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American Society for Microbiology
1752 N Street, N.W.
Washington, DC 20036-2904

Library of Congress Cataloging-in-Publication Data

Walsh, Christopher.
Antibiotics : actions, origins, resistance / by Christopher Walsh.
p. ; cm.
Includes bibliographical references and index.
ISBN 1-55581-254-6
   QV 350 W223a 2003]  I. Title.

RM267 .W357 2003
615 '.329—dc21  2002152389

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Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Address editorial correspondence to: ASM Press, 1752 N St., N.W., Washington, DC 20036-2904, U.S.A.

Send orders to: ASM Press, P.O. Box 605, Herndon, VA 20172, U.S.A.
Phone: 800-546-2416; 703-661-1593
Fax: 703-661-1501
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Online: www.asmypress.org
Dedicated to

Diana
Allison
Thomas
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Preface

This book has developed from four sustained, convergent interests in my research group: enzyme inhibitors; bacterial cell wall biosynthetic pathways; the mechanism of action of antibiotics and the development of resistance mechanisms; and the biosynthesis of polyketide and nonribosomal peptide natural products.

The basic premise of the approach is that one can understand and categorize antibiotic action, both historically and prospectively, by analysis of how these small molecules interfere selectively with one or more processes central to the survival of bacterial cells. Most of the attention in this book is on natural products with antibiotic activity elaborated by microbes to act as chemical weapons on neighboring bacteria, but synthetic chemicals with antibiotic activity are also examined. Thousands of molecules have been reported to have antibiotic activity, but only a few structural classes have had an impact in human infectious disease. The focus of this text is on those classes of antibiotics. This book is, then, not meant to be encyclopedic, nor a compendium of pharmacologic information, nor a microbiologic survey of pathogens and how to treat them. Authoritative texts already exist on those aspects of antimicrobial agents.

The current major classes of antibiotics act on only a small set of targets: bacterial cell wall biosynthesis, bacterial protein synthesis, DNA replication and repair, and the folate coenzyme-dependent pathway for thymidine biosynthesis. The first section of the book examines how antibiotics block specific proteins acting in these essential bacterial processes and how the molecular structure of the small-molecule drugs enables their antibiotic activity.

The middle section of the book takes up the development of bacterial resistance to antibiotics, starting with the molecular logic that microbial producers of antibiotics use for self-protection. The three major routes of resistance in antibiotic producers—destruction of the antibiotic, active extrusion of antibiotics by transmembrane pumps, and modification of target structures to antibiotic insensitivity—are seen to be the major mechanisms of resistance in bacterial pathogens.

The third part of the text takes up the molecular logic of antibiotic biosynthesis, starting with regulatory networks that control gene transcription of secondary metabolites in streptomycetes, those prolific producers of antibiotics. Polyketide and nonribosomal peptide antibiotics are manufactured on multimodal "assembly lines" that resemble fatty acid synthase machinery. The
modular assembly line strategy enables wide variation of structure in these classes of antibacterial agents and offers the prospect of directed combinatorial biosynthesis.

The last section of the book examines the prospects for broadening the base of bacterial targets and also where new antibiotics are likely to emerge. Bacterial genomic sequencing has moved antibacterial research from a target-poor to a target-rich arena. New antibiotics are likely to arise both from synthetic chemical efforts, perhaps via combinatorial chemistry efforts, and also from natural products, by combinatorial biosynthetic variants.

I am indebted to many members of my research group, over the past 5 years in particular, for many discussions and ideas about antibiotic action, biosynthesis, and resistance. I thank John Trauger for his design and execution of artwork on targets in bacterial cells that led to the book cover art and the chapter opener figures. I thank Gary Marshall, Raymond Chen, Hiten Patel, Steve Bruner, Mike Burkart, Susan Clugston, Rahul Kohli, Heather Losey, and Lusong Luo for their many contributions to artwork creation, design, and implementation, as well as the correction of numerous inconsistencies and errors along the way. I acknowledge the help and input of Tanya Schneider, Sarah O’Connor, and particularly Lusong Luo for efforts in literature citations. My special thanks go to Gary Marshall for his tremendous diligence and attention to the text and especially the bulk of the final artwork of the book.

Christopher Walsh
January 2003
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