REFLECTIONS ON RESEARCH IN CHEMOTHERAPY

Sir Ernst Chain

Professor of Biochemistry

Imperial College, London

I am greatly honoured by the invitation to give the opening address at this 9th International Congress of Chemotherapy, and am carrying out my assignment with greatest pleasure. The popularity of the subject can be gauged from the massive number of people who are gathered today in this largest hall in London.

Thirty-five years have passed since my colleagues and I published in 1940, in the Lancet, our first paper on the curative properties of one of the penicillins in experimental infections in mice, and a year later, in 1941, we published our second paper reporting the curative effect of this material in severe infection in man.

This discovery and its subsequent development which led to the production of benzylpenicillin on an industrial scale, and to the discovery and industrial production of a wide range of antibacterial substances of microbial origin, now known as antibiotics, with chemotherapeutic action against a wide range of bacterial infections, including some in which benzylpenicillin was not effective, marks a new era in antibacterial chemotherapy. The production technique for the antibiotics, with one exception, is based on fermentation technology which before the penicillin development was almost entirely unknown to the pharmaceutical industry, but since then has become one of the main pillars. Their use has revolutionised the treatment and brought under control the large majority of bacterial infections. The antibiotics development, therefore, constitutes one of the major achievements of medical research, and I should like to devote this introductory talk to some comments of general interest pertinent to the whole approach to medical research in the field of chemotherapy, not
just antibacterial, but drug therapy in general, arising partly from my own experience in the history of the penicillin discovery. I shall also try to make some brief comment on the future of chemotherapy, as I see it.

The history of the penicillin discovery is perfectly simple and straightforward, but has been distorted beyond recognition by mass media and sometimes even the professional medical press. Even the short introductory statement in the program of this Congress has not got the facts quite right. Yet it contains a number of facts of considerable general interest relevant to the basic principles of medical research in the field of chemotherapy, and demonstrates some of the difficulties, both conceptual and financial - administrative, which the investigator in the field encounters, before and even after he has been successful.

The work on penicillin, which I started at the end of 1938, was undertaken as a study of purely scientific interest, without any idea that it could have practical application in therapeutic medicine. It was the direct continuation of a previous investigation on the mode of action of lysozyme, which had occupied a Ph.D. student, L.A. Epstein, and myself in the years 1936-1938. The aim of this investigation was to establish the mode of action of this powerful bacteriolytic substance, discovered in 1922 by the London bacteriologist, Alexander Fleming, in tears, nasal secretion, and egg white, and capable of dissolving thick suspensions of a non-pathogenic micro-organism, b.lysodeicticus. We achieved our aim and were able to show that lysozyme was an enzyme hydrolising a polysaccharide substrate in the cell wall of b.lysodeicticus with the liberation of n-acetyl glucosamine. The full structure of the substrate of lysozyme was established later; it contained another sugar, n-acetyl-muramic acid, as part of the basic disaccharide unit.

When our work on the mode of action of lysozyme neared its end, we undertook a literature survey to find out whether other bacteriolytic substances, similar to lysozyme, had been described. This literature survey led me to the discovery of quite a large number of descriptions of the phenomenon of microbial antagonism, i.e. the capability of some micro-organisms, bacteria, moulds, and yeasts to produce substances inhibiting the growth of other micro-organisms, but to very few description of bacteriolytic substances, similar to lysozyme. However, I came across a paper published in 1929 by the same Alexander Fleming, in which he reported a striking lytic action of a mould metabolite against the staphylococcus, and the growth inhibitory action, without actual lysis, against many gram-positive and a few gram-negative pathogenic cocci of the culture fluid on which the mould was grown.