Introduction

Penicillin is a familiar word to everyone. The first idea that comes to people's mind is Penicillin is a group of antibiotics, as Penicillin is a very common antibiotic that kills bacteria. Apart from killing bacteria, what else do people know? Probably is nothing. In this project, I would like to find out what do Penicillin is and how people discovery Penicillin.

First of all, go with the basic thing, what antibiotic[1] is. Antibiotics are molecules that stop microbes, both bacteria and fungi, from growing or kill them outright. Antibiotics can be classified as either bactericidal or bacteriostatic. Antibiotics that stop bacteria from growing are bacteriostatic. Antibiotics that cause bacterial cell death are bactericidal. They lower the bacterial count, penicillin, is bactericidal. Some antibiotics can display bacteriostatic activity in some circumstances and bactericidal activity in other, where sufficient damage to one or more cell pathways or structures occurs such that a net bactericidal response is triggered. Many antibiotics are bacteriostatic at low concentrations and bactericidal at higher concentrations[2]. This distinction is often not important clinically.

Antibiotic can either be natural products or man-made synthetic chemicals. Most of the antibiotic introduced into human clinical use to treat infections disease in the past 60 years have been natural products, elaborated by the one microorganism in a particular habitat and set of environmental condition to affect neighboring microbes, either to regulate their growth or to rigger their elimination. Antibiotic natural products are produced by the both bacteria and fungi, with the major group of antibiotic-producing bacteria being the actinomycetes.[3]

When a new antibiotic molecule was detected in a microbial culture broth or a screen in a synthetic medicinal chemistry program, it will compare against benchmark antibiotics with known mechanisms of action. A novel mechanism suggested a new target could be delineated through biochemical analysis. In turn, knowledge of the

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[1] "Antibiotics: actions, origins, resistance " by Christopher Walsh

[2] "Pharmacology – for the health care professions " by Christine M. Thorp

[3] "Encyclopaedia of antibiotics" by Glasby, John S

targets and mechanism of action of major antibacterial drug classes also gave a range of assays that would allow categorization of newly discovered antibacterial by mechanism of action. For example, against cell wall biosynthesis or as inhibitors of protein biosynthesis. The evaluation of new antibacterial molecules typically follows a hierarchical procedure. First, a new compound is tested against a panel of bacterial strains, many of them pathogens arising from clinical isolates, and many of those possessing resistance to prior generations of antibiotics. If a new antibiotic candidate show that sufficient potency against marker strains, then the molecule may be evaluated in animals inoculated to have high levels of infections with specific strains of bacteria in particular tissues, such as bacterial infections of blood and bacteremia, to see if the candidate molecule is protective and curative. The new antibiotic may then be compared against standard antibiotics use against such bacterial infections, with both of the antibiotic -sensitive and antibiotic-resistant strains of pathogens. If the new molecule passes those test, it may well be on its way as a development candidates.[4]

Penicillin was first used in the 1940s, afterwards, they remain the most important group of antibiotics even though many other antibiotics produced and new penicillin derivative continues to be developed. Penicillin binds to the cell wall of bacteria[5]. Bacteria are single cell organisms, which can be rod-shaped or spherical. Spherical bacteria are known as cocci, and they can be single or double, in clumps or in strings. Bacteria have a cell wall, DNA and the means to synthesize protein, but no nucleus. Bacteria have many biochemical differences compared with human cells, and some antibiotics are apparently non-toxic to humans. Other, however, can cause harmful effects as a result of their effects on normal healthy cells. Most antibiotics are effective against rapidly dividing cells.

Discovery and history of penicillin

Most of the people think the discovery of penicillin is attributed to Scottish scientist Alexander Fleming in 1928. He showed that, if

[4] "Antibiotics: actions, origins, resistance " by Christopher Walsh
[5] "Pharmacology – for the health care professions " by Christine M. Thorp

Penicillium notatum was grown in the appropriate substrate, it would exude a substance with antibiotic properties, which he dubbed penicillin. This accidental observation began the modern era of antibiotic discovery. However, several people reported the bacteriostatic effects of Penicillium earlier than Fleming. Such as since the middle ages, the use of bread with a blue mould (presumably penicillium) as a means of treating suppurating wounds was a principal of folk medicine in Europe[6].

Actually, early in the ancient times[7], many different cultures such as the Greek, India, already used mould and also other plants to deal with infection. However, due to poor knowledge about medicine, they couldn't distinguish or distill the efficacious component in the moulds. The moulds involved in many old treatments. Around 1550 BC in Egypt, an Egyptian physician, stated that if a "wound rots…then bind on it spoiled barley bread"[8]. In fact, the Egyptian used all types of moulds to treat surface infections. It showed that early in 1550 BC in the historical records, were already records describing the use of fermented materials in and moulds in the treatment of disease. Because those treatments were carried out without any understanding of cellular and biochemical processes of the human body or any understanding on the nature of cure, there was a chance of the patient dying from the treatment as well as being remedy.

In China, the Chinese also put mouldy soybean curd on boils, used mould for carbuncles and other kinds of skin infection. In Russia, the Russian farmer used warm soil as treatment for infected wounds. In Greece, mouldy bread was a traditional treatment for infection and wounds. About 161-137 BC, soldiers in the army of Sri Lankan in order to make plaster of the oil cakes (a traditional Sri Lankan sweetmeat) to treat wounds, they stored oil cakes for long periods in their hearth lofts before their campaign start. It shows that they assumed that the oil cakes can work for desiccant and antibacterial. In Babylonia, Babylonian doctors use a mixture of frog bile and sour milk to remedy the eyes. Also, the Sumerian doctors gave patients beer soup mixed with turtle shells and snake skins. At that time, from the techniques they

[6] http://www.news-medical.net/health/Penicillin-Biosynthesis.aspx
[7] http://www.experiment-resources.com/history-of-antibiotics.html
[8] "Natural Alternative to antibiotics" by Dr. John McKenna

used, it could be said that they cannot define what component in those food that can remedy illness and did not fully understand the nature of the medicine.

Till 1640, John Parkington[9], who is a Pharmacist, wrote a book which is about using mould as an antibiotic for treatment. Afterwards, there was more knowledge about moulds. Also on pharmacology, mould became respected as a treatment and more pharmacists started to study mould to extend the knowledge. In 1871, John Burdon-Sanderson[10], who graduated in Edinburgh University with a degree of Medicinal Doctor and started to work at St. Mary's Hospital as a lecturer after graduate, found out by covering mould and drying the air current, bacteria will be easily killed. This inspired Joseph Lister[11], the father of antisepsis, who is a surgeon to continue the research. In his research, he found out a phenomenon that the urine samples had been contaminated with mould would not allow the bacteria to grow. He called the antibacterial action on human tissue as "Penicillium Glaucum". He wrote to his brother[12] saying 'There should a suitable case present, I shall endeavour to employ Penicillium glaucum and observe if the growth of the organisms be habited in the human tissues.' However, he never published his results, so no one knows how far and how long he pursued the question. But in 1884, at King's College Hospital a nurse had wounds that did not respond to any antiseptic, Lister gave another substance that cured her. She was so astonished and so grateful at her seemingly miraculous cure that he asked Lister's registrar to write the name of this substance in her scrap-book. It was called "Penicillium". From 1870 to 1874, William Roberts, who is a physician in Manchester, studied the dissolution of bacteria in cultures contaminated by a mould. He also specifically studied the impact of Penicillium glaucum too. In 1874, he noticed that when penicillium glaucum is present, it did not allow the growth of some forms of bacteria. In 1875, an Irish physicist John Tyndall after reading John Burdon-Sanderson's research, he decided to follow up on his work. He

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9 http://www.associatedcontent.com/article/100649/a_brief_history_of_antibiotics.html

10 "Sir John Burdon Sanderson" by S. MacNalty

11 http://www.associatedcontent.com/article/100649/a_brief_history_of_antibiotics.html

12 "Bad Medicine" by David Wootton

demonstrated the antibiotic effects of the Penicillum glaucum fungus to the Royal Society in London and reported that it had caused some of the bacteria to burst. In the same year, there was a first demonstration that a specific bacterium - Bacillus Anthracis was shown to cause a specific disease, anthrax. In 1877, experiments in Paris demonstrated the benefits of using harmless, "good" bacteria to treat pathogenic or harmful bacteria. These experiment did indeed prove that harmless bacteria could be used to compete with pathogens (harmful bacteria), although they did not kill the pathogens. These 'good' bacteria assist the body by producing certain vitamins while at the same time protecting the body against the growth of harmful, disease-causing bacteria. Also in Paris, Louis Pasteur[13] who is a famous for the invention of the process of pasteurization, coordinated efforts with his colleague Jules Francois Joubery to observe that cultures of acillus Anthracis, when contaminated with the penicillium notatum, it could not easily sustain growth, became inhibited. Many other experiments[14] on anthrax and cholera confirmed these findings and proved that harmless bacteria can inhibit the growth of disease-causing bacteria.

It didn't help matters that in 1895, when the Italian Vicenzo Tiberio of Naples made an extract of penicillium mould and injected into the bloodstream of virulent animals, but the results were inconclusive. Two years later in France, Ernest Duchesne had completed his Ph.D. on the evolutionary competition among microorganisms. Specifically, he studied focusing on the interaction between E. coli and Penicillium glaucum. Some of Duchesne's observations included how the bacteria was eliminated by the fungus when both were grown on the same culture, and in inoculation of laboratory animals with lethal typhoid bacilli and P. glaucum, the mould prevented the animal from contracting typhoid. Although, he urged that further research be carried out, he was unable to do so. After graduated, he became a teacher at the Army Medical Academy, he observed stable boys using slices of mouldy bread to treat skin infections in horses. But the results were inconsistent because different strains of penicillium were used, some of which weren't effective, making the treatment look as though it had a spotty success rate. He published a dissertation about his

[13] http://www.associatedcontent.com/article/100649/a_brief_history_of_antibiotics.html

[14] "Natural Alternatives to Antibiotics " By Dr. John McKenna

successful treatment of typhoid via injected penicillium, but it was ignored. He did not claim that the mould contained any antibacterial substance; he claimed that the mould protected the animals.

In the 1920, there were two unknown scientist[15], Sara Dath and Andre Gratia who researched a fungal contamination in one of their Staphylococcus cultures was showed that it was inhibited to the growth of the bacterium. They distinguished that this as a species of Penicillium. They wrote their observations on a paper but they did not further to do the research. Perhaps it was due to not a realization as to what they had or because other scientists who had heard their paper did not have any interest about it. In spite of the reason, these two scientists missed being a major part of discovery penicillin because of not follow their research further. In 1927, Costa Rican Scientist Dr. Clodomiro Picado[16] published the results of research which demonstrated the inhibitory action of the bacillus genus penicillium sp on the proliferation of the bacteria staphylococcus and streptococcus, which helped in the development of penicillin.

Everything changed in 1928 by a British bacteriologist Alexander Fleming[17]. In September, 1928, Fleming returned from holiday and began to sort through the mess in his laboratory. At first, he discarded a culture plate that had been lying in the open air for some weeks. On it a blob of mould had interfered with the development of the staphylococci that had been sown on the jellied broth. Glancing at it again, Fleming rescued the plate from the bath of disinfectant in which it was about to be immersed. Six years before, he had discovered a substance called lysozyme – a substance found in tears, mucus and saliva, which had shown a similar capacity to kill off bacteria. Lysozyme, it had turned out, had little effect on those bacteria that cause dangerous diseases, but Fleming's experience with it meant he only needed a glance at his contaminated plate to recognize that something important might be happening, for on this plate the unknown mould was killing an organism which was a common source of dangerous infections, a staphylococcus.

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[15] http://www.botany.hawaii.edu/faculty/wong/BOT135/Lect22.htm
[16] http://www.wipo.int/wipo_magazine/en/pdf/2000/wipo_pub_121_2000_07-08.pdf
[17] "Bad Medicine" by David Wootton

It was straightforward to establish that the mould as a member of Penicillin family, and that it was active against numerous dangerous bacteria. Fleming could easily show that it did no harm to white blood cells: this was important because the laboratory he worked in, handed by Almroth Wright, had long been committed to the idea that the key to effective treatment was to mobilize the body's own capacity for defense. Fleming himself, during the First World War, had studied infections in soldiers' wounds and had argued that conventional antiseptics both killed off white blood cells faster than they killed bacteria, and failed to penetrate into the jagged interstices of gunshot wounds: they were, he thought, positively fostering infection. He could also striaghtforwardly show, by injecting the broth derived from his mould into a very small number of mice and rabbits, that it was not toxic. And he could also show that it quickly lost its anti-bacterial effect when mixed with disgestive juices: there would be no point in taking it as a pill. Fleming was surely moving towards injecting ''mould broth filtrate'' - penicillin into infected animals to see if would cure them.

By April 1929, Fleming seems to have lost all interest in injecting penicillin into bloodstream. As penicillin took around four hours to kill bacteria, but tests showed that both in animals and in the test tube it ceased to be active in blood after two hours. This seems to have persuaded him that it would be pointless introducing penicillin into a diseased body. The possibility that penicillin might have a future use as an antiseptic was mentioned in Fleming's first and only major publication on his new discovery, which appeared in 1929. He wrote: "It was suggested that it may be an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes."

Between 1930 and 1940, [18]Fleming made no effort to develop a clinical use of penicillin. Throughout this period, however, he employed it regularly for the one use that was outlined in his key publication. While penicillin killed many bacteria, it did not kill a bacterium called Pfeiffer's bacterium. Fleming found that if he took a sample of mucus and spread it over a petri dish treated with penicillin, then he could grow a pure sample of Pfeiffer's bacterium, because it was immune to penicillin, while the bacteria that normally overwhelmed it were sensitive to it.

[18] "Natural Alternative to antibiotics" by Dr. John McKenna

Fleming was happy with this discovery because the laboratory in which he worked was funded by the production of vaccines.

Although Fleming recognized that penicillin might possibly have a therapeutic use, he was far too interested in the production of vaccines to waste much time exploring the possibility. A few discouraging findings, and he dropped all work on it. He was also quite uninterested in the problem of how to problem of how to produce purer, stronger samples of his drugs. Two students of him, Ridley and Craddock, did astonishingly able work, under horribly primitive conditions – worked on tables in a corridor, and had to go to the ext floor to find running water, to produce a purer drugs. They evaporated a broth made from the penicillin under a vacuum, and dissolved the penicillin in alcohol, in the process purifying it further. Their first preparations were highly unstable, but they discovered that they could make the penicillin stable by adding acid. Fleming seems to have had virtually no interest in their work. He even misreported some of their findings in his first publication, and later claimed that the problem of producing stable penicillin is because of insoluble. When others set about producing purer and more stable penicillin, they had to rediscover everything that Ridley and Craddock had discovered because Fleming never mentioned their work to late investigators. Fleming himself was quite happy about using the impure penicillin broth, which was perfectly adequate for the production of uncontaminated samples of Pfeiffer's bacillus.

In September, 1939, eleven years after Fleming's discovery, Howard Florey[19], in Oxford, began to seek funding for penicillin research – for a year or so his colleague Ernst Chain and Norman Heatley had been cultivating penicillin derived from Fleming's original strain. Florey and Chain were engaged in a systematic search to find biological agents which would be capable of killing the bacteria that caused fatal infections, and penicillin was only one agent on their shortlist of promising substances. In May 1940[20], they had enough purified penicillin to carry out a straightforward experiment. They carried out precise experiments on cats, rat, rabbits, and mice to quantify exactly how penicillin was absorbed and excreted and what, if any, toxicity it

[19] "Bad Medicine" by David Wootton
[20] "The Mould in Dr. Florey's Coat" by Eric Lax

possessed. They injecting penicillin into four mice that had been infected with streptococci – four others were infected but not given penicillin. The result were dramatic, for the mice treated with penicillin survived in good health and those not treated died. They were confirmed when the experiment was repeated the next day.

After two month of the mouse experiment, Howard and his colleague published an article entitled "Penicillin as a Chemotherapeutic Agent"[21]. The article showed that penicillin does not appear to be related to any chemotherapeutic substance in present use, and is particularly remarkable for its activity against the anaerobic organisms associated with gas gangrene. The news was as explosive as the prose is calm and flat. In fact, there were someone who took a strong interest in the article. Dr. Martin Henry Dawson, a specialist in bacterial endocarditis at the Columbia University College of Physician and Surgeons in New York, hoped that penicillin would save patients with his staphylococcal infection of the lining of the heart or its valves that infects the blood as well and was then nearly uniformly fatal disease. By October, Dawson and his colleagues had enough crude penicillin to inject two patient with small doses, there sere the first humans to be given injections of the drugs and receive what is known as systemic treatment. Unfortunately, there was not enough penicillin to improve the condition of the patients. Dawson delivered a paper on their findings at the May, 1941 meeting of the American Society for Clinical Investigation. The "New York Times'' reported details of it.

Dr. Wallace Herrell of the Mayo Clinic in Minnesota immediately started research into drugs after the news reports out. Also, few American drugs companies also began to do some preliminary research. Dr. Selman Waksman, a soil biologist at Rutgers University, convinced scientists there to look into penicillin. Also, Dr. Geoffrey Rake a t E. R. Squibb and Sons began some experiments with penicillin.

On the other hand, the third, fourth, fifth, and sixth patients were treated with penicillin, with results that were alternately promising and heartbreaking. Percy Hawkins, a forty-eight years old man, had a deep, four-inch-long staphylococcal infection called a carbuncle embedded

[21] "The Mould in Dr. Florey's Coat" by Eric Lax

in his back, and caused by the infection. He was given five hourly 200mg doses of penicillin, then 100mg every hour following. After few days, there was clear improvement, and his doses were cut in half. This stronger regimen maintained a continuously detectable concentration of penicillin in the blood for the first time. After a week, the carbuncle was almost completely healed. It was the first in which the patient had received an adequate dose of penicillin, and he made a recovery unequalled without the drug.

Penicillin saved the lives of many soldiers in World War II[22], but the supply was extremely limited, and the drug was rapidly excreted from the body, so the patients had to be dosed frequently. It was common practice at this point to save the urine from patients undergoing penicillin treatment so that the penicillin could be isolated and reused.

In 27th August, 1942[23], a three hundred words editorial London Times seconded the plea in a recent Lancet(general medical journal) article that the government promote the industrial production of penicillin. Entitled "Penicillium", the article described the 'strong antibacterial powers' of the mould discovered ' some thirteen years ago', and it cited current work in Oxford that showed the drug was not toxic, was ' many hundred times as active as the sulphonamides', and was able to overcome bacteria the sulphonamides did not affect. No scientists were named. 'The prospect is certainly an alluring one,' the article said and, quoting The Lancet, 'in view of its potentialities, methods for producing penicillin on a larger scale should be developed as quickly as possible." The times was the first to widely publicize news of penicillin. This cause people started to pay attention to penicillin. In the same year, Florey and Chain invented the manufacturing process for Penicillin G Procaine. Afterthat, Penicillin could be sold as a drug. Also, Fleming, Florey, and Chain were awarded the Nobel Prize in medicine in 1945 for the discovery and development of penicillin.

After the news publicize, a lot of scientists started to do further experiments of penicillin. In 1948, Andrew J. Moyer, the lab's expert on the nutrition of molds, had succeeded, with the assistance of Dr.

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[22] http://www.wisegeek.com/how-was-penicillin-discovered-and-developed.htm
[23] "The Mould in Dr. Florey's Coat" by Eric Lax

Heatley, in increasing the yields of penicillin 10 times. The required clinical trials were performed and penicillin was shown to be the most effective antibacterial agent to date. Penicillin production was quickly scaled up and available in quantity to treat Allied soldiers wounded on D-Day. He was inducted into the National Inventors Hall of Fame for his process of creating penicillin in high quantity.

In 1952, Dr. Ernst Brand (now known as Sandoz) developed the first acid-stable penicillin for oral administration, Penicillin V[24](phenoxymethylpenicillin). It works by interfering with the formation of the bacteria's cell wall while it is growing, weakening the wall and killing the bacteria.

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 nucleus of penicillin, allowed for the preparation of semisynthetic penicillins, with various improvements over benzylpenicillin. The first major development was ampicillin, which offered a broader spectrum of activity than either of the original penicillins. Further development yielded beta-lactamase-resistant penicillins including flucloxacillin, dicloxacillin an d methicillin. These were significant for their activity against beta-lactamase-producing bacteria species. 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.

After penicillin could be more cheaply produced in large quantities, it became widely prescribed. Unfortunately, penicillin soon became too-widely prescribed, and was often taken in an attempt to treat minor illnesses that are usually a result of viral infections. Patients also had , and continue to have, a tendency to stop taking their antibiotic prescription before the course of treatment is finished. These two practices have led to the development of antibiotic-resistant strains of bacteria, which are a serious health concern.

[24] http://www.drugs.com/penicillin.html

There is little doubt that penicillin has saved millions of lives. Even victims of diseases that do not respond to penicillin treatment have benefited from the development of this drug. The discovery prompted scientists to begin searching for other antibiotics that could be used to treat infections penicillin could not.

Conclusion

Penicillin had many advantages at the time of its discovery and remains an important drug today. Anyone able to associate a name with the development of penicillin almost invariably thinks of Alexander Fleming, all the praiseworthy achievement to develop penicillin have towards to Alexander Fleming. In fact, there were lots of records of using Penicillin before 1928 – Fleming discovered Penicillin. In ancient times, the Chinese used mould which presumably is penicillium for carbuncles and other kinds of skin infection. Unfortunately, due to lack of professional techniques and lack of understanding the nature of the medicine, they cannot define what component in mould that can remedy illness. Till 1600s, more and more knowledge in nature of medicine and also about antibiotics. One of the successful happened in 1884, a nurse in King's College Hospital had wounds that did not respond to any antiseptic, Lister gave Penicillium that cured her.

Although there were records showed that people using Penicillin before Fleming discover it, the observation of Penicillin exist on Earth does begin with Fleming, but because of his lack of interest in Penicillin, he didn't did much further research. The statesmen with great achievements should goes to Dr. Howard Florey and his colleagues, Ernst Chain and Norman Heatley. They were the persons who did further research about Penicillin. They truly proved that Penicillin can cure people.

In fact, Penicillin was not the first antibiotic, although it was the first to prove effective against many infections. The first relatively useful antibiotic was probably Salvarsan, a drug discovered in 1909 by Paul Ehrlich. Salvarsan was a compound made from arsenic that was effective in the treatment of syphilis and other diseases caused by spirochete bacteria. Other antibiotics became available after penicillin

had been discovered, but before it was available to the public. However, they were more limited in their use than penicillin was , so a lot of people will not count Salvarsan as the first antibiotic.

The development of antibiotics is one of the most successful stories in the history of medicine, but it is unclear whether its ending will be a completely happy one[25]. As improper use of penicillin would lead to its becoming ineffective. The danger was not taking too much, it was in taking too little to kill the bacteria but 'enough to educate them to resist penicillin'. This is unfortunate because there are not many ways to fight microbes, and fewer and fewer antibiotics are being developed. Also, develop a new antibacterial drug is largely economic[26]. As antibiotics often are good for only two or three years before bacteria become resistant to them, pharmaceutical companies do not have the financial incentive to develop new ones. When a company loses interest, its researcher adept at developing and testing antibiotics must move to more profitable areas.

[25] http://www.guardian.co.uk/ - 9th September,2010 by Sarah Boseley
[26] Interview with a pharmacist – Sherrie Hair