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OK. So I'm Claudette Gardel. And I am in the instructor of this course. And I've been asked to do the second immunology lecture because Professor Jacks is out of town. So he talked to you on Friday. And he introduced the topic of immunology. And he talked about the cells that one finds in the blood. And these are the cells that are important for immunology. They're responsible for the immune response. And he mentioned, I believe he mentioned mast cells and macrophages and neutrophils and plasma cells and B cells and T cells. And those are really the main players of immunology. He also, no, no, no. He also talked to you about the incredible diversity, incredible, tremendous repertoire of antibodies that we have that recognize variable, based on their variable regions they can recognize a whole slew of antigens. OK? And this is like a graphic depiction of an antibody. This is a hetero-dimer, excuse me, tetramer. And this diversity is a result of gene rearrangement in the variable region of the antibody chains. And so you heard VDJ recombination. So this is at the level of DNA recombination. Similar to the gene rearrangement that occurs in B cells that results in the diversity of antibodies, T cells also have rearrangement for their variable region of their T cell receptors. So we have a population of B cells and T cells that can recognize a wide array of foreign antigens. OK. So this is immunology. This is a topic that makes grown scientists run away. And partly it is because there are so many terms and so much jargon and it just seems so confusing to get it all straight. And it is. There is a lot of jargon. So my goal in this lecture is to try and make you understand conceptually what's going on. OK? And I don't have handouts, but I promise I will put this on, now, this isn't very helpful. But I will put this PowerPoint presentation on the Web. And I have like tried to elucidate the main concepts of immunology, which is so cool. It is like such a cool topic. OK? So we're going to get through this. OK. So what is immunology? It's how we fight infections. And what causes infections? Pathogens. So let's have a look and see what we're up against. This is what we're fighting. OK? There are parasites and funguses, fungi and bacteria and viruses. And they cause a whole slew of diseases. You've heard of some of them, right? Smallpox we've heard of. Influenza. We're going to study AIDS. We talked about polio a little bit. We had cholera perhaps. And tetanus we talked about. And what must every pathogen do to cause disease? They must enter you. They want to live on you. They want to grow on you. You are their food source. So they want to enter you. They want to evade the immune system, which we're about to learn about. They want to colonize and multiply and grow. And then they want to spread to other hosts. That's all they want. Whether you get hurt in the process they don't care. They can cause disease three different ways. Pathogens have basically three main strategies to cause disease. They can cause disease from an extracellular point of view. And so here I've drawn some, could you keep it down? Some epithelial cells. These little spots here are nuclei. The pink represents damage. So these pathogens can cause damage without being in close proximity to the cell. This is usually the result of secreting a toxin. And this occurs with tetanus, anthrax, gangrene. Other pathogens have to be right up close to the cell surface to cause disease. And this is true of the positive agent of cholera. So they get up close and then they can cause damage. And then there are others that are intracellular. They actually get within the cell. And this is true of many bacterial pathogens like chlamydia and the causative agents of tuberculosis. And it's true of every single virus. OK. So we have developed strategies to deal with this. And this strategy goes under the main umbrella called the immune response. And the immune response can be divided into two main parts, innate or nonspecific and/or acquire adaptive and specific. OK. So this slide is actually my summary slide. And it's going to blow you away a little bit, but by the end of the talk you're going to understand it. OK? So we're going to go through it really quickly, you're going to like glaze over, and then we're going to go through it. Oops. What happened? Tom? OK. Oh, that was good. OK. So the innate. The innate response is composed of things that we have all the time, natural barriers to the disease. They're always present, it's a quick response, and it doesn't result in anything long-lived. The acquired or adaptive response takes longer. And it's divided into two kinds, humoral and/or the other kind is cell-mediated or sometimes it's called cellular and sometimes it's called cell-based. This is why immunology is so confusing. Professor Jacks used the word cell-based. And the main players of these, they're going to be shown here. So humoral has macrophages, helper T cells and B cells. The main player of the cell-base is killer T cells. This is the pathway that they work. You're going to learn about this in detail. Lysosome breaks up the antigen into epitopes. It's presented on MHC-2 molecules. In the case of cell-based it's a proteasome that breaks it up into epitopes presented on MHC-1 molecules. And it's presented to the helper T cell by way of its receptor which is associated with CD4 or to the killer T cell which has a T cell receptor with an accessory protein called CD8. The end result of the humoral response, antibodies and memory B cells. The end result of the cell-based response, memory T cells. That's it. OK. So that's what you're going to know by the end of the lecture. Here's the immune response. Excuse me. Here's the innate. We're going to discuss the innate. This is like an exploded diagram of a human sort of. Now, I talked about pathogens and I talked about bacteria being pathogens, but not all bacteria are pathogens. In fact, we are colonized by bacteria. We are colonized by microbes. In fact, they outnumber us. There are ten to the thirteen cells that we have and there are ten to the fourteen bacteria. They live on your skin. They live in our large intestine. And this is a good thing, OK, because they're commensals and they take up space to prevent real professional pathogens from honing in on that space. So commensals are beneficial. Plus we have this thing called skin. Skin is a good barrier. It prevents us from looking like a piece of meat. You know, it's tough. It's thick. It's salty. It has a low pH. It's not exactly 37 degrees. It's a little bit cooler. Pathogens like to be at 37 degrees. It has fatty acids which is sort of anti-microbial. Skin is good, yet some pathogens have evolved systems to get through the skin. For instance, malaria gets in on a mosquito bite. Yersinia pestis, the causative agent of bubonic plague which gets in on a flee bite. OK. So some can get through the skin. And then, of course, there are cuts. The eye is mostly sterile due to lysozyme which is an enzyme that breaks down bacterial cell walls. Your respiratory tract is surprisingly sterile considering there are 500 to 1, 00 microbes per cubic meter of air. And as you're sitting here at rest in 10-250 breathing in about six liters a minute, that translates to about 10, 00 microbes a day. And why is this? But I just told you that your respiratory tract is relatively sterile. And that's because it's lined

with mucus which traps the microbes. And the cells along the respiratory tract have these little cilia that look like little hair-like projectiles. And they're beating up, constantly beating up the microbes. And they get to the back of your throat and you swallow them. OK? So you swallow them. And then the stomach, a sterile environment because of the low pH. There are some microbes that can live in the stomach and they cause ulcers. Small intestine. Is that sterile or not? Nobody knows. It's very sterile. It's a hostile environment. It's full of bile. If you can live there, like vibrio cholerae, you'll be causing disease. The large intestine. Is that sterile? No. No. There are so many bacteria in the large intestine that per gram of feces there's ten to the eleventh bacteria. That's a one with 11 zeros after it. So it's a lot of bacteria. And this is a good thing. E. coli secretes little vitamin K for us and there are commensals. The bladder should be sterile. The kidneys should be sterile. And the flushing action of urine is constantly pushing down microbes that might be wanting to infect us. OK. Within the blood there are also some innate components. One of them is the complement system. The complement system is a series of serum proteins that can recognize nonspecifically many different bacterial pathogens. And they come, and it's an enzymatic cascade, and they land on the surface of the bacteria. And then they can either recruit other members of the immune system or they can actually physically drill a hole in the bacteria and then kill it like a little oil rig. And then there are macrophages which I like to abbreviate this way, macrophage. Macrophages are white blood cells that engulf, they swallow, they phagocitize. Phago means to eat. Macro means a lot. They eat a lot, and they eat nonspecifically. They just swallow and take things away nonspecifically. There are also interferons, a component of the innate response. And that's interesting in that when a cell is infected with a virus sometimes it will secrete. And it knows it's infected. Sometimes it knows it's infected, and sometimes it has the ability to secrete interferon. And there are other cells that have receptors for interferon. And when it's through a signal transduction mediated pathway they go into an anti-virus state and they stop making protein and they start cutting away RNAs. And so, actually, some of the bad feelings that we have when we have flu is not really the flu virus. It's the result of interferons being globally secreted in our body and our cells sort of shutting down. OK. So here's the inflammatory response. OK? And here we have a splinter. This is a piece of wood coming in and look. Oh, look, it's coated with little bacteria. OK? And, actually, this experiment was done by Mesnekoff many, many years ago where he took a splinter and he put it in a starfish leg. Leg? You know, one of those little projectiles of the starfish. And he looked. And he saw these cells trying to engulf, actually trying to engulf the wood. And that turned out to be the macrophage. OK? So he was actually the first person who discovered the macrophage. So here we see the splinter penetrating the dermis. And these cells here are called mast cells. And they're full of vesicles that secrete histamines. And the histamines cause the blood vessel that's underlying to become more permeable such that the macrophages and neutrophils, phagocytes can come to the area and swallow the bacteria. So this is histamine, these are the macrophages that are coming and swallowing. And also you can see these little red dots are complement. Those are the serum proteins that will come and land nonspecifically on bacteria and lyse them. And the macrophage will also secrete something we call cytokines. Cytokines are signaling molecules that immune cells use. And there is a whole array of cytokines and they have a whole different variety of affects. Some cytokines have global affects upon us. They cause us to have fever and not feel too well. OK. So after the infection you'll notice the macrophage is swallowing a dead, infected cell. They clean up. And then these cells with grow and will be repaired. So this is the inflammatory response. The hallmark is redness and swelling and heat. So now let's discuss the acquired response. The acquired takes longer. There was the humoral cell-mediated. The end result of the humoral response are antibodies and memory B cells. The end response of cell-mediated are killer T cells. We're going to talk about the humoral response right now. And I'm going to give you an example of a disease. This is vibrio cholerae. It's a bacterium that causes cholera. There are some places in the world where some people get cholera. And this person is suffering. And the doctor has squeezed her skin, and you can still see that the skin is upright because she is severely dehydrated. The disease is marked by severe diarrhea that can lead to death within hours. And they measure -- What they do to treat cholera is they measure the amount of diarrhea that happens, and that is the exact amount that they replace in fluids. The lifecycle of the bacterium is shown here. You ingest contaminated food or water. The bacteria get through the low pH of the stomach. They swim through the mucus gel overlying the small intestine epithelial cells at which point they adhere. And they start to elaborate cholera toxin and other factors that allow them to colonize and multiply. It's the action of cholera toxin which causes the severe diarrhea, and it releases the vibrios into the environment and the cycle continues. And some of you had in your signal transduction the action of cholera toxin where it like turns on the alpha protein in the intestinal cell causing high levels of cyclic AMP which results in chloride ions and salt followed by water going into the lumen of the small intestine. A person can die in as little as eight hours due to the action of the toxin, and yet it's absolutely treatable with oral hydration. And yet still 50,000 people die each year because it can take up to 40 liters of liquids to restore hydration. And sometimes it takes place in areas where there's not water or for some reason small babies cannot take in the water. Without treatment 70% will die. With treatment less than 1% will die. Now, there are some places in the world where cholera is endemic. People get it and they get treated with oral rehydration. And once you get it you don't get it again. You will have developed long-lived immunity to cholera. And this long-lived immunity is a result of the humoral response. So the next slide will show you the two key members, actually three key members of the humoral response dealing with a pathogen. So here we have a macrophage, here we have a B cell. And look, this little red dot could be a pathogen, it could be an antigen, and it's about to be engulfed by the macrophage and it's about to be recognized on the surface, it's about to be recognized by the variable region of the antibody which is on the surface of this B cell. This is the B cell. This is macrophage. OK. So the macrophage swallows it and it goes into an endosome. It endocytosis it or phagocytosis. It could be a phagosome or an endosome it's called. The B cell does exactly the same thing. It brings it in on the antibody. And so it's also in an endosome or phagosome. And see this little circle here? That's a lysosome. Do you remember lysosome? We had them early. This is not lysozyme which is the enzyme that's in the tears that break down cell walls. No. This is an organelle that is found in cells, and it's full of degradative enzymes.

proteases, nucleases, lipases. And it just fuses with the phagosome and chews it up into little itty bitty pieces. And these little itty bitty pieces are loaded onto these molecules called MHC class II molecules. And they display little eight or nine amino acid snippets of what was just chewed up. The only two cells in the body that make MHC-2 molecules are the macrophages and the B cells. And who are they displaying it to? Well, there's this third cell right here. It's the helper T cell. And the helper T cell recognizes the MHC-2 class molecule in conjunction with the epitope by virtue of its T cell receptor. OK. And here are some helper T cells. Here's either a macrophage or a B cell. This sort of looks like a B cell. It's an antigen presenting cell of which there are only two kinds, B cells and macrophages, and they have MHC class II. OK. Here's another way of looking at it, pathogen engulf. There's the phagosome or endosome. It looks like the lysosome is already fused. It's broken up into little fragments. Peptide fragments are called epitopes. They're loaded onto MCH class II molecules. Presented to the helper T cell. And now, look, here's the T cell receptor. It has an accessory protein. The helper T cell receptor's accessory protein is called CD4. OK. So, now, remember the helper T cell is going to bind to the macrophage? And it's going to -- Only if it recognizes the epitope in conjunction with MHC-2. And should that happen the macrophage sends out some cytokines, special cytokines that causes the helper T cell to also send out cytokines to itself and causes it to clonally expand. OK? So many more of these helper T cells are around. So here we go. It's found the macrophage. It becomes activated. It becomes in an activated state. It clonally expands but it still remains in its sort of activated state. And should it encounter a B cell that has swallowed the exact same antigen or pathogen and is displaying the exact same epitope then it causes the B cell to do something through the action of cytokines. So here it's finding the B cell. It has the exact same epitope. And it sends these cytokines and it causes the B cell to clonally expand into memory B cells and also to differentiate into plasma B cells that are now secreting the antibody that originally recognized the surface of the bacterium or the antigen. And now these are now being secreted into the blood or wherever they are. OK. Here it is again, helper T cell recognizes the B cell, sends a signal, clonal expansion. The ones where the antibodies remain on the surface are called memory cells. Now they're in greater abundance. Some of them differentiate into these cells that have lots of endoplasmic reticulum because they're synthesizing a secreted protein. Now it's secreted and it's called antibody. So we've got all these secreted antibodies and all these memory T cells, excuse me, B cells. And this is the reason why the secondary response is greater. OK? So the first time you encounter a pathogen or an antigen it takes a while and it's not as great the magnitude of antibodies. But the second time, because we have all those extra memory cells around, it's much quicker and it's also a greater magnitude. Now, if some of you were observing that there are these things called IgM and IgG. Well, this refers to different classes of antibodies. And there are different classes. IgM are the ones that are sort of on the surface of the B cells. They're sort of still tethered at some point. And then as they become plasma cells they actually have secreted antibodies. And there are different classes depending upon what fluids the antibodies will be found in. For instance, IgG is the predominant antibody found in the blood. IgA is found in some mucouses and tears and mother's milk. So babies don't have any immune system, but if they're nursed they get the IgA from their mother. And, actually, it goes into their small intestine and just goes right across into their bloodstream. So it actually helps them because it takes the babies a while to develop antibody-making systems. IgE is an antibody that has been implicated in allergic responses. Do you remember the mast cells that have those ready pockets of histamine ready to like secrete out and cause like a ray of affects? Well, they also have receptors for IgE. And so some of us have allergies, right? And when we have allergies we develop IgE to ragweed or cat dander. And as a result, if we're exposed to this antigen we can have this reaction involving IgE in mast cells resulting in histamine release. And if it's very bad then it can actually result in anaphylactic shock. OK. So antibodies, you know, we have a whole production of antibodies made. But how do they actually fight disease? What do they do? So we've got them floating in our blood? How do they rid ourselves of the infection? Well, they do it three ways. OK. Remember vibrio cholerae? It wants to get to the intestinal epithelium to cause disease. Here's a bacterium here. Here are antibodies that are specific to the surface of vibrio cholerae, this bacterium here. It is coated with this furriness of antibodies. Can it touch the tissue? No it cannot. It is sterically hindered from getting to its surface. And this would be true of a toxin, too, of a toxin, a protein toxin. A toxin is coated with antibodies. It cannot get to a receptor and cause ill effects. OK. So now we've got these antigens and bacteria and they're coated with antibodies. Opsonization. This is derived from a Greek word which means seasoning on food like salt and pepper. So here's a pathogen. It's coated with antibodies. In comes a macrophage and swallows it up. Now, the macrophage would devour this thing anyway without the antibodies. But it might be slower. It might be a little pokey. When you have -- It's like seasoning on food. When you have antibodies it's going to do it voraciously. And why is that? It's because the variable region binds to the bacterium or the pathogen or the antigen. What's sticking out is the constant region of the antibody. No matter what's on the variable region the constant region is the same. So the macrophages have receptors that recognize this constant region and they zip it up and they swallow it. Likewise antibody triggers the complement system, so although the complement system might come in slowly, when it sees antibodies bound to a bacterium it comes in and it does its little oil drill thing instantly. OK. So that's how antibodies prevent disease. Here's a picture of the macrophage with its receptors. This end of the molecule of the antibody is called FC. So the receptor is called the FC receptor. And it just coats it and brings it in and ingests it. OK. So we've got antibodies as a result of the humoral response. Would they be affective in preventing a toxin from binding to a surface if we had antibodies against that toxin? You bet. It's very good for pathogens that cause extracellular disease away from the cell. It's very good for toxins, extremely good. What about preventing cholera again? Can it prevent a pathogen from binding to a surface, an adherent bacterium? Yes. We just showed you it did. Sterical hindrance. But what about the case of viruses or other things that are intracellular, that cause disease from within, would antibodies be effective there? Only if they were caught before they got in. But once they're in they're protected from macrophages. They're protected from antibodies. They're in a nice, warm, nutrient-rich environment. They're looking pretty good. And many professional pathogens have opted for this tact. So what we've done is we've developed the other wing of the immune system called cell-

have opted for this task. So what we've done is we've developed the other thing of the immune system called cell-mediated to deal with intracellular pathogens. And these are the stars of the cell-mediated or cell-based or cellular system. And they are called killer T cells. And they are the coolest cell in your body. They're like the Terminator, you know, Arnold Schwarzenegger, the Terminator. And so they go around and they like will protect us. So let's show you this. OK. This thing that looks like a suitcase is my drawing of let's say an epithelial cell that has been like sandblasted away. OK? One side of it is sandblasted away so we can look in. Oh, look, there's its nucleus and there's its endoplasmic reticulum. And what are these things on the surface of the cell? Well, it's called MHC class I molecule and it's presenting and epitope of eight to nine amino acids. All nucleated cells in the body. Every cell in your body that has a nucleus is presenting MHC class I molecules on their surface, presenting epitopes on MHC class I. And where did these epitopes come from? They come from proteins that are found in the cytoplasm. At some point routinely proteins are channeled through this organelle called a proteasome. They get threaded through and they get broken up into eight or nine amino acid snippets, and they get loaded onto MHC class I molecules in their final stages of being transported to the membrane. And who are they presenting, these MHC class I molecules to? They're presenting them to killer T cells by way of the T cell receptor. Now, although most of the epitopes that are presented on these MHC class I molecules are derived from your own proteins, host proteins. Any killer T cell that could have recognized a host protein, in conjunction with the MHC-1 molecule, has been eliminated early in development. Early in development if there is recognition. That killer T cell has been targeted for apoptosis and dies. And this is true with B cells, too. So if they have an antibody on their surface that can recognize a self protein they are eliminated. And this is called clonal deletion. So what is left in our blood are only killer T cells that can recognize foreign epitopes in conjunction with the MHC class I molecule. And so if the cell is infected, and it is because I drew in these chlamydia, and if some of these proteins are chlamydia proteins and they are being presented on these MHC class I molecules, and the right killer T cell with the receptor that comes by and recognizes it, if recognition occurs two things happen. OK. Here's the killer T cell. Here's the MHC-1 with the chlamydia epitope or a pathogenic epitope. A foreign epitope sitting right there. The killer T cell says oh, my God. We have a cell that's infected. Maybe there are other cells that are infected. I've got to make more of me. And it clonally expands to make more of itself with the exact same T cell receptor that's going to recognize this epitope. It also punches a whole in the cell using perforin. It secretes this thing called perforin. It punches a hole in the cell. And if that's not good enough, it also secretes something called granzyme B which causes this cell to undergo apoptosis. So it like double kills it. OK? And here's like another picture of it. So here's the virus. The proteins are loaded onto MHC class I molecules. The killer T cell recognizes it by way of its T cell receptor. And its successor protein is CD8. OK. Here's the infected cell. Here is the killer T cell. There's the CD8. This is perforin which is going to puncture a hole in the infected cell. It figures it better kill this cell now and save the rest of the body. It decides to sacrifice the infected cell. And here's granzyme that causes apoptosis. And this cell then ends up looking like this with holes punched in it, cytoplasm streaming away and starts to undergo apoptosis. And it makes more of itself. So you end up with an army of memory killer T cells that are going to recognize this exact pathogenic epitope. Here's a killer T cell. Here's an infected cell. And here's a movie. Remember I said Terminator, right? OK. There's the T cell. There's the cytoplasm streaming away. And look it. It just keeps going. It doesn't stop. It just keeps going. Punching away. Wasn't that awesome? Let's do it again. OK. That is so cool. Yup. OK. And they're on our side, you know. This is the army we have going in our blood. It's just awesome. It's just awesome. OK. OK. So this is the T cell receptor. This is found in both helper T cells and killer T cells. Notice it has a variable region. Early in its development the T cell precursor actually has both CD4 and CD8. And it's immature at this point. It doesn't know what it is yet. It has both. And then as it develops it has only one left. So if it remains with the CD4 it is a helper T cell. If it has a CD8 in its final differentiated state it is a killer T cell. And it's this accessory protein that, actually that's it, that's what causes it. And so if we look up close and personal at an MHC receptor, this could be MHC-1 or MHC-2. This accessory protein could be CD4, CD8. So if it's MHC-1 the accessory protein is CD8. If it's MHC-2 the accessory protein that fits MHC class II would be CD4. So now I'm hoping that this will become a little bit more clear for you. So the innate response had lysozyme, the mucus, ciliary ladder, skin and complement, and macrophages and mast cells. It doesn't last very long. And it's really not completely effective in, you know. It wouldn't really work that alone. We'd need the acquired and adaptive response which takes a couple of weeks the first time. And so the humoral response and the cell-mediated or cellular or cell-based response. The humoral response has the macrophage that first engulfs the antigen and the B cell that recognizes the antigen through its specific tethered on its surface antibodies. Both of them engulf it, break it down and present to the helper T cell. The cell-based response involves killer T cells. So inside the macrophage and the B cell a lysosome comes over, it fuses with the endosome, breaks it into epitopes which get loaded on MHC class II molecules. Inside every nucleated cell in our body we have a proteasome that is breaking anything that's found in the cytoplasm onto epitopes. And if the cell is infected those are going to get broken into epitopes and loaded on MHC-1 molecule to be hunted down by killer T cells. This is recognized by a T cell receptor with an accessory protein CD4. This one's recognized by a T cell receptor with an accessory protein that's CD8. See, it's not so hard, right? It seems a little bit wordy, but conceptually -- So the T cell causes the blood, the B cell to clonally expand. Some of them become plasma cells which secrete antibodies. Some of them become long-lived memory B cells. The killer T cell, recognizing an infected cell, will secrete perforin to punch holes in it, granzyme B to kill it through apoptosis. And it also creates lines of memory killer T cells such that the next time we see the same pathogen, if any, we're ready. OK. So, now, if we didn't have the mechanism to make antibodies or T cell receptors, what if we only had the innate response? And there are people who don't have the acquired or adaptive response. Oh, excuse me. These are other terms. And they're called the Ã¬bubble boyÃ®. Have you heard of the bubble boy? They have to live inside a bubble, basically a plastic shell that's completely sterile. They either don't have B or T cells or they don't have any antibody or T cell variation. And so the innate response is not quite good enough. And so, on the other hand, sometimes you can have an overactive immune response. For instance, you could have killer T cells or even antibodies that recognize or start to recognize host

response. For instance, you could have killer T cells or even antibodies that recognize or start to recognize host proteins. And this happens. And the end result of this is autoimmune disease. So here's an example of an autoimmune disease that's caused by killer T cells that have now started to recognize beta cells in the pancreas as being infected and they kill them. And the beta cells in the pancreas are cells that respond to levels of glucose in your blood. So you have like a candy bar, you eat a meal, there are high levels of glucose in your blood. The beta cells secrete insulin so that your entire body, the cells in your body will make glucose receptors to take that glucose out of the blood and utilize it. So if you don't have beta cells because they've been killed by the killer T cells you don't make insulin and you get diabetes. Let's see. What other autoimmune diseases? Lupus is an autoimmune disease. Sometimes you can have antibodies that recognize the myelin sheath, the cells that make up the myelin sheath, and then those cells are destroyed. And that results in multiple sclerosis. So these are autoimmune diseases, when the immune system goes wild or goes bad. OK. So I've just sort of built up the immune system as being really great and wonderful. But some of you might have questions and some of you are thinking, well, you know, gee, I've had the flu twice. My roommate has had strep throat a couple of times. What gives? What's with this secondary response, this acquired response? Well, pathogens, some pathogens, it's an ongoing war, have developed strategies to overcome our immune system. And that's why we use antibiotics to kill them sometimes. OK? And they're nasty, you know, and they grow fast and they mutate. And they can develop ways of getting around our immune system. For instance, this is a picture of Bacillus anthracis. It has developed this enormous polysaccharide capsule that absolutely prevents it from being phagocytosed by macrophages. Without the capsule it is absolutely harmless. It absolutely requires the capsule to cause disease, as well as a toxin. That's the only thing it needs, a toxin that is on a plasmid and in a capsule. Or, let's say we develop antibodies to neisseria gonorrhea, or we develop antibodies to malaria. What they do, these pathogens, some of them very clever ones, is they say OK, antibodies are recognizing things on my surface. I know. I'll just change my surface. And they'll change their surface. They'll put up a different protein for phase variation or they'll mutate. And the antibodies are so specific that they cannot recognize this mutated protein, and it's like we're getting it again for the first time. And this actually happens with cholera. So in places where it's endemic, people get it once, they develop long-term resistance, and then 20 to 40 years suddenly adults start getting cholera again. Actually, I'm not even sure it happens that quickly. The last one happened in the late 1990s where it just started wiping out adults. And so whole clinics had to be developed in town squares for oral rehydration. And what had happened was that the bacterium, the vibrio cholerae bacterium changed one sugar residue on its surface. Just one little sugar changes. A fructose turned into a mannose, right? And that was it, because that was what the antibody recognized. So now new antibodies have to be made to that one so people will get it twice. There are some bacteria that make proteases that are designed to cut our antibodies in half. So horrible. So they just go in there and they just secrete these proteases, and the antibodies have just like degraded. Let's see. Some pathogens can survive phagocytosis. They send out little messages that prevent the lysosome from coming over, and they live in the phagosome. And, oh, I'm going to be leaving you on a sad note, ha? But, all right, do we have any questions? Do we have any questions? No? Perfectly clear? OK. You can go.