Antibiotics

Containing the Beta-Lactam Structure I

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

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Part I

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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.

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CHAPTER 1

History of β-Lactam Antibiotics

E. P. ABRAHAM

A. The Past Fifty Years

I. Fleming's Discovery

During the second half of the nineteenth century observations of the antagonism of fungi of the genus *Penicillium* to the growth of bacteria were recorded by JOHN TYNDALL, JOHN BURDON-SANDERSON, JOSEPH LISTER, T. H. HUXLEY, ERNEST DUCHESNE, who was a French medical student, and others. Whether any of these examples of microbial antagonism was due to the presence of penicillin is unknown. However that may be, they bore no fruit. It was not until 1929 that ALEXANDER FLEMING, in a paper from St. Mary's Hospital, London, introduced the term "penicillin" for an entity with well-defined antibacterial properties (FLEMING 1929).

While looking at plates that had been seeded with staphylococci and left on a laboratory bench during a vacation, Fleming noticed that one plate had been contaminated by a mold and that in the vicinity of this contaminant the bacteria were apparently undergoing lysis. He grew the mold *(Penicillium notatum)* in broth and showed that the resulting culture filtrate powerfully inhibited the growth of a number of gram-positive pathogenic bacteria and gram-negative cocci, but not that of gram-negative bacilli; and he decided to use the name penicillin for the more cumbersome phrase "mold broth filtrate."

The phenomenon seen by FLEMING is not easily reproducible in the laboratory, because penicillin brings about the lysis of growing staphylococci but not that of staphylococci in cultures that have reached the end of their growth. It appears that a period of cool weather allowed the *Penicillium* to form a large colony and produce penicillin before growth of the bacteria was completed as a result of a rise in the ambient temperature. FLEMING's great achievement lay in his flair for seizing on the unexpected, which he had revealed earlier in his discovery of lysozyme. He found that his penicillin was no more toxic than ordinary broth to a rabbit, a mouse, or the leukocyte and he tried it as a local antiseptic. But there is nothing to indicate that he ever envisaged that it could be injected into the blood stream to act as a chemotherapeutic agent in systemic infections. His interest focused on its use as a selective antibacterial agent in differential cultures.

FLEMING's two assistants, F. RIDLEY and S. R. CRADDOCK, prepared crude extracts of penicillin. In 1932 CLUTTERBUCK, LOVELL and RAISTRICK made an attempt to isolate penicillin, but abandoned it after finding that the antibacterial activity of the substance could readily be lost. Clearly no one imagined, at this time, that penicillin was of outstanding medical value. It must be remembered that the

therapeutic properties of the sulfonamides were then unknown and that the possibility of finding chemical substances that could cope with bacterial septicaemia was viewed with pessismism. Nevertheless, when the successful use of prontosil and sulfanilamide was revealed in 1935, no interest in penicillin was rekindled.

II. Discovery of the Therapeutic Power of Penicillin in Systemic Infections

A second chapter in the history of penicillin began in 1938, when Professor H. W. FLOREY and Dr. E. B. CHAIN, in the Sir William Dunn School of Pathology at Oxford University, decided to make a systematic survey of the antibacterial substances known to be produced by microorganisms. This project was suggested by CHAIN during the course of discussions on these substances with FLOREY and it arose out of FLOREY's interest in lysozyme. It was motivated by scientific interest and not by the hope that such substances would prove to have medical value. Nevertheless, in 1939, after attempts to purify bactericidal substances produced by *P. notatum* and *Pseudomonas pyocyanea* had begun, the possibility that such substances might have clinical application was noted in a successful request to the Rockefeller Foundation for support.

The use of a solvent-transfer process for the purification of penicillin, suggested independently in Oxford by N. G. HEATLEY following its earlier unpublished use by L. B. HOLT at St. Mary's Hospital, led to the preparation of material that was not more than 1% pure. Between May and July 1940 FLOREY showed conclusively that this crude penicillin, given subcutaneously, could protect mice from otherwise fatal infections with the streptococcus or the staphylococcus. By this time, A. D. GARDNER, A. G. SANDERS, E. P. ABRAHAM and others had also begun to work on the penicillin project and a major effort was made to purify it further and produce enough material for a small clinical trial. The treatment in Oxford of five patients who were gravely ill with streptococcal or staphylococcal infections was carried out by FLOREY and C. M. FLETCHER early in 1941. The purity of the penicillin used varied from 0.3% to 7% and the supply was inadequate, even though it was supplemented by material recovered from the urine. Nevertheless, the results of this trial indicated that penicillin was not toxic to man and could control very severe infections.

III. Large-Scale Production

In view of the wartime situation in Britain FLOREY and HEATLEY went to the United States in June 1941, with FLEMING's strain of *P. notatum* and in the hope that penicillin could be made there in larger quantities. Their visit was facilitated by the Medical Research Council and supported by the Rockefeller Foundation. Work on penicillin at Columbia University was already being done by DAWSON, HOBBY, MEYER and CHAFFEE. At the Northern Regional Research Laboratory (NRRL) in Peoria Dr. COGHILL suggested that the use of deep fermentation, rather than stationary surface culture, might facilitate commercial production. A. J. MOYER, who worked with HEATLEY, introduced the use of corn-steep liquor (which contained

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