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Penicillum Notatum Westling

Chemical Report
Jim Hughes
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Periods 3 & 4

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"The practice of medicine has been revolutionized by the phenomenal success of certain drugs, notably the sulfa drugs and antibiotics."[1] The majority of all doctors' prescriptions rely on one or more of these so called miracle drugs. These miracle drugs come under chemical therapy or chemotherapy. Chemotherapy is the "use of chemicals for selective destruction"[2] of germs without harming the host. Chemotherapy has two phases and they are as follows: (1) locating natural selective drugs, and (2) the changing of the molecular structure to improve the drug for optimum effects with little harmful residual after-effects.

Investigation on using bacteria against disease started back in the ninteenth century. For an example, the French scientist named Babés stated in 1885 that "if the study of mutual antagonism of bacteria were sufficiently far advanced, a disease caused by one bacteria could probably be cured by another."[3]

Penicillin is a member of the antibiotic family. The term "antibiotic" is used for a growing list of the so called wonder drugs which have the power to destroy or inhibit the growth of bacteria (germs). When a few germs became resistant to the sulfa drugs, the power and scope of the antibiotics was discovered just in the "nick of time." The word "antibiotic" has a Greek origin which means "life against life." Antibiotics are produced, believe it or not, by almost every form of life - tomatos, cabbage, algae, bacteria, yeasts, and molds, just to name a few. Penicillin is a mold commonly found on fruit, cheese, or stale bread.

Dr. Alexander Fleming is the one to whom goes the credit of discovering the penicillin mold. Fleming was born on a farm in Scotland in August, 1881. He lost his father when he was seven years old. When Fleming was fourteen, he left home and went south to London where he worked for a shipping company. A few years later his brother died and left him some money, suggesting that he use it in his education toward becoming a doctor.

He went to St. Mary's Hospital, London, were he studied under the famous bacteriologist, Almroth Wright. Later Fleming became a doctor.

At the hospital, Fleming's job was to prepare the dangerous streptococcus bacteria for use in tests in trying to inhibit such blood destroying germs. It was at this time when Fleming was doing a routine lab job of taking the tops off of the culture plates. Later during the day Fleming noticed that the bacteria in one dish was dead with a living blue-green mold around it. The streptococcus bateria had been killed! The year was 1928. It seems that a mold spore had made a "crash landing" on one of the culture plates. The plate was only four inches in diameter. Fleming later remarked that "it was like winning the Irish Sweepstakes."[4] Fleming called the blue mold "penicillin."

The penicillin discovered by Fleming was Penicillium notatum Westling, a member of the Penicillium chrysogenum Thom family. Experiments with penicillin were slowed up because it was unstable, hard to isolate, and lost its activity during the

process of extraction. Fleming published his findings in the British Journal of Experimental Pathology.

No one noticed the report until about ten years later (1938), Dr. Howard W. Florey and Dr. E. B. Chain, scientists at Oxford University, were doing research on microbes versus microbes. One day while looking through dozens of reports, Chain came across Fleming's article on the discovery of penicillin.

Florey tested penicillin on lab mice, with promising results: 25 control mice, 25 treated mice; 25 control mice died, 1 treated mouse died. Florey and Chain "set out" to try penicillin on humans. By June, 1941, a total of five blood poisioning cases had been treated with penicillin. Three were cured, two died: a policeman - penicillin supply gave out, and a small child - in a semiconscious state when treated. The great potentiality of penicillin had been proved. The future was still dark in one respect: penicillin could still be prepared only in small amounts. Also, at the time Britain was under the threat of German invasion.

Florey took the valuable mold with him and flew to America, which was not yet at war. Under the Office for Emergency Management, penicillin experiments were carried on in the United States. In 1943, penicillin went into mass production by the country's largest pharmaceutical manufacturers (Merck and Company, Inc.; Charles Pfizer and Company, Inc.; E. R. Squibb; The Abbott Laboratories; and the Winthrop Chemical Company).

By October, 1943, seven other firms had entered the scene, and by 1944, twenty-one companies were producing penicillin from molds which represented an investment of twenty million dollars.

It's interesting to note that Florey found that penicillin could be diluted 50,000,000 times without losing its effectivness. Florey and Chain calculated that one drop of water diluted 50,000,000 times would fill 6,000 whiskey bottles.

Fleming, Florey, and Chain jointly received the Nobel Prize. Fleming died in March, 1955. His old friend Professor C. A. Pannett said "...by his work he relieved more suffering than any other man; perhaps more than any man who has ever lived."[5]

At the beginning of the manufacture of penicillin, even in powder form it still contained impurities, they had to measure it not by quantity but by what it could do. To make measurement universal, Florey established the so called "Oxford Unit". This amount (whatever its weight) was the amount necessary to inhibit the Straphylococcus aureus present in $\frac{1}{2}$ cubic centimeters (C.C.) of medium. Penicillin used to be measured by "units" because of the limited amount. The price has even been radically slashed from twenty dollars per dose (1943) to $ .007 per dose (1956)! In the preceeding example, one dose equals to 100,000 Oxford units.

The manufacture of penicillin is a delicate and detailed

process. Molds are grown and fermented in huge, two story vats, its contents being constantly stirred by a drive shaft. The inside of the vat looks like a large washing machine. Sterile air is piped in to keep the molds growing. Water is circulated in coils of pipe to maintain constant temperature in the vat. In due time the vat is tapped and the penicillin liquid is drawn off and made completely sterile. The penicillin is then crystallized by drying it. Usually the drying process takes twenty-four hours, but by 1955, the Radio Corporation of America had invented an all-electronic penicillin drying system which drys penicillin in only thirty minutes. Before each shipment leaves the factory, each batch of penicillin is tested for purity in the laboratory.

Research by Dorothy Hodgkin of Oxford University, using X-ray methods, revealed the structure of the penicillin molecule. This has made synthetic manufacture of penicillin possible. The structure of penicillin is not particularly complex nor is it sluggish or inert by chemical standards. The problem has been that penicillin is so reactive. This has puzzled chemists for more than ten years because it is hard to change just a part of a penicillin molecule. In 1957, John C. Sheehan, of the Massachusetts Institute of Technology, succeeded in the synthesis of penicillin by usage of a series of methods, all of which require only mild conditions. Penicillin is still mass produced by molds because its natural process is inexpensive.

The antibiotics are sometimes referred to as the "broad spectrum" antibiotics because each antibiotic cures more than one disease. For example, see page 10 for a view of the "broad spectrum".

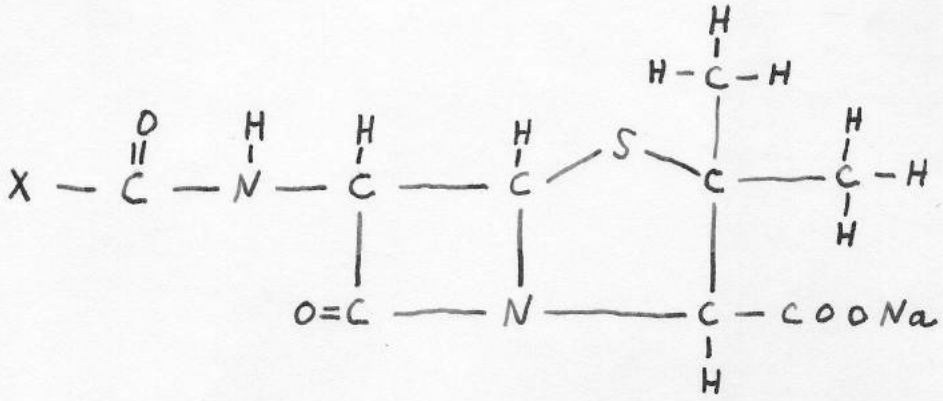
Two problems arise in the use of penicillin. The first problem is the side effects caused, such as dizziness, ringing in the ears, and so forth. Side effects will not occur very often if the doctor controls the usage of penicillin. It seems that side effects are the result of individual metabolism differences. The second problem in the use of penicillin is the development of resistance to the pneicillin. The reason is not known why this happens. Some doctors make this problem a joke by saying, "Use a new drug quickly, gentlemen, while it still has the power to cure."[6]

Penicillin attacks bacteria in the following methods. Penicillin interferes with bacteria by "tying up" some item indispensable to their nutritional processes, and thus renders them incapable of reproduction. It is also known that some gram-negative bacteria, which are insensitive to penicillin, produce an enzyme (when attacked by penicillin) called penicillinase. The enzyme penicillinase then decomposes the harmful bacteria. Among those which decompose are the Bacillus coli and Typhoid bacillus.

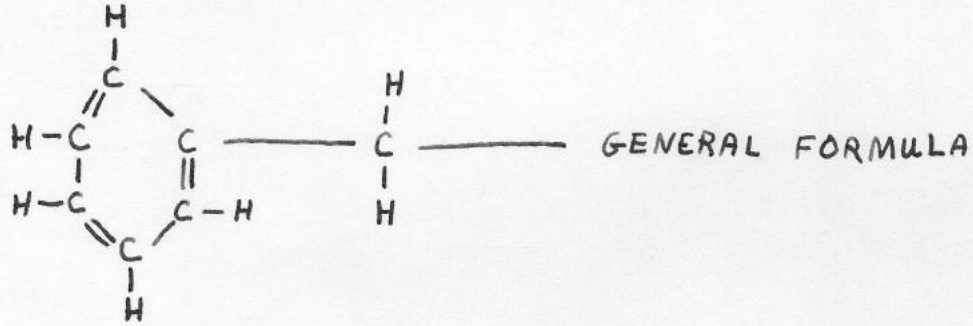
Penicillin (common name of the Penicillum notatum mold) is a member of the plant family, thus making it organic. Its characteristics are that of "branching plants with frequent

cross walls. No cholorophyll is produced, thus the plants are dependent upon organic matter."[7] Penicillin belongs to the phylum of carpomycetae (fungi), the class of ascomyceteae, and the order of aspergillales. Penicillin is sometimes called the "Blue Mold".

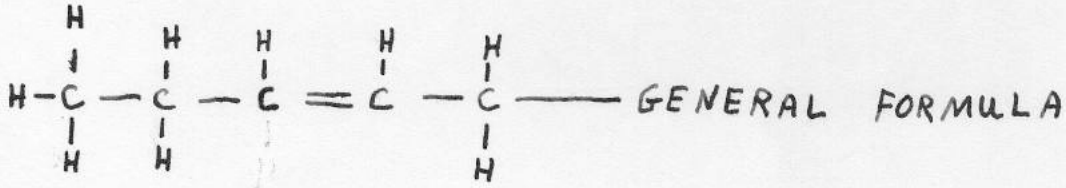
The general formula of structure of penicillin can be seen on page 8. The "X" symbolizes the different additives which can be added to make different types of penicillins. The structures of a few additives are drawn below the general formula structure.[8]



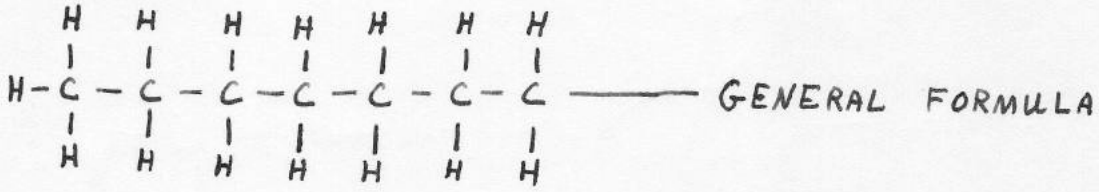
The General Formula Structure



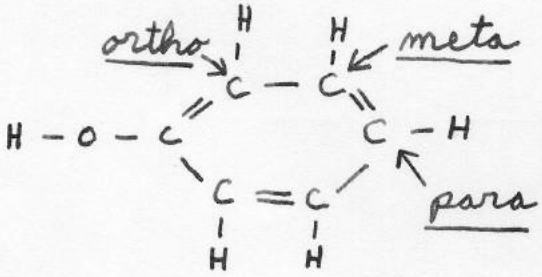
Type "G" Penicillin: Benzyl Penicillin



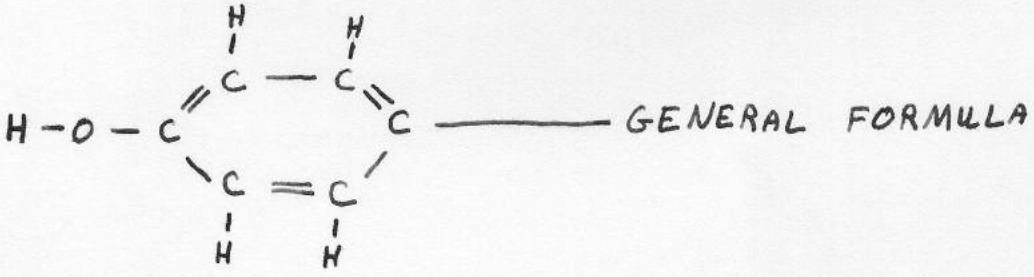
Type "F" Penicillin: 2-Pentenyl Penicillin



N-Heptyl Group Penicillin



Hydroxbenzyl Group (names indicate the location of the general formula, and thus naming the group)



P-Hydroxbenzyl Penicillin

	penicillin	strepto-mycin	chloro-mycin
pneumonia	✓	✓	✓
diphtheria	✓	✓	X
scarlet fever	✓	X	X
tetanus	X	X	X
typhoid fever	X	X	✓
whooping cough	X	✓	✓
tuberculosis	X	✓	X

Effectiveness of Selected Antibiotics.[9]

✓ effective; X ineffective

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Footnotes

[1]Ferguson, Lloyd N., Textbook of Organic Chemistry, p. 508

[2]Ibid, p. 509

[3]Reinfeld, Fred, Miracle Drugs and the New Age of Medicine,

[4]Ludovici, L. J., The World of the Microscope, p. 117

[5]Ibid, p. 120

[6]Ferguson, op. cit., p. 514

[7]"Plants, Classification of", The Encyclopedia Americana, p. 169

[8]Brewster Ph.D., Roy Q., Organic Chemistry, p. 784

[9]Ferguson, op. cit., p. 513