Announcer: Bulletproof Radio: A State of High Performance.

Dave: You're listening to Bulletproof Radio with Dave Asprey. Today's cool fact of the day is that there is such a thing as a music mind meld. It turns out when you watch live music together with other people, your brain synchronizes with theirs and that brain bonding is linked with having a better time when you're listening to music. This comes from neuroscientists at Western University in Canada. It's actually London, Canada, because they name things weird up here. They split people into two different groups. Some of them watched a live concert, some watched a recording of the concert, and watched the recording with a large audience or just a few other people. They did this wearing electrodes on their head, EEG caps, looking incredibly cool.

What they found was that the delta brainwaves of audience members who watched the music live were more synchronized than people in the other two groups. And these delta brainwaves fall under frequency range that corresponds roughly with the beat of the music, which means that maybe the beat of the music is driving synchronicity, which would drive all those weird ancient drumming tribal practices that we keep finding across almost every old culture on the planet. The new findings are just a reminder that we are social creatures and doing things all by yourself isn't always the right thing to do. So, maybe go to a live concert, 'cause well, science says you should, and it's kind of cool. This came out of the Cognitive Neuroscience Society is where I found that research for you.

As we get into today's show, I'd love it if you went to Bulletproof.com/iTunes and just left a quick review for this, because today's episode is going to be awesome, so you can actually review before the episode, 'cause it's going to be that good. Today's guest is none other than Dr. Peter Attia. Dr. Attia grew up in Toronto, Canada. And I really like his work, because he's a mechanical engineer and applied math guy who wanted to be an aerospace engineering guy, you know, go to space kind of thing until he volunteered at a children's Hospital, so he decided he'd get an MBA from Stanford, trained in surgery for five years at Johns Hopkins, two years with MIH as a surgical oncology fellow at the National Cancer Institute, and then because that's what they always do, he went on to become a consultant at the global medical firm called McKinsey, which is like the top of the top for consulting people. He said, "Well, that wasn't enough. I'll go back into healthcare and start NSI, the Nutrition Science Institute that's funded human clinical trials in nutrition and metabolic disease, and I believe NSI, the other guy there was Gary Tobbs, right?

Peter: Mm-hmm (affirmative).

Dave: And Gary Tobbs is actually one of the original sort of keto writers, and also guy who introduced me to my very first book agent years ago, and he spoke at my non-profit. So anyway, I'm a fan, Peter, and the fact that you're an engineering mind turned medical mind who can solve consulting things means that you're going to think about everything differently compared to the average human being, which is awesome, because who wants to be average anyway. So welcome to the show.

Peter: Thanks for having me Dave.

Dave: You're welcome. How was that for an intro?

Peter: That was a little over the top, but-

Dave: What'd I miss?

Peter: I don't think you missed anything. I think it was just more then they needed, but-

Dave: Well there you go. The point here is I like to interview people who just think differently and are working to really change things, and kinda change the game. And I think you're one of those guys, and you've really thought about medicine in a very different way than I've come across almost anyone else. And what I wanted to talk with you about is kind of how you got to where you are. But I wanna talk something about human longevity. I've been very public about saying I'm gonna live to at least 180 years old. And as someone who's really talked with a lot of the top people in the field of this, and someone who's been through that problem of, you were 40 pounds overweight, and you had problems with cholesterol and things that I had, metabolic syndrome, someone who's hacked it, but maybe more knowledgeable than I am, 'cause you're a practicing doctor. Am I gonna make it?

Peter: I don't know. I mean, I think if we wanted to really talk about that rigorously, you'd have to think of it not so much in a binary sense, but in a probabilistic sense.

Dave: Yes.

Peter: And I would say that there have only been a handful of changes in our understanding of longevity that have led to what I would call step function increases in lifespan. So the first thing is, you have to acknowledge that, how old are you Dave?

Dave: I'm 45.

Peter: Oh, so we're the exact same age. I'm 45.

Dave: Cool.

Peter: So for you and I to live to be 180, it will not happen on the basis of business as usual.

Dave: Correct.

Peter: So it requires a step function improvement, not an incremental improvement in lifespan extension. So when you look at the previous examples of this, of which there are several, but probably the most recent was the introduction of germ theory and the understanding of how that works, and systemic antibiotics and things like that. We haven't had one since. So we're certainly due for one or more of these things. So the way I would think about this if I were gonna evaluate it probabilistically, I'd say question one is what is the probability that in our lifetime we will see one or more of these step

function improvements, and happy to talk about what I think some of those may or may not be.

Dave: Yes.

Peter: And then secondly, absent that, or if those come about, what's the likelihood that we are still sitting around doing well enough, are healthy enough to be able to actually exploit those things.

Dave: Yes.

Peter: So I guess it's hard for me to say, and I know you weren't asking in a, you know, it's sort of a bit glib, but it's an important question, because it's a question I think speaks to the nature of how difficult it is to sorta see into the future. If anything has been taught to us by history, it's that we are notoriously horrible at predicting the future.

Dave: Amen. So here's my thinking, and I want you to dissect this and tell me where you disagree or you do agree. And partly this is enlightened self interest. But also, I think for people listening, I would like to inspire them to think maybe this is possible, because if you don't think something's possible, you're probably not gonna do it.

The way I look at it is, we have enough examples of people who live to 120. So I'll say that's achievable and doable with what we have now. It doesn't happen that often, but if you start 80 plus years before you think you've hit 120, and you start minimizing the things that cause mitochondrial harm, things that cause aging, and you basically take care of the hardware you've got to the best of your abilities, you increase your chances of being around and being healthy towards those advanced ages, not having Alzheimer's, not having cancer, not having heart disease, diabetes, Parkinson's, ALS, dementia, high blood pressure, all those things that are manageable if you catch them very early on, you can take course corrections long before they become really serious and cause other damage in the system, managing just the inflammation levels in general, things like that. So, and that's why I also drive a heavy vehicle, 'cause physics is part of living a long time. So, sorry, if we get in a car accident, I'm probably gonna be the one who walks away. And I don't wanna be rude about it, but if you're driving a really light car and you wanna live to 180, you're doing it wrong. At least drive a really safe light car if you're gonna do that.

So that's half the equation. The other half of the equation is will we have-

Peter: Well, before-

Dave: Okay.

Peter: Before we leave that half though, I wanna say one thing. Not to be the party pooper, but you're absolutely correct. There's certainly plenty of examples of people who lived to be 100 or beyond, and we give them a special name, of course, is centenarians. They're about .4% of the population, so four out of 1000 people are gonna live to be 100 or

longer, currently, meaning I can't say what that number is going to be of people born today, but of people coming into that field of maturity, it's 4 in 1,000. But here's what we do know about them Dave. They're not doing jack shit to be-

Dave: Exactly.

Peter: Like they're not doing anything to stack the odds in their favor. This is a pure genetic lottery. So we have a little bit of a true, true, and unrelated here. So it's true that there are people who live to be 100, 120, and it's true that you can do a bunch of things to exact the outcome you've just described, which is, "Can I do things to reduce mitochondrial injury? Can I do things to reduce inflammation?" Yes, yes, yes, yes, yes. Those two are parallel and seemingly at this point in time unrelated. So the old joke in longevity research is the single most important thing you can do is pick the right parents.

Dave: Amen.

Peter: And right now we know that those centenarians, on average, are doing things worse than the rest of us. They're actually a little more likely to smoke, a little bit less likely to exercise, a little bit less likely to eat well. And so their longevity is actually despite their lifestyle, not because of it. So fortunately this problem's been studied pretty extensively, and we have a pretty good sense of what the genes are that are offering those people protection. And again, I don't think it's necessarily that interesting to go into every which one of those genes, but whether you look at these genes, so for example, they might have hypofunctioning APOC3 genes or hypofunctioning PCSK9 genes, or they're more likely to have an APOE2 versus and APOE3 or 4. We could rattle off about a dozen genes that seem to come up consistently in these people. I think the more interesting, though probably less sexy insight form that is all of those genes with one exception, there's only one that is the THSR that I can't entirely make this case for, but of all the others, they all offer protection from one of the major chronic diseases.

Dave: Yes.

Peter: So they basically, centenarians get the same diseases the rest of us get, and they'd actually die in almost the same distribution, although they get slightly more heart disease and slightly less cancer. They just seem to get the diseases about 20 years later. And so step one, if you wanna live to be 180 or reserve the right to play that game is do everything in your power to avoid the onset of atherosclerosis, which means sort of anything that predisposes you to heart disease or stroke, anything that predisposes you to cancer or Alzheimer's Disease, 'cause those are, statistically speaking, along with accidents as you pointed out, kind of for most people who make it to 40 who don't smoke, those are more likely to be your downfalls.

Dave: Amen brother on that front. So we are, we're aligned on our thinking on that. And when you look at each of those genes that are over expressed in those people live a long time, or you might even just argue properly expressed in those people, they each cause changes in the metabolism, and I believe that we can cause, we can do some of those

similar things by changing our environment, using the epigenetics, or supplements, or lifestyle modifications, so things like that. So we know one gene causes certain things to happen downstream from it. Can we replicate those as best we can using technology. And I'm thinking that not perfectly, but can we at least tilt the odds in our favor? I'm thinking if I do that, I should be able to get to 100 and still be highly functioning, probably even 120 given that I'm willing and able to do all sorts of bizarre things that most people haven't even heard of, that can, in certain circumstances, be the right thing to do.

So for instance, if I'm injured, I probably have the ability to recover more rapidly than the average person because I have access to stem cell people, and just because I'm really fortunate. So I'm hopeful on that front. But I'm also betting like 50% of this increase, the other 60 years that you stack on the 120, that's gonna come from a step function, that we are now using machine learning. We have more data than we ever had. The human genome is mapped. And we're really finally starting to understand epigenetics. I have substantial concerns about mismatch between mitochondrial DNA and nuclear DNA, which, if you're listening, you got your mitochondria from your mom, the power plants in your cells that also are the things that seem to monitor the environment to trigger the epigenetic changes.

And you also have this nuclear DNA, which is like the wiring for your heart. Not the wiring, but the plans for your hardware, how your body's gonna be built. And the problem is if you have the power plant from say a commercial building and you've got the physical plans for a home, and those are mismatched, that might affect your aging. And I think that's probably something a lot of us have, and there's emerging science about that. So maybe we need to hack our mitochondrial DNA. I'm all over doing that. I just think that's one of those step function changes that might come over the next 50 years, which seems to be enough time for me to live to 180. Is that, I mean, over a 50 year time span, do you forecast at least one of these step function things?

Peter: Well again, I try to avoid forecasting, because every time I do it, I seem to be wrong. And there's two things to forecast, right, which one is what is the plausibility of-

Dave: Right.

Peter: ... something happening. And then the second thing is how long will it take to come online. I think we do a slightly better job at forecasting ... Well, maybe this isn't [inaudible 00:13:25] true. In my own biased way I think both of those are really hard. I'm actually, on this one, more willing to place a bet on some things actually happening than actually trying to understand when they could happen.

Dave: Yeah.

Peter: So for example, I do believe we will absolutely be able to manipulate the Torr pathway, which is in my opinion the single most important pathway in biology. And I believe we will be able to manipulate it with much more specific molecules than we can do today. In other words, we can do things that are gonna be very specific in the future that today,

we can't really do. Now, I also have the fortune of knowing the people who work on that problem day in and day out, and therefore I have probably a little bit of, I share some of their humility in how complicated that is. I mean, nature took a billion years to make that system, so a couple of whiz kids from MIT don't necessarily get to undo that in a decade.

Dave: Yes.

Peter: But I think, I view that as a very plausible step towards longevity. Another example that I think is actually gonna be a more challenging problem is going to be a reprogramming senescent cells.

Dave: Mm-hmm (affirmative).

Peter: So certainly we've had proof of concept along that, and there's companies like Unity Biohealth that are actually doing really exciting work in that space. But you know, I think to get to the point where Dave Asprey can show up and say, "Hey, I want all my senescent cells zapped." That's sort of the engineering problem that comes after the proof of concept. And so I think that, to me, is much harder to understand.

I think the third thing that interests me the most is probably, given that atherosclerosis seems to be the only inevitable disease in our entire evolution. So once people reach their 8th or 9th decade, if they haven't got cancer or dementia, their odds of those things actually start to go down. So the only disease that increases in its risk monotonically, without fail, is atherosclerosis. And so, I know, unfortunately, it is really popular in the blogosphere to talk about how heart disease has nothing to do with LDL and it has nothing to do with cholesterol, and all of these things. But the reality of it is that's just patently false. This is clearly a disease that is driven by lipoproteins, inflammation, and endothelial dysfunction. And those things, when you are exposed to those things in a time dependent manner, your risk of those diseases almost universally just goes up as time goes on. So while age is the single greatest risk for atherosclerosis, it's the confluence of the lipoproteins, the inflammation, the endothelial dysfunction that provide the explanation for why.

So how would one ... So in other words, so taking a step back, to get to your step function, no step function improvement in longevity can come without addressing atherosclerosis. This problem must be addressed. If you wanna live to 180, we absolutely have to fundamentally change the way your coronary arteries and other arteries interface with lipoproteins, oxidized cholesterol and the like. And so when you start to look at what nano particles could potentially do, if you could build nano particles that can replicate the functionality of an HDL particle, which is to say those things that could enter the subendothelial space and delipidate oxidized sterols, clean our foam cells, that's a step function. Now you've changed the course of the game. And you might even get a two for one, because if you can take nano particles and actually start having them behave like T-cells, you now start to get enhanced immune function, which probably is going to play a pretty important role in reducing our risk of cancer.

So again, I think all of these things, from an engineering standpoint are plausible.

Dave: Right.

Peter: And I, my view is, just being a relatively unsophisticated longevity guy, unsophisticated in that all I talk about is the basic, you know, blocking and tackling of food, and exercise, and sleep, and stress management, and drugs, and supplements, nothing really unheard of in that tool space. The goal is can you generate even that extra 10 to 15 years above business as usual. 'Cause it might be that period of time is what's necessary to allow you to be around for the step function.

Dave: This is that idea of achieving escape velocity, the way Ray Kurzweil talks about, where if you can just live long enough and be healthy enough long enough, technology will save us. And I think there's merit to that line of thinking, which is we don't know when we're going to get these step functions. And I'm not sure that I agree it's just a step function. There's probably, in fact I wouldn't say probably. We know that there's more than just atherosclerosis, although it's a major thing. And for instance, reducing cancer risk, and Alzheimer's, these other things that we talked about. And there's many different pathways that we understand now. So what I'm thinking is that there are some things that are linear functions but not step functions. So you got a year here, you got two years here, you got three years here. You reduce your risk by 50% on this, but you didn't eliminate it. And so I'm hoping that gets us to the point where there are some really big things, like engineered molecules or the ability to do things that cause your body to grow new body parts, for instance.

I mean, I've seen some phenomenal things with stem cells. A family member was gonna go in for cardiac surgery for a heart valve problem. And six weeks after he had stem cells, his own cells, introduced intravenously, his heart spontaneously healed. And the surgeon went in and did a scan before they were gonna book him for surgery and was like, "uh, you don't have this problem anymore." So there are things like that that are happening today. And who knows how long it'll be before we can resurface our arteries using things that we just don't know about today. So I'm hopeful that there's some biological manipulations we could do that maybe don't require artificial molecules. I could be wrong. I just feel like we're getting more and more control over our cellular biology, so there's at least hope, whether I'd be betting only on that. No. I'm doing everything I can think of, probably like you are, that's gonna increase the odds. And I'm willing to die trying too, which I think happens to all of us.

Peter: Yep.

Dave: What do you think about stem cells as a part of this equation for living a long time? Are you bullish, bearish?

Peter: Pretty neutral at this point, frankly.

Dave: Yeah.

Peter: I think I haven't really been that impressed with the data thus far. I think the challenge when you try to assess something like that, even inside of clinical settings, clinical trials rather, is the anecdotes tend to speak louder than probably the real data. So it's a question I get asked a lot because a number of my patients either go through stem cell therapy or PRP, especially around orthopedic stuff.

Dave: Yeah.

Peter: And my view is, you know, you have to evaluate two risks, which is what's the risk of doing this, and what's the risk of not doing this. And so, again, I, it's hard for me to provide a blanket sort of statement on my views on this.

Dave: Sure.

Peter: But with each patient, I sort of spend time going through the, what's the problem you're trying to have addressed? If we do nothing, or if we do everything that we think we can, outside of doing this, what is the natural history of this going to look like? And then, how does that compare to what we think is the risk of doing something with stem cells. So this strikes me as a problem that's a little bit harder than we think it is right now, which doesn't, that's obviously stating the obvious, but honestly Dave, it just speaks to a bigger issue, which is biology's freaking hard. It's way harder-

Dave: Yes.

Peter: ... than physics. It's way harder than chemistry. It's way harder than mathematics. In a different way, right?

Dave: Right.

Peter: I mean, those things are slightly more ordered, slightly neater. It's slightly easier to differentiate between convergent and divergent systems. And biology is, I don't know, we just have like the most still, relatively crude understanding of it. And that's of course the fun of it.

Dave: Yeah.

Peter: I mean, in many ways, that's the fun of being in any field. I mean, when you look at what physicists went through at the turn of the last century, so going from the 19th into the 20th century. There could not have been a better time to be a physicist. Now I'm not saying that to be disparaging to someone who's a physicist today, because obviously physics is still exciting. But its amazing era was 100 years ago. And in that sense, I think we are entering that space in biology, but that also speaks to how little we know at this moment in time, and hopefully what, 100 years from now, maybe you'll be interviewing somebody else, and you guys will wax philosophically about, "Oh my God. You remember how little we understood," fill in the blank, stem cells, or whatever, "back in 2018?"

Dave: You said once the science of longevity and the art of longevity are basically an interdiscipline of engineering, which is not something that you'll hear most doctors say. And I think it speaks to your training as an engineer before you went to medical school. And a lot of your answers sound like an engineer more so than your typical MD. How, I mean, how do you reverse engineer that problem if you put on your pure engineering hat but with your set of medical knowledge? And we've talked about, you have to solve atherosclerosis, and probably cancer and Alzheimer's, but what's the first step to reverse engineering?

Peter: I think it always starts with defining the objective, so you wanna know where you need to go. So if you're trying to build a bridge and you wanna cross this thing, you sort of have to understand the basic parameters of where you wanna go, which is the bridge needs to be this long. The span needs to be this wide. It needs to be this high. It needs to be able to bear this load, et cetera, et cetera. And then you sort of, you work backwards from that position of understanding. So with respect to longevity, I mean, I think the first thing I, and I had this discussion with a patient this morning. And it's always a morbid discussion, but it's like, "How are you gonna die?" Let's, we've now got a really good sense of what your genome looks like. We've got a really good sense of your family history. And I mean, I think even a geneticist will probably agree with me on this, though they might not, that a really, really well done family history provides far greater insight into the genetic risks that are predisposing people to death than a whole genome sequence.

But the point is, once you finish doing a complete risk assessment, you then should be able to start answering the question, which is if you don't change anything in what you're doing today, this is kind of how you're likely to die. This is the probability distribution map of your demise. So you have to start with that. And the reason you have to start with that is you have to know how to back out of that. And not everybody's gonna be the same here, and that's why there really isn't a one size fits all. This gets to your earlier part about this is where the art comes in. The art is in taking the scientific principles, what are those principles? Inflammation, as a general rule, is bad. Immune function, as a general rule, is good. T-cells do good things and macrophages, when they run amok, do bad things, that sort of thing. There are these general principles, but you know, if someone has two copies of an APOE4 gene, and their family history is also suggestive of a high degree of penetrance of these things, then avoiding neurogenerative disease is the highest priority, and it might even come at the exception of increasing or allowing an increase in the risk of something else, like cancer.

So that's what I mean by reverse engineering is you sort of see where the iceberg is, you see where you are, and you ask a question. How far am I from the iceberg? How fast am I traveling? How much do I need to shift the direction of my ship, and what new iceberg does that put me in the line of?

Dave: Do you think we have enough knowledge yet for the average person listening to sort of know what the first iceberg is, the first big problem? Or is it really just a family history sort of thing?

Peter: I think, to me, a really, really good family history coupled with a really good set of diagnostic tests, most of which can be done within the blood, can get you partly there. This might be more nuance than I can get into without a white board, even though I realize I have one behind me, I'm not gonna jump on it. I try to explain to patients that when it comes to the main three diseases, so the atherosclerotic diseases, the neoplasms and the neurodegenerative diseases, depending on your age, what we learn from family history, and what the blood test shows, we can get somewhere between I think 70 to 90 percent of our predictive insights on cardiovascular disease from blood, probably only about 30 to 40 percent from cancer, and probably about 60 to 70 percent on neurodegenerative disease, but specifically dementia. Now, the earlier you start in life, I think the better you can handicap those risks. The later you get, I think the more you have to look at other means of testing to stratify risk.

I'll give you one very simple example. Is there a role for coronary calcium scoring and CT angiograms and things like that? Sure, there's a role for them. But the younger you are, the less valuable those tools become for predicting risk, and the more value you can get by understanding the lipoproteins, the inflammation, the endothelial health.

Dave: We have a long body of science, a lot of history saying cholesterol is really important. And you've shifted the way you talk about that from not just general cholesterol, but you talk about oxidized cholesterol and specific lipoproteins. Thank you for that, by the way. Because HDL does something different than other ones, just like people say protein's good or bad for you. It's like, well, spider venom and nerve gas, both which are proteins, neither one of those is good for you. Different proteins might do different things, you know. And so, but like, there's a nuance to this, and so thank you for helping on that one.

Peter: Yeah.

Dave: If someone has unfavorable, we'll say lipoproteins, but they have no markers of inflammation, which one is more important? I mean, are you concerned as a doctor, if someone's like, "I have zero LPPLA2, that enzyme's that released when your arteries are being damaged, and I have no inflammation to speak of in my body, but my cholesterol's dysregulated. Do you care?

Peter: I mean, I think that's a really difficult question, and I don't think it's one we know the answer to. The first thing I do wanna clarify is that I wanna make sure patients understand, I don't like the word cholesterol just willy nilly because it has so much-

Dave: Right.

Peter: So I try to get very specific on that. So when I'm evaluating a patient for risk, I am paying attention to four lipoproteins in the following order. I need to know their LPa.

Dave: Yay.

Peter: And ideally, I wanna know that through NMR. In other words, I don't wanna know the mass of LPa, and I don't wanna know the cholesterol content of LPa. I wanna know the number in nanomole per liter of LPa particles. So that's the first thing. So we know that about 8% of the population have that genetically inherited, and it's elevated. In fact, Anahad O'Connor did a really nice piece in the New York Times, probably about two or three months ago, on this silent killer, which unfortunately by most physicians is just completely unacknowledged. And it's a tragedy because it is a greater cause of familial heart disease than any other genetic mutation we're aware of.

Second thing I wanna know is what is their LDL particle number. I don't care about their LDL cholesterol. I'm honestly more interested in their eye color than their LDL cholesterol. If their LDL cholesterol agrees with their LDL particle, then that's fine, but if it doesn't, I don't care. It is unambiguously clear in looking at the Mesa population and the Framingham population that when there is discordance between LDLp and LDLc, LDLp wins every time. So I wanna know their LDLp.

I wanna know their small lDLp. Now this is still an area that I think is a little bit gray in the space. I think you still have two camps, sort of the camp that says particle for particle size doesn't matter, and then the camp that says no, actually a small particle is an independent predictor of risk and therefore has atherosclerotic properties that are unique to it. Since we can't really target small particles directly, it might be a little bit of a moot point other than tho help risk stratify.

The fourth thing I care about then is the VLDL remnant, and the best way we can look at that is to look at the VLDL cholesterol, and the best way we can estimate that is to take the non HDL cholesterol and subtract from the LDL cholesterol. So I guess I'll take back what I said a moment ago. There is one time I care about the LDL cholesterol, which is to calculate the VLDL cholesterol, which then serves as a proxy for VLDL remnants. Again, a VLDL remnant is problematic if you have enough of them, because it is a atherosclerotic particle. It is an APOB100 bearing particle.

So now let's reframe the question. If a patient shows up and they have some of those or all of those elevated ... So again, notice I don't care what their total cholesterol is-

Dave: Right.

Peter: ... or LDL cholesterol. I don't care if their HDL cholesterol's low either by the way, because everybody gets phosphorolated over low HDL cholesterol. But we are way too early in the infancy of lipoproteins to actually even pretend we know what that means. In fact, you could make an argument that a low HDL cholesterol serves to have a more functional HDL particle. And we certainly know the opposite is true, that the more you fill an HDL with cholesterol, I.e. the higher the HDLC gets, the less functional they can be. And we've seen three clinical trials of CETP inhibitors that have all raised HDL cholesterol, and two of the three increased mortality.

Dave: Right.

Peter: The third was actually just pulled off the market, 'cause it had no effect. So HDL biology is I think way more complicated than LDL biology. So if you have somebody who's elevated in all of those risks, and now they say, "Well, but Peter, my LPPLA2," as you pointed out, "is normal. My CRP is normal. My fibrinogen is normal. My homocystine is normal. My Ox LDL is normal. What do you want, do we need to do anything?" I think the question is do you feel lucky? Because you need three things to be not firing on all cylinders to get disease. So we've ruled out effectively, in this case, the inflammation that we can measure seems okay. But of course, we have far more advanced inflammatory tests that I'll typically look to if I wanna get a better understanding of that. None of those things give me a sense of how the endothelium is functioning, and of the main drivers of atherosclerosis, I think endothelial function is the hardest one to assess in the blood.

So we do look at things like asymmetric and symmetric dimethylarginine. Insulin itself probably speaks to endothelial health, and certainly homocystine does. But that's relatively crude compared to the precision with which we can look at things like lipoproteins. So I would say look, most risk models that would evaluate a patient are looking at 10 years of risk. Now, 10 years of risk doesn't really mean that much to someone like you who's 45, who wants to be 180.

Dave: Yeah.

Peter: If you're 45, and you wanna be 180, the fact that your 10 year risk is low shouldn't tell me to back off. So my view on this is actually quite a long view, which is that we have to be able to address these things through the lens of what's the 60 year risk or longer for what we're talking about? And in that sense, I think it's actually quite unambiguous, that lower LDLp, and frankly even LDLc always corresponds to less heart disease. Now, I know what some people are gonna say. You can always find an exception to these things. But the body of work through the mendelian randomizations and all of the naturally occurring experiments including the PCS canine gain and loss of function people, make this pretty clear.

In fact, so much so that the European Society of Cardiology actually recently published at the end of last year a very strong statement saying, "Look. It is becoming impossible to ignore the role of APOB in atherosclerosis as a causative agent." So maybe the way to frame this question, and I apologize it's taken so long to get to it, but this is a nuanced point is, if someone's sitting there with perfect inflammation and elevated lipoproteins and saying, "Do I need to do anything?" The question is do you wanna be even better? So you might be in good shape. You might actually still do okay, but do you wanna do better than okay, because in having lower lipoproteins, you're gonna do better than okay.

And the question is how do you achieve that without causing another problem?

Dave: Yeah.

Peter: So this is where I tend to then deviate from the kinda mainstream cariology approach and where I probably have just as many arguments on the other side, which is I think from a cardiac standpoint, you can't go too low on LDL.

Dave: Interesting.

Peter: The problem is, you can go too low on LDL from the standpoint of other diseases.

Dave: Right. Like cancer?

Peter: Well, I think actually more so of neurodegenerative disease.

Dave: Okay.

Peter: My biggest concern. So I tend to get very concerned when a patient has a complete suppression of cholesterol synthesis, and their risk of Alzheimer's Disease, either through genetics or non-genetic sources is deemed anything high. So I actually treat every patient as thought they're modest risk for Alzheimer's Disease, and I sort of never wanna see their cholesterol synthesis suppressed below a certain level, which we can measure, and that has been documented through some pretty interesting research to significantly increase the risk of neurodegeneration.

So that gets back to your point about what's the art. Well the art is how do you finesse two different fields of literature that aren't actually looking at the same problem necessarily, but directly, but indirectly they are. And then your job is to sort of understand well if it's happening this way over here, and it's happening this way over here, how do we thread a needle to give us the best of both worlds?

Dave: During my years of biohacking and experimenting, I got my cholesterol, my total cholesterol down to 136, when I was a raw vegan, eating huge buckets of food every day to try and have enough food. Didn't do very well on that over the course of time, and I definitely experienced way more brain fog and like the neurological things that can happen when your cholesterol is too low. And I don't know that from that long ago, this was a good 15 years ago. I don't know that I have, I don't know that we could get some of these markers that we can get today. Is there a level where if someone came in and their cholesterol is that low, or at 100, where you sorta scratch your head and go, "This is not a good thing." Or even then you wanna see the particles.

Peter: Yeah. Again, I never really concern myself with the cholesterol. What I'm looking at when I'm looking at the particles that I talked about is I wanna understand four things, three of which we can measure, one of which we can't measure, but we can infer it by the other three.

So the first is I need to understand what their volume of triglycerides are. So lipoproteins are there to traffic cholesterol, but they also traffic triglycerides, and so you want your serum triglycerides as low as possible, and the more of those guys you have

floating around, the more you're wasting precious space on your lipoproteins to make use of the cholesterol space.

The second thing I wanna understand is how much cholesterol do they make? So every cell in the body makes cholesterol. In fact, every cell [Interviewer] he body makes almost enough cholesterol to meet its own needs, but of course, that's not always the case. So for example, if you are sick, the adrenal glands are probably gonna need more cholesterol than they can make, and they're gonna have to beg, borrow, and steal from someone else, which is why we have these lipoproteins to traffic cholesterol around the body. We can measure that. We can measure how much cholesterol the body makes.

The next thing I wanna understand is how does your body recirculate cholesterol. So all that cholesterol's getting made, it's getting trafficked. It ends up back at the liver, and the LAL particle gets brought into the liver through the LDL receptor, and the process then results in the cholesterol being put into bio and then partially being reabsorbed in the gut. And again, we can measure that. So now we get a sense of what that dynamic looks like and how that's being circulated.

Finally, the thing we can't measure directly is how well does the liver clear the lipoprotein out of circulation. So when I'm trying to evaluate if a patient's cholesterol or particles are too low, I have to do it in the context of all of those things. But as a general rule, no. I don't find myself being concerned with low cholesterol unless the synthesis per se is being low and I see an obvious endocrine problem along the way. So from a symptom standpoint, and I don't think I've actually, I'm trying to think. I might've seen this once, where when you're working up hypergonadism, it looks like the problem is just insufficient cholesterol. But I gotta be honest with you. That could also be true, true, and unrelated. And I'm not sure that, yeah, I'm just not sure that that's even causely related. Because the challenge of looking in the bloodstream is you're not getting tissue specific information.

Dave: Right.

Peter: So you'd have to believe that the gonads aren't smart enough to make enough cholesterol when they need it. So I really think that the hypergonadism diagnosis in a patient like that is probably more due to something else, deficient pituitary signaling and or lading cell disfunction more than it is, "God, everything's on fire and also [inaudible 00:39:08] Dave, we just don't have enough cholesterol." I just, I don't know. I don't think that's the case.

By the way, I was a vegan 15 years ago as well. So when I was 30.

Dave: How'd that work for you?

Peter: You know, so I don't wanna take too much credit for my veganism. I just did it for 6 months as an experiment. But I remember distinctly when I did it. So first of all, I enjoyed it tremendously. I think a lot of people.

Dave: Oh yeah, so did I.

Peter: I think a lot of people who assume that I'm the guy who spent all this time in ketosis, I'd be like the anti-vegan. But the reality of it is I love vegetables beyond words, and I wasn't the healthiest vegan, I must admit. There was a lot of vegetarian Subway stuff, and-

Dave: Okay. I never did that.

Peter: I wasn't like the ... But I was in my residency at the time, so it's like-

Dave: Oh, [crosstalk 00:39:48].

Peter: I was on a pretty shoestring budget when I was doing this. I'll tell you a couple thing that I observed. So the first thing is I gained a little bit of weight doing it. That was a little bit frustrating, 'cause this was kind of in a time when I was trying to understand why I couldn't lose weight. The second thing that I found really interesting, and I'm sure you can relate to this, as can others, is I was amazed how when I went back to eating meat, how my appetite for it had decreased. And so I had-

Dave: Yeah.

Peter: ... agreed a priority, I was going to do this for 6 months. And I was counting down the days until I could go have that steak on the first day of the next month. And I remember going to a steakhouse, and not being able to eat the steak. And I remember thinking that is weird man. Doesn't that speak to how malleable and adaptive we are to our environments. Obviously in time I was able to learn to eat a steak again. But it gave me a bigger insight and empathy into patients who we ask to make significant changes in how they eat.

Dave: It does take time, no matter when you make a change. Although I find once some people get some ketones flowing, their cravings drop very substantially, so they're able to say no to sugar more easily and things like that. But I remember I said, I'll do this forever. I would eat gravel every day if I thought it was gonna make me live longer, and I felt good when I did it. And it was when I started to get even worse brain fog, not better. And then I cracked a tooth that had no business cracking. And I was a very conscientious vegan. I prepared everything, went to the farmer's market, fresh vegetables. I did everything you could do and just found that alright, at a certain point I realized this just isn't working, same as some of the other things I had tried to do to lose weight over the years, although I did lose weight as a vegan. It just, I didn't lose all the weight I wanted to lose, and a lot of it was muscle mass, not necessarily fat mass. It was an interesting experiment, but it makes me think, what did my cholesterol do?

But you talked about something that I think listeners would care about. You talked about this cholesterol recirculation, and some percentage of us, roughly some 28% have an HLADR, or one of several HLADR genetic polymorphisms, where, and for, if you're listening to this, the basic thing is you have some different genes, for lack of a easier

way to say that, that cause us to more effectively recirculate our bile, and thus our cholesterol. And those are the 28% of people who are more susceptible to lipophoric toxins. These are basically toxins that dissolve into fatty stuff in the body and get recirculated in the nervous system that are tied in some studies to Alzheimer's, ALS, Parkinson's, a bunch of other things. And things like Lyme disease make lipophoric toxins. Things like toxic mold make lipophoric toxins. And I think that there's some very interesting anti-aging things like that. If you re one of those people who has that difference genetically, you're more likely to survive in some environments throughout history, for instance times of famine, because you're better at recirculating these precious molecules. But you're less likely to survive if you have things that dissolve into your fat that keep getting recirculated versus excreted and then remanufactured fresh.

Do you look at that as a part of your anti-aging perspective?

Peter: I look at something a little bit different along that same spectrum which is I'm interested in a different polymorphism, which is around something called the ATP binding cassette, G5, G8. So this is the specific ... So when you have that biliary cholesterol coming down your intestine, a transporter called the Niemann-Pick C1-Like 1 transporter brings any non-esterified sterol into the enterocyte. So esterified is just the chemical, for the listener, it's just a chemical structure that has two molecules that are joined by a covalent bond around their oxygen atom. But if you don't have something that's esterified, meaning it's less bulky, it can be brought in that transporter. And then you have a whole set of sensing molecules inside the cell that says, "Hey, do you have too much of this stuff in you? And if so, we need to get it out. So we're gonna kick it out through that ATP binding cassette."

Now here's where it kinda, you can get into trouble. The last numbers I'd seen were somewhere between about 8 to 12 percent of the population have defective or suboptimally working ATP binding cassettes. These are people that have a much harder time getting phytosterols out of their system. So sterols can, like cholesterol is just the sterol from an animal. Phytosterol is the sterol or cholesterol equivalent from a plant. Now it's been largely known that if you take high doses of phytosterols, you can actually lower your cholesterol. And this explains the mechanism why. You basically overcrowd the system, the Niemann-Pick C1-Like 1 transporter, and all of a sudden the body just can't absorb as much cholesterol. So you look at your cholesterol numbers and you say, "Oh yay. This is great news." The problem is phytosterols turn out to be more atherogenic than cholesterol. So I care deeply about a patient's phytosterols level, their level of phytosterols because of their atherosclerotic properties, and as a general rule, I don't advocate using phytosterols as a tool to lower cholesterol. In other words, I'm not saying don't go out and eat as much plant matter as you want. I think you can't overdo it just eating. But certainly taking these exogenous phytosterols is problematic.

Now to the point you're making, I think we see that example lots of places in biology. I mean, that again speaks to this idea of biology's a bitch. There's no two ways about it, right? Look at the APOE gene. We used to all be APOE4s up until about 200,000 years ago. Meant we were all "high risk" for Alzheimer's Disease up until about 200,000 years ago. Well, what was the advantage of an APOE4 gene when compared to the APO3 which showed up 200,000 years ago or even the APO2 which showed up 50,000 years

ago. It turned out it offered you enormous protection against parasitic infections. So if you didn't wanna get parasite infections, especially those that got to the brain, having an APOE4 gene would be a better thing. But of course, today we know that the APOE4 is not an advantage gene, but a disadvantage gene at least with respect to Alzheimer's Disease and atherosclerosis.

So the example you referred to, I'm actually not familiar with that example, but certainly by plausibility it would certainly make sense that different polymorphisms are going to predispose people to different scenarios or more specifically allow them to thrive in one environment or offer protection, and yet come with a disadvantage or a drawback in another environment.

Dave: And these are the nuances where, when we talk about living to 180 or longer even. Like you said, biology's a bitch. But your individual biology's even worse, 'cause you gotta be able to map all this stuff out, at least enough of it to move the needle, and then make the appropriate changes. And I'm seeing a lot more things going on around gut bacteria. You have different gut bacteria, so you change the bacteria. They change what's happening inside your biology, and we're just now getting to the point we have a good data set there. We can start applying that data set to looking at that as an independent risk profile or risk factor in your profile. And it just seems like we're only gonna be getting more and more and more data, which makes teasing out what matters for you versus the guy sitting next to you maybe more difficult, but also more accurate. Do you believe that our ability to make sense of the data will grow at the same speed that the data that we're getting is growing, or are we just dealing with way too much data?

Peter: No.

Dave: Okay.

Peter: Absolutely not. Not a chance in hell. The availability of data is going to outpace our ability to understand what to do with it at a log order. And in fact, as time goes on, I think the signal to noise ratio is going down, not up. So I think that is a problem. And I also thing the problem is, among other things, and I'm as guilty of this as anyone, I think we just generally are more confident than we should be. I mean like, I sometimes stop and say, "Wait a minute. Peter, why are you so confident in what you're saying?" I mean, is that reasonable? And then of course I get all self doubting and self loathing, and think well, I don't know anything, and every time I think I know something, I learn something new that tells me I didn't know what I thought I knew. And so, I don't know. I'm troubled in some sense by my inability to make sense of all the data out there.

You brought up gut biome. There's an example of something I just think it's a complete shit show, no pun intended, of just completely useless meaningless data that just really strikes me as a bit of a drunk in the streetlight problem, which is, you know, you see the drunk guy standing below the streetlight and you say, "Hey dude. What are you doing looking under the streetlight?" He says, "I'm looking for my keys." You say, "Is that where you last left them?" "No, but this is where the light is." And so, we've, you know, every time our practice, our analysts take a hard and fast look at the gut biome stuff, we come up empty handed, which is one, these data do not provide us with actionable

insights that seem to materially move the needle. Two, it is not clear if these findings are associative or causative to the things we care about. So I'm not saying that those things won't turn out to be true. But every time over the past seven years we've looked into it, and looked into it at a level of excruciating detail that I think few people could appreciate. Including very recently. We just went through this exercise with yet another sequencing company. I mean, gosh, I just got the final report on that from my team a week ago. And again, it was another disappointment. So we wanna believe that this stuff can help us, 'cause we're looking for any edge we can get. If we were gonna use the example of being hedge fund managers, we're looking for any legal edge that can create the maximum alpha at the lowest risk. That's effectively the model of longevity. So no stone should be left unturned. But oh my God. Half the stones you turn over, you don't know what to do with what's under them.

Dave: So the amount of data is definitely changing. I'm reminded that at one time, when I was doing the research on the Bulletproof diet, not just the pub med research, but also just the experimentation, like well this study says this oughta kinda work. Let's just try this for a while and see what happens. I got it dialed in where I could be at a level of leanness and energy that I'd never had in my life, and I could keep it. And I kept it for a couple years. Then all of a sudden, over the course of about 6 to 8 weeks, I gained 20 pounds.

Peter: Wow.

Dave: And I'm like, this is not okay. And all the tools that I used just didn't work. And at that point, I'm like, "I've got this. I own my biology," at least at that level, where this is something I can dial up and down. And I was really frustrated, so I ... What could this be? And a bunch of lab tests. And it turns out I had high levels of blastocystis. It's stuff that grows in your gut that shouldn't grow there that is correlated pretty heavily with autoimmune conditions, and new food allergies, which I also achieved at the time. And this was after coming off a few months of like, we'll call it extreme keto, where I probably feeding much at all to my gut bacteria that they liked. It was fat and protein and very few anything else. When I treated the blasto, I lost the weight in another like three weeks, like it just fell off, right. And I'm pretty darn-

Peter: And you treated it by doing what?

Dave: I took whatever antibiotic kills blasto. Actually it might've been metronidazole. I don't actually remember what I took. This was a while ago.

Peter: But did you also correct the dietary imbalance that led to it?

Dave: I tried correcting the dietary imbalance before I did that. So I played around with the diet. Alright, I'll go off the extreme keto thing, like that, but nothing moved the needle. None of the dietary changes that should have, whether dialing carbs up or down-

Peter: Got it. Yeah.

Dave: And it was pretty obvious, when I took the stuff to kill it, I felt better, and then, and the weight just came off very dramatically. And you look at the studies on something like that, knowing you've got that going on. Or more recently I had apparently giardia and an amoeba that eats your brain, if it gets into your brain anyway. I'm forgetting its name. It was a histolytica.

Peter: Don't say E Histolytica.

Dave: It was.

Peter: Okay.

Dave: Why? Do tell me if, especially if it was skeptical. I wanna hear this. I'd say I had four months of disaster pants, like 20 times a day, where you're like, okay. Nothing will stop this. And also, soon as I got this, I got it from salad at a restaurant, you know.

Peter: So I will say this.

Dave: Yeah.

Peter: You don't need a gut sequence-

Dave: No.

Peter: You don't need to sequence your gut biome to know those things. So those are well understood parasites. I think giardia is certainly, I mean, my guess, Dave, not trying to play doctor on a podcast, is all of your difficulties were due to the giardia, not the E Histolytica. E Histolytica is probably an innocent bystander in that situation. But regardless, even if we would buy the argument that E Histolytica is the problem, we don't need to sequence-

Dave: No. No sequence in this.

Peter: ... the multi-trillion [crosstalk 00:53:12] bacterial. I mean, this is the kind of, this is just basic parasitology.

Dave: Although I can tell you, three different labs missed these things.

Peter: Oh no. I'm not saying it's trivial.

Dave: Okay.

Peter: But I'm just saying like that is basic parasitology and that is, God if ... And my guess is you were some place where you drank water that is where you got that from. Yeah, usually shows up from sort of a contaminated water source. A lot of people get it hiking or camping or being in some unusual place.

Dave: This was probably a restaurant in Phoenix as far as we can tell. And I mean, Phoenix is a rough and wild place.

Peter: Yeah.

Dave: And it's, one practitioner said, "Oh, it looks like you've had this giardia in your system for a while." But whatever's going on there, four months of trying different drugs and different natural techniques, and everything that I knew, nothing touched it, and it was ... Finally, an 80 year old guy in New York who's written 6 textbooks on tropical parasites ... Well the reason I'm saying this is there's a lot going on in the gut. That sure was a long time to say that. But there's ...

Peter: No, no, no. And I don't disagree. I think what I was just, the point I was making is I'm not disputing the importance of the gut. I'm not disputing that there are many times when a pathology can be found in the gut, treated directly, and lead to an improvement.

Dave: There you go.

Peter: I think, yeah. I think what I'm generally going to reserve my optimism around is that, and I won't name names of companies. I was just about to use a company's name as a verb, to blank blank your gut biome sequence is the panacea to health. I'm just waiting on the evidence that demonstrates that that's gonna provide more actionable insight than the other stuff. And my hope is that ... First of all, right now, the sequencing is still prohibitively slow on this stuff.

Dave: Yep.

Peter: So every time we've gone to sequence, it's really hard to make changes when you don't have somewhat real time feedback. So if you come to me and say, "Peter, I'm feeling really horrible, and blah, blah, blah, blah, blah," and we do a sequence, and I have to wait 12 weeks to get the results back, it's gonna be really hard to make a decision and tie it back to where you were. So they have to get faster. They have to get better. And those are engineering problems. That basically just requires capital and engineering. Those are solvable problems.

The most thoughtful person, to me, on this topic, is a guy named Larry Smarr, and I don't know if your readers are familiar with Larry. But-

Dave: I love Larry. I've actually held his 3D printed colon. In fact, I took a picture of his own colon, I took a picture of it on a sushi plate, with all the trimmings, and I put it on, whatever, Twitter, and I said, "Can anyone tell me what kind of sushi this is," 'cause it looks like a piece of sushi, but it's actually his colon. So this is UC San Diego scientist. He's a complete [crosstalk 00:55:51].

Peter: Yeah. So Larry's a close friend, and actually we're having dinner probably in about three weeks. And so the question is can you take the types of insights, not you, but can one take the types of insights that Larry has generated through just raw computing power,

and sheer brute force, and how long will it be before we can take that to the masses? And as you probably know Larry's whole story, I mean, Larry's basically the guy that single handedly figured out his own GI pathology just through sequencing and understanding how colitis could be related to these patterns. So yep, there's absolutely something there.

Dave: You just think we aren't, we aren't quite there yet from a technology.

Peter: I just don't think we're ready for prime time yet, which means let's keep rooting for it.

Dave: I actually share your perspective in that. There's so much we don't know, and when I get a full workup, like 90% of the things that they find, we don't know what that means yet. So your like, "Well how actionable is that?" I have some cool bacteria from a sea squirt growing in my gut that are apparently good for me, but I'm not sure what to do with that yet. But I know we're gonna get there.

Peter: Right.

Dave: And I'm excited about some of the innovations there.

Well so, let's talk for a minute about not just Alzheimer's, but executive function, processing speeds, short term memory, things like that. These are things that you can actually look at as people age. And they go down relatively reliably, like your working memory doesn't work as well. What are the things you're doing for yourself or for patients to protect executive function?

Peter: Well, I mean, I think the reality of it is I don't have a great sense of how one augments those things in healthy individuals. We certainly have a sense, based on some work we've done in collaboration on how you would go about addressing those in people who are imminently facing decline. So what we do then is by extension, we make a logical posit, which may or may not be true, which is whatever things that are necessary to delay conative impairment in people who are susceptible, should also provide a benefit to those who are perfectly functional.

Now, that's, those aren't logically equivalent, and therefore, we have to acknowledge that that could be incorrect. It could be that whatever steps are necessary to take someone who's in early cognitive impairment and reverse it are not the same things that would take someone like you, who's presumably got no impairment going on, and saying, okay, how can we boost your performance by 20%?

But nevertheless, I thin there are a number of factors that have to be considered. So the one you can't change is genetics. There are a handful of genes that are gonna certainly predispose people to conative decline. APOE being by far the most common. If you're an E4 verus an E3 or an E2. But there are other snips as well, so TOMM40, that's T-O, that's double M 40, is a snip that's actually very close to the APOE gene. May or may not be an independent predictor outside of it, TGF, and a few others. Now, you got those, you got those. We can't change them. But when you start to-

Dave: Hold on. Can't change them yet.

Peter: Yeah. Well, I don't hold out a lot of hope that we're gonna be making-

Dave: Okay.

Peter: ... germline changes yet, for any time soon, in terms of gene therapy.

Dave: Even over a 50 year timeline, you don't think that's possible? Serious question.

Peter: No, I think that's a fair question. I don't know, Dave. I mean, I think that's-

Dave: I don't either. I just hope it is.

Peter: Sure. I hope it is too. But let's look at the things that we can actually impact today. It's, the first thing is gonna be metabolism. Second thing is gonna be vascular health. The third thing's gonna be exposure to toxins. I think those are your big three. And so our way of thinking around brain health is identifying your risks according to the four metrics, genes, vascular health, metabolic health, and toxins, understanding what we can and can't measure. So we have a great ability to measure your genetic susceptibility to AD. That's one time where the genes actually, the genetic testing is actually helpful. We have a really good sense of how to measure your vascular risk factor. We have a really good sense of measuring how your metabolic stuff. We don't have great tools for measuring toxins. So it's very indirect.

Dave: Yeah.

Peter: So I can measure all these things in your blood. But only at our most high high high risk patients are we doing lumbar punctures to look at CSF levels. So cerebral spinal fluid, of course, which you can capture through a lumbar puncture, we'll only look at that in the most high risk patients. But certainly I would not consider that ready for prime time. So what do you want to do to achieve maximum brain health? You know at the risk of sounding a bit trite, it's anything that you do that maximizes insulin sensitivity and reduces your risk of cardiovascular disease is almost assuredly also reducing your risk of neurodegenerative disease. Our view internally is that Alzheimer's Disease is actually several diseases, and the inability to have stratified them into different diseases is probably partially what explains the epic failures in pharmacotherapy, which is when you try to treat all diseases at once with one drug, you're very likely to see a strong enough signal in the subset that's most susceptible. So when you look at that group of Alzheimer's patients whose disease seems to be most manifested by a metabolic phenotype ... So these would be patients who, if you give them intranasal insulin, they get better transiently.

Dave: Yep.

Peter: So, but that doesn't happen with all patients. So what's happening in those patients? Well in those patients, intranasal insulin is probably offsetting some of the insulin

resistance that pyruvate dehydrogenase, that's preventing pyruvate from getting into the mitochondria of the neuron to generate the real lion's share of ATP.

Dave: Just for people listening, intranasal insulin is a relatively recent thing. You can literally take the insulin you would inject, put it in a nasal spray, and take a couple puffs in each nostril. And man, if I was taking medical school exams, which I never have, but I would probably be doing that before I walked in to take the test, because I noticed a massive boost in cognitive function when I do that. And my insulin sensitivity is actually perfect on the, at least the last time I measured it. But it goes into the brain, you're like, "Dang, what just happened? My visual acuity improves." It's noticeable.

Peter: How long did the effect last?

Dave: Oh it's good for like an hour or two. I don't know. It's not a super long effect for me.

Peter: Interesting. I've never tried intranasal insulin. I'll have to try it.

Dave: It's worth a shot. Get it? Oh, sorry. I had to say that. But it's one of those fringe area conative enhancement short term strategies for when, like if you're gonna write something, or you're gonna be onstage, and you wanna pull out all the stops. Take 1mg of nicotine, a little bit of intranasal insulin, and watch what your brain can do. You wouldn't even believe it. It's those sorts of things. But if you do it all the time, intranasal insulin is probably gonna increase your risk of Alzheimer's Disease.

Peter: Well it's interesting. I have to give it some thought. I haven't really thought about it through that lens, if constitutive use would ...

Dave: If you believe Dale Bresdon's work, it probably would. That scared me. I don't ... By the way, for people listening who are gonna go out and try this, you should try it if it's not gonna be risky for your own biology, 'cause it's really interesting. But should you do it every single day? I would say there's no evidence that says it's not harmful, so ...

Peter: Well, I mean, it's like the null hypothesis should be it is harmful given that it's completely unnatural.

Dave: Exactly.

Peter: But interesting, it'd be interesting to see if there is a benefit My guess is the more insulin resistant somebody is centrally, the more benefit they'd experience from this. That's generally the case with these things. But yeah. Anyway. That's interesting.

Dave: Not to take you off your track. I just realized a lot of people might not know what internasal insulin was, 'cause it's not well-known outside of weird biohacker circles or some people looking at diabetes and things.

Peter: There you go.

Dave: So I totally took you off your path what you were saying there around-

Peter: I think I was pretty much done, which was basically you want to, you want to do all things that reduce cognitive decline, and those things ... Those thing probably then parse out into these things.

Now, what I don't think is entirely clear, although I think there are smarter people than me who are working specifically on this problem, is are there specific gains that we can play that hone our skills around these things? So like if I took a Raven Test every day, does that make my executive function higher? Probably not, although I do find the Raven Test to be incredibly fun, Raven Test being sort of one of the tests that we use to assess executive function.

Dave: You'd probably just get better at taking the Raven Test, just like IQ tests, right?

Peter: Exactly, and I think that's the point here. So we did an internal experiment. I don't know if I'm allowed to discuss this.

Dave: That means you should, definitely. Using the null hypothesis.

Peter: Yeah, yeah. Just loosely, we did a very informal experiment around a bunch of neurocognitive tests-

Dave: Cool.

Peter: ... which is what I wanted to understand how much could you offset a known driver of decline by just having more experience with the game. So the experiment was basically getting a whole bunch of the analysts together to take the test, and then take a shot of alcohol, and then take the test again, and then take a shot of alcohol, and then take the test again. So what you were basically doing was getting drunk while you were taking a test, and looking to see if performance would go down. And it turned out performance stayed completely flat during the period of debauchery, which suggested to us that the learning effect was equally offsetting to the cognitive impairment-

Dave: Interesting.

Peter: ... that was coming through the alcohol. And this went on for like 8 rounds of shots.

Dave: Wow.

Peter: This was 8 rounds, 8 hours, or something like that. It was a non-trivial amount of impairment. And again, we were looking at this internally because this was before we discovered, we have a great collaborator now at, his name is Richard Isaacson. He's a neurologist at Cornell, and he and his team have the largest Alzheimer's prevention clinic in the United States, and so what, and I had known Richard before this, but we didn't decide to start collaborating til after this, because what I came away realizing was off the shelf cognitive testing was pretty useless. And you really needed clinical grade,

like NIH toolkit powered cognitive testing to really measure meaningful changes in cognition. And we, internally, at our practice, just didn't have the expertise to be able to administer those tests, whereas in Richard's clinic, because that's all they do day in and day out is high risk, treat patients who are not yet having dementia but who are high risk, it was the perfect sweet spot.

Dave: You said something earlier. You said that assuming everyone has, or assuming a person has normal or healthy cognitive function, that there probably isn't much we can do. My experience working with people and just with myself is that very few people have well functioning or perfectly functioning cognitive function at any take, at any place in time.

Peter: Sure.

Dave: And that's because we're all exposed to some toxins. Our mitochondria are a little unhappy. We didn't sleep well last night, and we had a drink of some kind of inflammatory thing. So there's, I think for 99% of the population, there's low hanging cognitive enhancement fruit that comes from just giving you access to all that's already there. And then there's another set of training exercises, some of them neurofeedback based, where there's IQ improvement shown in multiple studies. There's dual N-back training. I write about some of this stuff in my new book that's coming out in December. Like these are things that are shown in multiple studies to have the potential to raise IQ. But even then, we don't know, are these in people who maybe that was their natural IQ and we just, they're tapping into what was there.

Peter: They're recouping.

Dave: Or are we taking someone and saying, well now you have more fluid intelligence. And it looks like fluid intelligence is trainable. It's just really unpleasant to train it, which is why no one does it.

Peter: We are looking into this, like I mean a lot. So the way I would describe this is what's the basic blocking and tackling everyone should be doing to maximize their cognition? And it basically comes down to the same very unsexy cast of characters which is what you do with respect to your nutrition matters. So the less you can create glucose fluctuations, the less you can create insulin surges, the more steady the influx of energy to your brain.

Dave: Yes. Yes.

Peter: So even those people who are on a ketogenic diet, there is no denying that even under George Cahill's most extreme example of starvation-

Dave: Yeah.

Peter: These were 40 days starved subjects. They were still getting at least 40% of their brain's energy was coming from glucose through the gluconeogenic turnover. So even when, and that's starving ketosis, with ketones of 7 to 8 millimolar. So the average person

walking around in nutritional ketosis, still probably relying on 60 to 70 percent of their brain energy from glucose. So glucose always matters. Glucose homeostasis always matters.

Sleep.

Dave: Yeah.

Peter: I mean not to harp on it, because it's become so obvious now that most people don't even wanna hear about it anymore. But you know, you and I were bullshitting about the Oura ring before we went on the podcast, and you now, I'm a huge fan of it. You're a huge fan of it. There's a reason for it.

Dave: Right.

Peter: It's like, it's the most accurate tool out there to measure one of the most important things that we do. And the difference in my cognitive performance when I wake up and my Oura score was 85% versus 65%, I mean it's night and freaking day.

Dave: Yep.

Peter: And I'm even at the point where I could not look at my score first thing in the morning, and wait and see how I feel for a couple hours and almost kind of predict my readiness score and my sleep score, just a function of how I feel. Sleep. Exercise.

Then we talk about management of distress. Well I think that the biggest epidemic that certainly is facing many of us, including many of my patients is just distraction.

Dave: Yeah.

Peter: I mean, we are so distracted. I get a lot of patients that complain to me that they think they're in early stages of dementia. You know, they're 45 years old and they're worried that they're ... A CEO of a company was telling me like, "I can't remember the names of my employees anymore." And I said, "Okay. It's possible it could be early onset dementia. But a far more likely scenario is you are getting 375 emails a day that require your attention and you're constantly being tugged into this meeting versus that meeting versus this meeting. And you're simply prioritizing, like do I really need to remember the name of every person who works in this company, or can I just, you know, limit it to the 12 people who report directly to me? So I think that we are all highly distracted, and that tends to produce a state that is suboptimal with respect to these metrics, executive function, processing speed, and short term memory in particular.

Dave: Very well put. Now, I've noticed, you said something really good about controlling blood sugar in the brain. And I've noticed that my cognitive function is much better when I have ketones, and some glucose present, which is one of the reasons I think Bulletproof coffee has taken off is it gives you background ketones even if you had some carbs the night before. And I've found that, I'm sorry, one of my companies is a neuroscience

clinic that does cognitive enhancement stuff, custom hardware, software, 24-channel QEG, a bunch of stuff like that, in Seattle. And it's a five day intensive program where we have people for 10 hours a day doing neural feedback and personal development kind of stuff. But if I give them a brain octane, so they get exogenous ketones from that, just a baseline low level stuff, and they're eating a clean diet, which is good. We have a chef on site, so I can enforce that. They can do tow and a half times more of this intensive meditation stuff with electrodes before they just hit the wall. It's like a willpower wall, where they're like "There's nothing left in my brain. I've hit my," like in a marathon, like I can't run another step. You can do that with meditation.

Peter: Right.

Dave: But we can push that wall out about two and a half times with some ketones. But if they're on a zero carb diet, unless they're highly adapted, they can't do it either. So it's like if they're all sugar, it doesn't work. If they're all carbs it doesn't work. Do you have any thoughts on, not just from a willpower cognitive enhancement thing, but on this unnatural state of having some glucose but not high glucose and some ketones from an external source, what that would do biologically?

Peter: I haven't really thought about it. I mean, I think evolution probably offers us a bit of insight. I don't think our ancestors, at least most of them would've walked around constitutively in a state of nutritional ketosis.

Dave: You can't. Yeah.

Peter: Because even if you have spiking feeds, that will generally knock you out of ketosis, because if-

Dave: Even if it's protein.

Peter: Yeah. Just the protein alone will typically knock you out. So I wish we had better insight as to what our evolution would've looked like. And I know many people have spent countless blog posts arguing as vehemently as they would argue their religious beliefs and political beliefs, that they know the answer to this question.

Dave: Well put.

Peter: They're smarter than I am. I don't know the answer to that question. But again, I think my intuition would suggest that it's probably not an entirely unreasonable state to be walking around with a flux of intermittent ketosis.

Dave: There you go.

Peter: Now, the next question, which is one I definitely won't pretend to know the answer to is how much of that is a function of the benefits you get from a nutritional approach alone where your ketones are endogenous, versus the addition of an exogenous ketone. So obviously today there are a number of companies that are out there that can actually

sell and produce these exogenous ketones. So as every, maybe the reader doesn't know. There's three ketones. There's beta-hydroxybutyrate , acetoacetate, and acetone. Acetone is a metabolically inert ketone. We don't particularly care about it and it exists in a one way equilibrium or non-equilibrium, but from acetoacetate all the way down. But the two that matter are acetoacetate and BHB, beta-hydroxybutyrate, and they exist in an equilibrium that tends to favor BHB, although actually it varies by physiologic state, so I won't even say that.

Now, you can make those either as esters or salts, and therefore ingest them. So in theory, there's three ways to get these things, 'cause there's no acetoacetate salt to my knowledge. So you can either have acetoacetate ester, beta-hydroxybutyrate ester, or beta-hydroxybutyrate salts. The net effect though is you ingest these things, and in a very short period of time you will have ketone levels that go from zero, which would be the default state, to as high as 3, 4, or even 6 millimolar. And this can last for a couple of hours. Now, it's been a while since I've mainlined exogenous ketones. I guess I was probably doing it before it was trendy.

Dave: Me too.

Peter: And I gotta tell you, I don't really recall getting a huge cognitive boost from it. It might be that because every time I was doing this, I was already in a state of ketosis. It might be that there was very little incremental benefit that came from it, and maybe the better experiment would be if you take someone who's got no ketones, who's eating a high carb diet, can you do what you're describing, which is just put in a slight amount of exogenous ketone here and there and achieve the benefits. I don't know the answer.

Dave: I was ready to launch, like we formulated a BHB salt product at Bulletproof, where we had the label done, the flavoring done, the mix of the different salts done, and it even tastes so good. I was ready to launch. And I pulled it from the market before we put it out there because it turns out that half the ketones in those salts are isomers, and no one knows what they do. And the one expert I could find who looked into this, who studied with Hans Krebs, basically said he thought they cause mitochondrial harm. And I know that the brain octane and the stuff we make also converts one step up from BHB. It converts into BHB metabolically. So it'll raise ketones reliably, but not as high as the salts. And I'm not certain that you need a huge spike in ketones versus you want some. You don't want a huge spike in blood sugar either. We don't know, having these starvation level of ketones turn on like that, we don't know whether it's beneficial or not. But I chose to forgo the business opportunity there just because I wasn't convinced of the safety, even though I tried a variety of those things, enough to be comfortable with formulating it.

So it's, I think the jury's out on that stuff. But I do know if you can have some ketones present, which I do with the oil, and some glucose, but not sugar, just some base starchy carbs, that it seems like your cognitive resilience goes up. And that's something that I benefit from almost every single day.

But I think there isn't science out there, but if anyone would know, I was hoping that you would have some great big spark of insight about what's going on with that state,

because we were wired to only have ketones or basically be metabolizing carbs, but not to be able to do both. And it seems beneficial, but who knows.

Peter: Well I think we are wired to be able to go back and forth between the two quite easily, actually.

Dave: Yeah.

Peter: 'Cause I don't think there would be a state when we could be so fortunate that we would never go more than about 20 hours without access to glucose.

Dave: Yep.

Peter: And you'd have to believe that that's the case for us to be specifically wired to be purely functioning on glucose. Again, having not lived 10,000 years ago, I can't speak with any authority, but it just strikes me as highly improbable before agriculture that we could've reliably assumed we'd have that much access to glucose.

Dave: Yep.

Peter: So that means we have to have had this capacity to quickly turn over and utilize ketones. And then as we said a moment ago, it's equally implausible to me that that would be the default state, because there's too many times when you have to get out of that state.

Dave: Yeah.

Peter: So-

Dave: Okay.

Peter: And you know, there's even more subtle stuff here, which is like maybe it's a function of where you're evolving from. We certainly deviated long enough ago from our central ancestors to acknowledge that look, maybe someone who's coming from northern Europe or somebody who's coming from Asia proper, or someone who's coming from the Arctic Circle, or someone who's coming from the high plains of Africa, you spent a couple hundred thousand years there. You might actually produce different phenotypes from each other.

So even that question then becomes complicated. That stuff's interesting to me actually. You know you and I probably come from a pretty different genetic background just based on, you're a white dude. I'm not quite a white guy.

Dave: Where is Attia from? I can't even, I have no idea.

Peter: Well, my parents are both from Egypt.

Dave: Okay. Got it. So your Egyptian.

Peter: So I'm a, yeah. My mom likes to tell me I'm a descendant of the Pharaohs. I guess I need to do Ancestry.com to see if that's really true. But point being is we're just, you and I have obviously only recently come to cohabitate the same area-

Dave: Right.

Peter: ... on an evolutionary scale. So the question then it, isn't it at least plausible that whatever conditions are necessary to optimize your health might be different from those that are necessary to optimize mine? It seems plausible.

Dave: It's beyond plausible, and when you look at some of the epigenetic arguments, and some of the studies on, what I mentioned earlier, the mismatch of your mitochondrial DNA with your nuclear DNA. They've done some studies with sparrows or some other species, a finch of something, that diverged a few thousand years ago. Some live very far north. Some live very far south. And when they crossbreed the two things, they get this weird mismatch where it takes a few generations for it all to start working right again. So we are the product of our environment, right?

Peter: Yeah.

Dave: And it's an interesting world we live in. That's for sure.

Well Peter, I know that we both have stuff coming up next. I've got one more question for you on the show, and I think your answer's gonna be really interesting.

Peter: Oh, you've got me scared now.

Dave: I've only asked-

Peter: You weren't just gonna say goodbye?

Dave: I've only asked like 489 other people or something, so no pressure.

If someone comes to you tomorrow and says, "Peter, I wanna perform better at everything I do as a human being. What are the three most important pieces of advice you have for me?" What would you tell them? It doesn't have to be all medical stuff. I mean, you're a medical guy, but just from your life's experience.

Peter: The first would be change the way you eat. The second would be change the way you sleep. And the third would be change the way you move.

Dave: Wow. Alright, the big three, eat, sleep, and move.

Peter: Yeah, and the devil's in the details.

Dave: There you go.

Peter: I mean, yeah, yeah. But if you completely completely optimize those three things, I think you're getting 60 to 70 percent of the possible benefit that exists out there.

Dave: Very succinct, well put, and well thought out. Peter, your URL is PeterAttiaMD.com. You're one of the leading thinkers and more interesting cross functional disrupters out there, I would say, just because you've brought all these different disciplines together into what you're doing with medicine. And just thanks for your work. I'm a fan, and I appreciate the way you think about things.

Peter: Thanks for having me on Dave. It was great to chat today.

Dave: If you enjoyed today's episode, you know what to do. Check out Peter's work. It's actually really cool stuff, and you'll have fun with it. And if you feel so inclined, head on over to Amazon and leave a review for a book that you enjoyed. And if it happened to be headstrong, I wouldn't really object. But if it's any other book you enjoy, tell authors and other people who do lots of work that their work is worthwhile just by leaving a review. It's an easy way to show gratitude. And trust me, us authors, we pay attention. Have an awesome day.