200: Resiliency Radio with Dr. Jill: Bridging Beauty & Health with Nitric Oxide - Dr. Nathan Bryan

00:13
Dr. Jill: When I really knew something was wrong, was when I started having trouble walking up the stairs. I was supposed to be grateful and happy and healing and well and thriving, but I did not feel that way. I was so sick. Like always, I wanted to find an answer, and I had to figure it out. And I had to figure it out to save my own life. So I dove in.

00:38
James Maskell: Jill is the leading voice in biotoxin illness and chronic conditions that are driven by toxicity.

00:43
Bree Argetsinger: Oh my gosh, you're dealing with mold? You have to work with Dr. Jill Carnahan.

00:47
Patient 1: Dr. Jill is the first person that actually began to shed some light on the problem.

00:53
Dr. Jill: What I do is listen to the patient, and we together talk about what else is possible.

00:59
Patient 2: I don't know why I'm crying.

01:02
Patient 3: She saved my life.

01:06
Dr. Jill: The deepest lessons and most profound insights come in the suffering, come in the dark moments. Self-compassion is the healing transition that shifts something inside of us. It's actually the thing that we need most in order to heal.

01:26
Narrator: *Doctor/Patient*—available now at DoctorPatientMovie.com.

Dr. Jill 01:43
Welcome to *Resiliency Radio*, your go-to podcast for the most cutting-edge insights in integrative and functional medicine. I'm Dr. Jill, your host, and in each episode we dive into the heart of healing and personal transformation. Join us as we connect with renowned experts, thought leaders, and innovators at the forefront of medical research and practice, empowering you with knowledge and inspiration and aiding you on your journey to optimal health.

Dr. Jill 02:09
Hey guys, it's out! You've probably heard me say this now if you've been watching my podcast. But my documentary, which has been many years in the process, is now available—streaming online—at DoctorPatientMovie.com. It has been a joy and a treasure and a little bit terrifying to share this very, very intimate personal journey with you. And I hope you'll go share it with friends and inspire someone that you love.

Dr. Jill 02:32
Today, I've got a special guest, Dr. Bryan. He is an international expert on nitric biochemistry and molecular medicine. He has more than 20 years in academic research leading to many seminal discoveries, and this has resulted in dozens of issued US and international patents. Today, we're going to quiz him on this—I think, cutting-edge—so important topic of nitric oxide. If you don't know much about it, stay tuned. We're going to dive in. Products from his innovations are the most successful nitric oxide products in the market and are responsible for hundreds of millions of dollars in revenue around the globe and, most importantly, improved patient health.

Welcome, Dr. Bryan! I'm so glad you're here today.

Dr. Nathan Bryan 03:12
Hi, Dr. Jill. It's so good to be with you! Thanks for having me.

Dr. Jill 03:14
You're welcome. Before we dive into nitric oxide, which I just dove into last fall—I gave a presentation, and I really started to dive into it, especially for women of menopausal age, which is me, and we'll dive into that—I always love to know: What's your background? How did you get into the science of nitric oxide? Tell us a little bit about your story.

Dr. Nathan Bryan 03:34
I was introduced to the science of nitric oxide in the late '90s, early 2000s. I was a student at the LSU School of Medicine. I was working on a PhD in molecular and cellular physiology, and a Nobel Prize had just been awarded for the discovery of nitric oxide. Lou Ignarro, one of the gentlemen who shared the Nobel Prize, came to the LSU School of Medicine and gave a talk. I had a chance to have a conversation with him. I went and had dinner with him that night. I was fascinated by this molecule. There was a pharmacologist at that school and I trained under him, Martin Feelisch, who had been in the nitric oxide field for 20 years prior to that.

Dr. Nathan Bryan 04:10
My work was trying to figure out: How do we detect this gas? Nitric oxide is a gas. It's naturally produced in the body. And once it's produced, it's gone in less than a second. At the time, 25 years ago, there were no sensitive and selective methods to detect this gas at physiological levels. So, that was the basis for my PhD work: How do we create a detection method where we could detect physiological amounts of nitric oxide in blood, tissue, saliva, and biopsies? We figured that out. We developed the methods and the analytical tools to do that and create a fingerprint of xenobiology in many different diseases, from cardiovascular disease to diabetes, ischemia-reperfusion injury, stroke, and brain injury. That armed us with tools and techniques with which we could answer a lot of important biological questions in science and medicine.

Dr. Nathan Bryan 05:03
We started publishing 10 to 12 papers a year. I finished my PhD in less than two years because we had solved some major problems in diagnostic and nitric oxide biochemistry. Then I went to Boston and trained as a cardiology fellow in Whitaker Cardiovascular Institute for two years. Then I joined the faculty of UT Medical

School in Houston as a professor of molecular medicine. And Ferid Murad, one of the other guys who won the Nobel Prize, was my department chair. He recruited me to join the faculty. We had a drug discovery program.

Dr. Nathan Bryan 05:31
Since day one, our whole mission has been to understand the mechanism of disease to the extent that we could fix it and develop rational therapies. We've come a long way because nitric oxide is fundamental to many chronic disease processes. It's really foundational. As you know, as a physician, there are many things you've got to see through, diagnose, and get to the root cause. But what we're finding is that nitric oxide deficiency is one of the earliest signs of the onset and progression of chronic disease.

Dr. Jill 06:05
Yes. That is why I am here, and I am so absolutely delighted and honored to have you as a guest. As I dove in, I was like: "Wow! This is the biggest discovery that no one's talking about." And in medicine—I went to medical school 20 years ago—there was no discussion of nitric oxide. What was the year that it was really discovered and you started publishing?

Dr. Nathan Bryan 06:26
The molecule was discovered in 1987. It was the first seminal paper showing that this endothelium-derived relaxing factor that was discovered in the 1980s was nitric oxide. From '87—discovery; a Nobel Prize was awarded in 1998. Now we're 26 years post-Nobel Prize and [there are] close to 200,000 scientific papers published on nitric oxide.

Dr. Nathan Bryan 06:52
Even when I was a professor of medicine and taught in medical schools, there was one course that we taught—it was the molecular basis of cell signaling—but it was only [for] the MD-PhD students. I taught that course. I think that was the only mention of nitric oxide throughout the entire medical school curriculum. There's a little bit of mention of it in first-year physiology courses. Maybe a little bit in pharmacology when you talk about PDE5 inhibitors and organic nitrates for ischemic heart disease. That's it. But it's so fundamental to medicine. It's very

difficult to change the curriculum in medical schools and how we train future physicians.

Dr. Jill 07:29
Yes. This is kind of a pattern. We have an amazing medical system in the U.S., and we have wonderful training. But often, if there isn't a blockbuster drug that is related to the concept, or if there isn't a financial reason to really promote it… Now, again, this is so core to so much physiology.

Dr. Jill 07:46
One of the things that really surprised me was—and you can correct me if I have the stat wrong—I think I heard that over the age of 40, we have about 50% production of nitric oxide. And over the age of 60, it might be more like 15%. To me, this is one of the core foundational concepts of anti-aging: How do we make more nitric oxide naturally?

Dr. Nathan Bryan 08:08
That's right. If you look at the general population and age-dependent loss of nitric oxide, really, what we're determining is endothelial dysfunction. The endothelial cells are the cells that line all the blood vessels. There's an enzyme contained in the endothelial cells called nitric oxide synthase. When that enzyme becomes uncoupled and dysfunctional, then that's the basis for endothelial dysfunction. The older we get, the less we make. There's this age-related decline: a 10% to 12% reduction per decade. By the time you're 40 or 50, on average, you have about 50% less nitric oxide. But that doesn't have to be the case because we figured out how to prevent that age-related decline. We can certainly accelerate it by the Western lifestyle.

Dr. Nathan Bryan 08:54
We're seeing 20- and 30-year-old young men and women with the vascular age of a 60- or 70-year-old. I'm the exact opposite of that. I turned 50 in November, but I've got the vascular age of a 32-year-old. So we can certainly slow that progression and, in the best-case scenario, prevent that age-related decline. But it's things like the sedentary lifestyle. It's the standard American diet. It's exposure to things like herbicides, pesticides, glyphosate. Basically, all the standard cardiovascular risk

factors lead to this dose-dependent or stepwise reduction in nitric oxide production.

Dr. Jill 09:33
Oh gosh, I have so many questions for you. This is so relevant. Whether—if you're listening—you're in your 20s, 30s, 40s, 50s, or 60s, it's relevant to every single one of you out there.

Dr. Jill 09:46
It's a fascinating story—how we make nitric oxide and why the microbiome of even the mouth matters. Do you want to start with a story there and tell people listening why that is such a big deal and why the pesticides in our food could affect the mouth and could affect production?

Dr. Nathan Bryan 10:01
When I got started in this field, there was one primary pathway for the production of nitric oxide—the nitric oxide synthase enzyme. It's found in endothelial cells. It's found in neurons and it's expressed by our immune cells. It's responsible for killing bacteria, viruses, or any pathogen. As a biochemist, this is an energetically and kinetically unfavorable reaction. So my whole thought process, trained in biochemistry and physiology, is that there's enormous redundancy in the human body. There's always a backup compensatory system. If nitric oxide was this critical fundamental molecule that we all thought it was, why is there only one pathway to make it? And why is that pathway so damn complicated biochemically?

Dr. Nathan Bryan 10:43
Fast forward: Now we know that the microbiome [and] the bacteria that live in and on our body part of their job and role is to produce nitric oxide. It does this through inorganic nitrate that's found primarily in green leafy vegetables. They metabolize this two-electron reduction to inorganic nitrite. Then we swallow it, and we make nitric oxide in the lumen of the stomach. So the oral bacteria are absolutely essential for this pathway because humans do not have this enzyme. We lack a functional nitrate reductase enzyme.

Dr. Nathan Bryan 11:17

When you think about things we do on a daily basis, like mouthwash, two out of three Americans use mouthwash every day and two out of three Americans have an unsafe elevation in blood pressure. We and others have published that that's not coincidental; it's causal. And then things like fluoride—fluoride's an antiseptic, it's a neurotoxin, and it's just down your thyroid function. When we start to understand, "How do we improve and support the diversity of the microbiome and then eliminate things that destroy it or disrupt it?" then we can start to improve this ecology—improve nitric oxide production.

Dr. Nathan Bryan 11:52
We're starting to see remarkably that we can reverse resistant hypertension and get people off of anti-hypertensive medications because, as we're finding in a lot of cases, for patients with resistant hypertension, their hypertension is a consequence of oral dysbiosis. So the ARBs, the ACE inhibitors, and the calcium channel antagonists aren't going to normalize the blood pressure because it's not a renin-angiotensin problem; it's not a calcium mobilization issue. It's an oral dysbiosis.

Dr. Nathan Bryan 12:22
If you interrogate your patients and say, "Are you using mouthwash or fluoride in your toothpaste?" two out of three people say yes on the mouthwash and ten out of ten people say yes on the fluoride. Then you go: "Okay, do me a favor. Stop using mouthwash. Get rid of fluoride. Give me 30 days and let's come back and we'll test your blood pressure." Remarkably, it's somewhat normal. That's remarkable that you can just support the microbiome, improve nitric oxide production, and normalize your blood pressure.

Dr. Jill 12:48
Yes. This was one of my massive ahas when I did the research. I was still using natural mouthwash, but it doesn't matter—you're destroying the microbiome with antiseptics. That was a massive aha!

Dr. Jill 13:00
For people listening, let's go to this mechanism. Basically, nitric oxide is a vasodilator. It opens everything. If you have this constriction and a lack of nitric oxide, that's one of the drivers of blood pressure rise. What percentage would you

say are related to this? Is it 100%? Is it 80%? Obviously, there can be kidney issues and other issues. What percentage would you say is related to nitric oxide production at some level for blood pressure issues?

Dr. Nathan Bryan 13:28
I think probably 95% of essential hypertension is related to a loss of nitric oxide production. It's about vascular reactivity, regulating blood flow, and vasodilation. Blood pressure control is a balance between vasoconstrictors and vasodilators. Nitric oxide is the primary vasodilator. If you lose the ability to produce nitric oxide, the vasoconstrictors take over. Now you're pumping the same volume of blood through smaller pipes. As a consequence, you see an increase in pressure. If we can just restore the production of nitric oxide... And the ACE2 inhibitors have a nitric oxide effect because they downregulate these two receptors. There's always a crosstalk in that. It may not be a renin-angiotensin problem. If we can just provide nitric oxide, restoring the endothelial function, then not only do we improve the vasodilatory capacity of the blood vessels, but you actually improve the compliance of the blood vessels. So now, with each heartbeat, you can dampen that pulse response and it'll lead to less damage to the endothelial cells.

Dr. Jill 14:36
Yes. And I want to get real because many of you who have blood pressure issues may not feel it, and you may not care because you don't feel differently. But if you're a man who has sexual dysfunction or a woman who is anorgasmic (has trouble with orgasm) or even activation of lubrication and all those things, these things—which people do care about, right?—are very related to nitric oxide as well. Do you want to comment on why it's so important for men and women, for normal sexual function, to have good nitric oxide production? Because this is where it matters to people, right?

Dr. Nathan Bryan 15:07
Yes, that's right. I see people all the time. They're at an increased risk for cardiovascular disease, and they don't pay attention to it. But once they start to develop sexual dysfunction, then it becomes a crisis.

Dr. Jill 15:17
Yes! It gets their attention.

Dr. Nathan Bryan 15:21
It's all about the regulation of blood flow. To get an erection in men or women, you have to have dilation of the blood vessels. That dilation is dependent upon the blood vessels supplying that sex organ to be able to produce nitric oxide. Without nitric oxide, there's no dilation; you can't get engorgement. In men, it leads to erectile dysfunction. But it's the same thing in women. You have to dilate the blood vessels of the clitoris. For women to become orgasmic, you've got to see an increase in labial pressure, clitoral pressure. That pressure comes from an increase in blood flow, which is due to nitric oxide production. So if there's no nitric oxide in the lining of the blood vessels, there's no dilation, there's no engorgement, there's no increase in pressure, and you cannot reach orgasm.

Dr. Nathan Bryan 16:07
We call that the canary in the coal mine because if you have vascular dysfunction in the vascular bed of the sex organs, it's not just isolated there; it's systemic. It's in your coronary arteries. It's in your cerebral arteries. It's in your pulmonary arteries. It's systemic disease that you have to pay attention to and correct. Or else that sexual dysfunction is going to lead to advanced coronary artery disease, heart attack, or stroke, and you become a statistic. But we can avoid that.

Dr. Jill (pre-reording) 16:32
Hey, everybody. I just stopped by to let you know that my new book, *Unexpected: Finding Resilience through Functional Medicine, Science, and Faith*, is now available for order wherever you purchase books. In this book, I share my own journey of overcoming a life-threatening illness and the tools, tips, tricks, hope, and resilience I found along the way. This book includes practical advice for things like cancer and Crohn's disease and other autoimmune conditions, infections like Lyme or Epstein-Barr, and mold- and biotoxin-related illnesses. What I really hope is that as you read this book, you find transformational wisdom for health and healing. If you want to get your own copy, stop by ReadUnexpected.com. There, you can also collect your free bonuses. So grab your copy today and begin your own transformational journey through functional medicine and finding resilience.

Dr. Jill 17:29

Yes. And I love that we're talking about this because, obviously, it gets people's attention. But more importantly is what you said: This is a signal that there's endothelial dysfunction in your body. So if you're a woman or a man who's having trouble… And this can come as early as [one's] 30s. It's surprising to me how many people, early in life, are starting to have dysfunction. It's a signal that, if they don't address this issue, they're going to have issues.

Dr. Jill 17:52
If the sexual dysfunction didn't get your attention, let's talk about the brain. People are thinking about the heart and the blood pressure, but this is absolutely critical to blood flow to the brain. Talk a little bit about cognition. Is there any relation to studies with dementia or cognitive decline and nitric oxide?

Dr. Nathan Bryan 18:10
Absolutely. If you look at the work of Daniel Amen and you look at SPECT scans—whether it's functional MRI or SPECT scans—really, what we're looking at in those imaging modalities is how well-profused the brain or an organ is. In this particular case, it's the brain. In any neurocognitive disorder, whether it's mild cognitive disorders—vascular dementia, Alzheimer's, or bipolar—there's always a loss of regulation of blood flow. There's a vascular component to every disease, including every neurological disease.

Dr. Nathan Bryan 18:38
But in terms of cognition, dementia, and the progression of Alzheimer's, it's called diabetes type 3. It's loss of insulin signaling, and it's loss of glucose uptake. When you define the disease process of Alzheimer's, it's low blood flow, inflammation, oxidative stress, immune dysfunction, and insulin resistance. Remarkably, nitric oxide, this single molecule, addresses every single one of those. It improves blood flow, mitigates the inflammation, inhibits oxidative stress, and prevents the immune dysfunction. And based on a paper we published in 2009, nitric oxide is part of the insulin signaling pathway. So it can potentiate insulin signaling and enhance glucose uptake. And now the brain can take in an energy substrate where it can do its job.

Dr. Nathan Bryan 19:26

We have a drug in phase 3 trials now for Alzheimer's and mild cognitive disorders because it gets to the root cause of the disease. We're up against a big hurdle here because all Alzheimer's drugs have failed. I think they've all failed because these companies are going after the wrong target. They're targeting the amyloid, the plaque, and the tau tangles. Those are consequences of the disease; they're not the cause of disease. What we're doing is getting to the root cause of disease. And I think this is going to be a game changer for Alzheimer's and vascular dementia.

Dr. Jill 19:58
Wow, I can't wait to see that.

Let's just shift just a little bit more into the post-pandemic because this particular virus we've been dealing with has a pretty dramatic effect on the endothelium. And for me, I'm now considering COVID an endothelial disease. We're seeing a lot more patients post-COVID and long COVID, and it's all about the endothelium. Where do you see, in your research, this being connected? I feel like as we restore that nitric oxide and that healthy endothelial lining, we get resolution of long COVID and post-COVID symptoms, right?

Dr. Nathan Bryan 20:30
Yes, no doubt. We've learned a lot over the past four years about the vascular complications of COVID. In fact, we had a drug in phase 3 trials for COVID early on in 2020. What we were finding was that the people who were getting sick and dying from COVID were the people who could not make nitric oxide—the elderly, people with a prior heart attack, diabetics, smokers, African Americans. These are the people who clinically present with nitric oxide deficiency.

Dr. Nathan Bryan 20:59
In 2005, it was published that nitric oxide prevents the coronavirus from replicating. That was SARS-CoV-1; this was SARS-CoV-2. If you can't make nitric oxide, then you get an upregulation of adhesion molecules. You get the ACE2 receptor, which is the primary target of the spike protein. Now you've got multiple targets being expressed for this virus to attach to. And if you have nitric oxide deficiency, you can't mobilize an immune response. So now the virus goes into the cell, hijacks our DNA, replicates, and propagates throughout the body. Then it allows for the platelets, monocytes, and neutrophils to stick to the lining of the

blood vessels. You get microclots. And there's the vascular inflammation from long COVID.

Dr. Nathan Bryan 21:40
Our approach was: Let's give nitric oxide to these high-risk patients. That way, you can 1) prevent the virus from replicating and 2) nitric oxide downregulates the ACE2 receptor so there's less target for the virus to bind to and you completely mitigate the vascular inflammation from the spike protein. You completely detoxify it.

Dr. Nathan Bryan 22:02
So that's been our approach, and it worked well. We were keeping patients out of the hospital. But as you know, COVID changed, the virus mutated, and it became a moving goalpost. So there was no way we were ever going to reach our clinical endpoints because everything was changing. And now we know that there was a lot of politics involved in the COVID virus. But we established safety. We treated over 600 really sick, highly medicated patients. There was not a single safety signal with our nitric oxide therapy. So now we're moving straight into phase 3 trials because we've established safety for our drug programs.

Dr. Jill 22:40
Absolutely amazing! Let's talk briefly about the products you developed, because we're going to mention that. If you guys want to check that out, we'll give you links in the show notes. But the N1O1—is that your brainchild and your research? And it sounds like you've got some pharmaceuticals. Tell us about the different categories and what you've got.

Dr. Nathan Bryan 23:01
My objective early on was, as I mentioned, to develop safe and effective drug therapy. But what we're doing is completely different. Most drug companies employ the principles of pharmacology: Create a synthetic compound that inhibits a biochemical reaction to treat a symptom or a consequence of some biochemical reaction. What we do is completely different. We employ the principles of restorative physiology. As it relates to nitric oxide, what we're finding is that most chronic diseases are associated with a loss of nitric oxide. What we want to do is figure out what's missing and give back this missing molecule at doses that

recapitulate endogenous signaling and endogenous production. That's restorative physiology.

Dr. Nathan Bryan 23:43
What we're finding is that there's no indication where nitric oxide at the right dose at the right time in the right patient wouldn't be beneficial. But as you know, it takes many years and tens of millions, if not hundreds of millions, of dollars to get a drug approved and on the market. So what we did early on was, we developed over-the-counter dietary supplements because we're basically restoring the function and supporting the structure and function of the human body. We can do that through nitric oxide.

Dr. Nathan Bryan 24:08
But the challenge—for the past 40 years—is: How do you deliver nitric oxide gas in an outpatient setting? The only way you do it in a clinical setting is through a nasal cannula. This is approved for premature babies with pulmonary hypertension or adults undergoing cardiopulmonary bypass to maintain some tissue oxygenation. But it's a gas. My claim to fame is that I made the first and only solid-dose form of nitric oxide gas. We do this through an orally disintegrating tablet. You put this lozenge in your mouth and it dissolves over five to six minutes. You just move it around. As it's moving around, it's liberating NO gas. We can detect it. We can do an ultrasound. We can see dilation of your carotid arteries within 10, 12, 15 seconds. The nitric oxide that we're releasing is vasoactive. And we recouple the NOS enzyme. So we're overcoming and fixing the underlying endothelial dysfunction.

Dr. Nathan Bryan 25:00
We understand the enzymology—that we can prevent BH4 oxidation, maintain NOS coupling. And because it's an orally disintegrating tablet, what we're finding is that it's killing the pathogenic bacteria in the mouth. And it's helping to wake up and restore the nitrate reducers, the nitric oxide-producing bacteria. So if your body can't make nitric oxide, our products do it for you. But more importantly, we fix the reason your body couldn't make it in the first place. And that's what makes our products different from any other product technology on the market in the world.

Dr. Nathan Bryan 25:32

All other companies are giving you precursors and substrates. They cross their fingers, close their eyes, and hope and pray that your body can convert it. But the basis for a patient's deficiency is that they cannot utilize those precursors or substrates to make it. So we have to fix that, and that's what we do.

Dr. Jill 25:48
Wow! I'm in awe because I know about some competitors out there and what they claim. That's one reason I wanted to bring you on and talk to you because I know you are at the forefront of really doing the research and showing and proving.

Dr. Nathan Bryan 26:00
It's the source of my daily frustration because, in the supplement space, as you know, it's the wild, wild west. Everybody says the same thing, but very few products actually deliver on that. Nitric oxide is a molecule that, as I mentioned, is a gas. It's gone in less than a second. So a lot of these people, I think, are well-intended. They're just naive on the science and the biochemistry. And other people out there are intentionally defrauding and deceiving their customers because they know better. So that's my frustration. That's why I appreciate the opportunity to come and inform and educate on the science of nitric oxide. I'm not here to sell you products. I'm here to try to tell you how to fix it naturally. But if you need a little bit of help, then we have products that will certainly help you.

Dr. Jill 26:42
Gosh, I love this! Let's briefly talk. There are foods—obviously, leafy greens. This is why every diet that's ever had any good scientific evidence, whether it's Mediterranean or [others], includes leafy greens as one of the primary substrates—because this is so core—and beets and root vegetables. Do you want to name some of the top food sources of this?

Dr. Nathan Bryan 27:00
The darker the green leafy vegetable, the more the nitrate content. That's based on this whole field of agronomy. The plants that are grown in the soil, if we add nitrogen to them, assimilate nitrogen in the form of nitrate. The more nitrate—the highly fertilized fields—the greener the vegetable. If you look at kale, spinach, arugula... Beets have become pretty popular over the past 10–15 years, but beets aren't really the major source of nitrate. They're the third least-liked vegetable in the world.

Dr. Nathan Bryan 27:34
We published a paper in 2015 where we looked at the regional differences in the nitrate content of common vegetables—broccoli, spinach, celery, lettuce, and things like that. There's as much as a 50- to 100-fold difference in the nitrate content of vegetables grown in New York versus Chicago, Dallas, or Los Angeles. So, it's almost impossible to determine or know if you're getting enough nitrate from the foods you're eating. But I think what we're finding is that, as you mentioned earlier—the Japanese diet, the dietary approach to stopping hypertension, the Mediterranean diet—all the nutritional epidemiology on these time-tested and proven dietary patterns can be explained by the nitrate content and the oral microbiome metabolizing this into nitric oxide gas and dilating the blood vessels, normalizing blood pressure, and reversing coronary artery disease.

Dr. Nathan Bryan 28:26
The work of Caldwell Esselstyn and our colleagues like Joe O'Connell use a plant-based diet for the regression of cardiovascular disease. That mechanism is very well elucidated. It's a nitric oxide-related phenomenon. But we're also finding, having conversations with Dr. Esselstyn and Dr. O'Connell, that some patients don't see the benefit. So I asked them: "Are those patients the ones that are using mouthwash or are they using fluoride?" Because if you don't have the right oral microbiome, you can eat a straight plant-based diet until the cows come home, but you're never going to be able to metabolize this into nitric oxide. You're going to sweat it out, you're going to poop it out, and you're going to pee it out. So now they interrogate their patients. They go, "Oh, well, maybe that explains the non-responders." And that's, I think, a major step forward in understanding the mechanism and this whole field of nutritional epidemiology.

Dr. Jill 29:15
I love this, and I'm smiling so big, Dr. Bryan, because the 2013 paper was one of the reasons I contacted you. I grew up on a farm in Illinois. My brothers now do thousands and thousands of acres. They have all non-GMO, and they have started to do organic, which is not done for corn and soybean farms in Illinois, right? You know how that goes. I'm so proud of them. But obviously, we talk. I always talk to my brother. He's like the functional guy of the soils, so we talk about the nitrogen application and some of these things. So I know enough about that. When I read

your paper, the thing that shocked me—I want to share this, and you can maybe clarify—is here, I pride myself on eating almost all organic. But your paper talked about organic because of the limitations of fertilizer applications. I'll let you explain. There was a much lower amount of nitrate in the vegetables that were organic, right? So then there's this conundrum: What do we do? Talk a little bit about that. That was a surprise to me and a really big deal for people who are eating all organic.

Dr. Nathan Bryan 30:15
It's a jaw-dropper for us too. We expected some regional variability. Lightning fixation is what fixes nitrogen in the environment—there's 78% nitrogen in the air—into usable forms in the soil. This Rust Belt in the south, where a lot of farmland is, is naturally enriched in nitrate because of the lightning storms. And most people don't understand what organic means. We're conditioned to eat organic because there are no herbicides or pesticides. That's a good thing. But to get an organic label in the US, there are restrictions on adding standardized nitrogen to the soil. You can add manure, compost, and things like that. But there's no standardization of the nitrogen in that compost.

Dr. Nathan Bryan 31:02
I live on 800 acres here in Texas, where we raise our own beef and grow our own vegetables. I do soil samples. I figure out what's missing from the soil, and then I add back to make sure it's a nutrient-dense soil. Then I grow the vegetables. But I don't add the herbicides or the pesticides. So what we're getting are nutrient-dense foods. They're not labeled formally as organic because we're adding nitrogen and other nutrients to the soil. But what you get is an enormously nutrient-dense food that's free of chemicals.

Dr. Nathan Bryan 31:34
I tell people: Go to your local farmer; go to your local market. Get to know your farmers. Even if you live in big cities, there are still people out there who are growing good food free of herbicides or pesticides. But understand how to grow food, add nitrogen, and assimilate all these nutrients into the foods we eat. And I think that's a major problem.

Dr. Jill 31:55
Yes. I loved reading about that because I read about your farm. I was so fascinated

because my brothers and my dad are still doing that. And the same thing—they're testing every soil, and they're adding back. We always talk about the deficiencies in humans. Magnesium in the soils used to be very prevalent. Now, I think it's about a fifth or less of the magnesium. People are like, "Why do I need supplements?" Even if you're getting a good organic product that has a soil depletion… I've been talking to Jeff Bland lately. We used to say the gut is where autoimmunity and disease starts. Well, now I think it's the soils, and I'm sure you would agree. The soils are where the disease starts because we're getting deficient products.

Gosh, this is fascinating because I could talk all day.

Dr. Nathan Bryan 32:37
There's data now going back to the 1940s tracking the basic micronutrients in the food grown in America. There's a 78% decline in basic micronutrients like magnesium, selenium, and chromium in the foods that were grown in the 1940s up until 2017. The pressures of feeding a growing population are at the expense of nutrient density. It's a major problem. I tell people: You almost have to supplement because we're not getting the nutrients from the foods we eat.

Dr. Nathan Bryan 33:07
I think that's why micronutrient analysis and personalized medicine are so important, because, as you know, there's not a one-size-fits-all. You have to personalize these supplements and nutrients and figure out: What is the body missing? Or what is the body exposed to? And then you've got to detoxify that. When you replace missing nutrients and remove toxins from the body, then the human body heals itself. I think, after watching your documentary, that's certainly your philosophy. I think that's why you've changed so many people's lives because you get to the basic principles of physiology. I think we've lost that in medicine because medicine originally was applied physiology. Today, it's applied pharmacology. And obviously, that's not making anybody better. [laughs]

Dr. Jill 33:48
What a brilliant statement in that sense! We do micronutrient testing all the time, and I'm always shocked at [how] even a seven-year-old will come back with all kinds of mineral depletions at that young age. It's probably from the womb because the mother wasn't repleted with nutrients.

Dr. Jill 34:03
There are a lot of products out there, like we said, that really aren't doing the trick. Years and years ago, there was arginine and precursors there. Do you want to talk about those?—because there are a couple of pathways. To me, that is way less effective, may be very problematic, and may cause more harm than good. Maybe just share because I know we have a lot of practitioners listening and they're looking at their bottles of what they're using. I want them to know why this N1O1 may be a better option.

Dr. Nathan Bryan 34:28
The enzymology of the nitric oxide synthase enzyme takes arginine and, through a five-electron oxidation, produces nitric oxide. And then you get a byproduct, L-citrulline, as a consequence of it. So L-citrulline is a byproduct. The binding constant—we call this the Michaelis constant in biochemistry—the concentration needed to theoretically saturate 50% of the binding sites for arginine, is five micromolar. But even in the sickest of sick patients, intracellular and plasma levels of L-arginine are 100 to 200 micromolar—20 to 40 to 50 times higher than what's needed to theoretically saturate the binding site of the enzyme. The whole point is that you're never deficient in L-arginine. Giving L-arginine doesn't fix the problem. It's like putting gas in a car with a blown-up engine. You're not out of fuel. The enzyme to convert the arginine to nitric oxide is what's uncoupled and dysfunctional.

Dr. Nathan Bryan 35:23
Now there's data showing that if you give L-arginine to a patient with endothelial dysfunction, either post-infarct patients or PAD, they get worse. Post-infarct patients had a higher mortality [rate]. PAD patients—intermittent claudication got worse and quality of life got worse. So L-arginine is contraindicated in post-infarct patients and patients with peripheral arterial disease. But the common denominator in post-infarct and PAD patients is endothelial dysfunction. So, [with] arginine and citrulline, you're never deficient. There's never a reason to supplement. Plus, your body makes arginine and citrulline through the urea cycle. It's a semi-essential amino acid. You get it from the breakdown of proteins, but it's produced in sufficient flux through the parts of the urea cycle, which is present in every cell in the human body. So you always have a constant flux of arginine.

Dr. Nathan Bryan 36:15
[There is] no need to take arginine products. Save your money. They don't work. They may provide other benefits, but it's not a nitric oxide benefit. And a lot of these companies are putting arginine with a bunch of resveratrol and antioxidants. They contain a lot of good ingredients. They're just not nitric oxide products. So call it a multivitamin; don't call it nitric oxide.

Dr. Jill 36:38
I love it. And I couldn't agree more. Like I said, you bring the science to this at a great level.

I've got a couple of things going on here in my head; one is mast cell activation. I did some research and read that nitric oxide can help the mast cells and especially the gut lining. Gut is a lot of times where there's inflammation dysfunction happening. Do you want to talk a little bit about what nitric oxide might have to affect the leaky gut, permeability, and mast cell activation?

Dr. Nathan Bryan 37:08
It's the same in endothelial cells or epithelial cells—we have to maintain that barrier function. [As] part of that intracellular communication, nitric oxide is one of these intracellular signaling molecules. Endothelial cells—you've got the tight junctions in the brain; you've got the fenestrations in the liver. There are different types of vascular beds and different organ types. But in terms of leaky gut, when you lose that barrier function—peptides and undigested fragments start leaking across the gut and your body develops an antibody against it and foodborne allergies and autoimmune disease—then we've got to fix that.

Dr. Nathan Bryan 37:44
I think what you preach is that you have to figure out: What is the offending agent? Is it gluten? Is it dairy? Is it some other foodborne allergen? Is it exposure to some chemical? But then you've got to support that. What we're finding is that the gut microbiome is extremely important in that communication. Not only the epithelial cells are producing nitric oxide, but the bacteria in the distal colon are also part of this to maintain the epithelial barrier and that function. What we're finding is that

nitric oxide can mitigate that inflammatory response. But until you remove the offending agent, you've got this chronic inflammatory cycle.

Dr. Nathan Bryan 38:24
I think in 2004, we published on this in ulcerative colitis and Crohn's disease. If you look at the literature, people go: "Oh, well, nitric oxide is always present in UC patients and colitis, so nitric oxide is contributing to the pathology." But that's not the case at all. I tell people that cops always show up at a crime scene, but the cops didn't cause the crime. They're there to prevent further damage. In this paper, in 2004, we published that Crohn's patients get chronic inflammation in the gut, so you're getting this overproduction of nitric oxide to suppress the inflammation, but it leads to a feedback inhibition on the constitutive isoforms.

Dr. Nathan Bryan 39:03
[In] people with chronic inflammation, even though they may have a local overproduction of nitric oxide at that site—whether it's in the gut in ulcerative colitis or Crohn's disease—the endothelial production of nitric oxide is completely shut down. Now they have systemic inflammation; they have runaway oxidative stress. If we can restore the production of nitric oxide, you mitigate the inflammation, inhibit the oxidative stress, and basically heal the gut. But you have to identify: What was the offending agent in the first place?

Dr. Jill 39:32
Wow! You just read my mind, because my next question was going to be: In these super complex chronic [cases], especially POTS dysautonomia, where they're hypotensive and they're having this runaway activation... I wanted to understand: I know they need nitric oxide, but sometimes in the acute phase, they're producing too much locally, which is what you just explained. Would there be any contraindications? Say someone runs a blood pressure [of] 90 over 60 and they're having POTS dysautonomia. Is there any way to take your products and supplements that would be safe? Or would you avoid it for a certain time? Talk about that kind of patient.

Dr. Nathan Bryan 40:06
Dose dictates poison. The only toxicities of nitric oxide are hypotension and then methemoglobinemia. We tested this before we ever brought these products to

market because if you have low or normal blood pressure, the last thing you want to do is further reduce blood pressure. It can cause syncope and people pass out. That's not a good response. We've done this through 24-hour ambulatory blood pressure monitoring. I'm always the N=1 experiment or the guinea pig.

Dr. Jill 40:36
Me too!

Dr. Nathan Bryan 40:38
That's very important, right? We have to test it.

My blood pressure is 116 over 72. I take a lozenge; there's no drop in blood pressure. And then, if you take people with POTS or chronic hypothyroidism, with a blood pressure of 90 over 60, there's no further reduction in blood pressure. But what we're finding in these pediatric patients that we published on is that we can take a blood pressure of 200 over 110 and, in four hours, bring it down to 130 over 80. It's a safe, steady decline in nitric oxide production, but there's no orthostatic hypotension. So to answer your question, there's been no contraindication where we would see that the nitric oxide that we're producing through this lozenge wouldn't be beneficial. There's no unsafe drop in blood pressure. There's certainly no methemoglobin formation when taken as instructed. But you'll develop low blood pressure long before you develop any cyanosis from the methemoglobin.

Dr. Jill 41:38
Oh, that makes so much sense.

And maybe you can clarify too: There's an eNOS and an iNOS. And they're a little bit different. Do you want to explain those two? Because I think one can be activated with inflammation and the other is the endothelial—the eNOS.

Dr. Nathan Bryan 41:51
Yes. There are two, what we call, constitutive isoforms. There's the neuronal NOS that's found in the neurons of the brain, and then there's the eNOS, which is found throughout all the blood vessels. Those are constitutively expressed, meaning they're constantly active; they're producing nitric oxide at any given time. The inducible is only induced from a cytokine storm. When we see an infection or an

injury, four hours after we see that injury, there's an upregulation of this iNOS enzyme. Now that enzyme produces about 1,000 or 10,000 times more nitric oxide than the constitutive isoforms. If it's an infection, then that overproduction of nitric oxide binds to the iron-sulfur centers of the bacteria and completely shuts down the respiration. So it kills the bacterial infection, and it prevents the virus from replicating. And it's not just the coronavirus. It's RSV. It's the seasonal flu. It's any respiratory virus. It's any virus for that matter; it doesn't have to be respiratory. But it also walls off the site of infection or injury, and that's the redness and the heat—all the hallmarks of inflammation.

Dr. Nathan Bryan 42:59
The local inflammatory response is absolutely essential for mitigating infections and for the wound healing response. The problem is when you have chronic inflammation and that system never gets shut off because now it leads to feedback inhibition of the constitutive isoforms. You've got to remove the offending agent, figure out what's causing the inflammation, and then reset the nitric oxide. That's what we do through our technology. We recouple the NOS enzyme and downregulate the TNF-α-mediated response and all these cytokines.

Dr. Jill 43:31
Okay, this is so clarifying. And you talk about our N-of-1 experiment—because I do that on myself.

You know a little bit about my history. I had Crohn's disease at 26 after breast cancer. And now there's this big aha I just had as I'm listening to you speak. Number one, I have a real high-risk gene for Crohn's, which is NOD2. What that means is that my response to a normal microbiome is incredibly aggressive. So that kind of makes sense. I also have this thing that's very, very unique: My iNOS is very upregulated. I'm like one in a million as far as the amount of iNOS, which makes sense. What happened in Crohn's is that my iNOS went crazy and was reactive to the normal microbiome and after chemo, it caused more permeability in the gut and this whole thing started.

Dr. Nathan Bryan 44:10
The perfect storm.

Dr. Jill 44:11
Right? It's so fascinating. And it's interesting because that's what I've been trying to understand myself: How do we do this with patients like myself who have the iNOS out of control? But what you're saying is that if we upregulate iNOS and correct some of that, that will improve permeability, improve overall efficacy, and decrease that iNOS—that reaction to infection or toxin.

Dr. Nathan Bryan 44:32
That's right. It may seem a little bit counterintuitive, especially in that local inflammatory site of the gut. But if we give the nitric oxide, you can downregulate that. But I think, more importantly, you restore the constitutive isoforms where you get normal signaling and you basically shut down superoxide production from NADPH oxidase, the electron transport chain, and an uncoupled NOS. Oxidative stress goes away, you mitigate the inflammatory response, and then the body can heal.

Dr. Jill 44:58
Amazing! That makes so much sense. It also makes sense because if I have an objective nitric oxide strip on my mouth, it's going to be none. Would that strip be a test more for the eNOS, the healthy nitric oxide from the bacteria in the mouth, versus iNOS?—because iNOS is localized to some area of the body. When you test someone's saliva, you're going to probably get their...

Dr. Nathan Bryan 45:21
What we're measuring is salivary nitrite. So what we have to understand is: Where is that coming from? I developed those test strips 15 years ago. I don't use them anymore because there are false positives. What we're finding is that in people with active oral infections, it's an iNOS-mediated response; it's a local immune response to [inaudible] infection.

Dr. Jill 45:41
Yes. So they have periodontitis or a cavitation.

Dr. Nathan Bryan 45:44
Yes. It has nothing to do with the reflection of systemic nitric oxide availability. It's a diagnostic for poor oral hygiene—either periodontal disease or an asymptomatic infection in the oral cavity. That gives people a false sense of security because we

see the 50-year-old overweight diabetic hypertensive patient with AD and he lights up the test strip and you go, 'What?' He's got all the classical symptoms of nitric oxide deficiency but he's lighting it up. Then you find out, if you do an oral exam or ask questions, that this guy has poor oral hygiene; he's got infections through the roof. That's a false positive. So we just have to be aware of that.

Dr. Jill 46:24
I love that clarification because those are a dime a dozen now and getting out there. People are handing them out at conferences. I always wondered: "Is this really accurate?" And for someone like me who has very unique genetics on this, that makes so much sense. You clarified a lot.

Dr. Jill 46:43
I would love to tell people: Where can they find more about you and more about your work? You've been such a leader in this industry and we're so grateful for your research! Tell us where people can find you.

Dr. Nathan Bryan 46:54
First, I've got a YouTube channel. We'll probably host this podcast on the YouTube [channel]. It's podcasts; it's lectures. I've got an educational website: DrNathanSBryan.com. I do a monthly blog. There are six-minute videos on there that'll tell you everything about nitric oxide. You can find me on PubMed—I've published over 100 peer-reviewed papers—if you want to read the published literature. Our products are [at] n1o1.com. I'm on Instagram: @drnathansbryan. Twitter: @drnitric. I've got a couple of books out. I've got a new book coming out, probably this fall, called *The Secret of Nitric Oxide: Bringing Nitric Oxide to Life*.

Dr. Nathan Bryan 47:39
I was watching your documentary, Jill. It was really inspirational. But my book is part autobiographical, also telling the story of the discovery of nitric oxide and why this molecule is so important so that hopefully we can empower people all around the world to understand this molecule and take the steps to maintain adequate production, stop doing the things to disrupt it, and start doing the things that promote it. And they'll see a change in their own health and lives. So thank you for the documentary and for being a source of inspiration!

Dr. Jill 48:11

Oh, Dr. Bryan, thank you for your work over these many decades!—because this, to me, is probably the most important issue in chronic health conditions. I don't think there's anything more important that we could be talking about. And I think a lot of people are still very unaware. I think this podcast will be really interesting to people who don't have any idea that that's the underlying root. So thank you from the bottom of my heart for your research. If you're listening, wherever you're listening to this podcast, you will find in the show notes links to Dr. Bryan, his research, and the N1O1 site. And thank you again for coming on and sharing your wisdom. We'll have to have you back when your book's out, because I want to share that as well!