[MUSIC PLAYING]

TERENCE STARZ: My name is Dr. Terry Starz. I'm a clinical professor of medicine here at the University of Pittsburgh School of Medicine. I have recently transitioned from practice. I also do clinical research in rheumatoid arthritis, pain, including fibromyalgia, as well as outcome studies.

So this is the last lecture. We've reached the end of this year's update in internal medicine. And the last lecture, I think, is very important because, in these lectures, I think one thing that we all like is to learn new things. And I'm going to be talking to you about rheumatoid arthritis. And I'd like to share with you certainly about the most common inflammatory type of arthritis, but also we're going to look at new ways of thinking about rheumatoid arthritis, new ways that we, as rheumatologists, are approaching the disease.

Over the years, I've taken care of many, many cases of rheumatoid arthritis. And one thing that is so interesting is that not any two of them are perfectly similar. There's a lot of variation. And that is true of many of the diseases that all of us take care of in internal medicine.

So here are our goals for this lecture. So I would like to begin by providing principles that are used to determine exactly how we create a disease model for inflammatory rheumatic diseases, including rheumatoid arthritis. This is applicable to other inflammatory diseases, lupus and the like.

I'm going to describe with you about how we think about rheumatoid arthritis. And that's actually the origin of the topic. And that is, I'm going to talk to you about thought barriers for how we understand rheumatic disease. And then in the course, we're going to determine how we look at information and determine what's most important in determining the diagnosis, how we focus on targeted management activities, and how we determine and project outcomes in rheumatoid arthritis.

I'd like to, in the course of the lecture, for you to think about two questions. And they're pretty straightforward questions, but not simple. And I hope that, as we go through the lecture, you'll get perspective on how these are essential in terms of our treatment of rheumatoid arthritis, and how it really helps you, as a physician and health care professional, to manage the disease.

The first question is, what is the single most important factor that will predict the outcome of rheumatoid arthritis? Now, obviously, there are many factors involved, but there is one factor that is essential in terms of the outcome. And secondly are what measures do we use to determine our treatment outcomes and our treatment choices.

So let's start. And I want to start with this slide by a very perceptive doctor, Dr. Halstead Holman. He was chairman of the Department of Medicine, head of Rheumatology, head of the training program at Stanford. And he had really a very eclectic career. He did basic research. He certainly was involved in clinical care. He had a tremendous focus on the patient, as well as creating models for the disease.

And he wrote this article in 1993, which I think is really important, and helps us to put this into a framework that allows an evolution of our knowledge. And the first is that medical teaching has traditionally been centered on acute disease. And that is really true in rheumatology. But most of the diseases we take care of are chronic. So that part of the model really creates challenges, as well as the fact that we use the single-lesion perception of disease causation derived from infectious disease. And remember, infections were a paramount problem in terms of medicine until the advent of antibiotics, especially.

The third barrier is about interactive biologic pathways. As human beings, we like to have things be relatively definable and straightforward. And as I'll show you, that's a challenge with looking at these rheumatic disease because it's not exactly one pathway. There are many different factors involved.

And one of the challenges is, when we look at these inflammatory diseases, that autoimmune abnormalities are not necessarily harmful. And that creates a challenge for us, as well. And our task as physicians and other health care professionals is to manage this course of disease, this chronic problem over time, never forgetting that the patient is at the center of achieving and monitoring our progress.

One of the things in rheumatology, we have gone through different stages of lumping all of the diseases together and then splitting them. And now we can really look at categories of problems. And I'll talk to you about how we diagnose rheumatoid arthritis, but you must remember there is a tremendous spectrum of the disorder. And one thing, as well, is that when we look at clinical trials, because a lot of them are based upon this acute or defined interval of the disease, and that really is challenging because trying to project that information on the long-term course of rheumatoid arthritis maybe creates situations that are not ideal.

So I want to start by taking you back to June 24, 1971. I was an intern. That was my first day here at Presby. In the morning, we made rounds. And as I was finishing rounds, my resident, Ed Procoff, said Terry, you have clinic this afternoon.

So I dutifully reported to the fifth floor of Falk Clinic. I was given my schedule. I had six patients. The mentor that day was Dr. Gerald Rodman, the head of Rheumatology. And that was the tradition here at the University of Pittsburgh, was to have all the physicians in the department precepting a clinic.

I'll never forget, the third patient I had was a 58-year-old woman who had presented with a six-month history of pain and swelling that was insidious in onset, but definitely persisted and progressed. The swelling was very pronounced in some of the small joints of her hands, especially the PIPs and MCPs, with DIP sparing. The symptoms were certainly discomfort or pain.

There was significant morning stiffness. And she was having considerable impairment of her function. She saw her primary care physician. A rheumatoid factor was performed. It was positive. And she was referred here to the general medical clinic.

As tradition, one of the cases was chosen to present to the preceptor of clinic. And of course, this was the case. I can't tell you how little I knew about rheumatoid arthritis. Fortunately, Dr. Rodman, who was my chief when I was in training here, was reasonably benevolent. I presented the case.

And three years hence, Dr. Rodman was the president of what was called the American Rheumatism Association, now the [INAUDIBLE] Rheumatology. And he was a very perceptive, very smart individual. But his recommendations at that time was to take 12 aspirin a day, go to physical therapy, and come back and see us in three months. This was 1971. And my, how things have changed, because I like this slide. When we look at this disease in rheumatoid arthritis, we almost never see this any longer. How do we prevent that from happening?

So when we take a look here at rheumatoid arthritis, this is one thing I want you to keep in mind when you think about RA. This is a synovial biopsy. Normally, the synovium has a one to three-cell layer of synoviocytes on the surface. There's loose areolar connective tissue, and certainly this inflammatory infiltrate is not present. Remember, this synovial membrane makes the joint fluid, which is what nourishes the cartilage. And this synovial fluid from an inflamed synovium like this is very abnormal.

I want to talk to you about, in general, the model of autoimmune rheumatic diseases. And I think this gives you a perspective. And I'll show you how this applies to rheumatoid arthritis, but it also applies to the other rheumatic inflammatory diseases.

So we take a look here at the etiologic factors. Genetic factors, of course, are very important, but there is no one single factor that identifies rheumatoid arthritis, like with the spondyloarthropathies, the HLA-B27. Even those patients do not always have that present.

And then we look at what are the environmental factors. Smoking certainly increases the likelihood of developing rheumatoid arthritis, as well as does have an impact, a negative impact on treatment. Microorganisms are really very important. And significant advances have been made by identifying microorganisms, but I'll tell you, we still do not have a single microorganism, nor do we have a full understanding.

In conditions like lupus, the sun can cause damage to an organ, in this case the sun releasing certain sequences, which can stimulate an immune response. This is something I find to be so interesting, though, is where does the problem begin. And that's the whole issue of taking a look at it, and what happens right in here.

Rheumatoid arthritis is certainly a disease of joints, but it is a systemic disease. And when we take a look at it and we look at this whole situation, and we'll be talking about the course of rheumatoid arthritis. And it's interesting that rheumatoid factor, for example, can be present for a significant period of time before the disease becomes manifested. And in addition, people can have a positive rheumatoid factor, especially as the individuals age, and it have no significant whatsoever.

And then when we take a look at this is what are the target areas affected. And we're going to talk about this. And we're going to talk about this in the context of looking at our barriers. I mean, there's a lot of stuff here. And when we look at the acute disease model that Halstead was talking about, bacteria and other microorganisms almost certainly play a role in the initiation of that whole process. But looking at this other whole situation of what are the areas of the body affected, what do the immune abnormalities represent, and how do we target treatment within the context of our understanding.

So let's look at what rheumatoid arthritis is. We mentioned it's a systemic inflammatory disease. It's certainly autoimmune. But the primary expression, unlike something like lupus, in which certainly arthritis can occur, but we also have a lot more organ involvement. The kidneys, for example, are not affected directly in rheumatoid arthritis. It's the most common form of inflammatory polyarthritis. It occurs in 0.5% to 1% of the population.

As I mentioned to you, the clinical presentation is very heterogeneous. Some people present with one or two joints. Some people have a more abrupt onset. But usually, it begins very insidiously. And it occurs usually between the third and the sixth decade, with a significant female to male predominance. This suggests that factors including hormones could be very important in the disease process. Men tend to get rheumatoid arthritis later in life. And again, that may be some reflection about hormones.

This insidious onset, and there's varying degrees of intensity. But one thing that's important is the disease in the joints persists. And there's the stiffness, especially in the morning. That's because we have swelling in there overnight. And when we wake up in the morning, we have to move the joints in order to get that fluid out of the interstitium from the inflammation. There is a specific pattern of joint involvement in rheumatoid arthritis, especially the hands and the feet with the MCPs and PIP joints, but the distal inner fail phalangeal joints are spared. The MTPs are another very important joint, but any synovial joint can be effective.

When we ask patients about the disease or when I'm teaching about it, if I use one word to describe it, it would be insidious. It persists. It's not a whole lot different, usually, yesterday than today, but there tends to be this gradual progression of the disease process.

Well, let's take a look at a little of the history. Dr. Rodman loved the history of medicine, and he taught us about it. But the term rheumatoid arthritis was really only separated by Dr. Garrod in 1859 in his treatise on gout and what was called rheumatic gout in the past. And he was the first to use the term rheumatoid arthritis. The rheum is derived from the Greek, and it's a humor that circulates in the blood. And that probably is still very accurate. He described here the clinical findings.

I just wanted to show you this little thing from Short, who said this about the naming of the disease. But it was really a question because, remember, rheumatic fever was much more common back then. And there was a problem of separating it. The pattern of joint involvement can be somewhat similar. But he said that this was a vague term fitting for the subject. It has no etiologic implications when we look at the description of it.

But when we look at this whole thing, it does talk about rheumatology and the importance of developing criteria. And these are the criteria. And the ones that we've already mentioned to you-- morning stiffness, joint swelling, swelling of another joint. And that's very important to have this be described. There is certainly pain with movement. It's symmetric. And just for your own knowledge, one of the reasons why symmetry is important because that's the way we separate between rheumatoid arthritis and psoriatic arthritis.

Rheumatoid nodules are not common. They occur less than 5% of people. And rheumatoid factor we'll be talking about, and radiographic changes, as well, because rheumatoid factor does occur in the normal population. And not everybody with RA has a positive rheumatoid factor, nor does everybody with a positive rheumatoid factor have RA. Radiographic changes are important, and do have prognostic implications. But again, not everybody develops this.

And you can see that some of the factors is morning stiffness, where we see this particular pattern of joint involvement. Symmetry. Nodules, as you see, does not occur often. And this is still about the frequency that we see rheumatoid factor positivity. And the x-rays, especially erosions, they do occur, but especially periarticular osteoporosis. When we have inflammation, cytokines tend to promote decreased bone formation.

Well, these are our new criteria that we use. And we're looking at these criteria that we take a look at this, is joint involvement obviously is very important. And we want to have multiple joints being involved. Certainly, we can see large joints, but small joints are very important. I mean, rheumatoid arthritis can begin in about a quarter of people in large joints, like the knees, but it progresses to involve the small joints of the hands, and also it can be the feet.

We can see here, and we'll be talking about rheumatoid factor. This is the CCP test. And we can see about this. And it still is part of the criteria. And positivity does help somewhat, especially early in the course. And when we take a look at this, we look at measures of inflammation. You see the weight that is given to this is small because these are so nonspecific.

And duration of symptoms. Unlike this case I had talked to you about, if there is persistent symptomatology of greater than six weeks with the criteria, you know, multiple joints being involved with the rheumatoid factor positivity, unfortunately, rheumatoid factor positivity is only present early in the disease in about 30%. And it becomes increasingly positive, especially over the first year.

And these criteria, we've been through them, and they've been modified and the rest. But when we look at the 2010 criteria, they identified more patients, but there are limitations to the criteria. And so that's one of the challenges, what I told you before, is that rheumatoid arthritis has so much variability. But we focus on the findings in the joints. We take a look at other data, specifically like the rheumatoid factor. We take a look at morning stiffness as very important, as well.

So when we look at rheumatoid arthritis, remember I told you we need to think about the synovium. And this is the site of the problem. Did it begin there? That's where it's still not clear, because when we take a look at what's going on and the pattern of joint being affected, it really is a challenge.

But there is no question that this inflammatory activity has a significant amount of immune response here. And that immune response causes an abnormal fluid, which not only causes damage to the joint, cartilage especially, but also to the bone. And this synovial inflammation acts almost like a malignant tissue because it can erode away the bone, as we see right there.

And when we take a look at this pathogenesis, this is where we have to kind of expand our thought barriers. I wish it was as simple as that we could say that it's like, gee, it's hitting your finger with a hammer, and that's what caused it. That's a problem because when we take a look, there certainly is interaction between genetics, although, again, what the specific genetic information, there is definitely some twin studies that suggest that.

But when we look at these environmental activities, we mentioned about smoking and infections. And infections are interesting. It's not just one organism per se, but it's different organisms. And we haven't been able to identify that one single organism, not like with Borrelia burgdorferi organism in Lyme disease. But we can see a gingival infection, GI infection. You can see pulmonary problems. And something happens.

And it turns out that there probably, when we look at this, is that when we look at this prearticular phase, I mentioned to you that antibodies, rheumatoid factor and CCP can be present before clinical manifestations occur. And what exactly is going on here? And then how do we take this prearticular phase, and how does it become right here? Right here, the trigger occurs. And what is it?

And there's certainly a strong suggestion that it takes an initial infection, and then there can be a second infection. And that's why the single event with a single pathway is just not operative. But this causes the synovitis. And when we look at these organisms, I mean, in the past, antibiotics and the rest have been used. Tetracycline was one agent, especially. But that just doesn't get rid of it. You have somebody with Lyme disease, you use tetracycline, that is very specific.

And then we take a look at this. And this is a challenge. It's a challenge for you, as primary care, health care professionals, but certainly for us, as well, because of this tremendous variability in the course, certainly where it is in here. And the interesting thing is how do we target treatment so as to be able to impact this. A few people, the disease will go away relatively spontaneously. But in the overwhelming majority, not. And when there's persistence, one can see irreversible damage, especially related to the degree of inflammation, where we get that abnormal fluid, the cartilage becomes narrow, and then we can actually get erosions.

We must never forget that this is not just a disease of joints. It's not like osteoarthritis, in which the joints are the primary area. We have lots of other areas involved. And that's also very challenging to understand, what's symptomatic and what's asymptomatic in the disease. You can see changes, for example, in the pleura and the pericardium with some inflammatory and then fibrotic change, but although it happens, it does not clinically become manifest often.

We can certainly see localized problems neurologically. One thing really of concern is atherosclerosis. When you have this inflammatory reaction going on, that is of concern. And when we take a look at this whole situation, I mentioned to you about the osteoporosis in and around bones.

When rheumatoid arthritis so-called burns out, the joints have been damaged, and we get secondary osteoarthritis. I'll talk to you a little bit later about pain in rheumatoid arthritis. And fibromyalgia occurs in over 20% of patients.

So as I mentioned to you, there is no pathognomonic test for rheumatoid arthritis. This anti-cyclic citrullinated peptide antibody, now we call it the CCP, usually, as well as the rheumatoid factor, IGM, we can see them at about 75%. And it can precede the disease onset, but it's not specific. And you cannot use that alone. That's why you have to be very careful about ordering it.

And we used to divide people-- and there is no question that people who are seropositive have a positive rheumatoid factor or CCP, that may indicate more severe disease. These other laboratory measures just look at are very nonspecific. Baseline X-rays are useful to provide a perspective as to whether there are erosive changes. And we do check them periodically, depending on the symptoms.

I just want to review for a moment about rheumatoid factor. We've known about rheumatoid factor since the late 1940s. And 75% to 85% can become positive. But it just doesn't have, in terms of following the course of the disease, once you have a positive rheumatoid factor, it almost always stays positive. But if there is a high titer, it can indicate more severe disease. It's just not a specific test because we can see it in a lot of other conditions, especially with aging.

CCP is another antibody. And again, it's a real issue. It's not that sensitive, but it is pretty specific. And again, there is a predictive value to it. And that's why we usually get both of these tests.

The acute phase reactants, again, they just represent with sed rate, the fibrinogen is really what's important. And the CRP, they just don't give us that much additional information. You can have a flare of rheumatoid arthritis, and more than 20% of people will have a normal sed rate.

So when we look at this clinical spectrum of the disease, how do we keep it from going from the left to the right there? And there's this enormous variability in the course of the disease. We now, as we see on television, there is great expectations for impact in the disease. We try to focus on treating the target, to stopping the disease process. And when we look at that situation and we look at the so-called disease-modifying antirheumatic drugs, they have expanded enormously. And they are definitely more targeted, but there's a great cost to them.

And so when we look at the treatment of rheumatoid arthritis, we see these algorithms. But the key to it is that our goal is to maximize quality of life through controlling the symptoms. We want to stop structural damage. We want to normalize function and want to keep people physically active.

And it's a difficult disease, and a rheumatologist is very helpful to determine exactly what the position of the disease is right there and how to very early treat the disease process with conventional synthetic drugs like methotrexate, but there are certainly others that we can use. We use steroids on a short-term basis, orally or by injections. But methotrexate is the gold standard to which everything else is really compared.

And this slide, again, just illustrates to you one of the things is all of this variability. And we do definitely focus on high degree of activity. And that really is related to the number of joints involved. And so this is the key, though. The key focus is early diagnosis. And that is the key. And when we take a look at our drugs, anti-inflammatories can help, but these are the drugs that influence the disease process.

As we mentioned, methotrexate is the initial drug. It can be used alone, or in combination with other drugs. We could use triple therapy with sulfasalazine and hydroxychloroquine. And there's an art to that whole situation. But the key is we cannot put our head in the sand. We've got to treat people aggressively early. And if they don't respond to the conventional drugs, we need to really focus on biologics.

And when we take a look, you know, you've seen slides like these. These can be pretty overwhelming. I was just at the Pennsylvania Rheumatology Society. And now, we're looking at how-- we look at the drugs targeting the specific cytokines, the mediators of inflammation.

One thing, and actually I'd ask the speaker, about how if you inhibit like TNF, how does that stop the whole process? It's still not clear whether we do that or IL-6 or other drugs of the many. And that's what we're really looking at, do we look at levels of the cytokines in the blood that is being investigated very intensely? But the key is this, as we just summarize, early disease, persistent disease, and once it starts to get in here, and that's where we need to take a look at how to use methotrexate, adding other drugs to it and then if that does not achieve the results looking at others.

And so when we take a look at this, I mentioned to you what are the most important factors? Well, certainly, the presence of joint inflammation and that is why joint examination is so important to see if there's swelling and tenderness, listening to the patient about morning stiffness. And the other is pain and function. Those are really the key criteria that impact enormously our decision-making about treatment of rheumatoid arthritis.

This is now, there is not a barrier anymore. It used to be that you had to have rheumatoid arthritis for two years before we'd use gold therapy. Gold was OK, but there were a lot of side effects to it. When I said to you what is the single most important factor, the single most important factor is treating the disease earlier because there is just no question about it, that as the disease persists not only can there be more joint damage but there is more resistance to treatment. So that's why we need to treat people. And that's why the criteria have changed, you have those findings of joint swelling with or without rheumatoid factor, and the rest, we treat people, start them early with methotrexate. We know how to use methotrexate, it's been around actually since the 1940s but in rheumatoid arthritis since 1983. We use it and you just have to monitor the drug.

One thing that's important about pain in rheumatoid arthritis because it is really another part of the challenge, there's a lot of genetic influence that impacts pain, there's psychological distress, which is not inappropriate, of course. And then we have this altered central processing, this sensitization because when people have this chronic pain it does sensitize our brain. And so there can be amplification of the discomfort and that is fibromyalgia. And that's something again, that's why we want to stop inflammation and stop the pain.

I thought that this was really an interesting little slide that talks about difficult challenges. And we have to-- about this window of opportunity of treat to target, yes it is, you've got to treat early. And what's the most effective treatment? The problem is it has to be done very dynamically. The rheumatologists and other health care professionals involved have to see these patients frequently to determine using disease activity measures to look at the outcomes and how to most effectively. And it really does challenge us because of the cost of treatment.

So when we look at outcomes, remember pain and function are so important in terms of quality of life, and they really impact it. And again, that's our focus, that's why therapy measures are very important, that's why engagement of the patient is important, acceptance of it. That's why I encourage people when they come into the office like Dr. Halstead did, is bring me a list, I want to know what your symptoms are. That's why we examine people. We did a study looking at joint counts and it turns out that nurses can do as good a joint count as physicians. So we need to look at how to get other individuals involved in that management to create that health care team because looking at the joints, seeing which joints are affected helps enormously.

And so now we're starting to look at new ways. I mentioned to you about targeting specific cytokines, measuring levels. Now we look at molecular portraits to try to see in terms of whether in the joint fluid or synovial biopsies, whether we're going to be able to identify factors that help us to determine what the course of the disease is going to be and how to best treat.

And so when we look at this biosocial model, and I like this because when we look at this, these are the-- we don't want to get those thought barriers. We want to look at the disease as a spectrum. We want to take a look at the synovitis, we want to know and treat this as early as possible. We want to look at pain and function and inflammation. And then to take a look at these different factors. So as we can have quality of life be maintained so that we can take a look at a patient's psychosocial situation and to focus on that.

And we must never forget as Dr. Halstead said, the patient is what's most important. And that's not meant to be trite, and we all agree with that but I would hope that what we've done in the course of our discussion today is we've taken a look at rheumatoid arthritis, the most common inflammatory type of arthritis and we've shown you a model of how we deal with it. It's definable. Yes, there is a lot of variability. But that's why we have to listen to patients, we have to diagnose them early, we have to look at targeted treatment.

If the treatment is not working, we have to figure out how to modify that so as to bring that inflammation under control. And by doing so, and by using other measures, by using therapy measures, keeping the patient's muscles strong, by helping them from a psychosocial point of view, involving them in that to get them engaged, to get their families engaged, that's how we can remove those barriers. And that's how we can provide the most effective treatment for rheumatoid arthritis. Thank you.