

Germ Theory

- “In earlier ages, pestilences were mysterious visitations, expressions of the wrath of higher powers which came out of a dark nowhere, pitiless, dreadful, and inescapable”
- So says historian Hans Zinsser in his classic book *Rats, Lice and History*...
- Imagine what it must have been like to live in a world where germs had not yet been discovered
- When we had to watch our loved ones wither and die before our eyes, not knowing what was killing them, not having any hope for a cure
- Before we could begin to solve the puzzle of disease, we first had to realize that diseases
 - > were not the wrath of a vengeful god
 - > weren't due to an unfortunate conjunction of stars and planets
 - > weren't caused by an imbalance of bodily fluids
 - > weren't caused by mysterious vapors
- Diseases were caused by the incessant nibbling of tiny little creatures feeding on our bodies
- Creatures that live in us, that live on us, that live all around us - creatures so small that they were invisible for most of human history
- The history of human civilization is in one sense a history of epidemic diseases
- Every once in a while, a pathogen comes along that through exquisite adaptation, through random mutation, or through plain blind luck, breaches our defenses, overwhelms our immune system, and leaves entire cities dead and dying in its wake
- During the Spring of 2009, the latest swine flu epidemic (an unusual summer flu) was pushing panic buttons all around the world
- In early July 2009, the UN's World Health Organization listed 94,512 confirmed cases of swine flu, in 122 countries, with 429 already dead
- Once it crossed national boundaries, the swine flu epidemic officially became a pandemic
- An epidemic is a contagious disease that spreads very rapidly through a population
- We call it a pandemic if it occurs over a wide geographic area
- As the pandemic continued to spread, the Centers for Disease Control predicted that as many as 40% of Americans could catch it
- And several hundred thousand of us could die unless we were vaccinated!

- I was one of thousands who searched far and wide for the swine flu shot, pestering drug store pharmacists and campus health care nurses to find out when and where the scarce vaccine would be available
- I finally got lucky – and it only hurt for a minute (but I didn't get a lollipop) ...
- In fact, the swine flu pandemic sputtered out, as many epidemics seem to do, and the final death toll was only 18,449, including 8,533 in North and South America
- Bad enough, but not the killer flu the CDC and the UN's WHO had warned about
- Under intense criticism for unnecessarily frightening the public, the World Health Organization finally admitted that they might have overreacted
- But what if they had been right?
- What if this had been the super flu that we think may be out there somewhere?
- Doctors and health officials are concerned for a good reason, as we'll learn in our series of three lectures on the 1918 Flu pandemic
- What if this had been that one special microbe that finally slipped the leash, killing millions worldwide, and leaving social and economic chaos in its wake
- A truly frightening scenario...
- Now, try to imagine how much more frightening it would be if you had no idea why everyone around you was dying
- Think about it... In the days before the invention of the microscope, before the rise of modern medicine, how would *you* have explained a killer plague?
- Well, the common explanation for plagues was cosmic forces beyond our control, the whims of gods and demons
- And we're reminded of this every time someone sneezes in a crowded room
- What do we say when somebody sneezes? We say "Gesundheit", or we say "God bless you"
- Gesundheit is the more mundane of the two, an old German and Yiddish word meaning health
- So - good health to you
- But the expression "God bless you" has a much richer heritage
- This simple custom may have started in ancient Rome
- Where sneezes were thought to be a trick of demons...

- Demons would sneak up on you, and get you to sneeze, and the sneeze would expel your soul from your body so the demon could pounce on it
- Saying “Jupiter preserve you” would foil the demon, and save your soul
- Over the centuries, this customary saying may have evolved into the more Christian “God bless you”
- It was Pope Gregory, incidentally, who may have made it official, in 590 AD
- During an outbreak of the Black Death he is supposed to have announced everyone should say “God bless you” anytime someone sneezed
- But more enlightened folks knew that diseases were not caused by divine wrath, or demons - they were simply a consequence of astrological fate
- The word “influenza” reminds us of that ancient belief – it refers to the influence of the moon, the planets, and the stars
- The ancient Greeks thought that disease was caused by an imbalance of bodily fluids, which they called the humors
- Black bile, yellow bile, phlegm, and blood
- The idea is derived from the four elements of antiquity – earth, air, fire and water, each element represented by its respective humor
- Earth = black bile, air = blood, fire = yellow bile, water = phlegm
- The imbalance of humors was usually due to some outside force – bad air, climate, diet, occupation, personality, mood etc.
- From this perspective, there was no such thing as a specific disease
- What disease you got depended on
 - > what humors were involved
 - > where they had accumulated
 - > where they were being expelled from (runny nose, loose bowels) etc.
- So any disease could theoretically become any other disease - measles could become smallpox, if that balance were somehow shifted
- This meant there was absolutely no predictability in medical diagnosis or medical treatment
- The cure consisted of restoring the individual’s balance of humors, either through purges, or enemas, or bloodletting, or by changes in diet or climate

- Fever meant you had an imbalance of heat and moisture, so cold and dry foods were prescribed to help restore the balance
- If you suffered from an excess of phlegm, you could be cured by drinking wine - the perfect cure for a runny nose!
- Blood contained all four elements (earth, air, fire and water), so bloodletting would restore any type of imbalance
- Pretty convenient, considering how easy it was to extract...
- So bloodletting became a common cure for almost any serious health problem
- So widespread was the custom of using leeches to balance the patient's humors, that the medicinal leech is still an endangered species today
- At the height of the leech craze, between 1828 and 1836, France alone was importing over 34 million medicinal leeches a year!
- Another ancient theory of disease was that contagious diseases were caused by a miasma
- Miasma was bad air, air polluted with bits of decomposing matter (Mal-aria = bad air)
- Belief in miasmas dates back to classical antiquity
- Hippocrates, in his 5th Century BC treatise "Airs, Waters and Places", warns people not to live near stagnant water, or swampy areas
- Tell that to the people in New Orleans – we must be the miasma capitol of the world
- We used to fire powder charges from cannons on Canal Street during the "plague season", thinking that the sulfurous smoke would purify the miasma from the surrounding swamps
- And how many times has a southern belle has attributed her indisposition to an "attack of the vapors"
- Now, all these ideas might sound a bit foolish...
- But remember that, up until the late 17th Century, no one on Earth had ever actually seen a microorganism!
- They were simply too small...
- It's hard for us to really conceive of just how remarkably tiny bacteria really are
- They are so small we have to measure them in micrometers, also called microns (symbol is μm)
- There are 1,000 microns in a millimeter, and around 25,000 microns in an inch

- We talked about some of the advantages and disadvantages of being small in our first lecture
- The largest known bacteria are truly giants, compared to their tinier brethren
- They are the Blue Whales of the bacterial realm
- *Epulopiscium fishelsoni* , for example, lives inside a surgeonfish in the Red Sea
- They get to be about 600 microns long (over half a millimeter)
- *Thiomargarita namibiensis*, which lives at the bottom of the ocean, reaches a mighty 750 microns (~ 0.03 inch, or 0.75 mm)
- Both species are actually visible to the naked eye, though you might have to squint
- But most bacteria are much smaller than that...
- Typical bacteria are only about 0.2 to 5 microns across, with many species barely reaching half a micron or less
- A single period at the end of a sentence is large enough to enclose hundreds of thousands of bacteria
- In 1683 Leeuwenhoek peered through his microscope, and observed the tiny creatures that inhabit the microbial world
- What an amazing experience that must have been, to be the first person in human history to see the world in a teardrop
- But Leeuwenhoek didn't connect microorganisms to disease or decay
- Microorganisms were often found in decay and putrefaction – that didn't necessarily mean that they had *caused* it
- Maybe they were simply attracted to it, or even produced from it by spontaneous generation, spontaneously created from the vital force thought to be inherent in all organic matter
- The discovery of many good bacteria in the body also made it harder to see bacteria as any kind of threat
- One of the early pioneers of germ theory was Girolamo Fracastoro, a brilliant and precocious scholar who became a professor at the University of Padua at the ripe old age of 19
- He was the quintessential Renaissance man – an expert doctor, mathematician, astronomer, geographer and a poet into the bargain...

- He was the first to use the word pole, in reference to the Earth's axis
- He was a friend of Copernicus, and wrote about the nature of comets
- He was an early pioneer in the study of light, and may have been the first to suggest using combinations of lenses to improve vision
- He was the first to fully describe and name syphilis, and wrote an epic poem about it, as we'll discuss in our lecture on virulence
- His classic text, *On Contagion and Contagious Diseases*, published in 1546, theorized that diseases were caused by tiny spores, that could be spread by contact, through clothing, or through the air
- His theory of infection was very modern in some respects, but very primitive in others
- It's not entirely clear if his *seminaria* are really minute organisms, in the modern sense, or more of a physical and chemical agglomeration, spontaneously generated by putrefaction in disease – most probably the latter, given the prevailing theories of his day
- But Fracastoro was just too far ahead of his times, and his ideas gradually faded away, to be revived three centuries later, in the work of Robert Koch and Louis Pasteur
- The germ theory of disease wasn't accepted until the late 19th Century!
- It took pioneers like Louis Pasteur and Robert Koch to discover that microbes were the real cause of disease
- They relied on careful experimentation, instead of the more traditional clinical observations
- People didn't pay a lot of attention to germ theory until it hit them in a particularly sensitive spot – their wallets!
- It wasn't human misery, it was bad wine and dead silkworms that finally brought people around
- Louis Pasteur didn't set out to prove that human diseases were caused by microorganisms
- He was really interested in wine...
- Pasteur was working with wine and beer, to disprove Justus von Liebig's hypothesis that fermentation was a purely chemical process
- Fermentation, we now know, is an ancient microbial metabolic pathway, which breaks down glucose into alcohol (ethanol) and carbon dioxide
- Pasteur was able to show that wine fermentation was caused by the yeast *Saccharomyces cerevisiae*, a microscopic fungus
- But first he had to prove that yeast was actually a living microorganism, something that could grow and reproduce, not just a blob of chemicals

- He spent hours and hours hunched over his microscope, watching little blobs become bigger blobs, and budding off tiny offspring
- He proved that yeast was alive, and that it was responsible for the fermentation of wine
- But along the way, he also saw other microorganisms in wine, in beer, in vinegar
- He concluded that different germs could have different effects, a major breakthrough
- Sometimes the brewing process failed, with very costly results
- Pasteur went on to prove that these failures were due to various bacteria contaminating the yeast cultures
- He invented Pasteurization, carefully heating wine to kill the bacteria that would otherwise cause the wine to sour
- So now people knew what to look for in their wine, and could head off disaster before they ended up in the poor house
- John Tyndall [blue sky] and Joseph Lister [father of antiseptic surgery] studied Pasteur's results
- They both concluded that similar microbes must also be the cause of human diseases
- But Pasteur himself was not convinced - until the silkworms began to die...
- The French silk industry had survived six centuries of political and economic turmoil
- It was just starting to recover from the rather dramatic change in fashion brought about by the French Revolution - not a good time to be walking around in silks and satins...
- But in the 1860's, just when things were looking up, a mysterious disease called pébrine, swept through the country, killing millions of silkworms
- Pasteur insisted that pébrine was hereditary
- He even savaged his colleague Antoine Béchamp for insisting that the disease was caused by little burrowing parasites
- It took five long years of work to finally convince Pasteur that pébrine was in fact a contagious disease
- And that realization totally changed the focus of his remaining years, putting him on the track of human diseases, and ultimately leading to his discovery of the first anthrax vaccine
- Sadly, Pasteur's relentless quest to find a cure for infectious diseases was fueled by personal tragedy - three of his five children had died of typhoid fever...

- Pasteur was a linchpin in connecting microbes to human diseases
- But it fell to Robert Koch to firmly establish modern germ theory in the 1870's
- Koch connected anthrax, tuberculosis, and cholera to specific bacteria
- That was a huge step, from connecting germs to a handful of animal diseases, to the more general connection of microbes to human diseases
- But Koch faced a major challenge
- How to tell the good germs from the bad germs?
- The sheer abundance of different kinds of bacteria made this challenging (there are over 700 species in your mouth alone!)
- Plus the difficulty of telling them apart!
- He had to find a way to isolate individual types of bacteria, to create pure cultures of bacteria
- Oddly enough, his breakthrough involved someone's favorite jelly recipe
- In the usual fluid culture, bacteria were hopelessly mixed together
- So he had to invent a solid culture surface to grow them on
- Because on a solid surface, they would form isolated little colonies or clumps
- So he started with slices of boiled potato (too damp - fungus), then he tried gelatin (too mushy)
- He finally settled on a Japanese seaweed extract called carrageenan – (just right!)
- It was suggested by Fannie Hesse, a lab assistant, whose mother used it to make jelly
- And thus was born the familiar agar plates of the modern medical laboratory
- Carrageenan comes from a red algae, *Chondrus crispus*, also known as Irish moss)
- Koch put heavy stress on laboratory culture, and the identification of microbes, a medical tradition that continues to this day
- And culture is still a major hurdle, only about 1% of known bacteria have ever been successfully cultured!
- Koch invented a series of steps to prove which specific microbe is causing a particular disease
- These steps became known as Koch's postulates

- Koch's postulates
 - > First, the bacteria had to be present in every case of the disease
 - > Second, it had to be isolated and cultured
 - > Third, injecting the cultured bacteria into a healthy host must cause the disease
 - > Fourth, you had to be able to recover the bacteria from the infected host
- So that's the long and winding road that led to germ theory
- Starting with gods and demons, through humors and miasmas, to contagion & germs
- Finally, let's consider one early pioneer who paid a big price for his efforts to fight contagious disease, Ignaz Semmelweis
- Childbed fever is an ancient killer of young mothers
- It's also called puerperal fever - puer is Latin for child
- It was first described by Hippocrates over 2,000 years ago
- The death rate runs as high as 20%, occasionally spiking in epidemics to nearly 100%
- Henry the 8th lost his mother and one of his queens, Jane Seymour, to childbed fever
- It can be caused by a variety of staph and strep bacteria
- Ignaz Semmelweis worked at the Vienna General Hospital in the 1840's
- In 1846, he was appointed assistant to the professor of the maternity clinic, which included two maternity wards
- One ward had a mortality rate of up to 16%, the other only about 2-3% mortality
- Women were well aware of the difference, and often begged on their knees not to be admitted to the more deadly ward
- They actually preferred to give birth in the streets outside the hospital, where the mortality rate was much lower
- And they could still get their medical benefits, by claiming to have been en route to the ward at the time!
- Semmelweis says that:
 - > "To me, it appeared logical that patients who experienced street births would become ill at least as frequently as those who delivered in the clinic...What protected those who delivered outside the clinic from these destructive unknown endemic influences?"
- The big breakthrough came when one of his male medical colleagues died a few days after pricking his finger during an autopsy on a young mother
- His body was riddled with the same type of damage seen in victims of childbed fever

- Semmelweis says:
- “Totally shattered, I brooded over the case with intense emotion until suddenly a thought crossed my mind; at once it became clear to me that childbed fever, the fatal sickness of the newborn and the disease of Professor Kolletschka were one and the same, because they all consist pathologically of the same anatomic changes.”
- The high-mortality ward turned out to be attended by medical students
- Students were going from autopsies on dead mothers directly to the delivery room
- Ignaz was able to show that these students, along with doctors and nurses, were unintentionally spreading the disease
- There must be some particles in the cadavers that were the source of this mysterious disease
- In the days before Pasteur and Koch, he had no real clue as to the cause of the disease
- But he was able to show that deaths were much lower if doctors and nurses disinfected their hands with chlorinated lime
- You’d think that everybody in the world would be lined up to shake his hand
- Well...maybe not to shake his hand, but to wish him well...
- But exactly the opposite was true
- No doctor wanted to admit that he had inadvertently killed hundreds of innocent young women
- Besides, great social unrest and even open rebellion in Vienna at the time (1848) meant that if you wanted to keep your job, you didn’t make waves
- And it didn’t help that his boss believed that diseases were caused by cosmic disharmony, and were therefore beyond human control
- He fired Semmelweis for making waves, and for daring to suggest that doctors and medical students were killing patients
- Ignaz continued his pioneering research elsewhere, but was increasingly ignored or ridiculed by his colleagues and the press
- It’s not all one sided - his growing arrogance, his sloppy experiments, and his unwillingness to share or publish his data until late in life (1861), didn’t help convince his contemporaries

- Even his staunchest supporters drew back as he began to lash out at the indifference of doctors to his results
- In his frequent open letters to his peers he called them ignorant and irresponsible murderers
- He writes:
- “You see, Herr Hofrath, I have deprived your teachings of the basis which you found in the murderous deeds which were committed as a result of your ignorance by the midwives of Wurzburg and its vicinity...I have, in fact, devoted 103 pages of my publication on childbed fever solely to a refutation of all the errors and deceptions which hold you in their spell.”
- He became increasingly unstable, alcoholic, and even perverse, and was finally confined to a mental institution
- He died two weeks later, from an infection following a severe beating, a bitter and broken man at the age of 47
- Despite all his efforts, doctors who don't wash their hands are still a problem today
- Recent studies show that the rate of hand washing is at best 50%!
- Around 2 million people every year end up with hospital acquired infections due to doctors and nurses who don't wash their hands
- Semmelweis, Pasteur and Koch proved the value of the scientific method, breaking with the earlier tradition of case studies and conjecture
- Their objective and analytical approach allowed medicine to finally become a predictive science
- Pasteur's career also reminds us of the serendipity of scientific discovery - he started with sour wine, and ended up with a vaccine for anthrax
- These pioneers of germ theory opened our eyes to an invisible realm
- And along with the realization that microbes were the cause of many human diseases, came a growing awareness that we were engaged in an ongoing evolutionary struggle with these microscopic creatures
- In our next lecture, we'll explore this evolutionary arms race, and learn about the strategies that microbes have evolved to attack us, and the strategies that we've evolved to defend ourselves

- Sadly, one of the casualties of our increasing paranoia about epidemic diseases and dirty hands is a growing reluctance to shake hands with one another
- Shaking hands is one of our most ancient customs – it showed you weren't carrying a weapon
- James Joyce, incidentally, was once approached by a young fan who asked him “May I kiss the hand that wrote Ulysses?”
- To which Joyce replied “No, it did lots of other things too.”...