MCAS And Neural Inflammation

Tom Moorcroft, DO With
Theo Theoharides, MD

Tom Moorcroft, DO
Hi, everyone and welcome back to this episode of the Reversing Mast Cell Activation Syndrome and Histamine Intolerance Summit. And I'm your cohost Dr. Tom Moorcroft, and today we're all in for a really amazing treat. I had the great honor to speak with the mast cell master himself, Dr. Theo Theoharides. and he's one of the top mast cell researchers in the entire world. He's a professor of immunology, and his research is really focused on the mechanism of selective secretion of cytokines and other pro-inflammatory molecules from mast cells. He has a broad background in immunology and has been studying the regulation of mast cells and their role in allergic and inflammatory diseases for over 30 years. He is one of the most widely published people I've ever met. He's published over 400 peer reviewed medical journals and is cited as one of the top 5% of authors in the immunologic research field. He discovered that mast cells are inhibited by certain natural flavonoids including and especially luteolin and tetrahydroxy luteolin and subsequently developed a well known mast cell blocking supplement NeuroProtek. So I am just so honored to have an opportunity to talk with you, Dr. Theo, and welcome to the Summit.

Theo Theoharides, MD
Well, thank you very much for the invite. I'm delighted, especially since I'll be talking hopefully about a subject that I'm absolutely passionate about.

Tom Moorcroft, DO
Yeah, I'm very interested. I was remarking with you as we were, you know, getting started before we hit record that, you know, I just remember back at an ILADS conference, you know, we're all studying Lyme, and it was like the first time I had really gotten exposed to your work, and it really changed the way I looked at my patients with chronic illness. So I'm really excited to be able to

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share some of that with our listeners today as we talk about mast cells and neuroinflammation. So what got you interested in mast cells of all things, and what's this journey been like?

Theo Theoharides, MD
It's a very interesting story. Back in 1972, long time ago, in the summer, I had just graduated from Yale, and I had spent a few weeks at Albert Einstein College of Medicine where a very well known dual was going on between two professors. There was evidently an annual event, and in that particular time the dual were between Professor Padawer who was a Histopathologist, Jacques Padawer, Canadian and Sam Seifter who was a biochemist. And they chose to hash out a topic which was mast cells. And I was like, wow. And the biochemist, Sam Seifter, felt that it was an incredible cell because it either contains and or can make as many as 100 different biologically active mediators. And Jacques Padawer felt that it was actually a useless cell because he had done a very important experiment.

He had injected in the peritoneal cavity of rats gold particles, and the mast cell is notorious about taking things from the outside and storing them in their granules. So the mast cells took up the gold, and then he sacrificed the animals over time until all dates and the gold was still there. So therefore he said, under laboratory normal circumstances, the mast cells don't degranulate because if they had the gold would've been released, the macrophages would have removed it. So these were the two extremes. At that time I was starting my PhD thesis at Yale. I was undergraduate doctorate of pharmacology and my medical school was at Yale, and I was working between two very strong minded but very good friends, professors. So one was Bill Douglas who was a neuroanatomist and Paul Greengard who was mostly sort of a biochemist.

And Paul Greengard had gotten the Noble Prize actually in physiology and medicine a few years into my PhD. And we were looking for a good secretory cell to study. So Bill Douglas was very interested in the pituitary gland. Paul Greengard was interested in neurons specifically in general. And they told me, go find a good cell. And I recall the discussion at Albert Einstein, and I said, how about the mast cell? Here's a cell that has 1,000 secretory granules. Each secretary granule stores about 50 or so molecules that we know, and that when it's triggered it makes another 50 or so. And it is not only triggered by allergens. So I said, what better secretory cell to study than the mast cell? And I did all my PhD thesis on the mast cell between 72 and 78, so to speak. And I've been hooked ever since.

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Tom Moorcroft, DO
Ever since. Wow, that's kind of cool like, the mast cell seems like, it's interesting cause I was thinking as you're talking about that in medical school, it's sort of like the mast cell lets out histamine, and it's a white cell, and that's kinda like all you need to know. And that's.

Theo Theoharides, MD
Unfortunately this is pretty much what it is still being taught even at the National Institute of Health where they ought to know better than that. And here's a little story as well, The mast cell were discovered by Paul Ehrlich in 1887. It was part of his doctoral thesis, but at about the same time in 1901 there was an experiment that was being conducted out of the Oceanographic Museum at the principality of Monaco by two French scientists, Portier and Richet. And the experiment was they took jellyfish tentacles because jellyfish, Man o' War were rampant at that time. They ground them up. They gave them to dogs, they injected the dogs, and they were pretty sure the dogs would be protected from subsequent stings. So they had a term ready for it. They were going to call it prophylaxis. However, when they immunized the dogs, and they're-exposed them to the jellyfish. They dropped the blood pressure, the bronchi constricted. They went into acute anaphylaxis, and they died. So they called it anaphylaxis. So the term anaphylaxis and mast cells were discovered at about the same time, two years apart. But they were never connected until 1947 when histamine was discovered in mast cells. So hundreds of years went by,

Tom Moorcroft, DO
Oh, my God.

Theo Theoharides, MD
Before we realized, and now since 1947 we're still kicking the same idea that histamine is the main problem in all of these conditions, which it's not.

Tom Moorcroft, DO
It's just like so remarkable because it's like literally it's like I'm like everything I've been taught is just, that's really what it is. So what else is in, and you know, anaphylaxis is obviously a thing that all of us learn in medical school, and a lot of people know about bee stings or shrimp, and it's a scary thing. But so what else is going on with the mast cell and in our health? Like what are the

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things that we need to know about it to start to learn, to kind of set the record straight, if you will, about what they're doing?

Theo Theoharides, MD
So first of all, we've gotta realize that one does not have to be allergic in order for the mast cells to fire. So they're individuals. And as you know in medicine, if we don't know something we call it idiopathic. So there's idiopathic anaphylaxis, out of the blue someone responds. And one of the key molecules in wasp venom is called Mastoparan. And you're not allergic to Mastoparan. Mastoparan will trigger the mast cells in its own right. So we have to stop thinking of the mast cells responding only to allergens, which is a big deal. I'm not trying to minimize that.

Tom Moorcroft, DO
Oh, right.

Theo Theoharides, MD
But they can respond to molecules released under stress, molecules released from, you know, viruses, from bacteria, fungi. Mycotoxins can trigger the mast cells. And probably the most important message for today as far as I'm concerned is that the mast cell is very dynamic. It's not just a static cell you trigger it, it will release something, and that's the end of it. It changes as you go along. So mast cells are very different in the skin, in the gut, in your mouth, and if we have time to talk about in the brain. And when the mast cells are triggered, their reactivity to other stimuli changes enormously. And I'm sure you and other colleagues, certainly I have had numerous patients who had a little kind of allergic diathesis, I prefer sometimes atopic diathesis because that's a little broader than just straight allergy, and then they undergo major surgery, trauma, God forbid someone dies in the family, and now they respond to everything under the sun. So the mast cells can change their reactivity, and we have to be very cognizant of that because if we think we're gonna stop the mast cell at one point in time, we're just missing the dynamics of what is happening, not only with the mast cell but in the whole body.

Tom Moorcroft, DO
So what's leading to that? I mean it's like, cause, I mean, you know, we talk a lot about the hyper-responsiveness, almost like the mast cell being a sentinel to protect us, but then it gets, it's on guard all the time rather than only certain times. But like what is leading to this, and what is that pathway that we need to be looking at?

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Theo Theoharides, MD
Well that's easier said than done. Let me start historically. The mast cell has has been identified in species over 400 million years. So all the way from mollusks to octopi to zebra fish has tons of mast cells to invertebrates, vertebrates, and of course, you know, humans. So obviously the mast cell played a role at some point, and I'm sure it still plays a role now that's not necessarily detrimental. But maybe go back to millions of years ago. So those invertebrates or you know small vertebrates, et cetera did not necessarily have developed immune nervous hormonal systems. So the mast cell, both other colleagues and I believe played a role because it makes, synthesizes and releases all such molecules.

It makes and it responds to endorphins. It makes and responds to Catecholamines. It makes and response to sex hormones, so forth, so on. And as we developed other systems to cover and the mast cell sort of maybe remained as sentinel cell for maybe poisons, maybe toxins, maybe parasites going up in our behind, et cetera. And as we've evolved even more and then we had antibiotics, you know, we were purified by being inside homes with, you know, air conditioning or vacuum cleaners and whatever, the mast cell probably didn't have that much to do with protecting us. But it was still there as the canary in the mine for things that might still be dangerous. And it probably does that in some individuals more than others for genetic reasons as well.

However, when it comes to stimulation, we know that even stimulation with an allergen, which is through immunoglobulin E can actually talk to other receptors on the surface. And a good example of that, jumping way ahead, is the drug Xolair that neutralizes circulating IGE. But it has been shown with publications that it is helpful in vibration urticaria, in pressure urticaria. There's no IGE involved there. So that by definition means that when you strip the IGE from the surface, this is what Xolair does or other similar drugs, then the body doesn't see IGE anymore. And what do the cells normally do? They interiorize the receptors. I don't need that many receptors anymore. There's no IGE around.

Tom Moorcroft, DO
Right.

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Theo Theoharides, MD
And I think that as the cell does that, other receptors that might be linked covalently might also be drawn and internalized and destroyed. And vice versa, if you stimulate something too much, maybe other receptors get expressed, and then now you have, you know, co-reactivity. So I just submitted two weeks ago an invited review on mast cell activation, and one of the tables shows that the mast cell expresses about 50 different receptors on the surface, other than the receptor for IGE. So obviously the receptors are there. They're there for some reason. And even though there are also some inhibitory receptors, no one has ever found natural or synthetic molecules to stimulate the inhibitory receptors to shut the mast cell down. So we're still basically in the dark.

Tom Moorcroft, DO
Interesting.

Theo Theoharides, MD
So answering more precisely your question, I don't think there's just one pathway that we might address to inhibit the mast cells, but I tend to think how can we actually block the last steps of the mast cell activation. So you have 50 receptors, you know, different stimuli. They'll go through various pathways. Eventually they have to release something. So if we can block that final release step that might be our best bet to shut the mast cell down.

Tom Moorcroft, DO
Right, and it's kind of like the holy grail it seems like because I mean, you know, it is almost, I'm thinking as you're talking, this is one of the things a lot of us are just like, let's block histamine, and it doesn't, it doesn't always seem to work that easily.

Theo Theoharides, MD
Not at all. Besides now you might have put your finger to something very important. We always say histamine is in the secretory granules. There are about 1,000 of them per cell, okay? Presumably in those granules we also have enzymes like tryptase and chymase and carboxypeptidase, just to give you some. We always thought that all of these are released together, and that doesn't seem to be true at all. We have many cases in mast cell activation where histamine is released, but tryptase is not released. And very recently, over the last few months there are three publications, independent publications that in individuals that suffered from COVID-19, chymase was elevated in the blood but not histamine and not tryptase. So how

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on earth is then chymase being released from the same granules without tryptase and histamine since we always said this is degranulation? And a paper that will just published this week, and maybe we'll return to this if we talk about COVID was quite fascinating because it showed convincingly that the spike protein binds two chymase, and the two together can damage the blood brain barrier. Okay, this was just published. So the whole idea of what the mast cells do in certain conditions including COVID-19 is really changing rapidly.

Tom Moorcroft, DO
Man this is like, this is like opening Pandora's box, right? I mean cause I, one of the points I wanna highlight is like testing for folks like, and COVID is so critical, and we need to talk about it as well as neuroinflammation. And with testing a lot of times like I just remember as you're speaking I'm like oh yeah, you know, it's like a lot of us will run like a tryptase and stuff to verify it's anaphylaxis or whatever or earlier, you know, phase of anaphylaxis. So, but a lot of people I think get frustrated. They say I have mast cell activation syndrome, and our testing is kind of miserable for it. But it's almost sounding like the symptoms that you can get from mast cell activation may not just always be histamine-related.

Theo Theoharides, MD
Not at all. Back in 2015, two colleagues of mine, Cem Akin and Peter Valent and I wrote a review in "The New England Journal of Medicine," and I was grateful to the journal, I still am because the title was "Mast Cells, Mastocytosis, "and Related Disorders." So it opened up the door to the possibility other molecules are being released, and in fact one of the diagrams that we have in that journal shows the mast cell in the middle, and depending what the trigger, the outcome is different, and it can affect every organ of the body. And I want to stress that paper because many colleagues might not know there was a supplemental file to that paper.

Tom Moorcroft, DO
Okay.

Theo Theoharides, MD
So if you visit "New England Journal of Medicine," I was the first author, so you can easily pick it up. There was a supplemental file that has never existed before and has not existed since showing a human mast cell degranulating in real time. So I have a mast cell in three dimensions between two cover slips, profusing it with a neuro peptide, and within five seconds it goes ba

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boo boo boo boom, and it degranulates, okay? So once you see that, you know how dynamic and powerful the cell is, and we're not talking about histamine. So I would urge you, go back to the journal and go to the supplemental file, and you'll be really impressed. And I'm not saying this because I took the video. It just, it's so powerful to see how dynamic and you see thousands of granules spitting their content out. That's what happens in anaphylaxis, but not necessarily during infections, et cetera when the cell releases molecules without undergoing degranulation, without tryptase, without histamine. So in this last review that I submitted, hopefully it will be accepted, I have a list of what I propose should be potential markers of mast cell activation beyond histamine and tryptase.

Tom Moorcroft, DO
Right, I'm sure all of us are gonna be so interested in seeing this and checking it. I mean are there particular things that are we should be kind of maybe considering clinically to start looking at or?

Theo Theoharides, MD
Well, we should. So first of all, I mean it's obviously important to measure tryptase because if tryptase is high, it's telling us something. So either you've got, you know, mastocytosis or you've got this genetic condition, you know, alpha hyper tryptasemia which is also very confusing because these patients have a lot of symptoms in many organs and yet in alpha hyper tryptasemia it is the alpha tryptase monomers that are released, and they're inactive. While in the granules it is the beta tryptase tetramer that becomes active when it's released. So it's beyond me how an inactive monomer can still cause symptoms in about five different organs. You know, so we still don't know what it means, and of course we don't have any drug to block tryptase period anyhow.

So having said that, to the extent possible, it is important to measure at least the prostaglandin, leukotriene, and histamine metabolite in the urine because that is telling us that the mast cells are spitting out other mediators than just tryptase. And it used to be that we need only 24 hour urine to measure that. Now it suffices at least at the Bayer Clinic to give them first morning void, but it has to be cold. If it comes up to room temperature, they're gone. So you're gonna get negative results. And then finally there were four papers, one was published from my group, the other from Dr. Metcalfe at NIH, the other from Dr. Scribano in Spain showing that interleukin-6 levels reflected disease activity better than tryptase or histamine. And of course my colleagues

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say, you know, we can't really measure L-6 because L-6 can be released in other inflammatory diseases. Of course, but if there's no other comorbidity, why not measure it? You know, if someone has inflammatory bowel disease, well, it might be coming from the bowel, et cetera. And a paper was published recently confirming what we had also published extensively that vascular endothelial growth factor is actually increased both in mastocytosis and mast cell activation patients. And I always measure that because it tells me whether the vasculature is actually leaky, in which case it will promote inflammation, et cetera. Finally, and I'm trying very hard to come up with a way to measure platelet activating factor, PAF.

PAF has been known for many years, but it is impossibly difficult to measure in a clinical laboratory. However, there have been very good papers including a paper in "The New England Journal of Medicine" from Dr. Vadas in Canada that showed that levels of PAF in the blood were more reflective of severity of anaphylaxis than either histamine or tryptase. But because we cannot measure it, we ignore it. However, even if we cannot measure it, there are ways to block PAF, and that should be actually a regular component of treatment of mast cell activation diseases moving forward. Again, if we have time, I'll get back to this.

Tom Moorcroft, DO
Yeah, I think that maybe the way we can kind of structure flowing through the rest of this, cause I think that blocking PAF is like, I mean, these are the things that we need to know because as you mentioned earlier, there's different triggers, stress, viruses, and I'd love for you to touch on things cause a lot of our patients that we're talking with are exposed to mycotoxins, candida, maybe even, a lot of people have tick borne illness or even community acquired pneumonia, bugs that are persistent. And then obviously as you mentioned, we should maybe talk a little stress and dovetail right into COVID if you wanna kind of like play with that a little bit because I think that this is what our audience is, these are some of the things our audience is experiencing, and certainly obviously knowing what to do after COVID and how COVID impacts mast cells and then how to block some of this is certainly totally high yield stuff here.

Theo Theoharides, MD
Sure.

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Tom Moorcroft, DO
It's super exciting. This is like, I feel like a kid on Christmas right now. I mean such great information.

Theo Theoharides, MD
Well, let me, before we get into, you know, COVID and the like, let me just first say that the terminology used is very confusing, still very confusing. So let me just start out by saying, generally separate mast cell diseases into the primary, and as an example would be either systemic mastocytosis or cutaneous mastocytosis. So by definition you have a lot more mast cells. Then you have the second, and in most cases of the primary, the mast cells are also activated. So we should reserve the word activation for many different settings, not just mast cell activation syndrome to which I will return. So whether you have systemic mastocytosis, in probably 100% of the people, the mast cells are activated by X, Y, and Z.

In cutaneous mastocytosis, the mast cells are not as activated as in systemic, but they're more activated if you rub, you know, the lesions, et cetera, et cetera, you know, heat. So that takes us to the secondary, which might be allergic rhinitis, allergic, you know, pruritus. It might be what we call pressure urticarias or physical urticarias. And then the third category is idiopathic. So you've got idiopathic anaphylaxis, idiopathic angioedema, idiopathic whatever. And now you have a category mast cell activation syndrome, which according to my colleagues, it has to have tryptase elevation within 48 hours of an episode, which is almost impossible to measure unless you have an indwelling catheter, and most laboratories will not even measure it. Most emergency rooms don't know what it is, let alone measure it.

And then you have the category of muscle activation, unspecified and that has its own diagnostic code. So we don't have to necessarily be going crazy, is this really mast cell activation syndrome because if it doesn't have tryptase, let's just call it muscle activation, unspecified. It still has a diagnostic code. You can still do a whole bunch of testing on it, et cetera. Okay? So but most everybody talks about the MCAS, the syndrome, and I think that just derails us from thinking that mast cells can be activated in many, many other conditions. Give you an example unrelated to all of this. In solid tumors, whether it's breast, pancreatic, ovarian cancer, prostate cancer, we have accumulation of mast cells. No one knows why. We always thought they were being accumulated to kill the tumor, and yet the tumor cells are smarter than us. They prevent the mast cell from degranulating. I've never seen degranulated mass cells around tumors, yet

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they stimulate the mast cells to release VGF and other angiopoietins that allows neovascularization, growth of the cancer metastasis. So the cancer cell can do what I have not been able to do in 40 years, can tell the mast cell what to do to its advantage.

Tom Moorcroft, DO
Interesting.

Theo Theoharides, MD
If I could tell the mast cell what to do, I can tell the mast cell don't release angiogenic factors, release tumor necrosis factor and kill the tumor cells, and I dunno how to do it. So that's why the mast cell is fascinating. I mean, in my mind, it's like a microcosmic pharmacology circulating in the body. If I could put a microchip on the mast cell and tell it what to release in what part of the body, I'll have the best treatment ever for many conditions.

Tom Moorcroft, DO
For real.

Theo Theoharides, MD
Maybe 100 years from now, that's exactly where we'll be having. So coming back now, what is the original approach for treatment? And I will leave the good stuff for the end. Once you identify that there is activation of mast cells, you have a clinical history, you know, you give them some antihistamines, a little better. You know something is brewing, and if you actually scratch their under arm, and you get dermatographia, then you know the mast cells are activated just by pressure, which means that they're ready to fire. No allergens involved. So I always do this scratch test.

Tom Moorcroft, DO
Yep.

Theo Theoharides, MD
Because if they're positive, that is telling me that antihistamines probably are not gonna be enough to take care of this patient because the mast cell responded to pressure and not necessarily to an allergen. So what do we do? We try some antihistamines. Three things to know about antihistamine that we usually don't think about. Number one, they're not all the same.

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Number two, about 15% of the people get wired even though we're supposed to be sedating to some extent. So a lot of people just don't tolerate them. There you go. So it's very hard to tell a patient, oh, take you know X. It's good for you, and the patient's, you know, pulling their hair because they're now wired. Number three, there are some antihistamines that have additional properties. Give you an example, Hydroxyzine or Atarax. It's slightly sedating, and it's slightly anti-exciting. Many times you give them to children that have Enuresis at night. They might have had a very difficult day. I find it very useful to give it at night for instance. It puts you in a deep sleep, so people, you know, before they go to Ambien, or you know, whatever for, you know, not being able to sleep, I'll give them a little Atarax. So then you have antihistamines, one of which I'll mention, then I'll return to it, which is Rupatadine.

Rupatadine has existed in Europe for 20 years, in Canada for three years, still not in the United States, but it's as good an antihistamine as any. It partially blocks mast cells, and it was designed to be a PAF inhibitor. So you get three birds with one stone. And by the way, anybody can get Rupall from Canada with a US prescription through a Canadian online pharmacy. You don't have to compound it. Lots of patients, you know, physicians get it from Canada. I'll return to this when it comes to COVID as well. So then what do you do after that? Well you try to block the mast cells, and you know, most everybody reads about Cromolyn blocking the mast cells. I published on Cromolyn as an undergraduate at Yale in 1971. It worked perfectly in rats. It was very bad in mice, and it really doesn't block human mast cells. Okay, it just doesn't.

Tom Moorcroft, DO
Interesting.

Theo Theoharides, MD
It became word of mouth that it's a good blocker because they called it mast cell blocker. It gets absorbed less than 5% from the gut. Does it inhibit anything? Yes, it inhibits histamine release, maybe about 20%, mostly in the gut. It doesn't do anything else, and the body gets used to it very quickly. We call that Tachyphylaxis. So we start with 100 milligrams, you know, vial a day that it becomes before you know it, about three months, it's 400 milligrams four times a day, and by that time you have about 15% of explosive diarrhea. So it's not an easy drug, and it's very expensive as well. So don't get me wrong, if someone has GI symptoms, and they take it and do well, all par to their elbow, and I find NasalCrom quite useful. So NasalCrom is nasal spray. So I find it for allergic rhinitis quite useful, but not the oral Cromolyn. But anyhow, some colleagues

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will try Cromolyn because it's available. Then what do you do? Well you think maybe Leukotrienes are involved. We know Leukotrienes are extreme bronchial constrictive, that's why we have Singulair. But because we don't know what to do, we might say, okay, nothing else is helping. Let's put you on 10 milligram Singulair and hope for the best. Sometimes it works, sometimes it doesn't. It really doesn't have that many side effects. I'm leaving the polyphenols out. I'm talking about the sort of, the straightforward, you know, colleague who doesn't think outside the box. If someone has tremendous itching, they might think about Xolair, okay. And that's about it in terms of what they will do.

Some will go crazy, and they'll show I'll put someone on Plaquenil. God forbid, so, but they do, okay, they do. You might also put someone on more exotic tyrosine kinase inhibitors, those that work well for mastocytosis, but they do not block mast cell activation. So you know, for some of that doesn't have mastocytosis, they're not gonna work. So that takes me back now to almost 40 years ago when I was studying Cromolyn. And if you think of Cromolyn, it's a butterfly with two wings, and I did one of the first searches on molecular mimicry back then. And what do you know, the basic structure of a polyphenolic compound is almost identical to one of the wings of the butterfly.

Tom Moorcroft, DO
Nice.

Theo Theoharides, MD
So it was very similar to Cromolyn, and that's what got me interested in flavonoids to begin with. In addition to the fact that probably the guru on flavonoids was Dr. Middleton, who unfortunately died many years ago. And his colleague had called me up about 1998 or so, and he said that he had left in his will that I actually take his work on flavonoids and write a review. And I was, I was really taken and honored.

Tom Moorcroft, DO
Wow.

Theo Theoharides, MD
We published a review in "Pharmacological Reviews" in 2000 about flavonoids, and its become classic basically in terms of citations. So the flavonoids are very antioxidant.

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They're anti-inflammatory and they can block mast cells, but there are 3000 of them in nature, and all of them are not the same, and all of them don't do the same. And some are bad actually. So when we talk later about polyphenolic compounds, I have to actually differentiate and say why we have to be very careful about what we choose and how we give it. Taking me back, we were amazed over the years that many patients with mast cell or allergic-like problems would get worse when they were stressed. I mean that was well known. And of course what did we used to hear? It's all in your head. Go see a shrink.

Tom Moorcroft, DO
Right, supratentorial.

Theo Theoharides, MD
We were the first that published that the main hormone released under stress, corticotropin releasing hormone or CRH, it's released outside the brain, and it stimulates the mast cells to release molecules without histamine and tryptase, and changes the reactivity of the mast cells to allergens as well. So there's no question that stress via CRH can actually do a job on the mast cells. Therefore, in treating or attempting to treat any of the patients we're talking about, reducing stress in any way possible is very important in my mind. If they continue to swim in stress, no matter what do we do, they'll continue to have problems.

So I had one patient from Brussels who used to trade diamonds in the upper parts of Russia. And he would come back, and he would be covered with eczema and all kind of other problems. And I said, well, what do you do when you go up there? Well, you know, I've got some bags with diamonds, and, you know, bags with dollars and a couple people with Kalashnikovs, and I dunno if I'll come back alive. I say, you're crazy. I mean you're swimming in stress. So I said, look, he was also Greek American. I mean, Belgian American, so Belgian/Greek. So I said, just go to a Greek island, you know, for a couple of years and forget trading diamonds.

Tom Moorcroft, DO
Chill out a little bit, right?

Theo Theoharides, MD
Yeah, chill out. And and he did phenomenally well. I mean, you know, it's obviously anecdotal, but it was true. and I had received actually five US patents on how to block CRH as it relates to

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mast cell related diseases. But now was interested in bringing them, as the lawyers say, reducing it to practice. So 70 years have gone by, and the patents are gone, and we still don't have any way of blocking, these were CRH receptor antagonists for such kind of diseases. So to finish this part, from the very beginning I was amazed by the fact that the median eminence, the little stock that connects the hypothalamus to the pituitary has as many mast cells per unit volume as our skin. Yet, the mast, the brain doesn't get allergic reactions. So what do they do?

Tom Moorcroft, DO
Interesting.

Theo Theoharides, MD
Immunoglobulin E cannot cross the blood brain barrier unless it becomes, you know, leaky.

Tom Moorcroft, DO
Compromised.

Theo Theoharides, MD
So they must be doing something, and of course CRH is right there, hypothalamus makes CRH, in addition to other molecules. So it became apparent that the mast cells may be contributing to sort of neuropsychiatric symptoms both indirectly by releasing things outside the brain that might cross the blood brain barrier as well as about being activated inside the brain. But to this day, no one really has focused on mast cells in the brain in spite of, you know, numerous publications by myself and other colleagues. So let me stop and let you ask.

Tom Moorcroft, DO
Yeah, well I mean I just think it's phenomenal. I could listen to this all day cause there's so many pieces that are kind of bringing together some of the questions we have, and I know that we don't have maybe all the answers like you just alluded to, but I feel like it gives me comfort that, and hopefully to our, any of the patients who are experiencing these symptoms watching that we we're starting to understand why you're reacting the way you're reacting. And we may not have all the answers yet, but we've got scientists leading us in that direction, and I love the fact that stress, like we keep saying everybody's, oh, de-stress, de-stress, and that's all nice, right? But for us to be able to understand there's a scientific basis.

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Theo Theoharides, MD
Correct.

Tom Moorcroft, DO
And we know that de-stressing will for sure help balance out our mast cell, you know, response. That's a lot of hope because you have so much control, you have more control over stress it sounds like, than our supplements or our medications have over your mast cells.

Theo Theoharides, MD
Correct. We published two separate papers and another colleague published a third paper, in one instance we had a patient with cutaneous mastocytosis that after a very stressful event she was covered. You know, she went from a few lesions to hundreds of lesions, and we measured CRH in the blood, and it was off the roof. We had another patient that we published who had systemic mastocytosis, notoriously will get worse under stress. And in that instance, not only we measured and we showed CRH was high in the blood, but we took your biopsies that were done in Michigan, and we restained the biopsy where there were clusters or mast cells with a fluorescent antibody to a CRH receptor, and the mast cells lit up like light bulbs. So we know what is happening. It's just that we don't have a way of blocking the release of CRH or the action of CRH as of yet. So, but there are ways to reduce stress that might not necessarily require, you know, Benzodiazepines and other things. And again, if we have time we can get into that.

Tom Moorcroft, DO
Yeah, I think there's, and so much, and we've, you know, we definitely have some, it's great to hear this because a lot, some of the other speakers in the Summit are, do talk about like limbic stuff and stress reduction too. So, but we now we have, we're seeing the science of it. One of the things that I really would love to hear about too is you had mentioned COVID, and I'm sure we've talked about it several times here as one of the things that might have a unique relationship with mast cells, and I would wanna make sure we put that in and then give you a chance to talk about polyphenols and how to properly utilize them.

Theo Theoharides, MD
Sure. Well, just as COVID started, you know, I published a couple of papers two and a half years ago immediately saying that most of the action, at least at that time appeared to be in the lungs. We know mast cells are in the lungs. We know mast cells contain lots of cytokines and pretty

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much patients were dying because what was called cytokine storm. Yet the ability of the virus to bind to its key receptor, which is Angiotensin-converting enzyme 2, ACE-2 receptor, had nothing to do with cytokines. The ACE-2 receptor is important for the virus to get in, get into the nucleus and multiply. So where were the cytokines coming from? So that was question number one. Question number two was, can we actually block the mast cells in the lung? And of course if one could actually squeeze something in the nose or have them inhale it, that would be tremendous. But no one ever did that, and they still haven't done it. Number three, can we measure anything that comes out of the mast cells in the blood to see if in fact there is some outcome or through bronchoscopy in you know, Bronchoalveolar lavage fluid.

So while I was writing this reviews, and they were published in different journals, one paper came out from France showing that in the alveolar septum of patients that had died, and they did pathology, the mast cells were activated, they didn't measure what, but it was the first paper. And a second paper came out showing that chymase was high but not tryptase. Then a third paper came out a few months ago showing that when they infected mice with COVID, well, the SARS-COV-2 protein not COVID, the mast cells in the lungs got activated, but they only released chymase. And when they went to patients, and they looked at asymptomatic, symptomatic and severe patients, chymase was actually tracking with the severity of the disease. Again, no tryptase, no histamine. So there was clear evidence that the mast cells were being activated, although it threw us for a loop as to why molecules that are in the same granules are not released together. We still dunno the answer to that.

At the same time, a paper was published that very few people paid attention to, and that was actually published in Proceedings of the National Academy of Sciences where they looked at 81 countries. They looked at the level of pollen and the incidence of COVID, and they tracked together. The more pollen, the more COVID. And they said that maybe because you breathe the virus, and if you have an allergic response in the nose because of the allergen et cetera, the type of immunity shifts and doesn't protect against the virus. To me it was an obvious indication that if the mast cells are activated there, maybe they were making things more likely to occur vis-à-vis COVID infection since it goes through the nose.

Tom Moorcroft, DO
Through the, right.

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Theo Theoharides, MD
And finally we did some experiments which since only one paper recently actually published because we didn't have time to publish because they shut our lab down. But we showed that the spike protein, recombinant spike protein, can stimulate the mast cells. So you didn't need the whole virus, just the spike protein. And at the same time, because we were very interested about what happens in the brain, brain fog, long COVID, et cetera, we also took human cultured microglia, which as you know are the defenders of the brain and the spike protein recombinant also stimulated the microglia. And two papers now have been published showing the same thing. So you don't necessarily need the whole virus, which to some extent worried me because if the spike protein can cross the blood brain barrier or damage the blood brain barrier, then it can get in and set up sort of a local perivascular inflammation.

And that's exactly what had been shown in pathology of patients who died. There's perivascular inflammation, and I wrote a paper in "Molecular Neurobiology" about a year ago, less than a year ago. And the question was could the spike protein be responsible for COVID-19 neurologic symptoms? And we actually showed in a diagram whether you have microglia or mast cells, how basically the spike protein can do that. And we proposed that it might be through toll-like receptors that respond to viruses, fungi, and bacteria. And since then three papers have be published, one in "Nature," showing that the spike protein can stimulate toll-like receptors, unrelated to its main receptor for invasion, which is ACE-2. So for about two years we were missing the boat basically focusing on ACE-2 while the mast cell expresses all toll-like receptors, one through nine. You know, four is for LPS. Two is for fungi, et cetera.

So with that in mind, immediately I said can we block the mast cells by using at least whatever we have available? And what was available was literally Quercetin and luteolin in terms of inhibiting the mast cells. Both we and others have published on that. Immediately a Canadian group did a clinical study on Quercetin, and it showed that you could actually reduce symptoms. Another study was done in India with very few patients showing the Quercetin could again inhibit the symptoms to some extent. We're not focusing on mast cells necessarily, right? But the difficulties that Quercetin is absorbed less than 10% from the gut and so is Luteolin. That's why we focused on how to increase absorption of both Quercetin and Luteolin. So we put both Quercetin and Luteolin together in two preparations. One is called NeuroProtek. It's a smaller capsule because some individuals cannot swallow bigger capsules, and the other is called

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FibroProtek. That is almost double the amount of both Quercetin and Luteolin. Again in olive pomace oil to increase absorption. Since then we have two clinical studies ongoing. One is actually about to start in the Miami VA Long-COVID clinic, and one is going on in Greece, and we published one paper which was literally changed our thinking. This was a lady well known from a big city in Florida, two years ago went down with COVID. She had all the symptoms you can imagine. She was given everything that was available at the time including, you know, convalescent serum and, you know, azithromycin and dexamethasone, you know, the works.

Tom Moorcroft, DO
Everything, yeah.

Theo Theoharides, MD
And her lungs basically were so damaged that she was put on double lung transplant list, and she was living on 10 liters oxygen, okay.

Tom Moorcroft, DO
Holy cow.

Theo Theoharides, MD
So what we decided, I was asked to consult through a friend and her primary physicians went along, God bless them. So we put them actually on FibroProtek, you know, four of those a day. We put her on another supplement called Brain Gain that is much more helpful if you have brain fog, not necessarily symptoms all over the place. We put her on Rupall from Canada because as I said earlier, it blocks also PAF, and there are independent papers that PAF is involved in COVID, including two papers we wrote, and then we put her also on an old drug that we don't think about anymore, Cytotec. So Cytotec is a Prostaglandin E, you know, agonist. We used to give it to protect the stomach for old timers taking non-steroidal anti-inflammatory drugs, but it's antifibrotic. And in this patient the lungs were actually fibrosing, 100 micrograms per day, not milligrams. Okay, don't make a mistake. And then because she was not exchanging enough oxygen, we put her actually on Erythropoietin injections, Sub-Q three times a week. In three months her lungs will look so perfect, she was taken off the transplant list, and she's back to low practice. Now that doesn't mean to say that every patient, you know, will have such amazing, you know, turnaround, but it points to the fact that we have ways to address aspects of COVID, and

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what is really most important for the brain, the polyphenolic compounds are called phenolic because they had hydroxy groups attached to the benzene rings, and that's called a phenolic ring. The more hydroxy groups you have, the more phenolic you are. The more antioxidant you are. But the less anti-inflammatory you are, and the more phenolic groups, the less likely you'll get into the brain. That's why we focused on Luteolin because unlike Quercetin, which has a five hydroxy groups, Luteolin has four, and it's likelier to get into the brain. So the Quercetin part of the NeuroProtek and the FibroProtek catches the mast cells outside the brain, and it acts like a decoy because it gets metabolized to allow luteolin to escape and get into the brain.

Tom Moorcroft, DO
I love it cause like, you know, it's so funny. So many of the folks speaking with us here and obviously yourself and myself are scientists, and yet we're still looking at sort of functional medicine and quote unquote alternative. And I think that this is like for me like so much hope because we're using real science to get real results, and we understand that maybe we need, you know, a side of, you know, one of these medications or maybe we need a supplement and to do that. So one of the things that we had talked about that I think is really important is when you talk about the the polyphenols, I mean do you have particular tips for the public to kind of navigate? Cause like what you just said is there's certain ones we should and we shouldn't use. And then there's also dosing considerations.

Theo Theoharides, MD
So number one, please try to find out the source, the purity, and the amount. No one mandates that. The FDA does not mandate that. So many supplements will say proprietary blend, and they will not tell you what they have.

Tom Moorcroft, DO
Right.

Theo Theoharides, MD
In fact, many of them do that. That's number one. Number two, the polyphenolic compounds, all of them are yellow. The more hydroxy groups you have, the more color you have. So if you open up, whether it's a capsule or a pill, and it's not yellow, there's no Quercetin in there. There's no Luteolin in there. Okay, so that's kind of a quick way to find out if someone is pulling your leg. Then the source is very important. And again, supplements don't tell you the source, as you will

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see in the supplements I helped develop, they'll say in parenthesis with Latin because that's how it's supposed to be by the FDA what it is.

Tom Moorcroft, DO
Right.

Theo Theoharides, MD
The reason is because the cheapest source of Quercetin and some of the flavonoids is actually peanut shells. But no one is telling you it's from peanuts. So if you're allergic to peanuts, well, you know what will happen.

Tom Moorcroft, DO
And you're taking peanuts.

Theo Theoharides, MD
The next cheapest source is fava beans. But about 20% of Mediterranean extraction people like myself, you know, Greeks, Italians, you know, Jewish, Northern Africans, they lack G6PD. If you lack G6PD and eat fava beans, you get Hemolytic anemia. Go chase your tail now, you know. You're gonna be running to hematologist while all of a sudden your cells are going to pieces. And the third, which is also very important, is the most polyphenolic something is the more likely about 20% of the people to get hyper on it. These are people that have phenol-intolerance, and we know why because the enzymes that break down phenols, mutations. So I always ask for, you know, gene mutations for about six different enzymes because they will direct me not only about supplements, but about drugs, what to give them, how much to give them. As you know, we separate people in fast metabolizers and slow metabolizers. So if someone is slow metabolizer, one gram of Quercetin might be five grams for them, and you know, it might cause problems. So try to find out source, purity, and amount.

Tom Moorcroft, DO
Okay.

Theo Theoharides, MD
The second is that too much of something is not necessarily good. So I'll give you the example that I gave you before we started. Some of my colleagues will say, well, you know, flavonoids are

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absorbed less than 10%. Let's give them two grams. That means it will absorb 200 milligrams, 1800 milligrams will stay in the gut. They will shut down your bioflora, and it will cause dysbiosis, and then you start chasing your tail as to how do I fix dysbiosis. That's why we mix them up with olive pomace oil. And what is olive pomace oil? If you take the olive oil, you're left with a pit, and a little bit of the shell of the olive. If you squeeze that, you get a thicker oil. And in Greece we use it as a salad dressing, but it is cheaper than olive oil in trying to keep actually the cost down. And it's not like you can take any pomace oil because as you know, the oleic acid content of either the olive oil or the olive pomace oil is what causes you to have heartburn. You know, it's, if the oleic acid is too much, you kind of get a heartburn.

So the typical olive oil that you buy, you know, anywhere is actually one to 2% oleic acid. The olive pomace oil we use is 0.1%, so 10 times less to make sure that we don't run into that problem. And the third problem to watch out, which maybe I should have said earlier is that soy flavonoids, many times you see soy bioflavonoids, soy flavonoids, soy flavonoids are estrogenic. So if God forbid a lady has, you know, ovarian cancer, you know, breast cancer, those would be a no, no, absolutely no, no. So again, not everything is the same unfortunately. And at the end of the day, duration of time is more important the amount. I always, especially when we don't know who the patients are, sometimes they'll just order something, and you don't have the chance to talk to them. I always say start with one and slowly increase to the extent tolerated.

And then of course, you know, if someone were to come to you, it could be important, do they have any endocrine problems? Do they have thyroid disease? Because at two grams a day, Quercetin will shut down thyroxin production. But if you have some who is hyperthyroid, then it would be good because you want to shut down thyroid production in hyperthyroidism. So there's so many things that enter. You really need to know, and unfortunately so many patients just buy over the counter or on the internet, and it's just impossible to be able to help them all and help them navigate through.

Tom Moorcroft, DO
Yeah, you know it's interesting. I mean, I think of a couple things, and one is that so much of what I do like, and I kind of learned about like sort of the conversation we're having in mast cell activation syndrome and the Summit and today with you is, comes through the world of Lyme and tick borne illness. And I hear myself saying all the time, it's low and slow and long is often

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better. If I had a choice between really high dose and really long course at a low dose, I'd take the second one most.

Theo Theoharides, MD
I'm 100% with you on that.

Tom Moorcroft, DO
And that's what we see with mold. That's what we see with mast cells. And so I'm really glad to hear you say that.

Theo Theoharides, MD
Yeah, mycotoxins are very high on my list. I've got numerous patients who were just horribly affected by exposure to mold and or mycotoxins. And just to be clear, for the audience that might not be aware of it, mold, types of mold make different types of mycotoxins, and mycotoxins stick to everything. I wrote a little editorial about mycotoxins and inflammation, and I quoted actually from the Old Testament. So the rabbi, the rabbi said, we're talking about 3000 years ago, "If you find a house that is infected by mold, "you tear it down." That's exactly quote by quote. And if someone has been wearing clothes that were exposed to mold, you burn the clothes. They could not have been more right.

Tom Moorcroft, DO
Wow.

Theo Theoharides, MD
If you don't pay attention to mycotoxins, you know, of course, if you have musty smell and you see, you know, water stain on the walls, you know you got a problem. But the mycotoxins are very difficult to measure in the air, and they stick to carpet, rugs, et cetera. So numerous occasions, I had people just leave their homes for two, three months if they could,

Tom Moorcroft, DO
And they feel so much better.

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Theo Theoharides, MD
And many of the symptoms got so much better, and we don't have good ways to measure mycotoxins. We tend to measure mycotoxins in the urine. But you know, I've sent urine in four different labs, and I get, you know, four different results back. And someone would argue some mycotoxins like ochratoxin is found also in food, you know, sources. So I always say, you know, wash, if you don't wanna peel the fruit, wash it with a little bit of soap first. You've gotta get the mycotoxins out.

Tom Moorcroft, DO
You gotta clean 'em.

Theo Theoharides, MD
No matter where they come from, but you have to address them.

Tom Moorcroft, DO
It's so important because, and it's like this taking out a little bit of toxin over time, doing the duration and kind of getting the understanding that we don't need to do everything all at once, I think too, I mean except maybe the long haul COVID lady who's gonna get a lung transplant.

Theo Theoharides, MD
Of course.

Tom Moorcroft, DO
You kind of have to, sometimes, some people throw the kitchen sink. One of the things I did wanna highlight though that I kind of heard you sort of saying is there's, maybe directly saying, there is a quality of product in, you know, medication and supplement and the sourcing. So I know that a lot of us have spent a lot of time getting different supplements, different places. The protocols get bigger, they get costly. But please like remember to work with your practitioners to make sure that you're, when you're spending money on something that maybe your insurance isn't covering, get the good stuff rather than, cause otherwise you're gonna be doing this for a little while, and if you're using lower quality stuff, you can actually be making your symptoms worse, not better.

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Theo Theoharides, MD
Correct. We're actually, so you know, the company Algonot has made, you know, a number of the supplements that we've been talking about, and it is actually on the Health Store as well. So where many physicians have their own kind of, you know, store, and I'm writing actually an article with one of the functional medicine physicians who's responsible in the Mayo Clinic. So we're trying to get out there, and it doesn't matter whether someone in my mind uses the term integrated medicine or functional medicine as long as they look for the reasons why. So functional medicine should not be necessarily that we should not be using medicine or we should not be actually looking for the science.

You know, functional medicine in my mind or integrated medicine is to look at the whole puzzle and not necessarily just a piece of the puzzle, but if for each piece or as many pieces of the puzzle, we can find a reason, that's how we should be making our selections, you know, moving forward. And in fact, I wrote a little tutorial called Luteolin Supplements: All that Glitters is not Gold type of thing, and I compared all the Luteolin supplements in the United States that were available, you know, two years ago when I wrote it. And you'll be surprised there'll be, for instance, one particular company says 100 milligrams of luteolin, but then when you read down only 10% of that is luteolin. The rest is rutin. And I'll say a word about rutin. There's another one that says 25 milligrams luteolin, which is, you know, a drop in the bucket. And then you read that it's actually two capsules for even the 25 milligrams.

Tom Moorcroft, DO
Oh, my God.

Theo Theoharides, MD
But the word luteolin shows up with big letters, and you've gotta read small letters to see that it's not enough luteolin in there. So the important thing is that Quercetin in life, in nature exists with a sugar attached to, and that's rutin. So rutin in Quercetin glycoside. So when someone buys Quercetin, they've removed the sugar. Now why is that important? I use Rutin too, whenever I have GI problems because rutin will be cleaved by GI bioflora and liberate Quercetin in the gut. So it's liberated slower. So for instance, in NeuroProtek, there's 100 milligrams luteolin, but 80 milligrams quercetin or 70 milligrams and 30 milligrams rutin because I'm trying to catch the gut, the rest of the body and the brain.

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Tom Moorcroft, DO
Brain.

Theo Theoharides, MD
So, but if you're gonna have 100 milligrams rutin. It's not gonna help you. It will all stay in the gut. So that's why I'm not saying rutin is bad. Sometimes I use the word inactive because if you take human cells in culture and you add rutin, it will not inhibit them because the cells don't have the way to cleave the sugar. So it, you know, sometimes when the words are used, you know, the mind is faster than your mouth so to speak. In terms of what you're trying to explain. The bottom line is I really believe we have good substances out there, and if they can be put into better formulations, we can be doing wonders. I've been trying for three years to create an intra-nasal with luteolin. I haven't been able to find funding, whether it's NIH or corporate America because there are no patents on it, but, so.

Tom Moorcroft, DO
Interesting. Yeah, it's one of those things. I think it's so, just everything you've shared with us today is just so inspiring.

Theo Theoharides, MD
Thank you.

Tom Moorcroft, DO
Because there is hope, and I think that so many of us feel that there may not be hope, but you know, and this is another reason too, like I really recommend people find a practitioner. If you're having symptoms like this, don't go it alone. There are people who know what they're doing. And like, even like, I mean, I know that like many of the guests including you on our Summit as well as our, you know, our host Beth O'Hara, like I love, she wanted to bring this whole group of people together because like you just said so eloquently, functional medicine is bringing science to all of this. It's not, and the way the body functions, not so much like no western medicine and all herbs and supplements or just meditate in a cave, and you'll be better. But it's the bringing together of all these things. So highlighting all that, I would, you know, I'm just so thankful for the time to talk and as we kind of land and bring all this together, are there any kind of closing words of hope you wanna share with? I mean, I feel like the whole thing's just been this amazing

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like masterclass and then also I feel so as a provider, sometimes I do feel like my patients are losing hope, and I might, so thank you for bringing that back for us.

Theo Theoharides, MD
So three parting comments if you wish. Number one, there's absolute hope. There's always hope, and if we don't have hope, then we're stressed out, and then we're spinning our wheels. Number two, as you said, find the right person. And if that person is not the best person, at least open the door that that person might talk to someone else who might know a little more. And I tend to think that functional integrated medicine colleagues are a little more open to talking to other colleagues than not. The third, probably the most important thing is in 40 years in research, I've never been funded by NIH to study the mast cell. I've always been funded through, you know, eczema, through psoriasis, through autism, et cetera.

There's gotta be a request for applications for just studying the mast cell at this point. It's way, way overdue. And in that vein, I've been fascinated, not necessarily pleasantly by the fact that patients who did very well, who before they got well, were saying, my God, I'll give you anything to make me feel better. And I've never asked for money other than give some money for research. They just disappear. There's gotta be some money to help. And not necessarily me. Whoever is out there struggling to find answers. Without money, there cannot be any research. So I'm begging people that are on the way to recovery or those who are begging for recovery who might be independently wealthy.

We need donations, tax deductible donations to the universities to help out with this research. I mean, we're lacking, we used to be many more in the area of mast cells. I could have counted 20 maybe colleagues. Now we're down to about seven who know about mast cells, and three of them are retiring. So if we don't have younger people coming into this because there isn't money into this. These are complicated patients. They require a lot of time. You know, insurance companies don't cover many of these things. So we've gotta find a better way to address the patients and do the research that eventually will help everybody, so.

Tom Moorcroft, DO
Well, a great call to action for everyone, and if maybe you don't fit into that, you know, into the ability to personally fund anything. One of the other things we've seen in the Lyme world is that public talking to their, you know, to the representatives and to their local governments and those

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folks who are representing them in Washington does make a change. And there are some changes that have gone on in the last couple of years that have really made a difference. And so if we can dovetail into the new work that's been going on with Lyme and all these other parts. Let's, I mean the mast cell seems like something that should be studied. So if you happen to think about it, just write to your congressperson or representative as well. And if you know anyone, so Dr. Theoharides, I mean, my goodness, thank you so much. You're so generous with your time and your knowledge.

Theo Theoharides, MD
Thank you.

Tom Moorcroft, DO
Thank you all you've done over the past like four plus decades to help all our patients get well.

Theo Theoharides, MD
Good luck to you and all of you listening out there.

Tom Moorcroft, DO
Great.

Theo Theoharides, MD
Thank you so much.

Tom Moorcroft, DO
So everyone, thank you again for joining us for this episode of the Reversing Mast Cell Activation Syndrome and Histamine Intolerance Syndrome and our Summit, I should say. And my name's Dr. Tom Moorcroft, and we'll see you in our next episode.

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