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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 fluid 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

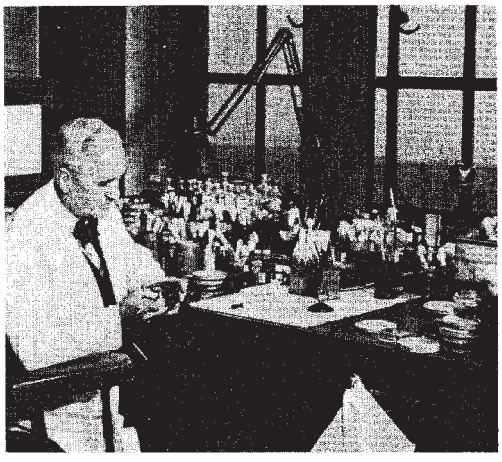

FIG. 1. Alexander Fleming at St. Mary's Hospital.

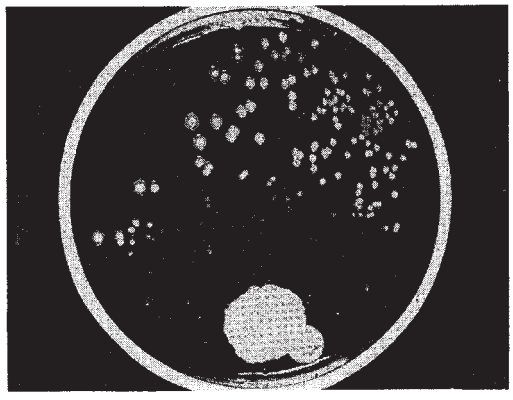

FIG. 2. Fleming's original plate isolation showing a colony of *Penicillium* and lysis of staphylococci (from Fleming, 1928).

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 Hare, 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.

FIG. 3. Howard Florey (top, left) at the Sir William Dunn School of Pathology after his appointment to the Chair of Pathology at Oxford. (Bottom, right) Sir Edward Mellanby (Secretary of the British Medical Research Council).

FIG. 4. Dr. Chain at the Sir William Dunn School of Pathology (about 1945).

At Florey's suggestion, Chain began working on lysozyme and thus became familiar with the already extensive literature on naturally occurring antimicrobial substances. In the course of their discussions, Florey and Chain formulated a plan to make a systematic investigation of substances of this kind and it may be worthwhile to mention the reasons which motivated them to do so. One was that the field invited further exploration from the point of view of scientific interest. The other was that a grant which supported Chain was coming to an end and that a project was needed which would attract a new grant to replace it. In applications to the Rockefeller Foundation and the British Medical Research Council, it was possible to hint that a study of naturally occurring antibacterial substances might lead to results which would be useful to medicine. But, in fact, the primary motivation was scientific curiosity and there was no serious expectation at the time that the work would lead to findings of clinical application. Indeed, Florey said much later that "the idea of helping suffering humanity never entered our minds."

At the beginning of the work several substances, whose existence had already been reported, were chosen for further investigation and one of these was penicillin. There were apparently two reasons why penicillin was included. First, it was an unstable substance whose isolation appeared to Chain, as a biochemist, to be a challenge. Secondly, it had been shown by Fleming to be active against the staphylococci, organisms against which the sulfonamides had proved relatively ineffective. At that time Florey had a rather personal interest in staphylococci because his young daughter, Paquita, was suffering from boils. Whatever the reasons for it, the choice must be regarded as a piece of

great good fortune, for any numbers of other substances could have been chosen and, however good the research, the results would have been of no significance to medicine.

Chain began the first experiments with penicillin at Oxford in 1938, under the impression, perhaps derived from his studies of lysozyme, that it was an enzyme. But no great priority was given to this work and no substantial progress was made in the purification of the substance until the spring of 1940. At that time N. G. Heatley suggested what seems, in retrospect, to be a very simple maneuver, but one that had not in fact been tried before. This was to extract penicillin from an acidified aqueous solution into an organic solvent, as had already been done, but then to re-extract it into water at pH 7 instead of evaporating the solvent. It was at this stage that Clutterbuck and Raistrick had lost all activity during a study of penicillin and had discontinued their work. This simple maneuver proved to be a key step in all subsequent purification processes of penicillin and Florey used the crude material so obtained at Oxford, still less than 5% pure, for chemotherapeutic experiments in mice. It was the astonishing success of these experiments which transformed our outlook on penicillin and led to the assembly of a small group of research workers and technicians who made what may perhaps be described fairly as heroic efforts, under war-time conditions and with make-shift apparatus, to obtain enough material by 1941 for small trials on man at the Radcliffe Infirmary. The gratifying results of these trials are well known.

FIG. 5. Dr. Heatley at work at the bench.

FIG. 6. Prof. Florey injecting into the tail vein of a mouse.

FIG. 7. Production of penicillin at Oxford, 1941.

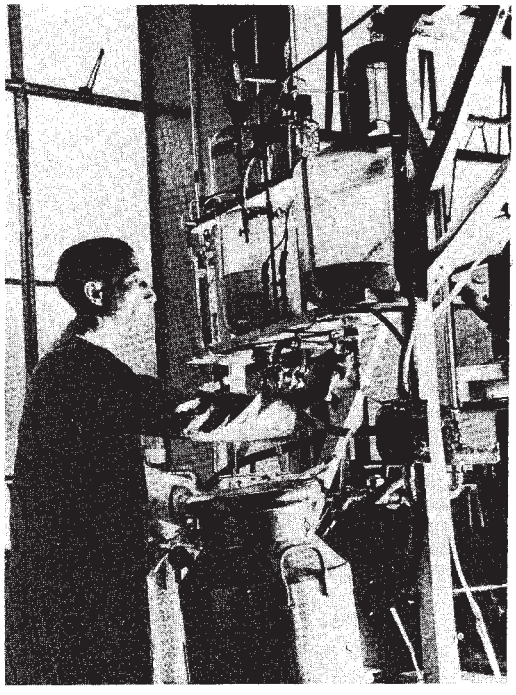

FIG. 8. Extraction of penicillin with make-shift apparatus at Oxford, 1942.

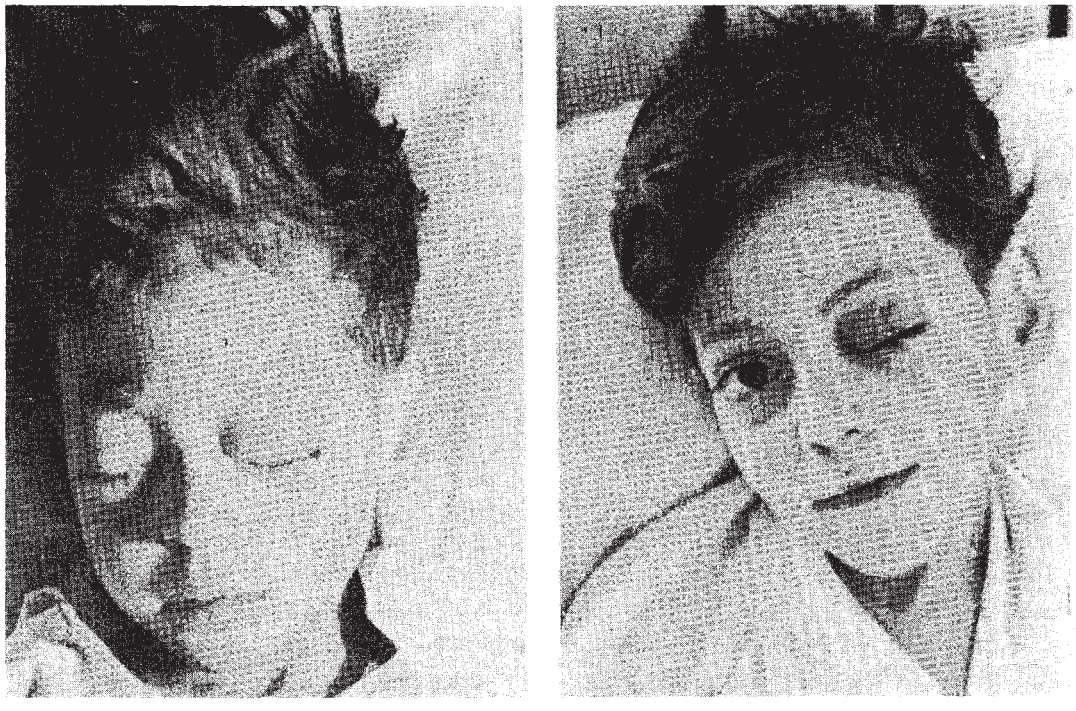

FIG. 9. Case of cavernous sinus thrombosis due to staphylococci. Left: The patient before treatment, a 4-year-old boy considered moribund. Right: after penicillin treatment (from Abraham et al., 1941).

Early in this period some biochemical and microbiological observations also were made which developed later into widespread areas of investigation. Thus, penicillin was known to be much less active against many gram-negative bacteria than against gram-positive organisms; Chain and I wondered whether this was because the gram-negative bacteria contained an enzyme which destroyed the antibiotic. In 1940 we ground the cells of a strain of *E. coli* in an old ball mill and found such an enzyme, which we named penicillinase, in the extract. Other experiments by A. D. Gardner showed that bacterial cells became swollen and distorted in the presence of subinhibitory concentrations of penicillin. In more recent times the work of Park, Lederberg, and Strominger and their colleagues has shown that penicillin interferes specifically with bacterial cell-wall synthesis and has begun to throw light on the details of the mechanism by which this occurs.

So far, I have said nothing about the contribution of industrial microbiology to the penicillin story, but we have only to remember that the yields of penicillin obtained in the early work at Oxford were about two units per milliliter, whereas the yields now obtained by pharmaceutical companies are many thousands of units per milliliter, to realize the importance of this contribution. It was made largely in the United States, partly because your technology was more advanced than ours and partly because we were engaged heavily in war. In the Northern Regional Research Laboratory at Peoria, which was visited by Florey and Heatley at the suggestion of Charles Thom, radical improvements were made quickly through the initiative of R. D. Coghill, A. J. Moyer, and others. Deep fermentation was introduced in place of stationary cultures and penicillin production was found to be stimulated by the addition of corn steep liquor, readily available locally, to the culture medium.

Nevertheless, when Florey and Heatley crossed the Atlantic in war-time to enlist American aid, penicillin was scarcely a soft sell. The difficulties of producing large amounts of material seemed formidable indeed, and Florey attributed the success of his mission partly to his friendship with A. N. Richards, then Chairman of the War-time Committee on Medical Research of the Office of Scientific Research and Development. What Florey described later as a pay-off from this connection was that the American Government was persuaded to inject a great deal of money into the project. In any event, we saw an unprecedented cooperation between scientists in American and British pharmaceutical firms, universities and Government institutions, the emergence of higher-yielding strains of *Penicillium chrysogenum* which transformed the outlook, and the production of enough penicillin to treat all serious battle casualties by D-day in Europe. To our disappointment, none of this penicillin reached Oxford for further research, and I learned why this was so shortly after the war, when I was in Rahway, N.J. I was told, to my astonishment, that George Merck would like to meet me. As it turned out, he wished to explain that Merck's undertaking to Florey to send some penicillin had not remained unfulfilled through lack of good will but because almost all the material produced had been requisitioned by the armed services.

Although the large-scale production of penicillin was a very great triumph for industrial microbiology during those war years, it would be wrong to imagine that the microbiologists had no competitors. In 1943 benzylpenicillin was crystallized by MacPhillamy, Wintersteiner, and Alicino at Squibb, and soon afterward crystalline pentenylpenicillin was obtained at Oxford. Definitive structures for the penicillin molecule could be proposed and a great deal of effort in the United States and England went into attempts to produce the substance by total synthesis. In the early stages of this

FIG. 10. Members of the group at Oxford who worked on the chemistry of penicillin. Right to left: Sir Robert Robinson, E. B. Chain, Wilson Baker, and E. P. Abraham.

work some, at least, of those involved had high hopes of rapid success. Indeed, it was rumored that the chemists of Merck & Company were willing to wager a case of whiskey that they would have synthetic penicillin within a few months. All this effort produced interesting chemistry but came to very little in practical terms. The chance of success was not increased by the fact that two different structures were then being advocated, containing a β-lactam-thiazolidine and a thiazolidine-oxazolone ring system, respectively, and that much of the effort went into attempts to synthesize the latter. But the work was regarded as sufficiently important to be classified as secret in both England and the United States and it clearly was also thought to be of some importance in other countries. When the reports in which it was embodied were finally declassified, a small squad of photographers descended on us from a foreign embassy and copied the collection.

For some years after the war, it would have been excusable to conclude that the major contributions of penicillin to chemotherapy had already been made and no one could have predicted the remarkable developments which were to follow. Dr. Behrens and his colleagues at Eli Lilly had shown that a variety of penicillins could be obtained from fermentations of *P. chrysogenum* by addition of appropriate side-chain precursors to the medium, but none of these substances appeared to offer substantial advantages over the benzylpenicillin already being produced on a large scale. Then, in the early 1950s, the picture began to change and the research which brought this about provides a good illustration of the international face of science. At M.I.T., John Sheehan took up the study of the chemical synthesis of penicillin and began to throw a good deal of new light on the chemistry of the molecule in investigations which culminated in its total synthesis by use of a new reagent for ring closure. In Japan, Kato produced circumstantial evidence that the nucleus of the penicillin molecule, now known as 6-APA, was present in fermentation broths; Sakaguchi and Murao reported that this nucleus could be obtained by hydrolysis of penicillin itself by an enzyme from *P. chrysogenum*. These studies later came to fruition with the isolation and characterization of 6-APA by workers in the

Beecham Research Laboratories, with its production in quantity and the demonstration that it could be acylated to give new and useful penicillins unobtainable by fermentation.

Even before this, what was to be a very fruitful discovery had been made by Professor Giuseppe Brotzu in Cagliari, Sardinia. Brotzu was a politician and administrator as well as a bacteriologist, but in 1948 he was sufficiently free from other commitments to undertake some personal research. He thought that antibiosis might play a role in the self-purification of sewage and he recovered from the sea, near a sewage outfall, a species of *Cephalosporium* which produced antibacterial material. He used a crude extract of the culture filtrate, apparently with some success, for the treatment of infections in man. Having failed to interest the Italian pharmaceutical industry, he published a lucid account of his findings in what appeared to us, when we first saw it, to be a journal called *The Works of the Institute of Hygiene of Cagliari.* In this he expressed the hope that others with greater facilities would continue the work. It seems unlikely that this publication would have received much attention had it not been that Dr. Blyth Brook, an English friend of Brotzu, wrote about it to the Medical Research Council in London. Indeed, when I asked Brotzu years later how often the Sardinian Journal appeared he replied that it was a unique issue, but that there would be a further volume should he ever make another discovery of comparable interest. In any event, and at the suggestion of the Medical Research Council, Brotzu sent his organism and a copy of his paper to Oxford.

In the Sir William Dunn School of Pathology the *Cephalosporium* sp. was first found to produce an antibiotic, named cephalosporin P, which was extractable into organic solvents, was entirely different in its antibacterial properties from the material studied by Brotzu, and which turned out to be a steroid. However, my colleague, G. G. F. Newton and I were somewhat more interested in the finding that it also produced a hydrophilic antibiotic, because this substance appeared to be an unstable peptide and the study of such substances had been one of our major research interests. We succeeded in isolating this compound and in showing that it was a new penicillin with a D-α-aminoadipyl

FIG. 11. Prof. Brotzu at his laboratory in Cagliari. (Photo courtesy the Glaxo Research Laboratories.)

FIG. 12. Plate showing inhibition of bacteria by the *Cephalosporium* isolate of Brotzu (from the original publication by Brotzu in 1948).

FIG. 13. Dr. Newton, about 1950.

side-chain. Its range of antibacterial activity corresponded with that described by Brotzu, but was quite different from that of derivatives of it obtained by acylation of the side-chain, or from that of benzylpenicillin. This was probably the first demonstration that a radical and potentially useful change in antibacterial properties could accompany an appropriate change in the side-chain of a penicillin. The new penicillin, now named penicillin N, turned out to be identical with a previously uncharacterized antibiotic, named synnematin, which had been obtained in a crude form from a different *Cephalosporium* sp. by Olson and his colleagues. The crude product was used, with considerable success, in small-scale clinical trials against typhoid fever and there were some pressures from both inside and outside the pharmaceutical industry to have it produced and purified in quantity. But its commercial production was never undertaken, apparently because the cost of developing a process to deal with this labile and hydrophilic antibiotic seemed to be too great in relation to the likely returns.

Cephalosporin P and penicillin N were the only antibiotics which we detected by antibacterial assay of culture filtrates and crude extracts of the Sardinian *Cephalosporium* sp., but a third antibiotic was discovered in a purely academic study of the chemistry of penicillin N. In 1953, during an experiment designed to isolate the penillic acid of penicillin N in a pure form from partially purified penicillin N itself, Newton and I observed that the penillic acid was followed from an ion exchange column by a second substance which had a characteristic ultraviolet absorption spectrum. This substance, named cephalosporin C, was isolated as a sodium salt in crystalline form. It was subsequently shown to have antibacterial activity, but the latter was too low for it to have been detected by antibacterial assay, at that time, in fermentation fluids. It thus seems unlikely that cephalosporin C would have been discovered in a conventional screening program. Its detection was, in fact, a totally unexpected bonus from our decision to put the finishing touches to the evidence for the structure of penicillin N.

Two findings persuaded us, at an early stage, that cephalosporin C was worth detailed investigation. One was that it resembled penicillin N in some of its chemical properties

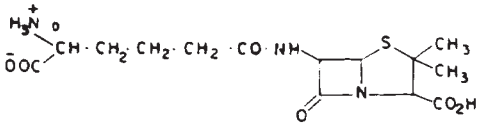

FIG. 14. Structure of Penicillin N (from Newton and Abraham, 1954).

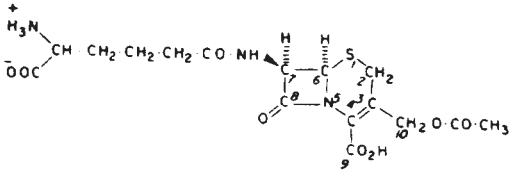

FIG. 16. Structure of Cephalosporin C (from Abraham and Newton, 1961).

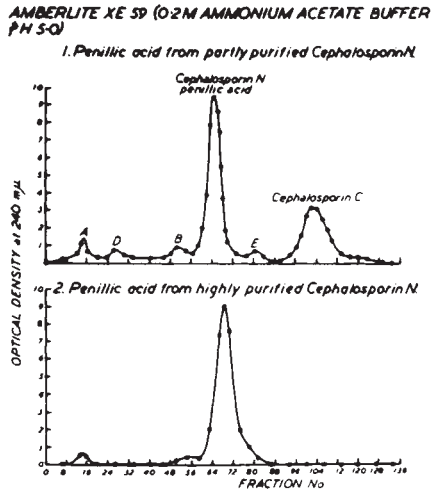

FIG. 15. Discovery of Cephalosporin C in partly purified penicillin N penillic acid (from New ton and Abraham, 1956).

but differed from it clearly in others, and the second was that it was resistant to the action of a penicillinase. These two properties gave it not only a scientific interest but also a potential interest to chemotherapy, for at that time the emergence of staphylococci which were highly resistant to penicillin (because they produced a penicillinase) was becoming a very serious clinical problem.

In some respects the problems which had to be overcome before cephalosporins were introduced into medicine were greater than those encountered with penicillin, despite the great increase in knowledge acquired by the industrial microbiologists in the intervening years. Cephalosporin C was produced in very small yield by the Sardinian *Cephalosporium* species, as was penicillin by the original strain of *Penicillium,* but the hydrophilic properties of cephalosporin C made it more difficult to purify. In obtaining sufficient material for chemical investigations and protective experiments in mice, we received indispensable help from the Antibiotics Research Station at Clevedon, near Bristol, a small institution which had been adapted for penicillin production during the war by the British Admiralty in the hope that the Navy might then have its own source of supply. The station had then been taken over by the Biochemical Group of The Distillers Company for the testing of culture fluids produced in a screening program and after the war had been acquired by the Medical Research Council. However, great difficulties were encountered by its staff in scaling-up cephalosporin C production until they isolated a mutant of the original organism which yielded larger amounts of this antibiotic than the parent Sardinian strain, although still very much less than strains now available. With the material finally produced, Newton and I were able to obtain enough information by 1959 to propose a definitive structure for cephalosporin C. By this time, also, Florey had shown that it had an extraordinarily low toxicity to mice, lower than that of benzylpenicillin, and that it was able to protect mice from infection with penicillinase-producing strains of staphylococci which did not respond to treatment with benzylpenicillin.

From soon after the time of its discovery, it had been clear that cephalosporin C suffered from one grave disadvantage, despite its highly desirable properties: although it

showed a wide range of antibacterial activity, its intrinsic activity was low and very much lower than that of benzylpenicillin against sensitive organisms. Nevertheless, the situation at that time with respect to the penicillinase-producing staphylococci was so serious that cephalosporin C itself might well have been used to treat infections with this organism, in large doses and by intravenous drip, had it not been for a new development in the penicillin field which came from the Beecham Research Laboratories. This was the chemical synthesis from 6-APA of methicillin (2-6-dimethoxyphenylpenicillin), which proved to be of great value because it had a very low affinity for the staphylococcal penicillinase and was hydrolyzed by it at only a negligible rate in therapeutic concentrations. However, we were able to demonstrate that chemical manipulation of the cephalosporin C molecule could lead to compounds with higher activity. By mild acid hydrolysis the α-aminoadipyl side-chain of cephalosporin C could be removed to yield (although in only minute amounts) the nucleus of the molecule 7-aminocephalosporanic acid, or 7-ACA. Acylation of 7-ACA with phenylacetylchloride produced a compound whose activity, as expected from analogy with benzylpenicillin and penicillin N, proved to be very much higher than that of the parent compound. In addition, we showed that the acetoxyl group of the acetoxymethyl attached to the dihydrothiazine ring of cephalosporin C could be replaced by nucleophiles, such as pyridine, and that derivatives so obtained were also more active against some organisms than cephalosporin C itself.

By this time it had become clear that the key to the door to further progress was the discovery of a method which would produce 7-ACA from cephalosporin C in high yield. I must admit that I felt quite confident that this would be achieved, without too much difficulty, by the discovery of an enzyme which would remove the α-aminoadipyl side-chain, but extensive searches by pharmaceutical companies in the United States and the United Kingdom failed to result in the discovery of such an enzyme. This was a period of considerable discouragement when it seemed possible that the whole cephalosporin project might come to nothing in a commercial or medical sense. At that time Florey went to a dinner at which he sat next to Harry Jephcott, then head of Glaxo, and was told that the firm was spending large sums of money on the cephalosporin project without any indication of a successful outcome in sight. Florey replied, "Don't lose your nerve." Whether this characteristic remark encouraged Glaxo to persist I don't know, but soon afterward the situation was transformed by the discovery, in the Lilly Research Laboratories, of a chemical process for removing the cephalosporin C side-chain to give 7-ACA in quantity. From then on the stage was set for the systematic production of a large series of compounds and the further testing of those which seemed likely to be of use in medicine. Among the latter were cephalothin, in which the α-aminoadipyl side-chain of cephalosporin C was replaced by a thienylacetyl group, and cephaloridine, in which the O-acetyl group of cephalothin was replaced by a pyridinium cation.

Surprisingly, and for reasons which are still not clear, the first cephalosporins to find clinical use were not absorbed, unlike comparable penicillins, from the gastrointestinal tract and could only be used parenterally. This limitation was overcome by the finding that cephalexin, which has the D-phenylglycyl side-chain of ampicillin but a methyl group instead of the acetoxymethyl group in cephalothin and cephalosporin C, is not only absorbed from the intestinal tract, but absorbed with extraordinary efficiency.

This was not to be the end of the cephalosporin story in so far as it impinged on industrial microbiology. One important development was the discovery in the Lilly Research Laboratories of ingenious chemical procedures for transforming the penicillin into the cephalosporin ring system. In consequence, only a penicillin fermentation is

needed, at least in principle, to produce cephalosporins as well as penicillins on a large scale. Another development coming from the Lilly and the Merck Laboratories has been the finding that 7-methoxycephalosporins, with a methoxyl group attached to a carbon of the β-lactam ring, are produced by certain strains of the prokaryotic organisms, *Streptomyces*. These compounds contain the same D-α-aminoadipyl side-chain as cephalosporin C. Even so, their discovery was surprising, for the cephalosporin ring system had previously appeared to be almost a unique product formed only by the Sardinian *Cephalosporium* sp. and mutants derived from it. We may perhaps wonder whether other surprises are in store for us in this field: whether, for example, deacetoxycephalosporins, containing the ring system of cephalexin, may not be obtainable by fermentation and, indeed, whether it may not be possible to find biosynthetic routes to cephalosporins with side-chains other than α-aminoadipic acid, just as a variety of penicillins may be obtained from fermentations with *Penicillium chrysogenum*. The biosynthesis of these related, yet quite distinct, families of antibiotics almost certainly follows a common pathway over part of its course. The nature of the bifurcation of this pathway is one of the fundamental problems that remain to be solved and whose solution could eventually lead to developments of practical significance.

In retrospect, it seems astonishing that a field which showed some signs of being worked out more than 20 years ago should subsequently have flowered in such a remarkable fashion as a result of the combined work of microbiologists and chemists. This has led to the production of new penicillins which have extended the range of bacterial chemotherapy and of cephalosporins which have extended it still further and which may be given with impunity, in mose cases, to penicillin-sensitive patients. But this, of course, is only one side of the coin. The so-called antibiotic era has been possible because among the innumerable secondary metabolites of microorganisms are some which are able to damage selectively features of microorganisms which differ from those of animal cells. How this has come about is still a matter of conjecture. If the selective pressure arose from the ability of these substances to protect some microorganisms from others, it does not now seem to be one of exquisite efficiency, for industrial microbiologists have had remarkable success in selecting, in the laboratory, strains which produce enormously more antibiotic than the wild types. But in the use of antibiotics we have imposed another selection pressure which has resulted, and continues to result, in the emergence of microorganisms resistant to the substances in common use. In the case of the penicillins and cephalosporins, this has been related to the appearance of a variety of different β-lactamases and of organisms which differ in their cell walls, or, at the molecular level, in a cell-wall synthesizing enzyme, from other organisms that are sensitive. Members of some genera, such as *Pseudomonas*, have continued to present a medical problem for one or more of these reasons.

I have emphasized here the role of chance in the successes of the antibiotic story and this is particularly apparent in the case of penicillin and cephalosporin C, which were not discovered by screening programs but as offshoots of more or less academic investigations. Once a lead has been obtained in this area, both microbiologists and chemists have shown that they are now well able to exploit it with great skill. But, although we can sometimes argue very profitably from analogy here, no one could have predicted from first principles that compounds with the penicillin or the cephalosporin ring system would be useful drugs, or that they would differ from each other in their biological properties in the useful ways they do. It is perhaps symptomatic of this state of affairs that 7-methoxycephalosporins, which arose from observation in screening programs, show

some signs of being useful antibiotics; whereas 6-methylpenicillins, which were synthesized chemically on the basis of a rational prediction from our present knowledge of bacterial cell-wall synthesis, do not.

In short, we know far too little about the detailed macromolecular structures with which such selective antibiotics react. In these days, in which governments are showing signs of restricting their grants for research more and more to those which they think may pay off in the near future, this is perhaps an argument for allowing some of our resources to be used to satisfy the long-term curiosity of scientists without requiring an immediate return.

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