Antibiotics

Containing the Beta-Lactam Structure II

Editors: A. L. Demain and N. A. Solomon

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Containing the Beta-Lactam Structure

Part II

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Preface

It is quite amazing that the oldest group of medically useful antibiotics, the β-lactams, are still providing basic microbiologists, biochemists, and clinicians with surprises over 50 years after Fleming's discovery of penicillin production by *Penicillium*. By the end of the 1950s, the future of the penicillins seemed doubtful as resistant strains of *Staphylococcus aureus* began to increase in hospital populations. However, the development of semisynthetic penicillins provided new structures with resistance to penicillinase and with broad-spectrum activity. In the 1960s, the discovery of cephalosporin C production by *Cephalosporium* and its conversion to valuable broad-spectrum antibiotics by semisynthetic means excited the world of chemotherapy. In the early 1970s, the 40-year-old notion that β-lactams were produced only by fungi was destroyed by the discovery of cephamycin production by *Streptomyces*. Again this basic discovery was exploited by the development of the semisynthetic cefoxitin, which has even broader activity than earlier β-lactams. Later in the 1970s came the discoveries of nocardicins from *Nocardia*, clavulanic acid from *Streptomyces*, and the carbapenems from *Streptomyces*. Now in the 1980s we learn that β-lactams are produced even by unicellular bacteria and that semisynthetic derivatives of these monobactams may find their way into medicine. Indeed, the future of the prolific β-lactam family seems brighter with each passing decade.

Considering the level of excitement in this area, we felt that this would be the right time for the leaders in the field to survey past and present research, development, and clinical applications of β-lactams and prospects for future progress. We were pleasantly surprised that so many busy people agreed to give up their time to contribute to this project. The result is this volume in two parts describing all aspects of β-lactam antibiotics.

Cambridge

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A. Introduction

Development of β-lactam antibiotics over the past 40 years represents an unparalleled effort in the history of antimicrobial chemotherapy. The continual emergence of new compounds, natural, semisynthetic, and synthetic, is a tribute to the research programs being carried out around the world. Alongside the intensive search for new and improved β-lactam antibiotics has been the study of enzymes that interact with these molecules.

Early studies were conducted on the penicillin-hydrolyzing enzymes (β-lactamases), initially detected by ABRAHAM and CHAIN in 1940. These enzymes, responsible for the penicillin resistance among staphylococci in the 1940s and 1950s, have since proved to be a major source of resistance in gram-negative organisms. Throughout the 40-year history of β-lactam antibiotics, β-lactamases have continually asserted their presence. They have proved to be extremely important as antibiotic resistance agents and, as such, have given impetus to antibiotic development programs. Other enzymes implicated in the hydrolysis of penicillins and cephalosporins are the acylases and esterases. Although of little importance as antibiotic-resistance agents, these enzymes have played a significant part in the production of semisynthetic β-lactam antibiotics.

The second group of enzymes interacting with β-lactam antibiotics have the opposite physiological role to the β-lactamases, i.e., they are inactivated by these compounds. The effects of penicillin on cell-wall structure and morphology were shown soon after its introduction, and by the late 1950s penicillin was reported to be a specific inhibitor of bacterial cell-wall synthesis. During the following decade, the structure of the bacterial cell wall and the mechanism of its synthesis were elucidated. Following on from these studies in the 1970s came the isolation and identification of the two types of bacterial enzymes sensitive to penicillin, peptidoglycan transpeptidase and DD-carboxypeptidase.

Abbreviations

6-APA, 6-Aminopenicillanic acid; pCMB, p-chloromercuribenzoate; Diac-L-Lys-D-Ala-D-Ala, α,ε-diacetyl-L-lysyl-D-alanyl-D-alanine; Diac-L-Lys-D-Ala-D-Lac, α,ε-diacetal-L-lysyl-D-alanyl-D-lactate; DFP, diisopropylfluorophosphate; DTNB, 5,5′-dithiobis (2-nitrobenzoic acid); pI, isoelectric point; MSF, methanesulfonyl fluoride; MIC, minimum inhibitory concentration; NEM, *N*-ethylmaleimide; PBP, penicillin-binding protein; PSE, penicillin-sensitive enzyme; SDS, sodium dodecylsulfate; UDP-MurNac-L-Ala-D-Glu-meso-Dap-D-Ala-D-Ala, UDP-*N*-acetylmuramyl-L-alanyl-γ-D-glutamyl-meso-2,6-diaminopimelyl-D-alanyl-D-alanine