Key:

T: Dr. Thomas

T: Greetings. Today I want to talk about pain and nociception, and I also am going to talk about how pain and nociception are measured, how they're studied and how the measurement of pain might impact the legal system, how it might be used in a legal system or not used in the legal system. So, I want to start by distinguishing between pain and nociception. You may not have heard of the term nociception. Maybe you have, but it's really easy to study. Nociception is simply when you get noxious stimulus to a body part, say your hand. You get a pinch. You get some heat, extreme cold, and you have little receptors in your skin. These receptors will get activated to tell your nerve that you have potential damage to your nerve, to your skin about to happen. Send a signal, and this data then goes to the brain. That's nociception, basically sensing noxious stimuli. It's not a problem. It's good that we have that, but pain is something different. Now when the stimuli come to the brain, they go all over the place. They go to memory areas. They go to sensing areas. They go to discrimination areas. They go to your affect. You have emotions around people, you feel the pain. It goes all over your brain, where it's sensed, where it's reacted to, where you learn from it. So, pain is a lot more complicated to understand, a lot more complicated to study. But let me just start by saying pain is good, okay? Now that might sound incorrect in a way for all the people suffering from pain, and I don't want to say people should suffer from pain, but pain is a very good sensation to have in general. It protects the individuals. You learn not to do what hurt you again. You learn to get away from what just hurt you. There are people that cannot feel pain. They're born with no pain ever in their life. It sounds like, well, "Wouldn't that be nice if I never had pain, never had to suffer?" but these people have very, very difficult lives. They hurt themselves. They lose fingers. They don't know when their body is being hurt, so they can't protect themselves. In species, I can't think of a species that doesn't feel pain because species that didn't react to being hurt, being injured, weren't around that long to exist in evolution. So, pain is very biologically important, and it helps us survive, as people, as a species. However, pain can also be very, very bad. About 100 million Americans suffer from pain, persistent pain. That's almost a third of our population. That's a lot of people that are suffering. So, although pain is adaptive, it's good to have pain, it's good that we can sense pain, it can also become very maladaptive. It can ruin people's lives. And let me talk about some sorts of pains that you might have. There's that pain that when you sense, you step on a tack, you should react to it. That's fine. You don't step on the tack again, or you take your hand out of the fire. There's also pain associated with diseases. So, let me give you one example: gout. Gout hurts your hands, it hurts your feet, and that disease is caused by the build up of acids in your extremities, and these acids form crystals. Crystals are often

sharp, and so what you really have, it's sort of like you're being poked by a pin, and you get nociception coming up your nerves. But you're being poked from the inside. So moving is poking you with pins from the insides, and a lot of diseases do something to your body that then causes you to have nociceptive information, data sent to your brain which then gets seen as pain by your brain. It gets interpreted as pain and it starts to hurt. In those cases, if you work on the disease and you can get rid of the disease. Say you get the pins not poking your skin from the inside anymore, the pain goes away. Even with disease, though, you still have to treat the pain until the disease goes away. However, pain itself can become a disease, its own disease, and that's why we have 100 million people in pain because a lot of them have the disease of pain. Your nerves, the ones carrying nociceptive information, they can just fire all the time saying, you have a lot of pain, you have a lot of pain. Your brain senses it and reacts and feels a lot of pain. That's neuropathic pain and that's very common, and hard to treat. But a newer type of pain that we're just starting to understand better now is centralized pain. Your brain actually gets inflamed in a way. You have these toxins that are released, and these inflammatory agents that are released. Your brain becomes very sensitive, much like if you've sprained your wrist. It hurts when you move it. Well, people with this centralized pain, any stimuli that comes in starts to hurt. It gets amplified so that it's hard for them to live their life because everything hurts. This is where I want to bring in two concepts: allodynia and hyperalgesia. Allodynia means that if you have some sort of sensory stimulation, say just touch, just taking a shower, wind blowing on you, that can really, really hurt. It becomes pain. Nonpainful stimuli then become painful, and your brain thinks that you're really being hurt, that you're being injured, but you're not. It's just the brain is misinterpreting the information it's getting. A second type of pain is hyperalgesia. That's when a normally painful stimulus becomes a lot more painful. It's kind of like allodynia where what you see is not what you get. Light pressure, cooling, heating that's a little painful, it's excruciating for these people. There's one thought that opioids, people take opioids for pain that in the long run, they might produce opioid induced hyperalgesia where the opioid itself starts to make more pain. So you're in pain, you take an opioid, pain goes down, but then after the opioid is done, your way pain goes up higher. So, you take a little more opioid to push it down, but your pain comes back more and more, not being driven necessarily by the nerves or by the injury but by the opioid itself. So, that's a vicious cycle that we're trying to get a better handle on and is of great concern, especially during an opioid crisis. Another distinction is between acute and chronic pain. I bring it up because a lot of people are familiar with that distinction. Acute pain is considered less than 3 or 6 months in duration. Chronic pain is over those periods of time, but it's really just a shortcut notation for clinicians. There's nothing mechanistic about it. If I go to a doctor and I've been in pain for 6 months and 1 day, the doctor should not say to me, "Guess what, Dave? You're now in chronic pain." Because nothing has really changed between the days. We need to look more at pain in

terms of its mechanism, and being a scientist, this distinction, acute versus chronic, well, it's fine if it hasn't lasted long, it has lasted a long time. But scientifically, we need to look inside what's going on and what's changed in the chronic pain state. So, pain can be a sensation, or it can be the symptom of a disease. Now people ask me about the pain matrix, "What is that exactly?" and I alluded to this earlier, but pain affects all sorts of parts of your brain. It affects your emotions, your memory, your sleep. It affects your affect. It's everywhere, and that makes sense because pain is such an important sensation for survival that a lot of brain areas are involved. But it also makes it complex because you can't measure, oh, there's pain right there, or you see it on a little imaging thing. That person is in level-four pain, or they have an eight for their pain. You can't do that. It's all over the place, all sorts of things are going on with the neurons, which are your typical brain cells. But it goes beyond neurons. There's genetics changes that happen. Your immune system, both peripherally, in your body, and also in your brain. Your immune system goes very active and can then escalate to more pain, and even things like your microbiome, your gut. It looks like the microbiome, the flora in your stomach, actually talk to your brain. It goes back and forth too. So, brain affects you on many, many levels. I want to make that very clear that pain affects on you on many, many levels. It affects your behavior, your psychology, your social interaction, even on the spiritual level. So, we have to do a better job at the National Institutes of Health and just in general in understanding what pain is. One big problem we've had in studying pain is how we measure it. It's all over the place. It's hard to get a handle on. The way we measure pain now is with self-report, and self-report is important. You should listen to people when they say they're in pain, but it's like if somebody came in to a doctor's office and said, "I feel hot. I feel like I have a fever." Would you say, "Okay, well, how big of a fire does it feel like, like a campfire? Does it feel like a really big campfire, or a little campfire?" You would do that, but with self-report on pain we have smiley faces, frownie faces, and somehow, we think that captures the experience of pain, or a number on a zero-to-10 scale. So, we have to do better than merely self-report. Pain is real. It affects you on many, many levels, and we can study these things on many, many levels, and that's what we're trying to do at the NIH. One thing that looked like, and is promising for studying pain, is FMRI. It's a way to look at glucose and blood flow in your brain to indicate activity. It's been around for at least 30 years. We do have some idea from there, from using FMRI, what's activated and what's not in pain. But it varies so much. It's not a camera into consciousness. You don't get the whole picture of pain from the FMRI. It's important to see. It's a good research tool, but it's not the whole story. Now in terms of legal assessment for pain, I likened it to genetics. Genetics took over 100 years before it could get into being used for evidence for court cases. We're not at the point where we can go beyond what a person says. If a person says that they are in pain, they probably are. What we're trying to do scientifically is to add to the self-report where we get some information that says, okay, you say you're in pain, but now we

know it's somewhat neuropathic. Maybe you have some central desensitization, maybe it's more nociceptive pain. Those are the sort of things we could a little better handle on is what type of pain you're in and what treatments might work. Just better than self-report. That's where we're at at this point in time. So, I don't think that the FMRI is ready for that, and I don't think it will be just used alone. It's unlikely that we'll be able to just image a person's brain, and based on glucose level and neurons activity in some growth areas of the brain, that we'll say, "Ah, you're in this much pain." But what we could do is use FMRI, and this is something we're working, is use FMRI with other things. That's true. Look at the brain activity, use fancy statistics, machine learning to see how things are connected, but then connect that with other things. Because if you see a person in pain, there's all sorts of things going on with them. It's clinical wisdom, and neurologists know this, that people in chronic pain are very sensitive to light. Their pupils act differently. We're starting to look at research that looks at brain waves that are different in people in pain. Genetics, facial expressions. You can have a computer read the face of a person or a rat in pain, and they're pretty good. The computers are pretty good at detecting whether that person is in pain. I mentioned before the microbiome, what we'd like to do, and this is what we're working on, is to use machine learning to take all this information, to look at genetics, look at the brain, look at everything, put it together and get a fingerprint of pain. That, I think, would really change the field where we'd be able to do better research on pain. We'd be able to diagnose pain and be able to select treatments better. Instead of going to a doctor and having them give you different pills, and seeing what works, and trying something else, and trying opioids, it would be nice to know what works best first. So, what we're trying to do at the National Institutes of Health is to promote better health. We're trying to get better pain diagnosis during the opioid crisis. We want to help people in pain, and we also think it could be good for the justice system at some point when we're ready to help people in pain. People in pain, they go to court, they might be in pain. You don't know they're in pain because you can't see it. I think they would get better justice within the criminal justice system but also people that were trying to game the system. Yeah, we should know that they're not in pain. If they're trying to game the system and pretend, they're in pain, they're hurting people in pain within the system, and that's a crime. So, I would like at some point for us to get these measures so they're really, really good. I think it would really help people in pain, and I would love to see the day where it could be used in the judicial system because that would mean we have such a handle on measuring pain that we've helped a lot of people in the scientific world. Thank you.