Dr. Jill

Your Functional Medicine Expert®

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#26: Dr Jill Interviews Bob Miller on Overstimulation of NOX and Functional Genomics

Dr. Jill 0:12

Hey, Bob Miller! We're live again. This is like the third now in our series. We're going to have to start numbering them so people can keep track. But I will say, like I said last time, that your lectures here have been some of the most popular, [which is] not surprising because the information you have to share is so relevant to some of the tough [challenges] and complexities that we see.

Dr. Jill 0:34

I've introduced you before, but I'm going to just give another brief intro for those of you who haven't met Bob Miller. And just a little background: If you would like to review this, it will be live on Facebook now. But it will be recorded. It will also be on my YouTube channel. You can search on YouTube for "Jill Carnahan", and all the videos are there. And the previous two, if you have not seen them, are there as well. Just search for "Bob Miller", and they'll be there. And like I said, we're going to do a little overview to start, but they are very interesting and very relevant to some of the complexities.

Dr. Jill 1:07

So let me introduce Bob Miller. He's a traditional naturopath specializing in genetic-specific nutrition. He earned his traditional naturopathic degree from the Trinity School of Natural Health and is board certified through the ANMA. In '93, he opened the Tree of Life Practice and served as a traditional naturopath for 27 years. For the past several years, he has been engaged exclusively with functional nutritional genetic variants and related research.

Dr. Jill 1:32

And what I really love is that he brings some clarity too. I always say that 20 years ago, when I first started, I would have patients come in with hypothyroid or menopausal symptoms or a sore throat. And within sometimes a few days, sometimes a few weeks, and definitely a few months, these patients would come back, and they felt great. That rarely happens anymore. One of the things we see that we are going to address today is the environmental toxic load. So we're going to also talk about Bob's conference coming up at the end. So stay tuned. We'll give you those dates, and you can sign up for that. It's all

virtual. He's going to especially address this year: The load of mycotoxins and mold. So that's all relevant to today. Welcome, Bob. Glad to have you here, as always.

Bob Miller 2:16

Well, what a pleasure to be back! You and I have had so much fun! The feedback has been incredible. People think the two of us bounce off each other nicely. They're quite enjoyable to watch. And I'm just having a blast doing them as well. So thank you for the opportunity.

Dr. Jill 2:29

Bob, I'm going to tell our secret. The very first time, we were texting back and forth—and I'm just checking on time and making sure he has the links, and I'm voice texting into my Siri—and I looked at the text. I hit send. And it said, "Hey, babe, are we on in 30 minutes?" [laughter] So I had to laugh. So then we joke: Bob's new name is Babe. Hey, Babe!

Bob Miller 2:48

There you go. Here in Pennsylvania, Dutch country, the old saying is: "Call me anything but late for dinner." [laughter]

Dr. Jill 2:56

Yes, so that's our little personal joke with Siri.

Bob Miller 2:59

A lot of fun.

Dr. Jill 3:00

So let's jump right into the overstimulation of NOX and NADPH. I know you have some slides to share. So you can hopefully share them. The child locks are off.

Bob Miller 3:10

They sure are. Okay, so here's what we're going to do. We are going to share the screen. And let's see. Do you see the screen there now?

Dr. Jill 3:21

Yes, perfect.

Bob Miller 3:22

Okay. So the subject is going to be the 'NADPH steal' and what I'm calling the 'Holmes cycle.' And I actually had this graphic drawn. I actually hired someone to draw this graphic because one of my favorite sayings is "There's nothing simple about this." As you said, things are getting more complex. So I call it the 3D chess game played underwater. And you'll see that as we go through everything today, you're going to understand. That's why I kind of like that little bit of analogy. Now I would encourage everyone to go back and watch our June Facebook Live, where we spoke about peroxynitrite. Now, we're going to do cliff notes on it, in case you didn't see it. And if you did, you may want to go back and see it. And if you didn't see it, go watch it.

Bob Miller 4:08

It's a very oxidizing and damaging molecule that actually damages DNA in cells and suppresses the immune system. Now, it's created when something called superoxide, which we'll talk about today, combines with nitric oxide. And then peroxynitrite creates carbonate radicals that actually damage the DNA. Now, there are a couple of ways to do this; it's not just one: The Fenton reaction, where iron combines with hydrogen peroxide. EMF—that may stimulate superoxide in the cell, and that makes peroxynitrite. There's something called the NOS enzyme—nitric oxide synthase—where we're supposed to make nitric oxide, [which was] Nobel Prize-winning back in the 1980s. But rather than making nitric oxide, we make superoxide, and again, then into peroxynitrite. And then, finally, if we don't take our oxidized glutathione, the master antioxidant, back to reduced due to an NADPH deficiency that was our other subject, that oxidized glutathione combines with oxygen, here we go again, makes superoxide, and combines with nitric oxide to make peroxynitrite.

Bob Miller 5:22

And we spoke about this on our other Facebook Lives: Sometimes glutathione is wondrous for individuals, but other times, people take it and do well for a short period of time, then it backfires. And that can be when the oxidized doesn't go back to the reduced. So all of those are ways that we can make peroxynitrite, and it does a lot of damage. Peroxynitrite weakens the immune system. It's behind inflammatory bowel disease. It's behind cancers. It's behind osteoporosis. I used to call it the elephant or gorilla in the room because of all the damage that it can do. So again, go back and listen to the other one if you want a whole seminar on peroxynitrite.

Bob Miller 6:09

Then last month, we talked about NAD+ and NADPH. You're hearing a lot about that—a lot of lectures. NAD+ supports PARP—DNA repair—that we just spoke about. Some important

enzymes called sirtuins and FOXO genes make very important antioxidants. We spoke a little bit before about the importance of mTOR and autophagy. NAD balances those. It supports vitamin D receptors. In our kidneys, we have something called the urea cycle that takes out ammonia. And it also provides energy to the mitochondria. I mean, that's a lot of stuff because NADH is at the top of the electron transport chain. And if that's not enough, it supports: Phase 1 detox. The transport of iron into ferritin, and if we don't do that properly, that iron can become one nasty free radical. The production of a very important antioxidant called bilirubin. The production of nitric oxide. And the recycling of oxidized glutathione and thioredoxin back to their reduced form. Dr. Jill, I can't think of another molecule that wears so many hats on the good side. But what's really unique about NADPH [is that] it's also used by another enzyme to actually make inflammation. And that's our subject today.

Dr. Jill 7:37

So I want to just jump in here really quick because, after our last Facebook live, we had a couple of questions. And one lady, in particular, said: "Well, if this is the case, why shouldn't everyone stop everything else and just take NAD+?" And that's part of the answer to today's lecture, as far as everything being in balance and everything depending on your genetics and your pathways. And there's a good and a bad side to every nutrient. So as Bob explained some of this, I'll hopefully bring some just clinical pearls of what I've seen because I have seen this at the exclusion of everything else, especially methylation factors. We'll kind of see how that works today. It can be detrimental, even though it's a wonderful molecule.

Bob Miller 8:19

Absolutely. We tend to get on bandwagons. We tend to think: "Oh, this is the latest and greatest thing. So everybody should be taking it all the time. And the more we take, the better." One of the analogies I always give [is that] without oxygen, we're dead within three to five minutes. [If you] breathe pure oxygen for a couple of days, you'll oxidize. No water; you've got a couple of days. Drink three or four gallons, and you'll wash out your electrolytes and your heart will stop. So one of my favorite jokes is that everything we really need to learn is [about] Goldilocks and the Three Bears. Not too hot, not too cold—balanced. Now, I am intrigued by NADPH oxidase. I learned about this a couple of years ago, and something instinctively said, "This is a big deal." Now, this enzyme has one purpose: To actually create free radicals, such as superoxide and hydrogen peroxide, and stimulate mast cells to fight an invading agent, such as bacteria and parasites.

Bob Miller 9:20

Now, we tend to categorize antioxidants as good [and] free radicals as bad. Obviously, excess free radicals are bad and are behind a lot of problems. But we do need free radicals when we have a fight to fight. So when we get a bacteria or a parasite, if we did not have the NOX enzyme, we would die of infection. In animal studies where they took the NOX out, the animal died. But as we just perfectly alluded to, it has to be in balance. And overactivation and overstimulation of the NOX enzyme by environmental factors may cause inflammation, over-activation of mast cells, and high histamine. And I'm sure, Dr. Jill, that when you started out in your practice, you probably didn't hear too much about mast cell activation. And now, it's quite common. Are you seeing that increase in mast cells?

Dr. Jill 10:19

Yes, absolutely. Again, it was almost unheard of. And it's literally been in the last decade, and for sure, extremely much more common in the last five years. And again, I feel like the mast cells are the canaries—the cells that are reactive to the environment, whether it's mold, infection, or other toxic exposures—so they tend to get activated. And again, we'll hear more about that in your lecture. But it's, I think, evidence of the increasing toxic load.

Bob Miller 10:47

Absolutely. Now, the NOX enzyme uses oxygen from iron—and listen to this—an electron from NADPH to create the superoxide. And I sort of coined this phrase because I don't think anybody else did. I'm calling it the 'NADPH steal,' where NADPH is used excessively to make superoxide, thus depriving [it of] the other ways it's used.

Bob Miller 11:11

Now, I sat back for a while and tried to figure out: "All right, why would God make us this way that this NADPH that's needed to do all these good things actually gets used to doing bad things?" And what I came to realize is that when we have a pathogen, we really want a full-court press of free radical damage for a short period of time. So then it makes sense that the body says: "Okay, we're going to shut down recycling of antioxidants. We're going to do a full-court press. We're going to be in battle. And we're going to kill this invader." [It makes] perfect sense unless it's happening all the time. Then we have a problem. So, as we said, NADPH supports phase 1 detox.

Bob Miller 11:52

We've mentioned all of those things. So here's the latest discovery we've made. And I'll show a chart here in just a moment. When we have this NOX enzyme upregulated… And it might be a good idea to do that right now. Let me pull this guy over. Are you seeing the chart there?

Dr. Jill 12:13

Yes, perfect.

Bob Miller 12:14

So here's the NOX enzyme—NADPH oxidase—and it grabs oxygen from iron [and] an electron from NADPH. And here we see that it stimulates hydrogen peroxide [and] superoxide. The superoxide combines with nitric oxide to make peroxynitrite, and we make the mast cells. So consequently, it's not going to be available for doing all those other things. And again, we want this to happen when we have that going on. However, what we're going to point out and probably the most important thing we're going to speak about today is—as we've combed the literature because, through the Nutrigenetic Research Institute, we have researchers who look these things up—as we learned, the superoxide makes peroxynitrite. We make the mast cells. And then we make the histamine. And I have a slide later [that] I'll show. We tend to think of histamine as just allergies. But it can affect a lot of body systems, not just allergic reactions.

Dr. Jill 13:22

And Bob, just like anything, you need some histamine. And too much is a big problem. We see that all the time with mast cell patients and rashes and dermatographia, where you can draw a line on your skin, and it's raised and read for several hours. And many, many other things, such as breathing issues, chest tightness, and congestion—all of these things are histamine-related. But what's very interesting, I find, is that there is some research on high histamine, intelligence, and IQ levels. So there is a connection because histamine is a much more red-alert molecule. And there is some evidence that those who run slightly higher histamine [levels] actually have more attention, focus, and higher IQs. Have you heard [about] that research?

Bob Miller 14:01

Oh, yes, I have. Yes, they call it the 'histadelic personality'. And many times, people who are leaders in industry... I heard one time that, for example, the Kennedy clan, many of those were considered histadelic. And that's why they had such power for such a long time. Yes, so it does make you intelligent. But it can also cause all kinds of inflammatory—

Dr. Jill 14:23

It causes problems, too, yes.

Bob Miller 14:26

Yes. The blessing and the curse at the same time. Now, I want to pay attention to this. This is really the crux of what we're going to be talking about today. And then I want to set this stage. Then we want to go through how all of these other factors can create a problem. But here's our main factor that we want to point out today: There's an enzyme called renin that takes something called angiotensinogen and turns it into angiotensin 1, which then goes into angiotensin 2, which makes aldosterone. And look what aldosterone does! It stimulates NOX. And then that begins the chain. And then what happens? They all feedback on each other. The histamine, the peroxynitrite, and the mast cells come back. And they stimulate renin and keep this guy spinning around in what I'm calling the 'Holmes cycle.' So here you see high glucose, peroxynitrite, mast cells, histamine, dopamine, and testosterone. All [of this] will stimulate the renin enzyme to take that angiotensinogen and push it down this pathway more robustly.

Bob Miller 15:42

Now, to complete our 3D chess game, there's an enzyme called ACE2. And ACE2 takes these inflammatory and vasoconstrictive molecules and turns them into angiotensin 1-7, which is anti-inflammatory and vasodilative. Now, I'm sure some people have heard that COVID comes in using ACE2. So one of the concerns we have is that if this is already weak and COVID comes in here—question, not a statement—might that make more of this happen, which stimulates NOX? And then you'll also notice that angiotensin 2 stimulates interleukin 6. Interleukin 6 is one of the players behind the cytokine storm, where lung inflammation makes COVID a very serious and/or deadly condition.

Dr. Jill 16:35

Yes. And they're studying IL-6 inhibitors, some of these expensive drugs, and many, many of these types of conditions, including a research study going on with the virus. So it's interesting to see that because IL-6 is such a big point of inflammation. I'm assuming you test genetics around IL-6 inactivity?

Bob Miller 16:54

Absolutely. Because of COVID, we started looking at this. But on the other hand, for people who don't have COVID and they had inflammation that we could never seem to crack the code, we're finding that when people have genetic mutations in renin, that's an upregulation; genetic mutations in ACE2 that inhibit these inflammatory molecules to go into anti-inflammatory; weakness in HMOX, heme oxygenase that inhibits angiotensin 2, and mutations in IL-6 that are upregulations; these are the people that have a lot of inflammation that nobody's able to crack the code. So I'm really excited about this.

Bob Miller 17:38

Now, I have a slide. I mean, we literally saw this two days ago. So this is the first time we're presenting this information. I literally drew this this afternoon. We're going to talk about glutamate. Just like histamine, glutamate makes you intelligent, highly motivated, [and a] go-getter. And I would tend to think the people on this call probably have some high glutamate. However, glutamate needs to turn into GABA. GABA is the don't worry, relax, be happy [amino acid]. I just about fell off my chair, Dr. Jill. I'll show you the literature. Glutamate inhibits ACE2.

Dr. Jill 18:17

Wow, this is amazing! I agree—the profoundness of this.

Bob Miller 18:23

Yes. So the more you make histamine, the more you make glutamate. The more you make glutamate, the more you inhibit ACE2. I have this slide. I'll show that a little bit later.

Dr. Jill 18:35

A quick question for you, Bob. This may or may not have an answer, but I'm seeing the list of things that stimulate REN: High glucose, peroxynitrite, mast cells, histamine, dopamine, and testosterone. Do you think there's any correlation [between] those synergistic factors making each other worse? They seem to me like independent risk factors, but I could also see a lot of people hanging in that category with higher dopamine due to gut issues, mast cell issues, and higher glucose. Do you think they're independent, or do you think there's a synergy of those things acting together or coming as more of a package?

Bob Miller 19:09

Well, it's an excellent question, and I think you're absolutely correct that the more factors you get together, the more it compounds. And I've been saying that for a long time. We're looking for simple answers. What causes this? What do we do for that? The pill for the ill. And as your opening statement was so correct, things are getting much more complex. So I think it is multiple factors that go together. So I would agree that if someone's diabetic and they've got higher testosterone and they've got clostridia or genetic issues, they don't convert dopamine and norepinephrine; it all compounds. Then, if you've got mutations that are an upregulation, mutations that are downregulation, all these factors go together in an incredibly complex method. So when people say, "What is the SNP that's important?" Or "What is the nutrient that's important?" I don't think we're going to have any of those in this complex world that we're living in today.

Dr. Jill 20:07

Yes. And this is going to be way out on a limb, but just for fun, I'm going to say it and say there's no evidence behind it. I love to go where my brain wants to speculate. And what I'm thinking is that you have these executive-driven, successful entrepreneurial types that we already talked about. You know, could the Kennedys have had high histamine and high dopamine?—because those can go together as well—the drive, the ambition. And then, a lot of times, that high stress level will create high cortisol, which creates glucose intolerance and insulin resistance. I wonder if you would look at studies of that type of personality and the risk of this virus or some of these inflammatory infections. Hmm, could there be a correlation? Again, I'm just purely speculating, but I'm interested because a lot of those factors are seen in those types of patients.

Bob Miller 20:53

Sure. Well, I mean, you're correct; it's speculation—hypothetical. But that's how we discover things. And my instinct would tell me that's probably correct, but obviously, universities need to do studies. This needs to be peer-reviewed and such.

Dr. Jill 21:04

Absolutely. It's fun to speculate. We're not saying any of this is fact. We're just interestingly observing. "Could that be?" I always like to say, "What if?"

Bob Miller 21:12

What if? Yes. Well, that's how we find things—by saying the what-ifs. So I was really excited about this glutamate because I believe that we are having a real problem with glutamate. If you talk to elementary school teachers who taught for more than five years and college professors who teach more than five years, and they ask them, "How are the kids today versus five years ago?" Every time they'll tell me: More anxious, more difficulty focusing, more behavioral issues, sensitive, can't handle stress. And I think it's a combination of glutamate, mast cells, and histamine. And also, when we just look at behavior—you know, when we just turn on the news—many of us are shaking our heads, saying: "What is going on with people? Why are they so irrational?" Clearly, [there are] multiple factors. And again, I wonder, I speculate, if some of this isn't accountable for some of the behavioral issues we're seeing, as people seem to be changing, becoming more angry.

Dr. Jill 22:15

Yes, yes.

Bob Miller 22:17

So this is what I call the 'Holme's hypothesis'. So what I want to [do is] go back to the slide, and then I'd like to go through each of these and show you how they can do that. So here's what I've come up with: The 'Holme's hypothesis'. Again, just that theory. Toxic environmental factors that we were not exposed to historically, with their negative effects, [are] amplified in those with genetic predispositions. So I often say that many people who are ill today, if they had their genetics but lived 75 years ago, would probably be just fine. It was good enough. But if you have a little genetic weakness, in the toxic soup that we're in today, it's pushing us over the edge.

Bob Miller 23:02

And then this is causing stimulation of NOX. We get superoxide, peroxynitrite, mast cells, histamine, and glutamate, [and] the 'NADPH steal' that we just talked about [and] all the things that it does. And then, as we just pointed out, these free radicals produced by NOX stimulate renin, angiotensin 1 and 2, [and] aldosterone. And let me just park on aldosterone for a second. Aldosterone is what causes you to hold on to sodium and excrete potassium. And that's when you get the edema—the swollen ankles. And as I do my health coaching and consulting, I'm asking people: "When you take your socks off at night, do you see an indentation?" I didn't ask that before, but I'm surprised at how many people are having just mild edema as a result of the higher levels of aldosterone. Are you seeing a little bit more of that as well?

Dr. Jill 23:54

Oh, I love that you mentioned this. First of all, in my personal experience with mold five years ago, I had 3-plus pitting edema for probably over a year. And you'll see a period of time where I taught in pants—I never wore dresses—because I had these huge elephant ankles. It was all related to that. And it was related to the toxic mold, probably stimulating the NOX enzyme in this whole pathway. I have another patient right now, as well, who's been really struggling with the edema. The same thing—mold exposure. And of course, there are other causes. But absolutely. In fact, we tested aldosterone. It's actually just normal now. And most of these patients, like myself, do very well on extra potassium, which makes sense.

Bob Miller 24:33

Absolutely. So that's what's happening—this aldosterone is going up. Then it stimulates interleukin 6, NOX, in a positive feedback loop that creates that perpetuating, vicious cycle of inflammation we've named the 'Holmes cycle.' So I think when we start looking at this, we realize this might be happening more often than we ever anticipated.

Bob Miller 24:55

Okay, just a couple of facts on NOX. As we said, it's the only known enzyme with the sole function of producing reactive oxygen species. We spoke about [how] it uses oxygen and an electron to create superoxide. Immune cells express the NOX enzyme. Mast cells may express NOX. And NOX may stimulate the mast cells. Another positive loop. And as we're going to demonstrate soon: If there's a relationship between mTOR, mammalian target of rapamycin. So I have a sneaking suspicion. This is a very short list of all that it does. But NOX activity has been associated with cardiovascular disease, neurodegeneration, organ failure, cancer, and autism. But let's think about this. If this creates histamine, glutamate, peroxynitrite, and aldosterone, what conditions could that create? How many ways could that make you ill? It almost becomes mind-boggling when you think of all the downstream effects this could be causing.

Dr. Jill 26:07

Yes, absolutely. I can see it dramatically affecting the gut. So almost any gut disorder, especially inflammatory bowel disease and IBS types of things, I could see it affecting the skin and tegmentum—so, sinuses, lungs, skin issues. I could see it potentially affecting the brain, as we saw in neurodegeneration—but even just classically, the non-medical term 'brain fog' that patients often tell me they have—and then any sort of inflammatory or autoimmune disorder that isn't listed there, and many, many more.

Bob Miller 26:37

Absolutely. The list goes on. And here we were referencing a study that says targeting these sources with natural compounds may be an important tool. Now hang on to your hat. NOX2 activation in COVID-19 published just July 25th. And it's saying "oxidative stress by NOX2 activation is associated [with the] severe disease in thrombotic events in COVID-19 patients." Isn't that mind-boggling, Dr. Jill?

Dr. Jill 27:06

Wow. It is, and yet, it isn't, right? It's amazing that this is published. But it makes so much sense, doesn't it, Bob?

Bob Miller 27:13

Absolutely. Yes, it sure does. And we've been saying that for a while. Now, I want to be very clear, we're not talking about [whether] taking care of NOX would cure or not have you get COVID, but the activation of NOX2 is what gives that cytokine storm. That's a part of it. So I think a lot of research needs to go into this. But we were very shocked that one of our researchers found this. And again, just a little over a month ago, this was published. So quite fascinating.

Bob Miller 27:49

And then I just wanted to show this slide. And you alluded to this a little earlier. We tend to think of histamine as allergies, but the skin, the cardiovascular system, vertigo, nausea, and vomiting, circadian rhythm, bone marrow, the gastrointestinal tract, as you mentioned, the uterus, and the respiratory tract—as this is upregulated, we make all this histamine—these are all the things that can be impacted by that histamine. So I just want to point out that we can't pigeonhole histamine into watery eyes and a runny nose.

Bob Miller 28:27

And then here's the study on [how] excessive glutamate stimulation impairs ACE2 activity. The bottom line here [is that] the study reveals a strong relationship between excessive glutamate stimulation and ADAM17-mediated impairment in ACE2 activity, suggesting a crosstalk between glutamate-induced excitotoxicity and dysregulated RAS. Wow. So therein, Dr. Jill, is the mind-body connection.

Dr. Jill 28:56

Yes. And again, in the patients that we see, of course, with any neurodegenerative disease, this is one of the pathways that's most of the time activated. But we also see this in patients with Lyme or mold, chronic infections, and chronic exposures, where, especially when the brain is affected, I find that to be relevant.

Bob Miller 29:15

Absolutely. Now, what I want to go through is help everybody understand all these epigenetic factors that will stimulate NOX. One of them is homocysteine. So let's talk a little bit about homocysteine. So I'm going to bring a map over here. And a lot of people are familiar with the methylation map. The MTHFR enzyme makes your methyl folate. Your MTR is what puts a methyl group on B12, and that takes your homocysteine back into methionine. That makes your SAMe, S-adenosyl methionine. Then there's also the middle pathway, where trimethylglycine combines with BHMT to turn homocysteine back into methionine.

Bob Miller 30:03

Just as a side note: SAMe does a lot, but it's needed by the COMT enzyme to clear dopamine. And if we don't have enough SAMe, we're going to have high dopamine. Histamine and methyltransferase need SAMe to take out histamine. So if you have perfect genetics on HNMT, no problems at all, but you don't have enough SAMe, your HNMT is not going to clear the histamine. So this is a very important cycle, and if this doesn't work, the

homocysteine goes high. And there's a lot that can go wrong in here, even at the folate receptor sites, the DHFR. A lot of people talk about MTHFR, and it's important, but there's a lot upstream from that here as well. And interestingly, in our first video, we spoke about the Fenton reaction that makes hydroxyl radicals. Hydroxyl radicals will impede the methyltransferase enzyme that puts your methionine into SAMe. So talk about the 3D chess game here, Dr. Jill. [There are] so many ways that things can get messed up.

Dr. Jill 31:12

And, of course, high homocysteine is known. I'm always looking for ways to bring that down with the methyl donors and all of the things we talked about here on the pathway. But would you like to comment just a moment on low homocysteine?—because that can be the opposite side of the coin. I see that as well. And it can cause its own set of issues when we have a homocysteine [level] of three or four, something very, very low.

Bob Miller 31:35

Sure, well, look at our chart here. You see, homocysteine comes down into cysteine. Then that combines with glutamate and glycine to make your glutathione. So, not enough homocysteine is not going to allow you to make glutathione. But also, let's look down here, where homocysteine comes down, turns into cystathionine, and then cysteine. And we're going to talk about this in a little bit.

Dr. Jill 32:01

Ah, CBS is what I was looking for there because rapid CBS can be one of those factors that pulls it. Is that correct?

Bob Miller 32:09

Yes, right here. Here's CBS. So rapid CBS can pull it down through. And then we can have too many sulfates, and these are the people who say, "I can't do sulfur foods," and they're sulfur sensitive. And what we need to do is figure out why they can't use them, not just totally not consume them. So there's a lot that can go wrong here. And we'll talk about this a little bit, sulfation, a very important phase 2 detox. We take out our catecholamines, our hormones, our xenobiotics, and many of our toxins through sulfation. And if that is not running properly, then these toxins once again build up inside the body. And in a couple of minutes here, we're going to talk about the SUOX enzyme.

Bob Miller 32:59

I saw recently on your Facebook page that you had articles on glyphosate. We're going to get into that in a moment, as to how glyphosate can impact the SUOX enzyme. So bottom

line, it's important to have homocysteine that is not too high, not too low, just right, as we said. And then there's an interesting book out there called *The H Factor.* It's written for the general public, and it talks about [how] the higher the homocysteine, the sooner you die from all causes. And there might be multiple mechanisms, but if this is stimulating the NOX enzyme… Well, it is. But if there are other mechanisms besides that that I'm not aware of, just stimulating that NOX enzyme could certainly be enough to cause many of the problems that we're seeing today by high homocysteine.

Bob Miller 33:50

Now let's move on to oxalates. Now, one of the interesting things that people do is, [when] they're not feeling well and they decide, "Well, I think I'm going to eat healthy," they start juicing. And they get their beets. And they get their spinach. And they get their kale. And they start juicing, feeling good about themselves because they're doing something good. Can that be excellent? You betcha. Can it backfire? Well, you know the answer. Yes, it can.

Bob Miller 34:20

So what can happen inside the body is… Here's your glyoxalate, and there are actually genes, the AGXT, the GRHPR, and they're not on here, the HOGA1 and SPP1. And if you get a leaky gut, what can happen is that these healthy foods—spinach, kale, beets—if you look at them very closely under a microscope, you'll see what are called little oxalates; they're like little razor blades. And normally, if your gut is doing well, they pass through the stool. They pass out. But if you maybe had a histamine issue, if you had other issues with the gut, a gluten issue, you get what's called a 'leaky gut,' and those oxalates leak in. And when those oxalates get into the tissue, people hurt. And this is why you just grab them on the arm and they yell, 'Ouch!' It's implicated in fibromyalgia.

Dr. Jill 35:22

Yes. I was just going to say that in fibromyalgia and even interstitial cystitis, there's been some implication with oxalate levels. Pain in general, almost anywhere in the body, can be exacerbated by oxalates. And one of the things I see—[going] back to my favorite topic—[is that] Aspergillus, candida, and different mold species will actually contribute. So I'm always looking at the load as well because the food can be part of it. If they have any Aspergillus colonization in the sinuses or exposure, or if they have candida, those things will all raise oxalates. So it's actually not just a low-oxalate diet that can help because I don't want them to be off these really good health foods forever, but I would have to deal with those fungal contributing factors. And clostridia, I believe, can also contribute to oxalates. So there are a bunch of different sources, and if we can bring those levels down, there's also something to be cautious about because if someone has a normal oxalate diet or a high-oxalate diet, and all of a sudden one day they say, "Okay, this is a problem; I go to zero oxalates," there's

a dumping effect that happens that can really exacerbate their symptoms. So I rarely recommend someone go totally off oxalates cold turkey unless they know what they're doing, because they can really get into trouble.

Bob Miller 36:30

Absolutely. We've seen that happen. We usually recommend you reduce them by about 10% per week.

Dr. Jill 36:35

Absolutly. Perfect. I agree totally.

Bob Miller 36:38

Take your time. Now, we're going to talk about mTOR, the mammalian target of rapamycin. We showed this chart before, but it's probably worth looking at again: mTOR, the mammalian target of rapamycin, is a very important process. When the sperm and the egg come together, they need mTOR to grow into the baby. We need mTOR to grow new cells. If we didn't have mTOR, we wouldn't have new cell growth. However, there's a lot of interest going into autophagy, the cleaning of the cells. And there needs to be a balance between mTOR and autophagy. So autophagy takes that old dead cell [and] either recycles it or clears it out of the body. And if we don't have this happening, this is where you'll see people who have age spots much more quickly because they're not cleaning out the cells; the sun oxidizes them. And when you see people in their mid-to-upper 40s and a lot of age spots, there could be other things going on. But many times their mTOR is excessive. Their autophagy is weak. And we can see genetic factors that will weaken autophagy.

Bob Miller 37:47

And back to epigenetics: Xenoestrogens—what are we doing? [There are] plastics everywhere, Dr. Jill. Even our polyester clothing is now getting into our water supply. We spoke about this before: That some people are doing too many amino acids, like bodybuilders, that stimulate mTOR. One of the things we're going to look back on someday is giving our animals growth hormones. "Well, they'll get fatter faster, and we can make more money." Well, great, but that stimulates mTOR. High glucose, high iron, and even methionine and SAMe will stimulate mTOR. Uh-oh, glutamate. Okay. So that's why I'm concerned that too many functional medicine doctors are giving too many glutamine powders under some circumstances, inadvertently up-regulating mTOR.

Bob Miller 38:47

The same with folate. Do we need folate? Do pregnant women need folate? You betcha. That's why if they don't have enough, they'll either not get pregnant, have a miscarriage, or [have] a deformed baby. But once again, in excess, [it] can stimulate mTOR. So that's why I get concerned if someone says: "Oh, I've got MTHFR C677; I better take a couple of milligrams of folate." Maybe. It suppresses your autophagy. And then what does it do? It stimulates the NOX enzyme. Allergens, air pollution—all of those things will also stimulate the NOX enzyme.

Dr. Jill 39:33

So Bob, I want to comment real quick because anyone in my listening area or California knows the air quality has been horrendous—probably the worst I've seen it in 10 years. And I have two Austin air filters going on in my home. At work, I have five of them. So we actually have pretty good indoor air quality. But I see so many patients right now [who are] really struggling. And what they look like is someone who's had a mast cell reaction or a mold exposure, but it's not either one of those things. It's actually the outdoor air quality from the smoke. So this is a very real thing for those of you listening if you're struggling, like, "What is going on here?" If you don't have a good HEPA air filter with a VOC filter inside your home, I highly recommend it. It's just such a great thing for us to have because it really does make a difference.

Bob Miller 40:20

Absolutely. Now let's talk about dopamine. Dopamine is one of the catecholamines. We already pointed out that it stimulates renin, and it all stimulates NOX. So once again, do I think we're seeing high [levels of] dopamine in individuals? Yes. And as we pointed out earlier, clostridia will inhibit what's called the DBH enzyme that takes your dopamine and turns it into norepinephrine. And then you can also have genetic mutations on the DBH enzyme itself. And one of the telltale signs is that people get irritated quickly. The least little thing sets them off. And it's not just the emotional thing that's happening; it is stimulating their NOX enzyme.

Dr. Jill 41:07

And there's clear evidence for neurodegeneration and chronically high dopamine. So that's another reason. I'll tell you what, Bob, I like my dopamine. I've done rock climbing. I have a motorcycle. So I do get it, but there are some really detrimental effects on the brain from high dopamine [levels over the] long term. So we've kind of got to break that addiction and fix the gut.

Bob Miller 41:25

Absolutely. All right, back to sulfites and sulfates. Interestingly, sulfites will stimulate the NOX enzyme. That's why in our clinic, when people come in, we actually use those little strips and measure the sulfites and sulfates to make sure that that conversion is happening okay.

Dr. Jill 41:44

Is that a urine or saliva test?

Bob Miller 41:46

That's just urine. Yes, just urine. And you can buy those strips on Amazon. So when you've got high sulfites and low sulfates, you know that this is not converting. Very, very simple test. So the SUOX enzyme, sulfur oxidase, takes sulfites and turns them into sulfates. Why is that important? Because we then go over to a very important phase 2 detox. Phase 1 is where we take toxins and put them into fat-soluble [form]. Phase 2 puts them into water-soluble [form]. And then we excrete them. Here you can see that this is excreted in the urine. And this is a very important detox process. We all, again, hear about methylation.

Bob Miller 42:28

You don't hear too many people talking about sulfation. But it really is an important detox process. It deactivates xenobiotics. [It helps with the] inactivation of catecholamines, the structure and function of macromolecules, and the elimination of the end products of catabolism. So if this isn't working, we have these toxins building up. And not only that, but sulfites stimulate NOX. The catecholamines and some of these xenobiotics stimulate NOX. Now, how can this get messed up? Well, we can have genetic mutations in the SUOX enzyme. There's a mineral that many people have not heard about: Melendimum. And that is a cofactor for SUOX.

Bob Miller 43:14

But here's what's not well known: Heme is a cofactor. And this is an area that we've been taught quite a bit [about] by one of our researchers, Beth O'Hara. And I want to go back over here and show everybody what happens. In your mitochondria… Of course, everybody knows that we take fats, carbohydrates, and proteins. There are your fats, carbohydrates, and proteins. They come down through, and they make something called succinyl-COA. That succinyl-COA combines with glycine. And that's an amino acid. I know you've heard many of these things from Stephanie Seneff, a brilliant woman who, by the way, is going to be speaking at our conference, about how glyphosate is impacting our glycine. It's controversial. You know, there are people who agree with her and people who disagree. But my personal opinion is that I think it's going to turn out that she was correct that the

glyphosate impacts the glycine, [which] then affects what's called the heme cycle, where through eight steps, we make heme.

Bob Miller 44:27

Now, there can be genetic mutations in any of these. Epigenetic factors: Lead will inhibit these too. So that's why lead can be so insidious. So if we don't have enough heme, look at what heme does. We tend to think of hemoglobin, but myoglobin, neuroglobin, phase 1 detox—it's a cofactor—peroxidase, catalyse, cofactor for NADPH, for tryptophan, nitric oxide synthase, and SUOX. Not too many people are looking at this. To make matters worse, if these porphyrins build up, they'll block the GABA receptor sites. And when this isn't working properly, this is where people get what's called 'hangry,' where they're all of a sudden feeling fearful, worried, and frustrated. They've got to have some food, and then they feel better after they eat. These are the folks who, when they try the ketogenic diet, fail miserably because they can't handle not having carbohydrates coming in on a regular basis.

Dr. Jill 45:36

And this is so important because, again, diets have to be individualized. Not everybody should be on a keto diet. There are a lot of people who actually do not do well. I love that you mentioned Stephanie Seneff. I was thinking about her when you were on the sulfation pathways because she's putting this all together and the effects of glyphosate, again, hypothesizing. One other thing is molybdenum. I love that. I remember years ago that I had lots of pain and lots of CBS upregulation, so lots of cysteine and taurine in my urine. I took molybdenum, just a milligram, and all of a sudden the pain went away. And for me, that was like an 'Aha!' moment. For me, I probably have a SUOX mutation. And the molybdenum and the B2, the riboflavin, completely took away that pain.

Bob Miller 46:17

Absolutely. One of the things that we just put into our software, Dr. Jill, that's fascinating, is that there are actually enzymes that make the cofactors that help molybdenum be used. And for some of these people who just can't seem to get to the root of their problem, we're finding they've got problems with their molybdenum cofactors. So the sulfites don't turn into sulfates. Now, a good way to know if this is a problem for you is if you take a couple of sips of red wine and all of a sudden are flushed and feel horrible. That means these sulfites are not converting. Oh, just one little quick, little interesting [point]. For people who have this problem, one of their favorite foods is ice cream because [it contains] glycine [and] carbohydrates. And a tablespoon of ice cream every couple of hours just really balances them out. Now, that's not the long-term solution. But that's why intermittent fasting

and/or keto are disastrous when somebody's got this pathway not working properly. So that's how we can have some problems with sulfites.

Bob Miller 47:32

Now, to make things just a little bit more complicated, the HMOX enzyme breaks down the heme. If this is not working, the iron from the heme gets dumped to be a free radical. And then here's where your iron goes into ferritin—your storage. So if this isn't working, you're going to have low ferritin. A well-meaning practitioner says, "Let me give you more iron." If this is just dumping, you can make more inflammation. And look up here: NADPH. Whoa! NADPH, a cofactor for HMOX, makes biliverdin and bilirubin. And guess what bilirubin does? It inhibits mast cells. And then it makes the carbon monoxide that stimulates KEEP1 and Nrf2, which is what controls the production of your antioxidants. So HMOX1 [is] really, really important. My son and I just did a poster that's going to be at the ILADS conference talking about the importance of HMOX in COVID [and] how it gets up-regulated. And we'll be presenting at that medical conference.

Dr. Jill 48:43

I can't wait to hear that, Bob. I look forward to hearing from you. One question for you. This may or may not have an answer. But Gilbert's syndrome, which I see a lot of, is a genetic predisposition to elevated bilirubin. Does that affect that pathway?—because it looks like bilirubin has a good role. But I'm assuming it's the breakdown of bilirubin that's impaired. I don't know for sure off the top of my head.

Bob Miller 49:05

Yes, I don't either. But I think it is the breakdown rather than overproduction. But it could be. I mean, it could be if HMOX gets upregulated. That'd be an interesting research project to see if HMOX is actually upregulated in those people.

Dr. Jill 49:21

We'll have to bring the answer in episode four, so stay tuned. [laughter]

Bob Miller 49:24

How about 34 on that one?

Dr. Jill 49:26

Yes, exactly. [laughter]

Bob Miller 49:28

That's a little too much pressure.

Dr. Jill 49:30

I know. I know. Me too. No promises.

Bob Miller 49:34

All right, well, air pollution—we talked about that. Glutamate—now this is, again, one of my favorite subjects. Glutamate makes you very intelligent, highly motivated, and a go-getter. However, in excess, it's a problem. It's a big problem. So look what happens here. Glutamate is really a multifactorial molecule. It will turn into glutamine, which is part of the healing of the gut. And then glutamine needs to turn into glutamate. However, inflammation or infection will inhibit the enzyme that turns glutamate into glutamine. So that means you can be high in glutamate. Also, glutamate turns into alpha-ketoglutarate and succinyl-COA. Remember, we just talked about that being in the heme cycle. If we don't have enough NAD+—and there are more enzymes in here that I do not have listed; there's the GOT enzyme and the GOT2—mutations here will again inhibit the [conversion of] glutamate to alpha-ketoglutarate. So you're not going to have energy, and you're going to have more excitatory glutamate.

Bob Miller 50:43

And again, we just learned two days ago, glutamate inhibits ACE2. It stimulates aldosterone. The GAD enzyme, along with B6 and magnesium, turns glutamate into GABA—the don't worry, relax, be happy [amino acid]. But as we just pointed out, if the heme cycle is not working, those porphyrins will block the GABA receptor sites. And that's where we get hangry. Then glutamate comes over and makes glutathione. And again, it is ATP-dependent, so if energy is not being produced or if we have genetic mutations on GCLM or GCLC, the glutamate doesn't come over here, and therefore we don't make our glutathione. So there's a lot that can go wrong with glutamate. And possibly this is why, when people get ill, like with Lyme or other conditions, and they've got the infection and the inflammation, they become more anxious because their glutamate is going high. And without glutamate, we don't have intuition.

Bob Miller 51:52

People who are high in glutamate are usually very intuitive and go-getters. But on the other hand, they're sensitive to light and sound and sometimes a little paranoid. High enough, you start having visual hallucinations where you think you see something off in the corner that's not there. And of course, as it goes higher, that's where you get your

bipolar and schizophrenia. So again, Goldilocks and the Three Bears—we need to keep it balanced. One of my favorite herbs is honokial. Honokiol reduces glutamate and supports glutamate-to-GABA conversion.

Dr. Jill 52:25

Oh, I love it. Magnolia is another name for that, I think, right?

Bob Miller 52:29

Yes. Magnolia bark, honokial. Now, we want to talk a little bit about mycotoxins. And you and I have had this discussion multiple times [about] how we believe that mycotoxins are more of a serious issue than we realize. But look where the mycotoxins are. They stimulate the mast cells. They're going to stimulate the histamine, the cytokines, and the glutamate. Then that's going to come back, stimulate renin, stimulate aldosterone, stimulate IL-6 and NOX, and just keep spinning around and around and around. So that's why mycotoxins can be so insidious. And then unfortunately, as you know, when someone has mycotoxins, they're around allergens, and they get Lyme disease and possibly EMF, they're in serious trouble.

Dr. Jill 53:28

It's a perfect storm. And sadly, we're seeing more and more of that where there's not just one factor.

Bob Miller 53:33

Exactly. And then EMF. And we spoke about that in our peroxynitrite, so we won't go into a lot of detail on that. But basically, the EMF causes the CACNA1C gene to put more calcium in. That can stimulate more superoxide, [which] combines with nitric oxide and makes peroxynitrite. And that's why we see some individuals who are very EMF-sensitive. And unfortunately, sometimes, people will make fun of them and say: "Oh, come on! You're making this up. This cell phone; this WiFi can't hurt you." But in some individuals, it does. And then, of course, the Lyme disease.

Bob Miller 54:12

Now, I'm not going to read these. Somebody can pause the video if they really want to look at these. But these are the genes that would cause overstimulation of the NOX enzyme. So sometimes, to get to the root cause of it, we've got to dig into functional genomics and see where it is. For example, ABP1 is what makes the diamine oxidase that breaks down histamine. HNMT breaks down histamine. So, [it's] a 3D chess game played underwater. Here are more genetic factors overstimulating NOX. If someone watching this is a health

professional and wants to learn this, we do have an online certification course that trains people on this. It's about 35–40 hours of instruction that helps you understand all the places you have to look to try to find [out] why this is upregulated.

Dr. Jill 55:06

Yes. And I just want to plug that, Bob. You've got great educational materials. What website can they find that on if they're a health professional?

Bob Miller 55:14

Well, all they have to do is go to dnasupplementation.com, and there's a link there for the online certification course. And what we do is give the first couple of modules for free, because I'll be the first to admit this isn't for everybody. This is not for the faint of heart. This is for the serious practitioner, because if they're looking for a piece of paper that says, "Do these three things," they won't get that. They've got to really dig in, learn, and look at it. So that's why it's not for everybody. That's why we give the opportunity to try it. And some people are like, "This is the coolest thing I've ever looked at," and others say: "Too much work. Nope, sorry." And that's okay. This is not for the faint of heart. So these are all the genetic factors that could overstimulate NOX. If someone would like these maps, just go to nutrigeneticresearch.org/research and they can download those PDFs. I have them there for you and for anybody who wants them.

Bob Miller 56:15

So there's that vicious cycle once again. So what do we have to do? Well, we have to see if there are genetic issues with any of the NAD+ and NADPH pathways because that 'NADPH steal' is using your NADPH up excessively. And if you have some issues that you don't make enough, that's when you're in a serious issue. Modulate and calm NOX. Easier said than done because we showed so many... Support, production and usage of NAD. Support glutamate to GABA. Reduce oxalates. Support the proper use of iron. Limit EMF exposure. I just recently had a physician whose wife was not doing very well, and she was literally in the office, sitting next to their Wi-Fi—literally two feet away from their Wi-Fi. [We] moved her away from that, [and there was] dramatic improvement. Support sulfite to sulfate conversion. Get that homocysteine where you want it. Get the dopamine where you want it, and then make sure you've got adequate Nrf2 and glutathione activity. Is that a lot? Yes. So do we have a pill for the ill? No. That's a lot of things.

Bob Miller 57:35

So to sum it up, let's just look at one other chart here. And this is one of the things that people can download. I put on that website the actual nutrient that will help either suppress... Like, here's: Suppress the histamine. Here's: Help clear the histamine. So these

are all the nutrients that could provide support to those enzymes that could be out of whack. And then, if someone wants to know: What are the genetic mutations that could contribute to that? These two charts are on the website. They're free; we don't sell anything. They're there for you to download. And you can actually see which genes, when they're mutated, could contribute it. Here are, for example, the enzymes that, if they're mutated, will relate to more oxalates. This could make more iron. The DAO and GAD would make more glutamate. ULK1, ULK2, and ATG13 would weaken autophagy strength and mTOR. And I just have fun with this. The renin or ACE genes will create more aldosterone. And anybody who really wants to geek out on these charts, there they are.

Bob Miller 58:53

So bottom line, it's hypothetical, but I think we've discovered something very significant. Epigenetic factors, [which] we weren't exposed to 50 to 75 years ago, stimulate superoxide, peroxynitrite, hydrogen peroxide, mast cells, histamine, and glutamate. And we just start a positive feedback loop that feeds it and keeps it going. And I believe that as we learn more about this and do more research on it, we're going to be able to help some people that we weren't able to help before.

Bob Miller 59:28

Finally, I want to mention that coming up very, very soon, September 18–20, is a three-day conference for health professionals. But since it's streaming, if someone's not a health professional and just wants to listen in, they certainly can. By the way, thank you, Dr. Jill, for being a speaker. And I'm not going to read these, but the who's who of functional medicine, particularly as it relates to mycotoxins. And we're going to spend three days—three long days—on mycotoxins. And we're hoping that when the doctors leave this conference, they're going to have some tools that they didn't have before because we're going into some really unique angles: How it affects the adrenals. How it affects interleukin 13 and nitric oxide. The mast cell relationship. And we'll be talking about some of the things that I just spoke about here today, [like] how this thing feeds upon itself. So if someone's a health professional and they want to attend, [go to] nutrigeneticresearch.org. It's the same website for the maps. And you can click or just put in '2020 conference'. So it should be a lot of fun. We're looking forward to it.

Bob Miller 1:00:41

There's our website, tolhealth.com. If you're a health professional and want to look into studying this and learning how to do it, there's the website, dnasupplementation.com.

Dr. Jill 1:00:56

Bob, as always, this information is so important. I really believe it's the kind of stuff that's going to take us to the next level in functional and integrative medicine. And we are all so grateful to you and your team for continuing to bring the research. I always learn something new when I talk to you. And I am all on board to help get the word out for you, as you well know, because I really believe in the work that you're doing. I believe in you. And what I love is that I also heard some things [about] how you give away the free documents, how you give away the first three modules, or whatever. You are a man of a generous heart, because I know your heart, as far as getting the research out to people, is in the right place.

Dr. Jill 1:01:36

So I hope that if you've listened to this and enjoyed this, [you'll] come back and listen to episodes one and two. If you're a professional who wants to join the conference or a layperson who wants to get really deep, join the conference and be sure to support Bob because he's just doing great work. And I am so grateful for all that you do for us, Bob.

Bob Miller 1:01:52

Well, it's my pleasure. Our whole mission is to be of benefit to humanity. That's what we do. And to me, what a blessing that someone who's just a traditional naturopath has this opportunity to bring this information to the world of functional medicine. And we're just hoping that it improves the lives of a lot of people. So that's our mission.

Dr. Jill 1:02:14

I know you already have. So thanks again for joining us. And stay tuned because I'm sure Bob will be setting up maybe the next three episodes for the fall. Take care!

Bob Miller 1:02:22

Okay, we're looking forward to it!