

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 the Industrial Revolution changed more than 10,000 years of human grain consumption. In 1870s we invented the modern steel roller mill, which completely changed how we milled grain. Compared to the old stone methods, it was really fast and efficient and it gave you really fine control over different parts of the kernel. So instead of just mashing it all together, you could separate the parts, allowing the purest and finest of white flour to come out at a very low cost.

Dave: And that meant that people with the very lowest levels of income could still afford the fancy flour. And the good thing about white flour is well, it ships better, it stores better, it allows for long distribution chain. In fact, you could keep it almost forever because it seems like nothing wants to eat it except for humans. We now know that's because it was stripped of nutrients and pest problems were less of an issue because well, bugs and rodents didn't want to eat it.

Dave: The problem was that well grains, even if they're not treated that way are not particularly good for humans because before the Industrial Revolution, we had the Agricultural Revolution, which is when humans dropped a foot in height in some places and we started getting cavities and other degenerative diseases we didn't have before. And there's really good science to help explain why that happened. Because yeah, pizza and croissants tastes good. Doesn't mean you need to make them out of grains.

Dave: There are other ways to do it and if you want to continue eating those things well, to put it really bluntly, you'll probably die sooner from something painful than if you choose not to do that and you'll probably not like the quality of your life as much as you would if you made better choices. I wish it wasn't so. However, that's what the science that I'm aware of says both from my own extensive research and self experimenting, and from having the opportunity to interview some of the world's smartest and best and most impactful people out there on Bulletproof Radio.

Dave: I'm really pleased to have a dear friend, just a fantastic human being, a guy with a crazy amount of education and experience across different fields of medicine, a famous author and someone who I featured in Game Changers on the show again. I'm talking about none other than Dr. David Perlmutter, author of Grain Brain. I think you're also the author of four other New York Times Best Sellers and practicing neurologist and well, just an overall fantastic guy. David, welcome to the show, man. That's the best I could do for you, but it's still isn't adequate.

David: Oh my gosh. It's an honor. Your listeners need to know that right back at you. We both do podcast. We both interview a lot of people, but you and I have had just the great fortune of taking it a step further and spending some really quality time together, family time together and it really has been very, very meaningful for us, that's for sure.

Dave: Well, it's inspiring for me and I'm going way off. There's plenty to talk about, but when I first got going on Bulletproof and Bulletproof Radio and all, you see these authors kind

of up in the clouds. They write these books, you read these books and you're sort of like, so like what kind of people are they? And then eventually with the work that I'm doing? I got a chance to meet you and there are a lot of people who don't have to write books and they write books because they've studied this for many years and because they think it matters and they just go around generally doing good work and helping people with an attitude that's amazing.

Dave: You're one of the probably the most giving guys I've met. Every time I've seen you interact with someone whoever they are, you're just, "How can I help?" That's something that's hard to see if you read your books or if just to look at you from afar, but just having gotten to know you, this is a hallmark of people who succeed really well and it's one of the things that came out from looking what 500 people do. People who learn how to be happy tend to be more successful and everything I know about you says that you've figured out how to do that and that that's powered some of what you do. True statement?

David: Yeah. I mean, I am eternally grateful every moment of my life for just the life that I've had the opportunity to live so far. I mean, the family that I have been gifted, the people I've gotten to know. Maybe it's rose colored glasses. I see things as being just extremely positive. I am a realist. I see what's going on around us, but I have complete faith in us as a species and in our ability to do the right things and move things in the right direction despite temporary setbacks.

David: I think it is more along the lines of being an investor and not a traitor. I'm looking at where we're going in the long run and I think the slope is exactly where we need it to be. Are there setbacks along the way? You bet there are, but this is looking at the climate as opposed to looking at the day-to-day weather and we know, and that's not necessarily a positive thing or not necessarily the best metaphor, but it again just speaks to the long view that I take in a very positive way.

David: I've always said that today is the best day of my life. The reason being is that it builds on yesterday and yesterday, until today, was the best day of my life. And the good things are cumulative. The bad things do not enter into that equation. So therefore, today has to be the best day of your life. If one tiny thing was good that happened, then it moves the ball a little bit further. So that's the attitude, I think.

Dave: It shows. Part of the reason that I put all the ... It was about 8,000 hours into Game Changers was to understand the mindset is one of the many things that that people who've had a big impact do. And when I say you have a big impact, you won the Linus Pauling Award for treating neurological disorders in a new way. You've spoken at the World Bank. You're now an author as a top expert in the field of the emerging science of microbiome and the brain. And just kind of the amazing list of accomplishments throughout your career in diverse fields, which are profound.

Dave: One of them is your book Grain Brain really helped people see that it's not just a bunch of cavemen or hippies saying, "Don't eat grain." And I have no problem with cavemen or hippies or cavemen hippies for that matter. But if you want to get people who aren't doing lots of research to make a change well here, I'm a highly credentialed neurologist,

and here's the hard science and it's accessible. So Grain Brain really helped to change the conversation, to make it normal to go to a restaurant and say, "Don't put gluten in that," and actually know what gluten is, but you just rewrote the entire book five years after it came out from the ground up.

David: We did. We really did and it was as much effort as went into the first book, but I will tell you with ... This time around there was so much enthusiasm in the project I think that was engendered because of the degree and level of science that has come in the past five years that has been so supportive and validating of our original, a very much disruptive contention. We were talking about gluten and sugar and carbohydrates as being toxins with reference to the brain at a time.

David: This was long ago. This is ancient history five years ago when there was plenty of pushback, though the science at that time was burgeoning. The original book was written based mostly ... I'd say significantly what brought it about at least was clinical experience in dealing with patients, then finding the support of science. But as you well know in the past five years the science surrounding lower carbohydrate dare I say even to the extent of ketogenesis, as well as the more recent science on gluten and non-celiac gluten sensitivity, we'll talk about that, has really been so extensive, so validating.

David: So it's great to have now gotten so much support. This book Grain Brain has been translated into 34 languages around the world. I saw one of my books this morning, somebody sent me an Instagram picture of it on a TV show in Turkey and it's just, these are people I will never see, never personally experience as a clinician, but yet to think that somebody on the other side of the world is going to get a simple message and that is that, hey, this aberrant diet that we feel is appropriate for, a diet quite unlike anything we've experienced in 99.6% of our time walking this planet, that we really need to consider, that this is a threat directly in terms of the provision of macronutrients, like carbohydrates, directly threatening to our health.

David: And also secondarily threatening to our health in that this is a diet that's sending really bad signals to our genome, which then expresses genes that enhance inflammation, that degrade our antioxidant quenching ability, that compromise our ability to detoxify. The very toxins that are now part of our environment when we desperately need to amp up our detoxification system.

David: So I think the one experiment, the one research project I think that really is I leverage the most in terms of validating these recommendations is a study that's been going on for two million years. It is called the human being and it's demonstrated that you bet a diet lower in carbs, higher in healthful fat, a diet that gives us lots of good nutrient fiber has kept us going for two million years. And suddenly, what did we learn in the past few days?

David: We learned that for the first time at least in recent history, that life expectancy for men and women in the United States has not only plateaued, but has now begun to decline. We haven't changed genetically. We certainly have changed the epigenetic signaling that we are now engaged with. So now more than ever I think we've got this robust data

that says, suddenly take a deep breath, what has changed and what can we do to make it right?

Dave: It's interesting that you talk about carbohydrates because in Game Changers, where I summarize all this knowledge, one of the 46 laws of high performance is feed the little bastards in your gut. And you're one of several experts I cite in that. This is what the people who are performing really well actually do. And I wrote a lot, it's just the bacteria in your gut control a lot more than you might imagine. They have the power to make you fat, tired and slow, to give you extra energy to tap into new power or even to make it a pressed. They're in the driver's seat and if you treat them poorly your performance will suffer. When you treat them well, they serve you, learn how to make them do your bidding. But they eat at least primarily carbohydrates in the form of fiber.

David: Correct.

Dave: Because fiber is a carb. And I'm a little concerned. I've seen, I've been experimenting with something very close to the carnivore diet where people are eating only meat or you get what I would like to call the [keto bros 00:12:26] where, well, if it's not a carb I'll just eat it. So I'm having pork rinds, bacon and that's it for the rest of my life. Is there some carbohydrate confusion?

David: Well, without a doubt.

Dave: Walk me through that.

David: Yeah, I'd be delighted to. I'd like your listeners to really tune in because I think ... I don't where we're going later in our time together, but this is very important. And indeed it is carbohydrate confusion because we desperately, desperately need carbs. So many people adopt a ketogenic program and totally abandon their carbohydrate intake and what happens? They feel crappy, they become constipated, they get brain fog, they don't sleep well, they're agitated and it's all because they fail to understand that we have to be quite specific when we talk about carbohydrates. That we are desperately in need of fiber in the diet, which is by definition a complex carbohydrate that we don't metabolize, but is yet metabolized by our gut bacteria.

David: When we throw that baby out with the bathwater, we set the stage for not nurturing what you mentioned, these 100 billion organisms that live within us that really depend on your food choices, 100 trillion, depend on your food choices to nurture them to allow you to not just be healthy, but be healthier, to be able to combat risk of illness moving forward. In other words, a preventive program. If you want to make it more simple then perhaps if you talk about the notion of net carbohydrates, which is fiber minus these simple carbohydrates and minus sugar alcohols for example.

David: So we want to understand that we do need fiber. We've eaten fiber and in fact, looking back at our ancestors, they ate a heck of a lot of fiber, as much as 100 to 120 grams of fiber a day and had many bowel movements a day and nurtured their gut bacteria. So it's a huge mistake and if that helps to unwind or unpack this notion of carbohydrate

confusion, I'm really happy because again, we want people to eat a lot of good fat, a lot of good fiber, not a lot of protein.

David: In fact, this recommendation that we're making is absolutely not an Atkins Redux. We don't want you sucking down pork rinds and meat all day long. I mean, The China Study, Dr. Campbell drew correlation between red meat consumption and risk for colorectal cancer. And, as a matter of fact, does Dr. Perlmutter agree with that? You bet I do. Why? Because first of all, there are some downsides of taking in too much protein with reference to certain biochemical pathways, activation of mTOR for example, ultimately-

Dave: You're talking about too much cysteine, too much methionine, the amino acids that come from eating too much protein.

David: Exactly right.

Dave: They cause aging basically. Right.

David: Correct. And turn on a cell signaling pathways that are disruptive. But beyond that, the data that is utilized for these studies involves dietary analysis with a question on the dietary question asking simply, how often do you eat red meat? How much red meat you eat? So that they're ultimately able to categorize people into eating high amounts of red meat versus low. Now, red meat by and large is a one of the most dangerous foods on the planet. And by that, I mean the factory farmed red meat that typifies the type of red meat that people generally consume.

David: If you're consuming a food that comes from an animal that's been antibiotic exposed, that's been fed glyphosate rich grains and has been stressed throughout its existence, there's no alchemy that occurs here. You're going to create a food product that is absolutely threatening to your health. On the other hand, if you choose to be omnivorous and choose to eat some red meat on occasion, then it must be grass-fed beef or other type of meat, really emulating how these animals did live prior to this industrialization of our food supply.

David: By and large though, I would indicate that the more plant-based is your diet the better off you will be. If you choose to have a garnish of red meat, then it should fulfill the criteria I just proposed. Wild fish as well, some free range chicken. Eggs, I think are really handy food and are really-

Dave: Those sound plant-based though.

David: No, they're not. I'm just saying.

Dave: It scares me when people say the more plant-based you are because that drives you to become a vegan. And I can tell you, I know very few long-term vegans who are even average health. It's exceptionally rare. Was that a plug for veganism?

David: No, not at all. I said by and large the diet should be plant-based.

Dave: Mostly plants, but it doesn't mean all plant-based. It's that nuance where I think people get stuck.

David: Absolutely.

Dave: And brother, I'm in alignment with you here. I think red meat can be great for you. You eat a couple ounces of it. You never eat industrial meat. It never has antibiotics in it. If you do that and you take care of your gut bacteria, you don't have the gut bacteria that make TMAO, which is a compound that causes the all of the risk factors, at least most of them I would say from these studies of red meat. And I've had my gut bacteria tested. Guess what? I don't have anything that makes TMAO because I don't eat antibiotic tainted meat.

Dave: There's nuances. There's also what kind of cut? Are you doing collagen from red meat, which has a different effect, which doesn't have all these amino acids. So it's such a complex thing, but I just want to make sure that unless you were meaning to do it, that people didn't say, "Oh, if mostly plant-based is good, therefore only plant-based is better." That has been my experience.

David: I am so glad that you're holding my feet to the fire on this because we don't want people to get the wrong idea. And I would agree with you that by and large, without certain important caveats, that vegans can get into trouble with low levels of certain things, vitamin D, vitamin B12, even not getting adequate levels of dietary fat. Who knew? I mean, who knew this was going to be an area of actual importance? That said, overdoing the meat side of this equation at multiple levels, not just the antibiotics, but as you well mention, the conversion of TMA into TMAO when a diet is rich in choline and carnitine.

David: We see even higher levels of trimethylamine oxide, TMAO, even in the spinal fluid. So this becomes not just a cardiovascular event increasing inflammatory changes within the coronary arteries, but it becomes an event with reference to the brain as well. So there are multiple levels upon which we can discuss these dietary nuances directly in terms of the macronutrients and micronutrients, but the second order, which really I think should probably the first order would be, how these things are viewed through the lens of the gut organisms?

David: And there are so many things to consider. I mean, I mentioned detoxification earlier. Our frontline of detox is the detox that happens as one of the tasks that our gut bacteria lovingly do for us day in and day out, which we certainly need these days in our very toxic world. We know that these gut bacteria are producing various metabolic products, the short-chain fatty acids that have effects throughout the body and even vitamin, some of the B vitamins.

David: We're learning, from my perspective as a brain specialist, that the gut bacteria actually are playing a role in the production of this really important chemical called brain-derived neurotropic factor. We'll probably touch on that later, but important for making connections in your brain, we call that neuroplasticity, for growing new brain cells,

which I still am not over. I still, it takes my breath away from the old school where I came where we didn't believe that could happen.

David: So there are many things, not the least of which and perhaps certainly towards the top of the list would be the very important role that our gut bacteria are playing in affecting the set point of inflammation in the human body. They do so in that they are in charge of maintaining the gut lining where we want to have a gut lining that is patent or intact or has integrity. When dietary issues, food issues, toxic issues, et cetera, threaten the integrity of our gut lining we enhance through some mechanisms that we may or may not have time to talk about, we enhance inflammation in the body.

David: Why is that a big deal? It's a big deal because we correlate higher levels of things that we measure that relate to inflammation with just about every chronic bad thing that you don't want to have, whether it's coronary artery disease or it's Alzheimer's or Parkinson's. Yes, the truth of the matter is there are higher markers of inflammatory mediators in the bodies of autistic individuals. Certainly a diabetes is inflammatory and even cancer. So our main mission here is to keep inflammation at bay, and that is what happens when we are good to our gut bacteria.

David: I think it's really interesting to consider a study that was published in the highly respected journal *Neurology* back in 2017. That is the journal that's put out by the board that says you're a board-certified neurologist. It's really the go-to neurology journal. And it was an interesting study that looked at 1,600 individuals and evaluated these people many years ago in their 30s and in their 40s, and did some blood work on them measuring markers of inflammation. And these were inflammatory markers back then, which we don't really use these days, but fibrinogen count, von Willebrand's factor, if anybody's interested, total white blood cell count. We use different ones today, C-reactive protein, TNF-alpha. But anyway.

Dave: By the way, those are in The Bulletproof Diet. Those are in *Headstrong*. Those are the core lab tests for inflammation, because it doesn't matter where you got inflammation. If you got it, you got to fix it. And then you start solving it.

David: You bet.

Dave: So anyway, thanks for repeating those. I love to look at those in every show.

David: But here is what this amazing study revealed. So they look at this group of 1,600 people in their 30s, in their 40s, and they follow them for 24 years, this ongoing study. The researchers dedicated and probably passed the torch a couple times. 24 years later there is a perfect correlation between the level 24 years ago of these inflammatory markers and decline in brain volume and even episodic memory today. In other words, they look at a group of people 24 years ago. Those who had the highest level these inflammatory markers in their 30s and their 40s today have the worst memory and shrunken brains.

David: The point is, a, it really correlates the importance of inflammation as a mechanism, but b, it also reinforces the notion that we've got to pay attention to these recommendations and ideas long before we are threatened or seemingly threatened by them. As a neurologist I deal with people who begin to have memory issues when they're 60, they're 70 and in their 80s and by then this is a process that's been going on for three or four decades.

David: So the message here, the take-home message. And in fact, I did talk about this the World Bank, is that we've got to target younger and younger audiences in terms of the long-term message to keep your brain healthy. Alzheimer's is a dialogue that happens between doctors and individuals once it's started raining. And John Kennedy, why I use the metaphor is, he told us in his inaugural address that the time to fix the roof is when the sun is shining. So now that makes sense.

David: I'm not going to say it's in your 30s before it is you need to start paying attention to this. I'm going to say it's in your adolescence when we're now seeing massive increases in type 2 diabetes and obesity and overweight. I'm going to say it's in childhood. I'm even going to go even a step further saying that it is during pregnancy that choices a mother makes will have outcome markers in terms of that adult. How do I come to say that?

David: I will say that based upon our understanding for example that women taking certain medications like proton pump inhibitors and antibiotics have a significantly increased risk of having a child who will then go on to develop issues related to immune function like type 1 diabetes and even obesity. Therefore, what mother does during pregnancy has a role to play in the risk of her son or daughter ultimately developing Alzheimer's disease.

Dave: It's real. I just love it that you said that. My very first book was what do you do before and during pregnancy to have the healthiest, smartest child possible? Because that's exactly it. What even your grandmother ate has a huge impact. So this is multi-generational, but I wanted to ask you a question there. If you're listening to this and you're saying, "Well, I'm 20 and I'm inflamed right now and 24 years later I'm going to have a high risk of all this stuff." It appears we can either fully or almost fully mitigate the problems of having inflammation when you're young as long as you undo the inflammation. That's been my own experience.

Dave: My hippocampal volume is in the 86th, 87th percentile for people my age. So my brain didn't shrink even though I was 300 pounds and screwed up and ate the wrong stuff and had inflammation everywhere you can probably have inflammation. And I keep it under control really dramatically and my brain works better now than it did in my 20s. But do you think I'm still going to pay the cost of all those years of hard living for the first quarter century of my life?

David: Well, I think that there is a debt and I think that you've probably paid the debt back and then some. I think you've put money back in the bank based upon the things that I know you're doing now. So I think you've undone the damage and you're ahead of the game. You've demonstrated that through your voxel imagery of your hippocampus, as you just

mentioned. But those people who do not do the work have great risk, and I'll give you another-

Dave: There you go.

David: So I hope you'll feel better.

Dave: Also, I don't know if people are listening, but you can start, you can change. I was the worst example, I think, of what you could get because of the pre-diabetes, the high risk of stroke and heart attack, the high inflammation markers across a whole bunch of different things. Pretty much everything bad on the list of aging other than maybe cancer. I didn't have Alzheimer's, but I had cognitive dysfunction, but just really, really not an autoimmune stuff. So if I can get to where I am, you probably weren't as far down the hole as I was. So it should take you less work than it did me, but if you do the work you can get yourself to where you're actually younger than you were before, which is kind of cool.

David: Well, I mean you just came back from an anti-aging conference and that's exactly what we're talking about right now. And we are talking about reversing this stuff, reversing these the clients which, with reference to the brain, we never were schooled in. We never thought the brain had a second chance. And that was the fundamental premise of Grain Brain, that you do get a second chance through this gift of neurogenesis and neuroplasticity and we spend so much time in the book talking about what you can do to enhance that process.

David: But you mentioned years ago that you had a lot of extra body fat and I think it's very instructive to talk about a study that was published way back in 2008, ancient history, again in the journal Neurology, where they looked at a group of individuals and this was a much larger, 6,580-something, 83 individuals. And similarly, they looked at these people at the beginning of the study and then said, "Check you later. We're going to see you in many years." They actually checked back with these people 34 years later, 34, 36 years later.

David: The only study they did at the beginning of the research was they measured their sagittal abdominal diameter. Basically, how big is your belly. They took a group of individuals close to 7,000 people, how big is your belly? Check you later. They checked back with these people 36 years later and they found a perfect correlation between the size of your belly three-plus decades ago and risk for dementia. In comparing those who had the largest sagittal abdominal diameter, biggest belly, versus those who had the smallest diameter, the risk for dementia was increased threefold. A threefold increased risk of dementia simply related to making the choice to having a bigger belly.

David: It is not a cosmetic issue anymore that you got a big belly. And yet, we tend in media to be normalizing this notion that being fat is okay. You know what, if you don't care what you look like, that's not what we're talking about. I'm going to ask you, do you care if you're at risk for dementia in 30 years? And maybe people don't care about that because they're placing their hope on the idea that there's some wonderful treatment

for Alzheimer's and I could tell you that there is no such treatment. There is zero treatment for Alzheimer's. There is no drug, Dave Asprey, as you and I have this conversation right now, that has any meaningful effect on that disease.

David: And I want to take this a little bit further. Last month The Journal of the American Medical Association published a meta-analysis, meaning a review of other studies, by researcher by the name of Richard Kennedy and his research looked at probably the best 10 studies that looked at the two major classes of so-called Alzheimer's drugs, the cholinesterase inhibitors, drugs like Aricept and another drug called memantine marketed as the drug Namenda.

David: And what he found was not only do these drugs not work, but as published in The Journal of the American Medical Association, those people taking these Alzheimer's drugs actually declined much more quickly in terms of their cognitive function. I want to tell you right now, I can barely talk about that with you because think about the literally millions. There are 5.4 million Alzheimer's patients in America, the millions of these individuals who are taking these drugs and whose families put their faith in these drugs because their doctor wrote the prescription and these drugs are actually making them worse. It'd be like giving somebody a blood pressure pill that raises their blood pressure or treatment of diabetes where your blood sugar goes up.

Dave: Or a diet soda that makes you obese. That seems like a business model that works.

David: Yeah, but why-

Dave: It's evil.

David: ... was this not on the front page of the New York Times or why didn't NBC News, CBS, ABC cover this, CNN. This was published and put out by the American Medical Association, that is that the very drugs that are being given to these people ... When I say given, they're being sold to these people. Financially, it's an issue and the heartbreak from my perspective. Having lost my father to Alzheimer's so I know what it's like, but the notion that these people put their faith in their doctors and in the pharmaceutical industry and the very drug that they're taking is causing mom, dad, husband or wife to actually decline more quickly. That's important news. Go to DrPerlmutter.com, read the blog I wrote about it and the full PDF is available there in the science section, the learn section on my website.

Dave: You said something profound in your new book, in the new Grain Brain that's actually got the same title, but it's a very different book than your first version. And you said 90% of literature peer-reviewed journals ever published about the human microbiome have been in the last five years. And that's since you published your last book.

David: Yeah.

Dave: So in addition to talking about Alzheimer's and inflammation what ... I mean, this is incredible. My really big diet book was 2014, so that's four years ago. So that's 80% of

this five-year period and. So all this new gut bacteria comes out. I read a lot of literature, probably not as much as you because you just wrote a book about it, but what really stood out as what's different now than when you first wrote the first edition of Grain Brain?

David: Well, it's a very good question. I think that so many people have been so hard at it in terms of the research. We have some wonderful leaders in the field, Dr. Rob Knight at UCSD for example, just putting out so much research that ties in the actions of these gut bacteria with some really fundamental processes that underlie whether we live or die, whether we get cancer or not, whether we develop inflammation or autoimmune conditions or not.

David: So I think in so many areas of medicine where we've been stymied with lack of opportunities to really be impactful, we're now learning that we have a brand new playing field that can be leveraged to give us wonderful, new, empowering opportunities and it is just beyond exciting to watch the literature every day. There's a wonderful online journal called Cell Host & Microbe. Actually, that is available in print copy if you choose, that on a weekly basis is just giving you these wonderful new studies that are just incredible aha moments for those of us in the field.

David: And for me, I like to portray it as that these new studies are connecting dots for me. I mean, we've got a lot of dots that have been connected, but there's a couple of funny pieces to the jigsaw puzzle that we haven't really found yet. But when you find that piece and you drop it in and it fits, oh my gosh, it really adds to continuity and you start to see the whole picture. Let me give you an example.

David: There's a researcher at the University of Louisville. His name is Yun Teng. And Yun Teng, again, in this journal Cell Host & Microbe recently published an article that came out actually when I was in Switzerland lecturing on this exact topic a couple of months ago. And he noted or discovered that plant cells that contain their own genetic material, RNA, when we eat plants, that encapsulations of their RNA called microsomes or exosomes once they leave the cell and are through digestion, that these exosomes of this genetic material travel in the gut, bind to the cell membranes of our gut bacteria, insert themselves into the gut bacteria and make their way to the genetic material of our gut bacteria and then influence the genetic expression of the gut bacteria's genome causing at least three things to happen.

David: Number one, changes in the reproductive activity of that particular species of bacteria. Number two, changing the metabolic products that that gut bacteria might make. And number three, actually changing the location of these gut bacteria, which is important when as mentioned earlier, we need some of our good gut bacteria to cluster around, especially the clostridial species, to make their way towards the gut lining where they can be at work helping us maintain the integrity of that gut lining.

David: But how incredible that we now understand that plants, yeah, we get prebiotic fiber and that's good for our gut bacteria. But no, we are influencing the genetic expression of the gut bacteria and make no mistake about it, that connects to another dot that's really important. And that is the dot that we've already understood whereby the genetic

expression of our gut bacteria influences our DNA, our genome. So this now connects the plants that we eat to the expression of our DNA. Wow, those are two very important dots that are now connected and I think that, as I say, what a very important piece of the jigsaw puzzle has now been put in place.

David: Beyond that, stay with me and think about the notion then if the RNA, the genetics of the plants that we eat is so important influential through the mechanism I just described. What then should our level of concern be as it relates to the notion of genetically modifying the plants that we eat? So people have said, "Well, there's no real evidence that genetically modified food is creating a health issue for us and plus, it's going to allow us to feed the planet whereas otherwise the planet would starve."

David: We can challenge that one on multiple fronts, that notion, but that said, now that we understand that the genetic material of the plant does in fact influence the genetic expression of our gut bacteria that plays a role in our DNA expression, then you bet it's time to take pause as it relates to modifying the genome of plants that we eat and look at it through a new lens and in terms of the doctrine of *primum non nocere*, above all, do no harm.

Dave: Very beautifully put. And there's something else that you came out with in your new version of Grain Brain, a study that I talked about a lot on social media and I believe blogged about last year. And they looked at just about all of the fatty plaque in people that have heart disease and they found that it doesn't come from egg yolks, it doesn't come from butter, it doesn't come from beef fat, it doesn't even come from bacon. It comes from microbes in your gut.

Dave: I actually mentioned this in a friendly discussion with a proponent of the vegan diet, saying meat causes heart disease. And the evidence is in, gut bacteria are what's causing heart disease because if you eat meat and you have the wrong gut bacteria, they make that TMAO stuff we talked about earlier. And even if you don't have that TMAO stuff, even if you eat vegetables if you have plaque in your arteries, it was made by your gut bacteria. Do you believe that's the case? I believe the study. It looked well done. There's no way to argue with the isotopes are looking at it and the stuff. But what's your take on that? How real is it?

David: It's not the end-all cause, but I think that again, it really speaks to this notion that the health vitality of our ... And diversity, perhaps the most operative word here, of our gut bacteria is massively important in determining our health destiny. And beyond that we understand that it isn't the quantity of certain fats or fat carriers, the lipoproteins that is really the issue.

David: Well, Madison Avenue, somebody came up with the notion of calling LDL bad cholesterol. They get a great prize for that because everybody's latched onto that. I want to get my bad cholesterol since it's bad, it should be as low as possible. And well, there must be a good cholesterol. Yes, there is, it's HDL. A, they're not cholesterol, they're proteins. B, they're both really, really good. Yes, LDL is what transports an important fact to your brain called cholesterol that we desperately need. It does a great job.

David: When you compromise LDL you're in big trouble. We know that LDL in terms of how it's modified, how it makes its way through the brain vasculature for example, the blood vessels within the brain crossing what we call the blood-brain barrier. When LDL has been damaged we see great relationships to mechanisms that underlie significant brain degeneration. So let's just first by characterizing LDL as good and HDL as good and that the issue and let's relate this back to our gut bacteria for a moment, that becomes important, it's not the amount of LDL. It's good to have LDL to transport our fats, but it's the state in which we find our LDL. Has it been damaged or has it not been damaged?

David: And what do I mean by that? LDL is damaged in a couple of ways. It can be oxidized. In other words, the action of free radicals. And that certainly is influenced dramatically by the foods we eat and how the foods influence the expression of our gut bacteria, whether we're on a ketogenic diet for example, whether we are eating types of vegetables that enhanced pathways to increase our antioxidants, like the Nrf2 pathway, i.e., why we want to eat broccoli and drink coffee and use turmeric in our cooking, et cetera.

David: But beyond that, another issue that is so influential in terms of our LDL is, has it been glycosylated? What does it mean? It means has it been not just oxidized, but now has it bound itself to sugar? Glycation process by which proteins bind to sugar and once they do so they are modified to become less functional. The main issue that we need from our LDL, which is not bad cholesterol. We love our LDL. It's keeping us alive. The main issue is, what we're looking for is functionality.

David: We will compromise the functionality of our LDL and therefore, be in great trouble like heart disease, like [inaudible 00:45:16] vascular disease, strokes, et cetera. We compromise functionality of our LDL, which is not bad cholesterol, when it is either oxidized by the excess activity of production of free radicals in the presence of inadequate antioxidants or it is glycosylated.

David: Now, let's just look at ... Not everybody can go and have their glycosylated LDL blood test done, but a terrific surrogate marker that anyone can tomorrow go to their doctors and have done that correlates almost perfectly with the level of glycosylated and even downstream oxidation of LDL is a very simple test, a glycosylated hemoglobin test. Is that unusual? That's the A1C that they talk about on the diabetes drug commercials that you see on the evening news.

David: Everybody knows about their A1C because there are 60% of Americans now, they're probably have their A1Cs checked because they are pre-diabetic or ... I mean adults or frankly, diabetic. So everyone's familiar with A1C. What is it mean? It means glycation in this case, sugar binding to a protein called hemoglobin. That's the oxygen carrying, carbon dioxide carrying molecule within a red blood cells. So that is the terrific surrogate marker for this LDL glycation and LDL oxidation or oxidatively damaged by the actions of free radicals.

Dave: So the glycosylated hemoglobin also tells you whether your LDL is oxidized, not just whether your LDL is glycosylated? Because those are different types of damage pathways.

David: Absolutely.

Dave: Both.

David: Great point. When things are glycosylated, they oxidize. Two things are triggered by the glycosylation of proteins, oxidation, higher levels of free radicals and who knew, inflammation. So these things all come together. Again, it's all about these dots and when you're pulling the research, writing a book or updating a book and these things come together you just say to yourself, "Why, that's fantastic." Or #WTF, why that's fantastic. Because it really is and you make these connections. I got to write a book about this. People have to know that lowering inflammation in your body and lowering your blood sugar to reduce glycosylation of proteins is so very important.

David: One graph that I included in Grain Brain and now with the new release of the revised edition I included because it's so compelling, is the relationship of A1C to brain shrinkage. Higher A1C, higher rate of brain shrinkage. It's linear. You've got to know that. And having an A1C of 6 when your doctor says, "Oh, you're not diabetic. Everything's cool. Go home. Keep doing what you're doing." That does not jive with the science. It's telling us that a hemoglobin A1C of 8.16 is good for you. That's BS. You need your A1C down to 5.2 and that's pretty much take that one to the bank one.

Dave: How low would you go if you could set it as low as you want it? I don't want to be average. I want to live 108.

David: I don't know the answer to that, but I will tell you that one thing I've learned over the years is that there is this notion of what we call the U-shaped curve or perhaps the sweet spot where too low ... Or Goldilocks area where once the porridge was too cold, the porridge was too hot and this one's just right. So we know that higher A1Cs for example are correlated to cognitive decline, but we've been talking for years about keeping not just your blood sugar, but actually your insulin level low.

David: I will note that a recent study that came out of Sweden looked at ... It was published just in May of this is 2018. I know this will be evergreen, but published earlier this year 2018. The study also published in one of my favorite journals called Neurology looked at 1,200 women between the ages of mid-30s somewhere up to age 60, followed them for 34 years and what did they find? Again, they measured one thing at the beginning to study and that was their fasting insulin levels.

David: They found that those individuals with the lowest level of insulin actually had an increased risk of dementia of about 2.3-fold. Those in the middle range of insulin levels as they defined it by definition of their study, their risk was put at one, and those in the higher ranges of insulin as you might expect also had a higher risk for dementia of 1.7. Not as high as the very, very low levels of insulin. So the notion of trying to keep your insulin level really, really low, I think we have to temper that.

David: The notion of over-exercising I think should be looked at in terms of the U-shaped curve, the sweet spot. The amount of sleep that we get, for example. The amount of nutrients

that we take in. The amount of fat we consume. Vitamins, we can overdo or under. So I think that the notion of the more the merrier, and I for one have been guilty of that personally. If I was told that it'd be good to do something I always did twice that or more than that. And I know you are the same way. I've been to where you're broadcasting or recording this studio, leave it at that.

David: So you are like me. We both have been aggressive about things and I think understanding that there is an ideal place. So the question then becomes, how do we zone in on that? How do we fine-tune that analog dial on the FM radio to get the very best signal? You turn the dial to the left, you get static. Turn it to the right, get static. You really want to fine-tune. That's what biohacking is all about. That's what understanding biometrics and crunching the data is all about.

Dave: What's really frustrating is when you see ... Well, here's how you scored your testosterone compared to the average 46-year-old. That's one of the laws in Game Changers is average is the enemy. I don't want to be the average 46-year-old because most of us are developing dad bod the way I had in my 20s and our muscle mass is going down, our testosterone is going down and don't compare me to average, you tell me ideal, but medicine has failed us in telling us what's ideal.

David: You're right.

Dave: So I'm like well if this works, let me try doubling that and tripling that and then try going back and tuning that dial myself, but I feel like even some of these studies that you talk about in Grain Brain over the last five years, we're starting to understand enough that maybe we can get these numbers dialed in so I don't have to do the guess work. So the biohackers listening, and certainly there is a lot of people listening who are not biohackers don't go out and do all these stuff. They just want to feel good and perform well.

Dave: I think we're sort of failing them by not saying, "Here's the number." And you did it right here, Dr. Perlmutter. Okay, you want to have a number of 5.2. You don't want it to be six and you probably don't want to be four, but that's based on very recent knowledge versus most of the other lab metrics when you get it back what the lab tells you is garbage for the reference range because you don't want to be normal. Normal people die.

David: Yeah, well that's in the normal range. And what is normal these days? Normal is by definition average. That's how they develop these lab values. They take a large number of people and then they use one standard deviation on either side of the peak and they say, "That's in the normal range." And I think that's a huge disservice to people who want to be optimized. So yeah, we can talk about a vitamin D level being in the normal range, 30 to 100, and that means that I'm okay at 31.

David: Well that you are not okay. You're not okay quite literally in my book. You're not okay in my book because I want as many people that I can touch over time to be their best. To be not only their best today in terms of their functionality, but to be their best

tomorrow in terms of being resistant to the degenerative processes that are so pervasive now in global society. So you have your opportunity to be your best when you begin to understand that you have to be that n of one that challenges the notion of normal range.

David: The medical model were as only as much as 3% of people ever ... Data from 3% of people are extrapolated to the remaining 97%, or actually the 100% because they're then included in that in terms of the recommendations that are made by mainstream medicine. That is, as my dad used to say bass-ackwards, and it raises this discussion of personalized medicine, where we want to know about Dave Asprey specifically. Not your wife. Not your neighbor. We want to know about you. What's your pedigree? What does your microbiome look like? What do your current biometrics look like? And from that, we'll develop a program that is best for you.

David: Now, having said that. I gave this talk at Jeff Bland's Personalized Lifestyle Medicine Institute conference. I guess it was two months ago. That's the future. That's the best we can do and we should extrapolate from that information back to the notion of making the broad stroke recommendations. There's great value in the broad stroke recommendations in terms of those ... The broader reach of the population that's not going to necessarily be able to participate in a very in-depth personalized medicine approach.

David: And those broad stroke recommendations are that you've got to cut down on your simple carbohydrates, you've got to understand what is the notion of net carbohydrates. And by all means, as we talked about at the beginning of this discussion, not eliminate the fiber, by definition, a complex carbohydrate from your diet. That dietary fat if you're careful about what that fat is in terms of its type, is fundamental to your health. Understand the discussion, Dave, that you and I had earlier with reference to meet and its quality.

David: And beyond that, look at the things like sleep and the restorative nature of sleep and exercise for example as broad-stroke recommendations that we really need to engage. The main premise of Grain Brain and now with the revision has always been to appeal to the larger audience. Yes, we made a few specific recommendations in terms of fasting insulin, a vitamin D level, a hemoglobin A1C, fasting blood sugar amount of exercise to get looking at your sleep, getting a sleep study as it were as one type of study to understand who you are and what your risks are, but by and large, it's the broad strokes that I believe everyone can do.

David: One of the recommendations I make in the book and again with the revision that's coming out next week. And that is, you do have to buy something. I am wanting you to buy something and here's the pitch. Here's what you got to buy. And people are saying, "Oh, I knew that was coming." Yes, you need to go out and buy a new pair of sneakers. That's it. I mean, if you have to do one thing and buy one thing, go out and get a new pair of sneakers. It's so undervalued that our sedentarity is killing us.

David: And people think, "I've just got to get the project finished. I've got a whatever it is." And by and large, our work is done by sitting and in front of the computer. You and I are

doing it right now. This is the only time of day that I'm going to really be doing this and I've already had my aerobic workout for the day and I'm going to do another one in just a bit, but that said, that's a huge issue. And again, it's something that everybody can do.

David: For me, I would say even if it's walking to the mailbox and coming back, that's a start if you didn't do that before. If you're in a wheelchair, you buy some free weights and you do something, but I think everyone should be really cognizant of the fact that aerobic exercise, and now we know resistance exercise as well, is a powerful way to change the expression of your life code, of your DNA for the better, and who wouldn't want to do that?

Dave: You talk about something else in the new Grain Brain that wasn't a big focus in old one. You talked about ketosis. And we've also talked about these Goldilocks zones. At the beginning of this you said what I think is going to be the title of the show, why you desperately need carbohydrates. Because like what? Well, you do, it's called-

David: Great idea. You should definitely do that with Dr. David Perlmutter. People are going to really say why, that's fantastic, WTF. Go ahead.

Dave: Totally. You're going to have to listen to the show and realize that you're actually correct. If you feed your gut bacteria wrong, but there's definitely people ... It'll cause a double-take for sure. And there's an ideal number for that stuff and clearly you and I are not going to be in the camp of high carbs ever. But also, the zero carb is maybe going too far.

Dave: With ketosis I see some of the the sort of hands of as long as it's not a carb, I'll eat it type of ketosis. Saying, "Oh, yeah, my blood levels are two, three, four. My ketones are higher than yours. I took these non-bio identical [inaudible 00:59:45] ketones and look what happened." I have a belief based on the studies I've seen it all about a good number of ketones for people, but I want to know what you think after writing the new Grain Brain because you've put a lot more focus on keto because you're a neurologist, because now, five years after you wrote the first, we know way more about ketones in the brain, you know there's something going on. What's the number the people? What's the max? What's the min? What's the average? Where should we be?

David: Well again, we want to try to find that Goldilocks zone. And I think it has to be contextual. I think we have to look at not just ketones and we'll get there in just a moment. But in the context of also your fasting blood sugar. So again, we want our fasting blood sugar, as I've said before in the 70s, in the 80s. I'm lower than that, but I'm okay with it. Again, these are just general recommendations. And I'd like to see people getting their beta-hydroxybutyrate as a specific ketone that is measured, which does require a finger prick, to be at least 0.5, 0.7, 0.8, in that range.

Dave: Hallelujah. I was going to say 0.5 to 0.8. That's all the numbers I've seen. Okay. It is not one. It is not three. It is not five. You might want to spike it for something, but having it high all the time is bad. Okay, why those ranges? I know there's two studies I love, but you probably have more.

David: Well, I think that that's a heck of a lot of beta-hydroxybutyrate floating around doing what it needs to do. And to be clear, the research demonstrates a absolute linear correlation between brain levels of beta-hydroxybutyrate emulating what we find in the blood. Research would demonstrate that these levels of beta-hydroxybutyrate in the brain are actually very active. And this is some of the research that Dr. Bredesen has leveraged in terms of his recommendations would fall in the same range as you and I just quoted, allowing people actually the ability to recover, to recover from Alzheimer's disease.

David: I take a big push from that. I also think that it is achievable by the common man, that it is ... It certainly may be enhanced by adding MCT oil or coconut oil to the regimen, but I think even with a fairly well-defined ketogenic diet, to get that level most of the time is a good thing. I also believe that the hormesis or the stress metabolically that is imparted by a little bit lower blood sugar from time to time and therefore, a slightly higher 121.5 range of beta-hydroxybutyrate has got to have some downstream positive effects when you stress the body that way mimicking fasting.

David: That brings up another idea of fasting mimicking, but mimicking caloric scarcity. And I think the body goes into it really protective mode. There's no food. We've got to start changing. What genes are expressing and what genes are not expressing? Because we don't have access to a caloric resource here. At the same time I would indicate that having a higher blood sugar from time to time, not higher than normal, but just letting it come up a little bit.

David: So cycling through this looks like based upon really fairly recent research to be more in line with mimicking our paleolithic environment and also allowing genes to be more adept at expressing themselves. But again, I think that you bring to mind these as long as it's not a carb, I'm going to eat it. You can absolutely have a very detrimental effect on your ability to get into ketosis and lower your blood sugar if you're eating lots and lots of meat for example, just protein in general.

David: I think that such an important concept through the notion that high levels of amino acids, the breakdown products of protein can be reassembled through a process in the liver called gluco, sugar, neo, new, genesis. Making new sugar. It's enhanced in that scenario where you're eating ... You go ahead and say, "If it's meat, I'm going to eat it." And basically again, Atkins Redux, apart from this mTOR consideration where you're activating a pathway that really is profoundly detrimental leading to cellular death, pre-programmed death and leading to mitochondrial failure.

David: Maybe what we're saying seems complicated. But again, I think that people should based on current data and let's be clear, you and I may get together five years from now saying we learn through current research that the world is flat. We were wrong that world, it wasn't round, it's flat. I guess I could be open to that. It'd a stretch, but what we understand now ... And again, it's bolstered, as I mentioned, by 2 million years of being tested on the racetrack that a diet that doesn't have simple carbohydrates, that has lots of carbs. Perlmutter is saying, "Eat a lot of carbs." The title of this podcast, but these are carbs that are fiber, that are nurturing your gut bacteria, that isn't eating meat

and eggs and cheese and milk products all day. No, that's not what we're saying, mostly plant-based, but not entirely if that is your choice.

Dave: Plant-based does not mean eating basically flour all the time, grains, only beans, rice, starch. So it was almost like mostly plants, but not plant babies. I don't know exactly how to express that to people. You're talking about green vegetables when you say mostly plants. Not so much potatoes that are also plants.

David: That's right. And we say basically above-ground vegetables, above ground, because these are vegetables that by and large, aside from their seeds, that we will get to in a moment, by and large don't store carbohydrate in the form of starch. So having a couple of potatoes ... Not potatoes, but a few pieces of potato or carrot which does grow in the ground, turnips, whatever. They're not unreasonable, but we certainly want to avoid the seeds of grass because the products derived therefrom are generally going to spike your blood sugar and if it's wheat, barley or rye and now even oats, of course, you're going to get exposed to gluten and specifically part of it called gliadin.

David: We really spoke about in Grain Brain five years ago the work of a British researcher Marios Hadjivassiliou, who I think was really the pioneer in terms of the notion that gluten can have extra intestinal effects, meaning affects outside of the digestive system. What a notion. He was even very clear that neurological conditions issues manifestations can occur in response to being sensitive to this protein called gluten.

David: And that was resounded, the rejection of his although he published in the journal Lancet, I might add, but there was a resounding rejection of his concepts, which I felt were very, very valid and since that time as you well know this notion of non-celiac gluten sensitivity has been absolutely supported globally by literature to the extent that even The Journal of the American Medical Association in 2017 published a very extensive review with Harvard researchers contributing to this review.

David: In fact, Dr. Alessio Fasano was a contributor to this study, absolutely affirming for us the notion of non-celiac gluten sensitivity and the notion that gluten sensitivity can have significant extra intestinal manifestations that may involve the brain. So when we talked five years ago about movement disorders, about ADHD, other issues with cognition headache for example, possibly being related to gluten sensitivity because science supported that, yeah, there was pushback, but now. My goodness now it's really becoming much more accepted and I'm really grateful to for the degree of validation.

David: I published a study several years ago with a Dr. Aristo Vojdani where we demonstrated markers in the blood demonstrating gluten sensitivity without celiac disease in a patient with about 28 years of intractable headaches having to take opioids to control his pain and going gluten-free and finally coming off opioids after more than two decades.

Dave: Well, Dr. Perlmutter, this is why your work matters and for people listening, you don't have notes in front of you. You know these studies because you write books and because you read these so you can be better in the clinic every day. And all the science is real. It's all out there. So if you're still stuck in that, I've got to have my sticky white

bun on my cheeseburger or something, just know, it is not free and the idea that I'm going to spend less on my food as long as it tastes good is not actually spending less because you're probably going to not like how you feel.

Dave: I just have to say thanks. Thanks for the new Grain Brain. Thanks for your decades of work in the field. It has made a big difference and I appreciate it. If you loved today's show, you should check out the new Grain Brain. And if you happen to order it on Amazon at the same time you order Game Changers, they'll be stuck together for other people [crosstalk 01:10:24]

David: There you go. Forever.

Dave: Exactly. Thanks again for being on the show. Thanks for being such a great friend and such a big ... Do I say Game Changer?

David: Well, I will tell you that I was very, very honored not only to be spoken about in terms of my work in your book, but to be supportive of the book in general because it's a really a great resource because we must learn from others and you've cultivated an incredible cadre of individuals who absolutely, by definition, have been Game Changers and are helping moving the ball down the field, challenging the status quo. Ronald Reagan reminded us ... Well, he didn't remind us, but he told us that the term status quo is Latin for the mess we're in. So to make changes and challenge the accepted dogma allows us to make progress. So I appreciate the fact that you do that and everything that you do because it's really ... Is it disruptive? Yes, and that's a really, really good thing.

Dave: If you like today's episode, well, I already told you what to do. Go ahead and read something good. You know the good stuff to read. Thanks for listening.