip the unwary. Rash generalizations from limited data can be very tempting when most calculations deal only with simulating the *in vacuo* state and neglect the solvent environment. It is easy to get drunk on enthusiasm about new developments, to be blind to mistakes and to be hypnotized by clever speculation.

The underlying assumption of this book is that it is possible to treat drug–receptor interaction purely as a chemical problem. This problem lies at the heart of pharmacology, but many pharmacologists seem unaware that it is surreptitiously being stolen from them by scientists from other specialist disciplines. A careful perusal of the references at the end of this book reveals that only a small number of pharmacological journals are quoted. Many of the important recent advances are to be found in literature that few pharmacologists would regularly scan. This is due, in part, to the fact that the overwhelming mass of research in pharmacology is, naturally, concerned with how particular drugs act on the body's physiological systems; there seems to be little commitment to understanding what is happening at the molecular level. Current awareness of recent developments in drug–receptor interaction is essential if the molecular nature of the problem is to remain accessible to us as the theoretical basis of pharmacology.

This book is limited to one small step in the chain of events of drug action. Only the very first stage is considered, namely the initial interaction between the drug molecule and its receptor site to form a molecular complex. Biochemical and biophysical consequences that follow from this step are not described since very little is, as yet, clearly understood about them. The initial events can loosely be described as molecular recognition. If recognition can be understood in the precise language of intermolecular forces, there will undoubtedly be important applications of molecular theory to the design of new drug molecules. This theme of recognition

forms a constant undercurrent throughout the book and its link to the rational design of novel ligands is frequently alluded to.

One of the great advantages that an author has when commissioned to write a book is that he is forced to sit down and read through the earlier literature to trace the historical development of his subject. It seems to me that one paper is pre-eminent in laying the molecular foundations of drug–receptor interaction. Sir Arnold Burgen's (1966) concise essay on 'The drug–receptor complex' is almost a manifesto for subsequent investigations, the results of which are now outlined here. What is surprising is that his paper was written before the application of computational chemistry to biomolecular interactions. These new techniques have, since then, simply filled in some of the details of the overall plan.

My own research interests are heavily invested in three chapters written here and so reflect the importance that I personally attach to those areas. Close involvement with one part of a topic may have led me to overemphasize it with respect to other related viewpoints. It is extremely difficult, when one is intimately involved with a subject, to stand at some vantage point and view the whole field impartially; thus I am aware of my own particular perspectives.

Chapter 1 outlines the historical development of theories about drug–receptor interaction beginning with the birth of the receptor concept by Langley and Ehrlich. Major steps in understanding drug action are highlighted over a period of nearly 100 years. This chapter will be familiar to classically trained pharmacologists, but I believe there is little mileage left in this approach which is essentially one of empirically fitting equations to gross measurements of tissue responses. The rest of the book concentrates on molecular details. There is a strong emphasis throughout the text on the need to understand and manipulate three-dimensional molecular structure. Chapter 2 provides some basic mathematical and crystallographic methods for handling molecular architectures. Work in the early 1980s on molecular databases is also outlined to provide the reader with ready access to these new and important facilities. Structural geometry gives rise to different spatial dispositions of intermolecular forces. Chapter 3 examines these forces and deals in detail with some of those that are believed to be crucial in drug–receptor interaction. Quantum chemistry is not dealt with in this book; an excellent treatment of it, and its application to molecular pharmacology, can be found elsewhere (Richards, 1983). If molecular shapes are to be handled by computer programs, methods must be developed to characterize and handle shape in any form (chapter 4). Only certain portions of the molecular receptor are concerned

with ligand binding. Different ways to examine these sites are explored in chapter 5. Most computational models for drug–receptor interaction ignore the solvent environment. This neglect is a substantial defect in current models. The behaviour of solvent molecules over small intermolecular distances is not well understood. What inroads have been made into this complex problem in the physical sciences (chapter 6)? The docking manoeuvre of a drug molecule into its receptor site is illustrated in chapter 7 where emphasis is placed on electrostatic interactions. Practical applications of computational chemistry to the rational design of new drugs are outlined in chapter 8. The final chapter attempts to predict the major avenues along which drug–receptor interaction will progress. Three important developments are already surfacing: protein engineering offers the pharmacologist the ability to re-design the receptor; knowledge engineering draws together key strands from artificial intelligence that are making it possible for new comprehensive and automated techniques to emerge for drug design; new computer hardware will, if the fifth generation project is successful, provide sufficient computing power to make molecular simulations significantly more complex and bring the research on drug–receptor interaction nearer to completeness.

I would like to acknowledge with gratitude the encouragement and financial support given to me over many years by the Wellcome Trust. Without the Trust's generosity it would not have been possible for me to pursue a research career largely unfettered by a heavy academic teaching load. Thanks go to colleagues in the department, and elsewhere in Cambridge, for providing stimulus and a lively environment for the exchange of new ideas. Lastly, but not least, I am indebted to Diana for patiently deciphering my writing for input to the word-processor and then nit-picking through the manuscript to remove many grammatical obscurities.

Cambridge, May 1986. P. M. Dean

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CONTENTS

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The development of theories about drug–receptor interaction

The reading of seminal papers in any scientific discipline, in the cool silence of a good library, is akin to the experience of visiting the cellars of a well-established wine-merchant. The pleasure of tasting the classed growths of Bordeaux in sequence through the years is punctuated at definite and widely recognized intervals by the great vintages. At these points in history the wines are remarkable for their intensity, complexity and finish; they manage to stand the test of time without deterioration. So with drug–receptor interaction, there are extraordinary periods of intellectual growth within the discipline, landmarks in time where developments have held together despite the changing tides of fashion.

For the pharmacologist, drug–receptor interaction is the very heart of his subject; yet despite the centrality of this theory to the practical development of new drugs, surprisingly little is known about the process. Only in the last decade or so, have we been able to characterize the molecular structures of a few receptors. Naturally, the pharmacologist's understanding has lagged behind the evolution of chemical theories of molecular reactions. Only with the advent of high-speed computers has it been possible to apply the rigours of computational chemistry to molecular biological problems. Recent progress in these different research areas has led to a flurry of new work; chemical theories inaccessible to experiment can be evaluated by careful computational simulation. This novel work forms the subject matter of the book. However, we must begin by placing these new ideas within an historical perspective. Ideas do not just happen in isolation, they emerge from a fertile milieu through a process of accretion. Ehrlich described this process as 'a host of individual facts which, being stored at a subconscious level, lead one to take involuntarily the right direction'. (Dale, 1956).

Inevitably, whenever a review of drug–receptor interaction is

contemplated the discussion revolves around the axis of Paul Ehrlich. His astonishing abilities, sheer hard work, and prophetic vision have contributed more to this subject than that of any other worker. In a key paper on structure–activity relationships which Ehrlich published in 1902 he expressed his hopes, his fears and his rationale in these words: 'Hence the expectation to be able to construct new drugs of predetermined action on the basis of theoretical conceptions will probably have to be deferred for a long time. To the initiate, the lack of sufficient positive knowledge is revealed by the inactivity which now characterizes a field once entered upon with so much promise. The innumerable drugs which have overwhelmed medicine in the past few years, of which only a few are of any value and thus denote any real progress, have sufficed speedily to allay the original enthusiasm. A feeling of indifference has thus been engendered, which is constantly being increased by the advertisements which are daily becoming more and more evident. Apart from these evils, however, this line of study is at present suffering especially from two other evils:

(1) The habit, when a drug has been partially accepted, of immediately following it with a dozen rivals of similar composition, and,

(2) The exclusive preference given to drugs acting purely symptomatically, which are not true curative agents.

A change for the better will occur only when purely biological points of view are adopted, ie if the initiative is transferred from the chemical to the biological laboratory. As physicians we must cease to be content with the auxiliary role of advisers in these important questions. In this subject, our very own since time immemorial, we must insist on taking first place. Now is the time that we must turn to more general, biological conceptions, and it is therefore the duty of everyone to contribute his brick to the construction of this new theory.' The cornerstone was destined to be laid by Ehrlich with his notion of receptors.

1.1 The concept of receptors

1.1.1 J. N. Langley

The notion of specific receptors for drug molecules or natural neurotransmitters developed slowly over the course of about 20 years. Two strands in the research can be detected. J. N. Langley, working in Cambridge under the influence of Michael Foster, began his studies of the nervous system linked initially to the mechanism of secretion. His early studies were on the action of the recently discovered cholinomimetic compound jaborandi. The drug stimulated salivary secretion and could be antagonized by atropine (Langley, 1873, 1878). In the discussion of his

1878 paper Langley speculated 'Until some definite conclusion as to the point of action of the poisons is arrived at it is not worth while to theorize much on their mode of action: but we may, I think, without much rashness, assume that there is some substance or substances in the nerve endings or gland cells with which both atropine and pilocarpin are capable of forming compounds. On this assumption then the atropine or pilocarpin compounds are formed according to some law of which their relative mass and chemical affinity for the substance are factors. In the analogous case with inorganic substances, other things being equal, these are the sole factors. To take the simplest case, if *a* and *b* are both able to form, with *y*, the compounds *ay* and *by*, then *ay* and *by* are both formed, the quantity of *ay* and *by* depending on the relative masses of *a* and *b* present and their relative chemical affinity to *y*.' Receptors, antagonism, chemical affinity, drug–receptor complex, all the ingredients for receptor theory are here, but they lay dormant for many years. Meanwhile, the results of these initial findings led to a number of papers on antagonism of various poisons by physiologically active alkaloids (Langley, 1880; Langley & Dickinson, 1890a, b). This research pathway focused on the nerve endings in ganglia, the neuromuscular junction and neural control of secretion.

1.1.2 *P. Ehrlich*

Ehrlich's contribution forms the second strand and was independent of Langley's work; it approached the notion of receptors from a different direction. An early training in the chemistry of dyestuffs provided Ehrlich with a great facility for research in staining biological tissues and he made numerous important contributions to histology. One observation in histology that fascinated Ehrlich was the fact that staining could be specific for a particular tissue. Furthermore, he noted that substances which stain neuronal tissues are lipid soluble. If the lipid solubility of the chromophore group is changed, for example by making a sulphonic acid derivative, although the colour remains the dye is not taken up by the tissue and the biological material is not stained. This simple observation led to the idea that different chemical structures could show different biological distributions and the distribution of a chromophore could be changed by modifying the molecular structure. The possibility that dyestuffs could combine with specific parts of biological tissue was not appreciated for many years because there were many competing theories about the staining process.

Ehrlich's work with dyestuffs had bearing on another idea that was popular at the end of the nineteenth century; this was the emerging notion of affinity. It had been observed that many of the biologically active