A Special Interview with Dr. Dominic D'Agostino

By Dr. Joseph Mercola

JM: Dr. Joseph Mercola

DD: Dr. Dominic D'Agostino

Introduction:

JM: Welcome, everyone. This is Dr. Mercola. You all are aware that cancer is a profoundly important problem that challenges most all of us at some point or certainly someone we know. We're really privileged today to speak with Dr. Dominic D'Agostino, who is an assistant professor at the University of South Florida College of Medicine.

He teaches courses in molecular pharmacology and physiology, and maintains involvement in several studies researching metabolic treatments for the neurological disorders such as seizures, Alzheimer's, ALS, and cancer. They're all really related. It's interesting that there's a central component that is really relevant for so many of these widely diverse diseases.

So, welcome and thank you for joining us today.

DD: Thank you. I'm glad to be here.

JM: We're really excited, because you've got so… You're really on the cutting edge research. I'm wondering if you could explain to our viewers how you first became interested in this area, because it's so fascinating. And I really look at you as one of the primary leaders in establishing some of the basic foundational precepts that we have to treat so many of these widespread diseases, especially cancer.

DD: Thank you. My entry into this field of cancer research was pretty unexpected, actually. I was funded to study the effects of gasses on the brain. Specifically, the funding was from the Office of Naval Research in 2007 to study seizures related to oxygen toxicity that are experienced by Navy SEAL divers using a closed-circuit breathing apparatus. As I delve into neuroprotective strategies to prevent oxygen-related seizures, I came across the ketogenic diet. I found it interesting that the ketogenic diet is very effective for drug refractory epilepsy and a variety of seizure disorders.

In studying this more intensely, I wanted to develop a ketogenic diet strategy for the war fighters to protect them from the effects of hyperbaric oxygen. I realized that your brain primarily runs off glucose for energy. During periods of carbohydrate restriction or calorie restriction, it can derive fuel from ketone bodies.

So, I delve into the nutritional physiology (I guess you could say) of ketone body metabolism. We further pursued ketosis as a strategy for oxygen toxicity and developed ketone supplements, which have been shown to be very effective. In addition to that, the research indicated that ketosis could be a therapeutic strategy for cancer.

I came across the work of Thomas Seyfried. I came across a large amount of evidence that suggested that cancer was unique, that it was metabolically unique. Genetically, it was very heterogeneous. There are a host of different genetic anomalies in the cancer cells, but one characteristic is that it had this ubiquitous metabolic phenotype, which was aerobic glycolysis.

Even in the presence of oxygen, it was shown that cancer cells continue to pump out lactate, suggesting that they're fuelling their metabolism from excess glucose consumption. From my perspective, the only reason cancer cells would be pumping out lactate and deriving energy from glucose at such a high rate would be because they are metabolically compromised with mitochondrial deficiency.

Insufficient oxidative phosphorylation, which takes place in the mitochondria, contributes to a compensatory fermentation, so that the cells are forced to get energy from somewhere and the mitochondria is not functioning. This destabilizes the nuclear genome and activates the oncogenes, which then kind of increases the glycolytic enzymes and enhances the ability of the cancer cells to derive energy from glycolysis.

In studying nutritional ketosis for an application related to seizures in Navy SEAL divers, I came across a body of evidence that suggest that not only was therapeutic ketosis neuroprotective, and ketone bodies function as an alternative fuel to enhance brain metabolism, decrease reactive oxygen species, but they also have a brain-stabilizing effect, which we can exploit with the ketogenic diet that we call nutritional ketosis or ketone supplements.

But there's a body of evidence suggesting that cancer itself would be responsive to therapeutic ketosis. Because nutritional ketosis involves carbohydrate restriction that would decrease glucose availability to cancer cells and it would increase the production of ketone bodies from the liver. Your normal cells have the normal flexibility to readily adapt to using ketone bodies for fuel. Cancer cells lack this metabolic flexibility to do that. They can't derive significant energy from ketone bodies, the large majority of cancer cells.

In testing our nutritional strategies or ketone strategies for seizures, we looked at a few cancer cell lines and saw a robust effect probably about four years ago. So it all started about four years ago, you know, just a simple observation in a glioblastoma cell line. That led to the work we're doing now.

JM: So, you're really on the beginning stages of this. Because four years isn't really a long time, as far as research goes.

DD: Yeah, I know. I'm brand new into this and even a junior faculty member. But it's such an exciting field to be in, because there are really not a lot of people doing it.

JM: Yes.

DD: The reasons for that are interesting, I guess you could say. There's not a whole lot of money, and there's really not a whole lot of… People understand nutritional biochemistry, but nutritional physiology is not really appreciated.

JM: Yes.

DD: It's kind of how our nutritional strategy influences the body as a whole. Not just at the level of, you know, the biochemical level, but as a whole.

JM: That's one of the reasons why I'm so excited about connecting with you and dialoguing and understanding what you're doing. You're really one of the upcoming researchers that are going to… I mean, you've got your whole career in front of you. You're really passionate about this. You're really going to uncover so many foundational key solutions to these challenges, these health challenges that so many of us or our relatives face.

What I'd like to do is deconstruct some of the very eloquent language that you use to explain what you're doing and sort of simplify it for a large number of our viewers who aren't as educated in nutritional biochemistry.

So, if I can summarize this – correct me, if I'm wrong – most of our cells in our body, our own cells have the metabolic flexibility to use either fat or sugar (which is basically the two fuels that we can do), except for cancer cells. There is some aberration that really allows them not to use this fat or the ketones as a fuel. They really can only use glucose. It's sort of a derivative of what Dr. Otto Warburg discovered and actually received a Nobel Prize for in the 1930s. He learned that glucose or sugar is really the primary fuel substrate for cancer cells.

Yet oncologists have ignored this for over 80 years and don't use it therapeutically, which is just reprehensible and almost criminal. So many people suffer needlessly because they don't have access to this simple nutritional therapeutic strategy. But essentially, that's it. To take advantage of this metabolic differential, that cancer cells just don't function on fat, that if you can shift over…

Here's, I guess, where the confusion is, at least in my understanding – please correct me, if I'm wrong, because you're the expert here – that most of us, we have a limited storage of sugar. We only store it in the form of glycogen typically in our muscles or our liver. But that storage is relatively short. Typically, 12 hours or so, maybe in some people it goes for two or three days, but it's relatively short. Whereas fat, we can go on for months, almost many of us.

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And it's this conversion. Essentially, if we eat carbohydrates all the time, we continually replete those glycogen stores, so we never get down. There's always sugar available for cancer cells. It's a matter of depleting those glycogen stores and going to ketosis. Maybe if you can expand on what I just attempted to simplify, what you mentioned.

DD: Yeah, that's a good point. You bring up a lot of, you know, a few interesting questions here. In theory, it's pretty simple, right? You eliminate carbohydrates, you decrease the glucose availability, and you should, in theory, starve cancer cells a bit…

JM: Right.

DD: Their primary source of energy, glucose. The thing is that our physiology is a little more complicated than that. When we restrict carbohydrates, we may prevent the spikes in blood glucose and the spikes in blood insulin. These spikes are actually very pro-inflammatory. They kick on a lot of… They can kick on oncogenes and enhance cancer cell proliferation and the metastatic process. These spikes can. The ketogenic diet and carbohydrate restriction can reduce these spikes in blood glucose and blood insulin. But it does not have a major effect on baseline levels of blood glucose unless the calories are restricted.

Kind of getting back to what you're talking about, the ketogenic diet is, I think, a… It's a very good strategy to make calorie restriction tolerable. Because when your brain in particular is craving glucose, and, say, for example, you go on a calorie-restricted diet, but it's a high-carbohydrate diet, you're still getting fluctuations in blood glucose. The brain goes through these intermittent periods of glucose deprivation. Your brain gets very hungry. It's not a very comfortable feeling.

Nutritional ketosis, which occurs with carbohydrate restriction and is further enhanced with calorie restriction, forces the physiological shift from a glucose-based metabolism to a fatty acid and ketone metabolism. When your body is, shall we say, keto-adapted, the brain energy metabolism is more stable and your mood is more stable. It may take a few weeks to adapt physiologically to this. But nutritional ketosis can be maintained and sustained with carbohydrate restriction and is further enhanced with calorie restriction.

I think that's kind of where you were getting at. The total calories really need to be restricted and also protein. Protein is gluconeogenic. There are gluconeogenic amino acids in protein. If protein is at, say, for example, two or three grams per kilogram per day, that is probably going to feed in through the gluconeogenic pathway. It will be hard to deplete their glycogen stores, which is necessary in the liver to drive the ketogenesis in the liver.

JM: Okay.

DD: You really need to decrease glucose availability, carbohydrates, and protein consumption to deplete liver glycogen to maintain and sustain nutritional ketosis.

JM: I would…

DD: That would be an optimized approach.

JM: I'd like to tease out those details just to, again, sort of simplify the process. You had mentioned this rate of protein consumption with two to three grams per kilogram.

DD: Yeah.

JM: The reason you mentioned that is that's the typical amount of protein that a person is consuming?

DD: It's what I consumed for many years when I was into…

JM: Bodybuilding?

DD: Athletics and more physically active. I'm physically active today, and my protein consumption is probably half of what it used to be. But my performance, surprisingly, is the same or higher, suggesting that all these years that I consumed high, very high amounts of protein, it was kind of unnecessary, because the ketones and fatty acids are protein-sparing.

If you replace the protein and the carbohydrates, but also restrict the protein and feed your body fatty acids, and elevate blood ketones, this will have a protein-sparing effect. We say an anti-catabolic effect. It will help you preserve lean body mass and a physical performance in the phase of a calorie deficit. This is why the ketogenic diet is an effective strategy for losing weight and retaining muscle, especially if it's complemented with resistance exercise or some kind of physical activity.

But we do find that in measuring blood ketone levels in humans and in animals, simple carbohydrate restriction isn't enough. You really need to lower the protein (the American diet is pretty high in protein) to achieve nutritional ketosis, which is an effective strategy for weight loss, but it may not be for everyone.

Because some people… It depends what the question is. If you're using it for weight loss or you're using it for a therapeutic intervention for cancer or seizures. In those cases, you would want a more strict, kind of like a classical ketogenic diet that involves a protein restriction and, to some extent, calorie restriction, especially if it's used for a cancer therapy.

JM: Well, let me continue to refine this a bit. Everyone here certainly has heard of Dr. Atkins, who, at his time, was really probably one of the most popular doctors in the world and was, of course, responsible for promoting the ketogenic diet. I think what you're discussing here is a revision of that, because typically the people… And there are many people who are still using the Atkin's approach. But that's typically low carbohydrate, high protein.

DD: Yeah.

JM: Which will not work. It will not give you the results that you're achieving. I think that is really the key and crucial element here. And this protein of two to three grams per kilogram, typically translates out to 100, 150, to 200 grams of protein per day for some people, which is an enormous amount.

I'm somewhat intrigued with the concept of one of my mentors, Dr. Ron Rosedale (whom I suspect you're familiar with also), who's advocating a much lower dose of actually a gram per kilogram or one gram of lean body mass. It's even lower than that. Typically, for someone like myself, it would be 50, maybe 60, or 70 grams per day. I'm

wondering if you could comment on that, especially in light of this calorie restriction, because that's another important tweak.

His take on it – and it has to do with, you know. The reason he promotes this so much is the protein influence and specifically some of the amino acids like the branch-chained amino acids' influence on mammalian target of rapamycin (mTOR), which is this massive pathway that seems to be largely responsible to much of the pathology we see in cancer growth. Protein actually has a stimulatory effect on this. When you lower that, then it's more inhibited, I guess.

I'd like to dialogue about that protein component and the importance of the calorie restriction. Because the calorie restriction is another twist that Dr. Rosedale doesn't go into. But I believe there may be some validity to that.

DD: Yeah. I think we need to define kind of what the question is and what the problem is that we want to address nutritionally.

JM: Okay.

DD: I tell people the ketogenic diet, it's not a one size fits all. Even carbohydrate restriction, it's really not a one size fits all. I think carbohydrates can be titrated in, perhaps individually. I mean, some people I know have a very high carbohydrate tolerance. They can get 800 grams of carbohydrates per day and they maintain a very lean physique. These are exceptions to the rule. And maybe they would get better results with carbohydrate restriction (but I haven't been able to convince them of that), although they need to get frequent meals.

One advantage to eating a low-carbohydrate, higher fat diet is that I can eat two meals a day and be totally fine. Whereas several people I know, including my girlfriend, actually, I mean, she needs to eat like every two or three hours, because she has dips in blood glucose levels. It's interesting. My lifestyle – I think most people can kind of put themselves into this category – would favor an eating pattern that's not so frequent.

Getting back to your original question, it depends on what you're using. If you're using it for health management and weight loss, shall we just put it under the blanket of metabolic health? Optimal metabolic health would be achieved with carbohydrate restriction definitely, but with some level of calorie restriction and either intermittent calorie restriction or some level of calorie restriction to promote a calorie deficit, at least, at certain periods of time.

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If there is a period of calorie surplus, it should be kind of given in and around exercise – during or immediately after exercise.

We run into the situation… I think it can all… Thomas Seyfried would probably agree with this. The benefits of nutrition are achieved when you can sustain a calorie deficit. We're all familiar with the benefits of calorie restriction. From my perspective, kind of

like a simple perspective, it's like how do we achieve the benefits of calorie restriction? How do we maintain low insulin and low glucose levels?

I agree that mTOR is an important signal once you have cancer. The amino acid leucine is a powerful activator of the mTOR pathway. Now, if a normal healthy person consumes boluses of leucine, you know, five grams a couple of times a day, which a lot of bodybuilders and athletes do, can this cause cancer? This is an interesting question. It's a question that I've been researching. We're about to set up a study where we give large doses of branch-chained amino acids in a metastatic model of cancer.

My opinion is that branch-chained amino acids, which activate mTOR, in a normal healthy person are not counterproductive. They do not increase one's susceptibility to cancer. The mTOR pathway is primarily activated in the skeletal muscle. The leucine is a very powerful stimulator of protein synthesis. By stimulating protein synthesis in the muscle, you can maintain and build more muscle. That's the metabolic tissue that consumes glucose and is basically the primary factor in your metabolic health.

So, by restricting your calories and perhaps supplementing with anabolic or anti-catabolic amino acids, we can maintain a greater proportion of lean body mass in the form of skeletal muscle, which will be a glucose disposal tissue and which can help us maintain lower blood glucose and lower insulin levels. This can, in the long run, potentially promote a metabolic physiology that can prevent cancer and perhaps treat cancer.

One of the questions that we want to address is that even if you have advanced metastatic cancer, if you do a ketogenic diet and add high levels of branch-chained amino acids, will that decrease survival time? This is a question that I waver back and forth on. We don't really know. That's why we're setting up the experiment to do this.

Scivation is a nutritional company that makes a very popular branch-chained amino acid product. They've given us a charitable donation. They have a product called XTEND. It's a very great branch-chained amino acid product. It's used by many people that I know in preparation for athletic events, bodybuilding, and such. There are anecdotal reports of cancer patients taking this throughout their chemo. It helped them retain their lean body mass and had an anti-catabolic effect. These anecdotal reports have led me to develop a study to test this.

JM: Well, that is kind of interesting, because…

DD: It's kind of stepping around your question, maybe not answering it exactly quite yet.

JM: Because in theory, anything that would stimulate mTOR, you would expect to make the cancer worse. But these anecdotal reports sort of, I guess, refute that belief.

DD: Yeah, well, the leucine is a powerful stimulator of mTOR in skeletal muscle, right? When you have a calorie deficit, your physiology is a little different. It's true that cancer cells do have a hyperactive mTOR pathway. It's kind of like the default pathway's already activated, right? Whether leucine can feed into that pathway and further activate

mTOR, which is already activated, is a question that I don't think has been addressed scientifically.

We have to realize that the activated mTOR is a downstream consequence of metabolic dysfunction, which triggers genomic instability that then activates the oncogenes. It's the mTOR activation. All oncogenes are kind of like downstream epiphenomenon of insufficient respiration due to mitochondrial dysfunction. That's in working back. It's kind of more of a downstream event.

JM: Okay.

DD: It's already activated.

JM: What, in your belief, activates it? Is this reliance on excess calories in conjunction with too many carbohydrates?

DD: Well, I think it's complicated. I think there are environmental factors. There's the issue of metabolic health. Over time, the aging process contributes to a progressive mitochondrial dysfunction and a decrease usually in overall metabolic health, inactivity, poor diet, environmental factors – radiation and chemicals. There are a lot of things that can feed into this. The bottom line is that the genome of the mitochondria is probably more vulnerable than the nuclear genome. The nuclear genome has more robust DNA repair mechanisms.

Over time, cellular damage, inflammation, and poor metabolic health will contribute to a progressive decline in mitochondrial function and ATP production. The cell needs to maintain its energy status to preserve the fidelity of the nuclear genome. When that's compromised by a defect in mitochondrial function and a collapse of the energy systems that maintain a proper genomic fidelity, that can activate, especially under certain conditions, the oncogenes.

If someone, for example, putting it into more of a practical perspective, has a poor metabolic health, maybe exposed to environmental toxins, things in the diet, they are challenged by a virus, for example, an illness, [inaudible 27:11] the immune system. That can set them up to be susceptible to cancer. We all have cancer in our body right now. Our immune system is fighting it off. It's the failure of the immune system to attack these pre-cancerous cells from becoming cancerous cells that could be important.

Having a robust metabolic health can allow us to adapt to these toxins in the environment, these metabolic insults, and these pathological situations, for example. We know viruses can cause cancer, but if our metabolic health and immune system is robust, we can fight it off.

JM: Okay.

DD: There are things in our environment that can prevent us from doing that. But I think optimal metabolic health is achieved when we make the mitochondria work hard, and we rely primarily on fats and ketone bodies for our metabolism. The way to do that is with carbohydrate restriction, which can be further enhanced with calorie restriction.

JM: And intermittent fasting, which we'll talk about in a moment. But before we hit intermittent fasting (I think that is an important part of this), I'd like to comment on the calorie restriction that you mentioned earlier, which I don't think any researcher would disagree with. I think there's a uniform consensus that calorie restriction has been well established to promote longevity, at least in the animal studies.

DD: Yeah.

JM: That's well accepted, non-disputable, and non-controversial.

DD: Yeah.

JM: Dr. Rosedale believes that a big portion of that benefit of calorie restriction is not necessarily related to the calories, but it's actually related to the restriction of the protein and inhibiting the mTOR pathway.

An observation I've made that I think most people would agree with is that most vegetarians are healthier than the typical American. There certainly are some unhealthy vegetarians. I state that fully believing and promoting that I believe we need animal foods to stay optimally healthy. But I think it may be a quantity issue. My current belief and understanding is that many vegetarians are healthy because they restrict their protein intake. Because it's really hard to get a lot of protein from vegetables; it's just a lot easier if you get it from animal foods.

I'm thinking – and my belief now is – that there's probably a happy merger between the two. It's that if you could radically reduce your protein intake closer to the one gram a day instead of two or three that most of us are taking… Make sure it's high-quality protein; we don't want animal protein from confined animal feeding operations, industrial farmed animals, of course, and you know, free of toxins. But it's just a matter of restricting that and having a lower protein intake in combination with the other healthy foods. That may have a profound influence and may, in fact, be one of the reasons why the vegetarians are so much healthier.

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I mean, obviously, there's benefit in eating vegetables. But many of them don't eat vegetables; they just restrict animal foods. I think the consistency is that this lower protein intake may be profoundly beneficial, maybe even more beneficial than restricting the carbs.

DD: Independent of calorie restriction.

JM: Right.

DD: That's where you're going.

JM: Yeah.

DD: Yeah, that's a possibility. I think when you're getting a surplus amount of calories from anywhere, you're setting yourself up for an unfavorable metabolic profile, you

know, elevated triglycerides, cholesterol, and high blood glucose. If you have a surplus of amino acids, I guess the question is: is that going to be more dangerous than a surplus of glucose floating around in the bloodstream? Amino acids have important signaling events that they can initiate. It's an interesting question.

But I believe that a lot of the vegans and a lot of vegetarians are very particular about the food that they eat. I think some of the benefits, the claimed benefits from a vegetarian diet or a vegan diet, are due to calorie restriction. It could be an inadvertent calorie restriction. Because a diet high in fiber, where you're ingesting a large portion of food that is not very digestible or readily broken down into usable fuel, although it's counted as calories. You kind of have this inadvertent calorie restriction phenomenon.

I think it may explain, for example, the Ornish Diet. It may explain some of these results that have been reported in several books like *The China Study*, where a plant-based diet has shown to be a good promoter of health.

I've seen a lot of bloodwork from people that can basically eliminate plants from their diet and go on a ketogenic diet – a high-fat, moderate-to-low protein, very-low carbohydrate ketogenic diet. And all the markers of metabolic health go in the right direction in most of these people. If they don't, typically, what's happening is they're not restricting their calories.

But most people who follow a ketogenic diet, they inadvertently restrict their calories without trying and reap the metabolic benefits of a calorie deficit, which is lowered blood glucose, lowered insulin, lowered triglycerides. Paradoxically, when you're eating more fat, your blood fats will go down, because you're out of calorie deficit. And HDL goes up. Almost everyone that I see on these high-fat ketogenic diets, their HDL actually goes up and improves.

JM: Well, let's talk about the fat, because I think that, really, the devil's in the details.

DD: Yeah.

JM: I think we're both in agreement on this, but we weren't really specific.

DD: Yeah.

JM: When we say increase the fat, we're not talking about the most common fat that people eat, which are highly processed vegetable oils that are full of omega-6 fats or trans fats like French fries and doughnuts.

DD: Yeah.

JM: We're talking about high-quality fats like avocados, butter, coconut oil, Macadamia nuts, and olives. These types of fats, which Dr. Rosedale believes are metabolically neutral, because they don't tend to trigger those hormonal signaling events like leptin, insulin, and the mTOR pathway, of course.

DD: That's right.

JM: They're sort of free calories that you can take. With respect to, I guess, the importance of maybe not so much calorie restriction, which you just mentioned in the example you've shared with these people not having plant-based diets, but having profound improvements metabolically by following a ketogenic diet.

DD: Yeah, I would agree. Fats are an important source of fuel. I think the optimal fuel substrate, really. Pro-inflammatory fats can really wreak havoc in the body. These are the ones that you mentioned. Many of the plant-derived oils, processed oils can cause real problems.

And yeah, there's a difference between, like, an Atkins-based ketogenic diet and a healthy ketogenic diet. When someone talks about being on a ketogenic diet, I'd like to find out specifically what they're eating. The classical ketogenic diet is very high in dairy. I think I've observed in people and myself that when I can minimize dairy protein… Dairy fat is another issue, which is not as problematic. But a ketogenic diet that's high in dairy protein can…

What I see is that people can have persistently high blood glucose levels and a low level of systemic inflammation from the allergens that are in dairy proteins. My body is very reactive to these things. I get eczema and all kinds of weird autoimmune kind of reactions. But it's kind of a persistent chronic level. Think about what's happening inside the body. I don't think, you know. It's not like one person has it, one person doesn't. There's a spectrum of immune response, depending on the person and level of intake of dairy proteins.

A lot of my friends are big, big fans of whey protein, you know, drinking whey protein shakes. I did that for many years. I don't think it's necessary. I think a lot of the fats can be used in place of protein. And I think fats are very protein sparing, decreasing the need for protein.

But a ketogenic diet – going back to the optimal diet – that's high in dairy, which is the traditional ketogenic diet, can be problematic and can prevent many of the health benefits that you can get from a low-carbohydrate ketogenic diet.

JM: Yeah.

DD: It really needs… And a lot of nutritionists aren't really up on kind of these distinctions between… They're just a few macromolecules.

JM: Right.

DD: They're just, "What are your macros?" I believe that more attention needs to be paid to the actual composition of the macronutrient profile that is given to these people. If you're a registered dietician, and you're assigning macronutrients to your client, kind of if-it-fits-your-macros kind of phenomenon that a lot of dieters are using, the composition of macronutrients is really important. Because some foods are potential allergens and can really be counterproductive for your health and for weight loss. These things need to be taken into account. It varies between individuals.

JM: Yeah. I believe Atkins is guilty of the same error. He didn't pay attention to the macronutrient composition.

DD: Yeah.

JM: Along those lines, specifically with respect to dairy… You know, I'm a firm believer that if you're going to have milk, it should be raw. The pasteurization of the milk actually changes the three-dimensional nutritional [inaudible 37:48] structure of the proteins, which can contribute to the allergenicity that you're taking.

But the other hidden component… I really strongly discourage people from drinking milk. I just don't think it's the optimal food for most people, even raw milk. Because not only does it have this protein issue, which you referenced, but it's also associated with sugars and the lactose. It's an interesting combination. But I personally consume about a pound of raw butter a week. I think the raw animal fats are profoundly beneficial. They're loaded with nutrients, of course, that are difficult to get otherwise.

DD: Yeah.

JM: I think you're onto something there in your observations that people who are following a ketogenic diet that includes dairy run into problems. Maybe you could… Are there any other distinctions you noticed in your observations? Let me give a frame here, too. Because you're not a medical doctor; you're a Ph.D. But you do help and assist many people in their attempts to apply what you're learning to treat their cancers. Maybe that's overstated or incorrect. That's the frame.

I'm wondering, in that process of helping and assisting others, what you've noticed and learned. Maybe you can share that with us and for people seeking to apply the proper ketogenic diet to achieve these benefits.

DD: Yeah, that's right. I'm not a medical doctor, and I'm not qualified to give medical advice. But a lot of people do come to me for information about metabolic therapies for everything – from ALS, seizures, to cancer. What I do is I direct them to information. One of the first websites is usually the KetogenicDietResource.com. A friend of mine maintains that website. They have a book on that, which is like a ketogenic diet handbook for patients. That's called the Ketogenic Diet Resource.

Thomas Seyfried's book, which is a good reference for people to go to, although it's a little too technical for most people to handle.

But when people come to me, I direct them to a variety of resources. I have a website KetoNutrition.org. I just put a lot of information on there.

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What I ask to see is, like, hard scientific evidence. I like to see biomarkers of metabolic health – bloodwork, blood glucose, blood ketones, and C-reactive protein and these things – before, during, and after they've maintained nutritional ketosis or calorie restriction. In hundreds of people that I looked at, I see all the markers of metabolic

health improving. Everything is going in the right direction with carbohydrate restriction and with calorie restriction.

So, yeah, I don't give diet advice specifically, but I give people the… I send them in the direction where they can find the information. There are many simple tools that people can use. For example, a blood ketone and glucose meter that you can buy at any drug store. These can quickly get blood glucose and blood ketones. You can assess your response to a nutritional intervention, and then titrate the calories and the macronutrient ratios to optimize your body to be in what we call the metabolic zone.

The metabolic zone – our definition of it – is that the blood ketone levels actually rise to the level of blood glucose and above. If you can produce sustained hypoglycemia with carbohydrate and calorie restriction and elevate blood ketones, it actually makes the hypoglycemia tolerable. The ketones replace the glucose as the primary energy fuel for the brain. It basically keeps the brain metabolism optimized and prevents fluctuations in your mood and your energy levels, if you can sustain therapeutic ketosis with carbohydrate and calorie restriction.

If a person can do that, they need to take it upon themselves. Because someone who's 250 pounds with metabolic syndrome is going to have a different adaptive response to calorie restriction and carbohydrate restriction than the lean athlete that's a 170 pounds who's using it to treat a condition. It's not a one size fits all. The carbohydrate threshold that's needed for individuals to maintain nutritional ketosis can vary widely. I can get 150 grams of carbohydrates a day sometimes if I'm really active and still maintain nutritional ketosis.

JM: Interesting.

DD: Yeah. Only if I'm very active.

JM: Most people…

DD: And it's high in fiber.

JM: Yeah, okay.

DD: That's a distinction, too. If someone's getting 100 grams of carbohydrates, well, are you getting it from broccoli and salads? Or are you getting it from cookies and candy? There needs to be clear… That's why, I think, just assigning macronutrients for diet can be counterproductive in some ways. I think the composition of the food is equally important, especially in some people that just have very stubborn, persistent allergies. That will impact their metabolic health and overall physiology. If your body is fighting something off with an allergic reaction, it's going to compromise the metabolic health. That's why removing allergens from the diet is important.

There are several books out there that address this issue. Elaine Cantin wrote a book called *The Cantin Ketogenic Diet*, and that's been a useful resource for a lot of people that come to me. They say, "I want to start the ketogenic diet, but I can't eat dairy. How do I follow it if I can't eat dairy or if I can't eat these other foods?" There are not a whole

lot of ketogenic diet books out there that promote the diet and give an outline of the diet that's dairy-free. Elaine Cantin's book addresses that.

I think that as people are becoming more aware of these issues that you mentioned, especially with dairy, I think people are looking to see resources that can guide them to maintaining nutritional ketosis with a restriction in dairy protein.

JM: Well, let's talk about the meter that you had mentioned that people can get in the drugstore. I'm assuming that's a finger-prick model, and that there's a strip.

DD: Yeah.

JM: Strips of regions that you would use and purchase independent of that.

DD: Yeah.

JM: Do these require a prescription from a physician? Or can anyone walk into the drugstore and pick up one of these?

DD: Yeah, there's a variety of models out there. I use the most common one that you hear people talking about. Abbott Labs makes it. It's called the Precision Xtra. Their glucose meter strips are about 50 cents per strip. But the ketone strips can range from three dollars to six dollars per strip.

JM: Wow.

DD: They can be expensive. But what I find is that patients may just use a blood glucose or blood ketone meter maybe once a week. And they'll use the urine ketone strips throughout the week to check their urine ketones. They may just do a couple of blood measurements. Typically, if your blood glucose stays 75 and below with carbohydrate restriction, there's a good chance that you'll be in nutritional ketosis.

JM: Okay.

DD: Another simple way to do it…

JM: That's what you've seen from the research when people do this. When they're below 75, you can save yourself the expense and inconvenience of doing the blood ketones. Because most of the time, you're going to be in ketosis.

DD: Yeah. And you know, a cheap way to do it is just with the urine ketone strips. If you're in ketosis by evidence of ketones in your urine, you're in a situation where you likely have depleted glycogen stores in the liver. You're maintaining a low blood glucose. The driver for hepatic ketogenesis is low blood glucose and low glycogen levels in the liver – depleted glycogen. Your body really won't make ketones, and they won't spill over in the urine unless you've achieved that level of glycogen depletion. That's a good biomarker in nutritional ketosis.

I opt to use the blood ketone meter, the Precision Xtra meter. There's a Nova Max Plus meter that measure ketones, but this measures them lower. We found that it's relatively

inaccurate. We found that the Precision Xtra meter, which I have a number of these meters. Another one is the CardioChek meter. This is an interesting meter, because it can measure glucose, ketones, HDL, LDL, triglycerides, and a number of things.

JM: Interesting.

DD: You can buy these at any CVS, Walgreen, or any drug or food stores.

JM: Is there a prescription that's required?

DD: No prescription required.

JM: Interesting.

DD: It requires money, though.

JM: Okay.

DD: These strips are pretty expensive. You can get them at American Diabetes Wholesale, you know, places online.

JM: Sure.

DD: Amazon.com sells them online. What I typically do… Ebay, you can get them on Ebay. I look for a sale, and I buy a whole bunch of them at one time, typically thousands of them, because we do so many experiments. I literally bought, like, 20,000 ketone strips, you know. Because we do so many blood measurements with the experiments that we do. I have a big stash here that we use.

We compare the measurements to the biochemical assays done with very expensive equipment at Case Western Reserve University. We found that these meters are actually very accurate. The ketone measurements are accurate, and the blood measurements, they're precise and they're accurate. They're measuring repeated measurements of the same sample. They give you the same numbers. They're also in the same ballpark.

JM: Yeah, well, it's wonderful stuff. Thanks to the exponential growth in technology. I suspect in the not too distant future we'll have a little sensor we can put into our smartphone.

DD: Yeah.

JM: And then be able to… We can analyze it that way, which would even be less expensive.

DD: That would be ideal. Yeah, like a little Band-Aid, you know. I'm working with… I know some companies or foundations that are working on this, where you just put something like a Band-Aid that has nanosensors that can detect the blood in your capillaries and basically give you a metabolomic profile of all the metabolites in your…

JM: Yeah.

DD: I think this technology is available to do this. It's going to take some R&D…

JM: Sure.

DD: To actually develop a commercialized product. But it's going to have big advantages.

JM: But ultimately, you're going to want to have a protocol that you follow to achieve metabolic excellence…

DD: Yeah.

JM: Which is really why we're meeting today: to help us understand what that protocol would be. I want to tap into your expertise, because you've guided so many people through this. So, for the average person who's interested or intrigued with this concept, either concerned about optimizing their health and longevity, treating an existing cancer, or preventing cancer…

The typical person is not fat-adapted. There are two fuels to burn: fat and carbs. Those people – I would say; I suspect to a degree – over 99 percent are adapted to burning carbs as their primary fuel.

DD: Yeah.

JM: Our goal is to help them transition to that and to achieve this metabolic excellence. But part of the reason for that, too, as you alluded to earlier, is that when you are adapted to burning fat as your primary fuel, you are flexible.

[----- 50:00 -----]

You don't have to eat every two to three hours.

DD: Yeah.

JM: You can go for a full day and not be hungry. That is the key. It just seems like we're blowing smoke. But your hunger disappears, because you have fuel to burn. If you're not adapted to burning fat, then you absolutely have to have those carbs. Otherwise you're going to be miserably hungry.

DD: It becomes a crisis situation.

JM: Absolutely. I mean, you'll kill for food.

DD: Yeah. The major practical advantage is to be fat-adapted.

JM: So, how do we do this? In my perspective… I've got less experience than you, certainly, in helping people apply this practically. But it's this concept called intermittent fasting, where we gradually allow people to restrict the window at which they're consuming foods. I tell people to stop eating anything – all food, except for water – for three hours before they go to bed, and then to gradually extend the time that they're

consuming their first meal to the point where they're skipping breakfast. They have a six to eight-hour window where they're restricting their calories.

In a sense, you must have to calorie restrict, although I don't tell them to calorie restrict. But it's sort of an artifact of following that concept, because you're not eating food as long as the day.

In that period, to provide substrates to make the transition to fat burning as their primary fuel, is to use fats that break down real easily, that are healthy and full of medium-chain triglycerides, like coconut oil, which can substitute frequently for the glucose, at least, given the energy that they don't have until they switch over.

So, I'm wondering what your comments are on that and any revisions that might make it easier for people to follow.

DD: A lot of good points you bring up there, a lot of good topics for discussion. You name it, I've tried it. I've tried intermittent fasting. I fasted for one week, and I found that it was very tolerable. I had the benefit of already being fat-adapted or keto-adapted. But the third day was a little bit, you know. I got a little bit hungry. But I wasn't hungry after about the fourth or fifth day. By the seventh day, it was very easy.

I actually gave a seminar, a nutritional seminar on the last day of my fasting, you know, showing people. I showed people my blood glucose which was 51. My ketones were like five or six millimolar. Earlier in the morning, I think, I was like 44 or something, my blood glucose. If a doctor saw that, he would think I would be in a coma. So, you name it, I've tried it.

I think from a practical standpoint, the important question is what's a person going to follow? From my perspective, the biggest hurdle here is compliance, compliance to a dietary strategy that makes calorie restriction feasible and possible. And you know, carbohydrate restriction, high-fat diet, and intermittent fasting is one way to achieve that.

I found that one meal per day kind of left me a little bit… I would tend to consume a little bit too much food I think on a single meal. I found two meals a day to be optimal for me. Although when I'm travelling, sometimes I'll go a whole day without eating. Or sometimes, I'll just eat once per day. For example, if I'm travelling in Europe – and foods are more expensive, or I have a pretty busy itinerary – one big meal at the end of the day is great. And it can cut down on your budget for food, too, you know.

There are a lot of advantages, as you alluded to, to this pattern of intermittent fasting. I think that it is a good strategy to promote metabolic health and to maintain nutritional ketosis, if the person can adapt to it. In some lifestyles, people cannot readily adapt to it. But I found that most people can if they give it a try. Most people are resistant. But once they try it, they're amazed at how much better they feel.

It's also, you know. You ask the question: are you an elite athlete? Why are you doing it? If your goal is to build muscle, if you're into powerlifting, intermittent fasting may not be the best strategy for you.

JM: Or how about a pregnant woman, which I would also include in that category?

DD: What was that?

JM: A pregnant woman, a woman who's…

DD: A pregnant woman.

JM: Yeah, for different nutritional requirements and it's a different goal. They're in a different phase in their life.

DD: Yeah. I think…

JM: Or someone with adrenal stress, too.

DD: Yeah. I think there's much to be said for just eating when you're hungry, right? And I think that we're programmed by the norms of society to eat breakfast, dinner, and lunch, with snacks in between, right?

JM: Right.

DD: We've also been told that eating more frequent meals is more beneficial. And that those meals…

JM: And that breakfast is the most important meal of the day.

DD: Yeah, and those meals should be high in carbohydrates. This creates a pattern of eating that I believe is unhealthy. And it's just not feasible. I mean, with my work schedule, it would just be hard. It would kind of tap into my productivity.

Frequently, I get bloodwork probably about four to five times a year. I've gradually shifted from eating six meals per day (which I use to eat when I was very active, more active in athletics) to this pattern of eating that is like two meals per day. My weight has come down a little bit, but I still maintain. I'm about 100 kilograms or 225 pounds. I can maintain that my metabolic health is good.

I'm overweight. But I've been able to use intermittent fasting, if you want to call eating just twice per day kind of like a weak intermittent fasting protocol. I've been able to maintain my strength and my power to weight ratio, if you want to call it that, by reducing my meal frequency. I'm actually stronger now pound for pound than I was when I was eating more.

JM: That is amazing. When you give the body what it needs.

DD: Yeah, and the body is pretty smart, you know. It just kind of takes what it needs when you give it the right foods. I find that if your overall physiological health is better, your body will kind of breakdown, assimilate, and utilize the nutrients that you give it much more efficiently. You'll have a re-partitioning effect. The nutrients will go preferentially to rebuilding and maintaining muscle and into energy pathways that kind of give you sustained energy effects.

Whereas if you're eating carbohydrates or you're overeating carbohydrates, it just causes a metabolic situation, where you have pro-inflammation. You have fluctuations in blood glucose, which can decrease your cognitive and physical performance.

A colleague of mine, Jeff Volek, he works with advanced athletes, you know, these ultra-endurance runners who run like 100 miles at altitude.

JM: Sure.

DD: In the rain, over hills. He developed several nutritional strategies. Jeff Volek has written books – *The Art and Science of Low Carbohydrate Performance* – and has shown conclusively that, at least in endurance athletes requiring stamina and strength, that carbohydrate restriction and even an intermittent fasting-type feeding schedule is actually optimal to enhance physical performance. He's demonstrated this and has a number of studies. Jeff has published probably over 250 peer-reviewed articles.

JM: Wow.

DD: He's definitely put out enough research…

JM: I'm not convinced…

DD: To validate this pattern, this way of eating, this carbohydrate restriction and decreased meal frequency.

JM: Yes. And that is a great strategy if you're going to use that. But if your goal, from my perspective, is longevity and optimal health…

DD: Yeah.

JM: I don't think that's a wise strategy to achieve that. I think it's going to be counterproductive. I'm a far more fan of the high-intensity, slower, and less-frequent type of exercise, although I use to do longer [inaudible 58:51]. I ran marathons when I was younger, and [inaudible 58:54].

DD: Yeah.

JM: But I want to comment on one point you mentioned earlier. I honor and respect that and recommend that principle also. It's listen to your body. Eat when you're hungry. But the caution and the caveat, I think, that one needs to apply here is that that's valid if you're adapted to burn fat as your primary fuel. If you're adapted to burning carbs, your body's going to lie to you, because it's going to want to fill those glycogen stores up.

So, I'm wondering, from your experience in guiding people through this process, what the range is, where in you find people required to make this shift that they're applying intermittent fasting is a tool to achieve fat adaptation.

DD: That's a good question. And there's no easy answer to it. I think it varies tremendously. Some people just like to eat. I mean, some people like the fact that they have the time and the money. They enjoy eating. Eating is a pleasurable thing. I don't

think people should deprive themselves of eating. If eating more frequently is pleasurable to them, and they can maintain metabolic health doing that, then I don't try to change their eating pattern if they don't want to.

[----- 1:00:00 -----]

People need to want to change. Usually, that results from some kind of underlying pathology. The doctor tells them they need to lose weight. They're trying to get in shape for an event or something.

JM: They've been diagnosed of cancer.

DD: Yes, exactly. In these situations, you need to assess the person's current eating strategy. You need to assess their metabolic health. Bloodwork is important. If they have some renal insufficiency, if they have different… If they have hypercholesterolemia, there are factors that need to be considered before giving someone advice for a nutritional strategy. But I think with calorie restriction, basically, the benefits cannot be denied. Any eating pattern that promotes a tolerable means for calorie restriction is going to improve overall health and metabolic health.

JM: What's the range of time do you think it takes people to achieve that, in your experience? Is it one week, two weeks, three weeks, or three months?

DD: It depends on where they're coming from. But I think within four to six weeks, most people can fully adapt and embrace a low-carbohydrate, reduced-meal-frequency eating pattern. I think it takes about four to six weeks.

Actually, this would correlate with the exercise performance studies done by Stephen Phinney and Jeff Volek that showed that the performance deficits that you see with carbohydrate restriction… Restricting carbohydrates can actually drop physical performance. And then this starts to come back up to baseline at about four weeks. In about six weeks, at least in advanced cyclists, they can achieve far better.

That's kind of an evidence for me, that they're keto-adapted in the sense that their body is better utilizing, transporting ketones maybe across the blood-brain barrier, and that they're fully utilizing and optimizing fats and ketones for fuel. This may correlate with just an overall sense of well-being. Being that their body is fat-adapted and keto-adapted, that their brain, organ, and whole physiology are in tune and adapted to this nutritional ketosis. And that can be hard for some people. Because it's literally forcing their body to use a fuel that it doesn't want to use.

JM: Right.

DD: Because it's mimicking the physiological phenomenon of starvation.

JM: Right.

DD: And the body doesn't want to be in starvation for survival. So, carbohydrate restriction mimics the physiological state of survival. They're fasting.

JM: I believe most likely the reason this works is that it follows one of the principles that I believe is pervasive to good health which is RAP. We replicate our ancestral practices. Our ancestors did not have access to food 24/7. They regularly went through periods of decreased calories. That's probably why this works. If our ancestors didn't, then we wouldn't need to do that. But we have to honor our biochemistry to achieve those benefits.

So, the four to six-week window is phenomenal. That's good to know. And then I would encourage people to stick with it. To get through that, use a lot of coconut oil to give yourself energy until you've achieved… I mean, you can do it with the meters that you mentioned.

But also – this is such a huge point – the hunger disappears. When your hunger for carb disappears, you know you are burning fat, because that's one of the side effects. It's obvious. It's plain as day. It's not a mystery. It's like turning the lights on in a room. You'll know as soon as it hits, because it's so obvious.

DD: Yes.

JM: And it's so consistent. I mean, it happens to almost everyone.

DD: I would agree. There are some people that fail to adapt to the ketogenic diet, but they're the exception rather than the rule. Most people who say, "I've tried a ketogenic diet. I just couldn't do it." I was like "Well, tell me what you did." They're like, "Well, I was eating like 200 grams of protein, 30 grams of fat, and zero carbs." I was like, "No, you're following a high-protein diet."

JM: Yeah.

DD: Your blood glucose was all over the place. You weren't making ketones, because you're not giving your body the fats that are needed. The ketones are a product of the liver. Basically, give your body fats, feed the liver fats from your adipose tissue or fats from your diet, and it will make ketones. I think it really comes down to having that sustained nutritional ketosis to fuel your brain and keep your brain happy, shall we say, during periods of reduced glucose availability.

It's those dips in blood glucose that's going to create that glucose withdrawal syndrome in the brain. It's a dysphoria, I guess you would say. You just don't feel good. I see it all the time in people that I know that skip a meal. They're like, "I got to eat now. We've got to stop some place. I've got to eat."

JM: Right.

DD: "Because I ate three hours ago. I ate carbohydrates. Now I'm hungry again. I got to eat something." When you're fat adapted, you forget what that feels like.

JM: Right. It's just off.

DD: I remember feeling... I used to eat a lot of fish, rice, and pasta. I grew up in an Italian family, where it was basically a pasta-based family, with lots of bread.

JM: Sure.

DD: I remember feeling hungry and like the feeling that I need to eat right now. I need to eat something. I don't feel that way anymore. I actually have to remind myself to eat sometimes.

JM: It's metabolic freedom and flexibility once you achieve this.

DD: Yeah.

JM: It's really worth the effort. It's four to six weeks of somewhat discomfort. No question, it's an uncomfortable feeling. But it's definitely worth the effort.

DD: Yeah.

JM: I want to comment on, you know. I would agree with you that two meals a day is probably optimal. What I find myself doing though, because of just the hassle factor and inconvenience. I mean, I will eat two meals a day. But frequently, when I'm at home, I'll eat one meal a day. But I substitute snacks around that.

The snacks are typically two: Macadamia nuts for two reasons: they have the highest fat in any nut that I know of and the lowest in protein, so it's closest to that metabolic window that you want. And then also, a candy that I make from coconut. It's primarily coconut oil, some coconut flour, coconut flakes, and some natural sweeteners like Stevia. I supplement that. I'm getting all their calories and fats around that big meal a day, which typically varies from 2:00 to 4:00 in the afternoon.

Have you ever tried to play with something like that, where you're having these smaller or little snack meals around that?

DD: I do that. My typical morning routine is to wake up and actual have an amino acid supplement – which, by the way, is leucine – a little bit of leucine, a little bit amino acid mixture, and some spirulina. Actually, it tends to be just a buffer for the amino acids. I'll have a little bit of an amino acid mixture when I wake up with some spirulina and a few things, plant-based proteins actually, just a small amount. And then I brew coffee. I don't know if you're familiar with bulletproof coffee.

JM: Oh, yes.

DD: Yeah, so, basically, I take almost a third of stick of butter and kind of blend it up and whip it up with some strong coffee. I'll sip on that and just kind of work. You know, wake up early in the morning [around] five. I'll have the most productive two, three, four hours of working just all fat.

JM: Yeah.

DD: Essentially, all off the butter. And then I kind of have to force myself to eat breakfast. This is kind of contrary to what I was just talking about. But I know if I don't eat breakfast, and I get into a work pattern (I'm at work until, like, 8:00 at night), I

probably will get hungry during the day. I might have a couple of free-range eggs, a little bit of sardines, and broccoli. That didn't sound like a very appetizing breakfast, right?

JM: Sure.

DD: Sardines in the morning. But…

JM: It works.

DD: But that's typically what I eat. Yes, it's really heavy on fat and kind of moderate with the protein. I used to eat like a dozen egg whites and oatmeal. I remember that being a staple breakfast. But now I eat a couple of eggs.

JM: I've made my mistakes, too.

DD: Yeah. I cook it in coconut oil. Usually, I have some kind of greens like broccoli, asparagus, or spinach omelet or something like that with some mushrooms. That will sustain me. The butter in the morning with my coffee… A high-fat, moderate-protein, low-carb breakfast will sustain me for half of the day, 12 hours. And then I might hit some MCT oil in the middle of the day, coconut oil. Add an amino acid supplement that I take occasionally.

And then I eat… Dinner is my bigger meal of the day. It typically follows some kind of physical activity whether it be walking the dog, going to the gym, or you know, some kind of physical activity. I kind of… I have it immediately after.

JM: Okay.

DD: It's typically protein, a big salad, and lots of fat.

JM: Yeah.

DD: My fat intake is probably about 300 grams a day.

JM: Wow.

DD: Believe it or not. I'm pretty high in fat.

JM: Percentage wise, how many calories would you say are from fat? Percentage wise, 70 percent of your calories are from fat?

DD: Yeah, I would say about that. On some days, it might be as low as 50. And on other days, it may be as high as 80 or 90.

JM: Okay.

DD: But about 70, that's a pretty accurate description.

JM: That's basically what I follow, so about 70 percent of fat.

DD: Yeah.

JM: Most people, most conventional nutritionists or dietitians would strongly disagree with that, of course.

[----- 1:10:00 -----]

I think you've provided us with a wealth of information that people can delve into. I'm wondering if you could maybe summarize some of the basic principles and then perhaps, most importantly, provide the resources – repeat what you have mentioned earlier – that people can follow. Go for more specific details if they're intrigued with this concept and want to integrate it into their lifestyle.

DD: Sure. So, just a summary of kind of my thoughts on it?

JM: Right.

DD: Okay, so just kind of taking a big step back from where we started, my research here has evolved by… Basically, I was studying the effect of neuroprotective agents against seizures, and I stumbled upon nutritional ketosis as an effective way to prevent seizures. That led to a number of projects. Probably five or six projects that are ongoing now and that are giving compelling evidence to show that metabolic therapies in the form of calorie restriction, ketogenic diet, or ketone supplements.

What I didn't really mention… Similar to MCT product, we developed and tested ketone esters and ketone salts. Creating nutritional or even starvation ketosis without dietary restriction is of interest to the military. Because they are aware that nutritional ketosis has a very powerful anti-seizure effect, which is important for Navy SEAL divers who use a closed-circuit rebreather.

If we can achieve that without calorie restriction or without carbohydrate restriction and elevate blood ketones to the level of fasting ketosis, we can, in essence, feed the brain an alternative fuel that can enhance brain metabolism and preserve brain function under periods of stress and periods of oxidative stress, for example, high-pressure oxygen breathing.

The ketone supplements – ketone esters and ketone salts – that we developed have been shown to be very neuroprotective. We've published a report on that in the *American Journal of Physiology*, actually. The title is "Therapeutic Ketosis with Ketone Ester Delays Central Nervous System Oxygen Toxicity Seizures in Rats."

Tomorrow, actually, there'll be a press report out, a press release on our paper that was recently accepted in *PLOS ONE* journal. It's an open-access journal. Readers will be able to get this. The tittle of it is "The Ketogenic Diet and Hyperbaric Oxygen Therapy Prolong Survival in Mice with Systemic Metastatic Cancer." As you know, most people who die of cancer die of not the tumor per se, but the metastatic process. There's really no treatment or cure for metastatic cancer. That's one of the reasons we wanted to study it. No one's really studying it, because it's hard to show efficacy in any kind of animal model of metastatic cancer.

We've demonstrated that the ketogenic diet by itself can extend survival in animal models of metastatic cancer. But when it's combined with hyperbaric oxygen therapy three times per week, there is an additive effect. You get a significant reduction in tumor growth, decrease in tumor size, and significant extension of life when therapeutic ketosis achieves what the ketogenic diet is combined with hyperbaric oxygen.

Tumors thrive in a low-oxygen environment. As a tumor grows, it exceeds its ability to supply oxygen to the center of the tumor. That low level of oxygen, really called hypoxia, actually further activates the oncogenes, the cancer promoting genes. It activates things like HIF-1-alpha and VEGF. IGF-1 signaling goes up. Hyperbaric oxygen can reverse tumor hypoxia intermittently. In doing that, it can actually turn off the oncogenes. There are published reports on this.

More importantly, the tumor thrives in a low-oxygen environment, and it's adapted to that low-oxygen environment. When you saturate a tumor with oxygen, because the mitochondria are damaged, it overproduces oxygen free radicals in the form of superoxide anion. This oxygen-induced increase in free radicals can actually cause the tumor to kill itself. It overproduces free radicals in the presence of the high levels of oxygen.

JM: [inaudible 1:15:00]

DD: And free radicals can damage the tumor. When that natural form of oxidative stress is given to the tumor during the ketogenic diet, the ketogenic diet will put metabolic stress on the tumor cells by limiting glucose availability and elevating blood ketones, which your normal cells can use, but cancer cells can't use. It compromises the metabolism of the tumor.

And then you hit the tumor with a high pressure of oxygen by hyperbaric oxygen, which is breathing 100 percent oxygen at an elevated hyperbaric pressure. We're at one atmosphere now. And we use like 2.2 atmospheres or 2.5 atmospheres of oxygen, which will probably increase the tumor oxygen 10-fold. We're using a natural form instead of radiation, which works by killing cancer by causing free radical formation by destroying the tissue and creating free radicals. Hyperbaric oxygen is just a more natural way to do it without damaging the natural cells, and it seems to be synergistic with the ketogenic diet.

There will be a report on this tomorrow, a press release. The paper will be available tomorrow.

JM: Well, please send us a link to that. We'll put it in the interview.

DD: Yes. I'm working with a foundation called Winning the Fight for neurodegenerative diseases. This is a foundation primarily to treat patients with ALS.

I've been testing what has been termed the Deanna Protocol. The Deanna Protocol is a metabolic therapy that elevates blood ketone levels and actually is a combination of nutritional supplements that includes alpha-ketoglutarate (which is a Krebs cycle intermediate, an energy metabolite), a soluble form of CoQ10, a soluble ubiquinol,

GABA, the amino acid GABA, and caprylic acid, which is an eight-carbon medium-chain triglyceride. These things in combination have been shown anecdotally in patients to stall the progression of ALS.

This observation was first shown in Deanna Tedone. Her father is a retired orthopedic surgeon. His name is Dr. Vince Tedone. They have a foundation. They contacted me. I met Deanna. I met with the family. I observed that they were getting a real therapeutic effect to this metabolic therapy, which involved elevating blood ketones and giving the body high-energy intermediates in combination with co-factors, like soluble CoQ10, to enhance metabolic efficiency.

The reason why this works is that all neurodegenerative diseases are associated with impaired energy metabolism. The impairment of the cell to make energy causes the membrane potential to collapse, and then it oversecretes glutamate, which is an excitatory amino acid transmitter that can activate the NMDA receptors and AMPA receptors, which can be excitotoxic. The hallmarks of ALS pathology are glutamate excitotoxicity, excess calcium, and oxidative stress.

These are, I believe, downstream epiphenomenon or downstream consequences of failed energy metabolism. If we address the issue upstream by giving a metabolic therapy that fuels the cells – in this case, the motor neurons for ALS – that helps the cells maintain ATP production within the cell, the cells will maintain their resting membrane potential, and it will prevent the collapse of the metabolism, which contributes to excess glutamate excitotoxicity.

Many of the therapies now are just blocking the glutamate receptors or blocking the accumulation of the protein, the toxic proteins that occur as a consequence of failed energy metabolism. The therapy that we're testing – and I think the therapies of the future – will be metabolic therapies that address the underlying metabolic dysfunction associated with the cell. For some reason, in patients that have ALS, they are responsive to a TCA cycle intermediates or Krebs cycle metabolites. When these are given at high doses, it seems to restore energy metabolism perhaps in the motor neurons, which decreases the symptoms.

So, the question is are we just decreasing the symptoms? Or are we stalling the pathology?

[----- 1:20:00 -----]

Deanna Tedone has been using this protocol for several years now. She has beaten the odds as far as progression of ALS, which is a terrible disease.

JM: Sure.

DD: And a number of other patients… I think there are a thousand of patients that have registered with the foundation at Johns Hopkins, Duke University, and Emory University. These are being evaluated. It's too early to tell, but our animal studies definitely showed an extension of survival with this metabolic therapy that elevates blood ketones.

JM: Do you think this would also be helpful for other neurodegenerative diseases like Alzheimer's and Parkinson's, or even autoimmune motor dysfunction diseases, like multiple muscular dystrophy?

DD: Yeah. It's funny you mentioned Alzheimer's disease. Actually, today, in the paper, *The Tampa Bay Times*, there's a story of Mary Newport.

JM: Oh, sure, coconut oil.

DD: I know Mary. She's a good friend of mine.

JM: Yeah.

DD: As you can see, Mary's in the corner there with her husband. And you know, another report showing that the Alzheimer's Institute here has actually started a clinical trial to determine… They have coconut oil and a placebo, which is olive oil or some kind of plant-based oil that they give to patients. I think there are 60 patients in the trial.

The question is does giving coconut oil enhance brain metabolism to delay the Alzheimer's pathology? They're going to look at not only cognitive function, but actually do an amyloid PET scan to see if it's impacting the progression of the pathological protein that it's contributing.

JM: Do you think the same supplements will be helpful? The same supplements that you're using for the ALS would be helpful in those diseases like Alzheimer's?

DD: Yeah. That's a very good question. I know the foundation is in discussion with the Alzheimer's Institute, because they have reports. Alzheimer's patients have contacted this foundation that primarily specializes in ALS therapy. But there are reports from Alzheimer's patients that are telling them that it's working for Alzheimer's disease. The tremors are decreasing. There's an improvement in cognitive function.

This perhaps may put pressure on the Institute to run a study to test the Deanna Protocol, which is being used in many ALS patients, to perhaps use it in Alzheimer's patients.

JM: Sure.

DD: And Parkinson's disease patients, too, have reported. I've had several contact me, because they know we're doing the animal studies on the transgenic animals that are models for these diseases. We saw a positive effect in… That won't be published soon. But other people have been contacting us.

JM: What about the possibility of using it for autoimmune motor disease like muscular dystrophy? Have you seen a benefit there?

DD: Yeah, I have. A student of mine has MS and maintains nutritional ketosis. He's on a calorie-restricted ketogenic diet. He essentially does intermittent fasting with coconut oil and MCT throughout the day. He appears to have stalled the progression of his MS. That's just one observation there.

But a number of people, maybe about four or five people with MS have contacted me and kind of given me the protocol that they're using, which typically involves some kind of ketogenic diet – calorie restricted or not – with lots of coconut oil and MCT oil. Some of them rubbed the MCT oil or coconut oil into their skin. It does have the ability to be transdermally crossed into. Whether it elevates blood ketones through that way or not, we have not tested that yet. But they seem to be getting a therapeutic benefit, at least, symptomatically in MS and other neurological diseases.

JM: Right.

DD: But MS is an interesting one. I think a nutritional strategy is very important in MS, because, I think, the immune system is obviously important in driving the progression of the pathology.

JM: Sure.

DD: MS is really a mystery. But removing toxins and removing potential allergens from the diet is very important.

JM: Now, can you also provide us with a list of those resources that someone could use if they wanted to apply this? Because that's I think… You've mentioned a number of books.

DD: Yeah.

JM: A number of websites.

DD: Yeah, I think a good place to start would actually be… For cancer, you're probably aware of Thomas Seyfried's book, *Cancer as a Metabolic Disease*. This is very academic. It's probably a little too technical for most people. But within this book, there are patient protocols that are being used for clinical trials with the restricted ketogenic diet for glioblastoma brain tumor. I know the protocols in this book are going to be the ones that are implemented in clinical trials. I think that's important to know. I highly recommend this book.

If a patient brings this book to their doctor, there is irrefutable evidence that Thom has amassed in this book to support cancer as a disease of metabolic origin and support showing that cancer of all types is genetically heterogeneous. They're diverse, but they have dissimilar metabolic phenotype, which is the Warburg effect, aerobic glycolysis. Even in the presence of oxygen, they continue to use glucose as a fuel and pump out lactate.

With that knowledge, we can exploit that. The protocols described in this book, the data presented in this book, gives the reader a firm understanding of what cancer is, how to prevent it, and how to treat it if one has it. There are a number of case reports in the book. There are specific protocols in the book. And there's a firm history of kind of how we got into the present state.

We've developed a large variety of genetic therapies that are having no effect. The Human Genome Project has given us a lot of different therapies, and none of them are working. Something has to change.

With a combination of anecdotal reports, animal studies, and case reports that are documented, I think that book is a very important resource for patients and for their doctors to support the use of these metabolic therapies.

Another book – I mean, I think we've talked about briefly more of the history of cancer – is *The Emperor of All Maladies: A Biography of Cancer*. This is a great book to read prior to reading Thom's book. Because it presents the whole history of cancer, right? The author is very articulate. It reads like a very suspenseful novel. But it leaves the reader kind of desperate for a therapy. It's basically kind of talking about the failure of modern medicine to provide us with an answer as to why cancer occurs, how to prevent it, and how to treat it.

I think Thom's book picks up where that book leaves off. It gives a firm scientific background and rationale for a metabolic origin for cancer and delves into the biochemistry and the physiology of how metabolic therapies work and how to implement them. And there are resources within the book that can guide the patient for that.

A friend of mine by the name of Ellen Davis maintains a website that has been really helpful for a lot of patients I come in contact with. It's one of the first websites I direct people to. That website is the KetogenicDietResource.com. The KetogenicDietResource.com is a very comprehensive website that describes how to implement the ketogenic diet. There are recipes on there. You're featured on there. There are a lot of links to your website.

Recently, Ellen Davis has finished a book that is a patient hand guide for using the ketogenic diet for the metabolic management of cancer. The problem I get with Thom's book – although it's very eloquent and he can kind of breakdown biochemistry in fairly simple terms – it's still over the head of many patients that seek a resource to help them. Ellen had completed a patient guide to the ketogenic diet. It's on her website. It's been a tremendous resource for people wanting to try this strategy.

The blood ketone and glucose meters that we talked about would be essential tools to assess the important biomarkers: the blood beta-hydroxybutyrate, which is one of the main ketones in blood glucose to ensure that you're in nutritional ketosis and you're in that metabolic zone that we talked about.

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Then if a patient achieves a metabolic zone, that therapeutic zone is when ketones are actually elevated above blood glucose. If those biomarkers can be achieved and maintained, typically what you see is it's either the tumor slows in growth, it completely stops growing, or it starts shrinking. You get three responses. Occasionally, you'll have people go into remission quickly after. There are some anecdotal reports of people with advanced metastatic cancer going into remission with nutritional ketosis.

In the people that I know, the few reports that I've seen, one of them, one person, I encouraged him to do a therapeutic fast. When implementing metabolic therapy for cancer, I think it should be encouraged that if the patient is healthy enough, they should undergo a therapeutic fast of five to 10 days or up to two weeks, if they're able to do it. If a patient's overweight, they should be able to achieve two weeks or 10 days of fasting, at least a week. I mean, I get a week, and it was fairly easy. But my health was good. I think the fastest way to get into nutritional ketosis is with a therapeutic fast.

During this fast, a patient can take non-caloric nutritional support, which could be in the form of chicken broth or coconut oil. I think coconut oil and MCT oil, although they provide calories, they can help someone overcome the glucose withdrawal symptoms that typically hit on day two or day three of a complete fasting. I found that that can be helpful in some patients. But a therapeutic fast followed by a restricted ketogenic diet is an effective way for a patient to implement a strategy to metabolically manage their cancer.

Now, they can use this as a standalone therapy, or they can combine it with standard of care. My recommendation would be to track the tumor growth with a CAT scan or MRI. If you implement a metabolic therapy, and the tumor shrinks or the tumor blood markers go down, then I would discourage someone from using chemotherapy or the standard of care, especially if the standard of care has been shown in their particular cancer to be largely ineffective for their type cancer, which is often the case, especially with metastatic cancer.

JM: Almost all.

DD: Only few cancers are responsive to the standard of care. Now, my colleague at Barrow Neurological Institute, Adrienne Scheck, is working on and, I think, has gotten the administration there to conduct a clinical trial that combines the ketogenic diet with radiation.

Now, I'm not a big fan of radiation, and Thom Seyfried is not a big fan of radiation. But Adrienne Scheck is a brilliant Ph.D. researcher at Barrow Neurological Institute. She's done some research on a brain tumor model in rodents and has been able to achieve complete remission in an aggressive brain tumor model with combining the ketogenic diet with radiation.

As we talked about, the ketogenic diet puts tremendous metabolic stress on the cancer cells by limiting glucose availability and elevating ketones, which may actually have an anti-cancer effect that we're studying right now. She's demonstrated that the ketogenic diet can prolong survival. But in several animals within the group that receive the ketogenic diet plus radiation, some of them were completely cured of their aggressive brain tumor.

I'm not aware of anyone that has been able to demonstrate this, this particular syngenic animal model of a brain tumor, which is most similar to a glioblastoma. Adrienne's work is published in *PLOS ONE* journal. If you just Google "the ketogenic diet and radiation," you'll come across this work. This is an example of someone that, you know, and a

study that combines the ketogenic diet with the standard of care (radiation), and showing a synergy there. That is important.

Once again though, the track record for the standard of care, particularly radiation, is not very good. But we have studied radiation with people eating a standard diet. In many cases, the people are encouraged to overconsume nutritional products like Ensure (which is basically just like sugary milk), and to overconsume excess calories to prevent the side effects associated with radiation, which is nausea and things like that.

The question is if perhaps we can unmask the potential benefits of the standard of care, if the patient is maintained in nutritional ketosis. That's a question that needs to be addressed and studied. My gut feeling is that all attempts should be made to pursue a non-toxic therapy...

JM: Sure.

DD: For cancer and other neurological diseases like ALS and Alzheimer's.

JM: Which is why I was interested in the synergy that you mentioned with the hyperbaric oxygen.

DD: Yeah.

JM: Which is available from many natural medicine physicians.

DD: Yes.

JM: It's not that difficult to find. But I'm wondering, if a person has metastatic cancer, what your gut feeling is. Because I know this probably hasn't been studied. But if a person had that, and they were to implement this radical… I mean, not radical, but very disciplined application of ketogenic diet with hyperbaric oxygen, what's the effect in this? What's your gut feeling? To me, probably over 70 to 80, maybe even 90 percent effective. Obviously, it depends on when you implement it and how rigid. What's your best guess as to how effective it might be?

DD: That's a difficult question to answer.

JM: Yeah, I know but just…

DD: My answer is that it will be more effective than metabolic therapy combined with hyperbaric oxygen. It will be more effective than anything currently available that I know of.

JM: Yeah.

DD: There are a lot of reports on the Internet of this or that working. Producing a sustained hypoglycemia with therapeutic ketosis and combining that with another modality that's non-toxic like hyperbaric oxygen therapy is a win-win situation in my book, because you're not compromising the long-term health of the patient. The main side effect of chemotherapy and radiation is cancer. You're damaging the genetic

material, the DNA of cancer cells by hitting them with a cytotoxic chemotherapy and radiation. Typically, what you're doing…

JM: It impairs your immune system**.**

DD: That's just buying time.

JM: Yeah, it impairs your immune system. And your immune system is what you need to fight the cancer.

DD: Good point.

JM: It's destroying the very process that your body desperately needs.

DD: Very good point. A robust immune system is very important for beating cancer long term. If your immune system is compromised, it's setting you up for getting a major recurrence of cancer, an aggressive form of the cancer, and setting you up for even different cancers in the future.

Hyperbaric oxygen has been shown to be very immune-stimulating. A colleague of mine that's at University of Pennsylvania, Stephen Thom, was there and demonstrated that hyperbaric oxygen can increase stem cells, the release of stem cells and the production of stem cells. You have drugs like GM-CSF (which is sold as Leukine) and G-CSF, which is sold as Neupogen, I believe. These things cost like a thousand dollars a week to take. And they work by elevating, by stimulating the release of stem cells in the body by stimulating your bone marrow.

Now, hyperbaric oxygen has essentially been shown to do the same thing. You have a mobilization of stem cells. So, where do stem cells go? If they're therapeutic, that's another question. But for example, if someone has a wound injury and they undergo hyperbaric oxygen, you have a mobilization of these stem cells. They tend to hone in on the site of injury and assist in the repair of the wound, for example.

How they're doing that is also another question. Whether they're releasing anti-inflammatory factors or actually becoming cells of the same phenotype to build the scaffolding for the wound itself is what people are studying. We're actually studying that.

There are modalities out there that are not in the pill form, that are not sold by Big Pharma. There may not be a whole lot of profit potential in suggesting that someone do fasting and the ketogenic diet. But we know from the science and anecdotal reports that these are very valid therapies…

JM: And they are.

DD: That can be implemented cost-effectively by the patient.

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Hyperbaric oxygen can be a cost burden. One of the questions that we want to address is do you need to get inside a hard-shell hyperbaric chamber to reap the benefits of

hyperbaric oxygen therapy? We're going to design a dose-response study where we use 100 percent oxygen at normal pressure, putting essentially, you know. A person can put on a mask and breathe…

JM: Sure.

DD: One hundred percent oxygen. Or using a low level of hyperbaric oxygen like 1.3 atmospheres of oxygen. There are various soft-shell chambers in the market, like, anywhere from 3,000 to 5,000 dollars that are available. That can increase the partial pressure, the barometric pressure in a 100 percent environment. You can get mild hyperbaric oxygen.

JM: Yeah, but you need…

DD: The question is will you get the same robust response in our animal model with that? That could be very useful from a practical…

JM: Well, you have to keep us posted. What you're seeking to find is the MED, the minimally effective dose.

DD: That's right.

JM: That would be a very profoundly useful information.

DD: Yeah. There's a big difference between telling someone that they need to do two atmospheres of hyperbaric oxygen five times per week, which is the standard protocol, to pay up to 200 dollars per session and go to a hyperbaric oxygen clinic, where perhaps 1.3 atmospheres of oxygen in a low-cost, soft-shell chamber or even 100 percent oxygen normal baric pressure just three times a week could yield the same benefit. These are questions that we want to address.

We tested the standard level of oxygen just because that's what people do. It's kind of an arbitrary number. But we figured we'd start with that, and then do a dose-response to see other benefits.

JM: But you have to keep us posted. If your future experiments show that they need a higher dose, it's a little more costly, but it's a lot less expensive than the alternative, and it's a lot more effective. So, ultimately, you want something that's going to work.

DD: Yeah, absolutely.

JM: It would be great to find what the lowest dose possible is working.

DD: Yeah.

JM: But even at a high dose, it's probably more than worth it.

DD: Yeah. And I need to stress, too, that the work that we've done was in an animal model of cancer. There have been reviews on the effects of hyperbaric oxygen therapy in cancer patients. The weight of the evidence supports a therapeutic benefit to

hyperbaric oxygen, especially for things like radiation necrosis and different… But all these studies we're not done in patients that have achieved nutritional ketosis.

Nutritional ketosis, I believe, will kind of synergize with hyperbaric oxygen therapy and will allow the benefits to take place. There are many reasons for that that I can go into biochemically. But I think that's what needs to be done. That's what we've shown even in our animal models: giving a standard diet with hyperbaric oxygen therapy, gave a trend for increased survival, but it wasn't like a major statistically significant finding. But it's only when we combine hyperbaric oxygen therapy with a nutritional therapy that we saw the true benefits being achieved.

JM: Sure. Full metabolic benefits, which is great.

DD: Yeah.

JM: Well, it has been an absolute delight to connect with you. You've enlightened so many of us on this really important topic. I'm sure it will be reviewed by many over and over again, because there's a lot of information here. So, I want to thank you for joining us. And I want you to continue your research. Hopefully, we'll have a long collaboration and you'll update us in the future with your finding.

DD: Yeah, we have a lot of projects ongoing right now. One will be released tomorrow, as I mentioned. But yeah, thank you for having me. It was a pleasure to be on your show here. Yeah, let's keep in contact. I can keep you abreast of what we're doing and new things on horizon.

The main goal is to get these therapies into clinical trials. For that to happen, we need funding. Right now, we've applied for funding, but as you know, the cancer industry or research, much of it is funded by the pharmaceutical companies.

JM: Sure.

DD: There are really no companies like that that are funding the kind of therapies that we're developing. We're positioned to make even a little bit of funding go far. So, if we can kind of develop the funding to validate these therapies in a pre-clinical model that sets us up for getting approval to do this in human clinical trials, which will give the evidence that people need to be able to embrace this therapy and for their doctors to help them.

The main problem we see is that patients want to do this. They know it's effective, but their doctors have never heard of it. They're not going to assist their patients and help their patients implement these metabolic therapies, simply because they're not trained in nutrition. That's one of the problems. But they're looking for the human clinical trial. There's the logistics behind doing a diet study and also who's going to fund it.

JM: Right.

DD: We really need to do this.

JM: A lot of work ahead of us. All right, well, thanks so much.

[END]