Dr. Jill

Your Functional Medicine Expert®
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#82: Dr. Jill interviews Bob Miller on The Carnahan Reaction and iNOS

Dr. Jill 00:15
Hey, everybody! We're live today. I know some of you have been waiting for this interview since the last little snippet we did last month. I am so excited to be here again with my good friend Bob Miller. We always have so much fun diving into pathways and trying to figure things out. This pathway in particular has a lot of personal relevance, as you can see from the title, 'The Carnahan Reaction'.

Dr. Jill 00:39
We're going to talk all about how that's affected me personally, how I've had some massive insights and breakthroughs by understanding this pathway in my own personal health, and how Bob and I have already probably worked together on almost half a dozen patients by conversing and finding this pathway. It's actually more common than we thought. Bob will dive in and tell you all the fun and fascinating information that he's been working on.

Dr. Jill 01:03
Before we do that, just a little background: You can find all of my blogs, literally 10+ years of content, at JillCarnahan.com. It's all free. If you want to know more about mold, environmental toxicity, benzene, Lyme and co-infections, or any sort of topic, it's all there. If you want any products, you can find them at DrJillHealth.com. If we ever mention any of those, you can find them there. And then, of course, the YouTube channel is Jill Carnahan, MD. You can find all of these interviews if you missed any of them live video. And for Bob and me, it's probably our half-a-dozen mark here. I think we're on number six. There's lots of great content there. You can also find me anywhere you listen to podcasts—YouTube or Stitcher—and you can listen there in your car or if you're walking if it's easier.

Dr. Jill 01:50
That's the background. I told Bob today that I wanted to get right in. I don't want to waste a lot of time. If you want to listen to my other interviews with Bob, you can get a formal introduction. He's a genius at putting together pathways. He does a lot of work in our field with teaching practitioners. And we're going to talk about the

certification course at the end. If you want to know more, you can join him. We'll give you links. We'll give you all that information. But without further ado, Bob, let's jump right into the 'Carnahan reaction.'

Bob Miller 02:19
Absolutely. I've been looking forward to this for a long time. I think a lot of people are going to have quite a few aha moments as we go through this today. I'm going to do a screen share here. I think we're seeing the screen, correct?

Dr. Jill 02:34
Yes, perfect. It looks great.

Bob Miller 02:37
As the title says, 'The Carnahan reaction.' And of course, this is not giving medical advice. This is educational and informational only. We're going to be talking about nitric oxide, BH4, and superoxide, and then how that can get out of balance and be caused by environmental and genetic factors that cause it to go wrong. What we're going to look at here is brief: What eNOS is and what iNOS is. What could be the potentially negative consequences of excess iNOS, environmental stimulators, or something called NOS uncoupling? And why is that so dangerous? And we're going to have a little more emphasis today on BH4, tetrahydrobiopterin, and the consequences of inadequate BH4. Maybe we'll touch on high-fructose corn syrup and aspartame. And then what we're talking about today is the 'Carnahan reaction'.

Bob Miller 03:32
At the very end, we're going to tell you about how health professionals can take our certification course and we'll have a Dr. Jill coupon code that'll save you $100. I want to thank a couple of people—Matthew, Beth, Mariam, and Mackay Rippey—who have contributed to this work. These are folks who have helped with the research.

Bob Miller 03:53
We're going to very quickly go through nitric oxide. Because we talked about this in our other video, we're going to burn through this pretty quickly. It's a very simple molecule. It's one atom of nitrogen and one atom of oxygen. But it's now regarded as one of the most significant molecules in the body. It's absolutely crucial to your well-being. Here's what it does: It acts as a vasodilator, causing the blood vessels to

expand. It stimulates the brain, helps men with erectile function and impotence, increases energy, supports wound healing, and supports the immune system. It's a signaling molecule present in the cardiovascular and nervous systems. It's an incredibly important molecule. The Nobel Prize, 1998, was given to three gentlemen for their research as it relates to cardiovascular health.

Bob Miller 04:44
I'm not going to read this because there are too many here and we're short on time. But what we might be able to do, Dr. Jill, is [provide] a PDF of these slides and link them. For people who really want to look at these carefully, they can. We can give you a link for that.

Dr. Jill 04:57
I love that. Everyone stay tuned, because wherever you're listening to this, I will be sure to include a special link where you can download these slides.

Bob Miller 05:06
Now let's look at how nitric oxide is made. I'm going to slide over another little map here. Don't panic; this isn't as bad as it looks. There's a substance called BH4 that's right here in the middle that combines with oxygen, something called NADPH, and an amino acid called arginine to make nitric oxide. It's all accomplished by the NOS3 enzyme or endothelial nitric oxide. On the other hand, when we are faced with a pathogen—a bacteria, virus, fungus, or parasite—iNOS kicks in and says: We've got a problem here. It's the same procedure, but it makes more of it to kill the pathogen. The problem arises when this gets carried away. We get tissue damage or organ dysfunction.

Bob Miller 06:01
And we're going to go through these, so I won't read them now. But over here are the environmental factors and these last two internal factors that will stimulate. Also of note, many people are dealing with mold. And we'll talk about your experience a little bit later. Clostridium, mold, and Bartonella are sources of lipopolysaccharides that stimulate NADPH oxidase, mast cells, and histamine in the iNOS enzyme. I'm speculating, but I think the reason this mutation probably got popular is because there was probably somewhere in time that there might have been a virus, fungus, or parasites and this was actually helpful. However, now what's

happening to us is that we have all these environmental factors stimulating it, then something else comes along and it gets carried away.

Bob Miller 06:54
If anybody saw our video before, we focused on the iNOS upregulation. We've been doing a lot of research and everything we said is true. We're going to put a little more focus on BH4 depletion because what happens is that if we use up this BH4, we're running off of BH2. And if we're running off BH2, we make superoxide—a nasty, nasty free radical—and then that makes something called peroxynitrite that may further inhibit the BH4. And we're on one little merry-go-round here.

Bob Miller 07:34
This one is new. We didn't have this last time. We've mapped out the whole pathway of how we make BH4, how it's dependent upon something called guanosine triphosphate from the Krebs cycle, and then how we need folate. And genetic mutations here could impact it as well. We'll get into that as we move along, but that's the big picture.

Bob Miller 07:56
As we said: BH4, oxygen, arginine, heme, and NADPH. And specifically for the nitric oxide that helps circulation, NOS3. Interestingly, there's one RS number; here it is, 3918226. 'Wild' means it's the one that's the most useful, and T means the 'risk' that it's less useful. Mutations on the T, either heterozygous or homozygous, will cause less than optimal nitric oxide production. If somebody has a 23andMe or they do the Functional Genomics [test], they can look at this. If they have one or two Ts, they may have less nitric oxide production—the endothelial nitric oxide.

Dr. Jill 08:41
Interesting. Bob, just to clarify, you're going to go into this in detail, but most of the mutations that we're going to talk about increase production. Is this the unique one that actually decreases it? Is that why you're bringing it to our attention?

Bob Miller 08:53
Yes. This is the one that's the NOS3 versus the NOS2. NOS3 is the one that helps us have circulation. NOS2 is the one we're concerned about being upregulated.

Dr. Jill 09:03
Okay. Just to clarify, because I think the listener will understand too, on the circulatory bit, this will lower nitric oxide, which could be a disadvantage because we need that vasodilation in the circulatory system. But in NOS2, a lot of the mutations are upregulated, which causes the reactive oxygen and all of those things that you just talked about.

Bob Miller 09:23
Absolutely. I'm going to make this very short because there are people who are a lot more qualified to speak on this than I am, and perhaps that'd be an interesting guess for you sometime. But I just want to mention that this is the pathway we're talking about with nitric oxide. There's another one called the nitrate pathway. And the L-arginine pathway is pH-dependent and oxygen-dependent. This one isn't. Interestingly, arugula is one of the highest sources of nitrates. What happens is that when we get nitrates, they'll turn into nitrites and nitric oxide. So there is a plan B here. Also, spinach, celery, butter lettuce, bok choy, beets, and kale. What we have to have are bacteria on the tongue that provide the nitrate reductases. That's why sometimes using mouthwashes and fluoride toothpaste, whitening, could degrade this. Antibiotics and antifungals could also decrease it.

Bob Miller 10:22
This is an additional pathway that could bring the good nitric oxide in. And what's interesting, and I just learned this from Beth Shirley: Nitrites and nitrates recouple the NOS—we'll talk about that later—and inhibit these enzymes (we don't have to read them, it gets complicated, they're inflammatory), support antioxidants, SOD, catalyst, SIRT1 and this GTP, which is at the beginning of the phase to make BH4 and an enzyme called heme oxygenase that helps us break down heme properly. Some food choices there could be a big part of it.

Bob Miller 11:06
Here's what we really want to get into today: iNOS. Remember, I said iNOS is what comes to your rescue to kill pathogens.

Dr. Jill 11:14
Bob, if I could give a really quick comment on the diet, because practically speaking, this is one of the reasons why leafy greens are such a core part of a healthy diet, no

matter what you're doing—paleo, keto, vegan, or anywhere in between. I always say a plant-based diet is still the best, no matter who you are or what you're doing. And you can do that with keto. It just means that plants, primarily, are still such a powerful source of nutrition. And this is just one more reason why leafy greens, in particular, are powerhouses. And if you don't have leafy greens in your diet, you're missing out. It's so crucial. I think if I had to pick one element of a healthy diet—of course, there's never one—leafy greens are right up there at the top.

Bob Miller 11:54
Absolutely. Let's get into iNOS here. As we said, iNOS is crucial for our immune defense, so iNOS generates a very high amount of nitric oxide to fight bacteria, viruses, and fungal [infections]. NOS3 is the one that makes little puffs of it to dilate your blood vessels. When we get total elimination of it, it increases the susceptibility to various infections. On the other hand, excessive [iNOS] has been associated with many health concerns. As you've said, Dr. Jill, we've spoken many times, and we keep coming back to Goldilocks and the Three Bears—not too much, not too little. And that balance—not too little, not too much—is so critical for almost no matter what we're talking about. If there's not enough iNOS, we don't kill pathogens. If there's too much, we can cause damage.

Dr. Jill 12:46
It is. And if you're listening out there, methylation has been a hot topic for several years now. And you and I, Bob, have talked all the time about how everybody is like, "Oh, methylation—let's do this" or "NAD—let's do this." So people go crazy with NAD precursors, methylated folate, or methylated B12. But if you are in a process and you're really toxic or your genetics are not ready for that load, a lot of times these things make people worse. And this is one of the reasons why—it's that happy medium.

Dr. Jill 13:14
I was diagnosed with breast cancer. After that, I realized I was deficient in methylated Bs. I went pretty crazy on getting methylated folate and methylated B12. I did horrendously because my body was not ready for that. So I love that. I wanted to reiterate to those of you who are listening that if you're getting excited about methylated Bs or you have MTHFR, you have an NADPH deficiency and you're getting NAD, too much of some of these things is not a good thing.

Bob Miller 13:39
Absolutely. One of my favorite sayings is that when the house is burning down, you don't paint the walls and mow the lawn. We have to put out the fire. As I said, this is mostly a literature review. People will notice that we're just bringing up peer-reviewed literature. This isn't just somebody's opinion. Excess production of nitric oxide appears to be linked to tissue damage and organ dysfunction, even when we get something like septic shock.

Bob Miller 14:10
Here's another one as it relates to the autoimmune thyroid. The enhanced expression of iNOS in autoimmune thyroiditis suggests that nitric oxide synthase plays an important role in the inflammatory phenomena observed in this disease. Alzheimer's—what a serious problem that's becoming. Here's a peer-reviewed study: iNOS seems to be a major instigator of beta-amyloid deposition in disease progression. Their conclusion: Inhibition of iNOS may be a therapeutic option in Alzheimer's disease. Clearly, we have to do more research into this.

Bob Miller 14:46
As we talked about, when you've got too much superoxide that's made, it combines with nitric oxide to make peroxynitrite. We're going to talk about that a little bit because more research is now showing peroxynitrite may not be as bad as we thought, but you'll still see differing opinions on this. But in this article, [it mentions that] cellular generation of peroxynitrite may contribute to carcinogenesis and tumor progression by weakening key cellular defense enzymes such as N-acetyltransferase 1.

Dr. Jill 15:20
Bob, I just want to comment because 20 years ago, at 25 years old, I had breast cancer. And part of my journey in helping patients has been [about figuring out] "Why did this happen at 25 to me?" I think of many, many, many things. One of them is poor detox, glutathione transferases, and pesticide exposure as a farm girl being raised in that environment. In this NOS, which we'll talk about, I've got some really specific deficiencies in the genetics there. And I think that was part of the factor—this reactive oxygen. And I've got a lot of issues with the absorption and methylation of B12. So it's all of these things together. And there's more, but those

are just a few of the pearls with the genetics that now allow me to understand things like: Why would someone like me who was living a healthy lifestyle get cancer at 25 years old?

Bob Miller 16:04
Absolutely. We have part of the answer in what we're talking about. Here's an article: Inhibiting iNOS improves triple-negative breast cancer. The relationship in gastric cancer: The expression of iNOS and VEGF are closely related to tumor angiogenesis and are involved in the advancement and the lymph node metastasis. Here we're talking about colon cancer: iNOS expression and tyrosine nitration may be an indicator of cancer development and progression in colitis and colon cancer. And part of your story was Crohn's disease, I believe, as well.

Dr. Jill 16:40
Yes, exactly. It makes a lot of sense now.

Bob Miller 16:43
Yes. High levels of iNOS expression in ovarian tumors are associated with a greater risk of disease, relapse, and patient death.

Dr. Jill 16:51
Real quick thought as you're going. I love these thoughts that just pop up. You talked about LPS earlier. LPS is the coating of bacteria. We talked a lot about the gut microbiome and this leakage of the coating of the bacteria into the immune system through a permeable gut. It's a massive trigger for autoimmunity, obesity, heart disease, cancer, and even mood and sleep disorders. So back to my story, the chemotherapy caused massive permeability, and LPS from the gut was one of those triggers that caused the Crohn's disease. Then we look back at this iNOS and LPS being a trigger there. In my personal story, that LPS had a big role, I think.

Bob Miller 17:28
Absolutely. Yes. Here is information on iNOS and osteoarthritis. People can look at the slides if they want to read all of the details. If you're joining us late, we are going to put a link to the slides so that you can get them as a PDF.

Bob Miller 17:48

Here is for the respiratory and vascular systems. What we're going to be talking about here is COVID. Of course, we're not saying there's any cure that we're providing here or a cure, but it's interesting what they're saying here. And this is a peer-reviewed study—it showed up in PubMed, a medical journal—on nitric oxide. "Implications of COVID on eNOS and iNOS activity: Consequences for the respiratory and vascular systems". Look at this slide. When COVID hits you hard and the antiviral effects come in, that can be a consequence of severe lung inflammation as it suppresses the eNOS—the blood clots. We're not saying this is a cure or prevention, but it may explain why some people are more impacted by COVID—because the iNOS is getting upregulated by the virus going too far, causing blood clots.

Bob Miller 18:44
It's interesting. We've been talking about all of this, and here's an article that says that data is accumulating on a protective effect of high-output nitric oxide synthesis and a protective stress response that simultaneously aids in downregulating the pro-inflammatory response. So it's like: "Uh-oh, Bob. You just made an argument that the iNOS is the problem. Now you're saying that it may not be." And of course, this information came from some of the researchers who were talking to me and saying that this is being re-evaluated. So I'm not taking a position on it, but the question is, who is the real villain?

Bob Miller 19:24
Everything we've said so far is correct. The upregulation of iNOS is a problem, so we're not saying it's not the problem. But here's the scientific debate: Is the inflammation from the nitric oxide, the superoxide created with the nitric oxide, or—we'll talk a little later about [it]—NOS uncoupling? It almost just becomes a scientific argument, not something that we need to be concerned about as much. But all of this that we've talked about might be the superoxide rather than the nitric oxide. This will probably be hotly debated for years. Beth surely gave me this quote: "When you see firemen at a fire, are they the cause of the fire?"

Dr. Jill 20:05
It's an association versus causation, Bob. We know this in research. I love that you're bringing this up. As you look at that list that you showed earlier, I'm sure we're going to dive into causes. Usually, someone like me or our patients have other

reasons why they're having massive inflammation. And it's actually our body's protective mechanism, but it goes too far.

Bob Miller 20:28
Absolutely. Maybe someday this will be something they're talking about at all the conferences. Clearly, the iNOS is elevated. No one's debating that. The question is, is it the iNOS making the superoxide or the nitric oxide? Stay tuned. But again, from what we're talking about, it doesn't matter much because it's causing damage.

Bob Miller 20:50
There's a saying that's been around for a long time: "Genetics loads the gun, the environment pulls the trigger." Here's your free radicals. Let's look at a couple of them: Aluminum, mercury, uranium, and plastics. Someday we may have to do a subject just on plastics.

Dr. Jill 21:08
I think we do. I do these tests—urinary analysis of metabolites from a couple of different labs—and I would say almost always, phthalates and BPA come up for most patients. And even for patients like myself who are using really clean beauty products, they are ubiquitous. It's really hard. And I always say that those BPA-free plastics, I don't think they're any better—you know, the new versions. I think plastic is plastic is plastic. Please avoid that.

Bob Miller 21:35
And we're polluting the ocean and the waterways. We're making a mess. [Continuing with the list]: Ethanol, EMF—we'll talk more about that and we spoke about Lyme and mold—even fluoride (I just found that today), clostridia, high fructose corn syrup (we're going to talk about that a little bit), gluten (we have a couple of slides on that), glyphosate and then homocysteine, if it's high, or iron, too high.

Bob Miller 21:58
So let's get into them. Here's a slide on gluten. Increased iNOS expression has been found in the small intestine of celiac disease patients during a small-scale clinical analysis. What they're saying here is that there were increased urinary nitric oxide products in children with celiac disease during at least three clinical analyses.

Increased iNOS expression was also reported in the small intestine. In those with celiac [disease], a gluten-free diet was found to result in a rapid decrease in plasma nitric oxide (NO) and NO products.

Bob Miller 22:31
If anyone's interested in [knowing], "Do we have gluten sensitivity?" there's an enzyme called KIAA1109. When there's one mutation, you're usually gluten sensitive and that really jacks up the chance of celiac—not a diagnosis, but a potential. And here we have listed the RS numbers, which is the good one, and which is the risk. You can see by this bar chart that the homozygosity only occurs in 2.6% and 2.5% of the population. It's not very common. But when someone has these, there's a very good chance that gluten is not their friend.

Bob Miller 23:09
Now we're going to talk about microwaves and EMF. Here we're talking about more iNOS when exposed to electromagnetic fields. Let me show you this first. These are some of the genes that are related to the calcium voltage channels that, when mutated, allow EMF to push calcium in more strongly and then make superoxide. We list the four here if anyone ever wants to look them up. The 'wild' means the good one, and the 'risk' is the mutation. Rather than go into it, in your video number 54, we spoke about EMF. So they can go back. For one hour and 21 minutes, we spoke about EMF. There we go into all the pathways, so we don't have to repeat it here. Find that video and go back and listen to it. We had fun on that one too.

Dr. Jill 24:08
We did.

Bob Miller 24:11
Mercury alone induces NF-κB activation. I probably went through it very quickly, but NF-κB, among other things, stimulates the iNOS enzyme. We all know that mercury is dangerous for us. We all know that glyphosate—more and more information is coming out—promoted NF-κB. That stimulates iNOS. It also stimulates iNOS and other inflammatory markers. Can you imagine the poor person who has gluten sensitivity where there's glyphosate sprayed at the beginning and end of the crop? These people are in real trouble.

Bob Miller 24:52
There are genetic polymorphisms that are determinants of pesticide toxicity. There are a couple of them listed here, but the most common one is called the PON1. That will help take out the pesticides. You can see here that for this one, only 1.3% of the population is heterozygous and 0.1% is homozygous. Knowing your PON1 status helps you understand how seriously we should take pesticides. We all should, but this even makes you more—

Dr. Jill 25:26
But those patients, in particular, we're really watching. And [eating] organic—really, there's no other way, because you want to prevent it after you're exposed. It's much harder to detoxify.

Bob Miller 25:35
Absolutely. You did a great show with Mackay Rippey. He gets into the BPA. It induces the uncoupling of the eNOS, which we'll talk about a little bit later. It uncouples the NOS3, which is the good one, and creates the peroxynitrite. I'm not sure which show number that is, but they could easily find it on your YouTube or somewhere else. Listen to the one you did with Mackay Rippey. It's a great video.

Bob Miller 26:06
Ammonia increases the expression and activity of the L-arginine transporter. I found this absolutely fascinating. I didn't put slides up for the urea cycle, but there is a genetic pattern that can mean that something called the urea cycle doesn't clear ammonia quite as well. Then that activates NF-κB, which leads to increased nitric oxide synthesis and protein nitration. It's really important to make sure that the urea cycle and ammonia are cleared.

Dr. Jill 26:42
Bob, I do have people who either smell ammonia or they have that smell in the urine of ammonia. I find it's not too uncommon in patients.

Bob Miller 26:54
Absolutely. That old person smell. Kitty litter or Windex, in case anybody's wondering [inaudible].

High fructose corn syrup. We're going to talk about this a little bit. This really came into being around the late '70s and early '80s. We're going to look back someday and say, 'Oops!' to this. It increases the iNOS enzyme and it suppresses a very important enzyme called SIRT1. Hopefully, we'll have time to get to that. Sirtuin 1 is a very important enzyme that's related to longevity.

Bob Miller 27:30
We talked about this. The lipopolysaccharides activate NF-κB. Then that stimulates the iNOS enzyme and other inflammatory cascades. Ethanol is able to upregulate both COX-2 and iNOS expression. Now let's look at some of the internal things that are pulling the trigger.

Dr. Jill 27:52
Bob, there are many other reasons, but I don't tolerate alcohol well. I just decided 15 years ago that I basically don't drink. Once in a while, at a party, I'll have one sip of wine. And I don't mind it. I don't miss it. But I'm assuming that probably some of the genetics that I have with the iNOS and all this, in addition to other things, are one of the reasons why I... Are there any other things that you would think about genetically when someone doesn't tolerate alcohol? Is there a set of aldehyde genetics too?

Bob Miller 28:20
That's part of it too. I'm also thinking of glutathione. If you don't take your oxidized glutathione back to the reduced [state], that's another factor.

Dr. Jill 28:29
Which is me too.

Bob Miller 28:31
There are probably multiple factors.

All right. Here we go. Hyperglycemia increases iNOS levels inside the body. This is possibly why diabetes is another morbidity that makes the COVID outcome worse. Here's another one on the advanced glycation end products. They induce the iNOS enzyme. When I was young, we used to call it "adult-onset diabetes." You're usually over 40 and rather overweight. Now children are getting diabetes. And then obesity

is another comorbidity. Obesity causes iNOS pathway upregulation. Of course, we are getting fatter all the time. Histamine stimulates iNOS expression. The more we create histamine, the more we're going to create excess iNOS activity.

Dr. Jill 29:33
So many of these are the perfect storm, Bob, because our mold exposure—and I deal with so many people with that—is one of the number one things that triggers mast cells. Mast cells then throw out prostaglandins, histamines, etc. And for those people who have trouble breaking down histamine production in excess, there are a bunch of different genetic variants. This just adds to the toxic mix.

Bob Miller 29:52
Absolutely. Rather than get into histamine today, go back and listen to interview 34 on histamine. We had a great time going through all the pathways. We're just mentioning it today. And if you want to learn more, listen to interview 34.

Estrogen upregulates inducible nitric oxide synthase and COX-2. And what are we doing? All the plastics [inaudible].

Dr. Jill 30:18
Those are called estrogen disruptors, if you haven't heard of them—and pesticides, organophosphates, and a lot of chemicals in our environment. And what's interesting, really quickly, is that toxicology classically will show these levels of toxicology. Basically, "Here's a level that causes a toxic effect." When we see these endocrine disruptors, sometimes their levels are tens and hundreds of times lower and they're synergistic with other chemicals. Extremely low levels that are not considered classically toxic exert a hormetic effect—that means a hormone-like effect in the body—and can cause real damage at very low levels. Our classical toxicologists haven't been warning us about this, but we see levels that are really low in the environment are still causing massive damage.

Bob Miller 31:00
Absolutely. We've made a mess of things, haven't we?

Dr. Jill 31:03
Yes, we have. Exactly.

Bob Miller 31:07
As you know, anybody who follows the things that I teach health professionals [knows that] I'm a big fan of NADPH oxidase. This is part of our protection. When we're faced with a pathogen of any kind, if we didn't have NADPH oxidase, we'd be in trouble. It stimulates the mast cells, histamine, and kills the pathogen, but environmental factors are upregulating it.

Bob Miller 31:32
Since blocking either NF-κB activation or NADPH oxidase is sufficient to present iNOS expression, they are now separate targets for therapeutic interventions that aim to modulate iNOS expression in sepsis. We'll be talking about that a little bit, I think, when we talk about your experience with mold. We could spend the next 20 minutes talking about NADPH oxidase. Just go to [interview] 26. We really dig into environmental factors that are overstimulating the NADPH oxidase. Dr. Jill, when we did all these videos, I had no clue that all of these dovetail together in a perfect puzzle.

Dr. Jill 32:12
I know. It's so amazing, Bob. That's the fun thing, as we just keep diving deeper. And for me, what's been so great is that I have a lot of ahas about patients. As you know, I see a lot of the most complex, chronic... I love mysteries, and I love detective work. But some of these patients have been ill and have tried everything, and it's not a matter of the standard protocol. There's no one size fits all. And these little pearls where you individualize the genetics are always so powerful in finding out what for you, as an individual patient with unique genetics, is the thing that's going to be a game changer.

Bob Miller 32:44
Absolutely. We've got to get away from the pill for the ill.

Dr. Jill 32:46
Yes, absolutely. And protocols. I'm not a protocol kind of doctor. Yes, we use protocols, but they're all individualized.

Bob Miller 32:54

Absolutely. They've got to be. NADP oxidase stimulates interleukin-6. And I believe that is still the most watched video on your YouTube channel.

Dr. Jill 33:04
I think so too.

Bob Miller 33:08
When I grabbed this some time ago, 2,500 people watched it on YouTube. That's amazing. That's in addition to your Facebook and other [inaudible]. And we went almost two hours on that one. If you want to see how this all interreacts, watch that interview on IL-6. We did a great job.

Dr. Jill 33:28
That was a really good one. And that was so relevant because of COVID, cytokines, and all the stuff that we've seen. I always say that one of the good things that happened with the pandemic was that it allowed the average population to understand [things] like cytokines and some of these words that you and I talk about and that a lot of us in functional medicine think about but that the average person hadn't been exposed to. Now most people have heard the word 'cytokines' and understand at least the basics of what that is.

Bob Miller 33:52
Absolutely. I believe IL-6 overexpression is a huge problem, as we talked about in that video, because of all the things that we're exposed to environmentally. Nitrates and nitric oxide actually downregulate that NOX enzyme. So back again to your diet. Those dietary nitrates may help calm that puppy down.

Bob Miller 34:13
The L-arginine paradox. If you look at some things on the internet and if you want to boost your nitric oxide, you'll see boatloads of supplements that have L-arginine in them. And the literature is very clear: L-arginine turns into nitric oxide. We tend to think, "The more L-Arginine, the better." And this is still being researched, but I go back to: There can be too little or too much. I'm afraid sometimes we're pushing it a little too much.

Bob Miller 34:47

A peer-reviewed study. What I circled here: "We demonstrated for the first time that increased concentrations of L-arginine further potentiate iNOS-dependent superoxide formation." Wow. We need to really emphasize this because superoxide is one nasty, nasty free radical, which further takes us back to the argument: It may be the superoxide rather than the iNOS. But either way, that extra nitric oxide combines with superoxide and creates this inflammatory process.

Bob Miller 35:31
We need to be thinking a little bit more about superoxide. I've been teaching about superoxide for the last 20 years. But since the last nine months or more, I believe that we need to look at superoxide even more strongly because I believe it's more of a problem than we ever anticipated made by this process right here that we're looking at and made by the EMFs and made by the Fenton reaction. There are many ways now that we're making more superoxide than we ever did before.

Dr. Jill 36:04
Question, Bob. You and I both love our hydrogen-breathing machines. That's, to me, this universal thing that neutralizes reactive oxygen. Is this one of the areas where that would be helpful, either the tabs or the breathing hydrogen?

Bob Miller 36:18
Absolutely. Yes. I was hoping to do it today, but I was working on slides.

Dr. Jill 36:27
I try to do it every morning and some days I'm like: "I really miss that. It's amazing." And if you want to know more, you can get hydrogen tabs on DrJillHealth.com. There are a couple of brands. Just look up H2 tablets. It's the cheap, easy version. The machines that Bob and I have, unfortunately, are about $5,000. You may not want to invest in that. But I love it. I use it almost every day.

Bob Miller 36:51
Absolutely. Now look at this slide. While arginine is a cofactor for nitric oxide synthase, it has a specific role in regulating that iNOS transcription and expression. In other words, too much of a good thing. This study really blew me away. Depleting arginine decreases iNOS even under conditions that would upregulate iNOS expression. I'm really excited about this. This is fascinating. That's why perhaps we

should do a future show just on arginine, because we're going to show you some really cool stuff here. Arginine does a lot of things, but it will also turn into glutamate, which is excitatory, which will stimulate interleukin-6, which will stimulate mast cells and histamine. It's also a neurotransmitter and can make us anxious. Excess glutamate can be a real problem.

Dr. Jill 37:54
Let's talk quickly about that because a lot of patients have this question. Glutamine is a precursor to glutamate. And GABA in some people can go down that pathway too. There's been a lot of controversy. When I teach, some of the doctors are like: "Glutamine powder is harmless. Everybody can take it. No problem." In my clinical experience, which is not a randomized controlled trial, there are subpopulations that do not do well on glutamine and glycine as well, because these pathways can cause excitatory issues with the brain and nervous system.

Bob Miller 38:26
Absolutely. I think some functional doctors have gotten a little carried away: "Oh, you have a leaky gut. Let me give you this glutamine powder." And it actually drives mTOR as well, which is [responsible for] the growth of new cells.

Bob Miller 38:41
This is something new that was just introduced to me: ADMA. A lot of people have not heard of this. I was rather intrigued. That's why I think we need to do a webinar just on this ADMA and what it can do to us. It's fascinating. Here's a quick preview. Proteins get arginine put in them. Then, through methylation, we make this ADMA. ADMA will inhibit the NOS enzyme to make nitric oxide. This gets cleared by something called the DDAH enzyme. We're working on making a new chip for our genetic testing. If at all possible, I want to make sure we've got these guys, because we've got to start looking at them. But look what happens. High cholesterol, high blood sugar, high homocysteine, or smoking inhibit this enzyme. More inhibition of nitric oxide. This is the good nitric oxide, the eNOS.

Bob Miller 39:51
There's a lot to learn here. I don't claim to be an expert on this. But here you can see SAM, which comes from methylation and that arginine protein. We need to dig into this deeply. What this ADMA does [is cause an] increased risk of

atherosclerosis, such as with increasing age, high cholesterol, hypertension, high triglycerides, diabetes, insulin sensitivity, high homocysteine, and renal failure. And here's what caught my attention: It's an independent risk factor for atherosclerosis, cardiovascular death, and all-cause mortality. Ouch.

Dr. Jill 40:33
Yes, that always catches attention when you say all-cause mortality. I always talk about gluten and people who have celiac genetics. When they eliminate gluten, their all-cause mortality goes down by 70%. That's dramatic. It's a big deal because these underlying inflammatory processes will lead to many, many different types of mortality issues.

Bob Miller 40:54
Absolutely. So stay tuned. I think we need to dig a little deeper into this.

Here's the reaction between nitric oxide, ADMA, and homocysteine. They're suggesting that they have a role in preeclampsia. It's fascinating. It's naturally produced in the body from arginine found in proteins and completely inhibits arginine utilization by NOS. It's been repeatedly associated with a variety of health conditions, such as endothelial function and cardiovascular health. And then, as we said, the homocysteine slows down that DDAH enzyme and further increases those levels, which could be a big part of why elevated homocysteine is such a significant factor in our cardiovascular health. Interestingly, though, we need homocysteine to make the cysteine that makes glutathione. So here we go again. If we didn't have homocysteine, we wouldn't have glutathione. When it goes too high, then we have a problem.

Dr. Jill 40:02
Any thoughts—you may not have a lot to say here, but I'm just curious if you do—on the really low homocysteine, like say four or five? Are those hypermethylators? Are there any thoughts around that, Bob?

Bob Miller 42:12
Yes. They may be hypermethylating. Through either the middle pathway or through methyl folate and methyl B12, they're overconverting. There might be other reasons

as well. There's a SAM [inaudible] ratio as well where that comes down through. That could be disrupted. I think it's a 3D chess game.

Dr. Jill 42:32
Yes, I totally agree.

Bob Miller 42:36
Here are some of the interactions. It induced nitric oxide production [via] NF-κB. For those who don't know it, this is a very strong inflammatory component, the NF-κB. In mice, it increased the iNOS expression threefold. It was also found to induce NOS uncoupling, increasing the reactive oxygen species. And this blew me away: It depleted intracellular levels of your tetrahydrobiopterin—that's the BH4—by 80%. That's a big deal!

Dr. Jill 43:13
That's a big deal.

Bob Miller 43:14
That's a big deal. Interestingly, in our health coaching, sometimes I'll say to people, "Has your doctor ever measured your homocysteine?" It's like, no. It's ignored. I believe that we really need to be paying attention to this. One takeaway, I think, is that everyone should be aware of where their homocysteine is because it's a really important [inaudible].

Dr. Jill 43:37
Bob, I could not agree more. I'll just say, if you're listening, here are a few things you want to ask your doctor if you haven't checked: A1C, average blood sugar (you should be checking that every year), homocysteine (for the reasons we just talked about), HSCRP (non-specific inflammatory marker) and other things like immunoglobulin G, and really all the immunoglobulins. Very few doctors are checking those, and I can't tell you the number of patients I've diagnosed with immunodeficiencies. And these are pretty simple tests to get.

Bob Miller 44:06
Absolutely. But with this number right here, I was like: "You've got to be kidding me! An 80% reduction in your tetrahydrobiopterin?" That's the BH4 we talked about

earlier, in case people are confused. That's what helps you make nitric oxide, rather than superoxide. How do we calm this puppy down? Vitamin D. Vitamin D has the potential to prevent oxidative damage by suppressing the iNOS enzyme. Zinc limits iNOS-derived high-output NO production in endothelial cells by inhibiting NF-κB-dependent iNOS expression. Lysine may reduce the arginine absorption. They're both absorbed through the same transporters. When we take the lysine, the arginine may not be absorbed as much. And just about everybody knows about how you can use lysine for cold sores.

Dr. Jill 45:04
Viruses, yes. Let me just comment clinically. For anyone who has frequent cold sores or genital herpes, either one is HSV virus. Taking a decent dose of lysine—usually, I have patients do a minimum of 1,000 [mg] per day, sometimes up to 2,000 [mg]—will inhibit that virus and often prevent you from having breakouts. This is a great pearl. It's an easy and cheap supplement. And as we're going to talk about with Bob, this has another effect on iNOS. It's funny, Bob; personally, I did have cold sores after my cancer, so I've always been a lysine for the past 20 years. I know I do really well on it, but I didn't know the secret of how lysine is also helpful at preventing that upregulation of iNOS. Unbeknownst to me, I was doing it for one reason and I was getting benefit from another. After we talked about this, I upped my dose, and it was pretty powerful.

Bob Miller 45:53
Yes, I'm anxious to hear about that. Thanks for the update.

And here we are in endotoxic shock. The bottom line: L-lysine has no effect in the absence of the endotoxin and thus appears to act as a selective modulator of iNOS activity. Curcumin has been shown to promote the degradation of iNOS. We all know about that. It's quite popular. Boswellia, that is, frankincense, showed a significant increase in a colitis group. Both pretreatment and treatment with Boswellia exhibited significantly reduced lipid peroxidation, nitric oxide, and iNOS and showed improvements in tissue injury [associated] with ulcerative colitis.

Bob Miller 46:40
There's something called ParActin. It's something that's manufactured, but it comes from Andrographis. It was found to reduce pain and mild to moderate

osteoarthritis, but it also decreases iNOS. Andrographolide has been shown to inhibit iNOS expression, and it also inhibited NOX2. That's one of your NADPH oxidases that we spoke about earlier. Green tea and black tea are helpful, and EGCG was the most active inhibitor of the iNOS enzyme.

Bob Miller 47:23
We're going to talk about NOS uncoupling, then we're going to get into the 'Carnahan reaction.' What happens here is that BH4 is needed to take L-arginine and turn it into nitric oxide. That's what we showed earlier. When it turns into BH2, we make the superoxide. We showed that earlier. But here we go: BH4 is the central character. That's why I said I'm putting more emphasis on the BH4. Here is the pathway that we [use to] make BH4, the de novo pathway. Then there's also a salvage pathway where the BH4 turns into BH2. And then we bring it back to BH4.

Bob Miller 48:07
Tetrahydrobiopterin—we've talked about this, but here's more: Phenylalanine is an amino acid. It needs to turn into tyrosine. It's not good if that doesn't happen. It's BH4-dependent. Then we need the tyrosine to turn into L-DOPA. And many people say, "Is that the problem with Parkinson's?" Then we need tryptophan to go into serotonin. Without serotonin, we're depressed. And it just appears as though more and more people are getting depressed. Are you observing that as well, Dr. Jill?

Dr. Jill 48:38
Absolutely. I think there was almost a 400% increase in prescriptions for SSRIs in the last year. Granted, we've had a pandemic, but I don't think that's the only thing. I think the toxic load and some of these things are really contributing.

Bob Miller 48:53
Absolutely. Look at this fascinating chart. Here it is. Here's that GTP-cyclohydrolase. That comes from the Krebs cycle. If we have anything that's impacting the Krebs cycle, we're not going to have that GTP—guanosine-5'-triphosphate. That helps you make your BH4. The BH4 turns into BH2. We need to bring it back. You spoke about this at length, the endothelial nitric oxide, but here's the phenylalanine into tyrosine, the tyrosine into L-DOPA, and the L-DOPA into dopamine. Look who's lurking over here: Reactive oxygen

species. The more inflammation, the less BH4, and it's another merry-go-round that we're on.

Bob Miller 49:47
Here is a little bit more specific on how we make it. In our Functional Genomic Analysis software, we've just recently put in all the SNPs that are related to the production of BH4. It's still too early to tell, but we're finding that when people have trouble producing, they have these strange inflammatory conditions they can't seem to resolve. I didn't list all of them, but here's one of them. You can see even a heterozygosity here is only in 1.6% of the people in our software. These are evidence-based SNPs that will be related to the production of the BH4. As we make a new chip in the future, we want to make sure we have all these evidence-based ones, so we can see if someone's having some difficulty making a BH4. I'm really thinking that we need to be spending more time thinking about BH4.

Dr. Jill 50:36
Years ago, Amy Yasko talked a lot about this. I haven't had her on the show, but you can find some information there too. This has been a really big thing in the world of autism, and the children that have been affected by that, adults too. This has been on the radar for a while. We continue to learn more and more about biopterin and how important it is.

Bob Miller 50:54
Yes. I didn't have time to find the slide, but I saw some things as I was looking, such as that some autistic children—not all, but some—are really helped considerably by boosting their BH4. Clearly, autism is very complex, and I don't think there's one thing that's [inaudible], but in some instances, that can be very helpful.

Dr. Jill 51:12
I will say that I used to compound it and prescribe it. It's so much harder to get. I think a drug company got the rights to produce it. I don't know what's happening with that, but years ago, I used to be able to prescribe it, and it's much harder to get nowadays.

Bob Miller 51:25

We're hoping that if we see the pathway properly, if we slow down the wasting of it, support the production of it, and support the recycling of it, that may be sufficient in some cases. This is a fascinating quote here. "It's believed that the intracellular BH4-to-BH2 ratio, rather than the absolute concentrations of BH4, is the key determinant of NOS3 uncoupling." That BH2, when combined with NOS, makes the superoxide, which kind of goes to the argument that it may be the superoxide that's the real villain here. So, stay tuned for that.

Bob Miller 52:04
Folic acid promotes the recycling of the BH2 to the BH4, and it protects against hypoxia-induced pulmonary hypertension by recoupling the eNOS. We're working on some nutritional formulas that may do this, but it's very complex. We want to look at: How do you support the guanosine triphosphate? How do you support the recycling? There's a lot to learn there.

Bob Miller 52:33
NADPH is needed for BH4 production. [See interview] 23. If you want to know how to boost your NADPH, listen to that pathway. And as you know, I'm a huge fan of NADPH. But just don't throw a lot of it at one time. You have to make sure you do it judiciously when other things are calmed down.

Dr. Jill 52:53
You do. And a real quick pearl on that, Bob. Last December, I was speaking in Vegas. I had a big month, and I was like, "Let me do some NAD." At that time, I was doing subcutaneous injections almost daily. And as you know, it requires methyl donors to process. I have issues with B12. I need a lot of B12. I have all kinds of genetic polymorphisms around B12. So, as you can imagine, for two weeks, I felt amazing. I was on top of the world, had great energy, felt perfect, and then I crashed. I started getting depressed, which is not like me at all, and really tired. And guess what? I completely depleted my methyl donors. From now on, for me, this is an N of 1. I always have to make sure I have methyl donors at good, high doses with my NAD. I don't do well with too much. So, for some patients out there, you don't want to overdo this until you know your genetics.

Bob Miller 53:43

Absolutely. And you might want to listen to [interview] 16. I think that might be one of the first ones we did where we talked about peroxynitrite.

Bob Miller 53:53
What happens if we deplete that BH4? Modulation of NOS2 activity by repletion of BH4 may be a safe and effective approach to reduce the frequency of atrial arrhythmias during heart failure.

Bob Miller 54:06
Here's another one: Tetrahydrobiopterin and cardiovascular disease. BH4 replacement may help treat hypertension, ischemia-reperfusion injury, cardiac hypertrophy, and chamber remodeling by restoring the NOS. It improves endothelial function in those who smoke, are diabetic or hypertensive, have cholesterol problems, have coronary artery disease, or even have heart failure. All of that can be the effect of supporting your BH4. But I go a step further, and it's like: Yes, supplementing that might be okay, but let's stop the wasting of it. Let's support the recycling of it. Let's support the making of it. And one of my favorite sayings is that I'd rather have you make it than take it. But we have to learn a lot about this.

Dr. Jill 54:53
I love it. We need a Bobisms file. These are good Bobisms. [laughter]

Bob Miller 54:57
[laughter] All right. We showed this before. Here you're seeing how folic acid, or methyl folate and SAMe are part of that BH2 to BH4. It's much more complex than this. This is a rather simple drawing.

Bob Miller 55:11
As I said, this is needed for phenylalanine-to-tyrosine conversion. Here's a little chart. PAH takes phenylalanine, which is an amino acid, and converts it to tyrosine. But look who's needed: BH4 and NADPH. Efficiency here can cause a problem. Most people know that when babies are born, they take a drop of blood and look for various serious illnesses that are genetic in nature, where, [if so], they have to have very serious dietary restrictions. One of the things I'm hypothesizing is: Are we getting mini versions of that—not severe, but mini versions—because of our BH4 and NADPH depletion?

Bob Miller 55:55
Just N of 1 and talking to some folks, there's some individuals that have brain fog and insomnia, and they're seeing some improvement as they stop things like aspartame, which is pure phenylalanine. We'll talk about that just briefly. There are foods that contain phenylalanine. If someone's having trouble with beef, lean chicken breast, or anything on this list, one of the things they may want to start considering is: Am I having some difficulty turning the phenylalanine in there into the tyrosine? And as we said, there's a serious issue called PKU that is medically diagnosed. But interestingly, supplementation with BH4 can drive that activity in some individuals with certain mutations, lowering the plasma phenylalanine. It's fascinating.

Dr. Jill 56:49
Bob, you may not have the answer to this, but I'm always thinking as we're talking, we have a lot of patients who have excess dopamine because of gut dysbiosis and that upregulation of some of those pathways. Would SAMe or some of these things drive if they already have too much dopamine? Do you think you would need to be concerned about that? Does that make sense?

Bob Miller 57:10
It does and I can't say for sure. I think that's absolutely true. I think we need to be careful with SAMe. I've seen as many people have bad effects as well as good effects to it.

Dr. Jill 57:21
I think that in the literature, you can almost induce mania in someone who is very, very prone to high dopamine. I agree. I always tell patients to watch. If you're taking SAMe, it's a great thing for mood. There were studies against all the common SSRIs where 1,200 milligrams a day actually outperformed most of the SSRIs. However, if you're prone to mania, insomnia, or anxiety, be very cautious because this could stimulate a little too much.

Bob Miller 57:45
Absolutely.

I think most people know what this is. It was first approved in '74. It only started being used in the late '70s and early '80s. It's in so many products—we won't read them here—but that's why I believe some people just can't handle those. It can even turn into formaldehyde. And these are some of the conditions that are associated with too much aspartame: Cancer, cardiovascular, Graves' [disease], Alzheimer's, seizures, stroke, dementia. We're going to look back someday and say, "What did we do?"

Dr. Jill 58:17
Right. What were we doing with these artificial sweeteners?

Bob Miller 58:20
Here we are. It's time to introduce the 'Carnahan reaction.' We named this after Dr. Jill for health concerns. So why don't you take a few moments and explain to us, perhaps, what happened with your mold exposure or however this ties into everything that happened to you? And then we'll explain what the 'Carnahan reaction' is.

Dr. Jill 58:43
Sure. I had a mystery and Bob helped me solve it. He's so cool to name it after me. What happened was that just a few months ago, I had some significant mold exposures to Chaetomium. Chaetomium is, for me, what I call the narcoleptic mold. To me, mold has personalities. Aspergillus and Penicillium cause more allergic redness, a lot of histamine reactions. But Chaetomium and Stachybotrys, some of the really toxic black molds for me personally, caused me to be out like a light. When I get exposure, I've got to lay down now. I can't even stand up.

Dr. Jill 59:18
And with these recent significant exposures, I was getting these episodes where I'd—not blackout, I'll tell you the symptoms in a moment—almost lose time. I equated it almost like if someone was an alcoholic—I don't drink alcohol—and would lose time and space and have these episodes where they just couldn't function. I was having these maybe once a week, a few times in August and September. And what would happen is that my blood pressure would go down to about 80 over 50. As you can imagine, that's not very compatible with standing up. So I realized it was the drop in blood pressure that would cause me to literally have to lie down and

sleep because I couldn't even stand and function. And of course, with that, I would have massive brain fog and exhaustion, and I just couldn't even function.

Dr. Jill 1:00:03
Bob and I, as we talked, realized that nitric oxide production in my genetics was upregulated. And we know mold would be a trigger. The likelihood of what was happening was that the mold was triggering the nitric oxide to be produced. That was a massive vasodilatory effect, almost like if I were septic, causing this really low blood pressure and the symptoms that I was experiencing.

Bob Miller 1:00:27
Absolutely. And that really took a toll on you.

Dr. Jill 1:00:30
It did. It was a rough one.

Bob Miller 1:00:33
So here it is. Gain of function mutations in NOS2 enzymes, mutations in other enzymes overstimulate iNOS, along with environmental and internal stimulation of NOS2, create inflammation from excess nitric oxide or maybe superoxide, excess superoxide through NOS uncoupling and depletion of BH4, creating more superoxide and potential disruption of the neurotransmitters. So that's what we're calling the 'Carnahan reaction.' I think 200 years from now, people will still be studying the 'Carnahan reaction'.

Bob Miller 1:01:17
These are two of the RS numbers that we found in the iNOS based on the literature. I suspect there's got to be more. It's 2779249. The A-allele has been associated with, hold on to your hat, 4.73 times increased iNOS expression. That's a lot. There were also increased plasma nitrite and nitrate levels. The heterozygous genotype was associated with increased levels of salivary nitrates and nitrites. Here it is: The 'wild' or the one that's good is a C, and the risk is an A. And you can see that it's only in 9.9% of the population that our software analyzes. Keep in mind that this software has people who are not well. I would imagine that among the general public, it's even less.

Dr. Jill 1:02:09
Bob, I want to mention one more little thing that's related as patients listen to this. This isn't related to the iNOS, but to me personally, years ago, I had really high cortisol. I've had high cortisol for most of my life. In the last several years, after I've done a lot and I've depleted my adrenals a little bit so that I'm more in the realm of normal or low cortisol, I think that having that cortisol slightly deficient also contributed because cortisol will regulate your electrolytes and your blood pressure as well. To me, part of this perfect storm was clearly the iNOS. But on top of that, why was this different from years ago? Now I have a little bit lower cortisol than I used to. And a whole other thing—I won't go into this—is that I was taking a medication that was lowering my cortisol even further. So I think that that contributed to the perfect storm of this being a massive drop and causing hypotension.

Bob Miller 1:03:00
Sure. And keep in mind that cortisol calms down the histamine, so if it wasn't doing that, that was further stimulating iNOS, further stimulating interleukin-6, which makes more superoxide. Here is RS2297518. The A-allele increased iNOS activity and was associated with the early onset of Crohn's ulcerative colitis and IBD. And there in the chart, you can see that this only occurs homozygously in 3.9% of the population.

Bob Miller 1:03:35
Here's what happened to Dr. Jill. You're very brave, by the way, for putting your genetic information online here. There's a genetic mutation called HFE H63D. That may increase the absorption of iron. And as you can see here, you've got one genetic mutation here. That only occurs in 23.9% of the population. Homozygous is only 2%. Now, if you remember when we looked earlier, excess iron stimulates iNOS. Mutations in HMOX may impact the production of biliverdin, which inhibits iNOS. And there are some mutations here. But here we go. Those two that we pointed out are homozygous on both of them. That just puts you in a position where your iNOS enzyme is, let's call it, trigger-happy. Perhaps it just likes to overreact and over respond.

Dr. Jill 1:04:32

Bob, on the good side of this, I've been super athletic and had good running ability. Years ago, I did track, volleyball, and cheerleading. On the other side of this, just like Goldilocks, I probably had some good ability for the athletic performance things that need oxygen to tissues because patients use this. It's just that going to the extreme is a problem.

Bob Miller 1:04:54
Absolutely. As we spoke about in our first interview, many people need to boost their nitric oxide, which we do, and we're not saying that's a bad thing.

Dr. Jill 1:05:03
And when we first talked about it, we were trying to figure out: Is this gain a function or loss a function? I remember telling you that I don't do well with beets. I never take arginine. And as we went through it, we were like, "I think this is a gain of function." And of course, you and your team have proven that to be the case.

Bob Miller 1:05:16
Absolutely. As we talked about, DHFR is part of the way we get the folate there. And this is an evidence-based SNP on DHFR. Part of making or recycling your BH2 into BH4 could have been compromised.

Bob Miller 1:05:32
We're going to very quickly talk about SIRT1, and then we [will have] managed to get through the slides. SIRT1 is a very important enzyme. It supports endothelium nitric oxide. It supports superoxide dismutase. It inhibits NOX and NF-κB. And if you remember—we're throwing out a lot of terms—these stimulate inflammation, but they also stimulate iNOS. High fructose corn syrup weakens SIRT1. However, resveratrol and nitrates support SIRT1. SIRT1 also inhibits mTOR, which can be inflammatory, which inhibits autophagy. It also supports, as we just found recently, the MAOA enzyme, which is one of the major ways to clear histamine, which, as we just said, stimulates iNOS.

Dr. Jill 1:06:23
Quick random question, Bob. The MAO SNPs: Are they mostly gain or loss of function or do they vary?

Bob Miller 1:06:30
From what we understand, they're loss of function.

Dr. Jill 1:06:32
Okay.

Bob Miller 1:06:35
And here are some of the things that SIRT1 is involved with. It's involved with obesity-associated metabolic diseases, cancer, adipose tissue, aging, cellular senescence, cardiac aging, neurodegeneration, and inflammatory signaling. All of these things are related to SIRT1. And there is one of them that is pathogenic when it's mutated.

Bob Miller 1:07:00
I'm not going to read all this. We don't have time. But if someone looks at the slides, these are all the positive things that SIRT1 does. And if you look at the statistics here, homozygosity is only 1.5% of the population. RS12778366, an evidence-based SIRT1 mutation. T is the wild or the good one. C is the risk.

Bob Miller 1:07:31
We'll go through this very quickly. High-fructose corn syrup—I think most people know what that is. It's just been around since the late '70s or early '80s. Which food products contain it? It's in everything from soft drinks, canned foods, jellies and jams, processed snacks, fast food items, sauces, and salad dressings. It is just everywhere. And that will inhibit your SIRT1.

Bob Miller 1:07:58
I put these graphics together. Let's just say you have a typical breakfast of coffee and donuts. If you put some aspartame in there, that's going to increase the phenylalanine. That's going to create brain fog, low dopamine, agitation, and insomnia. If your donut is made out of gluten and sprayed with glyphosate on it, that's going to stimulate the iNOS. If you've got some filling in there or an icing that has high fructose corn syrup: SIRT1 inhibition, decreased SOD and eNOS, increased NOX and NF-κB, NOS uncoupling, decreased phenylalanine conversion, increases in superoxide, increases in iNOS. If someone has mutations in iNOS or SOD mutations or BH4 or PAH mutations, these people are going to be on fire. When you think

about a perfect storm, you put some artificial sweetener, glyphosate, wheat, and high-fructose corn syrup. What a combination!

Dr. Jill 1:09:05
Bob, I just want to comment. People talk about Europe and a lot of times, when eating there, they're less toxic and less inflamed. One of the reasons is that if you look at the label of a certain product in the U.S. and then that equivalent, same brand, same manufacturer in Europe, they will not use corn syrup in Europe. They will throw it into the American-made products. I've seen this over and over again. It's amazing because our regulations are not as stringent as those in Europe and some other countries as well. Sadly, you really have to become a label reader. I would just recommend you completely avoid processed foods because you're going to get this everywhere if you're eating processed food.

Bob Miller 1:09:40
Absolutely. And how many people have coffee and donuts for breakfast?

I'm not going to read this. This is the whole list of all the mutations that could be contributing factors to upregulating iNOS.

Bob Miller 1:09:56
As we said, if you are a health professional, we have an opportunity for you to do some online education. People can take it as well, but there's no certification. I'm not going to read these, but these are the modules we now have up. Overview: Fenton reaction, nitric oxide, glutamate, gut-histamine-oxalates, heme and heme support, mast cells, the NADPH steal, and NADPH oxidase. And these are the videos that are listed here: Nrf2 and Keap1, more on NADPH, glutathione, SOD and catalase, the sirtuins that we just talked about, and phase III detox and autophagy.

Bob Miller 1:10:40
We're probably about halfway through. We're making them as we go along. More modules are added every one to three weeks. All you have to do is go to functionalgenomicanalysis.com. Right here, click on the certification. You get the first seven modules for free. What we do is say to doctors or health professionals, "Try this out and see if this is for you," because it's not for everybody. This is not for the faint of heart.

Dr. Jill 1:11:07
You have to want to dive deep, right, Bob?

Bob Miller 1:11:10
Yes, this isn't a genetic test and it tells you what to do. You do get to a point where you have to pay, and if you use the code DRJILL, you'll get $100 off. But you can try the first modules first, before you even have to do anything. And then we do have the Functional Genomic Analysis software. We have a supplement line. There's the genetic test. And there is [information about] who does the research.

Bob Miller 1:11:37
I know a lot of people are not health professionals. If they want to talk to us about health coaching, here's our phone number: 717-733-2003. Tolhealth.com. If you're a health professional only, this is the software we use for the analysis. And Yvonne Lucchese is the executive director, and her phone number is 717-466-5700. If someone wants to learn and you're there, hopefully in the spring or summer we may do a conference on the 'Carnahan reaction,' where we will spend probably three days with doctors talking about every aspect of this. I mean, we did a really quick review.

Dr. Jill 1:12:18
We did it, Bob. You are amazing! The amount of data you just got through is absolutely amazing. I hope you all listening out there appreciate Bob Miller and what he's bringing. I just have such great respect for you, Bob, and your tireless efforts. And what I love too is that you're genuinely doing it out of the good for humanity and the good for the people. And you continue to give, and you're so generous with your time, with me, and with everyone here. I mean, this is all free. This is your time, and it's valuable. And I know how hard you work. Sometimes it's nine o'clock at night, and you're just getting done with patients.

Dr. Jill 1:12:57
I want to publicly thank you for your efforts, and I and many, many other physicians are benefiting from your work, your team, and all the research. And I am so supportive of your educational courses. I completely endorse them and believe in the work that you're doing. So if you're a physician or a highly educated consumer

who wants to learn more, you can join that. You can get that link. And wherever you listen to this, we'll have those links posted with the code and everything. I can't thank you enough. I always enjoy our time. I always learn more. It's so fun.

Bob Miller 1:13:32
And any update for you on how you're doing now after all that?

Dr. Jill 1:13:35
So much better. So much better. I added lysine. I got rid of the excess and all the little pieces I think we talked about in our little promo. But I was taking tons of glutathione, which was oxidizing, so I got rid of some of that. I was doing IVs weekly. I stopped that. So let this be a lesson to you. This is my lifelong lesson: Less is more. I'm that kind of person who's like: "Oh, I want to fix this. I want to do this." Often, my downfall is just because I do too much. So if you're listening and you're crashing and you have a ton of supplements, often with my patients, I'm like, "What can we take out?"—because sometimes it's too much. I added a lot more lysine. I've been avoiding mold. I'm doing so much better, Bob. And thank you for asking.

Bob Miller 1:14:13
And our goal is that in 2022, you will just laugh at mold.

Dr. Jill 1:14:17
Yes, like: "Oh, it's nothing. It's merely a flesh wound." Thank you so much.

Bob Miller 1:14:26
It's always a pleasure.

Dr. Jill 1:14:27
And thank you, everyone, for joining us today. I hope you enjoyed it as much as I did. Please leave comments and maybe future topics. I know Bob and I are always brewing about what to bring next. As always, it was such a fun time. Thank you so much, Bob!

Bob Miller 1:14:39
My pleasure. Have a great rest of your day.