Alexander Fleming is credited with the discovery of penicillin; perhaps the greatest achievement in medicine in the 20th Century.

Having grown up in Scotland, Fleming moved to London where he attended medical school. After serving his country as a medic in World War I, he returned to London where he began his career as a bacteriologist. There he began his search for more effective antimicrobial agents. Having witnessed the death of many wounded soldiers in the war, he noticed that in many cases the use of harsh antiseptics did more harm than good.

By 1928, Fleming was investigating the properties of staphylococci. He was already well-known from his earlier work, and had developed a reputation as a brilliant researcher, but his laboratory in the basement of St. Mary’s Hospital in London was often untidy.

His famous discovery happened on the day that Fleming returned to his laboratory having spent August on holiday with his family. Before leaving, he had stacked all his cultures of staphylococci on a bench in a corner of his laboratory. On returning, Fleming noticed that one culture was contaminated with a fungus, and that the colonies of staphylococci that had immediately surrounded it had been destroyed, whereas other colonies farther away were normal.

"When I woke up just after dawn on September 28, 1928, I certainly didn't plan to..."
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 suppose that was exactly what I did."

Fleming grew the mold in a pure culture and found that it produced a substance that killed a number of pathogenic bacteria. He identified the mold as being from *Penicillium notatum*, and after some months of calling it "mold juice" named the substance it released penicillin in March of 1929.

Fleming published his discovery in 1929 in the British *Journal of Experimental Pathology*, but little attention was paid to his article.

He investigated its positive antibacterial effect on many organisms, and noticed that it affected bacteria such as staphylococci and many other Gram positive pathogens that cause scarlet fever, pneumonia, meningitis and diphtheria, but not typhoid fever or paratyphoid fever, which are caused by Gram-negative bacteria, for which he was seeking a cure at the time. It also effectively killed *Neisseria gonorrhoeae*, although this bacterium is Gram negative.

Fleming finally abandoned penicillin. Not long after he did, Howard Florey and Ernst Chain at the Radcliffe Infirmary in Oxford took up researching and mass-producing it with funds from the U.S. and British governments. They started mass production after the bombing of Pearl Harbor. When D-Day arrived, they had made enough penicillin to treat all the wounded Allied forces.

It was Ernst Chain and Edward Abraham who finally developed the method to isolate and concentrate penicillin. Shortly after the team published its first results in 1940, Fleming telephoned Howard Florey, Chain's head of department, to say that he would be visiting within the next few days. When Chain heard that he was coming, he remarked, "Good God! I thought he was dead."

After the team had developed a method of purifying penicillin to an effective first stable form in 1940, several clinical trials ensued. Their amazing success inspired the team to develop methods for mass production and distribution in 1945, which was just in time to be of use in World War II.
Fleming was modest about his part in the development of penicillin, describing his fame as the "Fleming Myth" and he praised Florey and Chain for transforming the laboratory curiosity into a practical drug. In fact, several others reported the bacteriostatic effects of *Penicillium* earlier than Fleming. The use of bread with a blue mold (it is presumed, *Penicillium*) as a means of treating infected wounds was a staple of folk medicine in Europe since the Middle Ages.

However, Fleming was the first to discover the properties of the active substance, giving him the privilege of naming it penicillin. He also kept, grew and distributed the original mold for twelve years, and continued until 1940 to try to get help from any chemist who had enough skill to make penicillin.

Fleming was very aware of the ensuing bacterial resistance to his new drug, and he cautioned about the over use of penicillin in his many speeches around the world. He warned not to use penicillin unless there was a properly diagnosed reason for it to be used, and that if it were used, never to use too little, or for too short a period, since these are the circumstances under which bacterial resistance to antibiotics develops.

The structure of the penicillin molecule features the β-Lactam ring, which inhibits the formation of the peptidoglycan cross-links in the bacterial cell wall, but has no direct effect on cell wall degradation. The relatively small size of the molecule allows it to deeply penetrate the cell wall.

In the early days, before resistance developed, penicillin was widely used and effective in treating Staph and Strep infections, as well as syphilis and gonorrhea. It is still highly effective against Groups A and B Strep infections.

The challenge of mass-producing this drug was daunting. In 1942, the first patient was treated for streptococcal septicemia with U.S. made penicillin produced by Merck & Co. Half of the total supply produced at the time was used on that one patient. In July 1943, the War Production Board drew up a plan for the mass distribution of penicillin stocks to Allied troops fighting in Europe.
Penicillin is actively excreted, and about 80% of a penicillin dose is cleared from the body within three to four hours of administration. Indeed, during the early penicillin era, the drug was so scarce and so highly valued that it became common to collect the urine from patients being treated, so that the penicillin in the urine could be isolated and reused.

In a 1946 to 1948 study in Guatemala, U.S. researchers used prostitutes to infect prison inmates, insane asylum patients, and Guatemalan soldiers with syphilis and other sexually transmitted diseases, in order to test the effectiveness of penicillin in treating sexually transmitted diseases. They later tried infecting people with "direct inoculations made from syphilis bacteria poured into the men's penises and on forearms and faces that were slightly abraded . . . or in a few cases through spinal punctures.” Approximately 1,300 people were infected as part of the study (including orphan children). This study, now highly criticized for its unethical treatment of its subjects, was sponsored by the Public Health Service, the National Institutes of Health and the Pan American Health Sanitary Bureau (now the World Health Organization's Pan American Health Organization) and the Guatemalan government. The director of this study, John Cuter, was also involved in the infamous Tuskegee syphilis experiments.

Since this famous discovery in 1928, many more effective antimicrobials have been developed which retain the beta lactam ring that is characteristic of penicillin, such as carbenicillin, methicillin, imipenem, and the cephalosporins.

For his important life saving discovery, he shared the Nobel Prize in Physiology or Medicine in 1945 with Howard Florey and Ernst Chain.

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