Kicking Off Episode Four: Longevity Molecules

0:00
- Welcome to the Lifespan podcast, where we discuss the science of aging and how to be healthier at any stage of life.
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I'm David Sinclair. I'm a professor at Harvard Medical School and Co-director of the Paul F. Glenn Center for Aging Research.
0:16
And I'm joined today by my lovely co-author and cohost, Matthew LaPlante. - Hey, how are we doing? - [David] Hey, welcome.
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- Feeling good today. - [Matthew] Back at it again. - We are. We're here today to talk about how to live longer and better.
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- As part of this podcast series, this deep dive into things that you can do to slow, stop, and reverse aging.
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- That is true and today is going to be a really interesting one. - This is going to be the one that everybody,
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I mean, this is the one that everybody's been begging for. - That is true. We've been monitoring the responses to tweets
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and Instagram posts, and most of them are, David, just tell us what to take.
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- [Matthew] The nice ones. - Yeah. - Some of those aren't very nice either, but yeah, please, please, please.
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Should I take NR? Should I take NMN? What should I do with Metformin? We're going to be talking about all of that today.
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- We are, and our research team has been spending weeks on this, and if you can't see, I'm actually sitting in front of many pages of notes here.
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We're going to go deep dive into what is fact and what is not fact. What is known, what is not known, because there's so much misinformation out there,
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especially with supplements. - Yeah. We do need to say we usually take a moment
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to thank our sponsors, we're going to do that of course, but we also have to take a moment to say we are not medical doctors. We are not medical doctors.
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We are not medical doctors. - What he said. I'm a PhD, I'm a researcher.
1:36
I can read the literature. I've been doing it for the last 30 years. I distill that for everybody.
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But of course, if you want to try supplement or even change your diet radically, please talk to your physician before you change anything.
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Because some of the things we'll talk about today can affect your body in, hopefully, many good ways, but sometimes can be dangerous depending on the person.
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And everybody's different. - And what we want to do is give people the ability to have a more intelligent
2:02
and informed conversation with their physician. - Exactly. - Okay, with that out of the way, now we should thank our sponsors.
2:09
- Let's do that, because this podcast is free to anybody who wants to watch or listen.

Thanking the Sponsors

2:15
Our first sponsor is Levels. Levels is an app that syncs with a continuous glucose monitor, which they provide,
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and it interprets your glucose data for you. I've been so impressed by Levels that I've recently joined them as an advisor.
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Monitoring your blood glucose allows you to see how different foods impact you. I've used Levels to see what foods impact me.
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I've learned that grapes spike my glucose, white rice, but actually potatoes aren't that bad.
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It's not just interesting, it's also a lot of fun to see what's going on inside your body.
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So if you'd like to try Levels, you can skip the 150,000 person wait list. And you can join today by going to levels.link/sinclair.
2:52
That's levels.link/sinclair. Today's podcast is also brought to us by Inside Tracker.
2:58
Inside Tracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better understand your body
3:05
and reach your health goals. I've been using Inside Tracker for over a decade and also serve as chair of their advisory board.
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I really like Inside Tracker because they make it easy to get your blood test. Either someone can come to your home like they do for me, or we can go to a clinic.
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They then present the blood analysis in an easy to understand dashboard that provides recommendations for improving your health.
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Their InnerAge 2.0 test, which I helped develop using an AI algorithm, even shows your biological age.
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If you'd like to try Inside Tracker, you should go visit them at insidetracker.com/sinclair
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and you'll get 25% off every Inside Tracker plan. Use sinclair as the code at the checkout.
3:46
Today's episode is also brought to us by Athletic Greens, the all-in-one daily drink to support
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better health and peak performance. Athletic Greens is a greens powder developed from a complex blend of 75 vitamins,
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minerals, and whole foods sourced ingredients. It's filled with adaptogens for calvary, probiotics and digestive enzymes for gut health,
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as well as vitamin C and zinc citrate for immune support. I've been drinking Athletic Greens
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in the morning for many years and I do that because I don't often eat perfectly and I travel a lot
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and I can rest assured that I'm getting all the nutrients I need for optimal health.
4:22
So if you'd like to try Athletic Greens, you can go to athleticgreens.com/sinclair
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to claim a special offer. They're giving away five free travel packs, plus a year supply of vitamin D3 for immune support
4:34
and vitamin K2 for keeping calcium out of your arteries and putting it where it's needed into your bones.
4:40
Again, go to athletic greens.com/sinclair to claim this special offer.

An Additional Boost Beyond Adversity Mimetics

4:46
Okay, Matt, let's dive in. There's a lot to get through today and I know everyone's waiting to hear
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what we have to say today. - In the last episode, David, we talked about adversity mimetics. These are the things that we can do in our modern lives
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to mirror the sorts of stresses we faced across our evolutionary history. But even if you're engaged in doing these things
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like we've talked about already, fasting and getting lots of exercise, getting out of your comfort zone,
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our modern lives are still designed around comfort and sedentariness, is that a word?
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- Sedentary lifestyles? - [Matthew] Sedentary lifestyles. And that's not to mention the fact that even before modern times we aged, right?
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So if we're going to combat aging we may need an additional boost.
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Do you believe we may need an additional boost? - Well I do and I've been doing this since my early thirties.
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We'll talk about my program at the end of this episode, but really what we want to do today
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is to talk about some of the major supplements and medicines that are thought and have the greatest
5:48
scientific evidence to be able to give you wellness now as well as long-term health in the future. - Supplements and medicines,

Drugs vs. Supplements and Highlight Points

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drugs and supplements, molecules and drugs. There are a lot of different terms that we're probably going to throw around
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and we're going to use them fairly synonymously. But in fairness, let's define drug versus supplement, at least.
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- Right, first of all, most drugs are chemicals, okay?
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But some are naturally occurring and some are freely available over the counter, OTC. And that's because they've been in our food supply before
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and the FDA doesn't regulate them. They fall under what's called generally recognized as safe, or GRAS.
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And that's why you can pick up whole variety of molecules from the plant world, 'cause they're already in our food supply.
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Therefore the government thinks, well, they're probably okay, even if they're a thousand times more
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concentrated than what you're eating. - Which may or may not be the case, right? - Right, and so that's why you always have to be careful.
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You have to monitor yourself, like I have been with my blood work for many years to make sure that you're not hurting parts of your body.
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Your liver particularly could be sensitive to some of these molecules, even if they are available freely at the pharmacy or the vitamin shop.
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A different story about drugs. Drugs are regulated molecules because they have the chance to actually cause damage.
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And many drugs actually do have serious side effects that need to be carefully monitored and discussed with the doctor.
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Even those that are very safe. Like we'll talk about Metformin. These are regulated by the government
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because they are not in the food supply. There are artificial molecules that could theoretically do damage.
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- And there are literally thousands of drugs and supplements that someone somewhere
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will tell you we'll help you with health spans and lifespans. We're not going to talk about
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thousands of drugs and supplements today. - No, maybe in future episodes we'll come back, but we want to hit the high points today.
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- And so that's why today we're going to move through some of the most popular and some of the most promising. These are things that most people can have access to,
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or find a physician who, if the need exists, will prescribe.
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- Right, and I get emails and I get all sorts of texts every day, DMs, what should I take?
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What about this? What about that? What's the dose. When should I take it? What should I take it with? Is it okay to take this drug with exercise or not?
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That's what we're going to cover today. Your most pressing questions answered here today.
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- And so we're going to talk about NAD boosters. We're going to talk about Metformin, berberine, rapamycin, spermidine, resveratrol,
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fisetin and quercetin, and probably a few others. But those were sort of the highlight points.
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If you're only interested in one of these, or if you watch this whole episode need a reminder,
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the show notes are going to be timestamped so that you can immediately go to berberine and find it and click on it.
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- That's right, included in the show notes are the scientific references that we now have in front of us that we're going to talk about
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so that people can do a deep dive, even deeper than what we're going to do here today. - There's one more thing that we'll link
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to in the show notes that's on your website that I think is valuable for people to know about. You're involved in a lot of different companies.
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You're an entrepreneur, you're a researcher. You have I don't know how many patents.
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There are plenty of people who would say, oh, this guy's just trying to sell stuff. If they suspect that you might have a conflict of interest,
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they can go and look at your disclosures. - I do disclose everything that I do. My lab has a website. You can Google Sinclair Lab.
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And if you click through my bio, there's a link to all the work that I do outside of Harvard,
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as well as what we do at Harvard, of course, but importantly, I've never sold any supplement in my life.
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- And that's not because you're a bad salesman. It's because you haven't actually tried to sell. I mean, there's a difference between
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having not sold a supplement and having tried to sell a supplement and not sold a supplement. - Right, I've actively kept myself away from the supplement industry because I want to be able
9:38
to talk about things without any bias. - Not for a lack of opportunity though,
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there's plenty of people who would love to put your face on a package. - Well, and they do, without my permission. You can see my face on the internet.
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But if you see that, know that it's not with my permission and I do actively try to stop that. - To get into this let's use some of the same framing

Longevity Molecules Target the Survival Circuit

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that we've used for the other conversation. And that's these three longevity pathways, three longevity genes that we've been talking about.
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sirtuins, AMPK, and mTOR. Different drugs and supplements are thought
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to work on these different pathways in different ways. And we'll sort of like categorize them in those three buckets today.
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- Exactly, and the thing to also remember is that these three survival pathways we've talked about, and in episode one we talked a lot about,
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are responding to our environment. Whether you're exercising or fasting they'll turn on, but also appreciate that they talk to each other
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and some drugs or supplements will activate one of these and talk to the other two. So it's a network and we're still
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trying to figure out exactly what the optimal combination for each individual might be. Whether to tweak it with this molecule
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and then exercise here and then fast that day. We don't know all the answers, but we are going to present the cutting
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edge science here today. - And I think it's been really interesting. I've been working with you for, what,
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like about four years now. And in that time a lot of the molecules that we knew to be working on one of these pathways,
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there's been further research that has said, oh, that's not just an AMPK effect. There's also an mTOR connection there.
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- Well they definitely talk to each other. Because if you're low on immuno acids and it'll turn on the mTOR protection pathway,
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that will then tell the other survival pathways to do their thing too.
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It's like the Pentagon where there's centrally coordinated defenses and basically what we're trying to do
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is to make prank phone call to the Pentagon to say there's an emergency and they'll send out the troops in various ways and protect the body,
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even though there's no immediate threat. - I like that analogy. That's fun. Let's talk about the class of molecules

NAD Boosters

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that you've worked most extensively on in your lab. These are known as NAD boosters.
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Talk a little bit about why NAD is important in our bodies.
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It's really important, if it disappears, we're screwed, right? - Well, we'd be dead in 30 seconds. We need it for energy but it was discovered
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about 100 years ago by Germans who were looking at extracts in yeast. And there was this component called NAD
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that was necessary for chemical reactions. - We didn't say what that stands for, that's?
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- So NAD stands for nicotinamide, which is vitamin B3, and adenine dinucleotide. This is a sugar and a phosphate.
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The important part about it is that our cells use NAD to transfer hydrogen atoms
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between proteins and even DNA. That is really important for life and without it
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we can't make chemical energy, which is in the form of ATP, which we'll talk about later
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because that's important for Metformin. NAD is found in abundance. There's many grams of it in the body.
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It's probably, with the exception of ATP, the most abundant molecule we have in the body. It helps us make energy but it
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also has this other function that's just as important that we worked on and just co-discovered in the 2000s.
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It activates the sirtuins and the sirtuins are these defensive enzymes that, like the Pentagon, send out the troops.
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The problem is as we get older we make less NAD and we also destroy it more for reasons
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that we don't fully understand, but it leads to a decline in our ability to fight off aging and the diseases that it causes.
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- And this is because NAD is a sensor for adversity.
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- It is, if you exercise, it's known, and fast, it's known to raise NAD levels.
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But even if you exercise and have the healthiest diet, you're still going to have lower NAD levels by the time,
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you know, you're in the latter half of your life. So that's why these supplements are thought to help because they'll boost up those older levels of NAD
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to where they were when you were young. - Okay. So let's talk about the first NAD booster.

Nicotinamide Riboside

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Probably the most well-known, it's definitely the most well studied of the NAD boosters, and probably the most taken used. That's NR.
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- Which stands for nicotinamide riboside. So that's the vitamin B3 plus the sugar.
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Without the N part, which is a phosphate, we'll get to the phosphate, that's important later.
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It may make a difference, but NR has been taken over the counter or through websites for, what, since 2014,
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either solely just as a capsule or there's some companies that sell it in combination with other molecules.
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- And because it's been pretty well studied in humans, there've been plenty of human studies,
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at least in the short term that show little to no side effects. This is a pretty safe molecule.
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- That's for sure. We know that if you take it as a supplement to swallow the pill, either 250 milligrams
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per day or a gram, there's no apparent negative side effects, and in fact, you will raise
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NAD levels in blood tests. - So I think this is an important distinction to make, though, like there's a difference between
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safe and effective, right? Just because we say something as safe, doesn't mean it's going to work enough. And in fact sometimes things that are the most safe

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aren't going to work at all. That's why they're so safe is they don't have any effect. But we do know that NR is largely safe, you know,
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millions of people around the world take it. NRs have been well studied in animals as well.
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And let's start with that because we actually know more about what NR does in the bodies of animals than we do in the bodies of humans.
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- Well let's start with yeast. Go even further back. - Okay, yeah. - So that's where it was first discovered.
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NR was a newly discovered molecule back in the early 2000s. It's found a little bit in milk and other food selves.
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And if it was fed to yeast, they lived longer by turning on the yeast sirtuin pathway. - Okay. How much longer were the yeast living?
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- Generally yeast live about 30% longer when you give them these molecules, similar to choleric restriction.
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And that's what this was doing, mimicking choleric restriction, 'cause both activate the sirtuins and give increased genome stability
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and epigenome stability that lengthens their life. - And those kinds of findings make you really interested
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because you're really interested the sirtuin activation. And so you've been part of a group of scientists
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that have been looking at this. - Yeah, one of the first things that we discovered, this is now, we're talking 2002, 2003 in my lab,
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is that there's an NAD synthesis gene called PNC1. In our body it's called NAMPT.
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And it gets activated by these mild stressors. In a yeast cell it's low salt, it's low sugar, heat.
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And that turns on the synthesis of NAD and we found that extended lifespan. And then a few years later it was shown
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you can mimic this effect with this NR. - How does the NR turn into NAD?
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- So NR has to go through an intermediate molecule. Let's start with the mouth. You swallow your NR, it'll go into the gut.
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Some of it will be metabolized by the gut bacteria, but most of it will go into the bloodstream
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and then flow around and then get taken up into your muscle, into your brain and other cells, by transport that's called ENTs.
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And there it's converted into NMN by what are called NRKs. And then you add the phosphate

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and you've got this thing, NMN. What's NMN? Nicotinamide mononucleotide.
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And then the cell puts two of those together to make NAD. - And when we do this in laboratory animals,
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you mentioned in yeast it extends life by 30%. What have we seen in mice,
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which are a little closer to you and I than yeast is? - Yeah, it's going back a number of years ago.
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It was found that NR, when given to mice, extends their lifespan by about 9%.
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But it was given to them late in life at about 700 days, which is a pretty old mouse, that'd be like a 70 year old human, but it still worked.
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But they're also in improvements in health, they had more mitochondria, which is the energy. They had more athleticism, less inflammation.
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And so that was the first real study that said, okay, maybe supplementing with these molecules
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like NR or NMN might have some long-term health benefits as well in humans. - Among the other health benefits
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that have been seen by researchers who have given NR to animals and lab enhanced oxidative metabolism.
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Let's talk about that. - So they burn more fat, they get thinner. And that also means that they're burning more oxygen and that's thought to be really good
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at staving off diabetes, type two diabetes, as well as improving lifespan. - Let's carry this now into the human studies because what we don't have for reasons
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that maybe are obvious, but I'm going to state it any way, which is that humans live a very long life. And it's really hard to put humans
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into a control group and a test group across a very long time, then control for every variable that's possible,
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is longitudinal studies that show increases in lifespan as a result of taking NR.
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But we do have studies that have sought to show similar health benefits
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to what we've seen in rodents. - Somewhat. I would say, NR,
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there've been a few positive results. Not a lot. Before we'd get to that I think
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it's worth talking about why can't we just take vitamin B3, which is a precursor to NR.
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You can but it doesn't raise NAD levels anywhere near the level that NR does. NR doesn't seem to be as effective as NMN.
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So the closer you get to NAD with your molecule, the better it seems. And that's probably because you need
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to bring in other components. So if you just take vitamin B3, you need a sugar and a phosphate. If you just take NR, you need the phosphate.
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Phosphate is pretty rare in the body. It's in your bones, it's in your DNA. And maybe when you take NR one of the issues
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is that you need to find a phosphate head on there before it becomes active. - Okay, back to the human studies on NR.
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We have sought to see, by we I mean the research community,
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I don't mean necessarily you and me, we've sought to see the same sorts of effects
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that have been seen in models, organism studies.
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Sometimes that's happened. Sometimes it's not. Is that fair to say?
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- That's very fair to say. With NR there've been a handful of studies in humans showing that low dose, 250 milligrams per day,
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up to a pretty large dose, a gram a day, does raise NAD levels, but it takes about 9 to 10 days to get to those peak levels.
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What we've also seen is, or others have seen, is lower inflammation as well as some other markers
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such as minor changes in body composition. But these other things which are lower blood sugar,
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improvements in insulin sensitivity, increased mitochondria, those haven't been born out just yet
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in these short term studies with NR. - Sorry, so these are the things that were present
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in the mice who also lived longer. - Right, yeah. Now it could be that you need a longer
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term exposure of these people. These have been fairly short-term studies. Or that humans are not the same as mice.
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- So would you say, I mean, if somebody tells you, oh, David, I've been taking NR for so many times,
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you're not rolling your eyes, but you're not convinced at this point. The jury's still out.
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- Well, it depends what you're asking. If it's to lower inflammation, yeah, it probably works. There's also a study that was put out by a group
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that combined NR with [indistinct], which is a resveratrol-like molecule, We'll talk about resveratrol next,
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that found that in ALS patients, Lou Gehrig's disease, there was an improvement in their daily function.
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So that is somewhat promising. I think that of course we need more studies. That's what we really need here to be able
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to make any sort of conclusion about what the long-term effects of taking this supplement are. - It's fair to say that in the sirtuin

Nicotinamide Mononucleotide

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activated compound research community, there's kind of team NR and then there's team NMN.
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Your lab really focuses on NMN and I think if people were sort of like following
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what you said earlier about how NR turns into NAD,
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they might go, oh, well, NR turns into NMN, NMN turns into NAD, so why don't we just
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take NMN to begin with anyway. And you had mentioned earlier phosphate, and that's an important component of this question.
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- Well, it is. NR is more popular because it's cheaper to make. It doesn't have that phosphate which can be expensive
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to put on the molecule through chemistry. And that's why most people started using NR first in humans and in mouse experiments.
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I didn't have a horse in the race. I didn't care which one. In fact, I'd prefer if both worked according to,
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you know, my theories, but what we found through empirical studies, basically,
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we're looking at which ones work better, my lab and others, including Matt [indistinct], who's at Wash U,
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who treated a mitochondrial disorder and we were treating regular mice on treadmills. We found that NMN just worked better at the same dose.
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We don't actually understand why it could be that this phosphate addition is one of the reasons, but, you know, just based on observations
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in our hands and in others, NMN works better than NR. - When we supplement with NMN,
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when NMN is given to organisms in the lab, what's happening?
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- Well, it's a little different, there's been an argument in the literature that NMN doesn't get into cells. And similarly, NAD is really a big molecule
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because it's got multiple components. And that also has a real struggle to get it into cells.
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Neurons take it up but other cells typically need to break it down into its various components and then re-uptake it.
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And that's important because some people actually are giving themselves NAD through the IV route. When it comes to NMN what happens
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is it was recently discovered by Shin Imai at Wash U, his team discovered that there's a specific transporter
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that takes NMN out of the liquid outside the cells inside the cell and its name is SLC128A.
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Still debated, a lot of things to figure out. But I think it's just best to say, okay,
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we know what's happening when you give it to animals, we are starting to learn what happens to people.
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We of course want to understand how it's working, but the fact that it does work is the most important point.
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- So when it comes to NMN, there's been a number of animals studies showing, for instance, similar to NR, restores NAD levels,
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it enhances insulin sensitivity. One of the things that was surprising to me is that we don't have a study that shows
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NMNs effect across analysis entire lifespan yet. - Well, we have half a life span.
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Shin Imai showed that it actually was pretty good at slowing down the effects of aging,
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but he stopped the experiment because he ran out of NMN. It used to be rare stuff. Now you can buy it.
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But we took up the challenge and we've been doing these studies for the last few years in my lab. Now, preliminarily, these mice have less frailty.
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We've reported that out in the scientific community. They seem to be younger, having better activity,
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better mitochondrial function. They run further. The lifespan looks promising. We've done it once and they do live longer on NMN.
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The doses are out 400mgs per kg. - How much longer? - At this point by recollections,
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about 10 to 15%, but particularly strong in females. - Okay, so not particularly, like, wholly different than what we saw
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in the NR cases with the mice. - Right, a little bit better than that, but certainly those mice are healthier
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and more active and are more youthful. - And you said it was more pronounced in the females,
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or at least according to the first phase of this it's more pronounced in the females. - Right, well we had fewer females
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so we have to repeat that. So we've now got a larger cohort of mice. We're repeating the whole thing. We'll see how it goes.
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But right now with the small number of females, yeah. They did do better than the male. - And even though mice live pretty short lives,
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what we have to understand here is that there's still live two, three years on average. Right, and so in order to see lifespan extension,
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especially if they live much longer, it takes some time to do these studies. - Yeah, it's quite painful actually,
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because you think about this, an average experiment takes three years and then you have to repeat it. So that's now six years.
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Then to analyze the data and publish it is another three or four. That's a decades worth of work for one experiment.
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And, you know, your career only goes for about five of those times. So, five experiments?
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- Well, that's how careers used to go. But we're going to change that, right? - We're going to live a lot longer.
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We run things in parallel as well. That's important. But we can also mimic things, not just in animals,
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but growing tissues in the dish will be the subject of a later episode. - So, so far what I'm hearing is in animals,
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NR and NMN both have some similar effects, right? Lengthening lifespan, restoring mitochondrial activity,
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restoring NAD levels, enhancing insulin sensitivity. But in NR the human studies haven't always
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confirmed that that's the exact same thing that's happening in humans. What are we seeing in the human studies for NMN?
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- I know a fair bit about the effect of NAD boosters in humans because I'm helping a group that is actually
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doing clinical trials at Harvard Medical School and they've been giving a molecule that's similar to NMN to subjects for many years now.
27:00

First of all, importantly, there's been no evidence of any negative side effects. That's important.
27:06
We're about to learn whether it actually does anything that's similar to the mice. We don't have results in yet, but hopefully by 2022,
27:14
we'll actually know if people have more energy, more mitochondrial function, better blood flow, more endurance, which is what we saw in those mice.
27:21
- There's been a little bit less human research on NMN then in NR,
27:26
but we're starting to see just in the last couple of years, especially sort of a flood of studies
27:32
being published, early results, for instance, from Yoshino et al. in 2021 showed increase
27:37
insulin stimulated glucose disposal. We talked about this a little bit when this study came out,
27:45
you were pretty excited about it. Tell me why. - It's one of the real first proofs that NMN does something in humans
27:51
the way it works in mice. So this was a 10 week study. It's well done, it's randomized, placebo controlled.
27:56
It was 250 milligrams, which is a relatively low dose. Remember, I'm taking in my clinical trials,
28:02
a gram and two grams, this is 250 milligrams. Nevertheless, it improved what you said,
28:07
insulin stimulated glucose disposal. That's basically insulin sensitivity. And that's a hallmark of longevity.
28:13
Keeping the glucose out of the bloodstream, keeping it low levels is a hallmark of wellness and ultimately longer life.
28:20
So that's the beginning but we have a lot more to figure out. We need to figure out if that increased endurance that we see in my lab with NMN
28:26
treated mice is true for humans. We also want to note, are organs protected? Other labs, not mine, but other labs have shown that NMN
28:33
protects the organs when they're damaged. Kidney and heart, the two main ones. Even increased wound healing.
28:39
I'd love to know if NMN does that in humans. That'd be a big deal. Kidney injury is huge.
28:44
And particularly, I don't know if you know this, but most surgeries on the heart end up
28:49
damaging the kidneys and there's not much you can do about it. So ultimately we've seen a glimpse with Yoshino et al.
28:56

My studies that I'm involved with at Harvard Medical School are looking promising, we'll know more next year,
29:01
but yeah, there's a lot more in the works. And there are other NAD boosting molecules that have been made that are even better than NMN.
29:09
So-called NCEs called, new chemical entities. And those I'm aware of probably in the next year
29:14
will go into the first human study. - I mean, that can be a whole episode of this podcast in and of itself, yeah.
29:21
- We should do it. - Yeah, okay. Why don't we just give NAD directly?

NAD Intravenous Drips

29:27
We're talking about like NAD boosters. NR creates NMN, NMN creates NAD, that boosts NAD.
29:32
Or NMN boosts NAD, but it all gets us to NAD. So why don't we just, you know, set up the drip line and get it going?
29:42
- Well, we don't, but others do. There's a lot of activity going on in Florida and LA,
29:47
particularly, of having large drips, long drips of over an hour of NAD.
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- These are not in a study settings. This is not in a research setting. This are like people trying this out.
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- Well, they're done under medical supervision, but I haven't yet seen a placebo-controlled trial
30:05
that would tell us for sure if it's just wishful thinking or not. I don't think so given how many people
30:11
have been now treated and there's a serious amount of anecdotal data on this, better mood,
30:17
better energy, but you know, you cannot conclude anything unless you actually have one of these placebo-controlled trials.
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I'd love to be involved if anybody's going to do one, I'd love to help. But I'm asked this probably every day.
30:29
NAD IVs, do they work? My answer has to be we don't know yet. - What do we think they might be doing?
30:35
I mean, what are people trying them for? - Well they're used for various things. It's been used for many years are to treat addiction,
30:41
whether it's drug or alcohol, it's also used for depression, and also increasingly for hangovers.
30:48
- Is it as good as the Australian hangover cure that you've given me a few times? - Oh, the raw egg and the Vegemite?

30:55
I hope it's better than that. - Because the truth is that doesn't work. I just pretend it works because it makes you happy.
31:02
- That's true and you're one of the few people that eat my Vegemite. But the reason that it probably works
31:07
is there's an enzyme that detoxifies alcohol called alcohol dehydrogenase, and a lot of Asians are susceptible
31:14
to high levels of alcohol because they lack a lot of this enzyme. Alcohol dehydrogenase needs NAD.
31:20
And so what's probably happening is when you wake up with a hangover, you lack NAD, your liver is depleted,
31:26
and if you take NMN or NR, you can raise those levels back up, get your liver working again,
31:31
and get rid of the excess alcohol. - So you think chances are that is actually,
31:37
it's not just like a placebo effect. That there's a chance that, like, it makes sense that that would work.
31:43
- I think makes sense is the right words to use, you know, I'm a Harvard professor. I'm not going to say something works
31:48
unless I've seen hardcore proof. And I hope that'll come in the next year or so. - Just so I'm clear on this though,
31:55
'cause it's still a little fuzzy to me. I can understand why we might want to use NAD.
32:03
I'm not understanding why we're not starting, for instance, all the research with NAD and then
32:09
moving backwards to NMN and then moving backwards to NR. - It all started in yeast when I was at Harvard early 2000s.
32:16
Even in yeast if you give them NAD it doesn't work because it's too big, it doesn't get taken up into the cells.
32:22
So what we want to do is back off in size. So the next smaller molecule behind NAD is NMN
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and there we know there's a transporter protein that sucks it into cells and NR is even smaller and it gets taken up even better into cells.
32:36
And so that's the reason why it may be that NMN is at the sweet spot of the right size,
32:42
but also has the right components to make just the right amount of NAD. - It feels like a good time to talk about bioavailability and making things

Bioavailability of NAD Boosters

32:48
available to our body's machinery. How do we make NR and NMN most bioavailable?
32:56
- Just swallowing it is enough in our studies to raise NAD by two to three fold. - So if you buy the, for instance,
33:02
the capsules, they're often sold in capsules, just swallowing. That's going to be? - Or the powder, just drink it.
33:08
We make tablets and give it to the patients that way, the subjects, but there were others, there was a sublingual version.
33:15
I have heard there's evidence that works. I haven't yet seen it. It makes sense that it would be
33:20
absorbed under the tongue, or you can inject it. - In terms of the research right now,
33:27
it doesn't seem like there's a huge advantage one way or another? - No, I haven't seen any reason for saying that you need to put it onto your tongue versus swallow it.
33:34
What I can say for sure is that I've seen so much data on swallowing it that it definitely works to raise NAD levels.

NAD and Cancer

33:40
- There has been some concern around the use of NAD boosters
33:46
when it comes to the potential that it might stimulate cancer growth.
33:52
And obviously that's something that we don't want to be dismissive of. It does you no good to be boosting your NADs
33:58
and extending your lifespan if you're just giving yourself cancer. What's the latest research on that
34:04
and how concerned should people be? - Well, so most of these studies, actually, there's only two main studies have been done in mice.
34:10
So here's what they are. There was one, again, out of Washington University by a different group that found
34:15
that knocking down the levels of NAD in brain tumors slowed the growth of the tumor.
34:20
And unfortunately the news story ended up being, oh, NAD causes cancer, which is not the same, right? That's the complete opposite.
34:27
So that study, I wouldn't put a lot of stock into, but there is one other study that came out in 2019
34:32

by [indistinct] and they found that NAMPT, this NAD boosting gene,
34:38
it increases the number of senescent cells and makes them more inflammatory, giving out these SAS proteins as they're called,
34:45
the senescence associated secretory phenotype is the word, but also there were mice that were predisposed
34:51
to pancreatic cancer and when given NMN they developed more precancerous and cancerous growths
34:57
when they consumed this NMN. Exactly how it works we're not sure, but it might be because it was down-regulating
35:04
a tumor suppressor gene called P53. - And this was a subgroup of mice that were already predisposed.
35:09
They had a gene that made them more likely to get cancer. - Right, but remember we fed NMN to mice,
35:14
but normal mice, not predisposed, and if anything they lived longer and healthier. So it's a question whether it's this
35:20
predisposition that's the difference. - Something to watch for and to think about and to work into anyone's calculations
35:27
if they're going to be considering an NAD booster in any case. - For sure and another reason to consult your physician.

Resveratrol

35:33
- Absolutely. Okay. Now there are other NAD boosters,
35:39
sirtuin inactivating compounds. One of the ones that you've been really interested in that I think a lot of people are interested
35:46
in, probably really widely used, is resveratrol. You started working with resveratrol
35:54
back when you were trying to understand sirtuin inactivation in yeast.
35:59
- Right. I was just a kid. I was in my early thirties and I'd just come out of MIT with Lenny Guarente where
36:05
we'd found that up-regulating the sirtuin gene in yeast extends their lifespan.
36:10
But of course we can't up-regulate genes easily in our body. We're not going to genetically modify ourselves anytime soon.
36:16
- Not anytime soon. - We can but we're not going to. IT's easier to find a safe, natural molecule that does the same thing.
36:24

And so our goal back in the early 2000s at Harvard was to look for any molecule that we could find
36:30
that was safe that would activate the protein, not the gene, but the protein, it's an enzyme that controls other proteins, remember.
36:37
And so he set up an essay that looks for what's called Sirt-1 activation. Sirt-1 is the first out of seven of them in the body,
36:45
and Conrad Howards, my collaborator, and I were using an essay in a test tube that would fluoresce when you had more activity.
36:54
And so we added these chemicals, we added a dozen. Then we added thousands and eventually tens of thousands
37:00
to Sirt-1 and found which ones raised the level of fluorescence.
37:05
- And you've found a bunch of them. There were like 20 of them that did. - We published 20. Yeah, in Nature 2003. The one that was the best at the time,
37:11
which activated 13 fold Sirt-1 activity was resveratrol. And there were others, of course, [indistinct],
37:18
which are actually now used by others for longevity. But resveratrol got most of the attention
37:23
because it's found in red wine. - And you've told me this a bunch of times, red wine stock went out the roof, right?
37:29
Like people started buying red wine like crazy. - 30% Sales, and they've stayed up ever since. And I've started drinking more red wine as a result as well.
37:37
- The truth is though, how much red wine would you actually need to drink in order to increase your levels of resveratrol
37:46
and get an actual effect out of this? - You know, you can't drink enough red wine to get the kind of doses that are efficacious.
37:51
- You can't. - Well you can try, but I don't recommend it. You'd need hundreds of glasses of red wine a day,
37:57
which I don't recommend. Even if your doctor says so, not recommended. - That's not going to extend your life.
38:04
- Probably not, no. But what you can do is you can purify it out of grapevines or polygonum cuspidatum,
38:11
which is an herb, a plant mostly grown in Asia. - When you say that, can you just take your pen?
38:16
All right, now say that word again and go like this when you do it. - Polygonum cuspidatum.
38:22

- Okay. Thank you. I appreciate that. - This is magic I think. Harry Potter? - How much resveratrol do we actually need to see an effect?
38:29
- There are a lot of human studies now. The minimum that I've seen is 250 milligrams a day.
38:34
And some people take 1000 or 2000 milligrams a day. - This is a Sirt activator like the other
38:41
NAD boosters we've been talking about, works a little bit differently, but like you said,
38:47
really well studied and for almost 20 years now. What's happening when we put resveratrol,
38:53
let's start with the animal studies. What do we know? - Well, we know, first of all,
38:58
if you just give it to them in their water supply, it's not going to work. You can't just swallow it and expect it to get in easily.
39:03
- Why not? - Well, resveratrol is the equivalent of brick dust, it's really insoluble. If you put it in a glass of water
39:09
it will fall to the bottom. So what you need to do is we found in both mice and humans, mix it with some food.
39:15
You can use yogurt, you can use that kind of olive oil, that kind of oily food, and it will dissolve. It's hydrophobic. This is the problem, it's scared of water.
39:23
- And this is actually why you suggested that maybe some resveratrol studies that have shown that it doesn't work
39:30
as well as other studies show, those studies may have involved people who were feeding mice resveratrol
39:37
without that additional fat. - Yeah, that's the case.
39:43
Some of these studies didn't include food. We found that early on in the mid-2000s that if we gave it with a meal,
39:49
the levels in the blood went way up. - There have been a number of animal studies
39:55
on resveratrol going back almost 20 years. Now we're seeing extended replicative lifespan in yeast.
40:04
We're seeing activation of AMPK in rodents.
40:10
What are these things telling you? - Well, they're similar to what we expected from the sirtuins.
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They defend the body. They raise the metabolic rate. They protect against free radicals.
40:23
And when we see research given to these rodents, what the biggest surprise was was that they were protected
40:29

against a high-fat so-called Western diet. Those mice on resveratrol, even though they were really obese
40:36
on this really chunky meal, they lived as long as the lean mice that we had as the control group.
40:42
And that was really, as far as I know, the first study of any that showed that you could mimic caloric restriction with a molecule and be fat
40:49
but live as healthy as a lean animal. - Have those findings translated over
40:55
as we've moved resveratrol into human studies? - Yeah, somewhat.
41:00
Not all studies have worked, but there are a number of them that have. And for instance, resveratrol has been shown
41:06
to reduce fasting glucose and significantly increase insulin sensitivity. This was a study in 2019, and then again, in 2020,
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Battista and George et al. showed that a randomized control study of 25 individuals
41:21
ranging from 30 to 60 year olds with a slightly high BMI of 30 were able to lower their cholesterol levels,
41:29
their urea levels, which is important for kidney function, as well as raise their good cholesterol, the HDL.
41:36
- Well, once again, we don't know long-term what this is going to do but the trajectory seems good when we consider it
41:44
in the context of what we've seen in animals and what we are seeing in these early human studies.
41:49
- Yeah I think so. Even before I worked on resveratrol, it was known to be an agent that suppressed cancer.
41:57
If you put a carcinogen on the skin of mice and then rub resveratrol on it, a 1999 science paper showed that those cancers
42:04
are much smaller in those treated mice. So the anticancer activity of resveratrol
42:10
has been known before I came along. And since then we've seen effects on body composition, on metabolic rate,
42:16
mitochondrial boosting, glucose levels. The list goes on, there's probably 1000 papers now
42:22
showing at least the benefits in animals and a dozen in humans. Cardiovascular disease I haven't mentioned,

Red Wine and The French Paradox

42:28
but that's a big one. May help explain the French paradox. The French can eat high-fat foods
42:33
and with this glass or two of red wine every day, it helps mitigate the effects. - I mean like, but what you've just said,
42:39
like you actually have to drink so much red wine in order to get this effect, but then we're thinking maybe the French
42:44
who don't drink that much red wine, even though they do drink a lot of red wine, but they don't drink that much red wine.
42:50
- There's two considerations here. One is that drinking red wine over 30 years
42:55
could have a cumulative effect and a buildup in the body. And the second is that red wine
43:00
has more than resveratrol and it has some of these other xenohermetic polyphenols that we talked about in earlier episodes
43:06
that could give a combination effect. - Okay. The two other molecules I wanted to mention, you mentioned them earlier actually by name,

Fisetin and Quercetin

43:13
these were part of the group molecules that were identified in those early experiments
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with the yeast that identified resveratrol as a potential sirtuin activating compound,
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these are fisetin and quercetin. And both in addition to being serotonin activators
43:33
potentially also seemed to have this other property to them that is making them sort of like a hot number now.
43:39
- Right, they are what are called senolytic. Kill senescent cells. - Senescent cells.
43:45
- Are zombie-like cells. The ones that accumulate over time in your body probably because their epigenome gets screwed up.
43:52
But what they do is they shut down, they stop dividing and they start secreting inflammatory factors and also factors that cause cancer.
43:59
- Yeah, and so getting rid of those would be presumably a good thing. And that's what fisetin and quercetin appear to do.
44:07
- They do in the dish and in mice and there even some human studies now that show that killing off these senescent cells

44:14
in the body can improve health. And ultimately, we think, could extend lifespan. - And these have been shown,
44:19
in the case of fisetin at least, to extend lifespans in some model organisms.
44:25
- Like fruit flies? - Yeah. - And even in mice recently. I was particularly impressed by the mouse studies.
44:31
Couple of colleagues out at the University of Minnesota were able to show that fisetin put in either in the food of the mouse when it's young
44:39
or even late in life after 700 days, which is like a 75 year old human, was able to extend lifespan quite dramatically,
44:46
up to 30%, including improving their health. And that's extensively because both
44:52
it's removing those senescent cells and activating the Sirt-1 defenses. - And there's been human studies in both of these as well.
45:00
I know we kind of talk about these in a group because they were discovered as sirtuin activators and now they're being seen also as potential senolytics
45:07
but maybe we can differentiate a little. - Well, a lot more is known about quercetin.
45:14
That was discovered first as a senolytic by Jim Kirkland at the Mayo Clinic who combined it with a drug called dasatinib
45:20
and together those two molecules are potent killers of senescent cells. And those have been put into mice and into humans
45:26
where they are showing really remarkable effects in treating age-related diseases.
45:31
- And we've had some randomized controlled trials with humans and quercetin. The effects are? - Reduces liver steatosis, or fatty liver,
45:40
as well as other effects like inflammation in the body. You can actually see that the number
45:46
of senescent cells in the body goes away when you treat with quercetin and dasatinib. - Dasatinib is a drug that's used to treat leukemia.
45:54
It's got a lot of promise as a senolytic too, it seems. As of right now you can really only
46:00
get it for treatment for leukemia. - That's right. You can only get it if you're part of a clinical trial,
46:06
you can't just go buy it on the internet. It's a regulated drug as well as another drug that's senolytic which is called [indistinct].
46:13

These are being tested. They're not ready for prime time at all. But fisetin is the interesting one. That one is a plant molecule, it's found in grapes.
46:20
It's found in apples. Relatively high levels in strawberries. You can now buy that relatively cheaply on the internet.
46:27
- So if people are like, man, I really like want to get into senolytics, the gateway right now,
46:33
the most accessible place for people is fisetin. - Well, it is, but it's early days. There's not a lot of data compared to,
46:39
quercetin and dasatinib. Really we know that it reduces inflammation.
46:45
That's about it in humans. I think we still have to wait to see whether it's really truly safe before people rush out and try this.
46:52
I'm excited about this affirm light study by Jim Kirkland with fisetin. He's got a number of patients are on 20 milligrams
46:59
per kilogram of body weight and this, over the next year or so, should tell us whether fisetin is truly a senolytic
47:07
in humans and can have some health benefits too. - Okay, so there's a third class

Rapamycin and Rapalogs

47:12
of drugs we want to talk about today. We're not going to spend too much time with them because, broadly speaking,
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they're not available for purchase or even prescription right now, except for very, very narrow instances.
47:24
I'm talking about rapamycin and these drugs, rapalogs, drugs are supposed to mimic
47:31
the effects of rapamycin perhaps without all the toxicity. These drugs have a really interesting history.
47:38
- Well, they do, these are drugs that inhibit mTOR, which is mimicking fasting. They were discovered a number of years ago on Easter Island.
47:46
Rapanui, which is why it's called rapamycin. On the back of a statue, I believe, somebody found.
47:51
- [Matthew] Yeah, there's like the mold and they are some fungus and they scraped it off and lo and behold,
47:57
we have a drug that actually has been used for other purposes. - Immune suppression. - Yeah. - Cancer.
48:03
- Like, really, I mean, this is a life saving drug. We just don't know yet if it's a life extending drug
48:09

that's going to be useful in humans. - I'd put good money on it. The reason is that it's extended the life span of every organism it's been given to in low doses,
48:15
not immune suppressing doses. In humans it's considered around 10 milligrams per week,
48:21
but you definitely don't want to suppress your immune system. But even from yeast to worms to flies and mice,
48:27
if you give it late in life it still extends lifespan. It's really quite potent.
48:33
The only downside is that it could be toxic. So you have to be extremely careful and right now it's not available.
48:38
- And rapamycin works by inhibiting mTOR. - Yeah, actually, TOR stands for Target Of Rapamycin.
48:45
So that's how mTOR was discovered. And when you give animals rapamycin, you're mimicking low protein intake.
48:53
- You're mimicking this adversity that we've been talking about throughout this entire series. - Right, so your body says, oh my goodness,
48:59
I'm running out of protein. I need to scavenge protein from within. And so the body starts recycling old proteins
49:06
in this process we talked about earlier called autophagy. - And that brings us to another drug, spermidine,

Spermidine

49:16
which is also working on this autophagy process.
49:22
- It does. So, spermidine is more recent. You've only recently been able to get it on the internet. It has an interesting history.
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Anton van Leeuwenhoek, the inventor, basically, of microscopy, was looking at his sperm.
49:33
No one believed him that there were these swimming things down there, but he started to get crystals in the sperm,
49:38
and that was spermidine, hence the name. - Kids, if you want to get into science. And what do we know about spermidine now?
49:48
Because this is really old. I mean, this has got an old history, but like really new research that's showing potentially extensions of lifespan.
49:56
Well, we know it extends lifespan of yeast and flies and worms. - And even mice. - And mice.
50:02

- There's a new study that was really compelling. If you give spermidine to mice, either when they're young or even late in life,
50:08
they live longer and they have better heart function or other youthful capacities. There are two ways that spermidine
50:14
is known to work in mammalian cells. One is it stimulates autophagy, just like rapamycin does in the mTOR pathway.
50:21
There's another really interesting property that seems to be true which is it also stabilizes changes to the epigenome, which as you know,
50:29
is one of the major causes of aging. - There have been a number of human studies on spermidine, particularly revolving around enhancing memory
50:38
and dealing with memory loss in older Americans. - That's true. We don't know a lot about aging itself
50:43
but cognition has greatly improved in a number of studies. The one that stands out for me is the one by Schwartz et al., 2018.
50:50
They were giving people 1.2 grams per day over three months and there was significant enhancement of memory.
50:55
- I want to go back to the history of this stuff. You mentioned earlier the Antony van Leeuwenhoek
51:01
discovered the crystalline structures that led us to spermidine by examining his own sperm,
51:07
presumably his own sperm, in a microscope. Is that still where we're getting spermidine?
51:15
- No, not that I know of. - Where are we getting it from? - We're getting it from wheat germ. It's a lot easier. It's much more abundant.
51:22
You can also find it in soy products. - That makes me feel better about it. All right. We've talked about sirtuin activators.

Metformin

51:30
We've talked about mTOR inhibitors, but really one of the most exciting classes of drugs
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is also sort of actually kind of the most boring because it's been around for so very long,
51:45
an AMPK activator called metformin,
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which hundreds of millions of people around the world already take for diabetes.
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- Yeah, it's been used since the 1950s as the frontline medicine to bring down glucose levels in type two diabetics.
52:02

And it is relatively safe as a drug goes. Half the world it's available over counter at pharmacies.
52:07
Here in the US and in Europe, and UK, Australia, you need a prescription. - And we know that Metformin works by activating AMPK.
52:16
Do we know how that process kind of unveils itself? - Well, there are a lot of theories
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and it's been debated for over 50 years. One thought is that the microbiome changes, but a leading school of thought that most scientists agree
52:29
on is that it activates a protein complex called complex one which is involved
52:35
in making energy in mitochondria. And what it does is it lowers the amount of energy that the cell has in the form of ATP,
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this chemical that we use for energy. And then you get mitohormesis, mitochondrial hormesis, what doesn't kill the cell makes it stronger.
52:48
And the reaction is two fold. One is to make more mitochondria, so you get more energy a few days later,
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but also by inhibiting mTOR it'll improve what's called insulin signaling so that the blood sugar
53:01
that's in your blood, and if you're a type two diabetic, it's too high, it gets sucked out of the bloodstream and utilized,
53:08
which is why it's used to treat type two diabetes. - And this is another one of those cases where there
53:13
is a perceived diversity and then not just one of these pathways but multiple
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pathways in this case are impacted. - Yeah, similarly to all of these factors
53:23
which are talking to each other, this is a good example. Metformin will lower energy, inhibit mTOR. It will activate AMPK, obviously,
53:30
we talked about that's what it's mainly doing, but it also raises NAD levels, which as we all know will activate the sirtuin.
53:38
So Metformin is a remarkable molecule, comes from the plant world, is very simple.
53:44
The French hellebore or lilac plant produces what's called guanidines,
53:49
and these have been known to treat diabetes for many years, in fact, over a century, and then chemists have put methyls on them,
53:56
chemically modified it so that it's more stable. And we call this Metformin and that's what we have as the drug today.
54:01
- And we've given this drug to animals. In worms it's extended lifespans, 30 to 40 days,

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which is no small amount of extension for a worm. - Yeah I was involved in the mouse study
54:15
with Rafael de Cabo down at the NIH and we found that the mice were healthier and longer lived on Metformin.
54:21
- And what are the other things, 'cause again, what we want to look for if we want to know if Metformin is working in humans
54:27
like it works in animals, you know, we're not necessarily just going to look at the lifespan extension 'cause that takes a long time.
54:33
What are sort of the intermediary things that we're seeing with Metformin? - In humans, you mean? - Well in animals and that we can look for in humans?
54:41
- Well, the main one of course is glucose lowering, but we also see more energy, more mitochondria, less inflammation, and muscle switching.
54:48
We haven't talked much about muscle type switching, but muscles, as you get older, become more glycolytic.
54:53
They start to use more anaerobic mechanisms and you can see that switch back when you give them Metformin.
54:59
Like they're more like an athlete. - And we're seeing all of these things in animals and also in humans.
55:05
- Right, and this is where we can speak to a lot of data. Because millions of people have taken Metformin.
55:11
And one of the most interesting things about it is you can do a retrospective study of tens of thousands of elderly people
55:18
on Metformin and ask, okay, their type two diabetes may be reduced and slowed down,
55:23
but what about other diseases that they're susceptible to? Cancer, heart disease, Alzheimer's, frailty. And the answer that's quite remarkable
55:30
is that Metformin lowers the risk of all those other diseases. - So when we control for everything else
55:36
what we see is that the people who were on Metformin are living longer. - Than people who don't have type two diabetes.
55:43
It's a remarkable fact. - So now the question becomes, okay, take the type two diabetes part of the equation out,
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will we still see an effect? And that is something that's being investigated in this really large study that's underway. The tame study.
55:59

- Yeah, you're right. The targeting of aging by Metformin study run by [indistinct] down at Albert Einstein College of Medicine,
56:05
this is a very large study over many different institutes and hospitals. It's costing tens of millions of dollars.
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It's taken a while to raise that money. But ultimately the goal is to show to the American FDA
56:17
that you can target aging with a drug and slow it down. The ultimate goal being having aging
56:22
a treatable medical condition. - Why is it taking so long to raise money for this? Because this is really, I mean,
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everybody I know in the aging space is excited about this and yet the money's hard to come by because?
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- Well, this is where capitalism has a little bit of a downside, which is that Metformin is very cheap.
56:41
It costs a few cents and it's off patent. - Which means anybody can make it. There's no profit motive for making this drug right now.
56:50
- Right, so [indistinct] has relied on the government and they've given half the money and the rest of the half
56:55
he's relying on donors and he's still raising that money, but he's getting started. Fortunately he's off to the races and we should know in the next few years
57:01
if he's seeing signs of slowing aging and he's looking at a number of things, not just diseases, but also things like stability, ability to walk,
57:11
strength, these kinds of things, mental acuity, these are things that would indicate that aging itself is being slowed down.
57:17
And he's even now able to measure the human biological clock with accuracy. And that should also be slowed down
57:22
if this is truly an anti-aging medicine. - We're seeing a lot of doctors get a lot more comfortable
57:29
with the idea of prescribing Metformin off-label. Just a few years ago, you know,
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the constraints of what Metformin was actually approved for was keeping it out of the hands of a lot of people
57:41
who thought that it might be good for them in their efforts to slow their aging. There's starting to be a little bit of a shift there.
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- Well, yeah, I'm seeing a lot more people taking Metformin with the approval of their physician.
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And part of it is education. Typically when a doctor sees the evidence

57:59
and there's extensive literature, and sometimes it's the patient takes the information to the doctor or our book.
58:06
The doctor in most cases is convinced that this is worth the risk. Now, it's not risk-free.
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We should mention that Metformin has some downsides. One is that it can cause lactic acidosis,
58:16
which is quite a severe condition. It can be fatal. You have to be very careful there,
58:21
but most people are fine on Metformin. The biggest thing that happens to them is that they have an upset stomach, lack of hunger,
58:29
which can actually be a good thing if you want to lose weight as well. - But doctors now are saying, okay,
58:36
they're advising their patients as to these potential side effects and also saying, yeah,
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either because that doctor is sold on the idea that there's a potential aging benefit here,
58:50
or anti-aging benefit here, or one of the other things you and I have talked about before is doctors are increasingly getting sick
58:58
of waiting until patients are full-blown sick to prescribe the medications and they're prescribing it to pre-diabetic people and pre,
59:05
what we might call pre-pre-diabetic people. - Well, there's a shift in medicine and the way doctors are looking at their patients.
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More and more doctors are saying, okay, let's not wait until the patient is so sick that we have to treat them. Let's get ahead of that.
59:17
And let's start treating them earlier. - The one other thing that people should talk to the doctors about if they're considering trying to get on Metformin
59:26
is the concerns about the connection between Metformin and muscle loss.
59:34
- Right, particularly in the elderly this is an issue, but actually if you look at the data and there's been a couple of human studies,
59:40
Metformin doesn't make a big difference to muscle size. It probably makes a difference if you're trying to win Mr. Universe.
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But other than that the difference is really slight. If you look at the graphs it's only a 5% difference, and actually 5% difference,
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I'll give up 5% body size for longevity any day. But the other important thing is that those muscles
59:59

on Metformin were just as strong as the others and had less inflammation. So there's other benefits to that.
1:00:05
What some people are doing just in an abundance of caution is taking Metformin on days that they don't exercise. And if you're wondering, why does it affect exercise?
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Well, really it's pretty obvious. It reduces the body's ability to make energy. And so you don't feel as strong on the days
1:00:19
that you take Metformin so you do less reps, fewer reps. And so what you could really do is just put a little bit of extra effort in and probably make up that 5% difference.

Berberine

1:00:27
- If people are interested in the effects of Metformin, but are not able to work with a doctor
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to get a prescription for it, or if they've tried out Metformin and it just doesn't sit well with them,
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which is the case with about 20% of people, there's another alternative that works on some of the same pathways activating AMPK.
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That's berberine. - That's right. This is a molecule from the plant world bark and roots.
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You can find it's a yellow substance. Again, it's fairly insoluble. So if you want to take it, take it with some food.
1:00:58
Yogurt, olive oil, all this kind of stuff, but it's been remarkable what's been found in animals. And even in people that it can mimic
1:01:05
the effects of Metformin. Specifically what it does, is it, again, it binds to this complex one and reduces
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chemical energy in the body. And in reaction this mitohormesis is to amplify up mitochondria and make the body
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more sensitive to insulin and lower the blood glucose. We've seen this in my lab in mice and human studies
1:01:22
have actually validated this as well. The doses are high, one to two grams per day,
1:01:28
but it does seem to work. - And when you say it does seem to work, you mean not just showing, you know,
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the activation of AMPK and increased mitochondrial energy, but we actually in mice have seen increases,
1:01:41
pretty substantial increases, in lifespan. - Actually, it's really interesting. In mice berberine will extend the lifespan
1:01:47

of mice treated with chemotherapy and have a pretty big lifespan extension of normally aged mice. That's also true in fruit flies.
1:01:55
So it seems to be a common mechanism that you lower the energy in an animal and it responds by living longer.
1:02:01
- And I think you said you got to take quite a bit of this stuff, though. - Yeah, the clinical studies, it's at least a gram,
1:02:06
there's one that worked with two grams, but it does seem to work just like Metformin in improving the body's sensitivity
1:02:12
to insulin and lowering the blood glucose levels, which is a good sign that it's going to have future health benefits.
1:02:18
- Any concerns about side effects with berberine? - I'm unaware of any downside of berberine.
1:02:23
- We should say berberine does have some of the similar side effects of Metformin. We don't know in different groups of people
1:02:28
might be different, but you're looking at diarrhea, constipation, gas, potentially upset stomach.
1:02:33
- Right. Yeah, no molecule's perfect. But this one's really interesting because it's a natural and commonly available one that you can try at home.
1:02:41
Of course, talk to your doctor first though. - All right. Well, that kind of brings us to try at home.

Dr. Sinclair’s Protocol for Longevity Molecules

1:02:47
And again, with the caveat that we're not telling anybody what to do, we're not giving them medical advice. You're not a doctor.
1:02:55
I know you have been really open about what you do. That has changed over the years,
1:03:03
but let's just sort of take it through the things that you started doing, you know, 20 years ago, 10 years ago,
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five years ago, just start from sort of a chronology. When you started investigating resveratrol,
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you also started taking resveratrol. How did you know how much to take though?
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Because you were giving resveratrol to yeast and eventually to mice. - It's not a one-to-one,
1:03:28
it's not like you should take 3000 times as much as the mouse had. - If you were 3000 times bigger than the mouse is.
1:03:34
- Right, it's not just proportional. It's actually more related to our surface area and how much the drug can get into

1:03:39
our bodies versus the mouse and the calculation for a mouse, which is called the allometric scaling, is about 12.
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So you multiply it, let's say, if the mouse has 100 milligrams, 1.2 grams for a human.
1:03:50
For a rat it's 3, for a mini pig it's 1 to 1. Turns out we have about the same
1:03:55
surface area as a mini pig. - And so you take about a gram of resveratrol every day.
1:04:01
- I do and I've been taking that since about 2004. But like I said, you can't just
1:04:07
put it in water and drink it. - You have to add some fat to it. - Yeah, so I typically have some yogurt,
1:04:13
a couple of spoonfuls, not a lot because I'm trying to fast until dinner, but I could mix it with olive oil. Olive oil, recently, as we mentioned
1:04:18
earlier in a previous episode, seems to be really good for activating sirtuins, but also you can dissolve resveratrol in it.
1:04:24
- So you get a twofer. - You do. I don't have a lot of it. There's a lot of calories in olive oil. I don't want to break the fast severely, but you know,
1:04:30
mix it with bit of vinegar and basil leaves and it doesn't taste too bad. - Okay, so resveratrol,
1:04:37
you're taking about a gram a day in the morning, Also in the morning you take NMN.
1:04:43
- I do, and there you don't have to worry about food. It's dissolved easily. You can put it in water or swallow it, put it under your tongue. And so I do that.
1:04:50
That's my main combo in the morning. - How much NMN are you taking? - Again, it's a gram, but that's not a guess.
1:04:55
That's actually based on the human studies that we've done that show that a gram over 10 days raises your NAD levels about two-fold.
1:05:02
- And that's sort of the dosing amount that we're seeing in a lot of the human studies now. Both the past studies and the current studies.
1:05:09
- I take one gram of NMN every morning along with my resveratrol. The reason is in humans we know that
1:05:15
that doubles NAD levels which is important because someone my age has half the levels of NAD than I did when I was 20.
1:05:21
But you can go as high as two grams and triple the amount. It's important to mention that I take these
1:05:27
at a certain time of day based on science as well. I take these in the morning because that's when the natural rise in NAD and Sirt-1 activity should happen.

1:05:35
And we actually know this, that the Sirt-1 NAD cycle is part of our body's natural 24-hour clock.
1:05:41
Sirt-1 regulates a protein called BML that controls the genes that tell us whether it's night or day, should we be hungry or not?
1:05:47
Whether we have jet lag or not. And I do find anecdotally that NMN is remarkably good at preventing jet lag as well.
1:05:56
I can reset my body's clock ostensibly through the Sirt-1 BML pathway. - You're also taking Metformin.
1:06:02
- Yes. - How much? When? - I take 800 milligrams at night. - Okay, and you take that at night because?
1:06:09
- Well, because doctors tell me that it's a good time simulate a fast. I take it with my dinner, just after.
1:06:16
And then through the night, I'm presumably having low levels of glucose and my body has all the benefits
1:06:22
of stimulating those repair pathways, those survival genes. - And that's the most recent thing that you've added to your regimen?
1:06:28
- It is. Actually what happened was I had terrible blood biochemistry. I was eating badly, I gained weight.
1:06:34
I wasn't sleeping. I was stressed. And those numbers just went through the roof. And I said, I got to do something. So I went on NMN and things were somewhat rectified.
1:06:42
And then I added Metformin and they really got back to my optimal. - We mentioned earlier some concerns about exercise,
1:06:51
Metformin, your practices, where that's concerned? - Yeah, I pause Metformin.
1:06:57
It doesn't sit well in my stomach anyway. So on days where I know next day I'm going to exercise and lift weights,
1:07:02
I might skip Metformin that night before. - And then there's also spermidine.
1:07:07
- There is. You can buy it now. There's a company that makes it in pure from very low levels of gluten.
1:07:13
And just the last few months I've added that to my protocol and we'll have to see how my numbers look on Inside Tracker.
1:07:19
- Okay, so that's not something you've adopted and you're like, I'm definitely taken with it. This is I'm adopted and I'm testing
1:07:25
it out to see how it works. - I am. And actually, I advise that company. The first supplement company I am advising
1:07:30

and I did that because I wanted to look at the human clinical trials and they look really promising as well.
1:07:36
- How much of that are you taking? - A gram as well. - [Matthew] Okay. You are also periodically taking fisetin,
1:07:44
quercetin, aimed at senescent cells. - There are clinical trials being run out of the Mayo Clinic
1:07:52
for fisetin and for quercetin. These are high doses. They're typically two grams taken one day a week for a matter of months,
1:07:59
Myself, I'm on a maintenance dose. I take about half a gram of each every day.
1:08:04
- Let's take this morning through night just really quickly. Resveratrol, one gram. - In the morning with yogurt or olive oil.
1:08:10
- NMN as well. - A gram, yep. - Fisetin and quercetin. - Half a gram in the yogurt.
1:08:16
- Spermidine. - Definitely spermidine in the morning, about a gram. - And then in the evenings,
1:08:21
if you're not working out the next day, Metformin. How much? - 800 milligrams. - Okay. - That's it. - That's it.
1:08:28
Now, you're not most people. A lot of other people are going to be different. You don't advise people,
1:08:34
but it might be a good place for people to start their conversation with their doctor though, yeah?
1:08:39
- Well, I think so. Most doctors are open to looking at, say, Inside Tracker data and hearing about the latest science.
1:08:47
It's very difficult for them to keep up with it. It's one of the reasons we're doing this podcast in the first place. - So David, this has been a really

Wrap-up and Next Week’s Episode: Interventions on the Cutting Edge

1:08:53
comprehensive conversation. Even still we could have gone deeper on any one of these drugs or supplements.
1:09:00
Maybe we'll do that in future episodes, in a future season of Lifespan podcast.
1:09:06
But what we're trying to do today is really give people an opportunity
1:09:11
to really start thinking about whether this might be something that they want to bring into their lives.
1:09:17
And if so, how, of course, again, in consultation with their physician.
1:09:24

- And monitoring, this is important. You don't know if you're doing good or harm to your body unless you measure it, particularly your liver.
1:09:30
You can measure what's called ASTALT. I do that routinely just to make sure nothing's going wrong in that regard.
1:09:36
- Our next episode is? - Things that are not supplements things. Maybe you could regard them as being on more
1:09:42
on the cutting edge, things like testosterone, growth hormone, exosomes, peptides. We're going to dive deep into those as well.
1:09:48
- All right. - Sounds like fun? - Yeah. - Let's do it. If you're enjoying this podcast and would like to support us, please subscribe on YouTube,

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