Antimicrobial Drug Resistance

Edited by

L. E. BRYAN

Antimicrobial Drug Resistance

Edited by
L. E. Bryan
Department of Microbiology and Infectious Disease
University of Calgary
Health Sciences Centre
Calgary, Alberta, Canada

1984

ACADEMIC PRESS, INC.
(Harcourt Brace Jovanovich, Publishers)
Orlando San Diego San Francisco New York London
Toronto Montreal Sydney Tokyo São Paulo

ACADEMIC PRESS, INC.
Orlando, Florida 32887

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

Library of Congress Cataloging in Publication Data

Main entry under title:

Antimicrobial drug resistance.

Includes index.
1. Drug resistance in micro-organisms. I. Bryan, L. E.
[DNLM: 1. Antibiotics--Pharmacodynamics. 2. Anti-Infective agents--Pharmacodynamics. 3. Drug resistance, Microbial. 4. Plasmids--Pharmacodynamics. QW 52 A631]
QR177.A58 1983 616'.01 83-22377
ISBN 0-12-138120-X (alk. paper)

PRINTED IN THE UNITED STATES OF AMERICA

84 85 86 87 9 8 7 6 5 4 3 2 1

Antimicrobial Drug Resistance

Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

W. L. ALBRITTON* (515), Sexually Transmitted Diseases Laboratory Program, Centers for Disease Control, Atlanta, Georgia 30333

J. BRUNTON (529), Department of Medicine, Mount Sinai Hospital, and Departments of Medicine and Medical Microbiology, University of Toronto, Toronto, Ontario M5G 1X5, Canada

L. E. BRYAN (81, 113, 241), Department of Microbiology and Infectious Disease, University of Calgary, Health Sciences Centre, Calgary, Alberta T2N 4N1, Canada

JANE L. BURNS (293), Division of Infectious Disease, Children's Orthopedic Hospital and Medical Center, and Department of Pediatrics, School of Medicine, University of Washington, Seattle, Washington 98105

KAREN BUSH (1), The Squibb Institute for Medical Research, Princeton, New Jersey 08540

NAOMI DATTA (487), Department of Bacteriology, Royal Postgraduate Medical School, University of London, Hammersmith Hospital, London W12 OHS, England

E. B. DOBERSTYN (461), World Health Organization, Bangkok, Thailand

JED FISHER (33), Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

M. JOHN GILL (369), Departments of Medicine and Biochemistry, University of Alberta, Edmonton, Alberta T6G 2H7, Canada

A. J. GODFREY (113), Department of Microbiology and Infectious Disease, University of Calgary, Health Sciences Centre, Calgary, Alberta T2N 4N1, Canada

J. M. T. HAMILTON-MILLER (173), Department of Medical Microbiology, The Royal Free Hospital and School of Medicine, London NW3 2QG, England

*Present address: Department of Microbiology, University of Saskatchewan, Saskatoon, Saskatchewan, S7N 0W0, Canada.

ROBERT E. W. HANCOCK (147), Department of Microbiology, University of British Columbia, Vancouver, British Columbia V6T 1W5, Canada

INOUE (279), Department of Microbiology, Laboratory of Drug Resistance in Bacteria, School of Medicine, Gunma University, Maebashi, Japan

GEORGE A. JACOBY (497), Infectious Disease Unit, Massachusetts General Hospital, Boston, Massachusetts 02114

STUART B. LEVY (191), Departments of Molecular Biology and Microbiology and of Medicine, Tufts University School of Medicine, and New England Medical Center, Boston, Massachusetts 02111

D. L. LOCKERBY (317), Departments of Medicine and Microbiology and Infectious Disease, University of Calgary, Health Sciences Centre, Calgary, Alberta T2N 4N1, Canada

S. MITSUHASHI* (279), Department of Microbiology, Laboratory of Drug Resistance in Bacteria, School of Medicine, Gunma University, Maebashi, Japan

THALIA I. NICAS† (147), Department of Microbiology, University of British Columbia, Vancouver, British Columbia V6T 1W5, Canada

THOMAS R. PARR, JR. (81), Department of Microbiology and Infectious Disease, University of Calgary, Health Sciences Centre, Calgary, Alberta T2N 4N1, Canada

ANNEMARIE POLAK (393), Pharmaceutical Research Division, F. Hoffman–LaRoche and Co., Ltd., CH-4002 Basle, Switzerland

H. R. RABIN (317), Departments of Medicine and Microbiology and Infectious Disease, University of Calgary, Health Sciences Centre, Calgary, Alberta T2N 4N1, Canada

H. J. SCHOLER (393), Pharmaceutical Research Division, F. Hoffman–LaRoche and Co., Ltd., Ch-4002 Basle, Switzerland

ARNOLD L. SMITH (293), Division of Infectious Disease, Children's Orthopedic Hospital and Medical Center, and Department of Pediatrics, School of Medicine, University of Washington, Seattle, Washington 98105

ANNE O. SUMMERS (345), Department of Microbiology, University of Georgia, Athens, Georgia 30602

RICHARD B. SYKES (1), The Squibb Institute for Medical Research, Princeton, New Jersey 08540

D. LORNE TYRRELL (369), Departments of Medicine and Biochemistry, University of Alberta, Edmonton, Alberta T6G 2H7, Canada

*Professor Mitsuhashi is also Director, Episome Institute, Kogure Fujimi-mura, Seta-gun, Gunma-ken, Japan.

†Present address: Department of Microbiology and Immunology, University of Oregon, Health Sciences Center, Portland, Oregon 97201.

Foreword

The discovery of antimicrobial agents has created a new era of medicine. The control of infectious diseases is now based on the choice and prudent use of a large group of low molecular weight inhibitors with diverse mechanisms of action and varying spectra of antibacterial and antifungal activity. To withstand this ever-increasing menace to their existence and survival, microorganisms have developed a variety of defense mechanisms. New and better antibiotics are sought continually because of the capacity of microorganisms to survive this threat.

The biochemical rules determining the resistance of microorganisms to antibiotics have been recognized for some time. In 1952, B. D. Davis and W. K. Maas predicted, with extraordinary perspicacity, the most likely mechanisms of antibiotic resistance to be (1) decreased penetration of the drug; (2) increased destruction of the drug (or decreased conversion of an inactive compound to an active compound); (3) increased concentration of a metabolite antagonizing the drug; (4) increased concentration of an enzyme utilizing this metabolite; (5) decreased quantitative requirement for a product of the metabolite; (6) an alternative metabolic pathway bypassing the metabolite; and (7) an enzyme with decreased affinity for the drug compared with the metabolite. Notwithstanding this clear delineation of an important set of concepts (which now form the basis for this book), geneticists were less receptive to notions that bacteria might develop stable resistance. Resistance to antibiotics was judged to be of low probability, and the idea of multiple drug resistance was unthinkable. In a 1955 review, V. Bryson and W. Szybalski considered it unlikely that sexual mechanisms would contribute to any great extent in the development of drug-resistant bacterial strains. Such discussions (as well as those dealing with more aesthetic concepts such as adaptation in the presence of drugs) took place in spite of the fact that penicillinase had already been identified (1940) and that increasing numbers of bacterial isolates were, in consequence, resistant to penicillin. Thus it was some time before antibiotic resistance became, as it is now, a fact of life.

My own interest in this field began in 1962, when I began a study of bacterial mutants resistant to streptomycin, in the laboratories of B. D. Davis and L. Gorini. I took a leave of absence to learn genetics at the Institut Pasteur with F. Jacob and met Yukinori Hirota, who told me about multiple drug resistance and gave me an *E. coli* strain carrying resistance plasmid R100. I could not resist doing a few experiments on this strain, and I found that the streptomycin resistance was nonribosomal (target) and that extracts from the R^+ strain would inactivate streptomycin in the presence of ATP. I continued work on the mechanism of resistance to aminoglycoside antibiotics when I moved to the University of Wisconsin in 1967. My efforts seem like a drop in the bucket when one considers all the aspects of resistance described in this book. It has now become a field of research in its own right, as one sees from the reviews of various developments accrued over the past 10 years or so. This admirable collection of articles is, however, only a description of the state of the art; it is not a final report on the subject since the protagonists in the field, the microorganisms and the pharmaceutical industry, continue to look for ways of defeating each other. Unfortunately for human medicine, we know who will win in the end! In spite of many new and newer antibiotics, bacteria will continue to exert their incredible capacity for survival by developing mechanisms to inactivate, exclude, or simply to ignore the most up-to-date products of pharmaceutical research. It is most impressive to realize that in the past years hundreds of tons of antimicrobial agents have been released on the bacterial population in hospitals, farms, etc. Microbes, however, have not only survived but even flourished in such hostile environments.

The advent of an almost bewildering number of new β-lactam derivatives with novel properties and broad antimicrobial spectra has been heralded as a nail in the coffin of antibiotic-resistant microbial infections. These compounds are refractory to and even inhibit the known microbial β-lactamases. However, as is set forth in this book, bacteria have been able to exploit another property of the existing β-lactamases, as reagents to bind tightly and titrate out the β-lactam, reducing their intracellular concentrations to levels acceptable to continued bacterial growth and survival.

In another sense, studies of antibiotic resistance have been of great utility with respect to the analysis of novel biochemical modifications, small molecule transport, gene transfer, transposition, and gene evolution. Antibiotic resistance plasmids have become important tools in the study of genome replication and interactions, and the analysis of a number of transferable genetic systems has paved the way for the development of gene cloning vectors used in almost all genetic engineering studies; resistance has even been put to good use since the combination of an antibiotic with its cognate resistance gene is an important component of all genetic engineering host–vector systems. The dominance of expression of the resistance mechanisms described in clinical isolates is thus of

importance. The most widely known and used plasmid, pBR322, relies on its β-lactamase and tetracycline resistance to serve for selection and maintenance of its vector function in a variety of hosts. Use of other antibiotic resistance mechanisms allows selection of gene transfer throughout a wide spectrum of cell types. The biochemical mechanism of resistance to inhibitors of dihydrofolate reductase enzymes (a bypass mechanism) has been used to advantage as a means for selecting specific gene amplification to provide high-level gene expression in eukaryotes.

After reading a book such as this, in which so many novel reactions have been analyzed in detail in a genetic and biochemical sense, one has to ask, What comes next? It is evident that antibiotic resistance will continue to be a source of concern but also of interesting research in infectious diseases. The field has, however, now expanded beyond microorganisms; the resistance of parasites to drugs is a problem of some magnitude in the Third World. In addition, increasing resistance of insects, tumor cells, etc., to their chosen predators and inhibitors will create ever-increasing efforts to control diseases that affect large percentages of the human population. Studies on antibiotic resistance, of the type described in this excellent collection of chapters, are of considerable relevance to these fundamental problems of the future and have pointed out the flexibility and capability of living organisms to survive in hostile environments. These are practical and soluble problems, and with the wealth of information on the resistance of organisms to natural and synthetically derived inhibitors as reviewed here, there need be no surprise in the future.

J. E. Davies

Preface

The study of antimicrobial resistance has been a major driving force in the understanding of many genetic and biochemical processes in bacterial cells. In addition, it has had direct medical value in making more effective use and development of antibiotics. The time is right to provide a detailed overview of progress and the state-of-the-art of study of antimicrobial resistance. Previous discussions of resistance have, for the most part, been a chapter in a book or part of a chapter on mechanisms of action of antimicrobial agents. A more comprehensive approach devoted entirely to resistance seems an important addition to the literature on antimicrobial agents. This volume should demonstrate to the reader the major contributions made by the study of antimicrobial resistance, where we stand presently in terms of the extent of the problem, and hopefully some idea where future problems may arise and where emphasis in future studies should be placed.

The present book devotes itself to discussion of resistance to antibacterial, antifungal, antiviral, and antimalarial agents as well as metal ions. It provides the views of a group of authors who have made significant contributions to an understanding of resistance. In general, except for those chapters devoted to plasmids, the book emphasizes in particular mechanisms of resistance and the extent and significance of resistance to various agents; many chapters also provide some discussion of the genetic basis of resistance to individual agents.

One group of chapters covers resistance to β-lactams, design of new β-lactams to circumvent such resistance, and alternative forms of resistance to β-lactam and other antibiotics through permeability and alteration of target mechanisms. A second group of chapters covers resistance to most other major antibacterial agents, including metal ions. In view of the increasing use of antiviral compounds, a significant potential for resistance, and an appreciation that resistance to antimalarial agents is a major international problem, another group of chapters treats resistance to antiviral, antimalarial, and antifungal compounds. The final group of chapters is devoted to a discussion of resistance plasmids of most of the clinically important bacteria.

The book should appeal to those in microbiological and pharmaceutical research on antimicrobial agents, to those in clinical infectious diseases and medical microbiology who must use and direct use of these compounds in ways to prevent and overcome resistance, to those teaching microbiology and pharmacology to provide information not only on resistance but also on genetics, cell physiology, and biochemistry as well as microbial pathogenesis, to individuals in pharmaceutical marketing to aid in an understanding of where specific agents fit, and to those in infection control to assist in the control of local, national, and international problems of resistance.

We hope that readers of this volume will have at their fingertips most of the valuable information and views on antimicrobial resistance to assist in the more effective use and design of new agents as well as use of current agents. It should provide to those readers the benefits of the experience and perspectives of a group of authors who have contributed to our understanding of antimicrobial resistance from a variety of countries and a spectrum of backgrounds.

L. E. Bryan

Contents

Contents