



Transcript – Keying in on Ketones with Dominic D’Agostino - #325



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Speaker 1: Bulletproof Radio, a state of high performance.

Dave: Hey, it's Dave Asprey with Bulletproof Radio. Today's cool fact of the day is that most people talk about measuring ketones, these fat burning molecules in the urine. You pee on these little test strips. Did you know that ketones can be detected just by smell? The simplest ketone is called acetone. That's actually nail polish remover, and it leaves through the lungs and can give you a sweet, fruity smelling breath. If you stay in ketosis for long enough, the primary ketone will not show the same intensity in your urine, but you can definitely measure it with your breath. In fact, I have a ketone breath meter somewhere in my stack of toys, and I imagine today's guest probably has more of them than I do.

Before we get on to today's guest, if you haven't heard about Fresh Books yet, listen up. These folks are on a serious mission to help small business owners save time and avoid a lot of the stress that comes with running a business. As a small business owner myself, I pay a lot of attention to not wasting my time and not wasting my staff's time, and one of the things that makes a big difference is pain free invoicing for freelancers and small business owners. Using Fresh Books, you can take about thirty seconds to create and send an invoice, and you get paid online because Fresh Books gives your clients tons of ways. They can just pay you with credit cards or other ways, which can seriously improve how quickly you get paid. In fact, customers get paid five days faster on average. You also get an instant notification to tell you whether your client's looked at the invoice the second they view it, so you don't have anymore excuses from people saying they never received an invoice that you know they got.

Fresh Book also lets you keep track of your expenses. It's ridiculously simple. No more boxes full of receipts. For me, that's some of my personal kryptonite. Expense reporting drives me nuts. Making it simple with Fresh Books is really cool. The Fresh Books mobile app lets you take photos of your receipts, and Fresh Books organizes them for you later. It can create expense reports for you, and it also makes claiming expenses at tax time a breeze. Fresh Books is offering thirty days of unrestricted use to all Bulletproof listeners totally free right now, and you don't need a credit card to sign up. To claim your thirty day free trial, go to freshbooks.com/bulletproof and enter Bulletproof Radio in the "how you heard about us" section.

I'm a little bit of a coffee snob. I love trying new coffee, but I learned a few years ago that I don't like how I feel when I try new coffee because there are extensive problems in coffee with mold toxins and other things that just simply aren't Bulletproof. I enjoy the taste, but I don't like the after effects. That's why I developed the original Bulletproof process to create Bulletproof, and we developed a medium roast profile that has a ton of flavor. I wanted a little bit more variety in my coffee, so we've been working for the last year with one of the top coffee tasters on earth, Paul Songer who trains the judges for the Cup of Excellence, which is like the world championship of coffee. I am so pleased to announce two new roasts of Bulletproof processed coffee beans. These are mold free, independently lab tested coffees, and they're made at our Bulletproof plantations. We just changed how we roast them.



The first new roast is called the Mentalist. It's available in whole bean and ground. It's a medium to dark roast, kind of right in the middle there. It's got dark cocoa and vanilla aromatics that open up to a rich, full-bodied coffee with some cherry sweetness and notes of almond and caramel in there as well. It's profoundly good. I've been putting it in my espresso machine, and man, it's crazy. You take it, and it's engineered to taste amazing with butter and brain octane oil. A lot of coffee tastes bitter and weird when you put butter in it. Not this stuff because we built it that way.

The next one is for you. If you really like your dark flavored, dark roast coffee, it's called French Kick. It's a dark roast, but it's not charcoal. It's smooth and sweet. It's pleasantly almost a little bit smokey, and it's got baking chocolate notes, but it finishes really clean and has a medium body. This is one of the few dark roasts coffees I like. I am not a fan of those burned things that you might find at the corner coffee shop. This isn't one of those, but we pushed it as close to dark as we could get and still maintain that flavor for you. You will be amazed at how you feel when you have this coffee, just like you are with our existing coffee. Now you've got a whole palette of coffees you can play with depending on if you like espresso, French press, immersion, or just drip brewing. However you like your coffee, you can do it, and you're going to just be amazed at the flavors. I'm excited to share these with you.

Today's guest is someone who's been on this show before. In fact, several years ago, he was somewhere around episode eighty guest, and it's none other than Dr. Dominic D'Agostino. He's an associate professor at Morsani College of Medicine at the University of South Florida, travelling senior research scholar at the Florida Institute for Human and Machine Cognition, a neuropharmacologist, and he's probably best known as one of the top ketogenic diet researchers out there, specifically looking at neurological diseases, cancer, and other chronic illnesses. Certainly one of the bio-hackers I respect the most. Dominic, welcome to the show.

Dominic: Thanks for having me Dave.

Dave: I wanted to have you back on the show because it's been too long and because we had such a fun time on the first show. We'll put a link in the show notes, so people can go back and hear the first interview, which was, I think, one of the very early ones you were giving about ketosis in the overall public sphere as far as I know. I learned a lot on that one, realized we had some similar recipe ideas around chocolate and huge amounts of fats and how it could make you feel amazing. Before we jump into the main reason, which is I had Dr. Veech on the show recently. Dr. Veech is a major researcher in ketones as well, and he had some really interesting comments on things I had not heard anything about in the ketone community. We're going to get into that stuff.

For people listening who aren't super ketogenic already, let's talk about just ketogenic diets in general, do a little bit of a primer, catch up from one of the top researchers in the field here. If you're a longtime listener, you probably already know what ketosis is, but we are now getting two, sometimes a little bit more than two, million downloads a month on Bulletproof Radio. There are lots of new listeners who are just getting into this, so we're going to go a little bit basic on ketosis. Then we're going to go deep on what kind of supplements should you be using, what

kind of diet should you be using, and we'll just have lots of fun because we always do. All right, what are the top benefits of a ketogenic diet that you've come across in your research? You know stuff about this that most people don't. What is it, just the two cents version, and then, what's it doing for people that you're seeing in the labs?

Dominic: The history of the ketogenic diet is really interesting. We wrote a three part article, actually, with Travis Christofferson. I think he'd be good to have on your show. It's on Rob Wolfe's podcast. It's "The History of the Ketogenic Diet" part one, two, and three if your listeners want to check that out. I got interested in the ketogenic diet because it mimics the metabolic physiology of fasting. We knew for centuries if not millennia that fasting is very effective for controlling seizures when drugs fail. Millennia, a thousand years ago, they didn't have drugs. The diet was designed to mimic the physiological effects of fasting and prevent seizures. That was the original application was specifically for seizures that result from oxygen toxicity that are experienced by the Navy SEALs using a closed circuit rebreather.

That work has expanded to a broad range of other seizure disorders, including things like glucose transporter type I deficiency syndrome, Angelman syndrome. We have other models of seizures we're looking at. Neurodegenerative diseases, including Alzheimer's disease, traumatic brain injury, wound healing. Cancer is a big area of research in our lab. We have three people just working on cancer right now. Then performance in extreme environments, so that could be resilience against hypoxia, resilience against extreme increase in oxygen or pressure. These are the things that we're looking at. We've broadened out into many different applications. My original application was very esoteric.

Oxygen toxicity seizures are experienced in a pretty small subset of the environment. The limits are pushed with hyperbaric oxygen therapy. Oxygen toxicity is a limitation of hyperbaric oxygen therapy and will limit the therapeutic efficacy of oxygen therapy, hyperbaric. That's used for things like carbon monoxide poisoning. You can really only go to about three atmospheres, two point five to three atmospheres of hyperbaric oxygen if you have carbon monoxide poisoning. If you could go to five or six, if you were to put someone in ketosis, we have evidence that you could go to five and be okay and probably push the limits of safety. Then you could push the carbon monoxide molecule off the hemoglobin molecule with enough oxygen. That's sort of the area that we're going into to make diving for special ops safer and to decrease the side effects associated with the high pressure oxygen over time.

Then from the work that we did on that project, we observed all these other benefits. That expanded into a number of other projects that we assign PhD students to or post-docs to, and they are just running with it. We're doing a lot of pharmacokinetic studies, a lot of safety studies on the racemic salts, and also, we're comparing the R versus racemic and various formulations. We probably got twenty different formulations that we're looking at. The most important thing, for me, is to establish that they are, not only efficacious, but also safe. I think safety is the number one priority. I've served on a lot of different panels to assess the safety of other types of ketone esters and salts, so I'm very familiar with the whole body of literature, very familiar with Dr. Veech. He's one of the first people that I reached out to. Actually, one of the first ketone esters that we tested, but it wasn't effective against oxygen toxicity seizures because you also have to elevate acetoacetate in a certain ratio. Then that got me to look into my own methods

of development and looking at different esters from there.

Dave: If you're listening to this and going, "What the heck? Racemic mixtures, hyperbaric stuff," we're getting pretty deep on this. The reason this is so profound is that ... In fact, I'm working on a new book about mitochondrial functions. I'll have to ask you a few questions off air about some nuances of ATP formation. What's happening is we have something called the Krebs cycle inside our cells, and this is how your cell makes ATP and how it turns food into electrons. You use those electrons to, basically, run your brain, run your cells, run your pumping systems, basically everything in your body. It's an incredibly complex thing, and it was only hypothesized, theorized in 1937. In the last eighty or so years, we've come to understand what is, really, a little semi-conductor inside our cells that has amazing properties. That it's affected by light. It's affected by temperature. It's affected by all sorts of environmental things.

We thought for years it only burned glucose except if you were really, really sick. It turns out that when it goes into its fat burning mode, ketosis, that, essentially, things that shouldn't be possible become possible. I think you and I, Dominic, are not the first people to figure this out. Probably the first people to figure this out were thousands of years ago when they were fasting in caves because after four days of fasting your brain wakes up. You're like, "Wow, I feel amazing even though I've had no food. What's going on?" What's going on there is what happens when your mitochondria have more power because they're using ketones or at least have different power. What you've done is you've opened this giant maze because you start out by looking at oxygen toxicity in special forces divers, such a niche thing, and all of a sudden, you're like, "Wait. Alzheimer's, ALS, Parkinson's, heart disease, diabetes." Is there any chronic disease that you don't think ketosis would help?

Dominic: Yeah. That's a good question. From a neurological perspective, all neurological diseases are linked pathophysiologically to energy dysregulation.

Dave: Yeah.

Dominic: Alzheimer's disease, the gold standard for assessing someone with Alzheimer's dementia is the PET scan. A dim PET scan shows impaired glucose metabolism, and ketones can fill that gap and help you restore brain energy metabolism. You generate more energy per oxygen molecule with ketones than you do with glucose. For example, the energetic efficiency of the mitochondria is increased, so the electron flow through the mitochondria to generate the hydrogen ion gradient that spins the ATP synthase is greater. You have less reactive oxygen species produced when you generate ATP from ketones than you do with glucose. Dr. Veech probably went into how oxidizes chio and then you have less superoxide anion production.

That actually attracted me because oxygen toxicity, the theories were that it was generating reactive oxygen species. Then that was contributing to the seizures, but it's really the source of reactive oxygen species is the mitochondria. If you enhance the bio-energetics of the cells by enhancing mitochondrial ATP production, then you don't make as much superoxide. Instead of throwing antioxidants onto the brain and trying to prevent oxygen free radicals during it, why don't we just enhance mitochondrial function? Then we could preserve the bio-energetic state of the cell in the face of the oxidated stress, which it would be the high oxygen content. That's

why it works. You can say that with a number of epilepsies, so the ideology of epilepsy is largely unknown for many cases. Nutritional ketosis and fasting work independent of the ideology across all different seizure types by enhancing the bio-energetic function of the brain cells. I think we're just beginning to understand how that's working, and it's not one pathway like drugs to heart, one pathway. It's many different pathways synergistically working together in synchrony to enhance and preserve brain homeostasis. That's really important to understand.

That's metabolic physiology, and it's important to distinguish metabolic biochemistry from metabolic physiology because a biochemist, which Dr. Veech is a biochemist, and he's very knowledgeable, and he also has knowledge about physiology. When you view it from a systems level, that's truly important to understand even the neural control of autonomic regulation, so how it's impacting our central nervous system, which are things we're looking at. We're studying the effects of ketones on anxiety. Just simply reducing anxiety, we find it's like a whole other variable. We see a thirty percent reduction in anxiety. We just presented this work in Budapest last week. The reduction in anxiety may be contributing to the delay in seizures that we're seeing, so we need to weed all this out. There's many factors.

Dave: I've been giving some talks. I gave a talk at Jim Quick's SuperheroYou, like a brain hacking summit, this weekend, and I'm talking about the bio-energetic effects of anxiety. It burns energy to focus on stuff that like a brain paying attention uses more electrons than a brain doing nothing or a brain at peace. If you're burning more energy because you're worrying because you have bad programming and you're hungry, of course hunger makes anxiety worse. If you have hunger, which is a problem with energy regulation, there's not enough energy and that's why I have a hunger signal, of course anxiety is going to be worse. What do you do? Eat enough so that you're not hungry when you're done eating would be a good way to start, add more fat, and get some ketones in there and magically, people, they feel less anxiety. You actually quantified it, which is awesome.

Dominic: Yeah. When you achieve a flow state, your brain energy metabolism goes down or that the cross talk in your brain is shut off. When you achieve a flow state, you dynamically activate the areas of the brain that you need for the specific task while tuning out the others, and that's important to understand. I think that being in a state of ketosis may help with that, and some drugs help with that too. Nutritional ketosis is very effective we think.

Dave: It's one of those things where if you look at mitochondria as being really important, ketosis because it affects so many different parts of the mitochondria is probably the biggest hack you can do to have better functioning mitochondria. Are you familiar with Dr. Shallenberger work on ozone therapy?

Dominic: No. I get that question a lot though because a lot of people ask about ozone therapy from cancer and for other things.

Dave: The similarity it has with ketosis is that it changes the NAD plus to NADH ratio by adding electrons directly from ozone, like there's a free electron in ozone. You end up having a mitochondrial effect that is not dissimilar to the stuff that you're doing, but the reason I'm asking is he has found that about half of people, forty-six percent of people have early onset

mitochondrial dysfunction before age forty as measured with breathing oxygens. Essentially, looking at oxygen consumption rates. Okay, that's one in two of us has broken mitochondria and don't know it. With the work you're doing around mitochondrial uses of ketones, just like you said before, you're reducing free radicals here. You can actually fix that.

I'm spending a lot of my energy working on, how do we take people who don't know that their mitochondria are jacked and then getting them jacked in a muscle building jacked kind of way? My goal is if you were to take one of my cells out and look at it under a really fat microscope, you'd see incredibly ripped and muscular mitochondria just completely covering the thing. I don't want to be a body builder on the surface. I want to be a cellular body builder. I'm focusing on, what are the things I could do to grow better and stronger mitochondria? Given all of your ketone research, what are ketones going to do for someone listening to this who wants to have better functioning cellular energetics, like better mitochondria?

Dominic: That's a good question because they work through multiple mechanisms to enhance mitochondrial efficiency and also, ultimately, from a more long-term perspective, mitochondrial biogenesis.

Dave: Yeah.

Dominic: ATP production is limited, and if we do isolated mitochondria, there's a state one, state two, state three. You can characterize how the ATP is being limited, and one of the states is reduced TCA cycle intermediates. You could have reduced energy flow to the mitochondria to produce ATP. Now ketones, being in a state of nutritional ketosis is anaplerotic. It helps generate the Krebs cycle or the TCA cycle intermediates, so it sucks in alpha-ketoglutarate. All these are elevated by twofold. They're even up to threefold higher in the brain and in the serum. When you're in a state of nutritional ketosis

Dave: Let's pause for a second for people that are listening. The TCA cycle is the same as the Krebs cycle. This is how we make ATP in our cells. Okay.

Dominic: The Krebs cycle should really be called the Kremp Georgia cycle because there's a guy in Hungary who also probably did most of the work on the cycle. It's kind of interesting history there. Generating Krebs cycle intermediates is one way, so increasing the bio-energetic molecules that create energy is one way. Increasing oxygen flow to the mitochondria, the ketones enhance. One thing we're looking at in our wound model is vasodilation. Ketones seem to couple. They help couple the energetic state of the cell with oxygen and substrate flow. It seems to enhance the vasodilate areas that need it most, which would be in ischemic wound. In our aged model of ischemia where the wounds do not regenerate efficiently, we can do a Doppler blood flow measurement and show a thirty percent increase in blood flow to the wound tissue, which has a ninety percent deficiency in ATP production because it's not getting enough. Then that was shown years ago, showing a thirty percent increase in brain blood flow or oxygen brain blood flow with ketosis.

Dave: Now, what about burn victims and people with injuries outside the brain? Is that still going to be really effective?

Dominic: Yeah, we think so. Of all the things that we've tested so far and the model of wound healing, the ketones are one of the most effective things that we've seen. What's interesting with all wound healing therapies are tried topically where you put the substance on the wound. Where what we're doing is inducing acute and sustained nutritional ketosis with a supplement by altering metabolic physiology from a systems level, just by lowering blood glucose. We know that if we give an acute bolus of exogenous ketones, blood glucose goes down. If you bring blood glucose down by virtue of decreasing, making your blood less sludgy, you'll increase perfusion of the tissue. It lowers blood glucose. It elevates ketone levels. It also elevates adenosine levels, which is a potent vasodilator. It helps to perfuse the tissue.

Just getting back to the mitochondria, it's anaplerotic, so you get more TCA cycle intermediates. You get more oxygen and substrate to the mitochondria. It enhances the bio-energetic capacity, the electron flow through the mitochondria. It helps, obviously, to generate the reduced intermediates that drive the electron transport chain through the anaplerotic reactions. Then there's less reactive oxygen species production. At the semi ubiquinone site of the mitochondria, there's less superoxide. Making superoxide at the level of the mitochondria could be damaging because that superoxide, if it goes to hydrogen peroxide in the presence of copper or ferric iron, you can generate reactive oxygen species through the fenton reaction. That can directly damage the mitochondrial membrane and decrease mitochondrial efficiency. You get electron leak. Then you just make less ATP. That's four things right there. There's probably about ten things in my head that I could talk about. TCA cycle intermediates, electron flow, more oxygen, less production.

There's a lot of ways. Even taking a step back, the role it has on glucose homeostasis and all the other signaling pathways that could be activated. That gets into a whole bunch of secondary reactions or signaling pathways that I could talk about. Importantly too, from ... I described to you acute things that can enhance energy, mitochondrial production. Then we know that ketones are more than just an energy metabolite. They function as a histaminase inhibitor class one and two. There was a science paper-

Dave: Talk about the impact of that. Just people listening don't know what that is.

Dominic: Okay. If we're in a state of ketosis and we have beta-hydroxybutyrate elevated in our blood stream, that's impacting gene expression in a way that's altering our physiology over time. It's decreasing oxidated stress. It's conferring protection against aging and oxidated stress over time by increasing activity of things like superoxide dismutase, by activating a whole genetic program that parallels our calorie restriction. We know all the benefits of calorie restriction have been really talked about in the literature. It's easy to find that literature on PubMed. One of our colleagues, actually, and collaborators from Yale, Deep Dixit, contacted me and did a lot of work with calorie restriction and fasting. He said, "We think beta-hydroxybutyrate may be like the metabolite that's actually conferring all these benefits to fasting."

Dave: Wow.

Dominic: Contacted me, and we formulated a diet. We basically took the standard diet and formulated a

diet with our ketone ester. We collaborated with him, and he ran a study. He found that elevating beta-hydroxybutyrate suppresses the NLRP3 inflammasome. That inflammasome is linked to a whole host. It's like the hub inflammasome that kicks on the inflammatory cytokines that are associated with many age related chronic diseases. It was published in Nature Medicine. It's like the gold standard of scientific publications.

Dave: It's kind of interesting. Bulletproof intermittent fasting where you have Bulletproof coffee made with brain octane in the morning at the end of the fast to help you sleep. Brain octane raises BHB more than MCT oil and more than coconut oil. I've been doing that every morning for more than seven years now, and it's completely changed my life. I believe it's a mitochondrial energetics thing.

I also think that one of the reasons caloric restriction works, and by the way, I have no scientific basis for this other than I'm a systems guy and I'm a bio-hacker. Mitochondria, when they're burning sugar, when they're burning anything, they do produce free radicals, so if you eat less food, you make less energy, you have less free radicals, you get less damage. Therefore, that could confer some of the benefits, but they come at substantial cost as well. You're cold and tired and having less energy sucks. I like to be exploding with energy, but I don't want to die when I'm fifty. How do you manage to have more energy without incurring the damage from the energy? That's my quest right now, and I think ketosis is at the core of it.

Dominic: Yeah. Your brain octane has been something that has been a staple in what I do. The C8 is a pretty potent ... The more we're studying these synthetic, expensive ketones and ketone esters and ketone salts, but the more that we look at what's in brain octane C8, the more impressed I get. It's a little bit biased because in rats, they have such fast, hepatic metabolism that you get blood ketones levels ... You get the same effect as a ketone ester as you do with C8, so you can easily get-

Dave: In rats, but not in people, right?

Dominic: Rats. Yeah. The C8's interesting because it goes directly to ... It actually profuses the liver with the oil when you drink it instead of going through ... Instead of it being packaged into chylomicrons and going through the lymphatics. You get obligate oxidation of the fatty acids exclusively in the liver, and not much C8 actually escapes the liver if you keep the dosages even in the moderate to high range. It almost completely gets oxidized in a healthy liver to beta-hydroxybutyrate. The MCTs and C8 especially, they're not esterified. It's poorly esterified. It doesn't get transported by CPT1, the carrier, and it can be independently go right into the mitochondria. It doesn't need a lot of carriers.

We also found another benefit of MCTs that I didn't know until I did the metabolomics is that they readily cross the blood brain barrier. Not only do ninety percent of it gets generated, eighty to ninety seem to be generated into beta-hydroxybutyrate. Then what does get into circulation can readily cross the blood brain barrier. I thought fatty acids didn't, but short chain and medium chain do. We only took tissue when we took the hippocampus out and did metabolomics on it. We found pretty high levels of C8 and C10. We did MCT and C8. Yeah, so the MCTs are very versatile, ketogenic compounds that can be ... They taste good. You can

formulate so many great carriers.

Dave: Some of them though. This is something that I've helped to push the MCT thing out there. There are companies selling some that contain C6, which is a really strong gastric irritant, so you end up, frankly, shitting out the rest of your MCTs when you have that. Then C12, which is good for you. It's doesn't go to BHB. It acts like a long chain fat, but it's legal to call it an MCT. You're seeing coconut oil companies pretend that there's a sixty percent MCT when it's really fifteen percent of the MCTs that actually work. I'm seeing a lot of slimy marketing activity. I'm sure you are too. MCTs, at least the ones that work, they're just like step one of ways you can increase ketones. You've got like two other ways of increasing ketones that I wanted to pick your brain about here because I synthesized my own esters three years ago. It was thirty thousand dollars a kilo. I'm like, "I can't even afford to take these myself, but I took like two samples and it worked." Then there's salts too.

Dominic: What ester was it that you synthesized? Do you remember?

Dave: I would have to look in my notes, but I worked with a third party lab. It came in a little vial, and it was insured when we shipped it because it was so darn expensive. Gees, I'd actually probably have to open up an old email to find it.

Dominic: Actually, yeah, the first time, this goes back to 2009, that we acquired different ketone esters and to test which ones were going to be effective against oxygen toxicity. My original proposal to the Office of Navy Research was to feed it for one week because I was convinced that you needed to keto-adapt the animal or at least get levels ... The tissue saturated, the brain. I only had enough to really give one dose, and I did it thirty minutes prior to a super deep oxygen dive. I was like, "I don't have enough to really run the study that I want to do, but I have enough to give one dose prior to." We gave one dose prior to the dive, and in every single animal we dove, we saw an astronomical increase in the latency of seizure. We published that, and it was like a five hundred and seventy-five percent increase in the latency of seizure. That pretty much outdoes all anticonvulsants that the military has looked at for this.

We still have not gone back and did a study where we feed it continuously. We're doing some work now, but I was basically figuring if it's this effective just getting one dose in an animal that's eating a high carbohydrate diet prior to the dive, really, that's what the military wants. They don't want to have to feed something for a week. They want to give like one shot, and then hit your mission. We have long-term chronic feeding studies for other disorders, but when it comes to oxygen toxicity, we're really just looking at a single dose prior to the mission. We screened out the different types of exogenous ketones in that project in the beginning and identified the one that was most effective and just been really focusing on that. Getting that synthesized was a project. It was a lot of back and forth with the chemist.

Dave: Yeah. I don't think that problem is solved, but manufacturing that stuff is just complex. People listening like, "Big companies can just make whatever they want." This is one of those game changing supplements that has the possibility to transform a lot of athletic performance and a lot of ... If you want to feel young when you're old, have mitochondria that work. The average seventy year old has half the mitochondrial function of someone who's thirty, and it's one of the

reasons it sucks to be old. Let's get ketones in older people, and magically, they'll get up and dance. It's that big of a difference. I'm very hopeful, and I don't think Bulletproof is big enough to fund the kind of manufacturing research that's required to do this. It is a giant project, but I'm working on it, and I'm supporting everyone I know in every way I can including just by talking about how important this is.

Let's talk about salts before we get into esters. There's a hierarchy of ketones. The first thing you do is you go on a low carb, high specific fat diet. That alone can put you in ketosis. Atkin's, stuff like that. Then the next thing you could do is add brain octane, which is basically the Bulletproof diet, which gets you in ketosis. Especially in the morning, do this Bulletproof intermittent fasting. No carbs in the morning. No protein in the morning. Extra, extra fat in the form of brain octane as much as you can take without filling your pants. You do that. Like, "Okay, something different just happened." I can get my levels up to point eight or one point oh in my blood just from brain octane. Nutritional ketosis starts at about point eight. Then from there though, there's ketone salts.

Talk about what the salts are, the four kinds of salts, what are the pros, what are the cons, and if you could, address what Dr. Veech in his interview was like, "Some of these based on whether they're bio-identical isomers," this is called basically mirror image molecules of each other, whether that's an issue or not. Walk me through the salt story.

Dominic: Yeah, it's important to address the ascemic issue because it can create a lot of confusion. I'd like to address danger. Are they dangerous, and are they efficacious? I think that's what I'll address upfront. When we approach this question, it's important to distinguish and separate someone's opinion from the scientific fact and what has been published and observed in the literature. I listened to about half of the podcast. I was driving, so I don't remember all the ...

Dave: I get it.

Dominic: I doubt that he referenced any papers when he said ketone salts were dangerous.

Dave: Yeah, he did.

Dominic: I've sat on many boards, and it was actually in talking with him it was a concern that I had because we were testing a number of different compounds. The ones that were most effective for my applications tend to be the ones that were racemic.

Dave: Explain what racemic is for people listening who don't have the chemistry background.

Dominic: Yeah. Probably be good to look up the word "enantiomer," and it's a stereo image of when you think of your hands as the mirror image of it. The molecules in your body ... Most drugs that we consume actually are racemic, so if you go back to general chemistry when you did all the stereo chemistry of the molecules, and you were studying that, if your listeners out there had general chemistry, you probably remember. You probably came across the word racemic. If you pull out your general chem book, you can look up the definition of that. Essentially, there are molecules in your body, amino acids, lactate for example. L-lactate would be the physiological enantiomer,

and D-beta-hydroxybutyrate would be the physiological enantiomer. The opposite enantiomer has a configuration that would mirror it sort of like two hands coming together. Depending on the specific metabolic pathways, the body will reject it or consume it or some may have a weak interaction at the receptor if it's a drug or a stronger interaction with a receptor.

I studied lactate, the effects of lactate like ketones. Lactate is an alternative energy substrate. Before I got into oxygen toxicity, I was looking at hypoxia. Lactate is actually a very effective fuel. When you exercise, your body produces a lot of lactate, and the lactate actually goes to your brain and functions like ketones. It's an alternative energy substrate, and through the Cori cycle, it gets recycled back to glucose. I was interested in using lactate to preserve, protect the brain from hypoxia and ischemia. Alpha L-polylactate is something that I was interested in. As a cyclist, it's in a product called Xytomax, and I was interesting in developing different forms of lactate.

I saw that racemic lactate was being used as Ringer solution. Any heart doctor, any medical doc out in the field, when you're shot, when you lose blood, when you're in the emergency room, they fill you up with Ringer lactate, which is racemic lactate. According to Dr. Veech that would be dangerous. That would kill you, but it saved millions of people's lives. They always use racemic lactate for that.

Dave: For people who didn't take general chemistry, imagine that every molecule in your body likes left-handed things, but sometimes you have right-handed things. It's still a hand, but it's not the same hand. Sometimes it'll fit into the glove-like receptors in the body. That's a gross simplification, but the idea there is that they're almost the same, but they're just mirror images. If we're left to our own devices biologically, we typically make the L form, but the opposite form we can make in the labs. When we use it as a food supplement or as drug, it does all sorts of cool stuff in the body including sometimes kill you. Quite often, it's useful.

Dr. Veech concern when he was on the show was that if you're going to be magically raising ketones, which, frankly, give you superpowers. You get more energy than you had before, like Captain America kind of stuff. You want to make sure that you're not doing something that's going to give you cancer or increase oxidated stress or otherwise shorten your life or mess you up. Dr. Veech had a pretty good concern here, and what you're saying now is kind of the counterpoint that says, "Okay, here's all these times when we use the wrong hand in our bodies, and it completely saves lives, and it completely works," which is a pretty powerful argument I'd say Dom. You got a point there.

Dominic: We don't progress as a species unless we move forward on truth. From my perspective as a scientist, the truth should be in the science. If there's evidence out there that racemic salts are dangerous or that lactate is dangerous, it saved millions of lives in the emergency room and on the field. That using these racemic compounds are dangerous, there's just no evidence. One could ask the question, is one optimal over the other? I know lots of work was done early on on Ringer's lactate, and they compared L versus racemic, and there was no change in metabolic state, on its buffering capacity, and its capacity to save people's lives. I would assume the same thing would apply for ketones, but we're interested in studying that. That's why we're studying that now.

Dave: There are people selling it right now who haven't tested it.

Dominic: Yeah.

Dave: What do you think about that?

Dominic: Yeah. I was a little bit concerned until I went ... At about the same time that marketers started commercializing ketone salts was about the same time that I was on various panels, expert panels to really spend weeks just going through the literature to see if these things could have any potential for danger. I just couldn't find any. I kind of wanted to find something because I thought people, marketers were jumping the gun, but I couldn't find evidence to suggest that they were dangerous or less efficacious. To that argument, you see Ringer's lactate has been used for decades.

The DL, the racemic beta-hydroxybutyrate has been used for decades to treat a disorder called MADD. MADD stands for multiple acyl coa dehydrogenase deficiency, MADD. The kids with this, the ketogenic diet doesn't work for them, but exogenous ketones do. They're given very high doses of pure sodium beta-hydroxybutyrate to stay alive. This has been published. There's lots of publications on it. There's a publication in the Lancet, which has an impact factor of forty-five showing the safety and efficacy of sodium racemic beta-hydroxybutyrate given in massive quantities to kids over years to manage their disorder. That's just one example.

I was going through a list of emails this morning with parents that have kids that have glucose transporter type one deficiency syndrome. For reasons, a lot of these kids tend to be picky with their diet, and they found these ketone salts on the market. They ordered them, and I've gotten emails from parents that said when their child drank these ketone salts they literally just woke up. It's like they came out of a coma, and they're energetic. They're lucid. They're active for hours until it starts to wear off, and the ketones come back down, and then they dose them up again. You have like four companies out there making them, and they're all ... They have sodium beta-hydroxybutyrate in it, but there's also potassium and calcium and magnesium.

I know Dr. Veech talked about the sodium being an issue, but sodium has not been an issue for all the applications that it's been used for. The products on the market, they spread the beta-hydroxybutyrate across a number of different monovalent and divalent cations. That's really important, and that's really what I want to do is formulate something that has at least a dozen or more different carriers of beta-hydroxybutyrate. You can use a list of amino acids, calcium, sodium, potassium, magnesium. I have magnesium beta-hydroxybutyrate right here I was just testing. [crosstalk 00:45:59] I just took pure magnesium beta-hydroxybutyrate and can get up to about a half of a millimolar by itself with no GI issues with this particular magnesium product. You can envision getting about six different either amino acids or monovalent, divalent cations and formulating something that tastes good. That's really important too because some of them don't taste good. They need to be buffered.

When we talk about ketone salts, a lot of people just think sodium. I have a sodium free ketone salt that I've been testing that has no sodium in it, and it tastes really good and gets me up in

the two millimolar range. The sodium is not really an issue. I personally don't have an issue with sodium. When you're on a ketogenic diet, your insulin tends to be a little bit low, so you excrete a little more sodium. If your RDA is like twenty-five hundred milligrams per day, you should probably be taking more like thirty-five hundred or four thousand. That would allow for a pretty significant amount of sodium beta-hydroxybutyrate to get your ketone levels up without any problems at all.

Dave: I actually target four to six grams of sodium in my diet per day, and there's abundant evidence that that is safe. In fact, lowering it to the current limits that the FDA recommends actually increases heart attack risk in studies. Sodium, if you're a salt sensitive hypertensive, basically you have high blood pressure from salt, two percent of people are like that, restrict sodium. For the rest of you, if you're stressed, you need more salt. Go for it. It's fine. If you take the salt with ketones, okay. That's totally cool.

Dominic: It's funny. That's about what I get per day too. I get my sodium load. For awhile when I was testing just the sodium, I was getting about ten grams per day, and I didn't have a problem with that.

Dave: I've done ten a day, and it helped me recover. I don't need that much now, but absolutely. It's just fine.

Dominic: Especially if you're out ... We live in Florida, so it's like if you're sweating, if you're outside working out, I think ten grams a day may actually be optimal. If your energy levels are low, just take in some sodium with ketones, and it'll wake you up and energize you.

Dave: When I was in South America, I was doing some high altitude mountaineering at Mount Cotopaxi in Ecuador. I was literally adding a teaspoon or two of sea salt to my water bottle and so amino acids. All my other climbers were like, "What the hell are you doing?" I'm like, "I'm feeling good is what I'm doing." You need the sodium. It's one of those things where if you're doing too much salt your body will tell you very abundantly.

Dominic: Yep.

Dave: We just pissed off half the physicians in the country. Sorry guys. Read your science.

Dominic: When people talk about the dangers of a high sodium diet, we're administering the sodium in processed food with refined carbohydrates, which spike your insulin. The insulin makes you retain the sodium, so that sodium retention, it's really not about sodium intake. It's about sodium retention, and insulin causes you to massively retain sodium. Just look at someone who's done a pre-contest physique dieting for a body building show or something. They go from calorie restriction or low carb to high carb, and just going high carb, that insulin spike with sodium, they blow up so fast. It's the insulin really that's causing the sodium retention. Your insulin levels are suppressed on the Bulletproof diet, on the ketogenic diet, low carb. If your ketones are elevated, a part of ketogenesis is driven by suppression of the hormone insulin. You are excreting more sodium just by virtue of keeping your insulin low, driving beta oxidation in the liver. That whole process is just excreting more sodium, so it makes sense to get more into

your diet. That's good because I like the taste of salty food.

Dave: I actually travel with a little vial of salt. Some restaurants don't put salt out. I'm like, "What's wrong with you?" I just put it on myself. I have a question for you about mitochondrial physiology here. I'm writing my next book. It's like how do you hack your mitochondria, and I'm really into it. One of the things that really matters is the size of the mitochondria because if you basically move molecules apart a little bit, it takes a lot longer, there's a percentage, for these little electrons to move. One of the concerns about using ketone salts is that if you're using the racemic form that it's going to reduce mitochondrial NAD, which causes oxidation of [kyoo 00:50:29], which basically increases the redox span between these two parts of the electron transport system.

If you're listening to that and you're going, "What the hell did Dave just say," what I'm saying is if you imagine that you have to take this little packet, an electron, you have to move it from step one to step two to step three. If you move the steps further apart, it's going to take a lot longer. If you have to do it a hundred thousand times, all of a sudden, that increase in distance becomes really meaningful. Are you concerned about that?

Dominic: No because I understand the metabolic biochemistry of it. What our lab does is this top down approach where we feed the ketogenic diet or we feed ketone supplementation, and then we go back and look at the brain tissue, the skeletal muscle, and we do metabolomics. What we see is all the evidence points to enhanced, more robust mitochondrial function. We can look at using electron microscopy. We can count the number of mitochondria, and now we can also look at the morphological structure of the mitochondria. I just got back from Budapest, and I was talking with an MD PhD over there that has hundreds of brain tumors. He said even in low magnification when you look at a tumor, the mitochondria, the inner mitochondrial membrane is all mucked up. Even in low magnification, you can see total crystallosis.

You can see malformed mitochondria. Some of them are enlarged. Some of them are small. Some of them are split in two. A lot of times, you see them forming little circular structures, which means they're stressed. Then in healthy tissue, we just see a very dynamic dispersal of mitochondria and also the ability to mitochondria for them to migrate, for example, in brain tissue to the synapses where there's robust bio-energetic processes happening. A lot of electrochemical radiance being shifted from firing action potentials and things like that. The mitochondria are sort of transported through the cell in different ways. In healthy cells, what you see is they all have the same uniform circular, football kind of shaped structures. Then in diseased tissue or diseased model, you just see a range of different mitochondrial sizes and shapes and morphology. With the ketogenic diet or animals or humans are fat adapted. You do see more mitochondria, and people have reported this. We have a lot of tissues to look at.

The architecture of the mitochondria are more consistent with healthy mitochondria. They have a more intact cristae and that's really where all the action is happening, the inner mitochondrial membrane right at the level of the cristae. That's really the indication of the bio-energetic capacity of the mitochondria, the health of the inner mitochondrial membrane. That's held together by different substances and probably most important being cardiolipin. In cancer, you find a shift towards more immature cardiolipin, so the inner mitochondrial membrane doesn't

stay together. With the ketogenic diet and with healthy mitochondria, you see a shift towards more mature cardiolipin that holds the ... Plays a big role in mitochondrial health and mitochondrial efficiency by preserving the integrity of the inner mitochondrial membrane. That's really a function of ketones, the ketogenic diet, a healthy compliment of essential fatty acids, phosphatidylpoline, phosphatidylserine things like that that can enhance healthy mitochondria over time.

Dave: It's such a complex topic, and that's why I decided that my next book needed to be about mitochondria. I've been following the work of guys like Nick Lane, and I just realized everything I've ever done that really made a huge difference including back in the day I used to shine an infrared LED, one of the first LEDs you could get, on my head where there's the most mitochondria. Light affects mitochondria dramatically, so I've been doing a lot of light based interventions for mitochondria for more than ten years. I see what happens when I mix ketones, which is our topic, with other things like cryotherapy that actually makes mitochondria work better because they get a little smaller when they're colder, so electrons move faster with ketones. You stack ketones on almost anything that makes you perform better, and you're like, "Oh, something magic happens." I'm excited to explain this in a way that is less sciency, but it's pushing my limits of being able to simplify because it is such a complex topic.

Dominic: These books won't make you simplify, but these are excellent books that ...

Dave: Hold those still. I'll read them. "Mitochondria" is one of them. Who wrote that one?

Dominic: Yeah. There's a number of authors, so there's editors basically. There's probably to dozen authors to get into the level of detail that you need to. In here, you have a whole bunch of authors.

Dave: Okay. Got it. Those are basically medical textbook level things.

Dominic: Scheffler is the author of this book.

Dave: I may have that one. I don't have the "Mitochondria and Cancer" book. We'll put the names of these ... There's probably twenty percent of people listening to this right now are in the medical or healing field. It's amazing the number of emails I get from people who are like, "I'm at this big hospital, and I'm doing this kind of research." They listen because we're willing to go deep enough, and there's tons of people who aren't in medicine at all who are just like, "Is it really true that you can do this?" Of all the guys I ever talk to, you're one of the top ketone experts out there. Ketones are a superstar when it comes to performing at a new level. I wouldn't be sitting here today without ketones for really more than a decade because my brain was such junk without them to be perfectly honest.

Dominic: Yeah. I don't think I could do ... I just flew in over night last night, and I've been awake for ... I'm not even counting the hours now. I don't really think I could function in the capacity that I do with the productivity that I have been doing to get tenure recently at my university-

Dave: Congratulations by the way.

Dominic: Thank you. It took a lot of over nights, working on grants and publications and things like that. I don't think I could do it if I didn't follow a nutritional program that allowed me to have the resilience and just stay up night after night and work on things. I'm in a pharmacology department, so I'm really supposed to be working on drug research. When the drugs didn't work for the type of seizures I was looking at, and I found out that the ketogenic diet through the Charlie Foundation was being used at John's Hopkins for hundreds and thousands of kids and that it worked about sixty to seventy percent of the time even when drugs failed, I realized it was something I had to look into.

Then when I realized that you can actually create exogenous ketones to mimic that, then I got really interested because that's like the combination of nutrition and pharmacology to get ... It was accepted. Doing high fat diet research for neurological diseases in a pharmacology department is a little strange, but if you're developing a dozen or more different types of synthetic agents that can mimic that neuro protective state of nutritional ketosis, that's something you can build a career off of. I realize I'm very fortunate that I just stumbled across Dr. Veech and Henri Brunengraber who's at Case Western. He helped me out a lot. Sami Hashim, Theodore, he's like ninety-six or ninety-five now, ketogenic diet guy. These are like the pioneers in the field, and these are super smart guys who really understood metabolic physiology. Dr. Cahill, George Cahill at Harvard Medical School did the experiments fasting subjects for forty days, and he passed away a few years ago. When I was in my post-doc, I was calling him up all the time. I was calling all these guys up. I was probably really annoying to them.

Dave: They probably loved it. I don't think you're annoying at all. You know what it's like when someone who really cares about something calls up. I get calls like that sometimes, and you're like, "Of course you want to talk about it because it's your life's work."

Dominic: Yeah. They had great stories to tell, a lot of stories. They were inspired that a younger guy was picking this research up, and they inspired me just because of their background that this was something real that I needed to get into more and study for the applications I was looking at.

Dave: From a personal perspective, about three months ago I got food poisoning, and I threw up so hard I passed out, and I smacked my head on the tile and got a concussion. I actually seized for a few seconds. It helps to be married to an emergency room doctor, but I can tell you with absolute certainty that I used every possible way of raising ketosis that I had on hand, which was basically brain octane oil. I absolutely did that, and I took a bunch of mitochondrial energizers. I manufacture a bunch of them, and I pretty much have all of them on hand because I'm always hacking my mitochondria. I use red lights and other things like that, infrared and recovered very quickly, didn't get any long-term damage. Even with that, for about a week I was kind of a zombie. My working memory was shot. I couldn't remember words. I swore a lot. All kinds of weird stuff.

I think if I hadn't had ketones present in my body during that time, I would probably still be swearing. I would not have recovered at the rate that I did. I did neuro feedback and a bunch of other stuff. I came back actually remarkably quickly. Thanks for pointing out the things you point out in your work. Because of that, I knew what to do. That's not the sort of thing you Google for.

I also have hyperbaric oxygen downstairs. We talked about that earlier. I'm lucky to have a human hacking lab. I look forward to the day when that knowledge is just common sense, and when a kid takes a hit on a football field, which happens tens of thousands of times a year, that we actually put them on ketones, and we put them in hyperbaric, and we do all those things because that will actually change enormous numbers of lives. Just huge lives.

Dominic: Yeah. I get emails from parents, and their kid, they're high school or even PV football, they've gotten a concussion. They ask, "What's the best way to get my kid into nutritional ketosis?"

Dave: Keep answering that.

Dominic: Yeah. I get a lot of questions. People ask, "Are ketones" ... It sounds like they're a panacea for everything. Soon we'll be saying they can cure the common cold, and when I think about it-

Dave: They do.

Dominic: I see three colds a year, and it's been about seven years since I've been on a ketogenic diet, and I've only had one cold that I can remember. One or two maybe. It was just little sniffles. We get less colds as we age, but I went from getting two or three a year to one or two that I can remember over the last six or seven years. That's really strange for me, and that's through a lot of stress. Usually, stress always triggered it because right around finals time when I was in college, I would always get a cold.

Dave: I'll sound like the first chapter in the mitochondria book. Everything your body does is based on mitochondria other than your red blood cells that don't seem to have them. If you could do anything that just even gives you a ten percent boost in the way they function, it's ten percent more of everything including immune function, including everything in the body. I look at that as the ultimate hack for the body where of course your immune system is going to work better because anytime a cell needs to respond to an invader, it's got more energy. If you have more energy, you're going to do a better job. I think that works at the very micro level and at the very macro level. I've used ketones to build my company, to write my books, to be a better parent, and you could use sugar as well. It just doesn't work as well, and so I don't. I'm not sick like I used to be.

Dominic: Yeah. Ketones are an easy sell for me because I was a patch clamp electro-physiologist in my PhD. That's what I did with electro-physiology, with patch clamping, and I did something called a wholesale perforated patch where you take a glass electrode, and you put it on a neuron. You don't dialyze the cell, but you seal onto it. Then you have nystatin and the pipette, and it pokes little holes in the membrane, and then you gain electrical access. Then you get the action potentials and the membrane potential. It was very clear to me even early on in my doctoral work that we're just like a bunch of batteries, and we have these bio-energetic potentials.

That was completely driven by ATP, ran the pumps that created the membrane potential. When I would deenergize the cell either by cutting off the substrate or cutting off the oxygen, which my background is looking at hypoxia, that's when life ceases to exist. That's when you shut off the energy pathways, and you can't maintain that membrane potential. That membrane

potential really is the definition of life. It drives all the biological processes that we call life. Preserving the ATP levels and the bio-energetic state of the cell with ketones, it just made a lot of sense to me. That's when I first started studying lactate, and then other alternative energy substrates, and I came across ketones. It seemed such a versatile thing. There was ways to do it through fasting with the ketogenic diet. Then I discovered other ways to enhance ketone production. It was really like a super fuel. If you're at the gas station and you have four choices to choose from, it's the super high octane stuff. I wanted to study that.

It was a pretty easy sell for me especially since all these other therapies, all these other disorders will respond to this type of metabolic therapy. It's a very powerful metabolic therapy that has so many different applications. If you look at my CV or what I'm doing, it looks like I'm all over the place, but that's just because nutritional ketosis or therapeutic ketosis can be applied to so many different pathologies.

Dave: It takes you there. If you follow the ketones, you are going to realize that they're responsible for just about everything we do because they have more energy in them than sugar does. More energy means doing more.

Dominic: Fat does too.

Dave: Fair point. Fat, which drives ketones.

Dominic: I always like to preface it by saying, "Being fat and keto adapted."

Dave: There you go. That's a good point. Now we're over a little bit on the length of the show, and I know you've just got off an airplane from Budapest. I appreciate you making time to be on Bulletproof Radio. I've got one more question for you that I'm sure you don't remember your answer for because it was a couple years ago last time you were on the show. If someone came up to you tomorrow and said, "I want to kick ass at everything I do. I want to be better at everything I do. What are the three most important things I should know," what would you tell them?

Dominic: Get enough sleep. The most important thing is just to follow what you're passionate about. I think even if you have ... You probably run into people who follow a crappy diet and don't get any sleep, but if they're really driven from a gut level and very passionate about what they're doing, and if what they're doing is not self-serving and it provides a service for someone else, then they become more intrinsically motivated to work harder and be more successful. I would say, sounds cliché, but follow your heart or just follow really what you're passionate about. If you follow nutritional ketosis and proper sleep and get sunshine or fresh air and exercise on top of that, then you're really going to kick ass.

Dave: Love it.

Dominic: You got to focus on what you're passionate about and just don't have any fears and go for it.

Dave: I knew you were going to say ketones in there, and you didn't.



Dominic: I said diet, yeah.

Dave: There you go.

Dominic: Fortify that passion with nutrition and sleep and everything else. Nutrition and that includes ketones.

Dave: There you go. I love it. Dominic D'Agostino, where can people find out more about your work? Are you going to write a book for all of us at some point or something? What's the deal there?

Dominic: Yeah. I'm thinking about it, but right now, I think what's important for me is to build a big foundation of research that the book will be about. I'm really deep into doing that kind of research. We have a lot of research projects that are going full steam right now, and in the process, I'm writing a lot of manuscripts and reviews and book chapters and things like that. That will ultimately become part of probably a book in the future, so I'm entertaining that thought. Ketonutrition.org is a website that I maintain and basically just put a bunch of links up there. Metabolic optimization is also a website that I started and did a few podcasts and intend to have more people on that show.

Dave: Beautiful.

Dominic: Those two links right there.

Dave: Thank you. I look forward to having you back on Bulletproof Radio maybe in another six or eight months. It's always a pleasure.

Dominic: Thanks for having me Dave.

Dave: Don't miss out. To keep getting great videos like this that help you kick more ass at life, subscribe to the Bulletproof YouTube channel at [Bulletproofexec.com/YouTube](https://bulletproofexec.com/YouTube) and stay Bulletproof.