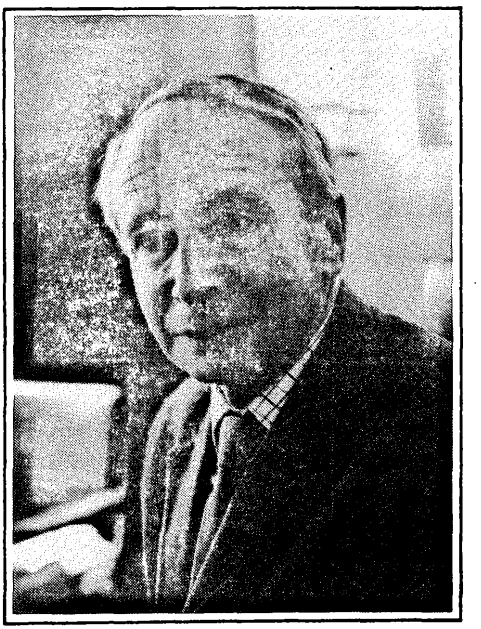

REFLECTIONS ON THE DEVELOPMENT OF THE PENICILLINS AND CEPHALOSPORINS

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George Sarton was a pioneer of independent means who is widely acknowledged to be the founder of the history of science as an intellectual discipline. I feel greatly honoured to have been selected for the award of this Sarton Chair, particularly since I can make no claim to be a professional historian of science or medicine. But I have happened to live through the fifty years of what may be called 'the antibiotic era' and to have had the good fortune to be in personal contact with some of the ways in which it has developed and the people who figured in it.

In a previous and intriguing Sarton lecture Robert Merton, a student and friend of Sarton, spoke on 'The Matthew effect in Science'. He was concerned with the distribution of credit and reward in science and went for his title to the first gospel where a parable is used to explain how it can be that to those who have shall be given, but from those who have not even that which they have shall be taken away. The present lecture will be in some respects somewhat more specific. But I will try to indicate how chance events, scientific curiosity, personalities, industry and government policies were all involved in developments that led to one of the great medical advances of the 20th century. Little more than fifty years have passed since the time when physicians could do little in the face of life-threatening bacterial infections, when bacterial endocarditis was almost invariably fatal and meningococcal meningitis left its few survivors with pitiable disabilities.

Observations of the activity of some microorganisms against others and the idea that microbial products might have therapeutic use can be traced back at least to the time of Lister and Pasteur, but the early observations had little impact on medicine. There are several reasons why this was so. Time has shown that only a very small proportion of such substances have a low enough toxicity to man to be injected safely into the blood stream; many of the earlier observations were made by microbiologists who had no chemical or biochemical collaborators; and the methods available for the isolation and characterisation of substances from natural sources were far less advanced than they are today.

In World War I Alexander Fleming studied the effect of a number of antiseptics applied locally to war wounds and came to the conclusion that those in common use were not only ineffectual but harmful, because of their toxicity to animal cells. By the end of the nineteen-twenties it was widely believed that searches for a substance that was highly active against pathogenic bacteria but innocuous to man would be fruitless. That this pessimism was not justified became evident only a few years later after the chance discovery of an antibacterial substance that was not a product of the microbial world but of the dye industry. Following the interest of Paul Ehrlich in the selective staining of dyes, Domagk tested a number of dyes synthesised by the I. G. Farben industry. He found that one of them, prontosil, would protect mice from streptococcal infections. It is fortunate indeed that his tests were done *in vivo* and not in the test tube, for prontosil is inactive *in vitro*. Soon after Domagk's finding prontosil was shown by others to be split in the body to an inactive compound and to sulphanilamide, the first of the sulphonamides.
Sulphanilamide had been described in the chemical literature in 1908, but there had been no reason to suspect that it would have chemotherapeutic properties and it had never been tested for antibacterial activity.

The sulphonamides caused a dramatic reduction in deaths from streptococcal infections, particularly those responsible for puerperal fever in childbirth. Incidentally, a sulphonamide provided my first

encounter with a clinically useful antibacterial substance. Just after the outbreak of World War II, when I was Rockefeller Fellow in Stockholm, I became infected with a streptococcus. My Swedish physician told me that unless I took the tablets he had prescribed I should only be travelling home, if at all, in a wooden box. So I took the tablets, managed to reach Oxford alive, and became involved in research on penicillin. However, the sulphonamides had serious limitations; they were not very effective, for example, against infections with staphylococci.

Fleming's good fortune

Domagk should have counted himself fortunate that prontosil was included among the azo dyes that he tested, for he did not realise that it was a colourless derivative of this dye which was medically important. The role of chance was far more striking, however, in Alexander Fleming's discovery of penicillin in 1929. Despite his discouraging experience with antiseptics in the local treatment of war wounds, he was not looking for a better substance. He had been asked to write a review on the staphylococcus and left plates of nutrient broth seeded with this organism on his laboratory bench while he went on vacation. On his return he noticed that one of these plates had been contaminated with a *Penicillium* and that in the area around this fungus the staphylococci appeared to be undergoing lysis. But, since penicillin lyses growing staphylococci but not those in fully grown cultures, how did this phenomenon occur ? Ronald Hare, a contemporary of Fleming, established that a spell of cool weather happened to be followed by a warm spell at that time. The *Penicillium*, grows best at a lower temperature than the staphylococcus. Hence the fungus could have grown and secreted penicillin before the staphylococcal colonies were fully established.

It is to Fleming's great credit that he did not ignore his unexpected discovery, although it was extraneous to the work he had in hand. He preserved the fungus and grew it to obtain an active culture fluid and gave the name penicillin to this 'mold broth filtrate'. He

showed that this solution was highly active against some bacteria, but not others, and that it was not toxic to white blood cells and to a rabbit.

Fleming made some use of his 'mold broth filtrate' as a dressing for septic wounds, but said later that there was no miraculous success.

He then appeared to lose interest in penicillin as a therapeutic agent event after the advent of the sulphonamides and in 1940 wrote that 'the trouble of making it seemed not worth while'. It is of interest to speculate why this was so and why he never tried to find out, as he might have done, whether it was able to protect mice from lethal streptococcal and staphylococcal infections when injected into the blood stream. The answers to these questions probably lie in his personality, which was not conducive to his entry into a new field; in the discouraging climate of opinion at the time; and in the fact that he was not equipped, as a medical bacteriologist, to grapple with the problem of handling and purifying a relatively unstable substance.

However, Fleming's good fortune extended beyond the unusual events that enabled him to bring penicillin to light : he lived to obtain the lion's share of the public acclaim after others had revealed the outstanding importance of this discovery. Whether this provides an illustration of the Matthew effect I hesitate to say. But it clearly demonstrates the power of the media to influence the public's perception of history.

Florey, Chain their colleagues and the rôle of chance

The dramatic transformation of penicillin from little more than a curiosity to a substance of great therapeutic value came, more than ten years after it had been revealed by Fleming, with the discovery in Oxford of its ability to cure systemic bacterial infections — first in mice and then in man. How did this come about ? The stage for the new development was set by Howard Florey, an Australian who came to Oxford as a young man to study physiology and became a Universi-

ty Professor of Pathology in the Sir William Dunn School of Pathology in 1935.

Florey had first wished to study chemistry, but was advised that there were few jobs for chemists in Australia at that time and he therefore turned to medicine. But he retained a strong interest in chemical substances with biological activity, one of which was the bacteriolytic enzyme lysozyme that had been discovered by Fleming in 1921. He was convinced that this subject needed the collaboration of experimental pathologists with those in other disciplines and when he obtained the Chair in Oxford he found positions for chemists and biochemists in his Department. The first to come was Ernst Chain, a refugee from Hitler's Germany. He was followed by Norman Heatley and then, in January 1940, by me.

At Florey's suggestion Chain began to study the mode of action of lysozyme and during this work made a survey of the extensive literature on antimicrobial substances produced by microorganisms. In the course of many discussions in 1937-1938 with Florey, who drew his attention to a review of the field by Papacostas and Gaté in 1928, Chain suggested and Florey agreed that a systematic investigation of such substances should be undertaken. Three substances were first chosen for study and one of them was penicillin.

Chance intervened in several of these events and those that followed. Florey's election to the Chair of Pathology in Oxford nearly failed to occur, because his strongest supporter was late for a crucial meeting of the Electoral Board and only arrived just in time to prevent the despatch of an offer to another candidate. Florey's first choice for a chemical collaborator turned out to be unavailable and Chain was suggested in his place by Gowland Hopkins at Cambridge. Heatley had planned to go to Denmark in the autumn of 1939 to work with Linderstrom-Lang, but was prevented form doing so by the outbreak of war. And had it not been for the war and the reorganisation of research to which it led it is unlikely that I would have become a

member of the Sir William Dunn School of Pathology when I returned to Oxford from Sweden.

However, the war, or the prospect of war, was in no way responsible for the decision to investigate naturally occuring antimicrobial substances. What motivated this decision ? One factor was probably the poverty of the School of Pathology in the 1930's and the knowledge that a grant from which Chain was paid was coming to an end; a project that might attract a new grant was thus highly desirable. Another was that the project appeared to be one of wide scientific interest. Both Florey and Chain insisted later that they had no expectations that it would yield results of clinical value. Indeed, Chain wrote that he had believed penicillin to be a microbial protein that would provoke an immune reaction and thus be disqualified from systemic medical use. Florey stated in a short recording of his life : "I don't think that the idea of helping suffering humanity ever entered our minds". Nevertheless, in subsequent applications for support from the Rockefeller Foundation and the medical Research Council it was mentioned that the study might lead to medically useful substances. Perhaps this is an example of a not uncommon tendency of academic applicants for grants to point to the possible utility of the research they propose in the hope that this will increase the chance that their application will be successful.

But why was penicillin included in the substances chosen for study ? Chain stated that he regarded the reported instability of penicillin as a challenge to the biochemist and Florey appears to have been interested in its activity against the staphylococcus. In any event, it was by great good fortune that the choice was made, for in 1949 Florey could say that the outcome was so gratifying as to be almost unbelievable.

I do not propose here to go into the details of the work which led to Florey's demonstration in May 1940 that penicillin would cure generalised infections in mice and then to the first clinical trial in the

Radcliffe Infirmary in Oxford. But it may be of interest to recall some of the problems that arose and the attempts to overcome them.

One major problem, of course, arose from the minute amount of penicillin (about 1μg/ml) that was produced in surface culture by Fleming's *Penicillium notatum*. Moreover, some of the fermentations failed because of contamination with bacteria that produced a penicillin-destroying penicillinase, a type of enzyme that we discovered in 1940 in *E. coli*, while looking for an explanation of the fact that some bacteria were relatively resistant to penicillin.

Heatley achieved a ten-fold purification of the early penicillin-containing extracts by transfer between solvents. Nevertheless the resulting purity of product used in the mouse experiments was probably less than 0.1 and 0.2%. The purity of most of the material prepared subsequently for clinical trial was between 2 and 3%. It was fortunate indeed that the great mass of impurity in these early preparations was itself relatively innocuous, for if it had been toxic the therapeutic power of penicillin would have been concealed. However, the first penicillin to be injected into a patient produced a disconcerting rise in temperature and a rigor and a second patient reacted similarly. But fortunately it was soon shown that this was not caused by penicillin itself for by that time I had introduced a chromatographic step into the purification process which removed the pyrogenic material.

Larger scale production

The success of the early clinical trials and the potential value of penicillin for the treatment of war wounds made it evident that serious attempts should be made to produce enough penicillin for it to become widely available. Florey decided that this would not be possible in war-time Britain, then under heavy bombing, and he went with Heatley to the United States, where he had good friends, to enlist American support. This visit produced gratifying results, although it did not enable Florey to obtain the penicillin he urgently needed for further clinical trials. At the Northern Regional Research Laboratory in

Peoria, where Heatley described the current Oxford process, fermentation in deep aerated cultures was introduced and production stimulated by the addition of corn steep liquor, a by-product of the maize industry that was readily available in the Mid-West. Later, after a world-wide search for higher yielding strains of *Penicillium*, a superior strain of *Penicillium chrysogenum* was isolated by the group at Peoria from a mouldy canteloupe in the local market. Eventually the yield of penicillin obtained by fermentation in pharmaceutical companies was more than ten thousand times that produced originally by surface culture in Oxford. George Merck later explained to me why very little American penicillin came to Oxford : it was commandeered, he said, by the armed forces.

Despite this disappointment enough penicillin was obtained in the Sir William Dunn School of Pathology and from commercial British sources for a further clinical trial by Howard and Ethel Florey in 1942. The patients with very serious infections included one with a sulphonamide-resistant streptococcal meningitis and ten with either staphylococcal-osteomyelitis, septicaemia or cavernous sinus thrombosis. All these patients recovered after penicillin had been administered by intramuscular injection and there were no toxic effects. In addition, mastoid infections were treated locally and successfully by instilling penicillin, after mastoidectomy, through a tube sutured into the wound. This type of procedure involving early suture and the instillation of penicillin was used with success in North Africa when Florey and later Hugh Cairns went there in 1943 to study the best use of the still trivial amounts of penicillin available for the treatment of infected war wounds.

Isolation, structure and attempted synthesis of penicillin

When Florey had visited American pharmaceutical firms in 1941 some, including Merck, Squibb and Pfizer were seriously interested in penicillin production, others less so and some not at all. One reason for a lack of wider enthusiasm was probably the formidable difficulties that would face commercial production with the trivial

yields of penicillin obtainable by fermentation at that time. But another may well have been the expectation that fermentation would be supplanted by total chemical synthesis. Fleming had been bold enough to prophesy in 1940 that penicillin would not be used in war surgery "until some chemist comes along and finds out what it is and if possible manufactures it".

Before rational attempts could be made to synthesise penicillin it was clearly necessary to know its structure. Clutterbuck, Lovell and Raistrick had abandoned an attempt to isolate it in 1932. Chain and I began to purify penicillin in 1940 and by 1942 we had a product which proved later to be nearly 50% pure. Chain was so excited by the high antibacterial activity of this product that he became optimistic enough to say to me that nothing could be so active if it were not pure. But almost a year elapsed before we obtained nearly pure material. By this time we had isolated several characteristic degradation products of penicillin and had begun to collaborate with Professor Sir Robert Robinson and Dr Wilson Baker in the Dyson Perrins organic chemistry laboratory in Oxford, while work in a number of American Institutions was under way. In July 1943 our earlier belief that sulphur was absent from the penicillin molecule, based on the failure of a micro-analyst to find it, was shown to be wrong.

In august 1943 a telegram from Squibb gave the exciting news that their penicillin had been crytallised as a sodium salt. I then converted our purest material, which was in the form of a barium salt, to a sodium salt and the latter was found to crystallise spontaneously. It was evident, however, that the British and American penicillins were not identical. They had a common nucleus but different side-chains, due to the presence of a side-chain precursor in the corn steep liquor added to the American fermentations.

By October 1943 it seemed clear that the penicillin structure was to be obtained by the removal of the elements of water from a known degradation product of penicillin. But how was this to be done ? On the basis of my finding that penicillin contained no basic group, I proposed the well known ß-lactam structure in October 1943.

However, Sir Robert Robinson disliked this structure intensely and proposed an alternative one. Controversy continued until 1945, when a crystallographic analysis by Dorothy Hodgkin and Barbara Low finally showed that the ß-lactam structure was correct.

Immense efforts were made in Britian and the United States during the war to synthesise penicillin — many of them with the wrong structure in mind. But despite the activities of at least a thousand chemists in some thirty-nine major laboratories, only traces of the drug were ever obtained. One reason was the unavailability at that time of a reagent that was mild enough to close the four-membered ß-lactam ring without inactivating the resulting penicillin. A few years after the war such a reagent was found by John Sheehan at MIT, who used it in a rational synthesis of penicillin. However, the production of penicillin by fermentation had then become so efficient that chemical synthesis had no chance of competing with it. Later, however, chemical studies were to make major contributions to the field.

The penicillin nucleus and new penicillins

At the end of the war the astonishing therapeutic properties and the limitations of penicillin were well established. It seemed possible that the final chapter in the history of its great contribution to bacterial chemotherapy had already been written and indeed that its value might decline because of the emergence of resistant bacteria. A number of penicillins with different side-chains were obtained in the Eli Lilly laboratories by the addition of appropriate precursors to the fermentation, but the type of side-chain that could be introduced in this way was limited and the resulting compounds were not clearly superior in antibacterial activity to the original penicillins.

However, two unpredictable events changed this situation. One was the isolation of the nucleus of the penicillin molecule, 6-aminopenicillanic acid, and the other was the discovery of the first cephalosporin and the production of its corresponding nucleus, 7-aminocephalo-

sporanic acid. To these nuclei innumerable side-chains could be added by chemical procedures.

The penicillin nucleus was first observed by Sakaguchi and Murao in Japan in 1950. They reported that it was formed when the side-chain of benzylpenicillin was removed by an enzyme in *P. chrysogenum*. Three years later indirect evidence for its existence in fermentations to which no side-chain was added was obtained by Kato, also in Japan. But these findings were not pursued further in Japan and we may ask why this was so, since an important development was in sight. One reason was that the Japanese workers had no chemical collaborators, and another was that Murao and Kato went to other institutions where there was little interest in penicillin research. However, in 1956 Batchelor and Robinson independently made observations similar to those of Kato while working in Chain's laboratory in Rome. After their return to Beecham they concluded that their results were due to the presence of the penicillin nucleus (6-APA). In 1958 this substance was isolated and characterised and a series of new and clinically valuable penicillins with an extended range of activity was then obtained from it by semi-synthesis.

Chance and the Cephalosporins

The discovery of the cephalosporins came from a decision of Giuseppi Brotzu, a Sardinian medical bacteriologist who had been Rector of the University of Cagliari and was later Mayor of the city, to look for new antibiotic-producing organisms near a sewage outfall. He supposed that the self-purification of sewage was partly due to antibiosis. Although it is doubtful whether this idea was well-founded, he quickly isolated in 1945 a *Cephalosporium* fungus that produced material with a broad range of antibacterial activity. He boldly injected this crude material into patients and concluded that it had a beneficial effect, particularly in cases of typhoid fever. But he had neither the facilities nor the expertise to carry these observations further and his attempt to arouse the interest of an Italian pharmaceutical company was unsuccessful.

Brotzu then wrote to a British acquaintance who consulted the Medical Research Council in London and it thus came about that he kindly sent his organism and a copy of a publication, entitled 'Richerche' su di un Nuovo Antibiotico', to the Sir William Dunn School of Pathology, Oxford, in 1948. For some time we imagined that this paper was a contribution to an unfamiliar Sardinian journal called 'Lavore dell'Istituto d'Igiene di Cagliari'. But years later, when I met Brotzu for the first time and asked him how often this journal appeared, he smiled and said that it had never appeared before or since but that there would be a second issue if he made another discovery that was of comparable interest. Had it not been for an unforeseen sequence of events it is highly unlikely that we would have been aware of his work.

It turned out that what Brotzu had described as 'A new antibiotic' was in fact a mixture of at least seven different antibiotics. Five of them were acidic steroids extractable by organic solvents.

However, it became clear to me that this group of substances could not have alone been responsible for the broad range of activity observed in Sardinia. I therefore studied the aqueous solution remaining after their extraction and found that it contained a different antibiotic with a wider range of activity. In deciding to investigate this substance further, my colleague Guy Newton and I were not at first motivated by the expectation that it would be of value in medicine, but by the fact that it had some of the chemical and physical properties of an unstable peptide and might therefore belong to a class of substances in which I had been interested since my earliest days of research. In the event we showed that it was a peptide-like penicillin with a new type of side-chain, consisting of an amino acid, which endowed it with a new type of antibacterial activity. It was finally named penicillin N.

Penicillin N was undoubtedly the antibiotic whose activity had been detected by Brotzu. It received a small clinical trial in Mexico and was reported to be superior for the treatment of typhoid to the widely used and quite different antibiotic chloramphenicol. But it was

never produced commercially. One reason for this may have been that it was difficult to purify and that its large-scale production would not have been financially rewarding.

However, it was the difficulty of purifying penicillin N and our interest in its structure that led Newton and me to the discovery in 1953 of a third antibiotic which was the first of the group of compounds now generally known as the cephalosporins. This substance, which we named cephalosporin C, was present as a minor impurity in our preparations of penicillin N. But it was readily separated from the product obtained when penicillin N was inactivated by dilute acid and it then crystallised as a sodium salt, and it was only shown after its isolation to have antibacterial activity.

We had two incentives to pursue a study of cephalosporin C. One came from the finding that it resembled penicillin N in having an amino acid-chain attached to a four-membered ß-lactam ring. These resemblances to a penicillin led us to hope that it would be relatively non-toxic. Another was the finding that cephalosporin C was resistant to hydrolysis by a penicillinase that hydrolysed the original penicillins then known. At that time the emergence of staphylococci in hospitals that were penicillin-resistant because they produced a penicillinase was becoming a serious medical problem and it seemed that penicillin might lose one of its most important properties.

What was the nature of the structural difference between the penicillin and cephalosporin molecule ? In our attempts to establish this by the methods of classical organic chemistry, Newton and I encountered more difficulties than we had anticipated, despite the fact that we received help in the production of material by a small Antibiotics Research Station that had been set up by the Medical Research Council.

However, while thinking about our problems during a skiing holiday in the spring of 1958, I decided that the only possible structure was one in which a ß-lactam ring was fused with an unsaturated six-

membered ring instead of with the saturated five-membered ring in penicillin.

It was not immediately obvious that this structure would account for the absorption of cephalosporin C by ultraviolet light and at first not everyone was willing to accept it. In 1960, on the evening before I was due to present our compelling evidence for it at a meeting in Australia, I was disconcerted to receive a telegram from London which stated baldly 'your structure believed to be wrong'. I could only try to ignore this telegram. But on returning to Oxford through America I stopped at Harvard and showed the structure to R. B. Woodward, perhaps the post eminent organic chemist of his generation. He remarked 'If I had proposed that structure for a compound with that absorption spectrum I would be very unhappy'.

Despite these events there was no prolonged controversy over the structure for cephalosporin C, as there had been over that for penicillin, for Dorothy Hodgkin, to whom we have given crystals of cephalosporin C soon after they had first been obtained, completed an X-ray crystallographic analysis with E.N. Maslen which comfirmed the structure that had been proposed.

Arguing by analogy with penicillin N and other penicillins we were tempted to make a number of predictions about the biological properties of this structure, some of which turned out to be true while others did not. We expected that appropriate changes in the amino acid side-chain of cephalosporin C would result in a large increase in activity against certain bacteria. We showed that this was so and also that interesting changes in activity followed changes that could be made in a group attached to the six-membered ring. On the other hand our naive hope that the resistance of cephalosporin C to staphylococcal penicillinase would extend to penicillinases from almost all other bacteria was highly optimistic, for time has revealed the existence of a multiplicity of such enzymes with different substrate profiles. We also hoped that many cephalosporins would be well absorbed when given by mouth, because they were relatively stable to acid and would thus

be able, like penicillin V, to survive gastric acidity. But in fact it was several years before the first orally active cephalosporin was produced. Finally we thought that the structural difference between the penicillin and the cephalosporin nucleus might enable penicillin-sensitive individuals to be given cephalosporins with impunity. Although this has appeared to be true in many cases it is not so in all. It is evident that these biological phenomena are too complex at the molecular level for predictions based on simple analogies to have a high chance of success.

Development by pharmaceutical companies

Florey showed that cephalosporin C itself would protect mice from lethal infections with penicillin-resistant staphylococci and that it was even less toxic than penicillin G. He believed that it would find a use in medicine and it was in fact used succesfully in a few cases, but there were two reasons why it did not come into general use. First, the isolation of the penicillin nucleus was followed by the semi synthesis of new penicillins, one of the first of which, methicillin, could cope with penicillin-resistant staphylococci. Secondly, semi-synthetic cephalosporins that were much more active than cephalosporin C could be obtained from the nucleus of cephalosporin C.

Two pharmaceutical companies, Glaxo and Eli Lilly, showed serious interest in cephalosporin at an early stage. Glaxo's involvement was stimulated by Florey's acquaintance with its then Chairman, Sir Harry Jephcott. Eli Lilly were particularly interested because they had been hoping to isolate the penicillin nucleus but had been forestalled by Beecham.

An unforeseen difficulty faced the large-scale development of the cephalosporins. The penicillin nucleus could already be obtained by removal of the side-chain of penicillin G with an enzyme, but no enzyme that would remove the side-chain of cephalosporin C should be found.

We had obtained the nucleus of cephalosporin C by mild acid treatment, but only in very low yield. However, in the Lilly Research Laboratories a chemical process was devised for preparing this nucleus in quantity. This opened the way to the study of innumerable cephalosporins with different side-chains.

Among the many thousands of semi-synthetic cephalosporins produced by pharmaceutical companies and containing a variety of different side-chains and substituents on their six-membered ring, twenty or more have proved to be of value in medicine. They have extended the range of bacterial chemotherapy from the staphylococcus to a number of Gram negative bacteria, including some that are penicillinresistant, and share with the penicillins the indispensible property of low toxicity. In short, they can be regarded as complementary to the penicillins and have an important place in the search for new non-toxic substances that can cope with the continuing emergence of new resistant organisms. The considerable demand for these substances by clinicans, has led to world sales that are now said to be nearly £4,000 million per year.

Oxford and patents

This brings me to another unanticipated aspect of our involvement with the cephalosporins. Before and during the war it was widely felt that commercially valuable findings by those in academic medical research should be made freely available. This view was held in Britain by the then President of the Royal Society and the Secretary of the Medical Research Council and in the USA by members of the Rockefeller Foundation. Chain, whose father had been an industrial chemist, made strenuous efforts to change these views with respect to penicillin, but was entirely unsuccessful. In retrospect I doubt whether a rewarding patent for the Oxford work on penicillin could have been obtained, at least after the publication of the clinical paper, but it was a principle that was at stake.

Towards the end of the war, however, when thoughts were turning to post-war reconstruction, it appeared to the British Government that a failure to exploit and protect scientific discoveries had imposed a significant financial loss on the country. An outcome of this conclusion was the setting up of a National Research Development Corporation (NRDC) to support potentially valuable inventions in the national interest and a volte-face by the Medical Research Council.

At an early stage of our work on the products of Brotzu's *Cephalosporium* I was surprised to receive a letter from the Medical Research Council expressing the hope that we would patent, through NRDC, findings that might be of medical value.

At that time (though no longer) the University of Oxford disclaimed any interest in patent royalties and its members were free agents provided only that they did not use the University's name in commercial transactions. In fact we assigned cephalosporin patents to NRDC, which carried out all negotiations with pharmaceutical companies but had a standard revenue sharing agreement with inventors. Our key patents were cephalosporin C and its nucleus.

When royalty payments from NRDC began to come in, at first in relatively small amounts, I began to think about what to do with the money. I soon decided, with my wife's encouragement, to divert most of my royalties into two Charitable Trust Funds, the first to support medical, biological and chemical research in the University of Oxford; and the second to include education as well as research in these sciences and the Royal Society and an independent school among possible beneficiaries. Guy Newton, who had less to dispose of because he had been employed by the Medical Research Council as well as by the University, told me that he wished to set up a smaller Fund.

The setting up of charitable Trust Funds was not a simple legal procedure, for my lawyers told me that it might be claimed that I had disposed of a marketable asset and was thus liable for a substantial tax on what had been given away. Fortunately, however, the Board of

Inland Revenue eventually agreed that such tax would not be claimed. Had they decided otherwise I do not know what we should have done. One adviser suggested that we should emigrate, but this was a painful solution that we never seriously contemplated.

The income from these Trust Funds has so far enabled the Trustees to endow three Chairs and a variety of Fellowships and to support many new developments in the medical, biological and chemical sciences.

Comments on the past and prospects for the future

Sir William Dunn left the residue of his estate for the relief of human suffering. The money was partly used to build the Sir William Dunn School of Pathology in 1927, but only after a High Court ruling that this would not conflict with the benefactor's intentions. It now seems clear that the Dunn School has been able to comply with the terms of Dunn's Will.

Unlike most of the later antibiotics of clinical value the first penicillin and cephalosporin came from academic institutions in which research was largely motivated by scientific curiosity. But a good many years elapsed between the early discoveries and the wide use of these families of antibiotics in medicine that was only made possible by the skill and resources of the pharmaceutical industry.

For pharmaceutical companies the finding of products of commercial value is a prime objective of research and comes before a disinterested pursuit of scientific knowledge. The academic's need to publish and a company's wish to protect its property are possible sources of friction in a collaborative enterprise. But I can say here that we encountered no serious problems of this kind in our relationship with NRDC and its licensees. Moreover, in assessing what was done in pharmaceutical companies it would often be difficult to distinguish between applied and basic research.

In the present lecture I have emphasised the roles of chance and luck. But good luck often needs to be complemented by the gift of some ability. During a discourse in 1854 Pasteur told his audience to remember that in the field of observation "Le hasard ne favorise que les esprits préparés"; and later Paul Ehrlich included patience, skill and money, as well as luck, in his list of four helpful things in scientific research — Geduld, Geschick, Gluck, Geld.

Despite the remarkable contributions to medicine that have been made by the penicillins and cephalosporins now available, strains of bacteria with resistance to them continue to emerge, particularly in hospitals. Thus the search for new compounds has not come to an end. More sensitive methods have been introduced for screening the microbial world. Rapid progress is being made in the isolation of genes that code for enzymes involved in the biosynthesis of ß-lactam antibiotics and in resistance to them. With such fundamental knowledge a less empirical approach to this area of chemotherapy may eventually be feasible.