Long-COVID, autoimmunity and PANS/PANDAS

Guest: Dr. Sam Yanuck

Disclaimer: The contents of this interview are for informational purposes only and are not intended to be a substitute for professional medical advice, diagnosis, or treatment. This interview does not provide medical advice, diagnosis, or treatment. Always seek the advice of your physician or other qualified health provider with any questions you may have regarding a medical condition.

Claire Sehinson - [00:00:16]

Hello and welcome back to the Fatigue Super Conference, I'm Claire, the Head of Research at the Optimum Health Clinic, and today I'm really excited to be talking to Dr. Sam Yanuck about long-COVID, autoimmunity and PANS/PANDAS.

Dr. Yanuck is CEO and director of education for Cogence Immunology, an online functional immunology course, with over 5000 clinician participants from more than 60 countries around the world. He's an adjunct assistant professor in the program on Integrative Medicine, in the Department of Physical Medicine and Rehabilitation at the University of North Carolina School of Medicine, where he teaches topics in functional immunology.

Dr. Yanuck runs the Yanuck Center for Life and Health, a functional medicine clinic in Chapel Hill, North Carolina, where he sees patients with complex autoimmune disorders and other immunologically challenging cases. He also provides online consultations to clinicians around the world. Dr. Yanuck and colleagues recently published a functional medicine perspective on COVID-19. In the paper, *'Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery*'. Dr. Yanuck is also the author of a key paper called '*Microglial Phagocytosis of Neurons - Diminishing Neuronal Loss in Traumatic, Infectious, Inflammatory, and Autoimmune CNS Disorders*'.

Welcome, Dr. Yanuck, to the conference. We're so pleased to have you here. And a huge thank you from myself and my colleagues and all practitioners who've really gained a lot of knowledge and experience and clinical prowess from your course, I mean, it's really been a game changer in treating some of the complex patients. So thank you for that, too.

Dr. Sam Yanuck

Absolutely. That's very gratifying to hear.

Claire Sehinson

Yeah, brilliant. So I thought we'd just dive in, firstly, with the current pandemic and sort of what makes COVID-19, I guess, or SARS-CoV-2 so special in terms of a virus? I know traditionally we think of epidemiology as the more contagious something is, so less deadly, I guess the infection can be. But with COVID-19 it seems to have this quite transmissible, contagious aspect as well as seemingly being very deadly. So is anything special about the virus or the current infection that's caused this global pandemic?

Dr. Sam Yanuck

I think you look at COVID, for example, compared to something like Ebola, you know, with Ebola, and granted I'm not an Ebola expert by any means, but, you know, it's fairly intuitive that the symptom onset is pretty fast and the symptoms are sort of horrifying. And so it's very natural that people keep

their distance. And the people who have Ebola virus are rapidly identified because there's not a giant window of lag between when a person becomes infected and when they become symptomatic.

The problem with COVID is that it's a combination of aggressiveness, when it's aggressive and a symptom lag. So, if you get infected on day number one and you start to show symptoms on day number five, there's plenty of time when you spread it around. And certainly in my own practice, every patient who has gotten COVID, has gotten it through some descriptive narrative that includes phrases like I didn't realize or I thought my choice was going to be OK because. And so they then discover like, oh, you know, it turns out I got COVID. I thought I was handling the process reasonably and it turned out I wasn't. And I only realized in retrospect that I had made myself vulnerable to receiving transmission of the virus.

So that lag makes it rather invisible. Now a lot of people get COVID and they're fine, but the trouble is that for those that are susceptible, it's potentially deadly. And then, of course, there are also post-COVID effects that involve damage to lungs or kidneys or heart or liver or other vasculature, including brain vasculature. You get this microvascular damage. Now you have hypoxic tissue. Now you're into the way that hypoxia induces inflammation, not to mention other kinds of things like fatigue and so on. And you're off to the races. So if it doesn't kill you, you can still have life long sequelae that are that are profoundly problematic.

And that's a piece of this that I think we're going to discover over the next several years is, how many of the people who got COVID and recovered now have long term consequences? And are those consequences reversible and to what extent in which people and so on?

Claire Sehinson - [00:05:38]

And I guess, I think one of the numbers, the figures that are being thrown around here is, 1 in 10 people with COVID will go on to develop a longer form of COVID. So, experiencing symptoms for weeks or potentially much longer, months and months longer. I guess for you, how does it become long-COVID in certain people and completely asymptomatic in other people?

Dr. Sam Yanuck

Well, I think the first thing to say is that there's enough complexity here that it's unlikely that we'll be able to say the singular way that it happens is... It's much more likely that we're going to need to unpack each person's biology individually and say, OK, what appears to be happening in this person is that persistent microvascular damage to the lungs is yielding them effects. Or persistent microvascular or persistent fibrotic damage to the kidneys is yielding them such and such an effect. Or development of soft tissue antibodies, as a consequence of tissue damage and therefore presentation of the debris of that damage as antigen, has cultivated the development of an autoimmune process in this patient.

So there are going to be lots of different manifestations of this. And the clinician's job is going to be, they should be able to unpack, on an individualized basis, what's going on. And that's going to put us into a zone in which, as I think we've seen in other circumstances, an attempt to name the thing and put a diagnostic code number on it, as though everybody has that thing is identical, that attempt will fail.

We've seen the same kind of thing, for example, with chronic fatigue syndrome, where people have fatigue for a whole variety of different reasons, and there are subgroups categorized by certain things. But the idea of chronic fatigue syndrome or myalgic encephalomyelitis as a singular entity where everybody who has it is identical in relation to that entity, is probably not real.

Claire Sehinson

Yeah, and I think it's been highlighted more with the onset of the long-COVID. I've got a lot of patience to, it's sort of going two ways. I'm really frustrated that all of this emerging research is coming out with the current pandemic, when they ignored post-viral fatigue or potentially not even believed. And the

other is, just really excited of these new developments in inflammation and immunology. So, I think it will ultimately be a good thing.

I guess with some of our clients, in particular what we're seeing with long-COVID or even COVID itself, it can present really atypically. So I've seen a complete absence of lung involvement and sometimes neurological, gut, completely gut manifestations of COVID, is that what you are seeing in this area? Is that down to the individual again?

Dr. Sam Yanuck - [00:08:45]

It's all over. It's what the virus turned out to have done. Or what the immune response being overly exuberant turns out to have done. You know, and it's hard to tell sometimes if, let's say, let's say a person has impairment of kidney function. Sometimes, you know, OK, this person had impaired kidney function going in, right, and so it's not a surprise that they had some decrements, some further decrements in their renal capacity. OK, that's straightforward to understand.

Sometimes the person can be a civilian at baseline, biologically speaking, and they get effects from the kidneys. And you say to yourself, did the virus just, from a sort of where it went point of view, did the virus simply affect the kidneys more? Or is it that we didn't really understand or appreciate that this person already was a bit marginal in their renal function? Or perhaps a bit closer to expression of an inflammatory effect, from a threshold's point of view, in their kidneys, so that when they went into a cytokine storm, the kidneys were already so close to falling into that ditch, that they had a deeper manifestation in the kidneys than they had elsewhere. It's difficult to know.

Claire Sehinson

And I guess, you talk so well on purposeful and non-purposeful inflammation. And I think, traditionally we're used to thinking of inflammation as a bad thing, switch it off and non and anti-inflammatory are very good. And I think we're now understanding, obviously a bit more about the immune system, and that in order to fight a viral infection, we actually need to induce a purposeful, inflammatory response. Can you elaborate a bit more on what is purposeful and what's non-purposeful inflammation?

Dr. Sam Yanuck

I mean, we talk in the paper that doctors, Pizzorno, Messier and Fitzgerald and I wrote, we talk a lot about the staging of how to deal with COVID. And so, we're trying to describe a process by which it's important to have adequate Th1 mediated and M1 macrophages mediated response to viral illness, so that you have a crescendo of your immune response. And what the research shows is that, if the interferon mediated crescendo of immune response can happen sooner and more vigorously than the crescendo of viral copy numbers in the patient, then you beat the virus. You don't go into the inflammatory escalation phase, that is the severe COVID.

So, that purposeful immune activation carries with it, inherently, some inflammation, but there's no such thing as killing pathogens in a way that doesn't involve being inflamed. That's not real, right? Because neutrophils have to go in and then monocytes go in, turn to macrophages, gobble up the neutrophils, clear them from the tissue and so on. And in that initial stage we are also setting the stage for antigen presenting cells to present the antigen to T cells and so on. And you want that T cell activation. You want that clonal expansion so that you can have those T cells migrate to where the infection is and kill the infection.

That's all fine if it's efficient. But if you get this grinding perpetuation, where where the immune response itself creates enough inflammation, that now you're getting an immune response to the signals from tissue damage, as well as getting an immune response to the signals from the pathogen being present. Now, you have an inflammatory activation that's too elaborate, right?

So, you can get an immune response from damage and you can get an immune response from pathogens. Both will trigger inflammatory activation. Once you begin to drift over into getting an immune response to the damaged tissue itself, then you risk perpetuating an over, and overly

extended and an overly large elaboration of inflammation. So horizontally through time, but also vertically in terms of intensity, your area under the curve for how inflamed you are, can be too big. Then now you're into damage, now you're into the prospect of promoting autoimmunity, depending on what else is going on, and so on.

Claire Sehinson - [00:13:51]

I guess severe illness, and I guess a lot of what you speak on and work with your clients is subtracting all of the non-purposeful additional inflammatory disorders. And there's so many of them, it almost feels like there is actually a lot we can control. So, could you perhaps kind of touch on what you might subtract from a client's current inflammatory baseline?

Dr. Sam Yanuck

Sure, sure. So there are a lot of things that are part of routine life that can invite the biology toward being inflamed. The simplest one is stress. And, you know, stress is one of these things where it's like, OK, sure, I know I should do yoga. OK, fine, move on. But really, what you'd like to figure out in a case always is, which parts of the case are mysterious and which parts of the case are not mysterious.

Now. You know, when a patient has a complex, multifactorial case, there are parts that you really have to dig into to figure out what's going on. But I always emphasize with patients that if there are parts of the case that are not mysterious, where you can create advantages, increments of advantage by attending to those parts, that's of enormous value. Even if what you have to do to get that done isn't the coolest, newest thing. So people tend to devalue things that aren't the coolest, newest things. But that's a mistake.

So lowering stress level is a pretty straightforward thing. It's just that, you know, the mysterious parts of the case, that's my job. And the patient doesn't have anything to do until I figure that stuff out. But the not mysterious parts of the case, I can tell them what they need to do right away, that's their job. So, lowering stress is very important because stress is inherently inflammatory.

And the problem is that the chemistry of inflammation then turns on in the brain the mechanisms that turn on the stress response. So you can have a very activated biology of stress, even if you don't feel especially emotionally stressed. Some of what you can do to attend to that has to do with like, taking adaptations like ginseng and things like that, that diminish the extent to which you make the chemicals of stress, even though you would feel the emotionality of stress, or even if your stress responses are being evoked by inflammation. So some people have stressed chemistry, even though they have a lot of emotional equanimity. Sometimes the adaptogens are useful there.

Claire Sehinson

Yeah, absolutely. I think a lot of our clients, the more complex ones, have actually been working with our psychology department for quite a long time, and actually say, I'm not actually feeling stressed. And you look at their markers, their bloodwork, and it will be off the chart, off the scales. So yeah, absolutely.

Dr. Sam Yanuck

Yeah. So stress is not, doesn't have to be emotional. You know, if you look at the stress chemistry of a person who delivers packages for a living, let's say in Chicago, in the U.S. or in Sweden or in Scotland or whatever, you know, warm shop, cold outside, warm building, cold outside, warm truck, that constant oscillation of thermal stress. Now that person's stress chemistry is off the charts, even though they're very happy and calm.

So stress can come in a lot of different forms. We're talking about the biology of stress. So that's one of them, in terms of ways to subtract non-purposeful inflammation. So what you want to be left with, the inflammation that's a consequence of responding to the virus. So subtracting stress is important,

attending to dysregulation of the GI tract is very important, dysbiosis things like that, sleep biology is very important.

Very, very useful paper in Nature Reviews Immunology I believe it was by, Irwin is the last name, came out in 2019 or 2020, taught me about the immunology of sleep. And the bottom line of it is that when you have good, solid, deep sleep, it's profoundly anti-inflammatory and you have the adequacy of the Th1 response. When your sleep is too shallow or too disrupted, you have less slow wave sleep, you have more REM sleep, you have more Th2 response, which is not what you want with viral infection, and you have more inflammation.

So one sign of this may be, and some people will simply know, yeah, my sleep was messed up, but for others it may be, yes, I have a ton of dreams all the time. People have a ton of dreams all the time, that may be a sign that their sleep is inefficient. And instead of a lot of slow wave sleep, they have a lot of REM sleep and that needs attention.

Then foods are a big issue, driving inflammation as well. Subtracting problematic foods is very, very important. And people need to understand that if they have antibodies to a certain food, first thing to understand is that we're talking about IgG antibodies, not IgE. IgE antibodies to a food would be a food allergy. Allergy means IgE response. Most food responses are IgG responses, immunoglobulin G. And when you have IgG responses to a food, that's a food sensitivity reaction. It's not an allergy, but nonetheless it's an immune response that's provoking of inflammatory activation.

And people need to be exact about their avoidance of those foods. They can't go from, I eat that all the time to, I eat a little bit but that's probably OK, it's better than what I was doing. No, that's not going to get you anything. You know, setting a forest fire once a week is not OK. Right? You were setting the forest fire every day and now you're setting it once a week or once every two weeks, the forest can be on fire every day of the month when you're setting a forest fire once every two weeks, so you have to go to zero.

Claire Sehinson - [00:20:27]

Absolutely, and do you find in that scenario, do you find lab testing helpful as motivating your client? And would you, or are there certain foods that you find inherently inflammatory in most cases and you might ask clients to remove those food groups?

Dr. Sam Yanuck

Sure. I tend to favor lab testing. It's quite useful. If lab testing is not available, then what I tend to do, if the patient has autoimmunity, just based on what the research shows, I tend to drop out, or I always drop out, things like gluten and dairy. If I don't have any way to understand from a lab testing point of view their responses to gluten cross-reactive foods, then I'll get rid of those as well. There are 8 of those, dairy, yeast, sesame, what am I missing? Dairy, yeast, sesame, corn, millet, rice, oats, coffee.

Claire Sehinson

OK, yeah, that's a significant amount of, I think foods that people, that kind of make up the standard American diet and the British diet and also that people enjoy the most. So it's often quite hard to make those changes I guess for the clients.

Just touching on sleep because you mentioned sleep, and we know that's one of the first things we go to when we're looking to heal, help some of these bodies naturally heal. What are your thoughts on the use of, both melatonin and also, some clients come to us and they'll have a sleep medication, is there any evidence, that you've seen, for detrimental effects of those medications on the proper sleep cycles?

Dr. Sam Yanuck - [00:22:11]

Yeah, I think, if I understand the research correctly, benzodiazepines may tend to diminish the efficiency with which a person gets into stage four sleep, in other words deep sleep. The thing is, that you make 85 percent of your growth hormone in stage four sleep. And growth hormone is necessary for tissue repair. So what you tend to want to prefer is to get into deep sleep efficiently. Now, you can quantify some of this. You know, there are things like, for example, an Oura Ring where it will show you what your sleep architecture is like, so that you know if this theoretical concern about a sleep agent is actually manifesting in the patient.

So always, if a medication is turning out to be quite useful for a person and helps to solve a sleep problem for them, you don't necessarily want to propose to cancel their use of it based on a concern about what might be happening. So that's a person for whom an investment of an Oura Ring, might be an appropriate way to get quantified data to help them track, OK, what's going on? Is this medication creating a problem or not?

Now, as regards melatonin, melatonin is a Th1 support, and so in the context of viral illness certainly, might be quite useful. And then just circling back to growth hormone for a second. One of the things that's very important, you mentioned at the top, you mentioned the paper that I wrote in Frontiers in Psychiatry about neurons and microglial cells. So one of the things to understand there is that everyone loses some neurons, which are the signaling cells in the brain, some neurons every day. That's normal for humans. It's a higher number than you would think. The different estimates put it between 7000 and 50,000 a day.

Claire Sehinson

Wow, that's significant isn't it?

Dr. Sam Yanuck

So let's say it's 10,000, just to pick a number in that region. How do the microglial cells, which are the white blood cells that live in the brain, how do the microglial cells know which are the dead neurons? You can't just gobble up any random 10,000 neurons a day, it's got to be the dead ones. If you're gobbling up the dead ones, you're cleaning up the brain and keeping it, you know, keeping it from getting into necrotic inflammatory stuff, you know.

So the way this is done is through signals between the neurons and the microglial cells, microglial cells just being specialized maps. Now, one of the main signals that neurons send to microglial cells to say, hey, I'm a live neuron alone, is this cluster of growth factors. Nerve growth factor, brain-derived neurotrophic factor and so on. So if you're production of growth factors is diminished, that may not be very good for your brain.

Claire Sehinson

And I guess that leads into things like neurodegenerative conditions, Alzheimer's, Parkinson's and things that we're linking more to the neuroinflammatory processes.

Dr. Sam Yanuck

Right. And PANDAS as well.

Claire Sehinson

Yes, absolutely, which we'll go on to. One thing I learnt from you, Sam was the brain is the biggest immune organ, which I thought that was mind blowing, excuse the pun. But it's, can you speak a little bit more on that? And how does that come to happen? We originally, obviously thought the immune system was the biggest immune organ, and then it turned out it was gut. And now we're thinking a bit more about the brain.

Dr. Sam Yanuck - [00:26:09]

Right. So the immune system is a disseminated system. You got white cells and other immune factors everywhere. So there are three systems like that. There's the nervous system, which is sort of structurally, mechanically everywhere. You have the hormones, the underground system, we're talking about the glands and then there are the things the glands secrete, and those things circulate everywhere. Then you have the immune system. And so, you've got a spleen and lymph nodes, but then you've got all these circulating white cells and antibodies and all kinds of things like that. In the fourth system there is the circulation itself.

But the immune system really is, it is the surveillance mechanism for all of the self, non-self stuff, and given the current realization of how much, if you count by cell numbers, this realization that there's so much not self that's sort of inherently part of biology. But you have your gut microbiome, skin microbiome, you've got organisms everywhere. And the way you make that OK is with this negotiated settlement that is mediated by the immune system. OK, these are commensal bacteria in my intestine. I'm not going to try to attack those, they're doing good things for me. They're manufacturing chemicals that my intestinal lining needs and so on. So there is this process of negotiation.

Now, in terms of brain, the signaling cells are the ones that we think of as the brain. And when you see these wonderful animations about brain cells talking to each other and the signals going down the axon to the next nerve and so, we think to ourselves, oh, yeah, that's the brain. And we think the brain is this giant mass of neurons. But for every neuron there are 10 microglial cells, which are macrophages, white blood cells that live in the brain and that do surveillance on the neurons and keep them from becoming inflamed and prune unuseful synapses. And essentially, they're the gardeners of the brain. And that's all great unless the brain gets too inflamed or develops an autoimmune process, in which case microglial cells begin to become mischief makers.

Claire Sehinson

Yeah, and I guess there's quite a lot of, I guess, symptoms when you look at the survivor corpus survey, large scale patient survey and we have another one in the U.K., Body Politic. And you look at the the top symptoms of the COVID, they're not what you think they are, for a start they're not necessarily respiratory, but fatigue and brain fog are right up there. So I guess that must be part of the neuroinflammatory process as well.

Dr. Sam Yanuck

Yeah, well it's very clear in the research that body inflammatory process is a substantial driver of brain inflammatory process. So even just with that simple mode of understanding, you can imagine that COVID is going to create a fair amount of body inflammation, certainly when it's severe, and that's going to yield you brain inflammation. Now, in a lot of people, when the body information goes away, the brain inflammation goes away. All right, all done. But there are certain circumstances in which one of the consequences of COVID is some kind of respiratory impairment or fibrotic change and so on, that can yield a longer term mild reduction of oxygenation.

Now, hypoxia, low oxygen states, are inherently inflammatory. Now you have a way of perpetuating body inflammation in a way that perpetuates brain inflammation, or you can have some microvascular damage to the brain itself. And that may give you profound fatigue and brain fog. Or you may have a central nervous system inflammatory process that can persist even after the body inflammation has quieted down, or you may have developed in the course of COVID, you may have developed an autoimmune process. We can talk about how that all happens. So there are a lot of ways to end up with a perpetuation of body inflammation that drives brain inflammation or a perpetuation of brain inflammation that persists despite recovery in the body.

Claire Sehinson

And I guess touching on hypoxia a little bit, so much of what we do to support stress chemistry, like meditation and breath work, I guess people with COVID are going to find that quite hard if they have lung scarring, ongoing shortness of breath. So that's kind of a new barrier to people helping

themselves in the most simple way. You find, are there any kind of alternative or other ideas of people who are struggling to breathe that you found useful in your clinic?

Dr. Sam Yanuck - [00:31:32]

Now then, I think that thinking about the biology, that there are a couple of important points. One is, there are indeed so-called long haulers who do very well with hyperbaric oxygen. And that becomes important, not only therapeutically, but also diagnostically. If a person has very substantial improvements with hyperbaric oxygen, then you know that substandard oxygenation, a decrement to the oxygenation, is part of the picture.

Now, one of the problems is if a person has microvascular damage in an organ, that isn't the lungs. Then they may be having trouble, let's say, if they've got microvascular damage in brain or in kidneys or in heart, right, then what you may see is that if you put a pulse oximeter on their finger they may have perfectly adequate oxygenation in their hand, but that doesn't prove to you that their kidney oxygenation is OK.

Claire Sehinson

Yeah, so it depends on circulatory function as well.

Dr. Sam Yanuck

You just have to try to understand what's what in the case.

Now, the other thing to consider is that, if a person has had, has gone through COVID, the concern would be that if they have fibrotic change somewhere in their body, the increased activation of fibroblasts is likely to have caused them to make more transforming growth factor beta, TGF beta, and there's a loop activation between TGF beta and fibroblasts that gets very, very active in COVID. And there's a whole sort of cluster of processes there involving the NLRP3 Inflammasome and neutrophil extracellular traps, and that drives the extra clotting and the microvascular damage, that's a whole different topic.

But the key point is that fibroblasts make TGF beta and TGF beta encourages the activity of fibroblasts. So that's a loop that can drive a persistence of fibrosis. And even as a person who is in recovery from COVID, the concern would be that that biology might continue to persist so that the person begins to accrue more fibrosis, even though they're coming down the other side of the mountain. The crescendo of their disease, and then to the decrescendo, you say to yourself, this person's in recovery, so all is well, but you still have plenty of area under the curve there where a persistent activation of fibrotic change can still be happening. So I always want to push back against that by shutting down that TGF beta activity. And I tend to use, for example, glutathione and n-acetylcysteine to do that.

Claire Sehinson

And when you're approaching your COVID clients and also I guess, some of the chronic immune dysregulation, you often talk about using the right intervention at the right stage of the illness. Can you expand on what a normal trajectory of recovery would look like, given the right nutrients at the right time?

Dr. Sam Yanuck

Yeah, so I always want you know, we talk in the paper about four stages, right. There's prevention, there's when the patient first has COVID, there's if it escalates into this cytokine storm, hyperinflammatory process, then there's recovery. So, in the prevention phase, I always want to make sure a patient comes in and says, I don't have COVID, but I had MS, I have rheumatoid arthritis or I'm just a civilian and I want to make sure that I'm set up in such a way that I'm likely to be as robust as I can be. So in that stage I'm always looking at baseline levels of vitamin D and C and A and B and so

on, making sure their potassium level is adequate because the NLRP3 Inflammasome that's been shown to be so involved and up regulation of inflammatory process in COVID, that NLRP3 Inflammasome was known to be inhibited by potassium. So I just want to make sure that they're topped up there.

And then I want to know what their essential fatty acid status is. I want to know, as you described before, what I can subtract to reduce their baseline inflammatory status. What's their food like? What's their nutrition like? And so on. So their starting point isn't an already on fire starting point.

Then what's been shown in the research is, as I mentioned before, if early in the game you can have an adequate interferon response, so that's going to be favorable. So I'm always wanting to support the adequacy of the Th1 response, the adequacy of the natural killer cell response, all of that kind of stuff. The innate response of M1 macrophages, if you can support that early in the game, they tend to do better, according to the research. And also, observations bear that out.

But if the patient shifts into the escalation of the inflammatory intensity, then you have to let go of support for the Th1 response, support for the natural kill cells and shift over into a vigorous push toward reduction of inflammation. And you have to also make sure that you're doing surveillance on clotting. You have to make sure they don't clot up so quickly. And that kind of process can shift rapidly, you know so you can get COVID.

I'm aware of one case, not a patient of mine, but someone I have a connection with. That person's 40 year old son felt flu-like on Friday, and died of a stroke on Monday.

Claire Sehinson - [00:38:10]

Wow. Dramatic.

Dr. Sam Yanuck

So in the natural medicine world, we tend to deal with patients whose illness is chronic. So we have this sort of, the pace of how to unpack and unfold a case, reflects that sense of chronicity. You may say to a person, OK, you know, we're going to do these things, you're going to come back in a week or two and tell me what you observed and so on. And that's not how COVID is at all. You can't think that your cycles of work are a couple of weeks long before you connect again. You've got to be just on it.

Claire Sehinson

Yeah, it's, I mean, we have had cases of, not necessarily COVID, but viral infections where you're normally expecting someone to have chronically developed the burden on the immune system but actually some people just say, I was fine one day and the next day it was like someone just unplugged the system, which is. Yeah, that's quite key.

I'm just wondering and, you know, a lot of our, the more of the complex people who might have Lyme, berylliosis, kind of chronic viral infections, is it harder to get their natural killer cells and their innate immune response to be adequate? And often in that dual suppressed innate response and chronic inflammatory state, so does that become even more of a challenge to work with?

Dr. Sam Yanuck

That's right. And in those people, you know, what you're looking for is an inventory of the many ways in which people can be drifted over toward being Th2 dominant. And that's very, very common and the problem is that Th2 dominant people tend to have a very inadequate Th1 response. So, stress is a promoter of Th2 dominance, it's inhibitory to Th1 so it will drift over to Th2. Any kind of inflammatory process in a hollow space, like an intestine or a sinus or a lung, is going to move people toward Th2 dominance, head injury moves people towards Th2 dominance, exposure to pesticides, accumulation of plastics in the tissue. Both those pesticides and plastics are things that diminish glutathione status. And so you can't have an adequate Th1 response without glutathione, so those people will be

inadequate in their Th1 response as well. And the list goes on. People who are histaminic are Th2 dominant and so on.

So addressing those kinds of things to diminish the overabundance of their Th2 dominance is a way of helping their Th1 response to move forward.

Claire Sehinson - [00:40:57]

Yeah, absolutely. And I guess it's sort of, touching on autoimmunity and actually what has, I know bacterial viral infections have long been associated with the onset of certain types of autoimmune conditions. Can you expand on what's the mechanism there? How does a viral infection actually trigger the immune system to go wrong?

Dr. Sam Yanuck

Yes. So let me give you a two part answer. The first part is, since we're talking about Th1 response, Th1 cells and natural killer cells and M1 macrophages and CD8 cytotoxic T lymphocytes, that's the group of cell types that helps you kill viruses. So, in a person who's got problems with viral burdens, you want to have more efficient Th1 response, M1 macrophages response, natural killer cells and so on.

What's also true, though, is that if a person develops autoimmunity, the tissue destructive component of autoimmunity is going to be driven by its Th17 cells. We want to down regulate Th17 cells by promoting tolerance, by promoting regulatory T cells, also called Tregs, but we also want to promote Th1. Back in the old days, like in 2002. We only knew about Th1 and Th2. And we thought Th2 was anti inflammatory and Th1 was inflammatory. And Th1 also drove autoimmunity. Well, that's a 19 year old idea that turns out to be entirely wrong. It turns out that the interferon gamma of the Th1 response inhibits Th17 cell activity. So we actually want both regulatory T cells and Th1 cells. So that's the first piece.

Then the question about, OK, how does viral illness cause autoimmunity in the first place? So, there are two tracks here. One track is, you want the Th1's response to be adequate to knock down viruses. The other track is you want the Th1 response to be adequate to knock down Th17 cells. Those two things aren't actually directly connected to each other. So it's a little bit confusing.

The way that the viruses induce autoimmunity isn't about particular T cell polarization necessarily. It's really about the fact that when a cell gets infected with the virus, a bunch of cells let's say, and the virus starts to destroy those tissues. Now you have the debris of that tissue and you have a bunch of viruses there.

Now an antigen presenting cell, which is a white blood cell type, it's going to come in and it's going to try to clean up. And that means that it's going to internalize, it's going to gobble in to itself into that cell, that antigen presenting cell, it's going to gobble into itself some debris of soft tissue and virus. Now it's going to have to present, it's going to go to a lymph node, it's going to go from where that damaged tissue is, to the draining lymph nodes of that tissue and it's going present both that fragment of soft tissue and that virus. And it's going to present them to two different T cells, one of which has a receptor that matches that fragment of soft tissue and one of which has a receptor that matches the virus. But it can only release chemical signals for kill or tolerate. And it's going to release them into the local tissue environment.

So it's done two antigen presentations, one for soft tissue, one for a virus. But is it going to release a kill signal or is it going to release a tolerate signal? If it releases a kill signal, the T cell that has a piece of soft tissue, that the antigen presenting cell gave to it, that T cell has now been instructed to kill soft tissue.

Now you have an autoimmune response, but at least the T cell that's got it's hand on the virus has been told to kill the virus. So that part is pretty good. On the other hand, if you do both handoffs and you release a tolerate signal, you're going to tolerate the soft tissue, that's good, but you're also going to tolerate the virus, which is not OK. So this is why viral illness can tend to create a signal scramble.

That makes it likely, or at least a risk that you will end up with some autoimmune process somewhere down the line.

Claire Sehinson - [00:45:50]

It's so fascinating. It's so inherently complex as well from moving from that seesaw Th1, Th2 model to kind of what you're teaching now. I'm just wondering actually, on a tangent, when we think of the microbiome and people are quite used to having beneficial bacteria now, I think we're just only starting to understand or even identify the human virome. To your knowledge, are there any kind of beneficial viruses that you know that might be helping our bodies?

Dr. Sam Yanuck

That's a topic area that I don't know much about. I suspect that Helen Messier, a wonderful immunologist in the States, who's one of the co-authors on the paper we've been talking about. I expect that she will know a lot more about that than I will. One thing that she does talk about that I find quite fascinating is that on the topic of fecal transplants, for example, what's coming to be understood is that when the microbiome of the donor is given to the recipient, that microbiome includes the virome of the intestine. Which is something that I think hadn't really been thought much about before.

And very much to the point of your question, that's not necessarily a bad thing, but it's probably a good idea to quantify what's going on there, instead of not thinking about it at all. And it might be that some intentionality in that domain to make sure, for example, the certain favorable viruses are there and also make sure certain unfavorable viruses are not there. But that's very much outside, you know, my area of expertise.

Claire Sehinson

Thanks for answering that. That's actually really, it's hugely interesting.

So going back to autoimmunity as well. And, you know, sort of going towards PANS/PANDAS, that presentation of autoimmune, which is quite specific to the central nervous system. We're used to seeing, probably more used to seeing it in children. And I'm not sure whether that's because it's picked up a bit more or the behavioral changes are noticed more in children, whereas adults have all kinds of ways of presenting. So just wondering if you could maybe just explain what PANS/PANDAS is and maybe autoimmune encephalitis, what we might want to call it for something like COVID and you know, how that might present differently in children and adults.

Dr. Sam Yanuck

Yeah, so. To go to the beginning of it, a wonderful researcher named Susan Swedo at NIH noticed that there was this whole group of kids, she was studying Sydenham chorea. And what she noticed was there's a group of kids who had Sydenham chorea and had had strep. And she became very interested in strep cross-reactivity to the brain, which was not a recognized thing at all. And so she began to work with Madeleine Cunningham at Oklahoma and so, the reason she did that was, Dr. Cunningham is an expert in cardiac manifestations of cross-reactivity and strep, so she's a person who knows a giant amount about soft tissue cross-reactivity of strep, so she'd be a natural collaborator, right? So what they began to do was unpack and publish all of this biology about the way that strep can cross-react with the tissue of the basal ganglia and in particular the dopamine receptors in basal ganglia.

So in short, what they observed and discovered was that these antibodies were hitting these dopamine receptors and causing activation of the basal ganglia. So the problem is that when you have that dopaminergic stimulation, you're going to fire up an activation process there. Now, it can turn into tics, that essentially in a simplistic way you can think of it like this. The direct basal ganglionic loop is like a lever that the cortex uses to help itself get going. So it signals fire from the cortex down to the direct basal ganglionic loop, and that fires back up through the thalamus, up into the cortex,

and it's an accelerator, it's a gas pedal, it helps you get going. It's good to have some of that otherwise none of us would ever be able to get up out of bed in the morning or much less, you know, move in anyway. So that accelerator is helpful.

But if it gets stuck on, imagine that you're hurtling down the road with brakes that don't work and a gas pedal that's stuck on. That's what it's like to be a kid who's got PANDAS. And you'd very much like to not be doing that. It's like being stuck in that car and people are yelling at you, slow down, slow down. And you're saying, I'm trying, but it doesn't work, because the brain mechanisms involved in attenuating that overactivated direct basal ganglionic loop can't overcome how overactivated it is.

Now. So if those overactivation signals go down into the body, then that's a tic disorder or it's Tourette's or it's Sydenham chorea. If that overactivation process stays up in the cortex that's OCD. So tic is a body manifestation of repetitive motor activity. OCD is a mind manifestation of overactive motor activity. So instead of twitch, twitch, twitch, it's same thoughts, same thoughts, same thoughts. And all of that is about basal ganglionic overactivation driven by an autoimmune process.

Now, it was identified in kids because Dr. Swedo's a pediatrician. So that's her population. But, there is no biology preventing this from occurring in adults.

Claire Sehinson - [00:52:46]

Yes, absolutely. And I guess with, clinically, when you've seen PANS/PANDAS or autoimmune encephalitis in adults, how fast is the onset from the infection? I mean, they might not know when they actually contracted the infection, that's a whole other thing as well. But how fast do you think that response is in the brain? Is it something that, again, varies? Or could it be, in children often ask the parents how fast, were there any sudden behavioral changes? What can the clinician ask, I guess, to establish if this might need ruling out?

Dr. Sam Yanuck

Yeah, you know, I think that, it's easiest when the manifestation is very rapid. It's easiest to recognize and categorize as PANDAS or PANS. And PANDAS is Pediatric Autoimmune Neuropsychiatric Disorder Associated with Strep. PANS is the realization that strep is not the only thing that can do this. So you need an acronym that doesn't mention strep. So PANS is Pediatric acute-onset neuropsychiatric syndrome.

So it's easiest to recognize an autoimmune encephalitis, an autoimmune drive to an OCD, for example, when it's acute onset. That's the easiest because the parents say, my kid was fine, then my kid's sibling got strep and then the kid just went haywire. That's the easiest categorization. But you will see brain antibodies in kids and adults for whom the onset wasn't perfectly matched to the acute onset criterion. So I always run a Cunningham panel from a company called Moleculera in the States. And Moleculera is the word molecule with RA at the end, Moleculera.

And essentially that company began to exist because there was a need for a commercially available tests. That, when you can imagine when you start publishing research on PANDAS, parents are going to be frantic for the tests that your research is based on. But if you're a researcher, you can't just get contacted by parents and sent blood samples, that's not a thing. So you have to figure out how to make that test available to them. And that means you need a clear, in the U.S. at least, you need a clear certified commercial lab that can routinely receive samples and send reports. That's, at least in the U.S., that's how lab testing is done in a clinical setting.

So Moleculera is the lab that was set up so that that work would go forward. And I use that lab all the time when I have a question about, OK, is there an autoimmune component to this? And you will see it after infection, you will see it after head injury. You will see it when the symptoms get you wondering, even though there's been no obvious infection and no obvious injury, you just got to find out what's going on.

Claire Sehinson - [00:56:14]

And I guess also, you mentioned, traumatic head injury. How about traumatic stress, like PTSD? Is that known to you? Could that induce an autoimmune encephalitis also?

Dr. Sam Yanuck

Well, in order to have an autoimmune encephalitis, you need to have the signaling conditions and you need to have tissue debris. Right, because if there's no debris of soft tissue, there's no presentation of that tissue debris as antigen. So, or you need to have cross-reactivity that gets the immune system to mistakenly attack the brain in the first place.

So you can start the process with cross-reactivity from strep or mycoplasma or what have you. That's commonly the way it gets going. But in the absence of any kind of infection and the absence of any kind of injury, that gives you a debris field in the brain because of a bump on the head. Just getting upregulated inflammation by itself shouldn't do it.

Now, if you've got all the other preconditions there and the only thing missing is the brain getting inflamed enough. Then PTSD could do it. See what I mean? You could have regulatory mechanisms keeping a damper on things and you don't know that's happening because it's working and then that sort of, tenuous but working homeostasis could get disrupted by something like PTSD.

Claire Sehinson

And I guess someone could be walking around with that, just below threshold, all of those factors and then potentially something like COVID-19 could also trigger, potentially trigger that condition. I mean, have you seen any research around sARS-CoV-2 and that potentially activating autoimmune encephalitis too?

Dr. Sam Yanuck

Well, it wouldn't surprise me, I have not seen specific research, but it wouldn't surprise me because even if you simply get microvascular damage in the brain, triggering hypoxic inflammatory process, if, and this may also go back to the PTSD question, if the brain is inflamed enough to create a field of debris in the brain as a consequence of inflammatory damage, then it's a question of whether that debris is cleared effectively in a way that doesn't promote the immune system being interested in the debris that it's clearing.

Or if the immune system clearing that debris, which means that those microglial cells, for example, are in possession of that debris. Being in possession of that debris, is combined with the wrong kinds of signals, then maybe you're off to the races. But, you know, that sounds like a kind of a scary thing. But the important thing to realize is every human has debris clearance going on all the time and we are not all going up in flames all the time with autoimmunity that just completely takes you down. The fact that that's not happening constantly all the time is an indication of how powerfully efficient the tolerance promoting mechanisms in biology are.

Claire Sehinson

Yeah. Absolutely, I think it's amazing how much our bodies can actually withstand, if you think of all the cellular processes, you sort of think, how do we even cope? But, yeah, that's kind of illustrated perfectly.

I'm really conscience of the time because they've kept you quite a while. But thank you very much for that conversation. I think we covered so much ground. And I know people want to be knowing more about Cogence Immunology and your work at the clinic. So where can they go? Where would you direct them to get more information?

Dr. Sam Yanuck

Sure. So there are two places, and you mentioned, cogenceimmunology.com. And that's where clinicians can go to study the information.

And then the clinicians who want consultation can go to yanuckcenter.com and you'll see contact information there. And then just contact the office and the staff will know how to set up consultation.

Claire Sehinson

Thank you so much Sam, for joining us today.

Dr. Sam Yanuck

It's a pleasure Claire, glad to do it.