ANTIBIOTICS and AGRICULTURE - THE HISTORY and the DOWNFALL

The 2 biggest events which have extended Humans' life expectancy were the evolution of proper sanitation systems (18th and 19th centuries) and the development of antibiotics (only the last 70 years). Prior to the beginning of the 20th Century, infectious diseases accounted for high morbidity and mortality worldwide. The average life expectancy at birth was 47 years, 46 for men and 48 for women, even in the industrialized world. Today life expectancy ranges from the mid 60's in poorer, less developed countries, to the 90's, lifestyle depending of course. Click here for a reference. Although antibiotics have undoubtedly cured many life-threatening infections and saved many lives, one could argue that because of their overuse in humans, but mostly in the agricultural industry, they have contributed to much more illness and resulted in many more deaths than it has saved. Their overuse has resulted in the creation of a number of drug resistant organisms which might well be the downfall of Humanity. The World Health Organization sites drug-resistant infections as the most concerning problem facing humanity. Not global war or climate change.

Antibiotics have been used for millennia to treat infections, although until the last century or so people did not know the infections were caused by bacteria. Various molds and plant extracts were used to treat infections by some of the earliest civilizations. The ancient Egyptians applied moldy bread to infected wounds. It wasn't until the late 19th century that scientists began to observe antibacterial chemicals in action. German physician Paul Ehrlich noted that certain chemical dyes colored some bacterial cells but not others. He concluded that, according to this principle, it must be possible to create substances that can kill certain bacteria selectively without harming other cells. In 1909, he discovered that a chemical called arsphenamine was an effective treatment for syphilis. This became the first modern antibiotic, although Ehrlich himself referred to his discovery as 'chemotherapy', the use of a chemical to treat a disease. The word 'antibiotics' was first used over 30 years later by the Ukrainian-American inventor and microbiologist Selman Waksman, who in his lifetime developed over 20 different antibiotics.

The discovery of penicillin was made in 1928 by Scottish biologist Sir Alexander Fleming (1881-1955) who was doing experiments on the bacterium Staphylococcus, a normal skin microbe. He opened his lab windows one day, introducing penicillium mold from outside which contaminated his petri dishes and he noted that some of them died as a result of the contamination. He found that the fungus Penicillium notatum proved extremely effective at preventing Staphylococcus growth, even when diluted 800 times, and was less toxic than the chemical disinfectants used at the time. It was first tested on humans in 1941 and biochemists Ernst Chain and Howard Florey purified the first penicillin, penicillin G. It was first used in 1942 during World War 2 and it undoubtedly saved many thousands of lives of wounded soldiers. It was dubbed the "miracle drug". In 1949 and it became widely available outside the Allied military and again, it saved many thousands of civilian lives from mortal infections.

During the war, there was a constant demand for meat to feed the military and the meat industry was encouraged to expand to meet this need. That guaranteed market disappeared after the war was over. In addition, there were problems with crop failure after the war in Europe and Asia. To make up for both of these problems, the agricultural industry started looking for ways to save money. In other words, try to continue to maintain the increased capacity but cut costs at the same time. They switched from feeding pulverized fish feed from the California coast (highlighted in John Steinbeck's famous novel "Cannery Row") to using cheaper grains which were not as nutritious. This heralded the "supplement" industry.

In 1948, a scientist named Thomas Jukes, who was forking for the pharmaceutical company Lederle Labs, was working of supplementing animal feed. He did an experiment where he fed newborn chicks various established feeds and compared their growth with chicks fed the leftover, throw-away remnants

from the formation of the antibiotic tetracycline. He found that despite being fed less nutritious feed, the "residue"-fed chicks grew almost twice as much as any other group. They found that there were small traces of the antibiotic still in the remnants and this was felt to be responsible for this "growth promotion". The main mechanism by which antibiotics increase the efficiency of animal growth is thought to be by inhibiting the growth of microbes in the gastrointestinal tract which trigger immune responses. Simply put, if the animal's body doesn't have to expend energy combating microbes in their gut, it can expend more energy on growth. In addition, the antibiotics prevent the development of life threatening infections because of the horrible, close-quarters living conditions which breed disease.

In addition to the growth promoting effects these small amounts of antibiotics provided, they discovered that slightly higher doses also prevented many diseases leading to increased livestock survivability.

Within 5 years of these discoveries, livestock growers were using antibiotics regularly in their productions, feeding their animals more than 500,000 pounds a year. Today, the US uses more than 30 million lbs. of antibiotics in livestock including chickens and other poultry, beef, pork, sheep and even fish. Worldwide, over 260 million lbs. are used. The vast majority of these antibiotics are not used to treat disease but to promote growth and prevent disease.

Before the development of antibiotics, most people didn't die of the lifestyle-diseases people die from today. Most didn't live long enough to develop those diseases. Most died of injuries; gored by an ox, injured during a battle, crushed in an industrial accident, as was common in the early days of industrialization, and, most of the time, from the infections which finished those injuries off.

In an instant, usually lethal infections became curable literally within days. This has been a "golden era" of medicine because of antibiotics. This era has lasted barely 70 years and now we are on the precipice of the end of this era with the development of antibiotic resistance. People are already dying of infections, not responsive to antibiotics, at a rate which is rapidly approaching epidemic levels.

Bacteria compete against each other, just like any other organism, for resources and food. They compete by producing lethal compounds directed against each other. Other bacteria develop defenses against that attack. Antibiotics were developed to attack bacteria and in a similar way as occurs in nature, bacteria develop defenses to thwart our attack. They develop such resistance quickly. The first antibiotic discovered, penicillin, started to become ineffective within 2 years! Resistance to vancomycin in 16 years. Imipenem in 13 years and a more recent antibiotic, Daptomycin in only 1 year!

With EVERY dose of antibiotic, the bacteria have an opportunity to develop resistance. The CDC estimates that almost 50% of antibiotics prescribed to humans in the US are inappropriate, meaning the infections are probably viral or the symptoms are not even because of an infection. If you are treating a life-threatening bacterial infection, the risk may be worth it but as a growth stimulant or as a preventative means, we are playing Russian Roulette. The bacteria will eventually win. Humans will lose.

We are constantly playing "leapfrog" with bacteria and it is frightening and soon coming to an end. Some pharmaceutical companies are no longer developing antibiotics because they just lose money doing so. There are over 100 different antibiotics on the market. Some microbes are resistant to all but 1 or 2 and a few are resistant to all of them.

In 2000, a single case of *Klebsiella pneumoniae carbapenemase* (KPC) was identified in a hospital in North Carolina. This microbe is resistant to all but 2 antibiotics. By 2015, cases spread to all but 3 states in the US, South America, Europe and the Middle East. In 2008, an Indian patient was identified in Sweden with an infection resistant to all but 1 antibiotic. The microbe causing this infection carried a gene mutation known as *New Delhi metallo-beta-lactamase,* NDM-1. This mutation allows a bacterium

to develop resistance easier. This gene mutation has now spread to China, Asia, Africa, Europe, Canada and the US.

In the US and Europe, more than 50,000 people a year die from infections not treatable with antibiotics because of resistance. Worldwide, the estimation is that 700,000 deaths (2015 data) occur because of resistance. They also predict that if we can't get this under control, by 2050, the worldwide toll will be over 10 million deaths a year.

If we lose antibiotics, all of the following would also be lost:

- Any protection for at risk, immunosuppressed individuals like:
  - Cancer patients
  - HIV and AIDS patients
  - Transplant recipients
  - Premature babies
- Any treatment which involves implanted devices (1 out of 6 would probably die):
  - Stents for heart attacks, strokes, aneurysms, kidney infections…
  - Pumps for diabetes and pain management
  - Pacemakers and defibrillators
  - Dialysis catheters
  - Joint replacements (think of all the hips, knees and shoulders which are implanted yearly).
- Surgery in general since many procedures are proven to be safer with a prophylactic dose of antibiotics.
  - No heart operations
  - No prostate biopsies
  - No cesarean sections…
- We would now have to fear routine infections:
  - Strep throat which can lead to heart failure and joint destruction. George Washington died of an infection caused by Strep.
  - Skin infections will lead to amputations.
  - Giving birth had a 1% death rate from infections alone, even in the cleanest hospitals.
  - Pneumonia killed 30% of kids.

If you knew that ANY injury could lead to death from infections, would you live your life the way you do now? Would you ride a mountain bike, let your kid slide into 1st base, climb a tree…? In fact, the first person to receive penicillin, a British police officer named Albert Alexander, whose infection resulted in him losing an eye and oozing pus from his skin, became infected by simply going into is garden and scratching his face on a thorn.

We have done this to ourselves in only 70 years.

- Penicillin used to be sold over the counter in the 1950's in the US. Antibiotics are still available that way in much of the developing world.
- In the US, 50% of antibiotics given in hospitals are given unnecessarily.
- 45% of out-patient antibiotic prescriptions in doctors' offices are inappropriate and not indicated.
- HOWEVER, the majority of antibiotics used are for livestock and fish farms, not to treat illnesses but as a growth stimulant and to prevent infections because of horrible, stressful and unsanitary factory-farm living conditions. In the US, 80% of the antibiotics used are for livestock, not Humans.
- Even in agriculture, antibiotics are used for crops like apples, citrus and pears to prevent infection.
- Some herbicides, like glyphosate found in Roundup, are actually antibiotics and are used not only to kill weeds but also as a drying agent to make harvesting easier.

THIS WAS NOT ONLY PREDICTABLE, IT WAS PREDICTED.

The father of the antibiotic era, Alexander Flemming, the scientist who first identified penicillin, predicted this catastrophe. In 1945, only 2 years after his discovery, he was given the Nobel Prize. Shortly after, he said in an interview "The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with penicillin-resistant organism. I hope this evil can be averted." He was concerned specifically that antibiotics, given at too low a dose, would allow resistance to develop more rapidly and he was exactly right. That is exactly what the meat and agriculture industries do. 2 years after his comments in 1947, penicillin-resistant staph arise in hospitals first in Great Britain, then Australia then in the US in 1955.

This same issue with resistance seen in humans was also seen in animals. The first signs were seen in dairy. Kids, who naturally drank a lot more milk than adults, started to develop penicillin allergies because there was so much penicillin in the milk they were consuming. Cheese makers started complaining that they could not make cheese since the antibiotics were killing the beneficial bacteria, they used to ferment the cheese. Then there was an outbreak of drug-resistant staph in southern England with over 100 people getting ill with 6 deaths. A drug-resistant outbreak of E. Coli broke out in Yorkshire killing 13 children.

In 1969, Britain was the first government to restrict antibiotic use in the agriculture industry and took growth promoters completely out of farming. What did the US do since we were the agricultural power in the world and were the first to use antibiotics and growth promoters in the industry and use the most in the world? Unfortunately, NOT MUCH! Not until 2017, when after decades of consumer pressure, was some minimal regulation implemented.

In 1976, Tufts professor and physician Dr. Stuart Levy staged the first US experiment proving that antibiotics in feed was a grave threat to human health. He set up an experimental chicken farm outside of Boston. He fed one small group of chickens on the farm antibiotic-laced feed and very soon, those chickens started to develop drug-resistant bacteria in their intestines. Those same resistant bacteria started to appear in the intestines of the non-antibiotic fed chickens and then eventually, the human farm family became colonized with the same drug resistant bacteria. That recognition resulted in… NOTHING! The next year, when the FDA tried to withdraw the licenses that it granted to growth promoters in the 1950's, powerful congressmen, under the influence of and beholden to the even more powerful agricultural industry (meaning they were paying them), threatened to hold the FDA's entire budget hostage and forced it to back down. It stayed that way, allowing resistant bacteria to flourish and allowing people to become sick and die.

In 2014, drug resistant salmonella from just one California chicken processing plant, caused more than 600 people to get sick in 29 states, including Puerto Rico. The CDC estimates that for every diagnosed case of food-borne illness, there are another 30 that go undiagnosed. So in reality, this outbreak probably sickened close to 20,000 people!

We can try and try and try to keep developing new effective drugs, but evolution always wins. Bacteria produce a new generation every 20 minutes. It takes drug companies 10 years to create a usable new drug. Every time we use an antibiotic, regardless of what setting it is in, we give the bacteria billions of chances to crack the codes of the defenses we've constructed. There has never been a drug they have not overcome.

Is it hopeless? Maybe not but it would take extreme effort on everyone's part. Here are some examples of what we would need to do:

- The livestock, fish and agricultural industries would have to stop using antibiotics. If not voluntarily, then by force with legislation.

- Systems monitoring use of antibiotics and disease outcomes n Humans can be implemented to better tailor treatments.
- Gatekeeping monitoring systems requiring a second look at all prescriptions ordered could be implemented.
- Surveillance systems monitoring resistance worldwide could be implemented.
- People have to stop expecting and demanding medications for themselves and their children. We need to be patient and trust that most illnesses get better on their own. It may be inconvenient, but it's necessary.
- We can refuse to purchase animal products and produce known to have come from farms where antibiotics are used. As mentioned above, it was not until 2017 that after public pressure, followed by some institutional fast food companies like McDonalds starting to speak up, did the government implement some minimal regulation. It's not enough, but it's a start.