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Six Microbes that Changed the World

Tuberculosis

WHAT IS TUBERCULOSIS?

"Tuberculosis is believed to be the most lethal disease in history, having claimed more than a billion lives since it was first identified in ancient Greece." (Goetz, 102)

The disease known as tuberculosis has been around for millennia. It was first documented by the ancient Greeks, who called it "consumption." (*The Forgotten Plague*, 2:05) Since then, the disease has gone by various other names including "phthisis" and "The White Plague," and has had a significant impact on human history. The symptoms of tuberculosis are what earned it the name consumption, as it "eats away" at its victim. Some of these symptoms include fever, chills, fatigue, emaciation, pain in the chest, incessant coughing, and, the telltale sign of tuberculosis, coughing up blood. (Mayo Clinic) The duration of the disease varies: some die quickly and violently, while others live with the disease for decades before ultimately succumbing. (*The Forgotten Plague*, 2:59)

The cause of tuberculosis is infection by a bacterium known as *Mycobacterium tuberculosis*. An obligate human pathogen, *M. tuberculosis* has survived all these centuries solely by infecting human hosts. (Glickman, 477) This means that since the time the disease was first identified, there has never been a single moment at which no human was infected. Because the bacterium requires high levels of oxygen, it is primarily a pathogen of the respiratory system, although it has been known to spread to other parts of the body as well. (478) An airborne microbe, the primary mechanism of transmission of *M. tuberculosis* is via particles spread through the air by the coughing, sneezing, and/or spitting of infected individuals. (478)

The one "saving grace" of *M. tuberculosis*, and perhaps the sole reason why it has not succeeded in decimating the human population, is that most infections are latent. This means that the bacteria are simply lying dormant in the carrier's body, and no symptoms are being shown. A person cannot die of a latent tuberculosis infection, nor can they spread the bacteria to anyone else while it is in this state. (Glickman, 478) However, sometimes latent infections become active. More often than not, this can be attributed to a weakened immune system. Once the disease becomes active, symptoms begin to appear, and the infected individual is capable of transmitting the disease to others.

19TH CENTURY – WHITE PLAGUE, HEREDITY, AND THE CLIMATE CURE

Tuberculosis was especially prevalent during the 19th century—this was the time during which it was referred to as "The White Plague." (Goetz, 91) This was because, by the beginning of the 19th century,

tuberculosis had killed 1 in 7 of all people who had ever lived, making it the most common cause of death. (*The Forgotten Plague*, 1:54)

At this point in history, there were many competing theories as to how a person might contract tuberculosis. The most prevalent of these theories was that the disease was hereditary in origin. (*The Forgotten Plague*, 6:12) This was based on the fact that it often afflicted multiple members of the same family. Nowadays, we can attribute this phenomenon to fact that families spent so much time together, and were very likely to spread the disease to one another. In the 1800s, however, the germ theory of disease was not yet widely accepted, so people simply did not know that such a method of transmission was even possible.

The hereditary theory brought with it some negative stigma for those who suffered from tuberculosis. If you contracted the disease, it was not your fault—it was unfortunate, to be sure, but it was simply your lot in life. However, this led to the notion that there was something wrong with lineages that had especially high rates of tuberculosis: "…the hereditary explanation for tuberculosis compounded the stigma of the disease. If tuberculosis was a manifestation of weakness, of poor stock, then consumptives were clearly genetically inferior creatures." (Goetz, 101) Given the sheer number of people who contracted the disease, however, it is unlikely that this stigma was especially damaging. After all, everyone knew someone who had tuberculosis.

In America, tuberculosis hit especially hard in the early 1800s. (*The Forgotten Plague*, 3:08) This was also around the time that the American West was opening up to settlers. It promised a return to nature – undeveloped land, wide open skies, and plenty of fresh air. This attracted, among others, the chronically ill. There was a strongly held belief that the best treatment for diseases like tuberculosis was to get away from the city and to expose yourself to the air of the country. This "climate cure," as it was often called, was advocated by physicians, and brought settlers out west in droves. (Goetz, 170)

As railroad tracks were laid down across the country in the 1870s, it became easier for more and more people to move out to new settlements. To attract people, growing cities started ad campaigns that touted the region's fresh air. Cities like Denver, L.A., Albuquerque, Colorado Springs, and Tucson all sprang up around this time. Some who traveled west got healthy, but most didn't. (*The Forgotten Plague*, 9:00-11:10) Before long, these new western cities became full of sick people with no resources available to care for them.

SANATORIUMS

In the 1840s, institutions called sanatoriums began to pop up all over Europe. (Goetz, 170) They took primarily tuberculosis patients and emphasized the climate cure, exposing their patients to plenty of fresh air. Inspired by the Europeans, Edward Trudeau opened the first American sanatorium in the Adirondacks in 1882. (*The Forgotten Plague*, 30:49) He was especially fond of the idea, as a longtime

tuberculosis sufferer who had experienced some relief upon moving to the Adirondacks from the city years before. Following Trudeau's lead, sanatoriums quickly began to spread across the U.S.

As sanatoriums opened, tuberculosis patients flocked to them. It was not uncommon for people to leave their family without any notice to check themselves into a sanatorium. Some went in the hopes of recovering; others went simply to die. Once there, patients would often stay at sanatoriums for extended periods of time, sometimes even years. In the first decades of the 1900s, 1 out of every 170 Americans lived in a sanatorium. (*The Forgotten Plague*, 32:22) Patients were prescribed lots of bed rest and healthy meals, and their beds were often placed outside so that they could get fresh air. This led to the popularization of front porches and sunrooms, which developed as ways to expose patients to the outdoors in a controlled manner. Reclining chairs can also be traced back to sanatoriums, where they were useful for patients transitioning from sitting to lying down, as even moving from a chair to a bed was often hard for fatigued patients. (37:54) Despite the popularity of sanatoriums, only about 1 in 3 people who entered them actually recovered. (40:07)

KOCH'S DISCOVERY

The cause of tuberculosis wasn't discovered until 1882, when Robert Koch identified the culprit bacterium. (Goetz, 85) His discovery came when germ theory was at the brink of widespread acceptance. It had been gaining a following within the scientific community for years, but was still staunchly opposed by some, who thought it was simply too fantastical to be true. These opponents held firmly to miasma theory and/or the belief that tuberculosis had hereditary origins.

There were many opponents who saw germ theory as a direct threat to their own work. Scientists whose entire bodies of work would be rendered irrelevant by the advent of germ theory recognized that the validity of their careers was at stake. Once such scientist was Rudolph Virchow, who believed that tuberculosis was a hereditary form of cancer. Over the length of his career, his held faithfully to his mantra: "all disease from cells," meaning that disease could only arise from problems within *human* cells. (Goetz, 101) While the scientific community was divided on germ theory, the medical community entirely discounted it. Whether or not it was a valid theory, they argued, it had yet to provide any useful applications, and so had no relevance to their profession. (120)

However, this would all change with Koch's discovery. His work would prove so convincing, so outright irrefutable, that the scientific community would have no choice but to accept it. "His theory was, all at once, accepted as proven. Rarely had medicine ever experienced, wrote the *British Medical Journal*, 'so sudden and complete casting aside of tradition.'" (Goetz, 106) It is said that immediately following Koch's initial presentation of his findings, his audience stood in shocked silence. Virchow, apparently recognizing the lethal blow to his life's work, simply put on his hat and left the room. (88) "In a single presentation built on just a few months of work, Koch had rendered obsolete libraries of medical textbooks representing decades of work by thousands of men." (102) With his discovery, Koch had just

launched germ theory into the public consciousness. Even the medical community began to implement new techniques and procedures flavored by germ theory.

PARADIGM SHIFT

Koch's discovery and the subsequent adoption of germ theory were major scientific milestones, and they brought with them both positive and negative social consequences. To increase public awareness of the mechanism of tuberculosis transmission and of germs in general, a massive public health campaign was launched in the U.S. in the early 1900s, the first of its kind. (*The Forgotten Plague*, 23:30) This brought about various changes in public views of sanitation, from a sharp decline in spitting (so as to avoid spreading disease via saliva), to the shortening of women's skirts (so they didn't drag along the ground), to an increase in clean-shaven men, who didn't want to harbor germs in their beards after sneezing or coughing. (24:06) This campaign would also lead to the invention of the waffle cone as a replacement for the "penny lick," a glass cup that customers would lick their ice cream out of and then hand back to the scooper to be used again, and the Dixie cup, as a single-use alternative to "tin dippers," which were metal cups placed at public water sources. (Goetz, 205) Overall, these improvements to personal hygiene along with a heightened awareness of germs began to reduce the rate of tuberculosis even before a cure was developed. (*The Forgotten Plague*, 25:04)

Now that tuberculosis had been proven to be communicable and not, in fact, hereditary, perceptions of the disease began to change. No longer was having tuberculosis simply "your lot in life"—now, it was your fault for having caught it. The disease's stigma began to shift, and so-called "sick-shaming" ensued. If you had tuberculosis, it was likely because you were poor, messy, and unsanitary. (*The Forgotten Plague*, 20:44) Unfortunately, this stigma wasn't entirely without merit. Poor neighborhoods that didn't have access to the same resources as better-off communities often had higher rates of tuberculosis. (25:15) Public health officials monitored these neighborhoods, performing inspections and even committing diseased people to hospitals and sanatoriums against their will. It was a battle between individual freedom and the "greater good" of public health, and the greater good was winning out. (26:06) Even the western cities that had once welcomed tuberculosis patients with open arms now tried to keep them out. (21:54)

THE CURE

Koch, who died in 1910, wouldn't live to see a real cure for the disease he had devoted so much of his life to studying. (Goetz, 234) In fact, such a cure wouldn't be found until 1943 by the work of Selman Watzman and Albert Schatz. (245) After the birth of penicillin, and its subsequent failure to cure tuberculosis in the 1940s, Watzman believed he could find another drug that would. His lab conducted research that focused on isolating antibiotics form soil-dwelling microorganisms. Schatz, a research assistant in the lab, made it his personal mission to find the antibiotic that would cure tuberculosis. After 3 months and countless hours spent in the lab, Schatz had found it—a substance that inhibited the growth of *M. tuberculosis,* among other penicillin-resistant bacteria. This substance, which would

be named Streptomycin, was derived from the bacterium *Streptomyces griseus*. In November of 1944, Streptomycin was tested on a patient with active tuberculosis, and was shown to work—the patient had been cured. (*The Forgotten Plague*, 41:29-46:05) After centuries of affliction, humanity had finally found a way to defend itself against its greatest plague. Of course, since it was in Watzman's lab that the discovery had been made, he alone received the Nobel Prize for Streptomycin in 1952. (Goetz, 247)

Before antibiotics, half of all people with tuberculosis were expected to die within 5 years. By 1950, the majority of tuberculosis cases were able to be cured. (*The Forgotten Plague*, 48:17) Rates of tuberculosis plummeted worldwide, and sanatoriums began to shut down as patients were treated. Within a couple decades, "the general public lost any perception of tuberculosis as a true concern." (Goetz, 248)

In the late 1940s, some tuberculosis patients started to relapse—Streptomycin didn't quite get the job done, and the bacteria it didn't kill came back with a vengeance. New drugs were added to the treatment regimen alongside Streptomycin to reinforce its effects. This drug cocktail was shown to be entirely effective, and was used from then on. (Goetz, 247-248) Though this was just a small blip in the history of tuberculosis, it was the first harbinger of what was to come.

RE-EMERGENCE

By the 1980s, tuberculosis was a long-forgotten plague, having been relegated to the likes of the Black Death as a disease that just didn't come around anymore. However, this would all change with the onset of the AIDS epidemic. (*The Forgotten Plague*, 50:50) As it turned out, tuberculosis hadn't actually gone anywhere—it had just been lying dormant. The disease became active in response to the weakened immune systems of newly-infected HIV patients who had been carrying the latent form. (Goetz, 249) To make matters worse, active tuberculosis, unlike the latent form, is infectious, and can easily be spread to others. Within a few years, a full-blown tuberculosis epidemic had broken out alongside AIDS.

As is inevitably the case with most antibiotic-treated diseases, strains of tuberculosis began to develop drug resistance in response to poor adherence to proper treatment practices. (Goetz, 249) In a disease that had been so far removed from the public consciousness for so long, this was a terrifying development. Would there be enough antibiotics available to treat these newly-resistant strains? If not, what was going to happen?

MODERN TUBERCULOSIS

Today, the tuberculosis crisis has only worsened: there are currently about 9 million active cases of tuberculosis worldwide. (*The Forgotten Plague*, 51:06) It is estimated that one in every three people in the world carries *M. tuberculosis*. (Sharma, 354) Strains of drug-resistant tuberculosis are widespread across the globe, and are particularly devastating in areas with high rates of HIV infection, where those

with weakened immune systems are more likely to contract the active form of the disease. (Duncan, 243) So why are more and more resistant strains developing? As we learned, starting and failing to finish treatment is often what gives rise to resistant strains. If the bacteria aren't entirely wiped out, they have a tendency to come back with a vengeance–that is, those who have mutated to become resistant to the antibiotic will flourish given the opportunity to do so.

Antibiotics used to treat tuberculosis can be broken down into first-line and second-line drugs. When a patient is first diagnosed with tuberculosis, it is assumed not to be drug-resistant, and first-line antibiotics are employed to combat it. If, after sufficient treatment time has passed on these drugs, no noticeable change has occurred, the disease is assumed to be MDR-TB, or "multidrug-resistant" tuberculosis. (Migliori, 423) At this point, second-line drugs are employed. These drugs are saved for these severe cases so as to avoid over-prescribing them and increasing the chances of resistant strains emerging. However, such measures have not been entirely successful. If at least three second-line drugs are shown to be ineffective after sufficient treatment time for MDR, the diagnosis becomes XDR-TB, or "extensively drug-resistant" tuberculosis. (423) At this point in time, a diagnosis of XDR is essentially a death sentence: there are often no antibiotics available that can cure the disease. (*TB Silent Killer*)

Tuberculosis treatment, especially in MDR and XDR cases, can be long, harrowing, and costly. Treatment can take from months to years, and can involve a strict and demanding medicine schedule involving a multitude of pills and injections that must be administered daily. (*TB Silent Killer*) This alone is enough to discourage many, but the real drawback to treatment is that the side effects are often worse than the symptoms of the disease itself. Spending months to years in abject misery, having no idea whether or not you will be cured is hardly an appealing scenario. Some simply refuse treatment. Others attempt treatment for a time, only to give up once the all-consuming nature begins to take its toll. (*TB Silent Killer*) For those who make it all the way through treatment only to be delivered the grim diagnosis of XDR, the news is impossibly devastating. The reality that they devoted years of their life to horrific, fruitless treatment is often too much to handle, and it is not uncommon for these patients to commit suicide. (*TB Silent Killer*)

The fact that few people successfully complete treatment for tuberculosis, especially for MDR and XDR, is what has led to the emergence of even more resistant strains. However, all hope is not lost. In 1998, the genome of *M. tuberculosis* was sequenced. (Duncan, 245) This has proven to be a huge aid in the development of new antibiotics for tuberculosis treatment. There has also been a bigger push in recent years to fund antibiotic research due the severity of the crisis. (245) At this point, our best hope to combat the disease is to continue developing new antibiotics that could cure XDR and that could reduce the treatment time and/or difficulty of MDR, so that more patients can successfully complete their treatment.

TUBERCULOSIS IN SIX MICROBES

M. tuberculosis is a perfect candidate for inclusion in future iterations of Six Microbes. Of any disease that could be studied, I would argue that tuberculosis has one of the most intriguing stories, and that it has had *the* greatest impact on humanity. (It has, after all, killed more people than any other disease in history.)

It should be noted that the cholera unit was in fact my favorite unit in Six Microbes, and that there was absolutely nothing wrong with it. So when I say that I think tuberculosis would be an even better disease to study than cholera, I do not say so lightly.

Let's start with what makes tuberculosis a worthy substitute for cholera. The paradigm shift to germ theory is at the heart of the tuberculosis story, making it similar in function to that of the current cholera unit. *The Remedy* by Thomas Goetz (the book I read for this project), like *The Ghost Map*, offers a gripping narrative that makes it hard to put down. The story has a compelling and intriguing protagonist in Koch (whose life had more ups and downs than I was able to mention in this paper), just like *The Ghost Map* has in Snow. There's even an antihero who opposes the paradigm shift: Rudolph Virchow's "all disease from cells" mantra runs directly parallel to Edwin Chadwick's "all smell is disease" mentality. Both stories are perfect case studies in the same scientific revolution, with proponents of the old and new paradigms battling for dominance.

With this in mind, it's not hard to see how tuberculosis and cholera could be easily interchanged. But what gives tuberculosis the edge? What makes it more compelling to study than cholera?

For one thing, Koch's discovery was the single most crucial event in driving the scientific revolution. If it were possible to point to one specific instance in history and say "this is when the paradigm shift to germ theory occurred," Koch's discovery would have to be that instance. Thus, the story lends itself to a much more extensive narrative than that of cholera, encompassing the effects that the paradigm shift had on the scientific and medical communities, and on society as a whole: from the rise and fall of sanatoriums, to the "climate cure" and the settling of the American West, to the societal changes brought about by public awareness of the germ theory of disease, to the story of the discovery of Streptomycin. While Snow certainly helped bring the idea of germ theory to the forefront, the actual shift occurred after his time, so the cholera narrative leaves many questions unanswered.

At first glance, it might appear that the biggest obstacle to integrating tuberculosis into Six Microbes would be to come up with an appropriate laboratory study, as *M. tuberculosis* itself is hardly a suitable microbe to work with. However, I would argue that by connecting aspects of the tuberculosis story to previous laboratory work in the class, an ideal study could be developed. Recall Waksman and Schatz's work in discovering antibiotics via soil-dwelling microbes in the era of penicillin. This is a direct callback to the first unit, and ties in perfectly with the first laboratory study, in which we do exactly the

same thing. This could easily be connected to the recent sequencing of the *M. tuberculosis* genome to produce a study in which students identify potential points of weakness within the genome that could be targeted by antibiotics such as the ones they may have discovered in the penicillin unit's lab study.

Building on this proposed laboratory study, perhaps the most significant aspect of the tuberculosis story, and what makes it most compelling, is the current-day drug resistance crisis. A callback to what we learned about antibiotic resistance in the penicillin unit, this is a prime example of the very real dangers of resistance and what is being done to deal with it. I think many people would be shocked to realize that tuberculosis is still prevalent today, nevermind the fact that tuberculosis drug resistance is one of the most pressing global medical issues. The ongoing nature of this crisis leaves plenty of room for exploration, from identifying the different strains of resistant tuberculosis and how they arose, to the difficulties surrounding adherence to treatment regimens, to the development of new drugs and what the future looks like for tuberculosis treatment.

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