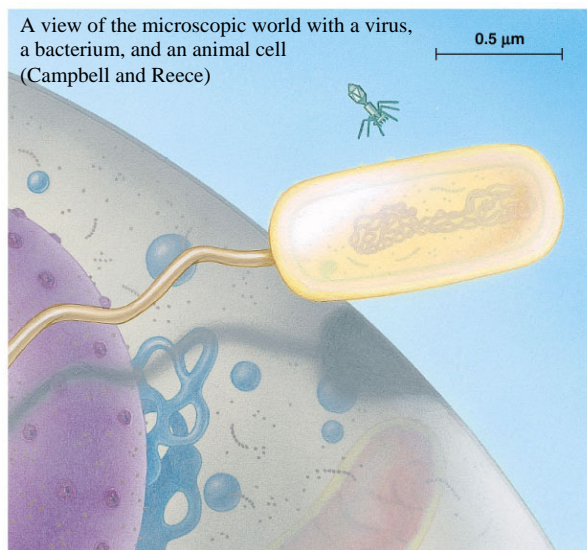


The Resistance from Microscopic Rebels: The Invisible Assassins

Before the advent of antibiotics, the world was a deadly place. Disease ravaged populations. However the discovery of penicillin, the first antibiotic, changed the balance. Mankind now possessed the ability to cure, to heal the afflicted. Within a few decades infection death tolls dropped. The United States Surgeon General even declared that bacterial infections would disappear in the near future. He did not know the war against bacteria had just begun. Man may have dealt a swift and deadly blow, but the enemy grew stronger. The antibiotics weeded out the weak bacteria and made way for the strong. Bacteria evolved following Darwin's process of natural selection. The bacteria themselves did not change; instead, the composition of the bacterial populations changed. Gifted with the ability to resist some antibiotics, these populations could once again prey on mankind. They reversed the dominance man had gained. The war against bacteria has just begun.

Until the advent of antibiotics, untreatable diseases would more often than not kill. Treatments such as plant extracts and cheese molds had been used for centuries to treat disease. However, the first antimicrobial created



A view of the microscopic world with a virus, a bacterium, and an animal cell (Campbell and Reece)

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from a living organism was discovered by Sir Alexander Fleming in 1928 ("Antibiotics", par. 3). Sir Fleming accidentally discovered the effectiveness of the mold *Penicillium notatum* against bacteria. Even with this discovery, it took until World War II for penicillin to be purified enough for effective human use. After the successful use of antibiotics, the world changed drastically. Previously untreatable diseases became treatable. Survival rates for surgeries and other medical practices increased. The advent of antibiotics is one of the

greatest achievements of mankind. We can only hope to maintain this achievement.

After the first antibiotic, many more were discovered and produced. With these new drugs, bacterial differences became more pronounced. Significant differences in the outer membrane of bacteria often affect which antibiotic can attack that specific bacterial strain. The two types of outer membrane are Gram-positive and Gram-negative. The distinction between the two strains is the thickness of the outer membrane. Gram-positive have a

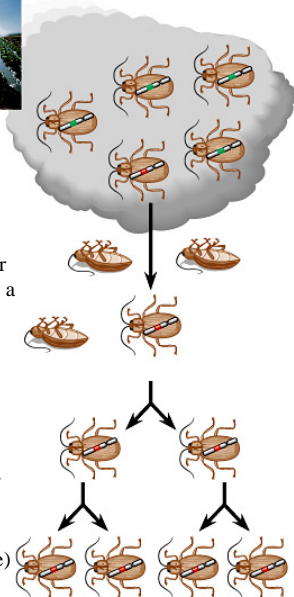
thicker outer membrane while Gram-negative have a thin outer membrane. Because of the difference in outer membranes between the Gram-negative and the Gram-positive, an antibiotic is unlikely to affect both types of bacteria. However, if an antibiotic can kill both types of bacteria, it is designated 'broad spectrum'. These antibiotics work like double edged swords. On one end, they can cut down any possible bacterial intruder. On the other, they act against the natural, beneficial bacteria within a human body. In this way they are counter-productive. Even the bacteria that do not directly benefit their human hosts often benefit them indirectly by out competing the deadly, pathogenic bacteria that would otherwise causing harmful infections. Antibiotics succeed because of their ability to attack multiple species of bacteria. However, a broad spectrum antibiotic is verifiably like a nuclear device. It may work to kill what one wants to kill; and, it will kill anything else that happens to be in the vicinity.

The antibiotic was hailed as the savior of mankind. It was the 'silver bullet' that would, as the United States Surgeon General suggested, eliminate bacteria once and for all. This mindset was not surprising. "Antibiotics have saved more lives than any other drugs in the history of humankind..." (Sulakvelidze 807). Antibiotics have saved innumerable lives; however, this came at a price. Thanks to the over-use of these silver bullets, we are now facing bacterial strains that have become resistant to antibiotics. This trend of antimicrobial resistance will continue, and hopefully mankind will find another stratagem because the enemy learns.

Bacteria have evolved resistance to many antibiotics. The process by which bacteria have developed this resistance is an excellent example of Darwin's theory of natural selection. His theory can be summarized in three main points. "Natural selection is differential success in reproduction. Natural selection occurs through an interaction between the environment and the variability inherent among the individual organisms making up a population. The product of natural selection is the adaptation of populations of organisms to their environment" (Campbell 435). Evolution occurs at the level of the population. A single organism does not change; instead certain characteristics expand within a given population as a percentage. The reason for the shift in population is the ability of offspring of a specific pair of individuals to survive because of an advantage given to them from their genes. The selection of specific



This picture exhibits natural selection. Humans introduce pesticides to kill the insects. All of the insects die, except for the insect that carries a resistance gene. This insect survives to reproduce. Thus, the population shifts toward resistance to the pesticide because the pesticide kills off the non-resistant insects. (Campbell and Reece)



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traits occurs in the context of the organism's environment. Fish are adept at swimming in the ocean, but they can not survive in the desert. The differential ability of specific individuals to survive and reproduce in a given environment shapes the genetic makeup of the species.

Populations take generations to change and shift. The short lifespan of bacteria means that evolution and adaptation to the environment can take place quickly. Some bacteria create a new generation every twenty minutes, doubling their population size. This short generation period also makes bacteria easy to study. Microbiologists, unlike other scientists, can receive almost instantaneous data. Microbiological experiments on resistance and inhibition using agar plates and an incubation chamber can take only one day. Within a single twenty-four hour period a microbiologist can test his theories. However this speed of bacteria reproduction allows them to seemingly adapt almost immediately to their environment, gaining resistance to the substances that harm them. Not all bacteria have to become resistant to pose a threat. A population needs only a small percentage of its population to contain a trait allowing it to survive in an antibiotic environment. The antibiotic kills the other bacteria that are not resistant. The resistant bacteria survive and reproduce. The subsequent generations become stronger and resistant, making antibiotics ineffective.

Antibiotic resistance has been on the rise. Misuse and overuse of antibiotics have been the two largest contributing factors. In many developed nations antibiotics have caused the mortality rates of deadly diseases to decline, but now the bacteria have grown stronger and possess the capability of resisting these treatments. Treatable bacteria have once again become deadly. Research at Atlanta Georgia, "...judged that a full third of the 150 million outpatient prescriptions for antibiotics written each year in the United States were unnecessary: either the infection turned out to be viral or the wrong drug was prescribed" (Shnayerson & Plotkin 15). Antibiotics often prescribed did not treat the infection. A placebo, a sugar pill, would have treated the infection just as well, because all viruses are resistant to antibiotics. Antibiotics specifically target bacteria. Viruses can not be attacked by the same substances that can kill the bacteria. Viral structures differ significantly from bacteria cells. Viruses are non-living structures of protein with genetic material. Thus, some antibiotic treatments are prescribed to patients who do not need them because the perpetrator is not a bacterium, but a virus. Another major factor would be livestock antibiotic treatments. "Nearly all livestock in America were also fed small, daily doses of antibiotics..." (Shnayerson & Plotkin 19). These antibiotics may be beneficial to the livestock industry, yet this constant inoculation of livestock creates a breeding ground for resistant bacteria. This constant presence of antibiotics selects bacterial strains that can

live with the antibiotics or that cannot be affected by antibiotics. These resistant bacterial strains can then be passed on to anyone who comes into contact with the animal or its by-products. It is true that livestock and humans do not use the exact same antibiotic; however, antibiotics effectiveness is not measured by individual antibiotic effectiveness. Although antibiotics may be different, they can still possess the same method of attack. The bacteria will usually become resistant to the method of attack rather than the antibiotic itself. For this reason scientists search specifically for antibiotics with new attack strategies.

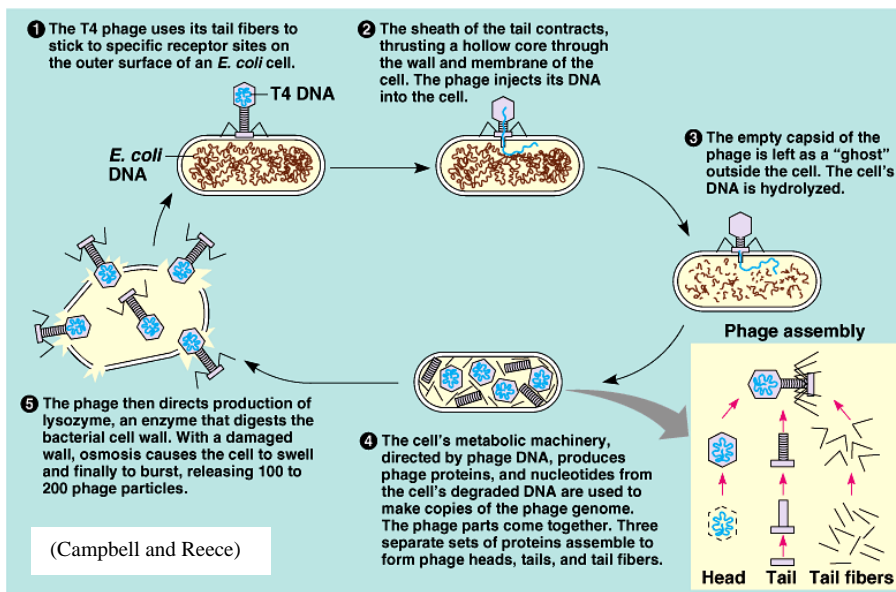
Hospitals provide a breeding ground for drug resistant bacteria. Antibiotics are used frequently. Therefore, the bacteria are constantly exposed to these treatments and any bacterium that evolves a resistance to the treatment will thrive where others would die. Generally the bacteria infect and kill the patients that are in the hospital with weakened immune systems. Yet, others can be infected; soldiers often suffer from diseases that entered their bodies through open wounds. Currently, in the American War in Iraq, soldiers are having difficulty with the bacteria *Acinetobacter baumannii*. This is not the first time this bacteria has attacked American forces. During the Vietnam War the United States Medical Staff had to deal with these bacteria strains. *Acinetobacter baumannii* thrives in soil and water. On the other hand, this bacteria is easier to deal with than some. "It is not difficult to treat," said Colonel Burno Petrucelli... "If the antibiotic works, it works easily. It easily dies" (qtd. Grady A.15). Nevertheless, these bacteria remain particularly problematic; they are both hardy and resistant. Not only can they live on or in any tissue, but they can survive for twenty days without substantial nourishment (Grady A.15). This longevity makes them dangerous in the hospital environment. If any sanitation procedures are forgotten, patients can easily become infected. There is one other problem with *Acinetobacter baumannii*. It is resistant to many commonly used antibiotics, although specific drugs, like amikacin and imipenem can easily treat the bacteria. However, their resistance still threatens the medical society (Grady A.15). "These bacteria pose a challenge because they have natural defenses that let them fight off many antibiotics, and they are also good at improvising ways to out-fox new drugs that are thrown at them," (qtd. Grady A.15).

After the recent surge in antibiotic medicine, many companies began to research treatments for more specific medical conditions rather than for new antibiotics. They saw no need to spend money on new antibiotics when the old ones would always be good. Besides, within a few years all these antibiotics would become superfluous, bacteria having been wiped out. So, drug companies cut funding for antibiotics. However, they did not predict the surge in antibiotic resistant bacteria. "The world may soon be faced with previously treatable diseases

that have again become untreatable, as in the pre-antibiotic era” (qtd. Sulakvelidze 807). Now these companies must race against time to find new treatments. Development takes years in itself and with the Food and Drug Administration’s testing procedures, it takes decades to take any new treatment to a consumer market – this is why drug companies feel justified in their high prices. Researching new antibiotics is a slow and lengthy process. “...Only nine new antibiotics were approved by the FDA during 1998 to 2003...” (Sulakvelidze 807). The long process of approval and development shows that antibiotics can not be produced fast enough to deal with the resistant bacterium, and even if there were many antibiotics created, some would become ineffective much faster than others. “...and only two of them [the nine new antibiotics approved during 1998 to 2003] had a novel mode of action...” (Sulakvelidze 807). The search for new antibiotics is made more difficult because of the way antibiotics work. Antibiotics attack the bacterium in some way, disrupting reproduction, tearing at the cell wall, bonding to amino acids, etc. If two antibiotics use the same method of attack, then a bacterial strain that becomes resistant to one of the methods will become resistant to the other. To treat a bacterial infection effectively, one must use different tactics. In a game of chess, if a person uses the same strategy every single game, he will lose. Eventually, his opponent will learn the strategy, and discover how to defeat it. Therefore, in the game of bacterial resistance mankind must always have a backup strategy. Just as the rook is not enough by itself to destroy its opponent, with the aid of the other pieces the game of chess becomes winnable.

Before the widespread use of antibiotics, there was another treatment that was gaining widespread use.

Bacteriophages were discovered in the early 20th century by two scientists, Frederick Twort and Felix d’Herelle. At



first phages were thought to be the wave of the future. However, phage therapy became less common after the rise of modern antibiotics (Sulakvelidze 808). Phages are viruses that prey on bacteria. After they reproduce their structures with the host’s cellular

organs, they lyse, causing the host cell to burst open. They are an effective method of treatment, but their power is somewhat limited. A bacteriophage can prey on only one or a few bacterial strains. Therefore the infecting agent must be known or the wrong phage could be administered. Using the incorrect phage would be only indirectly harmful. The phages can only attack their prey, so a human is safe, but if one is treated with the wrong phage, the bacteria would not be inhibited. The bacteriophages, however, offer a very large boon. They evolve with their hosts. While antibiotics could become useless within a few years, a phage strain constantly evolves with its prey population. The phage has a paramount potential in medical use, yet it is rarely used in urbanized countries due to the availability of antibiotics. Yes, phages can kill many bacterial strains, but in the case of an emergency, when the bacterial culprit is unknown, a doctor would choose an antibiotic. Antibiotics have a much wider spectrum of treatment, a multitude of strains against the phages single strain. This makes the phage like a special operations agent. In regular combat, a soldier fights just as well as a special operations agent; however, when a specific target needs to be destroyed, then that agent is the precise choice for the mission.

Another field of bacteria treatment, peptides, has potential, but only in the distant future. Peptides are protein chains that attack foreign agents within the animal that creates it. All animals create peptides. The animals' cells create these protein chains. The peptides attack bacteria by breaking a hole in their outer bacterial membrane. This hole causes the bacteria to lose control over the substances that enter it through the membrane. A cell, like a castle has walls, bacterial cell membranes; when there is a hole in the wall, then the invaders, in this case water, can enter. This influx of water causes the cell to swell and burst. This process is called lysing. Peptides attach to the bacterial membrane, punch a hole in the membrane, and then lyse the bacterium - like a battering ram used in the Middle Ages to break down the gate so that the invaders could enter the castle. However, because the peptides must attach to the membrane, they can only hook on to a specific membrane. Thus, the peptides are very specific to the bacteria they attack. This also allows them to work as the body's natural defenders. They are formed specifically to lyse foreign cells and not the body's natural cells. The largest downside to peptide use in patients is their selectiveness. Human bodies recognize the peptides of other creatures as foreign objects and expel them. At this stage of their development, they are unable to be used in any creature other than the one in which they are created. Their selectiveness also makes them share the same problem that bacteriophages face; the doctor must know exactly what the infectious agent is. The next step in peptide research is to find a way to allow peptides from other creatures to take effect within humans. Until then, peptides are an unlikely candidate to succeed antibiotics.

Antibiotics drastically changed the world and are an unparalleled achievement of mankind. However there is still much left to do. Bacteria are once again becoming an unstoppable force. Within a few decades or even a few years man will have lost the ability to cure with the current antibiotics. In this game of life and death humans are just puzzling out the implications of the rules Darwin proposed. As humans learn more about the world around and within themselves, new cures can be discovered. Other strategies exist to fight bacteria, but they are not as effective as antibiotics are. The essential value of time is being discovered. If man loses this battle before reinforcements can arrive, the world will recede and again become a dark place. Intuition and perseverance will be the saving graces of mankind. Without them we will surely lose this war.

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