Invitational ONR Lecture

Some Aspects of the Development of the Penicillins and Cephalosporins

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It is with interest that I note that The Society for Industrial Microbiology was first organized in 1949, soon after a new and important development in industrial microbiology, the production of antibiotics, had begun to get into its stride. I have lived through the period of these developments and have been fortunate enough, in a small way, to be personally involved in them. Therefore, I should like to reminisce about how some of these things happened, as I saw them, as well as to make some assessment of the situation today. Ultimately, almost all new scientific and industrial developments of major importance depend on the abilities and environment of small numbers of individuals. What I propose to do is to talk about the development of penicillins and cephalosporins, as it was influenced by people whom I knew and, in some cases, worked with. Such an account will necessarily be personal and far from comprehensive, since it will not include references to the outstanding work on antibiotics which was initiated by the researches of Selman Waksman, whose death occurred only a few days ago; but I hope that it will not be slanted, or give the impression that I am making use too light-heartedly of the generous support to the Society provided by the Office of Naval Research.

The idea of using antimicrobial substances produced by microorganisms for therapeutic purposes was an old one, going back to the time of Pasteur; but penicillin, which was observed by Alexander Fleming in 1929 in the course of a study of staphylococcal variants, was the first substance of this kind to make any real impact on chemotherapy. As is well known, Fleming observed that a plate seeded with staphylococci, which had been left on his laboratory bench during a vacation, had become contaminated with Penicillium notatum and that in the vicinity of the fungus the bacteria were undergoing lysis. He then grew the fungus in liquid medium and found that the culture liquid showed high activity against certain bacteria but was nontoxic to leukocytes. He named the active substance penicillin and thought that it might be useful for the treatment of certain bacterial infections by local application. But he never seems to have envisaged the injection of penicillin into the blood stream and its use as a systemic chemotherapeutic agent, even after the sulfonamides had been introduced into medicine and it had been established that they could cure certain systemic infections.

Most of us, I suppose, would acknowledge that chance has played an important role in some of the most significant events of our lives and this was certainly so with Fleming's observation. It is not at all easy to reproduce the phenomenon he observed. Penicillin kills and lyses staphylococci only when they are growing and there would have been no lysis if
the plate had been incubated at 37 C before, or soon after, the contamination had occurred. The temperature changes in the laboratory must have been just right for penicillin to have been first produced by the fungus and then to have encountered growing bacteria. Thus, the odds against discovering penicillin in this way were very high.

Fleming was an acute observer dedicated to research and to his great credit he did not throw penicillin away, even though it was extraneous to the work in which he was then engaged. He was a bacteriologist and it is not surprising that he did not purify the active substance, but it is strange, nevertheless, that he never attempted to use it systemically in mice in the crude form in which it was available to him, for this would have been technically possible. Perhaps the climate of opinion at that time in the laboratory at St. Mary’s Hospital, headed by Almroth Wright, was responsible for this omission; for a contemporary, Ronald Harc, has stated that animal experiments were thought to be unfruitful on the grounds that they gave no certain indication of what would happen in man. In the event, more than 10 years elapsed before the crucial experiment in animals was done and penicillin was transformed from a bacteriological curiosity into a substance of great potential medical interest.

The central figure in this development was Howard Walter Florey, an Australian who qualified in medicine and then came to Oxford as a Rhodes Scholar. It is probably relevant to the story of penicillin that Florey wanted to study chemistry at the University of Adelaide. He was dissuaded from doing so by the headmaster of his school, who told his father that there were few jobs for chemists in Australia, and he thus studied medicine. But, although he was no chemist, his interest in chemistry persisted and when he became a Lecturer in Pathology at Cambridge and later Professor of Pathology in Sheffield, he began to study lysozyme, a chemical substance with antibacterial properties which had been discovered earlier by Fleming in the nasal mucus of a patient with acute coryza. He tried hard to obtain a grant for the salary of a chemical collaborator, but in those days even small sums of money for research were hard to come by and he only succeeded, some years later, on his appointment to the Chair of Pathology at Oxford in 1935. Then, at the suggestion of Gowland Hopkins, he took on Ernst Chain, a refugee from Hitler’s Germany who was completing his second Ph.D. at Cambridge, to work in the Sir William Dunn School of Pathology.