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**Dave:** [00:00:00] You're listening to The Human Upgrade with Dave Asprey. [00:00:05] This is going to be a really fun episode recorded live in the studios here in [00:00:10] Austin, Texas. Because I like talking with really, really smart people [00:00:15] who've done a lot of big things in the world. There's so much we can learn. The episode [00:00:20] today is about longevity.

It's about NAD. And it's [00:00:25] with a guy who's only written like a hundred and seventy scientific [00:00:30] publications, fifty patents, and the guy who created the first PARP1 [00:00:35] inhibitor, which is really, really useful in preventing cancer. He's [00:00:40] Also, the chief medical officer for Wonderfeel, which is a [00:00:45] new NAD focused company making some supplements that are, I would say, [00:00:50] the next generation of what's happening in the world of NAD.

If you're new to the show and you [00:00:55] don't know what NAD is, we're going to go into that. This is a compound I wrote about in my [00:01:00] longevity book, and it's a compound that you've heard from maybe David [00:01:05] Sinclair on the show talking about it. And it's something that's very fascinating because if you can [00:01:10] control your NAD levels You can control one of the many pathways of aging [00:01:15] that you need to control if you want to live to at least 180, like me.

So let's bring one of the luminaries in the [00:01:20] field onto the show to go deep on it. None other than Dr. Andy [00:01:25] Salzman. Andy, welcome to the show. Thank you very much. You're an interesting guy. So you were [00:01:30] a practicing physician, Harvard kind of guy, and then you suddenly [00:01:35] one day decided, I'm going to wake up and go do research and make drugs instead of being a [00:01:40] doctor.

**Andrew:** I love taking care of patients and being at the bedside and helping [00:01:45] people, helping children, talking to the families. I went into intensive care because I deeply cared [00:01:50] about critically ill kids. But you know, after about 10 years at the bedside, [00:01:55] I realized that I wasn't able to do enough. I, I could work all [00:02:00] night, I could take care of kids, but ultimately the real advance is when you [00:02:05] develop a new drug or a new intervention that can save not one kid at the bedside, but [00:02:10] thousands, thousands that you haven't even met.

And so I committed myself to research, research to do [00:02:15] that. Does it have to be drugs? I mean, could it just be No, no, any kind of intervention, but something different, something [00:02:20] outside of the normal pattern of medical behavior that we are accustomed to in the

**Dave:** hospital. So [00:02:25] something that scales better than let's send everyone to the hospital, let's give them something that can work even [00:02:30] if they don't have to go to the hospital.

That's right. You're working with a supplement company, but you did a [00:02:35] 600 million deal on a cancer drug you invented that you sold to [00:02:40] Genentech. So why the cutover from pharmaceuticals to [00:02:45] nutritionals? Well, I work

**Andrew:** in both areas. Okay. Okay, so I don't have a [00:02:50] preference. Well, I will say, I do have a preference actually.

I think that the non pharmaceutical [00:02:55] approach today has become faster, it's richer in terms of the possibilities [00:03:00] you can exploit. Uh, the pharmaceutical world, For all of the good it can do, it's just [00:03:05] very tedious and slow and I want to get a lot done. I'm ambitious. I have

**Dave:** a lot of things I have to [00:03:10] do.

We're going to go deep on NAD in a minute. Sure. You have some interesting perspectives on this. If [00:03:15] you wanted to create a new pharmaceutical, and I know you invent them on napkins in your sleep probably, [00:03:20] so you have this idea. How much money would it take on [00:03:25] average to get a pharmaceutical to market in the U.

S.?

**Andrew:** Oh, at a [00:03:30] minimum, you're talking 75 to 100 million. Ten years.

**Dave:** If you came up with a [00:03:35] new nutraceutical, how much money would it take to get that to market?

**Andrew:** Two hundred and [00:03:40] fifty to five hundred thousand dollars in six months.

**Dave:** Okay. Why such a difference?

**Andrew:** [00:03:45] Regulation.

**Dave:** Yeah.

**Andrew:** Look, the concept of the FDA was good at the beginning in [00:03:50] the 1930s.

They cared about people. They didn't want anyone to get hurt. They wanted a [00:03:55] certain type of procedure and protocol to follow every kind of new [00:04:00] development for the sake of the good. Do no harm. But it metastasized. It became [00:04:05] so extraordinarily complex and involved that it just takes a [00:04:10] lot of different things to do.

And it adds up costing money and time. No way around that. [00:04:15] Did you just say the FDA

**Dave:** metastasized? I'm afraid so, I've never [00:04:20] heard that before and I can't disagree. And I've been involved in longevity [00:04:25] medicine for 25 years on the nonprofit side and just with what I do. And [00:04:30] I've seen so many companies just leave the United States in order to get things [00:04:35] done.

And it doesn't feel like it's serving Americans or even the world when we [00:04:40] have this kind of resistance. And I can see why you'd say, well, if I can solve a problem [00:04:45] with a half a million dollar investment. Or a hundred million dollar investment. It's [00:04:50] almost like they're punishing pharmaceuticals.

**Andrew:** At some point, perfection becomes the enemy of the good.[00:04:55]

And it's a brilliant thing to have an absolutely bulletproof drug that's been through all of these [00:05:00] myriad tests. Love to have it, but it takes too long. And if we, [00:05:05] if we rely entirely upon that process for the discovery of the next generation of [00:05:10] drugs, we're going to be waiting a long time. I don't have the time.

**Dave:** There you go.

**Andrew:** And a [00:05:15] lot of other people don't have the time. The people who need help, who want interventions, who want [00:05:20] improvements, they're not going to wait 10 or 20 years. We need to do it now. We have the knowledge. Let's [00:05:25] apply

**Dave:** it. One of the things that drives me nuts in the world of longevity is you'll see so many [00:05:30] people saying, well, we have no evidence that you can extend human life, therefore you can't.

And there never [00:05:35] will be evidence because they would have to die. Meanwhile, we do have aging clocks and we [00:05:40] have the ability to measure all sorts of aspects of aging. So we can say, well. Let's do what's most [00:05:45] likely to be beneficial and let's see what happens and I'm on that path. What do you think [00:05:50] about the ability to measure someone's age and to predict whether we can extend their lives?[00:05:55]

**Andrew:** Well, aging is really two things. Aging is measured in years, [00:06:00] which can be, as you said, a very long process and we have to wait for people to succumb in order [00:06:05] to know whether we've made a difference in mortality. But aging is also reflected in the quality of our [00:06:10] health and our organ function. And we can use that as a proxy for longevity.

**Dave:** Uh, that's where I [00:06:15] am, and I'm saying if I can make my organs younger, I can make my mitochondria work better, and we can [00:06:20] measure all these things, at a minimum, I'm gonna have a really good [00:06:25] time when I'm 80, and if I die at 86 on average or something, I still win. [00:06:30] And the odds are very high that it'll be longer than that.

And I know our current best [00:06:35] is 120 or so years. Given what we know with AI, with new [00:06:40] research, all the work you've done in your life. How long do you think humans could [00:06:45] live if we just pull out all the stops?

**Andrew:** We have to ask ourselves whether [00:06:50] the ultimate longevity of the species is determined in some type [00:06:55] of inexorable and unchangeable way or whether it's the [00:07:00] accumulation of damage over time that ultimately, uh, forces us to succumb.

[00:07:05] If we look at More broadly at the ecology, we see animals that live two weeks [00:07:10] and we see animals that live 400 years, like the lake shark. What we're learning by these [00:07:15] experiments of nature is to better understand what are the underlying principles that guide their [00:07:20] ultimate demise. And we know, for example, in the lake shark, which is such an interesting [00:07:25] animal, 400 years old.

This animal has massive duplications [00:07:30] of DNA repair enzymes. So they have a tremendous investment on [00:07:35] making sure they don't accumulate mutations. It takes so much energy to do that that the [00:07:40] darn creature can hardly move. He doesn't have much energy left for anything else. But he sure lives a long time.

[00:07:45] So there's a trade off from an evolutionary perspective where every species [00:07:50] has evolved either to have a wonderful quick life with tons of [00:07:55] energy like the mosquito or the housefly or a very long and somewhat a slow life [00:08:00] like the tortoise or a giant tree that doesn't do very much or in the case of the [00:08:05] lake shark.

So if we understand what are the fundamental determinants of a long [00:08:10] life then we can start to make interventions. to specifically interdict these. And [00:08:15] what we've learned from these experiments is that the lake shark and other animals like that [00:08:20] have invested massively in protection of their genes.

Because [00:08:25] ultimately it is the accumulation of mistakes, of mutations, will [00:08:30] ultimately lead to dysfunction. Aging is, in the broad sense, [00:08:35] and

**Dave:** death. The logo for my company, Upgrade Labs, the AI exercise [00:08:40] longevity company, is the axolotl, which is an animal that can regenerate limbs, [00:08:45] or even its entire spinal cord, over and over and over.

I'm like, okay, it can be [00:08:50] done. How do I install that in myself? There's

**Andrew:** the possi one, look, everything's based on [00:08:55] knowledge. Knowledge is power. As we start to understand, really, what are the fundamental [00:09:00] drivers of longevity and of, and of death, that will give us the [00:09:05] information from a scientific perspective to go out and make the right interventions.

So I don't think 120 years [00:09:10] is the ultimate barrier. It is right now because we really haven't made [00:09:15] those changes we need to, but Science is moving very quickly, so I would predict [00:09:20] that in 5 to 10 years, we're going to start to see changes. It's not, it's going to be 130, 140, [00:09:25] you know, at some point maybe we'll be like the lake shark.

I don't think so, that far. Who would [00:09:30] want to live 400 years? But I think we will make, we will crack that barrier.

**Dave:** I certainly [00:09:35] think we can, and I'm totally willing to be wrong and just have a great life in the meantime. [00:09:40] Uh, I've seen in my 20s when my health was failing. I remember [00:09:45] my, my friend Mike, who's on the board of the Anti Aging Nonprofit, he would call me at [00:09:50] 1130 at night and he had more energy than I did.

And just, I, I watched people reverse their age when they [00:09:55] were in pretty events and I'm like, I wish I had that much energy. And so I've, I've seen it, they're [00:10:00] outliers. But if one person can do it, then we gotta study them and figure out what [00:10:05] caused that. And your relentless curiosity in your career, I think is, is pretty [00:10:10] interesting.

Because you've done a lot of different areas of work and [00:10:15] you arrived at NAD as something to Oh, I've been

**Andrew:** focused on NAD since [00:10:20] 1985.

**Dave:** Oh, wow.

**Andrew:** Okay. So you were early,

**Dave:** early adopter.

**Andrew:** Oh yes. [00:10:25] By 1994, my career was focused on, uh, was focused on NAD. [00:10:30] When I became involved in the PARP work, I recognized that NAD was the centerpiece of [00:10:35] biology as far as I was concerned in the ICU.

**Dave:** Because NAD powers PARP. [00:10:40]

**Andrew:** Well, NAD has many important functions, but for PARP, it is [00:10:45] absolutely the critical cofactor. PARP without NAD, it doesn't work. [00:10:50] Okay, let's,

**Dave:** let's explain what NAD is and what PARP is. So first, what is [00:10:55] NAD and why do we care?

**Andrew:** Well, NAD is a small molecule, but like I said, it's the centerpiece of biology [00:11:00] and it really does three things in our body.

First of all, NAD is absolutely essential [00:11:05] for energy. NAD controls the production of ATP, which is the currency we use in order [00:11:10] to, to think, to move our muscles, to have our digestion work, to metabolize. [00:11:15] So, NAD is absolutely essential for the energy in your body. You have low NAD, you have low [00:11:20] energy. Mm hmm.

Okay, so that's the first thing. Second thing. NAD is absolutely [00:11:25] essential for the production of an antioxidant defense. We are [00:11:30] bombarded continuously by the environment, by cosmic rays, by oxidants we make. We are [00:11:35] in a bath in a world of oxidants. We must have an efficient and [00:11:40] effective antioxidant defense.

NAD. It produces or is converted [00:11:45] to NADPH, and NADPH is the driver that protects [00:11:50] us. It produces glutathione, it produces all of the antioxidant functionalities. So we need [00:11:55] NAD to survive in an oxygen rich environment. That's the second thing. Third, [00:12:00] NAD is used by PARP. PARP is the second most abundant protein in our [00:12:05] nucleus.

It enshrouds all of our DNA, all our genetic material. Every [00:12:10] minute we are undergoing changes in the DNA because of the environment, because of oxidants [00:12:15] and cosmic rays, and there are breaks. There are little, you know, DNA is a double strand. It's a [00:12:20] helix. Though that helix is susceptible. to nicks or breaks in one of the [00:12:25] strands and they're happening about 70 times a minute.

So over the day, [00:12:30] every day, we are having an assault on our genetic material. If we do not immediately [00:12:35] recognize that and correct it on the spot, those breaks persist. [00:12:40] And when the cells divide, if there is a break, You will have a mutation. [00:12:45] Well, when you're 10 years old, maybe you won't have many. By the time you're 30, you're going to have a bunch.

By [00:12:50] the time you're 50 or 60, if it's not corrected, you will have loads and loads of [00:12:55] mutations, and that spells malignancy. If you remove any of the DNA repair enzymes, [00:13:00] you are going to get cancer, and the best example, of course, are BRCA deficiencies. Mm hmm. So, [00:13:05] PARP is the enzyme in the nucleus. Identifies the problem, [00:13:10] the nicked DNA, it gloms onto it, and then twists and becomes active, and [00:13:15] then NAD flows into it, and it uses the NAD to repair.[00:13:20]

So, low DNA, no DNA repair, mutations, ultimately malignancy. [00:13:25] So those are the three things that NAD does. It gives us our energy, it protects us against oxidants, and [00:13:30] it saves us from cancer. And the protection from oxidants is going to provide cardiovascular protection, [00:13:35] right? Oh my goodness, yes, if you look at the vascular system, the oxidants that [00:13:40] bathe our blood vessels over time, those lead to endothelial dysfunction.

It leads to [00:13:45] hypertension, calcification, uh, all of the problems we have with plaque buildup. [00:13:50] So yes, it is a critical part of the vascular system. And then of course of the [00:13:55] cardiovascular, of the, of the heart, the oxidant injury to the heart impairs the [00:14:00] muscle function. So as we get older, we have a heart that beats less strongly and [00:14:05] blood vessels that are more rigid.

They don't provide the kind of blood flow and nutrition we need to [00:14:10] sustain us. So, uh, the role of NAD and the cardiovascular health cannot be underestimated.

**Dave:** [00:14:15] It's funny. In the world of longevity, I talk about there's these four killers. [00:14:20] If you want to live a long time, don't die first. So that would be don't get cancer, which [00:14:25] we're talking about with NAD and PARP, and then don't get cardiovascular disease, which is actually more [00:14:30] deadly than cancer.

And then what's behind both of those is don't get diabetes [00:14:35] and then don't get Alzheimer's. I look at diabetes as kind of the, the first of [00:14:40] the four. 'cause if you get that, your risk of the other three big things that'll kill you goes up. [00:14:45] What's we, were the first

**Andrew:** to show that in Diabe we published in nature that in [00:14:50] diabetes you get a fallen NAD.

**Dave:** There you go.

**Andrew:** Right? And that leads to, uh, [00:14:55] the all, all the complications of diabetes on the blood vessels, on [00:15:00] uh, on insulin sensitivity. This is all bound up. with having a healthy level of [00:15:05] NAD. It's got, you've got to maintain

**Dave:** NAD to maintain your health. A long time listeners [00:15:10] have heard me talk about niacinamide, which is the very oldest way of raising NAD.

[00:15:15] And then the first research came out about NR, about 18 years ago or [00:15:20] something. I started taking it then. Uh, and then NMN came out. And so I've been on [00:15:25] these things for a long time. I've done the IVs and talked about. What would that look like? What [00:15:30] is the benefit of taking NAD and what is the, or NAD precursors, and what is the [00:15:35] downside of taking NAD?

**Andrew:** In order to boost NAD, there are only two things you have to keep in [00:15:40] mind. One is you have to have enough there. You've got to have a supply. And [00:15:45] secondly You need to prevent its consumption or its depletion. So let's look at each one of those. Okay. [00:15:50] You were taking supplements, NR initially, then NMN. Why did you do that?

Because [00:15:55] NAD itself cannot be swallowed and expect to cross the gut into the [00:16:00] blood and get into our cells. NADs, I mentioned how important it is, but it's important [00:16:05] inside the cells. Right. That's where it works. So if it's outside the cells, it's not going to [00:16:10] do anything. Even with an intravenous infusion?

Even with an intravenous infusion. It'll be in your [00:16:15] blood. But that doesn't mean it's in your cells. And when it works, it's got to be inside the cell. [00:16:20] That's where it does those three things I mentioned. So how do we get it into the body? How do we get it through the [00:16:25] gut? How do we get it from the blood into the cells?

We use nature's own way to do [00:16:30] it. Nature has designed a thought about this. So in our bodies, we have [00:16:35] precursors NMN and NR, and they're there for a reason. Because there are specific shuttles [00:16:40] that exist in the cell membrane that move these from the outside to the inside. to the [00:16:45] inside. Remember, NAD is a very precious molecule.

God made it with charges on it. It's [00:16:50] a polar charge molecule. It will not leave the cell and it will not get into the cell. It [00:16:55] can't cross a fatty lipid membrane because it's charged. So in order to [00:17:00] get stuff into the cell, there was a jacket created around it, if you will. That's [00:17:05] what NR and NMN are.

They're, they're, they're a jacket on NAD. And that [00:17:10] jacket is recognized by a shuttle, which whisks it in to the cell and there the [00:17:15] jacket comes off and NAD is alive and well and ready to go inside the cell. So the supplement [00:17:20] industry recognizes this and that's why NR and NMN dominate that industry. You [00:17:25] have to supply those in some manner to get enough NAD.

That's the [00:17:30] first goal. The second goal is you got to keep it there. Right. Doesn't do you any good to [00:17:35] boost the stuff and get it all in there and then only find out that there are depleting mechanisms [00:17:40] that scarf it away, that steal it away.

**Dave:** I think this is a problem that I ran into, but actually [00:17:45] first I have to ask, there's pretty good evidence that alcoholics who get [00:17:50] 10 to 20 NAD infusions have a much lower risk of starting to [00:17:55] drink again.

And if it can't enter the cells at all intravenously, why are we seeing clinical [00:18:00] results? Because

**Andrew:** NAD in the blood can be converted by enzymes in [00:18:05] the blood and in the tissues to NMN and NR.

**Dave:** So when I get an NAD [00:18:10] IV, my body's converting it back to NMN? Yes. I did not know that. Okay. Yes, [00:18:15] yes. So you can save a lot of money by just taking the right supplements without having to do the [00:18:20] IVs.

Not many people want to walk around with an IV. Plus, it's pretty uncomfortable. [00:18:25] NAD IVs, I finally got to where I could do a gram in about 45 minutes. [00:18:30] But it's like something sitting on your chest and you're turning red, it's a [00:18:35] methylation thing. Yeah. So we can just stop doing that.

**Andrew:** Yes, I would recommend good oral supplements that make [00:18:40] sense, that provide the precursors, these jacketed forms of NAD.

Do

**Dave:** you know how much time I've [00:18:45] spent with needles in my arm that I didn't need to, with the knowledge that we now have that we didn't used to? Yes. [00:18:50] Okay, that's fascinating. So let's say that I've taken some NR or some NMN, [00:18:55] What's going to steal it?

**Andrew:** Well, there is, uh, [00:19:00] there are a lot of interesting theories on this, but now we know a lot more than we did five [00:19:05] years ago.

It turns out that there is a major enzyme in our body [00:19:10] which has the specific role of clipping [00:19:15] NAD or NMN and cutting it in half and destroying it, and that is called [00:19:20] CD38. You may have heard of this. CD38 is an enzyme that's present in most of [00:19:25] our tissues. When we're young, we have just enough that we need, but as we [00:19:30] age, there's more and more and more.

So by the time we're 70, we've [00:19:35] got way too much of this. This enzyme is positioned in different places in the [00:19:40] cell. There are actually three different places, but the one we care about is on the cell membrane [00:19:45] itself. It sticks out into the blood. And as NMN whisks by It [00:19:50] says, ha ha, there you are, I gotcha, and it cuts it in half.

**Dave:** Why would this [00:19:55] exist in ourselves?

**Andrew:** Because it needs to do that in order to fight infection. It [00:20:00] is something involved in the inflammatory response, so a little bit of this, [00:20:05] great thing. There are three enzymes that use NAD or NMN. One of them is PARP, I [00:20:10] already mentioned, to affect DNA repair. The second one is the sirtuins, which changes a lot of the [00:20:15] physiology we need.

And the third one is CD38, which uses it to fight infection. A [00:20:20] little bit of something is a good thing. It's natural. We need it. Unfortunately, as we [00:20:25] get older, we get more and more inflammation, probably from leaky gut, and [00:20:30] CD38 responds to that by being more and more expressed. And as we get way [00:20:35] too much of it, by the time we're 50 and 60, it is out there and it is destroying the [00:20:40] NAD.

So you can take all the supplements you want, you can load yourself up with NMN, NR, [00:20:45] but this enzyme's out there when you're 50 and 60, and it's chewing it up. [00:20:50] So the right approach is give the supplement, yes, great idea, but [00:20:55] concomitantly with that at the same time, slow down [00:21:00] CD38. And, and this is the key combination approach, which we [00:21:05] think is the next generation

**Dave:** approach.

So if you were taking extra NMN and [00:21:10] extra NR, your CD38 activity is going to go up and CD38

**Andrew:** is going up because of [00:21:15] your age.

**Dave:** Does it go up even more when you have NMN and [00:21:20] NR?

**Andrew:** I thought it consumed, it does, but it doesn't, it's an enzyme. It's not used [00:21:25] up when it catalyzes the degradation of NAD. It is, it is [00:21:30] an enzyme.

It's being regenerated. You don't lose it. Okay. It's just there and it's, it's [00:21:35] doing its thing, which is

**Dave:** eating up your NAD. So if you wanted to live a very long time. You probably should brush [00:21:40] your teeth really well because if you have a lot of oral bacteria, which drives your whole microbiome and [00:21:45] also escapes directly into the bloodstream, you're pissing off your immune system.[00:21:50]

You're living in a house with toxic mold like I did as a kid, which causes stroke throat to grow as well. You're [00:21:55] pissing off your immune system. So the more chronic infections you have, even low grade, the [00:22:00] more you're going to have an aggressive immune response. And the more likely I'm just, I'm kind of [00:22:05] making this up as I go along, but I'm well, All of the things you've said are

**Andrew:** absolutely true.

But there's [00:22:10] an even bigger gorilla in the room here. What is it? The real cause of, the major [00:22:15] cause of progressive inflammation as you age is the ability of [00:22:20] your intestine to seal itself and not permit [00:22:25] the egress. of endotoxin, other bacterial constituents from inside the gut [00:22:30] to the blood. We know that the major protein in the gut, which is the seal, [00:22:35] the gasket,

**Dave:** is

**Andrew:** ZO1.

And ZO1, unfortunately, [00:22:40] uh, as we get older, its levels go down. The gut gets [00:22:45] leakier and leakier. Look, if you take a 25 year old person, they have trillions of bacteria [00:22:50] inside them. None of them get into their blood. You take a 60 year old. There's [00:22:55] lots of garbage coming in. And that garbage stimulates our immune system and it says, Whoa, [00:23:00] time for inflammation.

We have infection. And that infection, if you took a 70 year old [00:23:05] person, they're inflamed. Aging is an inflammatory event. And that [00:23:10] inflammation turns on the expression of CD38. That's where it's coming from. So the [00:23:15] microbiome and our ability to protect our gut is key. Proper diet, the various things we can do [00:23:20] about the microbiome.

I'm sure you've talked about that in other shows. This is central to [00:23:25] maintaining longevity because that starts the whole process. Our gut is the driver, [00:23:30] ultimately, the initiator.

**Dave:** In my longevity book, I referenced a couple [00:23:35] of papers that showed taking activated charcoal, which just binds to endotoxins [00:23:40] in the gut, is associated with about a 15 percent lifespan increase just from [00:23:45] reducing some of those.

Yeah. And when you look at things like germ free mice. Where they have [00:23:50] no microbiome because they live in little bubbles, they live a long time, they're ripped, they can eat whatever they [00:23:55] want.

**Andrew:** This is where I began my career, really, in 1988, I was in the [00:24:00] intensive care unit, and there was a brilliant young professor that I teamed up with named [00:24:05] Mitchell Fink.

We had the idea at that time that the barrier dis barrier of the gut [00:24:10] mm-hmm . Might change during disease. No one had thought about that. Wow. And I discovered that [00:24:15] endotoxin can actually open up the gut. Uh, and we published these papers from [00:24:20] 88 to 92 showing that it was malleable, that the gut sealed the, the [00:24:25] barrier is not fixed.

It can respond, and we found a lot of, we [00:24:30] found that hypoxia will do that, we found that acidosis would do that, uh, certain cytokines, [00:24:35] and all of that work show that it's

**Dave:** dynamic. That they're opening and closing the Yes, [00:24:40] yes. the gut junction. Yes. How would you go about sealing, as best as possible, [00:24:45] the gut so that nothing leaks out of it over the course of decades?

**Andrew:** That's going to [00:24:50] require, I think, understanding of diet and the role of the microbiome. Right. That's [00:24:55] not an area that I'm in anymore, but there's tremendously good research looking at that. And that's [00:25:00] very important. That is a major factor in longevity that should be emphasized. There needs to be more [00:25:05] research

**Dave:** in that area.

I've been, uh, for almost the last eight years [00:25:10] now, uh, advising Viome, which has a really good data set now where they're starting to figure that out. [00:25:15] I know that because I was on antibiotics for 15 years every month because I had [00:25:20] chronic. Uh, Sinusitis and strep throat because I lived in a house with toxic mold, [00:25:25] um, that I probably don't have a, an advantage there.

In fact, the fact I'm [00:25:30] not obese right now is kind of shocking given all the crap that I went through. And so I [00:25:35] feel like I'm coming from behind in my longevity journey here. For an average [00:25:40] person, maybe they're a little obese, but they haven't had that big of a problem. Is there a pharmaceutical [00:25:45] intervention?

Or is taking these NAD things like you're making with Wonderfeel, [00:25:50] where do you start? Well, it's actually

**Andrew:** interesting. Now you're talking about a positive feedback loop. It [00:25:55] turns out that, and this is also work that I did in 1992, the [00:26:00] energy of the cell in the gut is directly [00:26:05] responsible for how well the gut seals itself.

We published the first [00:26:10] paper on this where we related NAD and ATP levels inside the gut cells [00:26:15] to their ability to maintain the integrity and not let molecules slip through. [00:26:20] So you can imagine if that gets out of hand, out of whack, and then you start to [00:26:25] leak. And you get inflammation. CD38 expression goes up, NAD goes down.

[00:26:30] The gut now is, doesn't have enough NAD to maintain itself and it gets [00:26:35] progressively leakier. It's a snowball effect. So the key thing is keep the NAD at a [00:26:40] healthy level, have a good healthy gut, do whatever interventions science is telling us to do, [00:26:45] keep our gut good and healthy, and then, to further augment that, take NAD [00:26:50] supplements, or actually NAMN or NR, and find a way Which I'll [00:26:55] talk about a little later to stop the activity of CD 38, [00:27:00] depleting this precious NAD that we have.

**Dave:** So even if you have immune [00:27:05] activation as you age, you can stop the CD 38 so that you can, can slow it down. There are

**Andrew:** [00:27:10] two, you don't

**Dave:** stop it. Yep. Slow it

**Andrew:** down. There are two approaches. There's the pharmaceutical approach. Mm-hmm . I wish them well. [00:27:15] It'll be another 10 or 15 years. I'll be a little bit old at that time to enjoy the benefits, but I do wish [00:27:20] them well 'cause CD 38.

It is a target that the pharmaceutical industry should go [00:27:25] after. While I'm waiting, we have botanical approaches, natural [00:27:30] approaches, which we include actually in our WonderPhil product, which slow down the activity [00:27:35] of CD38. So that combination I mentioned is so critical. Give a boost with a [00:27:40] supplement, but stop the depletion.

**Dave:** You mentioned ATP, and I think a lot of [00:27:45] listeners know what ATP is. Just in case we have some new listeners, [00:27:50] talk about ATP for a minute and what it does in the gut.

**Andrew:** ATP is the ultimate [00:27:55] means. It is a currency. Think of it as a cryptocurrency. It's a [00:28:00] currency in every cell that is there, and it is the [00:28:05] final common molecule that provides energy to [00:28:10] various processes, whether they're metabolic processes, um, [00:28:15] hormonal processes, movement of muscle, activity of neurons in our brain [00:28:20] thinking.

Ultimately, ATP provides us. Transcribed The electron reducing [00:28:25] equivalent is providing the power to do things, to make the body work. [00:28:30] NAD creates the ATP, so if you don't have NAD, you don't get ATP. [00:28:35] And why did I care about this as an intensive care specialist? We're not worried about longevity in the [00:28:40] long term in the ICU, we're worried about whether you live the next hour or two.

Okay, when someone comes in [00:28:45] with a heart attack, for example, they have an acute interruption of blood flow and oxygen to their heart. [00:28:50] Okay. What happens when you have no oxygen coming into your heart? You [00:28:55] don't have enough NAD. PARP is activated within about 5 seconds. [00:29:00] NAD is massively consumed. And there's no ATP made.

And [00:29:05] because there's no ATP made, that heart muscle, which is at risk in the first few minutes, [00:29:10] Sadly, it goes on to die, to infarct. So if you maintain NAD, [00:29:15] you maintain ATP, during the heart attack, you won't get the [00:29:20] infarct and you won't die. So we made every effort and we designed drugs. And this is what I licensed through [00:29:25] Genentech.

By blocking PARP activation, it didn't consume the NAD [00:29:30] during the heart attack. ATP levels were maintained and the heart did not get an infarct. [00:29:35] Wow. Same with stroke. Strokes the same way. A lot of these, uh, and I could go [00:29:40] on and on and on, but, but PARP is very important in these acute events. For [00:29:45] aging, though, this is not done over minutes.

This is a problem over decades. [00:29:50] So the principles are the same, but it's not

**Dave:** as dramatic. So PARP is helpful because [00:29:55] it repairs your genes, but if there's a traumatic event or an over [00:30:00] activation, it stops being useful for gene repair and it causes all kinds of damage by stopping [00:30:05] ATP.

**Andrew:** So we showed this if you take an animal or a person.

And [00:30:10] you interrupt blood flow to their coronary arteries. Their heart is deprived of the oxygen [00:30:15] it needs. Within about one to one and a half minutes, you get a massive influx [00:30:20] of oxidants in that cell that attack the DNA, attack your [00:30:25] genes, cause huge numbers of DNA single strand breaks, millions in the [00:30:30] cell of the heart.

Those activate PARP like crazy. Suddenly, [00:30:35] PARP consumes NAD within about two to three minutes. If you measure the NAD levels [00:30:40] in the heart after two to three minutes after heart attack, zero. Undetectable. [00:30:45] And of course you wait one more minute, no ATP. You wait another five minutes, [00:30:50] dead cell. Mm hmm. So yes, PARP over activation in [00:30:55] the

**Dave:** acute setting is a killer.

Would it make sense to block PARP before you play a football [00:31:00] game? Because you know you're going to get hit and add?

**Andrew:** That is something I never heard anybody suggest. It's a wild [00:31:05] idea, but it's an interesting concept. We did prophylaxis animals, many, [00:31:10] after head, we did traumatic brain injury studies with PARP.

And yes, you can preserve [00:31:15] brain function, reduce neuronal injury. I'm not suggesting anyone do this. I am. But, but, [00:31:20] okay. Okay. I'm with

**Dave:** you. But I mean, if you're an MMA fighter or a [00:31:25] professional football player, I have protocols for what to do before.

**Andrew:** Oh, no doubt. No, it would help there. [00:31:30] Yes. Yes. We have done dozens of studies in traumatic brain injury.

We've done them [00:31:35] in sheep. We've done them in mice and rats. And we have shown conclusively that you can. [00:31:40] ameliorate and prevent the sequelae of a concussive or [00:31:45] a worse event. Yes, it is protective in that sense. Not making a recommendation,

**Dave:** but it [00:31:50] works. No one that I'm aware of is using PARP drugs like the one you invented for this, [00:31:55] and there may be side effects I don't even know about.

Uh, but what I do know, having had a titanium [00:32:00] knee to the head at high speed and gotten a brain injury, I'm fortunate that I know what to do for that. I have a [00:32:05] neuroscience clinic, so I was able to repair my brain and as soon as we knew what happened, I started with the [00:32:10] antioxidants and all. Yes. But the incidence of brain injury, even in kids or in highly [00:32:15] functioning adults, you get a car accident, you get whiplash, and it ruins marriages.

That is it. It [00:32:20] messes with people. It's a major

**Andrew:** killer, and not just killer, but it leads to [00:32:25] very sad situations where people have chronic brain injury that just doesn't get better. [00:32:30] I know six

**Dave:** weeks after I took that knee to the head, I sent Tim Ferriss an angry email [00:32:35] about something he didn't even do.

Like, I was out of my mind. I was swearing all the time, and you're like, what [00:32:40] is going on? And some of this has to do with the fact that my brain, which actually [00:32:45] at the time especially didn't even have enough blood flow regularly, according to Amin Clinics. And [00:32:50] then I ran out of ATP for the parts where I scrambled my eggs, and so it took me a [00:32:55] little while to recover.

And the good news is we have neuroplasticity, you can recover. Yes. But I look [00:33:00] at people who are at risk of these things and saying, all right, I know having ketones present [00:33:05] reduces oxidative damage. There's all sorts of different strategies that are all mitochondrial [00:33:10] enhancing. And when you peel all that stuff away.

Ultimately, it seems like NAD is the [00:33:15] most important of all of those. It's the centerpiece. It's the major player. Wow. All right. [00:33:20] So, what about liposomal NAD? I've seen some formulations of that. Does

**Andrew:** that work? Well, [00:33:25] there's liposomal NMN. That's been looked at because people want to optimize the [00:33:30] amount of NR or NMN that's coming in.

I'm all for that, but it needs to be done in a [00:33:35] way that's effective. So far, we haven't seen studies that really [00:33:40] prove to me that liposomal NMN is better than just regular NMN. It might [00:33:45] be, but I haven't seen the studies. I will say that liposomes are not easy to work with. [00:33:50] Having spent quite a bit of time with those, they leak.

They leak over time, so [00:33:55] there's stability issues even on the shelf. So it's a difficult modality to [00:34:00] work with. More power to them. They should do great research and maybe that will improve it in the long [00:34:05] run, but But I haven't seen that yet. Got

**Dave:** it. And I realize I'm using big words, uh, if you're [00:34:10] listening, lipo, whatever.

Liposome is a little, call it a bubble of fat [00:34:15] that you can use to put a pharmaceutical or a nutraceutical inside it. So it'll absorb through the gut lining [00:34:20] or absorb into cells. So the very first liposomal glutathione on the [00:34:25] market, I helped to bring that to market years and years ago. And then I had a dry liposome at Bulletproof, and like you [00:34:30] said, They're very hard to work with.

My friends at Quicksilver make some cool stuff. [00:34:35] Um, there's even like liposomal testosterone formulations and things now. So it's a [00:34:40] cool delivery system that's very finicky. Finicky, that's the right word. Yeah. Difficult. Unstable. Yeah. [00:34:45] And what you have with the stuff you're doing at Wonderfeel is you're, you're doing [00:34:50] Uh, NMN, plus you're blocking CD38 at the same time.

Right, we have

**Andrew:** two [00:34:55] natural products and their ingredients, if you will, in our solution. One of them is [00:35:00] resveratrol, which of course is from red grapes, and that has been, and it's in wine, red wine, and that [00:35:05] has been shown to block CD38. Very interesting. And the other is from [00:35:10] olive oil, hydroxytyrosol, okay, in the Mediterranean diet there.

And [00:35:15] that is also a blocker of CD38. So that's why we took those two and we added [00:35:20] those to NMN so that we would increase the supply but we would block the [00:35:25] depletion simultaneously.

**Dave:** You're the only person who's ever talked about [00:35:30] hydroxytyrosol on the show. And I looked at a lot of the research [00:35:35] around olive oil and there's plenty of evidence that says 30 grams of olive oil a day [00:35:40] is good for you.

Above that, it's a bit of a, [00:35:45] it's a bit challenging. If you take a lot of oleic acid, the primary fat in [00:35:50] there, it increases something called D5D and D6D, [00:35:55] which means that your body way more easily oxidizes all the other omega 6s. [00:36:00] So, olive oil good. Excessive olive oil drives oxidation. [00:36:05] Well, we don't provide olive oil.

No, you don't. hydroxytyrozole. Exactly. Right. [00:36:10] So, hydroxytyrozole is the most likely beneficial compound [00:36:15] in olive oil. So, when I put together one of my, I think it was my fat, [00:36:20] uh, my omega 3 formula back when I was at Bulletproof. And guys, I don't have anything to do with [00:36:25] Bulletproof. I don't I don't believe they're following my formulas.

I don't even track it. So no, [00:36:30] no commentary there I can offer you. But the thing I formulated years ago, I put hydroxy tyros [00:36:35] all on it and my formulators were like, what is this? And I said, now there's a supplier. We gotta do [00:36:40] this. Because I wanted the benefits of drinking a gallon of olive oil. I just don't want to drink the olive oil.

'cause I [00:36:45] don't think it's. good for you at high doses, right? Hydroxy tyrosol, of

**Andrew:** course, is an antioxidant has lots of different [00:36:50] functions. One of them is the CD38 blockade, but the height, the, um, the antioxidant effect [00:36:55] is also important. And to that end, by the way, we've added another ingredient in [00:37:00] our wonder field, which is ergothionine.

So this is a natural amino acid. It's [00:37:05] very, very powerful as an antioxidant. And the reason we did that. was that we [00:37:10] didn't want to have a lot of DNA damage. DNA [00:37:15] damage activates PARP, PARP consumes NAD. So [00:37:20] by giving that heavy hit with ergothionine, we have a lot of antioxidant [00:37:25] power in there now that reduces the amount of DNA damage and reduces the [00:37:30] need for PARP to fix something which would consume NAD.

So all of this was focused [00:37:35] on keeping NAD levels high using antioxidants in conjunction with [00:37:40] PARP. with boosting the NAD, very important. And that's why it was necessary to include [00:37:45] ergothionine.

**Dave:** Ergothionine is another one of these longevity molecules that most people haven't even [00:37:50] heard of. And I look at this as, as foundational as glutathione.[00:37:55]

And when I started the whole biohacking movement, glutathione was the rock star, and it [00:38:00] still is. You need this for your liver, for your brain, inside all your cells. Uh, and Orgothionion is, [00:38:05] is as potent via different mechanisms. Yes, it is. And most people don't know it.

**Andrew:** I should also add [00:38:10] that glutathione, just to make a full circle here, where does that come from?

Glutathione is [00:38:15] produced by a, um, glutathione reductase and [00:38:20] the energy To make glutathione comes from [00:38:25] NADPH through, and where's NADPH, what is that? That's from NAD, so NAD is [00:38:30] acted on by NAD kinase. It makes NADPH, which then creates glutathione, [00:38:35] which is a major, major important antioxidant. If you can, if you take [00:38:40] animals that can't make glutathione, They die.

They do not do well. [00:38:45] Okay? And any kind of limited injury, even a minor trivial injury, becomes a major [00:38:50] problem. So glutathione is one of the most important natural antioxidants that we have and that's [00:38:55] all dependent on having NAD there to make it. Without NAD, you [00:39:00] cannot make glutathione. Wow. Be very clear about that.

Yeah. So, NAD has a [00:39:05] very important antioxidant functionality

**Dave:** in that way. One of the concerns [00:39:10] that I've had, and this goes back to when I started in longevity, it was actually the late 90s, [00:39:15] uh, where I'm in my 20s and I'm learning from people in their 80s, and we were taking a lot of [00:39:20] antioxidants, sort of like oxidation's the devil.

And The problem is [00:39:25] we have this ox redox reaction that makes ATP. How do we [00:39:30] know that when we take Wonderfuel and now we're getting ergothionine and we're getting [00:39:35] resveratrol? And we're getting all the other antioxidants like hydroxytyrosyl. How do we know that we're not [00:39:40] suppressing oxidation to the point that it's a problem?

You do need some redox stress.

**Andrew:** [00:39:45] It's very important in terms of signaling. We were the first to show that oxy radical [00:39:50] signaling is very important in terms of the anti inflammatory effect in cells. I [00:39:55] published that in 1995 when I was at Children's in Cincinnati. So yes, [00:40:00] oxy radical signaling is important.

You need a limited amount of redox stress, of oxidant [00:40:05] stress. Too much, of course, causes all these other problems. How do we know that we're not giving too many [00:40:10] antioxidants? Well, we listen to our customers. We have a registry where [00:40:15] every single person who takes our product writes back to us, and most of them do because they're repeat [00:40:20] customers.

We don't really advertise. We don't need to. People like the product. They come back. They buy more. [00:40:25] And so they generously give us their thoughts and their feedback. And we've seen No [00:40:30] evidence of any kind of toxicity or any evidence of a problem [00:40:35] with the material of the solution that would get us concerned.

We're always watching though. We [00:40:40] have a respect for listening to the patients, to the customers. So if we do see any [00:40:45] problem, we would quickly, you know, investigate that. So far, We haven't seen that. What we [00:40:50] do see are numerous reports coming back that exemplify just how [00:40:55] effective this is. And it's really surprised me, you know, I was a little bit cynical before about [00:41:00] supplements.

I was in the pharmaceutical industry, so I was on the bad side, right? So, I was kind of suspicious, [00:41:05] what are these guys doing, but when you read these reports, you have to stand up and pay attention. We [00:41:10] had a, a 60 year old person with arthritis, uh, she used to be a tennis player, [00:41:15] she could hardly get off her couch, and she's back and she's playing tennis now.

We had a [00:41:20] 75 year old lady who unfortunately had pretty advanced vascular dementia, her husband was [00:41:25] having to take care of her. She loved to do crossword puzzles before all of this. She was doing maybe one. [00:41:30] Every day or two, she's now doing four a day. Her husband's crazy. He's the one buying it. [00:41:35] Um, sexual health, all of the nitric oxide metabolism in sexual [00:41:40] health is driven by the need to have NADPH activate [00:41:45] EC NOS.

So we found people, uh, both men and women, a woman who was 61 [00:41:50] Who is reporting much stronger orgasms and vaginal lubrication. We published, we're the [00:41:55] first to publish on vaginal lubrication. I did that in 2004, showing [00:42:00] that this whole mechanism causes increased blood flow to the vagina and increased [00:42:05] lubrication.

And that's entirely dependent. on NAD being there. So NAD [00:42:10] drives sexual function? Oh, yes. Erectile dysfunction is based on ECDOS. Look at Viagra. What does [00:42:15] Viagra do? It prevents the breakdown, okay, of cyclic GMP. But [00:42:20] what is making cyclic GMP? Nitric oxide. What makes nitric oxide? Nitric [00:42:25] oxide is formed by the activity of the ECDOS.

[00:42:30] NO synthase, the nitric oxide synthase. That enzyme, which is present in the [00:42:35] cavernosa of the penis, that enzyme requires NADPH in order to [00:42:40] work. The electron, which comes on to nitrogen to make [00:42:45] nitric oxide, that comes, that literally comes from NADPH. Well, [00:42:50] NADPH is formed from NAD. So if you have NAD deficiency, You can take all the [00:42:55] Viagra you want in the world.

It will not help.

**Dave:** No kidding.

**Andrew:** No. Viagra is [00:43:00] great if you're making nitric oxide, because it prevents the cyclic GMP from being wiped out. If [00:43:05] you don't have nitric oxide, forget it. The Viagra, the Viagra just doesn't work. And we [00:43:10] know that Viagra works in maybe half the population that, that needs help. It doesn't work in [00:43:15] everybody because some people cannot make nitric oxide.

Wow. So [00:43:20] this NAD is interesting because it will facilitate making nitric [00:43:25] oxide. So it'd be very interesting actually to look at our product in conjunction with Viagra. We haven't [00:43:30] done that yet, but the reports we're getting of sexual health from our customers suggest [00:43:35] that something important is going on, and that deserves more

**Dave:** attention.

This is [00:43:40] fascinating. One of the longevity pharmaceuticals that I take is low dose [00:43:45] Cialis. I take five milligrams most days. Right, and this [00:43:50] isn't for sexual function, it's for vascular function because I don't want to get Alzheimer's disease [00:43:55] and because I like having veins. It works very, very well. Low [00:44:00] levels,

**Andrew:** low levels of nitric oxide are absolutely essential to the preservation of your [00:44:05] vascular system in several ways.

First of all, nitric oxide causes [00:44:10] vasodilatation, not just of the large vessels, but of the micro vessels. The micro vessels are what nourish the [00:44:15] intestine, the gut, the liver, and especially the brain. You have to have good, healthy blood flow. As [00:44:20] we get older, we get calcifications and other changes, the vessels get stiffer.

So you [00:44:25] need low levels of NO, okay, in order to maintain your health. So NO [00:44:30] is very important. in the entire vasculature. The other thing is that nitric [00:44:35] oxide, uh, it, it inhibits platelet activation [00:44:40] by increasing the cyclic GMP in the platelets. So, platelets are great [00:44:45] if you get a cut, you don't want to bleed, you need your platelets.

But platelets can also adhere [00:44:50] to the vessels, especially in the heart and in the brain. It can cause a stroke or a [00:44:55] myocardial infarction. So you don't want, Excessive platelet activation, [00:45:00] that happens as we get older. Again, nitric oxide is key in keeping the platelets quiescent, [00:45:05] keeping them happy and non activated.

So again, NAD, by [00:45:10] facilitating NO expression, is critical to vascular health. And that's been [00:45:15] shown now even in clinical studies with NMN supplementation. They've shown, for example, [00:45:20] an improvement in blood pressure. In fact, if you remove CD38, [00:45:25] which, as I mentioned, breaks down NAD, so you have more NAD, you see a fall in blood pressure.[00:45:30]

Interesting. Yeah, so nitric oxide, CD38, NAD, they're [00:45:35] all connected, but the centerpiece is NAD. Have you seen people's blood pressure drop [00:45:40] when they take one study. Okay. Yes, that's been shown now. If you take people who are [00:45:45] on heavy NMN supplementation, the, the Buck Institute of Aging and a [00:45:50] number of the NIH places have recommended 900 milligrams total per day.

Some of [00:45:55] the studies have used much less and they haven't seen this good results. There was one study with 200. Yes, there [00:46:00] was a study with 250 milligrams in patients. They had an inkling of something good [00:46:05] happening, but it was not the right dose. But when you get to the right dose, you can see changes that are [00:46:10] favorable, not only in blood pressure falling, but you get better insulin sensitivities, so less [00:46:15] diabetes.

All of these things are happening because NAD levels are rising [00:46:20] to the level where they can, uh, produce nitric oxide and relax the blood vessel and [00:46:25] provide a defense against oxidant

**Dave:** stress in the blood vessel. If someone is [00:46:30] at normal blood pressure and they increase their NAD levels, is it going to drop even further?[00:46:35]

**Andrew:** No, it wouldn't do that excessively, but when you measure your blood pressure, [00:46:40] uh, with a cuff on your arm, you're looking at the, you're not looking at blood flow, [00:46:45] you're looking at blood pressure. What we really care about is not really just the pressure, we're looking at the [00:46:50] blood getting to where it's supposed to go.

Uh, and that can happen in a number of ways with NAD. [00:46:55] First of all, as it opens up the small blood vessels, it allows it to go everywhere. But in the [00:47:00] longer term, NAD Higher levels of NAD increase [00:47:05] mitochondrial supply and the blood vessels, therefore, are able to [00:47:10] enlarge and form. So, a person, like a basketball player, someone who's out there going back and [00:47:15] forth on the court, he has far more mitochondria than I do.

And that's because, [00:47:20] uh, he's been exercising, he has NAD being produced, you get more mitochondria. [00:47:25] So, in the long run, not only does it help your immediate health, but it makes you in better shape. [00:47:30] You actually condition a runner. We'll have much more, uh, blood supply [00:47:35] throughout his muscles because of this NAD

**Dave:** increase.

It makes so much sense. There [00:47:40] are about 30 million people in the U. S. alone who [00:47:45] have a COVID vaccine injury, also known as long COVID. Yes, I know. I just [00:47:50] trolled a bunch of people with that, but, um. What's the role of NAD in long [00:47:55] COVID?

**Andrew:** Actually, there was a study looking at the effect of NMN in [00:48:00] people who had had COVID in terms of their vascular function, and it actually [00:48:05] was much better.

So that's a population that is at risk. People who've had the vaccine or COVID, [00:48:10] you know, they've had the spike protein, the vaccine has the spike protein, COVID has the spike protein. [00:48:15] So that is an activator of endothelial damage, potentially. And [00:48:20] so NO and NAD will protect the blood vessels. Uh, so if you've [00:48:25] got COVID, it's recommended from this article, it's an NIH publication.

Uh, it's something to think about, [00:48:30] and certainly if you have long COVID, it's something also to think about.

**Dave:** I had chronic fatigue [00:48:35] syndrome and fibromyalgia diagnosed in my 20s. Those are exactly the same thing as long COVID. You can have [00:48:40] different things that trigger the whole cascade of mast cells and all the stuff that's involved in those.

So this [00:48:45] has been an area where I was able to recover from that, and I did get COVID and [00:48:50] did not get long COVID because I take care of my mitochondria. So I look [00:48:55] at all of those conditions as mitochondrial and inflammatory things, and if [00:49:00] you want to turn off inflammation, you turn on mitochondria, and as you just described, NAD [00:49:05] is most important.

**Andrew:** You know, we used to think about diseases as being sort of these [00:49:10] isolated instances of bad luck. Oh, I got diabetes. Oh my [00:49:15] goodness, I got cancer. Oh my gosh, I have fatty liver disease. Oh, I'm [00:49:20] having a renal problem. Oh, I'm having Alzheimer's. And we had departments set up and then we had [00:49:25] doctors who would specialize their entire lives in each of these very distinct areas.

And [00:49:30] that's one way to look at medicine, but that's the 1950 ways to look. Today, we have to see these. [00:49:35] Really, as an integrated whole, why do we get sicker as we get older? Is [00:49:40] it just bad luck? No, the aging process is a core fundamental [00:49:45] derangement that then spawns injury in all these different organs. If you happen to have [00:49:50] an injury in your.

Knee, suddenly you have arthritis,

**Dave:** but if

**Andrew:** it's really not [00:49:55] arthritis, really what it is fundamentally is aging. And so we can spend all [00:50:00] our time trying to treat arthritis, or maybe we need to go upstream and spend our time thinking [00:50:05] about the aging process itself.

**Dave:** I look at it like this. If [00:50:10] I age, it's my fault.

It means I haven't figured out [00:50:15] what I could be doing or I could have done to do a better job of it. Right? [00:50:20] We know all these different pathways and maybe there's some things we don't know. Well, that means I haven't discovered them yet or you [00:50:25] haven't discovered them yet. That's

**Andrew:** right. And it's never too early.

You know, a lot of people think that aging starts when you're [00:50:30] 60 and 70. They're elderly, right? You get your senior discount. I just got mine. I was so excited. [00:50:35] Made my day. But, but actually, aging doesn't start when you're 65. [00:50:40] Aging actually starts in your early 20s. I'm sorry to say that, but it's true. If you look [00:50:45] at a baseball player, you know, the rookies are great, 20 years old.

By the time they're 30, [00:50:50] they're kind of not rookies. By the time they're 36, they can't run as fast, they can't [00:50:55] dive, they can't slide as fast. It's not the same person. So if you care If [00:51:00] you're in your early 30s or in your late 20s and you want to maintain vigor, [00:51:05] you're an ambitious person, you know, you want to master your skills, you want to, you want [00:51:10] to exceed in, you know, do everything you can in your, in your profession, do really well there, succeed there.[00:51:15]

You want to have good pleasure in your life and good sexual health. It is not [00:51:20] sensible to wait till you're 60 to 70 to wake up, wake up now. When you're [00:51:25] in your 20s, start thinking what can I do to maintain my NAD at a healthy [00:51:30] level so that I don't develop these problems. I don't have to work backwards to fix them.

Let's prevent them.

**Dave:** [00:51:35] The reason that I, I called what I do biohacking is that I [00:51:40] learned, because I had the unfortunate problem of being old when I was young, the things that [00:51:45] make old people young make young people powerful. And all of a sudden I think, what [00:51:50] if I talk about it in a way I would have listened when I was 19?

Wow, I get to [00:51:55] choose to not be obese. I get to choose the skin I want. I get to choose the brain function I want. [00:52:00] And as a side effect, you have way more stamina and you have a better [00:52:05] life and you don't age the way everyone else does. That's right. I mean,

**Andrew:** people in their 20s care really [00:52:10] about three things, I would say.

They want to be mastering things, whether it's at [00:52:15] work or in sports, they want to master things. They're ambitious. They have drive. They have [00:52:20] energy. They want to flourish, whether it's in sports or whether it's at work. And they want to have fun, they want [00:52:25] to have pleasure, they want to have a good life for their family.

This is, this is what, well, all of these [00:52:30] things will be derailed if you don't have an NAD level that can [00:52:35] support you in, in your endeavors, in your goals. I mean, you've got to be alert. You've [00:52:40] got to be sharp at work. You've got to be, if you're on the tennis court, you've got to win. You've got to have [00:52:45] muscle, you have to have power.

You have to have pleasure and fun. You have to have a normal sexual life. [00:52:50] So all of these things can be derailed, but you don't have to let that happen. You have a choice.

**Dave:** [00:52:55] And it it's funny. Alcohol is just a bad idea in general. And [00:53:00] I wish I hadn't have drunk when I was in college because I know now what it [00:53:05] does.

What is the role of alcohol and NAD?

**Andrew:** Well, [00:53:10] alcohol, first of all, can spawn the generation of oxidant stress. It [00:53:15] directly damages tissues with the alcohol because it gets into the membranes, but more than that, it can lead to a lot [00:53:20] of oxidant injury. And so that damages DNA, activates PARP, consumes [00:53:25] NAD. So NAD levels in an alcoholic are suboptimal.

[00:53:30] Best thing, of course, is to stop the alcohol. But, uh, over and above that, you want to maintain [00:53:35] your levels of NAD in the face of alcoholism. Got it. The best thing is to stop the alcohol. Yeah. [00:53:40] That's the. Do you drink? I, I drink on, on Shabbat. I have a glass of wine.

**Dave:** [00:53:45] Okay. I live with it as that. Yeah. I, I have a rule.

I drink if it's older than I am. [00:53:50] Okay. So there's an economic reason to not drink, right? So maybe once a year [00:53:55] I'll have. Yeah. Good sake with sushi or something. But yeah, it's for me not even a monthly thing [00:54:00] because I'm into cognitive function and longevity and I know what it does. [00:54:05] And frankly Alcohol is

**Andrew:** just about the worst thing you can do for brain function.

It just is. It's a neuronal,

**Dave:** [00:54:10] um, injurious agent, pure and simple. I've been hearing a lot lately about what they call [00:54:15] California sober people. In fact, I'm one of those. We're saying, I don't drink, but I might eat [00:54:20] some microdose mushrooms at a party. Right. Anything that we know about NAD and psychedelics? [00:54:25] Um, no, I don't, not that I [00:54:30] know of.

My experience as a long time Burning Man guy, and I have a [00:54:35] ketamine as an offering through a medical doctor up at my neuroscience clinic. Uh, in fact, a lot of my new [00:54:40] book, I have a big section on psychedelics, any psychedelic [00:54:45] journey or deep meditation or breath work, it doesn't really matter what's getting you into these altered [00:54:50] states.

Yeah. If you can upregulate mitochondrial function, you have a much deeper, more [00:54:55] powerful experience. And it follows then that having adequate NAD, [00:55:00] when you're calling on the brain to go into these altered states, whether they're self induced or chemically induced, [00:55:05] it, it's a very, very big difference in the quality and intensity of the experience.

**Andrew:** Well, [00:55:10] we know that, I mean, now I'm thinking about it in light of what you're saying there, the psychedelics [00:55:15] upregulate. in a very acute fashion, the metabolic activity of the [00:55:20] brain. And the brain actually is the most metabolically active organ in our body. It uses [00:55:25] 25 percent of our blood supply. The oxygen demand by the brain outstrips [00:55:30] everything, including the heart.

So, uh, anything that you can do that, anything that you [00:55:35] are doing that causes increased brain activity and function will require a [00:55:40] commensurate amount of oxygen to support that and NADs. So I guess if this [00:55:45] psychedelic experience you're describing is energy demanding, then it's obligatory [00:55:50] that

**Dave:** you have sufficient NAD to support that.

So when I'm going to go on a journey, and [00:55:55] because I'm not recommending any of this stuff, I'm just talking about my practice and what I've found works best, [00:56:00] um, I want to have some ketones present and I don't care if it's from MCT or ketone dials, [00:56:05] uh, which are, I think my preferred way to do that at this point.

And, uh, [00:56:10] human makes that HBMN. Uh, and then I take a bunch of mitochondrial enhancers and [00:56:15] wonder feel, of course, because what you want is for every cell in your body to be able [00:56:20] to do everything that it's capable of doing effortlessly. Mm-hmm . Because [00:56:25] there's this beautiful thing that, that I've noticed in biology.

I'm a distributed systems computer hacker [00:56:30] guy. Like, well, if you don't have enough compute power, you stop doing some things that are critical. And the [00:56:35] body is the same thing. If I don't have enough metabolic power in the form of NAD, ATP, [00:56:40] mitochondrial function, well, what are the things that aren't necessary to be alive right now?

Let's not do those. So if [00:56:45] I can stack all of my energy metabolism and all of my antioxidant metabolism to their [00:56:50] fullest, then when I'm doing something, whether it's an athletic thing or it's a spiritual [00:56:55] journey kind of thing, then I'm going to have the full experience. That leads me to, [00:57:00]

**Andrew:** I want to add something there because there is a positive feedback loop, which of course, [00:57:05] you being a computer engineer, you know what I'm talking about.

When you are in a [00:57:10] situation where you have a fall in the amount of NAD [00:57:15] and systems start to go awry, Mm hmm. Those will actually increase the damage in the [00:57:20] gut that allows leakiness, which increases CD38, which further lowers NAD. So [00:57:25] it is a positive feedback loop in the bad way. It gets worse and worse and worse.

Right. [00:57:30] In contrast, if you can do the proper things in terms of your [00:57:35] health and maintain NAD, you will have a positive feedback loop in the other direction in [00:57:40] terms of restoration and prevention of disease. So, it's a very highly [00:57:45] amplified system, it's sensitive. If you are taking, say, any, uh, NMN [00:57:50] supplements or our product, for example, and all is going well, and we've had all of these people comment [00:57:55] about how their lives have changed.

We've had several people who went traveling and [00:58:00] forgot their stuff. Now, those people seem to regress pretty quickly after about two [00:58:05] to three weeks and, and, and it, it, so it can get better quickly, but it can [00:58:10] get worse if you're not doing these right things. So it's the sort of thing where you need [00:58:15] to be mindful to do it every day.

I mean, this is a journey. Longevity [00:58:20] treatments are not something you can do. If you're committed [00:58:25] to taking care of your health, it's something that you've got to do every day. We recommend, for example, [00:58:30] that our capsules taken at the time you brush your teeth, because you remember that in the morning. [00:58:35] And you want to do this every day.

All of these things you're discussing, we're talking about here [00:58:40] today, require commitment. It's something, it's lifelong. If you want to make a [00:58:45] difference, you have to maintain that momentum, and you can't be skipping out. You [00:58:50] gotta be consistent.

**Dave:** You saw my supplement room. Yes. [00:58:55] Where I take about 150 pills a day.

I never saw anything like this before. I've been doing [00:59:00] this for 20 plus years. Wow. Because Just hanging out with people [00:59:05] in their 80s when I was in my 20s, I, I, I know what's possible and also because I was [00:59:10] pretty sick too at the beginning of this and the benefits keep coming in where [00:59:15] I'm not slowing down.

My brain works. Look, the evidence

**Andrew:** is out there for us to see. We all know [00:59:20] people. My mother, for example, God bless her. She's 92 and a half. Her house burnt [00:59:25] down last week, but, but, but she ran out of the house and she's all ready to rebuild the new house. [00:59:30] She's excited. She can't wait. That's a 92 year old with energy, with activity, [00:59:35] with drive, but I know.

A lot of other people, the same age, and they're [00:59:40] shuffling, they can hardly walk, they have limited activity, they don't, my mother's [00:59:45] out there running down buses to go to the symphony, go to the museum, and other people they're, [00:59:50] you know, they need care, they're at home, so that, 92 is not 92. 92 is [00:59:55] just a number.

If you want to maintain your health and you're good about this, you can be a very [01:00:00] vigorous, active citizen well into your 90s, maybe longer. Wow. But it requires a [01:00:05] lifelong commitment to stay in good health. And some good genes. That doesn't hurt. Genes do not hurt. [01:00:10] Yeah. How much wonder fuel does your mom take?

**Dave:** She doesn't take it yet. She doesn't? And she's just [01:00:15] naturally doing this.

**Andrew:** Well, all her relatives live to be 100. I'm sure her PARP activity is [01:00:20] probably off the wall compared to most people. So she's not getting these genetic damage [01:00:25] accumulations. But, you know, not all of us have that. We all know people who live to be [01:00:30] very old.

But there are a lot of people who are in their 60s. Frankly, they look like they're 80 or 90. I have [01:00:35] friends like that. Uh, they're not doing anything wrong, they feel, but, but really they [01:00:40] could be doing more. They could prevent this. What are the biggest mistakes that people

**Dave:** make with NAD [01:00:45] supplements?

**Andrew:** I think that just taking an NMN or an [01:00:50] NR supplement by itself is a good first step, but I think the [01:00:55] mistake is not recognizing that depletion of the material is just [01:01:00] as important as its supply.

I, I really believe in the concept of combination. [01:01:05] So I think, I wouldn't call it a mistake, I don't want to assign blame to anybody, but I think we know [01:01:10] enough now from the biology to recognize that things like CD38 over [01:01:15] activation are going to cause a problem. So I think that's very important. Second thing is [01:01:20] consistency, like I said, this is not occasional, let me try some supplement, [01:01:25] it's a commitment.

Okay. You need, so that's a mistake if you don't maintain that reliability [01:01:30] and compliance and take it every day. Other mistakes, um, they [01:01:35] are not recognizing that the NAD story is part of a systems biology [01:01:40] thing. You have to exercise. You have to keep your weight down. You have to be doing all the [01:01:45] other important things with your diet and all the important things with your nutrition and [01:01:50] taking care of yourself.

So it's, it's part of a program. It is not a solution by [01:01:55] itself.

**Dave:** What do we know about NAD and the brain?

**Andrew:** Well, there are studies actually [01:02:00] looking very carefully at this and, uh, clinical studies even showing that NMN supplementation [01:02:05] or NR supplementation have a real effect on memory, on the [01:02:10] rapidity of your thinking, uh, they get rid of brain fog, they allow you to be sharper, [01:02:15] um, all of the things that you would expect from a molecule that is at the [01:02:20] centerpiece of the energy of the brain.

I mean, the brain is a motor. [01:02:25] It's like a computer, it runs on, it doesn't run on electricity, well it does run on electricity actually, but it has [01:02:30] power. And if you strip the power away, you turn it down 50%, what do you expect? [01:02:35] You're not going to be sharp. So NAD is absolutely front and center, in fact it is the organ [01:02:40] most demanding of NAD.

Why do I say that? Uh, if [01:02:45] you lose, if you have a traumatic brain injury or a stroke or there's [01:02:50] any kind of interruption to blood flow in the brain, you have eight minutes. Wow. [01:02:55] That's it. Eight minutes go by without oxygen. You have irreversible [01:03:00] neuronal injury and severe brain injury. So there is no [01:03:05] time and no tolerance for a lack of NAD.

Minutes [01:03:10] are life threatening. So great that you brought that up. The most important organ in the body [01:03:15] dependent on NAD.

**Dave:** Are there synergies between NAD and coffee [01:03:20] or caffeine, my favorite biochemical?

**Andrew:** Well, caffeine is a stimulant [01:03:25] and it's going to activate the metabolism of cells. And by, when I say [01:03:30] activate, what does that mean?

It means that it increases The energy production and [01:03:35] consumption in the cell, it's like being in a car driving 20 miles an hour or [01:03:40] 100 miles an hour more. When you drive 100 miles an hour, your car engine is working like [01:03:45] crazy. You're using more gas. You're going faster. All of those things happen when you take [01:03:50] caffeine.

So your need for [01:03:55] NAD in those situations is heightened. If you take caffeine and you [01:04:00] don't have the NAD that you should have, you will have a relative deficiency and it could [01:04:05] probably cause you some harm. So if you're going to be a heavy coffee drinker, make sure that you're [01:04:10] youthful in your cells and that you have your NAD maintained.

**Dave:** We know there's dozens of [01:04:15] studies now associating coffee consumption, not necessarily caffeine, but coffee consumption [01:04:20] with longer life. And I think some of that is because of the [01:04:25] antioxidants that are present in the coffee. But if you were to stack those with ergothionine [01:04:30] And the other compounds you have in Wonderfuel and you have adequate NAD, [01:04:35] you're going to get more benefits.

And I think either, either one by themselves work, the combination [01:04:40] together seems like a better idea.

**Andrew:** Yes, we're actually doing research in this area right now, because we [01:04:45] think that adding a stimulant To our products may be important, not in the long [01:04:50] run, but in the short term, it allows you to be sharper, faster, better during the day.

Everybody wants that. If you're an [01:04:55] ambitious young guy or girl, you want to be full of energy and do what you need to do. But at [01:05:00] the same time, we know that, like you said, stimulation without the commensurate [01:05:05] increases in energy supply is asking for trouble. So that's why we're thinking about a [01:05:10] further combination therapy like that.

**Dave:** What does NAD do for ketosis? [01:05:15]

**Andrew:** Well, fat metabolism is a, of course, ketones are produced [01:05:20] when fat is metabolized, right? And when fat is metabolized, that [01:05:25] requires, uh, energy, okay? Because the process of beta oxidation of fats, [01:05:30] that's how fats are removed in adipocytes in the fat cells. It's an energetic [01:05:35] process when insulin isn't present.

And that process requires [01:05:40] energy in order to process the processing of fats, in order to degrade them. So when you [01:05:45] are ketotic, because you're breaking down fats, you need energy to facilitate that [01:05:50] process.

**Dave:** So NAD can help with breaking down fats so you can be in ketosis. [01:05:55]

**Andrew:** The other thing to keep in mind is that NAD is very important in the Krebs cycle.[01:06:00]

Okay. There are two molecules of NAD which enter into the Krebs cycle and the Krebs cycle is [01:06:05] using ketones, uh, and incorporating them. So it is a very [01:06:10] central part of intermediary metabolism. So yes, you do need to have good NAD levels when you're [01:06:15] ketotic.

**Dave:** There are a lot of different longevity pathways, uh, that we cover on the show and [01:06:20] I'm trying to manage all of them for myself.

We have things like mTOR, [01:06:25] AMPK, and sirtuins. How does NAD compare to each of those?

**Andrew:** Well, [01:06:30] sirtuins, of course, are related because sirtuins use NAD, uh, [01:06:35] they use it to ribosylate proteins, which causes deacetylation. So [01:06:40] sirtuins and NAD are intrinsically connected with each other. [01:06:45] Um, for other pathways, Uh, all of them will interact with metabolic [01:06:50] machinery and oxidant flux and all of these things, uh, more or less depending on the [01:06:55] specifics.

So I don't know, I can't answer that generally, but on the specifics, [01:07:00] yes, there will be research that we are doing and other people are doing to make those connections.

**Dave:** [01:07:05] The mTOR front is really fascinating to me because for, for [01:07:10] listeners. Um, mTOR causes tissue growth, which is good, [01:07:15] unless it's on all the time, in which case you might get cancer.

So what I like to do is, [01:07:20] is suppress my mTOR, because the more you suppress it, then the stronger it rebounds. [01:07:25] So the three things that we know suppress it are, let's see, coffee. [01:07:30] Suppresses mTOR, exercise suppresses mTOR, and fasting suppresses mTOR. [01:07:35] So the tripling down on mTOR thing is, well, wake up in the [01:07:40] morning, have some coffee, don't eat breakfast.

Exercise. [01:07:45] And at that point you've smashed mTOR down and then you have some protein and some [01:07:50] carbs which raise mTOR. So then you get a big surge right when you want to put on muscle after the [01:07:55] exercise. But if you want to put on muscle and you don't have enough metabolic energy [01:08:00] because you're low in NAD, you simply won't be able to put on muscle.

You just get the systemic [01:08:05] stress of all that behavior, but you can't adapt to it. You gotta have your minerals, you gotta have [01:08:10] your Your substrate in the cells to be able to do this and that means you're getting [01:08:15] more results and less time from the exercise So there might not be a study but mechanistically [01:08:20] we know if you're gonna build any protein in the body what's powering that It's [01:08:25] NAD through ATP, right?

**Andrew:** That's right. When you're weightlifting or when you're doing any kind [01:08:30] of regular exercise, there's a period of stress where your muscles are undergoing [01:08:35] hypoxia. They're not getting enough oxygen because you're vigorously exercising. lifting weights, [01:08:40] whatever. And that is a stimulus for growth of new muscle, for growth of new [01:08:45] protein and for fission and production by fish.

And I mean separate [01:08:50] reproduction of mitochondria, right? So someone who's an active runner [01:08:55] or a weightlifter or a bicycler is causing stress to his system during the activity. And [01:09:00] then when he. Waits a day or two before he does it again. During that time, there's a regrowth, a new growth [01:09:05] of muscle. All of that requires an incredible amount of energy in order to facilitate [01:09:10] protein production.

Protein synthesis is a highly energy dependent process. [01:09:15] So, you've got to have adequate levels of ATP and NAD to sustain and [01:09:20] support that. So, that is why the good nutrition is critical to have the [01:09:25] ingredients for protein. You need amino acids, you need to have the right diet, but then you have to have a [01:09:30] steady state level maintained of NAD in your cell to facilitate the [01:09:35] expansion of the muscle.

**Dave:** What do you know about NAD and willpower? I

**Andrew:** [01:09:40] mean, in terms of your mind, in terms of your energy, I've never explored. That's a [01:09:45] great question.

**Dave:** Can I share something with you? This is my favorite study, maybe of all the [01:09:50] studies ever. And I wrote about this in my brain enhancement book. It's a [01:09:55] study from Israel, where you live.

And a group of scientists got together and they [01:10:00] said what predicts whether someone's going to get parole to get out of prison? [01:10:05] Is it their gender, is it their race, is it where they're from, socioeconomic, what [01:10:10] crime they committed, all of that. And after they comb through the data, what [01:10:15] predicts whether you get parole or you get sent back to prison is what time is your meeting with the [01:10:20] parole board.

Because decisions take mitochondrial energy. So in the [01:10:25] morning, if you get your meeting, you're very likely to get out because they'll consider your case. Well, [01:10:30] okay, you can go. And. If they're tired at the end of the day, blood sugar levels are lower, [01:10:35] mitochondrial activity is lower, brain function is lower, it's just too much work to think about it, stay [01:10:40] in prison.

And there was a brief spike right after lunch, when their blood sugar peaked and then dropped [01:10:45] again, and you're screwed if you have an african american meeting. Right. So I found the studies. There was two [01:10:50] studies that directly associate mitochondrial function with willpower, which only makes sense because this [01:10:55] drives everything.

**Andrew:** Well, I think that the whole issue about the NAD level [01:11:00] being susceptible both to or influenced both by supply and [01:11:05] depletion is important. If you take a supplement in the morning, you're, and this has been shown in [01:11:10] animals as well as in humans. Uh, it, when you take a supplement, you will get a boost in your blood [01:11:15] levels of, uh, NAD and NMN.

It goes up. But it's not going to stay up [01:11:20] because over time, the activity of CD38 on the outside of these cells will chew it up as well [01:11:25] as it being used up. So that is why. We feel so [01:11:30] important, uh, it's so important to have this combination, so that you have a [01:11:35] sustainable level of NAD throughout the day and it's not just a brief burst or [01:11:40] episode in the morning after you've taken the, uh, the, uh, [01:11:45] supplement.

**Dave:** So this you wonder feel in the morning and at lunch?

**Andrew:** No, you take it [01:11:50] once a day, but by blocking CD38 activation, by inhibiting [01:11:55] CD38, you prevent the subsequent breakdown that would occur, [01:12:00] uh, later in the day. So think of it as a, as a bathtub. You have [01:12:05] water going in and you have a drain with water going out.

You can fill up the bathtub in the [01:12:10] morning. But if there's a big hole in it, during the day, it's going to run down. The only [01:12:15] way to maintain a steady state level of something is to make sure that the water [01:12:20] going in is good, and that the hole letting it out is small. Right. [01:12:25] And this is the point of having that combination.

That's why I think you'd have a more sustainable level when you're blocking [01:12:30] CD38 and not just giving the supplement.

**Dave:** That makes so much sense. [01:12:35] The other process that's driven by mitochondria is the glymphatic [01:12:40] system, which is something that happens when you're asleep at night and your [01:12:45] brain basically washes itself out via a recently A recently discovered [01:12:50] mechanism.

And I did find a couple studies showing that that's also derived from [01:12:55] mitochondrial things. You have to pump this stuff out, and this isn't the kind of pumping that happens when you walk. It's the kind of pumping [01:13:00] that happens when you're asleep. Is there a case for increasing NAD for [01:13:05] sleep efficiency?

**Andrew:** We have had, uh, and not just we, many people have [01:13:10] commented that NAD supplementation has a very profound effect. on the [01:13:15] quality of sleep. We have seen this from our customers, many anecdotes. This is one of the most [01:13:20] common things that come back, but not just us. There are numerous reports with NAD [01:13:25] supplements like the NMN and NR commenting on exactly this point.

The, I don't know why [01:13:30] that is the case. We don't, I mean, there's very little research really on the [01:13:35] type of energy requirement during sleep and where and how it's done, but let's face it, [01:13:40] sleep. is a process which is removing adenosine. That's one of the main, I mean, it does [01:13:45] many things. There's neuronal plasticity, there's incorporation of events into [01:13:50] long term memory.

But fundamentally, during the day, the brain, [01:13:55] like any organ, is having to consume, uh, [01:14:00] energy in order to do its job. And as a consequence of that, the brain [01:14:05] is accumulating Metabolites of ATP that break down, [01:14:10] it uses ATP to make it go. The ATP becomes ADP and AMP and [01:14:15] ultimately adenosine. So when that all happens by the end of the day, say 10, 11 o'clock at [01:14:20] night, your brain is chock full of adenosine.

It's exhausted to put it [01:14:25] in another way during the night. And the, and the adenosine by the way, is what makes you sleepy, [01:14:30] right? And that's why coffee keeps you awake because coffee is an [01:14:35] antagonist of the receptor. Of adenosine. Yeah. So a person who takes [01:14:40] coffee and takes caffeine doesn't allow the adenosine within their brain to make them [01:14:45] sleepy.

Adenosine says to you, I'm sleepy. Go to sleep. Mm [01:14:50] hmm. Okay. So when you start to go to sleep, the adenosine is then taken up into the cells [01:14:55] and ATP with help of NAD regenerates the ATP for the [01:15:00] next day. When you wake up in the morning, you're feeling pretty good.

**Dave:** Your

**Andrew:** adenosine levels are low. Your brain is full of [01:15:05] ATP.

You're ready to think. You're ready to act. So NAD during the night is the [01:15:10] key driver of the process, which is restoring your [01:15:15] ATP levels and lowering your adenosine. So you're using NAD at night to [01:15:20] get back to where you were for the next morning. Do

**Dave:** you always take Wonderfuel in the morning?

**Andrew:** We [01:15:25] take it in the morning.

**Dave:** What happens if you take it at night?

**Andrew:** Well, it [01:15:30] probably would be okay, but think about it. You're going to have some type of burst of [01:15:35] activity or levels. I mean, when you take any molecule, whether it's a [01:15:40] drug or a supplement, whatever, you take it in the morning at eight o'clock, your peak level will typically [01:15:45] occur between 30 minutes and two hours.

Almost all drugs, there are a few exceptions, but most [01:15:50] take Tylenol, for example. 15 to 20 minute peak, uh, Advil, 30 [01:15:55] minute peak. So, so when you take wonderfield in the morning, you're going to get your peak early [01:16:00] when you want to have the highest levels because you're moving around, you're active, you're, you're going to work, [01:16:05] you're bicycling, you're, you're, you're thinking a lot.

So you want to have super high levels right then [01:16:10] to take it right before you go to sleep. Seems like kind of a waste of time. You need a steady state level while you're [01:16:15] sleeping, but you don't need a big burst. You're not doing a huge amount of activity when you're sleeping in [01:16:20] general.

**Dave:** One of the things that a lot of humans will do is if something's good for [01:16:25] you, more is better.

I believe this about exercise. I, for 18 months, I worked [01:16:30] out 90 minutes a day, six days a week, religiously. I never lost a pound [01:16:35] because I was over training and under recovering. Right. Is there such a thing as [01:16:40] having too much NAD because you're just popping supplements all the time?

**Andrew:** Well, there have been [01:16:45] studies of this, uh, going up to 900 milligrams a day.

And about four or five [01:16:50] studies now have all shown that the best effects were at 900 milligrams. There was [01:16:55] one study that showed also good effects at 600 milligrams, but slightly better at 900. [01:17:00] And there is actually, uh, courtesy of Dr. Sinclair's study of where he actually went [01:17:05] up to grams.

**Dave:** Mm

**Andrew:** hmm. Several grams.

He claims in that [01:17:10] study that no one was hurt, which is good. It means there's a nice safety factor so we can all step back and [01:17:15] relax a bit. Whether you need more than 900 milligrams to be effective has [01:17:20] not been examined. There has not been a careful comparison between 900 milligrams [01:17:25] and 2 grams. It might be better.

At some point though, having said [01:17:30] that, too much of something may not be a good thing. And all of the, [01:17:35] when you think about biology as a whole and the way our system works, the [01:17:40] entire organism in the human biology and any kind of biology [01:17:45] is based on having the foot on the gas and the foot on the brake simultaneously.

This is how we [01:17:50] create control. Uh, we don't have a system where just the gas is on or just the [01:17:55] brake is. So you need to have. Uh, a certain amount of something, [01:18:00] but if it becomes grossly excessive, you're going to have other factors involved, [01:18:05] uh, if NAD is spinning the Krebs cycle too fast, that could create byproducts [01:18:10] that can't be handled.

So there could be a lot of things where excessive NAD [01:18:15] is not, um, Needed, certainly, and could actually be injurious.

**Dave:** [01:18:20] Okay, so you like the recommended dose, and that doesn't change For the moment,

**Andrew:** there should be research [01:18:25] examining all doses, but this is where the research currently tells us it's best.[01:18:30]

**Dave:** Anecdotally, I did notice, especially with [01:18:35] NR, uh, which I started taking a long time ago, I felt a difference at two grams. I didn't feel it [01:18:40] a gram or less, but especially in the early days, that stuff was really expensive. It was like 500 a month to [01:18:45] take that much, you know, which is. It's kind of absurd for most people.

Keep

**Andrew:** in mind that when you're taking NR, you're [01:18:50] gonna get a boost, but then it's gonna come down because of the CD38. And we didn't

**Dave:** know the [01:18:55] CD38 yet and done all the research, and so these are old days, so maybe now the lower [01:19:00] dose with blocking CD38 is

**Andrew:** And I wanna emphasize that at Wonderfield at least and just [01:19:05] in my life, I'm a deep I'm a big believer in the importance of doing research.

I don't just like to [01:19:10] recommend something or even think about it. Uh, my entire career has been based on, [01:19:15] uh, researching everything. I'm not just curious, but it can help people and we, we need to do these studies. So [01:19:20] this whole, uh, health area with NAD, I'm telling you what I know today. I hope we'll know a lot [01:19:25] more next year and that'll be from research.

**Dave:** And we're, we're carrying

**Andrew:** out that research, by the way, [01:19:30] we have a big biology lab where we conduct, uh, research activities constantly at [01:19:35] the cellular level, at the animal level. We're asking questions about this all the time.

**Dave:** Well, thanks for [01:19:40] your relentless curiosity. That's what it takes to really discover this instead of just [01:19:45] deciding something works and then sticking to your guns.

Yeah. I have a final question for you as [01:19:50] we wrap up the interview. And you've studied all the different biochemistry, [01:19:55] you've treated people in hospitals. Uh, is there a hard truth about [01:20:00] biological aging that even biohackers want to accept?

**Andrew:** [01:20:05] I don't think that pessimism or cynicism or [01:20:10] resignation, capitulation is, is appropriate for people.

[01:20:15] If you just look historically where we were 200 years ago, where [01:20:20] Very few people live beyond the age of 49 if we go back 5, 000 [01:20:25] years ago where very few people lived ever beyond the age of 25 [01:20:30] All I see are good things happening and I don't think just like the four minute [01:20:35] mile, you know There was that whole debate before Roger Bannister ran

**Dave:** and

**Andrew:** they asked him afterwards.

Did you [01:20:40] think there was a physical impossibility to run a four minute mile. He said, no, [01:20:45] I just had to work hard to train. So I don't think there is a barrier as long as [01:20:50] we are wedded to the commitment to do the research, to understand why we're [01:20:55] aging. We need to do a lot of research, but I am gun ho. I'm ready to be part of that [01:21:00] research.

And I think the sky's the limit. We just have to. We have to push hard, [01:21:05] be optimistic.

**Dave:** Well, Dr. Andy Selzman, thanks for your lifetime [01:21:10] of just incredible work and going out there and saying, how do I do stuff that affects more people? I think you've [01:21:15] had a meaningful impact on our understanding of biology and aging and cell [01:21:20] metabolism, a bunch of other stuff, cancer.

So you had an impact and I love it that you're [01:21:25] not slowing down. So

**Andrew:** I appreciate it. Thank you. It was a pleasure to be here. Thank you.

**Dave:** Guys, [01:21:30] wonderfield. com is where you can learn about all this stuff and a lot of your writing [01:21:35] is on that web page as well. Or you can just read his 170 publications if you want to.

There's, there's that. [01:21:40] If you like this episode, you know what to do. Have more NAD in your life. It seems [01:21:45] like that's a good strategy. It's not the first time you've heard it on the show, but this is the first time we've gone deep on [01:21:50] CD38, ergothionine, and hydroxytyrosol. So this [01:21:55] is a good combination. And as you know, If you listen to the show for the [01:22:00] last 10 plus years, I take 150 supplements a day [01:22:05] and they're carefully designed for my metabolism.

I don't publish the entire list because if you did what I did, [01:22:10] you'd probably get disaster pants or as my daughter calls it, underwear surprise. So [01:22:15] you want to figure out what is the load on your life? What kind of stress are you [01:22:20] under? What kind of aging do you want to have? What kind of power do you want to have in your In your brain right [01:22:25] now, and you try things.

Say, I'm going to try Wonderfeel. So you try it [01:22:30] for, I would say, at least three months, and see what happens. And we're great at [01:22:35] understanding. I felt I felt good today. I felt good tomorrow. But some of these effects [01:22:40] build up over the course of weeks, and we're terrible as a species at noticing effects [01:22:45] that are just downstream.

So this is one of those things. Get your NAD up and your CD38 [01:22:50] down, and just watch what happens over time. And you might say, I've always felt this good. And then, [01:22:55] let's say you stop it for a month. And you go, oh, look, my aura ring, or in [01:23:00] this case, not my ultra human ring, I'm wearing both. Oh, wow. [01:23:05] My heart rate variability started to drop.

I didn't get as much sleep. My morning readiness score isn't [01:23:10] where it was. And you realize, oh, there's these gentle patterns that happen over time. And you want to live a very long [01:23:15] time, like I do, you want to watch those as well. And there's [01:23:20] so much evidence at this point. This is probably the 10th episode on NAD, [01:23:25] and the first one to go in this level, that this should be a part of your longevity strategy.

And maybe you say, I [01:23:30] can't live longer. I'm a Peter Attia fan who believes you can't extend human life. That's [01:23:35] okay. You can still improve human performance and the quality of your health span if that's your [01:23:40] only goal. I think your goal should be lifespan plus health span. And that's my [01:23:45] goal. So if you share that, get your entity levels up via any means necessary.

Thanks for [01:23:50] listening. See you next time on the Human [01:23:55] Upgrade Podcast.