Bacteria versus Antibacterial Agents
AN INTEGRATED APPROACH
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This book is dedicated to the memory of Dr. Guillermo O. Cobeñas, a rural medical doctor in Salliquelo, Buenos Aires Province, Argentina, where I was born and raised and where I received my elementary and secondary education. Dr. Cobeñas introduced me to what it means to be a university graduate. He embodied professional excellence and was a humanitarian, always committed to give his best to his patients.
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Since they were first introduced in the 1940s, antibiotics have transformed medicine; most infectious diseases can be effectively controlled by the appropriate use of the correct drugs. Bacterial diseases which frequently decimated the world’s population throughout history, such as plague, typhus, cholera, and tuberculosis, are little more than history to most people living in industrialized countries. The situation is such that antibiotics are taken for granted by the physicians who prescribe them and the public that consumes them. For most of the latter half of the past century, the production and sale of antibiotics have been highly competitive, with billions of dollars a year in sales. More recently, the competition has intensified in another sense; bacteria are responding to antibiotics by a variety of avoidance tactics, and the next phase of antibiotic development will take on a different focus: restoring their efficacy. This will require considerable research effort.

Thus, the importance of antibiotics to public health and well-being worldwide cannot be underestimated, and the availability of a text that describes all aspects of these magical small molecules is welcomed. *Bacteria versus Antibacterial Agents: an Integrated Approach* is such a text, and it will be welcomed as a source for university and medical school use.

In addition to the discovery and production of antibiotics, studies of the modes of action by which these compounds act on target cells have revealed fascinating biochemical stories. This information has been important in elucidating the mechanisms of replication, transcription, translation, and cell wall synthesis in bacteria and other living organisms. It also provided the experimental and conceptual basis for what is now known as chemical biology, wherein complex biological processes are dissected by analyzing inhibition by small molecules and using mutants refractory to inhibition as a means to identify key components of reactions.

Subsequent studies by three-dimensional structure analyses provided a detailed understanding of inhibitor-receptor interactions and the underlying
structure-activity relationships. Such has been the case for many of the inhibitors of ribosome function and DNA synthesis.

Along with its many notable successes in therapy and in basic science, the use of antibiotics has had its downside; the target organisms can employ a variety of genetic and biochemical strategies to evade inhibition by small molecules, and there exists a real threat that many antibiotics will become useless as a result. New approaches to the discovery of novel inhibitors are desperately needed, and a great deal of effort is going into attempts to find new active molecules or to redesign old ones in order to stem the threat of emerging resistant pathogens.

These goals can be realized only by an understanding of the biology of the target organism, the biochemical action of the antibiotic, and the potential resistance mechanisms, not to mention the participation of the host response. Oreste Mascaretti touches on all of these matters in this book and has done a real service in providing a readable and well-illustrated account of the world of antibiotics.

Finally, while this book focuses on antibacterials, the same principles of chemistry, microbiology, genetics, and biochemistry apply in the development of antivirals and anticancer agents. The work done on antibacterials that is so clearly described here has meaningful lessons beyond infectious diseases.

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Preface

This book presents an integrated approach to both the basic concepts and the most recent developments in the field in a form which is suitable for the needs of those who are studying clinical and molecular microbiology, biotechnology, biochemistry, chemical biology, bioorganic chemistry, pharmacy, or any of the related biomedical sciences.

The book was designed as an introductory text on antibacterial agents with broad coverage of the subject. I have tried to provide a comprehensive and concise overview of important subject areas. Supplanting a more detailed discussion of each topic, a list of references is included at the end of each chapter. The reference lists are limited mostly to some leading books, recent reviews, and a few classic articles where appropriate.

The understanding of the mechanisms of bacterial resistance has rapidly advanced in recent years, opening the way for the design of new antibacterial agents tailored to overcome the mechanisms that bacteria use to resist the action of traditional antibacterial agents.

In compiling diverse information into a single and comprehensive book, I have attempted to give a clear presentation of cutting-edge knowledge. The key features I present are as follows:

• The basics of bacterial cell structure and function for a better understanding of cellular metabolism and mechanisms of antibiotic action, as well as the mechanisms developed by prokaryotic cells to overcome the action of antibiotics
• The characteristic features of bacterial pathogenicity
• How antibacterial drugs reach their targets in gram-positive and gram-negative bacteria
• How the human immune system is involved in a wide range of immune responses in the battle against bacterial infections
• The genetic basis of resistance to antibacterial drugs


• The biochemical mechanisms of action of antibacterial drugs
• Improved penicillins, cephalosporins, tetracyclines, quinolones, macrolides, and glycopeptides developed by pharmaceutical companies to restock the antibacterial arsenal
• Recent advances in the research on and development of new classes of antibacterial drugs to combat the rising tide of drug-resistant bacterial infections

In preparing this textbook, I have striven for a coherent overall presentation. I have had the chapters read by experts (see the acknowledgments) who helped me to eliminate errors. However, any shortcomings of the book are solely my responsibility. There is no doubt that I have omitted some topics and given too much room to others, but the field of antibiotics covers such a broad area of interest that I had to make a personal judgment on what had to be included and what could be left out.

Where appropriate, mechanistic aspects of the action of antibacterial agents and β-lactamase inhibitors are discussed to help the reader understand the underlying principles of action on a particular target in bacteria. Additionally, each chapter on a group or subgroup of antibiotics or other antibacterial class also surveys the topic of structure-activity relationships.

The most recent and most significant developments in new antibacterial agents with novel modes of action are presented by using selected examples. Key terms are printed in bold type, and their definitions are given, when they are first encountered in the text.

I hope that medicinal and bioorganic chemists, molecular biologists, microbiologists, geneticists, and immunologists each will find relevant topics from disciplines that they are not too familiar with. I expect that some of the information provided in this book will be useful in the development of new antibiotics and synthetic antibacterial agents, and I also hope to see more interdisciplinary cooperation between scientists in these different disciplines.

Any comments or suggestions for improvements in future editions would be gratefully received.

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