Dr. Jill

Your Functional Medicine Expert®

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#119: Dr. Jill with Bob Miller: Why the Heme Oxygenase Enzyme is Critical

Dr. Jill 00:13

Well, good afternoon, everybody! Welcome to another episode of Dr. Jill Live. You can find all other episodes on YouTube, on Stitcher, on iTunes, or wherever you watch or listen to podcasts. Hopefully, you're enjoying this, and I hope you subscribe and leave some reviews there for us. Today I have a special guest, who is no secret to you all if you've been watching Dr. Jill Live. As I've heard in some of the reviews, he's one of your favorites because we go deep and go into the mechanistic pathways, and today is no different.

Dr. Jill 0:43

Every single time I talk to Bob, we have some new groundbreaking information on these enzymatic pathways and how they affect our health, especially if you're listening and you've dealt with chronic Lyme disease, mold toxicity, post-COVID, or symptoms after Epstein-Barr virus. It's really common that often these genetic pathways are the secret to why you're suffering or why you can't figure it out. And you're going to learn something really exciting today about heme oxygenase.

Dr. Jill 1:10

Before I jump in, you probably know Bob, but I'll give a brief introduction. He's a Traditional Naturopath specializing in the field of genetic-specific nutrition. He earned his traditional naturopathic degree at the Trinity School of Natural Health and is board certified through the ANMA. About 20 years ago he opened the Tree of Life practice and served as a Traditional Naturopath for 27 years. In the last several years, he's been engaging exclusively with functional nutritional genetics. If you're a practitioner listening, and we have lots of practitioners, you have probably used or seen his tests. I don't know of anyone who hasn't been familiar with some of these pathways.

Dr. Jill 1:46

Bob, welcome, welcome! As always, it is an absolute pleasure and an honor to have you here today, and I'm super excited about our path. Before we jump in, any brief little teaser on what we might find today with the heme oxygenase or why it's important to the listener?

Bob Miller 2:03

Oh sure. We've been looking at some of our other podcasts on how we make inflammation. We've looked at things like glutathione, superoxide dismutase, and all those helpful things. I was really surprised to learn that what we're going to talk about today is a major pathway that we use for detoxification and reducing inflammation. As you so aptly said, if you've got mycotoxins or Lyme or some other chronic inflammatory [disease], this may be one of the pathways that might be disrupted and that we need to work on. So hang on, put your seat belt on, because we're going to go for a ride here today.

Dr. Jill 2:38

I'm super excited. Take it away, Bob!

Bob Miller 2:43

All right. We're going to do a screen share here with the slides. Let's see. I think you got these slides there?

Dr. Jill 2:54

I see the screen. There we go! Looks good. Oh yes.

Bob Miller 2:57

Okay. All right, our topic is: "Why the Heme Oxygenase Enzyme is Critical for Your Health". Of course, we're not practicing medicine here. We're just giving you information. It's a literature review. And people have seen this before. So I say, "Heme Oxygenase, 'Another' Three-D Chess Game Played Underwater & the Environmental and Genetic Factors That Impact It."

Bob Miller 3:20

I just drew this little diagram from the literature that we found. We're going to be talking about an enzyme called heme oxygenase. Just in case anybody doesn't know, your DNA gives instructions on how to make enzymes. Enzymes either make something, clear something, or have some other function inside the body. When they're mutated, most of the time they don't do their job as well, but sometimes they do their job too well. Either one can cause a problem.

Bob Miller 3:48

So, let's take a look up here. You see that the heme oxygenase can decrease the oxidative damage to the pancreas; it helps kidney function; it actually can help reduce joint swelling and inflammation; it's actually involved with non-alcoholic fatty liver disease that can be associated with obesity and diabetes; it can help reduce gut inflammation and reduce the secretion of pro-inflammatory cytokines; it helps with the cardiovascular system and metabolic function. There are very few enzymes that have such a myriad of impacts on the body.

Bob Miller 4:24

Now, I wanted to show this first because, as you know, Dr. Jill, we are seeing such an increase in autism. I believe it used to be one out of a thousand, and I think the latest might be one out of 44 or 45, or something like that. Someone did a study of low heme oxygenase serum levels in children with autism. The conclusion is, as the study suggests, that oxidative stress is higher in children with autism and that heme oxygenase levels are insufficient to achieve oxidative balance. That one was quite surprising because when you talk to elementary school teachers who've just taught for five years, even aside from autism, we're just seeing so much ADD, ADHD—an inability to concentrate. It's becoming a very serious problem, and clearly, this isn't the only issue; there may be neuroinflammation from other factors, but the heme oxygenase may be playing a role in helping to reduce it.

Bob Miller 5:26

Now, you [wrote] an excellent article, and I'm encouraging everybody to read this article to learn about the heme oxygenase benefits. It's on your website, you called it "Heme Oxygenase-1: Can Boosting HO-1 Help in Autoimmunity… " And you very well described in one sentence what heme oxygenase is: "An enzyme involved in a process known as heme group degradation." We're going to talk about what a heme is. It breaks down and assembles the type of molecule known as heme. It has an important role in various biological processes. It's designed to be bound to other compounds. I'm going to show you what it does. When it's not, it becomes a potent inducer of inflammation. However, your body has an all-natural built-in defense mechanism and that's the heme oxygenase.

Bob Miller 6:19

This might be a topic for another show, so I'm going to go through this one very briefly. But what happens is that glycine and succinyl-CoA go through eight steps called the heme cycle. The very last step, the FECH enzyme, puts iron on the heme. And you've got your heme. Look on the right here. Heme plays a role in [the following]: Hemoglobin, myoglobin, neuroglobin, cytochrome p450; that's your

phase 1 detox; cytochrome c-electron transport, peroxidase, catalase, these are catalase major antioxidant, NADPH; as you know, we did a whole show on the importance of NADPH; tryptophan for your serotonin, nitric oxide synthase; we did an entire show on nitric oxide and the infamous 'Carnahan reaction'; and the SUOX enzyme, which is your sulfite to sulfates.

Bob Miller 7:16

So it's pretty amazing what this is involved with. And you can have genetic mutations anywhere along the pathway here. Or possibly glyphosate might be impacting glycine, and if your mitochondria are not doing a very good job, you may not have enough succinyl-CoA. So there are a lot of things here. In our genetic health consulting, we are finding that many people who are struggling may have some genetic issues along the pathway, or lead—lead will impede this as well.

Bob Miller 7:49

This is a diagram that shows all of the enzymes, and these are cytochrome p450s. Every one of these are dependent upon heme to function properly. Cytochrome p450 is [involved in] many of your phase 1 detoxes that clear medications, is also involved with your steroid hormones, and is involved in many, many processes. We're just beginning to learn the extent of the CYPs. You'll also see at the bottom that your nitric oxide is involved and that your SUOX is involved. So if we don't have enough heme, we can have no mutations on these whatsoever; they're not going to work because they don't have what they need to work.

Dr. Jill 8:32

It makes so much sense, Bob, as far as why it's such a big deal, which is exciting that we're talking about this.

Bob Miller 8:39

Absolutely. Now, again, I really encourage you to read this article. You go into the details; I just gave the key points here: [It's] cytoprotective, antioxidant, immunosuppressive—and it's like, "What, why is that a good thing?" You explain that: Anti-inflammatory support in autoimmune and inflammatory diseases, and [it's] antimicrobial. So, go to your website and read the whole article. You really did a fantastic job on that, Dr. Jill.

Dr. Jill 9:04

Thank you, Bob, and I just have to credit you because you were the one who got me thinking about it. I thought, "I'm going to start writing about this," and I think it was based on some of the articles we've shared. So, believe me, it was really at your instigation. I want to mention the immune thing because I think people are learning this and understanding it; if you're a practitioner, you're seeing this, but really, at the crux of so much of the chronic, complex [diseases], whether it's mold or Lyme or long COVID, it is either an overly activated immune system or an underactive [one]. It's [due to] this dysfunction of the immune system, and we're going to dive into that and why the heme is so important to that.

Bob Miller 9:34

Absolutely! Very well said. So here's what we're going to do today; we're going to really move quickly. We're going to review the inflammation pathways discussed in platelet activation and the RANTES pathway, which was episode number 102. I would really encourage people to go back to that one because we go into detail. I'm going to do the cliff notes in about two minutes for what we covered in an hour and a half. Then, the purpose and function of heme oxygenase. This is going to surprise people: It makes small amounts of carbon monoxide, which may be protective. People might be thinking: "Now, wait. Isn't that what kills you?" Yes, but a small amount of it that the body makes can actually be helpful. It converts your iron into ferritin; if we don't do that, we have a real problem.

Bob Miller 10:17

And the thing we're going to talk about the most today is making the powerful antioxidant bilirubin. Now, a lot of people say, "No, wait a minute. Isn't that what people have too much of sometimes, like Gilbert syndrome, or when babies are born, they're yellow and they need to go under a light?" Yes, but interestingly, at the right amount, bilirubin is right up there with glutathione as an antioxidant. [We'll discuss] how it protects us; why NADPH—one of my favorite subjects—is so important; we're going to talk about a new enzyme, POR; then we'll talk about the environmental genetic issues, the various SNPs; and then we're going to take a look at your heme oxygenase pathway, sharing it with the world. You're brave, Dr. Jill.

Dr. Jill 11:00

I always love being the guinea pig. Thank goodness I have so many good genetic mutations; we'll have hours and hours of discussion!

Bob Miller 11:11

And then, the bottom line: What can we do lifestyle-wise, diet-wise, or [through] supplementation that might be beneficial?

Bob Miller 11:17

Now, this is a somewhat revised map from what we had done before. I want to make this a little bit bigger. There we go. This is what we covered in the previous podcast, and I'm going to go through it very, very quickly. There's an enzyme called TNF-α (tumor necrosis factor-alpha). This is our friend unless it's not, because this will be stimulated by any lipopolysaccharides, mycotoxins, viruses, clostridia, or Borrelia. All of those will stimulate, and that's okay unless it's overactive. And you can have mutations on this that are gain of function.

Bob Miller 12:07

Iron—critical for life, but there are genetic mutations as you can absorb extra and that will also stimulate TNF-α. Then, it stimulates another nasty free radical producer called NF-kappa B. Maybe I shouldn't use that name because we need it in some instances to kill pathogens. Then it stimulates the NOX enzyme NADPH oxidase. We did a whole webinar on how this is our friend because it makes mast cells to kill pathogens, but if upregulated, we'd have too many mast cells and we'd have mast cell activation. And we've spoken about this before—that 20 years ago we barely saw any of this, and now it's rampant. What percentage of the people that you see, as a functional doctor, do you think have extra mast cells going on?

Dr. Jill 13:01

Oh, Bob! I think it's upwards of 50%. It's almost always coexistent now with all the things we talked about: The chronic infections, the toxicity, the mold, the Lyme, etc. Many, many people—I'd say half of them—have mast cell activation as part of the picture.

Bob Miller 13:16

Mast cells are our friends unless they're not. If they're overactive, that's a problem. The SIRT1 enzyme inhibits NF-kappa B, [which] inhibits NOX. You can have genetic mutations on here, or unfortunately, high fructose corn syrup inhibits it. We can have mutations in the KIT gene that will make more mast cells, and then we make histamine. We did a whole recording on histamine, and when that's in excess, we have enzymes called HNMT, MAO-A, MAO-B, the aldehydes, there's UGT1A4, there's diamine oxidase (ABP1) that clears histamine, and you can have issues here where you don't clear your histamine or lipopolysaccharides can stimulate the HDC enzyme to make more histamine.

Bob Miller 14:05

Then here comes the infamous 'Carnahan reaction,' where the histamine stimulates an enzyme called iNOS. I really encourage everybody to watch the video we did on iNOS. Just go to your YouTube channel or any other place where you have them and just search for 'iNOS'. We really do a deep dive as to what happens when this gets upregulated; it downregulates the eNOS, and you lose your BH4. Then, rather than making nitric oxide, you make superoxide. Then, you make peroxynitrite; this is called NOS uncoupling—it's very common. People who have Raynaud's or just circulatory issues have this.

Dr. Jill 14:49

Bob, I'm just going to put it in perspective. With iNOS, what we see is that we love nitric oxide. Athletes try to make more by taking beet juice. It's really popular to enhance nitric oxide for blood flow and vasodilation. However, too much [of it reminds us of] the Goldilocks principle. Like always, too little or too much is not a good thing. For many people, like myself, with the iNOS mutations, it's upregulated, so they produce too much and how that could present clinically is in syndromes like POTS. So many of you have heard of postural orthostatic tachycardia, where you basically vasodilate, drop your pressure to 85 over 45 or 50, and you have hypotension, dizziness, and fatigue. That's very commonly related to this iNOS upregulation, especially—is it iNOS2, the one you just showed us?

Bob Miller 15:33

It's NOS2 or iNOS. So it's iNOS or NOS2. Now, some of the recent research is indicating that it may not be the extra nitric oxide, but that this is running too fast, we're running out of BH4, and we're making superoxide rather than excess nitric oxide. So you'll see literature on both. But the current scientific thinking is [basically] that yes, the iNOS is running, but it may not be the nitric oxide and may be the superoxide. Either way, it's semantical which one it is. It's a problem, and it's inflammatory, but I just wanted to point out that there's debate as to which one it is.

Bob Miller 16:12

Anytime iNOS runs too fast, you're going to have a problem because you get NOS uncoupling. Then we activate our platelets. As you know, thick blood, varicose veins, clots, and strokes are on the rise because [when] these platelets get activated, it creates something called RANTES. Again, we're not going to cover that. Watch our platelet activation video for that.

Bob Miller 16:37

But then, we need our good fats. We need our omega-3s used by the FADS enzymes to make what are called protectins and resolvins that can calm this down. We didn't talk about this in the previous webinar; we didn't have this information, but NADPH is the cofactor for these. So, if NOX is constantly upregulated, we may not even be able to use our FADS properly, and using the Omega-3s could actually be pro-inflammatory.

Bob Miller 17:06

Then, to wrap it up, TNF-α stimulates an enzyme called PLA2. I have to admit, I'm enamored by this because I believe this is really being upregulated, where it pulls arachidonic acid out of the cell membrane. Now, arachidonic acid plays important roles in the body; it's not all bad, but when it's pulled out of the cell membrane, it can go down through multiple pathways to make inflammation. The one we're just going to show here is an enzyme called 5-LOX that makes leukotrienes. What's interesting is that we're finding that there is one SNP that is a gain of function on 5-LOX, and there's a CYP4F2 that inhibits leukotrienes. And what we're finding is that when people have this [5-LOX] upregulated and this [CYP4F2] downregulated, they have inflammation that they just can't seem to get under control. We'll show that when we look at your map.

Bob Miller 18:08

I'm not going to go into this, but just very briefly, it can stimulate interleukin-6, and it can stimulate angiotensin II, which is involved with blood pressure but also stimulates interleukin-6. I'm just mentioning that because heme oxygenase can calm that down as well. So that is the problem that we identified. So when we talked about platelet activation, we gave the problem, but I didn't realize at the time that heme oxygenase plays a very important role in calming all of this down. I have that in the next slide here. But before we do that, I just want to show when the heme is made. Here are your heme oxygenase enzymes. We need NADPH to turn that broken-down heme into carbon monoxide, and yes, that is the one that kills us if we get too much of it. It helps your iron go into ferritin so it doesn't become a free radical.

Bob Miller 19:10

And then, our emphasis today is going to be on the biliverdin and the bilirubin. Again, we think of bilirubin being too high as a problem. It sure is. But I think people

are going to be stunned that bilirubin is right up there with glutathione as an antioxidant.

Bob Miller 19:28

Now, we're going to get into the iron here. We're just going to have a couple of slides on iron, then a couple on carbon monoxide, but then really focus on the bilirubin. So, iron-derived reactive oxygen species are involved in the pathology of numerous vascular disorders, and that is the iron and the heme, which is dangerous when it escapes from its physiologic site. Then, the endothelial cells upregulate this enzyme, heme oxygenase, and ferritin. What they're saying is that it has been shown to be effective in the protection of the endothelium against the damaging effects of heme and oxidants; lack of adaptation in an iron-rich environment led to extensive endothelial damage in humans.

Bob Miller 20:18

What they're saying here, to sum it up: The heme oxygenase takes what could be a nasty free radical, that iron, and puts it into something safe. Here is a chart that shows it. Here are your heme oxygenases 1 and 2, and we're saying they're degraded by heme oxygenase, leading to the generation of this ferrous iron. However, the heme oxygenase activation also increases ferritin expression, which can bind the ferrous iron and detoxify its pro-oxidant effect. Here you can see as it goes into the ferritin, it can negate that pro-inflammatory. So you can see here, if you don't have heme oxygenase working, this iron can be very, very inflammatory. I believe one of our early recordings was on the dangers of iron, and we talked about the Fenton reaction, where iron combines with hydrogen peroxide.

Dr. Jill 21:20

Yes. And Bob, I always love to talk about this with patients to give them a really clear [idea]. It's like if you have an old car and it starts getting rusty—the iron rusts. That's basically what can happen in your body; this oxidative stress creates rusty iron. I'm exaggerating a little, but the idea is that this oxidative stress in the body combined with iron is really nasty. And so many doctors and people are like, "Oh, every woman should be on iron supplements." Yes, there's a place for it. We need iron, clearly. But if you have excess iron, are not binding iron, or have oxidative stress, iron can be very problematic too. There's a neutral place where it's very good for us, but there's a problematic place where it becomes very dangerous.

Bob Miller 22:02

Absolutely. As we've had these discussions over the years, we keep coming back to the same thing: Doing a little or too much of anything can be helpful or harmful. There's that Goldilocks [principle], as you said, that spot in the middle where everything is balanced.

Dr. Jill 22:17

I want to mention that this is just from my memory, so I may be quoting myself a little wrong—way back 20 years ago in medical school. But, with carbon monoxide, there's a big shift in the acid-alkaline [balance] of the body—the pH. I'm suspecting one of the ways that it could be beneficial is enzymes are all regulated by pH in the blood, and there can be just the smallest 0.1 change of the pH and there are shifts in enzymes opening up or closing or active or non-active. I'm guessing in this situation that the benefits of a little carbon monoxide are actually changing the pH of the blood in a beneficial direction.

Bob Miller 22:50

It sounds like a plausible thought to me. So here it summarizes [it this way]: It takes care of the iron, makes a little bit of carbon monoxide, which is vasodilatory, anti-inflammatory, antithrombotic, and then also makes the biliverdin that turns into the bilirubin that we're going to be talking about shortly.

Bob Miller 23:12

Clearly, carbon monoxide is a killer. It kills many people every year, and way back in the 19th century, they figured out that it might be overcoming the [available] oxygen. Therefore, we're asphyxiated, so clearly this is a killer, no doubt. I know no one would do it, but don't expose yourself to carbon monoxide thinking you're doing something good because your body makes it in very small amounts. So please, don't think that you're going to help yourself by breathing carbon monoxide.

Bob Miller 23:45

Here it's talking about: It's a gaseous second messenger produced when heme oxygenase [enzymes] catabolize heme. Now, what's interesting [is that] here they're saying "low-concentration carbon monoxide as a neuroprotective agent for combination treatment of... stroke, and its beneficial effect would be at least partially mediated by activation of the Nrf2 pathway." I've been pondering this a little bit, and you can't find any literature that's definitive, but I'm wondering if its effect isn't that it just gives a little kick to Nrf2. And I know we've spoken about this before, but if someone's new, it's worth repeating. Nrf2 is what stimulates the production, utilization, and recycling of your antioxidants. It's also involved with all

of your detox pathways. So there might be multiple [pathways], like you mentioned as well, but it may also stimulate Nrf2.

Dr. Jill 24:41

That makes sense. The other thing that's really interesting, Bob, is anything in excess—oxygen can kill too because of reactive oxygen, too much oxygen. So, in my mind, this could also help modulate if there's too much reactive oxygen, especially neurologically because that's such a problem with oxidative stress in the brain.

Bob Miller 24:59

Absolutely. So here we're saying carbon monoxide can quell inflammation, defend tissue from oxidative stress, prevent cell death, and more. At high levels, it causes cell death; at low levels—again, created by heme oxygenase, not anyone using it on their own—it can actually prevent cell death. This is an interesting quote here: It helps with lung transplants, "lung fibrosis, ulcerative colitis, cancer, and heart disease." Here's a quote from a lung disease expert at Cornell Medical College: "There is no molecule that's been shown to be this cytoprotective in just about every organ tissue injury—brain, lung, pancreas, heart, kidney, you name it."

Bob Miller 25:44

When I was preparing for this, I was really surprised at this because we all think of carbon monoxide as a killer. And here's this article that was printed back in 2011: "Carbon monoxide-activated Nrf2 pathway leads to protection against... ischemia." That's why I believe that there might be a component to this, and they're even actually saying that the "beneficial effect would be at least partially mediated by activation of the Nrf2 pathway."

Bob Miller 26:14

All right. Carbon monoxide induces vasodilation and nitric oxide release. Interestingly, high levels inhibit nitric oxide synthase activity; lower concentrations release nitric oxide from a large intracellular pool and therefore may mimic the vascular effects of nitric oxide. So here again, its dosage, and I've probably said it too many times, but just again, it's what your body creates, not what you'd expose yourself to.

Bob Miller 26:44

Now, here's an interesting chart that shows that the carbon monoxide stimulates the antioxidant response element for your KEAP1 and Nrf2, which then increases

your antioxidants. As we'll talk about later, Nrf2 stimulates and controls heme oxygenase. So it's like we've got a loop here, and it's fascinating how the body works.

Bob Miller 27:11

Now, we want to get into what bilirubin does. So, you remember, we very quickly went through it, but we talked about the dangers of tumor necrosis factor alpha being too high. Again, we need it, but when it's excessive, this is when you get your autoimmune diseases. Your NF-kappa B—we need it, but in excess, it can be very inflammatory. By the way, just as a clinical observation, Dr. Jill, those who seem to be incredibly ill from Lyme disease, we're finding that they have a homozygous mutation on the one NF-kappa B that's a gain of function. The NOX enzyme, again, creates the mast cells. I think the video we did on IL-6 is still your most viewed video.

Dr. Jill 28:00

I do too. Yes, people are really loving that one.

Bob Miller 28:03

Yes, so all of these are pro-inflammatory; SIRT1 holds it back. Look what bilirubin does: It inhibits TNF-α, it inhibits NF-kappa B, the heme oxygenase enzyme supports SIRT1, bilirubin puts down the NOX enzyme (NADPH oxidase), and it inhibits interleukin-6. I don't have it on this chart because it's way down the chart, but it also inhibits iNOS—Carnahan reaction—all from bilirubin. I was quite stunned when I started researching what it does!

Bob Miller 28:49

So, here are the heme oxidase enzymes, and then what we're going to do today is talk about how this is all controlled by Nrf2, which was controlled by KEAP1. Then, we're going to talk about one of my favorite subjects, NADPH, because we're going to talk about how there's an enzyme called POR that donates the NADPH to heme oxygenase. Now, let's think about this a little bit. If you've got the NOX enzyme chewing up your NADPH, you may not have enough over here [see slide]. Then, you can also have genetic mutations in G6PD and ME1. By the way, this is one of the most common worldwide mutations. You may not be making enough NADPH for the enzyme to give there. Nrf2 turns these guys [G6PD and ME1] on; KEAP1 shuts them down. There are a whole lot of things that can go wrong here.

Bob Miller 29:46

Clinical observation: Those people who are really struggling with Lyme, mold, or mycotoxins usually have some issues with their heme oxygenase, the delivery of NADPH, or the heme cycle that delivers the heme. So this really is the 3D chess game. You could see people with low bilirubin or low heme oxygenase, and you could probably have 30 to 50 different ways that you got there. So there isn't a one-size-fits-all [solution]. There isn't a, "Oh, take this herb for that." It's complex. We like simple answers, and wouldn't it be nice if there were, but there aren't when it comes to this; it's rather complex.

Dr. Jill 30:34

Bob, I just want to comment. I was giving a lecture for a group this morning, and one of the comments was, "Is this substance good or bad?" I had to laugh because it depends, right? That's the answer for most of the stuff. Really, the more we do personalized precision medicine, the more it is important because you could have turmeric cause histamine in someone or be the best antioxidant in another person, so there's never a one-size-fits-all [solution]. We have to kind of become uncomfortable with that uncertainty that there isn't just a protocolized approach and the best treatment is this real, individualized deep dive.

Bob Miller

Yes. I tell my clients: "If somebody says 'everyone should,' if it's anything other than drinking water and breathing air, get very worried."

Dr. Jill 31:16

Absolutely, I agree with you.

Bob Miller 31:18

Yes. So here's a little more detail. The heme cycle helps make heme. That's what we talked about earlier. So succinynl-CoA comes from our Krebs cycle. Glycine comes from our diet; it's an amino acid. And this is controversial: Stephanie Seneff talks about how glyphosate—she believes—interferes with glycine. You will see other sincere scientists say, "We don't think so."

Bob Miller 32:09

Succynl-CoA, which comes from the Krebs cycle, and glycine, which comes from our diet, start the process and go through these eight steps to make heme. As I was saying, with glyphosate or roundup, some very sincere people say that it interferes,

and some people say they don't think it does. So it may or may not. I tend to think it does, but I want to hold open the thought that it may not be totally accurate. But nonetheless, it's not good for us.

Bob Miller 32:42

So if we don't have enough heme, we then don't have the ability to make the carbon monoxide, take the iron, and break it down. I'm looking for the literature, and I didn't find it yet. I was hoping to find it before this podcast, but I couldn't find it, but it would make sense that if heme oxygenase isn't working quite well, this heme in the iron becomes very inflammatory. I couldn't find any papers on it, but I'm sure it's there. Then, as we talked about, ME1 and G6PD deliver it to the POR enzyme. And we're going to talk about this one; we've never talked about POR before, but I'm really blown away by how important this is because it donates the NADPH to the heme oxygenase. So we can have perfect heme oxygenase; we can have all the heme we want; Nrf2 can be functioning; but if we don't have NADPH being delivered, it's like having a brand new car without any gas.

Bob Miller 33:40

Now, I am very enamored by riboflavin. I think we've spoken about this before. Riboflavin is needed to make FAD, which is needed for the POR enzyme to work, and you can have genetic mutations on these transporters or the FLAD1 enzyme that makes the FAD. So there's a heck of a lot here that can go wrong, Dr. Jill. I think it's important for the functional doctor to be able to see where the problem is because yes, there are herbs that stimulate heme oxygenase, but if you're not getting G6PD and ME1 to deliver the NADPH, it's not going to help. If you don't have this cycle working properly, you're not going to have the supply of heme, and stimulating it isn't going to help. It's really a complex situation.

Dr. Jill 34:29

Yes, and Bob, I just want to comment. [After] seeing a lot of organic acid tests, we talked about this before too. I know you're now incorporating those results into your testing, but glutaric acid is a marker on organic testing that shows riboflavin deficiency, and I will say it is probably the number one deficiency I see in organic acids. Honestly, I think a lot of colleagues ignore that, [saying], "Oh, riboflavin isn't that big a deal." I find it is a big deal, especially in something like migraines and many other processes. That riboflavin is huge. We tend to give glory to methyl B12 and methyl folate. I think riboflavin is right up there in importance.

Bob Miller 35:09

Oh, absolutely. I've been doing some webinars for doctors on methylation, and I call it "get your ducks in a row," and that is, don't even think about giving methyl folate if you're low in riboflavin because riboflavin is one of the cofactors for the methyl group to go onto the folate. You hear this all the time: Some well-meaning person, either on their own or through a practitioner, says, "Oh, I've got MTHFR, therefore I need to take methyl folate." They feel phenomenal for 10 days, and then it's like, "What just happened to me?" They get irritable; they get inflamed. Just as a side note, and maybe this could be another show we do, but the histamine and methyl transferase get stimulated by methyl folate. If in the downstream from that the MAO-A and the MAO-B can't handle it, it actually makes the situation worse. So we have to be really careful with methyl folate. I tend to think that in the functional world, it's being given just a little too much. Now, obviously, if somebody's pregnant, we've got to have it. If you've got high homocysteine that's related to this, maybe it's time to be done. But other than that, I think we're overdoing it just a bit.

Dr. Jill 36:22

Bob, I agree, and I just want to comment and clarify what you just said. Histamine intolerance, mast cell activation—a lot of these are [the result of] a poor breakdown of histamine, among other things. And methylation breaks down histamine. But like you just said, I just want to clarify because if you have a poor MAO or one of those other enzymes, you can actually be in a worse situation with histamine if you give too much methyl folate. Is that what you're basically saying?

Bob Miller 36:44

Yes, exactly. You're absolutely right. So when people have mutations in MAO-A and MAO-B or the SIRT1 that controls it, I tend to think that if there's any chance that you're creating excess histamine, take care of that first before you support methylation. So I've done some webinars on that effect. I think I actually presented that for Great Plains one time. I call it "getting your ducks in a row." And in addition to histamine, you also have to be careful with dopamine because folate and SAMI can drive dopamine.

Bob Miller 37:20

Anyway, as I said, we also need FAD for the PPOX enzyme. There are other cofactors along here, and we're investigating how maybe we can help practitioners make a custom supplement that may not only give succinyl-CoA and glycine but, where they have weaknesses, find where the cofactor help is needed. So that's one of the things we're researching. But as I said, lead will impact some of these, and glycine deficiency [also].

Bob Miller 37:50

Just as a little side note—again, a clinical observation—when people have difficulty here [with the HEME cycle] unless they have a dairy problem, they love ice cream because it provides the glycine and the carbohydrates. And here we go. And when people have trouble here [with the HEME cycle], they often get what we call 'hangry,' where intermittent fasting on our ketogenic diet is a disaster. which goes back to what we just said. Intermittent fasting can be fabulous, but if this pathway isn't working, it bombs on you. The same with keto: It can be fabulous, but these people need carbohydrates on a regular basis. So that was a little side trail there, but probably worth putting out.

Dr. Jill 38:40

Actually, this is really important, Bob, because again, right now there's so much emphasis on intermittent fasting for everyone and the keto diet for everyone. And I agree with you that there are many patients who do not tolerate that and actually do far worse. So you really have to know who you're dealing with in order to use those kinds of things.

Bob Miller 38:56

Yes, just a clinical observation. When I've seen people that have a lot of issues here, I say: "Did you ever try keto or intermittent fasting, and did it go poorly?" And it's like, "How did you know?" Again, it goes back to 'everyone should' is not a good thing to say.

Bob Miller 39:17

All right. Now, let's get into the crux of the matter: What's bilirubin? It's the result of the breakdown of red blood cells. Now there are conditions [under which] you can have high bilirubin; this is a problem. Once in the liver, the bilirubin becomes conjugated, which means it's water-soluble and the body can excrete it. We're actually going to look at the glucuronidation enzymes that turn it into something that can be removed because unconjugated is toxic. It's usually not [toxic], because it can come out of the body as long as nothing interferes with its removal.

Bob Miller 39:51

All right. When it's too high, this is when the liver is not working properly and can't make the bilirubin water-soluble. Then it builds up in the liver. Causes can be hepatitis, alcoholic liver disease, some medicine overdoses, or autoimmunity—all of those things can cause the bilirubin to go too high. We get yellowing of the whites

of the eyes, dark-colored urine, itchy skin, and pale stool. We can have nausea, vomiting, stomach pain, bloating, weight loss, headaches, confusion, fatigue, and drowsiness—all from bilirubin [being] too high.

Bob Miller 40:29

Now, this is probably the slide that's going to blow everybody away. Everybody knows about glutathione and how wonderful it is. And everything you've heard is absolutely true. Some people might want to just put these words in and read the whole paper. [It says], "Water-soluble glutathione primarily protects water-soluble proteins, whereas the lipophilic bilirubin protects lipids from oxidation." Whoa! When I saw that one, it was like, "Seriously?" This was published all the way back in 2009. So in my opinion, in the functional world, functional doctors need to be aware of this and not always look to glutathione as being the savior every time.

Dr. Jill 41:18

I love that, Bob, and I'm wondering because we're doing tests that show lipid peroxides, which is the oxidation of lipids. So when someone shows those high lipid peroxides, this is something we need to really be thinking about.

Bob Miller 41:29

Absolutely. So in mice, they deleted the heme oxygenase enzyme, which generates the biliverdin and they displayed greater lipid than protein oxidation, while the reverse holds true for glutathione depletion. So this is something that I believe the functional world needs to start looking at. I was quite surprised. There's even more: Bilirubin scavenges superoxide—one nasty free radical. It inhibits—one of my favorite subjects—NADPH oxidase.

Bob Miller 42:06

Very quickly, NOX or NADPH oxidase is our friend because when we have a virus, bacteria, or pathogen, it kicks in and says: We've got an enemy here; we've got to fight and kill. Without that, we die. But I believe there are many environmental or genetic factors overstimulating the NOX enzyme. And here we have it: Bilirubin will calm that down. So what they're saying is that the expression of an inducible form of heme oxygenase—this is the one that kicks in when it's challenged—can be boosted by oxidative stress, sometimes from the NADPH oxidase activity, and then it puts the protection in. It starts creating the bilirubin that feeds back to quell this oxidative stress.

Bob Miller 42:51

So if something is stimulating the NOX enzyme and we don't have the bilirubin, that's when things can get carried away. I keep going back to it: I believe a major thing we're seeing today is the upregulation of the NADPH oxidase enzyme. It's our army; it's what kills the pathogens, but it hurts us if it's running too fast. I believe we did a Facebook live just on that subject of all the things that upregulate the NOX enzyme.

Dr. Jill 43:23

Yes, we did, and there's a lot. There's the list. Again, this is our environment; we're all swimming in toxic soup. So part of what we're seeing is that we're all getting exposed more and more to higher levels. And then, what can our bodies handle? Those who have genetic mutations are starting to get ill.

Bob Miller 43:39

Absolutely. As we've said many times, genetics loads the gun, but the environment pulls the trigger. So here's an article that says bilirubin inhibits the activation process of the NADPH oxidase. We said the same thing, but another article reinforces that concept.

Bob Miller 43:56

Now, this really surprised me. It's a potent antioxidant that can protect the cells from a 10,000-fold increase in excess hydrogen peroxide. Hydrogen peroxide can be used to kill pathogens, but [when it's] too high, [it] creates a problem for us. So it says bilirubin acts as an antioxidant, then it's oxidized to biliverdin and then recycled by biliverdin reductase back to bilirubin. We'll show that on the charts when we look at your DNA. There's more: [It] inhibited the secretion of tumor necrosis factor and interleukin-6, indicating the inhibition of the NF-kappa B pathway. I mean, it just keeps going on—what this does. It could therefore be considered an endogenous regulatory molecule modulating inflammation.

Bob Miller 44:51

Now, this is fascinating. This was—let's see. I don't see a published date. Oh yes, September 2009. Moderate-high bilirubin is associated with a reduced incidence of cardiovascular disease, including hypertension. Now, we talked about this more when we talked about the Holme cycle, so we don't have time to get into it today. But the angiotensin II is what can cause the body to hold on to sodium and excrete potassium. Moderately high bilirubin prevents angiotensin II dependent

hypertension. So there we go. And of course, we're seeing so much high blood pressure, and we see the sodium retention with the edema that goes with it.

Bob Miller 45:45

Bilirubin exerts reno—reno is [related to] kidney—in angiotensin hypertension. As we know, hypertension can affect the kidneys, and they're saying they conclude that the bilirubin exerts renal protective effects on the angiotensin II dependent hypertension.

Bob Miller 46:07

Unconjugated bilirubin modulates nitric oxide production via iNOS regulation. As we said earlier, this is 'the Carnahan reaction.' We're going to show once again where you inherited from both mother and father mutations on the two iNOS' that make it overactive. And they're saying here that they've created a significant reduction of iNOS gene expression. So there you go, Dr. Jill. We now have a way to help reduce the effect of 'the Carnahan reaction' on you.

Dr. Jill 46:38

Unbelievable. This is amazing!

Bob Miller 46:42

Now, we spoke about SIRT1, and I don't think I put a chart in this time. But SIRT1 also helps you make superoxide dismutase and eNOS, as well as knock down inflammation. It's saying that heme oxygenase has the ability to restore cellular redox and rescue SIRT1. So you can see there's a relationship between SIRT1 and heme oxygenase—they help each other out in a feedback loop.

Bob Miller 47:16

This is something we're just beginning to research, and we don't have a lot of data on it, but when bilirubin is released into the plasma, it is taken up by albumin, which serves as its transporter throughout the body. The binding is extremely high. Under ideal conditions, unconjugated bilirubin is seen in the plasma. I was hoping to get a little more research on this done before our broadcast here, but I didn't.

Bob Miller 47:45

But this is an interesting study, which was published in February 2020: "The role of the bilirubin development ratio as a predictor for mortality in critically ill patients"

without other problems. So they were saying that high bilirubin and low albumin frequently appeared and were associated with poor prognosis and critically ill patients. Their conclusion was that a higher bilirubin-to-albumin ratio is related to an unfavorable prognosis and mortality in critically ill patients. So maybe sometime we can come back when we have more information on this to learn how the albumin carries it around. I'll be honest; I don't have a strong understanding of this yet. But we need the albumin, so if the albumin goes down, then we don't get the positive effects of the bilirubin.

Bob Miller 48:37

As we know, Gilbert syndrome is a condition where people have occasional and short-lived episodes of yellowing of the skin in the whites of the eyes caused by a buildup of bilirubin in the blood. We'll show this in the software. There's an enzyme called UGT1A1 that is part of a process called glucuronidation where it takes the unconjugated bilirubin, conjugates it, and then excretes it. So if we have genetic issues here, we may not be able to excrete it properly, and then the bilirubin becomes a problem.

Bob Miller 49:12

Interestingly, homocysteine downregulates the heme oxygenase-1 enzyme. We could do a whole show on homocysteine. There are books out there that say high homocysteine virtually causes so many things that will cause you to live less longer because it does so much damage. I knew some of the damage that homocysteine did. I was not aware that it downregulated heme oxygenase. So measuring that homocysteine is so important. I'm sure, as a functional doctor, you do that all the time. You probably look at people's homocysteine [levels].

Dr. Jill 49:46

I do, routinely. And I totally agree with you. I've seen some in people in their 20s, and it's very concerning.

Bob Miller 49:53

Absolutely, and the catch-22 is that sometimes it's folate and B12, but then that can backfire in other ways. So it really becomes a tightrope [walk] as to how you want to bring that down safely. What percentage of your patients do you think have high homocysteine?

Dr. Jill 50:12

This is definitely less than mast cells. I'd say maybe 15%-20%. It's still like maybe one in five, but not as high.

Bob Miller 50:21

Yes, and unfortunately it's not measured very often. Often, when I do consultations with folks in our health coaching, we would say, "Have you ever measured your homocysteine?" [They say]: "I never heard of it. No one's ever measured it." It can be very, very important.

Dr. Jill 50:35

If you're listening out there, I like to see it below nine, but in the Bredesen Protocol with dementia and those kinds of things, we're even going below seven. Then, on the other hand, below four is an issue too, so there's a happy medium as well.

Bob Miller 50:47

Yes, absolutely, because we need homocysteine to go down through transsulfuration to make our glutathione. So again, every time we do a show here, we talk about not too little, not too much. So I now want to focus on the POR enzyme. I'm very intrigued by this guy because it donates NADPH to heme oxygenase-1, but not only heme oxygenase-1; most of your cytochrome P450s use POR to donate the NADPH. So you can have genetic mutations, and I'll show you those when we look at your genome. You can have mutations in G6PD [and/or] ME1. We mentioned this earlier: You need FAD to be the cofactor—not enough riboflavin causes that. Then you can have mutations in G6PD or ME1 or they can be just fine, but if you've got Nrf2 issues or KEAP1 issues, they don't get stimulated and they don't do their job. Let's go back to riboflavin. What is your favorite dosage for riboflavin?

Dr. Jill 51:54

It's funny because riboflavin 5'-phosphate is the active form, and it comes in the 30s [mg], which is, I think, way too little. I usually start at 100 [mg], and with migraines, I'll go up to 400 [mg] per day.

Bob Miller 52:06

Okay. All right. I was curious [about] what your dosage was.

Now, people probably have never heard of the POR gene, and I think we need to look at this guy because it provides instructions for making the enzyme cytochrome

p450 oxidoreductase; 50 enzymes depend upon it, and they are involved with the synthesis and breakdown of various molecules and chemicals within cells. So if we don't have those CYPs working, these are the folks that have all the negative effects with medications or are exposed to any chemicals and can't handle them. As we said, it's involved with the metabolism of ingested substances, such as medications, in the liver. Now, this is going to surprise you: It's involved in your drug metabolism, your steroid metabolism, your xenobiotics, and your heme oxygenase. So if this guy doesn't have a source of NADPH or it's got mutations where it doesn't have FAD, it's not going to do this job.

Bob Miller 53:13

Now, we're not going to spend a lot of time on this one, but look at this guy. This is a chart of how POR is involved in all of your hormones. Here are your cholesterol, your pregnenolone, your progesterone, and your testosterone. Every time you see this little orange here, POR is involved, so you're going to have hormonal disruption.

Bob Miller 53:37

And then here it talks about bone formation, the steroid metabolism we just talked about, drug metabolism, detoxification, your hemoglobin, metabolism, and your cholesterol—all controlled by POR. And I just want to illustrate again the importance of NADPH because it helps recycle your thioredoxin (TrxR), your glutathione, your catalase, it helps DHFR deliver folate, and it helps the POR. But here's NOX (NADPH oxidase). NOX will use it to make free radicals, and if this guy is upregulated, likely all of these others are going to suffer. And that's why I keep going back to [saying that] we've got to be looking at the NOX enzyme.

Bob Miller 54:27

So again, I talked about this a little bit, but just a quick review: The succinyl-CoA comes from the Krebs cycle; dietary deficiencies or possibly glyphosate may impede it; mutations in any of the heme cycle enzymes may lower it; and lead may lower it. And then the porphyrins go from one to another through the cycle, and they may block the GABA receptor sites where people get hangry, where it's like: "I'm upset. I'm frustrated. I've got to have some food." They feel better after they eat.

Bob Miller 55:02

Now, action steps. Again, I would encourage people to watch episode 102. Remove exposure to mold in your environment. I can't emphasize that enough, and I'm sure you talk to people about mold, and they'll tell you, "Oh, I don't have any mold in my

house," because they don't see anything black growing on the walls. That doesn't mean you don't have mold. It can hide in many places. And I know you've done other webinars on mold. I'd encourage people to watch them. But take it seriously. Make sure you don't have any virus, clostridia, or any source of lipopolysaccharides. Here are a couple of nutrients that can support TNF-α: Black cumin, milk thistle, EGCG, and Boswellia. All of those can help with TNF-α.

Bob Miller 55:49

NF-Kappa B—remove exposure to mercury; treat viruses; consider reducing exposure to glyphosate; reduce TNF-α over stimulation. We're just beginning to dig into this because we may make a supplement for NF-kappa B. The vitamin E GAMMA version, curcumin, fish oils, alpha-lipoic acid, NAC, but you've got to be careful, reishi mushroom, green tea, and resveratrol calm down NF-Kappa B. In other words, what we're doing here is saying: Let's not stress heme oxygenase as much.

Bob Miller 56:24

NADPH oxidase—take care of the histamine, the oxalates, and glutamate, and get away from air pollution. I remember you saying that when you had a big fire in your town, it really impacted people.

Dr. Jill 56:38

Yes, we saw TNF-α, TGF-β, and all kinds of things rise just from the smoke exposure because it was so toxic.

Bob Miller 56:45

Yes.

Keep homocysteine at a healthy level, keep dopamine at a healthy level, keep sulfites at a healthy level, keep aldosterone at a healthy level, [as well as] IL-6, mTOR, and autophagy. There's a lot there, but all of those have to be taken care of. Curcumin, spirulina, and then any lifestyle nutrients that would support healthy levels of the stimulators listed above.

Bob Miller 57:10

[Episode 42 on] interleukin-6. Again, when I copied this, there were 3,300 people who viewed it, and that's where we spoke about interleukin-6. And probably the

interest comes from the cytokine storm everybody was trying to look at. Mold, Lyme disease, the lipopolysaccharides, EMF, radon air pollution, particulates, lead, mercury, aluminum, glyphosate, the omega-6s, particularly canola oil, VOCs, pesticides, and any mTOR stimulator—those will all stimulate IL-6.

Bob Miller 57:48

What we've talked about here is: How do we take the pressure off of heme oxygenase? I'm not going to read these. If somebody's watching, they can just pause it and write these down. But all of these things will again stimulate interleukin-6, and then you can have a genetic gain of function on interleukin-6. And here are some of the things that can reduce it: Hydrogen water, thiamine and riboflavin, black cumin, apigenin, pine bark, oxytocin, PEMF—I'm going to have a slide just on that; I know that's one of your favorite subjects, Dr. Jill—vitamin D, EPA and DHA, hyperbaric, selenium because it supports glutathione, make sure your blood sugars are controlled, [maintain a] healthy weight, and [perform] moderate exercise.

Bob Miller 58:36

Then how do you support SIRT1? SIRT1 supports endothelial nitric oxide, good blood flow, supports a major antioxidant, and knocks down those two inflammatory enzymes. Reduce or eliminate high fructose corn syrup. We're going to look back on this someday and say, "What were we doing?" SIRT1 is part of our anti-aging. High fructose corn syrup inhibits it. Intermittent fasting—again, if you don't have problems with the heme cycle—supports heme oxygenase, because that supports it. This is dependent on NAD+. [To] reduce the overstimulation of it, resveratrol, and pterostilbene.

Dr. Jill 59:24

And Bob I was just going to say that this is where people are talking a lot about autophagy. Autophagy is basically cell-programmed death, so it prevents those cells that go rogue from becoming cancerous. It's very, very important for anti-aging because this senescence of the cells as they get older—if they're not dying off, that's the most common thing that causes aging. So everything you're describing here I just want to put in practical application as basically anti-aging and prevention of cancer.

Dr. Jill 59:51

Two other drugs that I don't recommend but that also have SIRT1 activity and [induce] autophagy are rapamycin and metformin, so those are the popular [ones]. They have side effects too, so again, you wouldn't want to use them without a

physician's help. But this is all about anti-aging and the prevention of cancer in the end.

Bob Miller 1:00:11

Absolutely. Well, here you can see SIRT1 inhibits mTOR, which inhibits autophagy. So that's why SIRT1 is one of my favorites. When people have homozygosity on SIRT1, they're usually struggling. They've gone to 20 clinics, and nobody can figure out what's happening.

Bob Miller 1:00:30

All right. How do we support heme oxygenase? Support KEAP1 and Nrf2. Particularly when I see a homozygous mutation on the KEAP1 overactive, these folks are in trouble. Here's your sulforaphane—milk thistle, turmeric, resveratrol—again, [they] support adequate NADPH by not having an overactive NOX. We call that the NADPH steal. Spirulina calms that down a little bit. Again, adequate NAD, but after you've calmed down, NOX. And then hops [extract], panex ginseng, sage, rosemary, turmeric, broccoli, and probably others support the enzyme. But again, I go back to if you think you're going to take care of it all just by doing this—as you've learned, there are so many other pieces to this puzzle that you have to take care of.

Bob Miller 1:01:20

All right. I thought you would enjoy this, Dr. Jill. The pulsed electromagnetic field increases heme oxygenase 1 and superoxide dismutase.

Dr. Jill 1:01:34

Yes, wow!

Bob Miller 1:01:36

And I believe you have something on your website—the PEMF that you recommend.

Dr. Jill 1:01:42

Yes. I love the higher dose. It's, actually, if you look right down there on the floor down there… I use it every single day. And I'll tell you something else, Bob, that's related to the whole stuff we talked about platelet activation RANTES—my theory, and I have evidence to back it up, is that it actually helps with the viscosity of blood. So, people who are struggling after COVID or after Lyme, with blood viscosity, I think it actually helps circulation. And I almost wonder if sometimes that's the most

important thing that we feel because our blood is flowing better because it's like a magnet that actually helps the blood flow—circulation.

Bob Miller 1:02:13

Sure. If you go back to that video, we talked about it. It's the upregulation of iNOS that activates the platelets. So if upstream you're able to slow that whole pathway down, it would make sense that it's going to improve the circulation.

Bob Miller 1:02:30

We've also talked about molecular hydrogen. So what they're saying is that hydrogen-rich water reduces reactive oxygen species production by inhibiting NADPH oxidase activity. So that, of course, is going to take some strain off of your heme oxygenase. In case anybody doesn't know, you can get machines that'll knock the hydrogen loose from your water, or you can get some capsules.

Dr. Jill 1:03:00

That's what we have here, Bob. This is a hydrogen machine. I have it right next to my desk here because I know we love to use this. You can keep explaining, but I want to show [everyone]. They are expensive, but for me and probably for you too, I think they're so worth it because it neutralizes this reactive oxygen in the water, so it's very, very safe.

Bob Miller 1:03:20

Absolutely. So you can breathe the hydrogen, or there are actually little tablets that you can drop into water that'll at least not get loose from the water, and it inhibits the NADPH oxidase activity plus a lot more.

Bob Miller 1:03:36

So here we have molecular hydrogen against sepsis. It upregulates SOD, heme oxygenase-1, and catalase and suppresses NADPH oxidase activity. So I've been asked already, and they said, "Bob, if you could do one thing from a functional standpoint, what would it be?" I think I'd pick hydrogen.

Dr. Jill 1:04:01

Bob I agree. I want to just pause there because I just had this vision. What if, in ICUs in hospitals, every bedside had the breathing... You just talked about sepsis and prevention. I wonder how much really severe illness we could prevent if we got

these ill people breathing hydrogen or taking the tablets—but breathing it is even more powerful. Wouldn't that be amazing?

Bob Miller 1:04:23

Yes. I mean, look at all it does. It neutralizes peroxynitrite (-ONOO). Here's your hydroxyl radical (-NO). It slows down iNOS. It slows down NADPH oxidase. It increases SOD, heme oxygenase (HO-1), and catalase (CAT). It's all from number one on the periodic table of elements—hydrogen.

Dr. Jill 1:04:44

Yes, it's so simple.

Bob Miller 1:04:45

It's so simple, and maybe that's why we're not talking about it much. A little bit of exercise will increase the heme oxygenase as well.

Okay, now we come to looking at you. Are you ready for this?

Dr. Jill 1:05:04

I'm ready.

Bob Miller 1:05:05

All right. Here you are. This comes from the functional genomic analysis software. This is the whole of what we call the RANTES map. Each of these circles is an enzyme. What we can do is click on any one of these, and it'll actually show us what's happening. So you can see here, Dr. Jill, your tumor necrosis factor—see it pop up on the side here. You're fine. But we talked about this before in 'the Carnahan reaction.' You do have one mutation on the HFE that causes you to absorb a little bit more iron. We didn't talk about this before because we didn't have it, but you do have a gain of function on one of the NF-kappa Bs.

Dr. Jill 1:05:49

And just for those watching, if maybe your doctor tested you for hemochromatosis, HFE is one of the main genes for that. If you have two copies, you have hemochromatosis. But as we're talking here, carrier one copy does make a difference, even if you don't have full-blown hemochromatosis.

Bob Miller 1:06:04

Absolutely. It can cause you to absorb a little more iron. It's incredibly common among people of English and Irish descent. So then we continue down the pathway, and we need SIRT1 to hold it back. And you're fortunate; you do not have SIRT1. What we're finding [is that] the people that are just really struggling might have TNFA, HFE, a weakness in SIRT1, exposure to mycotoxins, and Lyme disease. These are the people who are just struggling so badly.

Bob Miller 1:06:35

Then we stimulate the NOX enzymes. Then there's an enzyme called KIT that will cause the mast cells to be a little overactive. I don't know if we spoke about this, but you've got one little heterozygous on a KIT chain that could cause your mast cells to be a little overactive. Then we make histamine. Again, watch our video on histamine. And here are the histamine and methyltransferase enzymes. I don't have it on here, but that's what we spoke about. If you've got histamine and you take folate, B12, or SAMI, you'll make more n-methylhistamine. And then, if you're MAO-A and MOA-B can't handle it, this is worse than the original histamine.

Dr. Jill 1:17:16

Yes, and in my experience, Bob, in the early days right after my breast cancer, I realized I had methylation issues—MTHFR, one gene mutation—and I took a lot of methyl folate, and it did not go well, as you can imagine. Later on, as I've detoxified and done other things with the genes, I can definitely tolerate a milligram or two, but in the early days, it was disastrous, just like you said.

Bob Miller 1:07:35

Yes.

And then histidine decarboxylase. This actually causes the body to take the amino acid histidine and make histamine. You do not have any of the evidence-based ones. In other words, these are the ones where there's literature that says this really impacts it. However, when we look at the ones for which there's no evidence, there are still a few, but we don't know what they do. But they could be a gain of function, but we don't know for sure.

Bob Miller 1:08:01

Then here we go: 'The Carnahan reaction.' NOS2 is what makes a lot of nitric oxide to kill pathogens. And you've got an upregulation. It may be a little hard to see, but there's an up arrow here. Mother and father gave you a mutation. Up arrow here, your mother and father gave you a mutation. And then that will stimulate the NOS uncoupling, which makes the superoxide, which then makes our ONOO (peroxynitrite), which then further depletes the BH4. It's worth noting that BH4 is needed to make your serotonin and is involved with your dopamine as well. Many times people are depressed because they don't have enough BH4.

Bob Miller 1:08:50

All right, then we come over here and we activate the platelets. We activate the platelets. And then we need our good fats—let me just make that a little bit bigger—made by the FADS enzymes. You're not too bad here; you just have a little bit on FADS2, nothing on FADS1, and one on ELOVL2, which is the EPA to DHA.

Dr. Jill 1:09:25

I just want to mention it there, Bob, because you mentioned this, I think it's important for people listening [to know] that with protectins and resolvins, you basically bypass that pathway if you have issues. Those are the SPMs—SPM active, SPM supreme—there are a lot of them out there. I found that to be incredibly helpful for me with inflammation, and it makes sense because I'm bypassing all of those FAD enzymes. And the riboflavin for me for 20 years, now I know why, but I've always taken at least 100 or 200 [mcg] a day of riboflavin for years because I really do better with the riboflavin, which makes sense with the FAD enzyme.

Bob Miller 1:09:54

Absolutely.

Now, this could be a future show to talk about because I'm really becoming enamored by arachidonic acid. The tumor necrosis factor through PLA2 brings out the arachidonic acid. There are a couple of pathways—I don't have that chart ready—but one of them is to take the ALOX enzyme and make leukotriene B4, which is a nasty, nasty leukotriene. You don't have any mutations here, but some people have a gain of function, and the CYP, this one right here (CYP4F2), calms down leukotrienes. Clinical observation: When somebody has homozygous here and homozygous here, they've got inflammation that they just can't seem to figure out why. So we're researching that. So you're fortunate that you're clean as a whistle there.

Bob Miller 1:10:49

All right, now, drum roll! We're going to look at your heme oxygenase. So here you can see that your HMOX1 and your HMOX2 make the biliverdin and the bilirubin. You can see that you've got one homozygous and two heterozygous on your HMOX1. Then you've got a homozygous on HMOX2. Now, you are incredibly lucky because you do not have the gain of function on KEAP1. It's the folks who have this one, either one or two, particularly the twos, who are sometimes even bedridden from mycotoxin exposure. And you're very fortunate; I don't see this very often. You're perfect on all your Nrf2s. So you don't see this often: Perfect on KEAP1, perfect on Nrf2. But you do have weaknesses on HMOX1 and HMOX2.

Bob Miller 1:11:49

Now, talking about riboflavin, here are the riboflavin transporters. You can see: perfect. FLAD1, which is making your POR perfect. So you really lucked out here. Your POR enzyme [is] perfect. G6PD—not a thing—not one little thing. ME-1—perfect. As I said, the Nrf2 and KEAP1, when I look at these, very seldom is this area this good. So you're very fortunate there because it could have been worse if you had issues here.

Bob Miller 1:12:35

Now, let's look at your heme cycle. You do have a couple of PON1s that clear your glyphosate. Have you ever tested for glyphosate?

Dr. Jill 1:12:43

Oh, yes, Bob. Again, I grew up on a farm—organophosphates, glyphosates—[and] massive exposures, I think, contributed to some of my history of illness. When I first tested, when they very first came out with testing, I was three times the normal limit for farmers on application day. And that, actually, was with an organic diet and a pretty clean lifestyle. So this is absolutely valid for me as far as exposure and accumulation of glyphosate.

Bob Miller 1:13:08

Yes. Have you tested recently?

Dr. Jill 1:13:10

I'm better. I'm low now, finally, with all the detox I've done.

Bob Miller 1:13:14

Good, good, good.

PON1, which, by the way, stands for paraoxonase, clears the pesticides. You've got to be very careful. Sometimes people go golfing, and some people will smoke a cigar and put the cigar on the grass. It's not a good idea.

Dr. Jill 1:13:38

You know, Bob, they're talking with Dale Bredesen about writing 'Golf Course Alzheimer's' because there's so much related to exposure on golf courses and pesticides and the brain. So it's a very real phenomenon. I always ask people: Where do you live? Do you live near a golf course?—because they're likely going to be exposed to a lot more pesticides.

Bob Miller 1:13:55

Absolutely.

Now, your ALAD enzyme, as you can see here, you've got two heterozygous mutations. Then on the UROS, you've got one, and on the CPOX, this is a new one that we've just added, literally in the last couple of weeks.

And this is a rather significant downregulation of the CPOX enzyme. So we could make an argument—there's ALAD, and the keyword is potential—that you may not be doing this as strongly as you should.

Bob Miller 1:14:28

Then you get over to the HMOX, and it's not doing its best. But again, you're extremely fortunate—KEAP1, Nrf2, POR, and G6PD. So what's interesting is that you really got hit hard on the iNOS, but I would say that [you're] probably one out of a thousand, if not less, that has everything perfect right here. So you're very fortunate there. That's you for this section. Like I said, you might have a little [inaudible] because of the HFE and the NF-Kappa B. This could be pushed a little bit. Fortunately, your SIRT is good. But for you, supporting this heme oxygenase might be to your advantage. I believe you did start a couple of things that support—didn't you? Some sage or something?

Dr. Jill 1:15:26

I did. I'm trying to think of what we talked about because first the iNOS was lysine, and Resveratrol I added back in. I did SPMs. I'm thinking recently with heme ox[ygenase]... B5 was that one of the cofactors?— pyridoxine. Or am I thinking about adrenals, maybe?

Bill Miller 1:15:44

I think you're thinking about adrenals, yes.

Dr. Jill 1:15:45

Okay.

Bill Miller 1:15:48

Okay, well, there you go. We can now see why you had some of the struggles that you had.

Dr. Jill 1:15:55

And I'll just say one little thing about that because we've been talking about pathways as we keep learning new things and you share all your amazing knowledge. And I think I've shared on other [things] with the iNOS video that we did about how I was struggling with low blood pressure and all of this. I just told you before we started, but I want to say this for people who are thinking, "Oh, there's no mold in my house." I'm kind of the mold queen. I'll just say it. I love mold and I deal with mold; I really help so many patients with mold, and it's one of my favorite things to do.

Dr. Jill 1:16:23

Just recently, Bob, I told you that two or three weeks ago I found chaetomium, which is one of the nastiest [species], behind my fridge because there was a small leak in my home. Now I am feeling so much better. I'm only just saying this because here I am: I know mold, I know how to prevent mold, and I do all the right things. And [yet], even in my [own] home, I found mold recently, and there's no doubt all the stuff we've been talking about the last six months with the low blood pressure and the fatigue and some of the symptoms I was having related to that iNOS pathway were related to the mold in my kitchen. So if you think there's no mold in your house, check again because often there are hidden things, even for the best of us who know what to do, that are causing illness.

Bob Miller 1:17:00

Absolutely. I'm so glad you found it, and I'm sure it was a relief for you to know that there was a cause behind this.

Dr. Jill 1:17:08

Right, yes.

Bob Miller 1:17:09

All right. Just a little commercial: If you're a health professional, this is not for the general public. The software and the maps we looked at were made by the software "Your Functional Genomics." If you'd like to check us out, just go to functionalgenomicanalysis.com. We have an online certification, and you can save $100 by using the code 'Dr. Jill'. The first couple of modules are free, then there's a charge, and you can save $100 by using the code 'Dr. Jill'. If somebody wants to talk to us here at the office about health coaching, [go to] tolhealth.com, [or call] 717-733-2003. Again, the software is "Functional Genomic Analysis", and Yvonne Lucchese or Chrissy can help health professionals.

Bob Miller 1:17:58

So there we go. That's a really quick [explanation of] why we need to be aware of heme oxygenase. To wrap it up, what we need to do is take away the environmental factors that would stress it, not have the enzymes that also stress it upregulated, and then find out if the heme oxygenase enzyme needs help, if the heme pathway needs help, or if we need NADPH through the POR enzyme.

Dr. Jill 1:18:25

Bob, thank you as always. I love going deep, and I know so many of our listeners do. I think this is going to get thousands of more viewers. I'm going to share it everywhere that I can. I just want to thank you for your work. I always love promoting you and helping you get more practitioners trained because truly, I feel like this personalized approach is the thing that's the game changer for my most complicated patients, and I know you've seen that as well.

Dr. Jill 1:18:47

So I just want to thank you publicly again for all of your hard work and all of your brilliance in helping us find the pathways. Even my own health has benefited from you, and I want to say that publicly because we're all grateful for all the work that

you do and that you continue to educate. And I really believe this is the future. I've said before that I have a book coming out next year in a documentary, and I would say I want to teach the teachers and influence the influencers because the more we can impact those who are out on the front lines, like functional medicine and doctors… And you're one of those people. You're one of those people who teaches the teachers and influences the influencers in a very positive way that's changing health and the world. So truly, thank you for your work; I'm so grateful.

Bob Miller 1:19:25

Well, it's my pleasure. And I do have to also give credit; I'm very fortunate that my son is following in my footsteps. Now he has his Masters [degree] in pharmacogenomics. So a lot of these things that I pointed out today, he's the one who pointed them out. He pointed out the POR. He found the gain of function in the 5-LOX. So we're having fun geeking out together and working on it.

Dr. Jill 1:19:48

That is even more beautiful.

So as always, thank you. Thank you all for listening. Leave some feedback, share it with your friends, and we'll see you next time.

Bob Miller 1:19:58

Okay, [it was a] pleasure to be here.