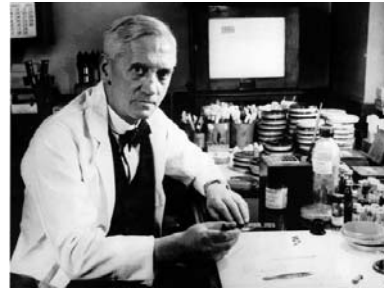


Penicillin

The Story of Penicillin



Alexander Fleming: Discovered antibiotic, penicillin

The Story of Penicillin

- Definition of **antibiotic**.
 - A chemical substance derivable from a mold or bacterium that kills microorganisms and cures infections
 - Also defined as any chemical substances that are able to kill microorganisms and cure infections.

The Story of Penicillin

- Use of antibiotics is common place today.
 - Treatment of various bacterial diseases.
 - Treat or prevent infections in wounds and following operations.
- Prior to discovery of antibiotics, bacterial diseases and infections were serious matter.

The Story of Penicillin



Filter pads with antibiotics inhibiting bacterial growth

The Story of Penicillin

- Story of discovery of penicillin only given as brief summary in introductory biology text books.
 - Alexander Fleming found a fungal infection in his bacterial cultures.
 - Noticed bacterial growth was inhibited by fungus.
 - Fungus was inhibiting bacteria with metabolite it was producing that Fleming named penicillin after fungus, *Penicillium*.

The Story of Penicillin

- Story of discovery of penicillin given as brief summary in introductory biology text books (continued).
 - Published results in 1929.
 - Discovery led to a knighthood, in 1943.
 - Was also awarded Nobel Prize, in 1945.
- A great deal more to the story.

The Story of Penicillin

- Fleming would always say because he was able to stand "on the shoulders of giants", discovery of penicillin was possible:
 - Over 3000 years ago, Chinese, Egyptians and Indians of Central America used molds to treat rashes and infected wounds.
 - **Pasteur's Germ Theory** 1860: Diseases were spread by microorganisms.

The Story of Penicillin

- Fleming would always say because he was able to stand "on the shoulders of giants", discovery of penicillin was possible:
 - **William Robert** (1874) Bacterial growth absent in cultures of *Penicillium glaucum*.
 - **Joseph Lister** (1871): Urine sample contaminated with mold did not allow bacterial growth.

The Story of Penicillin

- Fleming would always say because he was able to stand "on the shoulders of giants", discovery of penicillin was possible:
 - **Louis Pasteur** (1877): Anthrax could be rendered harmless by bacteria in soil.
 - **Rudolf Emmerich** (1887): Cholera could be prevented in animals by injection with *Streptococcus* bacterium.

The Story of Penicillin

- Fleming would always say because he was able to stand "on the shoulders of giants", discovery of penicillin was possible:
 - **Rudolf Emmerich and Oscar Low** (1899) Isolated **pyocyanase** from *Bacillus pyocyaneus* killed many different bacteria. Inconsistent!
 - **Andre Gratia & Sara Dath** (1920s): Observed *Penicillium* contamination in one culture inhibited *Staphylococcus aureus* growth.

The Story of Penicillin

- Fleming would always say because he was able to stand "on the shoulders of giants", discovery of penicillin was possible:
 - A number of people saw same phenomenon before Fleming.

The Story of Penicillin

- A number of incidents that could have changed Fleming's life if he had made sensible choices:
 - In 1900, during the Boer War, Fleming and his two brothers enlisted in a Scottish regiment .
 - Much of time, they were shooting, swimming, and played water polo.
 - Returning home from the war, he and his brothers were left with a sizable inheritance.

The Story of Penicillin

- A number of incidents that could have changed Fleming's life if he had made sensible choices:
 - His oldest brother suggested that he use the money to attend medical school.
 - Accepted at 3 medical schools. Selected St. Mary's because he had once played water polo against them.
 - Trained to be a surgeon, but for no particular reason.

The Story of Penicillin

- A number of incidents that could have changed Fleming's life if he had made sensible choices:
 - Had two choices after graduation:
 - Stayed at St. Mary's because he was convinced by the captain of the rifle team to stay.
 - Stay at St. Mary's or take position as surgeon he was offered and leave.

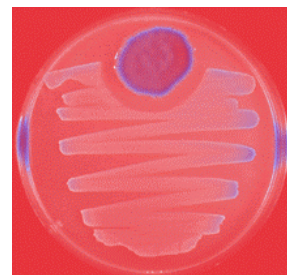
The Story of Penicillin

- Fleming, as early as 1920, was already looking for anti-bacterial agents because of number of death of soldiers due to **septicemia**, during WWI.
 - Lister's antiseptic procedures just introduced at time.
 - Antiseptic compounds also harmful to human tissue, which led Fleming to discovery of **lysozymes**: enzymes in body that cause bacterial cells to burst.

The Story of Penicillin

- Fleming, as early as 1920, was already looking for anti-bacterial agents because of number of death of soldiers due to **septicemia**, during WWI.
 - This was what Fleming was working on in 1928 when he made his discovery.

The Story of Penicillin



Charles Thom identified fungus as *Penicillium notatum*. Thus, the name **penicillin**

The Story of Penicillin

- Fleming worked on penicillin between 1928-31
 - Found penicillin more powerful than lysozymes even when diluted 1000X.
 - Determined not toxic to lab animals.
 - Unable to produce it in quantities necessary to make it of practical use.
 - Colleagues began to tire of his penicillin story and Fleming dropped this research until 1939.
- Other researchers continued his work

The Story of Penicillin

- Dr. Cecil Paine, the forgotten man
 - Was inspired to work with penicillin by Fleming's original publication. Not by Fleming!
 - Quote: "A shocking lecturer, the worst you can imagine".
 - First attempt at treating patient was infection with *Sycosis barbae*.
 - Second attempt was eye infection caused by laceration by stone.
 - Third attempt was hereditary gonorrhoea.

The Story of Penicillin

- Dr. Cecil Paine, the forgotten man
 - Never published results nor gave a paper on results.
 - Later took position, elsewhere, and research went in different direction.
- By mid 1930s **sulfa drugs** were discovered to treat bacterial infections.
 - Gerhard Domagk produced first sulfa drug **Prontosil** used to treat bacterial diseases caused by *Streptococcus* and other diseases. 1939 Nobel Prize.

The Story of Penicillin

- **Howard W. Florey**, at Oxford, began working with penicillin in 1938.
 - Reason for pursuing penicillin was Florey's conversation with Paine, in 1932.
 - Unlike Fleming, had a well equipped lab, lots of scientists and staff support.
 - Battle of egos between Florey and Ernst Chain, one of scientist working on penicillin.
 - Rift between Florey and Chain grew greater with time.

The Story of Penicillin

- One thing they agree on:

I became interested - immediately - in Fleming's paper, not because I hoped to discover a miraculous drug for the treatment of bacterial infection which for some reason had been overlooked, but because I thought it had great scientific interest. In fact, if I had been working at that time in aim-directed scientific surroundings, say in the laboratory of a pharmaceutical firm, it is my belief that I would never have obtained the agreement of my bosses to proceed with my project to work with penicillin.

The Story of Penicillin

- Negative interactions would slow research.
 - Chain purified extract of penicillin and wanted to do injection on lab animals.
- With successful test with lab animals, decided to test human subjects .
 - First test was Albert Alexander, 48 year old London policeman nicked himself shaving. Patient died
 - The next two patients treated successfully, but next one died.

The Story of Penicillin

- Fleming also successfully treated a patient suffering from meningitis.
 - Harry Lambert was patient and friend of Fleming.
 - Penicillin was supplied by Florey.
 - Injection of penicillin into spine was successful, but Florey at same time had injected spine of lab animals with penicillin that had been infected.
 - Although at first amiable, relationship between Florey and Fleming would sour.

The Story of Penicillin

- By 1941, it was acknowledged that penicillin could be a worthwhile drug.
 - Penicillin extraction process by Chain and Florey produced 1 part penicillin in 1 million part culture medium.
 - With England being bombarded by Germany during WWII, all resources were put into war effort
 - Rockefeller Foundation funded research on penicillin at this time.

The Story of Penicillin

- Amount of penicillin extracted even under optimum condition was insufficient.
 - Original culture of *P. notatum* unable to produce enough penicillin.
 - A search was made to find another species of *Penicillium* that would yield higher quantity of penicillin
 - Eventually *P. chrysogenum* was isolated from moldy cataloupe, in Peoria, Illinois.
 - *Penicillium chrysogenum* produced 200X more penicillin than *P. notatum*

The Story of Penicillin

- Amount of penicillin extracted even under optimum condition was insufficient (continued).
 - Amount of penicillin extracted from *P. chrysogenum* increased through irradiation with X-ray and UV ray.
 - A new means of producing penicillin also was developed.

The Story of Penicillin



For initial tests, by Florey, in 1940, on human subjects, it had required two professors, five graduates and ten assistants working almost every day of the week for several months to produce enough penicillin to treat six patients.

The Story of Penicillin



Tops of numerous fermentation tanks for growing penicillin, in U.S.A., during 1940s.

The Story of Penicillin



Purification of penicillin

The Story of Penicillin



Refrigeration units for penicillin

The Story of Penicillin

- With this new method for producing penicillin, enough could be produced to make it financially worthwhile.
 - By end of WWII, enough penicillin was produced to produce 7 million patients/year.
 - Greatly reduced number of deaths during WWII.
 - Many diseases successfully treated with penicillin, e.g., pneumonia, blood poisoning, strep throat, scarlet fever, diphtheria, meningitis, etc.

The Story of Penicillin

- By this time Fleming had nothing to do with penicillin.
 - In 1943, rescued from oblivion, was knighted with Florey.
 - In 1945, Fleming, Florey and Chain awarded Nobel Prize in Physiology and Medicine.
- Thus, many people had a role in the development of the application and use of penicillin.

The Story of Penicillin

- With development of penicillin, more antibiotics were being sought.
- Fleming predicted that penicillin should be used sparingly because genetic recombination of bacteria would make bacteria more resistant to penicillin.
 - By 1952, resistance by bacteria to penicillin was already being observed.