

## PREFACE

The dedication of this volume of Heterocycles to Hamao Umezawa on his 65th birthday is a fitting and welcome tribute to a man who has become the leading chemical microbiologist in Japan. He has long had an international reputation for his discovery of a remarkable series of microbial products with biological activity and for his fundamental investigations of their properties. Most of these substances are from Actinomycetes, many of them contain new and intriguing heterocyclic systems, and some are of value in medicine or agriculture.

Hamao Umezawa is one of a family of distinguished brothers. He began to work on antibiotics in 1944, when he was Assistant Professor in the Institute for Infectious Diseases at the University of Tokyo. Three years later he became Director of the Department of Antibiotics at the National Institute of Health. The prevalence of tuberculosis in Japan at that time led him to search for water-soluble substances with high activity against the tubercle bacillus, and in 1956 he discovered Kanamycin, an aminoglycosidic antibiotic produced by Streptomyces kanamyceticus, which found wide clinical use. One important consequence of this discovery was the decision of the Japanese Ministry of Health and Welfare to establish a Microbial Chemistry Research Foundation to receive royalties from the Kanamycin patent and to build an Institute of Microbial Chemistry for the study of antibiotics and other useful microbial products.

Professor Umezawa was appointed Director of the new Institute, which celebrated its 15th anniversary with a Symposium in Tokyo two years ago. He became the initiator and guiding spirit of an immense body of research in chemical microbiology which has produced results of basic importance and practical value. In 1962 he began a search for a substance which would cope with a serious infection of rice plants by Piricularia oryzae, and in 1965 he and his colleagues discovered in culture filtrates of Streptomyces kasugaensis

the aminoglycoside Kasugamycin, which has been widely used for the prevention of rice blast.

Before the Institute had been established he had also begun to look for substances with anti-tumour properties. The first substance to show therapeutic promise was discovered in 1956 and named Phleomycin, but this produced irreversible renal damage in dogs. However, in 1965, a continued search for similar substances revealed the chemically related Bleomycin, produced by Streptomyces verticillus, which has found use in the treatment of squamous cell carcinoma, Hodgkin's disease, and tumours of the testis.

In addition to his extensive researches on antimicrobial and anti-tumour substances, he initiated a search for enzyme inhibitors in the culture filtrates of microorganisms. A considerable number of such substances have already been found, some of which have well defined and useful pharmacological properties, and this approach to the discovery of new drugs has now become of wide interest. Two inhibitors of  $\beta$ -lactamases, discovered in the course of his screening programme in 1977, were the forerunners of clavulanic acid and the olivanic acids, which are of potential clinical value.

Professor Umezawa and his colleagues have not only isolated a great number of new and interesting microbial secondary metabolites but have determined the structures of more than 70 of them. The structural work on Bleomycin, which consists of a family of substances having a novel peptide linked to a disaccharide, is particularly impressive and has been followed by the production of semi-synthetic Bleomycins. Among the recent novel structures is that of Aplasmomycin, a complex molecule from a marine Streptomyces sp. with activity against plasmodia, which has been shown to contain boron at its centre.

Furthermore, the chemical and biological characterisation of some of these substances has been accompanied by studies relating to their biosynthesis and to the elucidation of their modes of action. Evidence has been produced for the involvement of plasmids in the biosynthesis of several antibiotics. Kanamycin was shown to be inactivated in resistant strains of bacteria by a phosphotransferase, a nucleotidyl transferase and an acyl transferase and on the basis of these findings structures were predicted for related compounds which were expected to be active against resistant organisms. This rational approach led to the synthesis of dideoxykanamycin, which has found clinical use.

Hamao Umezawa's outstanding achievements are embodied in more than 800

publications and the Journal of Antibiotics, with which he is closely associated, has become essential reading for all who study microbial secondary metabolites. He is the author of three books in English and five in Japanese. His "Index of Antibiotics from Actinomycetes", now in two large volumes and including more than 2000 substances, has met a widely felt need. His "Enzyme Inhibitors of Microbial Origin", embodying the Squibb Lectures for 1972, reveals how he came to extend research on antibiotics to "new and potentially fruitful areas" and describes the results, at that time, of his decision to do so. The work in his Institute has made it clear that the screening of microorganisms for new therapeutic substances and the introduction of new methods of screening are still fruitful and necessary occupations. It has also demonstrated the value of *liaison between academic research and that carried out by pharmaceutical companies.*

The contributions of Professor Umezawa to science, medicine and agriculture have been recognised by his membership of the Japan Academy and receipt of the Academy Prize, by the award of the Culture Medal from the Emperor, and by a doctorate Honoris causa from the Karolinska Institut in Stockholm. His dry humour, pleasing and helpful personality, his generosity and his memorable abilities as a host are widely known in Europe, the United States and Japan. I hope that the publication of this Volume as a token of admiration will please him, as it will his many friends.

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