Alexander Fleming, 1881-1955

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ALEXANDER FLEMING
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Alexander Fleming was the youngest of four children born to an Ayrshire farmer, Hugh Fleming, by his second wife Grace (née Morton) on 6 August 1881. His education, up to the age of twelve, was at the village school (Darvel) and, for a further two years, at the Kilmarnock Academy. At fourteen he joined his brothers in London, where he worked for a time as a clerk in a shipping office, and also attended some classes at the Regent Street Polytechnic.

His eldest brother Thomas was already practising as an ophthalmologist and, perhaps influenced by his example, Alexander also decided to study medicine. His choice of a medical school (which was to prove all important) seems to have been largely determined by the fact that he had competed in a water polo match against the students of St Mary’s Hospital. He therefore sat for an Entrance Scholarship at that Medical School, and won it, in 1901. After winning many other prizes as a student, he duly obtained his London University degree, M.B., B.S., in 1906.

At that time he seems to have had no strong predilection towards any particular sphere of medical practice. Surgical work evidently made some appeal to him for he proceeded to take his F.R.C.S. examination, and it may well be that, if he had pursued that career, his great technical ability and high intelligence would have made him an outstanding surgeon, and won him a substantial fortune.

But another road opened for him—in ‘laboratory medicine’. As a student he had come under the influence of Almroth Wright, who had come to St Mary’s in 1902, nominally as Professor of Pathology, but actually with the intention of developing a new road in medicine—that of therapeutic immunization against infectious disease. Wright had already, while serving in the Army Medical Service, successfully launched preventive immunization against typhoid fever. The new proposal went further. It aimed at stimulating the patient already suffering from a bacterial infection to make an immediate response to that infection by the elaboration of ‘antibodies’; and it sought to follow that process by measurement of these antibodies in the patient’s blood. This called for new techniques and considerable labour. The group of young men who had joined Wright, including John Freeman, Bernard Spilsbury and John Wells, were already unable to cope with it. So it happened that Fleming was invited to join the team as soon as he obtained his degree in 1906. (The choice fell on him partly because he was a good rifle shot and his
Having thus found his way into the first research laboratory to be attached to a hospital in this country, Fleming remained there until his death 50 years later, having ultimately, in 1946, succeeded Sir Almroth Wright as Director of a greatly enlarged Institute, and having himself become world-famous as the discoverer of penicillin.

During those 50 years he made many notable contributions to medical progress, for, like his chief Wright, he was an explorer—his mind was always moving on. The first of these, like several later contributions, was in the sphere of technical methods. Wright had introduced many ingenious procedures for micro-measurement by means of capillary glass tubes, rubber teats, and calibration by mercury. Fleming was quick to see that these could lend themselves to the new diagnostic methods for the detection of syphilis, which had been developed by Wassermann and others in Germany. His modification made it possible to carry out the test with half a millilitre of the patient's blood, derived from a finger prick, instead of five ml. obtained from a vein.

Very soon other technical problems arose in connexion with syphilis, for Wright became greatly interested in Ehrlich's discovery of the wonderful curative properties of dioxy-diamino-arsenobenzene dihydrochloride, known more familiarly as 'Salvarsan' or '606'. This had to be given by injection into veins—an almost unknown procedure in those days. Fleming undertook this work, and in one of the first reports to be published in English he described a satisfactory technique, and the results he had obtained in 46 patients.

Then came the First World War and Fleming at once became involved in quite different problems. It was quickly apparent that bacterial infection of the terrible wounds caused by high explosives was going to cost us very many lives and limbs. Wright was called upon to set up a laboratory in France for the study of these infections, and he took Fleming with him—with the rank of Captain, R.A.M.C. That first war-time laboratory for medical research was established at the Casino in Boulogne (since destroyed in the last war).

Fleming's first report upon his findings, early in 1915, stressed the great number of microbic species present in the wounds—some of them quite unfamiliar to most bacteriologists at that time; but it also showed that in the most serious infections, when the patient's blood stream was invaded, streptococci were chiefly responsible. It seemed probable that many of the wound infections were caused by microbes carried on fragments of clothing, mud, etc., which had been driven deeply into the tissues by the projectile.

These early observations of the wounds also brought out another important point, viz., that thorough application of the antiseptics in common use, either at the Front within a few hours of wounding, or somewhat later at the Base, was not sufficing to check bacterial infection, as many surgeons
had hoped it would. To Wright this was not surprising but he, and Fleming, had to spend many months of strenuous work investigating the matter in order to convince the surgeons that they were on the wrong road.

They concluded (Wright and Fleming) that two factors were chiefly responsible for the failure: First, the antiseptics did not reach the microbes because these had very often been implanted deeply in the substance of bones, cartilage, muscles, etc. And, secondly, the antibacterial potency of the solutions used was very much, and very quickly, reduced by combination with albuminous and cellular elements in exuded lymph, pus, blood, and the fixed tissues in the wounds; and the solutions thus reduced in strength were sometimes actually harmful, because they destroyed the patient's leucocytes, which, if unharmed and given favourable conditions, constituted a very effective natural defence mechanism.

The intellectual work which lay behind the formulation of these two important conclusions (and others) was almost entirely Wright's (he 'saw with his mind' where the truth must lie,) but Fleming, who shared in the work, made valuable contributions to it—especially in the technical sphere. It was he who made and experimented with 'artificial wounds' by drawing out spikes on the lower end of test tubes and filling them with serum, or serum broth, implanted with all the organisms from a dirty wound. When the latter had grown out freely the fluid was emptied out and the tube refilled with an antiseptic solution and left, sometimes as long as 24 hours. When this in turn was thrown out and replaced by sterile culture fluid a new outgrowth of microbes always occurred. Evidently the antiseptic had failed to reach and kill the organisms in the tips of the glass spikes. Most of the wounds caused by high explosives had far more inaccessible corners than Fleming's spiked tubes.

Another simple device which Fleming adapted (with due acknowledgment to its author, Dr Beattie) to the investigation of antiseptics was that of covering fluid cultures of a suitable gas-forming organism with melted Vaseline. As growth proceeded the confined gases pushed up the column of Vaseline and their volume gave a rough indication of the amount of growth. By this trick it was easy to demonstrate the greatly diminished potency of many antiseptics in albuminous fluids such as serum; and also the surprising fact that, with certain concentrations of many commonly used antiseptics (including carbolic acid, iodine, hypochlorous acid and sodium hypochlorite and also chloramine-T) bacterial growth was actually increased. (By this same device Fleming was able to demonstrate that the Clostridia associated with gas gangrene gave a much more abundant culture when grown in symbiosis with aerobic organisms from the wounds, such as staphylococci and streptococci.)

Yet another facet of 'the antiseptic problem' was revealed when Wright and Fleming transferred their attention to the anti-bacterial efficiency of the leucocytes in an infected wound. Briefly, they found that, given favourable conditions, the leucocytes of pus or blood were able to kill very large
numbers of staphylococci and streptococci; and that, under the influence of antiseptics, this beneficent activity was often interfered with. Here again Fleming's genius for simple devices brought striking results. His 'impression cultures', i.e., cultures made by applying a cover glass lightly to a wound surface and then immediately transferring it to a plate of nutrient agar, often demonstrated very prettily the anti-bacterial effect of the pus. And when such impression cultures were repeated before, and at intervals after, flushing a wound with an antiseptic it was often found that the bacterial growth was greater in the later cultures. Apparently the antiseptic had destroyed the leucocytes which had been holding the microbes in check.

Strong support was given to that conclusion by other experiments carried out by Fleming after the War, using the 'slide cell' technique which Wright had then introduced. By suitably adjusting the number of microbes implanted into the blood in these cells it was easy to show that, when the normal proportion of leucocytes was present, they exerted a very considerable bactericidal effect; and that, when additions of antiseptics had been made to the blood, that effect was greatly reduced, or abolished altogether.

Fleming's masterly summary of his researches on wound infections is to be found in his Hunterian Lecture to the Royal College of Surgeons in 1919 and in his communication to the Royal Society in 1924 entitled 'A comparison of the activities of antiseptics on bacteria and on leucocytes'.

His preoccupation, along with Wright, on the physiological defence mechanisms concerned in wound infections prepared his mind in some measure for the discovery, in 1922, of the remarkable microbe-dissolving ferment in nasal secretions which he named 'lysozyme'. In a sense this was a double discovery: that of the unfamiliar lytic agent, and, by an extraordinary chance, that of an equally unfamiliar microbe which happened to be exceptionally sensitive to its action.

Fleming's account of it to the Royal Society told how he was making daily cultures from a patient's nasal secretion (his own in fact) in the course of a 'common cold'. Until the fourth day his cultures grew little or nothing, but on that day there appeared 'a large number of small colonies which . . . proved to be large Gram-positive cocci arranged irregularly but with a tendency to diplococcal and tetrad formation'.* With Wright's help he subsequently christened this microbe, which was previously unknown to him, the Micrococcus lysodeikticus (i.e., capable of being dissolved).

It is not quite clear what led Fleming to suspect that there was something in the nasal mucus which would exert a powerful lytic action on this microbe. Probably there were some areas on his plate cultures where the growth of the Micrococcus was inhibited or prevented by particles of mucus. At any rate he did suspect it, and his suspicion was confirmed, when he prepared a thick suspension of the microbe from a fresh culture and added to it a drop of

* Dr V. D. Allison, who collaborated with Fleming in much of his lysozyme work, tells me that Fleming thought these micrococci did not actually come from his nose, but were chance contaminants blown on to the plate from the air.
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diluted nasal mucus. To his astonishment the suspension became quite clear in a minute or two.

Subsequent experiments showed that a similar solvent action on this sensitive microbe could be demonstrated with human tears, and sputum, and saliva, with extracts of many tissues of the human body, as well as with egg white and other animal and plant tissues.

Oddly enough no other microbe was found, nor, I think, has since been found, which was as sensitive to the solvent action as *Micrococcus lypselekticus*, although many others, including most of those associated with human diseases, were acted upon and destroyed to a lesser extent. A very significant finding, the full importance of which is probably still not known, was that the ferment lysozyme could be obtained from human leucocytes. The bactericidal effects which Wright and Fleming had demonstrated during the war with leucocytes derived from human blood and from wound exudates may well have been due in part to this ferment action.

The actual discovery of lysozyme was not perhaps a great intellectual feat but it should be remembered that hundreds of bacteriologists all over the world had been examining nasal secretions for years in the hope of finding the organism responsible for 'the common cold', and none of them had hit upon this remarkable ferment. Fleming also failed to find the cause of colds, but his questing mind and perceptive genius undoubtedly opened a new and important chapter in immunology by the discovery of lysozyme.

And a few years later (1928) he discovered another anti-bacterial agent, which he named ‘penicillin’, which was also elaborated by a living organism. The manner of that discovery was very similar to that of lysozyme. In the course of day-to-day observations of some staphylococcal colonies on an agar plate culture he noticed that some of them which were growing in the neighbourhood of a contaminating mould, were becoming translucent—apparently undergoing lysis.

This at once arrested his attention as something unusual. He grew the mould (afterwards identified as *Penicillium notatum*) on the surface of nutrient broth and found that the latter had become strongly antibacterial—its growth inhibiting power for *Staphylococcus* was nearly three times that of carbolic acid. Further investigation proved it to have other remarkable properties: it was very readily diffusible, and it was almost non-toxic for human leucocytes and for laboratory animals.

These were just the properties which Fleming’s earlier experience had led him to expect would be useful in the treatment of infected wounds. Unfortunately, in addition to these desirable qualities, the crude penicillin of Fleming’s filtrates had one great disadvantage—it was very unstable.

Fleming was not a chemist, and he saw no prospect of being able to extract and purify the active principle. He did not, therefore, seriously pursue the possible usefulness of penicillin as a therapeutic agent, but it is quite clear from his first paper on the subject that such an application was in his mind. He wrote:
Penicillin, in regard to infections with sensitive microbes, appears to have some advantages over the well-known chemical antiseptics. A good sample will completely inhibit staphylococci, *Streptococcus pyogenes* and *Pneumococcus* in a dilution of 1 in 800. It is, therefore, a more powerful inhibitory agent than is carbolic acid, and it can be applied to an infected surface undiluted, as it is non-irritant and non-toxic. If applied, therefore, on a dressing, it will still be effective when diluted 800 times, which is more than can be said of the chemical antiseptics in use. Experiments in connexion with its value in the treatment of pyogenic infections are in progress.

The last-mentioned experiments were not reported. It should be noted that at this time Fleming seems to have had in mind only the local application of penicillin—he did not foresee that (to quote Florey) 'It could circulate in the blood and body fluids in sufficient quantity to destroy sensitive bacteria in combination with the natural body defences without the least harm to those defences or to other tissues.'

Before turning to other problems Fleming did, however, show how even his crude filtrates containing penicillin could be usefully employed in bacteriological work—as a means of suppressing the growth of unwanted microbes in certain cultures, e.g., for the isolation of *B. pertussis* in whooping cough.

The subsequent history of the development of penicillin is too well known to need more than brief mention. After Raistrick and his colleagues had failed to extract and purify the active principle a fresh attempt was made by Chain and Florey at Oxford in 1940. By extraction with ether they succeeded in preparing enough partially purified material for preliminary trials of its antibacterial potency in laboratory animals infected respectively with virulent staphylococci, streptococci and *Clostridium septicum*. (Later experience showed that the penicillin used in these trials was only about 1 per cent pure.) These were remarkably successful and encouraged Florey and his team to seek further improvements in the extraction process. Solution in ether was replaced by an amyl acetate process, followed rapidly by acidification. By this and other means more stable samples of penicillin were gradually obtained, and undesirable impurities eliminated.

Fleming's findings as to the non-toxicity for laboratory animals and human leucocytes were confirmed and extended, and by 1941 favourable results were reported in the treatment of a few severe human infections. Others quickly followed, making it clear that penicillin was destined to take a unique position among the remedies effective against human diseases. Osteomyelitis and staphylococcal septicaemia, puerperal fever and other invasive streptococcal infections, pneumonia, infections of wounds and burns, gas gangrene, syphilis and gonorrhoea—all these and other human infections were treated with such happy and striking results as to justify large-scale manufacture. By 1944, thanks to the immense effort and energy of the American manufacturers and research teams, it was possible to treat every man wounded on the different war fronts, with incalculable benefit. When the war ended
supplies were adequate for the treatment of the civilian population in this country and North America. In the post-war years it was found that even bacterial endocarditis, which had previously been fatal in nearly 100 per cent of patients, could frequently be arrested by massive dosage.

All this, and much besides, has followed from the initial effort of Fleming on the one hand in 1928-29, and of Chain and Florey with their colleagues on the other in 1940-43. In view of this two-stage process of discovery, and the great importance of penicillin to the whole human race, it was perhaps inevitable that questions of priority and apportionment of credit should arise. It was pointed out,* with some truth, that Fleming’s work with *Penicillium notatum* was only in line with that of several earlier workers on the Continent. One of these, Vaudremer of the Pasteur Institute in Paris,† had reported that prolonged contact with a mould, *Aspergillus fumigatus*, destroyed the infectivity of the tubercle bacillus; and, on the strength of that observation, he had treated more than 200 patients suffering from tuberculosis with an extract made from that mould. The results, as very briefly reported, were quite inconclusive. Similar claims had been made in respect of other moulds, and some bacteria. It is clear that antagonism between different microbiological genera and species had been ‘in the air’ for some years, and Fleming himself admitted this in his Nobel lecture in 1945.

It is also clear that Fleming’s work had brought to light a new and exceptionally potent example of bacterial antagonism, the active principle of which happened to be remarkably non-toxic for animal tissues, and for human leucocytes. There it was left for a decade, and had it not been for the discernment of Florey and the chemical know-how of Chain, and their combined patience and enthusiasm in overcoming many difficulties, penicillin might still be unborn as a practical therapeutic agent. The share of credit due to these two workers must therefore be a large one.

The award of the Nobel Prize for Medicine jointly to Fleming, Florey and Chain in 1945 happily recognized the credit due to all three; and in his latter years Fleming was the recipient of very many other honours, notably that of Knighthood, Fellowship of the Royal Society and of the Royal College of Physicians, in 1943, Commander of the Légion d’Honneur in 1945, the Rectorate of the University of Edinburgh in 1951, and honorary degrees from universities all over the world. His long and fruitful association with Sir Almroth Wright in the development of ‘The Inoculation Department’ at St Mary’s Hospital was commemorated by its re-naming, in 1947, The Wright-Fleming Institute.

At the end of his life, from a heart attack on 11 March 1955, while still working in the Institute after his retirement from the Principalship, Alexander Fleming was buried among the illustrious dead in St Paul’s Cathedral.

Fleming was a man of few words—and ideas did not greatly interest him.

Women, on meeting him for the first time, were often nonplussed by the unemotional, ‘almost basilisk’ stare, which some of them mistook for rudeness, while others were fascinated. But there was much friendliness and kindness behind that apparently cold exterior, as many can testify.

‘Pain in the mind’ was not the spur that drove him to do research, as it was with Wright, but rather an urge to do a job better than the next man. Competition was the breath of life to him. Wright and he made a fine team. Wright supplied the ideas, which Fleming usually received in silence, and then went away and devised some neat trick for working them out. It was a joy to see him at work at his bench—the slick, apparently casual, but always efficient technique. If anything went wrong he was quite unperturbed and proceeded to do the job better.

Wright, chaffing him, used to say that medical research was just a game to him—and there was some truth in that. On one occasion, when King George and Queen Mary were due to visit the laboratories at St Mary’s, Wright wanted Fleming to display some of his bench technique. He did, but suspecting that it might not interest them very much, he also prepared one of his famous bacterial ‘rock gardens’ from all the available microbes which produced growths of vivid colouring. The story goes that when the Queen saw this she whispered to King George ‘What is the use of this?’ It was no use—but it amused Fleming.

Fleming was twice married, first, in 1917 to Sarah Marion, daughter of Mr John McElroy. She died in 1949. His second wife, whom he married in 1953, was Dr Amalia Coutsouris, who had worked with him at the Wright-Fleming Institute.

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