>> Today, all day, October 25, this is lecture 19 in Phys, and we're setting the circulatory system aside for a bit, and talking about a system which is not so much an organ system, but a broad, protective mechanism for your protection. Essentially defense mechanisms in your body. It's amazing to think that bacteria outnumber your cells by a factor of 10. That means on or in your body, there are more bacteria than there are your cells. In short, bacteria are everywhere, and they are, well, infectious for the most part. And it is amazing then that we survive, and we do because of these mechanisms. Not a singular mechanism, but a cooperation of many somewhat independent although somewhat overlapping defense mechanisms. So classically, these mechanisms are divided into two camps, two groups. First, the so-called nonspecific defenses, and then followed up and backed up by what are called specific defenses. A nonspecific defense is a generic kind of response. In other words, these defenses that we are about to list do not, cannot recognize specific foreign cells. They react the same way to any intruder. I like to compare these to a burglar alarm, or a fence around your property. Does a burglar alarm know the difference between a burglar and grandma? Reacts the same way to any intruder. And so does a fence. A fence doesn't really discriminate or identify intruders, it behaves the same way to any potential threat. So what are these in the order of their encounter? The first and most successful of these is the skin and mucous membranes. This is a physical, chemical barrier to infection. And it works pretty good. But does it work without exception? Is it perfect? No. Can the skin be broken down? Can this barrier be breached? Yes. But when we deal with intact skin, it's pretty good. It is designed to provide a physical or chemical barrier to infection. Quite often, as a result of injury or disease, it does fail. And typically that is the result of a wound, W-O-U-N-D, some kind of cut, or abrasion. Next, then, phagocytosis will essentially take over. Phagocytosis involves mainly non–I should say granular leukocytes which arrive in the vicinity of a wound, specifically and mainly neutrophils. And phagocytosis, as you know, is the consumption, the destruction of foreign microbes, often with great casualty. That is, a great many neutrophils succumb to this effort. And what we see as a result of this battle, is pus. We think of pus as infectious, but it is actually just a combination of dead white blood cells, and the bacteria that they have destroyed. So, in short, phagocytosis is evidence, evidence of a battle between those cells that are phagocytotic, specifically, granular leukocytes and macrophages. Does this get the job done? Does phagocytosis always succeed or nip the infection in the bud? No. Not always. And so what is next? Or what might occur even simultaneously is inflammation. We think of inflammation as a disease. It's not. We think of inflammation as bad. It's not. Inflammation is redness, pain, and swelling, in the area of an injury or wound, and even though it's not fun, even though it's painful, it's really a sign of an effort to eradicate an infectious threat. Essentially, basophils on the scene release histamine, which you know mediates pain, but also sets in motion vasodilation and edema. Edema means swelling in the area and in fact, swelling and inflammation are practically synonymous terms. But what good is all of that? The vasodilation and the swelling tends to slow the physical spread of the infectious agents. It keeps them confined to the

area. And the histamines and other vasodilators also improve extra vascular phagocytosis. In other words, if the capillaries are made more permeable, now some of the macrophages can leak into the interstitial spaces, so this provides better access. Better access for this process of extracellular phagocytosis. And incidentally it also allows antibodies, which we will discuss shortly to infiltrate the area too. So even though this is painful, even though it's unpleasant, even though we go to great limits to do what? When we see inflammation, what is our natural tendency or desire? Reduce the inflammation, because it hurts. But keep in mind, it's a natural defense mechanism, and it really is an indication of an effort in your behalf. And so is item D. Fever is not a disease. And at least in small ways fever is not particularly life-threatening. We know that fever is an increase in body temperature, and you might wonder, how can that be good? Well, basically fever is the result of agents that are released in an infectious response. These are called today interleukin-1. They used to be called pyrogens, which actually I like better, but anyway, these pyrogens, or interleukins stimulate the hypothalamus and cause the body temperature to rise. Now, how is that helpful? Certainly not fun. It's not pleasant. A fever is very uncomfortable. But this tends to raise the metabolic rate of all of your cells. It helps in a better response to heal or recover from an infection and remember, fever, high body temperature tends to denature enzymes, and that can act on the bacteria and reduce their levels too. But, please don't get me wrong, is a prolonged fever potentially dangerous? Yes. Because it can, indeed, cause harm especially as it denatures your own enzymes. So a little bit of fever is good. A lot of fever is not so good. But even a fever is not always successful in this first line of defense. And so the last ingredient, the last response that can be considered nonspecific, are compounds called interferons. Interferons are biological proteins which are produced and released where? From viral infected cells. When your cells become infected with a virus, they produce interferons, which leak out of the area, and essentially enhance, that means alert and activate NK cells. And these same compounds also stimulate, they basically alert nearby host cells, and gets them busy to produce antiviral enzymes. So, the message here is interferons are more of a signal. They signal the arrival of a virus, and they prepare the NK cells, and they prepare your healthy cells for an imminent battle. That is, they help stimulate healthy cells to begin the process of synthesizing antiviral enzymes. So there is our list of what? Nonspecific defenses. And in their entirety, we can describe these as the first line of defense. These are the ones that are the first responders. And they react generically and uniformly to any threat. Remember, they don't recognize specific foreign cells. Are these sometimes enough? Do these sometimes succeed? Absolutely. But do they always? No. So, if all of these are the first line of defense, what is the second line of defense? Actually quite impressive, quite elaborate, and the name, of course, suggests that these are surgical. That is, very precise. These are specific defenses that have the ability to actually distinguish your cells from anything that is not yours. They recognize self from non-self cells. I like to compare this to the big guns which have smart bullets. Now, of course, unfortunately there are no guns that have smart bullets. But if there was such a gun, what would a smart bullet be? A

smart–go with this, a smart bullet would go out there, and would go around what? The good guys, and what? Hit the bad guys. That would be a smart bullet, right? And so that is kind of the analogy here. Because specific defenses recognize the good guys from the bad guys. And how does that–how does that work? Well, we are about to see. And essentially, these mechanisms are spoken of as immune mechanisms. The word immune means to be exempt, and these are mechanisms that make you exempt, or at least give you great resistance to diseases which is, of course, can often overwhelm the nonspecific defenses. So, if this approach recognizes self from non-self, how is that done? Well, essentially it is done by the presence of identifying molecules found on all cells called antigens. And so your immune system is able to recognize, and in ways that we'll see destroy, foreign macromolecules by cellular or chemical means. These macromolecules are otherwise known as antigens, and a further definition, an antigen is simply a specific protein that provides identity and located on the surfaces or cell membranes of all cells. So what I've just said is, all of us have a different profile of what? Antigens. And that allows our body to be recognized as distinct from others. Not unlike a license plate on a vehicle. Supposed to identify that, right? And are there two license plates that are the same? No. So can we tell one vehicle from another based on that license plate? Yes. And so all of our cells have a profile of antigens which identify us from others. The only exception to that statement is if you have an identical twin. If you have an identical twin, then there are two people on the planet that have the same antigens. And are in effect the same person. But with that exception, all of us have a different profile of antigens, and it is based on these antigens that this system is able to tell you from something that is not you. And remember, antigens don't just apply to human beings. They apply to animals, and infectious agents, including bacteria and other pathogens. So, the function of an antigen, then, is to help establish a way to recognize self from non-self, and so establishes identity. And these antigens, then, provide a way to trigger or initiate or begin the immune responses that we are about to talk about. At least in many cases the immune responses to antigens, which are found on all living cells, is created by the production of these proteins called antibodies. Now, let's be clear. Antibodies are not antibiotics. Antibiotics are drugs that you buy at a drugstore. Antibodies are specific proteins manufactured by your immune system, and these are also known as immunoglobins. IG. They are synthesized on demand to combine with specific antigens, and therefore, bring about a clumping, that means a sticking together, of cells that bear foreign antigens, and therefore, make these foreign cells more approachable, more easily eradicated by phagocytosis. Here is a statement that you will hear, which is false. You will hear people say antibodies kill antigens. Or you will hear people say antibodies kill cells. Antibodies don't kill anything. They certainly don't kill antigens. Because what is an antigen? An antigen is just a protein attached to a cell. So let's not use the word kill. Essentially, these antibodies attach to antigens, very much like substrates attach to a–substrates attach to enzymes. And it is a kind of geometric recognition there. But the attachment of an antibody to an antigen doesn't kill the antigen, because the antigen is not alive.

The antigen is just a part of a cell which has been recognized as non-self. Turns out there are five classes of antibodies. We are not going to get to them all. You may cover many of these in microbiology. The two that matter for human physiology, at least in this context, are IGM and IGG. These are major classes of immunoglobins. Their function, again, is to attach to foreign antigens. And therefore, bring about a clumping of these foreign cells, which makes them more amenable to phagocytosis and destruction. Now, this establishment, this ability to recognize self from non-self, actually occurs before birth, which is amazing, because before birth you were in a sterile environment, which had no threat from outside invaders. But on the day of your birth, your immune system is ready to go. It has the ability to recognize you from non-you, and so when this system is functional, you're said to be immunocompetent. And when it is dysfunctional, a couple of terms or references are often used. One is immunodeficiency. Another is autoimmunity. Very different. So let's pause. Immunodeficiency is what it sounds like. It's a deficiency of immunity. And certainly one classic acronym comes into mind. What is AIDS? Acquired Immune Deficiency Syndrome. So that is a classic case of immunodeficiency. Which puts you in jeopardy of massive infection, perhaps death. Not to be confused with autoimmunity which is a strange combination of words. Auto means self. So what's the literal translation? Self-immunity. This is actually a bizarre and unfortunate situation where your body produces antibodies to who? Produces antibodies to your own cells. A complete and total chaotic series of events. And this is exemplified in such things as myasthenia gravis, multiple sclerosis, and others. Lupus. And these diseases are really defects of the immune system, which are hard to deal with, because in these cases, of course, your body is attacking your own cells. But all of us would certainly enjoy and appreciate the importance, then of immunocompetence, which means you have the ability to manufacture antibodies in response to foreign antigens. But that is a statement. How does it get done? What are the methods? What are the sequences that occur to bring about the production of antibodies? The important thing to say up front is that antibodies are not made just willy nilly. Antibodies are made only in response to some triggering event. You don't make antibodies to a particular disease until you're exposed to that disease. At least not naturally. So what are the steps in this process of antibody mediated immunity? The process means making antibodies in response to invading microbes. And the assumption is that these microbes have breached what defenses? What defenses have to be surpassed before this even comes into play? All the nonspecific. So again, this is plan B. This is the second line of defense, which steps in when invading microbes have breached that first series of defenses. And so we assume the arrival of microbes. Let's say bacteria. And usually they gain access to your body not through the circulatory system, but they get into the lymphatic system. Because when you have a wound, you're bleeding, right? Blood is coming out. And that in itself helps to eliminate, or at least retard the entry of bacteria. But the lymphatic system has a negative pressure, meaning more or less inviting bacteria in, and as you know from anatomy, the lymphatic system consists of lymphatic capillaries and lymph vessels, which eventually arrive at these bean-like structures called

lymph nodes, lymph nodes located strategically in the axillary area, neck, groin, and so forth. So basically by one means or another, bacteria arrive in a lymph organ, more often than not, a lymph node. And what's waiting there? What's there to greet these foreign bacteria? Basically we have specific B cells. B cells which are hanging out there, and these bacteria will be dealt with, that is, a certain degree of phagocytosis will occur, and the microbial antigen, which is that protein on the surface of those bacteria, that protein will be incorporated, that is, welcomed by the specific B cells, and specific B cells will begin to multiply. The word is mitosis. Not all B cells react, but those that are pre-programmed to produce the opposing antibody to that antigen. So essentially, this arriving antigen, this microbe, with the antigen, will stimulate a certain subset, a certain population of B cells, which is called a clone, and will cause them to multiply. And once these specific B cells have been activated, well, they are now called activated B cells. And they will be then converted. That is, they will be transformed into one of two types of active cells at this point. They're transformed into plasma cells, or memory cells. One of the two. Plasma cells are basically antibody factories, and they crank out, at least in the beginning, a class of antibodies called IGM. If these cells are exposed a second time to the same microbe, weeks, months, or even years later, they crank out a different kind of antibody called IGG. This occurs in the second response. So let's put this on a timeline, because it's interesting and important. Vertical axis is simply the production and concentration of a given antibody. Horizontal axis, we see time. But notice, we're not talking hours. We are talking days. So here, at the zero mark, is the first exposure. That means the arrival of these microbes. And we're plotting the production. The presence, the concentration of antibodies in the blood. Now, what is interesting about this is that it doesn't really occur that quickly. Look at this graph. How long does it take for any antibodies to really show up? What is the time lag between exposure and the presence of any of these antibodies? It's almost what? Seven days. And that should be scary. And it is. Because it means the first week you're really not putting out much in the way of defense. In short, this antibody response is sometimes too little and too late. And therefore, you can certainly get very sick. Maybe even die. And as if that weren't bad enough, even though the antibodies do peak at let's say two weeks, unless you're exposed again, what happens to those antibodies is they basically disappear. So this response is slow and temporary and you could say, therefore, pretty weak. But what if you're exposed to that same antigen a second time? Whether sooner or later, a whole different response occurs. Because remember, in the first response, not only did you get plasma cells, but you also had this second subset called memory cells. And it's a pretty decent name, because a memory cell obviously has some memory, meaning it remembers these microbes. These memory cells remain dormant. That is, they don't crank out antibodies until the second exposure. And then they not only produce IGM, but also IGG, and notice, the IGG stays high for months, years, maybe a lifetime. So clearly this second response reinforces and reacts quicker and often provides immunity or at least antibody levels for a considerable period of time. In fact, the second response is not always something you want to wait for. And what I mean is,

today's medicine, the second response is actually artificially induced in the form of vaccine. And we will talk about vaccines in a minute. But certainly you've heard the notion I need to get a booster, I need to get a second vaccination. Because that second exposure provides a much more long-lasting level of these antibodies than the first. So what's next? I mean, we've got these antibodies, but remember, how do they actually provide for health? Item 5, then, these antibodies, attach. Notice the word, it's attach, not attack. They attach to foreign cells that bear what? There is a foreign cell. It has a foreign antigen. The antibodies attach to that antigen, and therefore, they flag that cell. We could say they mark that cell, so that it's easy to see, easy to identify, easy to eliminate through phagocytosis. Sometimes you're driving down the road, and you'll see a car abandoned, and it has got a sticker on it, from the CHP or something, you know what I mean? So that's what I mean by marking it. The antibody attaches to the antigen, and that marks that cells as a target. It basically puts a target on its back, so that the NK cells can see it, and eliminate it. And that is the final conclusion to this process. A conclusion that will bring about some resolution to the infection. Here is a diagram from your textbook. You can find it elsewhere of course. And before we discuss it entirely, it's clear, or should be clear that there are two mechanisms here. Right here is the center. Everything to the left of center is what we've been talking about. Antibody mediated immunity. Everything to the right of center, we're about to discuss something called cell mediated immunity. So here, we have macrophages. Which have, of course, encountered these microbes in the lymph node. And these little green or yellow shapes are the antigens, which are passed over to these B cells. And remember, the B cells then evolve into one of two types. What were the two types that come from activated B cells? Plasma cells and memory cells. Plasma cells crank out antibodies right away. That is the good news. The bad news is these antibodies don't persist, and so a second exposure activates the so-called memory cells, which cranks out a different family of antibodies for a long period of time. So, to repeat, everything from the left of center here is a diagram of antibody mediated immunity. And this is all predicated on the arrival of a foreign antigen, which is on board, or part of an infectious microbe. Very specific, that means reacting to a specific microbe by producing a specific antibody against that microbe's antigen. Now, the second kind of specific defense is called cell mediated. The first one was called antibody mediated. This is called cell mediated. And this uses a different type of approach. Not B cells, but T cells. T cells basically mount an attack, especially this time, against intracellular microbes. Now, we need to make that distinction. A microbe is a microbe, meaning a small organism. But intracellular microbe means that we're dealing with one that occupies the interior of your cells, and we're talking virus. An extracellular microbe is basically families of bacteria. So this approach is directed not to extracellular, but intracellular microbes. But many of the steps will seem similar, and will certainly involve, once again, phagocytosis, from the very beginning. So in chronological order, here is what happens. Once again, the microbe gets past what? What does it have to overcome or get through? The non-specific defenses. Then it finds its way to lymph nodes, where it is greeted by–greeted

by macrophages, which begin to phagocytize, that is, essentially attack and destroy these cells, and releasing and utilizing the antigen. These cells, these macrophages, sometimes also B cells, are called antigen-presenting cells. A, P, C. Antigen presenting cells. And they present this antigen to specific T cells that are in the vicinity. This is kind of like, kind of like, taking an automobile, and beating the hell out of it, destroying it, and then taking the what? License plate, and handing it over to the cops. Okay, crude analogy but it works for me. So what's been done here, we've phagocytized this invader. But we picked apart, and essentially saved the antigen, and handed that over to T cells. It's like saying "here you go," and what do the T cells do? They process this antigen. That is, they analyze, and eventually they, the T cells, become activated, stimulated, and mobilize into two types of cells that get going. First are the cytotoxic T cells. Cytotoxic T cells used to be just regular T cells, but now they've been sort of promoted. Kind of the seal team here. And what do they do? They mosey out, that is, they survey or otherwise comb the body, and they chemically recognize, I should say they recognize and chemically destroy viral infected cells. That is, your cells that have been infected with a virus. Which is an amazing feat, if you really get down to the science of it, because it's must like a SWAT team going into a neighborhood where there is supposed to be a bad guy. I mean, how does the SWAT team know where the bad guy is? Are we just going to blow up the whole neighborhood? How do they recognize where the bad guys are? They recognize cells that are infected, because those bear what? The foreign antigens. The interesting thing is when a virus infects a cell, it leaves its antigen on the doorstep. So how do these cytotoxic cells know that those cells are infected? Because of the presence of the foreign antigen. So this is very surgical. Meaning, it destroys those cells that are infected, but not those that are currently uninfected. So it's a very precise process. And just like any, you know, combat, there are always troops that are behind. And the troops that are not on the front lines are called helper T cells, which is a good name, because they're not out there with the hand to hand combat. What do helper cells do? Here we go. They secrete a whole family of chemicals, which support the activity of cytotoxic T cells, and others. They secrete interlukin-2, which is both a T cell and an NK cell growth factor. Self-explanatory. And they also secrete interleukin-6, which is a what? B cell growth factor. And they also secrete what are called chemotaxins, which are compounds that lure, to lure means to bring in what? Bring in macrophages. So really, looking at these two types of T cells, it would be hard to establish which one is more important. Certainly the cytotoxics are doing the actual killing, but the helper T cells make possible and support the efforts of the cytotoxic T cells, and notice, their effect goes beyond T cells, because we've got a what? We've got interlukin-6, which is a B cell growth factor. So, you know, if you had to pin a blue ribbon on the most important cell here, I'd be inclined to give the award to these guys. Because even though they're not out there in the hand to hand combat, they are main possible the whole functionality not only of cell mediated immunity, but also of chemical mediated immunity because they promote, what? B cell growth. And the reason I'm harping on this is that there is one virus which you know

is the AIDS virus, which specifically targets, and eventually eliminates these cells. And when your helper T cells are down to none, game is over. Right? So in case this is not clear, I'm sure it is, people with HIV don't usually die from the virus. They die from what? A secondary infection. Because after all, what does AIDS even mean? Acquired immune deficiency syndrome. And it all boils down to a total lack of helper Ts. Which completely annihilates your cell-mediated immunity. It also cripples antibody-mediated immunity. And therefore, you're defenseless. Literally defenseless, except for the puny, inadequate what? Nonspecific defenses. So again, helper T cells deserve our respect, because without these guys, not much of the rest really will work. So this is the process of cell-mediated immunity, which backs up and provides additional support, especially for viral infections. Now, there's way more detail to that, which you may get in microbiology, or you can go to YouTube, or whatever you want. But our focus for now is to simply ask, okay, fine, we know what nonspecific defenses are, and we can't do much to really change or prop up those. They are what they are. But how can we acquire active immunity? How can we acquire specific immunity? What are the methods of acquiring immunity? Essentially there are two. The first method is simply called active immunity. And there are two ways to get this. But what does it mean? Active immunity means that your body, your immune system, has actually produced, on its own, antibodies following what? Following exposure to a foreign microbe. Following exposure to a foreign antigen. That's the whole policy here. That's the way it works. And if you think about it, it makes perfect sense. Why should the body go to the trouble of making an antibody for an antigen that it's never going to see? So the body is very efficient. It doesn't begin to produce an antibody until it's exposed to that antigen. It's just the way it works, for better or worse. So how is this exposure made possible? Well, at least historically, there was only one way to be exposed to a foreign antigen. And that was to be exposed. Meaning, to get the disease. And so this is called natural. In fact, the full name would be natural active immunity. This requires that you have personal exposure to living what? Living microbes. In other words, you have to take the gamble, often times it's not a choice, but you've inadvertently been infected. And so now you have the opportunity at least to acquire what? Natural active immunity. What's the good news? What's the bad news? Might you survive this? Yes. Will you have antibodies? Yes. Will you be immune, therefore? Yes. What is the bad news? You might die [laughter]. So it's kind of a crap shoot. Flip of a coin. Die, not die. If you don't die, party time. If you do die, well... rest in peace. So this is the history that is, this is, this was, the only way to acquire active immunity. Until–until the advent of vaccines. If you take microbiology you know about Jenner, this was back in the late 1700s, cowpox, and the whole story. Anyway, what is a vaccination? A vaccination is a prepared solution which contains killed or sometimes what they call attenuated microbes, with what intact? In other words, we take these microbes, we cripple them, so they can't reproduce, but we're careful not to destroy what? I mean what is the identity that we want to preserve that will ultimately trigger and produce in you active immunity? Antigens. So this is a delicate thing. Because

for microbiology, and from general knowledge, how do you kill bacteria? Hmm. Heat them up. But when you heat them up, you run the risk of doing what to antigens, which you're trying to save? You are denaturing. So this whole business of preparing vaccines has been, in the past, kind of tricky. And it has given rise to a lot of suspicion about vaccinations, because many people say oh no, I don't want that vaccine. I'm just going to get sick. It's going to give me the disease. Well that's just non-science B.S., but there has been, in the past, some instances where some of these microbes have not been fully attenuated, so you know, that's exaggerating what now is completely an antiquated notion. In fact, today we don't even rely on killing the microbes. You can actually genetically what? Genetically put together the antigens without any microbe involvement at all. And so naturally this approach is desirable, and has saved, you know, hundreds of thousands of people over the world. But it continues to be suspect. Because we worship celebrity. And so Jenny McCarthy, who was a Playboy bunny, somehow gets more respect, you know? Don't take those vaccines, they cause autism. Complete nonsense. But you have people that are fearful of and will withhold vaccination from their children. A classic new one is this. This is a virus which is pretty nasty. HPV. It causes cervical cancer, and genital cancer. Until recently, we had no protection. Now we have this, called what? Gardasil. It eliminates most of these HPV viruses, which can lead to cervical cancer. Why should it be controversial? Again, fear of vaccines. And parents say, well, I don't know, I don't want to give my daughter that. Then she'll be free to have sex [laughs], well news flash here! They're free to have sex whether they're protected or not, so as a parent, you make the call, but it is silly how we are so suspicious of actual hard science which can save lives, but I'm getting too emotional. Let's go on. Now, this is all great, and vaccination is a wonderful thing. Unfortunately we don't have vaccines for everything yet. And so there are gaps in our ability to vaccinate. And furthermore, even if we had a vaccine for this or that, what if you weren't vaccinated? And you decide, well, I'm going to go to that country. Oh, that country is infested with what? Whatever it is. You can't go out and get vaccinated the night before you go to that country because it takes time to build up active immunity. So an alternative, which is kind of a stopgap measure, is passive immunity which means what it says. Active means that you produce the antibodies. But if somebody else already produced those antibodies, could you borrow those, inject them into yourself, and would they be just as good as if you'd made them? Of course. And so passive immunity is the transfer of antibodies that somebody else made to give you a kind of coverage for at least a short-term exposure. The transfer of pre-formed antibodies obtained from an already immune donor. Two ways to get this. One is natural. And you all took advantage of this, because you all had mothers. And you all received what from your mothers, before you even left the womb? You received antibodies. Did you make those antibodies? No. How come? Well, because you weren't exposed to anything in there, because it is all sterile. So any antibodies that you were born with, that were not made by you, they were made by who? Mom. And whatever they are, basically reflect mom's exposure through her lifetime. So it gives you kind of a jumpstart,

because it provides you with a supply of antibodies during those early months. And I guess some of you know that it continues even after birth, that is, you're not only born with some of mom's antibodies, but you get more of hers how? Breastfeeding. Now none of you are still breastfeeding, I assume, joking, and so this is basically a done deal. How can you get passive immunity if not from your mom? Well, this requires, again, borrowing antibodies from somebody who already made them. This is in the form of something called an anti-serum or an anti-toxin. In other words, a concentrated solution. A concentrated serum, which is usually just a grab bag of miscellaneous antibodies, most commonly called simply immune gamma globulins. Is this the same as a vaccine? Does artificial passive immunity provide life-long immunity? No. Because all you're doing is borrowing antibodies, and let's be clear, do antibodies cause the production of antibodies? No. Only antigens. So this is temporary, and it's good, because it works quick, and provides some protection. Especially in cases where we don't even have anti–I should say vaccines for a particular antigen. The most notable recent case was the Ebola epidemic. Remember that? In Africa. People were dropping like flies, right? And there was no what? No V word. No vaccine. No treatment whatsoever. You either made it, or you didn't. And 99% what? Didn't. Were there any that survived? Yes. And did they, therefore, presumably have antibodies? And a few of those folks were magnanimous enough to what? They actually donated their plasma knowing that it contained what? And that was used to treat healthcare workers, and it was a very nice gesture, because it did save lives. We're still waiting for the V word here, a vaccine. But the point is that passive immunity, as good as it is, is temporary and depends upon somebody making antibodies that you can basically borrow. So that is our brief story about immune mechanisms. With no fanfare, let's move right into the second topic, which has almost nothing to do with it, something called hemostasis. Not to be confused with homeostasis. You've heard the term homeostasis, which means the body's attempt to maintain the status quo to keep everything happy and fine. This is not homeo, it's what? Hemo. Literally hemo means blood, stasis means to stop. So rough translation, stopping blood. In a sense, it's anything and everything that prevents blood loss. And we're all for that, right? In fact, in case it's not obvious, what's the danger of blood loss? Blood loss, AKA hemorrhage, AKA low venous return, AKA no EDV, no stroke volume, you get it right? So we don't have to build the case for hemostasis. It's common knowledge that bleeding can be life-threatening. But what are the means? What are the mechanisms for hemostasis? The natural hemostatic mechanisms. There are two. The first one doesn't get a lot of attention or publicity. It is called vascular spasm. This means a response from what vessels? Arterials, not arteries, not veins, not capillaries, what? Arterioles. Arterioles have, as you know, smooth muscle. And they have the capacity to–C word–constrict. And they will. They will when they're cut. And the mechanism is as follows. The pain of an injury or cut will cause a nerve reflex which will come back through not parasympathetic, but what? Sympathetic fibers. Which causes local vasoconstriction in the area that has been cut. This is a beautiful mechanism because it happens almost instantly and causes the vessel to clamp

down. To clamp down. In fact, that is why it's called vascular spasm. It's reinforced by the presence of platelets, which are typically trapped or sticking to the wound. What's the other word for a platelet? Thrombocytes. And you remember that platelets produce and release a compound called serotonin, not related to the neurotransmitter. This serotonin further causes the smooth muscle to contract. So let's be clear. What causes vascular spasm is sympathetic action coupled with serotonin, which is released from platelets at the injury site. And clearly, what this does, it clamps down on vessels, and therefore stops or at least reduces what? Reduces blood loss. The beauty of this is that it's quick, and that it is pretty simple. But is it enough? Does it do the job? Does it always stop blood flow at the injury? The answer is no. Especially when there are massive wounds or many wounds. So vascular spasm is fine, but the more familiar and more important hemostatic response is coagulation. Coagulation is the formation of a fibrous protein network which basically serves as a net, N-E-T, which then spans the wound, and captures red blood cells, creating a plug. P-L-U-G. On a microscopic level, this is very striking. It looks like a volleyball net. Got that? A volleyball net, with a lot of volleyballs against it. In other words, that is what a clot looks like microscopically. The creation of a thrombus or a clot is predicated on making a protein network which then spans the wound and captures–captures red blood cells to create a clot, also known as a thrombus. One thing we want to be clear about here is that a blood clot is not dried blood. We hear that a lot. It's dried blood. Do clots have to have contact with air to form? Now, so it's totally unrelated. Clotting mechanisms are complex and follow what is called a cascade of events. We are giving you the simplified version here. If you want the whole story, it's in your book, it's beautiful. But these are the highlights of what is called the coagulation cascade, starting from obviously an injury. Got a razor blade there. Doesn't have to be a razor blade. So the vessel has been cut. And keep in mind, what is going to happen, aside from coagulation? Vascular vasospasm, right? So, okay, apart from that, what is coagulation all about? The injury itself creates a rough and irregular surface. Even something as surgical as a razor blade, the actual vessel looks pretty ragged on a microscopic level. It creates a very rough, a very rough injured surface. And that causes platelets, AKA thrombocytes, to adhere. They stick to a rough surface. And the tissues themselves, that is, the cells of the vessel, also release compounds. And those compounds recall simply tissue factors. They're derived from the destruction of the cells of the blood vessel that has been injured. Platelet adhesion releases their factors, including serotonin, but others, others that we're just going to call platelet factor. If you want the whole name, they're all in your book. We are trying to streamline this. So platelet factors, combined with–combined with tissue factors, to produce something we're going to call prothrombin activator, which obviously apparently is something that activates prothrombin. But what is prothrombin? All the time, 24/7, your liver is cranking out prothrombin, which by itself has no function. Prothrombin is inert. It's a precursor. Prothrombin does nothing. Incidentally, though, the liver requires what vitamin to make prothrombin? Vitamin what? K. Let's be clear. Prothrombin is not vitamin K. Prothrombin does not include

vitamin K. Prothrombin is made in the liver but what is required to do that is vitamin K. So anyway, prothrombin is circulating in your blood right now, and has no function. But it will be activated by what? It will be converted actually to thrombin in the presence of these prothrombin activators derived from platelet adhesion and tissue factors. Another ingredient, which activates this enzyme, and that is an enzyme, thrombin is an enzyme, which requires the co-factor CA plus 2. What's that? Calcium. Now, just as a matter of fact, calcium is rarely, in fact never, absent in the human bloodstream. So it's not like this has to come from anywhere, or that it's ever in short supply. But I'm mentioning it, only because when we bank blood, what does that mean? To bank blood? To collect it, and store it in bags? Those people who bank blood take out the calcium deliberately so that it won't coagulate. But let's be clear. Normally calcium is not a limiting factor and even though we mentioned it, it is always present, and not a part of this equation in most cases. So, backing up. Tissue injury, platelets stick to the wound. The tissues, that is the cells of the injured vessel, are releasing their own factors, combining with platelet factors. The two of those create prothrombin activator, which converts what? Converts prothrombin into thrombin. Thrombin is an enzyme, which converts fibrinogen to fibrin. Fibrinogen is a soluble plasma protein, which is also manufactured by the liver, and fibrinogen itself has no function. That is, no immediate function, until it's acted on by what? Until it is acted upon by this enzyme called thrombin. Where it is converted to fibrin. The only difference between fibrinogen and fibrin is solubility. Fibrinogen is water-soluble. Fibrin is not. And remember, it is this network of protein, now known to you as fibrin, which actually creates the clot. So in this cascade, we can see lots of things that could go wrong. And therefore, delay, or slow down the C word, what's that? Coagulation. What about liver disease? Does liver disease promote or at least put people at risk for bleeding or poor coagulation? Yes. Liver disease, you're not going to be manufacturing fibrinogen. You're not going to be manufacturing prothrombin. So bleeding tendencies certainly associated with liver disease. What about low platelets? Obviously. And what about a shortage of vitamin K? You can see lots of things that would conspire or otherwise reduce this process of coagulation. And, in fact, there is one–there is one approach which is actually deliberately exploited for the sake of eliminating or at least reducing coagulation. This is a little off topic, but let's go there. Is all coagulation good all the time? Is coagulation sometimes inappropriate and unwelcome? Especially when we have a clot forming for no good reason, right? That's called a thrombus. And if that thrombus, as small as it is, breaks off, and starts moving downstream, it's going to go into veins, then it's going to go back to the heart, then it's going to go out to the vessels of the lungs. And a clot, which is on the move, is called a different name. A clot that is on the move is called a–embolus. And an embolus will sooner or later end up in the brain or the lungs, where it's going to do a lot of damage, because it's going to obstruct blood flow. So people who have a tendency to form clots, inappropriately, obviously would be advised to somehow, somehow protect themselves from that. And one cheap and simple approach is aspirin. Probably you've heard of that, right? Aspirin is not just

for headaches. Aspirin, taken at an 81 mg dose, once a day, something called baby aspirin will work by blocking, or at least reducing this process, what is it? Platelet adhesion. Therefore, will an aspirin retard coagulation? And would it be a good strategy for those people who have a tendency to develop inappropriate clots? Yeah? In fact, not uncommonly, first responders who come on to the scene of a heart attack victim will often give them an aspirin, and they might say, well wait a minute, I don't have a headache, I have a heart attack here. Well no, no, we're giving you this aspirin to provide some degree of protection against inappropriate what? Coagulation, which might affect their coronary vessels. So anyway, my point was, that coagulation can be good. It can be bad. And of course, even a good clot, even a good clot, do we want that clot to be there forever? So clots are good, but we don't want them to hang around indefinitely. There are at least two natural anticoagulating systems that provide for anticoagulation. And the first are those that are called simply anticoagulants. There is a natural anticoagulant called Heparin. First discovered in the liver. Now we know it comes from basophils, and even the lungs, but basically it's an enzyme inhibitor. What enzyme does heparin inhibit? It's right there. It inhibits what? Thrombin. And therefore, it tends to–well, slow down the process of what? Coagulation. Do we all have heparin in our body? Yes. Should we? Yes. Because are clots sometimes inappropriate and unwanted? Yes. What prevents an inappropriate clot from getting worse, and worse, and worse, is the natural presence of Heparin. So we all celebrate and appreciate the role that Heparin is doing. There are also not so natural anticoagulants, one of which is called coumarin, which is actually a vitamin K antagonist. What does that mean? Inhibits the action of vitamin K. And therefore prevents the making of–prothrombin. Therefore prevents the production of thrombin. Coumarin, also known as Coumadin, also known as Warfarin, also sold today as Xarelto. All of these are essentially the same, because they inhibit what vitamin? Vitamin K. Who would take this? Well hopefully not everybody because not everybody needs to have high exposure. Because is coagulation for most of us a good thing? Yeah? Incidentally, these are quite erroneously called blood thinners. Which is a pet peeve of mine. Makes my skin crawl. Because there is no such thing as a blood thinner, except water. And why do they call them blood thinners? I don't know, they figure people really can't understand the concepts of anticoagulation, but they're not blood thinners. They're what? They're anticoagulants. So the next time you hear somebody say blood thinner, say "excuse me, excuse me, excuse me, they're not blood thinners, they're anticoagulants." All right. Anyway. Then there are fibrinolysins [assumed spelling], but wait a minute, before we go there, will these anticoagulants dissolve existing clots? Will either of these dissolve an existing clot? No. They're only going to make a clot less likely to get what? Bigger. Or to not form in the first place. So these are not clot busters. These do not bust clots. And they don't thin the blood either. Okay. What does bust a clot are fibrinolysins. And these are naturally occurring too in the form of an active compound called plasmin. And what does it mean to bust a clot? What is a clot? What is holding a clot together is this protein. What is that protein? So anything that would hydrolyze

fibrin would dissolve a clot. And plasmin is just that. It is actually extracted from and produced by vascular, that means blood vessel, endothelium, and is first released and now available as TPA. Now available meaning, available as a drug. And does plasmin have an everyday value to you and I? Even in healthy people? Are there times when we want to dissolve a clot? Sure. When do we want to dissolve a clot? After it has done what it's supposed to do. You want that clot there forever? No. The vessel is healed. Time to bust the clot. So this has an everyday role for anybody. But does TPA have a clinical value in emergency rooms or in medical settings? Sure. Because after all somebody comes in with chest pain, chances are it is what? Chances are it's a myocardial infarction, which is probably due to a T word, thrombus. So what would be the approach? Okay, the first responders already gave aspirin. That's wonderful. That's going to prevent what? The aspirin is going to prevent that clot from getting any bigger. So we are happy about that. But meanwhile, they're having chest pain, and they're losing cardiac muscle. Going to give them two aspirins? Five aspirins? A whole bottle of aspirin is not going to help. What they need now is a fibrinolysin. So you give them what? TPA. After they check in and show their Blue Cross card, because this is expensive. About three thousand bucks. So you're not going to just, you know, pass this out like candy. But as long as you have good health care, you'll get the TPA. And will that dissolve those clots? Will that save your life? Or at least save some cardiac muscle? Yeah. And so this works indiscriminately. That is, it dissolves all what? Might you have fibrin elsewhere in the body that maybe you don't want to dissolve at the same time? Sorry. You're going to dissolve them all. So you know, there's a little bit of a risk here. And just in a closing remark, this is very valuable in treatment of heart attacks, but what about a stroke? A stroke is, or could be a thrombus or even an embolism where? And every second that is there, you're losing brain cells this time, right? So you would say well, that's great, let's give them TPA. And it might work. But not all strokes are due to thrombus. Sometimes a stroke is caused by hemorrhage. In other words, a bleed. So that is tricky, right? Because somebody is stroking there. You don't know whether it's a blood clot or a hemorrhage. And if you give them TPA, well, you just sort of brought it along, you brought their death on, there. So obviously first thing you have to establish is, is this a clot, or is this a hemorrhage? And if it's a clot, go ahead and give TPA. If not, hold off on that. So it's tricky. And it's expensive, but it is life-saving. These are very different. To repeat, an anticoagulant does not dissolve a clot, it simply prevents or slows down the development of a clot. Naturally occurring compounds, heparin, and those that are artificially available in drugs, pill form and so forth, Coumarin, and these. TPA, available, again in an emergency context to dissolve clots. So wrapping it up, hemo what? Hemostasis. What were the two methods? Vascular spasm and coagulation. Working hand in hand, or actually not hand in hand, but working together. Have a great weekend. We will see you on Monday. Sure hope!