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Antibiotics

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Preface

In three decades or so of widespread use, antibiotics have wrought a revolution in the medical, veterinary, and agricultural sciences; indeed, in all of the biological sciences. Early research on antibiotics was necessarily directed at the production, isolation, characterization, and pharmacology of this important class of natural products. It was soon apparent that microorganisms could develop resistance to antibiotics and that this resistance was due, at least in part, to the possession of enzymes that could, in some fashion, chemically modify the antibiotic. To keep ahead (or even abreast) of antibiotic resistance, it is necessary either to constantly discover new antibiotics or to develop derivatives that are insensitive to the enzymes that cause inactivation of the natural compound. Both avenues have been tried. It is evident that the search for new antibiotics must eventually reach the point of diminishing returns and that the second approach offers the best hope of extending the life of an antibiotic. Research on the biosyntheses of antibiotics as well as on enzymatic means of degradation has received less emphasis than other aspects of antibiotic chemistry, but, as it has become apparent that a knowledge of biosynthetic pathways can assist in isolating intermediate compounds capable of being modified chemically, this area has received more attention. Similarly, degradative enzymes have been found that are capable of providing antibiotic derivatives which can be chemically modified, allowing production of large numbers of semisynthetic antibiotics. Other practical uses of antibiotic enzymology include the use of enzymes as analytical reagents in determining the concentrations of antibiotics in samples and in the effective removal of antibiotics from reaction mixtures by converting them to inactive compounds.

Aside from the utilitarian aspects of antibiotic enzymology a principal driving force behind research on these enzymes is the intellectual curiosity as to the *raison d'etre* of antibiotic synthesis. The production of these secondary metabolites, which serve no evident function in the producing organism, requires large quantities of energy and considerable metabolic machinery. In some instances very complicated pathways involving 20–30 enzymes are required to synthesize an antibiotic. As the pathways are unraveled and the branch points with normal metabolic routes are established, light may be shed on the mechanisms of antibiotic synthesis.

Even with the renewed interest in antibiotic enzymology, the extent and scope of research in this area are uneven, and the published results are scattered throughout the scientific literature. The aim of this volume is to collate in one source as much information concerning antibiotic

enzymology as possible. The work is divided into three sections. The first is concerned with methods used in the study of antibiotics, and covers techniques from culturing the producing organism to various chromatographic methods to sophisticated physical techniques. The second and third sections are devoted to enzymes involved in antibiotic biosynthesis and antibiotic degradation and modification, respectively. In some cases the division between the second and third section is quite arbitrary because it is not always clear whether an enzyme belongs in a biosynthetic or degradative pathway. The coverage of enzymes represents the state of the art of antibiotic enzymology; the range extends from pure enzymes that have been sequenced to enzymes that have been studied only in crude extracts. Many other enzymes that act on antibiotics, antibiotic precursors, or antibiotic derivatives have been detected in extracts or whole cells. Most of these had to be omitted because of a paucity of information. It is evident that only a small part of antibiotic enzymology has reached the stage where it can be consolidated into a treatise of this kind, and it is hoped that this volume will serve as a stimulus for further research on the enzymes involved with this important class of compounds.

I am indebted to many people for many ideas and suggestions, but I am especially indebted to investigators in pharmaceutical laboratories throughout the world for their ideas and contributions.

JOHN H. HASH

METHODS IN ENZYMOLOGY

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Section I

Methods for the Study of Antibiotics