Health Effects of The Carnivore Diet: A Special Interview With Dr. Paul Saladino

By Dr. Joseph Mercola

JM: Dr. Joseph Mercola
PS: Dr. Paul Saladino

JM: Welcome, everyone. This is Dr. Mercola, helping you take control of your health. Today we are joined by Dr. Paul Saladino, who's going to enlighten us about the carnivore diet, which I'm sure you've heard a lot about recently, primarily used to treat autoimmune disease. Initially, I was highly skeptical, except for those who clearly found benefit from treating their autoimmune problems. But once I listened to Paul explain the detailed analysis and justification for this approach, I really changed my position.

What surprises me though is that he is a relative newcomer to the field. He's still finishing his training. He's still a resident. I mean, soon-to-be-graduated, but still a resident nevertheless. What I want to explore initially. You'll see real quickly how bright this guy is. He really is an exception. Most physicians do not dive deep into the literature and develop an expertise that is so profound. I want to explore that first because you'll see real quickly the level of his knowledge on this subject. It will astound you, I assure you. Welcome and thank you for joining us.

PS: It's so good to be here. Thanks for having me. I'm really excited to have this conversation with you and share it with everybody.

JM: Yeah. They're going to be really astounded by what you have to share. But before we start – I'll let you take it over. But I want to understand deeply – I emailed you this last night – how you got to be so comprehensively knowledgeable about this topic. As I said in the intro, most physicians do not dive deep into the literature, and you're still a physician in training, although you were a physician assistant (PA) before you started. You had some experience there. Walk us through your journey to get here.

PS: It's been a pretty interesting journey, quite circuitous. I graduated from college in 1999. I went to the College of William and Mary, studied chemistry and biology and did a whole bunch of molecular biology research there. My dad's a doctor, so I kind of had this – I [was] kind of steeped in medicine throughout my career, throughout my pre-career years and throughout my childhood. I've always seen medicine as something I was interested in. I've always been interested in the way that health and disease affected quality of life and the way that food affected the way that I felt as a human being.

I've been an athlete for most of my life, running and backcountry skiing and climbing mountains and so on. I was always kind of tuned into connections between food and health and disease. But when I got out of college, I thought, "You know what? I'm going to take some time off." Maybe this was the genesis of trying to think outside of the box or wanting to think about things differently or being curious about different ways of looking at paradigms. But I took six years off after college and just spent the time in the mountains, exploring and adventuring.

JM: Wow.

PS: Perhaps I already had this sort of seed within me of just questioning norms and asking interesting questions or being very curious. But I didn't, that time certainly, kind of fed that. I hiked the Pacific Crest Trail, which is a trail that goes from Mexico to Canada. It's 2,700 miles. I climbed mountains throughout the Pacific Northwest, the Rockies in Colorado. I got into mountaineering and backcountry skiing. Eventually, I realized that I really loved biology. I was really curious about some of these health questions. I wanted to go back to school. My dad is a doctor. He's an internist, an incredible man who spent so much of his life caring for patients. But I also saw him spend a lot of time working and not a lot of time being able to achieve balance and real self-work.

My original inclination was to go to physician assistant school. I went to PA school at the George Washington University, and then eventually started working in cardiology with a group of cardiologists in Bend, Oregon. Cardiology was kind of originally a good fit for me because I thought I was a runner at the time. I was so interested. Cardiology is fascinating as you know. It's just such an interesting conglomerate of blood pressure and lipids and interesting drugs and how we can manipulate the body in these fascinating ways. I just thought it was such an interesting field to go into. But what I realized quickly, this is what maybe is unique about my training. It's that I kind of cheated. I went to medical school twice. Not everybody gets to go to medical school twice. What happened was that –

JM: Why don't you stop there? Because some people may not understand what a PA is. In my view, it's a shortcut to being a physician. You essentially have almost nearly identical practicing privileges, although they're under the authority of a supervising physician. You would see the same two years of basic clinical science. It's accelerated. You did go to med school essentially twice.

PS: Yeah. I mean the PA school was pretty wild. The process of getting into PA school is often felt to be just as rigorous as getting into medical school, because they know they only have you for two years, and they have to teach you essentially what you're going to learn in four years of medical school. I went two years of PA school. I loved it. I just loved it. But you know, the first time I learned medicine, I could only see it as a neophyte. I could only see it as a new person. I couldn't get the perspective.

This was what was so interesting about my training. It's that once I started practicing as a PA, that was sort of my first medical career. In the beginning, I was just interested in like this beta-blocker or that beta-blocker or nuances of one statin or another or nuances of one type of arrhythmia and reading electrocardiographs (EKGs). But what quickly happened for me and my training was that I had this curiosity just bubble up. It became a passion and obsession to understand what was at the root of the disease, whether it was atherosclerosis or hypertension or atrial fibrillation.

I was primarily dealing with cardiovascular diseases, but I didn't expect this to happen. It took maybe about a year of actual clinical practice after PA school, but I started just having this massive curiosity about what was causing these things. I wanted to know how to change the course of a disease, how to get to the root cause of the disease. I know this is what you're fascinated by too. It

unites a lot of us in these fields. It's, "What is causing a disease?" This is the most interesting question to me and medicine. It's just fascinating.

That similarly birthed my second career in medicine. It was the beginning of the end of my first career in medicine. Because I realized very quickly into my career as a PA that I was going to want to go back to medical school to get an M.D., to get a doctoral degree, to continue my training, to have the ability to practice as a physician, and to do that practice from a perspective of someone looking for root causes of diseases. That's really been my focus. I ended up working as a PA in cardiology for four years. At that point, I went back to medical school at the University of Arizona in Tucson, which has a pretty strong history of integrative medicine. That's where Andrew Weil is.

JM: Sure.

PS: They have the Center for Integrative Medicine there. I was able to work with those physicians. At that time, I sort of discovered functional medicine. There are all sorts of names that people give to root cause medicine now. I think they're all good, whether it's integrative or functional medicine or whatever. This is really what became my passion. As I'm sure you will understand, when I began to describe for myself, what I began to discover in medical school. As I looked at medicine differently was that food seemed to be such a huge part. The things that we are putting into our body really seem to be a big part of what created health and disease.

JM: Let me stop you there, because we have so much to go into. I just want to applaud and acknowledge that you are indeed a pretty uncommon anomaly in this field, at least in my experience. It's the rare physician who has this type of motivation to seek the fundamental cause of disease and have this intrinsic, just burning curiosity that drives you. My guess is it's less than 1%. It probably is less than 1% of 1%. You are an anomaly. Thank God for people like you, because it's only individuals like you who are going to push us ahead. I really applaud your efforts.

Thank you for sharing that perspective of how you got into this, because I'm sure virtually anyone who is really curious about what you're going to share next is going to ask the same question. Because when I looked at your – I watched two to four hours of your previous interviews. The first question I had, "How did you get to be so darn knowledgeable about this field?" Your explanation provides this. Why don't you step us through your journey into your first encounter and exploration of the carnivore diet and just take it from there?

PS: This is where the story I think really gets interesting. Just like my time as a PA was instructive and kind of set the stage for my kind of self-examination and my realization that root cause medicine was what I wanted to do, it was probably the seven years that followed that, four years in medical school and my first three years of residency. Right now, I'm in my last month of my four years of residency at the University of Washington. I've got one month left to finish residency. But it was really the first seven years of my medical training after being a PA that kind of set the stage for this next sort of exploration, curiosity, realization for me.

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What those seven years were for me was – I mean, I already knew a lot of medicine. I went to PA school. I've been practicing for four years. I had this incredible privilege to see medicine through the eyes of someone who had been in the trenches. I thought, "Okay. Now I'm learning medicine again. What is going on here?" Every time I learned something, I thought, "What is the root cause here? What is going on?"

What happened for me was this constant kind of disappointment, this constant sort of struggle realizing, "The pharmaceuticals are incredible, but they're not treating the root cause. People don't often get better."

What I say now is that I was looking for sharp tools. I was looking for tools that worked. What I found for the first seven years for the most part – I hope this won't sound flippant – what I found for the first seven years of my training was tools that didn't work. I've joked with my colleagues that I feel like for most of residency and the medical school, I was being tasked with fighting a tyrannosaurus rex with a plastic spork. You're being tasked with treating complex disease, whether it's psychiatric disease or autoimmune disease. I would actually formulate most psychiatric disease is autoimmune.

But I was being asked to treat, in medical school, complex autoimmune disease, complex chronic disease, diabetes, inflammatory diseases, with a plastic spork. By that, I mean I was asked to treat those things with tools that didn't treat the root cause, which weren't that powerful. What I saw for seven years was people who got a little bit of relief, 5% relief, 3% relief and then relapsed, got worse or had a bad side effect or had a bad complication of a medication that we gave them.

For seven years, it was this process of sort of losing my religion again and thinking, "Oh, man." I just haven't seen powerful tools. I'd seen glimmers. I'd seen glimpses of powerful tools, but I was on the search for powerful tools. I wanted something that looked like it could really start to address the actual root causes. Like I said, I kind of had the suspicion that it was diet. What I'm learning is that there may be an ideal diet for everyone or it might be individualized. It might be some of both in there.

When I discovered the carnivore diet, I've been thinking about ancestral norms and evolutionary ideas. "Where have humans come from? What is written in our book of life? How do we eat? What is the most congruent way of eating for humans that is going to give us optimal health?" I've kind of been thinking about them throughout medical school and residency. But all of my iterations hadn't really been as effective as I'd hoped they would be, and then I discovered kind of this notion that it's the carnivore diet. It's super radical. I'm so excited to tell people about it and share more with you about it.

But, you know, when I first heard about it – I think I heard Jordan Peterson on the Joe Rogan podcast. He talked about his daughter Mikhaila. Mikhaila Peterson has an incredible story. She had very bad juvenile rheumatoid arthritis (JRA), which is a significant autoimmune inflammatory issue, which caused her to have multiple joint replacements at a young age. It pretty much crippled her. She kind of discovered this way of eating only animal meat.

We can go into how I would construct a carnivore diet. I really believe you should eat the whole animal. What happened for her slowly – She describes this kind of arduous journey over months, weeks to months, was that her symptoms slowly started to improve. I thought, "That is a wild story."

In medicine, we talk about case reports. I love case reports because I wanted to see how things actually worked at a real level. I love seeing someone with a problem and something improving it. It was so striking to me that someone like Mikhaila Peterson could essentially reverse and completely heal from JRA and then the depression that was connected with it, probably because of the concomitant immunologic and inflammatory mechanisms with this radical dietary change. I thought, "That is really striking. I want to study that." Then Jordan Peterson talks about the fact that he had kind of anxiety and sleep apnea and other issues himself. They improved when he started eating an animal-based diet.

I thought, "Isn't that fascinating?" Because for the last seven, 12 years I've been thinking, "We've sort of been told plants are good for you. Plants are the answer. Plants are the best thing for humans." I love that this notion just turned it all on its head. It just tipped everything over and I thought, "Wait a minute. It kind of makes sense. Maybe plants don't want to get eaten. Maybe plants aren't good for humans?"

At the beginning, I was very skeptical and I thought, "I really need to dig into this," and so I did. I loved the adventure. I think that's the previous life, you know? That's the ski bum. That's the thru-hiker on the Pacific Crest Trail. It was such an intriguing idea. It was like somebody handed me a treasure map and said, "Hey. This is cool. You should see what's at the end of this map. You should see where X marks the spot." I thought, "This is such an intriguing concept. I want to pursue it. I really want to dive in here."

This fundamental premise, this idea that plants and humans, plants and herbivores or plants and animals have coevolved, and every one of us, every life form really has one goal. That's to push its DNA into the next species and to continue the lineage of that species. A mustard plant wants the mustard plant to continue. An oak tree wants the oak tree to continue. Life and ecology is this beautiful intermingling of all these species working together but fighting and eating each other and trying to kill each other, but sometimes being symbiotic. This concept that "Maybe plants don't want to get eaten after all," maybe this narrative, this unconditional narrative I should say, that all plants are good for you all the time, maybe we should question that.

That's a pretty radical concept, because I think even within the functional medicine sphere, there's this notion that all plants are good for you and the more plants you eat, the better. But this really counterculture, disruptive concept that for some people, perhaps for all of us, perhaps just for some people, plants can be triggering autoimmunity through a variety of mechanisms is really intriguing. That's been the most exciting adventure in my medical career, this treasure map that I've been following. Here I am, just like way down the rabbit hole, just digging in.

JM: Great. Did you integrate any of Dr. Steven Gundry's information on the lectins that may be contributing to autoimmune disease in his book, "The Plant Paradox?" Which pretty accurately describes his premise, how plants, which are allegedly beneficial for us, can be harmful at times.

PS: Absolutely. I had heard of lectins before I kind of dove into the carnivore world. Those seven years in medical school and in residency, I'd experimented with all sorts of different diets. I had kind of my own issues that I was trying to improve. I had eczema. As a kid, I had asthma. I've always had this kind of atopic tendency. Eczema is this kind of itchy skin condition that people will know about. It goes hand in hand with asthma in this sort of atopic sphere, this atopic group of conditions.

I was thinking throughout medical school and residency, why did I have this eczema? It gets really bad sometimes. I got very much into jiu-jitsu when I was in medical school. At one point, I got such bad eczema on my knees that I got impetigo. The eczema got super infected. That's impetigo, when the skin gets super infected with the strep bacteria. I had these things that were kind of just nagging. I thought, "You know, I'm doing paleo. I'm doing autoimmune paleo. I'm eating 100% organic. I'm trying to remove the highest lectin foods and I'm still having these issues. There's something I'm missing here. There's something I'm missing." That was kind of always the driver.

I always wanted to optimize because I wanted to understand, could I be a little better because I knew that my experience would be the first step toward understanding what my patients were going through. I think that one of the fascinating ideas in medicine or one of the ways that I differ greatly from mainstream medicine in my conceptualization, in my nosology, is I don't believe in 76,000 diseases. I believe in like five diseases. Everybody manifests them a little differently. I kind of knew that my autoimmune disease was probably the same as almost everybody else's autoimmune disease.

If I could understand what was triggering my autoimmune disease, maybe that will be the first start of this journey, this first thread that I could pull on to understand what was causing other people's autoimmune diseases because autoimmunity, inflammation, these are almost synonyms. Gosh. If we can understand that, we can help a lot of people. A lot of people need that help. I was just going through this process. Steven Gundry's work was a part of it. I think that now I would disagree with him on many issues.

JM: Really? That's surprising. I'd be curious to see where your disagreements are.

PS: Well, you know, he was recently on Ben Greenfield's podcast. One of the ideas – Say that again.

JM: Just a week or two ago.

PS: Yeah, yeah. Steven has some great ideas about lectins. He's done a great job at sort of popularizing the notion that lectins are contributing to disease. He has said – I don't want to put words in his mouth, but I've heard him say that he's a plant predator. I think that what he's done is sort of create this paradigm whereby he's tried to create the lowest lectin, plant-based diet that he can with a small amount of meat.

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I've spoken about this before. But I think that he and many others are misunderstanding a series of studies done in the '60s and '70s with rodents and methionine overfeeding that suggested excess levels of methionine would shorten the lives of these rodents. Because Steven Gundry and some other people have said, "Animal protein shortens lives of humans." I've heard him say this. I wish it wasn't the case, but it is. I'm thinking, "Why do you think animal protein shortens human's lives?" We can get into this if we talk about mTOR and leucine and stuff as well.

JM: Colin Campbell has written a lot about that too. There are a lot of vegan physicians who hold that position.

PS: Right, right. My impression – I always try really hard. I was actually a vegan 13 or 14 years ago. I kind of explored that. I'm fascinated by that way of thinking. I'd like to understand the plant-based article and see what they're offering as well. My impression is that most of the plant-based physicians, when they're saying the animal protein shortens lives, they're referring to these methionine studies. The idea here was that in rodents, in mice and rats, when they overfeed methionine, which is one of the sulfur-containing amino acids, they do see shortening of the lifespan. Mice and rat diets are very different than humans'. They have chow and they're not eating like mice salad and mice steaks. It's this contrived model in some sense. We can adjust how much methionine is in a mouse or a rat diet.

What they see is that when they push the amount of methionine in a diet up to 2% or a little more, they'll get a decrease, a significant decrease in the lifespan of the rodent. Their conclusion originally was, "Oh. Their excess methionine is shortening people's lives or it could shorten human lives as well." There's actual human biochemistry to suggest why that might be the case. Animal protein is richer in methionine. Animal protein could shorten human lives, or animal protein may be leading to shorter or smaller amounts of longevity for humans.

Steven Gundry has kind of said this. I always think like – I really want to sit down with him at coffee and say like, "Let's talk about this." Because if you look at the rest of the studies, what they show – this is the fascinating part – is that when they did the next study they did, they took the methionine out of the diet a little bit. They did methionine restriction. What did they see? They saw lengthening of the life of the rats. "Okay. That's interesting." That was sort of further strengthening their first hypothesis.

But then the magical thing happened. They gave them a large amount of methionine or the same amount of methionine, 2% of the diet with more glycine. What did they see? They saw extension of the lifespan. Then they realized – This is what I think everybody's leaving out. It's that it's not about the excess methionine. It's about the imbalance and the methionine-glycine ratio. We know this from human biochemistry.

If you look at the folate cycle, if you look at methylation, if you look at the way we handle methyl groups, methionine is a methyl-containing amino acid. We know that homocysteine is converted to methionine by a series of enzymes. This involves the methylenetetrahydrofolate (MTHFR) gene, which makes L-5-methylfolate. Your body uses L-5-methylfolate with homocysteine and the enzymes methionine synthase (MTR) and methionine synthase reductase (MTRR). I hope I'm not getting too granular for people to convert, to add a methyl group to homocysteine to make

methionine. Methionine is the methyl donor for S-adenosyl methionine (SAM-e). SAM-e does all these methylation reactions – Or methionine, I should say, is the precursor to SAM-e. SAM-e is S-adenosylmethionine. SAM-e does all these methylation reactions in the body.

But what we know is that excess methionine is buffered by glycine. Our body will use glycine to buffer methionine. If we get too many methyl groups and we don't have the corresponding amino acids to buffer them, the biochemistry can get kind of messed up. Then the hypothesis, which I think is fairly compelling, is that too many sulfur-containing amino acids can create oxidative stress. Homocysteine is a sulfur-containing amino acid. I think there's good evidence that too much homocysteine probably causes oxidative stress by the same mechanism.

What we're looking at is a balance between sulfur- and non-sulfur-containing amino acids. We need the glycine, which doesn't have any sulfur, to sort of balance and buffer the methionine. There is this interesting concept that if we eat too much methionine, we will imbalance glycine. Glycine is such a crucial amino acid. If we use up all of our glycine to buffer methionine, we won't have enough glycine to make two very critical proteins. That would be collagen and glutathione. I know you've spoken a ton about glutathione, and your listeners will know about that.

JM: Let me just insert here also that aside from those important amino acids for sure, another one of our passions are nicotinamide adenine dinucleotide (NAD), the coenzymes NAD and nicotinamide adenine dinucleotide phosphate (NADPH). You could perhaps expand on that a little bit. But glycine – you're absolutely correct – is one of the important amino acids to construct glutathione. But it's also really important to increase your NADPH levels, which is massively crucial to keep your antioxidants recharged. Why don't you talk about that and then how the glycine isn't part of the nose-to-tail concept that you're promoting?

PS: Yeah. This is super fascinating. If we look at glycine, it's this magical little amino acid. I think it's got to be the simplest amino acid.

JM: Smallest for sure. Yes.

PS: Yeah. It's an interesting idea, because if you look at where methionine and glycine are found in animals, in muscle meat, muscle meat is about 2% methionine and about 7% to 8% glycine. So there's more glycine than methionine in muscle meat. But then if you look at connective tissue, connective tissue is about 0.9% methionine and about 23% to 24% glycine, which isn't surprising because connective tissue is essentially mostly collagen.

We know that collagen is usually constructed with three amino acids, which are glycine, proline and hydroxyproline. We would expect that a collagenous tissue would be mostly glycine, proline and hydroxyproline. Essentially, a one-to-one-to-one ratio, making up about 90% of it. About 30% of the amino acids in collagen are glycine, because it's one-third of the molecule. What we see is that there's a real difference in the collagenous tissue versus the muscle meat.

When we are thinking about eating a carnivorous diet, I am a strong advocate for this concept of nose-to-tail eating, this idea that evolutionarily, our ancestors were certainly eating the whole

animal, both from a spiritual perspective or a respective perspective for the animal and from a functional pragmatic perspective. They wanted all the calories and all the nutrients.

If you look at an animal, there are unique nutrients in the muscle meat. There's a whole unique set of nutrients in the liver, and a whole set of unique sort of amino acid composition in the connective tissue. There are unique nutrients in the bones. There are unique nutrients in the bone marrow and the fatty tissues. You can see this animal as this sort of fascinating partitioning of nutrients. The idea of a carnivore diet or a whole-foods, animal-based diet became much more viable for me when I realized and I remembered and sort of relearned studying anthropology that our ancestors were in fact eating the whole animal.

Every indigenous culture that I'm aware of on the planet that's living now eats the whole animal. Then you think, "Now it makes sense." It's not just about eating steak. You're really getting this incredibly diverse array of nutrients in the whole animal. When you sort of look at this from a first principles approach and break it down, we have a pretty good sense. I don't ever want to believe that as physicians or in the medical profession, we understand everything that a human needs, but we have a pretty darn good sense of the vitamins and minerals that a human needs.

One of the most elegant symmetries in this process for this hypothesis of eating animals nose to tail is this idea that you and I strongly believe that there's evidence that you can get all the nutrients that a human needs to function optimally eating an animal nose to tail. You can get every single thing that we need. It's really interesting to kind of break it down and say, "You're getting calcium in the bones. You're getting copper to balance the zinc in the liver. You're getting this B vitamin in the liver. You're getting this B vitamin in the muscle meat." But what we find is that we have to eat the whole animal. If we just eat the muscle meat, we're really going to be missing out on nutrients.

But that's such an incredible postulate to say, "Wait a minute. I can get all the nutrients that I need as a human by eating an animal nose-to-tail? That's incredible. It's like a multivitamin. It's like the best multivitamin ever." I would argue further that animal-based nutrients are much more bioavailable than plant-based nutrients. They're in the right ratio, which are incredible if you look at zinc, copper, calcium and magnesium.

Then it kind of makes sense when you think about it from an evolutionary perspective. A deer or an elephant is a mammal. They're much more similar to a human operating system, to a human physiology, than a plant is. We can get some nutrients from plants, but an animal looks so much more like us, that it's so much more compatible with our biochemistry when we take it in. The last part of the equation is that we can do all that, eating animals nose-to-tail without any of the anti-nutrients, which we can talk about that might be present in plants. It appears that some people may be uniquely sensitive to those anti-nutrients.

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My hypothesis, my postulate about that is that may be the root cause for a lot of autoimmunity. But going back to your original question, this is totally true, what you're saying. It's that when we eat nose-to-tail, we're getting glycine in the connective tissue to balance the methionine in the muscle meat. The glycine does help us make NADPH. If we look at the red blood cell, it's a great

illustration of how NADPH is involved in glutathione, because you get this enzyme, G6PD, which is glucose-6-phosphate dehydrogenase. This is a very elegant illustration of what happens here.

What happens is that when you ingest glucose, your body makes glucose-6-phosphate. This enzyme, glucose-6-phosphate dehydrogenase dehydrogenates glucose-6-phosphate into a very complex molecule. But that process generates NADPH. Your body uses that NADPH to reduce oxidized glutathione as you were referring to. That process, that cycle of glutathione being reduced once it's been oxidized is crucial to human life. Glutathione is this molecular policeman. We talked about it.

One of the amino acids in glutathione is glycine, which we need. The glutathione molecule moves around the body, donating electrons. Glutathione becomes oxidized, lots of electrons in this oxidation. Glutathione donates electrons, two free radical-containing molecules, lipid peroxides in order to sort of quell that reactive species. It's this molecular policeman who says, "Hey. Calm down. You're acting a fool. Calm down." It's taking people who are disorderly and calming them down, and then glutathione has lost an electron. Now that NADPH molecule serves a crucial purpose of giving glutathione back that electron, regenerating all of our police force and keeping us safe from oxidative stress.

What happens in people who have G6PD deficiency is that they can't do that conversion between glucose-6-phosphate and the dehydrogenation step. They don't generate enough NADPH. They don't regenerate glutathione in the red blood cells. Because red blood cells don't have any mitochondria, that's the only way that they can generate glutathione.

When we put oxidative stressors into the system of people who have G6PD deficiency, whether that's fava beans with their oxidatively active compound, which I think is called divicine, we can create hemolysis or hemolytic crisis in people with G6PD. It's just an illustration of how important glycine is to make NADPH, to make glutathione, the way that glutathione is this molecular policeman. Again, it's kind of a roundabout way of also saying that there are these plant molecules. Favism, there are these plant toxins in fava beans that can be dangerous to people who can't do that conversion well. It's this really kind of intricate system that works together very elegantly.

JM: Great. Thank you for the explanation. Of course, you've mentioned that the red blood cells don't have mitochondria – really one of the only cells in the body or types of cells in the body that doesn't. Not only is it important for them to make glutathione, but that pathway, the G6PD pathway is also responsible for creating the energy for them to function. Thank you for sharing that. I want you to now comment on your perception of the percentage of people who are following a carnivore diet, like you advocate nose-to-tail. Certainly, Mikhaila Peterson is not.

Just as an aside too, I'm absolutely convinced because I've treated thousands of patients with rheumatoid arthritis. JRA is very rare. It's way less that 1% of the rheumatoid arthritis population. But I've treated a number of those too. But one of the important components of JRA or adult rheumatoid arthritis (ARA) is that they're almost universally vitamin D-deficient. Mikhaila lives in Canada. Any Canadian is vitamin D-deficient unless they're swallowing a lot of oral vitamin D. I am certain from listening to her story that she wasn't. That was an element too. But the direct

question, and you can take it from there, is what percentage of the people currently recommending and adhering to the carnivore diet are eating those?

PS: I think it's growing, hopefully. I would say my estimate would be 50%.

JM: Wow. That high.

PS: Maybe. I mean maybe it's only 30%. I suppose I'm gathering folks gradually. There are others in the community who are also advocating for nose-to-tail. Interestingly, I actually spoke to Mikhaila recently. She did say that she's eating liver. Yes, yes. I think she's doing better. I believe that Jordan is also eating liver now.

JM: Great.

PS: They're eating close to nose-to-tail now. That, I think, is a huge, huge piece of the equation. They're getting close. I think they're doing better with that. I was really happy to hear that.

JM: You just have to give them collagen or the connective tissue.

PS: Yeah. They're getting there. That can also depend on which cut of meat we eat too, you know? This idea that some people find the connective tissue and the collagen to be the easiest way to get glycine or probably if we just eat connective tissue from the animal, if we were eating tendons or not cutting the chewy tendon or the chewy bits off your steak, you're going to get collagen and glycine that way too.

It's sort of a redefinition of the way that we imagine eating steaks. If you're going to eat nose-to-tail, you don't want to cut out all the fatty bits, all the collagenous chewy bits of your steak. Those are precious nutrition. I think that maybe – I don't know. Maybe it's an overly optimistic thing. But I think that at least 40% of people are trying to do it. I see more and more people.

I get these messages on Instagram every day now, which really make me happy. They say, "I did carnivore once. I didn't feel great." Some people do carnivore as meat-only and feel good. That's awesome. I do have worries about long-term nutrient deficiencies. But if they're feeling good, then I'm happy for them. But then a lot of people try it and they don't feel good on just meats or meat and eggs, and then they try more of a nose-to-tail approach and they'll send me a message and say, "Hey. I tried the nose-to-tail approach and it's working better. My digestion is better. I have more energy," or "I feel better." That makes me really happy. I think, "That's great. I'm so happy that they're doing better with that suggestion." Yeah. I think it's growing.

JM: That's good, that's good. Do you think it is possible for those who don't particularly enjoy connective tissue or collagen supplements to receive most of the benefits from just using the glycine supplement? Which is relatively inexpensive. It actually tastes sweet, like sugar, so it's really easy to consume. It's not bitter at all. A lot of people are advocating it. I personally take some glycine supplements. I take collagen. I take 30 or 40 grams of collagen protein a day, but I still take the glycine because it's such a magnificent amino acid.

PS: I agree 100% with you. I agree 100%. I recommend this to my patients when they have histamine issues or if we're trying to figure out sensitivities to bone broth. The histamine thing is quite complicated. But it seems that some people, probably because of glutamate and the formation of bone broths or the hydrolysis process of collagen may form compounds that are glutamatergic in the brain, they seem to have some sensitivities to those things. In that case, glycine is a great option for people. Like you said, it's kind of a magic hack, for lack of a better word. It's sweet like sugar, so people could add it to a warm beverage.

I mean as we talk about it, I have some concerns about tannins and teas maybe potentially causing irritation of the gut. But they can add it to things and it is sweet. It's not a hard thing to take at all. Even if you just put collagen in – glycine in water, people will find – I've used it. It's like a recovery drink or something after a workout. It's very easy to take. It's very pleasant. The other thing – Yeah. Go ahead.

JM: No. Finish it. Finish your comment.

PS: The other thing that I've run into sometimes is that people struggle to eat organ meats. This is a really unique thing that I think is happening now. There are all sorts of great companies, like Ancestral Supplements and some of these other companies that are now providing organ meats and desiccated organ tablets.

I love this trend in these companies. We're starting to see supplements that are actually animals. People can supplement with like desiccated liver. If they absolutely can't get their own liver, these companies are sourcing grass fed animals from New Zealand. They could get brain, liver, pancreas and spleen. A lot of people are finding improvements in histamine issues with kidney. The best thing would be to eat kidney, because it has diamine oxidase, which is sort of this interesting thing. But a lot of people are taking now now the desiccated organ complex with kidney from Ancestral Supplements or another manufacturer and getting improvements in histamine issues because of the DAO, the diamine oxidase, that's in that.

I love that the field is growing and there's a space in the market for it. Not everyone wants to eat liver or has access to kidney or access to brain. It's a new trend happening as well. It's becoming more and more doable because that's one of the criticisms of what nose-to-tail is. "I don't like liver. How am I going to get liver?" It's like – "You can get this now. It's available."

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JM: Or they may be concerned about getting prions from the brain too.

PS: Yeah.

JM: But I want to talk now about one of the concerns and one of my skepticism about the benefits and the value of a carnivore diet, which is the chronic activation of mTOR.

PS: Sure.

JM: But as I thought about it and as I've been listening to some of your presentations, it became obvious to me that it seems like a perfect hybrid and marriage would be to integrate this strong activation of mTOR, which is useful. A lot of people are afraid of mTOR. They're taking rapamycin supplements to suppress it all the time. But you need to activate mTOR, especially for your own health if you have any hope of ever gaining increased muscle mass. But if you activate it continuously, I think that's a prescription for metabolic disaster.

If you integrate an autophagy cycle where you're going through fasting or partial fasting on a regular basis, I think you can mitigate that effect and really radically improve it, and then you'd be activating autophagy. I want you to talk to that and also to the fact that it wasn't intuitively obvious to anyone, but when you are a carnivore guy, this is about as low-carb as you get. There's virtually no carbohydrates. You're going to be generating massive amounts of ketones as a result. You're already in ketosis. That doesn't necessarily mean you're activating autophagy because you're actually inhibiting it and activating mTOR. Talk about that and integrating both of those approaches. Then we'll dive into autophagy and some of the polyphenols you referenced earlier, because that's another fascinating discussion.

PS: Yeah. This is such an interesting discussion. I think it really illustrates some points for people that are important to note at this point. You and I have had some awesome conversations prior to this about how we activate mTOR. What I have learned in speaking with you and Ben Bikman and people who are deep in the space is that there are a couple of ways to activate mTOR. I'm sure your listeners are aware. But in case they're not, mTOR is the mammalian target of rapamycin.

It would be – In a gross oversimplification, it's kind of like the anabolic lever. It's the "build your body up" side of your metabolism. It's balanced by 5' adenosine monophosphate-activated protein kinase (AMPK), which is kind of the more catabolic. When we're eating whatever we're eating, whether it's carbohydrates of protein, we're sort of activating mTOR. We'll dig into that. When we're not eating, we're generally triggering AMPK.

The mTOR is the mammalian target of rapamycin. There's that fascinating story about the discovery of rapamycin on Rapa Nui, which is Easter Island. But it's this incredible interesting molecule that seems to inhibit mTOR. It has differential inhibition of mTOR, mTOR 1 versus mTOR 2, which are the two complexes of mTOR. But what we generally – I would agree with you. We probably don't want to over-activate mTOR. Again, this is an oversimplification.

Our overall understanding of this is evolving in medicine. But it does seem that over-activation of mTOR is too much. We don't want that. That makes sense. You don't always want to be anabolic in your life. There has to be a balance. This is sort of a Daoist concept. This is the yin and the yang. We need on. We need off. We need balance and flow. What's fascinating to me about the mTOR story is that when I really dug into this, the literature would suggest there are two ways to activate mTOR. There are different mechanisms, but they both do it. One of them is proteins, specifically leucine. One of them is insulin. What we see in the literature – And there's not a ton about this, but there are a few studies.

JM: Exercise.

PS: Yeah. In terms of insulin and leucine, if we compare those, if we look in cell culture, I think it was done in human myotubes, insulin had a much greater effect on mTOR turning it on. The insulin effect acted much longer on the order of three to four hours. Leucine certainly will turn mTOR on, but it has a lesser effect. I think relatively speaking at the risk of putting a number on it, it was about 30% less, and then it did it for only about 45 minutes to one hour.

What we're seeing here is we can activate mTOR with protein, specifically leucine load. Where there's going to be lots of leucine and P-protein or animal meat. People who are trying to build muscle on a vegan diet are going to use P-protein specifically, because it's the only real source of enough leucine to get mTOR activation probably. But if we activate mTOR with leucine, it's kind of on and then off about an hour later. If we activate mTOR with insulin, then it's going to be on for three to four hours. People can leverage this in whatever direction they want.

But with regard to a carnivore diet, some of the interesting discussion is around the question, "Will eating meat and a lot of meat –" again, you're eating nose to tail so you're not just eating meat, you're also eating connective tissue and fats and organ meats – "But will eating a large amount of meat, probably much more than the average person eats, over-activate mTOR?" I think what's interesting is it probably won't if we look at the molecular mechanisms, because it will primarily be a leucine switch of mTOR that we're turning on. It'll be kind of like on-off, on-off, rather than the insulin switch of mTOR.

Relatively speaking here, I think there's an interesting possibility that if we're eating carbohydrates, we're going to trigger more mTOR through the actions of insulin and the insulin-glucagon ratio than we are with protein. The carnivore diet is kind of like a unique example. Because like you said, there's essentially no carbohydrate. When we look at ketogenic diets, like a carnivore diet, we know that insulin is very low. When we look at fasting insulin, it's like less than three. I've seen some carnivores with fasting insulin that are like 2 or 1.5, the lowest fasting insulin levels I've ever seen. You know, when we eat food, insulin is going to rise. But on a ketogenic state, we know that insulin and glucagon are going to rise together. That ratio is not really going to change.

This comes up a lot in discussions with people. They say, "Isn't eating a lot of protein going to spike my insulin? Isn't eating a lot of protein going to turn on gluconeogenesis? My blood sugar is going to spike." That's not what we see at all, especially on a carnivore diet, because the insulin and the glucagon are going to rise a little bit, and they rise concomitantly, so then the insulin-glucagon ratio doesn't change. When the insulin-glucagon ratio stays consistent, you're not really activating mTOR through insulin. You're not getting a big insulin spike at all. You're not really switching over to – You're not really giving that big insulin hit that you'll see if you were to eat protein in a mixed state. If someone's not in ketosis, if they're not fat-adapted and you eat a bunch of protein, yes, you're going to get a big spike in your insulin. That insulin-glucagon ratio is going to change drastically.

But this is in stark contradistinction to the way that insulin responds when you're in a ketogenic state. This is what's kind of interesting about those two things. I would say that there's pretty good evidence that we're not going to over-activate mTOR with leucine on a carnivore diet. We're really not going to activate mTOR with insulin on a carnivore diet. Then the corollary is if we're really

worried about over-activating mTOR, we should think about carbohydrates more than we think about protein. This gets into this.

The next part of the discussion is also really interesting around what this means for humans who are trying to do bodybuilding or who are trying to activate autophagy. I totally agree with you. I think it's totally evolutionarily consistent to imagine that we were hunting animals. We were hunting a lot of animals. We were hunting big animals and eating a nose-to-tail carnivore diet at times in our lives evolutionarily. But then we were also fasting a lot when we didn't have an animal.

I think that, yeah. I think there's absolutely a role for intermittent fasting, time-restricted eating, longer fasts – 24, 48, 72 hours, where you really shut everything off and you turn AMPK. You think about really shutting mTOR down permanently for a little while, and then turning it back on with protein and meat. I think it's interesting. I think it's nice to have this more – I would argue that the meat or the animal foods are a little bit more of a precise switch for mTOR. You can just be like, "On, off, on, off." Like I said, you can exercise, turn it on, get anabolic, work, build muscle, regrow and then do other phases where you're kind of breaking down, doing autophagy or apoptosis even and totally recycling your cells. I think it's an interesting kind of this yin and yang cycle.

JM: Good. That was a great explanation. Thank you for bringing up the distinction. I don't think that most people are aware – I certainly wasn't until we dialogued about this – that the insulin is a far more profound activator of mTOR than the leucine is in a ketogenic state, which is a really important distinction. For me, one of the primary metabolic justifications for a carnivore diet. Let's step into the autophagy phase. You're in agreement with the need for that.

You'll generate some autophagy with intermittent fasting. I believe it's probably the ideal is six to eight hours to eat. I've come to the recognition that we're designed to sleep for eight hours, at least most of us. Wouldn't it make sense that we're designed to eat for eight hours and rest our gut for 16 to 18 hours? Doing that on a daily basis is a pattern I follow, but I may be mistaken. I'm not convinced that that significantly increases autophagy. It increases to a certain extent, but not a lot.

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To increase autophagy to the level that you'd like, you've got to go beyond 24 hours, probably into the 40-hour range and even beyond that. I don't know if it's necessary to go beyond that, because I think you might get 80% to 90% of the benefit at that level. I came up with the book, "KetoFast," which is published in April 30th. It's a brand new book that discusses this partial fasting, which you can do once or even twice a week, assuming that you're not losing too much weight.

I'm very curious because you've been in this field for a while now and really delve into the literature and certainly applying it on a personal level. I'm curious as to what your insights are into the frequency of this, because I think that is the relevant question. It's how frequent should you engage in this process? What is the timing of it? Is it once a week? Is it twice a week? Certainly

the longer fasts are going to be less frequent. I'm wondering if you've reached any conclusions or at least insights at this point.

PS: I think you bring up some great points there that I want to highlight around autophagy and stuff. I totally agree that the fasting is a crucial part of it. I recommend to all my clients. I think a piece of the carnivore diet, the way that I see it is absolutely, like you say, a time-restricted eating window. I think six to eight is probably ideal for most people as well. The other interesting piece of this is that a lot of people doing carnivore diets find themselves so satiated that they'll do one meal a day, so they get a 23-hour fasting window and a one-hour or a two-hour [eating window]. They'll eat for like two hours. They'll go to one of these Brazilian steakhouses and just eat. That's it. They eat one meal a day. They're having a long window.

But personally, I eat two meals a day. I would say 90% of the days, I'll get it within a six- to seven-hour window. Probably at 95% of the days, I get it within an eight-hour window. I've personally found that my sleep is better when I just eat breakfast and lunch and then skipped dinner. I have more time to digest. Everything is kind of done. I'm not digesting. I'm not doing anything really in terms of processing food by the time I go to sleep. A lot of people, in terms of time-restricted eating will do lunch and dinner. I think, "That's kind of the reverse. That doesn't make as much sense to me." But I do agree with the time-restricted eating.

JM: Do you want to hear an interesting insight on that?

PS: Yeah.

JM: As far as I know, I'm the one who figured this out. I haven't heard of anyone talk about it, but I'm sure you would appreciate this. It's that one of the other reasons, aside from putting your gut at rest, is that many people are unaware that the primary consumer of NADPH, which you referenced earlier, is creating fatty acids. If you're eating food before you go to bed and you're providing your body with energy that you're not using, then you have to do something with that energy, so you store it as fat. In other words, your body needs to make fatty acids.

As a result of that creation, your NADPH levels plummet, thus reducing your body's ability to recharge your antioxidant structure. I think that is really one of the most important features of not eating three or four hours before bedtime.

PS: I love it. I haven't thought about that. But I think that that makes a ton of sense to me. I mean I've heard all kinds of people report that benefit. I've heard Dr. Rhonda Patrick say, "I realize that I eat a long time before bed. I feel better." I like to extend that window as long as I can and do like maybe seven hours or six hours before bed. Yeah. I think it's something that people should talk and experiment with. Now that we've got all these devices, like the Oura ring and all these bands and stuff, people can see if their sleep quality changes.

But I know I've seen guys like Dr. Dom D'Agostino and Dr. Peter Attia post about decreased sleep quality when they eat too close to bed or do a workout even too late. It's such an interesting idea. But in terms of frequency of longer fasts, I think that that's a brave new world. I think you're

asking great questions there that I hopefully you and I will keep trying to answer and experiment in.

I don't know. I mean I think it would depend on body composition goals, potentially, on the overall health of the individual and what they can tolerate. I have some clients who are really working hard to leverage autophagy for weight loss and loose skin. I think, in that case, you could do it more often, as long as the metabolic parameters and all the electrolytes look good and you're under the supervision of a medical provider. You can do it more often. You could potentially do it – You could do 72 hours and then refeed and then do another 72 hours and refeed. You know, I think you have to keep an eye on markers of inflammation, markers of uric acid and markers you can check-reduce and oxidize glutathione and make sure you're not overdoing it. But like you're saying, I think that there probably comes a point at which it becomes counterproductive.

It's interesting when I see these five-day fasts or these seven-day fasts and people start to see their testosterone tank, the reverse T3 go through the roof, and the thyroid labs get really far down. It's quite interesting to see, like, is that at the 72-hour mark or is it – I think at the point that that starts happening, it's like maybe that's where you're getting maximum autophagy, or maybe that's when your body is like, "I'm done. I'm just shutting down right now." I think you can make a case at least theoretically that once you start to see testosterone drop and the reverse T3 go way up and the thyroid labs change, you're like, "Okay. Now it's time to refeed and then do it again," depending on what your goal is. For me, I try and do one extended fast per month, but I may not be doing it enough. I'm sort of flirting with that 48-hour –

JM: How long is your extended fast?

PS: Thirty-eight to 48 hours.

JM: Okay. Yeah.

PS: Two days.

JM: I think you're right. I think it really depends on what your personal goals are. Obviously, with 80% of the country being overweight, or 70% to 80%, depending on what region of the country you live, their primary goal is going to be to lose weight. They may need to do it more frequently. But for someone like myself and others that their goal is to improve your lean muscle mass – I'd like to gain about 20 pounds if I could. I was doing the partial fast twice a week, but I think that's too frequent for me. I'm going to bump it down to one. I think I could gain about 1 or 2 pounds a week of muscle mass.

PS: Yeah.

JM: Not visceral fat. I'm going to play with that. I think it really does depend. You've got to customize it for your specific circumstances.

PS: Yeah. I've noticed that if I do it too much, I will lose muscle mass too. For where I'm at, like with surfing and jiu-jitsu and working out and Muay Thai and stuff, I think I want to keep the

muscle mass I've got. I'm not trying to be a bodybuilder. If you look at me next to Mark Bell, I look pretty skinny.

JM: He was on the podcast you were on for a few hours.

PS: Yes, yes. Who I just interviewed for my podcast the other day. I love Mark. Those guys are great. Those guys are huge. There are all these different degrees of what we're looking for. I like having a moderate amount of muscles so I still have flexibility. It's not to say he's not super flexible, but for hitting the punching bag and jiu-jitsu, it allows me to kind of walk that line between endurance and strength. That's kind of the sweet spot for me. Yeah.

JM: Alright. Let's talk about this polyphenols. I sort of went on a deep dive on many of them. These are all, of course, mostly plant-based compounds. They seem to have enormous potential therapeutic value, especially with respect to doing two things. One is increasing, pretty radically, the benefits of autophagy and activating these metabolic pathways. Examples would be like resveratrol for sirtuin 1 (SIRT1). There are so many others – GGCG, berberine and curcumin.

I initially believed that it was probably wise to take them on a regular basis before you go to bed, where you have a little bit of autophagy activating to begin with. But I realized there's not much autophagy. It's probably not a good idea. Now I'm only doing it when I partial fast, which is only once a week now. I'm wondering what conclusions you've reached and any concerns that you may have about using these polyphenols.

As sort of an extension of that, there is a specific polyphenol called fisetin and quercetin, which are now being used for senolytic therapy. Senolytic therapy is sort of leading-edge longevity strategies to remove senescent cells. Senescent cells are senile cells that essentially stop reproducing but they're still active and they create these inflammatory molecules, typically cytokines that cause metabolic havoc in your body. You don't need a large percentage of them to radically accelerate the aging process. We're using these polyphenols to eliminate these senescent cells called senolytic therapy. Why don't you give a comment on that?

PS: Yeah. This is probably the most interesting part of the whole discussion for me and perhaps the place where I differ from many people in opinion. That could mean that I'm radically wrong. I'm radical. I could be radically wrong and about to radically get schooled and learned, or I've got a disruptive concept here.

But the interesting part about polyphenols – So if you think about plants, the idea when I try and talk to people I say, "Why do you eat plants? What benefits do the plants have for humans?" They'll say fiber, vitamins and minerals and phytonutrients, presumably they're referring to polyphenols. Well, we don't need to go down the first two rabbit holes. I've thoroughly discussed non-human need for fiber.

JM: Nothing on this one. But if we have time maybe we can mention that.

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

PS: Yeah. We can. Yeah.

JM: But I want you to finish this discussion first.

PS: Yeah. If we have time, we'll go back to fiber. But the basic idea of fiber is that if we really look at the literature, it's quite questionable whether fiber has any real benefit for humans. We can talk about the microbiome and fiber, which is very interesting.

And then if we look at nutrients, it goes back to kind of that first principle, the nutritional approach that says, "Well, actually, there aren't really any unique nutrients in plants that humans need in terms of vitamins and minerals." We actually even know now that we can get plenty of vitamin C for optimal antioxidant function just from eating animal foods nose-to-tail. The last part is really the cool stuff, which is the polyphenols. This is where I would say my ideas break from the norm most radically. I'll try and lay this out for people.

I think that the mainstream – or I shouldn't say the mainstream – but I think the predominant idea is that polyphenols have benefits for humans in a variety of ways, most of which are hormetic, this concept of hormesis, or epigenetic. I think resveratrol, people would think, is epigenetic because it's modifying. It's affecting the transcription of the sirtuin genes. But molecules like sulforaphane and some of these other molecules are hormetics.

What's so interesting to me about this concept is that once I started looking at this, I saw a pattern begin to emerge. The patterns are really interesting to me. The pattern that I began to see was that, harkening back to what I said earlier, animals and plants are really from a different operating system. I've used this metaphor before, that animals sort of work on Macintosh and plants are sort of like IBM. You can tell my intrinsic bias there, right?

JM: Yeah, yeah. Of course.

PS: But the idea is that if we look at the way that plant molecules act in humans, my hypothesis or my suggestion is –

JM: You should change that metaphor. Have the plants be the Apple operating system because it's Apple right?

PS: I know. That's true. People have pointed that out to me. Maybe I should. But I like my Mac.

JM: Okay.

PS: It's my intrinsic bias. I'm not affiliated with Apple. Apple is not a sponsor unfortunately. But the idea is that when we consume these plant molecules, they're from a different operating system. I'm super excited about all the research and the thinking that's going on with regard to plant molecules and saying, "Can these assist with longevity or human health?" But I'm sort of the voice in the background tempering that and saying, "Wait. Do they have a unique effect?" That's my first question about polyphenols. "Is what they are doing something that we cannot achieve naturally through exercise, heat stress or cold stress or ketosis?" I'll illustrate that in a second. "Do they have a unique effect?"

The pattern that I begin to see is that because they're from a different operating system, there's usually somewhere that we can find they're harming people on the backend. My concern is that the research often focuses on the benefit, which is awesome because people want to see the benefit. But if we look through the whole body – This is, I think, where we sometimes get a little too excited and we jump to conclusions. We often see dangerous effects in other parts of the body.

I'll illustrate this with sulforaphane. Sulforaphane is this compound that is widely touted as beneficial. Everyone is now eating broccoli sprouts, tons and tons of broccoli sprouts, because broccoli sprouts have sulforaphane.

Well, the way sulforaphane works is this. In the brassica family of vegetables – this is all the mustard vegetables: kale, collard greens, Brussel sprouts, broccoli and cabbage – there are a series of compounds that are called glucosinolates. If we actually look at the botanical classification, if we look at the botany, glucosinolates are plant pesticides, meaning they are compounds produced by the plants that are meant to harm insects and animals eating the plant. They are pesticides. There are pesticides we spray on plants, but the majority of pesticides that we humans ingest are endogenous pesticides. These are compounds that are produced by the plants to discourage us from eating them.

There's a great paper by Bruce Ames. It's called "Dietary Pesticides (99.99% All Natural)." On the second page of that paper, there's a chart. The chart is 44 plant pesticides found in cabbage. Glucosinolates are one of those families. Also included are things like allyl isothiocyanate. But we're talking about isothiocyanates here. If you look up isothyocyanates on the internet, 98% of what you'll find is very positive. But we need to tell the whole story. The way this works is that sulforaphane is produced when the precursor, which is glucoraphanin, combines with the enzymes myrosinase, and then sulforaphane is produced.

Now we know how sulforaphane works in the human body. It's an oxidant. It's an oxidant, which means it's a hormetic molecule. If sulforaphane has benefit, it does so by triggering the nuclear factor-like 2 (Nrf2) pathway in the human body, which is the pathway in the liver that responds to oxidative stressors. We know that things like smoking, tobacco, even polycyclic aromatic hydrocarbons and heterocyclic amines produced in the charring of meat trigger the same pathway.

JM: Excuse me for interrupting, but it has four of the mechanisms too. It increases heat-shock proteins. It increases the rate-limiting enzyme in glutathione production. And it's a histone deacetylase inhibitor.

PS: Yeah. But with regard to glutathione, so it's going to pump up the glutathione by hitting Nrf2, right?

JM: No, no. It actually hits the rate-limiting enzyme. It increases the production of the rate-limiting enzyme.

PS: Of glutathione.

JM: Of glutamate and cysteine.

PS: Yeah.

JM: Glutamate cysteine ligase.

PS: Yeah. Gamma-glutamate ligase – Yeah. What's interesting about this molecule is that we know that sulforaphane is going to increase our endogenous supply of glutathione. That's probably happening because it's doing these mechanisms directly and because it's an oxidant triggering the Nrf2 pathway, which is sort of the toxin pathway. But what we never hear about is that it can go in and do these good things, but then it also circulates in the human body. Because it's from a different operating system, it's been found to have negative effects as well, both in rodent models and in humans.

This family of plants, the brassica plants, are responsible for a huge number of cases of goiter, endemic goiter in the world. They're probably the biggest contributor to that, because they are goitrogenic molecules. Goitrogenic molecules also include molecules like amiodarone, lithium, toxic molecules that inhibit or compete with iodine for absorption of the level of the thyroid. But systemically or population-wise in the world, the major cause of endemic goiter and cretinism, which is a prenatal condition of inadequate iodine, are goitrogenic plants, like the brassica vegetables. It's a really big deal.

What we're seeing here is this is how the plant – This is what the molecule's really made for by the plant. It doesn't actually exist as sulforaphane in broccoli or in kale or anything. That molecule is so oxidatively reactive with other molecules – meaning that it will go in and lose electrons and create free radicals in plants – that it will kill the plants. It can't exist. We see this pattern. Again, this goes back to the pattern of plants.

My concerns about this is when plants have this, they have this sort of poisonous oxidant molecule, and they store it in a precursor form. The only way that sulforaphane is produced in the mustard family is when you chew the plant. Sulforaphane is not a molecule the plant is using. Evolutionarily, it's a molecule the plant is producing to deter predators from eating it.

You're making a great point that we do see some benefits from it. But the thing that concerns me is that, "Oh, but we also see negatives from it." We see dangerous things happening with sulforaphane. There are so many people having now potential hypothyroidism or issues with thyroid that could be connected with broccoli sprouts. I've posted sort of case studies or people who have messaged me on Instagram, talking about how they were doing broccoli sprouts and they develop thyroid issues, et cetera. At this level, it's kind of at the case report, anecdotal level. But it's a really interesting idea. So, sulforaphane is actually a plant toxin.

In response to the points that you illustrate, I think there's this fascinating idea that none of those mechanisms is unique to sulforaphane. We know that through things like heat stress, cold stress, exercise, fasting and ketosis, we can do all those things. We can increase glutathione. We can achieve histone deacetylase inhibition with betahydroxy butyrate. We can get adequate levels of glutathione. In fact, there's a fascinating study of swimmers in Berlin who swim in the frigid waters

in the winter. It shows that cold plunging can increase all these same enzymes and activate all of these mechanisms around glutathione.

The way that I would illustrate it for people with sulforaphane as sort of an example molecule here is that it can do some good things through these hormetic mechanisms, but these are not unique to sulforaphane. We can do this on our own by living what I could call a radical life. Then there are dangers on the backend. My hypothesis, one of the points that I'd like to suggest to people, is perhaps many of these plant polyphenols are net negative. It kind of argues more toward, "Live a radical life and get the optimal positive." This is what we're expanding and where we're learning. I don't think we fully know. There are so many polyphenols. I could also talk about resveratrol a little bit, which is another good illustration of this concept.

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

JM: Well, thank you for bringing out those concerns and dangers. I think it is appropriate. It's actually one of the reasons why I reduced my ingestion by probably 90%. But sulforaphane is not a polyphenol. It's an isothiocyanate.

PS: Yes, yes, yes.

JM: But the other polyphenols are different. I'm wondering – I mean, clearly, there's just no question and your reasoning is rational and solid and strongly supported against the continuous use of these polyphenols. But I'm wondering if smaller amounts, less frequently – I don't think more than once a week, but maybe even once a month – may be a really powerful hormetic biohack to massively increase the benefits of autophagy or senolytic therapy.

PS: It's possible. I love the idea. It's just like – Yeah. I think that's what we're trying to figure out. But I think that my concern is that most people are eating a heck load of broccoli sprouts every day right now. I mean I just put an article on my Instagram the other day. There was a case report of oxalate and nephropathy with a green smoothie cleanse. Oxalates are –

JM: Oh, geez.

PS: What's that?

JM: Probably from kale or spinach.

PS: It was from spinach. Yeah. Depending on the variety of kale. There's a smaller amount of oxalate. But spinach has a very high amount of oxalates. I did an interview with Sally K. Norton on my YouTube channel. It'll be out in my podcast soon. But, yeah. Oxalates are a big deal. We didn't even talk about oxalates. But yeah. We know that daily consumption of these plant molecules is just like, well, it's probably not a good thing.

JM: Oxalates are obtained primarily through plants, right?

PS: Yeah, yeah. They're exclusive. Oxalates are a byproduct of human metabolism, but we only produce a small amount from the catabolism of hydroxyproline, and then we're able to excrete it.

But the majority, the vast majority of our intake of oxalates, which is a 2-carbon molecule, two carbons and a bunch of oxygens, the vast majority of our intake is from plants, because plants use oxalate to hold on to minerals.

Humans don't use oxalates. It's just a waste byproduct. Glycine could be metabolized through the glyoxal pathway and hydroxyproline can be metabolized through a B6-dependent pathway to form oxalates, and then we excrete it in very small amounts. But one green smoothie can have 800 to 1,000 mg of oxalate, which is probably 20 times what we would produce in a day from our normal metabolism. We might make 25 or 50 milligrams of oxalate excreted every day. But one green smoothie, with spinach especially, could have 1,000 milligrams.

Apparently, in the literature, the lethal dose of lethal dose$_{50}$ (LD50) for oxalate is between 3.5 grams and 30 grams. It's completely obtainable from a diet. Like if you ate 3 pounds of spinach, you could get a dose of oxalate that has killed someone in the past. There's a case report of somebody dying from a 4-gram dose of oxalates eating a bunch of sorrel soup. Sorrel is oxalis genus. Anyway, oxalate is a whole different story other than the plant pesticides and plant molecules. But sulforaphane is not a polyphenol, but these plant molecules are like that. Resveratrol is a polyphenol.

JM: That's a very good point. I'm glad you brought that up. You can mediate against the oxalate toxicity by sprinkling in some non-well absorbed calcium, like calcium oxide. That one is not absorbed pretty well. It'll bind to the oxalates.

PS: Yes, you can.

JM: And then you don't absorb it because you just eliminate it in your stool. But it's still – It's sort of a mood issue, because you have so many other strong arguments not to have these plants on a regular basis. I guess we're getting close to the amount of time we have left. I really want you to comment on some of the strongest arguments against avoiding these plants. You've been off of plants for a long time now.

PS: Yeah. Eight months.

JM: Yeah, yeah. You're still reaping the benefits. We don't know. It's still relatively short-term.

PS: Yes, yes.

JM: But you're really enjoying good health and you're in fantastic shape.

PS: Yeah. One of the things that I really like is I love doing bloodwork on myself. I've probably done 350 blood tests in the last eight months. I've done C-reactive protein tests (CRPs) six times, every single time it's less than 0.03. This is high sensitivity C-reactive protein test (hsCRPs), so the units are milligrams per liter, so it's the most highly sensitive CRP. It's essentially undetectable times six. Eating a diet that's like all-meat, I've checked lipids and markers of endothelial function, et cetera, et cetera. I've checked micronutrients multiple times. I've checked my gut flora twice. I'm looking at quantitative polymerase chain reaction (PCR). I've done organic acids. It's this

fascinating experiment for me. I've done things like 8-hydroxy-2-deoxyguanosine, which is a measure of DNA damage. I've looked at heavy metals.

JM: What was it? I'm assuming it was –

PS: It was two. It was very low. And then lipid peroxides. Yeah. You can check. I've looked at my glutathione levels. Incidentally, my coenzyme Q10 (CoQ10) levels are off-the-chart high.

JM: Really? What would you attribute that to?

PS: There's just so much CoQ10 in me and muscle meat. I mean they were like 3.5. They're off-the-chart. All the carnivores I've seen have super, super high levels of CoQ10. You've got to think like – That's not a direct indicator of mitochondrial function. That part of the electron transport chain is greased. That is greased lightning, man. I think it's interesting.

I think this is one of the conversations that I really like having in the carnivore space. It's saying, "Hey. This is a radical thing. We really need to examine this carefully and do blood testing and make sure it's safe for people, because it seems to help people with autoimmune disease, you know?" I've seen people with Crohn's and ulcerative colitis and eczema and psoriasis resolve, which is just mind-boggling. It just really was what originally drew me to it. But the flipside is you need to make sure – I'm excited to be part of this movement and say, "Are people going to get deficiencies?" I don't think so. I think there's an evolutionary basis for this. But how do we show this is safe and then get some pilot studies going? Because it's my strengthening suspicion that this is going to be a very useful tool for us in the medical world moving forward.

JM: Yes. I couldn't agree with that more. Now you're very close to finishing your residency and will be going into private practice – or maybe not private practice, but you're going to practice. I'm wondering two things. One is, why the heck did you pick psychiatry? Why wouldn't you be an internist or a cardiologist if you come from that background? But then, what are your plans for practice?

PS: Psychiatry is an interesting story. When I was in medical school, I thought very strongly about internal medicine. I actually really – I applied to some joint programs, internal medicine psychiatry, family medicine psychiatry. But ultimately, I decided on psychiatry because I liked how human it was. I like the human story. I also realized that psychiatry needed a lot of help. Of any of the medical specialties, I felt like the paradigm in psychiatry was the most antiquated.

Really, if you look at the burden of mental health in this country, it is colossal. I think the most recent Centers for Disease Control and Prevention (CDC) estimates are that depression and anxiety are the No. 1 source of morbidity in our country. There's more productivity lost to depression and anxiety than anything else. Heart attack, stroke, any cardiovascular disease or cancer, depression and anxiety are the biggest. And so I thought, "Well, that's the biggest piece of the pie."

I love the human side of it. I never want to forget my internal medicine. I'm constantly geeking out with my internist friends and my gastroenterologist friends and having them remind me of things and looking at mechanisms and doing all of these, trying to keep my internal medicine

knowledge, but I love the human story in psychiatry. That when someone comes to you and they say, "Hey. I'm so depressed. I don't even have a will to live." That just hits me in my gut. That's a human-to-human interaction.

I really liked in medical school that when I did psychiatry, the patient didn't get lost in the labs. I love that I could keep the human story. I was much more able to connect with the person at a human level. It kept me human. It kept me young, so I love that. It's really satisfying to be able to help people with psychiatric illness, because if the mind isn't right, nothing else works well. It's totally true. It's like foundational, you know? Our outlook is so crucial that if someone's depressed or anxious, they're not going to be able to do anything else for their health.

I would argue that a lot of our issues with health behaviors and people not choosing to eat well or not exercising are based on the fact that there's underlying depression and anxiety and just demoralization. They're just not living the life that they're passionate about. They don't have love, emotion and passion in their life. It's just really cool to be able to start there. The second question –

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

JM: Yeah. Let me just comment that there's another – now-deceased – leading pioneer in natural medicine, Abram Hoffer.

PS: Yes.

JM: Interestingly, he really pioneered the work of niacin and, secondarily, NAD+.

PS: Yeah, yeah. It's fascinating. Your second question is interesting for me. I'm so excited about this carnivore movement and the potential for diet in general and food to continue helping people. In the near future, my plan is to move to San Diego and open a private practice there doing functional medicine.

What I've quickly learned about functional medicine is that it all starts in the gut. Every functional medicine doctor has to be a gastroenterologist. I have a friend who's a gastroenterologist who says that all medicine is gastroenterology. I, at least, say, "Yeah. That's probably true. It all starts there." I'm going to be treating patients in my practice who are psychiatric and non-psychiatric because I really think it's all connected.

You know, as I pointed out earlier, I really believe that a lot of psychiatric illness is autoimmune in nature and that a big part of improving that in the future is going to be treating people from that perspective in a very holistic way. I really like that perspective. I'll be treating people with all sorts of conditions, from GI to autoimmune. Yeah. I think it's going to be really exciting. Then I'm also doing all kinds of cool stuff. I'm writing a book, which is going to be out in about four or five months. I'll send you a copy.

JM: I'd like to have you again for that.

PS: Yeah. Absolutely.

JM: We could go on for hours.

PS: I know. We'll have to do a Part 2.

JM: There's just so much to dialogue about.

PS: Yeah. I'm starting to speak at conferences. I'm going to be at KetoCon in Austin, in June. I'm writing a book. I've got my own podcast, which is called Fundamental Health With Paul Saladino M.D.

JM: How do people find that? They go to YouTube and they type in Fundamental Health?

PS: Yeah. Fundamental Health is going to be launched on iTunes, Stitcher and Spotify this week. It's already on YouTube. If people Google my name on YouTube, it's on my channel. It's on the Paul Saladino M.D. channel on YouTube. The podcast is called Fundamental Health. They'll find it under that on all of the sort of streaming audio outlets. But yeah, I'm going to be in San Diego. I'm probably going to be in North County, San Diego. I'm on Instagram.

JM: Do you plan on doing virtual consults too?

PS: Yes. I do.

JM: Alright. By the time this interview airs, you'll have finished your residency. You'll probably be established in your practice. If someone was interested in seeing you for some conditions – and I would strongly recommend it. You're like such an amazing resource. Because literally in the not-too-distant future, you're not going to be able to get an appointment with you. I'm very confident about that. This is an amazing opportunity if you want to access your knowledge and really apply it to yourself. How would they contact you?

PS: The best way to get in touch with me for a virtual consultation or in-person consultation right now is just directly through email. My email is PaulSaladinoMD@gmail.com. In the greatest stroke of irony, my last name is Saladino, so it's S-A-L-A-D-I-N-O. There's salad in my last name, but there's also dinosaur in my last name. There's both. If people want to reach out to me for a consultation, they can just send me an email directly.

JM: Alright. Boy, this has been awesome. I've been so looking forward to this dialogue. I look forward to future dialogues. I really want to extend my deep appreciation for all you're doing and really serving as a model for other physicians to really honor their internal curiosity and really seek the foundational causes and continue to push the frontiers, because we just don't know a fraction of a fraction what we need to know. People like you are helping us increase the depth of our understanding in vitally important areas.

PS: Thank you so much. That means so much to me coming from you, who's really like a pioneer in the field and someone who I've looked up to. I've heard of you for years. When I was in medical

school, I was reading your stuff. We go way back. You just didn't know that I was reading your stuff then.

JM: Yeah.

PS: That means so much to me coming from you. I feel so much gratitude to be able to do this. It's such a privilege. My father always said that it was a privilege to be a physician. I feel privileged to be a physician and just to be able to contribute to this. It's so meaningful to be able to offer people some pathway to improve quality of life and help however that is. If it's carnivore or whatever we all discover as we're all continuing to explore is the optimal way for people to live well. Thank you so much for having me on. It's a total pleasure.

JM: You're welcome. Again, you're really knocking it out of the park. We just need a lot more people like you to raise the bar.

PS: Thank you, thank you.

JM: Alright. We'll be in touch soon. I look forward to reading the draft. You've got my email contact.

PS: I do. Yeah.

JM: Forward me the copy of your draft as soon as you have it done, because it's going to take me a while to read it. Then we have to schedule your interview. I'd like to launch that interview before your book is published.

PS: Sounds great. Thank you so much.

JM: Alright.

PS: Talk to you soon.

JM: Okay.

[END]