

Paleo Solution - 417

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Robb: Hey, folks, Robb Wolf here. Super, super cool podcast today. Dr. David Perlmutter, one of my very dear friends and just such a cool guy. He had his first publication in the journal *Neurology* at the age of 19. The guy is absolutely brilliant. He has a fascinating career because he went from a very kind of mainstream, orthodox, high-carb, low-fat kind of orientation. And then over the course of time, looking at the literature, working with patients on a variety of neurological issues, the guy has circled around to kind of a low-carb, ketogenic leaning, Paleo-friendly type of approach, very aware of immunogenic foods, aware of the importance of finding the proper glycemic load for individuals.

He was on the podcast quite a while back, Episode 200, and that's fantastic if you want to check that out. This episode is looking at his updated *Grain Brain* book, which has been out for five years. We covered a ton of different topics: intermittent fasting, autophagy, the pluses and minuses of ketosis, the healthcare system. We just covered a lot of ground. Love this guy. Really, really a good friend and I think you guys will enjoy this one a lot.

Dr. Perlmutter, how are you?

David: Well, I don't think I could be better. If I was any better, I'd be Robb Wolf.

Robb: Oh, man. Well, you would be less good-looking because you're much more handsome than I am at a minimum.

David: We'll see about that.

Robb: Well, just a huge honor to have you back on the show. I'm not sure if you're aware of this, but when you appeared on Episode 200, I believe, of the *Paleo Solution Podcast*, that has gone on to be in probably the top four to six most popular shows that we've ever done.

David: Well, that makes me feel very, very good.

Robb: Yeah, yeah. I mean the love and adulation that one receives when mentioning on Instagram that I was going to chat with you this day, it was pretty amazing. Like you have a lot of folks that just absolutely love you, are so appreciative of your work, and I am definitely at the top of that list.

David: Well, I have a big smile on my face right now, just so you know. To hear that, it's so encouraging to continue doing what we do because, frankly, the work is seeing the science as best and interpreting it as best we can and then making that available for everybody to utilize. That's the job. It's been what I've been doing for I guess 40 years now, and to hear that people are appreciating it makes me feel encouraged to continue working.

Robb: Well, it's a very fascinating time because as problematic as I think some of social media and the internet can be, there's also a really cool opportunity to share ideas, put out these ideas, have people tinker with them. Like so much of what I've observed in this kind of ancestral health space, like the past couple of randomized control trials looking at the autoimmune Paleo diet, that happened as an outgrowth of anecdotal collaboration that provided enough noise that some folks in the legitimate academic circles said okay, well, we can probably justify at least doing a pilot study around this and a feasibility study.

It's funny, when you look back at the history of say like the Mediterranean diet, it too started with an idea basically around a couple of review papers, and then people started tinkering with it, and then more rigorous science and testing has gone on since then. But you are still at this interface, in my opinion, that is just really, really controversial. Grain Brain focused on the health risks of sugar, refined carbohydrate, gluten, different immunogenic compounds like gluten being problematic. Clearly, I'm pretty sold on that as a big vector in the modern health problems that we face. There are a lot of people out there though that are still not, but how has the science on these different topics progressed in the last five years since you first published Grain Brain?

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David: Well, it's a great place for you and me to start. I've been asked that question, what was right, what was wrong about Grain Brain, and I have to say that by and large what we talked about, the subtitle of Grain Brain is The Surprising Truth About Wheat, Carbs and Sugar, Your Brain's Silent Killers. That was a bit bold, but it turns out over the ensuing five years that there's been a high degree of validation of what we originally were contesting and that was that a high sugar, high carbohydrate diet is going to translate into a higher blood sugar, which is basically a bad thing for your brain. As we looked at the correlative studies that we talked about in the original Grain Brain showing that a higher A1c or average blood sugar correlated with a higher dementia risk, we've seen follow-up studies, one published in the journal Diabetologia this year, matter of fact, that correlates the A1c with cognitive decline. We've seen the work of Dr. Rosebud Roberts at Mayo Clinic publishing in the Journal of Alzheimer's Disease showing that diets that are favoring carbohydrates as a primary source of calories are

associated with 83% increased risk of dementia to be contrasted with the diet that's higher in fat with a 46% lower risk of developing dementia.

Over these five years, there has been a really high degree of validation of these fundamental principles that basically having a higher blood sugar is not a good thing, that this is a diet that contradicts really 99.5% of the time we've been on this planet. There's been a terrific ongoing experiment for 2.5 million years that has really proven itself quite well that a relationship to an ancestral type of diet seems to be what has allowed us to have this conversation today. I'm aware of the nuances of dietary recommendations. I mean chapter one of *Wired to Eat*, your book, is one size does not fit all, and indeed, I think we have to be cognizant of the fact that while we can talk about the broad stroke recommendations, which are very important because they will reach a large number of people, there is absolutely merit in being more specific for people based upon their heritage, their medications, their current body morphology, their microbiomes, their genomes, et cetera.

I think it's been a very, very interesting and very encouraging past five years. It really has done a lot to strengthen our position, the fundamental position being that lifestyle choices affect your brain's destiny. We start there and now we take that apart and determine exactly what the implications are of the specifics of this discussion.

Robb: Absolutely, yeah. It's so fascinating to me and it's frustrating at times too. There are these camps that I would characterize as being maybe a little bit more in the kind of like fitness, bodybuilding kind of orientation where they're very calorie focused and not as food quality focused, and they tend to be remarkably dismissive of say like these immunogenic properties of foods. I've honestly modified my position on say like the insulin hypothesis underlying this whole story, like I've maybe gone a little bit more middle of the road. Clearly, insulin is important, but overall caloric load is important. I don't argue with any of these things, but I'm perplexed by kind of the position of some of these folks when we're facing just the diabetes crisis that Westernized societies are facing. Outlets like the Congressional Budget Office have a pretty modest projection that 15-20 years from now the US is bankrupt from diabetes-related issues, and this is before we get to neurodegenerative diseases.

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Diabetes, although hard to manage, but there's a huge suite of drugs and the person can be provided medication and trained in how to implement those use of glucometer. Although it's a very shoddy treatment protocol in my opinion, it's comparatively low cost compared to a massive number of people entering this neurodegenerative tsunami that we're going to face, Parkinson's, Alzheimer's,

dementia, in which these individuals will require 24/7 nursing care effectively. That is something that people have not even thought about.

We're in this kind of battle, and I'm sorry I'm jabbering so much, but I'm trying to set this whole thing up so I can get your thoughts on it. But we're in this kind of pissing match back and forth of it's the carbs, it's the fat, and I tend to think it's the processed food, which is a combination of them both, that really massively gets us into trouble. Nobody sits down and eats pearl barley anymore, so I don't really think that that's the issue. But while we're having these debates, we're kind of rearranging deck chairs on the Titanic and there seem to be no sense of urgency on the part of the people that are really trying to shoot holes in these ideas that like gluten may be a really potent immunogenic product, that refined carbohydrates and fat have addictive properties. What are your thoughts around that whole topic?

David: Well, I think I need to take a step back and just set this up to the understanding that I like sugar, I like gluten-containing foods, I like staying up late and I don't like exercising. The truth of the matter is those are statements that come from a more primitive part of the brain. A lot of that is immediate gratification, immediate activation of the reward pathway mediated by dopamine that gives us this sudden surge that ultimately activates within the brain these opiate-like receptors. In a very real sense, we become habituated and in a real sense addicted to these things that are omnipresent in our society today. It really takes a reconnection to our more sophisticated part of the brain called the prefrontal cortex, which is absolutely a gift along with the opposable thumb that we uniquely have as humans, to say yes, I want to eat sweet foods 24/7/365.

But I think in the long run it's not the right thing for me to do. How that translates to your statement earlier is I think that society-wide decisions are made similarly, that what we're observing is that recommendations and actions are being made in order to placate people who want a quick fix, whether it's related to growing our economy or what have you without really any regard to long-term consequences. Really, beyond just our personal actions, it seems that as a society, we're moving to a place of really wanting just to live for today and not understand the long-term consequences of our actions or even in the short medium term, which means again, we are acting from a very primitive place in our brains and not tapping into the prefrontal cortex where we can project the effect of our actions, we can experience empathy and compassion and participate in those types of engagements as opposed to just wanting to satisfy our immediate concerns.

Actually, I'm writing a book with my son that we will publish in January of 2020 that's absolutely focused on this topic. The book is called Brain Wash and it really talks about how highly influenced we are through things like social media,

specifically how our brains are being hacked and targeted by the way our social media is manipulated to entice us, to satisfy our urges immediately by just clicking in this space, click bait being specifically designed for your brain or my brain, and truthfully, we are being aggressively manipulated.

What's really concerning about that mentality is that it relates back to our dietary shift that has occurred. The more carbs we eat, the higher our levels of inflammation, the less able we are to access our prefrontal rational executive function brain, and the more we are likely to act impulsively from our more amygdala-based action center. It all fits into a very, very disturbing package, and I think once you call it out, the moment you call it out and make it real for people, then they suddenly realize their level of manipulation and hopefully want to tap into more of a prefrontal cortex type activity to distance themselves from having their brains hacked.

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I also experience your frustration when you were mentioning earlier about those who want to be somewhat derogatory towards what your messaging is and focus more specifically on caloric load. I think it's really helpful, or it's been helpful for me anyway, to get to a place of not just being comfortable with the criticism and the pushback, but really embracing it. Because if you're not being criticized, if people are not derogating you, then you're probably not doing the work if the work is to help move the ball down the field towards the goal and make progress. Because if you're not challenging people, if you're not being disruptive, I don't see how you're going to make any significant advancement. Our goal is to advance and move the ball down the field and our goal is to remain dynamic and limber in our recommendations.

Oftentimes, you and I and others in this arena are criticized because we change our messaging. I mean your most recent book, *Wired to Eat*, is clearly a change. It's clearly not necessarily in line with the Paleo solution. And that is a great thing. I'm so grateful that people like yourself are out there willing to say you know, I wrote this book a few years ago, here is what I believe then, but based on what we're learning now, I think we need to refine the message and maybe change the message. Plenty of people are readily available to criticize us for the fact that our messaging changes, but in reality, that's what our duty is. Our duty is to be dynamic and be able to move forward and make advances and make different recommendations as we learn the science.

Robb: Absolutely, yeah. It is a funny no-win scenario, like if you dig your heels in, then you rightly get characterized as perhaps a bit of a zealot. But then if you modify your position as the data maybe compels you to do so, then there's something

untoward about that somehow, which is just perplexing. But yeah, I really like that. That helps a ton.

In this whole process, the different macronutrients have kind of gone in and out of vogue with being demonized. Like fat was demonized and then carbs have been demonized. Now we're in this really interesting position where protein is being demonized. Like you have, interestingly, people in the ketogenic diet camp and the vegan camp who are so terrified of mTOR and IgF that they're basically making very similar recommendations with regards to protein intake. But circling back to fat, how have our positions around dietary fat, what has changed in that story, say, in the last five years? How have we gotten more granular on that topic?

David: I'd say that, first of all, there's been a huge push, not the least of which from even our United States dietary guidelines back three years ago. I think that people have really recognized that what went on, what went down in the late '60s and '70s with respect to influence of medical literature based upon industries underwriting of research, people really I think got that story that it wasn't the carbs that we needed to embrace. It absolutely was still fat. Fat shouldn't have been so demonized. The story was just starting to break around Grain Brain time and certainly as I was calling for higher levels of fat. The pushback I got on the Amazon comments and social media, higher levels of fat are going to make terrible things happen, your kids will be born naked, you'll have a heart attack, who knows what. Indeed, books have continued to be written by individuals with whom I have sat on panels and debated in front of major organizations who still dig their heels in based upon data that's 15-20 years old at least.

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I think the big shift has been embracing the fact that something that has been an integral part of the human experience for over two million years actually turned out to be a pretty darn good thing, and that is fat. What has really happened over the past five years is we've really seen a lot of work that's tried to distill out what it is about fat that we should be embracing and what it is that we should be fearful of, i.e. good versus bad fats in terms of what we should be consuming. I think there's been a lot of public exposure to what it means to be good versus bad fat. Unfortunately, when I say a lot of public exposure, it's really in the world that you and I live in. I think by and large, we still see the general public consuming those fats, those modified high omega-6 grocery store shelved, long-lasting fats that really are ultimately going to lead to increased inflammation and all the downstream effects that relate to that in terms of chronic degenerative conditions.

But I think there's been a very significant increase in the awareness of fat and certainly how fat work in the body, how we can amplify ketones by increasing dietary fat and specifically adding things like MCT oil, et cetera. I think the fat story is just gaining its traction, just beginning to gain its foothold in terms of how people are going to understand it and embrace it. I think, ultimately, the commercial side of this will see that as well.

I had the opportunity last month to visit the Nestle Corporation and headquarters in Switzerland and had the opportunity to give a lecture there and then meet with their top level executives. That may surprise your listeners. I know it surprised many people who follow my work. It surprised many of my family members. Truth of the matter is I was just taken away by the degree of commitment that Nestle Health Sciences is showing towards looking at what really matters in terms of giving people access to food that is supported by peer-reviewed current science. Here is the largest purveyor of food on planet Earth and certainly they got a long way to go. They have some products that we wouldn't necessarily define as being healthful. But nevertheless, the Health Sciences Division is really dialed in and understands leading science to a degree that is breathtaking and really looking at what they can do to lead by giving people foods that are good for them as opposed to just foods that are targeting their primitive desire for sweet, salty and fat. So I'm feeling very, very optimistic.

Robb: That's awesome. It's interesting. It makes me think a little bit of when EPIC was acquired by General Mills. There was a pretty good outcry around that, and it's tough. If folks want these ideas to be more broadly applied, they've got to go mainstream, and to go mainstream, they can't remain grassroots. So there are these mutually-exclusive things, and oftentimes, going mainstream means that a big organization like a Costco or a Wal-Mart or a Pfizer or something like that is going to take an interest and people can be maybe a little bit jaded about it and say, well, there's just a financial motive there. Yeah, there is, but it's still maybe moving things in a much more favorable direction.

David: No question. I think that what we're seeing in the world is the impact of influencers on trends towards people's buying trends. I think that large companies are starting to understand that people are generally tending to listen to these influencers perhaps a little bit more than they used to and perhaps more so in relation to simple straightforward advertising.

Again, I was very encouraged and I'm feeling very good about things. You know what? There's no question that these days, in my world of brain health and brain disease, you can become very discouraged by looking at the statistics and certainly at the projections about what we're looking at in the coming years. But yeah, you have to look at the darkness. You don't necessarily have to curse the

darkness, but you definitely have to light that candle. That's what the mission is all about. If we move the needle one-tenth of 1%, that's very, very important.

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Robb: That's awesome. That's super cool. Is that talk available, by the way, or is it internal?

David: Oh, no. That was in-house, internal.

Robb: Okay, okay, okay. That's awesome. I was somewhat tickled with how folks received my last book, *Wired to Eat*. I didn't make it obvious, but the whole book is effectively a sales funnel for a ketogenic diet. Like I lay all the stuff about personalized nutrition and different glycemic loads and try to present a very sound, rational case that people need to tinker and figure out on their own what they need to do. But then at the end of the day, kind of the way that I set the game up, almost everybody would probably benefit from a ketogenic diet, at least intermittently. Some people have kind of connected the dots on that. I know that you really detail the benefits of a ketogenic diet in your book. I know all this stuff travels in cycles, but why do you think a ketogenic diet specifically has become so incredibly popular? I have some ideas around it, but I'm curious why you think specifically ketosis has become so popular both in the mainstream and in academic circles. The number of research papers on PubMed hit this exponential that started maybe about three years ago and it's just exploding in research circles.

David: I think the answer to that question is results focused. I mean I think when you see what is happening to people who are achieving higher levels of ketones in their bodies either by caloric restriction, intermittent fasting, fasting-mimicking diet or simply adding in exogenous ketones or at the very least MCT oil and realizing benefit, that's the kind of stuff that travels quickly. As you mentioned earlier, that's the kind of stuff that really propels researchers to fill in the blanks quickly and do the work now that they're hearing that there's such an interest in terms of the public. Ultimately, as you've said, I think you are quoted in the *Paleo Keto Definitive Guide* as talking about how this is basically the diet of our ancestors. As I've said, for a couple million years, we're pretty much in ketosis all the time with the exception of the late summer, early fall when the fruit would ripen and we would have access.

I think that we've come a long way since 1928 in terms of utilization of ketogenic diet for the treatment of epilepsy when we see incredible research done by the Valter Longos of the world in cooperation with our most well-respected institutions and people like Thomas Seyfried and others talking about how a ketogenic diet does all of its magic. Then we get into the depths of that, the

understanding of re-establishing insulin sensitivity, reducing inflammation, enhancing brain-derived neurotrophic factor, activating G protein receptors throughout the body that help increase antioxidant production, help decrease the production of inflammatory chemicals, serving as an incredibly powerful fuel for brain mitochondria and multiple other things that ketones can do. How could we possibly turn our backs on that? I think that's what researchers are doing.

In the field of neurology, in my area, I think that the interest in ketogenic diet has really been pushed because of the lack of anything else that's really effective. I mean Pfizer, the global pharmaceutical company, in February of this year indicated they're going to stop, or they did stop, all research in terms of trying to find a therapeutic option for Alzheimer's disease. They quit. It would too difficult playing field in terms of looking at the return on investment. They said we're not going to do it anymore.

Just earlier this month in the Journal of the American Medical Association was published a very compelling article, a study, a meta-analysis of the top ten research studies that looked at the effectiveness of the two main classes of Alzheimer's drugs, memantine and then what are called cholinesterase inhibitors, drugs like Aricept. What was published in the Journal of the American Medical Association wasn't just that the drugs didn't work, but was that the drugs actually enhanced the cognitive decline in the patients who were taking these drugs.

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Now, let's just frame that again. These are patients whose family members took them to the doctor. "Doctor, what can we do to help mom or dad or my husband or my wife?" The doctors write prescriptions for drugs that are actually speeding their cognitive decline. This was put out a couple weeks ago by the American Medical Association. Did this appear on the nightly news? Was this on the front page of the New York Times? No, it wasn't. And yet, what we still see are advertisements for these exact drugs.

I guess we're getting back to cursing the darkness a little bit. I think it's the mission of many of us to call attention to the peer-reviewed research. It's not like Dr. Perlmutter is dreaming these things up. This was published in the Journal of the American Medical Association. Similarly, peer-reviewed research has shown, for example, that statin drugs increase the risk of diabetes in men by 46% and in women, the Women's Health Initiative study, 162,000 women increasing their risk of diabetes by 71%.

Why does that matter? Well, you alluded a few moments ago to the epidemic of diabetes. From my perspective, when you become a type 2 diabetic, you have

now quadrupled your risk for Alzheimer's, a disease for which there is no treatment. These statin medications that are being given out left, right and center for everybody who happens to have a mild elevation of their cholesterol are associated with a dramatic increased risk of diabetes. I really believe that we have to talk about that. People need to know when they're taking a medication what are the potential downsides. I can promise you, if you have a 71% increased risk of becoming a diabetic, what does that mean? Well, then I'll pop a few metformin along with my statin, and as we know, this is absolutely typical in patients. They'll come in with a list of the actual medications and you can be sure statins are on the list as well as their type 2 diabetes medications. You're not treating diabetes with these drugs. You are lowering their blood sugar, but you really haven't treated the diabetes. You really haven't addressed the insulin receptor issue where the insulin receptor is no longer being receptive to the signals of insulin.

Indeed, that gets to the heart of treating this situation, which is, getting back to your question, wonderfully achievable on the ketogenic diet, as was so beautifully described by Dr. Sarah Hallberg in one year, comparing standard treatment for type 2 diabetes, in which case patients progressively increased their medications over the course of one year versus putting patients on a ketogenic diet, in which case their medications were reduced dramatically. One hundred percent of the ketogenic side of the study stopped medications of the sulfonylurea class, which is a major type of medication used in diabetes, and every one of her patients, virtually every one of them on the ketogenic program was able to either stop or significantly reduce their insulin. By and large, they lost more weight, obviously their A1Cs went down, their HOMA score of insulin sensitivity improved and across the board these patients did great just from a lifestyle change by embracing a diet lower in carbs and sugar, higher in fat, emulating the diet of our ancestors. You can be sure that diabetes wasn't rampant in our Paleolithic ancestors.

Robb: It's interesting that you wrapped up with the Paleolithic ancestor point. Clearly, I'm earlobe-deep in this kind of Paleo scene, but for a very long time I've had this kind of gut sense that the complexity of relating the totality of that whole kind of original Loren Cordain Paleo approach, it really is a remarkable number of rules and exceptions and have kind of burn this stuff down for me to the following: finding an appropriate glycemic load, which I actually have some thoughts around that, or blood sugar excursions should be much, much lower in magnitude and volume than what is generally accepted, and then keep an eye open for immunogenic foods.

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If we do that, we arrive at something that's probably going to be pretty close to a ketogenic diet, even just intermittent ketosis and we'll keep an eye open for gut and systemic inflammatory issues that may be driven by immunogenic foods. What do you think about that? Am I out on a limb or is that a good way to pare this down?

David: No, I think that you're very well-dialed in. I think that we have increased our susceptibility as the host to having an immunoreactive response to food. So it's not necessarily that our food has become more immunogenic, but think we also have to look at the host. So the more that we are involved in lifestyle choices that are threatening to our microbiome the more we enhance the likelihood that certain foods that might not have been as threatening in the past would today be more threatening. So recognizing that what goes on in the gut is certainly responsible to a significant degree in terms of whether our foods are immunogenic or not, we have to ask what goes on there, where are the regulatory mechanisms. One thing we understand is that the more diverse our gut microbes are, the less likely we are to respond to certain foods and other things in our environment in terms of having an inflammatory or an autoimmune response.

I would say that the fundamental principle underlying the Paleolithic movement that Loren Cordain harped on is sound. That is that we have this intimate relationship with our genome. Our genome hasn't change to any significant degree in 70,000 years. That when we communicate with our genome we can either send it good signals or send it inappropriate signals that lead it to express genes that are not going to be salubrious for us. I think that's the fundamental of at least looking at what life what must have been like for our Paleolithic ancestors. Having said that, we have to make concessions based upon the fact that we live when we live. We can't walk around naked in the sunshine day in and day out. That's not going to work. You're going to end up in jail where you're not going to get all sunshine and then really won't have activated your vitamin D receptors. We can't kill things. We're not going to be able to eat things off the ground that have already started to ferment.

But that said, understanding that we relate to our foods well beyond the macronutrients and the micronutrients for that matter, but we relate to our foods through the information that our foods transmit to us at multiple checkpoints, multiple levels. We understand that through changes in the gut, bacteria as a consequence of the foods we eat from a macronutrient level are important in terms of decrease or increase in diversity, et cetera. We understand how prebiotic fiber is nutritious for our microbes, allows them to increase their production of the various metabolic products that we need, the B vitamins, the short chain fatty acids, their maintenance of the gut lining, et cetera.

But truthfully, I think the real mechanism or one of the important mechanisms for that is really at play in this relationship was absolutely just revealed to us in the middle part of this month, just a couple weeks ago in research that appeared in the journal *Cell Host and Microbe*, a research from Dr. Yun Teng and his group at the University of Louisville I think it was. What Dr. Teng demonstrated was that plants are able to influence the gene expression of our gut bacteria through encapsulation of the plant's genetic material. The encapsulation of the plant's genetic material, their RNA in what are called exosomes are then liberated when we chew plants and they're digested in the gut. This packet, an exosome of the plant genetic material then works its way into gut bacteria and changes the expression of the RNA of the bacteria that live within our gut. It changes their metabolic activity, it changes their population numbers and it changes even their location in the gut. So it enhances, for example, the ability of certain gut bacteria to move around and, let's say, go to the gut lining and do the maintenance that needs to happen to keep the gut lining intact.

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This was, I believe, landmark research. We've moved through the prebiotic fiber, the content of dietary fat, the role that alcohol plays, other phytonutrients, et cetera to really understanding that this is a gene to gene discussion between plants and bacteria, and then the bacteria communicate with our genome, influence the expression of our DNA through their various metabolic products, et cetera.

This really connected some dots for me. Obviously, I get excited about this kind of stuff because this was a bit of a hanging chad and now those dots have been connected, how eating plants and various plants, therefore -- that's a powerful argument for increase in the diversity to the plants that we consume -- will influence our gut bacteria, will ultimately influence the expression of our life code, the legacy that we have from our Paleolithic ancestors.

Robb: Oh, that's so fascinating. I was not aware of that. That is just such another layer in this information processing story. Like we were so cocksure when we started sequencing the genome and we're like, man, once we get this dialed in, then we're going to have the whole figured out. Then we've been peeling back more and more layers of epigenetics, and now we're actually this kind of quasi-promiscuous sharing of our RNA from plants that's modifying the gut bacteria that then go on to modify our own gene expression. That is a ridiculous level of complexity.

David: And simplicity when you think that's the way it's been done for, dare I say, tens of millions, hundreds of millions of years, that this relationship that animals and plants have. Certainly, we know that it goes the other direction as well, that the

organisms in the soil have an effect upon plants. There's this incredible level of connection that we really very much need to embrace. The two operative words are connection and diversity. The more of those two things we have at multiple levels, where it's reconnecting to our genomes, reconnecting our microbiomes, reconnecting to our families, our communities, our planet, it's all about the importance of that connection to establish what will ultimately play out as being better for all of us.

Robb: That's so interesting. Wow, wow. I need to track down that paper. I would love that.

David: I'll send it to you.

Robb: So doc, we've been talking a lot about what we are eating and some of the kind of consequences of that, both good and bad. What about the process of not eating, the fasting story? I am deluged with questions. Folks will ask should I do bulletproof coffee? Should I do a 16/8 fast? Should I do three-day, five-day, seven-day fast? My sense on this is that it's very context driven. Could you break down the story of fasting for us and maybe give us some thoughts around when and where we're going to get upside versus downside, like a time-restricted feeding versus three-day, five-day fasting? Like when and how do we want to roll these things out?

David: I think the answer to that question will take us back to understanding the individual. I think that there's a little bit of personalized medicine that needs to be at play here. But just the global overview I think would be that, first of all, clearly fasting is part of our legacy. We know that our ancestors obviously had times of caloric scarcity and had times of caloric abundance and that operant within the human body are mechanisms that allow us to store calories as a hedge against times of caloric scarcity, i.e. the activation of change within our microbiomes to a metabolic state that would allow us to make body fat -- much has been studied in bears during foraging versus hibernating -- as well as changes in something as simple as insulin signaling brought on by eating carbohydrates in, as mentioned, the late summer, early fall when berries are ripe. Our ancestors would eat them, higher sugar, higher insulin and thus increase body fat as a hedge against caloric scarcity during the winter months.

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But that said, these days, everybody wants to know about what does the ketogenic diet mean and what is this term intermittent fasting and what is fasting all about. This is a question of degree, not of kind. By that I mean when you're not eating food, by definition I guess you're fasting. You're either eating or you're not eating. We all fast, unless you are somnambulous and you hit the

refrigerator in the middle of the night or have Kleine-Levin syndrome. You'll probably need to look that one up. Kleine-Levin syndrome is a very rare malady in teenage boys where they get up in the middle of the night and just gorge in the refrigerator and go back to bed and then sleep for days and days. Anyway.

Robb: I maybe did that. I may have done that, possibly.

David: Anyhow, we all are fasting pretty much every single day until we eat. We can have gained more advantage from not eating until noon or 1:00 or 2:00 in the afternoon. And then when we finally do eat, we have a very special name for that meal. It's called break-fast when we break our fast. So the notion of protracting that event until later in a day is one that is associated with benefits of higher levels of ketones in the body and ultimately could help to restore insulin sensitivity and blood sugar balance as well.

We all grew up with mothers telling us that breakfast is the most important meal of the day. What was that breakfast? Well, it came out of a box along with a 12-ounce glass of orange juice, which provided us nine teaspoons of sugar, 36 grams of carbohydrates in addition to some toast or a bagel or something very exotic that couldn't be bad for us called a croissant or whatever it was. So we all grew up with that and had to live through these incredible blood sugar and subsequent insulin surges. No wonder we crashed at midmorning and by lunch time we're just ravenous where we would get our next carbohydrate fix.

We're hearing a lot then about at the very least protracting breakfast till later in the afternoon, maybe missing eating for the entire day one day a week or one day a month because, again, we've seen work over the years from Dr. Veech beginning in the '60s looking at some interesting genetic changes that happen, as well as obviously metabolic changes that happen when we caloric restrict, when we basically are fasting if you will.

I think we're hot on the trail right now of trying to determine overall what are the best recommendations, whether it's a Valter Longo-based fasting mimicking diet where we try to emulate those biochemical and genetically expressed changes that occur during fasting without actually formally fasting completely or we do engage in a fast or we try to get a bit of an end around by consuming something that will help boost our ketones, something like MCT oil, for example, to maybe harvest some of the benefits, if not most of the benefits, of fasting which happens to be the creation of ketones within our bodies.

I was recently asked at a conference how we compare all of these in terms of a process called autophagy. What autophagy is for your listeners, it's the way the body ridding itself of defective cells. I had to think about it for a moment because this is never going to be a controlled trial that anyone would approve as

being blinded. I mean how could it be? How could you compare a fasting mimicking diet with adding exogenous ketones, with simply protracting breakfast, et cetera? How can you?

I think a very important player in this discussion that seems to be overlooked but is important nonetheless is the fact that with fasting, if it's prolonging breakfast or even a day or two, it is associated with some degree of stress for a number of reasons. A, it's challenging, it's not what you normally do; and B, the sudden deprivation of calories and in an individual who's been eating three squares a day is suddenly a metabolic stress as well.

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I raise the point because I think there's some very important upsides to hormesis or low level stress. Those upsides actually include some good things that occur, some gene activation pathways that occur that are activated and even the increase, for example, in autophagy brought on by low level stress. That could be by fasting. It could be by cold water immersion. Any type of stress like that tends to be something that will increase one of the benefits of fasting. I'm hoping I'm answering the question.

Robb: No, you are.

David: It's difficult to look at the various forms of fasting in isolation because we have to consider what degree of stress is imparted by fasting for three days versus simply eating a special food, prepared food that is going to increase ketones, for example. Those are very, very different approaches to attempting to achieve the same goal.

Robb: You did a beautiful treatment of that. Some of the things that I'm perplexed in this story, we know that one of the things that we definitely don't want to experience as we age is muscle loss. Sarcopenia is so terrible for what it can do to people both metabolically and just their physical ability. This is what puts people in retirement homes, just the inability to get up and down and take care of oneself, protect oneself. I'm kind of nervous about really frisky amounts of fasting, particularly as folks get older, particularly when I overlay that picture with maybe you do two meals a day. I'm still kind of back and forth on whether or not it would be better to frontload the calories versus backload the calories, like there's some circadian and then entrainment stories there, but then just getting people to lift weights three-four days a week. It doesn't have to be a huge amount but just a full body circuit training process a couple of times a week. And the benefits that we see both with regards to hormonal status, muscle gain, and, interestingly, things like lifting weights stimulate autophagy. Drinking coffee stimulates autophagy.

It's kind of funny, the first article that I wrote on intermittent fasting was back in 2005, and it was mainly exposed to a very CrossFit-oriented crowd. I tell you, the people that are willing to CrossFit five days a week, eat two grams of carbs a month and then intermittent fast 22 hours a day, that combination seems to be pretty deadly. It's too many of those hormetic stressors layered on. I've honestly been a little conservative on that, I guess. I almost would rather see people do a moderate carb leaning towards ketogenic diet, maybe some time-restricted feeding, but hit the weights. Make sure you're getting out and getting sun on your skin and stuff like that. If that seems to be a better fit, then maybe like a three-day fast because I am nervous about that muscle loss. Do you think I'm being a nervous ninny with that or do you think there's appropriate situations where that might be the preferred protocol?

David: I think that what we're up against here are, in fact, these overzealous exercisers who are overzealous with respect to their carb restriction and fasting protocols. I think we have to embrace the U-shaped curve. I mean, for example, we've always said that we got to drive our insulin levels as low as possible. Frankly, most people's insulin levels, at least in America, are pretty darn high. This year we saw a very interesting study that came out of Sweden that demonstrated that women who at the beginning of the study -- it was a 30-year study, believe it or not -- who had the lowest insulin levels actually had a higher risk for developing dementia. So it's like alcohol consumption. It's even like sleep. We know that too little sleep is associated with Alzheimer's risk and greater than 10 hours a day is also associated with increased Alzheimer's risk. I think it is about embracing the middle ground. The question then is how do you define it?

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Getting back to your discussion of sarcopenia, which is certainly muscle loss, certainly loss of lean body mass, something that is a concern for people who not only are carb restricting but feel that they need to do protein restrict as well, I think it's actually very real. I mean when I say protein restrict I'm not saying, therefore, we would embrace whatever level of protein you want to ingest. Again, I think we have to look at the U-shaped curve and ask ourselves what is ideal and, of course, that's very individualized. But we are aware of a research that clearly shows, for example, that individuals who are on extremely low calorie diet that is ketogenic, when they are supplemented with amino acids, don't lose muscle mass. It's very interesting to take a look at that because it means that just having amino acids present, at least in some research that was performed in Italy, demonstrated that this is the way that you can avert muscle breakdown and ultimately the need for those cycling of those amino acids ultimately for gluconeogenesis to power your body because you're caloric restricted.

In individuals wanting, for example, to lose fat that we can preserve their muscle mass, allowing them to exercise, et cetera, and really just sort of target body fat by instituting program where they're on extremely low calorie in ketosis, but yet have been given an amino acid supplement, for example, and I would say certainly along with minerals -- we'll talk about that in a moment -- to allow them to salvage and preserve their muscle mass and remain in the game, remain in the game in terms of feeling well, in terms of also being able to continue with exercise.

I think we have to look at some of this research and really take a lesson from what it's telling us. It really gets to the point of where do people bail, where do they crash out when we're trying to be on the ketogenic diet. I would submit that these five times a week individuals doing CrossFit with the extreme carb reduction and fasting 24 hours a day, they're on track to crash and burn and go back to whatever it was that motivated them in the first place to change their lifestyles.

But there are various things along the way that people need to be aware of that are really important in order to embrace the ketogenic diet, to reap its benefits, to tolerate it, and even beyond to tolerate it to thrive while they're in ketosis. One of the biggest issues is certainly the fact that being on the ketogenic diet induces diuresis. You're going to lose a lot of fluid. You've got to drink a lot of water. When you're losing that fluid, you're taking potassium, sodium and magnesium with it, also to some degree B vitamins. Water-soluble B vitamins are being lost as well. So a word to the wise is to make sure that you're hydrating and make sure that you're getting adequate amounts of these minerals in a supplement form. Because if you're really in ketosis, it's great to eat foods that are organically grown so richer in minerals, but not likely you're going to get what you need unless you actually supplement.

The next thing that is so darn common aside from feeling crummy and keto flu because of the loss of electrolytes and dehydration is just gastrointestinal issues like constipation. Super common and the reason that has become clear to me is because people in their zeal to cut their carbs are cutting out all carbs and that includes the fiber, which, by definition, dietary fiber is fiber. I mean it's carbohydrate, a complex carbohydrate that is useful for digestion, certainly what the gut bacteria are looking for in your meals. I think we have to really concentrate on education in terms of hydration, mineral resupplementation as well as dietary fiber. These are the big pitfalls people get into.

Robb: I could not agree more. Doc, I could keep you on the show for four more hours and barely scratch the surface, but we're at an hour. I want to be respectful of your time. Doc, where do you see this Grain Brain concept going in the next five

years? Do you have any predictions that you might wrap up the show with? Like what do you think we're going to discover in the next five years or what do we write? Maybe there's some stuff that's suggestive, but we can't quite hang our hat on yet.

[1:00:04]

David: Robb, I'll tell you that several months ago I had the opportunity to speak at the World Bank and International Monetary Fund, and my presentation was simulcasted to 50 sites around the world. The focus of my talk, as you might expect, had more to do with the financial implications globally of the epidemics of neurodegenerative disease. But as I was talking, I shifted ultimately my conversation away from the notion that we're going to have a magic bullet in the next five, ten, 15 years or ever to the understanding that by and large, Alzheimer's, for example, which is costing us globally today as you and I have this conversation \$1 trillion, that Alzheimer's is significantly related to our lifestyle choices and as such, is significantly preventable.

That's where Grain Brain will go over the next five to ten years. It will continue to hammer away at the mainstream dogma that what have us believe that we should live our lives come what may and that modern science is right on the heels of developing a treatment for all of our maladies well beyond Alzheimer's and diabetes. It's going to hammer away at the notion that we are responsible for our health destiny; we are responsible for the destiny of our brains. We actually have a very big input in terms of the choice in terms of whether we're going to develop senile dementia of the Alzheimer's type or not.

So I think that's the message moving forward with respect to Grain Brain and we're going to stay at it. I think we explored a lot of interesting areas five years ago. We've sent some terrific support for those contentions, now in follow-up and my mission would be in another five or ten years to revise the book again and make changes and recommendations where perhaps we were wrong, amplify those recommendations that have been substantiated, but you know what? It's a job that will continue.

Robb: That's awesome. Well, doc, again it's such a huge honor to have you on the show. Super, super excited to see where all this is going. It's a fascinating time. I know some institutions like Swiss Re, which is one of the largest insurers in the world, like if one has a life insurance policy, chances are the final underwriter, you know with this long Byzantine chain of ownership may in fact be the Swiss Re folks. They are looking very, very closely at low-carb and ketogenic diets as the preferred intervention to extend life, because for a life insurer, the longer people live the better. Then they're also tied into the healthcare side of that also, so you don't just want them to live a long time, but you want to have them live a

long time and then die without a whole lot of medical cost. That can be achieved if we follow some of these more ancestral health approaches.

David: And Robb, it's not for lack of scientific support. What gets in the way is commercialization of our food, commercialization of healthcare. Unfortunately, those two things don't necessarily have our health in their interest. But every journey begins with the first step. This journey's begun quite some time ago. We're well into it, but to be sure there's still quite a ways to go.

Robb: Absolutely. Well, doc, remind everybody where they can track you down on the interwebs.

David: Let's see, my website is, oddly enough, drperlmutter.com. I have a YouTube television program which is called The Empowering Neurologist. We send out from drperlmutter.com each week a free newsletter, so that's available to people. My books are I guess all around, Amazon, bookstores, you name it.

Robb: Awesome. Well doc, we will have links to all that. We will have links to the updated edition of Grain Brain and can't wait to see you in real life. Are you going to be at Paleo f(x) or any of these other events coming up?

David: It looks like I am at Paleo f(x).

Robb: Okay, awesome.

[1:05:01]

David: It looks like we will be going there. Just to be sure, I will send you the full PDF of that very interesting article with reference to the plant-based RNA so you could share that with your listeners.

Robb: That would be amazing. Awesome, doc. Well, thank you again for coming on the show and can't wait to see you in real life.

David: Okay, my friend. Talk soon.

Robb: Take care. Bye-bye.

David: Bye.

[1:05:20] End of Audio