The Miracle Drug

It’s springtime. Imagine yourself walking around your garden, smelling and touching your freshly bloomed red roses. Ouch! What’s that? You accidentally pricked your finger on a thorn! If this were 2014, you would apply some Neosporin and bandage the wound. But this is 1920. No one has ever heard of Neosporin, or any other antibacterial medication for that matter. So what happens? Your prick becomes an infection, your glands swell up and you’re building up pus in your finger. You go to the doctor and he suggests cutting your finger off before the infection spreads elsewhere. Does this scare you? This was the world’s nightmare before penicillin was discovered.

Penicillin was discovered in 1928 as a naturally occurring antibiotic. Before its discovery, there were no effective treatments for infections. An accidental cut that is susceptible to an infection could potentially kill someone. Penicillin was accidentally discovered by Sir Alexander Fleming. Fleming was a bacteriology professor that studied Staphylococcus, the bacteria that causes boils, sore throats, and abscesses. He noticed that there was mold, later recognized as Penicillium notatum, growing on one of his Staphylococcus plate. Although the plate was covered with Staphylococcus colonies, there was a clear zone around the mold. Fleming found that the secretion made by the mold was capable of killing not only Staphylococcus bacteria, but also Streptococcus, Meningococcus, and other harmful bacteria. Although Fleming knew that a molecule in the secretion was responsible for antibacterial effects, he failed at isolating penicillin from the secretion because of its unstable property. It wasn’t until 1941 that penicillin was used to treat a human being.¹

The process of isolating penicillin from the mold secretion and changing it into a life-saving drug was done by Howard Florey, Ernst Chain, and Sir William Dunn. The first recipient of penicillin was Albert Alexander. Alexander was accidentally scratched by a rose thorn that caused Staphylococcus and Streptococcus infections. Upon given an injection of penicillin, Alexander showed remarkable recovery, but later died due to a supply shortage.² In addition, the use of penicillin to treat blood poisoning in children showed positive effects. Based off of these, and many other human trials, it was speculated that penicillin could quickly be available for British troops on the battlefield during World War II. However, due to wartime productions, there were not enough resources for Florey and his team to mass-produce penicillin. Thus Florey came to the United States to continue the production of the world-changing drug. Production of penicillin in the United States increased from 21 billion in 1943 to more than 6.8 trillion in 1945. By 1949, the annual production of penicillin in the United States was 133,229 billion.¹ The effects of penicillin on the war was also very apparent. During World War I, the death rate from pneumonia in the American army totaled 18% while in World War II, it fell to less than 1%.³

Throughout the years, many variations have been made to the original penicillin antibiotic that there now exist six different groups within the class of penicillin antibiotics itself. Penicillin antibiotics prevent bacterial cell wall synthesis by binding to enzymes called penicillin binding proteins. Without a cell wall, the bacterial cannot grow and thus growth is inhibited and the bacteria ultimately die. All penicillin type antibiotics are composed of an acyl side chain, a beta lactam ring, and a thiazolidine ring.
Variations to the side chain give rise to six different groups within the class. The six groups are: natural penicillins, beta lactamase resistant penicillins, aminopenicillins, carboxypenicillins, ureidopenicillins, and penicillin/inhibitor combinations.

Natural penicillins include penicillin G and penicillin VK. Natural penicillins target *Strep. Pyogenes*, Group B Strep., viridans group Strep., *Staphylococcus aureus* (non-penicillinase producing strains), *Enterococcus faecalis*, *Enterococcus faecium*, *Neisseria meningitides*, *Treponema pallidum* (syphilis), *Listeria monocytogenes*, *Corynebacterium diphtheria*, and anaerobes. Penicillin G is the most potent compound of all the penicillins for susceptible gram positive bacteria. Penicillin V is normally used for oral administration because it is more acid stable. However, *Strep. pneumoniae* shows increasing resistance to natural penicillins.

The second group of antibiotics within the penicillin class is the beta lactamase resistant penicillins. The side chain on this group of antibiotics prevents the destruction of the beta lactam.
ring by beta lactamases produced by Staphylococci. These penicillins include: methicillin, nafcillin, oxacillin, cloxacillin, and dicloxacillin. Beta lactamase resistant penicillins have positive effects on microorganisms similar to those of natural penicilins but also include Staphylococcus aureus and Staphylococcus epidermidis.

The third group of antibiotics within the penicillin class is the aminopenicillins. Aminopenicillins have an additional amino group on the side chain which helps increase the spectrum of activity to include aerobic gram negative bacilli. Aminopenicillins are not effective against Staphylococci like beta lactamase resistant penicillins, but are more active than penicillin against Enterococci. Aminopenicillins are also active against most gram negative aerobes that have no affect when treated with beta lactamase penicillins. The penicillins of this group are ampicillin and amoxicillin.

The fourth group of antibiotics within the penicillin class is the carboxypenicillins. Carboxypenicillins have a carboxy group and other groups in place of the amino group on the side chain. This modification increases the spectrum of activity to include other aerobic gram negative bacilli. Carboxypenicillins are less active than ampicillin against Enterococci and are not active against methicillin-susceptible Staphylococcus aureus. In comparison to aminopenicillins, carboxypenicillins are active against many hospital-acquired pathogens. Carboxypenicillins are usually administered with other antibiotics to treat aerobic gram negative infections, especially Pseudomonas aeruginosa. The antibiotics of this group are carbenicillin and ticarcillin.
The fifth group of antibiotics within the penicillin class is the ureidopenicillins. The side chains of this group were further modified to increase the spectrum of activity to include additional aerobic gram-negative bacilli. Ureidopenicillins are more active than carboxypenicillins against Enterococci and many hospital acquired pathogens such as *Pseudomonas aeruginosa* and *Klebsiella*. However, similar to carboxypenicillins, ureidopenicillins are usually administered with other antibiotics to treat aerobic gram negative infections. The antibiotics of this group are mezlocillin and piperacillin.

The sixth group of antibiotics within the penicillin class is the penicillin/inhibitor combinations. Various penicillins have been combined with beta lactamase inhibitors to overcome resistance due to beta lactamase enzymes. The inhibitors irreversibly inhibit beta lactamases in order for the antibiotic to be effective. The inhibitors that are used are sulbactam, clavulanate, and tazobactam. Sulbactam have little activity against Class I beta lactamases. Clavulanate are the strongest inducer of type I chromosomal beta lactamases. Tazobactam are the weakest inducer of type I chromosomal beta lactamases and also the most potent inhibitor. The penicillin/inhibitor combinations of this group are ampicillin/sulbactam, amoxillin/clavulanate, ticarcillin/clavulanate, and piperacillin/tazobactam.

Although penicillin is regarded as a miracle drug, it is not administered as frequently as before because approximately 10% of the population has penicillin allergies. In a penicillin allergy study done in 1994, out of 271 patients that participated, 21 of them reported penicillin allergy. The most common symptoms were localized rash, followed by unknown reaction symptoms, nausea with or without vomiting, generalized itchy rash with difficulty in breathing, and localized rash with chest pain. In most cases, penicillin is the most common cause of induced anaphylaxis and drug-induced allergic reactions. Penicillin causes approximately 75% of all anaphylactic deaths in the United States, which is 500 to 1,000 deaths each year. Luckily nowadays, penicillin skin testing can be done to see if a patient has allergic symptoms against penicillin.

The penicillin skin test demonstrates the presence or absence of specific IgE antibodies against major and minor penicillin determinants. If IgE antibodies are not present, the patient is not allergic to penicillin. Interestingly, there have been cases of desensitizing a penicillin allergic patient so that penicillin can be safely administered. Penicillin desensitization is a procedure where the patient is exposed to penicillin in increasing doses over a period of time. This process builds up the tolerance to the medication and lessens the allergic response by inhibiting the
release of mast cell mediators through prevention of IgE crosslinking. In a study performed by Wendal, 15 pregnant women with known penicillin allergies underwent desensitization with oral penicillin. At the end of the study, all 15 women showed no signs of adverse effects and each patient was able to receive their full treatment. This study showed that it is possible to administer penicillin to penicillin allergic patients for infections that are most susceptible to that drug.

The administration of penicillin has also gone down due to bacterial resistance to the antibiotic. At the end of his Nobel Prize lecture, Alexander Fleming warned “that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.” Several strains of bacteria became resistant to penicillin due to mutation of genes. Penicillin resistant *S. pneumonia* bacteria have developed a protein called MurM as an enzyme to help build dipeptide bridges within the peptidoglycan. A high level of dipeptide bridges in the peptidoglycan seems to be a pre-requisite for high resistance to penicillin. In 2009, Elias Mossialos told CNN that penicillin is becoming obsolete in France, Spain, Romania, and developing countries because of the over-prescription of the drug. Interestingly, there has been cases where death was caused by a class of bacteria that is resistant to all the antibiotics on the market. This class of antibiotic resistant bacteria is known as carbapenem-resistant *Enterobacteriacea* (CREs).

Although there are many different types of antibiotics on the market today, penicillin is the most influential antibiotic. Not only was penicillin the first naturally occurring antibiotic to be discovered, but also because its discovery gave rise to the idea that there are other molecules in other microbes with antimicrobial effects. Penicillin was able to cure millions of people in the mid 1900s, and it opened the door to the discovery of many other antibiotic groups in the years to come.
Works Cited


