**Chapter 1: Antibiotics and Antibiotic Resistance**

**Section 1: Antibiotic History and Overview**

Antibiotics are made up of microbes and are designed to inhibit or destroy other microbes. Over the past few years, some antibiotics have even been made fully synthetic in labs. Antibiotics must be able to stop the growth of bacteria or kill it altogether while keeping the host from harm. The age of antibiotics began in 1942 when Anne Miller became the first person to be cured with the use of Penicillin. Penicillins antibiotic potential was originally discovered by medical student Ernest Duchense in 1896, and then later rediscovered by Sir Alexander Flemming. Resistance to antibiotics has also grown over time making it increasingly hard for medical professionals to accurately and efficiently treat against a large array of diseases.

**Section 2: Antibiotic Mechanisms of Action**

A good target for antibiotics will be essential to the growth process for the cell while also standing out from the host cell. Because of these requirements, antibiotics must be able to attack a part of the cell that is unique to bacteria and not found in eukaryotic cells. This can be done in several ways including the interference in cell wall synthesis, translation, and DNA synthesis.

2.1 Cell Wall Synthesis

Bacterial cell walls are an easy target for antibiotics as bacterial cells contain the peptidoglycan layer that human cells do not. This makes it possible for the antibiotic to target the bacterial cell without disturbing the host cells. The peptidoglycan layer is made up of two sugar molecules named N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) and a pentapeptide side chain made up of amino acids ending in a double d-alanine.

One example of an antibiotic that attacks bacterial cell wall synthesis is Penicillin a beta lactam antibiotic. The structure of Penicillin mimcs the structure of the d-alanine peptide on the end of the peptide strand. By doing this it is able to interfere with the bonding of the precursor to the NAG-NAM molecule. This occurs only on growing bacteria that are actively making new peptidoglycan, and prevents the synthesis of the cell wall leading to cell death.

2.2 Translation

Translation involves the synthesis of proteins from RNA with the use of ribosomes. During translation mRna is converted into a ribosome which produces a polypeptide through a three stage process. Initiation brings the ribosomal subunits together, next elongation adds amino acids to the growing chain, and finally termination. There are antibiotics that can target all three stages of translation in order to inhibit or kill the cell.

One example of an antibiotic that inhibits translation is Aminoglycosides. Aminoglycosides contain a cyclohexane ring and amino sugars. This antibiotic inhibits the elongation stage by binding to the ribosomal subunit and causing a misreading of the mRNA which leads to premature termination. The premature termination eventually leads to cell death. Another example of an antibiotic that is clinically used to block translation is tetracycline. This antibiotic blocks elongation by binding to the A site and stopping anticodon binding. This prevents the accommodation of the next tRNA so that the growing peptide chain cannot elongate any further.

2.3 DNA Synthesis

Although both bacteria and mammals have similar processes for maintaing their DNA there is still one distinct difference that some antibiotics are able to target. Nucleic acids are synthesized using precursors such as tetrahydrofolic acid (THF). This is unique to bacterial cells because mammalian cells do not synthesize the precursor to THF. Instead they rely on their diet to procure the folic acid required for nucleic acid synthesis.

Sulfa drugs inhibit nucleic acid synthesis in bacterial cells by preventing the synthesis of THF. Bacterial cells make THF with the use of PABA. Because sulfa drugs are synthetic, a specific sulfa drug, sulfamethoxazole was designed to mimic PABA and compete for the enzymes used in folic acid synthesis.

**Section 3: Antibiotic Resistance**

Antibiotic resistance is defined as bacterial cell growth in the presence of an antibiotic that would otherwise stop cell growth or kill the cell. Antibiotic resistance can be acquired in a variety of ways including: Beta lactamase destruction, efflux pumps, and target mutation. All three of these methods are used to either modify, destroy, or pump the antibiotic out of the bacterial cell to ensure cell survival.

3.1 Beta Lactamase Destruction

As discussed above, penicillin is a beta lactam antibiotic whose ring binds to the end of the peptide strand and blocks cell wall synthesis from occurring. Beta lactamases are enzymes which are secreted in the presence of antibiotics whose key focus is to break open the ring of the penicillin structure. By breaking the ring of the antibiotic open, resistance can occur.

3.2 Efflux Pumps

Efflux pumps are proteins whose purpose in the cell is to pump out toxins. The pumps are powered by ATP, sodium, and protons. These pumps can be specific to antibiotics or can be more general and pump out many things from the cell. TetA is a specific pump powered by the proton gradient that pumps out tetracycline. Tetracycline has begun to become less popular in clinical settings because of the increasing resistance.

3.3 Target Mutation

Target mutations serve to modify the site of modification in the bacteria while also preserving the activity of the cell. This renders the antibiotic useless. Resistance to sulfa drugs is acquired in this way. Mutations will occur near the active site of the enzyme which is responsible for producing THF.

**Summary**

After the initial discovery of penicillin, many more have been discovered and even made artificially. Antibiotics serve the purpose of rendering a cell useless, or destroying the cell altogether. Antibiotics can do this through several mechanisms including: inhibition of cell wall synthesis, DNA synthesis, and translation. However, the growing resistance to these antibiotics has become a problem in many clinical settings.

It is important moving forward that there continues to be antibiotic discovery. However, many companies do not want to get into antibiotic research due to the high input cost, and low revenue. Many incentives are being put into place to entice people to invest in antibiotic discovery. These incentives include things like: grants, post market rewards, and intellectual property protection.