THE MOLECULAR BASIS OF ANTIBIOTIC ACTION

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SECOND EDITION

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Preface to the First Edition

In the thirty years which have elapsed since the Second World War there have been many great achievements in medicine and the biological sciences, among which one of the most impressive has been the discovery and development of antibiotics. It is commonplace to remark that antibiotics have revolutionized the treatment of infectious disease, and perhaps equally so to point to their contribution as tools for basic biological research. In both these areas, the remarkable specificity of action of antibiotics has been harnessed to meet a need, for antibiotics have indeed fulfilled the role of 'magic bullets' as originally conceived by Ehrlich. In chemotherapy the magic of the bullets is manifested in selective attack against pathogenic microorganisms. In biological research the magic is no less evident in the use of antibiotics as agents endowed with the capacity to interfere with one or a small number of processes in the complex, integrated reactions of cell metabolism. Small wonder that a knowledge of antibiotic action has become indispensable to the training of medical and biological students.

Most of the antibiotics were discovered before any detailed knowledge was available of the biochemistry underlying their effects. Much of the early work was therefore directed towards uncovering the general sites of action. With the birth and rapid growth of molecular biology it was natural that attempts should be made to elucidate the molecular basis of antibiotic selectivity. Already much has been learned, and it is equally clear that many more important advances lie just around the corner. This book represents an attempt to summarize and take stock of the position to date. There is more to this endeavour than mere curiosity or academic exercise, for it is an axiom of our age that deeper understanding of fundamental biological processes must ultimately be applicable in the service of mankind. In this case a part of the aim must be to improve the efficacy of chemotherapy in medical practice, the philosophy being that a thorough understanding of the nature of such selectivity as is shown by agents known at the present time will help to delineate sites and mechanisms through which selectivity may be achieved, and that, armed with this information, new drugs may be developed to combat disease. In short, the study of the molecular basis of antibiotic action must help to pave the way for a rational approach to

chemotherapy. In this light we have allowed ourselves to indulge in a little reflection and speculation at the beginning and end of the book, including topics such as drug resistance which might not *a priori* be considered relevant to our title. Similarly, we have not slavishly restricted our attention to antibiotics in the strict sense, i.e. substances of natural (microbial) origin, for in several places we felt that the topic could only be satisfactorily treated in context by including discussion of synthetic antimicrobial drugs, and occasionally even substances which are not chemotherapeutic agents at all.

We make no excuses for choosing to write at the present time: we are all too conscious that, if we were to wait a little longer, there would be many more exciting developments to record and the story would be that much more complete. Such will always be the case to some extent, and at the same time the volume of pertinent literature will increase in its relentlessly exponential fashion, requiring a commensurate increase in the number and/or capacity of authors to deal with it. It could fairly be claimed that we are already too late to hope to deal adequately with the relevant material, and to this contention we would be forced to bow. We cannot know everything, and in the course of writing we have become painfully aware of the enormity of the task and our inadequacy to cope with it as we should like. On the other side of the coin, we have been privileged to consult manuscripts and pre-publication material provided by a number of authors, whose interest and help we gratefully acknowledge, and we have occasionally taken the liberty of including unpublished information obtained in our own and other laboratories. In these instances acknowledgment is given in the text. To cope with the potentially enormous number of references worthy of citation we have, in general, adopted the policy of relying on recent reviews to cover the earlier literature and have tried to concentrate on providing references to the most recent and up-to-date original papers. Very often we have reluctantly decided not to give a direct reference to a classic paper when it is treated in reviews. Any errors, omissions, misinterpretations or other infelicities are of course our own responsibility. In attempting to provide a reasonably comprehensive coverage of the field we have, naturally, each written as individuals on those areas in which we 'specialize'. If, as a result, we have failed to achieve uniformity of style and have afforded a ready means of identifying the writers of particular chapters, we shall not complain if we are each held responsible for our own words.

One of our major problems was to decide how much background biochemistry to include. We have not always been consistent but, in general, have assumed knowledge of basic biochemical matters and, where possible, referred the reader to recent reviews for detailed treatment.

Finally, we should like to acknowledge our debt to colleagues in many laboratories, to students, visitors and correspondents who have discussed, argued, criticized and so helped the development of our ideas over the years.

We also want to thank Mrs B. Gill for her invaluable help in assembling and preparing the manuscript.

Cambridge, August 1971

E.F.G.
E.C.
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Preface to the Second Edition

In the nine years that have elapsed since the first edition was written there have, inevitably, been many advances in our knowledge of the ways in which antibiotics work and a vast increase in the number of papers published on relevant topics. New antibiotics have been isolated and characterized. We have not attempted to produce a comprehensive guide to all the antibiotics that have been described but have concentrated on those which have been studied in sufficient detail to throw light on their action at a molecular level. In general, advances of recent years have not revealed totally new principles of action but have led to a greater depth of understanding of the interplay between antibiotic structure and the properties of the cellular target. Consequently we have retained the same format as that adopted in the first edition but the new developments have meant that, with the exception of Chapter 1 and parts of Chapter 2, the greater part of the book has been rewritten. As before we have included synthetic drugs where consideration of these has aided our understanding of antibiotic action but, generally, not otherwise.

Again we would like to express our gratitude to many colleagues for the advice, criticisms, and discussions they have provided and especially to those who have allowed us to see and quote papers in preparation for publication. We also want to thank Mrs M. Cumpsty for her invaluable assistance in preparing and collecting the manuscript and particularly for rescuing us from a series of crises in the final stages of that preparation.

Cambridge, May 1980

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