The **history of penicillin** was shaped by the contributions of numerous scientists. The ultimate result was the discovery of the mould *Penicillium's* antibiotic activity and the subsequent development of penicillins, the most widely used antibiotics. Following the identification of *Penicillium rubens* as the source of the compound (1928) and the production of a pure compound (1942), penicillin became the first naturally derived antibiotic. There is anecdotal evidence of ancient societies using moulds to treat infections and of awareness that various moulds inhibited bacterial growth. However, it is not clear if *Penicillium* species were the species traditionally used or if the antimicrobial substances produced were penicillin.

In 1928, while working at St Mary's Hospital in London, Scottish physician Alexander Fleming was the first to discover that a *Penicillium* mould secretes an antibacterial substance and concentrate the active substance involved, which he named penicillin. The mould was determined to be a rare variant of *Penicillium notatum* (now *Penicillium rubens*), a laboratory contaminant in his lab. For the next 16 years, he pursued better methods of production of penicillin, medicinal use and clinical trial. His success in treating Harry Lambert' streptococcal meningitis, an infection until then fatal, proved to be a critical moment in the medical use of penicillin.

Many later scientists were involved in the stabilization and mass production of penicillin and in the search for more productive strains of *Penicillium*. Among the most Important contributors to the development of present day antibiotics are Ernst Chain, Howard Florey, Norman Heatley and Edward Abraham. Fleming, Chain and Florey shared the 1945 Nobel Prize in Physiology or Medicine for the discovery and development of penicillin. Dorothy Hodgkin received the 1964 Nobel Prize in Chemistry for determining the structures of important biochemical substances including penicillin. Shortly after the discovery of penicillin, there were reports of penicillin resistance in many bacteria. Research that aims to circumvent and understand the mechanisms of antibiotic resistance continues today.

SUGGESTED SUMMARY:

The **history of penicillin** was shaped by the contributions of numerous scientists. The ultimate result was the discovery of the mould *Penicillium's* antibiotic activity and the subsequent development of penicillins, the most widely used antibiotics. Following the identification of *Penicillium rubens* as the source of the compound (1928) and the production of a pure compound (1942), penicillin became the first naturally derived antibiotic. There is anecdotal evidence of ancient societies using moulds to treat infections and of awareness that various moulds inhibited bacterial growth. However, it is not clear if *Penicillium* species were the species traditionally used or if the antimicrobial substances produced were penicillin.

In 1928, Alexander Fleming was the first to discover the antibacterial substance secreted by the Penicillium mould and concentrate the active substance involved. . His success in treating Harry Lambert' streptococcal meningitis, an infection until then fatal, proved to be a critical moment in the medical use of penicillin.

Many later scientists were involved in the stabilization and mass production of penicillin and in the search for more productive strains of *Penicillium*. Among the most Important

are Ernst Chain, Howard Florey, who shared with Fleming the 1945 Nobel Prize in Physiology or Medicine.

Early history[edit | edit source]

Penicillin (Figure 1) is the second antibiotic and the first naturally-occurring antibiotic discovered.[1][2] The first antibiotic discovered was arsphenamine, marketed as Salvarsan, by German physician Paul Ehrlich and his Japanese assistant Sahachiro Hata in 1909.[3] A modified compound of a highly toxic chemical arsenic[4], it was used for the treatment of sexually transmitted bacterial (*Treponema pallidum*) infection or syphilis, and became the most commonly prescribed drug in the early 20th century.[5] However, arsphenamine was overshadowed by penicillin, a safer and more efficacious antibiotic, that was effective against a wide range of Gram-positive bacteria,[6] as well as Gram-negative *T. pallidum*.[7]

Traditional curative practices preceded the discovery of penicillin as a component of the mould *Penicillium* (from the Latin word *penicillum*, meaning "painter's brush").[8] Ancient Egypt, Greece and India were aware of the curative properties of fungi and plants in treating bacterial infections[9] as shown by a 16th-century BCE record of the use of bread moulds by a healer treating wounded soldiers. Around the same time, Chinese traditional practitioners used moulds from soya bean for wound infections.[10]

In 17th-century Poland, wet bread was mixed with spider webs (which often contained fungal spores) to treat wounds, a technique, mentioned by Henryk Sienkiewicz in his 1884 book *With Fire and Sword*. In 1640, the idea of using mould as a form of medical treatment was recorded by English apothecaries such as John Parkinson, King's Herbarian, who advocated the use of mould in his book on pharmacology.[11] One of the common practices for treating impetigo (an infection due to the bacterium *Staphylococcus aureus)* was mould therapy with moulds obtained from bread and porridge.[12] A Canadian biologist, A.E. Cliffe left a vivid description:

"It was during a visit through central Europe in 1908 that I came across the fact that almost every farmhouse followed the practice of keeping a mouldy loaf on one of the beams in the kitchen. When I asked the reason for this I was told that this was an old custom and that when any member of the family received an injury such as a cut or bruise, a thin slice from the outside of the loaf was cut off, mixed into a paste with water and applied to the wound with a bandage. It was assumed that no infection would result from such a cut."[13]

One of the most detailed medical narratives was the successful treatment of Brenda Ward (*née* Whitnear)'s daughter of facial impetigo in 1929. After treating eight-year-old Brenda with all available medications, the family physician James Twomey resorted to traditional practice and advised the child's mother to prepare a starch paste. The paste was left in the pantry kept at the cellar head for several days until it became very mouldy. It was then applied on the girl's face as an ointment for over a week until she was completely healed.[14] Ward recalled that the mould initially appeared yellow in colour, grew into bronze colour, and finally turned into blue-green colonies, which indicates it was

either *Penicillium* or *Aspergillus*. There is no written record of the treatment except for a receipt of the consultation fee but, based on Ward's description, in 1989, British microbiologist Milton Wainright concluded that the more likely mould was *Penicillum* due to the growth pattern and antibacterial activty.[15]

Traditional treatments often worked because numerous organisms, including many species of mould, naturally produce antibiotic substances. However, it was not until recently that practitioners were able to identify or isolate the active components in these organisms.

Early scientific evidence[edit | edit source]

The modern history of penicillin research began in earnest in the 1870s in the United Kingdom. Sir John Scott Burdon-Sanderson, physiologist and later lecturer at St. Mary's Hospital, observed that culture fluid covered with mould produced no bacterial growth. **[NOTE: ADD DETAILS IN A FOOTNOTE]** Burdon-Sanderson's discovery prompted Joseph Lister, an English surgeon and the father of modern antisepsis, to discover in 1871 that urine samples contaminated with mould did not permit the growth of bacteria either.[16] Lister also described the antibacterial action on human tissue of a species of mould he called *Penicillium glaucum*, and reportedly cured a patient in 1877.[17] A nurse at King's College Hospital whose wounds did not respond to any traditional antiseptic was then given another substance that cured him, and Lister's registrar informed him that it was called *Penicillium*.

NOTE IT IS NOT CLEAR IF THE NURSE IS THE PATIENT MENTIONED IN THE PREVIOUS SENTENCE. IF HE IS, I WOULD MAKE THE FOLLOWING CHANGE:

and reportedly, in 1877, cured a nurse at King's College Hospital whose wounds did not respond to any traditional antiseptic. He was then given another substance that, according to Lister's registrar was *Penicillium.*[17]

In 1873, Welsh physician William Roberts, who later coined the term "enzyme", conducted experiments to test the hypothesis of spontaneous generation (abiogenesis) and observed glass tubes were easily contaminated by airborne bacteria and moulds.[18] In his 1874 report in the *Philosophical Transactions of the Royal Society* he stated: "I have repeatedly observed that liquids in which the *Penicillum glaucum* was growing luxuriantly could with difficulty be artificially infected with *Bacteria*; it seemed, in fact, as if this fungus played the part of the plants in an aquarium, and held in check the growth of *Bacteria,* with their attendant putrefactive changes."[19] John Tyndall, professor of physics at the Royal Institution of Great Britain, followed up on Roberts's work and demonstrated in 1875 the antibacterial action of the *P. glaucum*. His report, read before the Royal Society the following year (and published as a monograph in 1881), stated::[20]

"[The] two most actively charged tubes were in part crowned by beautiful tufts of Penicilllum Glaucum. This expanded gradually until it covered the entire surface with thick tough layer, which must have seriously intercepted the oxygen necessary to the Bacterial life. The bacteria lost their translatory power, fell to the bottom, and left the liquid between them and the superficial layer clear".[21]

In 1876, German biologist Robert Koch discovered that *Bacillus anthracis* was the causative pathogen of anthrax;[22] it was the first time a specific bacterium was proved to cause a specific disease, and the first direct evidence of the germ theory of diseases.[23] A year later, French biologists Louis Pasteur and Jules Francois Joubert observed that, when contaminated with moulds, cultures of the anthrax bacilli could be successfully inhibited.[24] Their findings were reported in the *Comptes Rendus de l'Académie des Sciences*:

"Neutral or slightly alkaline urine is an excellent medium for the bacteria... But if when the urine is inoculated with these bacteria an aerobic organism, for example one of the 'common bacteria,' is sown at the same time, the anthrax bacterium makes little or no growth and sooner or later dies out altogether. It is a remarkable thing that the same phenomenon is seen in the body even of those animals most susceptible to anthrax, leading to the astonishing result that anthrax bacteria can be introduced in profusion into an animal, which yet does not develop the disease; it is only necessary to add some 'common bacteria' at the same time to the liquid containing the suspension of anthrax bacteria. These facts perhaps justify the highest hopes for therapeutics."[25]

The phenomenon was described by Pasteur and Koch as antibacterial activity and, in 1877, was named as "antibiosis" by French biologist Jean Paul Vuillemin.[26][27] (The term antibiosis, meaning "against life", was adopted as "antibiotic" by American biologist and later Nobel laureate Selman Waksman in 1947.[28]) It has also been asserted that Pasteur identified the mould as *Penicillium notatum*. However, Paul de Kruif's *Microbe Hunters* (1926) disagrees, describing this incident as contamination by other bacteria rather than mould.[29] Ten years later, in 1887, Swiss physician Carl Alois Philipp Garré developed a test method using glass plate to see bacterial inhibition and obtained similar results.[27] Using his gelatin-based culture plate, Garré grew two different bacteria and found that their growths were inhibited differently:

"I inoculated on the untouched cooled [gelatin] plate alternate parallel strokes of *B. fluorescens* [*Pseudomonas fluorescens*] and *Staph. pyogenes* [*Streptococcus pyogenes*]... B. fluorescens grew more quickly... [This] is not a question of overgrowth or crowding out of one by another quicker-growing species, as in a garden where luxuriantly growing weeds kill the delicate plants. Nor is it due to the utilization of the available foodstuff by the more quickly growing organisms, rather there is an antagonism caused by the secretion of specific, easily diffusible substances which are inhibitory to the growth of some species but completely ineffective against others."[25]

At the University of Naples, the physician Vincenzo Tiberio published his research about moulds initially found in a water well in Arzano (1895); from his observations, he concluded that these moulds contained soluble substances having antibacterial action.[30][31][32]

Fleming's mould, *Penicillium rubens* CBS 205.57. A–C. Colonies 7 d old 25 °C. A. CYA. B. MEA. C. YES. D–H. Condiophores. I. Conidia. Bars = 10 µm.

Houbraken et al., 2011, CC-BY 4.0

French medical student Ernest Duchesne at École du Service de Santé Militaire (Military Service Health School) in Lyon independently discovered the healing properties of *P. glaucum.*[33] He was able to grow the mould on pieces of moist food. When he mixed the mould with the bacterium *Escherichia coli*, he found that the bacteria did not grow, and when he injected the mould juice into guinea pigs experimentally inoculated with typhoid bacteria (*Salmonella enterica*), the animals never developed the disease.[34] He described the experiment in his 1897 doctoral dissertation, *Contribution à l'étude de la concurrence vitale chez les microorganismes* (*Contribution to the study of vital competition between microorganisms: antagonism between moulds and microbes*), submitted to the Pasteur Institute.[35][36] Unfortunately, his discovery was ignored by the Institute and soon forgotten.[37] It was not until 50 years later that the thesis was found by a librarian, once penicillin had already been discovered.

Duchesne could not continue his experiments due to a severe illness (believed to be tuberculosis) he contracted five years later. He died in 1912 while serving in the French Army.[34] He himself was using moulds to treat horses, a method learned from Arab stable boys to cure the animals´ sores, but he did not claim that the mould contained any antibacterial substance, only that it somehow protected the animals.[24] His conclusion was nonetheless prognostic, stating that competition between bacteria and moulds could be useful in the medical management of infections.[38] Penicillin does not cure typhoid and so it remains unknown which substance might have been responsible for Duchesne's cure.[a] A similar antibiotic effect of Penicillium was recorded in 1923 by the Costa Rican Clodomiro Picado Twight, a Pasteur institute scientist. In these early stages of penicillin research, most species of *Penicillium* were non-specifically referred to as *P. glaucum*, so that it is impossible to know the exact species and whether it was really penicillin that prevented bacterial growth.[24]

The first to discover and isolate an antibiotic compound from *Penicillium* was the Italian physician Bartolomeo Gosio (1896).[39] Gosio was researching pellagra, which at the time was a common disease in southern Europe and America. It was known that the staple food of people having the disease was corn, and fungal contamination of corn was regarded as the source (American biochemist Conrad Elvehjem would identify in 1937, its aetiology as deficiency of niacin or vitamin B_3). In 1893, Gosio considered the mould *Penicillium brevicompactum* as a possible cause of pellagra,[40][41] so he developed a simple culture method to make pure culture extract in crystalline form. Three years later, he tested the substance on anthrax bacillus and found it to be highly potent against the bacteria.[42][43] Nonetheless, Gosio's discovery was largely forgotten as the substance was found not to be the cause of pellagra, and its medicinal potential was not obvious. Sixteen years later, American scientists, Carl Alsberg and Otis Fisher Black resynthesized Gosio's substance giving it the name mycophenolic acid, which is now used as an immunosuppressant.[41][44]

In 1924, Andre Gratia and Sara Dath at the Free University of Brussels (Belgium), found that dead *Staphylococcus aureus* cultures were contaminated by a mould, a streptomycete. On further experimentation, they showed that the mould extract could

kill not only *S. aureus*, but also *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis* and *Escherichia coli*.[45] Gratia called the antibacterial agent "mycolysate" (killer mould). The next year they found another killer mould that could inhibit anthrax bacterium (*B. anthracis*). Their article in *Comptes Rendus Des Séances de La Société de Biologie et de Ses Filiales*, identified the mould as *Penicillium glaucum,*[46] and in 1927, Gratia reported its medical use:

"A poor patient who during three years had suffered from furuncles [infection by *S. aureus*], inspite of all treatments, was sent to us in despair. Jaumain did not hesitate to continue the treatment by a series of injections of the mycolysat. The result was remarkable. Not only was the recovery rapid, but it is now three years that [*sic*] this recovery continues without the slightest relapse. Since that time we have given the mycolysat to a very large number of cases. It is the most effective treatment even of the most resistant types of staphylococcic diseases."[39]

Unfortunately, as in the case of Duchesne, these findings received little attention as the antibacterial agent and its medical values were not fully understood; moreover, Gratia's samples were lost.[45]

The breakthrough discovery[edit | edit source]

Background[edit | edit source]

Alexander Fleming in his laboratory at St Mary's Hospital, London.

Ministry of Information Photo Division Photographer, Public domain

Penicillin, as we know it today, was discovered by the Scottish physician Alexander Fleming in 1928. While working at St Mary's Hospital, London, Fleming was investigating the pattern of variation in *S. aureus* (Figures 2 and 3).[47][48] He was inspired by the recent discovery by the Irish physician Joseph Warwick Bigger and his two students C.R. Boland and R.A.Q. O'Meara who worked at Trinity College in Dublin (Ireland). Bigger and his students found that a particular strain of *S. aureus* bacterium (designated "Y") that they isolated a year before from the pus of an individual's axillary abscess grew into a variety of strains. They published their discovery as "Variant colonies of *Staphylococcus aureus*" in *The Journal of Pathology and Bacteriology*:

"We were surprised and rather disturbed to find, on a number of plates, various types of colonies which differed completely from the typical *aureus* colony. Some of these were quite white; some, either white or of the usual colour were rough on the surface and with crenated margins."[49]

Fleming and his research scholar Daniel Merlin Pryce pursued this experiment. However, as Pryce was transferred to another laboratory in early 1928, a new scholar, Stuart Craddock, joined Fleming a few months later to continue with the work. Their experiment was successful and Fleming wrote a report for *A System of Bacteriology* that was published by the Medical Research Council in late1928.[48] **[*NOTE: I am assuming he did write and published the report]**

Initial discovery[edit | edit source]

In August, before leaving on vacation, Fleming inoculated several culture plates with *S. aureus* (Figures 3 and 4) and left the plates aside on one corner of a lab table away from direct sunlight. While on vacation, he was appointed Professor of Bacteriology at the St Mary's Hospital Medical School on 1 September 1928 **[NOTE: Why is this relevant to the main topic? Explain]**. He returned to his laboratory on 3 September, where Pryce was waiting to greet him.[50] As he and Pryce examined the culture plates, they found one with an open lid and the culture contaminated with a blue-green mould. In the contaminated plate the bacteria around the mould did not grow, while those farther away grew normally, meaning that the mould killed the bacteria.[51] Fleming commented as he watched the plate: "That's funny".[50][52] Pryce remarked to Fleming: "That's how you discovered lysozyme."[53]

[This paragraph is confusing. Why was Pryce waiting for him? Where was Craddock? Unless Pryce continues to be part of the narrative, it would be clearer to simplify and follow the results] I would change it to:

When he arrived at his laboratory on 3 September and examined the culture plates, he found one with an open lid and the culture contaminated with a blue-green mould. In the contaminated plate the bacteria around the mould did not grow while those farther away grew normally, meaning that the mould killed the bacteria.[51]

Experiment[edit | edit source]

St Mary's Hospital showing Fleming's lab (on the second floor) and Praed Street, from where Fleming alleged the mould came from.

Fleming went off to resume his vacation and returned to his laboratory in late in September.[48] He collected the original mould and grew it in culture plates. After four days he found that the plates developed large colonies of the mould. A repetition of the experiment gave the same bacteria-killing results. He later recounted his experience:

“When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionize all medicine by discovering the world's first antibiotic, or bacteria killer. But I suppose that was exactly what I did.”[54]

He concluded that the mould was releasing a substance that was inhibiting bacterial growth, and he produced a culture broth of the mould and subsequently concentrated the antibacterial component.[55] After testing against different bacteria, he found that the mould could kill only specific bacteria. For example, *Staphylococcus*, *Streptococcus*, and diphtheria bacillus (*Corynebacterium diphtheriae*) were easily killed; but there was no effect on typhoid bacterium (*Salmonella typhimurium*) and influenza bacillus (*Haemophilus influenzae*). He prepared a large-culture method from which he could obtain large amounts of the mould juice that he called "penicillin" in order "to avoid the repetition of the rather cumbersome phrase 'Mould broth filtrate,'.[50] In his Nobel lecture he gave a further explanation:

"I have been frequently asked why I invented the name "Penicillin". I simply followed perfectly orthodox lines and coined a word which explained that the substance penicillin was derived from a plant of the genus *Penicillium* just as many years ago the word "Digitalin" was invented for a substance derived from the plant *Digitalis*."[57]

As Fleming had no training in chemistry, he left the chemical works to Craddock.[48] In January 1929, he [**NOTE: It is unclear who hired Ridley. Fleming?]** recruited Frederick Ridley, his former research scholar who had studied biochemistry, specifically to study the chemical properties of the mould.[52] **[NOTE: Again, the sentence is confusing as the subject is not clear. Did Ridley studied biochemistry to study the chemical properties of the mould or was he hired to study them?]** However, both Craddock and Ridley left Fleming before completing the experiments and isolating penicillin.[50] Their failure to isolate the compound resulted in Fleming practically abandoning further research on the chemical aspects of penicillin.[58] Nonetheless, he continued doing biological tests up to 1939.[50]

Identification of the mould[edit | edit source]

Penicillium rubens (type specimen).

Houbraken et al., 2011, *CC-BY 4.0*

After a structural comparison with different species of *Penicillium*, Fleming believed that his specimen was *Penicillium chrysogenum*, a species described by the American microbiologist Charles Thom in 1910. He was fortunate as Charles John Patrick La Touche, an Irish botanist, had just recently joined as a mycologist at St Mary's to investigate fungi as the cause of asthma. La Touche identified the specimen as *Penicillium rubrum,*[59][60] identification that Fleming used in his publication. **[NOTE: What publication?]**

THE FOLLOWING PARAGRAPH IS VERY CONFUSING. IT SHOULD BE REWORKED (MAYBE SIMPLIFIED) AND INTEGRATED BETTER TO MAKE IT MORE READABLE.

In 1931, Thom re-examined different *Penicillium* including that of Fleming's specimen. He came to a confusing conclusion, stating: "Ad. 35 [Fleming's specimen] is *P. notatum* WESTLING. This is a member of the *P. chrysogenum* series with smaller conidia than *P. chrysogenum* itself."[61] *P. notatum* was described by Swedish chemist Richard Westling in 1811. From then on, Fleming's mould was synonymously referred to as *P. notatum* and *P. chrysogenum.* But Thom adopted and popularised the use of *P. chrysogenum.*[62] In addition to *P. notatum*, newly discovered species such as *P. meleagrinum* and *P. cyaneofulvum* were recognised as members of *P. chrysogenum* in 1977.[63] To resolve the confusion, the Seventeenth International Botanical Congress held in Vienna, Austria, in 2005 formally adopted the name *P. chrysogenum* as the conserved name (*nomen conservandum*).[64] Whole genome sequence and phylogenetic analysis in 2011 revealed that Fleming's mould belongs to *P. rubens* (Figure 5), a species described

by Belgian microbiologist Philibert Biourge in 1923, and also that *P. chrysogenum* is a different species.[65][66]

AS THE PREVIOUS PARAGRAPH, THIS ONE NEEDS TO BE BETTER INTEGRATED INTO THE MAIN TOPIC. MAYBE MOVED TO PRECEDE THE PREVIOUS ONE?

The source of the fungal contamination in Fleming's experiment remained a matter of speculation for several decades. The Royal Society of Chemistry initially believed it was caused by a cup of coffee left by Fleming on the table.[37] In 1945, Fleming himself suggested that the fungal spores came through the window facing Praed Street. This story was popularised in the literature,[67] starting with George Lacken's 1945 book *The Story of Penicillin*.[50] However, it was later disputed by his co-workers including Pryce, who later testified that the laboratory window was kept shut all the time.[68] Years later, Ronald Hare agreed that the window was usually locked as the apparatus placed in front of it made it difficult to reach. In 1966, La Touche told Hare he had given Fleming 13 specimens of fungi (10 from his lab) and only one from his lab was showing penicillin-like antibacterial activity.[67] It was, therefore, concluded that Fleming's mould came from La Touche's lab, located in the floor below, and the spores had drifted in the air through the open doors.[69]

Reception and publication[edit | edit source]

Initially, Fleming's discovery was given importance and, as he showed his culture plates to his colleagues, all he received was an indifferent response. He described the discovery on 13 February 1929 before the Medical Research Club but his presentation titled "A medium for the isolation of Pfeiffer's bacillus" did not receive any particular attention.[48]

In May of the same year, Fleming reported his findings to the *British Journal of Experimental Pathology*, that published them in the next month's issue.[70][71] The publication failed to attract any serious attention; Fleming himself was quite unsure of the medical application and was more concerned about the application for bacterial isolation, as he concluded:

“In addition to its possible use in the treatment of bacterial infections penicillin is certainly useful to the bacteriologist for its power of inhibiting unwanted microbes in bacterial cultures so that penicillin insensitive bacteria can readily be isolated. A notable instance of this is the very easy, isolation of Pfeiffers bacillus of influenza when penicillin is used...It is suggested that it may be an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes.”[70]

G. E. Breen, a fellow member of the Chelsea Arts Club, once asked Fleming: "I just wanted you to tell me whether you think it will ever be possible to make practical use of the stuff [penicillin]. For instance, could I use it?" Fleming gazed vacantly for a moment and then replied: "I don't know. It's too unstable. It will have to be purified, and I can't do that by myself."[48] Even as late as in 1941, the *British Medical Journal* reported that: "the main facts emerging from a very comprehensive study [of penicillin] in which a large team of workers is engaged... does not appear to have been considered as possibly useful from any other point of view."[72][73][b]

Isolation[edit | edit source]

In 1936, Ernst Boris Chain, a chemist of Jewish-German origins, joined Australian scientist Howard Florey (later Baron Florey) at the Sir William Dunn School of Pathology (University of Oxford) to investigate antibiotics. Florey assigned him to investigate on lysozyme, an antibacterial enzyme discovered by Fleming in 1922.[75] In 1938, Chain came across Fleming's 1929 paper and informed his supervisor of the potential medical benefits of penicillin.[76] Although a year before, Florey had decided to concentrate on pyocyanase (a pigment from the bacterium *Bacillus pycyaneus,* now called *Pseudomonas aeruginosa*), he agreed with Chain that penicillin was medically more promising.[77] In 1939, Florey and Chain obtained a $25,000 research grant from the Rockefeller Foundation to study antibiotics[78][79] that allowed them to assemble a research team composed of Edward Abraham, Arthur Duncan Gardner, Norman Heatley, Margaret Jennings, J. Orr-Ewing and G. Sanders.[80][81]

The Oxford team prepared a concentrated extract of *P. rubens* as: "a brown powder" that: "has been obtained which is freely soluble in water".[82] They found that the powder was not only effective *in vitro* against bacterial cultures but also and *in vivo* against bacterial infection in mice. On 5 May 1939, they injected a group of eight mice with a virulent strain of *S. aureus*, and then injected four of them with the penicillin solution. After one day, all the untreated mice died while the penicillin-treated mice survived, "a miracle" in Chain's view.[76] The team published its findings in *The Lancet* in 1940.[82]

The team reported details of the isolation method in 1941 with a scheme for large-scale extraction. It also found that penicillin was most abundant as a yellow concentrate from the mould extract, [83] but it was able to produce only small quantities. By the early 1942, the Oxford team could prepare highly purified compound,[84] and derived the empirical chemical formula as $C_{24}H_{32}O_{10}N_2Ba$.[85] In the June 1942 issue of the *British Journal of Experimental Pathology*, Chain, Abraham and E. R. Holiday reported the production of the pure compound concluding that:

"The penicillin preparation described in this paper is the most powerful antibacterial agent with predominantly bacteriostatic action so far known. Though it has not yet been obtained crystalline there are indications that it possesses a considerable degree of purity... The unusual biological properties of penicillin are linked with an exceptionally unstable chemical configuration. Inactivation by acid, alkali, and by boiling at any pH has been shown to be accompanied by definite chemical changes."[86]

First medical use[edit | edit source]

In January 1929, Fleming performed the first clinical trial with penicillin on Stuart Craddock, Fleming's assistant. Craddock had developed a severe infection of the nasal antrum (sinusitis) for which had undergone surgery. Fleming made use of the surgical opening of the nasal passage and started injecting penicillin. The patient experienced no improvement, probably because the infection was caused by the influenza bacillus (*Haemophilus influenzae*), the bacterium which he had found not susceptible to penicillin.[87] It seems that Fleming gave some of his original penicillin samples to his colleague, the surgeon Arthur Dickson Wright for clinical test in 1928.[88][89] Although Wright

reportedly said that it: "seemed to work satisfactorily,"[17] there are no records of its specific use.

In November 1930, Cecil George Paine, a pathologist at the Royal Infirmary in Sheffield, was the first to use penicillin for medical treatment successfully.[14] Paine was a former student of Fleming who, after learning about penicillin, had requested a sample from his mentor.[90] He initially attempted to treat sycosis (eruptions in beard follicles) with penicillin but was unsuccessful, probably because the drug did not penetrate deeply enough. He then tried it successfully on four patients (one adult and three infants) who suffered ophthalmia neonatorum, a gonococcal infection in babies. Penicillin worked on eye infections.[91][92]

Nine years later, the Oxford team showed that *Penicillium* extract killed different bacteria (*Streptococcus pyogenes, Staphylococcus aureus,* and *Clostridium septique*) in culture and effectively cured *Streptococcus* infection in mice.[76] Thus, they reported their findings in the 24 August 1940 issue of *The Lancet* under the title "Penicillin as a chemotherapeutic agent":

“The results are clear cut and show that penicillin is active in vivo against at least three of the organisms inhibited in vitro. It would seem a reasonable hope that all organisms in high dilution in vitro will be found to be dealt with in vivo. Penicillin does not appear to be related to any chemotherapeutic substance at present in use and is particularly remarkable for its activity against the anaerobic organisms associated with gas gangrene.”[82]

The following year, the Oxford team treated a policeman, Albert Alexander, who had a severe face infection. Although his condition improved, he eventually died as the researchers ran out of penicillin. Subsequently, several other patients were treated successfully,[93] among them the survivors of the Cocoanut Grove fire in Boston (December 1942) who were the first burn patients to be successfully treated with penicillin.[94]

The most important clinical test took place in August 1942 when Fleming cured Harry Lambert (a work associate of Fleming's brother) of a fatal infection of the nervous system (streptococcal meningitis).[95] Fleming asked Florey for a purified penicillin sample, which he immediately injected into Lambert's spinal canal. Lambert showed signs of improvement the next day,[96] and completely recovered within a week.[97][98] Fleming reported his findings in *The Lancet* in 1943.[99] It was on this medical evidence that the British War Cabinet set up the Penicillin Committee on 5 April 1943 formed by Cecil Weir, Director General of Equipment, as Chairman, Sir Percival Hartley, Allison, Fleming, Florey, and representatives from pharmaceutical companies as members.[96] The establishment of the Committee opened the door to the mass production of penicillin the next year.[100][101]

Mass production[edit | edit source]

The cantaloupe strain of *Penicillum* (*P. chrysogenum* or *P. notatum*) which is the best source of penicillins and was used in the first mass production in US.

Crulina 98, CC-BY 3.0

Knowing that large-scale production for medical use was futile in a confined laboratory, the Oxford team tried to persuade the war-torn British government and private companies to undertake mass production.[102] In face of their reluctance, in June 1941, Florey and Heatley travelled to the United States (US) to persuade the American government and pharmaceutical companies there.[103] [DELETED] In July they met with Andrew Jackson Moyer and Robert D. Coghill at the National Center for Agricultural Utilization Research (NRRL) in Peoria, Illinois, where large-scale fermentations were done.[104] The Americans showed great interest and were able to make a culture by the end of July[102] but realised that Fleming's mould was not efficient enough to produce large quantities of penicillin.

With the help of US Army Transport Command, NRRL mycologist Kenneth Bryan Raper was able to locate similar but better moulds from Chungkin (China), Bombay (Mumbai, India) and Cape Town (South Africa). However, the single-best sample was obtained in 1943 from cantaloupe (a type of melon) sold in the local fruit market. The mould was identified as *P. chrysogenum* and designated as "NRRL 1951" or "cantaloupe strain" (Figure 6).[104][105] **[DELETED]**

Between 1941 and 1943, Moyer, Coghill and Raper developed methods for industrialized penicillin production and isolated higher-yielding strains of the *Penicillium* fungus.[110] Simultaneous research by Jasper H. Kane and other Pfizer scientists in Brooklyn developed the practical, deep-tank fermentation method for production of large quantities of pharmaceutical-grade penicillin.[111]

Penicillin ad for World War II servicemen, *c*. 1944.

National Institute of Health, Public domain

When production first began, one-litre containers had a yield of less than 1%, but improved to a yield of 80–90% in 10,000 gallon containers. This increase in efficiency happened between 1939 and 1945 as the result of continuous process innovation (Figure 7 shows one of the first mass applications). Orvill May, director of the Agricultural Research Service, had Robert Coghill, who was the chief of the fermentation division, use his experience with fermentation to increase the efficiency of extracting penicillin from the mould. Moyer replaced sucrose with lactose in the growth media, which resulted in an increased yield. An even larger increase occurred when Moyer added corn steep liquor.[103]

The inefficiency of growing the mould on the surface of their nutrient baths, rather than having it submerged was a major challenge to the scientists. Although a submerged process of growing the mould was more efficient, the strain used was not suitable for the required conditions. This led NRRL to a search for a more appropriate strain, and one

was found in a mouldy cantaloupe acquired from the Peoria market.[112] To improve on that strain, researchers subjected it to X-rays to facilitate mutations in its genome and managed to increase production capabilities.[113][112]

Now scientists had a mould that grew well submerged and produced an acceptable amount of penicillin. The next challenge was to provide the air required by the mould to grow. This problem was solved using an aerator but, due to the use of corn steep, aeration caused severe foaming; the addition of an anti-foaming agent known as glyceryl monoricinoleate solved this problem.[113]

Chemical analysis[edit | edit source]

The chemical structure of penicillin was first proposed by Edward Abraham in 1942[114] and three years later Dorothy Hodgkin, who worked at Oxford, determined the correct chemical structure of penicillin using X-ray crystallography.[115][116][117] The same year chemical analyses done at different universities, pharmaceutical companies and government research departments was published jointly by the US Committee on Medical Research and the British Medical Research Council in the journal *Science*. The report announced the existence of different forms of penicillin compounds that shared the same structural component called β-lactam.[118] In the United Kingdom the penicillins were called penicillin I, II, III, and IV (Roman numerals were used according to the order of their discovery) while in the US scientists used letters such as F, G, K, and X that referred to their origins or sources. (See Table below).

UK nomenclature	US nomenclature	Chemical name
Penicillin I	Penicillin F	2-Pentenylpenicillin
Penicillin II	Penicillin G	Benzylpenicillin
Penicillin III	Penicillin X	*p*-Hydroxybenzylpenicillin
Penicillin IV	Penicillin K	*n*-Heptylpenicillin

The use of two different names for each penicillin caused confusion.[119] As the chemical structures came to be known, the chemical names (based on the side chains of the compounds) further complicated their identification and application.[121] Thus, penicillin literature became a mixture of three naming systems. Chemists mostly adhered to the chemical names,[120][121] while biologists preferred the classic numbered or lettered names.[122][123] To prevent additional confusion, in 1948 Chain introduced the chemical names as standard nomenclature, remarking: "To make the nomenclature as far as

possible unambiguous it was decided to replace the system of numbers or letters by prefixes indicating the chemical nature of the side chain R."[124]

Further developments took place. In Austria, Hans Margreiter and Ernst Brandl of Biochemie (now Sandoz) developed the first acid-stable penicillin for oral administration, penicillin V in 1952.[125] American chemist John C. Sheehan at the Massachusetts Institute of Technology (MIT) completed the first chemical synthesis of penicillin in 1957.[126][127][128] Sheehan had started his studies into penicillin synthesis in 1948, and during these investigations developed new methods for the synthesis of peptides, as well as new protecting groups—groups that mask the reactivity of certain functional groups.[128][129] Although the initial synthesis developed by Sheehan was not appropriate for mass production of penicillins, one of the intermediate compounds in his synthesis was 6-aminopenicillanic acid (6-APA), the nucleus of penicillin.[130][131]

An important moment in the history of penicillin was the discovery of 6-APA itself. In 1957, researchers at Surrey's Beecham Research Laboratories (now the Beecham Group) isolated 6-APA from the culture media of *P. chrysogenum*. As published in *Nature* (1959), 6-APA was found to constitute the core 'nucleus' of penicillin (in fact, all β-lactam antibiotics) and was easily chemically modified by attaching side chains through chemical reactions.[132][133].[134] This discovery paved the way for new and improved drugs as all semi-synthetic penicillins are produced from chemical manipulation of 6-APA.[135]

The second-generation semi-synthetic β-lactam antibiotic methicillin, designed to counter first-generation-resistant penicillinases, was introduced in the United Kingdom in 1959. It is likely that Methicillin-resistant forms of *Staphylococcus aureus* already existed at the time.[136][137]

Outcomes[edit | edit source]

Penicillin patents became a matter of concern and conflict. Chain had wanted to apply for a patent but Florey and his teammates had objected arguing that penicillin should benefit all.[138] Chain then sought the advise of Sir Henry Hallett Dale (Chairman of the Wellcome Trust and member the Scientific Advisory Panel to the Cabinet of British government) and John William Trevan (Director of the Wellcome Trust Research Laboratory). On 26 and 27 March 1941, Dale and Trevan met to discuss the issue. Dale specifically advised that patenting penicillin woul be unethical.[139] Not giving up, Chain then approached Sir Edward Mellanby, then Secretary of the Medical Research Council, who also objected on ethical grounds.[140] As Chain later admitted, he had "many bitter fights" with Mellanby,[139] but Mellanby's decision was accepted as final.[140]

Methods for production and isolation of penicillin were patented by Andrew Jackson Moyer in US in 1945.[141][142][143] Moyer could not obtain a patent in the US as an employee of the NRRL, and filed his patent at the British Patent Office (now the Intellectual Property Office). He gave the license to the US company, Commercial Solvents Corporation. Although completely legal, his colleague Coghill felt it was an injustice for outsiders to have the royalties for the "British discovery." A year later, Moyer asked Coghill for permission to file another patent based on the use of phenylacetic acid to increase penicillin production by 66%, but as the principal researcher, Coghill refused.[144]

When Fleming learned of the American patents on penicillin production, he was infuriated and commented: “I found penicillin and have given it free for the benefit of humanity. Why should it become a profit-making monopoly of manufacturers in another country?”[145]

Fleming, Florey and Chain shared the 1945 Nobel Prize in Physiology or Medicine "for the discovery of penicillin and its curative effect in various infectious diseases."[146] Dorothy Hodgkin received the 1964 Nobel Prize in Chemistry "for her determinations by X-ray techniques of the structures of important biochemical substances." **[NOTE: EXPAND ON HODGKIN’S ROLE AND THE IMPORTANCE OF HER CONTRIBUTION]**

NOTE: THE PARAGRAPH “DEVELOPMENT OF PENICILLIN-DERIVATIVES WAS NOT EDITED.

Development of penicillin-derivatives[edit | edit source]

The narrow range of treatable diseases or "spectrum of activity" of the penicillins, along with the poor activity of the orally active phenoxymethylpenicillin, led to the search for derivatives of penicillin that could treat a wider range of infections. The isolation of 6-APA, the nucleus of penicillin, allowed for the preparation of semisynthetic penicillins, with various improvements over benzylpenicillin (bioavailability, spectrum, stability, tolerance). The first major development was ampicillin in 1961. It was produced by Beecham Research Laboratories in London.[147] It was more advantageous than the original penicillin as it offered a broader spectrum of activity against Gram-positive and Gram-negative bacteria.[147] Further development yielded β-lactamase-resistant penicillins, including flucloxacillin, dicloxacillin, and methicillin. These were significant for their activity against β-lactamase-producing bacterial species, but were ineffective against the methicillin-resistant *Staphylococcus aureus* strains that subsequently emerged.[148]

Another development of the line of true penicillins was the antipseudomonal penicillins, such as carbenicillin, ticarcillin, and piperacillin, useful for their activity against Gram-negative bacteria. However, the usefulness of the β-lactam ring was such that related antibiotics, including the mecillinams, the carbapenems and, most important, the cephalosporins, still retain it at the centre of their structures.[133][149]

The penicillins related to β-lactams have become the most widely used antibiotics in the world.[150] Amoxicillin, a semisynthetic penicillin developed by Beecham Research Laboratories in 1970,[151][152] is the most commonly used of all.[153][154]

Drug resistance[edit | edit source]

In his Nobel lecture, Fleming warned of the possibility of penicillin resistance in clinical conditions:

“The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant”.[155]

In 1940, Ernst Chain and Edward Abraham reported the first indication of antibiotic resistance to penicillin, an *E. coli* strain that produced the penicillinase enzyme, which was capable of breaking down penicillin and completely negating its antibacterial effect.[136][71][156] Chain and Abraham worked out the chemical nature of penicillinase which they reported in *Nature*:

"The conclusion that the active substance is an enzyme is drawn from the fact that it is destroyed by heating at 90° for 5 minutes and by incubation with papain activated with potassium cyanide at pH 6, and that it is non-dialysable through 'Cellophane' membranes."[157]

By 1942, some strains of *Staphylococcus aureus* had developed a strong resistance to penicillin, eighteen years later, most of the strains were resistant to penicillin, and by 1967, *Streptococcus pneumoniae* was reported to be penicillin resistant.[158] Many other strains of bacteria have eventually developed, and continue to develop a resistance to penicillin.[117][71]

NOTE: IN MY OPINION, A SHORT CONCLUSION SHOULD BE ADDED.

Notes[edit | edit source]

1. ↑ At the time, the term *Penicillium glaucum* was used as a catch-all phrase for a variety of different fungi, though not for *Penicillium notatum*. Duchesne's specific mold was unfortunately not preserved, which makes it impossible to be certain today which fungus might have been responsible for the cure and, consequently, even less certain which specific antibacterial substance was responsible.
2. ↑ The statement "does not appear to have been considered as possibly useful from any other point of view" seems to be later deleted, but is still apparent from Fleming's response (*BMJ*, 2 (4210): 386–386).

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