Topics in Infectious Diseases
Vol.1

**Drug Receptor Interactions
in Antimicrobial Chemotherapy**

Symposium, Vienna, September 4-6, 1974

Edited by
J. Drews and F. E. Hahn

Springer-Verlag
Wien New York

Drug Receptor Interactions
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With 130 figures

Prof. Dr. Jürgen Drews

Sandoz Forschungsinstitut Gesellschaft m. b. H.
Vienna, Austria

Prof. Fred E. Hahn, Ph. D.

Walter Reed Army Medical Center
Washington, D.C., U.S.A.

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ISBN-13:978-3-7091-8407-3 e-ISBN-13:978-3-7091-8405-9

DOI: 10.1007/978-3-7091-8405-9

Introduction

The concept of chemotherapy as originated by Paul Ehrlich is based on the premise that antiparasitic drugs must have two properties: they must first bind to specific structures of the parasite which Ehrlich called chemoreceptors. Subsequent to their attachment to the chemoreceptor and by virtue of this binding they must possess the capacity to kill the parasite. Since the host which is to be cured of an invading parasite also contains a large number of chemoreceptors, that have the potential to bind toxic compounds, the task of the chemotherapist is to identify chemoreceptors of the parasite which are not represented in the host and to design drugs which bind selectively to them. In this context, Ehrlich called for "the complete and exhaustive knowledge of all the different chemoreceptors of a certain parasite" as a "*sine qua non* for success in chemotherapy".

Paradoxically and in spite of the fact that chemotherapy has become a very advanced and successful therapeutic discipline, few of its triumphs have been achieved by following Ehrlich's original precepts. On the contrary, in the overwhelming majority of cases, effective drugs have been discovered without any knowledge of their chemoreceptors, and these drugs themselves have conversely been used as tools to study the nature of the chemoreceptors involved. In other words: chemotherapy, notably antibacterial chemotherapy, has been successful without ever living up to the fundamental standards put forward by Paul Ehrlich.

Two reasons should lead us to reassess the basic postulates of chemotherapy: the first one can be deduced from the present state of antimicrobial chemotherapy itself. Clearly, the rate of progress in this area as judged by the number of genuinely novel drugs becoming available to the physician each year has slowed down. The rediscovery problem in the search for new antibiotics and the paucity of known biochemical differences between parasites and hosts which might be exploited for the design of antimetabolites are contributory factors to the decreasing rate of discovery of new chemotherapeutic drugs. Moreover, the current situation is characterized by the appearance of new problems such as multiple drug resistance of bacteria and the increasing frequency of infections with gram-negative pathogens and fungi as well as by the persistence of old problems best exemplified by our distressing inability to make progress in the area of antiviral chemotherapy.

The second, and more positive reason is that since the days of Paul Ehrlich tremendous advances have been made in the fields of physical chemistry, biochemistry, biophysics, genetics and molecular biology. Studies on the molecular structure of drug-receptors and on the interaction of such receptors with antimicrobial compounds should, therefore, have a distinctly better chance of success today than they had

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sixty years ago when their necessity was first recognized. While during the first decades following Ehrlich's death (1915) chemotherapy research was constrained to use empirical search and development procedures, we feel that with the current state of the art the field can no longer afford the luxury of unguided empiricism; the time has arrived to apply the knowledge of principles and mechanisms of drug action which has been gained during three decades of intensive research to premediated efforts to develop novel chemotherapeutic agents.

It is for these reasons that the Sandoz Research Institute decided to ask a number of scientists well known for their work in areas such as structure-activity relationships, structure and function of plasmid DNA, bacterial protein biosynthesis and bacterial enzymes to reassess their own work in the context of its possible applicability to the search for new antimicrobial drugs or to the improvement of already existing compounds. In selecting the general topics for our symposium on drug-receptor interactions in antimicrobial chemotherapy we were led by the intention to include only such areas of research which had already contributed to the generation of novel chemotherapeutic agents or in which relevant practical contributions towards this goal could be expected in the foreseeable future. We believe that the general subjects, microbial enzymes as drug-receptors, ribosomes as drug-receptors, DNA as drug-receptors and, last but not least, a general consideration of the receptor hypothesis, satisfy these criteria.

The proceedings of this symposium are not meant to compete with more systematic texts on molecular aspects of chemotherapy or pharmacology. The exciting responses of basic scientists to the challenges and problems of drug therapy and drug development were revealed during this symposium. We hope that some of this excitement will be conveyed to the readers of this volume.

J. Drews
Vienna

F.E. Hahn
Washington

February 1975

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