

Dr. David Sinclair: The Biology of Slowing & Reversing Aging | Huberman Lab Podcast #52

In this episode, I am joined by Dr. David Sinclair, tenured Professor of Genetics at Harvard Medical School and an expert researcher in the field of longevity. Dr. Sinclair is also the author of the book *Lifespan: Why We Age & Why We Don't Have To*, and the host of the Lifespan Podcast, which launches January 5, 2022.

In this interview, we discuss the cellular and molecular mechanisms of aging and what we all can do to slow or reverse the aging process. We discuss fasting and supplementation with resveratrol, NAD, metformin, and NMN. We also discuss the use of caffeine, exercise, cold exposure, and why excessive iron load is bad for us. We discuss food choices for offsetting aging and promoting autophagy (clearance of dead cells). And we discuss the key blood markers everyone should monitor to determine your biological versus chronological age. We also discuss the future of longevity research and technology. This episode includes lots of basic science and specific, actionable protocols, right down to the details of what to do and when. By the end, you will have in-depth knowledge of the biology of aging and how to offset it.

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Timestamps:

00:00:00 Dr. David Sinclair, Harvard Medical School

00:03:30 ROKA, InsideTracker, Magic Spoon

00:07:45 "Aging as a Disease" vs. Longevity & Anti-Aging

00:10:23 What Causes Aging? The Epigenome

00:15:53 Cosmetic Aging

00:17:15 Development Never Stops, Horvath Clock

00:20:12 Puberty Rate as a Determinant of Aging Rate

00:23:00 Fasting, Hunger & Food Choices

00:32:44 Fasting Schedules, Long Fasts, (Macro)Autophagy

00:34:50 Caffeine, Electrolytes

00:35:56 Blood Glucose & the Sirtuins; mTOR

00:37:55 Amino Acids: Leucine, "Pulsing"

00:44:35 Metformin, Berberine

00:50:29 Resveratrol, Wine

00:53:20 What Breaks a Fast?

00:56:45 Resveratrol, NAD, NMN, NR; Dosage, Timing

01:09:10 Are Artificial Sweeteners Bad for Us?

01:12:04 Iron Load & Aging

01:15:05 Blood Work Analysis

01:19:37 C-Reactive Protein, Cholesterol: Serum & Dietary

01:26:02 Amino Acids, Plants, Antioxidants

01:33:45 Behaviors That Extend Lifespan, Testosterone, Estrogen

01:40:35 Neuroplasticity & Neural Repair

01:46:19 Ice Baths, Cold Showers, "Metabolic Winter"

01:48:07 Obesity & How It Accelerates Aging, GnRH

01:52:10 Methylation, Methylene Blue, Cigarettes

01:56:17 X-Rays

01:59:00 Public Science Education, Personal Health

02:05:40 The Sinclair Test You Can Take: www.doctorsinclair.com

02:08:13 Zero-Cost Support & Resources, Sponsors, Patreon, Supplements, Instagram

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- Welcome to the Huberman Lab Podcast, where we discuss science and science-based tools for everyday life. I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today, my guest is Dr. David Sinclair, professor of genetics at Harvard Medical School and co-director of the Paul F. Glenn Center for the Biology of Aging. Dr. Sinclair's work is focused on why we age and how to slow or reverse the effects of aging by focusing on the cellular and molecular pathways that exist in all cells of the body and that progress those cells over time from young cells to old cells. By elucidating the biology of cellular maturation and aging, Dr. Sinclair's group has figured out intervention points by which any of us indeed, all of us, can slow or reverse the effects of aging. What is unique about his work is that it focuses on behavioral interventions, nutritional interventions, as well as supplementation and prescription drug interventions that can help us all age more slowly and reverse the effects of aging in all tissues of the body. Dr. Sinclair holds a unique and revolutionary view of the aging process, which is that aging is not the normal and natural consequence that we all will suffer. But rather that aging is a disease that can be slowed or halted. Dr.

Sinclair continually publishes original research articles in the most prestigious and competitive scientific journals. In addition to that, he's published a popular book that was a New York Times bestseller. The title of that book, is 'Lifespan: Why We Age And Why We Don't Have To.' He is also very active in public facing efforts to educate people on the biology of aging and slowing the aging process. Dr. Sinclair, and I share a mutual interest and excitement in public education about science. And so I'm thrilled to share with you that we've partnered. And Dr. David Sinclair is going to be launching the lifespan podcast, which is all about the biology of aging and tools to intervene in the aging process. That podcast will launch Wednesday, January 5th. You can find it at the link in the show notes to this episode today as well. You can subscribe to that podcast on YouTube, Apple, or Spotify, or anywhere that you get your podcasts. Again, the lifespan podcast featuring Dr. David Sinclair, Claire begins Wednesday, January 5th, 2022, be sure to check it out. You're going to learn a tremendous amount of information, and you're going to learn both the mechanistic science behind aging, the mechanistic science behind reversing the aging process and practical tools that you can apply in your everyday life. In today's episode, Dr. Sinclair and I talk about the biology of aging and tools to intervene in that process. And so you might view today's episode as a primer for the lifespan podcast, because we delve deep into the behavioral tools, nutritional aspects, supplementation aspects of the biology of aging. We also talk about David's important discoveries of the sirtuins, particular components that influence what is called the epigenome. And if you don't know what the epigenome is, you will soon learn in today's episode. Coming away from today's episode, you will have in-depth knowledge about the biology of aging at the cellular, molecular, and what we call the circuit level, meaning how the different organs and tissues of the bodies age independently, and how they influence the aging of each other. Today's episode gets into discussion about many aspects of aging and tools to combat aging

00:03:30 ROKA, InsideTracker, Magic Spoon

that have not been discussed on any other podcasts or in the book lifespan. Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is however part of my desire and effort to bring zero cost to consumer information about science and science related tools to the general public. In keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first

sponsor is ROKA. ROKA makes eyeglasses and sunglasses that are the absolute highest quality. I've spent a lifetime working on the visual system. And I can tell you that the visual system has to contend with a number of different challenges, such as when you move from a bright area outside to an area where there are shadows, you have to adjust a number of things in your visual system so that you can still see things clearly. One problem with a lot of eyeglasses and sunglasses is they don't take that biological feature into account. And you have to take off your glasses and put them back on, depending on how bright or dim a given environment is. With ROKA eyeglasses and sunglasses, you always see things with the utmost clarity. In addition, they're very lightweight and they won't slip off your face. In fact, they were designed to be worn while biking or running and the various activities, but they also have a terrific aesthetic, so you could wear them to dinner or work. I wear readers at night and when I drive and I wear the sunglasses for most of the day. If you'd like to try ROKA sunglasses or eyeglasses, you can go to roka.com, that's roka.com and enter the code Huberman, to save 20% off your first order. Again, that's ROKA, roka.com and enter the code Huberman at checkout. Today's episode is also brought to us by InsideTracker. InsideTracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better understand your body and help you reach your health goals. I've long been a believer in getting regular blood work done for the simple reason that many of the factors that impact your immediate and long-term health can only be assessed from a quality blood test. And now with the advent of modern DNA tests, you can also get a clear picture of what your biological age is and compare that to your chronological age. And obviously your biological age is the important one because it predicts how long you will live and it's the one that you can control. The great thing about InsideTracker is that compared to a lot of other DNA tests and blood tests out there is that with InsideTracker, you don't just get your numbers back at the levels of various hormones, metabolic factors, blood lipids, et cetera, but it also offers clear directives to lifestyle factors, nutritional factors and supplementation that you can use in order to get the numbers into the ranges that are best for you and for your health. If you'd like to try InsideTracker, you can go to insidetracker.com/huberman to get 25% off any of InsideTracker's plans. Just use the code Huberman at checkout. Again, that's insidetracker.com/huberman to get 25% off any of InsideTracker's plans. Today's episode is also brought to us by Magic Spoon. Magic Spoon is a zero sugar, grain-free, keto friendly cereal. Now I don't follow a strictly ketogenic diet. What works best for me is to eat according to my desire to be alert

at certain times of day and to be sleepy at other times of day. So for me, that means fasting until about 11:00 AM or 12 noon most days. And then my lunch is typically a low carb, ketoish lunch, maybe a small piece of grass-fed meat, some salad, something of that sort. And then in the afternoon, I might have a snack that's also ketoish. And then at night is when I eat my carbohydrates, which for me helps me with the transition to sleep and allows me to get great deep sleep. That's what works for me. What that means is in the afternoon I'm craving a snack. And the snack for me is Magic Spoon. What I do lately is I put in some Bulgarian yogurt. Sometimes I just eat it straight. Each serving of Magic Spoon has zero grams of sugar, 13 to 14 grams of protein and only four grams of carbohydrates in each serving. So it really matches that low carb ketoish approach. There's only 140 calories per serving, and they have a variety of flavors. Coco, fruity, peanut butter or frosted. I particularly like frosted 'cause it tastes like donuts. I try not to eat donuts, but I do love the frost. And as I mentioned before, I lately mix it with yogurt polo cinnamon on there. I'm getting hungry just talking about it. Now, if you want to try Magic Spoon, you can go to magicspoon.com/huberman to grab a variety pack. Use the promo code Huberman at checkout, to get \$5 off your order. Again, that's magicspoon.com/huberman

00:07:45 "Aging as a Disease" vs. Longevity & Anti-Aging

and use the code Huberman to get \$5 off. And now my conversation with Dr. David Sinclair. Thank you for coming. - Thanks for having me here. It's good to see you. - This is mate by the way, that we're toasting at 11:00 AM. Unlike other podcasts, we, well, I don't drink alcohol, so I'm boring that way. But truly, thanks for being here, I have a ton of questions for you. We go way back in some sense, but that doesn't mean that I don't have many, many questions about aging, longevity, lifespan, actionable protocols to increase how long we live, et cetera. And I just want to start off with a very simple question. I'm not even sure there's an answer to, but what is the difference between longevity, anti-aging and aging as a disease? Because I associate you with the statement, aging is a disease. - Right? Well, so longevity is the more academic way we describe what we research. Anti-aging is kind of the same thing, but it's got a bad rap because it's been used by a whole bunch of people that don't know what they're talking about. So I really don't like that term anti-aging, but aging is a disease and longevity are perfectly valid ways to talk about this subject. So let's talk about aging as a disease.

When I started my research, disease here at Harvard Medical School, it was considered, if there's something that's wrong with you. and it's a rare thing, it has to be less than 50% of the population, that's definitely a disease, and then people work their whole lives to try and cure that condition. And so I looked up, what's the definition of aging and it says, well, it's a deterioration in health and sickness and you can die from it, typically you do. Something that sounds pretty much like a disease, but the caveat is that if more than half the population gets this condition, aging, it's put in a different bucket. Which is first of all, that's outrageous, 'cause it's just a totally arbitrary cutoff. But think about this, that we're ignoring the major 'cause of all these diseases. Aging is 80 to 90% the cause of heart disease, Alzheimer's. If we didn't get old and our bodies stayed youthful, we would not get those diseases. And actually what we're showing in my lab is, if you turn the clock back, in tissues, those diseases go away. So aging is the problem and instead through, most of the last 200 years, we've been sticking band-aids on diseases that have already occurred because of aging and then it's too late. So there are a couple of things. One is we want to slow aging down so we don't get those diseases and when they do occur, don't just take a bandaid on, reverse the age of the body

00:10:23 What Causes Aging? The Epigenome

and then the diseases will go away. - That clarifies a lot for me, thank you. Can we point to one specific general phenomenon in the body that underlies aging? - Yeah, well, that's contentious because scientists like to come up with new hypothesis. It's how they build their careers. But fortunately during the two thousands, we settled on eight or nine major causes of aging. We call them hallmarks 'cause causes was a little bit too strong, but these eight or nine causes, at least for the first time allowed us to come around and talk together. And we put them on a pizza so everyone got an equal weighting, equal slices. But before that, by the way, we were trying to kill each other in the field, that was horrible. - Interesting that you guys work on aging and you're trying to kill each other. - Yeah, isn't it? Well kill each other's careers. Well I like to think I was fairly generous, but I was one of the kids and the old guard really didn't like the new guard. We just came along in the 1990s and said, free radicals don't do much. They're actually genes called longevity genes. And that caused a whole ruckus. And there was this competition for what never happened, which was a Nobel prize for this. And it just led to a lot of competition. I would go to meetings and people would shout at each other and backstab,

it was horrible. But then unfortunately in the two thousands, we rallied around this new map of aging with these causes of hallmarks. But I think that there's one slice of the pizza that is way larger than the others. And we can get to that, but that's the information in the cell that we call the epigenome. - Well tell us a little bit more about the epigenome, frame it for us if you will, and then we'll get into ways that one can adjust the epigenome in positive ways. - Yeah, so in science, what I like to do, a reductionist is to boil it down and I actually ended up boiling, aging down to an equation, which is the loss of information due to entropy. It's a hard thing to overcome, second law of thermodynamics. That's fair, but this equation really represents the fact that I think aging is a loss of information in the same way that when you xerox something, a thousand times you'll lose that information or you try to copy a cassette tape. Or even if you send information across the internet, some of it will get lost. That's what I think is aging. And there were two types of information in the body. There is the genetic information, which is digital. ATCG the chemical letters of DNA, but there's this other part of the information in the body. that's just as important, it's essential, in fact, and that's the systems that control which genes are switched on and off in what cell at what time in response to what we eat, et cetera. And it turns out that 80% of our future longevity and health is controlled by the second part, the epigenetic information, the control systems. I liken the DNA to the music that's on a DVD or a compact disc for the younger people. We used to use these things. - I recall. - Yeah, and then the epigenome is the reader that says, okay, in this cell we need to play that set of songs and in this other cell, we have to play a different set of songs. But over time, aging is the equivalent of scratching, the CD and the DVD so that you, you're not playing the right songs and cells when they don't hear the right songs, they get messed up and they don't function well. And that is what I'm saying is the main driver of aging. And these other hallmarks are largely manifestations of that process. - Can we go a little deeper into what that these scratches are. Is it the way that the DNA are packed into a cell? Is it the way that they're spaced? What are the scratches that you're referring to? - So DNA is six foot long. So if you join your chromosomes together, you get a six foot post-sale. So there's enough to go to the moon and back eight times in your body. And it has to be wrapped up to exist inside us, but it's not just wrapped up willy-nilly. It's not just a bundle of string, it's wrapped up very carefully in ways that dictates which genes are switched on and off. And when we're developing in the embryo, the cell marks the DNA with chemicals that says, okay, this gene is for a nerve cell. Your cell will stay a nerve cell for the next a hundred years, if

you're lucky. Don't turn into a skin cell that would be bad. And those chemicals, there are many different types of chemicals, but one's called methylation. Those little methols will mark which songs get played for the rest of your life. And there are other that change daily. But in total, what we're saying is that the body controls the genome through the ability to mark the DNA and then compact some parts of it, silence those genes, don't read those genes and open others, keep others open that should stay open. And that pattern of genes that are silent and open, silent, open, is what dictates the cells type the cells function. And then the scratches are the disruption of that. So genes that were once silent and you could say, it's a gene that is involved in skin. It's starting to come on in the brain, shouldn't be there, but we see this happen and vice versa, the gene might get shut off over time during aging. Cells over time, lose these structures, lose their identity, they forget what they're supposed to do and we get diseases. We call that aging and we can measure that. In fact, we can measure it in such a way

00:15:53 Cosmetic Aging

that we can predict when somebody is going to die based on the changes in those chemicals. - Are these changes, the same sorts of changes that underlie the outward body surface manifestations of aging, that most of us are familiar with, graying of the hair, wrinkling of the skin, drooping of the face. Walking around New York lately, it's amazing to me, there are certain people that seem to walk looking down at the sidewalk because their spine is essentially in a C shape, right? A hallmark, if you will, of aging, that most of us are familiar with. Are the same sorts of DNA scratches associated with that? Or are we talking about people that are potentially are going to look older, but simply live longer? - Well, it's actually, you are as old as you look, if you want to generalize. So let's start with centenarian families. These are families that tend to live over a hundred. When they're 70, they still look 50 or less. So it is a good indicator. It's not perfect because you can like me growing up in Australia and accelerate the aging of your skin. But in general, how you look, and no one's ever died from gray hair, but overall you can get a sense just from the ability of skin to hold itself up, how thin it is, the number of wrinkles. A great paper just came out that said that an AI System looking at the face

00:17:15 Development Never Stops, Horvath Clock

could very accurately predict someone's age. - Very interesting. So I started off in developmental neurobiology. So one of the things that I learned early on that I still believe wholeheartedly is that development doesn't stop at age 12 or 15 or even 25 that your entire life is one long developmental arc. So in thinking about different portions of that developmental arc, the early portion of infancy, and especially puberty, seem like especially rapid stages of aging. And I know we normally look at babies and children and kids in puberty, and we think, oh, they're so vital, they're so young. And yet the way you describe these changes in the epigenome and the way you have framed aging as a disease leads me to ask are periods of immense vitality, the same periods when we're aging faster. - Yes, yes. And this is something I've never talked about, at least not publicly. So this is a really good question. So those chemicals we can measure, it's also known as the Horvath's clock. It's the biological clock, it's separate from your chronological age. So actually what I didn't mention is that when the AI looked at the faces of those people, they could predict their biological age, their internal age. So your skin represents the age of your organs as well. And the people that look after themselves, we can talk about how to do that later. But there are some people that are 10, 20 years younger than other people biologically and it turns out if you measure that clock from birth or even before birth, if you look at animals, there's a massive increase in age, based on that clock, early in life. So you're right, so that's a really important point, that you have accelerated aging during the first few years of life, and then it goes linear towards the rest of your life. But there's another interesting thing that you brought up, which is that we're finding that the genes that get messed up, that get scratched that are leading to aging are those early developmental genes. They come on late in life and just mess up the system and they seem to be particularly susceptible to those scratches. So what's causing the scratches? Well, we know of a couple of things in my lab, we figured out. One is broken chromosomes, DNA damage, particularly cuts to the DNA breaks. So if you have an x-ray or a cosmic ray, or even if you go out in the sun and you'll get your broken chromosomes that accelerates the unwinding of those beautiful DNA loops that I mentioned. We can actually do this to a mouse. We can accelerate that process and we get an old mouse, 50% older, and it has this bent spine kyphosis. it has gray hair, it's organs are old. So we now can control aging, the forwards direction. The other thing that accelerates aging is massive cell damage or stress.

00:20:12 Puberty Rate as a Determinant of Aging Rate

So we pinched nerves and we saw that their aging process was accelerated as well. - Incredible, this is more of an anecdotal phenomenon. It is an anecdotal phenomenon, but at this experience of in junior high school, going home for a summer and you come back and then high school in the US usually starts eighth or ninth grade, or grade eight or grade nine for you Canadians. And then some of the kids, like they grew beards over the summer, or they completely matured quickly over the summer. Do you think there's any reason to believe that rates of entry into and through puberty can predict overall rates of aging? In other words, if a kid is a slow burner, right? They basically acquire the traits of puberty slowly over many years. Can we make some course prediction that they are going to live a long time versus a kid that goes home for the summer and comes back a completely different organism or appearing to be a completely different organism. Like they basically age very quickly in the summer. Does that mean they're aging very quickly overall? - Well, yeah, I don't want to scare anybody. - Sure. - That there are studies that show that the slower you take to develop it also is predictive of having a longer, healthier life. And it may have something to do with growth hormone. We know that growth hormone is pro-aging. Anyone who's taking growth hormone, pay attention. - Just look at someone who's taking growth hormone. - Yeah. - They often will acquire these characteristics of vitality, like improved a smoothness of skin, but their whole body shape changes often. - Yeah, I mean you'll feel better for a short amount of time. You'll build up muscle, you feel great, but it's like burning your candle at both ends. Ultimately, if you want to live longer, you want less of that. And the animals that have been generated and mutants that have low growth hormone, or sometimes these are dwarfs, they live the longest by far. A guy in my lab, Michael Bankowski, he had the longest lived mouse, a mouse typically lives about two and a bit years. He had a mouse that lived five years and he gave it chloric restriction, so fasting, combined with one of these dwarf mutations, low growth hormone, I think he called it Yoda. You look at who lives the longest, it's the really small people. This is a bit anecdotal, but it sounds like it might be true, is that the people who played the munchkins in the Wizard of Oz, many of them went on to live into their nineties and beyond. - Really? - Yeah. - Huh, amazing. - And are there are some Lauren dwarfs as well? There are dwarf mutations in South America and they seem to be protected against many of the diseases of aging. You barely ever see heart disease

00:23:00 Fasting, Hunger & Food Choices

or cancer in these families. - So I having owned a very large dog breed, a bulldog Mastiff who lived a long life for a bulldog, 11 years, but there are many dogs that will live 12, 16 years that are smaller dogs. Can we say that there's a direct relationship between body size and longevity or duration of life? - Well, there is, but that doesn't mean that you're a slave to your early epigenome nor have to your genome. The good news is that the epigenome can change. Those loops and structures can be modified by how you live your life. And so if you're born tall and I wasn't, and I wished at the time I did grow, but no matter what size you are, you can have a bigger impact on your life than anything your genes give you. 80% is epigenetic not genetic. - So let's talk about some of the things that people can do. And I've kind of batch these into categories rather than just diving right into actionable protocols. So the first one relates to food, blood sugar, insulin. This is something I hear a lot about, that fasting is good for us, but rarely do I hear why it's good for us. One of the reasons I'm excited to talk to you today is because I want to drill into the details of this because I think understanding the mechanism will allow people to make better choices and not simply to just decide whether or not they're going to fast or not fast, or how long they're going to fast, I think should be dictated by someone understanding of the mechanism. So why is it that having elevated blood sugar, glucose and insulin ages us more quickly and or why is it that having periods of time each day or perhaps longer can extend our lifespan? - Well, let's start with what I think was a big mistake was the idea that people should never be hungry. We live in a world now where there's at least three meals a day, and then we've got companies selling bars and snacks in between. So the feeling of hunger, some people never experienced hunger in their whole lives. It's really, really bad for them. It was based, I believe on the 20th century view that you don't want to stress out the pancreas and you try to keep insulin levels pretty steady and not have this fluctuation. What we actually found, my colleagues and I, across this field of longevity is that when you look at first of all animals, whether it's a dog or a mouse or a monkey, the ones that live the longest by far 30% longer and stay healthy are the ones that don't eat all the time actually was first discovered back in the early 20th century, but people ignored it. And then it was rediscovered in the 1930s, Claude McKay did Clark restriction. He put cellulose in the food of rats, so they couldn't get as many calories even though they ate. And those rats

lived 30% longer, but then it went away and then it came back in the 2000's in a big way, when a couple of things happened, one is that my lab and others showed that there were longevity genes in the body that come on and protect us from aging and disease. The group of genes that I work on are called sirtuins there's seven of them. And we show it in 2005 in a science paper, that if you have low levels of insulin and another molecule called insulin like growth factor, those low levels turn on the longevity genes. One of them that's really important is called SIRT1. But by having high levels of insulin all day, being fed, means your longevity genes are not switched on. So you're falling apart, your epigenome, your information, that keeps your cells functioning over time, just degrades quick. Your clock is ticking faster by always being fed. Okay. The other thing that I think might be happening by always having food around is that it's not allowing the cell to have periods of rest and re-establish the epigenome. And so it also is accelerating in that direction. There's plenty of other reasons as well, that are not as profound, such as having low levels of glucose in your body will trigger your major muscles in your brain to become more sensitive to insulin and suck the glucose out of your bloodstream, which is very good. You don't want to have glucose flowing around too much, and that will ward off type two diabetes. - So hunger of course is associated with low blood glucose and low insulin. Do you think there's anything about the subjective experience of hunger itself that could be beneficial for longevity? - Yeah, I do, though you get used to the feeling of not eating, so I'm kind of screwed that way. - It's like cold water, you eventually adapt. - You get used to it, unfortunately, but there are some studies that are being done at the National Institutes of Health that are able to simulate the effect of hunger, but still provide the calories. And it's looking like there's a small component that's due to hunger, but most of it, actually, is because you've got these periods of not being fed and then the body turns on these defensive genes. There's a really interesting experiment that was published maybe a couple of years ago by Rafael de Cabo down at the NIH. What he did was he took over 10,000 mice and gave them different combinations of fat, carbohydrate, protein. And he was trying to figure out what was the best combination. And then you also cleverly had a group. Well, two groups, one that was fed all the time or ate as much as they wanted and the other group was only given food for an hour a day. And it turns out they ate roughly the same amount of calories, 'cause of course in an hour they're stuffing their faces. It turns out it didn't matter what diet he gave them, it was only the group that ate within that window that lived longer and dramatically longer. So my conclusion is, and mice are very similar to us, metabolically, I think that tells us

that it's not as important, what you eat, it's when you eat during the day. - What is the protocol that people can extrapolate from that? Or maybe I should just ask you, what is your protocol for when to eat and when to avoid food? Do you fast, do you ever fast, longer than 24 hours? What do you do? And what do you think is a good jumping off place if people want to explore this as a protocol? - Well, if there's one thing I could say, I would say definitely try to skip a meal a day, that's the best thing. - Does it matter which meal or they're essentially equivalent? - Well, as long as it's at the end or the beginning of the day, because then you add that to the sleep period where you're hopefully not eating. - I think that that's an excellent point. I realized it's a simple one, but I think it's an excellent one 'cause I think one of the things that people struggle with the most is knowing when and how to initiate this so-called intermittent and fasting. And the middle of the day obviously is not tacked to the sleep cycle in the same way. So it's much harder as well for many people. - Yeah, well, I'll tell you what I do. I skip breakfast, I have a tiny bit of yogurt or olive oil because the supplements I have need to be dissolved in it. And then I go throughout the whole day, as I'm doing right now, here with this glass of water here, I'm just keeping myself filled with liquids. And so I don't feel hungry, be aware that the first two to three weeks, when you try that you will feel hungry and you also have a habit of wanting just to chew on something that there's a lot of physical parts to it, but try to make it through the first three weeks and do without breakfast or do without dinner and you'll get through it. And I did that most for most of my life, actually, mainly because I wasn't hungry in the morning. Some people are very hungry in the morning and they may want to consider skipping dinner instead, but I will go throughout the whole day. I don't get the crashes of the high glucose and the low glucose that anyone who goes, oh man, it's three O'clock, I'm going to need a sleep. If you do what I do, you will not experience that anymore because what my body does is it regulates blood sugar levels naturally. My liver is putting out glucose when it needs to, and it's very steady and gives me pure focus throughout the day. And I don't have to even have to think about lunch, I'm just powering through. At dinner, I mean, I love food as much as anybody. So I will eat a regular, pretty healthy meal. I'll try to eat mostly vegetables, I can eat some fish, some shrimp, I rarely will eat a steak. In fact, my microbiome is so adapted to my diet now, if I eat a steak, it will not get digested very well. I'll feel terrible. - If I don't eat a steak, I feel terrible. [David laughs] - Argentine lineage, but we can talk about that some other time. - Well, everybody's different, that's the other thing. What works for me may not be perfect for you and we do have to measure things to know

what's working. I rarely eat dessert, I gave up dessert and sugar when I turned 40 and occasionally I'll steal a bit of dessert 'cause it doesn't hurt if you steal it, right.? But other than that I avoid sugar, which includes simple carbohydrates, bread, I try to avoid, I've actually noticed, this is just a side note. I used to get buildup of plaque pretty easily and every time I went to the dentist, they'd have to scrape it off. And I even bought tools to scrape it off. 'cause it was driving me nuts. I don't get pluck anymore and I think it's because of my diet. I don't have those sugars in my mouth that the bacteria feed on and then form the biofilm on the teeth. Much better breath, by the way. - That's a benefit. Should you ever fast longer than this. It sounds if you go to bed, well, you used to tend to stay up late. I know because I get texts from you

00:32:44 Fasting Schedules, Long Fasts, (Macro)Autophagy

at like two in the morning my time, which means you're out very late and up early as well. But assuming that people go to sleep sometime around 1130 or 12, plus or minus an hour and wake up sometime around 7:00 AM plus or minus 90 minutes, you're eating more or less on. It sounds something like a 20 hours of fasting, four hours of eating or 16 hours of fasting and eight hours of food intake, et cetera. But do you ever do longer fast, like 48 hours or 72 hours a week long, fast? - Occasionally I do. So my typical day I would only eat within a two hour window. Just usually I'm either eating out or. - 'Cause you're 22 too. - Yeah, but I love well. - And if you exercise, do you feel like you, then you just power through and maintain that fasted state? - Absolutely, I can exercise and now I've already so used to it. I don't feel like I need food after exercising, I used to. But have I gone longer? Yes, but not very often. I find it quite difficult to go more than 24 hours. But when I do it, maybe it's once a month, I'll go for two days after two and actually even better, if you go for three days without eating, it kicks in even greater longevity benefits. So there's a system called the autophagy system, which digests old and misfolded proteins in the body. And there's a natural cleansing that happens when you're hungry. Macroautophagy its name is but a good friend of mine, Ana Maria Cuervo at Albert Einstein College of Medicine discovered a deep cleanse called the chaperone mediated autophagy, which kicks in day two, day three, which really gets rid of the deep proteins. And what excites me is you just put out a big paper that said, if you trigger this process in an old mouse, it lives 35% longer. - [Andrew] Wow. - Yeah, so it's a big deal. If I could go longer, I would. But I just find that with my lifestyle and I'm going always day, 110% I

need to eat at least once a day unfortunately. - One more practical question then a mechanistic question

00:34:50 Caffeine, Electrolytes

related to this, the practical question is when you are fasting, regardless of how long, I know you're ingesting fluids like water and presumably some caffeine I heard you had several or more espresso today, which is impressive, but are you also ingesting electrolytes? Like I know some people get lightheaded, they start to feel shaky when they fast. And that the addition of sodium to their water or potassium magnesium is something that's becoming a little more invoke now. Is that something that you do or that you see a need for people to do? - Well, it makes sense, but I haven't had a need to do it. So I don't, I drink tea during the day and coffee when I'm first awake and I don't get the shakes. So I don't fix what's not broken. And I do add things to my protocol that I think will improve me and avoid those things of course that wont. But yeah, because I don't have a need for it, I don't try it. But it does make sense, especially if you've had a big night the night before, you'd probably want to supplement with that.

00:35:56 Blood Glucose & the Sirtuins; mTOR

But I think there's fair amount of good stuff in tea and coffee as it is. - Okay, so then the mechanistic question is, you've told us that there's ample evidence that keeping your blood sugar low for a period of time is 24 hours, can help trigger some of these pro longevity anti-aging mechanisms. And that extending them out two or three days can trigger yet additional mechanisms of gobbling up of dead cells and things of that sort. How is it that blood glucose triggers these mechanisms? Because we've said, okay, remove glucose and things get better. You've talked before maybe we could talk more now about some of the underlying cellular and genetic mechanisms, things like this are sirtuins, but how our glucose in the sirtuins actually tethered to one another mechanistically. - There's a really good question, that proves you're a scientist or a world-leading one. So what we've now know is that these longevity pathways, we call them these longevity genes, talk to each other. And we used to say, oh, my longevity genes is more important than yours. It was ridiculous. 'Cause they're all talking to each other, you pull one lever and the other one moves. And the way to think of it is that there

are systems set up to detect what you're eating. So the sirtuins will mainly respond to sugar and insulin. And then there's this other system called mTOR, which is sensing how much protein or amino acids are coming into your body. And they talk to each other, we can pull one and affect the other and vice versa. But together when you're fasting, you'll get the sirtuin activation, which is good for you. And you'll also through lack of amino acids, particularly three of them, leucine, lysine and valine. The body will down-regulate mTOR and it's that up sirtuin, down mTOR that is hugely beneficial and turns on all of the body's defenses, the pro chewing up the old proteins, improving insulin sensitivity, giving us more energy, repairing cells, all of that.

00:37:55 Amino Acids: Leucine, "Pulsing"

And so these two pathways, I think, are the most important for longevity. - So interesting, you mentioned leucine, within the resistance training slash body building slash fitness community. Leucine gets a lot of attention because there are long-standing debates about how much protein one needs per day and how much you want and can assimilate at each meal. It makes for many YouTube videos and not much else, frankly. However, it's clear that because of leucine's effects on the mTOR pathway, that there are many people, not just people in these particular fitness communities that are actively trying to ingest more leucine on a regular basis in order to maximize their wellness and fitness and in some cases muscle growth but also just wellness. But what I interpret your last statement to mean is that leucine, because it triggers cell growth is actually pro aging in some sense, is that right? - Well, it could be that's what the evidence suggests. And again it goes back to the debate. Should you supplement with growth hormone or testosterone? All of these activities will give you immediate benefits. You'll bulk up more. You'll feel better immediately, but based on the research, it's at the expense of long-term health. So my view of longevity, the way I treat my body is I don't burn both candles. I have one end of the candle lit, I'm very careful I don't blow on it, but I also do enough exercise that I'm building up my muscle, but I'm not huge. Anyone who's seen me, knows that I'm not a professional bodybuilder, but I tried to actually, here's the key. And I haven't said this publicly, that I can remember. I pulse things so that I get periods of fasting and then I eat, then I take a supplement, then I fast, then I exercise and I'm taking the supplements and eating in the right timing to allow me to build up muscle sometimes because you can't just expect to take something constantly and do

something constantly for it to work. And that's why it's taken me about 15 years to develop my protocol. And there's a lot of subtlety to it. - Yeah, it sounds like a very rational protocol. Does the name Ori Hofmekler mean anything to you? - No. - Okay, just briefly, I discovered Ori Hofmekler about 15 years ago, he was a in Israeli special forces. He's now got to be close to 70. Forgive me Ori, if that number is inflated. He wrote a book called 'The Warrior Diet', which got very little attention at the time. But what he said was when he was in Israeli special forces, they rarely ate more than once per day. And sometimes once every second or third day. And this is a guy who maintains incredible physical stature, he's very lean, very strong and very vital at, I wouldn't say an advanced age, but he's getting up there and he just seems to be getting better and better. Ori Hofmekler was the person who essentially founded, if you will, although our ancestors founded, to be completely fair, the so-called intermittent fasting diet. He called it the warrior diet and this book didn't get much attention. But one of the things that you just said really reminded me of Ori. I sat down with him, I actually went to his home and sat down with him and he said, fasting is wonderful but these pulses where you nourish the body or even slightly over nourish the body provided they aren't too frequent, have a tremendous effect on vitality. And so I want to use that as kind of a segue to address this issue of vitality versus longevity, because here you're telling me and certainly the evidence supports that growth hormone will make you feel better and younger taking testosterone or estrogen, we should probably say. There are women who take hormone therapies later in life who take estrogen, they experience a strong increase in vitality if it's done correctly, but there is an effect of aging, the body more rapidly, it's sort of a second puberty if you will, but this idea of restriction and then pulsing, not necessarily feast and famine, but certainly famine and feast in lowercase letters, there really seems to be something about that. So at a cellular level, we'd kind of go back to mTOR and the sirtuins. How do you think that the cells might be reacting to this kind of lowercased feast and upper case famine type protocol? - Right, well, the pulsing, I think is what you want to do is to get the cells to be perceiving adversity. Okay, 'cause our modern life we're sitting around, we're eating too much, we're not exercising. Our cells respond. They go, hey, everything's cool, no problem. And they become relaxed and their own turn on their defenses and we age rapidly. We can see it in the clock. People who exercise and eat less, have a slower ticking clock, it's a fact. But my protocol is different than most people's because I am pulsing it. Now, first of all, let's get to, why did I even think that might be possible? 'Cause I didn't read the warrior diet. What I found in my research was

that if we gave resveratrol on this red wine molecule, that became well known in the 2000's. If we gave it to mice, their whole lifespan, they were protected against a high-fat diet, which we call the Western diet. They had lean organs. They live slightly longer, but not a lot. And if we gave them a high-fat diet without resveratrol, they actually lived a lot shorter. So it resveratrol protected them against the high-fat diet. We gave it to them on a normal diet, they just ate it when they wanted, and there wasn't much effect. This is what's not known though it's in a supplemental data of the paper that nobody ever reads. The mice that were given resveratrol every second day on a normal diet live dramatically longer than any other group. - [Andrew] Interesting. - So people out there, my critics say, resveratrol didn't extend the lifespan of mice on a normal diet. Therefore it's not aging, it's just protecting against a high-fat diet. Well, look at the supplemental data, please. If you give it to the mice every other day, we had mice living over three years. - Wow, that's a long time, I have got many, many mice in my own ownership at my lab at Stanford and that's a very long life for a mouse.

00:44:35 Metformin, Berberine

- It was, by far. And so it was a long life span extension. And what that told me is that probably, you don't want to be taking a supplement every day. You can take it either every other day or give your body a rest. And I do the same with my meals, I rest during the day and then I give a nutritious dinner to my body and then give it a rest, same with exercise. And then I try to time it because there are times when I'm taking the drug Metformin, which mimics low energy. For those of you who don't know, Metformin is a drug given to type two diabetics to bring down their blood sugar levels. But it's been found that looking at tens of thousands of veterans and all those, that those two type two diabetics live longer than people that don't even get type two diabetes. So it's a longevity drug, right now you have to get it from your doctor in the US, in most of the countries you can just get it over the counter and you're protected. It looks like, based on epidemiological data, cancer, heart disease for LT. What else? Dementia. So I take Metformin. - In addition, you take Metformin end fast fasting each day. So when do you take it relative to the fasting? - Yeah, I always take Metformin in the morning, along with the resveratrol, because for a number of reasons, but mainly because my body responds better and I've been measuring my body for 12, 13 years. But here's the thing, if I'm going to exercise that day, I will skip the Metformin. And a lot of people who do pay attention to this kind of

thing, think that they should stop taking Metformin 'cause they're never going to get muscle, or it's going to affect their ability to build up muscle. But that's not true, what Metformin does to you, it actually just reduces your ability to have stamina because it's inhibiting your body's ability to make energy. And so what happens is when you're on Metformin, you do fewer reps. But guess what? Those muscles that you do build up on Metformin, have the same strength and have much lower inflammation and other markers of aging. You just won't have that extra 5% size of muscles. So if you want large muscles, don't take Metformin and you'll be fine during your exercise. But for me, I'm not trying to get giant. I want strong muscles and I want to live longer and healthier. So I just try to time it so that I get the most reps out of my exercise regime, but sometimes in scientific literature, it's worth bringing this up. If there's a 5% difference in a graph, then either the press release or some reporter will say, oh my goodness, big difference, 5% contact Metformin during exercise. That's the headline. And then you go in and it's barely significant. And the graph is distorted because they've changed the axes to make it look bigger. And now it's become a myth that Metformin greatly inhibits our ability to exercise, which is not true, but in an abundance of caution, I skipped my Metformin on days I'm going exercise. And not only that, I'm one of the 20% of people that has a stomach sensitivity to it. So if I'm not feeling great that day, I don't take it either. - You mentioned Metformin is available only by prescription from a doctor, at least in the US. Berberine is a substance that comes from Tree Barco. I also learned about many years ago from Ori. He said, if ever, I'm going to overeat like a Thanksgiving meal or something, I take berberine, those were his words. And I tried it and what's remarkable about berberine is that you can eat enormous quantities of food and not feel as if you've eaten enormous quantities of food. I'm not necessarily recommending people do this. But what I noticed was if I took berberine, which my understanding is it works very similarly to Metformin where some of the AMPK pathway and the mTOR pathway, et cetera, that if I didn't ingest food in particular carbohydrates, I would feel a little dizzy and kind of get a headache, like almost hypoglycemic. What are your thoughts on berberine as an alternative to Metformin? And are there any cautionary notes? Obviously people should talk to their doctor before adding or subtracting anything from their life, including breath order, anything that comes up, but with all of that set aside, what are your thoughts about berberine and timing of low blood sugar and these sorts of things? - Right, well, before I had access to Metformin, I was taking berberine. It's often known as the poor man's Metformin. - He just called me poor. - Women can take it too. So the

thing with berberine and we started it in my lab, it is effective at boosting energetics in the body, just like AMPK and Metformin does. And we've actually given it to rats and mice and seen that they are very healthy, especially on a high-fat diet. So I think it's likely to be good. There are some human studies that exist, clinical trials showing that it increases insulin sensitivity. You have to take high doses. - Which is a good thing, right? I think when people hear insulin sensitivity, sometimes people think, oh, well that's bad, right? No, but you want your cells to be insulin sensitive. You don't want a lot of blood sugar floating around that can't be sequestered into cells. - Exactly, so this is anti type two diabetes. And so that this berberine does have wonderful effects on the metabolism of animals and in some clinical trials on dozens of people that's being tested. Now, there's one cautionary tale, which just came up, Caenorhabditis lab published that berberine reduced the lifespan of worms, but I'm not sure worms trump human clinical trials at this point. - Not in my opinion, no disrespect to my *C. elegans* colleagues or rather my colleagues that work on *C.* - Yeah, well, what I like to do is to give all the information, people can decide what they want, but I would say based on the worm data, I wouldn't panic just yet.

00:50:29 Resveratrol, Wine

And I think berberine has been shown to be really safe in humans. - You mentioned resveratrol, think now would be a great time to talk a little bit about, protocols for resveratrol, great seed extract, et cetera. Let's start with the obvious one that I know you get a lot, but for the record, can't I just drink red wine and get enough resveratrol, David. - You can try, you need to drink about 200 glasses a day. - I'm sure it's been tried. - There are some, and I drink a glass of red wine a day if I get the chance, but any more than that, it's a lot of calories and your liver will get fatty and it's all bad. So, I mean, realistically, you can only get the thousand milligrams that I take a day from a supplement that's pure. Now there are a lot of people selling resveratrol. If it's not light gray or white in color, throw it away. The brown stuff has gone bad or is contaminated. And the contaminated stuff beware it'll cause diarrhea. But regular resveratrol should not do that. - So a thousand milligrams per day is what you do. - Yeah and I had for about 15 years now. And you ingest that with some fatty substance, like olive oil or yogurt, is that right? - Yeah, you have to, and other supplements of course it's in curcumin. These are crunchy things, that is not going to get through your gut. And I'm not just making this

up. I always base my statements on human studies. So we've done a lot of studies on resveratrol as have others since, and we know that from, we found out early, I was one of the first people to take a high dose for resveratrol. And when we included it with food, the levels in my blood went up five fold. And so you want to have something in there. If you just drink it with water, it's not going to get through. And unfortunately, some people have done clinical trials without even thinking that they might need to dissolve it in something. - So are you taking this all at once in the morning and chasing it with some olive oil or are you dissolving it in yogurt? What's the specific protocol? - Yeah, I've been improving perfecting what I do for about 10 years I would take some Greek yogurt, a couple of spoonfuls, put the resveratrol on there, mix it around, make sure it's dissolved and put that in my mouth and swallow that, these days, what I like to do, because I've realized that olive oil and particularly oleic acid, one of the mono unsaturated, fatty acids is also an activator of the sirtuin defenses. So I'm trying to ingest more of oleic acid. So I switched to olive oil. What I do is I put a couple of teaspoons of olive oil in a glass mix around the resveratrol, and maybe some Coresatin a similar molecule. Make sure it's dissolved. I put a little bit of vinegar and if I have a basil leaf, I'll put that in.

00:53:20 What Breaks a Fast?

And it's like drinking some salad dressing. And it's very- - Delicious, that raises a question that I want to ask before we get to NMN and NR and vitamin B3, which is by doing that, do you think that it breaks your fast? And I want to just frame this question of breaking the fast in a more general scientific theme. And I'd love your thoughts on this. One of the questions I get asked all the time is does ingesting blank break the fast, does eating this or drinking this, coffee? If I walk in the room and someone else is eating a cracker, does it break my fast? People get pretty extreme with this, my sense and please tell me if I'm wrong, but my sense is that it depends on the context of what you did the night before, whether or not you're diabetic, lots of things. So for instance, if I eat an enormous meal at midnight, go to sleep, wake up at 6:00 AM. I could imagine that black coffee or coffee with a little bit of cream might quote unquote, break my fast, but the body doesn't have a breaking the fast switch. The body only speaks in the language of glucose, AMPK, mTOR, et cetera. So do you worry that ingesting these calories is going to quote unquote break your fast? And more generally, how do you think about the issue of whether or not you're fasting enough to get these positive effects? Because not

everybody can manage on just water or just tea, or we should say not everybody is willing to manage on just water or just tea for a certain part of the day. - Well, my first answer is not scientific, it's philosophical. If you don't enjoy life, what's the point. And so I'd like a cup of coffee in the morning, a little bit of milk, spoonful of yogurt, it's not going to kill me. Olive oil doesn't have protein or carbs in it, not many. And so I'm probably not affecting those longevity pathways negatively, but without that, first of all, I wouldn't enjoy my life as much. Second, well, the olive oil isn't is not as great as the yogurt, but I'm trying to optimize and there's no perfect solution to what we're doing. And we're still learning. We don't know what's optimal for me, let alone everybody else. But I'm with you, I don't believe that taking a couple of spoonfuls of something, unless it's high fructose corn syrup is going to hurt you because I've now got the rest of the day till about eight, 9:00 PM of not eating anything. And that I forgive myself for that. And that there's a really good point here. You and I were discussing this earlier. The point about doing this is that you try to do your best. If you go from regular living to donate the whole day, you're going to fail. It's like quitting smoking, cold turkey. It's easy to chew gum and stick the patch on because your body has to get used to all sorts of habits. And it's social, it's physical, putting stuff in your mouth, chewing, not just the low blood sugar levels and your brain will fight it. Your limbic system is going to go, hey, do it, do it, do it. And you're going to have to fight it but once you get through it, you'll be better, but you do it in stages. Do breakfast first, then do small lunch and then eventually cut lunch out. Don't go cold turkey because everyone knows. It's a fact that if you try to do a strict diet right out of the gates, they'll almost always fail. - Now, I think that captures the essence

00:56:45 Resveratrol, NAD, NMN, NR; Dosage, Timing

of the fasting rationally and irrational approach to supplementation very well, along the lines of supplementation. What about NMN, NR and B3, niacin? How does one, I want to know what you do. I also want to know what I should do, and I think most people want to know what they should do. These are molecules that impact the sirtuin pathway impact the pathways that control aging or rates of aging in the epigenome. How do they do that? And how does one incorporate that into a supplementation protocol? Should they choose to do that? All right. - Well, disclaimer is I don't recommend anything, but I talk about what I do. So a bit of scientific background, these are two in genes that we discovered first in yeast cells when I was at MIT and then in animals as I moved to

Harvard in the 2000's one of my first post-docs, actually literally my first postdoc Haim Cohen, published a great paper just a couple of months ago and found that turning on the sirtuin six gene, middle of the seven, number six gene is very potent. It extended the lifespan dramatically of mice that he engineered both males and females, which is great. So what you want to do is so naturally boost the activity of these sirtuins. They are genes, but they also make proteins. That's what genes typically make or encode. And then those proteins take care of the body in many different ways as we've discussed. So how do you turn on these genes and make the proteins they make even more active? You want to rev up that system. So exercise will do it, fasting will do it. What about supplementation? Well, the first activator of the sirtuins that we discovered that acts on the enzyme to make it do a better job of cleaning up the body and protecting resveratrol We looked at thousands of different molecules, eventually tens of thousands. And the one that was the best was resveratrol in the dish. And then we gave it to little organisms, worms, and then flies and mice, eventually humans. And we saw that it activated that enzyme. So resveratrol is one way to activate it. And you can think of it as the accelerator pedal on a car. It revs it up, but there's something else that the sirtuins need to work and that's NAD and is a really small molecule, little chemical in the body that we need for life. It's used by the body for chemical reactions, for a hundred different reactions in the body. And without it, you're dead within seconds, you need NAD. The problem that we've seen is that NAD levels decline as you become obese, as you get older, if you don't ever get hungry and the body not only doesn't make enough of it, it's chewing it up as well. There's an enzyme called CD38 that Eric Verdin over at UCSF showed choose up. Now he's now at the Buck Institute in California, choose up NAD as you get older. So it's a double whammy. You don't make as much and chew it up, which is really bad because what we've shown in my lab and so have others is that NAD levels are really important for keeping those sirtuins and defenses at a useful level. And you can give a lot of resveratrol but if you don't have the fuel, you're basically accelerating a car that doesn't have enough gas. So you want to do both. And that's what I do. I take a precursor to NAD called NMN and the body uses that to make the NAD molecule in one step. And so I know from measuring dozens of human beings, that if you take NMN for the time period that I do, I've been taking it for years. But if you take it for about two weeks, you'll double on average, double your NAD levels in the blood. Okay, that's not public information. That's from clinical trials that are not yet published over the last two years. There are other ways to increase NAD levels in someone like me, who's getting

older, I'm 52 now. You can take NR, which is used to make an amend, which is used to make NAD, and both NMN and NR are sold by companies in the US. NR is laxter phosphate, the phosphate is a small chemical the body needs. You've probably heard of the atom, phosphorus. Let's go back one step. How do you make NR? NR gets made from vitamin B3, often. You can also find it in milk and other foods, but sometimes people ask me, why don't you just take vitamin B3? And won't that just force the body to make NAD? And the answer is no, it doesn't work very well. We know this just by doing the experiment, but the reason I think is is that NAD, I said, it's a small molecule, but relative to vitamin B3, it's big. It's got those phosphates on there, it's got a sugar, it's got the vitamin B attached. So you've got all these components that come together to make this very complicated little molecule called NAD. When you give NMN, it contains all three components that the body needs to make NAD. If you give NR or just vitamin B3, which is an even smaller molecule, the body has to find these other components from somewhere else. So where do you get phosphate, well, the body needs it for DNA, it needs it for bones. So high doses of something that requires additional phosphate makes me a little concerned. And we have compared to NMN and NR head-to-head in mouse studies, for instance in NMN, we've shown in a cell paper a few years ago, makes mice run further, old mice can run 50% further 'cause they had better blood flow, better energy. NR are at the same dose, did not do that. In fact, it had no effect. - I see, dosage wise, if I were elect to take NMN in supplement form to increase my NAD levels and presumably slow my aging, how much NMN should I take? What's the protocol that you do? And are the various forms that are out there, are some better or some worse? - Well, I'm always happy to tell you what I do and what my father does, my 82-year-old father, we take a gram of NMN every day. - So it's a gram resveratrol and a gram of NMN. - Right. - Okay a thousand milligrams. - Now another important point, which is, I'm not the same as everybody else. I have a different microbiome, age, sex, right? And so I've been measuring myself and so I know if something's, or I think I know if something's making me better or worse based on measuring 45 different things. So I just want people to be aware that what I do may not perfectly or work at all for others, but I have studied, as I said, dozens of people who take NMN, at a gram, sometimes two grams. And I know by looking at all those people that without any exceptions, that if you do what I do, your NAD levels go up by about two fold or more. And so I do that every day, the thousand milligrams. Now people sell it. Now I never get into brands and all that. First of all, I don't have the time to measure products. I don't know, though I should say, I do

want to say I'm working on a solution for people to know what works and what's real and what isn't, but I'm not there yet. And in the meantime, I would say, if you do want to buy this, let's say you want to buy NMN, look for a company that is well-established that has high levels of quality control. Look for three letters, GMP, which is good manufacturing practices. And so that means they make it under a certain level of quality control. You're not going to find iron filings in there and it probably has the stuff in it that they say it does. But so that's all I can say right now. I'm working on something that's going to be much more helpful, but overall, make sure it's white, crystalline NMN, and that to me, it tastes like burnt popcorn. - You crack open the capsules, and you'll take a little sample to make sure it tastes like burnt popcorn. - Well, when I'm making my capsules, I'll taste it and I do a lot of quality control on the stuff that I take. - Do you take that gram all at once with the resveratrol or do you take it spread throughout the day? - It's all in the morning for those things. So if I take Metformin, it's NMN and the resveratrol altogether. And there's a good reason for that. It's all scientific, I try to be. The levels of NAD go up in the morning in our bodies naturally. Our bodies actually have a cycle of NAD, it's not steady. - It's Arcadian? - It's Acadian. In fact, NAD controls your clock. This was shown by Shin Imai and colleagues in this nice science paper about a decade ago, that if you disrupt the NAD cycle, which is controlled by the sirtuin gene that we worked on, that is what's telling your body, oh, it's time to eat, it's time to go to sleep. And if you take these, the NMN late at night, for example, you can disrupt your circadian rhythms. - Interesting. - Conversely, when I travel and I want to reset my clock to the time zone, I will take a boost of NMN in the morning and I feel great. - Does this protocol for you, does it produce any immediate effects of increased energy, et cetera? You mentioned that one would, if it's right for them, would have to take it for at least two weeks to start to see the NAD levels increase. At that point, when NAD levels increase, could one possibly expect an increase in overall energy, focus, et cetera? I realize we're not making promises here, but I'm just wondering whether or not the only measure of whether or not this protocol is working is whether or not you die at age blank or blank plus 20. And of course, once you're dead, you can't really know if you would've lived longer if you'd done something differently and vice versa. - Sure, well, there was a study again by Shin Imai my good friend at Washington University in St. Louis that showed that improves, remember this insulin sensitivity, which is a good thing. But you can't know your insulin sensitivity unless you're measuring glucose, have a glucose monitor on your arm. - Do you have one on right now? - No, no, I used to, I learned a lot. - Yeah, last time I saw you had this

thing, it looks like a small leach, not a large leach and it was measuring your blood glucose. - They're very informative because you learn what your body reacts to and grapes were really bad. Rhonda Patrick agrees with that, but the issue was, was what, where were we, Andrew? - The issue is whether or not you can expect any immediate effects on energy, vitality, focus, just even subject. - So what do you feel, is the question. And anecdotally, 'cause I've been taking this for a long time, if I don't take it, I start to feel 50 years old, it's horrible. I can't think straight. It may be placebo, but who knows? But what we're doing now are very careful clinical trials. We've done the safety for two years, and we're now treating elderly patients at Harvard Medical School with some wonderful colleagues. And those people are actually going to be an currently in MRIs. So you can measure the energetics and the NAD levels in their legs as they exercise in real time. And that will tell us if what we see in the mice is increased endurance actually works. In the meantime, it's fun to talk about anecdotes. I have a number of athlete friends, some of which have increased their load, their time in marathons, for example. There's a good friend of ours in our circle that is winning marathons at age 50 now. And he attributes that to the protocol that he's on. - Interesting, I haven't started taking NMN, but I'm planning to do that when my next birthday arrives, which is in a couple months. But I do experiments on my sister and have for years, I have a sister who's three years older than I am, who is very enthusiastic about these protocols. And I'll tell you that after reading your book, I started purchasing for her and giving her an NMN supplement and she claims and I believe her. She has a quite sensitive system and she's very tuned into it. She feels far and away better when she takes it, as opposed to when she doesn't and I've done the control experiment of removing her supply, and then giving it back to her in this kind of thing.

01:09:10 Are Artificial Sweeteners Bad for Us?

So that's my other laboratory. This is what younger brothers do to their older sisters. I have a question about something that if it has no relevance, we can just treat it as a speed bump and then move right on. And the artificial sweeteners, these things that we should say non-glucose, increasing sweetener. So you've got Stevia, which is a plant basically. And then you've got sucralose and aspartame and all these things. There is some evidence that I know we're both aware of, they've been publishing quite reputable journals, showing that they can disrupt the gut microbiome in certain cases in particular

saccharin, the one that basically nobody uses anymore. And it's questionable as to whether or not Stevia has the same negative effects, et cetera. That's not what this is about, but in terms of the sensation of, or the perception of sweet taste, is that itself a possible detriment to these pro-longevity, forgive me for using the term, the pathways. If I were to drink a diet coke during a fast, am I somehow disrupting this? And I'm asking this question, because I get asked this question a lot. - Well, there may be small effects. I don't think they're worth worrying about. Joe Rogan laughed at me 'cause I was drinking a diet coke during the first interview I did with them. I will drink diet coke, I've read the scientific literature. And again, it's this 5% thing that I think is blowing out of proportion. If I was to put a number on it, I would say, if eating a high sugary meal or drinking a sugar-filled soda, what is that, 30 grams of sugar? Let's say that's a 10 out of 10 bad for you. A diet coke might be a one. And if I'm, which am I going to do? I could have a 10 or a one or go without in my life. I'll do the one on occasion. I try to avoid them because I don't like the ones as much. But you can't say that sucralose is equivalent to drinking a sugary soda. There's just no comparison. And I think suc, what is it? Stevia, I do use Stevia whenever I can, because it's a naturally sourced product. And I haven't seen any good evidence yet that it's bad for you. But I think a lot of this is overblown, and a lot of it's the media trying to give equal weight to stories as you know as a scientist. It can be frustrating when something's a 10 and something's a one, and they're equated. - How do I say this respectfully? I think if science journalists were required to post their credentials alongside their name, [chuckles] then people would take the articles into, with additional grain of salt, right? I mean, in other words, that I think that the science media is mainly generated around two specific goals. One is to make people very, very afraid or get people very, very excited, and oftentimes the get people excited part is sponsored content,

01:12:04 Iron Load & Aging

and I think that's overlooked in any case. Thank you for that. I want to talk about iron and iron load. We were talking earlier about ferritin. And of course, women menstruate. And so their iron needs are greater than people, men that don't menstruate or women that don't menstruate. I don't think we can get right down into how much iron somebody needs because it'll vary person to person. But I was surprised to learn that iron is actually going to accelerate the aging process in various contexts. - Well, this is a new

finding out of Spain. Manuel Serrano's lab has found that excess iron will increase the number of senescent cells in the body. And senescent cells are these zombie cells that accumulate as you get older and they sit there and they cause inflammation mainly and also can cause cancer. And it's found that if you get rid of these cells or never accumulate them, you stay younger. In animals, and there's some really interesting studies out of Mayo Clinic in humans as well. So iron is a pro-senescent metal. And so what I think is that if you're taking excess iron as a supplement, you're probably accelerating your aging process. The other thing that I found really interesting is I've looked at hundreds of thousands of people's metabolism and their blood biomarkers. I was one of the first people in InsideTracker as a board member, and I'm still their scientific lead guy. So I can look anonymously at hundreds of thousands of people's blood work. And we also know how fit they are, how old they are. Some of them are marathon runners, some of them are CrossFit. And there's a signature of health that actually is different than your average person. Now, I'm not going to say bad things about MDs 'cause a lot of my best friends are MDs and I work with them at Harvard Medical School. The issue though, is that with MD training, there's a scale of what's normal, and if you're out of that normal range, something must be wrong, that's the paradigm that they work under. But first of all, everybody's different, and you want to know their baseline and track people over years to know what's normal for them. And what I find for example, is people who are really healthy and live the way I do and have a diet that's fairly vegetarian, but not strict, still have slightly low hemoglobin levels, slightly low iron, slightly low ferritin, but we have super amounts of energy, we're not anemic. And we're getting along great in life. But a doctor who just looks at that might say, oh, we need to give you more iron. All right, so what I'm getting at is an example of, we need to personalize medicine and look at people over the long run to know what works for them and what's healthy for them,

01:15:05 Blood Work Analysis

and not just work towards the average human, but work towards what's optimal for human. - I love that answer. You mentioned tracking and tracking over time. And this is a really interesting area that I know you have been focused on for a long time. I've been getting blood worked on about every six months frankly, since I was in college. I just got, I like data and I got interested in supplementation and exercise 'cause it made me feel

better, but I also want to know what was going on under the hood. So you get numbers back, you get this hormone, that hormone, this blood glucose measure, et cetera. How do you make sense of the data? I mean, what InsideTracker is doing aside, how do you personally make sense of the data in ways that might differ from the way that a standard MD might look at one of these charts? Because the standard practice is to say, is it red, yellow, or green, right? Is it basically too high or too low? Is it somewhere close to the margins or are you okay? Are you in these ranges? Are there any things that you pay attention to that you think are particularly interesting for people to just take note of? I mean, we're not asking you to go against anybody's physician. But what sorts of things should people start to educate themselves about in terms of what these molecules are on their charts if they choose to get them, and what do you look at? - Yeah, well, there's a lot there. The first is that you should be tracking things, because one measurement isn't enough. These things vary and over time. And if you can have a decade or more of data, it's super important, informative, as you know, well know, as you know. So the physician, interestingly, my physician, let's take him as an example. So he sees me, he says, "How are you feeling?" "I'm feeling great." "Okay, see you next year," that's craziness. Anyway, so I say, okay, stop. Let's talk a little bit about. - Let me educate you, that's what David tells his physician. I imagine that the 12-year-old David Sinclair says to a physician, "Listen, let's have a different discussion." Is that how it works? - It is. He finds me pretty annoying as does my dentist. But so I say, so hang on, I've got this data. I've got the InsideTracker data. So I pull that up on the screen, and I'm showing him the changes in my cholesterol and my CRP, which is inflammatory marker as you know. And we're going through it, and you can see things change over time, and I've corrected them as they go slightly out of the optimal range for me, which is different than what he would do, of course. But what was funny is that he says, this is great, I love this data. But I'm not allowed to get this because of course, the insurance companies won't pay for it. So again, you can pay out of pocket. It's not super expensive. I would say, if you save a bit of money on a coffee, you can afford this kind of stuff. But the main point is that doctors do like this data. It's just that they're unable to spend the money on every one of their patients to get it. - Is there a code word that someone can use with their physician that will trigger a comprehensive blood test? I keep trying to figure out what's the code that one needs to ask or tell their doctor, I'm feeling blank so that they get a full blood panel. - Well. - Do you have to be hemorrhaging from the gut or something? - Well, I usually use the WTH method, which is what the hell? And then he says, "Okay, we'll do

it." - 'Cause I think a lot of people out there are thinking, look, I'd love to have blood work repeatedly over time, but that's hard to get for financial reasons, but also a lot of people just don't know how to approach the conversation. And this is one of the things that I hope that we can educate people on, that they deserve to know what's going on inside their body, and that it makes a doctor's visit worthwhile, and that you don't have to feign illness in order to do it. - Right, yeah, and a lot of people do. So I would say, if you can't afford these tests, there are increasing number of companies that offer these tests, InsideTracker is one of them. And you just do it a couple of times a year at a minimum. And then you can share that with your doctor. If you can't afford that, then I would say to your doctor, here are the main ones that Andrew and David do. - Yep, and we must. And there's an email that is something like 555, or a phone number, rather, it's 555-5555. I think if they have any complaints, they can just call that number. David will pick up on the east coast business hours and I'll pick up outside of those hours. - But there was the main ones, I would say. Your blood sugar levels, you want to do your HbA1c, which is your average glucose levels over the month.

01:19:37 C-Reactive Protein, Cholesterol: Serum & Dietary

There's CRP, which I mentioned for inflammation. - Yeah, let's talk about C-reactive protein for a second. 'Cause I think it's been shown to be an early marker of macular degeneration of heart disease, of a variety of different things. CRP is something that we don't hear enough about, I think. Maybe, what do you know about CRP that I don't, I'm guessing a lot, but. - Oh, it was originally picked up as something that was associated with heart disease in the Framingham study, I believe. It is the best marker for cardiovascular inflammation and is also, we use it as a predictor of longevity, and its levels go up with mortality. And so this is an association, but there's enough data that I would say, if you have high levels of CRP, you need to get your levels down quickly. And the levels usually go up with age and with levels of inflammation. So the ways to get it down would be to switch the diet, eat less, try to eat more vegetables. You'll find it will come down, and there are also drugs that can do it. Anti-inflammatories can do it as well. But CRP is, it's actually, hCRP, there's a high sensitive hCRP, your doctor will know. Get one of those readings. 'Cause if you've got normal blood sugar levels, your doctor, or fasting blood sugar levels, your doctor might say you're fine. But a lot of people have normal blood sugar, but have high CRP, which is just as bad for you

longterm, and can predict a future heart attack. - On the lines of heart attack. I want your thoughts on cholesterol and serum cholesterol and dietary cholesterol. I cannot, for the life of me, get my arms around this literature. And even if I ignore all the essentially nonsense that's out there in various social media groups, as saying cholesterol is the worst thing in the world, or cholesterol is not, or dietary cholesterol has nothing to do with serum cholesterol and nothing to do with longevity. I can't seem to sort through the very basic data that essentially ask, is having high levels of LDL going to kill me earlier? Should I be striving to always reduce LDL and increase HDL? Is that a reasonable goal? And if so, is dietary cholesterol the primary determinant of that? And just as a final point about this, I am aware of quite good data that shows that anorexics, people that essentially eat no food, unless you force them to, can often have very high LDL. So their dietary cholesterol is essentially zero, and so they're manufacturing a lot of their own. So realize this isn't your primary area of expertise, but you're a smart guy and you think about this kind of stuff a lot. What do you think is going on with the cholesterol literature? And will we ever get to the bottom of this as a scientific and medical community? Because to me, it is rather perplexing. - It is, but you can get through the politics. I know a fair bit about cholesterol 'cause it's in my family history. And I was headed for an early death, my grandmother had a stroke 30, that's how bad I am in terms of my genetics. So I went on a statin, and I know there's a lot of people who say that statins long-term are bad. It's associated with Alzheimer's disease. I've been taking a statin since I was 29. And that's 'cause I forced my same doctor to give me the statin, the conversation was something like this. You're too young to be on a statin. And I said, what? You want me to have a heart attack before you give me something, give it to me now. So 29, I'd been on a statin, and my cholesterol was way up in beyond 300, which is a massive mess up. Basically my blood was creamy to look at. So I've now got my cholesterol down to low, low levels to what would it be. You can check on my InsideTracker, but so my ratio of HDL to LDL, which you want to be less than five, is now two, and the LDL is below a hundred, so it's all good. And I've measured my cardiovascular health with an MRI. I've got a movie of my heart beating. I've still got a heart of a 20-year old, so that's working, I'm willing to forgo the risk that the statin is causing problems later because of my family history. But other people, I would say, be aware that statins aren't perfect drugs. There were some interesting new ones. There's one called the PCSK9 inhibitor, which is, I think fortnightly, every two weeks injection, that blocks the release of LDL from the liver. And then that seems to be great for lowering cholesterol, but also has other benefits that

might be prolongevity. And there were some people that I was just talking to on the cutting edge of this, and their doctors are trying them on this drug instead of the statin. So you could talk to your doctor about. - Do you avoid dietary cholesterol for that reason also? Red meat, butter. I mean, I have been to love butter. I love red meat. I realized there's some people who don't. My cholesterol is a little bit high, but I'm working to bring that down a bit, although not by altering my food intake yet. But what do you think is the relationship between dietary cholesterol and serum cholesterol, and what's going on with the liver? Why are anorexics? Why is there a certain cholesterol so high when they're eating nothing? - Well, there've been in a number of papers over the years that have been ignored. And our friend, Peter Attia, brought to my attention recently, a new study that I think definitively said that dietary cholesterol has almost zero impact on blood cholesterol levels. - Good. - Yeah, so I'm annoyed 'cause I'd been avoiding eggs and butter for most of my life and I didn't have to. So I have eggs- - Plenty of time, or at least in your case. - Yeah, yeah. So that's the thing. You can eat these foods that were ones banned because it's very difficult to take cholesterol up into the body from the gut. And most of it's being synthesized in the body. - Well, I'm just pausing there for a second because I think that it's what we've been told. Six meals a day, eat a lot of grains and fruits and this kind of thing, avoid cholesterol. I mean, basically everything we learned

01:26:02 Amino Acids, Plants, Antioxidants

in the '80s and '90s and early 2000s is getting flipped on its head now. But, and I think this is a very strong caveat that's important to mention, amino acids. In particular, the amino acids that come from animal products, right? Seem to have some pro aging effect on them, right? At least the way that I've heard you describe your diet. And I'm somebody who enjoys meat, I like it. But so I'm by no means, a vegan at all. But I've heard you say you eat mostly plants, but a little bit of fish or chicken or something of that sort of eggs or. But is that specifically to avoid excessive amino acid intake? Or is it something specific about plants that excites you with respect to? [chuckles] I mean, vegetables are delicious too, but what is it? Is it something great about plants or is it something bad about when I think of meat, I guess the biologist in me thinks amino acids, right? I don't think top sirloin, I think amino acids. And I think top sirloin as I'm eating it, but really what they are, are amino acids, including leucine. - Yeah, well, there are two good things about plants, and neither of them is taste for me. I would eat steak

all the time if I could. I did when I was a kid, I'm an Australian. But plants have two benefits. One is that they're highly nutritious, and they'll give you a lot of the vitamins and nutrients that I need. I don't take multivitamin, I don't want to have the excess iron in my body. So there's that high density nutrition. So those dark leaves, if it's a spinach salad, great. The second is that there is what's called xenohormetic molecules in plants. That term, xenohormesis is a term that I came up with with my friend, Conrad. How it's, which means stressed plants make molecules that benefit your health. I'll break it down. Xeno means between species, and hormesis is the term, whatever doesn't kill you makes you stronger and live longer. And the idea is that when plants are stressed out, think of a great vine that's dried out and then starting to harvest the grapes, which is typically how it's done. They are full with resveratrol, because resveratrol is a plant defense molecule that I think is made to activate those sirtuin genes in a plant. So plants have sirtuins just like we do. But by purifying or at least concentrating in a light-proof bottle and keeping it out of the air, we stabilize the xenohormetic molecule, or it's a cocktail, not just one, there's others in wine. We then ingest those and get the benefits of activating our own defenses, because our food was getting stressed out. And by stressed, I don't mean psychologically stressed. I mean, biologically stressed. And so I try to eat plants that have gone through a bit of stress. They might be brightly colored, they've had too much sun or got nibbled on by a caterpillar. So you go to places where it's organic or it's fresh, local, and those are the plants that aren't perfect, and they probably have high concentrations of these molecules. And in addition, I also buy the supplements to make sure I'm getting enough of those as well. - Which supplements mimic that? - So resveratrol will, there's another one called quercetin, or quercetin, some people call it, what you find in trace amounts in apples and onions. And we also showed back in 2003 that it activates sirtuins as well. But others have, 20 years later, found that it kills senescent cells or helps kill senescent cells. So it's a double whammy with that molecule. - And are you actively picking out the peaches that look like they were nibbled on by a caterpillar? - No, but I don't worry if they've been banged up a bit. - What's the story with antioxidants? Are they of any value whatsoever, because the way that you describe them at the beginning, and what I've heard recently is that they are not all the rage for anti-aging. What are they doing that's useful? Should we be seeking out antioxidants anyway for other seller health purposes? - Well, yeah, antioxidants are not going to hurt you unless you take mega doses. We do need some oxidants for our immune system. And there's even, what's called mitohormesis, which is your

mitochondria power packs, need to have a little bit of these free radicals to be able to function. So you don't want to overdose on these antioxidants, vitamin C, vitamin E, don't overdo it. - You don't take a multivitamin, correct? - Right. - I think I'm going to stop after this conversation 'cause I've always just taken one for the kind of insurance purpose, which is a stupid purpose. Not actual insurance, but just thinking, oh cap top off on my ACBD. - Right, and I'll pee out what I don't need, right, sure. - But that never bothered me. The whole expensive pee thing never got. That argument never got made because of that. A good vitamin is not that expensive. I just figured better safe than sorry, but it may be that it's detrimental. - Well, it can in the case of iron as we discussed and the antioxidants. So when I came into the aging field in the early 1990s, it was all about antioxidants. And we thought that enzymes by the name of catalyze and superoxide dismutase, well, they're going to be the key to longevity. It turns out that it's largely been a failure that giving animals and humans antioxidants, haven't had the longevity benefits that we dreamed of. And the main reason is that there's a lot more going on than just free radical damage. The epigenome gets disrupted, we've got these proteins misfolding. And so the problem really has been that we didn't realize that you need to turn on the body's natural defenses against that plus a whole host of other things to get the true benefits. But I'm not going to say it's a problem taking it, an antioxidant drink, pomegranate juice for one is full of good stuff, including xenohormetic molecules. But resveratrol is a good case in point, which is when I worked on resveratrol as a longevity molecule, first we showed it in yeast and worms and flies and mice. Before that, it was thought that resveratrol was good for your heart in red wine when you drink red wine, because it's an antioxidant. So then we showed that it extended the lifespan of yeast cells through this genetic pathway, the sirtuins. And we then tested whether resveratrol, if we change one atom to make it not an antioxidant, guess what? It still worked fine. So it wasn't its anti-oxidant activity that was extending lifespan. It was its ability to turn on the yeast's defenses against aging. Conversely, when we gave the yeast antioxidants, they lived shorter. So yeah, that was the beginning of my transformation into thinking turn on the body's defenses, don't give it the antioxidants. - This is an opportunity for me to say something that I've been wanting to say for a long time, which is that, what's so wonderful about science is that because the goal is mechanism, you can really start to understand as you just described, what actually mediates a process is very different than what modulates a process. I mean, if a fire alarm goes off in the building right now, it's going to modulate our attention. That doesn't

mean that it controls our attention, it's not mechanistically relevant. And so I think this thing about antioxidants is one of these cases, it sounds like where it's in the right ballpark, but until one really unveils the mechanism as you have, you can be, one can or in a field, can be badly wrong for a very long period of time. It sounds like the sirtuins

01:33:45 Behaviors That Extend Lifespan, Testosterone, Estrogen

and really getting down to the guts of the machinery of what causes cells to age is really what it's about. Zooming way out, what are the behavioral tools that one can start to think about in terms of ways to modulate these? Basically the way that DNA is being expressed and functioning. I've heard you talk before about hormesis of other sorts, cold exposure. We talked about fasting. We talked about exercise in broad terms, but what about any evidence, if it exists, as to whether or not aerobic training versus weight training, these sorts of things. In other words, what are the sorts of things that people can do to improve their sirtuin pathway? And I realized that there are caveats. We can't go directly from a behavior dissertations, but in the general theme, what can people do, what do you do? - Right, well, we know that that aerobic exercise in mice and rats raises their NAD levels and their levels of sirt, one of the genes goes up two actually, number one and number three. What we don't know yet is what type of exercise is optimal to get them to change. We will learn, we're doing work. Now it's revealed that we're doing work with the military in the US, to try and understand that kind of thing. And I'll always tell you and the public, when I don't know something I'm not going to extrapolate. But what do I do? I base my exercise on the scientific literature, which has shown that maintaining muscle mass is very important for a number of reasons. The two main ones are, you want to maintain your hormone levels. I'm an older male, losing my testosterone and muscle mass over time. And by exercising, I will maintain that and have, in fact, I probably haven't had a body like this since I was 20. So that's one of the benefits of having this lifestyle. - Sorry to interrupt you. You do know we did an episode on hormones and there are data in humans that show that there are some males in their '80s and '90s where their testosterone is equivalent to the average of 25 and 30-year-olds. I can get you that information, is really impressive studies. Unfortunately, they didn't include a lot of information about the lifestyle factors, et cetera. But this idea that testosterone goes down with age, it might be the trend, but it's not necessarily a prerequisite. - Right, I believe in naturally increasing and maintaining these hormone

levels and I've been measuring them for a long time. And I could see for me, my testosterone levels were steadily, levels were going down. - And then you got tenure and they went back up again. [both chuckle] - No, I actually became complacent. And it was the worst. Actually my age changed in the wrong direction after that, 'cause I was relaxed. - Interesting. - And not worried about the future. But then I got serious. And I actually, according to the InsideTracker algorithm, got my age down from 58 to 31 in a matter of months. So that was a big drop. And I've been getting steadily younger over the last 10 years, according to that measurement, the blood test. - What about estrogen? Because women are different in the sense that they do the number of eggs that they, and the ovaries change over time, right? Do you think that they can maintain estrogen levels in over longer periods of time using some of these same protocols? - Well, yeah, I get into trouble from a certain university when I talk about this too much. - About estrogen? - Just about fertility and long story. I don't want to get too much into the anecdotes, but I'll tell you the science, which is that if you take a mouse and put it on fasting or caloric restriction for up until the point where it should be in fertile, so that's about at a year of age, a mouse gets infertile, female mouse. - Due to fasting or due to simply to aging? - Due to aging, due to aging. The fasting, it's not extreme fast, it's just less calories. Then you put them back on a regular food, and they become fertile again for many, many months afterwards. So the effect on slowing down aging is also on the reproductive system. - Interesting. - And so that, I wouldn't say to any woman, I wouldn't think that they should become super skinny to try and preserve fertility, that's not what I'm saying. But these pathways that we work on these, sirtuins are known to delay infertility in female animals. Case in point, I'm one of the lead authors on a paper where we used NMN. Remember, this is the gas, the fuel, the petrol for the sirtuins. We gave old mice. One group of mice was 16 months old. Remember they became infertile at 12, gave them NMN. And I think it was only six weeks later, they had offspring. They became fertile again, which goes against biology, the textbook biology, which is that female mammals run out of eggs. Turns out that's not true. You can rejuvenate the female reproductive system, and even get them to come out of mouseopause as we call it. So that's a whole new paradigm in biology as well. - That's super interesting. Sorry to interrupt you, but I'm reminded by a set of studies that were done by your former colleagues 'cause they're no longer there, David Hubel and Torsten Wiesel, my scientific great grandparents. Won the Nobel prize for discovering, what are called critical periods, this phase of early development when the brain is extremely plastic. And a big part of

their work was to show that after a certain point, the critical period shuts down, essentially the brain can't change or not nearly as much. And then people came along later and showed that you could open up these critical periods again, but very briefly, and it takes a very specific stimulus, essentially, high degrees of focus, et cetera. However, there's a well-known phenomenon in this literature where if you take an animal and to some degree, this has been shown in humans as well, and you let them pass through the critical period, but then you essentially sensory deprive them. You take away experience, you close both eyes. You essentially reopen the critical period. So it seems like I couldn't help but mention this, that there's this parallel between what we're talking about here with fertility and neuroplasticity, where yes, there is a timer where certain things are available to the organism early in life, and then they tend to taper off. It's not an open and shut, but they taper off. But then a deprivation can actually reactivate the availability of that process. Forgive me, I just couldn't help him mention it, but to me, so both of those things are associated with youth, fertility and neuroplasticity. And so I think that it'd be so interesting.

01:40:35 Neuroplasticity & Neural Repair

I'd love to collaborate with you on this to explore how neuroplasticity might actually be regulated by these things like the sirtuins. - Right, and the sirtuins do control memory in neurons as well. So what I think is really interesting is that what we're learning from work that you and your colleagues have done and in my lab as well, is that the body has remarkable powers of healing and recovering from illness and injury. And what we once thought was a one-way street and you just can't repair, or you can't get over these diseases, you can reset the system, and the body can really get rejuvenated in ways that in the future will wonder, why didn't we work on this earlier? The future of humanity is more like us walking around like Deadpool. We'll probably be cleaner, and we won't smell as badly, but Deadpool, if you don't know, can get injured and just recover. It's very hard to injure this guy, and we're going to be the same. There are many species you cut off the limb, the limb grows back. - Salamanders or. - Yeah. We are now learning how to tap into that system. And in part, what we're doing is reversing the age of those cells, and telling them how to read the genes correctly again, reversing the age of that epigenome. And when you do that, the cells, the brain, for instance, the skin. We did the optic nerve. - Let's talk about those results for a second. Then I want to make sure that

we return to some of these behavioral protocols. You have this amazing paper at the end of last year, cover article, full article in nature, showing that essentially a small menu of transcription factors, which control gene expression, et cetera, could essentially reverse the age of neurons in the eye and rescue those cells against damage. Essentially allow blind mice to see again, and offset degeneration of these retinal cells, incredible paper, and such a boom to the field. Where does that stand now in terms of human clinical trials? I mean, how do, what are you envisioning in terms of the trajectory of those data from mice into human someday? - Right, well, to get to the point immediately, we're going to be testing the treatment on monkeys, just for safety reasons. And then the first patient should be done sometime in 2022, early 2023, and we're going to try to recover blindness. - This involves making an injection of a virus into the eye, right? Right now, there's no way that I am aware of to manipulate these transcription factors through a pill or some other? - And that's why, we working on in my lab at Harvard right now. So it will be - It will base moderation of - Well you pop a pill in the whole body gets rejuvenated by 20 years. That's what we're aiming for. Now we do it with gene therapy in the eye and other places. So in the IES, it's single injection, the genes go into the retina and we can turn it on, with a drug called doxycycline. And we do that in the mice for four to eight weeks, then the eye gets younger. We can measure that cause you can measure the clock. And then the vision comes back in those mice. And I don't see any reason, why it shouldn't work in people because it's the same structures and mechanisms that are on in the human as well. Now these - - And it's one injection. - It's one. - I should mention injections into the eye obviously nobody should do this outside of an ophthalmology clinic. And there definitely by an ophthalmologist but, the injections into the eye are painless if done correctly by the right person. It sounds dreadful, but it's actually, I've seen it done hundreds of times. I've done it, thousands of times and it's not to myself, but to other creatures. And there's a way of doing this as completely painless to the person - - Oh you don't feel it. It's a tiny, tiny needle too. But the great thing about this is that it's a one-time treatment. Those genes go into the back of the eye and stay there, forever. And you can just turn them on whenever you want. So what we found is you can turn them on in the mice, they get their vision back, and then you turn it off again. And so far, many months out, the benefit has remained, but if it does decline, we'll just turn it back on and reset the system, rinse and repeat. So one day what's exciting is that we could potentially do this across the entire body and just take this antibiotic, every five years and go back time and time again. - And thinking

about the body and what's going on under the head I'm amazed, still that there isn't a simple, affordable technology that would allow me to just look into my body and see whether or not there are any tumors growing anywhere. I mean, it's not that hard to look into the body. I mean that the technology exists. why hasn't anybody created an at home or pseudo at home solution, like a clinic where you can go and pay 50 bucks or a hundred bucks and see if you have any tumors growing anymore. - Yeah, it's still expensive. You can get your doctor to try to get you in, there's some companies that offer blood tests that look at circulating DNA, that'll measure it. We're getting there. It's still probably five to 10 years away from being really cheap. You can do things like a colon cancer test at home. I think it's a hundred and something dollars. You ship off your shit, excuse my language, and they measure it. And they tell you if you've got colon cancer, with high probability, I did that during the pandemic because I didn't want to get a colonoscopy. - Mhmh, is it more accurate or as accurate as a colonoscopy? - I believe it's close to being as accurate. The downside is that during a colonoscopy, they can pinch off the polyps that are looking dangerous, whereas this obviously isn't that, but it's certainly easier to do. And my father who's Australian tells me that it's free for Australians.

01:46:19 Ice Baths, Cold Showers, "Metabolic Winter"

They get this test routinely. - Mhmh, interesting. I want to return to the topic that I took us away from. So I apologize, which is behavioral protocols. Do you regularly do the cold shower thing? Ice baths, cold water swims, are you into that whole biz? [David chuckles] - Well, you do know that I've done it at least once 'cause we did it together. - That's right. Not the same bath, just to be very clear, same sauna, different ice baths, [David chuckles] the idea of Sinclair and Huberman taking an ice bath together it's a, it might warm some people's hearts, but just to be very clear, different, same ice bath, different, different times. - Yeah, thank you for clarifying. - [Andrew] Yeah. I don't do them regularly. I do try to sleep cool. I sleep better anyway. I try to dress without a lot of warm clothes. I'm here in a T-shirt and it's middle of summer, but in winter, I'll try to wear a T-shirt too. - So you're challenging your system to thermoregulate? - Right, right. I've got this, hypothesis with Ray Cronise. We published what's called The Metabolic Winter Hypothesis, which is, few tens of thousands of years ago, we were either hungry or cold or both and we really experience that now. And so, we try to give ourselves the

metabolic winter and part of the problem I think with the obesity epidemic is that we're never cold and cold, when you're cold you have to burn energy. It may be only slightly, but over the whole night, if you're a little bit cool, you'll actually expend more energy. So I try to do that, but I'm not a big fan of cold showers. The sauna, I don't have access to my gym as much as I did. So, but I do want to get back into it. I used to do it regularly with my son and I posted on Instagram once that he could stay in there for 15 minutes and I could only stay in for about three. Anyway, long story short,

01:48:07 Obesity & How It Accelerates Aging, GnRH

I try to compensate with changes in my diet and exercise until I get back into it. - You reminded me of something that I meant to ask earlier that obesity reduces NAD levels and accelerates aging. How? I mean, okay. So again, this is the, the scientist in the us, so someone's carrying a lot of excess adipose tissues, subcutaneous and, visceral fat. But why should that reduce NAD in any ways that are independent of effects on glucose and insulin? If it, you know, is there's something direct about white adipose tissue. And the reason I ask this, is not simply to dig into mechanism alone, but I think there are really interesting data now that fat actually gets neural innervation. I mean, it's not just a, it's not just stored fuel. It's stored fuel, that's acting as an endocrine organ, essentially. So, why would being fat make people age faster? - Yeah, that's a question that, is so obvious, but so few people ask it, that's what makes you a good scientist. And so that we don't know, but I'll give you my best answer, which is that, obesity comes along with a lot of problems that, include a lot of senescent cells in fat, if you stain old fat for senescent cells, it lights up. - Mhmh. And when you kill off those cells, at least in mice, and maybe in humans, it looks like the fat is less toxic to the body. 'Cause those senescent cells in their fat are secreting these inflammatory molecules that will accelerate aging as we now know. We talk about the sirtuins in NAD. So if we, if we just look philosophically, at why this would be the sirtuins only, like to come on or get activated when the body needs, is on the right adversity. And if a cell is surrounded by fat or contains a lot of fat, it's going to think times a good, it doesn't need to switch on. So that's the evolutionary argument. Mechanistically, we don't know, but it could have something to do with the response to glucose, which then responds to the sirtuin gene, but that hasn't been worked out very well. - And is there any evidence that leptin, this hormone from fat can actually, interact with the sirtuin pathway? - I don't recall seeing that- - Maybe I could do a sabbatical in

your lab and that'd be a fun one. - Definitely- - Because leptin during development is what triggers, the permission for the hypothalamus to enter puberty, right? - Yeah. - This is why kids that eat a lot when they're young and get overweight will also start to go and undergo puberty more quickly, although they have reproductive issues later. - Well yeah. We should study the hypothalamus together 'cause, the hypothalamus is, can control the aging of the body. - The most interesting part of the brain. [Andrew chuckles] - For sure. - Yeah, absolutely. - If you turn on the SIRT1 gene, the SIRT2 that we work on, in the hypothalamus that actually, will extend lifespan. Also, it's been shown by Dongsheng Cai at Albert Einstein College of Medicine, that if you, inhibit inflammation in the hypothalamus, in a mouse, it will increase or maintain the expression of what's called GnRH, which is the hormone that, he found actually controls longevity in the mouse in part. And so keeping inflammation down in the hypothalamus, is sufficient to extend the life span of animals. And I reviewed that paper for nature all about seven years ago. And that was the first demonstration that the hypothalamus is one of the leading regulators of the body's age. - I find this fascinating GnRH, for those of you that don't know actually comes from neurons in the hypothalamus that then, literally reached down into the pituitary and trigger the release of all the things that control fertility, luteinizing hormone, follicle-stimulating hormone, et cetera. It's such a powerful set of neurons, and it's never really been clear, what at a behavioral level triggers the release of GnRH. There's all the stories about pheromones and timers and puberty, et cetera, but environmental conditions and dietary conditions

01:52:10 Methylation, Methylene Blue, Cigarettes

and behaviors that can control GnRH release, I think, is an incredible area for exploration. I'd love to do that sabbatical by the way. I have a couple, well seemingly random questions, but I can't help, but ask because one thing I like to do is forage the internet for practices that at least more than a few people are doing, and then wonder whether or not there's any basis for it. You mentioned methylation as a detrimental process, the way it disrupts the epigenome and the CD reader, so to speak. There are people out there who are ingesting methylene blue. And when I was a kid, I used methylene blue to clean my fish tank. And I love fish tanks. I know you're into aquaria also, a different podcast episode, we'll talk about aquaria, but why in the world, would people ingest methylene blue? Meaning is their logic correct? And or is that a dangerous

practice? I'm not sure I'd want to ingest methylene blue, sounds not like a bad thing to do. - It stains your body if you've seen, yeah methylene blue- - Yeah, there was someone in my lab as a postdoc was using it to study a completely different process related to the blood-brain barrier and used to inject into animals and they would turn blue, but then again, people ingest colloid silver. You know they'll put in there, there's this, please people don't do this or if you do, just don't tell me, 'cause I won't like it. They, people put it in their eyes and some people actually stain their skin. They actually become kind of a silver purple brown color if they do it excessively. I mean, there's a lot of crazy stuff out there. But what do you think they're thinking with this methylene blue thing or should we just get them to a good psychiatrist? - I don't know, for sure. I think methylene blue was found to extend the lifespan of some lower organism and that's where it came from. My recollection- - With the emphasis on lower organisms. - Yes smaller organisms. I think doesn't, do you remember Andrew does it, interrupt or interfere with mitochondrial activity and that's- - Maybe that's why they are doing it. - Yeah. - [Andrew] Okay. - We need to look this up and post it. - [Andrew] Okay. - We'll get to the bottom of this, but those methods, let's talk about those. - [Andrew] Yeah. - Those methods have to be placed on the right, part of the genome. They get attached to the right genes in the wrong genes. And if you have a lot of methylation, it's going to mess up the epigenome. Smoking will do that, lack of exercise, all that good stuff. So you, what you actually want to do is you want to measure it and make sure what you're doing with your body, is working. How do you know that if you do this or that is actually helping. And so you can test your age. I could take, a swab from your mouth and tell you how old you are biologically. And then we could work on trying to bring that down and actually there were anecdotes now, that people are reversing their age by a decade or more just by doing some of the things that we've talked about and some other cutting edge stuff that I'm going to write about. But yet, but you have to measure stuff. That's, I didn't want to forget to bring that up. I'm measuring stuff all the time. I have blood tests like you, I've got this monitor that stuck to my chest right now that's measuring myself a thousand times a second and I measure my biological age. - What's it measuring a thousand times a second? A huge list of things. - Yeah, yeah. So this, this little device is stuck here and it's for two weeks that you just recharge it or send it back and get a new one. It's got a body temperature movement, heart rate variability. It's an FDA approved device, it's not a toy. It's not one of these recreational things. It also listens to my voice, eventually will tell me if I need a psychiatrist or if I'm depressed, it will tell me how I sleep,

obviously. But when you put all that data together and it's individualized and anonymized, it can now tell my doctor in real time, if I've got a cold that needs an antibiotic, or it's just a virus. If I am suffering from COVID-19 or even if I'm going to have a heart attack next week. And so these little devices are going to be with us

01:56:17 X-Rays

all the time, instead of going to your doctor once a year, which is ludicrous. - I have to ask you about x-rays. 'Cause every time I go through the scanner at the airport, I think, "Sinclair would never do this." And the argument I heard you give about this before was a really excellent one, which is that it's a low level amount of radiation, going through at the airport, but the argument is always, well, it's just as much as on the plane and your argument, your counter-argument I should say was, "Well then why would I want to do both, right? Why would?" So when you go to the airport, assuming you're not running late and you have to go through the standard line, what do you say to them? And do you say, "I'm David Sinclair." And then they shuttle you to your own line. What do you say? You do say, "I don't like this thing." Do you have to give them a reason? - No, you don't. You can say, "I don't want this." And they'll get annoyed 'cause it's hard for them to pat you down, but you get a pat down and you you're done as long as you're not in a hurry, it's fine. If you want to pay for the TSA Pre in America or the way to get around those scanners, you can do that. So I travel a lot, so it's worth it anyway, but I just go through the metal detector, I don't get scanned. - And the metal detector doesn't have the same, same problem. And what about x-rays at the dentist? Yeah. - Well, you know one x-ray is not going to kill you. Two's not going to kill you, but I - - Three will kill you. No, I'm just kidding. [Andrew chuckles] - I try to limit it because it's cumulative. - Right. - And I went for six years without having a dental x-ray and then my last visit, I just gave up. I was tired of arguing with my dentist. So they gave me one, but they've got lead coats on and they put lead all over your body. That's telling you something right there. And funnily enough, my teeth hadn't changed. Now you can balance that by saying, "Well, one x-ray, two x-ray, three x-rays is worth it if I have cavities." And that's true, you want to know what's in there, but doing it regularly, for me, I don't think it was worth it because it, my teeth are in perfect health and I've always been, I don't have any cavities, didn't have braces, they're fine. So stop scanning me. I mean, I know you have to pay for the machine, but you know, do I have a choice? Yes, so stop pressuring me. - You know,

who shared your sentiments about x-rays and the dentist in general? My apologies to the dentists out there, was the great physicist, Richard Feynman. This is a story about him that's not especially well-known, but he had very serious concerns, health concerns, about x-rays because he understood the physics and he understood enough biology that, he was actually quite vocal about his, dislike of dental technology and its dangers. And he talked about some of that.

01:59:00 Public Science Education, Personal Health

People can find that on the internet, if they like. Speaking of people who, are like Feynman, who've been engaged in public discourse about science. One of the things that I appreciate about you, in fact, the way that you and I, initially came to know one another is through your public health education efforts. So, obviously we're doing this podcast, you've done the Joe Rogan Podcast, Lex Fridman's Podcast, excuse me Lex, I'm still adjusting that. Lex Fridman's Podcast and many other podcasts, you've written an amazing book. What are you thinking these days in terms of what the world needs in terms of, education from scientists, education from MDs, education in general as it relates to these things because, I think if nothing else 2020 revealed to us that there's a gap, there's a gap in understanding. And that the scientists too are guilty of, not knowing what to do with all the information that's out there on pub med or elsewhere. I'm just, you know, what are you thinking for yourself and in general, I'd like to just know, what do you think the world needs there? Maybe we can recruit some more public educators. - Yeah. Well, we've gone from a time, when you and I were, in college and young professors where the only way, to get our voice out to the public was either through a newspaper or a very short radio interview, which for me was extremely frustrating 'cause particularly the newspapers and my topic, every time was twisted into something that was not just embarrassing, but Harvard university used to bring me into the back office and- - Frankenstein. - "How did you say such a thing? We're all going to live to a 250." I didn't say that. So, we're now also in a world where we're overwhelmed with information, and most of it is wrong and anyone can pretend to be an expert. So we've gone from early days to now the future, and we're experiencing it right now thanks to guys like you, people like you, is that the experts, some experts, a small number who are brilliant and good communicators are talking directly to the public. This has never been able to be possible, until this time, right now. So another five years from now, and certainly by 10

years, I would hope that there are trusted sources of information of people who can not just communicate, the ideas directly, but are able to talk about things that are going on that aren't even published yet to say, "Here's what's really going on. And this is what the future looks like." But this is somebody, like yourself who spent their whole life studying a particular topic and knows what they're talking about. And this, this is also something that I think most people don't know that we scientists, if we tell a lie, we burst into flames, we absolutely cannot tell something, that's untrue. And to the best of our knowledge, we say it as it is, because if we don't, we're beaten up, and we, or we kicked out of the university. So the people who survive to our age, and I'm a little older than you. So I've survived a bit longer. - But a lot younger inside. [Andrew chuckles] - Nah, but we have to measure you with- - Yeah we need, I probably need a little help, hopefully not too much. - We'll measure that, and we'll work on your eating, but this is really, really important is that, finally people like your are allowed by our universities to talk to the public. I used to do it, with a real threat to my survival. People would look at me, "Oh, he's a salesman, he's promoting this and that." It was seen as a real negative, but finally, I think we're in a world where, it's not negative anymore. And the pandemic showed that we needed voices of reason, voices of fact, that you could trust. And you can see the popularity of your podcast, shows that the public, they're desperate for facts that they can trust, 'cause they don't know what to believe anymore. - Well, I'm being completely honest when I say this, that, you know, I followed your lead. I saw you on the Joe Rogan Podcast and my jaw dropped. I was like, "This is amazing, like this." Because, you get out other good scientists on before but, you're tenure Professor Harvard Genetics, Department of Genetics. And for those of you don't know, there's the Harvard and of course, Harvard Medical School and they're both excellent, of course, but these are the top, top tiers of academia. And I certainly understand what it takes to get there and survive there and to thrive there, it's like a game of pinball. You never win. You just, you just get to, if you're doing really well, you get to keep playing. And that's the truth in academia. And if you're not, you stop playing basically. But when I saw you, explain what you were doing in a way that was accessible to people and also talking about, possible protocols that they might explore for themselves to see if those were, right for them. I was just, I was just dazzled and excited, and I made every effort to get in contact with you. And, the rest is history, but, I think what's really exciting to me these days is because of 2020 and with everything that's happened and it continues to happen. There's a thirst for knowledge. There's also this direct to the public route that you

mentioned. And, I think there's also an openness, I'd love your thoughts on this, but it seems to me that there's an openness in, from the general public, about health practices, that there are actually things that people can do to control their stress level, to control, their sleep, to control their cholesterol if that's what they to do, maybe they don't and to even control their lifespan, which I think is remarkable. And, I know I speak on behalf of so many people, when I just, I want to say, thank you. You've, truly changed the course of my life. I would not be sitting here doing this were it not for your example. And I always say Sinclair, many people have written books, many academics have written books, as you have, but in terms of doing podcasts and really getting out there with your message in a way that I have to assume raised your cortisol level and heart rate just a little bit, but you did it nonetheless. You are truly first man in and that, that deserves a nod. And, I have a great debt of gratitude to you for that. So thank you so much. - Oh thanks, Andrew. You're a, you've become a good friend and I'm super proud of what you've done and what you, I know what you will do. - So in addition to your book and your presence on social media, Instagram, and Twitter, and appearances on podcasts,

02:05:40 The Sinclair Test You Can Take: www.doctorsinclair.com

recently I've noticed that you've opened up, a survey email/website that people can, access, excuse me, to get some information about their own health and rates of aging. Tell us about that and what's being measured. And what is this test that you've been working on, secretly and now soon, not so secretly. - Yeah, well that, what I want, is a credit score for the body to make it easy for people to follow their health. And there is a number, there's a, there's a biological age that you can measure. Unfortunately, the test is many hundreds of dollars right now, but in my lab, we've been able to bring that down a lot. And so I want to democratize this test so that everybody has access to a score for their health that can predict their, not just their future health and time of death, but to change it. And I'm building a system that will point people in the right direction and give them discounts for certain things that will improve, not just their health now, but 10, 20, 30 years into the future. And we can measure that, and very cheaply, keep measuring it to know that you're on the right track, 'cause if you don't measure something, you can't optimize it. And so this is the biological age test, we've developed it, it's a simple mouth swab. We're rolling it out. We're building the system right now. And there was a sign up

sheet 'cause a lot of people want to get in line, go to doctorsinclair.com, you can get on that and you'll be one of the first people in the world to get this test and see what we're doing. - Oh, fantastic. Will people be celebrating their, biological age birthdays? In other words, if I'm minus, like if I can imagine, so I'm 45 right now, soon to be 46. But if I, if I were to be so lucky as to get my biological age to 35 within 12 months, maybe you can help me do that. Do I get to celebrate, a negative birthday? - Absolutely. And my plan is that those people who take their age back a year or more, we think we can go back 20 years eventually, they'll get a birthday card from me and it's a negative birthday card. [Andrew chuckles] - I love it. And probably very little, actual birthday cake being ingested but, who cares 'cause you're living that much longer. - That's full of stevia,* that'll be fine. [Both chuckle] And thank you for talking to us today. I realized I took us down deep into the guts of mechanism and as well, talking about global protocols, everything from what one can do and take if they choose, that's right for them to, how to think about this whole process that, that we talk about when we talk about lifespan as always an incredibly illuminating.

02:08:13 Zero-Cost Support & Resources, Sponsors, Patreon, Supplements, Instagram

Thank you, David. - Thanks Andrew. - Thank you for joining me for my conversation with Dr David Sinclair. If you're enjoying and or learning from this podcast, please subscribe to our YouTube channel. In addition, please subscribe on Apple and or Spotify. And on YouTube, you can leave us comments and you can leave us suggestions, for future podcast guests that you would like us to feature. In addition on Apple, you can leave us up to a five star review and you can leave us a comment. Please also check out the sponsors mentioned at the beginning of this episode, that's the best way to support this podcast. Also, I teach science and science related tools on Instagram. It's [hubermanlab](https://www.instagram.com/hubermanlab) on Instagram. I also have a Twitter which has also [hubermanlab](https://twitter.com/hubermanlab). So be sure to check those out. A lot of the material, covers things similar to the podcast, but oftentimes I'll cover a unique material, not featured at all on the podcast. So that's [hubermanlab](https://www.instagram.com/hubermanlab) on Instagram and on Twitter. In addition, we have a Patreon, it's patreon.com/andrewhuberman. And there you can support the podcast at any level that you like. Today, and in many other previous episodes of the Huberman Lab Podcast, we discuss supplements. While supplements aren't necessary or right for everybody, many people derive tremendous benefit from supplements. For that reason, we partnered with

Thorne, T-H-O-R-N-E, because Thorne Supplements are the absolute highest quality and the absolute highest precision, meaning what you see listed on the bottle is what's actually in the bottle, which is not the case for many supplement companies out there. Thorne is one of the partners of the Mayo Clinic and all the major sports teams. And so they really are very trusted, very highest quality. If you want to see the supplements that I personally take, you can go to thorne.com/u/huberman, and there you'll see the supplements that I take, you can get 20% off any of those supplements. And if you navigate deeper into the Thorne site, through that portal, you'll also get 20% off any of the other supplements that Thorne makes. So again, it's Thorne, thorne.com/u/huberman to get 20% off any of the supplements that Thorne makes. Also take note that the lifespan podcast featuring Dr David Sinclair as a host, launches Wednesday, January 5th, you can find the first episode here on the Huberman Lab Podcast channel. They also have their own independent channel. You can find the link to that channel in the show notes. So please go there, subscribe on YouTube, also on Apple and Spotify. I've seen these episodes, they are phenomenal, and you're going to learn a tremendous amount, about aging and how to slow and reverse aging from the world expert himself, Dr David Sinclair. And last, but certainly not least, thank you for your interest in science.