

## Discovery of Penicillin

It was the first and is still a widely used antibiotic agent. Penicillin, is defined by WordNet as, “any of various antibiotics obtained from *Penicillium* molds (or produced synthetically) and used in the treatment of various infections and diseases.” It is often abbreviated as PCN. In the old days, people had remedies that included fungi, but they did not know that it was the fungus that was treating the disease. Penicillin is often described as a wonder drug because it performs wonders such as curing infection. Before its discovery, a death would occur in what could be said to be from minor injuries and diseases. Now the taking of penicillin in such conditions has prevented death from occurring. Many diseases and minor injuries are now very comfortably treated due to the availability of antibiotics that hasn't always been available in the past.

The science of microbiology was a mere fifty years old by 1928, when Dr. Fleming first noted the penicillin phenomenon, yet remarkable progress had already been made in the study of bacteria, fungi, and viruses. Many of the microorganisms have the ability to cause devastating diseases such as cholera, histoplasmosis, and poliomyelitis. So what are antibiotics? Dictionary gives the following definition: Drugs from living organisms which prevent the growth and reproduction of other organisms. (Wainwright pp. 4-6)

The discovery of penicillin, the first antibiotic, has been a recent one. It was first discovered in 1928 by a Scottish scientist Alexander Fleming. The leitmotiv of Fleming's career was his search for a chemical substance which would eradicate infectious bacteria

without harming tissues or weakening the body's defenses. In 1928 an accidental observation, which was a direct result of his apparently disorderly habit of not discarding culture plates promptly, led to the fulfillment of his goal. Fleming noted that on a culture plate of staphylococci, a mold *Penicillium notatum*, which had been introduced by accidental contamination, had dissolved the colonies of staphylococci. He found that the broth containing the bactericidal substance (penicillin) produced by the mold was unstable and rapidly lost its activity. Furthermore, it could not be used for injections until freed from foreign protein. Clearly, a method of extraction and concentration of the crude substance was required. Fleming had no chemist or biochemist on his staff, and he encouraged others to attempt the task. (Fleming)

Fleming, who had been unable to identify the antibacterial agent in the mold, had used the mold broth itself in his experiments to kill the infections. Assisted in their research by a fellow scientist Norman Heatley, Chain and Florey began their work by growing large quantities of the mold in the Oxford laboratory. Once there were adequate supplies of the mold, Chain began the tedious process of isolating the "miracle" substance. Succeeding after several months in isolating small amounts of a powder which he obtained by freeze-drying the mold broth, Chain was ready for the first practical test. His experiments with laboratory mice were successful, and it was decided that more of the substance should be produced to try on humans. To do this, the scientists needed to ferment massive quantities of mold broth. It took 125 gallons of the broth to make enough penicillin powder for only one tablet. By 1941 Chain and his colleagues had finally gathered enough penicillin to conduct experiments with patients. The first two of

eight patients died from complications unrelated to their infections, but the remaining six, who had been on the verge of death, were completely cured.(Chain)

Cecil George Paine was the first person to try to find cures with the newly found penicillin. Paine was one of the students of Fleming. He had first heard of penicillin while still a student at St. Mary's, where he attended Fleming's classes in bacteriology. The first human medical cases to be cured by penicillin were three babies and a colliery manager. Dr. Paine was at doing hospital bacteriology in Sheffield in Britain at that time. Paine started off by repeating Fleming's work and finding that the mould did, and produce an antibacterial substance in the broth. When he had collected enough mould juice, Paine tried it out on his first three experimental patients. They were all staphylococcal infections of the skin, referred to him by a dermatologist. It seemed to Paine that this sort of infection could be treated by applying dressings of the antibacterial mould juice was the ideal way of proving the value of penicillin. But Paine's first three cases did not lead to any successes. Either the penicillin was too weak to prove effective, or perhaps more probably, it failed to reach the seat of the infection which lay deep in the hair follicle. Paine said, "The results were uniformly disappointing." (Wilson pp. 111)

Despite these failures, Paine did not give up. Dr. Paine had one more interesting case. This was the colliery manager, whose eye had been penetrated by a small chip of rock when he was in the mine. The wound then got infected, and when he was brought to the ophthalmic surgeon, it seemed as if he might lose the eyesight. The removal of small chip from the delicate parts of the eye was impossible in this infectious condition. Swabs from the infected areas of the eye showed a pure culture of pneumococcus. Pneumococcus was known to be sensitive to penicillin from Fleming's early experiments.

So it was decided to let Dr. Paine try his mold filtrate. Forty-eight hours of continuous irrigation of the eye with the mold juice completely wiped out pneumococcus. The operation for removal of the chip of the stone went ahead normally, and successfully the colliery manager's eyesight was saved. And it was the last time Dr. Paine used penicillin because it was difficult having to manufacture the mould juice in any regular way. Different types of infection Paine's results were more promising. While skin cases didn't respond well to penicillin, four Sheffield babies with eye infections were providing the first known examples of penicillin's curative power. The response of gonococcal infections was remarkable too. Penicillin was hailed as the cure for gonorrhoea, when all but four of 129 patients were completely cured. (Wilson pp. 114)

It was on December 27, 1940, when Albert Alexander, who was a policeman, was admitted to the Briscoe Ward Oxford's Radcliffe Infirmary. He originally suffered from nothing worse than a scratch on the face from a rose bush. Unfortunately, the slight wound became infected with *Staphylococcus aureus*, and as the weeks passed a streptococcal infection was added. The doctors treated him with the latest of the sulphonamides, and sulphapyridine. He had, by February of 1942, lost one eye and his lungs were beginning to be affected. On February 12, Dr. Fletcher started treating him with penicillin. A first dose of 400 milligrams was followed by an intravenous drip feeding him 100 mgs of the drug every three hours. Within twenty-four hours, the policeman was plainly very much better: fever started to go down, the abscesses ceased to discharge, the running from the eye stopped. But the penicillin was running out. Dr. Fletcher started collecting the policeman's urine and taking it back to the laboratory to have the penicillin extracted from urine. The patient was also given a large blood

transfusion, and his improvement continued as long as the penicillin held out. By the fifth day they had given him 4.5 grams of penicillin and they had no more to give. For ten days the policeman fought on his own against the half cured infection, but then the infection got the upper hand and the policeman died on March 15, 1942. (Wilson pp. 171-172) Now the effects of penicillin were proven, but due to the lack of enough supply of penicillin the cases were only half cured. Now it was time to take the manufacturing of penicillin to higher level.

It was obvious to that the best hope for the large scale penicillin production lay not in Britain, whose industry was being frequently disrupted by enemy bombing, but with the giant US pharmaceutical industry. Florey and Norman Heatley came to the United States since the US was not involved in the war at that time. Florey was assisted in the task of seeking US help by an old friend and fellow Rhodes Scholar, John Fulton. Fulton wasted no time. He immediately introduced Florey to Ross G. Harrison, the Chairman of the National Research Council. They finally met Percy A. Wells, the Director of the US Department of Agriculture's Research Service. Wells had been given the task of developing new uses for farm products, notably wastes. To promote this program the USDA had recently opened the Northern Regional Research Laboratory in Peoria, Illinois. Here the Department of Agriculture's scientists had become particularly well known for their work on mass-producing the products of fungal fermentations. They were therefore in an ideal position to take on the penicillin work." (Wainwright pp. 62)

Peoria was something new to the two British scientists. It had many facilities which were not even dreamed in Britain. The Director of Peoria and the head of the fermentation division promised full cooperation when Florey and Heatley arrived. First

problem faced at Peoria was to get the freeze-dried specimens of Fleming's mold to grow. Slowly and with difficulty they were persuaded to germinate again and fresh cultures were founded in Peoria's magnificent facilities. Moyer, a biochemist on the Peoria staff, was set to work with Heatley. There was no fresh yeast available at Peoria at that time. Moyer suggested the use of corn-steep liquor instead of yeast as an addition to the medium. It proved actually to work better than yeast at inducing the mould to increase its output of penicillin. Heatley spent a few days away from the laboratory and when he returned he found that Moyer had pushed up the yield of penicillin from mould even further. Lactose was found to be another important component of the medium. Heatley and Moyer wrote a few papers together on their work. It was later discovered by Heatley that Moyer had published paper in his name only. It was on the basis of this paper that Moyer filed three patents on the methods of penicillin production. Moyer never made a penny out of these patents. (Wilson pp. 191 – 192)

In 1943, the production of penicillin was given highest production priority, second only to the atom bomb program. By 1944, the cost of treating single severe bacterial infection with penicillin was about \$200, a figure which fell so rapidly that eventually penicillin would cost less to produce than did the packaging which contained it. During the First World War, 150 out of every 1,000 battle casualties died of infected wounds. While the appearance of the sulphonamides had a dramatic impact on battle casualty mortality in the opening years of the Second World War, penicillin was to have an even more miraculous effect, such that from D-day to the collapse of Germany the death rate as the result of infected wounds amongst Allied soldiers was reduced almost to zero! Open fractures showed a recovery rate of 94 to 100 per cent, and penicillin meant

that for the first time in the history of warfare, soldiers with burns of one fifth or less of their body surface made almost complete recoveries. (Wainwright pp. 63-65)

In 1947, an American woman was given an injection of penicillin, apparently without any ill effects. In August of the following year she was given a second dose of the antibiotic, after which she complained of a strange taste in her mouth, which was later accompanied by a swelling in her throat. Then, while leaning over the kitchen table, she suddenly collapsed and died. This was the first fatality ascribed to penicillin, but unfortunately it was not to prove the last. It seems that even despite its remarkably low toxicity, some people develop an allergy to penicillin, and in some cases this allergy response can cause death. (Wainwright pp. 84) The common adverse drug reactions associated with the use of penicillin include: diarrhea, nausea, rash, urticaria, and or superinfection (including candidiasis). Rare adverse effects include fever, vomiting, erythema, dermatitis, angioedema, seizures and pseudomembranous colitis. (Wilson pp. 270-271)

So how do the antibiotics work? Most of the antibiotics are bacteriostatic in clinical use, although some might act as bactericides, particularly when administered in large quantities. The former action inhibits the growth of the pathogen and relies upon the body's immune system to immobilize any remaining bacteria; bactericides, on the other hand, kill bacteria outright. They work by interfering with their ability to synthesize the proteins essential for their body components. The end result is, of course, suppression of growth, interference with cell multiplication and ultimately death. Penicillins are bacteriostats which interfere with the ability of the bacterial cell to form a wall, leading to the inevitable cellular disruption and ultimately death. As a result, penicillin kills only

those bacteria which are in the process of building new cell walls, or which are about to divide to form daughter cells. Since human cells don't have the cell walls, penicillin doesn't kill the human cells. (Wainwright pp. 84-85)

Penicillin cures cellulitis, bacterial endocarditis, gonorrhoea, meningitis, aspiration pneumonia, lung abscess, community acquired pneumonia, syphilis, septicaemia in children, tonsillitis, pharyngitis, skin infections, etc. Rossi. Discoverer of this miracle drug should be given some type of award. In popular mythology, the credit for the discovery and development of penicillin is solely given to Fleming, while little if any credit is given to the Oxford group. There is no doubt that Fleming has received too much of the credit for penicillin, but to a large extent the responsibility for this lay with Florey. It was Florey who made the decision to avoid the limelight and shun any publicity for the role of the Oxford group in the development of the penicillin. Wainwright 14 Fleming is often described as genius, but is he the real genius? Although the Scottish bacteriologist Alexander Fleming discovered the *penicillium notatum* mold in 1928, it was Chain who, together with Howard Florey, isolated the breakthrough substance that has saved countless victims of infections. For their work, Chain, Florey, and Fleming were awarded the Nobel Prize in physiology or medicine in 1945.

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