[MUSIC PLAYING]

TERENCE STARZ: One of the things I like is I like, when I present, to give people new thoughts of really how to think about things. And if you go back to what's been covered in the course, you've heard a huge amount about inflammation. You've heard a lot about genetics. And I want to try if I could in this last talk to give you a model of how to think about rheumatic diseases.

And that sounds like a big challenge, but given all of what we've talked about today, I think you'll be able to see. And you've heard this, and it is clear that one message that you must take away is that inflammation is at the root of most diseases. And if you'll think about when the last lecture you had on inflammation, if it's like me, the last I had was in medical school.

And it's not an area that I have considered. I haven't really thought about it. And it's something, if you have some of the basic principles, I'll show you how by understanding just the basic elements of it, how you'll be able to think about these diseases not only in terms of their clinical manifestations, but also how to most effectively treat them. And so when we look and think about the diseases we talk about, certainly not only with cardiovascular disease, with atherosclerosis, with cancer, inflammation plays an enormous role with neurodegenerative diseases, and certainly with the diseases I take care of.

So here's our goal for this next bit of time. And that is I'm going to talk to you a little bit about exactly what is inflammation. I'm going to talk to you about something that is seemingly very obvious, but something that we just don't understand well.

It's just like aging. A lot about aging that we just don't understand. And with inflammation, exactly what starts it and what stops it. Because that actually is critical to all of these disease states.

We're going to talk to you about the manifestations, the consequences. I'm going to talk to you about certain diseases. And then I'm going to talk to you about management.

So what exactly is inflammation? Quite simply, it's the body's immune system, it's its reaction against injury and infections. So when you think about inflammation, number one, it's our immune system. That is the mediator of what takes care of this. And it is our body's reaction against injuries and infections.

And so there are internal and external factors that I'll show you. And essentially, what the body is trying to do, it's trying to dispose of these microorganisms that have invaded our system. It's getting rid of foreign material. It's eliminating that injured tissue, and then it promotes repair. It's that simple.

There are various elements that I want to show you about the response, the vascular response, the cellular response. And essentially, that's what helps. And then the last, it's just like when we're hearing about pain. When we think about pain, we have to think of acute pain and chronic pain. They are very different.

When you think about inflammation, think about acute inflammation and then chronic inflammation. I'll show you they are very, very different, and our management of them is different. Our immune system-- and if you'll just look at the word immunis from Latin, it means safe. It's there to create safety for the body.

And so our immune system, it gathers information. So it has to recognize that there's a problem, whether it's an injury, or whether it's an organism that's invaded and broken through the innate barriers that we have. And then it is the reactor. And it has this ammunition to isolate, neutralize, destroy.

And so actually, it's interesting. It's about two pounds of our body, many, many cells. And although you saw it, and if you think about the different toxin, the different mediators, in a lot of levels, it's just not that complex. So when you're thinking about acute inflammation, remember it's of short duration.

And the cell that predominates are the neutrophils. So that is it. That is the soldier out there dealing with the acute inflammatory process.

Chronic is certainly much different. And many of the diseases that you've heard talk about today, this is what we're looking at. We're looking at chronic inflammation, whether it's rheumatoid arthritis, whether it's inflammation in a plaque in the aorta, whether it's associated with Alzheimer's disease. And these are different kinds of cells. These are mainly the macrophages and the lymphocytes.

And there's a whole different kind of reaction that's going in our body and we have this proliferation of blood vessels. We have fibrosis that's occurring in there. And we certainly have the damage. Neutrophils do participate, but much less so.

So when we look at the causes of inflammation, the ones that we're going to be focusing on for many of these diseases are microbial infections. And that is so essential. Certainly, we're aware of these other factors. But most of these diseases it's going to turn out, I believe, are going to be related to some reaction, some imbalance that's occurring related to all of these microbes in our body.

So remember, with acute inflammation, we have these three components so that when there is a signal given out, there is this injury that occurs, you have these vascular changes. So what happens is the blood vessels dilate and there's increased vascular permeability. That's why we get swelling. If we take a look at our joints that are involved, we get swollen joints because the blood vessels have dilated and there is fluid in the interstitium there.

In addition, we have these cellular events. And these cellular events essentially are the leukocytes, they come in from the circulation and they accumulate. And they're coming there to react, to deal with the process that's going on, whether it's a mechanical injury to the area, whether it's an organism that's there. And essentially, there are ways that those cells recognize what's going on there.

They have, and it's quite simple that the cells have receptors on the surface and they recognize the bacteria or the viruses, the fungus, or whatever. And there are reactions that are made and one of the major reactions is that they make mediators. And you heard when Dr. Moreland talked about, and we'll talk about treating rheumatoid arthritis a little later, but you know we target those mediators in terms of the treatment. And those mediators are involved in how we deal with the injury.

And so this is a simple. Cartoon and you have this splinter entering the finger. And in that, there is certainly an injury that's occurring. We have the organisms that are present. And the acute inflammatory response immediately begins. It occurs right there and then.

And so what happens is that we have these different mediators. We have these cells come. And they start signaling to have more cells come. They put out chemicals, which dilate the blood vessels. And we see associated with that, we have the heat and temperature. And so we're trying to get rid of that process . We're trying to localize that process right there.

And so we see the cardinal manifestations, the redness, and that's the dilation of the blood vessels, the increased blood flow, the heat, and we have that increased chemical activity and increased blood flow. We have the swelling of course. And then the pain. And that pain is the warning signal that there is an injury. It's because of the stimulation of the nerve fibers there the pain fibers by the chemical irritants.

What happens in something now when you're thinking about inflammation? We have the local problem. But there's also a systemic reaction. And the systemic reaction occurs because these mediators, the different chemicals that are produced, the interleukins and the chemokines, they go out throughout the body. And when they go into the brain through prostiglandins, they can stimulate the temperature centers and you get a fever right there.

Certainly we have this leukocytosis with all of the blood cells coming from storage areas like in the spleen and the rest. And they come, and then the body starts having a reaction, these acute phase reactants that we'll show you. So remember, when you have an invasion coming in there, a break in your innate system, something breaks your skin or other barriers, we have the local effects that's going on right there. But we start getting these reactions. We start making these different chemicals.

These are the chemicals actually we are targeting when we're treating. And we're targeting those cells. There are the systemic effects we can see on the brain. Those chemicals cause the liver to make the acute phase reactants, the C reactive protein and increase other proteins there, and certainly in the bone marrow as well.

And so we can see that there can be effects throughout the entire body. I think it's interesting to look at the acute phase reactants. You always wonder what these proteins are doing. And we don't exactly know what these proteins are doing. And if you look at that term C reactive protein, well, the term actually comes from the C is the capsular carbohydrate of the pneumococcus.

It happens to be a protein that reacts with it. That's how we detect it. An interesting fact is that that protein has about a 50% identity to the P component of amyloid. We've heard about amyloid. And so there's nothing magical about these proteins. And you know why we make them. And when you take a look at them we have this reaction that's occurred. Some of them last longer than the others, but once the stimulus is removed, you know it takes about a week or so and that reaction stops.

And so this really becomes the big question when you look at the diseases that are in rheumatology, but also these other diseases, whether it be rheumatologic diseases, inflammatory bowel disease, any of these chronic, inflammatory conditions, why aren't they shut off? You know, so in rheumatic diseases, we didn't know what started them, and we certainly didn't know what shut them off.

And so, when we take a look after the acute inflammation, there are these phases of healing. We essentially start having this-- we start removing the debris. We have this proliferative change, the scar tissue being formed right there. And that's how healing occurs. But that doesn't always happen.

And there's been-- if we take a look at this acute inflammatory response, certainly oftentimes it is self-limited. The cells come in and they remove the debris. We have mediators which communicate. And it's interesting, these are chemicals that you probably haven't, really are not part of the armamentarium. But there are actually chemicals here that are involved.

Just like if you think about the coagulation system that we have, we have the coagulation system, the different proteins, but they're ones that shut it off and stop it and cause it to resolve but we have these as well, you know, the resolvants and others involved here. And again, these are proteins. But how that all works is really still very questionable. And the question as well as how that relates to then the evolution of some process to become more chronic. so that we really just don't have that resolution.

And so when we look at it again, something is going on. There's this imbalance. Our bodies processes just are not shutting off the difficult. And so then we go from acute to chronic. And as I'll show you in rheumatic disease, there's more and more evidence that organisms are involved in this whole process.

And so when we think about this, you know, what are the mechanisms here that cause this impaired resolution? The acute inflammation somehow, it just doesn't stop. It just keeps going. And the inflammation is terrific at getting rid of these organisms, or if there's a foreign body or the rest. But it's not good when it persists. Because it can certainly go on to cause significant damage to the body.

And so, you know right now this is where we are, is that we don't understand exactly what happens. You know, is there a failure to eliminate whatever that offending agent is? Was it just not, in terms of the reaction, are those cells, are they staying there in that particular area? So what is this functional alteration?

And actually, we just don't know. It's just like the aging process that we don't understand exactly why that is. But certainly when we look at chronic inflammation, for your thinking, just remember, this is a whole different set of cells. So now, these cells have come in and the macrophages and the plasma cells which make immunoglobulin, they infiltrate. And there is then tissue destruction.

It's interesting, if you go back when I was in training and Larry said this the other day about rheumatoid arthritis, we used to wait. We used to wait for two years for people having rheumatoid arthritis before we would use so-called disease modifying drugs. And logic has it, and it is absolutely true, the earlier you intervene with these conditions, the more effective that we can be. Because once this tissue destruction, and then we have fibrosis and this angiogenesis, all of that occurs, it becomes much more difficult.

So when we take a look at chronic inflammation, so this is this prolonged activity that's going on. And you can see this is acute inflammation over here with the neutrophils. And we have a whole different set of cells and this whole process is going on. And another concept that's very important, and I'm to be showing you three examples actually. We'll talk about rheumatoid arthritis, osteoarthritis, and gout.

Gout for the most part, is pretty localized. But sometimes during the acute attack, people can have fevers. When we take a look at osteoarthritis, it is very localized. There are really not overt systemic manifestations of osteoarthritis. But rheumatoid arthritis is an interesting process, because not only do you have the activity going on in the joints, but there's a whole systemic process going on as well. And so that's what we'll talk about in a moment.

And so, the question that comes up to is that, how do we go from this acute inflammation to this chronic inflammation? What happens to our immune system, you know, the so-called autoimmune. We're actually making a reaction against our own body, and it's occurring within there.

And so, I want to go through this slide for you. Because this actually, and I'll show you within these models, once you see this, you'll be able to understand it. And when you see people with different current kinds of arthritis, as well as when you're taking care of inflammatory bowel disease or other inflammatory states, the models, the general model is the same. And so, when you take a look at these diseases, there are definitely genetic factors here. So that there are genetic factors we've been able to identify and rheumatoid arthritis.

The problem is that it's not like with ankylosing spondylitis, with the HLA B27, we just don't have those markers that fully defined. But then there are environmental factors. And you know, for example, with smoking, smoking certainly influences the lung, obviously and it can cause injury in there. And that injury probably exposes certain antigens that may not be exposed to normally.

And then we have this stochastic, which is the randomness. And there's this random, you know, exposure to something. And I'll tell you what that something is. It's organisms. And it's interesting when we take a look at rheumatoid arthritis, as we'll show you, it is almost certain that rheumatoid arthritis is initiated by a reaction against a bacteria, either in your mouth, especially in the gums, in the respiratory tract, or in the GI tract. And that is the initiator, that's what pulls the trigger.

So you take somebody who has genetic predisposition to this. And then there are some environmental factors as to whether it's a microorganism, you know lupus, sun can certainly with the skin damage and the DNA. And then what's so interesting about these is we start making a reaction. We make these autoantibodies.

And there are now studies which show that those antibodies can be there for long periods of time before the disease becomes clinically manifest. Now, why that is true is not clear. However, as I'll show you with rheumatoid arthritis, it is likely that you need to have a second insult that occurs.

So you have the initial process occurring at these sites. And you'll notice that these sites are not the joints. And so what occurs is that there are cells that are stimulated. They are immune cells, and then they travel to the joints. You know, possibly although, it's hard to look,-- it's not exactly the same analogy like with metastatic problems, but there is localization and I'll show you.

And then we start having this evolution of a benign immunity. Because you know, one thing that I see all the time is people come in with a positive ANA or a positive rheumatoid factor. And they do not have anything. There are no clinical manifestations. And certainly not everybody with those autoantibodies will develop a connective tissue disease.

But you know there is a much greater understanding now of how, once in a genetically susceptible individual that gets started, and then there's a second event that occurs that creates the disease. And we, thinking of the microbiome-- remember we've got more bacteria in our colon that we have cells in our body. And so it's unbelievable about this. And you know it's remarkable how we keep all of this in balance.

You know it's interesting, you know, we've heard talks today like on antibiotics, how that influences, how our diet influences all of this. So there are lots of questions. But certainly this balance between our microbiome and how are our immune system keeps that in check is certainly where we are headed. Because when we see, especially within the GI tract, you know, and think about this. Think about inflammatory bowel disease. You know, we certainly see arthritis associated with that, 20% or 30%.

It's interesting that in people with inflammatory bowel disease, they can get sacroilitis. They can get, even if they're not HLA B27 positive. So something is happening once that inflammatory process gets started, there then becomes localization of those cells to other areas.

One thing that has always intrigued to me about rheumatology. You know, if I said to you, gout, you know, everybody thinks of the great toe, you know your big toe. So why does gout affect that? And I'll tell you, there is certainly increasing understanding now about these. You know, when I teach about the-- teach to future residents or the students, we tell them that they're marker joints.

I mean for example, we know that osteoarthritis affects the distal pharyngeal joints. It affects the base of the thumb, the knee, and the hip. But osteoarthritis does not affect the ankle. You know, if we look at the first MTP joint, the bunion joint, I mean that's something in osteoarthritis. But the other MTP joints are usually not involved. So why is that?

And so there is a lot of information that is now being developed that, in different joints, the cells there are different. For example, you know, if you look at the cartilage in somebody's knee, it is different, not tremendously different, but different from the ankle, and other cell types. You know, why do some people get osteoophytes and others don't? It's almost certainly related to different cell types and different stimuli.

And then you have various systemic triggers. That's why, if you get these organisms, these reactions occurring, whether in the lung or the mouth or in the GI tract, you know, that trigger, and then all of a sudden, these cell types start to get triggered. And then you can have local factors as well that influence it.

And so you know, what's so interesting when we look at not only the pattern of joint, but also the pattern of organ involvement. You know, why is that some diseases affect some organ systems and others affect others? And why different patterns of joint are involved? And it turns out, quite simply, that our immune system can localize to these different areas, depending on different genetic factors. And that's certainly the way it is.

And we can turn off and on genetic information that relates to the activity of different joints. So like in your knee or like in your big toe or your DIP joints, you can turn on and off that genetic information. And that certainly likely helps us to understand why different joints are involved in different kinds of arthritis.

We certainly can see hormonal factors as well. What's so remarkable, you know, if we take a look at rheumatoid arthritis, the incidence of it before age 50 or so is primarily women. And so men who get rheumatoid arthritis are almost always over the age of 50. And so, we certainly can see that there are hormonal factors that are operative there.

And I mentioned to you about these autoantibodies. They are very intriguing in terms of what they do. Because we can see these and certainly healthy individuals. And now there's more and more looking at this preclinical stage. But certainly this must be balanced with the systemic findings that people have. And to really focus on why something doesn't cause a problem, it is very likely related to the fact that you need to have multiple hits to be able to develop.

So in the last couple of minutes, I want to show you these diseases and show you now how you really can understand them, both in terms of the pathophysiology and the clinical manifestation. And so rheumatoid arthritis is common. Women are certainly three times more likely than men. However, men, once they get over the age of 50, that's when we see people, the incidence in men and women over the age of 50 is about the same.

And we certainly have the risk, that heredity and cigarette smoking is certainly a factor. And remember, rheumatoid arthritis is not like osteoarthritis. Rheumatoid arthritis is a systemic disease. And that's what we really have to understand with this, is somehow the immune system just gets turned on in our body.

The immune system gets turned on our body in lupus. It gets turned on in our body in ankylosing spondylitis. Those are involving multiple areas. Osteoarthritis and gout tend to be very localized. For some reason, that process is just right there at the joint. And so, when we take a look, this just shows you that slide that I had referred to initially.

You have a genetic predisposition here. You have these factors, these organisms in different places, the gums, the respiratory tract, GI. And we get that first hit. And we start changing our proteins. You know, there's this test, the CCP, the Citric Citrullinated Protein. So now, proteins, very likely related to some bacterial plus the smoke in the lungs, all of a sudden we start citrullinating proteins. And they are recognized as being foreign by the body and we start making those antibodies.

As we mentioned, the second hit is very likely what is necessary then to have these cells go and localize to the joints and then start that inflammatory process. And so once this begins in here, you know, and Larry showed you, I mean, there's a lot of activity. And it's not a good thing to have that persistent inflammation. When you look at it there is just not a persisting antigen that we can identify.

It's so interesting, when we heard about AIDS, that you know that virus, you know it still can be found in different tissues. The question is, we just haven't gotten the sensitivity to find that organism right there. And so what we're focusing on is this window of opportunity, of taking a look to see if we can identify genetically, then if there are autoantibodies or other markers, and then to see how to keep this from coming like this.

And the bottom line is, the earlier we treat it-- and now, I'll tell you, we have somebody there with persistent inflammatory arthritis, in three months we begin disease modifying drugs. And that is the key. Because the earlier you treat it, the more effect-- and we target, and you heard about the different ones. Don't be overwhelmed by that. Essentially what we do is that we are targeting these various mediators of inflammation, and by doing so, it allows us to be able to put that to somehow get that process of inflammation resolution to occur.

You know the challenge, of course, is we have all of those drugs. And the other challenges, and a message to take away, is that it is bad to have chronic inflammation going on. Because that also has a very negative effect on the rest of the body. For example, as you saw, if we look at atherosclerotic heart disease, I'm telling you, that worries me enormously about people with rheumatoid arthritis. And the studies show that effective treatment can significantly decrease the chance of having problems there.

In the last minute, I just want to show you osteoarthritis. And osteoarthritis, here the wear and tear changes certainly can occur. But also, it is now clear that there's an inflammatory reaction going on in that synovium. It's not as intense. But that likely is what accounts for the progression of osteoarthritis in there.

And we need to really develop-- and there is a focus on developing mechanisms to treat. But the mediators that are involved in osteoarthritis are different than rheumatoid arthritis. And so we need to figure out how to target these cytokines to hopefully start the process. And the same is true when we look at gout, that you know when we see this flare and we can see the damage. And what's so interesting about gout, is we know it's the uric acid that's there. And that is the stimulus.

But what's so interesting is that for some reason, it doesn't always cause the problem. But certainly the same type of situation where we're focusing on these kinds of mechanisms here, that we know about the uric acid. We know how it stimulates. And that we can, and that's what we hopefully, will be able to do with these other processes remove that stimulator. We can remove the uric acid with Allopurinol.

So in my summary, I would say this to you. Remember, and hopefully, this talk has just given you a picture now, and it's pretty straightforward, that inflammation is critical to our body to protect itself. But it's also, when that acute inflammation, that whole process does not get fully resolved, then we develop these chronic processes. Infections likely are going to be critical, and focusing on them, but also focusing on treating these as absolutely as early as possible. Because when we do that, we can really stop the consequences.