

Announcer: Bulletproof Radio, a station of high performance.

Dave: You're listening to Bulletproof Radio with Dave Asprey. Today's cool fact of the day is that your brain might make new nerve cells as you age in fact even well into old age which is kind of cool even if you're not old knowing that someday when you're old, you're going to be able to do that. To know that healthy people there's somebody who's have just as many young nerve cells or neurons in the memory-related parts of the brains as teenagers and young adults do. Thus, research just came out in April of 2018.

What this means is that your hippocampus keeps generating neurons throughout your life, at least it does if you've taken enough of the right foods and things like that [inaudible 00:00:49] that process. This new study contradicts a study from March which said that neurogenesis and hippocampus stops in childhood. The new research [inaudible 00:00:59] showing that adult human brains can at least to some extent make new neurons.

In my own life, my hippocampal volume is that the 87th percentile for my age which is a sign that I'm doing something right and I would like to be in the 100th percentile, but hey, I'm pretty far up there. What we don't know though is I didn't get a study when I was young and fat and sick to see if it's smaller but I do have other brain imaging studies that parts of my brain were substantially damaged by toxins. These are specifically more toxins and those are all repaired now. We know that your brain can repair itself and there's new evidence that your hippocampus probably can keep doing new neurons at least if you're doing everything right.

Hopefully, that inspires you to think that there is some things you can do to keep your brain running the way it did when you were young and this came from sciencenews.org.

You're really going to like today's episode because we're going to talk about some things that do impact neurons. Today's guest is Dr. Charles Brenner. He's one of the world's experts in biochemistry because he's, well, a Roy J Carver chair and head of biochemistry at the University of Iowa and has a PhD from Stanford focusing on cancer biology and chemistry and biochemistry in his postdoc.

He's one of these guys who's really dug deep on what's going on in our mitochondria and is now an expert in something called NAD. If you're on Headstrong, you might have heard about NAD and NADH. Because Charles is an expert on this stuff and co-discovered something called nicotinamide riboside, which is one of the few compounds out there that can boost NAD in your body, I want to interview him because, hey, if you can get your NAD levels up via any pathway possible whether it's from exercise or fixing and/or eating the right things not inhibiting things or taking supplements, I think it's worth your time and attention to learn about that. Charles, welcome to the show.

Charles: I am so happy to be here.

Dave: You've had a pretty illustrious career in education and research and even being a professor. How did you get focused on mitochondria in NAD given that you started out with cancer?

Charles: I was minding my own business working on an enzyme back in the early 2000s. The end product of this enzyme pathway was production of NAD, the central regulator of metabolism. Initially, I just wanted to know how the enzyme works. It actually has two active sites. It's kind of a complicated enzyme, which is why I loved it but too complicated to go into at the moment.

There was a huge amount of interest in NAD arising just at that time because NAD is required for the function of sirtuins. Sirtuins are these longevity-promoting genes that are found in everything from yeast to human beings. Folks were starting to manipulate the NAD pathway to see if they could extend lifespan in something like a yeast cell. When I looked at the evidence basis for how NAD is made even in something as simple as a yeast, it seemed like there could be some missing steps. Essentially, when we knocked out this gene that I was working on, we found that there was another way to make NAD. That was through nicotinamide riboside. That's when we discovered NR as a vitamin and the nicotinamide riboside kinase pathway to NAD back in 2004.

Dave: This is going back a while. This is one of those kind of unusual supplements that you heard about sort of on the corners of the internet around longevity. Given that I'm looking to live to at least 180 maybe a little bit longer or a lot longer actually, I'm completely willing and able to find everything and try everything all at once to see if it works. This is definitely the things I've been aware of for a while. I've taken on and off over the years.

I'm thinking for people listening, do you believe given that you're very well qualified to understand about what's going on biologically, do you believe that by increasing NAD in our bodies that we have a reasonable chance of extending our lives even a little bit?

Charles: Let's take a step back and talk about what NAD actually does. [crosstalk 00:05:35].

Dave: Come on, Charles.

Charles: I'm going to take it head on, but I got to take it in peace. [crosstalk 00:05:42]. NAD is the central regulator of metabolism. There's actually four NAD coenzymes. You might read sometimes when read about NAD. Sometimes, they'll say NAD+, sometimes just NAD. There's actually four different coenzymes; NAD+, NADH, NADP, sometimes that's a plus, and NADPH. These coenzymes are essentially required for all the metabolic transformations that occur in every cell in every tissue.

Dave: You die without them straight up.

Charles: You wouldn't live without them. There is no life without them. Conversion of our fuels, protein, fat, and carbohydrate into energy requires NAD similarly maintaining our blood glucose at night and generating ketones requires NADH. It's actually reoxidized as NADH

to NAD<sup>+</sup>. NADH is also reoxidized to NAD<sup>+</sup> when we make ATP from that fuel that we ate. This is required for all of our muscles to work and for ideas to be transmitted along our nerves and for us to hear.

Then, this NADP, NADPH is required for making DNA and RNA and lipids and also protecting us from reactive oxygen species. The connection between NAD and longevity really has to do with two or three things. One is resistance to molecular stresses like reactive oxygen species, sunlight damage, oxygen damage that can damage DNA and other macromolecules. In addition, all of the NAD-dependent processes like converting fuel into energy and repairing DNA and maintaining our blood glucose and having an idea and sleeping at night, all of those things depend on NAD. NAD is under attack in some of these stress conditions and declines in aging.

The basic idea is by boosting our NAD with nicotinamide riboside were maintaining a higher level of resiliency against damage. We're going to basically age better. I still think that we're going to age. I don't know whether you're going to get to 180, Dave, because there's not a lot of human examples of people getting beyond 120, but there's a lot of examples of people being very debilitated in their 70s, 80s, and 90s. That's what we really want to avoid.

Dave: Step one, avoid that.

Charles: We want to square the curve so that people are living more capable lives for a longer period of time, and our aging better essentially. I think that NR has a definite role in that.

Dave: I'm really glad you mentioned 120 because my rationale for that 180 is that, look, I know we can do 120 because it's been done enough times. If you start when you're 35 or basically 30 like I have and you can dole some of the effects of aging, your chance of getting to 120 if a piano doesn't fall on your head are reasonably higher than average. I'm also betting that over the next 100d years of life, we might have a few other technology and biological breakthroughs. They're going to give me another 50%. It doesn't seem that crazy to make that bet given the number of advances we've had in the last 100 years when we didn't have things like artificial intelligence, cloud computing, things like voicemail. Come on.

Charles: Right. Absolutely.

Dave: [crosstalk 00:09:33] 180.

Charles: I think that there have been improvements in sort of hygiene and sanitation, water that have extended our lifespan. We're not predated any longer although in some we could start talking about handgun violence and the potential for lower lifespan in certain locations. I think that more of us can be centenarians. You're right that there's a potential for interaction between things that haven't been discovered yet or better applications of things that have been discovered, but not everybody is necessarily going

to have the genetics that support that. There will be some pianos that will fall on our head.

There is an aspect of aging that stuff happens and a part of the role of nicotinamide riboside really is boosting cellular resiliency because stress is actually experienced at a cellular level. I could give you about seven different examples of metabolic stresses that actually depress aspects of the NAD metabolism.

Dave: Talk about laying a couple of those. I think for people listening, this is a molecule that keeps you alive. You have more of it. You're going to a very high-quality resilient life. You have less of it. Your life is going to suck on multiple levels. We'll talk more about some of the other stuff you can do for NAD like something that regimens and injecting it and things like that later, but what are these examples of things that depress NAD?

Charles: The thing that we've known about for the longest time is alcohol. Alcohol is metabolized in the liver in two successive steps. The NAD goes from NAD<sup>+</sup> to NADH. You need the NAD in the plus form in order to burn fuels. The end result of excessive alcohol intoxication, excessive alcohol metabolism is essentially alcoholic fatty liver because we're not burning those fuels in generating ATP. Instead, we're storing the fuel as lipid droplets, hepatic steatosis, but a few years ago, my lab did an experiment in which we essentially wanted to look at obesity and type 2 diabetes in a mouse.

There was a lot of speculation that might depress liver NAD as well. It did, but it more strikingly depressed liver NADPH. NADPH is the central regulator of reactive oxygen species toxicity. When you generate ROS, the reactive oxygen species have to be detoxified in a manner that depends on NADPH. When you overfeed a mouse, you end up with a storm of reactive oxygen species that damages molecules systemically including in its nerves. These mice develop pre-diabetic and then diabetic neuropathy on the basis of their obesity and diabetes. We can prevent that with provision of nicotinamide riboside. That's just the first two.

Dave: [crosstalk 00:12:58] Let me go straight. If I'm going to go out and drink a lot, which by the way if you guys have read the Bulletproof stuff, there's all infographic on if you're going to drink how to prevent damage, are you saying that having higher amounts of nicotinamide riboside is a good idea pre or post a binge? By the way, you shouldn't be bingeing. You guys hear me, but ...

Charles: Yeah. Bingeing, not so good, but having higher level of NAD. By the way, the liver loves taking up nicotinamide riboside. Oral NR is very highly available to the liver. I would say that if you were like going into Passover Seder or some other reason why you're going to have four glasses of wine just as I did on Friday night last week, preparing your body with a little bit more NR is probably a pretty good idea. This is something where ...

Dave: I got to pause here for a second there, Charles.

Charles: Sure.

Dave: You're not allowed to say necessarily a strong claim on this. I totally get it, but I can say pretty freely that I think it's a good idea to upregulate your mitochondrial function in every way possible if we're going to drink. This is one of the possible ways.

Charles: But yeah. Upregulating mitochondrial function through physical activity, eating well, and potentially taking a supplement that would elevate your NAD is something that will maintain wellness.

Dave: What is the effect of nicotinamide riboside or [inaudible 00:15:14] NAD for someone who's in ketosis?

Charles: Not been studied. You need NADH to generate ketone bodies. You need NAD<sup>+</sup> to oxidize them. There's a fuel cycle that depends on NAD, NADH. The ketogenesis part occurs in the liver whether that would be depressed at low NAD. I don't think anybody's actually looked at that yet.

Dave: It almost certainly would even though ... I don't know of any science either. Just because everything that happens biologically requires mitochondrial activation in order to make electrons to feel recycle, so pretty much when you're not making enough energy in the body, every system in the body can be affected. You would imagine if you have adequate energy reserves and your mitochondria functioning well that system would work better, but like you said, there's [crosstalk 00:16:08].

Charles: Dave, I wasn't going to be the first person to say electrons in this hour. I thought that was going to be too technical, but since you said electrons ... [crosstalk 00:16:17].

Dave: ... electrons.

Charles: Since he said electrons, the difference between NAD<sup>+</sup> and NADH basically has to do with electrons is that NAD<sup>+</sup> is the hydride or electron carrier for all that fuel oxidation. NAD is the hydride-accepting coenzyme. When it's got those electrons, it's NADH. Then, that initiates the electron transfer chain. You can generate the ATP.

Dave: Now, I'm going to translate that as best I can. My book, Headstrong, goes through this. There's so much complexity around mitochondrial biology. I am not a university professor level guy, but when you write a deep book about how to hack this process, you want a thing or two. The deal here is that food and air are coming in. Your body turns them into electrons via the Krebs cycle. Then, the electron has to be carried somewhere. You got NAD to do that. You like that really basic assumption there or [crosstalk 00:17:18] basic explanation?

Charles: Pretty good communication.

Dave: There we go. Now, if you're listening to this going why should I care about this, this is PhD level biochemistry. Here's the deal. This is fundamental to you being alive. It's a process that either it works or doesn't work, it's not a light switch. It's a dimmer switch. What you want to be able to do is you want to be able to turn out the dimmer switch

because when you do this more effectively, all of the diseases of aging get better. You will kick more ass through the entire length of your life and hopefully have a longer one as well if you can achieve that. That's why I spent a couple years writing a book on it because I wanted to do that for myself.

That understanding is cool because the first place you're going to feel this probably isn't in your liver unless you have weird sensors in your liver. I don't. You're going to feel it in your brain because your brain does this the most.

Charles: Right. Your brain is a very bio-energetically demanding organ so were peripheral nerves. That's why in chemotherapy, people get painful nerve endings or insensate nerve endings again because it requires so much ATP to transmit touch sensation all the way back to the dorsal root ganglion. Since you mentioned air, well, let's give a shout-out to oxygen. Oxygen is the ultimate electron acceptor. NAD is sort of the first electron acceptor.

Oxygen is the ultimate electron acceptor, but at the inner mitochondrial membrane, when these electron transfers don't work perfectly well, you generate superoxide and other oxygen free radicals. Guess what detoxifies them? Electrons on NADPH. I like having the nerdy conversation with you, Dave, because there's a lot of people that got interested in NAD because of sirtuins. Sirtuins are interesting proteins. Like in yeast, I started out as a yeast person and the ability of a yeast cell to extend its lifespan when you calorie restrict. It depends upon a gene and protein called sirtu, but by no means are sirtuins the only or the major mediators of the effect of NAD.

The fundamental redox biology of these four NAD coenzymes is vital to life. As you said, the ability to do all of these NAD-dependent processes is essential for every organ function.

Dave: It's interesting. People probably unless you're nerdy, which is a great description actually, you probably don't know this is really an unusual form of vitamin B3.

Charles: It is. Right. The two previously known forms of vitamin B3 were discovered in 1938 up the road in Madison, Wisconsin by Conrad Elvehjem. A hundred years ago, in the American South were a million people with a disease called pellagra. Pellagra was characterized by diarrhea, dermatitis, and dementia, ultimately death. When people looked at it at first glance, it looked like a communicable disease and infectious disease because you would see in a village or in a mental hospital or something like this, you'd see a lot of people with pellagra.

The Public Health Service was created. This is the forerunner to the National Institutes on Health. The very first grantee in the PHS was Dr. Joseph Goldberger went down from the North to the American South and looked at these pellagrans, people with pellagra. He would notice that doctors and nurses in a hospital didn't have these symptoms whereas their patients did. When he looked at the diet, he said, "Well, look. The doctors can put milk in their coffee. They have eggs. They have some fresh food, whereas the people that had pellagra were on a diet of corn rations and lard." It's almost to be hate

to be disparaging ... I live in Iowa City, but it's like an extreme of a Mid-American unhealthy diet or a diet in, which you try to get all of your foodstuffs from the isles rather than the perimeter of the grocery store where the fresh food is located.

Now, today, you wouldn't get pellagra from eating a diet of just crackers and cookies because niacin is supplemented into the wheat. We don't get frank pellagra from that diet today, but 100 years ago, we did. When pellagra was turned into an animal model, Elvehjem discovered nicotinamide and nicotinic acid as the two vitamins that would prevent it. We've known about those two forms of vitamin B3 since 1937. Then, my lab came along in 2004 and found NR. It's a third vitamin precursor of NAD.

Dave: What about the other form of vitamin B3 that it's not politically correct to talk about nicotine?

Charles: No. Nicotine is not B3. [crosstalk 00:22:47].

Dave: It's molecularly similar, right?

Charles: It's similar, but does not generate NAD. There is another molecule that can become NAD in some of our cells. That's tryptophan, but tryptophan is an amino acid. Its primary function is to make protein. You could also make serotonin from it. The gene pathway from tryptophan to NAD is basically inefficient. It's not on in every single type of cell or tissue. Tryptophan turns out to be a very inefficient way of making NAD. It basically doesn't promote NAD synthesis in neurons for example. It doesn't have nearly as much use.

Dave: You could get a little bit of biscuit. Well, this is niacinamide, which is one of the forms of B vitamin we know about and something called ribose. What's funny enough, that's what's in MitoSweet, the Bulletproof sweetener we have is the ribose-based thing, but your body doesn't combine niacinamide and ribose very effectively to make nicotinamide riboside [crosstalk 00:23:52].

Charles: It doesn't do that. There's actually no example in all of biology in which a base like nicotinamide or adenine is just combined with ribose to form a nucleoside. It's sort of not the way it works. Nicotinamide can react with a compound called PRPP to form NMN. Then, NMN can go to NAD or nicotinamide riboside can be phosphorylated is the technical term to NMN and then form NAD. But the ribose and the nicotinamide is mites great. High-dose nicotinamide doesn't really do what you want it to do because high-dose nicotinamide will inhibit these enzyme sirtuins whereas high-dose nicotinamide riboside is an any deeper cursor that doesn't inhibit these sirtuins.

Nicotinic acid is great especially for lowering LDL cholesterol, lowering the bad cholesterol, and raising HDL cholesterol but has two limitations. One is that it doesn't regenerate NAD in all tissues. For example, it doesn't regenerate NAD in neurons which [crosstalk 00:25:15] talked about that matters the most. Also, high-dose nicotinic acid causes a flush reaction that's pretty uncomfortable. [crosstalk 00:25:24] is basically ...

it's available to all cells and tissues. It doesn't [inaudible 00:25:27] sirtuins. It doesn't give us a flush reaction. That's why it's a more valuable B3.

Dave: If a biohacker has been trying stuff for a while, you might have had a chance to try niacin, one of these other forms of vitamin B2. Niacin is known for causing a flush reaction. This is going back to use like the mid-90s when I was first like I've really got to figure out why I'm not losing this 100 pounds. I got some very expensive high-end multivitamin. It had a substantial dose of niacin in. I took this stuff. I was just an uneducated biohacker, frankly desperate because my brain wasn't working at the time. I was feeling like crap. I couldn't keep up at work. I took the stuff. Literally, I turned bright beet red. I'm like I'm getting rashes. I set the vitamin back. They're like, "Oh, yeah. You should get this stuff without niacin."

People with infrared saunas will often times take niacin when they're doing the sauna to help cause like sweating and flushing to get toxins out and things like that. It's an aggressive thing, but if you have heart disease and things like that higher-dose niacin is probably a good idea, but what you're saying, Charles, is that NR has benefits far beyond what niacin would do, but it does the same types of things that niacin does.

Charles: They're both NAD precursors. NR does not produce a flush. There's much more clinical research on high-dose nicotinic acid than high-dose NR. Thus far, there's only two published clinical trials of nicotinamide riboside of human being's the first one. Well, there's one that was a combination, but the combination was with a compound you shouldn't really combine NR with. We could get into the cardiovascular effects in that trial, but in the only two clinical trials that have been published a pure NR, mine was just to see whether it was orally available in people and it would safely increase their NAD who does that.

But there was one that was just published in, I think, the end of March of 2018. It was at one gram of NR per day. What was found is that the folks on trial who were pre-hypertensive meaning that their systolic blood pressure was between 120 and 139.9 so they were not medicated for hypertension, they got about a 10-millimeter of mercury benefit so a 10-point drop in their systolic blood pressure by being on this high-dose NR.

There's many more published studies of high-dose nicotinic acid at regulating plasma lipids. That's basically not been studied yet for NR, but what we know about NR is that like nicotinic acid, it's an NAD precursor. Nicotinic acid and niacin are the same thing. Unlike niacin, it does not cause flushing and better than niacin, it is available in tissues like neurons. It's a very exciting compound. It's available over-the-counter.

Dave: When I first tried NR or nicotinamide riboside, the stuff that we're talking about, I know this was a long time ago rather when it first came out. I'm the guy who like orders a bag of white powder kind of guy, but legal white powder. I found that I know what it feels like when I have to regulate my mitochondrial function like what things are working better like there's a spark in your brain and things work like you don't drop words. It's very hard to put a word to it, but there's a feeling like I'm running at full power the dimmer switches all the way up versus down 10 or 20%. As I became just more able to tune that system, most people are not running at full power.

I can feel when I'm doing it at least what I think is full power, maybe there's a level I haven't hit yet up. I'm still working on that, but I could feel a gram, which is a relatively high dose what you talked about in your study ready the nicotinamide riboside, but I couldn't feel any difference from like 250. This is not to say I wasn't doing something, but it didn't hit my mitochondria to the point my brain would feel it. What's the difference between taking 250 milligrams or taking a gram?

Charles: The first thing I want to preface by saying is it this is something that's available over-the-counter. It's not intended to treat a disease or condition. We're not making health claims ...

Dave: That would be wrong to make health claims over anything you sell. Even if they're true, you must not make them, Charles.

Charles: It's an over-the-counter supplement. It's being tested for diseases and conditions. Right now, you and I are having a conversation about wellness and how you feel.

Dave: Absolutely.

Charles: I would say that at the so-called recommended dose, which is 225-millimeter capsules most people take it in the morning, what you're getting is an improvement. It's like an antivirus software that's running. It's running in the background. If you didn't get a cold this winter or a bunch of your friends got colds, if you just experience less time zone disruption than your work partner or travel mate, that's kind of your effect. You were a bit more resilient. You didn't necessarily notice a huge boost. But as people get to higher doses like the folks in this recently published University of Colorado study who were taking a half a gram in the morning and a half a gram in the evening, those are more of a therapeutic dose. The therapeutic trials that are going on in at least I think 16 sites around the world are tending to use doses that are higher.

Dave: These are without claiming that it does thing.

If you can slow, delay, inhibit those things, you're probably going to like your life because it's like they hit you one day is that they're building up over the course of years and during the time they're building up, you start to feel a little bit more like crap every day. It sneaks up on you.

Charles: I promised you earlier something like seven different ways in which NAD and the NAD metabolome can be depressed by metabolic stresses. Cardiac is one of the most interesting to me. Let me just run through them really quickly and any of them that catch your interest, we could talk about more. Noise-induced hearing loss, so there's a study in New York where they subjected, sorry, but it was an animal experiment. They subjected mice to sufficient noise that it caused deafness. [crosstalk 00:32:41]

Dave: I don't know what kind of music were they listening to. [crosstalk 00:32:44].

Charles: No. It was probably like a human being that works with a jackhammer.

Dave: Got it.

Charles: I don't know quite how it translates to two human beings, but noise-induced hearing loss actually depresses NAD in the cochlea. Sun damage, oxygen, free radical stress, depress NAD. [crosstalk 00:33:09].

Dave: We have to talk more about this noise thing. There are a very substantial number of rock stars to listen to Bulletproof Radio because a few of them have reached out to me, which blows me away completely and like, wow, their stuff works. Guys who are in the music field, I would just tell you that if I was going to be on stage the way you guys are, this would be a really good thing to do any mitochondrial enhancement, but given that there's a study about that, who cares if it's in mice like your ears are how you make your living for some people. That's just a great use case. That's cool.

Charles: Sun and oxygen damage reactive oxygen species so when you talk about the mitochondrial dysfunction, then you're talking about electrons gone wild. Electrons could go wild, they generate reactive oxygen species. They require NADPH to detoxify them. NADPH is also required to make things like estrogens and androgens. You really don't want your NADPH tied up in repair processes when you need it for biosynthetic processes.

Changing time zones and time zone disruption, this regulates the NAD metabolome because the NAD metabolome is regulated by circadian 24-hour functions. We're not in a large group of people. I asked people how many people would like to hop on a jet and go to a visa for a few days of drinking wine and enjoying plenty of food and listening to maybe loud music in the sun in the fresh air. Everybody raises their hand. Well, you just talked about five enjoyable things that all dysregulate our NAD metabolome.

That's not even disease processes. Then, we get into neuro-degeneration and heart disease. There are acute situations where NAD declines. We recently showed in a mouse model of heart failure that not only does the NAD decline, but the nicotinamide riboside kinase gene gets turned on. It turns out that in a failing heart, the heart wants to have NR in order to replete, in order to fill up to NAD stores. Why, because it costs less ATP to generate NAD from NR than from the other precursors.

Dave: That makes so much sense. It's pretty incredible what can happen with these things. I've got to ask what about just straight out injecting NAD because I've had about 15 grams of NAD intravenously. We're doing it at Bulletproof Labs on occasion. It's been pretty profound, but I'm taking a gram of NAD in my bloodstream. What's the difference between nicotinamide riboside and just straight-up doing NAD?

Charles: Injecting NAD doesn't make any sense to me because NAD doesn't go into cells as NAD. [crosstalk 00:36:13].

Dave: Inject intravenously.

Charles: No. It stills get into cells. We've done the experiment where we ... I know that you're basically interested in neuroprotection. We did the experiment. Again, we have to engage small numbers of animals in order to do controlled experiments and figure out mechanisms of action. In a collaborative experiment with Eric Duplus group in Paris, we generated a model of excitotoxic brain injury. NMDA is a neurotransmitter. But a very high dose of NMDA will actually cause brain damage. We induced this type of excitotoxic brain damage and directly compared NAD and nicotinamide riboside. Nicotinamide riboside worked more than 15 times better than NAD.

The NAD worked at a very low level but in a manner that required its conversion to NR. NAD converted to NR in order to go into the neurons in order to protect. Think of it this way. As we age, our skin is losing collagen production. We don't take a cowhide with collagen and just rub it on our skin. That doesn't work. It's only collagen peptides that ultimately are degraded into collagen amino acids that can go into cells and that with new collagen gene expression in those skin cells, those skin cells can make their own collagen.

Dave: I don't you brought that up on purpose, but the purpose is the company that brought collagen peptides to market. It's like when you go to Whole Foods, that's our collagen peptide's other side. I love it that you just brought that. Was that on purpose or you just ...?

Charles: Were you at this NAD summit in San Diego?

Dave: A couple of guys for Bulletproof Labs were there, but I couldn't make it down in time.

Charles: I was trying to figure out how to communicate this concept because there are folks that are out there that are injecting NAD and swearing by the transformative ability of high-dose NAD to cut down on their cravings and to do amazing transformational things in their lives. Although that's not the same as a placebo-controlled trial, the anecdotal accounts were pretty remarkable, but in animal experiments, we can try to figure out how these things work. Then, in a lay audience, I've got to figure out how to communicate that. Why wouldn't NAD be better if a damaged brain is deficient in NAD? I want to give it NAD rather than nicotinamide riboside, which is a precursor.

Well, collagen is the perfect way to explain that. You can't get intact collagen into a cell. The best you can do is degrade collagen and those peptides are going to be further degraded into amino acids in order to be converted into collagen.

Dave: That's a great way of explaining it. You need the building blocks. It's interesting that the studies on intravenous NAD show a bunch of effects on your pain reduction in the body and specifically for drug and alcohol addiction. They're seeing just profound results, but it takes 10 infusions of relatively high doses. It's a particularly uncomfortable procedure. It takes about two hours minimum. You sort of feel like a weird pressure on your chest, but I did notice like lasting impact from having done 10 of those. I've also had traumatic brain injury. I had toxic-induced problems in my brain from mold toxins in the environment around me that were looked at with a SPECT scan.

Maybe, I'm an unusual case there, but I noticed a difference there, but I also have taken NR for a long time. The question is stacking these in multiple pathways good, but I'm intrigued when you say 15 times better from an oral, but what was the measure of better?

Charles: No. This wasn't oral. This was a direct infusion of NAD and NR right at the site of a brain injury where NR was much more powerful.

Dave: Can I buy NR intravenous? Is that available? Can you get ...

Charles: NR's not available intravenously. We've commercialized it as an oral product. We've shown it that it's orally available. In the fullness of time, there will be compositions and formulations of NR and NR-releasing compounds that may be more brain available than NR, but we've done a lot of neuroprotection things with nicotinamide riboside in mice and rats and orally available NR is neuroprotective. I mean that's been shown in peer-reviewed studies.

Dave: That is fascinating stuff. what I've found in my own path of losing this weight and just getting energy I've never had is that your ability to build core resilience means you can do more things you want to do.

It means you can take a hit and get up again. I think there's a case for this form of medical enhancements stacked with things like glutathione and all the other things that are out there that make it work. When you get all those things working at the same time, you're like, "I kind of like my life." If you realize, wait, okay, this isn't always cheap, but compared to any one of the nasty outcomes that can happen at the end of your life that involve a decade or two in a nursing home, this is dirt cheap. This is just my perspective on life. Do you think that's warranted?

Charles: Well, nerd that I am, I'm going to first respond to the molecules that you're calling. Glutathione, it turns out that reactivation of glutathione, which is a key regulator of a detoxifier of reactive oxygen species depends on NADPH. Then, it's been widely reported that in multiple tissues, our NAD declines in aging. NAD declines much more sharply in the conditions of metabolic stress that I've described with alcohol, the overnutrition, the noise, the sun damage and then these real disease models like nerve degeneration and heart disease, but there appears to be a decline of NAD and NAD metabolites in aging.

Concomitantly, there's also a decline in metabolism and cognitive function and resiliency. Yes, potentially, by keeping our NAD and NADPH high through aging we can stay more active. It's potentially a virtuous cycle where if you enjoy exercise and activity more, you're going to do it more if you recover more easily because exercise is actually a beneficial type of stress just like responding to a loud car horn so that you don't get run over by a vehicle. That's a beneficial type of stress. When we exercise our muscle is able to dispose of damaged mitochondria. We turn over a lot of macromolecules and refresh ourselves. All of these processes require NAD.

Dave: What about physical performance, like if you want to be a higher performing athlete? What does NR do to physical performance?

Charles: It's not been clinically tested in people although since most of the early clinical tests are done with healthy human volunteers, the signal that one would see would basically be being even better than healthy. That's actually a hard signal to see, but we do know anecdotally of a lot of athletes and even teams that are using nicotinamide riboside. It's not considered a performance-enhancing drug. There's NAD in the food that we eat. NAD gets broken down into the vitamins, NR, nicotinamide and nicotinic acid in the course of our digestion.

When you're supplementing with NR, you're basically getting sort of like a day's worth of NAD precursors in a capsule form as a supplement to the NAD precursors that you have in your food.

Dave: That was a very well coached reply that said if you're a high-performance athlete, if you enhance mitochondrial function via lots of different pathways, which may or may not include nicotinamide riboside, it's probably a good idea. Did I nail that?

Charles: Well, here's what I want to say. I want to say that it's safe. We've very extensively tested it for safety. Placebo control trials show that taking a gram a day does not cause adverse events. It's not been tested in every possible combination with every possible genotype of a human being or every possible medication that a person could be on, but people can try it. For people that know their mile time or their swim time or they have something of a health complaint like, gee, I wish I could sleep a little bit better or I wish that I could focus a little bit better in the afternoon and they keep a journal, when they try nicotinamide riboside, probably by the second or third week and some people notice something on the first day, but most of us notice something in this second or third week that they're just functioning at a sort of higher level. That's something that you can sort of notice if you keep a journal.

Dave: That's one of the things I started out when I was working in Silicon Valley. I was just having days where I just couldn't pay attention instead of working. It was like I was walking through mud. It just didn't work. I realized, wait, some days are worse than others. I would just in the site of my engineering notebook, I'd be like, oh, I have a ton of energy right now or I'm feeling like crap right now or like I can't keep my eyes open. They're crossing or whatever is going on. After a while, I just cultivated an ongoing process. You can tell him like a computer guy. I installed a little process that was just sort of saying how am I doing right now like how's my energy level.

Over the course of years, it becomes really finely attuned like, you know what, just something half hour later, I feel really good. Then, instead of immediately saying if I feel good, that's just my perception. If I really don't feel good, I really I sort of like just self-questioning just doing ... This was a sensation and either it happened or didn't happen and whether it was placebo or not is secondary to the fact that I feel like good right now, but you learn the placebo effects generally wear off over time. If you do it on a regular basis, you're like, wow, I feel better. My lap time is faster. I stayed awake for longer. I wanted poker whatever is they're trying to do. That's a pretty liable signal. For

stuff like this that's shown to be safe, there's a case for saying try something and just see how you do.

I would also say there's a case to say if you try something, you don't feel anything, you do it for a month or two, you're probably not getting a high ROI on it or it's a very long term effect. Try something else, but if you feel it, keep doing it as long as you feel it. That's a basic algorithm for biohacking, but you're a university scientist. You're nodding, but how much of a pussy bow should we be worried about if we're self-experimenting on something like this?

Charles: The early adopters are a self-selected bunch of people. It's not a super inexpensive supplement.

Dave: No, not at all.

Charles: There's a certain amount of commitment to it. People may go into it reading about the amazing science and thinking, wow, this is going to be great, but I think that you're right that people are not going to stick with it doesn't provide a return for them. One of the things that you will notice, it's a little on the trivial side, but it's noticeable is that hair and fingernails grow faster. That's actually the anabolic piece, the NADPH piece of nicotinamide riboside is that you need NADPH for biosynthetic processes. Your gut turns over. Your hair grows. I shaved my head.

It would just be the amount of biomass that is dropping into the sink in the morning, but people do notice that their fingernails grow faster and stronger. Then, people that work out typically find that a recovery happens more reliably, more faster and that they can hop on a plane and adjust to a timezone better than the person and the seat next to them.

Dave: The resiliency thing is really important. I take a very carefully crafted mitochondrial stack every time I fly because I like to land and be functional. I've flown quite a bit in my career. It used to be a really major thing even if it's a four-hour flight or something. I was just a zombie for the next even two days and usually when you fly somewhere, if it's on vacation, you don't want to be a zombie because you won't have fun. If it's for a business trip, you land and then you can't remember what you did. You're tired and you fall asleep in a meeting. It's just not a nice thing. That's probably the best way to test whether something you're doing is working is take it before you fly or maybe while you're flying for a longer trip.

If you have an amazing trip like, okay, you probably did something good just because you're this confluence of negative things where you have less oxygen, changes in pressure, vibration, bad light, timezone, a circadian disruption, all the bad things you could think of all at once, extra ionizing radiation like it's a bad scenario.

Charles: Right. Because NAD is circadian, almost everybody takes nicotinamide riboside in the morning when they get up. This is one of those things where if you already know enough about circadian regulation to stay up until 10:00 pm in wherever you're flying to

if you can and then melatonin if you need it and then get out and get some bright sunlight in the morning. You want to reset with the bright sunlight and nicotinamide riboside in the morning on arrival. That would be the most evidence-based way to use this product.

Dave: You don't recommend taking it before bed? Will it keep you up or there's I guess it spikes naturally in the morning? [crosstalk 00:52:07]

Charles: The research that we've done on it shows that there's a diurnal function of NAD. There's a daytime peak and a nighttime peak. The daytime peak is normally coming from our digestion of food. We eat food in the morning and our NAD gets broken down into NR and nicotinamide and nicotinic acid. You're boosting your day time NADP by taking NR in the morning. Some people including myself take their daily dose of NR split into an AM and a PM dose. This is extremely anecdotal for me, but I'm one of the people that thinks that he has a sleep benefit of taking NR. Again, that's not been clinically tested, but that's something that we're very interested in.

Dave: This is something I wrote about in Headstrong. I've noticed when I take mitochondrial enhancers before bed and Bulletproof makes some ketones or mitochondrial enhancement like there's tons of ways to do it. The whole book is like studded with everything I know about how to make them work better. I'm like, well, why is this that I sleep better when I take anything that makes my mitochondria work better. It turns out the pump that moves cerebrospinal fluid, the glymphatic system is regulated by mitochondria. I found a study for that I quoted in the book.

We have a plausible mechanism that says if you can make your mitochondria work better, you'll do a better job of flushing the brain with clean cerebrospinal fluid, which is one of the processes that happens during sleep. In fact, I know just from anecdotal myself if you can have less toxins in the brain, you're going to feel better the next day. If you just wake up and you feel great, you need less sleep. One of the things that can make that happen is better function of that pump, which has to come from electrons. I would say take everything that enhances your mitochondria before you go to sleep. It's amazing I feel the next morning. I think your effect would be there's a plausible mechanism for the fact that [crosstalk 00:54:13] in yourself without making any medical claims.

Charles: Right. Well, that restorative aspect of sleep is so important potentially in removing pre-Alzheimer tangles and allowing memories to form. You absolutely need good bioenergetics for good brain function. One of the things that we found by doing research is if I've made a contribution to NAD, it's in two areas. One is in the gene discovery piece and like finding all of the missing genes that were involved in NAD metabolism.

Then, the other is in a measurement piece. We developed something called targeted quantitative NAD metabolomics where we can basically take blood or a tissue from any kind of sample. We can basically put it in a machine. We can determine the levels of all of the NAD metabolites. With these two technologies can basically tell us whether NAD is involved in any process that you want like chronic fatigue syndrome. Someone asked

me about that recently. He said, "Do you think NAD might be dysregulated in chronic fatigue syndrome?" I said, "Well, I don't know, but I can figure out how we can tell," which is just get some tissue.

If we see the genes are dysregulated and the metabolites are dysregulated, it's telling us that NAD is misregulated. One of the most amazing things that we did in last year related to this heart failure story that I was telling you about where this mouse is on its way to getting heart failure. It's even pre-symptomatic. Its NAD starts dropping. Its NAD is dropping. Its nicotinamide riboside kinase 2 gene is spiking up so that the gene pathway to convert NR into NAD is going up while the NAD is going down. What turns that on is something called a MP kinase.

It's this low energy sensor. The low energy sensor is turning on this NR pathway so that if you're the lucky mouse who is supplementing with nicotinamide riboside, you have a much better of heart function because NR is available to those stressed cardiac cells that are having this bio-energetic crisis. To some degree, people will have a more noticeable performance issue after they're already somewhat debilitated, but there's a protective aspect, I think, of having NR available when stuff happens because when stuff happens and we have those kinds of stresses or NRK 2 gene maybe turning on, the NR is available to us, then it may protect that tissue.

I'm getting out the level of interpretation of animal experiments, but I think that's where the science is going in terms of looking at applications where NR could improve human health is that somebody says to me, "Do you think it could be involved in this disease?" We now have the tools to figure out if it will be.

Dave: It's interesting. You mentioned. For several years, I took metformin, the diabetes drug, which affects AMPK. Now, you're actually providing a missing piece of that puzzle for anti-aging why people have been doing that although I think there's a great argument, don't do, that because long-term use inhibits mitochondrial function, which is why I quit taking that stuff. I've never had diabetes. I was pre-diabetic in my mid-20s when I started down this path, but my blood sugar regulation is perfect at this point.

That drug though, it sounds like it would probably have this effect of increasing your levels of NAD via that pathway, but why do you need to go to that level if you can just increase levels without it?

Charles: You're actually going to need a precursor anyway. AMPK kinase activation will turn on the NRK pathway, but then, you need nicotinamide riboside to feed into that pathway in order to replenish the NAD.

Dave: You need it anyway.

Charles: Yes. I certainly don't advocate off prescription uses of drugs.

Dave: I do.

Charles: I don't take rapamycin. I don't take metformin. We always say, "Ask your doctor for people that have a disease or condition." Right now, NR is out there to promote wellness, but the great thing about it is that it's safe. It's natural to nature identical product. We think that it will promote wellness.

Dave: I think you've got a pretty clear case there or, frankly, I wouldn't had you on the show. I know you've done the real research and looked at the gene pathways and looked at the mitochondrial biology. I'm hoping that this show just serves to help people understand how important mitochondrial function is for how you perform right now and how you are going to look and feel and think 20, 50 or 70 years from now however old you are and why you're building stuff like this into your stack that you take over time and maybe probably don't need this if you're 18 and your biology is working really well. You might get a bigger bang for the buck somewhere else or you might take it just before an event or you might be 18 like I was in fat and not feeling very good and probably could have benefited greatly from it.

There's an individuality. There's always a place where you decide where and how you're going to invest your dollars and your energy and your time in feeling really good right now and probably taking away some of the bad things that can happen as you age. I think you've done admirable work on this stuff, Charles. Just thanks for being curious for those long periods of time. I get asked why did you get so curious about this like what makes you tick.

Charles: Well, I love discovery. I love asking questions that no one has asked before. As I said, when we started looking at the NAD synthesis pathway, everybody else in the field basically took the received wisdom and said, "Okay. There's one way to make NAD from tryptophan. There's a way to make NAD from niacin. There's a way to make NAD from nicotinamide. That's what these five publications all say. That must be it. We just realized that potentially it was a rare example where we knew what we didn't know. Usually, you don't know what you don't know. This was a rare example in, which we realized that not all of the underlying assumptions behind the wiring diagram for NAD had really been tested and that it was really up to us to do that test.

It's been non-stop fun ever since then. We've made a transition from doing enzymes and yeast to doing mice and rats and people seen this molecule safely commercialized. It's been a really exciting ride.

Dave: Were you one of those like super curious kids who always had to figure out how things ticks? Is this something that you this level of curiosity that come to you as an adult or is it just something that has always been built in?

Charles: Yeah. I broke a few things in my childhood.

Dave: You're one of those kids. By the way, those are the best kids. I'm just kidding. This is just something that's just built into your nature to just be curious and just get to the bottom of things. That's what you're doing professionally.

Charles: Yeah. We like to figure out how things work.

Dave: There's this great pleasure. I'm certainly one of those people too where you know how it works. You can do things to change it. That's cool. If someone came to you tomorrow, Charles and they said, "I want to perform better at everything I do as a human being," just based on your life's path including your research or not including your research, whatever, what advice would you have for someone who just came and said like, "What should I do?"

Charles: Well, I would say aging better involves managing stress, sleeping, and eating well, staying physically active, mentally challenged and probably socially engaged, but increasingly, we have evidence that keeping one's NAD up with NR protecting us against some of the inevitable stresses of life. Supplementing with something like Tru Niagen could potentially be an adjuvant, but you got to start off by managing stress, staying active, eating right, and trying to have a positive attitude.

Dave: It's amazing how many people and we're going up against I think about 500 episodes at this point. I've been paying attention. They're keeping a tally, which is part of some new work that I'll be publishing soon. It's amazing how many people come up without those big ones. It's about stress, sleep, eating, and exercise and things like that and of all the things you could have said and I think what you did say at the end there was and increase your resilience, which is why you're talking about, nicotinamide riboside, which is really cool. I do hear that answer on occasion as well and I know solely NR, but just do what it takes to be more resilient because into the day, you want to perform better as a human being.

If you stopped performing the second something happens it isn't idea, that's not going to work very well. Certainly, as a biohacker, my resilience is increased and mitochondria seem to be at the core of it.

Charles: Yeah. Don't forget mentally challenged and socially engaged. For me, what works well is to always be diving into the deep end of a swimming pool and trying to do something that I've never done before, taking up a new hobby or going to a new place, trying a new exercise routine, all of those things can be can be really good for you. I think that social engagement and positivity has got to be a part of the mix as well.

Dave: They're on your list as well. Well, thank you for sharing that. Thanks for being on Bulletproof Radio. Let's see. Your work with nicotinamide riboside is that Tru Niagen T-R-U-N-I-A-G-E-N.com and your lab is that Brenner B-R-E-N-N-E-R.lab.uiowa.edu. Did I get those right?

Charles: Exactly. You do.

Dave: Awesome. I will put those in the show notes. If you go to the Bulletproof blog, just blog of bulletproof.com, we'll have a whole transcript of this. If you're super geeky and you wanted to make sure that he got all those pathways right, I can tell you he did, at least all the ones I knew because you touched on a couple where I certainly don't have those

memorized. If you didn't get all those and you don't want to, that's alright. I think there's a lot in this episode for you that comes down to the core biology of what can you do to have more energy now.

The bottom line is do what it takes to make your mitochondria work better and that has benefits across all everything that you do and everything that's probably going to happen to you are not happening to you. This is a new technology for changing that curve for you. Charles, thanks.

Charles: Thank you, Dave.

Dave: If you enjoyed this episode, you know what to do, learn something. Go out there and check out the info on nicotinamide riboside and better yet, go out there and leave a review for the show at [bulletproof.com/itunes](https://bulletproof.com/itunes) will take you to the Apple page where you can say this show was worth your time. I always appreciate a good review. I see those numbers every day. Thanks for taking the time to do that.