Kuhn on Discovery and the Case of Penicillin

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1. Kuhn's Theory of Discovery in Science

Kuhn is of course most famous for his theory of scientific revolutions. However in this paper I want to consider his theory of discovery in science. This theory is connected to his theory of scientific revolutions, but is nonetheless somewhat separate and very interesting in its own right. Kuhn first published his theory in a paper entitled: 'The Historical Structure of Scientific Discovery'. This appeared shortly before *The Structure of Scientific Revolutions* in the same year (1962). It has been reprinted in the collection *The Essential Tension* from where I will take my quotations. Much of the material in the paper was used in *The Structure of Scientific Revolutions*. It reappears largely in Chapter VI and Chapter X, p. 114 of that work. I will base my account of Kuhn's theory both on his paper (1962a) and his book (1962b).

The plan of my own paper is as follows. I will begin in this section by expounding Kuhn's theory of discovery in science. I will then go on to describe a famous discovery which is not considered by Kuhn – namely the discovery of penicillin. I will give a historical account of this discovery in sections 2-4. Finally in section 5 I will consider how well Kuhn's theory fits this example. In some respects the fit is very good, and the example of the discovery of penicillin may be said to support some of Kuhn's general ideas on the subject of discovery very well. On the other hand the fit is not perfect and some modification of Kuhn's theory is needed to take account of the case of penicillin.

Kuhn is concerned to criticize the view of scientific discovery as (1962a, p. 165): 'a unitary event, one which, like seeing something, happens to an individual at a specifiable time and place.' Such an account he thinks applies at best to a relatively unproblematic kind of scientific discovery in which theory predicts a new sort of entity such as radio waves, and this entity is subsequently detected experimentally. There is, however, a different kind of scientific discovery which Kuhn refers to as 'troublesome',

and to which the account definitely does not apply. In such cases an entity is discovered which was not predicted by theory, and whose existence takes scientists by surprise. Often there seems to be an accidental element in such discoveries. This is how Kuhn himself makes the distinction (1962a, pp. 166-7):

'The troublesome class consists of those discoveries – including oxygen, the electric current, X rays, and the electron – which could not be predicted from accepted theory in advance and which therefore caught the assembled profession by surprise. … there is another sort and one which presents very few of the same problems. Into this second class of discoveries fall the neutrino, radio waves, and the elements which filled empty [47] places in the periodic table. The existence of all these objects had been predicted from theory before they were discovered, and the men who made the discoveries therefore knew from the start what to look for.'

Kuhn's theory is concerned mainly with discoveries of the 'troublesome' class. His main point is that such discoveries involve at least two steps, namely recognizing *that* something is, and recognizing *what* it is; or, to put the matter another way, observing something novel, and providing a theoretical explanation of that novelty. Because such discoveries are a complex process, they do not take place at an instant, and often more than one person is involved. As Kuhn says (1962a, p. 171):

' … discovering a new sort of phenomenon is necessarily a complex process which involves recognizing both *that* something is and *what* it is. Observation and conceptualization, fact and the assimilation of fact to theory, are inseparably linked in the discovery of scientific novelty. Inevitably, that process extends over time and may often involve a number of people. Only for discoveries in my second category – those whose nature is known in advance – can discovering *that* and discovering *what* occur together and in an instant.'

Kuhn illustrates his theory by the examples of the discovery of oxygen, of the planet Uranus, and of X rays. For this brief account of his views, I will confine myself to the example of the discovery of Uranus. Kuhn writes (1962a, p. 171):

'On the night of 13 March 1781, the astronomer William Herschel made the following entry in his journal: "In the quartile near Zeta Tauri … is a curious either nebulous star or perhaps a comet." That entry is generally said to record the discovery of the planet Uranus, but it cannot quite have done that.'

Indeed it cannot, because the discovery of Uranus was the discovery of a new planet unknown to previous astronomers. However, Herschel does not mention a planet, but speaks only of a 'nebulous star or perhaps a comet'. He does, however, observe that the object is 'curious'. Kuhn says (1962b, p. 114):

'On at least seventeen different occasions between 1690 and 1781, a number of astronomers, including several of Europe's most eminent observers, had seen a star in positions that we now suppose must have been occupied at the time by Uranus. One of

the best observers in this group had actually seen the star on four successive nights in 1769 without noting the motion that could have suggested another identification. Herschel, when he first observed the same object twelve years later, did so with a much improved telescope of his own manufacture. As a result, he was able to notice an apparent disk-size that was at least unusual for stars.'

The key point here is that ordinary stars are not magnified in size by a telescope however powerful. They are so far away that they become effectively points of light rather than disks. The effect of a more powerful telescope is to make stars brighter and hence more visible rather than bigger. If a celestial object is increased in size by a telescope it must be something in the solar system such as a planet or comet, or a nebula. A nebula consists of [48] a large collection of stars and so magnification in the sense of an increased separation of these stars becomes possible. Herschel would have been very familiar with this, and, as he observed a magnification of the star, he at once recognised this as 'curious'. He could have concluded that the object was a planet, a comet, or a nebula. In fact he rejected the correct one of these three possibilities and concluded that what he had seen was either a comet or a nebula. It was now easy to distinguish between these two possibilities. A comet would move against the background of the stars, while a nebula would remain fixed. Herschel observed his curious object on two further occasions, namely 17 and 19 March. The object moved, and he therefore concluded that it must be a comet. He therefore announced to the scientific community that he had discovered a new comet. Kuhn now continues the story as follows (1962a, p. 172):

' … astronomers throughout Europe were informed of the discovery, and the mathematicians among them began to compute the new comet's orbit. Only several months later, after all those attempts had repeatedly failed to square with observation, did the astronomer Lexell suggest that the object observed by Herschel might be a planet. And only when additional computations, using a planet's rather than a comet's orbit, proved reconcilable with observation was that suggestion generally accepted. At what point during 1781 do we want to say that the planet Uranus was discovered? And are we entirely and unequivocally clear that it was Herschel rather than Lexell who discovered it?'

The example of the discovery of Uranus illustrates perfectly the two main claims which Kuhn makes about discoveries of his 'troublesome' class. These are that (1) such a discovery is 'necessarily a complex process which involves recognizing both *that* something is and *what* it is', and (2) that 'inevitably, that process extends over time and may often involve a number of people'. The main features of the story seem to be the following. First of all Uranus was seen by astronomers no less than seventeen times before Herschel's crucial observation, but none of these astronomers realised that there was anything unusual about what they had seen. Herschel, in contrast to these predecessors, did realise that he had seen something which in his own words was curious. This is an example of what Kuhn refers to as (1962a, p. 173): 'the individual skill, wit, or genius to recognize that something has gone wrong in ways that may prove consequential.' But Kuhn also points out that Herschel's success was the result not just of greater 'wit or genius', but depended on his having a better telescope. We can add that

background knowledge also played a crucial part here. Herschel's better telescope enabled the magnification in size of Uranus to become more obvious, but it was his background knowledge which enabled him to realise that this was significant. An amateur without this background knowledge would not have made the discovery. But although Herschel realised that there was something unusual, he misinterpreted what he had seen as a comet. Thus the discovery was only complete when Lexell, as a result of elaborate theoretical calculations, did finally identify Uranus as a planet. So the discovery of Uranus did definitely extend over time, and did involve more than one person. We could perhaps say that Herschel discovered *that* there was something new and of interest, while Lexell discovered *what* it was. The example is [49] also in agreement with the ideas of Fleck who was a major influence on Kuhn. Fleck in fact writes (1935, p. 76):

'If any discovery is to be made accessible to investigation, the *social point of view* must be adopted; that is, the discovery must be regarded as a *social event*.'

This completes my account of Kuhn's theory of discoveries of the 'troublesome' class. I will now begin my examination of whether the discovery of penicillin is in accordance with Kuhn's model. The first point to notice is that the discovery of penicillin agrees with Kuhn in that it took place over a quite long period of time, and involved several people. We may in fact distinguish two phases in the discovery. The first phase was the one which involved Alexander Fleming. Fleming, as the result of a chance observation of a contaminated Petri dish, discovered the existence of a new substance which powerfully inhibited a variety of pathogenic bacteria. Indeed some might regard this as constituting the discovery of penicillin. However, to me it does not seem that this in itself was all that there was to the discovery, because Fleming did not discover that penicillin could be used as what we would now call an antibiotic. In fact he had reasons for supposing that penicillin would not work as an antibiotic, and he himself used penicillin for another purpose. This brings me to the second phase in the discovery of penicillin which involved Howard Florey and his team at Oxford. They were the ones who showed that the substance which Fleming had discovered could be used successfully as an antibiotic. It will be seen that there is an analogy here to the contributions which Herschel and Lexell made to the discovery of Uranus. However, I will return to philosophical analysis in section 5 of the paper. In the next 3 sections (2, 3, and 4), I will give a brief historical account of how penicillin was discovered.[1]

2. The Discovery of Penicillin Phase 1: Fleming's Work

It was early in September 1928 that Fleming noticed an experimental plate in his laboratory which had been contaminated with a penicillium mould. If, however, we are to understand his reaction to this fateful event, we must first examine some of the research which Fleming had carried out previously. There were in fact two episodes which had influenced Fleming in a crucial fashion. The first of these was Fleming's experiences in the First World War, and this will be described in section 2.1. The second was Fleming's discovery in 1921 of an important biochemical substance which was

named *lysozyme*. This will be dealt with in section 2.2. An understanding of how these two episodes had prepared Fleming's mind will enable us to understand why Fleming acted as he did when he stumbled on penicillin itself, and this will be described in section 2.3. [50]

2.1 Fleming's experiences in the First World War Fleming spent most of his career carrying out research in bacteriology in the inoculation department of St Mary's Hospital, London. This department was headed until his retirement in 1946 by Sir Almroth Wright. When the First World War broke out in 1914, Wright, Fleming and the rest of the department were sent to Boulogne to deal with the war wounded, and, in particular, to try to discover the best way of treating infected wounds. At that time wounds were routinely filled with powerful antiseptics which were known to kill bacteria outside the body. Fleming, however, soon made the remarkable discovery that bacteria seemed to flourish in wounds treated with antiseptics even more than they did in untreated wounds. The explanation of this apparent paradox was quite simple. In an untreated wound the bacteria causing the infection were attacked by the body's natural defences, the white cells, or *phagocytes*, which ingested the invading bacteria. If the wound was treated with an antiseptic, some bacteria were indeed killed, but the protective phagocytes were also killed, so that the net effect was to make the situation worse than before. Wright and his group therefore maintained (quite correctly) that wounds should not be treated with antiseptics. They advocated the earliest possible surgical removal of all dead tissue, dirt, foreign bodies, and so forth, and the irrigating the wound with strong sterile salt solution. The medical establishment of the day rejected this recommendation, and so the superior treatment was accorded only to those directly in the care of Wright and his team.

2.2 The discovery of lysozyme After the war, Fleming returned to the inoculation department in London, and here in 1921 he discovered an interesting substance which was given the name *lysozyme*. Lysozyme was capable of destroying a considerable range of bacteria, and was found to occur in a variety of tissues and natural secretions. Fleming first came across lysozyme while studying a plate-culture of some mucus which he took from his nose when he had a cold. He later discovered that lysozyme is to be found in tears, saliva, and sputum, as well as in mucus secretions. He extended his search quite widely in the animal and vegetable kingdoms, and found lysozyme in fish eggs, birds' eggs, flowers, plants, vegetables, and the tears of more than fifty species of animals. Lysozyme destroyed about 75% of the 104 strains of airborne bacteria and some other bacteria as well. Moreover, Fleming was able to show that, unlike chemical antiseptics, even the strongest preparations of lysozyme had no adverse effects on living phagocytes, which continued their work of ingesting bacteria just as before. From all this, it seemed that lysozyme was part of many organisms' natural defence mechanisms against bacterial infection. Lysozyme had only one drawback. It did not destroy any of the bacteria responsible for the most serious infections and diseases. The hypothesis naturally suggested itself that the pathogenic bacteria were pathogenic partly because of their resistance to lysozyme.

If we put together Fleming's research on war wounds and his research on lysozyme, a problem situation emerges which I will call the 'antiseptic problem situation'. On the one hand, the chemical antiseptics killed pathogenic bacteria outside

the body, but were less effective for infected wounds, partly because they destroyed the phagocytes as well. On the other hand, the naturally occurring antiseptic lysozyme did not kill the phagocytes, [51] but also failed to destroy the most important pathogenic bacteria. The problem then was to discover a 'perfect antiseptic' which would kill some important pathogenic bacteria without affecting the phagocytes. The work on lysozyme suggested that such antiseptics might be produced by naturally occurring organisms.

2.3 Fleming stumbles on penicillin This then is the background to Fleming's work on penicillin. Fleming actually stumbled on penicillin while he was carrying out a fairly routine investigation. He had been invited to contribute a section on the staphylococcus group of bacteria for the nine-volume *A System of Bacteriology* which was being produced by the Medical Research Council. Fleming's contribution did indeed appear in the second volume in 1929. Staphylococci are spherical bacteria which are responsible for a variety of infections. For example, the golden-coloured *Staphylococcus aureus* is responsible for skin infections such as boils and carbuncles, as well as for a variety of other diseases. While reading the literature on staphylococci, Fleming came across an article by Bigger, Boland, and O'Meara of Trinity College, Dublin, in which it was suggested that colour changes took place if cultures of staphylococci were kept at room temperature for several days. This interested Fleming, because the colour of a staphylococcus can be an indicator of its virulence in causing disease. He therefore decided to carry out an experimental investigation of the matter with the help of D.M.Pryce, a research scholar.

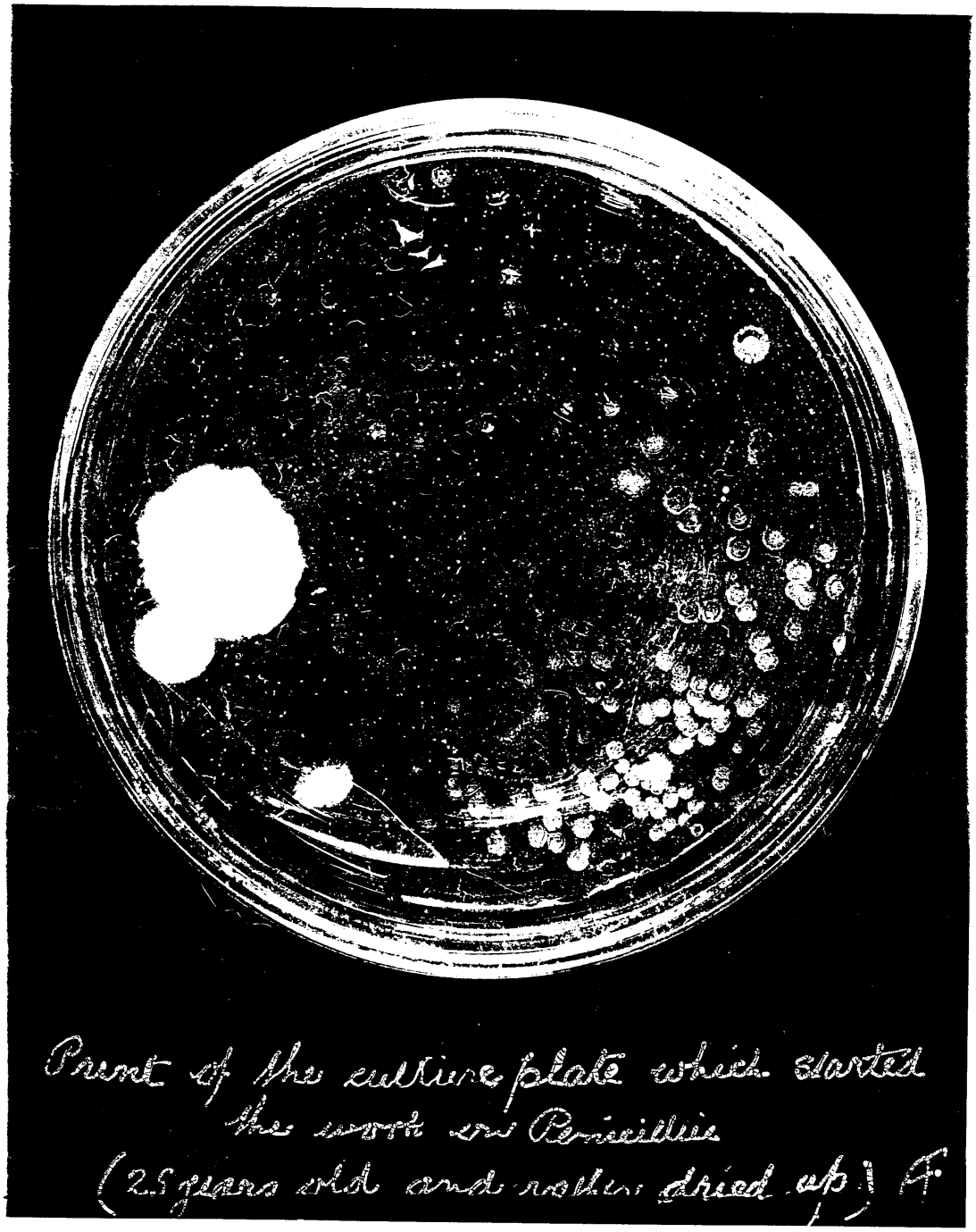
The staphylococci were cultured in glass dishes, usually 85 mm in diameter, known as *Petri dishes*. These dishes were filled with a thin layer of gelatinous substance called *agar* to which enough nutrients could be added to allow the microbes to multiply. Using a platinum wire, some staphylococci were spread across the surface of the agar, and the plate was then incubated at a suitable temperature (usually 37^{o}C), to allow the microbes to multiply. After this period of incubation, the dish was set aside on the bench, and was examined every few days to see if changes in the colour of some of the staphylococci could be observed.

While this investigation was continuing, Pryce left the laboratory in February 1928 to start another job, but Fleming continued the work on his own throughout the summer. At the end of July Fleming went off for his usual summer holiday, leaving a number of culture-plates piled at the end of the bench where they would be out of the sunlight. Early in September (probably on 3 September) when Fleming had returned from his holiday, Pryce dropped in to see him. Pryce found Fleming sorting out the pile of plates on his bench. Discarded plates were put in a shallow tray containing the antiseptic Lysol. This would kill the bacteria, and make the Petri dishes safe for the technicians to wash and prepare for use again. Fleming's tray was piled so high with dishes that some of them were protruding above the level of the Lysol. Fleming started complaining about the amount of work he had had to do since Pryce had left him. He then selected a few of the dishes to show to Pryce. More or less by chance he picked up one in the tray of discards but above the level of the Lysol. According to Pryce's later recollection, Fleming looked at the plate for a while, and then said: 'That's funny.' The plate was in fact the famous penicillin plate.

This is how Fleming himself described what happened in the paper which he published in June 1929 (p. 226):

‘While working with staphylococcus variants a number of culture-plates were set aside on the laboratory bench and examined from time to time. In the examinations [52] these plates were necessarily exposed to the air and they became contaminated with various micro-organisms. It was noticed that around a large colony of a contaminating mould the staphylococcus colonies became transparent and were obviously undergoing lysis.’

Fleming’s photograph of the original penicillin plate is reproduced in Plate 1, and it is easy to follow his description when examining the photograph.



Print of the culture plate which started the work on Penicillin
(25 years old and rather dried up.) F.

The colonies of staphylococci are the small circular blobs, and the contaminating mould is very obvious. Near the mould the staphylococci become transparent or disappear altogether. They are obviously, as Fleming says, undergoing *lysis*, which means the dissolution of cells or bacteria. From his observation of the plate, Fleming inferred that the mould was producing a substance capable of dissolving bacteria. The mould was identified as being a *Penicillium*. At first it was incorrectly classified as *Penicillium rubrum*, but later it was found to be the much rarer species *Penicillium notatum*. Fleming accordingly gave the name *penicillin* to the bacteriolytic substance which he thought was being produced by the mould.

The events described so far may make it look as if Fleming's discovery was simply a matter of luck. Indeed, there is no doubt that a lot of luck was involved. Hare subsequently tried to reproduce a plate similar to Fleming's original one, and found to his surprise that it was quite difficult (see Hare, 1970, pp. 66-80). The general effect of Fleming's plate could be produced only if the mould and the staphylococci were allowed to develop at rather a low temperature. Even room temperature in the summer would usually be too high, but here the vagaries of the English weather played their part. By examining the weather records at Kew, Hare discovered that for nine days after 28 July 1928 (just when Fleming had gone on holiday!), there was a spell of exceptionally cold weather. In addition to this, Hare concluded that [53] (1970, p. 79): ' … the plate cannot have been incubated in the usual way.' A final point is that the strain of penicillium which contaminated Fleming's plate is a very rare variety, and most penicillia do not produce penicillin in sufficient quantity to give rise to the effect which Fleming observed. How did such a rare mould find its way into Fleming's laboratory? The most likely explanation is a curious one. There was at that time a theory that asthma was caused by moulds growing in the basements of the houses in which the asthmatics lived. This theory was being investigated by the scientist C. J. La Touche in the laboratory immediately below Fleming's, and La Touche had as a result a large collection of moulds taken from the houses of asthma sufferers. It seems probable that *penicillium notatum* was one of these moulds.

There is no doubt then that a great deal of luck was involved in the discovery of penicillin. Yet it still needed creativity and insight on Fleming's part to seize the opportunity which chance had presented to him. Nothing shows this more clearly than a comparison of Fleming's reaction to the contaminated plate with that of his colleagues in the laboratory (including the head of the laboratory, Sir Almroth Wright) when he showed it to them. With characteristic candour, Hare describes the complete lack of interest shown by himself and the others (1970, p. 55):

'The rest of us, being engaged in researches that seemed far more important than a contaminated culture plate, merely glanced at it, thought that it was no more than another wonder of nature that Fleming seemed to be forever unearthing, and promptly forgot all about it.

The plate was also shown to Wright when he arrived in the afternoon. What he said, I do not recollect, but … one can assume that he was no more enthusiastic – he could not have been less – than the rest of us had been that morning.'

Fleming was by no means discouraged by his colleagues' cool reaction. He took a minute sample of the contaminating mould, and started cultivating it in a tube of liquid medium. At some later stage he photographed the plate, and made it permanent by exposing it to formalin vapour, which killed and fixed both the bacteria and the mould. Fleming kept the plate carefully, and it is now preserved in the British Museum. The whole episode then is a perfect instance of the famous claim made by Pasteur in his inaugural lecture as professor at Lille in 1854 when he said that: 'In the field of observation fortune favours only the prepared mind.'[2] Let us now examine how Fleming's mind had been prepared to appreciate the significance of his contaminated culture plate.

It is interesting in this context to compare Fleming with Herschel. Herschel needed a prepared mind to realise that a celestial body which was magnified by his telescope was something unusual. Specifically he needed the background knowledge that ordinary stars were not magnified by a telescope but only made brighter, and that, if something was magnified by a telescope, it had to be either an object within the solar system or a nebula. However, these bits of knowledge would have been part of the background of [54] any competent astronomer. The background knowledge which made Fleming appreciate the significance of the penicillin plate was, by contrast, rather unusual since it was not possessed by his very competent colleagues. It is not difficult, however, to see how this background knowledge which was specific to Fleming arose from his earlier researches.

Fleming, during his researches on lysozyme, had over and over again observed a substance produced from some naturally occurring organism destroying bacteria. This was a phenomenon with which he was very familiar. However, it would have struck him immediately that there was something new and curious about the penicillin case because the bacteria being inhibited were pathogenic staphylococci, whereas lysozyme only destroyed non-pathogenic bacteria. From the time of his work on the healing of wounds in the first world war, Fleming had been aware of the problem of finding a 'perfect antiseptic' – that is an antiseptic which would kill pathogenic bacteria without destroying the phagocytes. In the light of his knowledge of this problem, it is reasonable to suppose that, when he saw the penicillin plate, he conjectured that the mould might be producing a 'perfect antiseptic'.

The assumption that Fleming made such a conjecture is borne out by his subsequent actions. Fleming grew the mould on the surface of a meat broth, and then filtered off the mould to produce what he called 'mould juice'. He then tested the effect of this mould juice on a number of pathogenic bacteria. The results were encouraging. The virulent streptococcus, staphylococcus, pneumococcus, gonococcus, meningococcus, and diphtheria bacillus were all powerfully inhibited. In fact, mould juice was a more powerful germicide than carbolic acid. At the same time, mould juice had no ill effects on phagocytes. Here at last seemed to be a 'perfect antiseptic'. Indeed in his 1929 paper, Fleming wrote (p. 236): 'It is suggested that it [penicillin] may be an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes.'

However, at this point a series of difficulties began to emerge for Fleming and his colleagues who were working on penicillin. These difficulties led Fleming to the conclusion that penicillin would not after all be the kind of 'perfect antiseptic' which he had been hoping to find. He did, however, find another important use for penicillin.

There is a certain analogy here to Herschel who identified his curious heavenly body as a comet rather than a planet. This is why Herschel's work was only the first phase in the discovery of Uranus, and a second phase carried out by Lexell was needed to establish the existence of a hitherto unknown planet. In the same way Fleming's work was only the first phase in the discovery of penicillin, and a second phase carried out by Florey and his Oxford team was needed to establish that penicillin was after all a 'perfect antiseptic' – what we would now call a 'powerful antibiotic'. In the next section I will discuss the reasons which led Fleming and his team to give up the conjecture that penicillin would be a perfect antiseptic.

3. Why Fleming abandoned his hope that Penicillin would be a 'perfect antiseptic'

Fleming did not leave behind a diary or detailed notebook setting out the reasons behind his changes in research strategy, so that these reasons have to be inferred from what he did, and naturally this can lead to differences in opinion. There are, however, three factors [55] which most historians would agree might have influenced Fleming in abandoning his early attempts to demonstrate that penicillin was a powerful antibiotic. The first of these was the fact that some of the results of tests carried out by Fleming and his collaborators seemed to indicate that penicillin would not work against bacteria when injected into the body. In section 3.1, I will discuss these 'counter indications'. A second factor was that there were considerable difficulties in isolating penicillin from mould juice. These problems will be considered in section 3.2. The third factor was that neither Fleming nor any of his colleagues carried out what is known as an animal protection tests. By contrast, tests of this kind were done by Florey and his Oxford team. This issue will be discussed in section 3.3. We now come to another surprising twist in the story of the development of penicillin. Although Fleming seems to have given up his initial hope that penicillin might be a perfect antiseptic, he did not abandon penicillin altogether because he found another use for it. In section 3.4 I will explain what this use was, and why it had a very positive influence on the further development of research into penicillin.

3.1 The Counter-Indications Although the results of Fleming's first tests were encouraging, further experiments gave reasons to doubt whether penicillin would be an effective systemic antibacterial agent. First of all Fleming discovered that while chemical antiseptics killed microbes in a few minutes, his mould juice took several hours to do so. Then on 22 March 1929, Fleming's collaborator Craddock injected 20cc of penicillin into the ear vein of a rabbit. 30 minutes later a blood sample showed that almost all penicillin activity had disappeared. So if penicillin required about 4 hours to kill bacteria, but had disappeared 30 minutes after injection, it looked as if it could not work. Another finding of Craddock made the situation look even worse. Craddock discovered that penicillin lost about 75% of its activity in mixtures containing blood serum. Now as there is a great deal of serum in infected areas, this again strongly suggested that penicillin would not work as a 'perfect antiseptic' if injected into the body.

So we see that Fleming had good reasons for giving up his 'perfect antiseptic' hypothesis, but was he too Popperian in doing so? This example perhaps shows that Popper is too fiercely insistent on the need for scientists to give up hypotheses which appear to have been refuted.

3.2 Difficulties of Isolation Another problem facing Fleming was that of isolating the active ingredient (penicillin) from mould juice. Fleming was a bacteriologist not a chemist, and it could be argued that the chemical problems of isolating and storing penicillin were what caused him to abandon his research on it. This theory seems to me false, however, because 3 skilful chemists worked in Fleming's laboratory around this time, namely Craddock, Ridley and Holt. As we shall see, between them they took most of the key steps for the extraction of penicillin which were later carried out by the Oxford team. This leads me to think that, if Fleming had retained his belief that penicillin might be a 'perfect antiseptic', the chemical difficulties of extraction could have been overcome. However, he is unlikely to have thought it would be worth taking a lot of time and trouble to extract something which would not work. In other words, the counter-indications probably influenced Fleming more than the chemical difficulties of extracting penicillin from mould juice. [56]

3.3 Absence of an animal protection test There is another important factor connected with Fleming's early work on penicillin. Neither he nor his collaborators ever performed an animal protection test. This is a test in which an animal, e.g. a mouse, is infected, and then injected with the drug being investigated to see if it cures the animal. Craddock, as we have seen, carried out an experiment on a rabbit, but this was not an animal protection test in the sense just defined.

It is in this connection that the discovery of the sulphonamide drugs in 1935 was very important for the further development of penicillin. These drugs were discovered in Germany as a by-product of the activities of the giant chemical company I.G.Farben. The discovery was made by a team headed by Gerhard Domagk, who was born in 1895 and appointed at the early age of thirty-two as director of research in experimental pathology and bacteriology in the institute attached to the I.G.Farben works at Elberfeld. Domagk and his team had huge laboratories in which they routinely tested compounds produced by the firm's industrial chemists on thousands of infected animals to see if the compounds had any therapeutic value.

The I.G.Farben chemists Hoerlin, Dressel, and Kothe produced a rich red dye which was very effective with protein materials such as wool and silk. This was known as *prontosil rubrum*. Domagk and his team then discovered that this same compound possessed the definite ability to cure mice infected with haemolytic streptococci. Domagk published this finding in 1935, but referred back to experiments carried out in 1932.

Now the interesting thing about this case is that the pharmaceutical value of prontosil rubrum could not have been discovered without the use of animal protection tests for the simple reason that prontosil rubrum does not inhibit bacteria in Petri dishes (*in vitro*). It is only when prontosil rubrum is injected into living creatures (used *in vivo*) that it acts as an effective agent against bacteria.[3] This suggested that penicillin too, despite the discouraging *in vitro* results, might work *in vivo*.

A personal difference between Fleming and Florey may also have been important here. Fleming was the deputy of Almroth Wright who cast scorn on random experiments of the I.G.Farben type and argued that a good scientist should proceed by making deductions from a few carefully chosen tests. There is much to be said for Almroth Wright's approach, but, in this instance, it led to the wrong conclusion. Moreover, Almroth Wright and Fleming almost never conducted animal experiments. They worked *in vitro,* but not *in vivo*. Florey, on the other hand, had been trained at working on physiology through animal experiments, and was very skilled at experimental animal surgery. For him, animal experiments were a matter of routine.

3.4 Why Fleming nonetheless preserved the penicillin mould Despite abandoning his hopes that penicillin might be a 'perfect antiseptic', Fleming nonetheless continued the cultivation of the penicillin mould and the production of mould juice. This was extremely fortunate since the mould (*penicillium notatum*) was a very rare [57] type of penicillium, and most penicillia do not produce penicillin in the same quantity, if at all. If Fleming had ceased cultivating the mould, it would have been difficult to restart doing so. He continued the cultivation because he had found another use for mould juice.

The main source of income of the inoculation department where Fleming worked was the production and sale of vaccines. There was indeed an efficient unit for producing vaccine (a vaccine *laboratory*, as it was then called) within the walls of the department, and Fleming had been in charge of the production of vaccines since 1920. In particular, a vaccine was made against Pfeiffer's bacillus (*bacillus influenzae*) which was believed to cause influenza and other respiratory infections. It was difficult to isolate this bacillus because cultures were apt to be swamped by other micro-organisms. Fleming, however, had discovered that penicillin, despite its effect on so many virulent bacteria, left Pfeiffer's bacillus unaffected. By incorporating penicillin into the medium on which he was growing Pfeiffer's bacillus, he could eliminate the other germs, and produce good samples of the bacillus itself. Fleming in fact used this method for preparing the influenza vaccine in his vaccine laboratory for this purpose every week after its discovery. Significantly, the title of Fleming's 1929 paper on penicillin was: 'On the antibacterial action of cultures of a penicillium with special reference to their use in the isolation of *B. influenzae*'. Because of this application of penicillin, cultures of the mould were established at the Lister Institute, Sheffield University Medical School, and at George Dreyer's School of Pathology at Oxford. Thus, when Florey and his team decided to take up again the question of whether penicillin might be a 'perfect antiseptic', they were able to find samples of Fleming's strain of *penicillium notatum* just down the corridor in the Dreyer School of Pathology where they were working. This then is an appropriate moment to turn from Fleming to Florey and the Oxford team.

4. The Discovery of Penicillin Phase 2: The Work of Florey and his Oxford team

As we have seen, Fleming worked for a while on lysozyme, and this led on to his later work on penicillin. Curiously enough the head of the Oxford team, the Australian Howard Florey, followed the same route. In section 4.1 it will be explained why Florey got interested in lysozyme, what research he and his team carried out on it, and why this

research suggested that it might be useful to move on to investigate penicillin. Then in section 4.2 I will describe the Oxford team's work on penicillin between 6 Sept. 1939 and 27 March 1943. It was this work which established that penicillin was, after all, a very effective antibiotic.

4.1 The Oxford Team also started with lysozyme Curiously enough the Oxford team also started by working on lysozyme, and moved on from there to penicillin. Howard Florey first got interested in lysozyme from his studies on mucus and its function. Lysozyme is found mainly in mucus-containing body fluids. At any rate on 17 January 1929 he sent various organs and tissues from experimental rats which had been killed to Fleming, presumably for help in assaying the quantity of lysozyme they contained.

In the late 1930s, Florey was joined in Oxford by Ernst Chain, a Jewish refugee from Nazi Germany, and an expert biochemist. During the academic year 1938-9, Chain worked on lysozyme with Epstein, an American D.Phil student and Rhodes scholar. They [58] confirmed that lysozyme is an enzyme – a polysaccharidase, and then looked for the substrate in the bacterial cell wall which it broke down. This turned out to be N-acetyl glucosamine. This result was published in 1940.

While working on lysozyme, Chain surveyed the literature on other natural antibacterial substances which might be worth investigating. This is how he came across Fleming's 1929 paper on penicillin. This was in Vol. 10 of the British Journal of Experimental Pathology, while Fleming's papers on lysozyme were in Vols 3 & 8, and Florey's in Vol. 11. Chain at first thought that penicillin was a kind of mould lysozyme, a bacteriolytic enzyme on which he could repeat his investigation of lysozyme. Interestingly he did not realize at the time that Fleming was still alive.

After discussions with Florey, the two of them decided to investigate penicillin, and Florey prepared a grant application to support Chain.

4.2 The Oxford Team's work on penicillin (6 Sept. 1939 – 27 March 1943) Britain declared war on Germany on 3 Sept. 1939, and on 6 Sept. 1939 Florey sent in the grant application. Here is an extract (taken from Macfarlane, 1979, p. 299):

'Filtrates of certain strains of penicillium contain a bactericidal substance, called penicillin by its discoverer Fleming, which is especially effective against staphylococci, and acts also on pneumococci and streptococci. There exists no really effective substance acting against staphylococci *in vivo*, and the properties of penicillin which are similar to those of lysozyme hold out promise of its finding a practical application in the treatment of staphylococcal infections. Penicillin can easily be prepared in large amounts and is non-toxic to animals, even in large doses. Hitherto the work on penicillin has been carried out with very crude preparations and no attempt has been made to purify it. In our opinion the purification of penicillin can be carried out easily and rapidly.

In view of the possible great practical importance of the above mentioned bactericidal agents it is proposed to prepare these substances in a purified form suitable for intravenous injections and to study their antiseptic action *in vivo*.'

In October the Medical Research Council approved Chain's grant for £300 per annum, with £100 expenses for three years. This was not enough but Florey got an

additional grant from the Rockefeller Foundation of £1000 for the initial cost of equipment and £1670 per annum for 5 years. With this money, the work was able to go ahead.

The first step was to purify penicillin which Florey had rather optimistically said in his research proposal 'can be carried out easily and rapidly'. In fact it was a difficult task. The first result was that penicillin is soluble in alcohol. This had been shown earlier by Craddock and Ridley – Fleming's collaborators. This was interesting in that is showed that penicillin was not a protein. Chain confirmed this by demonstrating that penicillin would pass through micropore filters that retained proteins. So penicillin was not an enzyme and had a relatively small molecule. This must have disappointed Chain, but it did show that penicillin might be injectable without producing the allergic reactions due to foreign proteins.

The next result was that penicillin could be extracted by ether if the mixture was made acidic. This too had been discovered by a Professor of Biochemistry at the London School [59] of Hygiene and Tropical medicine (Harold Raistrick) in 1930, but Raistrick had been unable to get the penicillin back from the ether. This problem was solved by another of Florey's team at Oxford: Norman Heatley.

In March 1940 Heatley discovered back-extraction. The idea was simple. If an acidified solution was needed to make penicillin dissolve in ether, perhaps an alkaline solution would cause it to come out of the ether. Heatley shook ether, containing penicillin, with alkaline water, and, sure enough, the penicillin passed back into the water. Curiously enough this had already been discovered by Holt working in Fleming's laboratory in 1934, but had never been published.

Partially purified penicillin could now be prepared, and Florey conducted a systematic series of administration and toxicity tests in April & May of 1940. Penicillin was injected into rats, mice, rabbits, and cats with no ill-effects, though it was rapidly excreted and had largely disappeared from the bloodstream in 1 or 2 hours. (Penicillin is in fact toxic to guinea pigs. So it is fortunate that these were not used.) Penicillin was also shown to be harmless to the delicate white cells known as leucocytes. Fleming's findings regarding the inhibitory effect of penicillin on a wide range of pathogenic bacteria were confirmed, and it was realised that penicillin worked by blocking the normal bacterial process of cell-division.

So far the Oxford team had largely repeated Fleming's work, albeit more systematically and on a larger scale. The next step was their crucial innovation. On Saturday 25 May 1940, they carried out the first mouse protection test. 8 mice were injected by Florey at 11am intraperitoneally with 100 million streptococci. 4 (the controls) received no further treatment. Of the remaining 4, 2 (Group A) received an injection of 10 mg of penicillin subcutaneously at 12 pm and no further treatment, while the remaining 2 (Group B) received 5 injections of 5 mg at 2 hour intervals starting at 12 pm. The results are shown in figure 1.[4]

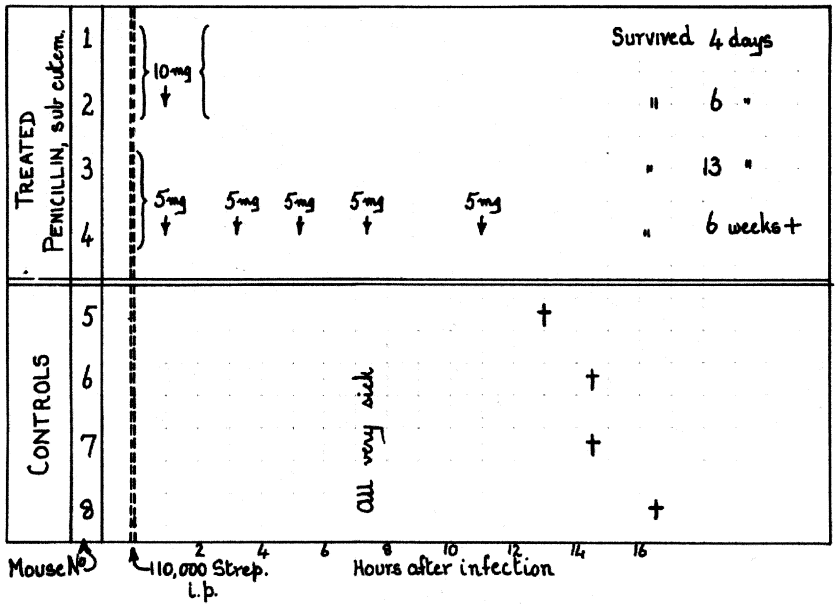


Fig. 1. Chart showing the timing of injections and the results of the experiments drawn by Dr. N. G. Heatley from his notes of the first mouse protection test on 25 May 1940.

[60]

The 4 control mice were all dead within 16 hours. The 2 group A mice survived 4 and 6 days. One group B mouse survived 13 days and the other 6 weeks +.

The result of this test was so striking that it could leave little doubt that penicillin was a highly effective antibiotic. However it was only the first of a series of animal trials carried out by the systematic Florey. These prepared the ground for the first clinical trial, but since a man is 3,000 times the weight of a mouse, the production of penicillin had to be greatly increased. Florey tried to interest several pharmaceutical firms but with little success. They were all occupied with seemingly more urgent war work. Undaunted, Florey decide to turn his laboratory into a factory, and was greatly helped in this by the innovative and resourceful Heatley. In 1941, the extraction of penicillin was improved by the use of column chromatography, which yielded penicillin ten times purer. This was necessary for the clinical trials, which were carried out by Fletcher, a doctor who worked with Florey.

The first clinical trial took place on 12 February 1941. This case illustrates the ravages which bacterial infections could cause in the pre-penicillin era. The patient was a 43 year old policeman, Albert Alexander, who had become infected after pricking himself on a rose bush. The infection had spread over his face, and his left eye had to be removed on 3 February. However, the infection spread further into his right shoulder and lungs. On 12 February, Fletcher gave him an intravenous injection of 200 mg of penicillin, followed by 100 mg at 3 hour intervals. The patient improved immediately. Within 4 days his temperature dropped to normal and his appetite returned. Unfortunately though, the penicillin was running out even though it was being extracted

from his urine and re-injected. Without further penicillin, his improved health continued for a while, but then he relapsed and died on 15 March 1941.

The third patient, Percy Hawkins, a 42 year old labourer, was a more unequivocal success. He had a 4 inch carbuncle on his back. Beginning on 3 May 1941, he was given 200 mg of penicillin every hour for five hours, then 100 mg hourly. After 7 May this dose was reduced to 50 mg. By 10 May the carbuncle had almost completely disappeared. This was a striking case of a successful treatment of a localised staphylococcal infection.

Of course these clinical trials were only the start. Howard Florey continued the work helped by is wife Ethel who was a doctor. On 27 March 1943, they published a paper in *The Lancet* describing 187 cases of sepsis treated with penicillin. This established beyond doubt the efficacy of penicillin as an antibiotic.

5. Suggested Modifications of Kuhn's Theory in the light of the Penicillin example

Let us now return to Kuhn and see how well the work of Fleming and the Oxford team fits his theory of discovery in science. It is certainly a striking confirmation of Kuhn's claim (1962a, p. 171):

' … the discovery of scientific novelty … extends over time and may often involve a number of people.'

And of Fleck's claim (1935, p. 76):

'… discovery must be regarded as a *social event*.' [61]

This feature of scientific discovery is still largely unrecognised by the general public. Alexander Fleming is famous everywhere as *the* discoverer of penicillin, while the name of Howard Florey and the work of the Oxford team remain largely unknown.

This attribution of credit in the popular imagination goes back to the time (August 1942) when news first leaked out of the new 'miracle cure' and the press got interested. A key factor was Sir Almroth Wright's letter to *The Times* of 31 August 1942 which ran (Macfarlane, 1979, p. 349):

'Sir,

In the leading article on penicillin in your issue yesterday you refrained from putting the laurel wreath for this discovery round anyone's brow. I would, with your permission, supplement your article by pointing out that, on the principle *palmam qui meruit ferat* it should be decreed to Professor Alexander Fleming of this laboratory. For he is the discoverer of penicillin and was the author of the original suggestion that this substance might prove to have important applications in medicine.'

In the outburst of press interest which followed, Fleming and Florey handled things very differently. Fleming saw reporters and gave interviews. Moreover this dour and laconic Scotsman proved to be a great favourite with the general public. Florey on the other hand refused to see any reporters and sent them away. It was natural then that the press should concentrate on Fleming whose name was the only one which became known to the public. The scientific community was more judicious. When a Nobel prize for the discovery of penicillin was awarded in 1945, it was divided between Fleming, Chain, and Florey. This was certainly quite reasonable, but it might well be argued that further members of the Oxford team, such as Norman Heatley, could have been included.

While the discovery of penicillin confirms Kuhn's views on the social nature of scientific discovery, it diverges from other aspects of his account. Kuhn essentially considers two types of discovery, viz. (i) *the unproblematic class*, in which an object is predicted and later discovered (e.g. radio waves), and (ii) *the troublesome class*, in which something strange is observed and its true nature only later elucidated. The discovery of penicillin does not fit exactly into either class. Penicillin was certainly not predicted, but, before its discovery, the concept of a perfect antiseptic had been formulated, and Fleming was on the look out for such an antiseptic without, however, any definite conviction that he would find one. It could be said that penicillin, or something similar, was hoped for rather than predicted.

In Kuhn's 'troublesome class' of discoveries, more than one scientist may be needed because the process requires (i) the initial observation of something unusual (e.g. Herschel's observation of a curious celestial object), and (ii) the elucidation of the nature of what was observed (e.g. Lexell's claim that Herschel's celestial object was a planet). In the penicillin case, however, more than one scientist was necessary because Fleming's initial hypothesis regarding penicillin, viz. that it was a perfect antiseptic appeared to be refuted by experiments, so that further work was needed to show that the initial hypothesis was correct after all. Thus, in addition, to Kuhn's two classes, we might introduce a third class of discovery in which researchers are looking for something with a particular set of properties. The discovery then consists of two stages: (i) becoming aware of something which might have the required set of properties, and (ii) the demonstration that it really does have these properties. [62]

Notes

1. My account of the discovery of penicillin is largely based on Hare (1970) and Macfarlane (1979 and 1984). Hare's book is partly an eye witness account since he was working in the same laboratory as Fleming when Fleming made his discovery. Macfarlane's two books are excellent historical works which are informed by a deep scientific knowledge of the area.

2. In Pasteur's original French, the quotation runs: 'Dans les champs de l'observation le hasard ne favorise que les esprits préparés'. This is slightly ambiguous since 'le hasard' in French can mean 'luck or fortune' as it is translated here, or 'chance' in the statistical sense.

3. Further details about the discovery of prontosil rubrum, and the explanation of why it works only *in vivo* and not *in vitro*, are to be found in Gillies, 1993, pp. 48-53.

4. This figure is taken from Macfarlane, 1979, p. 314.

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