Nitric oxide to enhance treatment and uptake of peptides and other bioactives

Matthew Cook, M.D. interviewing
Nathan Bryan, PhD

Matthew Cook, M.D.
Well, hi everybody. Welcome to the Peptide Summit. My name is Matthew Cook, M.D.. And I'm here with my friend, Dr. Nathan Bryan. In college I studied cell and molecular biology, but he went way beyond me and got a PhD in it. And I've actually known him for years. We met at a Cell Surgical Network meeting and he was talking about using nitric oxide to help overall health, vascular health, and stem cells and regenerative medicine. And I've been using his products probably for six or seven years now. And I've decided to have him on the summit because we're talking about peptides, but in a few important categories, I'm coming into some other molecules that I think are real important, either as a support in functional medicine or as something that may help peptides get where they need to go. And that's something that we're gonna dive into today. Dr. Bryan's probably the number one nitric oxide person in the world that I've known and is a fabulous teacher. And so we're delighted to have you on the show today.

Nathan Bryan, PhD
Thanks, Matt, it's great to be here. It's an honor.

Matthew Cook, M.D.
So tell us a little bit about nitric oxide and what's happening with it.

Nathan Bryan, PhD
Well, we've started so much over the past 20 or 30 years and it's still new in the scientific literature. It's only discovered in the late 70s, early 80s, but now it's recognized with I think probably over 175,000 scientific papers in the published literature. But it's one of the most important molecules produced in the human body. It controls a number of cellular activities, controls and regulates blood flow, blood pressure, oxygen delivery. And every single age-related disease is characterized or associated with a loss of nitric oxide production. So it's now

demonstrated or revealed to be causal for most, if not all, human chronic diseases. So it's clear now that your body cannot and will not get better until you restore the production of nitric oxide.

Matthew Cook, M.D.
Okay, what would be when you talk about major diseases, give me the top four or five that you think about that are related to nitric oxide.

Nathan Bryan, PhD
Well, certainly cardiovascular disease, hypertension. The number one with respect to cardiovascular disease is typically a loss of the production of the vasodilator and nitric oxide. So when you lose the ability to produce a major vasodilator in the systemic circulation, you get stiff artery and you get high blood pressure. The other is erectile dysfunction. That's the first sign and symptom of a nitric oxide vascular endothelial problem. The other is type 2 insulin resistant diabetes. There's a clear role now for nitric oxide that's part of the insulin signaling pathway. And then the thing that's most fearful for most Americans is vascular dementia and Alzheimer's. It's clear from a number of studies that the earliest stages, whether it's mild cognitive disorder and vascular dementia that precedes Alzheimer's is due to a lack of regulation of blood flow in certain regions of the brain. So you don't get the good nutrients in, waste products build up, you get beta-amyloid plaque deposition, hallmarks of Alzheimer's.

Matthew Cook, M.D.
So then that that's a good one. So then that basically means all of the biggest, most common aging problems that we know of relate in some way to blood vessels and blood vessel health. And if nitric oxide is low, that may be kind of a causal thing. There's a whole bunch of other things that we think about in integrative and functional medicine as strategies and ways to support that, but you've developed some ways to actually start to replace that nitric oxide in the body.

Nathan Bryan, PhD
Right, well, I take it a step further. There's inflammation is what kills, right? That's what causes heart attack, strokes. And we know that nitric oxide inhibits inflammation. And we're hit with a number of, infinite number of insults every day from the foods we eat to the environment we're exposed to to our lifestyle habits, but our body responds with three finite responses. It's inflammation, oxidative stress, and immune dysfunction. And nitric oxide is what controls all

three of those. So if your body loses the ability to make nitric oxide, your blood vessels become inflamed, you get oxidative stress, you get immune dysfunction. Then those show up as biomarkers that you can recognize as risk factors for certain diseases. So what I tell people is that it's really pretty simple. You have to do two things. You have to stop doing the things that disrupt nitric oxide production and start doing the things that are clinically proven to promote or activate nitric oxide production. Actually that simple, but then if you delve deeper, you gotta figure out, okay, well, what am I doing that's inhibiting my body's ability to make nitric oxide? The number one thing is mouthwash. In the United States, there are over 200 million Americans, 2/3 of the population that use mouthwash on a daily basis. It's not coincidental that two out of three Americans have an unsafe elevation of blood pressure putting them at risk for cardiovascular disease. Most recently it's been demonstrated that if you use mouthwash, you lose the protective effects of exercise. If you use mouthwash, you lose the protective effects of exercise. So these are things that people do I think with good intentions, but there's collateral damage. And people wanna go out and exercise and eat good food, but if you use a mouthwash, you completely eliminate the cardioprotective benefits of both.

So that's number one. Number two is fluoride toothpaste. You have to get rid of fluoride. It's an antiseptic, kills your thyroid function, and it's a neurotoxin. So get rid of thyroid, get rid of fluoride-based toothpaste. And then number three is antiseptic or antacids. Over 200 million prescriptions are written for proton pump inhibitors every year. That's not counting the over-the-counter purchases. We need stomach acid for our body to heal. We need stomach acid to make nitric oxide. So if people do those simple things, which is cost savings, stop using mouthwash, get a fluoride-free toothpaste, and stop using antacids, your body will thank you for it and you'll notice the difference. And then to promote or activate it, we gotta get up and move. We have to have moderate physical exercise, eat a lot of green leafy vegetables that are enriched in nitrate, and then get out and get sunlight. Sunlight, there's certain wavelengths of light that'll stimulate or activate nitric oxide production. So again it's really six things. Stop doing three, start doing the other three.

Matthew Cook, M.D.
Okay, I avoid the fluoride toothpaste like the plague. And interestingly, the idea from the literature is is even for people with real bad gastritis, most people are supposed to only be put on a proton pump inhibitor for a short period of time. And then even then, that generally doesn't

seem like a great idea a lot of times. A lot of times we find other integrative ways to kinda help people with those symptoms.

Nathan Bryan, PhD
That's right.

Matthew Cook, M.D.
And I echo that often that is the beginning of kind of a downhill slide for people. And I remember when I was in college, the doctor that I had gastritis after some weekend.

Nathan Bryan, PhD
It happens.

Matthew Cook, M.D.
And then I remember, right, the doctor said, "Oh you can just take this purple pill "and then you can just take it," and then I took it for about a week and then I thought this is the craziest thing, and then I stopped taking it, I basically never had really a stomach problem ever since then. So that was like an indication to me of something was screwed up about how we were thinking about things.

Nathan Bryan, PhD
Yeah, those drugs were never approved for chronic use. They're approved for acute use

Matthew Cook, M.D.
Right.

Nathan Bryan, PhD
For gastric acid refluxes, but now you can get them over the counter. And

Matthew Cook, M.D.
Yeah.

Nathan Bryan, PhD
Now you get H. pylori overgrowth, you get gastric ulcerations, you get overgrowth of other bacteria, you become more prone to foodborne pathogens, and you increase your risk of heart attack and stroke by about 30 to 40%.

Matthew Cook, M.D.
Right, that's because that stomach is supposed to be aesthetic as kind of like a nice, useful barrier that keeps problems. And so then if we lose that acidity, then bacteria can start to live in there and then the whole nitric oxide. So then what are the ways to start to, and Nat, before we go into that, you talked about three things. So unlock the how, because here we are in COVID days, and so then if you said immune dysregulation five years ago, everyone was like who's that? Now the whole world is suddenly interested in immune problems. Tell me about immune dysregulation and COVID and nitric oxide and how you think about that.

Nathan Bryan, PhD
Sure, well, any immune response, whether it's response to an infection or exposure to a virus or bacterium, or an immune response to heal a wound, a cut or some injury in the body, the body respond with mobilizing our immune system. You gotta activate your immune system and you mobilize those through the production of nitric oxide. And then interestingly, our own immune cells make nitric oxide when they're activated by cytokines. And then those immune cells generate a lot of nitric oxide at the site of infection or inflammation to kind of close off that, number one, to kill invading viruses or bacteria. So when your immune cells generate nitric oxide, it binds to the iron sulfur clusters of bacteria and shuts down the respiration and it prevents viral particle replication. So if your body can't make nitric oxide, you can't elicit a robust immune response and you become immunocompromised. And that right there explains what we've learned in two years of coronavirus, that who's most at risk for COVID infection? It's the elderly, it's people with high blood pressure, previous MI, diabetes, obese, and smokers. The reason they're at risk is because they're compromised to make nitric oxide. So when they get exposed to not just coronavirus, but any respiratory virus or any bacteria for that matter, their body can't elicit a robust immune response, the virus takes hold, replicates, propagates throughout the body. They get systemic disease, blood oxygen saturation decreases because there's no nitric oxide to signal oxygen release. They go to the hospital, they get ventilated, and typically that's the end of the story for most people. But it's those of us who have good nitric

oxide levels, like we have 26 clinical trials all over the US where we have a COVID drug now in phase three clinical trials, a nitric oxide drug. And I've never been sick with COVID. It doesn't mean that I haven't been exposed to COVID. I went on an airplane every week for the past two years, and I typically don't like to wear a mask and breathing in my own carbon dioxide, but I've never been sick from COVID. So that explains mechanistically everything we know about not just immune dysfunction and immunocompromised in COVID patients or patients at risk for COVID, but it explains every single infectious disease for that matter. Now we're seeing in our FDA-approved clinical trials for our nitric oxide drug, patients getting better. You take at risk patients, you start them on the therapy within 72 hours of onset of symptoms and they don't get sick. You keep them out of the hospital, you keep people out of the hospital, you keep people alive.

Matthew Cook, M.D.
What drug is that?

Nathan Bryan, PhD
It's a drug I developed called NOviricid, but it's a drug specifically for, it's a nitric oxide-releasing lozenge that we got an IND for for COVID patients at the start of the pandemic.

Matthew Cook, M.D.
Is that similar to the nitric oxide lozenge that I use?

Nathan Bryan, PhD
It is, so my drug company has a, so we've got a different drug company that has the license to the same patents, but rather than the field of use for dietary supplements and nutritionals, we've acquired the license for drug development. Same technology, same basic nitric oxide delivery, we just increased the potency because these patients need a little bit more nitric oxide than daily maintenance gives.

Matthew Cook, M.D.
It's kinda interesting because in my old life, I was an anesthesiologist. And it's kinda interesting also because then what I would do is I would meet people and then I would have like two or three minutes and I would have to make a real quick assessment. How's it going? Do you have

any asthma, diabetes, heart, lung, blood pressure, kidney, liver? And then if that was all normal, the probability that you have a problem with anesthesia is like one in a million.

Nathan Bryan, PhD
Right.

Matthew Cook, M.D.
And then on the other side of the coin, if somebody has vascular disease to any of the main arteries to their heart, their lungs, their brain, or their peripheral big blood vessels, and any heart disease or metabolic syndrome, you gotta think about it carefully because that's where almost all your complications are. And that's because when they go under a fairly significant physiological stress, I think one thing that's happening is almost all of those people are low in nitric oxide. We didn't even understand this really. I mean, we understood it mechanistically, but we didn't have anything we could do about it from

Nathan Bryan, PhD
Right.

Matthew Cook, M.D.
An anesthesia perspective. But that vascular sort of metabolic syndrome inflammatory pattern that people had, you'd walk in and you'd figure that, we would as anesthesiologists, you look at that and you're aware of that in about 30 seconds.

Nathan Bryan, PhD
That's right.

Matthew Cook, M.D.
And in a way that's almost like an analogy for COVID. COVID is like anesthesia but it's just like a hundred times more dangerous. And so then those are the patients that do struggle.

Nathan Bryan, PhD
That's right.

Matthew Cook, M.D.
So then interestingly, so then as a anti-aging or as a anti-inflammatory concept, then the one thing would be to potentially just try to start treating people and manage that inflammation and manage that immune dysfunction before they get exposed.

Nathan Bryan, PhD
Yeah, that's right and I think that explains part of the mechanism because there's so called long COVID where people get the systemic effects and the microemboli and the clots and the vascular inflammation and kidney dysfunction that last long after the active infection of COVID, even long after they stop testing positive. And that's because of the spike protein. So when a spike protein attaches, it activates platelets, it causes monocytes and neutrophils to stick to the lining of the blood vessel. That's all inflammation, that's vascular inflammation. If you give nitric oxide or restore endothelial production of nitric oxide, you completely inhibit platelet aggregation, you completely inhibit the adherence of monocytes and neutrophils to the side of the wall of the blood vessel, and you completely mitigate the inflammatory response. That is mechanistically the only thing that's gonna overcome that cytokine storm when you first get exposed to to the COVID virus.

Matthew Cook, M.D.
And so then it's interesting when, so when initially when somebody gets COVID, inflammation can happen, and if it gets into the blood vessels, and especially with the early versions of COVID.

Nathan Bryan, PhD
Right.

Matthew Cook, M.D.
Like the wild type and probably delta also. There would be an inflammatory situation that would happen in blood vessels, and when that happens, this population is the population that goes down by far the hardest. But then interestingly, along those lines, then with long COVID, it's almost like a similar process, but it's the simmering low level vascular inflammation that is. We talk about those cells, the monocytes, we're doing some tests where we look at the spike protein and see what their spike protein is, however, that's not 100% the total thing, because even when you treat that, it's not 100%. And what I have found on long COVID is that there's a diversity of things going on there, and there's vascular inflammation of probably more than one cause. And

interestingly, I've seen a lot of athletes that got COVID that end up, and they have no exercise tolerance, but those guys had been pro football players. And do you have a thought on what the mechanism is of people who were really at a 100% health and then they got COVID? They seem almost mechanistically a little different to me than the metabolic syndrome population.

Nathan Bryan, PhD
Yeah, well, look, there's no doubt nitric oxide is part of the problem in at risk patients for COVID and those with long COVID, but it's not the end all, be all, cure all. I think what we've learned is that if you have vitamin D levels less than 50 and you get exposed to COVID, there's a good chance you're gonna get sick for COVID. You may have really good vascular function, you got low vitamin D, you're at risk. The other thing, these other micronutrients like zinc and chromium and selenium, and you can't elicit normal cell signaling based on these micronutrients, you're gonna get sick from COVID. You can be a well-trained athlete, good vascular function, but these other components aren't in check, then it puts you at additional risk. So again nitric oxide is important, but it's not the end all, be all, cure all. You've got to optimize all systems. The human body is incredibly diverse and robust in its response provided that it has what it needs to do the job, right?

Matthew Cook, M.D.
Mm-hmm. I love that. So then talk me through how you think about replacing and supporting that whole process.

Nathan Bryan, PhD
In terms of nitric oxide production?

Matthew Cook, M.D.
Yep.

Nathan Bryan, PhD
Well, there's two ways the body makes nitric oxide. One is through an enzyme called nitric oxide synthase that's found in the lining of blood vessels, in the endothelial cells, it's found in nerve cells, and it's also part of our immune system. So bad enzyme converts arginine to nitric oxide and you get citrulline as the byproduct. But you're never, and I think this is important because a lot of people, there's a lot of nitric oxide products on the market that contain arginine, citrulline,

a lot of other nutrients. Problem is there's never a deficiency in these amino acids. The enzyme that converts arginine to nitric oxide is dysfunctional. So to give L-arginine or citrulline to a patient with endothelial dysfunction is like putting gas in a car with a blown-up engine. You're not out of fuel, your engine's broken. So it makes no sense. And in fact, you can push that reaction too far and generate superoxide instead of nitric oxide. So I tell people you don't need arginine or citrulline unless you've got a rare urea cycle disorder called argininosuccinic aciduria. That's the only known human condition where there's deficiency of arginine. And then the other, so you have to recouple the nitric oxide synthase enzyme. And that's not as simple as everyone believes. There's a certain redox potential or an electrical potential needed to recouple that enzyme. And so we know how to do that.

We put that in our product technology. And then the other part of the pathway is through diet from eating green leafy vegetables. It's the mechanism of action of a plant-based diet, Mediterranean diet, the dietary approaches to stop hypertension. It's eating a lot of green leafy vegetables that are enriched in nitrate. The body converts nitrate or the bacteria in the body convert nitrate to nitrite nitric oxide. So you gotta keep the bacteria, feed the bacteria that do this. You can do this through eating more nitrate or taking nitrate supplements, stop using antacids, allow that conversion in the acid environment of the stomach. And then when all else fails, and Matt, you and I both, change in lifestyle is the most difficult thing for people especially patients. With the way medicine is practiced here and well all over the world now, people want a quick fix, they wanna take a pill, they don't wanna change their lifestyle. So the easiest way and really the only way for people to get better is they gotta stop doing the things that make them sick and start doing the things that are gonna make them better.

And when they're not willing to do that, then we have to make product technology that makes them better. So that's where our technology comes in. If you don't wanna change your diet, if you don't wanna exercise or can't, then our thought process is if your body can't make nitric oxide, then we have technology that does it for you. And that's how we control and dictate the metabolic state of nitric oxide to orally disintegrating a lozenge that generates nitric oxide for you. So that's kind of the simplistic thing, but again you have to understand, it goes back to a very simple concept that people get sick for two reasons and two reasons only. You're exposed to something that you don't need or you're missing something that you need. So you've gotta remove the source of exposure of toxins or infections, give the body what's missing so your body can do its job. Get out of its way, it'll heal itself, right? But that's tough for people.

Matthew Cook, M.D.
Okay, good. Then so unpack for me what turns on nitric oxide synthase?

Nathan Bryan, PhD
Well, there are a number of things. Sheer stress, like for instance when we begin to exercise and we need more blood flow through the coronary arteries. As you know as an anesthesiologist, the only way to increase perfusion of the heart is through dilation. You can't recruit more capillaries because it's fully perfused. So the only way you do that is through the production of nitric oxide. So when we begin to exercise, there's increased metabolic demand on the heart, there's sheer stress in the heart that tells the coronary arteries to make nitric oxide. If they make nitric oxide, they dilate, and they meet the increased metabolic demands on the heart. You can't make nitric oxide, you become stressed, you get changes in electrical signal, and you fail an exercise stress test. That's basically diagnostic for lack of nitric oxide or the inability of coronary arteries to dilate. The other is histamine. When our immune system reacts, we get a histamine response, we get an increase in blood flow. There's certain wavelengths of light that will activate, UV will release nitric oxide from metals. Then ultraviolet light will actually cleave NO bond to a cysteine thiol and protein to glutathione. So that's kinda what stimulates the enzymatic production of nitric oxide. But there are a lot of things that disrupt that, oxidative stress, immune dysfunction, inflammation, superoxide production will all uncouple NOS and lead to endothelial dysfunction.

Matthew Cook, M.D.
Mm-hmm, and that is like this defining thing that wherever there's endothelial dysfunction, there's dysfunction.

Nathan Bryan, PhD
That's right. Well, all vascular beds are the same mechanistically. So if you have endothelial dysfunction in the sex organs and you can't dilate that to get more blood flow and get engorgement, we have erectile dysfunction, happens in men and women. If you can't dilate the coronary arteries, those who can't make nitric oxide, you get ischemic heart disease. You can't control and regulate blood flow and you have endothelial dysfunction in the blood vessels of the brain, you get vascular dementia, and you can look at this through spec scans and look at hypoperfusion, certain readings of the brain and certain neurological disorders. But the underlying common denominator in all of those is inability to regulate blood flow upon demand.

Matthew Cook, M.D.
It's interesting if you think about it and those are the same patients that I saw in anesthesia, but those are almost the same patient. So like in the guy.

Nathan Bryan, PhD
That's right.

Matthew Cook, M.D.
If you're a guy in your 50s with erectile dysfunction, then you gotta be thinking that's, they always say that's the canary in the coal mine.

Nathan Bryan, PhD
That's right.

Matthew Cook, M.D.
That's the first thing that starts to go, but then often those patients are on a spectrum of neurological dysfunction and issues and often they're on a spectrum of other vascular stuff, often high blood pressure and heart. So it's interesting to see that and it's reminiscent. It's almost like kind of a story. And so then one of the things is to try to take some nitric oxide. And now interestingly in the past, it was hard to get that without oxalates, because a lot of those green leafy vegetables are high in oxalates. Your nitric oxide lozenge doesn't have oxalates in it. How did you do that?

Nathan Bryan, PhD
Well, we kind of distill it down to the minimum necessary components to make nitric oxide, and then to recouple the NOS enzymes. So our philosophy is number one, if your body can't make nitric oxide, we gotta do it for you. So we also gotta fix the endothelial dysfunction. We've gotta recouple the nitric oxide synthase enzyme so that your body's ability to make nitric oxide improves. And so it's really very simple. It's biochemistry but it's also kinda like some energetic components too, because there's an electrical potential. You need a redox equilibrium that you need to prevent oxidation at pH four to pH two and then recouple the OS enzyme. So people historically just throw a bunch of ingredients together and call it a nitric oxide product, but 99% of the products on the market don't work 'cause they don't understand the enzymology and the

biochemistry to the extent that you can fix it. And that's where I spend more than 20 years in basic science and academia in understanding that reaction.

Matthew Cook, M.D.
Yeah, that's awesome. And how long do you think it takes? I take those daily lozenges. I take one of those every day that you make. How long would you say it takes the average person when you do 'cause you can do some salivary testing--

Nathan Bryan, PhD
Right.

Matthew Cook, M.D.
To start to look. How long does it typically take to get somebody replaced?

Nathan Bryan, PhD
Well, I think it depends on the endpoint. So if you're looking at, and look, we've done probably most if not all noninvasive as well as invasive in the cath lab looking at right and left heart caths and looking at their response. But the quickest is if you just take an ultrasound on the carotid, and we put the lozenge in somebody's mouth, within 30 seconds we can start to see the carotids dilate. So that's quick, I mean you don't feel it. When I take the lozenge, I don't feel my carotids dilate, I don't feel my other blood vessels dilate. But if you've got a history of TIAs or stenosis of the carotid or COPD, or you've got really some vascular problems and oxygen exchange issues, those are the people that they take that, they see a response within seconds. If you look at the response to blood pressure, for example, within 24-hour ambulatory blood pressure, and you'll start to see a reduction in blood pressure within 10 or 15 minutes. And that'll last out to six or eight hours and then stabilize. But that's only if you have high blood pressure. For instance, my blood pressure is about 118 over 68, and I take a lozenge or take a nitric oxide, and my blood pressure doesn't change. And that's very important because you only wanna lower blood pressure in people with high blood pressure. You don't wanna lower blood pressure in people with normal or low blood pressure, right?

Matthew Cook, M.D.
Mm-hmm. It's interesting when you talk about immune problems, then there's a interesting overlap with vascular stuff and then this happens in the long COVID people and then this also

happens in Lyme and mold and stuff like that where people will have something called dysautonomia and that basically is this imbalance of basically the fight or flight and relaxant aspects of the nervous system. And so then like for example, they'll stand up and get lightheaded, they call that POTS, postural orthostatic hypertension. But there's maybe a whole bunch of different variants of that. There's like a 100% of the time, there's some kind of immune dysregulation going on. And so then because of that, I always have the patients, and if you're one of those patients then, it'd be interesting to kinda think about and read about yourself in this 'cause I'll have people take that for that vasodilation, and my logic is I'm trying to dilate those arteries going to the brain to the limbic and to the deep brain autonomic structures to kinda basically get them

Nathan Bryan, PhD
Right.

Matthew Cook, M.D.
Physiologically turned on. We also do stellate ganglion blocks for a lot of these people, and then we'll give them nitric oxide lozenges before we do that so that we can kind of optimize when we open, the side effect of that injection is that it dilates the carotid artery.

Nathan Bryan, PhD
Right.

Matthew Cook, M.D.
And increases blood flow to the extent that they get a headache, but then once I started giving everybody the lozenges, people tolerate it better.

Nathan Bryan, PhD
Well, I think as you know there's receptors sensitization. And you'll see this in a very small portion of the population. And you see it primarily in patients who are taking organic nitrates like nitroglycerin or isosorbide. So those people have had so little nitric oxide for so long, they get an upregulation of an enzyme called soluble guanylate cyclase. So when you hit them with a lot of nitric oxide, whether it's through organic nitrate or through the lozenge, you saturate those receptors and you get massive vasodilation. But then as you continue, you'll downregulate those receptors. So that's kind of the desensitization that you'll see with that. I figured it's probably the

same with that acute vasodilation. These people have been sick. They upregulate their second messenger system because they're so low in nitric oxide. But then once you start to replete and restore nitric oxide, those receptors will desensitize and downregulate, and then there's no headaches or increase in cerebral pressure or anything like that.

Matthew Cook, M.D.
Right, no, the headache is a side effect of the stellate ganglion block, but when we do the nitric oxide, it seems to be less. It seems to sort of

Nathan Bryan, PhD
Oh, I get it.

Matthew Cook, M.D.
Balance the blood flow. What happens when you give the nitric oxide when you do the cath? You'll see increased blood flow basically.

Nathan Bryan, PhD
Yeah, one of the questions we had early on in patients with coronary artery disease is to prevent coronary steal, this phenomenon. And so we wanna when we dilate blood vessels, we don't wanna cause a coronary steal phenomenon. So that's what we investigated in the cath lab looking at left heart cath. Then we were looking at in heart failure patients with preserved ejection fractions and trying to look at reduction in pulmonary pressures on the right side of the heart. And so, number one, from a safety standpoint, we don't see any coronary steal with the technology. Number two, even in patients with half half or pulmonary hypertension, you can start to see a reduction in pulmonary pressures within 10 minutes of taking the lozenge. And it's unlike giving inhaled nitric oxide where you can drop pulmonary pressures, but when you turn the gas off, you see a rebound effect or maybe an overshoot of pulmonary pressures. With this, it seemed that with the lozenge, you reduce pulmonary pressures and you get a sustained effect. So it's not like when the lozenge is completely gone that the pressures go back up. We only had 20 minutes in the cath lab doing those studies so we don't know a lot about the long-term effects of that, but it certainly lasted 20 minutes long after the lozenge had fully dissolved.

Matthew Cook, M.D.
It was interesting that was something that we would do, nitric oxide for pulmonary hypertension. But it's interesting 'cause that's another one to think back, 'cause when I was at UCSF that we didn't have another way to get somebody nitric oxide at that time. It's kinda interesting.

Nathan Bryan, PhD
Yeah, you have to give it through the nasal cannula. Inhaled, right?

Matthew Cook, M.D.
Yeah, yeah. For the cardiovascular piece of it, if you had somebody and they had, let's say I have a patient I'm just thinking of who is a family member of one of my patients. And so we just got the call, oh. And I've been kinda worried about him for a while, but we just got the call, oh, he's gonna need to have either a cath, which is basically they stick a catheter into the heart to try to open up one of the blood vessels or maybe open heart surgery. So they're sorting that out. And so then this would be in a setting of coronary artery disease with probably a little bit of metabolic syndrome. If you could outline four or five things of how you think about that and how you would try to work with that from a nutritional and a nitric oxide perspective, what would you say?

Nathan Bryan, PhD
Well, certainly they gotta change their diet. I mean I think it's clear you've got to, and the work of Dr. Caldwell Esselstyn shows that plant-based diet completely reverses coronary artery disease, but that's an extreme measure, right? You gotta completely change your diet and lifestyle. Most people aren't willing to do that. But I think it's clear from our published data, clinical data on nitric oxide is you can see plaque regression, you can see perfusion and dilation of the coronary arteries as well as other arteries. And you stabilize the plaque. So as you know, it's not about the degree of stenosis of the coronary arteries. You've got people with less than 10-20% stenosis of the coronaries that have a MI, a fatal MI sometimes. They had subtle plaque, but that plaque is unstable and soft and it ruptures and creates an MI, where other people have lived with 90% stenosis of the coronary arteries, but it's stable plaque and you don't have a risk of it rupturing and causing acute MI, but you still got to increase the perfusion through that stenotic blood vessel, and the only way that I know how to do that is through restoration of nitric oxide. You can give it exogenously, but you have to restore the function of the endothelium of that to prevent

more immune cells and platelets from sticking to that existing plaque, and also stabilize that plaque if it becomes unstable. And probably in that patient, exercise is not gonna be an option for him because he's probably exercise intolerant, and especially with the underlying metabolic issues. But I think mechanistically we know that nitric oxide will improve the insulin signaling. We've seen a reduction in hyperinsulinemia and hyperglycemia with the nitric oxide, and then you perfuse the coronary arteries. But obviously he didn't get there overnight and he's not gonna revert back to normal overnight. This takes time.

Matthew Cook, M.D.
Mm-hmm. Yeah. It's interesting though 'cause I've got a couple other people that are kinda coming to my mind that we had somewhat of a come to Jesus conversation around, okay, let's really do this, let's really change your diet. The blood sugar piece is a, I think there's this endothelial, so this is the lining of the blood vessel, and then there's a blood sugar piece, and those two, if you've got both of those problems, that's a huge problem.

Nathan Bryan, PhD
Indeed.

Matthew Cook, M.D.
And so then managing that that's interesting. How long do you think it takes being on nitric oxide till people start to experience a little bit of a blood sugar? And have you had anybody track the nitric oxide with the continuous glucose monitor where they can track and see?

Nathan Bryan, PhD
We haven't. We published this in diabetic animals I think in 2009. And we treated them, I have to look back at the publication, either two weeks or 30 days. But there was a statistically significant reduction in both insulin levels and fasting glucose levels in these animals. And then we brought it back. Mechanistically we understood that it promotes GLUT4 translocation to improve glucose uptake when you get the nitric oxide. But I don't know if it happens within a couple of hours, a couple of days. I just knew in our experimental model in the lab, we could do it within 30 days. But I think it's a good experiment to do in humans would now with this continuous glucose monitoring. It'd be a cool experiment to do.

Matthew Cook, M.D.
And so basically for people out there, you can call us or go to your doctor and they put a little patch on, and then you just put your phone up and it just tells you what your blood sugar is. So like if you have to stick a needle into your finger, you're thinking, "I don't think I'm gonna check my blood sugar right now," but if you can just go like this and then do it, then you can begin to track it. And so then that's one of my number one things I do for this whole population of patients with cardiovascular stuff, because then we're trying to make it easy for them to get data. And they always say in Silicon Valley here, they say he who has or she who has the most data wins. And

Nathan Bryan, PhD
That's right.

Matthew Cook, M.D.
And so then we're trying to get you that data on your phone so that you can start to make those kind of lifestyle choices and make those easy.

Nathan Bryan, PhD
Well, that's empowering. And I mean people need to be responsible for their own health and wellness. You can't wait till you get sick to go to a doctor and then expect the doctor to prescribe a pill and change your health. I think the past 50 or 60 years in modern medicine has proven that that model does not work. You gotta make some fundamental changes. And if you can be proactive and understand these issues or changes based on lifestyle or diet, and then you proactively make those changes, then you can do what I think everybody's trying to do in medicine, and that's actually prevent disease, not try to treat disease but actually prevent it. And we understand today the mechanism of most if not all chronic diseases that we should be able to prevent a lot of these.

Matthew Cook, M.D.
Now in terms of blood vessel health, then one of the sort of the popular ideas in the last two years has been everybody got into NAD as a supplement

Nathan Bryan, PhD
Right.

Matthew Cook, M.D.
What's your thoughts about NAD in terms of vascular health?

Nathan Bryan, PhD
Well, I think it's critically important. I mean it's one of these things that it's a necessary co-factor in a number of different biochemical reactions not only in mitochondrial function, but we use NADPH as a critical co-factor for nitric oxide production. It's required for binding as a co-factor to make nitric oxide. So it's just a phosphorylated form of NAD. But again if your body, because of normal metabolism, isn't producing enough or there's not enough flux of NAD through these biochemical reactions, and you become deficient, things break down. If you give back what's missing, including NAD, the body responds. So I think again it fits this paradigm that, your body's exposed to something that it doesn't need or it's missing something that it needs, and if you give back what's missing, the body responds.

Matthew Cook, M.D.
Right. This is sort of like my, we have this idea of these essential vitamins and minerals and that they're crucial for health. And so you talk about vitamin D, and so then there's a whole bunch of them, but then NAD is just a derivative of B3, but it's crucial

Nathan Bryan, PhD
That's right.

Matthew Cook, M.D.
For the function in every cell. And I think part of the reason I wanted to have you on here is I think nitric oxide is like an essential, an essential thing that you have to get right. And if you don't get it right, you could do all of the peptides, all of the stem cells in the world, and then you may still have a fairly substantial problem.

Nathan Bryan, PhD
Now, I say, look, I obviously have a huge bias, but I think it's corroborated by 30 years of research that your body cannot and will not heal until you restore the production of nitric oxide. I think that's clear because until then, you're not gonna get perfusion into whatever organ you're trying to fix, and you can't deliver nutrients or other stem cells or other things deployed either IV or systemically to an ischemic organ. You have to open up the blood vessels and prevent the

inflammation, oxidative stress, and immune dysfunction in that vascular bed in order for that organ to heal.

Matthew Cook, M.D.
And so we were talking about immune problems, and obviously there's immune peptides, but then there's stuff that would be kind of an almost like a small molecular category like nitric oxide. And so then there's a diversity of ways we think about it that one other area we think about peptides is for sexual health, but sexual health, probably nitric oxide is gonna be one of the biggest factors. What's been your experience with people with erectile dysfunction who start taking regular supplementation?

Nathan Bryan, PhD
Well, interestingly number one was we saw people had, there's three main responses we saw when we first launched this more than 12 years ago, 10 years ago, 11 years ago. Number one was better energy, better sexual function, and better sleep. Obviously better energy comes from better mitochondrial function, better sex comes from better perfusion of the sex organs, better sleep, I still mechanistically I don't know how to explain it. But you get an understanding based on drugs like Viagra, right, that have been on the market now for more than a decade, couple decades. And these drugs are called phosphodiesterase inhibitors. And so they're not nitric oxide donors, as there was a so-called medical expert on major news a couple of weeks ago talking about Viagra being a nitric oxide donor. That's not the case at all. These drugs potentiate the effects of nitric oxide. And what we've learned from the vascular effects of erectile dysfunction is that 50% of the men that are prescribed Viagra or Levitra, the other ED drugs, don't respond.

So they don't respond with better symptoms of BPH and they don't respond with better erections. Why is that? Well, you need nitric oxide to activate cyclic GMP production, and these phosphodiesterase inhibitors prevent the breakdown of cyclic GMP. So if that particular vascular bed in that patient doesn't generate any nitric oxide, there's no cyclic GMP that's being produced, so you can't prevent its breakdown, so the drugs do not work. We did a clinical trial probably seven or eight years ago where we took non-responders to PDE5 inhibition therapy, gave them our nitric oxide, and we saw an improvement in both symptoms of BPH urinary scores and better erections. So that's very important because it tells us that PDE5 inhibition therapy doesn't work in patients because they don't make enough nitric oxide. And then if you can titrate up the nitric oxide, improve their oxide levels, you can take non-responders and make

them responsive, you can titrate down the dose to mitigate the side effects, and then everything works better. So erectile dysfunction is clearly endothelial dysfunction and a symptom of nitric oxide deficiency. It's very clear.

Matthew Cook, M.D.
Mm-hmm, that's been my experience. And another thing we do for that one is we do the shockwave therapy. And

Nathan Bryan, PhD
That's right.

Matthew Cook, M.D.
I noticed that the shockwave therapy works a lot better if people are taking nitric oxide. And then I've also noticed that the erectile dysfunction medications work better when people are taking it. And there's a part of me that would say just mechanistically, we're always thinking about those deep brain structures 'cause we see so many immune patients with dysfunction, autonomic dysfunction or emotional limbic dysfunction. And a lot of those people have sleep trouble. And there's a part of me that just wonders if the reason they're sleeping better is that there's vasodilating the blood vessels that are going to the brain and then that makes the brain healthier, and so then it's easier for the brain to fall asleep. I mean that's like an in simple terms, but.

Nathan Bryan, PhD
Right, no, it makes sense. I just don't know if it's through more production of melatonin or other peptides or neuropeptides that are controlling sleep. I've never been able to pinpoint it. But, yeah, look, if you perfuse, any improvement in perfusion of any organ, it's gonna perform better. Part of the function of the brain is to mediate sleep and patterns of sleep.

Matthew Cook, M.D.
Now just so you know as people research it 'cause there's a, you've had a pill and then you've had a lozenge. Can you tell me a little bit about the difference between those and when would somebody take one versus the other?

Nathan Bryan, PhD
Well, we evolve just like the science, and so we've understood that different people need different things. There's no one size fits all for anybody, right? I mean we think that nitric oxide is critically important, and no matter what the underlying cause of nitric oxide deficiency, we know the lozenge overcomes that 'cause we control the chemistry of that. There are other people that can just stop using mouthwash, stop using fluoride, stop using antacids, and their body heals to the extent that they can improve their endothelial function. And then other people can't or just addicted to mouthwash or can't get off antacids because of reflux disease or something like that, so they try to eat more vegetables. But we published in 2015 that there's as much as a fifty-fold difference in the amount of nitrate consumed from celery bought in Dallas and Chicago versus celery bought in New York. People cannot eat enough vegetables especially organically grown vegetables to get enough nitrate to make nitric oxide. So then what we've done is we've created a standardized nitrate capsule that if you wanna try that instead of eating 150 grams of spinach in Dallas, you could take two capsules and get enough nitrate of that spinach. And then that primes the bacteria, the nitrate-reducing bacteria. It works as a prebiotic so it gives these bacteria a substrate to work on, so you wake 'em up. Now you're able to utilize nitrate that comes from the diet as well as nitrate that's formed from the oxidation of nitric oxide. And so that gives you kind of an, and people can interrogate each step of the system and figure out what works for them. So what I do is I try to eat a balanced diet. I'm physically active. So those things work for me, but I still take my nitric oxide every day, especially when I'm traveling and eating on-the-go. So I take the standardized nitrate supplement to titrate my levels up, and then I take the lozenge when I'm feeling run down or before I go to the gym to stimulate nitric oxide or to give my body kind of that boost of nitric oxide.

Matthew Cook, M.D.
And then

Nathan Bryan, PhD
And then the other, some people can just, again just exercise, get sunlight. If you eat a good diet and you're not exposed to a toxic environment, you don't need to supplement anything, right?

Matthew Cook, M.D.
Mm-hmm.

Nathan Bryan, PhD
But nobody lives in a sterile non-toxic environment including the foods we eat. So we almost have to supplement because it's not just about nitric oxide, but a lot of the foods we eat today are deficient in magnesium and iodine and selenium and you gotta increase those.

Matthew Cook, M.D.
Mm-hmm.

Nathan Bryan, PhD
So you almost have to supplement.

Matthew Cook, M.D.
Now another thing that I have become a incredible fan of is the cream.

Nathan Bryan, PhD
Oh, that's really great.

Matthew Cook, M.D.
Speaking of cream, I noticed cream, I just had cream 'cause I see the Wu-Tang Clan behind you, which is kinda awesome. But tell me, I always like to get a music reference if I can in every podcast. But tell me about that one, because we are, that's my favorite aesthetic thing that I've actually literally ever found.

Nathan Bryan, PhD
Yep, well, you know, kind of my claim to fame is we know how to make nitric oxide. Then when you start thinking what other utility is there for nitric oxide. And just like the dermis, the skin is an organ, similar to the heart, it has functional cells, it has to get sufficient blood flow to those cells. And so aging, again whether it's an aging heart, aging brain, aging skin is a loss of nitric oxide protein. So what happens to the skin when you don't get enough nitric oxide, you lose collagen, you lose hydration, cells don't turn over to regenerate, you get fine lines and wrinkles, you get dermatitis, you get age spots. So I thought, okay, if we could make a topical nitric oxide that we can apply to the outermost dermis and open up those capillaries, perfuse those cells, then the skin should regenerate. We should have cellular turnover, we see collagen deposition, we see fine lines and wrinkles go away. It's antimicrobial. So people with acne, it kills the bacteria

and the pustules. And it's just a great product. We see amazing results. I think we have four published clinical trials on that. And in fact through the drug company now, we're about to submit an investigational drug application for diabetic and pressure ulcer, 'cause we've seen we've got some pretty impressive data on the antimicrobial, the antibacterial effects of it. We can kill things like pseudomonas, staph, a lot of these bugs that are inherent in infected wounds. And then as you know to heal a wound, you've gotta kill the infection and you've gotta get blood flow to the wound. That's the reason diabetic ulcers don't heal because there's poor blood flow and there's always an active infection in an open wound. So when we apply the topical, we kill the infection, we get a hyperemic response, we get granulation of tissue, and you heal the wound. So it's been remarkable. And I think that there's been no innovations in wound care for the past 50 years. People are still treating wounds the way they've did 40 50 years ago, negative pressure and then trying to kill the infection. We do both of those with a single topical. But for aesthetics, as you mentioned, the product that's on the market now is a cosmetic product that we're seeing great results with that. But again it just goes to show you the power of nitric oxide. When your organ is deficient, it becomes dysfunctional, and that's the outward appearance of aging, and we can overcome that.

Matthew Cook, M.D.
I always like to say that if you find something that works really well in terms of health for somebody that's really sick, it will help somebody who's healthy be healthier,

Nathan Bryan, PhD
That's right.

Matthew Cook, M.D.
Because things that, if somebody's really sick, you have to have a really good product for them to be able to take it, 'cause if it flares them at all, they could get worse. So it's kind of a nuance to finding those things that you can do for that population. So then by analogy it's kind of similar where you say, if there's something that you can put on a diabetic wound to make it better, it probably will make our face better. And I noticed that you told me, this is kinda crazy, but you did tell me that it's anti-infection. And then I had a couple patients with herpes outbreaks. And so then they put it on the herpes outbreaks, both genitally and on the face, and it helped them. We did other things as well, but they were like, oh,

Nathan Bryan, PhD
Right.

Matthew Cook, M.D.
That helped kind of right away which I found surprising. And so then this is basically you take two ingredients, there's a pump and you do one pump and then the other pump, and then you mix them and then you rub it on your face or you can rub it on other parts of the body. What's happening with that with that reaction when you do that?

Nathan Bryan, PhD
Well, I don't know if I've mentioned it, but nitric oxide is a gas. It's a gas under normal atmospheric temperature and pressure. So to create a gas that's bioactive is a challenge, right? And to make a solid dose form of a gas is kinda the code we cracked years ago. So to make this gas, you gotta create two separate components. I mean if you combined them and created this gas, you got a nice bomb, right? We don't wanna create bombs. So we have to keep these things separate. And so when you mix them together, the chemistry comes together and you generate nitric oxide gas. So this is very deliberately and strategically designed. It's pH balanced in both chambers. And then when you mix them together, the combining pH is about 5.5 to six, which is the pH of a healthy dermis or outer layer of the skin. And so when you do that, the nitric oxide gas is produced. It diffuses in all three dimensions. So above it, and we can detect that with a nitric oxide analyzer, but it diffuse into the dermis into the skin. And there's a limit of diffusion. So it's not gonna diffuse into, deep into the tissue and dilate resistance arteries. It just won't diffuse that far into the tissue, but it will diffuse several millimeters in and open up capillaries, dilate superficial blood vessels, and lead to an increase in blood flow or hyperemia to that area. And so when you flood that area with oxygen and nutrients, and you get better hydration, you get collagen deposition, you get the good stuff in, the bad stuff out, cells turnover and you get cellular regeneration. It's really that simple.

Matthew Cook, M.D.
And we have had people use it sort of from an aesthetic perspective for their face. I've also had people who have erectile dysfunction who will use it either, or both men and women have used it topically on the genitals, and they said they felt kind of an improved blood flow, and we've had some positive feedback. Have you guys heard that also?

Nathan Bryan, PhD
We have. Obviously we can't make those claims, but I tell people it gets the wrinkles out. You can apply it to wherever you wanna increase blood flow. So it works the same. But we market it as a cosmetic. As a physician, you can use your best medical judgment to give the patients what you think is gonna be best for their outcome. But, no, we have even thought about filing a drug application for that specific use because we have seen an improvement in both men and women. Now the challenge is to get it to where you can deliver that nitric oxide deep enough in the tissue to dilate the corpus cavernosum, the main conduit artery into the penis. And the technology we have in that cosmetic product will not allow diffused oxide gas far enough into that tissue. Now for the women, the blood vessels are a little bit more superficial in the clitoris to get engorgement, so we found that it works a little bit better in women just because the superficial nature of the blood vessels that supply that organ as opposed to men.

Matthew Cook, M.D.
But that's to basically, that encapsulates almost our whole conversation which is is that we have to think about blood flow, we have to think about where that blood flow is. For somebody like me, I'm trying to combine some combination of interventional things with injections of peptides or injections of other things to basically, we're kind of constantly trying to address nerves or arteries and blood flow into vascular beds. And then we're also, in parallel to that, thinking about what's happening at a cellular level inside the capillaries. And so nitric oxide is at some level implicated in all of that. And so it's kind of amazing. I'm delighted that we got to cover all of this stuff in one quick hour. It's awesome to talk to you. Any final thoughts for people?

Nathan Bryan, PhD
For your audience and listeners, I think it's important to do your own research, understand nitric oxide and how important it is on the body, and then just make those simple changes, and your body will thank you for it. I got an educational website, the drnathansbryan.com. I do a monthly blog to try to make it timely and practical in terms of hopefully provide some information that people didn't know prior and they can make some very simple steps in their life and see the improvements.

Matthew Cook, M.D.
Awesome, well, it's great to have you as a friend and it's great to be educated by you, and thank you for what you're doing 'cause you're making the world a healthier place. I really appreciate it.

Nathan Bryan, PhD
Well, thank you Dr. Cook. I certainly appreciate you, your friendship, and all you're doing to make people better.

Matthew Cook, M.D.
All right, well, have an awesome week. And try some nitric oxide, people.