[209: Resiliency Radio with Dr. Jill: Is Superoxide the cause of your inflammation with Bob Miller]

Dr. Jill 00:00
Welcome to *Resiliency Radio*, your go-to podcast for the most cutting-edge insights in functional and integrative medicine. I'm Dr. Jill, your host, and in each episode, we dive into the heart of healing and personal transformation. Join us as we connect with renowned experts, thought leaders, and innovators who are at the forefront of medical practice and clinical research, empowering you with knowledge and inspiration on your healing journey.

Dr. Jill 00:23
Today, I have a repeat guest who has been one of the podcast's absolute favorites. It's kind of a special edition because we share slides. We go really, really, really deep. I'm super, super excited to have Bob Miller back on the podcast.

Dr. Jill 00:42
Bob is a traditional naturopath specializing in the field of genetic-specific nutrition. In 1993, he opened the Tree of Life practice and has served as a traditional naturopath for 27 years. For the past several years, he's engaged exclusively with functional nutritional genetic variants and related research, specializing in nutritional support for those with chronic Lyme disease and many other chronic illnesses. We always relate so well because it's the same type of practice and patients that I see every day in clinical practice. To support his growing genetic research efforts, in 2015, he funded and founded the NutriGenetic Research Institute to research the relationship between genetic variants and presenting symptoms.

Dr. Jill 01:25
Today, guys, stay tuned; hold onto your hats. If you are driving, don't stop the car. Keep listening. But you may want to come back and look at the YouTube episode because we're going to share some visual effects. I'll try to comment if there's something that you can't see that would be helpful. Otherwise, wherever you're listening, you will find this information profoundly transformative, and today will be

no different. Today, our topic is: Superoxide—could this be the root cause of your inflammation?

Welcome, Bob!

Bob Miller 01:55
It's always good to be back. It's always a pleasure to be with you. As I said before we started, we get so much feedback. People say they appreciate the way the two of us talk back and forth and enjoy how we communicate together. Looking forward to it. It's going to be a lot of fun. I'd encourage everybody to put their seatbelts on because we're going to move along with some really cool stuff.

Dr. Jill 02:15
Yes. So go ahead and share your screen, Bob, and jump right in. We'll do like we always do. I'm going to put you on speaker view so whichever one of us is speaking, you guys will see us. We're going to dive right in, and I'll just let you get started.

Bob Miller 02:27
Okay. Do you see the slide there that says "superoxide"? Do you see that okay?

Dr. Jill 02:29
It looks great.

Bob Miller 02:30
Okay. The topic is "Superoxide: Is This the Root Cause of Your Inflammation?" If any of you are a health professional, you're like: "Superoxide—there's nothing new about that. We've been talking about that for a very long time." And we certainly have. I started talking about it probably 20 years ago. But as we dug a little deeper, you'll be surprised how significant this is. Of course, we always mention that this is [for] informational and educational purposes. We're not giving any advice on how to treat any disease.

Bob Miller 03:01
Here's what we're going to do: We want to look at superoxide 101, the damage from it, and how excess superoxide creates many health concerns that I wasn't aware of. Then we're going to look at all the pathways making superoxide. Then we're going

to look at the pathways of reducing superoxide. Of course, we always like to give some practical steps if this is something that you think you would like to address.

Bob Miller 03:28
First, I want to mention the people who helped this happen. It's not just me. Matthew Miller—he's the Head of Research. He has his Master's degree in Pharmagenomics from Manchester University. In case you're wondering, yes, that is my son. And Dr. Harold Landis—great guy. He graduated from the University of Maryland Dental School and is a Fellow in Integrative Medicine from the University of Arizona. Many times, we're still emailing each other studies at 12:00 or 1:00 o'clock in the morning as we say, "Isn't this cool?"

Bob Miller 04:00
I also think we need to honor the pioneers, the people who have come before us who have done some of this work. I've really come to appreciate biochemist Irwin Fridovich. He's from the James B. Duke School of Medicine. He was a professor emeritus of medicine. He was there from 1929 to 2019, passing at the age of 90. This guy published more than 500 academic papers. Dr. Jill, how in the world do you publish 500 papers?

Dr. Jill 04:31
Unbelievable! I love that you're honoring these people because so much of this research is leading us to these new discoveries. But it's so awesome to honor the people who've come before.

Bob Miller 04:45
Absolutely.

He wrote one article that was cited more than 51,000 times. He opened up an entirely new field of medicine in biology devoted to oxygen-free radicals. Here's the guy at 85 years old still lecturing at Duke University. Dr. Jill, that's one of my own personal goals—still lecturing at 85. We'll see if we can do that. He came up with the superoxide [theory]. [inaudible] of historical time. That's a blip. He said that superoxide is the origin of most reactive oxygen species and that it undergoes a chain reaction in the cell, playing a central role in the reactive oxygen species-producing system. Then he went on to say, [as] you'll see at the bottom of

the slide, that mitochondrial manganese SOD enzymes are your essential defense against that superoxide. That's because mitochondria are the major source of your superoxide.

Bob Miller 06:10
It was based on this that we started looking at our research. You can see here that Alzheimer's, Parkinson's, ALS, and other neurological diseases are caused by abnormalities in our biological defenses or increased intracellular reactive oxygen levels.

Bob Miller 06:28
We're going to get down to the real basics here, Dr. Jill. What is superoxide? People are going to say, "That's it?" If you're looking at the screen there, you'll see oxygen to the left. It's two oxygen atoms. The little blue dots.

By the way, do you see my cursor and what we're doing here?

Dr. Jill 06:48
Yes, it looks great.

Bob Miller 06:50
Yes. These little blue dots are the electrons, and they need to be paired. You can see they're all paired up. What happens with superoxide is an electron comes in and attaches by itself, and that's what creates all the trouble. To me, it's amazing that we're talking about one tiny little electron sticking on there and creating all the problems we're going to talk about.

Bob Miller 07:17
Here's what manganese SOD does. We thought we'd give you an idea of what that does. You'll see here that I'm pointing to superoxide, and then manganese comes along—this is not magnesium, this is manganese—and it's got a 3+ charge. It takes on that extra electron and turns it back into oxygen. How cool. Then you'll see that manganese 2+ combines with two hydrogens and turns it into hydrogen peroxide.

Bob Miller 07:53

Hydrogen peroxide can create problems inside the body, but we do have incredible mechanisms to get rid of this. The body makes something called catalase that will turn the hydrogen peroxide into oxygen. Glutathione—there's an enzyme called glutathione peroxidase 1 that uses glutathione to turn it into water, and something called thioredoxin. By the way, we could probably do a whole lot of podcasts on thioredoxin sometime—how that turns hydrogen peroxide into water as well. As you can imagine, you can have genetic mutations on SOD2 that make it not as effective. You can have genetic mutations on catalase, glutathione peroxidase 1, or thioredoxin, and it may not do its job as well as it should. If we don't clear that hydrogen peroxide, there's something called the Fenton reaction that takes Fe^{2+} and turns it into Fe^{3+} and makes hydroxyl radicals, which we're going to talk about a little later. But these are bad guys that do a lot of trouble because they oxidize and damage your lipids.

Dr. Jill 09:06
Bob, I have a quick question for you as you go. My thought is: One thing you and I both love is breathing our hydrogen, and a lot of people and patients do tabs that are hydrogen. I'm suspecting that there's a place for that in this pathway as far as neutralizing the reactive oxygen. Is that true? Would that just come in and add a hydrogen [molecule] in any particular place here? Or is that more a generalized reaction that can neutralize radicals?

Bob Miller 09:30
We talked about that among our crew. We do believe this is like the hydrogen you breathe or the hydrogen you take. I'm not surprised you caught that, by the way. Good catch. But that's why that hydrogen—water or breathing hydrogen—can be so effective.

Dr. Jill 09:46
But then it looks like if you had SOD mutations, you probably would benefit from that hydrogen, but maybe not as much because you still require the SOD in there, right?

Bob Miller 09:56
Absolutely, yes.

Dr. Jill 09:59
Beautiful.

Bob Miller 10:00
Yes. We're going to show what happens if we don't have SOD. We'll show that in a little bit.

This is a chart that I made up that illustrates the damage that superoxide can do. We're not talking about diseases or conditions. We're just talking about what it can make that's oxidizing. It was fun to make this chart. One of the things that superoxide will do is combine with nitric oxide. I know, Dr. Jill, you're a big fan of nitric oxide. I hear you speak about it and you talk about all the benefits of it, and that's all absolutely true. But we lose those benefits if superoxide combines to make something called peroxynitrite.

Bob Miller 10:42
We could talk about peroxynitrite, but what I encourage you to do is go back to one of our old videos, number 16, where we spoke about peroxynitrite. But the Cliff notes are that peroxynitrite is capable of initiating DNA single-strand breakage, leading to eventual severe energy depletion of the cells and necrotic-type cell death. By the way, it's interesting, the chemical symbols: ONOO.

Bob Miller 11:13
Peroxynitrite is not done there yet. We need to make nitric oxide. This is a very simplified version, but there's an enzyme called NOS. And there are three of them, but for simplicity, I just put one here. It uses arginine plus other things and it makes nitric oxide. But it's dependent upon BH4. BH4 turns into BH2, and BH2 has to be recycled back to BH4. A simplified drawing here, but if we're just running off BH2, rather than making nitric oxide, we make superoxide. And then that comes up here and creates a feedback loop, and we're in serious trouble as this thing just feeds upon itself. Additionally, that BH4 is needed to make dopamine and serotonin. Serotonin also goes into melatonin, and peroxynitrite inhibits that process. You can see here, Dr. Jill, how we get into this loop of inflammation.

Dr. Jill 12:22
That makes so much sense. And we've talked before in that previous episode about

BH4, the importance, and the sources because that can be one of those things. But it's not just as easy as taking BH4 because it doesn't come that easily to our bodies.

Bob Miller 12:36
It sure doesn't. We have another chart; we're going to look at that. The other thing that peroxynitrite does is inhibit manganese SOD2. What we just showed you that takes care of that—peroxynitrite—will inhibit it by something called nitration of one of the amino acids. We'll have another slide that shows that even more.

Bob Miller 12:59
If that's not enough, it gets involved over here. But first, let's look at what happens there. Here's your manganese SOD, as we just showed. The superoxide will turn into oxygen, a good thing, then it flips and makes hydrogen peroxide. As we said, that can combine with iron to make hydroxyl radicals. It makes your lipid peroxides. It takes your lipids, oxidizes them, and does cell membrane damage.

Bob Miller 13:30
Here we have just a little description. It's the most reactive oxygen radical known. It may cause lipid peroxidation and destroy cell membranes. It reacts with almost every type of molecule found in living cells, including sugars, amino acids, phospholipids, DNA, organic acids, and fatty acids. One nasty molecule. Look who will help with that BH4. But look what peroxynitrite does. It inhibits your BH4. You can see we've got multiple things going on here.

Bob Miller 14:08
We're going to talk later about manganese. It's a very important mineral. And we're going to talk to you later about how glyphosate may be impacting this. And if we run out of manganese, SOD2 keeps working but it uses iron.

Dr. Jill 14:25
That was one of my original questions. I'm sure you'll go into that, but I have seen [that] on testing patients who are manganese deficient more than ever before. Like you, I've suspected chemicals and glyphosate in the mix. I'm looking forward to hearing more about: What do we do when we don't have that element?

Bob Miller 14:41
Absolutely.

Yes, we have that later on in the presentation. If we're accessing iron, that will go into SOD2—we have another slide on this as well—and then it just makes your hydrogen peroxide, so you don't get the oxygen; you just get more hydroxyl radicals. As these lipids get damaged, it's called ferroptosis. This is a new form of cell death that results from the iron accumulation in the cells. It depletes antioxidant enzymes, resulting in lipid peroxidation and more oxidative stress.

Bob Miller 15:15
We're going to have more slides on this, but there's something called the electron transport chain. What that does is it takes these electrons and they just bebop down through here and they make ATP. It's interesting; they're dependent upon iron-sulfur clusters, as it's called. Dr. Jill, we could probably do a whole show on this one sometime because it's fascinating, an area we're digging into. But unfortunately, when we get too much hydrogen peroxide or superoxide, this iron can be ripped off to make this hydroxyl radical. And if we don't have iron-sulfur clusters, rather than make ATP—hang on to your hat—we make more superoxide.

Dr. Jill 16:03
Oh boy.

So not only does that damage cell membranes, it also steals from the mitochondria that are making this energy.

Bob Miller 16:12
Yes.

There are many reasons for fatigue. This isn't the only one. But this could be a big reason why people have fatigue or exercise intolerance—because they're not making enough adenosine triphosphate. That's the fuel that makes your body go.

Bob Miller 16:28
In a little while, we're going to show you a whole chart that shows you how these are made and what can go wrong. At the end of this podcast, we're actually going to show Dr. Jill's genome. She's brave enough to again let everyone see her genome. Congratulations on that. And we're going to show you that you may not be the best

producer of these iron-sulfur clusters, my friend.

Dr. Jill 16:51
No surprise.

Bob Miller 16:53
Yes. This may be of benefit to you.

And then finally, superoxide, as it destroys those iron-sulfur clusters, can affect your amino acid biosynthesis. I was pretty amazed as I started going through and looking at all the ways that it can hurt us, and I have a sneaking suspicion this isn't everything. I have a sneaking suspicion there's more.

Bob Miller 17:22
Just a real quick slide on ferroptosis. It's oxidative damage to the cell membrane leading to cell death. It's when you don't have that repair, the glutathione peroxidase 4. It's iron-dependent—distinct from apoptosis or necrosis—and it plays an important role in the development of various inflammation-related diseases, such as autism. In the fall and spring of '25, I'm going to be speaking at some autism conferences with an emphasis on ferroptosis being a player in that.

Bob Miller 17:57
Here's just a more simplified version. Here's your polyunsaturated fatty acids. Iron and hydrogen peroxide make reactive oxygen species, then damage your lipid peroxides, [causing] ferroptosis and cell membrane damage. Glutathione peroxidase 4 is dependent upon glutathione. GSH is the symbol for glutathione. And there's one pathogenic SNP, this one right here. When you've got a mutation on this one, your GPX4 may not be working as well as it should.

Bob Miller 18:31
In case anyone's not familiar [with] what we mean by a SNP, when you were conceived—when the sperm entered the egg—your DNA pattern was made and we can get what are called genetic SNPs or mutations or whatever you'd like to call them, where the enzyme that this makes isn't as effective. It's still working—it still gets turned off and on—but it's not as effective.

Bob Miller 18:54
In this example here, one parent gave a mutation on GPX4. And sometimes two parents too. If this GPX4 is weak and you make lipid peroxides, you're going to have less ability to turn that lipid peroxide into that lipid alcohol and more opportunity to go over to ferroptosis. Just as a clinical observation: We see a lot of leaky gut with this because the gut lining is being impacted.

Bob Miller 19:26
Here is a slightly expanded version. You might say, "No, wait, I saw this over here before you did." What we added to it was an enzyme called tumor necrosis factor-alpha, where mycotoxins or mold, excess iron, lipopolysaccharides, a virus, Borrelia, glyphosate, and clostridia will over-stimulate tumor necrosis factor. It stimulates the NADPH oxidase enzyme and makes your superoxide.

Bob Miller 20:00
Things we talked about before: The Fenton reaction. But on here we show you that the Fe^{2+} is called ferrous iron. This is what can bind your oxygen. Your Fe^{3+}—this is your ferric. It's non-functional and cannot bind oxygen. That's what happens the more this Fenton reaction occurs. Then we get those lipid peroxides, as we just spoke about. But here we show that CoQ10 is important. BH4 helps calm this down. Glutathione peroxidase 4—that we just showed you, and that comes from glutathione.

Bob Miller 20:40
We can have something called the NMDA receptor, which we'll talk about later, stimulated by glyphosate, homocysteine, high fructose corn syrup, electromagnetic fields, phthalates, and arsenic that will increase the glutamate, which can inhibit your body's ability to bring cysteine into the cell to make glutathione. Another three-ring circus here, Dr. Jill—how these can all interplay and all compound each other. This would be why some individuals might be inflamed and can't figure out why, despite whatever they try to do.

Dr. Jill 21:15
It makes sense.

Bob Miller 21:19

Here are a couple of conditions related to ferroptosis. I'm not going to read all of them, just the category: Nervous system, cardiovascular, bones, pancreas, kidneys, gastrointestinal, liver, lungs, and the eyes. They can all be affected by ferroptosis.

Bob Miller 21:38
And interestingly, they're now doing studies. Their study elucidated that there's an intricate correlation between ferroptosis and autism and provides a promising ferroptosis score model to predict molecular clusters and immune infiltration cell profiles of children with autism spectrum disorder. And clearly, this problem is just increasing dramatically. The amount of children now who are diagnosed with autism is going up. Our genetics haven't changed, but our environment has.

Dr. Jill 22:12
It's the elephant in the room—that environmental toxic load. And so many of the things you showed in the slide previously are increasing glyphosate, arsenic, and all of those types of things.

Bob Miller 22:24
Absolutely.

We're going to get into a little bit about what mitochondrial superoxide can do. It plays a critical role in Alzheimer's disease, increasing that dramatically. What a horrible illness that takes people's minds away. They don't know who they are anymore. They were able to show that increasing the expression of the mitochondrial antioxidant SOD2 prevents memory deficits and the plaque deposition that's associated with Alzheimer's disease. A lot to be studied there.

Bob Miller 23:01
Diabetic complications. The metabolic abnormalities of diabetes cause mitochondrial superoxide overproduction in the cells of both large and small vessels and also in the myocardium. This causes the activation of five major pathways involved in the complications.

Bob Miller 23:20

Interestingly, orally administered SOD, that's superoxide dismutase, can exhibit glucose-lowering effects via targeting the intestine of diabetic rats and the lipopolysaccharide influx.

Bob Miller 23:35
As we said, this is a manganese SOD. That's the manganese SOD. There are three of them, but we're talking about the SOD2. They're talking about [how it] inhibits the growth of antigen-independent prostate cancer cells.

Bob Miller 23:50
Atherosclerosis, clearly heart disease, is at the top of the list of conditions we have. Excessive generation of reactive oxygen species leads to a state of oxidative stress, which is the major risk factor for the development and progression of atherosclerosis. As we spoke earlier, eNOS endothelial nitric oxide can become uncoupled. Then superoxide reacts with nitric oxide to form peroxynitrite, which oxidizes the BH4, leading to BH4 deficiency. And once again, we're just on a merry-go-round here, Dr. Jill, of inflammation and heart disease.

Bob Miller 24:29
We even have a problem here with cataracts. Oxidative stress plays an important role in the onset and progression of cataracts. And here we have age-related macular degeneration. The low-glutathione peroxidase activity and antioxidant status are associated with advanced macular degeneration. The antioxidant enzymes and serum total antioxidant status could be promising markers for the prediction.

Bob Miller 24:59
And of course, as we get older, especially for women, their bones become brittle. Intracellular redox imbalance caused by SOD1 deficiency plays a pivotal role in the development of bone fragility in individuals.

Dr. Jill 25:14
I want to just pause there, Bob, and say that I think that osteoporosis, osteopenia, bone loss—a lot of women don't know that this is very inflammatory-driven. And I think this is a really important point. You might think, "Oh, it's my age" or "I'm not exercising enough"—and all of that is important—"or eating enough minerals" or

"low stomach acid." There are many other things that relate. But really, [with] a lot of these things that we don't suspect, inflammation is the root. So I love that you're bringing this all together, especially with bone health. And like I said, many women, I don't think, understand the connection between inflammation and loss of bone.

Bob Miller 25:50
Yes. I'm glad you brought that up because, clearly, calcium is important. But for too long of a time, if somebody has osteoporosis, they think they have to take more calcium. And that's not working very well. Interestingly, we'll show a little bit later that if the NMDA is upregulated, excess calcium can create inflammation as backward as that sounds. I know that flies in the face of everything we've ever heard. I'm not saying that you don't want calcium or take calcium, but if we get too much and NMDA is upregulated, it can create oxidative stress.

Bob Miller 26:26
This is talking about skin aging. Oxidative stress as a consequence of an imbalance in prooxidants and antioxidants has been demonstrated in the aged skin.

Bob Miller 26:37
And finally, increased superoxide in heart failure. A mechanism responsible for impaired endothelial function and heart failure is enhanced by a degradation of nitric oxide by the superoxide anion. I know that's one of your favorite subjects, the nitric oxide. When they combine with each other, they have a diffusion-limited radical reaction to form the peroxynitrite anion.

Bob Miller 27:03
This is interesting. In autism, SOD expression was found to be decreased during brain samples, doing a meta-analysis. Here's another one: Our data suggests that decreased serum SOD levels can be implicated in the progression of autism in children and can be used as an independent risk indicator of autism spectrum disorder.

Bob Miller 27:27
And here they're talking about the former hypothesis, where you're talking about [how] reactive oxygen and nitrogen species are now a certainty in autism. They're talking about superoxide, hydroxyl radical, hydrogen peroxide, singlet oxygen,

nitric oxide being used improperly, and peroxynitrite, respectively. They overwhelm the cellular buffering systems and may lead to cellular injury.

Bob Miller 27:58
We're talking now about adult ADD and ADHD. I just saw a statistic that among children, one out of nine children has ADHD. This is a tragedy. You've been in practice for a while; I'm sure you're seeing it among your patients. Are you seeing a rise in people that have ADD or ADHD, and they're having a hard time focusing and concentrating?

Dr. Jill 28:21
Absolutely. And yes, the kids are increasing in incidence, both autism and ADD, and all kinds of neuroinflammatory disorders. However, the adults, the same way. I would say I'm seeing just as much of a rise later in life with adults suffering from maybe something they've suffered with their whole life, but at least the prevalence in clinical practice is increasing pretty dramatically.

Bob Miller 28:45
Absolutely. We're seeing it here as well, that people have a hard time concentrating.

Okay, here it's even in Crohn's disease, which again is an autoimmune [disease]. And they're talking about [how] there's a relationship between oxidative stress and antioxidant defense in Crohn's disease.

Bob Miller 29:03
In pain, superoxide anion is overproduced in joint inflammation, rheumatoid arthritis, and osteoarthritis. It leads to tissue damage, degeneration, and pain. And in these conditions, the defense against superoxide, which you all now know [is] superoxide dismutase, is decreased. No great surprise there, Dr. Jill.

Bob Miller 29:32
How do we make this superoxide? Here we go. There isn't just one way. We're going to talk about NOS uncoupling by genetic and epigenetic factors, NOX, the electron transport chain, overaction of NMDA, glutathione not recycling properly, something called the aryl hydrocarbon receptor, and polycyclic aromatic hydrocarbons creating superoxide.

Bob Miller 30:01
I remember one of our recordings was one of the times that you were having the fires in Colorado. I don't remember what that was, but we discussed how so many people were struggling because all that smoke was—in some individuals more than others—creating all this superoxide. When was that? Do you remember?

Dr. Jill 30:22
That would have been about two years ago. Time flies when we're having fun. One other thought is I check TNF-α all the time in my mold patients, but as you elucidated earlier, it could be caused by multiple insults, infections, and toxins. And one thing I saw in the wildfires was that people's bloodwork was looking just like someone who had had an acute mold exposure. Of course, we knew this, but it was just showing that it's so many of the environmental chemicals that upregulate. And that makes sense in this case as well.

Bob Miller 30:52
Absolutely.

Now, if anyone's interested in what I'm going to talk about right now, go back to our interview, "The Carnahan Reaction and iNOS", where we talked about how Dr. Jill has an interesting pattern. You'll see this when we look at her genome of the NOS2 enzyme being a little overactive. I'm not going to go into a lot of detail, because you can just watch the video. We had a lot of fun on that one. But here's what happens. There's a NOS3 enzyme, or endothelial nitric oxide synthase, that makes nitric oxide. This is a gas that dilates our blood vessels. Everything you've heard about is absolutely true. We need it desperately. That's why some people need to take nitroglycerin. That's why men would use Viagra or Cialis to get the nitric oxide for blood flow. We need BH4, NADPH, and arginine to make the nitric oxide. NOS3 does that. Things like nitrates help that along, like your beets.

Bob Miller 31:52
Here you'll see the BH4. There are ways the BH4 gets made, and all these purple circles are enzymes that are made by your DNA. For example, if someone has mutations in their MTHFR A1298, they may not make as much BH4. And

interestingly, one of the things that helps with that is royal jelly. It's a naturally occurring source of BH4.

Dr. Jill 32:16
Oh, fascinating because, as we were talking before, I felt like it's difficult to come up with sources purely for that. I did not know about the royal jelly. That's amazing.

Bob Miller 32:26
Yes. In our health consulting, [for] probably one out of five people we suggest royal jelly. One of the funny things is that when we deal with young ladies, we tell them: "You're going to have to be careful. Everyone's going to have to address you as 'princess.'" [inaudible] [laughter].

Bob Miller 32:49
Also, when GTP (guanosine triphosphate) comes down through here through all these enzymes and makes BH4 as well. Again, mutations here can impact us.

Bob Miller 33:02
And here you'll see mercury, lead, aluminum, iron, sometimes too high of a protein diet, hydrogen peroxide, high ammonia, peroxynitrite, and sun (ultraviolet [light]) can suppress this.

Bob Miller 33:14
One of my favorite sayings is: "NOS2 is your friend, unless it isn't." In other words, this is there to create extra-high levels of nitric oxide if we need to kill some pathogen. If we've got a bacteria, virus, fungus or parasite, NOS2 will kick in and create extra to create a little bit of oxidative stress. But if this guy is overactive, we have a problem.

Bob Miller 33:41
And I think I had the slide—I should have put in this one, but I forgot—[showing how] COVID-19 overstimulates the NOS2 and suppresses the NOS3, possibly leading to the endothelial issues and the clotting. But the bottom line here is that if we run out of BH4 or some other things here, rather than making nitric oxide, you're going to make superoxide. Then that will combine with nitric oxide if we

don't have enough SOD and make peroxynitrite, which further suppresses your BH4. And the circus begins of just feeding upon itself.

Bob Miller 34:25
Here's another one. By the way, we did another recording—number 26—about the NOX enzyme. NADPH oxidase is one of my favorite enzymes. I've said this before: NOX is your friend, unless it isn't. This is part of your immune system response. When we're faced with something we need to kill, NOX makes superoxide to kill the pathogen and it can stimulate mast cells. That's okay unless it's overactive.

Dr. Jill, you've been practicing a little while. How much has mast cell activation increased from when you started to what you're seeing now?

Dr. Jill 35:03
Massively. There may not be another condition that I see more of an increase in clinical practice. It was almost unheard of when I graduated from medical school. The only thing we were taught in medical school was mastocytosis, which is the proliferation in the bone marrow—almost like a precancerous condition—that is very different from mast cell activation. In mast cell activation, it's the normal primordial immune cells that are a defense. But many, many people nowadays are having overreactive mast cells. And it leads to a host of illnesses and symptoms in all tissues, from the cardiovascular system to the brain, to the skin, to the gut. Pretty much any system you can name, I could tell you a mast cell effect. Thank you for bringing that up because I know a lot of people listening know someone, have heard of this, or are searching for information. It's a really big deal.

Bob Miller 35:53
Absolutely.

You talked earlier about TNF-α, tumor necrosis factor-alpha. This is your friend, unless it isn't. Here you can see there are two RS numbers, two SNPs that, when they're mutated, are considered gain of function. In other words, when they're stimulated by some pathogen, they overreact. Mycotoxins, viruses, lipopolysaccharides, clostridia, glyphosate, Borellia, and probably more will stimulate the tumor necrosis factor. If you have the SNP that's overactive, it overresponds and stimulates NOX.

Bob Miller 36:36
In addition to this pathway, there's an enzyme called SIRT1 that holds it back. You probably figured there you can have a mutation. There it is. There's the RS number. It's important to know if you have that mutation. That means your SIRT1 may not be as effective. By the way, resveratrol can help with that.

Bob Miller 36:56
I should have put this on. We did a whole video on IL-6, if you recall. If you just search "Dr. Jill Carnahan, Bob Miller, IL-6," I think we geeked out for about an hour and 45 minutes on IL-6. NOX stimulates IL-6. The reason for the interest in that [is] that's what created the cytokine storm in COVID. Interestingly, pine bark can calm this down. Black cumin seed oil can calm this down. The other thing that'll calm this down is biliverdin and bilirubin. I think one of the most fun podcasts we did [was] when we talked about why the heme oxygenase enzyme is critical. We geeked out for quite a while on the heme cycle, heme oxygenase, and now it makes biliverdin and bilirubin to calm this down.

Bob Miller 37:49
I know some of you are probably thinking, "I see a perfect storm occurring here." You're exposed to mycotoxins. Your TNF-α is overactive. Maybe your SIRT1 is underactive. Maybe your heme oxygenase isn't doing what it should. Maybe this isn't doing what it should. That is the prescription for massive overreaction to stimuli. That's why two people can live in the same home that's a little moldy and the one person is sick as can be and the other one says: "What mold? You must be imagining things because I don't feel anything." It really creates quite the dilemma for some people when the least little bit of stimulation puts them into a massive inflammation and the other person says: "What's wrong? I don't notice anything."

Bob Miller 38:43
When that happens, usually it's invariable. TNF-α is upregulated. By the way, excess iron can stimulate this. I didn't put the iron genes in here, but that can do it as well. Weakness here. I don't think we'll talk about Nrf2 and KEAP1 today, but they also impact this, and then if we have problems in the heme cycle. Usually that person who is as sick as can be with mold or Lyme usually has some weakness somewhere where this [TNF-α] is upregulated and SIRT1 and heme oxygenase is downregulated.

Bob Miller 39:18
Additionally, histamine will stimulate this. To learn all about histamine, go listen to our number 34, "Histamine Intolerance". Electromagnetic fields will also stimulate NOX. There we are on number 54. And then, as I said, I really encourage you to listen to the "Heme Oxygenase" [episode], number 119.
You know, Dr. Jill, we really have a cool library of stuff that's covering a lot of bases here.

Dr. Jill 39:44
I know! It's been so fun to continue. And like I said at the beginning, we have so many practitioners that appreciate this. If you're a layperson listening, this may be just slightly over your head, but I think there are so many practical applications.

Bob Miller 39:57
Absolutely. We're going to get to the practical applications in a little bit.

By the way, hops—yes, the same thing that's in beer—calm down heme oxygenase. BroccoRaphanin—you may have heard of that. That's the broccoli that supports the Nrf2.

Bob Miller 40:15
Just briefly, we're going to talk about iron-sulfur clusters. And you know what? In the future, I may come to you and say, "Dr. Jill, let's do a show on iron-sulfur clusters," because they're fascinating. We are not even putting our toe in the water here. They're essential cofactors known for their role in mediating electron transfer within the mitochondrial respiratory chain. That's what we spoke about earlier, the electron transport chain.

Bob Miller 40:40
It plays a critical role in transporting electrons through those complexes—I, II, and III—to cytochrome c before subsequent transfer to molecular oxygen. Folks, this is where you make your energy. This is where you make your ATP. This is what greases the wheels, so to speak, for you. It makes it happen.

Bob Miller 41:01

This is a chart that I just made. Up at the top here, you'll see complex I, II, III, IV, and V. Here's your ATP energy, and here are four iron [atoms] and four sulfur [atoms] in an iron-sulfur cluster. There's an enzyme called NFU1 that makes this. And Dr. Jill, when we look at your genome, you're going to see you've got a little bit of trouble there. Hang on, everybody, to watch for this.

Bob Miller 41:34
Also, we need iron. The enzyme FXN puts the iron into this pathway, and then here comes sulfur. And we're going to show you that you can have mutations on FXN. We're relatively new into this, but what we're finding is that when people have mutations on this FXN, they're tired and inflamed because they're not getting the iron up here, and the iron might be going off to be a bad boy.

Bob Miller 42:07
Also, [as] we mentioned earlier, the superoxide can steal some of this iron and go over here and make hydroxyl radicals. I didn't know this until we really started digging into the literature. What you need to grease your wheels here, so to speak, to help these electrons move along can be harmed by superoxide. But look what happens if we don't have this electron transfer going on; the electron combines with oxygen to make superoxide. Ouch. Ouch. Another three-ring circus here, Dr. Jill.

Bob Miller 42:50
We need sulfur to be part of that as well. There's an enzyme called NSF1 that gets its sulfur from cysteine. How many people have heard of cysteine—N-acetyl cysteine? It's part of the heme cycle. It forms pyruvate and taurine. For anybody who's looked at methylation, homocysteine comes down here and turns into cysteine. Cysteine is also one of the tripeptides that makes glutathione, along with glutamate and glycine, the master antioxidant.

Bob Miller 43:26
We're in the early, early stages of this. I debated whether to put it in because we're still early, but I thought, "For the practitioners, just introduce them to this concept because it might be something we're going to talk about later."

Bob Miller 43:41

I'm going to jump here to nitric oxide. Everything you've heard about it that's good is absolutely correct. The cGMP—this is what lowers your blood pressure by regulating vascular tone and inhibits platelet aggregation. All those good things that nitric oxide does. But as we also said, nitric oxide will combine with superoxide to make peroxynitrite.

And here's probably a new term to a lot of people: Aberrant nitric oxide. You've heard of that?

Dr. Jill 44:13
I have not heard of that term, but just clinically, from our previous discussions, I had a big aha, because I always was so puzzled as to why all the precursors of nitric oxide—like arginine or citrulline, or even beets—would cause me to fall flat on my face with exhaustion. We talked about that in our previous episodes. Go back and watch those. But I remember having such an aha when we first talked about it because it's wonderful and we need it, but if you have the... It's the second pathway, the iNOS, that's upregulated?

Bob Miller 44:46
Yes. The NOS2.

Dr. Jill 44:49
Yes. Exactly.

Bob Miller 44:52
Aberrant nitric oxide—we're going to talk about this a little bit—causes something called nitrosylation. One of the things it'll damage is cystine. Ouch. We were frantically trying to find literature that would support that this nitrosylation of cystine would impact the sulfur delivery. You'd almost think it would, but we don't have proof for it yet. So hang on, because what it does then is make S-nitrosylated cystine. Then that turns into S-nitroglutathione. And there's an enzyme called ADH5 that turns it into N-hydroxysulfonamide. And then that turns into oxidized glutathione and can be recycled. And then also something called thioredoxin will repair it. We've got two repair mechanisms. One is thioredoxin and one is through this ADH5. You've probably already jumped ahead of me and said, "What happens if you've got mutations here and here?" These people are not doing well.

Dr. Jill 46:04
Yes. And I have a subset of patients who do not do well on NAC. And this is back to one of the, I think, foundational principles that you and I talk about frequently: All of these nutrients, supplements, cofactors, and things can be so important in the right person. There are people who don't do well with glutathione because they oxidize it. Or, they don't do well with NAC or even sulfur, which I'm sure you're going to go into. But my clinical thought is I have a lot of people who really, really need sulfur and yet they're very reactive to sulfur. Sulfur is like yin and yang for those patients who need it, but they don't do well with too much sulfur.

Bob Miller 46:42
Yes, absolutely. Stay tuned. I was hoping to find it for this recording. I had my whole research team saying, "It's got to be out there," but nobody can seem to find it yet. My suspicion would be it would almost have to. But maybe not. And we're also looking [at]: Are there other sources of sulfur? That's undetermined yet. Yes, there are plenty of sources for sulfur, but we're talking about the sulfur that comes up here. We don't know yet. That's under research. And I'm going to show a mutation here and how that can affect someone.

Bob Miller 47:28
And now I'm going to back up another step because we'll get into this later. There's something called the NMDA receptor that, when it's stimulated by glyphosate, arsenic, phthalates, EMF or homocysteine, it brings excess calcium into the cell—excess intracellular calcium, by the way, which has been proven to be happening in autistic kids—stimulating the NOS1 enzyme, then overproducing the nitric oxide that becomes the aberrant nitric oxide.

Bob Miller 48:01
When we look at your genome, you'll see here, we're looking at all the things that make the cGMP, and we're trying to find out: Are there ways to encourage the nitric oxide to go here? Don't know yet. But clearly, when NOS1 is upregulated, we make this aberrant nitric oxide, which then makes more peroxynitrite. And you saw the circus that that creates.

Bob Miller 48:29

Superoxide promotes hydroxyl radical formation and consequent DNA damage in cells of all types. And superoxide may accelerate DNA damage—listen to this—by leaching iron from that 4-iron, 4-sulfur cluster. This is what helps us make energy, and superoxide takes it away. Another three-ring circus here, Jill.

Bob Miller 48:58
Superoxide and hydrogen peroxide oxidize this iron-sulfur into an unstable iron-sulfur intermediate, which is degraded to 3-iron, 4-sulfur. And what does this do, Dr. Jill? It releases free iron and inactivates the enzyme. Then here comes Mr. Fenton making more hydroxyl radicals. And then those hydroxyl radicals interact with all the macromolecules, including proteins, lipids, or DNA. And you can just see how there are multiple rings of inflammation going on here, Dr. Jill.

Dr. Jill 49:36
Yes.

Bob Miller 49:39
Superoxide inhibits the iron-sulfur cluster enzymes involved in amino acid biosynthesis. It's amazing how this thing just keeps doing damage everywhere it goes.

Bob Miller 49:54
I just want to illustrate, and we're not going to talk about this a lot because we're in the early stages, but here's that NMDA enzyme. When it gets stimulated, extra calcium stimulates the nNOS. Here's your nitric oxide; iNOS stimulates it. Superoxide and peroxynitrite. The good guy over here, [cGMP]. Organic nitrates increase that and inhibit the platelet aggregation. And then here's where your cysteine becomes nitrosylated.

Bob Miller 50:25
Interestingly—we've had this discussion many times—a little bit of something can be helpful; too much of it can be harmful. In small amounts, it can be neuroprotective, and then it can be attempting to protect brain cells. But in too much, it's neurodestructive. A lot to learn here. We're just in the early stages.

Bob Miller 50:48

Just a definition. S-nitrosylation regulates protein function via the reaction of nitric oxide-related species with a cysteine thiol group on the target protein. With aging or environmental toxins that generate excessive nitric oxide, aberrant S-nitrosylation reactions can occur and affect protein misfolding, mitochondrial fragmentations, synaptic function, apoptosis, or even impact that important autophagy.

Bob Miller 51:18
I'm not going to read these; I'll just highlight a few. Aberrant S-nitrosylation, decreased antioxidant activity, cell death, neuroinflammation, impaired metabolism, signal transduction, cell death, and inhibition of autophagy—those are all the things that can happen if we have aberrant nitrosylation.

Bob Miller 51:39
Again, I'm just showing that same slide again to summarize it. When we get these environmental toxins, we have our aberrant nitric oxide. It impacts our cysteine. Whether or not it affects this or not, it would have to affect your glutathione. You can have mutations here that you don't get your sulfur up. You can have mutations here that the iron doesn't come over. And you can have mutations here that you don't make that iron-sulfur cluster. Even if you do get here okay, superoxide can come along and undo it. No wonder so many people are fatigued.

Bob Miller 52:18
This comes from an 18-year-old boy with rather severe autism. He's got this NFS1. You can see this mutation occurs in 0.5% of the population. In the 80,000 samples in my software, there's no homozygous. None. I would imagine life couldn't exist if this was homozygous. This is where the cysteine comes up here, turns into alanine and brings that sulfur up through.

Bob Miller 52:55
This is the FXN gene. This is the one that we talked about that brings your iron in. You can see FXN coming in and combining with the sulfur to make your sulfur cluster. This protein functions in regulating mitochondrial iron transport. And look at this little chart here. When this guy is mutated, rather than making the OXPHOS, which is needed for the electron transport chain, there's iron accumulation inside the cell with mitochondrial impairment. In other words, they're going to be

inflamed and tired. This comes from a 20-some-year-old gentleman. He's embarrassed that he can hardly work because he's so tired. And he was so relieved to see, "Oh, that's why!"

Dr. Jill 53:42
Yes. An aha.

Bob Miller 53:45
Yes.

And here's the NFU1. This is what puts it together. And this puts together a protein that is localized and plays a critical role in the iron-sulfur cluster biogenesis. This comes from a rather severe autistic child. Homozygous—two, two, two, meaning that that last step can't be made. You're not going to have the iron-sulfur cluster. The electrons are not going to flow smoothly. They're going to fly off and make superoxide.

Bob Miller 54:20
This is just the NMDA receptor. I encourage people to go back to—I think this was our most recent one—[episode] 162, the lesser-known cause of mast cell activation, where we talked about how glyphosate, arsenic, homocysteine, high fructose corn syrup, electromagnetic fields, and phthalates, which come from all of our plastics... What a disaster we have with microplastics! We have really messed up big time. All of those will bring extra calcium in, and as we discussed, stimulate the iNOS, the nitric oxide, and create the peroxynitrite. But the NOX5 enzyme directly makes superoxide. So here's another way to make yet more superoxide. So, there's the 90-second [version]. If you want the hour-and-a-half version, listen to number 162.

Bob Miller 55:16
Here's just a real quick slide that shows that homocysteine induces cell death by the activation of that NMDA receptor. And by the way, that's what creates your osteopenia and osteoporosis.

Bob Miller 55:30
Fructose ingestion. High fructose corn syrup was only invented in 1977. Historically, not very long. What a disaster!—because it increases the activation of the NMDA

receptor function. Can you imagine some poor kid who's sitting for breakfast and is having a cereal with that in it, maybe some milk with growth hormones in it, maybe the cereal has glyphosate on it, and they're playing on their iPad? And we're wondering why they can't pay attention in school.

Dr. Jill 56:08
Yes, it's such a toxic storm. What I really enjoy about our conversations is that my biggest platform is the environmental toxic load and what it does to our body and how it really is the elephant in the room. And so often, even as we study these genetic mutations and SNPs, it comes back to so many of the environmental inputs that are causing it to escalate to a level of clinical significance.

Bob Miller 56:33
Absolutely. That's why, as we said, one person can be affected and the other person says, "I don't feel a thing."

Phthalates. Oh my goodness! What a mess we've done! That's what you get from your microplastics. I think it was January of this year [when] a study came out that showed that the microplastics in our water bottles are 10 to 100 times more than previously anticipated. Oh boy! It comes from ingestion, inhalation, and dermal absorption. I've heard some estimates that we each get a credit card a week in plastics.

Dr. Jill 57:08
Yes, I was going to mention that because that makes it so practical for people to think about. That's a lot of plastic that we ingest. This has been found in atherosclerotic plaques and all over our bodies and our blood vessels. It's creating not only damage but [also] inflammation.

Bob Miller 57:26
Absolutely. And you can even get dermal absorption from personal care products. I always encourage people to look at everything. If it says 'fragrance,' find something that doesn't. Even people who live near phthalate manufacturing are more likely to have phthalates in their bodies through dermal absorption.

Bob Miller 57:48

Research shows that because of phthalate structural similarity to tryptophan metabolites, they're capable of inhibiting two really important enzymes. I've often said that if somebody wanted to figure out how they could hurt humanity the most, I don't know that you could be this creative to come up with something that this does. What happens is tryptophan comes down through here and has to be turned into picolinic acid, which is needed to help your zinc and your chromium do their job. Zinc inhibits the NMDA receptor. If this substance right here, [3-amino 3-carboxymuconate 6-semialdehyde]—that I'm not even going to try to pronounce—doesn't come over this way, it'll make more of what's called quinolinic acid. Quinolinic acid is very inflammatory to the brain. Quinolinic acid will stimulate the NMDA receptor. And phthalates inhibit that as well. You can see how phthalates are the proverbial perfect storm.

Bob Miller 58:53
And then, as you can imagine, you can also have genetic mutations in ACMS. You can also have genetic mutations in clearing phthalates. If you don't clear phthalates—you microwave in plastic, or you drink out of plastic bottles, and you use a lot of personal care products—and you have mutations here, no wonder you can't focus and your brain's on fire, because this quinolinic acid is stimulating the NMDA receptor. As I said, I don't think if you wanted to, you could come up with something that creative to be harmful.

Bob Miller 59:33
The story even gets a little bit bigger. When this NMDA receptor gets upregulated, it also stimulates glutamate. Glutamate makes you intelligent, highly motivated, and a go-getter. But it can also make you very anxious and make it difficult to sleep. At the worst, it can even create some psychological problems for you as the glutamate goes out. So you've got this dance between the two of them—and you mentioned earlier about having difficulty with cysteine—while glutamate inhibits the enzyme that allows cysteine to come in to make the glutathione that's needed to deal with that ferropetosis that we spoke about earlier. Another three-ring circus here, Dr. Jill.

Bob Miller 01:00:23
We spoke earlier; I'm glad you brought that up—that glutathione [is a] master antioxidant. As it goes down, you're not going to do well. It takes out all the toxins,

so one would think: "Let's just take glutathione and you're going to do well." Some people do fabulous on it, some don't. What happens is that when glutathione does its job, it becomes oxidized, and we need an enzyme called GSR, NADPH, something called FAD, that comes from riboflavin. You can have genetic mutations on riboflavin. You can have genetic issues on GSR. Here you'll see one right here. This SNP right here is a pathological downregulation. If you've got difficulty recycling and you take too much glutathione thinking you're doing yourself good, look who's down here: Superoxide.

Dr. Jill 01:01:19
Yes, Bob, we've talked about this before since we've done so many episodes and talked about me. But that was me, especially right after the mold—maybe 10 years ago—where I could not take glutathione; I did not do well. And I know I had some of these genetic mutations.

Dr. Jill 01:01:31
And I just want to pause here. Whether you're a clinician or a patient, one of the important principles here is that there's no one-size-fits-all. I can't emphasize that enough because I hear patients all the time [say things like], "Well, I should be able to," or "I'm supposed to," or "This is good for me." The truth is that everybody is so individualized. I always have to say: "You know what? Maybe glutathione is not good for you," or "maybe excess NAC is not good for you."

Dr. Jill 01:01:58
And patients think [that] because they've read about the power of this or read about the importance of this antioxidant. And sadly, manufacturers, supplement companies, and influencers are making this even worse because they're out there promoting, "This one product is good for everybody." And I wanted to pause here and say that's just not true. One of the reasons I do these individualized cases and that you do the same is because it's so different for everyone, and there is no one-size-fits-all. And just because a nutrient is supposed to be good, it might be toxic to you if you have the wrong genetics.

Bob Miller 01:02:31
Dr. Jill, that was absolutely brilliant. You ought to maybe put that on one of your Facebook things as a little clip to put that out there. Brilliantly, brilliantly said. One

of the ways I put it is: "If somebody tells you everyone should, be very concerned." [laughter] Or, "Here is the protocol for," fill in the blank. It's like, "Well, maybe."

Bob Miller 1:03:02
Polycyclic aromatic hydrocarbons. What in the world is that? Chemicals consisting of numerous carbon atoms joined together to form multiple rings. There's 10,000 different PAH compounds. It's from the incomplete combustion of plant or animal matter or carbon fuels, such as coal or petroleum. They're the sooty part of smoke or ash—as we spoke about earlier—from forest fires, industrial processes, automobile exhaust, industrial emissions, and smoke from burning wood. Charcoal and tobacco contain high levels of PAH. Grilled, smoked, and charbroiled foods, especially meats, are sources of some PAH exposure. I'm sure you've run into this: Somebody just goes to a backyard barbecue and they're sick from the barbecue. Have you heard of that?

Dr. Jill 01:03:50
I have had multiple cases of [patients who were] very specifically exposed to this exhaust or smoke or charbroiled [cooking] or a restaurant where they have a grill. This is actually quite common. And patients are kind of confused because going out with the campfire is supposed to be this fun, wonderful family activity, or going to a charbroiled restaurant with a grill in front of you. These are things that people look forward to. And for some people, it literally takes some out of commission for days at a time.

Bob Miller 01:04:19
Absolutely. Here's why. There's something called the aryl hydrocarbon receptor. What is that? Normally enzymes take one substance, combine with something else, and make something new. Now, this is a completely different animal here, Dr. Jill. If—smoke, kyrurenine from the kyrurenine pathway, mold, high homocysteine, high iron, arachidonic acid—those hydrocarbons let a mercury [ion] go in, it stimulates that intracellular calcium that we spoke about that makes superoxide, stimulates ferroptosis, and makes these inflammatory genes upregulated, [leading to] reactive oxygen species and DNA damage. Then it stimulates interleukin 6 and NOX to make superoxide and one of the cytochromes—that should be CPY there—makes quinones and semi-quinones that make superoxide. Again, we're making superoxide. On the other hand, B12, folate, rosemary, resveratrol, fisetin, quercetin,

milk thistle, indole-3-carbinol, naringenin, and luteolin turn on the Nrf2 cycle.

Bob Miller 01:05:34
One of the most interesting clients I ever saw was a woman who said: "Bob, you're not going to believe me. I have to take 150 milk thistles a day to survive." That's like, "Seriously?" She'd have to take five to eight. It would last an hour and a half, and then the pain would be back again. What she was doing—she was so happy to see that she wasn't crazy—was having to stimulate this anti-inflammatory cycle. The last time we spoke, we had her down to 12 a day because we did some of the things over here and started working on the aromatic hydrocarbons and arachodonic acid. Some people even need an air purifier in their car. I don't know if you can do that or not, but you can actually get little things that sit in your coffee cup and run off the cigarette lighter and clean the air in the car. These people need very good air purification.

Dr. Jill 01:06:30
Bob, I have one of those, really expensive. It's not a small thing—it's larger than my head—and it goes behind the passenger seat.

Bob Miller 01:06:39
Oh, really?

Dr. Jill 01:06:40
Yes. It's from a company called IQAir. Of course, I love to experiment, so I was like, "I'm going to get one of these and try it." I happened to not have horrible, horrible issues with exhaust [but] definitely [with] molds and those kinds of things. But I was like, "Let's check this out." There are some pretty fancy devices you can get like that. There are many others. I have no association with the company, but that's just one of those.

Dr. Jill 01:07:02
And for those people who are really, really sensitive or who drive, say, in LA traffic… LA traffic is a perfect example. Maybe you have a two-hour commute to work or an hour and a half and you get so exhausted. I have patients that say, "I'm in my car for my commute, and I get home and I have to take a nap. I just don't feel well," or they have a headache.

Bob Miller 01:07:25
Absolutely. That's comes from that. And I've seen this with truck drivers and also people who do outside landscaping work where they're constantly using machines that are giving off smoke.

Bob Miller 01:07:37
Let's go back to our phthalates here now. Those phthalates will inhibit the QPRT enzyme that makes NAD that holds back the mast cells. You can see how this is like the proverbial perfect store. And this is why these are the people [who] just get a little bit of smoke and they're sick. They walk into a moldy house, they're sick. Even some perfumes will do this to some individuals. This likely isn't the only reason why people are like that, but this could be a reason why some people are struggling.

Bob Miller 01:08:17
There's an enzyme called NQO1, and this also reduces superoxide. It suggests that superoxide reductase activity does have cellular relevance. It's not a big one, but it does reduce superoxide in cardiovascular cells.

Bob Miller 01:08:33
Here's what happens. Again, back to the polycyclic aromatic hydrocarbons. They will stimulate these CYPs and they'll make something called quinones. And then that'll turn into a semiquinone. And then look what happens here, Dr. Jill. Oxygen and superoxide destroy your nitric oxide and stimulate ferroptosis and lipid peroxides. On the other hand, this NQO1 enzyme—and by the way, here's the RS numbers; you really should know if you have those or not—takes NADPH and hydrogen back to your breathing hydrogen or drinking hydrogen and turns that quinone back into oxygen. That's why this NQO1 is so important. It's controlled by Nrf2 and also controlled by KEAP1. I believe you're still breathing hydrogen therapy.

Dr. Jill 01:09:30
Oh, yes. It's right here beside me. I use it all the time.

Bob Miller 01:09:36
And then there are multiple SNPs in the CYP1A1 that can be gain of function. In addition to being exposed to that, you can have a gain of function. By the way, selenium and vitamin E can calm this guy down a little bit in addition to those other

things. [I recommend] drinking your hydrogen, breathing your hydrogen, and, more importantly, staying away from that air pollution as much as you can.

Bob Miller 01:10:03
We made a case as to how we can make it all. How do we break it down? We're going to talk about manganese, SOD2, B12, and PON1. We spoke about manganese earlier, and this is just a little easier to see. Here's your superoxide. Manganese grabs that electron—it's now got a spare electron here—and turns your superoxide into oxygen. The spare electron here—here are two hydrogens; it's what we just spoke about—takes the superoxide and turns it into hydrogen peroxide. That's manganese SOD or SOD2.

Bob Miller 01:10:46
We spoke about this at the very beginning. Glyphosate reduced seed and leaf concentrations of calcium, manganese, magnesium, and iron in soybeans. They're finding that glyphosate is reducing our manganese. In case anybody doesn't know it, that's Roundup. The way it works, you put it on the weeds and it kills them. It does that by just chelating their minerals, so they're essentially starving. Somebody should have thought about this: If it does it to the plant, what happens when we then eat the plant as well? I know Stephanie Seneff does a lot of work on this. She talks about how glyphosate may be impacting our manganese. Manganese is one of those minerals we don't talk about a lot, but we really need to be looking at our manganese.

Bob Miller 01:11:38
And here's a chart. There's a delicate balance. What no one should do is—based on what we said here today—start taking lots of anything, including manganese, because it can become toxic. Above 15 milligrams, it can become toxic, and anything less than 1.8 can be low. It is important that we have the right amount of manganese because of low or impaired growth and abnormal glucose tolerance. In here you've got all the things going right, but then over here you can have oxidative stress and mitochondrial dysfunction if you take too much. Word to the wise: Don't think, "I'm going to be really super here and take lots of manganese and I'll be much better"; you can actually be worse.

Dr. Jill 01:12:30
Bob, I love that you mentioned that because selenium can have a biphasic curve, and many of these other minerals that are trace minerals have this Goldilocks perfect balance. I am a huge fan of measuring. Or if we don't know and we suspect issues, sometimes the trace minerals or the fulvic acids or things that have just a little bit in a very neutral source is a way to go because you're not ever getting excessive amounts of one thing.

Bob Miller 01:13:59
Absolutely. I'm glad you brought that up because it's so important that we don't get too much or too little. I've heard that 50 micrograms is about the sweet spot for selenium. Have you heard the same thing?

Dr. Jill 01:13:11
Yes. A lot of people are taking 200 or 400 or much more, and I'm very cautious. I would say as I check RBC, magnesium levels in the blood—which is easy to do on a Quest or a Labcorp if you're a practitioner ordering these tests—and I see a decent amount that are high and almost toxic. I would say maybe 30% of the people we test who are taking what they think is a normal dose are too high in selenium.

Bob Miller 01:13:34
Yes, I always try to keep it at 50 micrograms.

This is a fun little chart.

Dr. Jill 01:13:39
For you and me maybe, right, Bob? [laughter] I love it.

Bob Miller 01:13:46
We thought, "Why don't we draw how SOD2 works?" I wish Irwin Fridovich was here to see this. Here's SOD2—manganese SOD—and there are two SNPs. There are the RS numbers. When you've got mutations on those, the enzyme itself isn't as strong as it should be. Here's manganese and here's superoxide. Superoxide turns into oxygen this way. Then we take the superoxide and two hydrogens and turn them into hydrogen peroxide. However, there are a lot of things that can go wrong here. Again, peroxynitrite. Peroxynitrite will do what's called the nitration of tyrosine. That can shut this down by almost 97%. Ouch. SIRT1 (sirtuins), there's a

mutation here. This one's the strongest. SIRT1 helps SOD2 do its job. F12 will help it do its job, but there are mutations on there that will inhibit it. There's also an amino acid called lysine. Interestingly, it normally has a positive charge. It will bring that negative electron in and say: Hey, Mr. Electron, come on inside here; I want to introduce you to Mr. Manganese, who's just going to help you out here a little bit. However, there's something called acetylation from acetyl-CoA that will take that negative charge off. SIRT3 (sirtuin 3) deacetylates lysine.

Bob Miller 01:15:40
If you had a little trouble following that, I get it. That's a lot of steps there. Lysine has a positive charge. This puts it back to negative. This puts it back to positive, and it's driven by NAD. And there's a whole bunch of genetic things that can go on here that make you not have enough NAD. And then there's an interleukin called interleukin 13 that the mutations can inhibit. The cysteine—this is what we talked about earlier—can be impaired by the nitrosylation. And then manganese can be impaired by glyphosate. There are what are called solute carriers that carry it in.

Bob Miller 01:16:24
You can see here that there is a lot that can go wrong if this guy's not working at 100%. And that's what we're doing now with our software, trying to figure out: Are they making too much peroxynitrite? Are there mutations on SIRT1 or F12? Is SIRT3 weak? And what you generally find is that when someone makes more superoxide and they're impaired, they're in trouble. They just can't seem to find out what to do.

Bob Miller 01:16:58
Here is just an example of this nitration of tyrosine from peroxynitrite. Here's that ONOO. That's your peroxynitrite. It's called nitration. It nitrates one of the tyrosine residues that can shut down that manganese SOD considerably. We need SIRT3 to help deacetylate that tyrosine. That's why SIRT3 is so important in helping that out. But also we have to slow down the peroxynitrite production.

Bob Miller 01:17:35
Here's the F12. Many people haven't heard of F12. Our genetic researcher found this one. This SNP has been strongly associated with altered SOD concentrations. Specifically, the A allele was associated with decreased mitochondrial SOD concentrations during a study of European ancestry. And the G allele was strongly

associated with increased SOD concentration. And here you can see [that with] this individual, both parents gave a mutation—8.7% of the population. One of these probably doesn't matter, but when they pile up on you, that's when it becomes a problem.

Bob Miller 01:18:17
Here I talked about the SIRT3. Clinical studies have shown that SIRT3 expression declines by 40% by age 65—I hate when that happens—paralleling the increased incidence of hypertension and metabolic conditions that further inactivate SIRT3 due to increased acetyl-CoA levels. And that's one of the areas we want to look at: Are there environmental or genetic factors that could create increased acetyl-CoA? Don't know yet. But SIRT3 impairment reduces the activity of superoxide dismutase 2, due to hyperacetylation. Interestingly, magnolia bark, milk thistle, NAD, and baicalin, or skullcap, support SIRT3.

Bob Miller 01:19:03
This is the genome of a little girl who's very autistic. I'm not saying this is the cause. It could be a contributing factor. You can see that she got it from both parents. It only occurs in 4.9% of the population. And you can see a little bit better. Acetyl-CoA comes down here, takes that positive charge off, and doesn't allow the electron to come in. SIRT3 comes to the rescue. But you can have this one here that ends in 20; that's a pathological downregulation. We've got to also figure out not only how we support SIRT3 but [also] how to slow down acetylation. We don't know yet. That's an area of research.

Bob Miller 01:19:56
I believe you just had Dr. Christy Sutton on recently talking about iron. A delightful young lady, by the way. She really knows her stuff on iron. What can happen is that we need that manganese in there to do the job. If we're manganese-sufficient, we're going to have that inoxidant capacity. But if we're manganese-deficient and iron-enriched, the iron goes into SOD2 instead and becomes pro-oxidant.

Dr. Jill 01:20:31
Bob, I just want to pause there really quick. We've talked about this in almost every session because the iron is such a yin and yang. We need it. We need it to make energy. But once again, just like excessive calcium, excessive manganese, and

excessive selenium, for the wrong person, iron can be incredibly... I always tell them it's like a car that's getting rusted. That's your iron getting oxidized. And if you have too much in the wrong location, like intracellularly without the right cofactors... We could do another two hours on this. But I just want to emphasize for those of you listening that a lot of the old medical school training was "Give all women iron" or this or that. And it's just not one-size-fits-all. If you're taking iron, you better be sure that you need it and that you're not creating rust on the inside, which is a metaphor for oxidative stress.

Bob Miller 01:21:19
Absolutely. I don't remember where I heard this, but unless you have bleeding or some other problem, one chicken leg a week may give you all the iron that you need.

Dr. Jill 01:21:28
I couldn't agree more. Clinically, I do not give a lot of people iron unless I'm certain that they're anemic or need it.

Bob Miller 01:21:34
Absolutely. But even with anemia, if the Fenton reaction is going on, it can be that the iron is just creating oxidative stress and not building the red blood cells. It's really tricky.

Bob Miller 01:21:46
This is the same chart, but you'll notice iron is in here rather than manganese. Guess what happens to your superoxide? Nothing. It just sits there and wreaks havoc. And you've already learned now what that does.

Bob Miller 01:22:07
B12. Interestingly, I wasn't aware of this until we started digging into it. We all know the benefits of B12, but B12 will take superoxide and turn it into hydrogen peroxide. And there's a lot that can go wrong. Here are your sources of B12 over here. There's an enzyme called TCN1 that gets it into the body. Then intrinsic factor gets it into the blood. And sometimes when you have mutations here, particularly on this TCN2, blood levels are high but tissue levels are low.

Dr. Jill 01:22:44
Oh, yes. Bob, I wanted to talk about this because I talk about this all the time. And now that I have a PA nurse practitioner in the clinic, I was teaching them recently. So many doctors get a B12 level for their patients. That's lovely. It's a serum B12 that's on Quest, Labcorp, or any hospital lab. Many times, as soon as we start supplementing, that serum level will go greater than 1,000, so it's very, very high. The reaction I most frequently see from other practitioners telling my patients [is]: "Oh, stop the B12. It's really, really high in the serum." And my thought is, yes, in some patients, it's too much, but most of the patients are not getting it intracellularly for one of these reasons. That sometimes can be a sign of them needing more or needing a transport.

Dr. Jill 01:23:26
And I think we talked one time about lithium as a cofactor. A very simplified version can open the doors. And there are other factors here. But I love that you're mentioning that because for those people listening who don't know, or maybe you're a physician out there who's telling people to stop B12, you really need to know what's going on because a high serum level could actually mean even more of an intracellular gradient.

Bob Miller 01:23:47
Absolutely brilliant. Yes. That's why we formulated a product of the three B12s, lithium, and folic acid.

Dr. Jill 01:23:53
Brilliant! I love it. I love it.

Bob Miller 01:23:56
To drive it in.

The nitric oxide and paraoxinase. PON1 in plasma decisively favors the activity of eNOS and therefore the production of nitric oxide, vasodilators, and platelet aggregates. You need to look at your PON1 enzyme as well.

Bob Miller 01:24:19

We're going to take some practical lifestyle steps, then, Dr. Jill, we're going to take a peek at you and see what's going on with your iron-sulfur clusters. Obvious: Avoid mold. Remediate if exposed. I'm sure you have a couple of comments on that.

Dr. Jill 01:24:37
Yes. Gosh, if you guys haven't got my free mold guide, you can download it. I'll be sure to put the link in the show notes. But the basics there are that you cannot get well if you are sensitive and in a moldy environment. That is a great step one.

Bob Miller 01:24:53
And then clean air. Consider purifiers. In my office, I have three of them. I have an IQAir, a Molekule, and a Dyson because we have to really keep the air clean. Organic food as much as possible. I know some people have trouble with the cost, but as much as possible, [buy] organic food. Avoid microplastics and fragrance as much as possible. When you get those water bottles that are flimsy plastic, during the summer, can you imagine if they're in a tractor-trailer and it gets 120 degrees or higher in there, what that plastic must be doing? It just must be pouring right in.

Bob Miller 01:25:29
Potential nutrient support. Pine bark or pycnogenol may reduce peroxynitrite. Black cumin seed oil may slow TNF-α if overactive. Hops can support the HMOX function. Catalase and glutathione reduce the hydrogen peroxide.

Bob Miller 01:25:45
SOD—I want to talk about this. Somebody might be watching this and say, "It sounds like I need SOD," so they'll go on the internet and buy some SOD. They'll feel good for a day or two, and then it's like, "What the heck just happened to me?" The reason you've got to be careful is because—it sounds backward—it works. What it does is make hydrogen peroxide, and if you don't have enough catalase or glutathione to reduce it, SOD is going to make you worse. What I do clinically sometimes is I'll give people catalase and glutathione for 10 days and then say, "Take one SOD tablet one day a week." And that works. But if you just pour in SOD, it can backfire on you terribly. I know there are some companies out there that make just SOD only. It probably works for some people, but it can backfire quickly.

Bob Miller 01:26:44

Nitrates may support healthy nitric oxide production. Do you have any thoughts on that?—because I know that's an area that you speak about quite a bit.

Dr. Jill 01:26:50
Yes. Once again, if you're super inflamed or are someone like me with these mutations, you have to be careful with that as well. But many people do benefit. I always say food is usually a great source. You almost can't go wrong by eating your leafy greens, and that's a great way to start if you're concerned about issues.

Bob Miller 01:27:10
Lycopene and riboflavin may help recycle glutathione. This is the list: Selenium, vitamin E, rosemary, fisetin, luteolin, quercetin, naringenin, indole-3-carbinol, and tart cherry juice—they may slow down that aryl hydrocarbon receptor. Taurine, magnesium, zinc, and cat's claw may slow the NMDA receptor. IP6—that's a form of inositol—may reduce inflammation from intracellular iron. And manganese at the right dose—not too much—can support your SOD.

Bob Miller 01:27:43
We'll look at this, then we'll go to your genome. Have your health professional check your homocysteine. Keep it in a normal range. Work with health professionals to check for mycotoxins or glyphosate. Monitor iron levels and take needed steps to balance. Check B12 and keep it in a normal range. Or, as Dr. Jill just very brilliantly said, sometimes needs are a little higher. Measure your functional genomics to see where there may be genomic weakness and apply targeted nutritional support.

Bob Miller 01:28:22
Before we go to look at Dr. Jill, I just want to mention that for the practitioners, we have our own genetic test called Functional Genomic Analysis. We have our own genetic sample. And then we have nutrition that works. If you're a practitioner—please, not consumers—you may want to check this out if you'd like to add this to your practice. We have an online certification course that teaches you. And if someone wants to contact our office, I've gotten so busy that it's hard to take on new people, but I'm very fortunate that I brought on Dr. Megan Ross. She's a naturopathic medical doctor who's doing consultations. There's our website and phone number. And there's the website for the practitioners. Yvonne Lucchese is support.

Bob Miller 01:29:10
Now let's look at you, Dr. Jill. If you go back and watch our program on iNOS, you'll see we went over that. So I'm going to breeze through this very quickly and then get into the new stuff. If you remember, Dr. Jill, you have the gene that you could overabsorb iron a little bit.

Dr. Jill 01:29:31
Yes, one copy of the hemochromatosis. The main one, right?

Bob Miller 01:29:34
Yes.

Then you have the SLC40A1 ferroportin that can bring a little more iron in. Fortunately, you don't have the upregulation of tumor necrosis factor. Your NF-κB could be a little trigger happy. Another NF-κB could be a little trigger happy. Fortunately, your SIRT1 is okay. But your HMOX is a little weak. And what's your saving grace here—I don't see this very often—[is that] your Nrf2 is perfect and your KEAP1 is perfect. You don't see that very often at all. Your HMOX may not have held things back very well. Then you may have a little bit of mast cells that are just a little trigger happy.

Dr. Jill 01:30:25
I do.

Bob Miller 01:30:27
Then your histamine, you may not make enough DAO. You have a homozygous—meaning from both parents—on the enzyme that can make more histamine. And then you have the MAOA and MAOB that can clear histamine.

Bob Miller 01:30:45
On our show where we spoke about the... If you look very carefully there, it says, 'Carnahan Reaction'. I have it right there in the software. You've got that named after you, Dr. Jill.

Dr. Jill 01:30:57

Honored.

Bob Miller 01:31:00
Yes.

You'll see here that there are two mutations on NOS2 that are considered gain of function and mom and dad giving mutation. This guy's trigger happy. The least little bit will cause them to go a little more active. That can suppress the NOS3. Fortunately, you don't have a lot on NOS3, but that NOS2 is going to suppress it. We don't know how much—genetics is a predisposition, not a diagnosis—but [there's] a good chance you're making a little bit of superoxide combining with the nitric oxide to make the peroxynitrite. You need thioredoxin to clear the peroxynitrite. One little mutation there.

Bob Miller 01:31:48
The good news here is that glutathione peroxidase 1, KEAP1, and Nrf2 [are] perfect. We very rarely see that good. Though we have some things that weren't so good, on the other hand, it's stellar right here. We don't see that very often.
Then you're making the peroxynitrite. And here's that chart we just showed you, but now this is actually in the software.

Dr. Jill 01:32:12
Amazing.

Bob Miller 01:32:13
Yes.

You can see here that there's that peroxynitrite possibly impacting the tyrosine. You are heterozygous on SOD2, so the SOD2 may not be as strong as it should be.

Dr. Jill 01:32:27
Quick question, Bob. Tyrosine in some patients—I more think about excessive production of neuroepinephrine, epinephrine, or neurotransmitters. It can cause some anxiety in people. Is there any correlation here with tyrosine driving or depleting that? Could you clinically give too much tyrosine or too little to someone? Is that a factor here?

Bob Miller 01:32:49
That's an excellent question. I'll have to take that back to my research team because what happens is the residues get changed on tyrosine. Does that mean that it's more susceptible or less susceptible to doing that? That's a good question. Next time, we'll talk about that.

Dr. Jill 01:33:07
Perfect. It sounds good.

Bob Miller 01:33:10
F12—you're perfect. SIRT1—you're perfect. Here's your lysine. You only have one little ding on one of them. You don't have the pathological one, so not too bad there. You're interleukin 13, just one. The bottom line is your ability for SOD2 is not perfect, but it's not bad. It's okay.

Dr. Jill 01:33:35
I want to just mention something you mentioned earlier that I think is so important because this is back—people going online and maybe self-medicate. Years and years ago—I'm sure when I was inflamed and depleted in glutathione—I took SOD and it did not go well. I want to emphasize that you said that because I think there are a lot of people who go out and try to fix themselves, which is wonderful. By all means, try to do things safely. But it often backfires. I really appreciate that you mentioned that because I remember the day I took SOD and it wasn't very good.

Bob Miller 01:34:07
Yes. What reaction did you have?

Dr. Jill 01:34:09
Gosh, it's been a long time ago. This was probably 20 years ago in the very beginning, maybe with Crohn's or whatever. I think it was just either fatigue or more inflammation or pain. I don't remember exactly, but I haven't tried it since.

Bob Miller 01:34:21
Yes.

More than likely, it worked and made hydrogen peroxide.

Dr. Jill 01:34:25
Yes, that would make sense.

Bob Miller 01:34:28
Now, here's your electron transport chain. Again, [as] we spoke about in the beginning of the podcast, there's this electron transport chain where your electrons are going to bebopping down through here and they make ATP. However, we spoke earlier about that we need the sulfur-iron complex, and NFU1 puts it together. And look what you've got there: Two, two, two. We tell people that when we find these things, we have solutions for it. We're working on this; we don't have it yet. This is what we're working on right now.

Bob Miller 01:35:10
Dr. Harold Landis is going to be doing a webinar in two weeks from Thursday. His assignment is: Let's learn about this guy and what to do about it. We don't know what amino acids it's made from. We don't know what breaks it down or what stimulates it. But in my mind, I see this guy as critical.

Dr. Jill 01:35:35
Oh boy, it makes so much sense.

Now, Bob, I'm going to throw something out there. You may have the answer now or maybe in our next webinar. First of all, long COVID, post-COVID, Lyme, infections, toxins—all the things we've been talking about—can affect the mitochondria for many of the reasons you've explained. Mitochondria produces ATP, as you've explained so well, and is energy-dependent. Many, many people at the root of their dysfunction have some sort of mitochondrial issue, which can come in many forms. But the research on methylene blue—I'm really curious to see what you heard or how much you know about where that fits in, because it's a redox. It decreases the oxidative stress in mitochondria, which is exactly what we're talking about. And I have seen it over and over again—in some of these really tough cases, including in myself—be a big shifter of energy and be something that dampens that oxidative stress. Have you guys done any research on methylene blue or thought about that?

Bob Miller 01:36:31
Not particularly, but it does seem to calm down some of that excess nitric oxide. We were wondering if that's part of it as well. That might be.

Dr. Jill 96:41
That would make sense. I've been wondering too, I'm like, "I think there's more to it than they know." And as you and I dive deeper, I think we'll find that would make sense if it dampened some of the excesses. Are you thinking [about] the peroxynitrite production?

Bob Miller 01:36:57
Well, no. The S-nitrosylation. That's going to be at the bottom of the chart here. I'll show you that when we get down there.

Dr. Jill 01:33:35
Perfect.

Bob Miller 01:37:05
Remember I talked to you about the FXN? It's what takes the iron and brings it in. And look what happened.

Dr. Jill 01:37:11
Oh boy.

Bob Miller 01:37:13
If we look at a bell curve here, you can see you're at the end of the bell curve.

Dr. Jill 01:37:18
Interesting. Now tell me practically again, is that getting excessive iron? I already have the hemocromatosis mutation, so I'm going to accumulate more iron. And this is keeping it intracellularly?

Bob Miller 01:37:29
Yes. In other words, it's going to keep it intracellularly. I can find the slide. Maybe I'll pull that in. Let me see if I can pull the slide in just for that. I know I have it here. It's not too far down my list. And there it is. Let me pull this slide over here.

Dr. Jill 01:37:56
As you're pulling up, I'll tell you a little clinical scenario. Years and years ago, I had Crohn's, which is completely in remission and gone now. But with Crohn's, you can have some malabsorption and nutrient depletion. I would show up as anemic because of that, which is interesting because I have always genetically had this hemocromatosis variant and probably accumulated intracellular iron at a higher level. I'm just saying that because if you're a clinician or you're a patient, you could actually be iron-excessive or iron-toxic and have iron creating the rust inside your cells and look anemic. That's a difficult thing because when it gets really low, you still need iron to survive. Any thoughts on that process of how someone could have hemocromatosis—one mutation or two or more—and have this issue with iron overload and also be anemic or borderline?

Bob Miller 01:38:48
Absolutely. If you look at the chart that we have up here now, you'll see that when you've got this mutation in FXN, the iron doesn't go over here to make the iron-sulfur complex; it goes inside the cell and makes oxidative stress and mitochondrial impairment. But then also, if you have the hydrogen peroxide that's not cleared, that will... Let's see if we have anything real quick here on that. If we don't clear the hydrogen peroxide by catalase, glutathione, and thioredoxin, here comes your iron and makes [inaudible] as well. You can overabsorb the iron, go through these processes, and be anemic. Some people just can't get their heads around that. "I can't be overabsorbing iron, because I'm anemic." It sounds like an oxymoron, but it can.

Dr. Jill 01:39:39
I love that you said that. You're consulting genetics on people. Do you see a lot of people who are insistent on [how] they need their iron and you're looking at their chart and saying, "No, please don't take that?"

Bob Miller 01:39:51
Yes.

Some rather sad cases as well where their nephrologist says, "I don't care what genetics they have; they're low in iron, and I don't want to hear anything about it" while their kidneys are being destroyed. Anyway, for you, I don't think this is a big deal, but with these FXNs here, there's the possibility that the iron is not getting up

here. And then if it does get up here, you're having a hard time making that iron-sulfur cluster, potentially. Again, genetics is just a predisposition.

Bob Miller 01:40:27
Here's your cysteine. We spoke about the cysteine. If you get this nitric oxide that's aberrant—again, let's go back to the nitric oxide—it can combine with oxygen to make superoxide. As you can see, we're just filling this in at this point. There's nothing in these guys. But this is the cGMP where you make the nitric oxide.

Bob Miller 01:40:57
And then we want to dig into the PDE5, because what Viagra and Cialis do is shut that down. The question we're exploring is: What environmentally or genetically might stimulate the PDE5? I don't know if they'll find anything, but that would be fascinating to look at. What we've got to do is get the nitric oxide to come down this pathway, not this pathway, and not the aberrant nitric oxide.

Bob Miller 01:41:25
You can see here that if your cysteine gets nitrosylated, you've got a little weakness on the thioredoxin enzyme. See the twos here? It would take it from the nitrosylated back. And then, if you go this way, you've got the ADH5 also mutated—there's one here that's evidence-based—that you're not going to go down and recycle. Much more to learn here.

Bob Miller 01:41:56
And then, if you're exposed to mold or a virus, we stimulate the NMDA. It stimulates the excess calcium. It stimulates your NOS1, 2, and 3, which is then going to potentially make excess nitric oxide. And then some of it may become aberrant and affect your thiols, which is then going to affect your production of glutathione.

Dr. Jill 01:42:28
Fascinating, Bob! As always, you put the puzzle together, and you keep working tirelessly to bring us as clinicians great information. If you're watching and you're a clinician, go back, rewind, and make sure to get Bob's information. If you want to learn more, this is a really, really great educational program that helps you fine-tune those complex chronic patients that we all see. And I find these are the kind of things that are one in a million or one in a thousand or those unique

characteristics that do move the needle. And as we do personalized precision medicine, we need to find these details to really help the patients. I'm saying that to say thank you for your brilliant work and for all that you've done in the many episodes before and even today! I always learn something new.

Bob Miller 01:43:18
Yes. It's a lot of fun, and there's much, much more to learn.

Again, if anyone wants to contact us, there's Tree of Life—clinicians only, please. There's the software that they can use. As you can tell, the software is not for the faint of heart. This isn't a printout of "Do this." It's for the serious clinician who's willing to do some homework.

Dr. Jill 01:43:45
It's amazing. And Bob, once again, just publicly, I am so grateful for your work in this field and for the times that you come on and talk with me about this stuff. It is so much fun. As always, today has been another great episode and I know people will benefit. And thank you for the tireless work that you put out there. We all appreciate you.

Bob Miller 01:44:03
Absolutely. And as soon as we know what to do for FXN or the iron-sulfur clusters, you will be the first to know.

Dr. Jill 01:44:10
Next episode. So stay tuned, everyone! Thanks again, Bob.

Bob Miller 01:44:14
It's been a lot of fun.

Dr. Jill 01:44:16
Yes.