162: Dr. Jill interviews Bob Miller on A Lesser Known Pathway for Mast Cell Activation (MCAS)

Dr. Jill 00:13
Well, hello everybody! It's another episode of Dr. Jill Live! As you know, you can find us on YouTube, Stitcher, iTunes, or anywhere that you watch or listen to podcasts. Today we're back with my good friend Bob Miller. Many of you have seen our podcast and know Bob well. And we were just talking before we got on [about how] your podcast episodes, Bob, are some of our most watched and favorite episodes. What's interesting is that we go really, really deep and really technical, but people seem to really like that. So hopefully, if you're out there joining us today live or if you're listening to the recording, you will enjoy diving in. This is one of those podcasts [where] I'll kind of give a little warning: You might want to watch it because Bob's going to share some slides. There are some very intense... Very fun; I say intense, but you and I love the intensity of the diagrams, right?

Bob Miller 01:00
Exactly.

Dr. Jill 01:02
So we're going to actually have some visuals that you might want to tune in. So if you're listening in your car, don't go off the road, but later on, if you get a chance, you might want to specifically watch this one on YouTube because there are going to be some cool graphics and things that might explain. What I'll try to do is just add in, [and] if you're out there listening and not watching, I'll try to explain if there are one or two things that need explanation.

Dr. Jill 01:23
Bob Miller is, again, a well-beloved guest and a wonderful friend of mine. He is a traditional naturopath specializing in the field of genetic-specific nutrition. In '93, he opened Tree of Life Practice and served as a traditional naturopath for 27 years. For the past several years, he's been engaged exclusively with functional nutritional genetic variants and related research, specializing in nutritional support for those with chronic Lyme disease—and I'll really say it goes way beyond that—chronic infections, mast cell activation, even mold exposure. But definitely, these complex chronic infections and toxins. And I could go on, Bob. You've got so many accolades. But what I love is your mind, what you bring to the table, and how you look at things. So welcome to another episode.

Bob Miller 02:09
It's always, always a pleasure to be here. And first, let me say congratulations on your book! What an incredible publication! I know you must be impacting the lives of so many people as they read it. So best of luck in continuing to promote it and changing lives as people learn some of the wisdom you're passing on.

Dr. Jill 02:24
Aw, thank you, Bob. That means so much. Yes, it's quite an ordeal, and I'm glad I'm on this side of it now, getting it out there. So today, our topic is called, "A Lesser Known Cause of Mast Cell Activation". Many of you may know—I'll just frame this and I'll give it right over to Bob—[that with] mast cell activation, these primordial cells that have been around probably before any other parts of the immune system are often reactive to our environment. So what we're seeing in this post-pandemic error, and error with an all-time high load of toxins in our environment, [are]: Parabens and phthalates in your makeup and beauty products. Heavy metals maybe when you get the silver amalgams in your mouth. Or lead in the old paint or as you sand off some old materials in your house. Or now fluorinated compounds. These PFAs are found in Colorado, where I live, and all of the water supplies are now contaminated with these forever chemicals.

Dr. Jill 03:21
I could go on and on about the toxic load in our world, but the significance of this is that it's driving our immune systems to be a little crazy and to act out more than they are supposed to. So this toxic load plus infectious burden is a perfect storm that's causing us to see more and more and more cases of something we didn't even talk about 10 years ago called mast cell activation. So the topic of our conversation today is going to be for Bob to really dive into some of the pathways behind this and explain something you may not have heard about relating to another cause of mast cell activation. So take it away, Bob!

Bob Miller 03:57
Okay, what a great introduction! I mean, you just gave a two-hour class on mast cells in 45 seconds. Excellent. Excellent. Are you seeing the screen?

Dr. Jill 04:09

Yes.

Bob Miller 04:10
Okay. So our topic is a lesser-known cause of mast cell activation. As Dr. Jill said, there are so many things impacting us. But today, I think we're going to take a really deep dive and look at what might be the mechanisms for all these environmental toxins causing this, and then, more importantly, what we can do to maybe slow that process down a little bit. There's a lot to be said about mast cells. And what we're going to be talking about is how they come from intracellular calcium, which probably surprises many people—it's like, "Wait, calcium; that's supposed to be good"—from something that probably no one has ever heard of, the aryl hydrocarbon receptor, the NMDA receptor. And then, of course, the last one most people have heard about is EMF. As we've said many times, this turns out to be a 3D chess game that's played underwater.

Bob Miller 05:03
Now, here's what we're going to talk about: Mast cells 101. And I mean, just really basic, because Dr. Jill just explained it. But then we're really going to dig into some of the causes, [such as] excess intracellular calcium, and we'll do a little bit on EMF. And then something very fascinating: The NMDA receptor stimulation and how glutamate is involved. Then we'll get into the aryl hydrocarbon receptor causing this problem, which is absolutely fascinating. Then we're going to look at the various chemicals that stimulate this aryl hydrocarbon receptor, a little bit of genetic predispositions, and then an action plan of lifestyle things you can do that may be able to slow down the possibility of this happening.

Bob Miller 05:43
Now we're going to spend about two minutes on what mast cells are. One of the experts on mast cells is Beth O'Hara, a functional naturopath. Dr. Jill has interviewed her twice. So if you really want to dig into the mast cells, I really encourage you to go back and listen to numbers 78, where they talk about mold, and 29—both of those—[that discusses] triggers and treatments for mast cells. So [those episodes have a duration of] 43 minutes, 52 minutes [respectively], [and provide] mast cell 101 in case this is a new subject for you because we're going to blow through it pretty quickly and then spend our time on why.

Bob Miller 06:20
I also have to do a shout-out to a good friend, Dr. Harold Landis. He graduated from the University of Maryland Dental School in '83, and then he went on to do integrative medicine at the University of Arizona in 2021. We call each other 'the geezer geeks' as we get into all of this and study it together. And Dr. Landis is now participating in the webinars that I have for physicians every other Thursday evening, so we're just having a good time. I'd be remiss if I didn't mention his valuable contribution to some of this information.

Bob Miller 06:59
Okay, we're going to blow through mast cells here, [which have an] important role in innate and adaptive immunity. As Dr. Jill said, they recognize harmful antigens by binding to them. And once they bind to them, it causes the release of inflammatory mediators. One of my favorite phrases is: "Is that a good thing? Yes, unless it isn't," meaning that if it's overactive, [it isn't].

Bob Miller 07:22
Again, it's very valuable. [Here are the roles and functions of mast cells]: Innate and adaptive immunity. Coordination of the immune defense when we have a virus, bacteria, mold, candida, or even venom detox. [They help with] wound healing, recovery of connective tissue after injury, formation of new blood vessels and vasodilation, homeostasis of tissues and organs, neurogenesis, angiogenesis, regulation of menstruation, and regulation of pregnancy.

Bob Miller 07:47
[They do] all these good things. However, we can get what's called mast cell activation syndrome, where they're dysregulated. They become overactive and over-release inflammatory mediators. When these slides were made up, which was some time ago, [it was] likely present in nine to 14% of the population. Dr. Jill, for the people that come in to see you—you're seeing more of the tougher cases—what percentage would you say you think are having some level of mast cell activation?

Dr. Jill 08:15
Yes, Bob, that's why I mentioned that 10 years ago, because 10 years ago, I didn't even know what it was. And nowadays, I would say 25% to 30% have some piece of it, so it's a huge percentage. And if you haven't watched, I know you didn't mention

this today, Bob, but we did a presentation on the 'Carnahan reaction', the iNOS pathway. And one thing I learned recently that I didn't know is that mast cells are also regulated by nitric oxide, which if it's uncoupled when there's oxidative stress will actually cause more reactive oxygen and less mast cell regulation. So this is all connected. And if you haven't seen our previous episode on the iNOS pathway, that's another one to watch.

Bob Miller 08:50
Absolutely. Yes, we named it after Dr. Carnahan. It's called the 'Carnahan reaction'. Here's a brief look at a chart that shows how when the mast cells get activated, they give off histamine; they're called interleukins. They stimulate a very powerful inflammation-creator: Tumor necrosis factor. And again, this is a good thing, unless it's overactive. Now, mast cell activation is when things get carried away. And that began the evolution of discussions about other forms of mast cell disorders, which became known as mast cell activation syndrome.

Bob Miller 09:26
When this occurs, we can have an allergy, some subtypes of autism, asthma, anaphylaxis, gastrointestinal disorders, many types of malignancies, and cardiovascular disease. They play a significant role in TBIs, PTSD, Alzheimer's, MS, and ischemic injuries. They might even be playing a role in autism spectrum disorder. They are really creating a lot of havoc. So what we had in our bodies to help us is now turning on us [and may play a significant role in] eczema, chronic dermatitis, migraines, neurological disorders, GI [disorders], including Crohn's and IBD, some autoimmune diseases, vascular inflammation, and unexplained multi-system illness. I tend to think there are more people struggling with this than they realize. Would you agree with that—that some people are chasing symptoms, not realizing it may be mast cell activation?

Dr. Jill 10:20
Yes, it's really Bob at the root of so many things. As you can see [from] this whole skew, it could be skin, it could be gut, it could be heart. Part of that is because histamine, one of the many mediators from mast cells, affects every tissue in the body.

Bob Miller 10:36
Absolutely. I'm not going to read all of these. If you're watching the video, you can

pause it if you want to look at it. But you can see it's widespread—all of the things that can be created by excess mast cells. Again, I'm not going to read this. If someone is watching, they may want to pause if they want to read it all. Overall, fatigue [and] muscular skeletal symptoms might be related to osteoporosis and osteopenia, [as well as] skin symptoms from the histamine, [such as] itching, flushing, and hives. By the way, Dr. Jill and I did an excellent podcast on histamine. And if you go back and look at that one, we really covered histamine quite well. [The list continues]: Cardiovascular, feeling faint, digestive, mouth burning, gum inflammation—again, I'm not going to read the whole list, but this is the who's who of digestive symptoms—brain and nervous symptoms, lungs, and respiratory symptoms, eye symptoms, trouble focusing, blurry, itchy, watery, irritated, reproductive system symptoms, endometriosis, painful periods, urinary tract issues, anaphylaxis, itchy hives, flushing or pale skin. As you can see, this is a very, very broad list of things that can happen. Fibro, chronic fatigue, IC, certain cancers, as we said, Crohn's disease, Ehlers-Danlos, where people are super flexible, POTS, where you get dizzy when you stand up quickly, as we mentioned, autism, and even some forms of auto-immunity such as rheumatoid arthritis, lupus, and Hashimoto's—the list goes on and on.

Bob Miller 12:13
All right, now what's the real problem? As you so succinctly said in the very beginning, it's many of the toxins that we're exposed to. It may even be an expression of what's called the cell danger response, where the cells go into somewhat of a shutdown. So we went along on a pretty good clip there because I just wanted to give a brief overview of mast cells. And again, go back and watch some of those other videos if you really want to dig into it. But we've now established that mast cells can be a problem.

Bob Miller 12:43
Now we're going to dig into some new research as to why this might be happening. It's probably pretty surprising that I'm going to be talking about calcium because everybody knows, "Well, calcium's important," right? It helps form your bones and teeth, helps maintain body strength, assists in the movement of muscles, assists with nerve messaging, helps blood flow as vessels relax and constrict, and releases hormones and enzymes that support body functions. We must have calcium. In the glands, it triggers the secretion. In nerve cells, it triggers the release of neurotransmitters. In muscle cells, it triggers muscle contraction. In cardiac

muscle, it prolongs heart contraction to ensure adequate ejection of the blood. All really important things. You'll notice down here I have the word 'unless'. There's now convincing evidence that the calcium ion can play a critical role in cell killing under certain conditions.

Bob Miller 13:47
[Notice] this peer-reviewed study: "The calcium ion and cell death". Who would have thought that something as important as calcium could actually, under the wrong conditions, turn on us? And what we're going to be talking about is when excess calcium comes into the intercell—the intercell calcium. There needs to be a balance between the extracellular and the intracellular. And you need a lot of extracellular; just a little bit of intracellular. And when too much comes in, that's when we start creating problems. So here's a peer-reviewed study. It is well known that mast cell activation is critically regulated by intracellular calcium ion.

Bob Miller 14:33
Now, I don't want anybody listening to this and saying, "Oh my gosh, I've got to stay away from calcium because it causes mast cells." It's not what we're saying at all. We're saying it's when calcium is used improperly, which we're going to explain in a little while. We also did some videos on iron. Iron is critical. Without iron, life doesn't exist. It carries oxygen through your red blood cells. However, iron can become a bad boy too, and cause all kinds of problems. So now we're going to be exploring how the mechanisms that cause calcium to be disrupted work and [how they] actually do some harm rather than be good for you.

Bob Miller 15:13
I'm going to try to get the annotation here and draw. Let me get the drawing tool. So here's what's called a calcium channel. What you're seeing here is the cell wall, and there are channels where calcium comes in. The key word here is overload,' if there's too much calcium inside the cell. So this is outside the cell over here. This is inside the cell here. The intracellular: Mitochondrial dysfunction, oxidative stress, generation of free radicals, DNA damage, and cell death if too much calcium comes intracellularly. Again, we're not saying calcium is bad, but when it's misused and comes into the cell inappropriately, that's when it creates a problem.

Bob Miller 16:09

Now, this chart—again, we're not going to go into the details here—shows three different ways that this calcium flux can cause mast cell activation. Here's the second one. Here's the third one. And we have the citation here. If anyone wants to look this up and read it, it's a long article, and somebody really wants to get into the specifics of how this causes mast cell activation. So here's another article: "If matrix calcium increases beyond physiological demands, it can promote the opening of the mitochondrial permeability transition pore and trigger apoptotic or necrotic cell death. In other words, the cells can be killed if too much calcium comes inside the cell. Here's another article: "The role of calcium and cell injury." Again, the bottom line is that it can result in membrane damage, mitochondrial calcification, and mast cell activation.

Bob Miller 17:13
So now the story is going, "Well, if that's the case, how does that occur?" We're going to get into that. But first, let's look at [how] this has been linked to neurodegenerative disorders, [such as] Alzheimer's and Parkinson's. Some even thought that it might be related to autism spectrum disorder [and] attention deficit hyperactivity disorder. I mean, if you talk to an elementary school teacher who's been teaching for five years or more and you ask them, "How are the students doing?" I don't know if that's happened to you as well, Dr. Jill, but everyone I've talked to says there's [been] a difference in the last five years. The children can't pay attention. They're more rambunctious. They're more agitated. At the worst, it can even go to schizophrenia. Are you noticing that same thing in children, Dr. Jill?

Dr. Jill (pre-recording) 18:00
Hey, everybody. I just stopped by to let you know that my new book, *Unexpected: Finding Resilience through Functional Medicine, Science, and Faith*, is now available for order wherever you purchase books. In this book, I share my own journey of overcoming a life-threatening illness and the tools, tips, tricks, hope, and resilience I found along the way. This book includes practical advice for things like cancer and Crohn's disease and other autoimmune conditions, infections like Lyme or Epstein-Barr, and mold- and biotoxin-related illnesses. What I really hope is that as you read this book, you find transformational wisdom for health and healing. If you want to get your own copy, stop by ReadUnexpected.com. There, you can also collect your free bonuses. So grab your copy today and begin your own transformational journey through functional medicine and finding resilience.

Dr. Jill 18:55
Yes. Yes, for a multitude of reasons, some of which you already talked about. Absolutely. I feel like there's a big exponential difference in the health and mental health of children and adults, and all the things we're discussing.

Bob Miller 19:09
Absolutely. Okay, now we're even looking at heart failure. They're saying that mitochondrial calcium overload is a key determinant of heart failure. Now, here's one of the ways that this can happen: This gene right here, CACNA1C, is called your calcium voltage channel, and this line right here is the cell wall. We need calcium to come into the cell. We need some in there. It's stimulated by voltage. Now, what's happening to us? We are living in a sea of electromagnetic fields like never before. No matter where you go—in houses and businesses or on the street with cell phones—we're being exposed to EMF. More and more research is looking at: Is this EMF triggering this calcium voltage channel to bring calcium in? And that's an area that's being researched quite a bit.

Bob Miller 20:07
Now, we're going to spend a little time on this chart right here that we made. It's just a little dense. But we're going to slow her down here and show you what can happen. [I was] absolutely fascinated by this. There's something called the NMDA receptor. And there's a glutamate binding site. Now, glutamate is a neurotransmitter that makes you intelligent, highly motivated, and a go-getter. Too much of it, though, and you're anxious. Glycine is an amino acid, and it binds on here. And if there is too much stimulation of this NMDA receptor, look what it does. It brings calcium into the cell—again, this is the outer cell up here, [and] this is the inner cell here—creating mast cells. Now, why might that be a problem? We're going to show you in a little while [how] glyphosate, which is Roundup, will drive the NMDA receptor and also homocysteine. This is something that I believe should be measured more often than it is. But it's a molecule that needs to be recycled through a process called methylation into something called SAMe. Many times, this homocysteine is too high, and it will also stimulate the NMDA receptor.

Bob Miller 21:36
Now, this gets a little bit more complex. Calcium, when it comes in, can be blocked by magnesium, and many of us are low in magnesium. So you can see here that this

little green [thing] right here is magnesium blocking it. Also, the amino acid taurine will inhibit it. So that's why we've been looking quite a bit at magnesium taurate, perhaps as a good magnesium source when this is an issue. Now, what's interesting [is that] there's something called quinolinic acid. We're going to have a slide for this, but it is neurotoxic, and it will cause some lipid peroxidation, but it will also stimulate NMDA. And this comes from something called the kyurenine pathway, which we're going to show you a little bit later.

Bob Miller 22:32
And, Dr. Jill, we have found a SNP that I've now put on my top 10 list. There's an enzyme called ACMSD. Right, there's the RS number (rs2121337), and that converts quinolinic acid into picolinic acid. And picolinic—we're going to show you a slide—is quite helpful, and it's very much needed for the proper use of zinc. So if we don't have enough picolinic acid… And what I'm going to show [you is that] you can also have genetic mutations in the transport of zinc. So maybe if you don't get enough from your diet, you don't convert quinolinic to picolinic. If you don't get enough zinc, you have trouble carrying it, [and] you do not have the ability to hold back this NMDA receptor.

Bob Miller 23:22
So as you can see here, there are multiple, multiple factors involved here. So you've got to make sure this quinolinic acid isn't too high. And by the way, interestingly, this nasty molecule turns into something called NAD by these enzymes. And NAD actually inhibits mast cells. So, Dr. Jill, that's why we're putting a lot of emphasis recently on making sure that this quinolinic acid isn't too high. And we are looking at—we're in the research phase now, [but] we're not there yet—[and] we've got to figure out how to get that quinolinic to come over to picolinic so that our zinc can hold this back.

Dr. Jill 24:06
This is amazing, Bob. I want to comment on two little things that came up as you were talking. First of all, for cardiovascular disease in general, there are four main nutrients that I always think about for heart health. Magnesium is one, taurine is number two, and then there's carnitine and CoQ10. But Mag-Taurine has always been a huge cardiovascular… As we know from your previous slide, this calcium channel is very important for cardiovascular disease and prevention and regulates

blood pressure and all kinds of other things as well. So that's interesting that on this other level, magnesium and taurine are so key. So that's number one.

Dr. Jill 24:42
Number two is that, as you mentioned, quinolinic acid is totally excitotoxic. You'll probably talk more about this, but I'll just frame it from a clinical perspective. When I see elevated quinolinic acid in the urine, it is literally the number one red flag for neurodegeneration, bipolar, schizophrenia, ADHD, or any sort of excitotoxic disease where there's a mental component or a nervous system component, because quinolinic acid [when] elevated will literally kill nerve cells. And there's a whole other pathway that's not shown here—again, you'll probably show it to us—that steals from our happy serotonin. Again, you know this well. So this is such an important pathway, Bob, that you're talking about. And I want our listeners to know that this is involved in a lot of depression, anxiety, bipolar [disorder], mood disorders, learning disorders, and neurodegeneration because, literally, elevated quinolinic acid will be so excitotoxic that it will kill your neurons and your brain cells.

Bob Miller 25:38
Absolutely. We're going to show a little later how it actually stimulates inflammation. So this just shows why we've got to be very careful with glyphosate and why we need to check our homocysteine and get it down. This is why some people do not do well on glycine, and this is also why some people, as you said, are so anxious. So we're looking at this NMDA receptor as being a big problem. And again, we're talking about mast cells. But as you pointed out, it's way, way beyond that.

Bob Miller 26:11
Now, here we're saying that massive activation of the glutamate receptors we just talked about can result in excessive rises in the calcium that's thought to underlie the fundamental processes leading to neuronal death. Preventing such cellular calcium rises in the brain may considerably reduce the neuronal damage produced by stroke, head trauma, or epilepsy. Here is another study. If anyone wants to read the whole study, just go to a search engine and type in that title, and that will pop up the whole study. I just took one sentence that summarizes it. "Excessive or

prolonged exposure to glutamate causes an elevation of intracellular calcium levels that can ultimately trigger neuronal death."

Bob Miller 26:56
Now, I've been talking about glutamate probably for the last 15 years from the standpoint that yes, it makes you intelligent, highly motivated, and a go-getter, but it can [also] make you anxious. And it can lead to a little bit of ADD, bipolar [disorder] or schizophrenia. Only recently have we dug in and realized this is also a very powerful way to create inflammation inside the body, and we'll be connecting those dots a little bit later.

Bob Miller 27:27
So here's just another study that says the activation of the NMDA receptors produces prolonged increases in that intracellular calcium concentration. All right. Now, we're going to get just a wee bit deeper here. So you'll see on the right here; that's what you just saw. So we went through all of that. Now what I'm going to talk about is glutamate. So right here is glutamate. It makes you intelligent, highly motivated, and a go-getter, and it's made from glutamine. There are actually genes that are enzymes that will cause the glutamine to turn into glutamate. Glutamate will go back into glutamine. There's an enzyme called DAO that, when there are mutations in it, will cause the glutamate to go even higher. There are enzymes called GLUD and GOT that will turn glutamate into alpha-ketoglutarate, which is energy inside the mitochondria. And you can have mutations in GLUD. You can have mutations in GOT. And one of the things, Dr. Jill, that I'm very excited about recently is oxaloacetate. This shows up in the Krebs cycle. It takes glutamate and turns it into alpha-ketoglutarate.

Bob Miller 28:47
Now, this is surprising. I mean, we just literally learned this in the last couple of months. Something called pyruvate turns into oxaloacetate. And one of the B vitamins is biotin. If you speak to most people about biotin, it's like, "Isn't that for the hair, the skin, the nails?" "Yes, sort of." I've just begun to learn recently that biotin is much more important than we ever realized because the pyruvate carboxylase enzyme will take biotin and turn it into oxaloacetate to clear the glutamate. So for some individuals, if you have a genetic mutation that you don't transport the biotin, that you don't recycle the biotin, that you don't use the biotin

to turn the pyruvate, you're low on oxaloacetate, which also impacts your Krebs cycle, but this glutamate is allowed to run wild.

Dr. Jill 29:47
And Bob, there's a product—I'm not going to mention brand names on here—an oxaloacetate that I've been starting to use in clinical practice because it was talked about with the cell danger response, which is kind of related to mast cell activation. The studies on this oxaloacetate [show that] using high doses can decrease that cell danger response and decrease mast cell activation. But I did not know this pathway. Now that I see it, it's like an 'Aha!' because, of course, that works. And of course, you can do it with more biotin or pyruvate in the right person too; I'm sure you'll tell us about that. But this is fascinating.

Bob Miller 30:18
Yes, absolutely. I'm starting to use that product as well, with very good results. And guess who else on this call [inaudible] like me, has high glutamate?

Dr. Jill 30:27
Ah, yes, both of you. I know I'm like, "I'm on this." Love it.

Bob Miller 30:32
Now, what gets interesting is that glutamate will stimulate the NMDA receptor that we just talked about. But there's even more. Now, this really surprised me. So this line here is your cell wall, and there's something called lipids that have to replace the cell wall and build the cell wall. As you all know, we're made of cells, and we've got this cell wall. It's made up of lipids, or fats. Well, what can happen is that iron and hydrogen peroxide—and by the way, this might be another podcast sometime just to dig into this, what's called ferroptosis—will damage this lipid. And if it joins the cell wall, it damages the cell wall.

Bob Miller 31:19
I was hoping to have another graph made up, [but I] just couldn't get it done. But there's a dance between this damage to the cell wall, the NMDA receptor, and something we're going to talk about later. Maybe that'll be our part two at some point. But what happens is that when this lipid gets damaged, there's an enzyme called GSS that makes something called glutathione, and then an enzyme called glutathione peroxidase 4 that takes the glutathione and fixes this guy so he can join the cell wall in a healthy way. It's called lipid peroxidation, or ferroptosis. So you can see that glutamine comes in. Cysteine comes in. And as you all know, glutathione is

a tripeptide, so it's got lysine, glutamine, and glutamate. But interestingly, look at this key point right here: Glutamate inhibits the enzyme that brings the cysteine in to make glutathione. Whoa! To me, that was a big deal.

Bob Miller 32:29
And then also, cysteine, if it doesn't turn into glutathione, can actually be inflammatory, especially if it can't go through what's called SUOX, and that'll actually make inflammation. So people might be taking cysteine like NAC, thinking, "Oh, cool, that's going to make me more glutathione." But if it's blocked and you might have problems with something called the SUOX enzyme that's downstream down here, you can actually make inflammation by taking NAC. Hate when that happens.

Dr. Jill 32:58
Bob, I love that you mentioned that. First of all, NAC is a precursor of cysteine. Everybody out there has heard of NAC, and many of you are taking it. And I would totally agree. Clinically, I have seen people get worse, usually when they have underlying infections or inflammation that's not controlled. Too much NAC can be a problem. So be very aware. All these nutrients have their good sides and bad sides. I have a question that you may or may not have the answer to. That alpha-ketoglutaric acid or glutarate at the top left there, I see your arrows going from glutamate, so I'm assuming your body can convert glutamate to that. And that's a good pathway because that converts to energy. Does taking alpha-ketoglutarate do anything to the glutamate itself? Is there any back pathway that you know of?

Bob Miller 33:39
Well, I've never studied that or dug into it, but it would just make clinical sense that if you take too much of it, it may cause the glutamate to back up. We've said this many times: Not too much, not too little, on just about everything.

Dr. Jill 33:55
Yes. And then another question real quick: Lipid membranes there—I'm assuming this could be measured with lipid peroxides, which we can measure in the urine and blood of patients.

Bob Miller 34:04
Yes, like the OGHD or something like that.

Dr. Jill 34:06
Yes. So if you have hydena organic acids and high lipid peroxides, that's just a sign that your membranes are being damaged. And this is what Bob's talking about with that inflammation and the lipids being oxidized there at the bottom left.

Bob Miller 34:17
Yes. And when we get a breakdown of the cell membrane, that's when the body breaks down because we live and die at the cellular level. So you can see now why I have a new appreciation for glutamate—not just [because it] makes you anxious and gives you nightmares. It can actually do serious damage to the body. Any other thoughts or questions on this before I move on?

Dr. Jill 34:42
Just one more caveat. If you're out there and you or a loved one has cancer, these pathways can be active in cancer. One thing I always look at if someone has cancer is: Are they making lipid peroxides or 8-DOH [*sic*], which is deoxy... I can't remember the full name there. But those two markers are related to oxidative stress and definitely related to DNA damage, which is a precursor of cancer. So this is relevant not only to inflammation and mast cells but [also to] patients with cancer.

Bob Miller 35:10
Let me talk about one of my other pet peeves. A lot of people think they have an upset intestinal tract, which they might. And too many times people reach for or are suggested glutamine. I'm not anti-glutamine. It does stimulate mTOR. It will rebuild the gut. But if you've already got this overactive, you can throw fuel on the fire by taking glutamine. And that can include things like bone broth, Chinese food, and collagen. All of those things that we tend to think are good for us, like bone broth, "Well, that can't be bad for you." Well, if you've got too much glutamate being made in some instances, that could happen. Now, again, I'm not anti-bone broth; it has a lot of benefits. But if this is an issue, maybe some caution is warranted.

Dr. Jill 35:57
Bob, I love that you said that because one thing that you find on labels, in health foods, and in different things is autolyzed yeast extract. It creates a great flavor in our brains. It's almost like natural MSG. And the same thing goes for that. That's a

precursor of glutamate, and MSG is as well. MSG is glutamate. So anything with MSG, anything with autolyzed yeast extract, anything with collagen or bone broth—those things can trigger this pathway.

Bob Miller 36:21
Absolutely. And now there are times when it's absolutely necessary. But if we're concerned that this guy is too upregulated, caution might be warranted. All right, quinolinic acid—and you did a good job talking about how dangerous it is—is an agonist, meaning it supports or stimulates that NMDR receptor. So it's a brain excitotoxin. And they're saying it's a neurotoxin, gliotoxin, proinflammatory mediator, and prooxidant molecule. It can alter the integrity and cohesion of the blood-brain barrier. I know you do look at a lot of organic acid tests. How often do you see that elevated, Dr. Jill?

Dr. Jill 37:00
I check pretty much every single person for this. It's on my organic acid panel. I would say on this, it's probably 10% to 20%, which is still one or two in 10, not as high as just the mast cell activation. But let's say even 10%; it's significant. And like I said, there are a few red flags in my practice that I see, and this is one of them that I'm like, "Oh, this is very bad." This will long-term lead to some sort of neurodegeneration and mood disorder or some long-term sequelae. So it's a really big deal if you have this elevated.

Bob Miller 37:31
Absolutely. Just another that kind of says the same thing: [It is] "implicated in the cause of many human neurological diseases." All right now, picolinic acid. If you remember back to my chart, I showed you there's an enzyme that turns quinolinic into picolinic. And I'm very intrigued by this because we found [in] a study that that AMSSD [gene] that I showed you, when it's homozygous, [there's a] much higher rate of depression and/or even suicidal ideations. So that quinolinic acid is really playing havoc on us, and I think we found the one RS number that can really impact it. Now, we're way early on this, but what I'm finding is that in many autistic children, they have a homozygous [mutation] on that one—they can't convert the quinolinic to the picolinic. So on the other hand, picolinic [acid] comes from L-tryptophan, which I'll show you in a little bit. [It has a] wide range of—

Dr. Jill 38:26
And Bob, repeat that gene real quick. I know you said it. I want to make sure people hear it, and I heard it. The gene that converts quinolinic to picolinic is what?

Bob Miller 38:34
ACSD. And there's the RS number: 2121337. I don't think I put that slide up, but there is a slide that [shows that] this is related to depression. Well, that would certainly make sense. So if anyone can check their genes for that, that's a good one to look at. So, as I said, we're seeing that quite often in autistic children. Okay, picolinic [acid has] neuroprotective, immunological, and antiproliferative effects. Picolinic acid increases the turnover of zinc in addition to enhancing its absorption and excretion. So it has implications for uses in zinc deficiency. So think about how this becomes the perfect storm. If you don't turn your quinolinic into picolinic, you're going to stimulate the NMDA. Then you might be inhibiting the one mineral that calms it down. The perfect storm. Now, just clinical observation only: We're seeing many individuals who have difficulty converting quinolinic to picolinic, along with trouble transporting zinc, as almost like the perfect storm. So we've been trying to put these people on a lot of zinc picolinate.

Dr. Jill 40:00
And Bob, interestingly, there's a German researcher who's doing DNA addicts. What he's doing is testing your DNA for things that stick to the DNA and damage the DNA. That could be aspergillus—mold. It could be metals. That could be all kinds of chemicals and toxins. He literally does a panel of the DNA for these adjuvants. But the core thing that he finds is that low intracellular zinc is the thing that triggers the worst reactions, which probably goes back to this research here and why zinc is so core and so important for detox.

Bob Miller 40:31
Absolutely. I'm glad you pointed that out. That's very valuable. All right, homocysteine, we mentioned this earlier, is known as an agonist—again, that means it helps it [whereas] antagonist means it goes against it—to that NMDAR. It's so important to keep your homocysteine levels in check. And I'm sure you check that, don't you, Dr. Jill?

Dr. Jill 40:52
I do—on every patient. My ideal [level] is below 9 if you're healthy and below 7 if you have a neurodegenerative disease.

Bob Miller 40:59
Absolutely. And I'm surprised how many doctors do not check it. Often, when we're consulting with folks, it's "What's your homocysteine?" "I don't know." There's a book out there called *The Higher Your Homocysteine, the Sooner You Die From All Causes* [*sic*]. And we're going to show you very briefly another pathway that homocysteine can stimulate—what's called the Fenton reaction, where iron becomes a free radical.

Bob Miller 41:29
Okay, just another article here: "Homocysteine-dependent NMDA receptor stimulation" and the resultant calcium influx "leads to rapid and sustained phosphorylation." Glyphosate—again, peer-reviewed study. You can look these up if you type all these words in. The whole thing will pop up. "Our results strongly suggest that activation of the NMDAR pathway, together with its downstream" calcium, "is caused by glyphosate." Fructose modifies the NMDA receptors and can make seizures worse. So what have we done in the last 40 or 50 years? By the way, one of my favorite jokes is… I was born in 1954, and when I'm speaking to younger people, I'll say, "Yes, I was born on a different planet," meaning that we didn't have all of these things that we have today. So we have high-fructose corn syrup. Then we have glyphosate. No wonder we're seeing so many people struggling and anxious.

Bob Miller 42:30
Now, this is fascinating. It's called the aryl hydrocarbon receptor. Not many people have heard about this yet. And I think in the functional and naturopathic worlds, we really need to dig into this because, in my opinion, this is a big deal. This is the cell. This is the cytosol, and this is the nucleus. A ligand is defined as any molecule or atom that binds to a receiving protein, otherwise known as a receptor. So here's a ligand. It attaches to the AhR enzyme. It then goes into the nucleus, and it binds with something called ARNT. And hold onto your hat. Depending on what the ligand is, it can be pro-inflammatory or antioxidant.

Bob Miller 43:20
As you know, Dr. Jill, most enzymes we look at can create free radicals or antioxidants. This one is a different animal, so I think you can see why I'm very intrigued by this guy. Then there's another one called AHRR that will calm this down. Now, we are really in the early stages of this. I know a lot of holistic health

practitioners watch your videos, and my message to them would be: You need to start looking at this because this is a big deal.

Bob Miller 43:55
A ligand, here we're saying, is defined as any molecule that binds to a receiving protein molecule. The aryl hydrocarbon receptor is ligand-activated. It takes in environmental, dietary, microbial, and metabolic cues to control complex transitional programs. And when we say complex, this is still being researched by the scientific community, and data is coming out. I mean, there are so many papers being written on this. This is being looked at, but I'd like to bring attention to it in the functional world because I think it's a missing piece.

Bob Miller 44:31
This is a little dense, but I do want to go through the whole thing slowly. It's a transcription factor and receptor for small molecule chemicals, including dioxins and environmental pollutants—as you pointed that out very succinctly in your opening comments—but it will also take in things such as flavonoids, byproducts of intestinal microbiomes, and drugs. Now, once this ligation occurs, it translates to the nucleus—in other words, it goes into the nucleus—then [it], this big word here, [heterodimerizes] the direct interaction between at least two different functional receptors, forming a complex with specific biochemical and functional properties different from those of the component receptor unit, boy, is that a mouthful, with the AhR nuclear translocator (ARNT) binds and regulates the expression of target genes. In other words, it will determine, based on what the ligand is, what it does.

Bob Miller 45:36
Now, one of the things that it turns on is CYP1A1, CYP1A2, and [CYP]1B1. And that's called cytochrome P-450, or phase I detox. Is that a good thing? Yes, unless it's excessive, because what happens is that this takes toxins and turns them into something that can be absolutely worse if it's not cleared by what's called phase II. So if your phase II enzymes are not doing their job properly and you start stimulating phase I, you can have a little bit of a problem. So the reactive oxygen species are generated during this process by these cytochrome P-450s or—this is so wild!—antioxidants through Nrf2. Nrf2 is what turns on all your antioxidants, so you can be turning on more inflammation or anti-inflammatory.

Bob Miller 46:33
Also, to make it a little more complex, there's an aryl hydrocarbon receptor repressor, and we haven't even begun to dig into that. Might there be some ways to turn this on? So, as you can see, this is incredibly complex. Perhaps someday, when we have all of this down, we could do a whole podcast just on how this guy works. But look at this visual. If you get some dioxin or other bad chemicals, it'll stimulate the CYPs and make oxidative stress that causes DNA damage and inflammatory cytokines. Or if the right flavonoids go in, it turns on Nrf2, the master antioxidant, and has antioxidant properties. So, Jill, are you a little surprised by how this one guy can do two different things?

Dr. Jill 47:26
This is amazing, Bob. And I knew you told me there was some really cool thing you were going to share today. And once again, my mind is blown. And you're right. I feel like I know a lot of what's going on. I have not studied this mechanism.

Bob Miller 47:40
Yes, I think we really need to. I think those of us in the functional world really need to understand this because, as we'll talk about later, some of these nasty chemicals that we weren't exposed to 50 years ago are stimulating it. So here we are. These aryl hydrocarbon receptors control mast cells. They result in calcium- and reactive oxygen species-dependent enhancement of mast cell activation. AhR is critical in controlling mast cell homeostasis. I'm sure you're already thinking this through in your mind, "So, Bob, how do we not stimulate the inflammatory side, and how do we stimulate more of the antioxidant side?" And we're getting to this a little bit. But again, this is all brand new, and we have a couple of clues, but we're going to be learning a lot more as we go along. So here's that AhR, and look at what it's doing: Stimulating the calcium channel to bring in calcium to combine with arachidonic acid, which is one nasty, nasty bad boy, and causes inflammation.

Bob Miller 48:55
And here again, this is just another chart. Here's the citation. If somebody wants to dig into the article, there's a whole article here [about] how AhR stimulates mast cells. Now, what's interesting is that AhR wears two hats. It can stimulate interleukin-6, which is inflammatory, and tumor necrosis factor. It can stimulate IL-2 and IL-4. But look at this. It stimulates NQO1, which is anti-inflammatory. It stimulates Nrf2 and again stimulates CYPs. So it's amazing how this one enzyme

here can have all these different properties. So what I believe is happening [is that] this is part of the wonderful creation that the body is, and it works fine until we muck it up with all these environmental factors.

Bob Miller 49:50
Here's another slide that shows some of the things that will stimulate it: Vascular disturbances, impaired blood-brain barrier integrity, neuro-inflammation, neurotoxicity, immune suppression, circadian disturbances, oxidative stress, increased angiotensin II—that's what puts your blood pressure up—decreased nitric oxide, vascular inflammation, cellular senescence, inhibition of autophagy [which is] the cleaning of the cells, and messing up with our circadian clocks. All of that can be affected by this AhR being out of whack. Sleep disorders, metabolic disorders, immune disturbances, a decline in autophagy, the decline in the mitochondria—we spoke about these—and the bottom line, a decline in the lifespan as this gets overstimulated.

Dr. Jill 50:41
Bob, I want to mention really quickly on that slide before there [about] that IDO enzyme, which is related to the quinolinic acid conversion. Years and years ago, it was a big aha—probably 15 years ago—on that IDO because it converts kynurenate to quinolinic acid, which is the bad boy we just talked about. And there are many things that stimulate the IDO enzyme. But one weird one that we haven't talked about that I want to mention is parasites. I have seen a correlation between parasite infestations and sleep disturbances. And as you mentioned here, this to me is another aha today, because I'm like: "Oh, this might be the pathway or one of them by which parasites that you have in your intestines that you maybe don't know about are impairing your circadian rhythm and impairing your sleep."

Bob Miller 51:21
Absolutely. And I had some slides in here, but then I took them out. But as you know, some research has been done at Stanford on how IDO1, when stimulated by tryptophan, goes along for a little bit and then conks out. So if somebody has mutations in IDO2, that can create something called a metabolic trap. But I took those slides out because I thought we were getting into a little too much today. These are all the parts about [AhR]. And, again, I'm not going to read them for [lack of] time. But just about everything can be affected when this AhR is out of whack.

Dr. Jill 51:56
My summary there is that the pizza is bad. It looks like a slice of pizza, right? You have bad pizza there.

Bob Miller 52:02
There you go. All right, here's another map that I made that we're going to spend a little bit of time on. Let me get the drawing tool. This is called the kynurenine pathway, where tryptophan, an amino acid—Dr. Jill just spoke about IDO1 and IDO2—make something called kynurenine. And then it'll go through a whole other process here, where it ends up with your quinoleic acid. And there's that ACMSD. And then that will eventually end up in NAD, which will calm down the mast cells. But for now, let's look at what happens when this kynurenine or any other substance stimulates AhR. And here's the one that suppresses it. This is where it combines and stimulates the aryl hydrocarbon receptor. Now, you'll notice that mycotoxins stimulate it. Arachidonic acid stimulates it. Now, we're going to talk about polycystic aromatic hydrocarbons as well as homocysteine, [which] will all stimulate this receptor.

Bob Miller 53:19
What I did here [was] I just drew all the things that will happen. It will stimulate interleukin-6—and we spoke about this, I believe, in our RANTES discussion—it then stimulates the NOX enzyme, then stimulates KIT, which stimulates mast cells. But hang on to your hat; it also creates an increase in intracellular calcium concentrations. And then, as we spoke about earlier, here's the map that we showed earlier, [showing] how glutamate through NMDA upregulation stimulates the problem. And we could have EMF and a voltage-gated calcium channel, creating this intracellular calcium, so there's a lot that can go wrong here. And then, of course, we show up here, the CYPs—xenobiotics—will be turned into carcinogenic compounds. I'm going to show you a little study later [that shows] that upregulation of the aryl hydrocarbon receptor can actually cause weight gain. I'm sure many people have looked at crowd pictures from the 1960s. If they look closely, there aren't many people who are obese. You look at a picture today, and… Well, I don't know. Do you know the statistics on how many people are now obese, Dr. Jill?
Dr. Jill 54:39
Oh gosh, I think about diabetes, which is closely related, and it's like one in three, I think, is predicted or even currently. And I want you to repeat what you just said

about that body mass, just because I think this is such an important point today. Just repeat what you just said there. I think it's so important.

Bob Miller 54:56
Oh, the cytochromes or the body mass gain?

Dr. Jill 54:58
The body mass gain.

Bob Miller 55:00
You know what? I have a slide coming up—one or two slides—that shows it in detail. So we have all these chemicals now, including kynurenine. I didn't put them in here, but there are genetic mutations that can get the kynurenine stuck when we actually look at the map. Dr. Jill is going to be brave. We're going to look at this map of her again. We'll take a peek at her map. So there are just so many things that stimulate this. Now, just a very quick clinical observation: We are noticing that when people have mutations on here, they're very inflamed because we believe that even the good flavonoids are not carried in to stimulate Nrf2. But that's just all speculative at this point. But I think now everybody can see why we're really excited about this and the potential for how we can alter this by what we're exposed to.

Bob Miller 55:54
So here they're talking about how kynurenine promotes mast cell activation. And what we're doing is talking about this guy right here. I probably should have put it in. There are enzymes here, [and there are] genetic mutations you can have where you get stuck here. But you can see that kynurenine will promote mast cell activation through that aryl hydrocarbon receptor. Here we go. This is what we were talking about. Kynurenine-induced aryl hydrocarbon receptor signaling in mice causes body mass gain, liver steatosis, and hyperglycemia. Isn't that astonishing?

Bob Miller 56:36
All right. Then here's another one. Inhibition of the aryl hydrocarbon receptor prevents Western diet-induced obesity. So this may be the key to why everyone's gaining so much weight. I mean, it's diet, lack of exercise, and many things. But this could certainly be a factor. So you can see that this leads to obesity. This study showed that "inhibition of the AhR blocks the cycle's output to prevent obesity."

Again, if anyone wants to read the whole article, just type that in on Google, and up will pop the entire article with all of this, if anyone wants to really dig in and learn more. Anything else on that, Dr. Jill? Oh, your microphone's off.

Dr. Jill 57:31
Here we go. Sorry, the tool got all hooked up there and tangled. Okay. All I was going to say is that this makes so much sense, as we started with the toxic load increasing obesity. This is one of the mechanisms you've just described as far as how all these chemicals in our environment are contributing, even if you're eating the same thing and exercising the same amount, to the increase in body weight gain, fatty liver, and obesity.

Bob Miller 57:54
Absolutely. The gut microbiota activates through the tryptophan metabolite kynurenine to mediate—in this case, they're talking about some kidney cancers. But we need to really dig into this because tryptophan can turn into something called tryptamine, which stimulates the aryl hydrocarbon. So we'd like to see if we can maybe find some probiotics that would inhibit that, but that's research for another day.

Bob Miller 58:25
Now, I'm not going to read all of this, but polycyclic aromatic hydrocarbons, or PAHs, are made whenever substances are burned. Coal gas sites, breathing smoke, or coming into contact with contaminated soil expose us to this. Now, what's been happening? I don't know if that's happening in your neck of the woods, but here in Pennsylvania, we really got impacted by the Canada forest fires. I don't know. I guess you weren't affected by that in Colorado, were you?

Dr. Jill 58:58
Slightly, but we have our own—so many—fires. Last year, [for example]. [And] it's just starting this year. And of course, we're recording this just days after the beautiful town of Lahaina in Maui was burned to the ground. And our love and prayers go out to all those people in Hawaii who lost [their] homes. But I want to mention something really important. We think mold is bad. And I test [and examine] the labs [for things] like TGF-beta and things after mold exposure. After the forest fires here and the wildfires here in Colorado, I saw the lab values actually much, much worse from the smoke and fire exposure than even from mold exposure. So

I've actually seen objective data [showing] that this inhalation of smoke is as bad or worse [than] mold exposure for most of my patients.

Bob Miller 59:41
Absolutely. These are the names of them. And if somebody wants them, they can pause the video and get them. But they're found throughout the environment in the air, water, and soil. They can persist for months or years. PAHs, short for polycyclic aromatic hydrocarbons, [are composed of] numerous carbon atoms joined together. There are at least 10,000 different [ones]. They can come from animal matter or carbon fuels such as coal or petroleum. They can come from the sooty parts of smoke or ash, automobile exhaust, industrial emissions, smoke from burning wood, charcoal, and tobacco. Interestingly, grilled, smoked, and charbroiled foods are sources of some PAH exposure. And here's an article that says that they're created by incomplete combustion and that they induce the cytochrome P450s that we just talked about through activating the aryl hydrocarbon receptor.

Bob Miller 1:00:45
All right, now off to dioxins. Again, through the activation of the aryl hydrocarbon receptor, our potent toxic substances are wildly distributed in the environment. So this could be doing it as well. They're often harmful to human health. They're sometimes called persistent organic pollutants because they take many years to break down. Some of this even comes from food, animal products, dairy, meat, and seafood. It can get into drinking water, according to the EPA. It could come from different sources. It's mainly the result of industrial processes.

Bob Miller 1:01:20
The EPA has listed dioxin as one of the 30 hazardous air pollutants that pose the greatest threat to urban areas, and this chart shows how dioxins come into the cell. They combine with the AhR and then with the ARNT and stimulate reactive oxygen species through cytochrome P450. High levels of dioxin are in cigarette smoke. So this might be one of the mechanisms by which cigarette smoking can be so bad for us. And we're stating the obvious: If you're a smoker, it's a really good idea not to.

Bob Miller 1:02:01

Now, I just put this in for fun. This is my office. And I just snapped these pictures. In my office, if you'd be sitting in my office, I have something with a carbon filter, something called Molekule—by the way, this is not a promotion for them at all, by any stretch; there are lots of them out there—and a Dyson. So I just mentioned one. When people come into my office, they look around. It's like, "You've got three air purifiers?" "Yes. That's the door coming in. This is next to my desk. This is a little countertop."

Dr. Jill 1:02:29
Bob, I have three in my 1400-square-foot condo, and I have five in my office. So totally, I'm right there with you.

Bob Miller 1:02:39
Yes. All right. This suggests that AhR has tumor suppressor-like activity for human lung cancer. So I know this guy isn't all bad, but arsenic can throw a monkey wrench into it. I believe we can get arsenic from chicken and rice, if I'm not mistaken. So again, homocysteine activates the AhR pathway. I am really becoming fascinated with arachidonic acid; this is one bad boy. It actually plays an important role inside the cell membrane.

Bob Miller 1:03:20
I'm going to show you a little chart—and this could be another topic to discuss—[of] the genetic and epigenetic patterns that cause arachidonic acid to come outside of the body. But the bottom line is that it will stimulate the AhR from the arachidonic acid. This is an omega-3 index. And this shows your omega-3s. And as you can see from this individual, it's low in the red. This is the omega-6 to 3 ratio. It's high. And here you can see the arachidonic acid EP ratio is high. You can see this goes up to 32.1, and it should be 2.5 to 11. I'm seeing this in the 50s, 60s, and 70s in some individuals. and I believe it's one of the bad boys that's really creating a lot of problems.

Bob Miller 1:04:13
Now, just very briefly, we'll show how we can get arachidonic acid. And we spoke about this. If somebody's really interested, we did the video a couple of months ago on RANTES, and we talked about the tumor necrosis factor. By the way, this is held back by something called heme oxygenase. So if you get a chance, watch the video Dr. Jill and I did on heme oxygenase because that holds this back. Mycotoxins,

viruses, clostridia, borrelia, and lipopolysaccharides stimulate TNF-α. You can also have genetic issues with TNF-α overactive. It'll stimulate an enzyme called PLA2 that pulls arachidonic acid out of the cell membrane.

Bob Miller 1:05:02
Then here's where it does its damage: It can create histamine. It can go through COX2 and cause pain and fever—this is the one I'm very intrigued with that we'll have to talk about another time—through 12-LOX and a process called ferroptosis or through COX1 and make something called thromboxane, which can activate your platelets and make your blood too thick. So that's why I'm very intrigued by arachidonic acid. And as we said, it stimulates that aryl hydrocarbon receptor, but it's also responsible for a process called ferroptosis, where iron combines with the arachidonic acid to again damage the lipid membranes.

Bob Miller 1:05:50
You spoke about this brilliantly in the opening. Aflatoxins and mycotoxins stimulate the aryl hydrocarbon receptor. The endocrine-disrupting potential of pesticides will stimulate the aryl hydrocarbon receptor. Now, these are talking about hepcidin deficiency, which resulted in iron overloading and heme accumulation. Again, it promotes AhR-mediated oxidative stress. So again, iron is critical. I mean, if we didn't have iron, life wouldn't exist. But in excess or [when] used improperly, in addition to doing some other things, it promotes this AhR enzyme. We all know that lead is not good for us. This is another one: Lead will stimulate the AhR and the CYP1A1 to create more inflammation. As we all know, many years ago, we had lead in our paint and gasoline. So lead toxicity is a huge problem. I don't know if you do it with everyone, but you probably do some testing for lead, I would imagine, Dr. Jill.

Dr. Jill 1:07:03
I do. At some point, I test everyone for lead as well.

Bob Miller 1:07:07
Yes. How prevalent is it?

Dr. Jill 1:07:09
I think less. We know that the chipping of paints and things is a big issue. I think it's less of an issue than it used to be, but I still see it.

Bob Miller 1:07:18
Absolutely. Mercury stimulates this process. Anyone who's in functional medicine knows this is the who-who of bad things. We are now learning [about] one of the effects that it might be having by stimulating this aryl hydrocarbon receptor.

Bob Miller 1:07:35
Now, here's an interesting chart that we kind of saw before, but this pulls it together a little more effectively. So here's tryptophan, an amino acid, and it needs to turn down into serotonin. And then it'll actually also turn into melatonin, which we need for sleep. There's a substance called BH4, which is needed to turn that tryptophan into serotonin. It's also needed to make nitric oxide. So I encourage you to go watch the video that Dr. Jill and I did on iNOS and the Carnahan reaction, where we looked at how what's called the NOS2 enzyme can be overactive and chew up your BH4. So if you chew up that BH4, you're going to be slightly depressed, and then you may have too much tryptophan. Well, that tryptophan, through IDO1 and IDO2, comes down through here and makes kynurenine. And if you remember earlier, we talked about how that can stimulate the aryl hydrocarbon receptor. There is one evidence-based SNP—I don't have the SNP number here—that will cause things to be blocked right here, so we don't go down this pathway and make something called NAD. We're also finding that there are some mutations on this kynu that also put the brakes on, so we don't get down to this.

Bob Miller 1:09:01
In case anyone doesn't know, NAD is critical for life. It's part of energy production inside the cell. It's responsible for making NADPH. And I think, Dr. Jill, we did a video on NAD and NADPH and the NADPH steel. If we don't get enough of this, we have a problem. We can also have genetic mutations on QPRT and NMNAT [where] we don't get enough NAD. Well, NAD suppresses the mast cells. So you can see how this kynurenine pathway and this whole pathway are becoming so important. I don't think we've put enough emphasis on it in the functional world.

Bob Miller 1:09:44
Here, you can see that NAD-boosting molecules suppress mast cell degranulation. So you can see if you go back to this map here, if we get clogged up right here, not only do we stimulate the aryl hydrocarbon receptor that causes more inflammation

in mast cells, but we don't have the NAD that helps knock it down. That's why we're beginning to believe this pathway is so vitally important. Resveratrol has antagonistic activity on the aryl hydrocarbon receptor, so it may even help with dioxin toxicity.

Bob Miller 1:10:23
Now, this is totally fascinating: Vitamin B12, and they're saying folic acid, but they probably mean folate, alleviate the symptoms of nutritional deficiency by antagonizing, or going against, the hydrocarbon receptor. So what they're saying is that only these two substances, B12 and folate, will actually slow down that aryl hydrocarbon receptor. So you can also have genetic mutations that I'll show in a couple of minutes here [by which] you may not transport your B12. Then, if you add to that dioxin exposure or those other environmental toxins, you've created the perfect storm.

Bob Miller 1:11:09
We've talked about this many times. Hydrogen is number one [on the] periodic table of elements. There are tablets that you can drop in a glass of water, and they fizz. I know both you and I are big fans of that. I know you also breathe hydrogen. So, who'd have thought that lowly hydrogen—number one on the periodic table of elements—will slow down that aryl hydrocarbon receptor? Artichoke—who'd have thought?—has something in it that induces, through AhR, Nrf2, the good side of it. So we're going to be learning so much more about this. And I'm sure, as research goes on, there are more things that are going to come to us.

Bob Miller 1:11:56
Artichokes upregulate Nrf2, which is what turns on all your antioxidants and one of my favorite enzymes, NQO1, which neutralizes superoxide and also helps properly use NAD. Here they're saying that it's activating it, but it's activating it on the antioxidant side, so it all depends on what goes in and what it does. Milk thistle prevents the expression of CYP1A1 and COX-2, which are genes targeted by the aryl hydrocarbon receptor. Indole-3-carbinol—it will actually also slow this down. It diminished the lipopolysaccharide-induced pro-inflammatory gene expression of iNOS and many of these others, and it slows down the aryl hydrocarbon receptor. Rosemary inhibits activation by dioxin. So if you're exposed to dioxin, the gentle little herb rosemary can help you out. [There is] a lot to be learned.

Bob Miller 1:13:05
I kind of summarized what you can do: Try to limit exposure to dioxins and PAHs. Consider high-grade air purifiers. If you're smoking, for gosh sakes, stop! Work with your doctor on homocystein and make sure that's okay. Make sure you have healthy levels of omega 3, 6, and arachidonic acid. Make sure you don't get exposed to lead, arsenic, or mercury. Try to eliminate exposure to mold and mycotoxins. And Dr. Jill has lots of videos on mycotoxins. And if you are filled with mycotoxins, work with a qualified health professional if needed. It might be a good idea to measure the quinolilic and kynurenine levels in the organic acid testing. And again, work with a qualified health professional to normalize it if it is out of balance. Make sure your phase II detox pathways are working. Make sure you have adequate levels of folate and B12. But you've got to be cautious. We've talked about this before. Too much folate can stimulate histamine. Consider hydrogen water, indole-3-carbinol, milk thistle, resveratrol, and artichokes.

Bob Miller 1:14:09
And if you really want to go deep, look at functional genomic testing to see if any of those things are there. Now, again, we're not giving any medical advice here. This is just for educational and informational purposes. But for those who want to know how you can lower the risk of that overactive AhR, there are some common things that everybody knows make sense, but these would be some of the things to look at. So anything to add to that, Dr. Jill?

Dr. Jill 1:14:35
No, fascinating. What a wonderful list. One thing you mentioned with B12 and folate [is that] we know that homocysteine stimulates B12 and folate—lower homocysteine. So I wonder if that may be just related to lowering homocysteine. Who knows?

Bob Miller 1:14:50
Yes, we don't know. It very well may. So what we're going to do now is very briefly look under the hood of Dr. Jill, who's very brave.

Dr. Jill 1:15:02
I'm the guinea pig for health, so I don't mind. Yes, genes to science here.

Bob Miller 1:15:08
Yes. So here is a map of Dr. Jill's data. Now, when we click on any of these here, it will show up. So very briefly, extremely briefly, I want to encourage you to go back and watch the video [in which] we talked about the 'Carnahan reaction'. There's an enzyme called NOS2 that, when it's upregulated, will cause you to make too much nitric oxide, which can be damaging and deplete BH4. And Dr. Jill's mother and father gave her mutations on two of the genes that cause this to be upregulated. That's why we call it the 'Carnahan reaction,' because everyone knows Dr. Jill's health history and how she struggled. I'm sure this wasn't all of it, but this had to be a piece of it. So that depletes your BH4. And by the way, another topic for another time, but ferroptosis depletes our BH4. You can actually have genetic mutations that cause you to not make enough BH4.

Bob Miller 1:16:09
But now let's go up here. Actually, Dr. Jill, you're in pretty good shape up here. You don't have the one enzyme that degrades tryptophan. So if someone doesn't degrade excess tryptophan, they can actually have extra. Here's that IDO2. You do have a homozygous on one of them. And as you can see here, it's not that uncommon. It occurs in 25% of the population. But it's called the metabolic trap, where if IDO1 gets pushed, it works, and then all of a sudden, it just kind of conks out and stops working. So if we have mutations in IDO2, we may not come down this pathway to make our NAD.

Bob Miller 1:16:52
Now, there's nothing evidence based here, but there are a couple that are slightly out of whack here. But I don't think that's serious. So here's your kynurenine. And then you are clear sailing. I mean, look at all that green. I mean, there's not a thing that went wrong. It's highly unusual to see somebody that looks that good. So this is the one that we talked about, the one ending in 37. I'm going to put this on my top 10 list of SNPs that are dangerous. It inhibits your body's ability to take quinolinic into picolinic. So we'll go back up here. If that picolinic [acid] is high, we show how that'll stimulate the NMDA receptor site. And as I mentioned, if somebody's got that one, plus if they have difficulty controlling zinc... And you can see here, Dr. Jill, you're perfect on your zinc transport; [there are] no problems there whatsoever.

Bob Miller 1:17:49

Obviously, everybody knows you're brilliant. So there are genes called GRIN. And you don't have the ones that are considered pathological, but you've got a few SNPs here that could increase your NMDA and your glutamate a little bit. We spoke earlier about oxaloacetate. And you do have an interesting mutation on the gene that causes you to recycle your biotin into biocytin. As you can see here, this only occurs in 4.3% of the population, so that's why it would probably be a good idea for you to take biotin. But you can see you don't have any other serious issues other than that you might make a little more glutamate, which is, again, no surprise because you are one of the more brilliant functional doctors in the United States. And that's why, because you got a little bit of extra glutamate there.

Bob Miller 1:18:47
And then, when we dig into your aryl hydrocarbon receptor, [it's] really a non-event here. You have hardly anything on the enzyme itself. Just clinical observation: When people have a lot of mutations on the ARNT, many times they're not bringing it in here, and they don't have the antioxidant capacity. But you're clean as a whistle here. If we do make some interleukin-6, you could have a slightly overactive interleukin-6. You do have one of the KIT genes that, if stimulated, mast cells could get carried away a little bit. And then what we did was—remember I said that B12 and folate are necessary to calm this down?—put in here an abbreviated methylation. And you do have one little copy of a folate transporter, DHFR, MTHFR C677. So maybe a little bit of folate would be a good idea. Again, not pushing the histamine.

Bob Miller 1:20:01
And then, interestingly, on your B12, there's something called the gastrointrinsic factor, which is the absorption of B12. The transport of B12—you've got a homozygous here—and the MTRR that puts the methyl group. So possibly a little bit of B12 and folate could be beneficial, but we've got to be really cautious because, as we said, folate can stimulate histamine. You and I have talked about that: that people get a home test and it's like, "Oh my god, I got MTHFR," and they start taking three to five milligrams of methyl folate. They feel great for 10 days, followed by [wondering], "What the heck just happened to me?" because they've pushed it too hard.

Dr. Jill 1:20:44
And that always makes so much sense when we talk because I've been on injectable

B12 since my Crohn's and my cancer because I was severely deficient before I ever knew any of this 20 years ago. And I do so well, but I need my B12. The same thing with methyl folate, and it's the same with patients; I always want to replete B12 before methyl folate because if you overdo the methyl folate and you have a deficiency of B12, things get way worse. This was the case for me because years ago, right after breast cancer, I realized, "Oh, folic acid—anti-cancer," at that point. And it would make me very, very ill to take the high dose of folic acid, just like what you're describing. And I should say that methyl folate was the one I took. But for years, B12 has been critical. I think it was probably a small contribution to my cancer and Crohn's—just a severe deficiency. And then you mentioned biotin. I've been on that for years and intuitively knew there was something important beyond hair, skin, and nails. And you've just told me recently about that pathway and that biotin gene, and it makes so much sense.

Bob Miller 1:21:38
Sure. And just to reiterate, this is where we need that oxaloacetate that turns that glutamate into alpha-ketoglutarate. And we're just clinically observing—just observing: Biotin can help some people with anxiety if they've got high glutamate and if they may need to turn some of that glutamate into alpha-ketoglutarate. So we can't say that biotin is anti-anxiety. I think that's where we get into trouble; we try to pin a nutrient to a condition. And somebody can be anxious, and if this isn't the issue, biotin won't hurt, but it won't help. So that's why we have to get into precision care, where we see exactly where the need is.
So, Dr. Jill, although you didn't do too well on the nitric oxide side, as we pointed out over here—you know, you had a little trouble over here—you were better than most. Very rarely do I see anybody who's got clear sailing all the way down through here. So just some typical things like avoiding some of those toxins [and taking] a little bit of B12 and biotin like you're doing would probably be all you need. So there you go. So thanks for being brave and letting everybody see.

Dr. Jill 1:22:55
You're welcome. Hopefully, you listening out there are getting some of this great information. You're probably going, like me, to want to watch this again. Bob, you give us such great information. And tell us where we can get more [information] about what you're doing and where we can find you. Give us that information.

Bob Miller 1:23:09
Sure. Yes. This slide is for health professionals. So if you're a health professional and would like to look at the genetic information, we have software called Functional Genomic Analysis that creates that map that you just saw. We have supplements. And then we also have a saliva test, of course, that measures the DNA. So if you're a health professional and you find this interesting, just go to FunctionalGenomicAnalysis.com. Get a free trial of the software. We also have an online certification course that talks people through. It's like 24 hours of instruction to learn it all. The first three modules are free. If you're not a health professional and you want to listen to it just for fun, you certainly can. There's no certification or anything, but a lot of lay people just say: "This sounds cool. I want to learn it."

Bob Miller 1:23:58
If someone wants to go onto certification, if you use the Dr. Jill coupon, save $100. It's only $595; save $100. And again, if you don't have some health degree, a layperson can't get this and then start practicing. This is for the person who's already qualified to just add that to it. And if someone wants to talk to us, Tree of Life Health, tolhealth.com. We still do consulting, although I've now been told I'm booking out until November, but we're still taking on new folks to try to help them. So there is our information. If you want to go to our website, give us a call. And again, health professionals can go here. So I think that is the end of the presentation. Let me find how to stop the sharing. There it is.

Dr. Jill 1:24:55
Awesome. Bob, as always, what a great tour de force of a new round of aryl hydrocarbons! I can't wait to continue diving in, and I'm sure we'll be doing this again in a few months on the next level. Thanks for all the work that you do in the world. Thanks for the brilliance you bring. Thank you all for listening. Again, you might want to go back and watch this one again. If you were listening on audio, you might want to watch the actual video on YouTube. And for all the things we mentioned with basic [supplements such as] methylated Bs, oxaloacetate, I'm going to put links to places where you might find some of those things in products if you're interested. Bob, thanks again for joining us today!

Bob Miller 1:25:28
It was a lot of fun! Was my promise true that this would be fascinating?

Dr. Jill 1:25:31
It was fascinating! I loved it! Thanks so much! And thank you, everybody, for joining us!