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'Rethinking the Pain and Inflammation Relationship'

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[00:00:10] Well, I'm really **happy to speak tonight**. I've enjoyed coming to these meetings and getting to learn a little bit about each of you and your stories. I am really happy to not only share my story, but also share with you some of the thoughts I've been having related to pain and specifically my specialty, which involves a lot of inflammation related to pain.

[00:00:45] So, as a rheumatologist, one of the main things I specialize in are **autoimmune diseases**. And these are diseases where the immune system gets really angry and revved up and starts to attack your own body. And often, it will attack joints, but it can attack the skin and internal organs and, some of these manifestations are annoying, and some of them are really debilitating, and often there's a lot of pain involved.

[00:01:16] One of the things that, I have, as a rheumatologist... So, one of the ways that we think about pain is that inflammation will activate nerve fibers and send a signal to the brain that is painful. And **my understanding** of that has **changed** slightly. And, I'm hoping to explain that change here over the next 30 minutes or so.

[00:01:45] So, one of the main things that I was trained on and had continued to think about for a long time is the **biomedical model of pain**. And in that model, there's a painful stimulus somewhere in the body, let's say it's a knee joint, and that painful

stimulus then sends a message up to the brain that tells the brain that there's pain there, and the brain then acknowledges that, and then you experience that pain.

[00:02:14] What I'm learning is that through the **biopsychosocial model**, which is really quite a striking change in me. This is something that really kind of shook me in my practice and helped me to really have to rethink how I take care of patients. Prior to coming to Corvallis, like I moved to Corvallis five years ago, I was previously living in New Hampshire, and I had been in New Hampshire for eight years as a rheumatologist. And much of my time was spent doing research. And most of the research was in the lab, and some of it was directly with patients. And one of the projects I worked on with my mentor was looking at osteoarthritis bone samples.

[00:03:06] So, when a patient would have a knee replacement from osteoarthritis, we'd get a sample of that bone, and then we would freeze the sample, and we would get proteins from the sample. And the intent was to see if we could find a **protein signature** or something in the bone that had a **correlation with pain**. And that's where much of the research is in rheumatology, looking at the joint to identify what the pain, why the person has pain. And I realized that that's only part of the story. So, when I first heard about the biopsychosocial model of pain, it was really, given to me as a sampling by Brent Godek and Lance McQuillan. And I heard them talking to residents, and they first talked about the Pain Triangle, which you all know has been championed by Dr. Kevin Cuccaro.

[00:04:07] And when I first heard about the **Pain Triangle**, I thought, "Yeah, okay, that sounds kind of interesting." But it didn't really click. I didn't really understand it. And then a year ago, I went to the Oregon Pain Summit in January, and at that summit, my mind was opened. And it started largely with the story about the **construction worker** who had a nail that went through his boot, and he was in exquisite pain, so much pain that when he went to the ER, they had to give him lots of IV morphine and some anti-anxiety medication to help decrease the pain. And yet, when they finally got the boot off, the skin wasn't even broken. The nail had gone between his toes.

[00:05:00] And that story was the key for me. That just triggered a change like, "Oh, okay, I've been thinking about pain differently. I've always been thinking about pain, in the context of some sort of inflammatory or damage situation, but in reality, the **pain is only influenced by inflammation and damage** but is interpreted by the brain in the context of that individual's current situation." That was mind blowing to me and it was also a little bit unstead... I, I felt unsteady. I was like, "Whoa, what's happening here?" It's almost like a midcareer crisis almost because I felt like it completely changed my view on how to approach patients with pain.

[00:05:56] And, I actually started asking myself the question, " Have I been doing things wrong? Have I been a bad physician?" And, and my answer to that is no. I've been practicing to the best of my understanding and knowledge, but I think I have greater understanding and have more tools now to help people. So much of the tools that I have used in the past are helpful, but I think that there are **even more tools now** to really help people out. So, with that in mind, I'd like to tell you a little bit about inflammation and pain and tell you kind of my thoughts about this.

[00:06:35] So, first of all, **what is inflammation**? This is one definition: redness, swelling, pain and/or a feeling of heat in the area of the body. And a really important part of this definition is that inflammation is **there to protect**. So, it's there to protect that tissue or that area of the body.

[00:07:04] So, most of the time, when we talk about inflammation, we talk about it in the context of the immune system. So, this [slide] is a little picture of several elements of the immune system. And this is not even exhaustive. There are other **elements of the immune system**. But, many of these are cells. Some of them are proteins, such as antibodies and this protein over on the left called 'complement'. These are elements of the immune system that start and drive inflammation. So, depending on what type of inflammation is present, you're going to have a mixture of some or all of these cells and proteins contributing. The more robust or expansive that the inflammatory response is, you're probably going to have more of these cells involved and there are some types of inflammation that's really going to be limited just a few of the cells.

[00:08:12] But, what I'm going to tell you that's really important is that **98% of the research** around autoimmune disease and around inflammation is really trying to dissect and understand all of the elements of the immune system, of these cells and proteins and how they interact with each other; how they perpetuate each other; and how they activate each other. So, that's what I have always thought about in the context of inflammation. And, as I mentioned earlier, I'm starting to modify that a little bit. And I'm going to show you how I'm modifying that, as I think about inflammation.

[00:09:01] So, here are some key points when we talk about inflammation and the importance of this. So, most of the time, inflammation occurs in the context of some sort of infection or as a response to some sort of damaged tissue. So, if you break a bone, some of the swelling that's accompanied with that includes inflammation to heal the bone. If you get an infection, such as a pneumonia, you have a great deal of swelling and cells that go to that area to **help fight off the infection**. So this really is the prime reason that we get inflammation much of the time. Now there are some cases where inflammation, which is meant to be protective, actually becomes too abundant. And that inflammation is overexpressed, and that leads to a **harmful form of inflammation**.

[00:10:12] So, in the example of COVID, when you have a viral infection such as COVID, your immune system, you want it to act in a way that it will recognize the virus, kill the virus, and prevent the virus from propagating throughout your body. And for most people, that's what's happened. But for the people who end up in the hospital because their lungs are filling up with fluid, and most of the people who end up dying because of severe COVID, is because they get a **hyperinflammatory response**. So, their immune system responds to the COVID, but it overresponds, and it becomes So, exuberant that you get fluid and cells all filling up your lungs and other tissues. And you get blood clots that form, and this ends up leading to death. Of course, this also happens in autoimmune disease. There's too much inflammation. And so we want to target that inflammation.

[00:11:17] In the context of pain, the main model of pain in relation to inflammation is that proteins made by the immune cells are released, and the nerve endings are stimulated by those proteins. We often call them **cytokines**. And, because those nerves are stimulated by those proteins, they send a signal to the brain, and that is why we have pain. But, what we're learning more and more is that, yes, the sensory nerves are stimulated by cytokines, but it also goes the other way. Nerves can release chemicals that stimulate the immune system and can drive inflammation. So, pain, and inflammation, and the neurofunction can actually go both ways. So, I think that's really interesting that it's not just the inflammation stimulating the nerves, leading to pain, but **also signals from the brain** through the nerves can stimulate inflammation.

[00:12:26] Okay, so, here is an example [slide]. In the left side of this picture, you get a splinter. And on that splinter, you have dirt, and bacteria, and maybe even a little fungus. And so, that gets stuck under the skin, and that's not good. We don't want that in our body, and so, our body wants to protect us. What happens to protect that tissue? Well, one thing we do is we get pain. And we **have pain so that we can pay attention to that area**. "Wow, look, I have a stick stuck in my skin. I need to get it out," or, "I need to stop what I'm doing so that I don't get more of these slivers in my skin." So the pain helps us to pay attention to that area and address it. And it might mean that we pull the sliver out. It might mean that we go soak our hand under warm water. But whatever, that's why we have pain.

[00:13:34] But the other response that happens is inflammation. So, from this graph, you see that the **immune cells** start to come out of the capillary there, the blood vessel, and they get into the tissue so that they can fight off any bacteria that are present. You also get leakiness of the vessels, so that there's increased swelling. That facilitates the white blood cells getting to where they need to go. And part of that whole process also leads to warmth and redness. Now, this is very interesting again because predominantly the model is that you have local immune cells who recognize that there's now a bacteria

there. And in order to get more immune cells and inflammation to the area, those local immune cells will **release the chemicals** that cause the inflammatory response.

[00:14:41] However, what we also know is that the **nerves in the area** similarly will release chemicals and cytokines to help increase the inflammation. So here we have both the nervous system and the immune system working together to protect this part of our body.

[00:15:00] I'm going to show you a study [slide] that illustrates how the nervous system contributes to inflammation. So, this is taking healthy patients or healthy individuals. And, what they're going to do is they're going to apply a noxious chemical to the forearm of the skin. And, the specific chemical is called **capsaicin**. And, that stimulates an inflammatory response, of the skin. And then what we're looking at is a thermographic image. So, this is showing us how much blood flow which is a surrogate marker of inflammation. So, they took some of these subjects and just took them in their normal state of mind. And these are the non-stressed individuals. And then they took individuals, and they exposed them to what they called **psychogenic stress**. So, they showed them multiple images that were disturbing and caused them to feel stress. And then they applied the capsaicin. And what this picture shows is that the individuals who were stressed, in other words, their nervous system was in a higher state of alert. When they had a noxious stimulus to their skin, the inflammation was higher.

[00:16:27] Why is this relevant? This again shows that the nerves are contributing to the inflammation. So, this is called **neurogenic inflammation**. And, of course, this picture is probably one of their best examples, and not everyone had quite as robust response. But, when they looked at several individuals, this same finding that having your mind in a stressed state led to an increased state of inflammation in response to the stimulus. Okay. So, I'm hoping that makes sense.

[00:17:00] So, we now have established that inflammation is not only driven by the immune system but also driven by the nerves and that the purpose of inflammation is to help protect our tissue. Sometimes that inflammation is overexpressed. So, let's think about a situation or a disease where that inflammatory response is overexpressed. One of my favorite illnesses is **rheumatoid arthritis**. And, while I was doing research, this is the main disease that I focused on. And, I continue to do some research in rheumatoid arthritis here in Corvallis. This is what is often considered a quintessential autoimmune disease, partly because it's one of the more common forms of autoimmune arthritis. About 1% of the US population will have rheumatoid arthritis.

[00:18:03] The key difference to rheumatoid arthritis as opposed to **osteoarthritis**, which is typically what you think of when the hands have deformities in someone who's over

50, usually that's from osteoarthritis where you get wear and tear in the cartilage and some bony overgrowth. But, with rheumatoid arthritis, the problem in the joints is too much inflammation. So, you can see [slide] from the diagram on the right, the kind of blown-up image that there is a tissue in there called the **synovium**. And the synovium in the joint normally is very thin, but in rheumatoid arthritis, that synovium becomes very inflamed. So, it's filled with immune cells; it's filled with fluid; and it's got all kinds of cytokines in there. And this leads to very swollen joints. And the inflammation also, contributes to the pain. Now again, the inflammation contributes. It's not the only reason people have pain. There are several other reasons, but it is a major contributor to the pain.

[00:19:22] Now if we think about rheumatoid arthritis and why people get this inflammation, there's a lot, this is a really complicated, and I don't want you to get too overwhelmed by this particular figure [slide]. But, what I'm going to show you or emphasize is that at the top panel, there are several things that are going to increase somebody's risk. So it might be their microbiome. It might be smoking. There's also some genetic component. And, this ultimately leads to an altered immune response. So, one of the ways that we know that someone has rheumatoid arthritis is by checking an autoantibody called **anti-CCP antibody**. And the interesting thing is that people can develop anti-CCP antibodies years before they ever get arthritis.

[00:20:18] So, lots and lots of effort has been put into understanding how people develop those anti-CCP antibodies. And we have a pretty good idea about how that works. But a real challenge is this step right here, this transition to arthritis. So, we know how people's immune system becomes altered, but we don't really know what step happens for the immune system to then get into the joints and cause inflammation in the joints. So, this is a real puzzle. You'll see that one of the **speculative reasons** put in this slide is **neuoimnune factors** , and I think that's where there's a considerable promise that that's one of the main reasons how the immune system starts getting into the joints. And, I'll explain that in just a little bit.

[00:21:13] Okay, so, here's several immune cells. So, let's say that you have a joint that somehow these immune cells get into the joint in rheumatoid arthritis. And, what they do is they're communicating with each other. So, one of the things that they're going to do is they're going to release a chemical called IL-6, **interleukin 6**. And this is going to give a signal to the other cells to stay very active, to keep searching in case there's an infection or something that needs to take care of, and that is a big driver of inflammation in rheumatoid arthritis. Another chemical or cytokine that's released is something called **TNF**. And this is a major driver. So these chemicals are being released, and the cells are talking together, and so you get this ongoing cycle of inflammation that just persists. And the immune cells tend to feed each other and it just goes and goes and goes. And, if we

didn't do anything to intervene, then this would just continue until the inflammation was so bad that people end up hospitalized or other things.

[00:22:27] So, fortunately, we do understand this, and so we've been able to develop really good medicines to try and stop this process. One of the medicines that I frequently use is called adalimumab, also known as **HUMIRA**, and this is an antibody that will block TNF. So, if I have someone with rheumatoid arthritis who has this very active inflammatory cycle, and I can give them adalimumab, it can block TNF. And, in the right person, it will stop that inflammatory cycle, so that the other cytokines go down, and all of these immune cells become quiet.

[00:23:09] Yes, that's what we want! We want the inflammation to go down. We want the pain to go away. And, this can really help people to feel quite good. One of the problems, though, with rheumatoid arthritis is that, if I then take away their adalimumab, the cycle comes back. Now, if it was just the immune cells causing that perpetual cycle, then you would expect that by stopping the cycle and them all being quiescent, that it should stop. But that's not the case. You stop the drug, and the cycle returns. So, here's a theory that I'm throwing out there, and other people throwing out, is maybe there's something feeding the cycle. Maybe the **nerves are releasing chemicals** into this tissue, and it's feeding and perpetuating the cycle, So, that if you block the TNF, you can stop the cycle. But, taking the drug away, it's going to start back up because the nerves are still there. So, that begs the question, "What can we do to stop the nerves from perpetuating the cycle?" And, that's still something that we have to really explore.

[00:24:31] Okay, so I want to show you a little bit of evidence [slide] that supports this theory that the nerves, again, signals from the brain traveling to the nerves, can initiate or perpetuate inflammation. So, one of the studies I want to show you is looking at the impact of adverse childhood events on childhood arthritis. So, **adverse childhood events** are traumatic episodes that happen to children. They can be things that have happened to them personally, such as physical abuse or neglect or sexual abuse, or it can be things they've observed such as abuse to a parent or something like that.

[00:25:19] So, what this study looked at is they took patients with arthritis who were kids, so these are **teenagers** usually who **had arthritis**, and this is inflammatory arthritis. And then they took healthy kids and they looked to see how many adverse childhood events there were, and what the risk of developing arthritis was. So, what you can see from this table is that, for the kids who had higher numbers of **ACEs**, their risk of getting arthritis went up substantially. So, for instance, in the unadjusted model, if you had more than four adverse childhood events, then your odds of getting arthritis increased sixteenfold, which is pretty amazing.

[00:26:10] In the adjusted model, it wasn't quite that high, but it was still quite high. So, this is not definitive. It doesn't define that ACEs caused this, but it suggests that there's a relationship between the **brain being in a higher state of threat** or danger and that contributes to inflammation in the joints.

[00:26:35] Here's another study [slide]. This is looking at adults now in patients with rheumatoid arthritis and the question was, "Have you had **trauma**? And if you have had trauma in the past, do you have symptoms suggestive of active **PTSD**?" So, the control were the group of patients who did not have trauma and did not have PTSD symptoms. And then they wanted to see what was the increased incidence of rheumatoid arthritis based on the prior history of trauma and symptoms of PTSD. And, what you can see from the, probably easiest to look at the, either the second or the third row because they're essentially the same, is that the more number of PTSD symptoms you have, the higher incidence of rheumatoid arthritis that you have. So, this study supports that, again, the brain having a sense of danger or threat leads to increased risk of rheumatoid arthritis.

[00:27:50] Okay, so, I'm going to show you another really interesting study [slide]. And, this is something that just has always fascinated me and I've never understood it until I started thinking about inflammation and the nervous system in a different way. So, this is a case of a patient who developed rheumatoid arthritis, which by the way, rheumatoid arthritis is **almost always symmetric**. So, it's both hands, both feet. And, two years later, he had a stroke on his left side. So, his left side was basically paralyzed. He no longer had nerve innervation or stimulation from the brain to that left hand. And, this is taken some time later. So, you what you can see in Box A is that the left hand looks quite normal, but the right hand shows severe destructive changes. The fingers are skewed off to the side. The bones in the hand, there's loss of joint space and there's lots of erosions. So, this is a very aggressive arthritis.

[00:29:05] And if you look at B, this is looking at heat, which is a surrogate marker of inflammation. You can see that their right hand has much more inflammation than the left hand. Why is it that **someone with rheumatoid arthritis who loses innervation to one side**, also loses inflammation in that side? Well, a possible explanation, again, is that the nerves are stimulating and perpetuating the inflammation or at least helping the immune cells to perpetuate that inflammation. I've seen this in my own patients. I've had probably two patients where I have seen this myself. So, this definitely is not, unique to this case.

[00:29:52] Okay, lastly, I want to show you this really interesting study [slide]. So, this is done out of, I think it was in Denmark or Sweden, one of those European countries. And, what they were asking was, "Could we lower inflammation and immune activity in patients with rheumatoid arthritis by stimulating the **vagal nerve**?" Now, the vagal nerve

mediates the part of our nervous system, part of the autonomic nervous system, called the parasympathetic nervous system. So, if you're not familiar with that, you will be aware of the concept of the fight or flight system. So, that's the sympathetic nervous system. When we have a fight or flight response, that increases our heart rate, it causes us to sweat, it gets our muscles tense and ready, and it helps us to be ready for action.

[00:30:51] The opposite of that is the **parasympathetic**, or rest and digest. And that is mediated by the vagal nerve. So, these doctors took patients with rheumatoid arthritis, and most of them had refractory disease. They'd been through four, five, six different biologic medications and still had active disease. And they had very active disease. So, these were patients who were not just a little bit inflamed and painful, they had very, very active disease. And what they did is they implanted a **vagal nerve stimulato**r in the neck. And they stimulated that vagal nerve for only four minutes a day. And then, they did that every day for 42 days, and then they stopped the vagal nerve stimulation.

[00:31:41] So, what you'll see in B is TNF found in the blood. So, you remember from before that TNF is one of those proteins that drives inflammation. And you can see that from day zero to day 42 of this vagal nerve stimulation, the amount of TNF went down considerably. When they stopped the vagal nerve stimulation on day 56, it went back up. If you look at C, this is change in a **disease activity measure** called DAS-28-CRP. So, this is a way of measuring active rheumatoid arthritis. The baseline DAS for most of these people was about six. So, you can see that the amount of drop in disease activity was approximately a third of their disease activity, which is amazing for a nonmedication intervention. So, here again is evidence to support that the nervous system is contributing to inflammation in rheumatoid arthritis.

[00:32:45] Okay, so this is a model [slide] that I mentioned to you before, and I'm going to change this just a little bit and pose **a new model of inflammation**. So, instead of inflammation primarily being there to fight infection, inflammation is a result of the immune system and nervous system activating the response to a threat to protect the tissue. This hasn't changed. There are many cases where that inflammation is overexuberant, especially autoimmune disease. But, while the immune system, those cells and proteins can perpetuate an inflammatory response. Neural activity may stimulate and direct the inflammatory response.

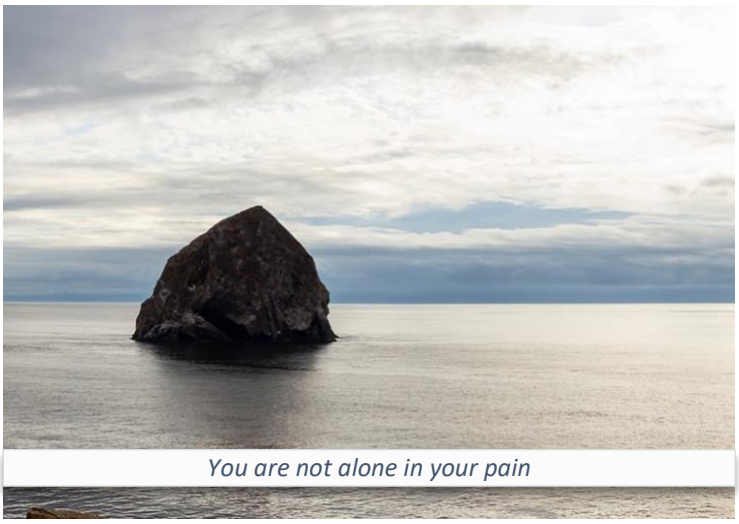
[00:33:32] Therefore, if I can get someone with rheumatoid arthritis to control the inflammation with the right medication, but I can also help to **change the neural stimulation** by decreasing the sense of threat and the need to protect the tissues, can I also then help them get off of that rheumatoid arthritis medication and let them to stay in remission of their disease? I'm hoping. I think it's interesting and intriguing. I don't know for sure, but that's kind of what I'm thinking about now.

[00:34:12] So, finally, this is the **last point** I wanted to say. What I have learned about pain with the biopsychosocial model of pain is that having a heightened sense of threat can lead to increased pain. And similarly, that same process may also lead to increased inflammation. Now, some people who have that increased threat may manifest without a lot of inflammation, but if you have the right genetics or potentially the right microbiome, then that may result in ending up in chronic inflammation. And, therefore, **treatment for rheumatoid arthritis** is not just focused on the immune cells, but also the state of the brain. And that's what I have.

About Pain Science Life Stories

Formed in 2018, the Oregon Pain Science Alliance (the Alliance) is an all-volunteer nonprofit 501(c)3 corporation. Our members come from the health care community, their patients, and others who follow pain science research.

We seek to share current information on how pain experiences are formed in the brain and influenced by biological, psychological, and/or social factors. Through community education events, health care workers describe how pain-science-based practices have changed their interaction with and care for patients, and patients tell stories about their experience with learned pain science tools used to help master chronic pain. We can now share these collected and curated stories, and other unique features, through the Alliance "story website" launched in early fall of 2022.



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Do new Pain Science insights and practices resonate with you?

We welcome anyone interested in collaborating to find or produce good stories and insights, then curating them to display on our website. Sharing in our discoveries and making them broadly available is both personally positive, and mutually satisfying.

The phone number or email address below will get you more information about us; then use the website link to the Member page for the steps to become an Alliance member, if that makes sense to you.

If you have a story using pain science tools and practices, and would like to share it with the larger community through our website, please send us an email. We would love to hear from you.

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