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Book Review

The "Molecular Logic" Underlying Antibiotic Activity and Structure

Antibiotics: Actions, Origins, Resistance
By Christopher Walsh
Washington, D.C.: ASM Press (2003). 335 pp. $99.95

The impact of infectious diseases on human health is dramatic and unquestionable. Prior to the twentieth century, the leading causes of death in the developed world were the result of infection (sadly, this remains the case in developing nations). Consequently, in 1900 life expectancy in the U.S. was 47 years. By the year 2000, life expectancy had climbed to over 76 years, and the leading causes of death are now heart disease and cancer (www.cdc.gov). One of the principle factors in this dramatic change over the past century was the discovery and clinical use of antibiotics. It is fair to say that these molecules have completely changed our view of the microbial world and infection, and for the most part we regard infectious agents as something we can control. This hubris, which arose from the incredible advances and clinical successes of the golden age of antibiotic discovery (roughly 1940–1970), has eroded over the past 20 years. The emergence of new infections and agents such as Legionnaire's disease (*Legionella pneumophila*), Lyme's disease (*Borrelia burgdorferi*), AIDS (HIV), and, most recently, SARS, along with the reemergence of old infections such as tuberculosis and the growing consciousness of our vulnerability to bioweapons, have contributed to an increased awareness that infectious agents still have the potential to dramatically impact our lives. Underlying this awareness is the inexorable march of antibiotic resistance. This process, driven by evolution and fueled by the selective pressure resulting from the use of antibiotics in medicine and agriculture, coupled with the short generation time of microbes, is unstoppable and requires continued cycles of antibiotic discovery and implementation.

Societal impression that infectious diseases were largely under control by existing agents has been paralleled by a retreat by the pharmaceutical industry from directed efforts to discover new antibiotics in favor of focusing their attention on other, largely chronic, diseases. At the same time, however, there have been dramatic advances in our understanding of antibiotic function, the molecular basis of resistance, and the genetics and biochemistry of antibiotic biosynthesis by microbes. These developments have come from diverse fields including synthetic organic chemistry, enzymology, macromolecular structure, molecular microbiology and genetics, and biotechnology. A new book authored by Prof. Christopher Walsh entitled *Antibiotics: Actions, Origins, Resistance* seeks to bring together this information from multiple fields and present it in a format friendly to chemists and other researchers interested in antibiotics and infectious disease.

Walsh is the author of over 500 scientific publications, a member of the editorial board of numerous journals, including *Chemistry & Biology*, and is the recipient of several awards celebrating his contributions to enzymology and chemical biology. Perhaps one of his most effective qualities is his outstanding ability to communicate science to both chemists and biologists. His 1979 text entitled *Enzymatic Reaction Mechanisms* inspired a generation of researchers and students from a variety of backgrounds to study enzymes and their function, and this new book has the potential to impact the field of antibiotic biochemistry in a similar fashion. Both of Walsh's books share a focus on the concept of "molecular logic," where molecular approaches used by organisms or enzymes that appear disparate at first examination are dissected to reveal common mechanisms that are approachable using the methods of biochemistry and molecular biology.

This new book is divided into five sections: (1) Introduction to Antibiotics, (2) Antibiotic Targets and Classes, (3) Antibiotic Resistance, (4) Antibiotic Biosynthesis, and (5) Strategies for Discovery of New Antibiotics. Each section focuses on the chemistry and biology of the subject and as such will appeal to a broad cross-section of interests and backgrounds. There are copious amounts of figures and tables used to illustrate concepts and mechanisms and a few color plates. In an age of PowerPoint presentations, more color figures would have perhaps been expected and would have been helpful (as in the early days of this journal), but publication costs likely would have been prohibitive. Perhaps this will be possible in a second edition? Each section is prefaced by a short overview that outlines the scope and key elements covered in the upcoming chapters.

Section one is short and is appropriately entitled "Introduction to Antibiotics." It reviews the concepts of antibiotic action, biosynthesis, and resistance and defines important nomenclature such as bacteriostatic versus bactericidal agents. The second section on antibiotic targets and classes includes five chapters divided by antibiotic target: cell wall, protein synthesis, DNA synthesis and repair, and others. An introductory chapter reviews the major classes of antibiotics, bacterial physiology, and diseases caused by bacteria. Each subsequent chapter in this section follows a general format with an introductory section detailing necessary background knowledge in physiology and biochemistry followed by a discussion of the classes and mechanisms of agents that inhibit these processes. The major advances in the past decade in the determination of the atomic structures of various antibiotic targets, such as the ribosome, frame the discussion of the effectiveness of each of the antibiotics and their respective targets and provide a current overview of the field.

The book continues with a third section describing antibiotic resistance, which contains four chapters. The first chapter provides some background on resistance and the distinction between acquired versus innate resistance, with emphasis on the strategies employed by

antibiotic producing organisms. This nicely introduces the next three chapters on enzymatic mechanisms of antibiotic modification, efflux protection approaches, and target modification. This is succeeded by the fourth segment which deals with the biosynthesis of antibiotics by microbes and is divided into four chapters: regulation of biosynthesis in producing organisms, polyketide assembly, nonribosomal peptide biosynthesis, as well as aminoglycosides, peptides, coumarins, and mixed polyketide and nonribosomal peptide strategies. This is a research area where Walsh and his colleagues have made a profound impact over the past decade. There is much promise in leveraging a molecular understanding of antibiotic biosynthesis in the synthesis of new antimicrobial compounds to address the challenges and bacterial evasion strategies outlined in the third section on antibiotic resistance. Walsh uses a number of examples, many of which are from his own research program, to illustrate the logic of biosynthesis and the interconnectedness of strategies microbes utilize to generate antibiotics and chemical diversity.

The fifth and final portion of the book focuses on current and future research areas and is comprised of three chapters on targets, new molecules, and a summary chapter on the challenges of the future. The first chapter discusses the validation and exploitation of new targets that are emerging from the massive amounts of information provided by efforts underway in genomics and related disciplines and a fresh look at some old targets. The application of chemical genetics and combinatorial biochemistry in particular are discussed in the new molecules chapter. This final section builds on the information presented in the previous sections of the book. It underlines the opportunities and challenges faced by the scientific community in the face of a growing understanding that antimicrobial drug discovery and the use of these agents requires a multidisciplinary approach and an acceptance that the future will require new cycles of discovery and prudent and creative use in both clinical and agricultural contexts.

The last comprehensive text (as opposed to edited compendium) to deal with the various aspects of antibiotics, their synthesis, and their action, was published in 1981 (Gale, E.F., Cundliffe, E., Reynolds, P.E., Richmond, M.H., and Waring, M.J. [1981]. The Molecular Basis of Antibiotic Action, Second Edition [London: Wiley]). Much has changed since then. Walsh's book provides an exceptional overview of the contemporary antibiotic field and integrates molecules, targets, biosynthesis, and resistance in a comprehensive and highly readable fashion. This book is written to transcend the divide between the chemistry and molecular microbiology of infectious diseases and will appeal to researchers of diverse backgrounds; this approach will also be of value to senior undergraduate or graduate students and will certainly find application in the classroom. Like his previous effort in enzyme mechanisms, Walsh's emphasis on molecular logic and the well-written prose delivered in this book will no doubt serve to inspire and instruct a new group of researchers to find interest and challenges in antibiotic biology and chemistry. Despite the present timidity of the pharmaceutical sector to reestablish or strengthen programs in infectious disease drug discovery, the predictability of the obsolescence of our current crop of antimicrobial drugs ensures that the time will come when this area will again see a golden age. This will require researchers with knowledge and passion for antibiotics. Perhaps this text can provide a measure of catalysis toward this effort.

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