Mark Mattson: I think caffeine is good. I published an article in Scientific American in 2015, and the whole take-home message of the article was that many of the chemicals that are in fruits, vegetables, tea, coffee, plants that are good for our health, the actual reason there in the plants, the evolutionary reason is that they're noxious agents. They're toxins, and caffeine's a good example.

Mark Mattson: If you take pure caffeine and put it on your tongue, you wouldn't want to eat it. It's a very bitter taste, and caffeine is a natural pesticide produced by coffee beans and tea leaves. If you take coffee beans or tea leaves, and put them on your counter, and put most any food next to it, and there's ants in your house, the ants will avoid the coffee beans and the tea, and they'll go for the other things that don't have the bitter-tasting chemical.

Announcer: Bulletproof Radio, a state of high performance.

Dave Asprey: You're listening to Bulletproof Radio with Dave Asprey. Today's cool fact of the day is that there are different ways to kickstart intermittent fasting, so it's easier for you. If you don't know about intermittent fasting, this is something I wrote about in the Bulletproof Diet. It's something I've been doing for a very long time. Basically, you eat the same amount of calories you're going to eat, you just eat them in a smaller eating window each day.

Dave Asprey: Basically, you have just lunch and dinner, skip breakfast, or have just lunch and breakfast, skip dinner. It's pretty straightforward. You don't want to eat in about six or eight hours. Here are a few different options that are out there for you. There's, one is fasting for 12 hours a day. There're studies for each of these things.

Dave Asprey: There's one fasting for 16 hours, and interestingly, in that study, men fasted for 16 hours, and women fasted for 14 hours because this is going to sound really, really bad, but men and women are actually different biologically. I know that's shocking for some of us. However, fasting can be hard on women, and I've seen this over and over since I started the Bulletproof blog, where the rules are different.

Dave Asprey: There's a couple really popular posts about why intermittent fasting can be bad for women that I've written over the time. There's also fasting two days a week, which is called the 5:2 diet. There's alternate day fasting, where you fast every other day, or have limited calories every other day. There's one weekly, 20-hour fast known as Eat Stop Eat, and people are just skipping occasional meal.

Dave Asprey: Then, there's this OMAD or the Warrior Diet, which is a 20-hour fasting window with a huge meal at night, stake and whatnot. You could do the same thing with a huge meal in the morning if you're the one who carry around steak, eggs and whatever else you're eating all day long. That might have some circadian benefits. Bottom line is six hours or sorry, six meals a day, so your body doesn't go into starvation mode, it is absolute bullshit.

Dave Asprey: It is a way to feel crappy, and probably stay fat. At least, that's what happened to me on something like that. That's not to say you couldn't do that. Sometimes, especially if you're working out a lot, but if you want to do that on a regular basis as a regular human being, you might not like the results of that. The number of processed foods, snacks you eat may go up dramatically if you do that.

Dave Asprey: Today's guest is the foremost scientific researcher on the topic of intermittent fasting. A guy that I'm really, really excited to talk with because there's so much academic research that goes back quite a while now about what intermittent fasting does, but it's one of these precious pieces of knowledge that hasn't entered our consciousness where it has been French knowledge.

Dave Asprey: It's just now becoming something that not just biohackers do, but your mom might do. In fact, my mom does do it. It makes a really big difference. Not only is this guest a top expert on what intermittent fasting does for you, he's also an expert on what it does for your brain, and he's one of the foremost researchers who are looking at cellular and molecular mechanisms of neurodegeneration like, Alzheimer's and Parkinson's.

Dave Asprey: If you read my book, Head Strong, I actually referenced some of his work in that book. I'm talking about Dr. Mark Mattson who's a professor of neuroscience at Johns Hopkins. Welcome to the show, Mark.

Mark Mattson: Thanks, Dave. I'm looking forward to talking to you. I've followed your Bulletproof website for a long time, and when I can, I listen to your podcast, which are always both informative and entertaining, so I'm looking forward to our discussion.

Dave Asprey: Well, thank you. I did not know that until we just got on, and you mentioned that. I'm truly honored because... I mean, in addition to the intro I just gave you, I mean, you are chief of the Laboratory of Neurosciences at the National Institute on Aging. At least, you were until you just retired last month. In terms of the anti-aging world that I live in, you're a godfather of that. The fact that you've ever heard the show is epic. Thank you.

Mark Mattson: Yeah. Well, there's a big... one of the big bottlenecks in getting science translated into the real world is communicating to the public. There're many scientists that either avoid intentionally, or just don't want to bother with taking the time to learn how to communicate with the general public.

Mark Mattson: That's like years, which really are evidence-based and communicate things in a way people can understand, I think our value. I do, and these podcasts are easy to listen to. I can even be working on a manuscript, while I've got a podcast in the background, so yeah. I do find time to listen.

Dave Asprey: Okay. That's really cool. I'm going to go there. There are not a lot of people here who can listen to one thing and write another thing. Have you always had that superpower?

Mark Mattson: I don't know if it's a... I think it started by, I'm an NPR nerd, so I'll have... and I telework. Even when I was lab chief at NIH, I used to telework one, and sometimes two days a week. I just have NPR on in the background, and I'd tune in and out. There're certain points when one writes that you can relax a little because you know what, you don't have to concentrate so much. Yeah. I've learned to do that.

Dave Asprey: One of my buddies, a real dynamic guy named Andrew, and I'm not going to drop his last name. I think he likes to hide behind the curtains, but I had dinner at his house and wrote about it in Game Changers, and he knows what I'm talking about. Entrepreneur friend. He told me that years ago, he started using Bluetooth headphones before the they actually had the Bluetooth standard done, and he listen to audio books 24 hours a day.

Dave Asprey: All the non-fiction stuff, just to learn things, and he just finally said, "After two years of it, my brain just started learning when I wasn't paying attention." He had to stop worrying about losing something. He just assumed some of it's going in. I haven't gotten to that level yet, but I have been able to listen to one thing and write on my latest book, but not the whole time.

Dave Asprey: Sometimes I would, but the load on my brain felt pretty high. Do you feel more loaded if you listen to podcast and write manuscript? I'm fascinated by this. I wasn't going to be-

Mark Mattson: Well, no. I'll pause. I'll turn off the volume on what I'm listening to when I get to where I have to really think for 10, 20 minutes straight or-

Dave Asprey: That's a neat little technique. I think most people listening are going, "Oh my God, it's possible to write and listen?" Anyway, that's a new skill for me. All right. You also talked about the difficulty of translating science from academia into public knowledge. I think some of my scientist friends are a little bit frustrated. They're saying, "I've spent my life doing all this crazy work, but no one knows about it."

Dave Asprey: They're feeling like, I did my part, but you've done something interesting. In academia and for research, there's an index of productivity in citation impact, so your h-index is over 200, which in academia means, you're super a Rockstar, gold record label. It's a pretty good number.

Mark Mattson: That's based on your total career, so it also means I'm getting old.

Dave Asprey: Okay. It's a fair point, but you've incited 150,000 times, or your work has been cited. You're up there, right? At the same time, you have three and a half million

TED views on your talk about intermittent fasting. You've crossed... I'm going to call it crossing the chasm to butcher that term into, all right.

Dave Asprey: You can now talk to the public about intermittent fasting and reach large numbers. You've talked to the academic and nutritional research on neuroscience world. What was the trick for you as a, I'm going to call hardcore aging neuroscience guy, to crossover and talk to the public well?

Mark Mattson: Talking to friends, and even students in the lab, and trying to learn to explain things initially in a very easy way, and then it's by looking at their facial expressions, you can tell whether they're understanding it or not. If they're not, back off and give some analogy, or take a little different pathway to try to help them understand what I'm trying to convey. I think it's just a matter of doing it.

Dave Asprey: Practice.

Mark Mattson: It's practice, yeah.

Dave Asprey: Okay. Just something you set out to do, was this a goal you set or it just emerged overtime?

Mark Mattson: It just emerged. Yeah.

Dave Asprey: Okay. Cool.

Mark Mattson: Although, now that I'm retired from NIH, so I'm semiretired. I'm still involved with working with clinicians at Hopkins doing trials of intermittent fasting in various patient populations, and I'm writing a book finally. Two books actually. The first is going to be with an intermittent fasting theme, and a historical perspective, and a lot of hardcore science hopefully, explaining in a way people can understand.

Mark Mattson: Then the second book is going to be pure neuroscience, which is what I'm really excited about. It's going to be something like, thought patterns, how the brain understands and escapes reality.

Dave Asprey: Okay. That-

Mark Mattson: Which is a-

Dave Asprey: That is going to be fascinating. In fact, when you write that book, we'll have you on. A big part of my understanding of the world is really, it's the challenge of not believing your own story, so you can see what's really going on, including your own food, right? The story in your head is if I don't have lunch, I'm going to die. It's probably not really true. Okay.

Mark Mattson: We wouldn't be here, would we?

Dave Asprey: Exactly, but man, it sure feels true at the time. That's the challenge of fasting in a nutshell is how do you feel good when you do that? Well, let's get in on fasting and just go in for people who... all right, and we've heard about fasting, you have pictures of people in robes fasting for days on end and things like that. Talk to me about the difference between calorie restriction, and actual fasting, and what you've learned about that over the course of your career?

Mark Mattson: The differences have to do with the frequency of food intake. A typical human liver can store about 700 calories worth of glucose in the form of glycogen. If you're this moderate activity like we are now, it takes 10 to 12 hours to use up those 700 calories. Then, when those calories go, then you start using fats. The fatty acids are released and those are the precursors of the ketones.

Mark Mattson: It's possible to reduce your daily calorie intake, but eat, as you mentioned in your introduction, eat meals frequently. Every time you eat a meal, you replenish the glucose storage in your liver, and so your fats are never mobilized. Your ketones never go up. Fasting by definition, if you're in a fasted ketogenic state, that's a sufficient time period with not eating to be designated as fasting. If your ketones never go up, you haven't hit a fasting state.

Dave Asprey: Okay. What do you do? You've been studying this stuff for a long time. What do you do when you wake up in the morning like, what's a typical day for you? What's a typical week?

Mark Mattson: I never eat breakfast. I usually try to work out midday or early afternoon.

Dave Asprey: Yeah.

Mark Mattson: I used to run a lot, do a lot of trail running. I had some knee osteoarthritis because I had a meniscus tear probably.

Dave Asprey: Yeah.

Mark Mattson: Now, I'm mountain biking. Maybe two or three days a week, I'm on the trails on mountain bike. The other days, I usually just do some walking or stationary bike. I pretty much always do that before I eat around midday, early afternoon, and then I eat all my food within usually, a six-hour time window. Sometimes five hours. The rationale for exercising at the end of the fasting period is it's pretty simple.

Mark Mattson: You get an extra boost in the ketogenic state, but there's also a number of we call pathways or signaling mechanisms that are activated by exercise, both exercise and fasting to get amplification of those pathways.

Dave Asprey: Is this mTOR you're talking about?

Mark Mattson: Well, yeah. That's one, and autophagy.

Dave Asprey: Okay. Some of my favorite words. Can you define them for people who don't know what they are? mTOR and autophagy?

Mark Mattson: Okay. This again, relates to the notion of the metabolic switch from glucose, to ketones, and what happens then. When your glucose levels are high, normal or particularly after eating a meal, there's a pathway called the mTOR pathway in cells that is activated. That pathway stimulates the uptake of the glucose. It also stimulates the uptake of amino acids from proteins in your diet.

Mark Mattson: Then, the cells increase their protein synthesis, and they're in a growth state. However, while they're in a growth state, they are also accumulating molecular garbage. When cells are in a growth state, and your glucose protein levels are up in your blood, it can help the cells grow. If that stays chronically on, there's accumulation of molecules damaged by free radicals, dysfunctional mitochondria.

Dave Asprey: Yeah.

Mark Mattson: Those damaged molecules are normally removed from the cells by a process called autophagy. It's the cell's garbage disposal.

Dave Asprey: In fact, we just had a recent interview on metabolic autophagy that was very well-received, and it's a very important thing like, getting rid of the garbage. You're saying that if you do an intermittent fast, and then exercise at the end of it, you're going to turn up autophagy, and you're going to turn up mTOR, which allows you to take amino acids, and put it into the cells or no? Because those don't go at the same time, right?

Mark Mattson: No. They're going up. During the fasting and exercise, mTOR pathway is inhibited. The cells go into a stress resistance mode. They're trying to conserve energy, molecules, recycle protein, so autophagy, it's a garbage disposal, but it's also a recycling bin.

Dave Asprey: You can incinerate garbage to make energy?

Mark Mattson: To make energy, but also to breakdown damaged proteins, but then take the amino acids from those proteins that are not damaged then use them to make new proteins.

Dave Asprey: Okay. You get this from fasting?

Mark Mattson: Exercise, both, and when you combine them, you get a further enhancement of the autophagy. Then, when you eat and rest, then what happens is the cells have cleaned out the garbage, and then when you eat and rest, the mTOR pathway is active. The cells synthesize a lot of new proteins, and they can grow. For example, to your muscle cells, when you exercise regularly, your muscle

cells don't get bigger during the exercise. They get physically bigger during the rest period, but-

Dave Asprey: It's about recovery?

Mark Mattson: Right. If you don't exercise, the cells never get the signals that enhance their ability to grow when you do rest.

Dave Asprey: Right.

Mark Mattson: These cycles of metabolic challenge, recovery challenge, recovery and the challenges of being fasting and exercise, and then eating and resting, sleeping is very important. Those intermittent challenges we think can optimize health.

Dave Asprey: Here's another question, and you may have gone into this in some of your prodigious research, and I wouldn't have happened to read all of it. When I wrote the Bulletproof Diet, I was looking for things that would suppress mTOR, so it would bound back more strongly.

Dave Asprey: The three things I found were certainly, exercise, we just talked about. Fasting we just talked about, but there's also studies on coffee in mTOR. Have you looked at the effect of coffee on either autophagy or mTOR?

Mark Mattson: We haven't, and it's a good question that I don't know the answer to. There's a lot of excitement from-

Dave Asprey: Okay.

Mark Mattson: It's actually a drug development standpoint in rapamycin, and I'm sure you've heard about that.

Dave Asprey: Yes.

Mark Mattson: That's a little bit scary because you can inhibit mTOR too much, and if you inhibit it too much too long, that's not good either. Again, these cycles of... but as far as caffeine goes, my opinion is it's good for your cells, but probably not if you have caffeine levels high 24/7.

Dave Asprey: Yeah, that whole sleep thing.

Mark Mattson: I think what most people do than drinking coffee or tea in the morning while fasting is a good idea. That caffeine certainly boosts your alertness and enhances your cognition.

Dave Asprey: Your ketones, right?

Mark Mattson: Yeah.

Dave Asprey: Cunnane's work at UC San Diego showed a ketone boost from it.

Mark Mattson: Yup.

Dave Asprey: Okay.

Mark Mattson: I think caffeine is good. I published an article in Scientific American in 2015. The whole take-home message of the article was that many of the chemicals that are in fruits, vegetables, tea, coffee, plants, that are good for our health, the actual reason there in the plants, the evolutionary reason is that they're noxious agents, they're toxins.

Dave Asprey: Right.

Mark Mattson: Caffeine is a good example. If you take pure caffeine, and put it on your tongue, you wouldn't want to eat it. It's very bitter tasting. Caffeine is a natural pesticide produced by coffee beans, and tea leaves. If you take coffee beans or tea leaves, and put them on your counter, and put most any food next to it, and there's ants in your house, the ants will avoid the coffee beans and the tea. They'll go for the other things that don't have the bitter-tasting chemicals.

Dave Asprey: It's fascinating. Nicotine is that way too. I mean, caffeine and nicotine are two of the smartest drugs from Asia that increase human cognitive performance. They both kill bugs, which doesn't mean they're bad for us. Both on nicotine in high doses from any mechanism is, but-

Mark Mattson: What's interesting here, Dave, is that some of those chemicals activate the exact same responses in cells, that are activated by fasting and exercise.

Dave Asprey: Wow.

Mark Mattson: One of those pathways, which I'm sure you've heard of is the Nrf2-ARE pathway. For example, there's a chemical sulforaphane, that's present in high levels in broccoli and-

Dave Asprey: Broccoli sprouts.

Mark Mattson: ... green leafy vegetables. The key thing of this pathway is it's an antioxidant defense pathway. When this Nrf2-ARE pathway is activated by exercise, fasting, some chemicals in plants, then cells boost their intrinsic antioxidant defenses, and are more resistant to being damaged by free radicals.

Mark Mattson: This was really why the trials of vitamin E, vitamin A, vitamin C, and a lot of different diseases, cancers, et cetera, pretty much uniformly failed. You don't want to swamp your cells continuously with these chemicals, it's scavenged the free radicals because the pathway such as the Nrf2 pathway are never activated.

Dave Asprey: Yeah.

Mark Mattson: Because they're activated by the stress of the fasting, the exercise or the-

Dave Asprey: It's interesting that free radicals themselves are signaling molecules. I interviewed, oh geez, Dr. Rowen, and then later... how can I blink on his name? That's really strange. I must need more ketones because I don't lose names that often. Sorry, at the tip of my brain. Anyhow, one of the preeminent ozone therapy guys, who looked at the ability of the free radicals from ozone, as a signaling molecule to trigger mitochondrial repair.

Dave Asprey: Not from breathing ozone, but from the other medical uses of it, even just topical on the skin and things like that. It's really interesting, if you take those antioxidants you talked about before exercise, you don't get the benefits of the exercise.

Mark Mattson: That's right.

Dave Asprey: What bout during fasting? I mean, should this mean when you're in flaccid state, don't take your vitamin E?

Mark Mattson: No, and as far as I know, I know this field pretty well. No one has done those experiments with fasting. That's only with exercising.

Dave Asprey: All right. Okay. Somebody listening is going to do those experiments, because all the right people are listening in. At least, I'm going to tell myself that. This is a fascinating thing. If you're working on your Ph.D., you're trying to figure out what to do, you're going to go to school, seriously investigate this. Just do fasted mice or whatever animals you like working with or humans. My favorite, guinea pigs.

Dave Asprey: See what happens if you fast, and just look at all the different markers in metabolism. Maybe you're on organic acids, and see what happens. If someone takes a fistful of vitamin E, vitamin C, even glutathione, which I'm a huge fun of. I use that during a fast, versus after a fast, versus after exercise. We already know what it does to exercise, but if fasting and exercise are mimics of each other, I'll bet you.

Dave Asprey: That you should take in antioxidants a while after the fast, not during the fast, or maybe at the beginning, but somebody tell me the answer so I can write about it, and I can do it. If you had to bet what the answer would be, what would you bet?

Mark Mattson: I would bet it'd be similar to exercise. Yeah.

Dave Asprey: Okay.

Mark Mattson: Yeah.

Dave Asprey: Interesting. I've never thought of this before, but I would agree with you that I'd place my bet in that same spot that said, "All right, let's look at that." Now, would you consider the... because there's different polyphenols, but I make polyphenol blends, there's chocolate polyphenols, there's coffee polyphenols, there's oregano, and pretty much any flavorful vegetable, fruit thing, or herb especially. Would you look at avoiding those during intermittent fast, or would you consider those to be useful during intermittent fast?

Mark Mattson: The noxious, the bitter tasting ones are probably useful.

Dave Asprey: Yeah. I think so too. I don't know any delicious polyphenols off the top of my head. They're all pretty nasty tasting, other than that. It turns out people who are fast caffeine metabolizers, they don't taste caffeine as bitter as people who are slow caffeine metabolizers, which is really interesting.

Mark Mattson: Yeah.

Dave Asprey: There's little subcellular mechanism. It's like, "You should get more of this." Okay. I'm going to keep doing that in the morning. Okay. Here's a great question. There are lots of studies on mice done with water-only fasting. There are other people say, "Oh well, they just had water," so usually only have water. All the stuff I know, even traditional Chinese medicine, they always had tea, or coffee, or pine bark tea, or whatever the heck depending on where you're from.

Dave Asprey: I always [inaudible 00:26:59] in fasting, have your coffee, have your tea, enjoy your life, but the purest. It's like, "We don't know what it does to your gut bacteria." Where are you in the spectrum of you should only do what the mice did versus have a little fun?

Mark Mattson: I think, it's actually good idea, at least from the standpoint of the brain to drink tea or coffee-

Dave Asprey: During a fast.

Mark Mattson: Yeah. Yeah, yeah.

Dave Asprey: Okay. All right. You'd be fine with an herbal tea as well then?

Mark Mattson: Yeah.

Dave Asprey: Okay. Got it. There're all sorts of different herbal teas you can do. What about mushrooms? Medicinal mushroom teas and people... I don't like chaga very much at all, but I've really gotten some benefits from lion's mane. I just had the lifecycle guys on about that, and I just had Paul Stamets on, who's famous mushroom guy.

Mark Mattson: Yeah.

Dave Asprey: I love Paul, he's so cool. Is there anything that you've come across on using mushroom extracts, not actually eating them because that'd be calories, during fasting?

Mark Mattson: No studies. I am interested in mushroom. Last few years I started foraging, I've got Paul's big thick book.

Dave Asprey: Mycelium Running, I think I've got it right back there.

Mark Mattson: Yeah. I actually bought some mice... what did I get, oyster and shiitake mycelia from his company in the spring. They're out in the woodchips right now.

Dave Asprey: Beautiful.

Mark Mattson: Yeah.

Dave Asprey: I'm just starting commercially growing cordyceps on my farm here in BC, which is really cool.

Mark Mattson: Oh nice. Paul is, he's from the neck of the woods.

Dave Asprey: Yeah. He's one island over. He came out for the interview. It was fantastic. Sounds like you guys know each other?

Mark Mattson: I don't know him, but there's fascinating chemicals in mushrooms. A lot more work needs to be done. There are some reasonable studies with things like turkey tail, tea, and some other things Paul talk about, but on the other hand, it's an area where there's a big need for a lot of better science.

Dave Asprey: Yeah.

Mark Mattson: As you know, finally, they're starting to do studies now with hallucinogenic mushrooms. One of the scientists at Hopkins in fact, has shown in a couple published studies now, that psilocybin mushrooms are beneficial in people with depression. They're not addictive. In contrast, the opioid, which is a huge problem. These chemicals in mushrooms that seem to have some interesting effects on the nervous system are not addictive, which seem to be a big advantage.

Dave Asprey: It seems nonsensical that alcohol, nicotine, and the opiates are legal, and cause a lot of harm, but I don't know how anyone could be really addicted to the strong hallucinogens. There are people who dissociate because there so traumatized to, but it's not an addiction. That's just deep-seated trauma response, which is different anomalies. My wife says so, and she's Karolinska-

trained drug and alcohol addiction emergency doctor, so I'm going to believe her there.

Dave Asprey: There are people who abuse them, but they're not addicted versus the actual addiction. All right. I'm really interested in compounds that I know that you're interested in. Nerve growth factor, NGF and BDNF, brain-derived neurotrophic factor, and I wrote about those in Head Strong. I used these old studies on mushrooms, there's a compound. I use one of my supplements from the fruit of coffee polyphenol raises BDNF.

Dave Asprey: Coffee itself probably does, according to some other research. Fasting I believe raises BDNF. Can you walk through your perspective on increasing nerve growth factor and brain-derived neurotrophic factor? What do you believe works, and how important is it for living a long time with a good brain?

Mark Mattson: Well, both BDNF and NGF are important for the development of the nervous system, for the survival growth synapse formation, and then the fine tuning of the structure of the brain during development. If you eliminate the genes of either NGF or BDNF from mice, they die during development. They're critical. In the adult brain, BDNF is particularly important throughout the brain, all over the brain in promoting the growth survival of neurons.

Mark Mattson: It's critical for learning and memory. We showed in my lab when I was back at the University of Kentucky in early 1990s that BDNF protects nerve cells against various types of stress. Oxidative stress, metabolic stress, something we call excitotoxic stress, which is unconstrained neural network activity occurs dramatically in epilepsy but we think to less dramatic extent in brain aging in Alzheimer's disease.

Mark Mattson: NGF on the other hand, they are only small, but important group of brain cells that response to BDNF in the adult brain. Exercise is a potent stimulator of BDNF production in the brain. Intermittent Fasting stimulates BDNF production, and the combination of exercise and fasting could have an additive effect in boosting BDNF.

Mark Mattson: I had a graduate student, Alexis Stranahan, who showed that many years ago in studies, where she combined running wheel exercise, and daily time restricted feeding daily, short fast, and found she got additive effect, an increase in BDNF, and then actually, protecting synapses against diabetes, which is another angle on this. It turns out that obesity and diabetes are not only bad for your heart, they're bad for your brain.

Dave Asprey: Yeah.

Mark Mattson: Particularly, as you get older. We think that intermittent fasting... well, I actually know it. Intermittent fasting and exercise can reverse diabetes, and obesity in humans if a person can switch their eating pattern, and get on an exercise

program. BDNF plays a role on that. In individuals who are obese and/or diabetic, BDNF levels are lower in their brains compared to normal weight metabolically healthy people.

Dave Asprey: One of the things that really changed my life when I weighed 300 pounds, and I was having all kinds of cognitive dysfunction in my 20s and early 30s, I started using a thing they called the Russian sleep machine, that's cerebral electrical stimulation with alternation current between the ears. It's very different than the tDCS we use now. It turns out there're studies that show both tDCS, and CES, or alternating current raise BDNF very meaningfully.

Mark Mattson: That's interesting, yeah.

Dave Asprey: I'd go to sleep with this thing. I saw that my brain helped to turn back on. Now, 40 years is in the brain upgrade place that I started, we use a clinical grade neuro science level system that lets you have specific frequencies that are tunable and controllable by a computer. We do that to prime the brain for better learning of altered states that you learn through neuro feedback.

Dave Asprey: You go all the way down to companies like Halo, who's been on the show, who makes a tDCS headset. When I do exercise, especially lately, I can't keep up very well with my nine-year-old at ping-pong. Ping-pong is a high reaction time thing, it keeps your brain young, Dr. Amen told me to buy the ping-pong table, I did. I started saying, "All right, I need some more BDNF here, my sons kicking my butt." We've got the pro-grade carbon fiber paddles and we're going at it.

Dave Asprey: He's good. Either that or I'm bad, but I was not a good competitor for him. I started running the electrical current over my brain. Again, using the Halo, and all of a sudden, my learning went up. 20 minutes after doing it, it's like the ball slows down, and I can hit it. I believe that's a BDNF thing. If you've seen electrical stimulation, magnets, lights, going to the bottom of swimming pools, any other crazy tech like that that's going to make our brains more plastic.

Mark Mattson: The answer is yes. Personally, I want to go back to when you were young and obese. You did this alternating current stimulation of your brain. Did that reduce your appetite? The reason I ask is, it turns out that BDNF suppresses appetite.

Dave Asprey: Interesting. I don't think it did. I'm going back to all the different times I'd use it. I would oftentimes use it when I was sleeping, or when I wanted to write, even when I was writing... actually, all my books. There were times where I'd change the frequency on my device to go up into the gamma ranges.

Mark Mattson: Did it help you lose weight?

Dave Asprey: It could have. I feel like the thing that really helped me lose weight was getting rid of the inflammatory food, and things that were inhibiting mitochondrial function was the number one thing.

Mark Mattson: Yeah.

Dave Asprey: It could have an impact, but for me it was, well, I just wanted ketosis. Then, I came out of ketosis, and I went in and out. I got half my weight down, and then the other half was, "Oh hey, guess what? Certain foods are going to make you inflamed no matter what, so you got to change the type of fat that makes you going [inaudible 00:37:34]." Yeah. Get rid of the night shades if you're sensitive like I am.

Dave Asprey: That was the genesis of the whole Bulletproof Diet approach, which was these foods may or may not be good for you, but don't assume that they're all good. Because if you're still fat after you tried hard... so for me, it was finding the guilty suspects.

Mark Mattson: Let's get back to stimulation and BDNF. BDNF was discovered in an animal model of epileptic seizures. There was a lab in California that was just looking for genes that are responsive to epileptic seizures. BDNF is highly responsive. As you know, one of the treatments for depression, which is still used in people who don't respond well to antidepressant drugs is electroconvulsive shock therapy.

Dave Asprey: Right.

Mark Mattson: It's highly antidepressant. It's highly potent in inducing BDNF expression.

Dave Asprey: Wow. I didn't know that.

Mark Mattson: Also, the antidepressant drugs themselves, the Serotonin and Norepinephrine reuptake inhibitors, Prozac packs, or etcetera, they increase BDNF levels in the brain. In animal studies, we have ways we can genetically manipulate the mice so that they can't respond to BDNF. Those mice do not show an antidepressant response to those drugs. Altogether, the available evidence says BDNF is, it's an antidepressant, endogenous antidepressant.

Mark Mattson: I mentioned it's potently up regulated by exercise. Exercise is a really good antidepressant. In fact, people who exercise regularly and then have some injury, and they stop exercising, that can often precipitate to episode of depression because they've been going a long exercising, and then all of a sudden, probably, their BDNF levels are going down.

Mark Mattson: Anyway, there is some evidence that even low direct current stimulation, or transcranial magnetic stimulation can increase BDNF levels. Caffeine, caffeine will increase BDNF levels, there you go.

Dave Asprey: I'm intrigued about what you do to manage your BDNF levels. I just want to warn everyone, look, you're an expert on aging, but you're also, the age you are, and you're a male, and you have your genetic lifestyle factors that we all have.

This isn't a do what you do, but I want to know what you do, specifically for BDNF and NGF to keep yourself strong in those things, and then I want to know why you do it? What's your personal practice for managing those, do you even measure them?

Mark Mattson: Well, that's a problem, because we'd have to measure them in the brain, or at least the cerebral spinal fluid. It turns out that there's BDNF and NGF in the blood, but the levels of those trophic factors in the blood and animal studies are not well correlated with levels in the brain. It turns out that nerve cells are not the only cells that produce BDNF.

Mark Mattson: Your heart cells interestingly produce BDNF, and there's other cells. Anyway, the bottom line is, unfortunately, unlike ketones, which we can easily measure from a finger stick and blood, we can't measure BDNF or NGF. There's no way noninvasively to do that. I'm just going by what the animal studies today.

Dave Asprey: Sure, sure.

Mark Mattson: Again, my normal routine is, don't eat breakfast, drink a lot of green tea in the morning, don't drink green tea a couple hours before I exercise, which I said is around mid-day, say 1:00. Because I found, I can get some gastric reflux actually, if I drink tea right before I exercise. Anyway, so then I exercise in the flaccid state.

Mark Mattson: My diet during the six-hour time window I eat, is what most people would consider a variety of healthy foods, vegetables, fruits, a lot of nuts, yogurt. If I eat meat it's usually fish, occasionally chicken, but not so much. Whole grains, there's a lot of literature out there on whole grains, one way and the other, and there are people who are sensitive over gluten and so on. My take on the scientific literature is that whole grains are generally good for health.

Dave Asprey: You eat whole grains?

Mark Mattson: I eat whole grains.

Dave Asprey: How do you stand ketosis if you eat whole grains and fruit?

Mark Mattson: I go into ketosis in the morning.

Dave Asprey: There you go, I was hoping you were going to say that.

Mark Mattson: Yeah.

Dave Asprey: We'll probably agree to disagree on whole grains for the average person, but some people tolerate them really well. I know they've completely shred other people over time. Those are in the system [crosstalk 00:43:00]-

Mark Mattson: Dave, well, I don't know. Refined grains are not good, but the whole grains have a lot of fiber, which is good for your gut, microbiota.

Dave Asprey: Unquestionably.

Mark Mattson: If you look at the actual scientific studies, there's epidemiological evidence that whole grains are good. Even in the blue zones, which most of your listeners will be familiar with, regions in the world where people, usually, large number of people live to be a hundred. Several of those areas, a lot of the calories are in whole grains, whether it's rice in Okinawa diet or so on.

Dave Asprey: Are the Okinawans eating white rice or brown rice? Its white.

Mark Mattson: Yeah, its white.

Dave Asprey: Yeah. It's not a whole grain, they got rid of the lectins from the outside, and all the phytic acid, all of the other stuff.

Mark Mattson: Well, but there you go is... but they have a low-calorie diet, and one thing that hasn't been studied in a lot in them as far as I know, no one has measured their ketone levels.

Dave Asprey: Interesting. Wouldn't that be fun?

Mark Mattson: Yeah. It would be interesting in those blue zone people that look, take blood at different time points throughout 24-hour period, with their eating patterns, they're not all eating three meals a day, spaced regularly. I think whether they're having the metabolic switching occurring would be an important thing to know. We think that that's much more important than diet composition, except for its definitely good to avoid simple sugars, it's definitely good to avoid a lot of saturated fats, but the whole-

Dave Asprey: What about in fried polyunsaturated fats that were never in our diet either? Those seem worse than-

Mark Mattson: Well, no. Yeah, the trans fats are worst, yeah.

Dave Asprey: Even just this heated, the stuff that your French fries are made in.

Mark Mattson: Yeah, that's bad.

Dave Asprey: Okay. I'm following what you're saying, on your overall daily thing, you are eating a moderate amount of carbs. It sounds like you're not going hog wild on the carbs. You're avoiding simple sugars in the afternoon, evening, and in the morning, you're eating nothing, so you can stay in that flaccid state. We also talk about ketones, and because you've developed this metabolic flexibility, when you measure ketones in the morning, where are they?

Mark Mattson: The ketone strips that you can buy commercially to measure ketone levels, they're only sensitive down to around 300 micromolar, below that, you can't tell what-

Dave Asprey: You can't tell, right.

Mark Mattson: It turns out there's two phases of ketone production that occur. As soon as the glycogen source in the liver are depleted, you get an increase from way down, below micromolar levels up to about two to 300 micromolar. They stay up in that level for between 10 up to 24 hours, and then there's a second bigger increase in ketones, where they go up into the millimolar levels.

Dave Asprey: That's over what timeframe was the second spike?

Mark Mattson: Beginning about 24 hours of complete fasting. My ketone levels, in the late morning, I get up to around the two to 300 micromolar level. Then actually, I haven't measured them after exercise, I should. I'm expecting to go up getting closer to the one millimolar level or above during the exercise. I think a lot of people will find that if they use the ketone strips, even after 12, even 16 hours of fasting. They may look and say, "My ketones aren't up at all," but probably they are up. It's just below the lower limited detection of those ketone strips.

Dave Asprey: If you use a finger stick, you can get the .1 level, right?

Mark Mattson: Not if you're using the ketone, the paper strips to measure.

Dave Asprey: No. I mean, there's the P strips and there's the finger stick strips, which strip are you talking about?

Mark Mattson: Either strip.

Dave Asprey: Interesting, even the finger stick.

Mark Mattson: Yeah. You have to use other methods that are more sensitive. There are commercially available, but they're from the scientific-

Dave Asprey: They're pricey.

Mark Mattson: Yeah. They're pricey.

Dave Asprey: Okay. That makes a lot of sense, in my research in just my own experience, if I do brain octane, the one of the four kinds of MCT that, actually, after I noticed the difference, the studies came out, and show that it raises ketones more than other MCTs, or short or long chain fats, or at least, probably butyric acid raises it as much, but anyway, it's the most powerful MCT, whatever.

Dave Asprey: I put that in my bulletproof coffee, I can have doughnuts for dinner, not that I actually eat doughnuts, but every carbs I want. More like, I'd probably eat sushi with white rice, wake up in the morning. I can have my bulletproof coffee, and I can get to 0.5 on a finger strip, right? In mice, there's things that happen with CCK and growing it 0.3 and 0.5.

Dave Asprey: Those seem to me, the magic levels, where I don't care about food anymore, and good stuff happens metabolically. You're the godfather of intermittent fasting here, am I reading too much into the mice studies and my own experiences there, or are those special levels, or is 0.7 better, or what are the levels?

Mark Mattson: Well, I guess my point in this biphasic, an initial, relatively small, but physiologically and probably health beneficial, this lower level like you're talking about, 0.5 millimolar. My view based on the animal studies, and human studies, and the time course that we know that ketones change. Those early increases in ketones are important for improving health, and including improving cognition, and suppressing appetite, which ketones do. You're Bulletproof MCT, is there five, six carbon length?

Dave Asprey: No, they are eight carbon.

Mark Mattson: Eight, yeah.

Dave Asprey: The six carbon is unfortunately, they might be slightly more ketogenic. They taste terrible, and they're huge gastric irritants. One of the problems with a lot of MCTs, those aren't adequately filtered out. You get a little bit of those or some C17s, and then you get that burning throat, or that real strong disaster pants. I managed engineer around that in the early days of Bulletproof, so that's not the issue it once was. You know what I'm talking about from MCTs.

Mark Mattson: Yeah, yeah.

Dave Asprey: It's the eights, and that's later Cunnane came along and said, "Look, four times more ketones than actually what you get from coconut oil."

Mark Mattson: Yeah. Steve Cunnane has done some... so we did work with the ketone ester in the animal model of Alzheimer's disease with [inaudible 00:50:46] with Richard Veech. He sent a postdoc up to my lab, and we did the experiments with our mouse model of Alzheimer's.

Mark Mattson: We published then 2013, and then, as you know, Steve is using PET imaging, positron emission tomography using radiolabeled acetoacetate, which is one of the two main ketones it elevated during fasting and extended exercise. The other being beta hydroxybutyrate. He could image, he could look at the brains of humans and see, are the brain cells using the ketones for energy, or are they using glucose for energy?

Mark Mattson: He takes these humans, puts them on a ketogenic diet, and they switch from using glucose to ketones, it's dramatic. We think Alzheimer's, we know the nerve cells in the brains of Alzheimer's patients, the nerve cells that is still alive, they have a big problem using glucose. We're pretty sure they could still use ketones.

Dave Asprey: You're talking about the neurons specifically?

Mark Mattson: Yeah, in people with Alzheimer's. If people with Alzheimer's are eating carbohydrates and their ketones are low, and their nerve cells cannot use the glucose very well, and the ketone levels are low, the nerve cells' ATP levels are low. However, if the Alzheimer's patients can increase their ketone levels, in the mice model as we know that, and the humans we think, at least based on the science is likely that they can still use the ketones.

Mark Mattson: Steve is involved in initial stages of the trial of the ketone ester in Alzheimer's patients. He already gave patients with mild cognitive impairment MCTs, which I don't... or was it your MCTs or was it-

Dave Asprey: Yes, as far as I understand.

Mark Mattson: Yeah, okay.

Dave Asprey: He's running multiple studies, but some of his studies are using specifically our MCTs, but I don't know if that was the study that was using ours.

Mark Mattson: Right. As you know, he's already published a paper in patients with mild cognitive impairment, which is often a precursor to Alzheimer's. That is to say, people with short term memory problems that are diagnosed with mild cognitive impairment, they're at increased risk for going on to develop Frank Alzheimer's. This was exciting news. There're no treatments for MCI or Alzheimer's. We know exercise helps in MCI patients.

Dave Asprey: Doesn't hyperbaric also help them?

Mark Mattson: Hyperbaric?

Dave Asprey: Yeah, hyperbaric.

Mark Mattson: I don't know. I think that would be not a good thing. This whole hormesis idea, and so if you increase oxygen levels, and the anti-oxidant defense pathways are toned down, they now have two pathway. Whereas, mild hypoxia, which is what occurs during exercise, that ramps up this intrinsic defense mechanism.

Dave Asprey: It's interesting because I interviewed Dr. Hart who wrote The Oxygen Advantage, and he's probably one of the preeminent hyperbaric guys. We talked about that.

Mark Mattson: Wow.

Dave Asprey: I understand that there's two sides of the coin, but the reason that it's interesting is that some of the other training that we do at Upgrade Labs, stuff I have right downstairs, is intermittent hypoxic training. We're actually on an exercise by breathing air that has no oxygen to drop your blood oxygen down to 87% to cause a hermetic reaction, so your hemoglobin can let go of oxygen more easily later.

Dave Asprey: It seems just like with food, you're fasting sometimes, there was no damn food. Sometimes there's only ketones, and sometimes there's glucose. It seems maybe for temperature, sometimes it's really hot, I'm in sauna. Sometimes it's really cold, I'm in cryotherapy, and then for oxygen, sometimes there's no air, and sometimes there's tons of air. It seems teaching the body to adapt, survive, and thrive in short term extremes, is a good strategy for living a long time and feeling good.

Mark Mattson: Yeah. One, not one, we did multiple studies looking at effects of alternate day fasting in rats on heart rate and blood pressure.

Dave Asprey: Wow, what did you find?

Mark Mattson: It's very dramatic, and it's very similar to what's seen with endurance athletes. They're with, not immediately, it takes two weeks to a month and by then, it's very clear. The animals on alternate day fasting, they're resting heart rate and blood pressure decrease. Their heart rate variability increases.

Dave Asprey: Which is a very good thing.

Mark Mattson: It's a good thing. It's what you see in endurance athletes. What's happening is, we found by measuring these things, the alternate day fasting similar to endurance training, increases the activity in the parasympathetic nervous system. Your heart rate is controlled, and blood pressure by a balance, and shifting between parasympathetic, and sympathetic nervous system.

Mark Mattson: Your parasympathetic nervous system slows heart rate, reduces blood pressure. Your sympathetic nervous system increases heart rate and blood pressure. What's happening with the intermittent fasting, is that your heart becomes more adaptable to shifts in load levels. For example, we did stress test in the animals. We subject them to a very stressful situation, where essentially, we put them on a strait jacket where they can't move.

Mark Mattson: That will cause a big activation of the sympathetic nervous system, the flight-or-fight response, their heart rate will go way up. In the animals that have adapted to alternate day fasting, their heart rate initially goes up when they're under a stressful situation. Then, it comes down more quickly after they adapt. They adapt more the stressful situation when they're adapted to intermittent fasting.

Dave Asprey: Resilience goes up.

Mark Mattson: Yeah.

Dave Asprey: Cool. Well, let's switch gears a bit. We know what you eat, and we know how you exercise. How about rapamycin? Have you ever taken it?

Mark Mattson: No, no.

Dave Asprey: No?

Mark Mattson: No.

Dave Asprey: How about the other anti-aging stuff, growth hormone, testosterone, supplements, I mean, you're the head anti-aging guy, you study all this stuff, you don't use any of it?

Mark Mattson: The only thing I'm taking now is, curcumin. Because I got some knee osteoarthritis, and vitamin D, and folic acid, that's it. I mentioned I eat a variety of vegetables, fruits, nuts, and so on, and so on. The studies we've done in animals, and others, manipulating specific nutrients and the NIA's lifespan studies. Compared to daily calorie restriction or intermittent fasting, none of those things have nearly as powerful effects. That's what I'm basing it on.

Dave Asprey: I got to agree with you there. Quality sleep, and some intermittent fasting, and moderate exercise, not even crazy exercise are ginormous variables. It does seem though. I mean, James Clements came on, and we talked a lot about increasing autophagy, including pharmaceutical stuff.

Dave Asprey: Aubrey de Grey, the seven different pillars of aging. It feels like we are making progress, and our David Sinclair is coming on and his NAD pathways on mitochondrial repair. It feels like this brave new world of anti-aging tech is it's all just coming online now, or am I just a hopeless optimist?

Mark Mattson: Rapamycin is very interesting, the NIA has supported three-center study of lifespan studies, where various people proposed things to try, metformin, rapamycin, sulforaphane, et cetera, et cetera. So far, they've completed studies with 30 some different test chemicals.

Mark Mattson: Rapamycin is the only one that has clear, highly, statistically, significant increase in the average lifespan in the mice in all three studies. In the animals, it's convincing that rapamycin can increase lifespan. It's the only single chemical intervention that's been clearly shown to increase lifespan.

Dave Asprey: What about metformin? I mean, that's another one, right?

Mark Mattson: In the three-center, there are some published studies suggesting it increased the lifespan, but in the three-center study, where all three centers do... they did metformin identically over 100 mice each study, they didn't see a statistical, significant effect.

Dave Asprey: Interesting. I am completely flummoxed by metformin. I started taking it many years ago, and the first studies came out from BioMarker pharmaceuticals. Then, I quit because of the B12 and mitochondrial harm things and switched to an herb for AMPK. Then I talked to James Clements recently and said, "Oh, that herb isn't so good either."

Dave Asprey: I go back and forth. Most of the anti-aging clinicians I know are using it in their practice, and seeing positive benefits even if it isn't life-extending. There's certain a quality of life performance and the labs look better. I'm torn on that one.

Mark Mattson: Yeah. The glucose regulation improves certainly.

Dave Asprey: You mostly don't do any of that stuff. I feel I don't eat for a while, and I get some sleep, and I get some exercise at the right time, which is at the end of a fast, and you're pretty much good to go with that.

Mark Mattson: Yeah.

Dave Asprey: All right.

Mark Mattson: As far as I know, the people in the blue zones aren't taking any metformin or rapamycin or any of these other things. They're saving their money and still living to be 100. It's diet and lifestyle, yeah.

Dave Asprey: That is true. At the same time, they also live in the blue zones, which says if you don't live in a blue zone, and you live in a highly polluted city, you might want to change what you do to match the environment, right?

Mark Mattson: Yeah.

Dave Asprey: I mean, there're a bunch of theories. There's glacial melt, water with extra minerals in it. There're all kinds of stuff around deuterium depleted, there's some French theories around that. There's lifestyle stress, and the diets are all over the place from 70% fat to 7% carbs. I'm having a hard time using epidemiology to get anything useful.

Mark Mattson: Yeah. I don't like epidemiology, whatever... yeah.

Dave Asprey: We're kind of in agreement. I wonder how it works, and I want to say if you do X, you reliably get Y, and then I'm going to do X even if I'm not a mouse and see

if I get Y. If so, I'm just going to have to deal with X because it's better than what I had before, which is random in and random out.

Dave Asprey: That offends some academics because it's N equals one, and I might be bias, but yeah, I'm bias, but I feel good. How do you sort that out? I talked to Dr. Newhouse, who wrote the first paper in 1988 on nicotine for Alzheimer's from Vanderbilt. He's like, "I've never used nicotine." How can you study this on your 30 years without taking a little hit of it once? Right?

Mark Mattson: Well, I do intermittent fasting, right? That's what I said.

Dave Asprey: Okay, good point. That's your number one intervention and you do it.

Mark Mattson: Yeah.

Dave Asprey: I'll give you that. Okay. The ways to raise ketones externally. There's MCT oils and different ones do different things. There's ketone salts and different ones do different things, and Dr. Veech raised the bioidentical issue there. I actually had a ketone salt product ready to ship, and I cancelled it because I'm not selling something that might feel good, but cause harm later.

Dave Asprey: There are people who are advocates of them, especially short-term use and things like that. Then, there's the esters, which Dr. Veech and I talked about, you talked about, and I actually synthesized some six years ago, but they're $40,000 a kilo, I couldn't commercialize them. They're still $100 for three doses, things wouldn't approve for people to do it.

Dave Asprey: There is a risk with blood sugar. If your blood sugar levels are high, it doesn't mean that you have more energy and you've done a good thing. It means you're not metabolizing blood sugar. If your ketone levels are exceptionally high, is there any similar situation where, "Hey, they're high because you can't metabolize them?" You're going to drain them as fast as you can, or should we not worry about, my ketone levels are higher than your ketone levels, sort of things?

Mark Mattson: Yeah. This is a good question. We know that with long-term fast, weeks or even months, we assume that it's important that the ketones be high because the cells are using the ketones for energy. As far as exogenously elevating ketones with MCTs or ketone ester, long term chronically, we don't know. My current thinking is intermittent elevations may be better than continuous.

Mark Mattson: The cycling between activating mTOR and inhibiting it, operating like autophagy then going into a growth mode, that switching back and forth is important. As much as the ketones play roles in that, and in fact, we showed ketones can stimulate BDNF production.

Dave Asprey: Wow.

Mark Mattson: However, this is very interesting. It turns out that BDNF is normally produced by neurons in an activity-dependent manner. That is, it's produced when the neuron is electrically active. It's produced when and where it's needed. We found if we swamp neurons with BDNF continuously, it's actually bad for them.

Dave Asprey: Interesting.

Mark Mattson: We did this in a published study where we were looking at the autonomic nervous system. Remember, I said that intermittent fasting increases parasympathetic activity and reduces heart rate. We had evidence, there was a role for BDNF in that, but it gets a little complicated. The parasympathetic neurons that send their axons to the heart, the neurons themselves are located in the brainstem.

Mark Mattson: They use acetylcholine as a neurotransmitter. BDNF, if we transiently apply BDNF to those neurons, they would produce more acetylcholine, heart rate goes down. However, if we continuously swamp those neurons with BDNF, then they deplete acetylcholine, and heart rate actually goes up.

Mark Mattson: My point is, your systems are very intricate, and are producing things where and when they're needed, and it may not be good to continuously swamp the system. We don't know for sure with ketones, but my intuition says maybe it's not such a good idea to just have ketones up 24/7 chronically.

Dave Asprey: Yeah. I'd say the jury is out on it. I've gone from using brain octane just in my morning coffee to I pretty much put on every meal. My ketone levels are generally not above .3, except in the morning. I think they're higher than physiological, but they're not high. What I feel like that does is that it affects my growing levels. I'm just not hungry, and so I can go long times without food. My brain, it just feels effortless.

Dave Asprey: We know that your neurons... neurons will use ketones in the presence of glucose because of the studies you talked about earlier. The glial cells and the repair cells in the brain, and I know I'm simplifying what glial cells do there, but they like glucose more than ketones. That's why I'm really concerned about the keto bro diets out there. If you eat another carb again, you're a bad human being. It feels like there's a role for carbs.

Mark Mattson: I think there is too, Dave.

Dave Asprey: Yeah.

Mark Mattson: There was a recently published study. It suggests that paleo diet is not good long-term. I don't think it's a good idea, just to eat only fats and protein. In fact, too much protein is definitely bad from the standpoint of aging.

Dave Asprey: Yeah. The paleo is, they're burned protein and way too much protein. In fact, my new anti-aging book that's coming out soon, I read a lot of protein restriction. In fact, there's one day a week of protein fasting, was part of the original Bulletproof Diet because it increases autophagy, you have less than 15 grams. For you, what kind of protein is worst and what kind is best?

Mark Mattson: Well, usually in animal meats, you've got a mixture of fats and protein. The fish story is strong. You can't go wrong eating fish. Ideally, some of the smaller fish with regards of the mercury issue. Red meat, you don't need it at all. You get plenty of protein... no, everything is all goofed up. Our parents told us don't get any dessert, which is sugar, unless you finish your meal. Eat a lot, over eat, and then you can have your sugar.

Dave Asprey: Yeah. You're over eating.

Mark Mattson: You got to eat your meat, drink your milk to get protein, so kids are getting too much protein. The mTOR pathway is overactivated, their cells aren't removing the garbage. In fact, the huge problem that's hard to tackle is how to change the family environment? Kid's habits, their eating habits, whether or not they exercise throughout their life for many people, it's determined by what their parents are doing.

Dave Asprey: At what age did you start intermittent fasting your kids?

Mark Mattson: I can't make a definitive statement on that.

Dave Asprey: If you had to bet, what would you bet?

Mark Mattson: Once they're sexually mature.

Dave Asprey: Okay. Basically, after puberty.

Mark Mattson: Yeah.

Dave Asprey: Yeah. I don't intermittent fast my kids. We're probably going to do once a month where we do 24-hour fast with the kids, just so they can see that we do it, and so they can toughen up a little bit, and you're not going to die if you don't have it. I've used intermittent fasting as a threat.

Dave Asprey: When they say, "I'm eating my broccoli," I'm like, "Oh, you've chosen to intermittent fast with me, let's all put our food away," then they eat their broccoli, and the conversation is over. It feels like it would not be a good thing to do that to a metabolism of a growing child, but we don't know. It might be fantastic.

Mark Mattson: Yeah. If you go up from my evolutionary perspective again, certainly kids, infants and young children used to nurse the breast milk a lot longer than they

do now. On the other hand, once they're weaned, they're probably eating intermittently before the agricultural revolution. I want to make one comment that I gave a talk at one of the annual meetings for the American Association for the Advancement of Science, the AAAS, and this woman came up to me after my talk.

Mark Mattson: She said, "That was a great talk." She said, "I'm glad I came to your talk. I'm so relieved now because my son who is in high school, he's not eating breakfast, he hasn't been eating breakfast for a year, and I've been worried about him. He's a straight student. He's active in sports. He's a really good athlete, but he hasn't eaten breakfast." She said, "I'm relieved now because he's doing well, and I'm not going to worry anymore about whether or not he eats breakfast."

Dave Asprey: That's great. I love that. Yeah. Just a little bit of metabolic flexibility, and different metabolism, and different things, and different ages too. I'll go with you there. Mark, I've got a final question for you, and I am intrigued at your answer because you have such a deep expertise in things like this. I've been pretty public on my... I'm counting on guys like you, and many other friends too, and expand over the next hundred years or so, expand the maximum human limit so I can reach at least 180.

Dave Asprey: I'm fully expecting skepticism from you there. My question for you though is a little bit more personal. How long do you think you're going to live given what you know about aging, what your colleagues know, and the tools you have access to? What's feasible for you? What do you think is going to happen assuming a truck doesn't hit you?

Mark Mattson: Yeah. My genetics is mixed. It's hard to really... so my mom and her siblings... my mom actually died at 67, but she was a two-pack-a-day smoker-

Dave Asprey: That whole epigenetics thing will get you

Mark Mattson: ... and had arthritis and was on Prednisone for years, and so on, and so on. She got a knee replacement, got sepsis, then had a hemorrhagic stroke. My father lived to be 90.

Dave Asprey: Okay.

Mark Mattson: I'm more like him from the standpoint of my, I guess you'd say, skinny as is my brother and sister are pretty skinny, our two kids are pretty skinny. I'd be happy if I made it to 90. If I made it 100, that'd be wonderful, but I'm not counting on it.

Dave Asprey: Don't you think you can do better than your parents? I mean, we know more than your parents did. We have better tools. We have radioactive imaging. We have DNA. We have mitochondria.

Mark Mattson: In the animal studies, the biggest impact of the intermittent fasting is on average lifespan.

Dave Asprey: Not total lifespan.

Mark Mattson: Not maximum, although there's some effect. The other thing is health span.

Dave Asprey: Yeah. That matters more.

Mark Mattson: Yeah, yeah. I'm starting to, I mentioned, get some orthopedic issues now, which is really my only health issues right now.

Dave Asprey: It's probably lack of red meat and that's what your mom said.

Mark Mattson: Well, she had really bad arthritis too.

Dave Asprey: Right.

Mark Mattson: At an earlier age.

Dave Asprey: Yeah.

Mark Mattson: You know what?

Dave Asprey: It does happen.

Mark Mattson: I think we should think about future generations. Think about your kids.

Dave Asprey: Okay. What's feasible for future generations?

Mark Mattson: Maybe, how many-

Dave Asprey: How long are my kids going to have a chance of living?

Mark Mattson: Well, they have a better chance of living longer than you did, just as we, I would say, I definitely have a better chance of living longer than the average of my father and mother.

Dave Asprey: Yeah.

Mark Mattson: We need something new though to extend maximum lifespan, rapamycin, I don't know. Maybe. Again, the animal study is remember that the control animals, that the rapamycin-treated group being compared to are overfed sedentary animals. Remember, that's also the control animals for the intermittent fasting studies is the control group has continuous access to food, they're in small cages, don't get much exercise, and a lot of strains of animals.

Mark Mattson: They become obese and even will become insulin-resistant as they ate. The animal study say if we take relatively sedentary, probably overindulgent animals, and we put them on intermittent fasting, combine it with exercise, it helps a little more, we can increase their lifespan. Rapamycin can increase their lifespan. What we need to do are combining say, intermittent fasting with rapamycin. Can we get a further increase? I don't know. I'm not sure we will.

Dave Asprey: Yeah. We definitely know until we try it. I look at the sum total of all the people doing all the research, and all the pathways, and just the ability to learn things from machine learning. I'm pretty optimistic that my kids are going to live longer than I am, and it feels like the last 30 years of work is now accessible on my iPhone. It wasn't 25 years ago. We had microfiche.

Mark Mattson: Yeah.

Dave Asprey: It's so much easier to... yeah, there is a connection there. I'm hopeful.

Mark Mattson: Yeah. I wrote my PhD dissertation was on a typewriter using whiteout to correct my typing errors.

Dave Asprey: Wow. The world has changed. I hope the world of anti-aging changes as well. I'm grateful for your contribution around this. You're right. Not eating is one of the key things. That doesn't mean being hungry all the time, but I mean it's not eating some of the time. I'm grateful that you came on the show.

Dave Asprey: People who are interested in your work, probably the easy way to find you is Googling Mark Mattson, and you're first couple pages of results. Your TED Talk is totally worth watching, and just thanks for the decades of work on anti-aging, and fasting, and neurology, and I find it fascinating. You've done a good thing.

Mark Mattson: Well, thanks, Dave. I've enjoyed a lot, and you keep up the good work too. As I said at the beginning of our conversation, there's a big need for translating this basic research and the practical things that people can apply to their own lives.

Dave Asprey: Well, I will keep doing my best. I'll ask the hard questions, and just to reiterate for people listening. I think we're both serious. If someone out there wants to do a PhD, or some other research project on antioxidants and intermittent fasting, it's a wide-open area that totally needs attention. I never thought about that until today, so you've stimulated a new idea. Thank you.

Mark Mattson: Okay, Dave.

Dave Asprey: All right. If you like today's episode, you know what to do. Head on out there and skip breakfast. You'll like your life better if you do that most likely. If you hate your life when you skip breakfast, you got to figure out, "All right, what's going on with my metabolism because I'm probably not as resilient as I'd like to be?"

Dave Asprey: Then, you can work on that. If you want to know how to do that, there's a whole variety of episodes at Bulletproof Radio. We talked about a few of them today. Listen to this one again, get to show notes. You could read the Bulletproof Diet, you could read Head Strong. I talk about intermittent fasting in both of those books.

Dave Asprey: There's just so much knowledge available right now on the blog in other places. Really, if you don't know what else to do, wake up, skip breakfast, don't put sugar in your coffee, don't put artificial sweeteners in it, and see what happens, and you just might be okay.