 From Affiliated Egyptian Universities and Cardiology Centers

Penicillin the Drug of War

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The darkest marks in our history are its vicious wars, and most people who were not present World War one (WW1, from 1914 to 1918), are usually stunned by the number of its fatalities. More than 15 million people were killed, making it one of the deadliest conflicts in history. The true causes of death were not only related to the numbers and sizes of the nations involved, but the inability to treat war causalities, wounds, infections and progressive septicemia at that time.

WW1 was called the "trench warfare", where fighting lines, consisted mostly of trenches, in which troops were immune to the enemy's small arms fire and were sheltered from artillery. The trenches were muddy, non sanitary, with human waste and even dead bodies. The area between opposing trenches was called "no-man land", where fire was opened from either side on any moving object. Medical services were primitive and antibiotics had not yet been discovered. Relatively minor injuries could prove fatal through the onset of infection and gangrene. The magnitude of infections related to mortality have been found in the American records. They recorded that 44% of casualties who developed gangrene died. 50% of those wounded in the head died and 99% of those wounded in the abdomen died.
During and immediately after WW1, management of wounds depended upon antiseptics in a trial to reduce infection. Many articles were published in the Lancet journal showing that antiseptics were the only option to treat infection. It was proved that they are effective for superficial wounds but for deep wounds they altered the patients' immunological defenses more than actually kill the invading bacteria.

From the end of the war to the early 1930s, there was no true antimicrobial available to fight infection. In the labs of the German pharmaceutical company Bayer AG, studies on a commercial sulfonamide dye named Prontosil, showed that it had no effect on the bacteria in vitro, but it can effectively treat a range of bacterial infections inside the body. Later it was discovered by a French research team, at the Pasteur Institute that the dye was pro drug and it is metabolized inside the body onto an active compound called sulfanilamide.

This discovery had a loud percussion, not only on medicine and management of infections, but on pharmaceutical and non pharmaceutical manufacturers. There was a huge Sulfa craze going on at that time, and there were no rules governing the official and non official Sulfa production and its selling. This and nonexistent testing requirements led to the Elixir Sulfanilamide disaster in 1937, during which at least 100 people were poisoned with diethylene glycol. The latter was used as a solvent for the non soluble sulfa. This incident led to the direct passing of the 1938 Food, Drug, and Cosmetic Act; which required that safety tests be performed on new medicines before they are released to the market.


Alexander Fleming

Sulfa as an antibiotic was the first true antimicrobial to be used before penicillin. The discovery of penicillin dates back to about ten years after the war in 1928, when Alexander Fleming (1881–1955), working at St Mary's Hospital in London, observed that a culture plate on which staphylococci were being grown had become contaminated with a mould of the genus Penicillium notatum, and that bacterial growth in the vicinity of the mould had been inhibited. He isolated the mould in pure culture and demonstrated that it produced an antibacterial substance, which he called penicillin.
He published several articles on his laboratory findings, that penicillin has anti-bacterial effect on many cultured organisms, and noticed that it affected staphylococci, and many other Gram-positive pathogens that cause scarlet fever, pneumonia, meningitis and diphtheria, but not Gram-negative bacteria. It also affected Neisseria gonorrhoeae, although this bacterium is Gram-negative.

Fleming continued his investigations, but unfortunately he found that cultivating penicillium was quite difficult, and that after having grown the mould, it was even more difficult to isolate the antibiotic agent. Fleming's impression was that because of the problem of producing it in quantity, and because its action appeared to be slow, penicillin would not be important in treating infection. Fleming also became convinced that penicillin would not last long enough in the human body (in vivo) to kill bacteria effectively. Many clinical tests were inconclusive, probably because it had been used as a surface antiseptic.
Fleming was not enthusiastic about spending effort and time on further researches on penicillin as he later said "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," Fleming would later say, "But I guess that was exactly what I did".

In the following years, there were several sporadic reports of its topical use with successful results in five patients with eye infections.
The remarkable antibacterial effects of penicillin in humans were clearly demonstrated in 1941. A small amount of penicillin, extracted from crude cultures in the laboratories of the Dunn School of Pathology in Oxford, was given to a policeman who had staphylococcal and streptococcal septicaemia with multiple abscesses, and osteomyelitis with discharging sinuses. He was in great pain and was desperately ill, and although sulfonamides were available, they would have had no effect in the presence of pus. Intravenous injections of penicillin were given to the policeman every 3 hours. All the patient's urine was collected, and each day the bulk of the excreted penicillin was extracted and reused. After 5 days, the patient's condition was vastly improved; his temperature was normal, he was eating well, and there was an obvious resolution in the abscesses. Furthermore, there seemed to be no toxic effects of the drug. Unfortunately, when the supply of penicillin was finally exhausted his condition gradually deteriorated and he died a month later.

With the rapidly growing industrial revolution, the World War two (WW2, from 1939 to 1945), was more vicious and its weapons were not only directed to opposing armies, but to innocent civilians. WW2 was called "the war against civilians", where from the 60 million people died in the war, 40 million were civilians and about 20 million were soldiers.
Penicillin was not used as an antibiotic at the beginning of the war, and sulfa powder was given to soldiers for topical use when wounded. It had many limitations in treating infected wounds in the presence of pus. Although Sulfa was discovered before penicillin, it was not considered to be the main drug of WW2.

In 1941, Howard Walter Florey (1898–1968), an Australian pharmacologist and pathologist, working in Oxford university with Ernst Boris Chain (1906–1979), a German-born British biochemist, revisited the work of Alexander Fleming, on penicillin described nine years previously. The research team investigated the large-scale production of the mould and efficient extraction of the active ingredient, succeeding to the point where, by 1945, penicillin production was an industrial process for the Allies in WW2.

Alexander Fleming shared the Nobel Prize in Physiology or Medicine in 1945 with Howard Florey and Ernst Boris Chain.

To know how much penicillin affected our lives is well expressed in 1999, when the Time Magazine named Fleming as one of the 100 Most Important People of the 20th Century for his discovery of penicillin, and stated; "It was a discovery that would change the course of history. The active ingredient in that mold, which Fleming named penicillin, turned out to be an infection-fighting agent of enormous potency. When it was finally recognized for what it was—the most efficacious life-saving drug in the world—penicillin would alter forever the treatment of bacterial infections. By the middle of the century, Fleming's discovery had spawned a huge pharmaceutical industry, churning out synthetic penicillins that would conquer some of mankind's most ancient scourges, including syphilis, gangrene and tuberculosis".

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