The following has been modified from the web-based educational tutorial made available through the Howard Hughes Medical Institute, found at http://www.hhmi.org/biointeractive/Antibiotics_Attack/frameset.html

What are antibiotics?

Antibiotics (or antimicrobials) are any natural substances secreted by one microorganism to ward off other microorganisms. Bacteria or molds might secrete chemicals that interfere with other microorganism to harm, kill, or slow them down. In the microbial world, antibiotics are ammunition.

Although humans have inadvertently used natural antibiotics for centuries, these powerful weapons were not discovered until the late 1920s and not harnessed until the late 1940s. The antibiotic age began in the late 1920s when Alexander Fleming serendipitously observed that the mold, *Penicillium*, contaminating his petri dish, was inhibiting the growth of nearby bacterial colonies. The inhibitory substance was purified and years later Alexander Fleming, along with the organic chemists Howard Florey, and Ernst Chain, won the Nobel Prize for Medicine for the discovery and application of penicillin.

Since then, antibiotics have been used as powerful treatments against bacterial infection. Although many antibiotics are chemically synthesized today, antibiotic substances are still being harvested from microorganisms.

Research has led to the discovery of a wide variety of antibiotics; however, only a fraction of these antibiotics can be used to eliminate infection without harming the patient. In order to selectively target bacteria, distinctions in structure and function must be made between the bacteria and the host. The basic theory of antibiotic attack is to target microbial cellular functions and structures that are different from the host. Simply, antimicrobial treatments look to stop infectious agents by throwing sticks in the spokes of their unique cellular wheels.

In this day and age, we may take the potent curing power of antibiotics for granted. Imagine catching strep throat or neglecting a cut and dying from infection. Antibiotics have acted as miracle drugs, from first curing wounded soldiers suffering from infectious disease in World War II to helping people in Singapore with typhus fever. Had antibiotics not been discovered nor isolated before World War II, at least 300,000 more people would have died. If we didn't have antibiotics today, many more men, women, and children would be very sick from bacterial infections.

Antimicrobial substances can have a range of structures and variations. Because structure determines function in biological systems, antibiotics with similar structures typically attack similar microbial targets. Likewise, antibiotics with different structures are able to attack very different microbial targets. Most antibiotic targets are found within the bacterial cell (the cytoplasm) or cell wall. In order for antibiotics to reach and attack targets within the bacterial cell, the antibiotic must be cell membrane permeable.

New drugs can be created by chemically altering the structure of naturally occurring antibiotics to generate new variations with increased bacterial cell permeability and/or toxicity. For example, variations of penicillin include ampicillin, methicillin, penicillin G, penicillin A, and gramicillin. Other research is focused on the identification drugs to supplement traditional antibiotics in order to block common bacterial mechanisms of resistance. By understanding these mechanisms more thoroughly, researchers can better design new drug therapies for enhanced potency.

How do bacteria become resistant?

As we use antibiotics and other antibacterial agents such as antibacterial lotions, soaps, and sprays to kill bacteria, we are pruning the microbial pool for the stronger bacteria. Since antibacterial agents do not kill 100% of bacteria, they leave a few of the bacteria that are resistant. These bacteria continue to grow, and in fact, they flourish due to an increase in nutrients that their weaker counterparts would have competed for.

Besides antibacterial agent use, over-prescription of antibiotics weeds out weak bacteria and leaves resistant strains. These remaining bacteria are able to survive the otherwise toxic effects of antibiotics by developing mechanisms to fight back.

The most common general mechanisms of bacterial antibiotic resistance include:

1. **Antibiotic membrane impermeability**— Bacterial cell walls with certain characteristics are impermeable to some structural classes of antibiotics. For instance, some exceptionally bulky antibiotics are unable to pass through the outer membrane of Gram negative bacteria. If an antibiotic is unable to pass through the cell wall components (necessary to reach and attack targets) it is non-toxic to the cell.

2. **Antibiotic efflux**—Some bacteria are very efficient at pumping some structural classes of antibiotics out of the cell (i.e. "efflux"). Efflux is mediated by membrane proteins specialized for the active transport of molecules with an *overall* conserved structure. In some cases, antibiotics with only slight structural differences can be transported by the same efflux pump. In the case of highly efficient efflux, although an antibiotic may initially enter the cell, it is pumped out so quickly that the drug is unable to attack its target and kill the cell. Unfortunately, this mechanism of drug resistance is also commonly found in many types of drug-resistant human cancers.

3. **Antibiotic degradation**—Some bacteria are able to destroy beta-lactam rings, a structural component critical to the function of some antibiotics. Beta-lactam rings are made of three carbons and one nitrogen atom—linked together in a ring shape. A carbonyl functional group (i.e. double bonded oxygen) is attached to one of the carbon atoms in the ring. When the beta-lactam ring in an antibiotic is degraded (along with the rest of the molecule) the drug is rendered inactive and non-toxic to the cell.

4. **Target alteration/mutation**—Antibiotics function by attacking a specific target within a bacterial cell. If a bacterial cell has altered its target (usually via beneficial mutation) in such a way that it is no longer recognized and thus susceptible to the antibiotic, the drug is rendered inactive and non-toxic to the cell. Because the modification of the cellular target is usually very subtle, small compensatory structural changes in a given antibiotic are often all that is necessary to restore bacterial sensitivity.