

Dr. Chris Palmer: Diet & Nutrition for Mental Health | Huberman Lab Podcast #99

My guest this episode is Chris Palmer, M.D., a board-certified psychiatrist and assistant professor of psychiatry at Harvard Medical School. He explains the important connection between nutrition, metabolism and mental health and his pioneering work using the ketogenic diet to successfully treat patients with various mental illnesses, including depression and schizophrenia. Dr. Palmer explains how the ketogenic diet is an evidenced-based treatment for epilepsy, mimics the fasted state and can offset the cognitive decline in Alzheimer's. He describes the key roles of mitochondria in mental health, how certain conditions likely arise from mitochondrial dysfunction, and how low-carbohydrate diets increase mitochondrial turnover to improve mental health. He also explains how low-carbohydrate diets positively impact the gut microbiome and weight loss, important risk factors for mitochondrial health such as marijuana and alcohol, and the best way to increase circulating ketones depending on individual needs. We also cover how a ketogenic diet impacts mood, sleep, and fertility. Dr. Palmer's work stands as a revolutionary approach to mental health and disease that, given the prevalence of mental health challenges, should be of interest to people of all backgrounds and ages.

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Dr. Chris Palmer

Dr. Palmer's website: <https://www.chrispalmermd.com>

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ANDREW HUBERMAN: Welcome to the Huberman Lab podcast, where we discuss science and science-based tools for everyday life. [MUSIC PLAYING] I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today, my guest is Dr. Chris Palmer. Dr. Chris Palmer is a medical doctor specializing in psychiatry at Harvard Medical School. He is the world expert in the relationship between metabolic disorders and psychiatric disorders. He treats a variety of different conditions, including psychosis, including schizophrenia, as well as attention deficit hyperactivity disorder, obsessive compulsive disorder, anxiety disorders, and depression among others. He is best known for understanding the relationship between how metabolism and these various disorders of the mind interact. And indeed, today, he

describes not only his own fascinating journey into the field of psychiatry but also his clinical and research experience using diet that is different forms of nutrition in order to treat various psychiatric disorders. He describes some remarkable case studies of individuals and groups of people who have achieved tremendous relief from the types of psychiatric disorders that I just mentioned a few moments ago, as well as new and emerging themes as to how metabolism and the mind interact to control things like obesity. Indeed, he raises the hypothesis that perhaps obesity, in many cases, is the consequence of a brain dysfunction as opposed to the consequence of a metabolic dysfunction that then impacts the brain. During today's episode, he shares with us his overriding hypotheses about the critical roles that mitochondrial function and dysfunction play in mental health and mental illness, and how various particular types of diets-- ranging from the ketogenic diet to modified ketogenic diet and even just slight adjustments in carbohydrate intake-- can be used in order to change mitochondrial function and bring relief for various psychiatric illnesses. He also highlights the essential and important theme that various diet interventions, including the ketogenic diet, were not first developed for sake of weight loss but rather were developed as treatments for neurologic conditions, such as epilepsy. Today, he shares with us how the foods that we eat alone and in combination, and how fasting-- both intermittent fasting and more lengthy fasts-- can interact with the way that our brain functions to strongly control the way that we think, feel, and behave. What's wonderful is that Dr. Palmer not only explains the science and his clinical expertise, but also points to various actionable measures that people can take in order to improve their mental health. I'd like to mention that Dr. Palmer is also the author of a terrific new book. The title is *Brain Energy: A Revolutionary Breakthrough in Understanding Mental Health and Improving Treatment for Anxiety, Depression, OCD, PTSD and More*. I've read the book, and it is a terrific read. I came away from this book with a much evolved understanding of how the various psychiatric disorders that I just described, as well as ADHD, emerge in people. And it has completely revised my understanding about the possible origins of various psychiatric disorders and the best ways to treat them, including both with medications but also with nutritional approaches. If you'd like to learn more about Dr. Palmer's

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work and the book, please go to chrispalmermd.com. We also provide links to the book

and to his website in our show note captions. Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is, however, part of my desire and effort to bring zero cost to consumer information about science and science-related tools for the general public. In keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first sponsor is Thesis. Thesis makes custom nootropics. And as I've said many times before on this podcast, I am not a fan of the word "nootropics" because it means smart drugs. And frankly, there are no specific neural circuits in the brain or body for being, quote unquote, "smart." Thesis understands this. And they've developed custom nootropics that are designed to bring your brain and body into the state that's ideal for what you need to accomplish. They use the highest quality ingredients, things like phosphatidylserine, alpha GPC, many ingredients that I've talked about before on this podcast and that I happen to use myself. I've been using Thesis for over a year now. And I can confidently say that their nootropics have been a game changer. For me, I like their nootropic for clarity. I use that before cognitive work often. And I like their nootropic for energy, and I often use that before workouts-- in particular, workouts that are especially intense. To get your own personalized nootropic starter kit, go online to takethesis.com/huberman. Take their 3-minute quiz, and Thesis will send you four different formulas to try in your first month. Again, that's takethesis.com/huberman. And use the code Huberman at checkout to get 10% off your first box. Today's episode is also brought to us by Eight Sleep. Eight Sleep makes smart mattress covers with cooling, heating, and sleep tracking capacity. I've talked many times on this podcast about the critical relationship between sleep and body temperature. That is, in order to fall asleep and stay deeply asleep throughout the night, our body temperature needs to drop by about 1 to 3 degrees. And conversely, when we wake up in the morning, that is, in large part, because of our body heating up by 1 to 3 degrees. Now, people have different core body temperatures. And they tend to run colder or hotter throughout the night. Eight Sleep allows you to adjust the temperature of your sleeping environment so that you have the optimal temperature that gets you the best night's sleep. I started sleeping on an Eight Sleep mattress cover about eight months ago, and it has completely transformed my sleep. I sleep so much deeper. I wake up far less during the middle of the night, if at all. And I wake up feeling far better than I ever have even after the same amount of sleep. If you want to try Eight Sleeping, you can go to eightsleep.com/huberman to save up to \$400 off their sleep fit holiday bundle, which includes their new Pod 3 cover. Eight Sleep currently ships in the USA,

Canada, United Kingdom, select countries in the EU, and Australia. Again, that's eightsleep.com/huberman. Today's episode is also brought to us by ROKA. ROKA makes eyeglasses and sunglasses that are of the absolute highest quality. The company was founded by two All-American swimmers from Stanford. And everything about ROKA eyeglasses and sunglasses were designed with performance in mind. I've spent a lifetime working on the biology, the visual system. And I can tell you that your visual system has to contend with an enormous number of challenges in order for you to see clearly-- for instance, when you move from a sunny area to a shady area and back again, whether or not you're looking at something up close or often to the distance. ROKA understands the biology of the visual system and has designed their eyeglasses and sunglasses accordingly so that you always see with perfect clarity. ROKA eyeglasses and sunglasses were initially designed for activities such as running and cycling. And indeed, they are very lightweight. Most of the time I can't even remember that they're on my face. They're so lightweight. But the important thing to know about ROKA eyeglasses and sunglasses is that while they can be used during sports activities, they also have a terrific aesthetic. And they can be used just as well for wearing to work or out to dinner, et cetera. If you'd like to try ROKA eyeglasses and sunglasses, you can go to ROKA-- that's roka.com, and enter the code Huberman to save 20% off on your first order. Again, that's ROKA, roka.com, and enter the code Huberman

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at checkout. And now, for my discussion with Dr. Chris Palmer. Chris, Dr. Palmer, thank you for being here. CHRIS PALMER: Thank you, Andrew, for having me. ANDREW HUBERMAN: I have a lot of questions for you. And I'm really excited about this topic because I think most people know what mental illness is-- or they have some idea what that is. Most people have some idea what nutrition is. Fewer people certainly know how closely those things can interact. And I think everybody is familiar with the feeling of a food or the ingestion of a food making them feel good in the short term. When we eat a food that tastes delicious to us or that we associate with something nice, then we feel good mentally and physically. Whereas, when we eat something that gives us food poisoning or maybe even something that just doesn't taste that great or that we associate with a bad experience, we feel less good in the short term. But I believe that very few people understand or are familiar with the fact that nutrition and our mental

health interact in this very intimate, maybe even causal, way and that is something that occurs over long periods of time. Meaning, what I ate yesterday or the day before, maybe even 10 years ago, could be impacting the way that my brain and body are making me feel now. So if you would, I'd love for you to just tell us about a little bit of the history, in particular, your history with exploring the relationship between nutrition and mental health. And then we can dive into some of the more particulars of ketogenic diets versus other diets, and some of the truly miraculous findings that you and others are coming up with based on real patients and real experiences of people who suffer and then find relief by altering their nutrition.

CHRIS PALMER: Sure. This story really starts with my own personal story. And I don't need to go into great detail. But to set the stage, when I was a kid, I definitely had mental illness, started with OCD. A series of events happened in my family. My mother had a horrible kind of psychotic break, and all sorts of adverse childhood events for me. She and I were actually homeless together for a while. I went on to have subsequent depression, suicidality, all sorts of things. But somehow or another, I pulled myself together and got through medical school-- actually did quite well in medical school, got an award for being one of the top students, and then was doing my internship and residency at Harvard. And at that point in time, I was diagnosed with metabolic syndrome. So I had high blood pressure, horrible lipids, and pre-diabetes. And I was doing everything right supposedly. I was on a low-fat diet, and I was exercising regularly. And year after year, my doctor kept telling me diet and exercise. I kept asking him, what diet? What exercise? I was doing everything he kept telling me to do. Everything was getting worse. My blood pressure kept going higher. And at some point, he kind of said, you're going to have to go on medication. I need to put you on something for your pre-diabetes, something for your cholesterol, and something for your blood pressure. So three pills out of the gate. And I'm like, I'm only in my 20s.

ANDREW HUBERMAN: Were you overweight?

CHRIS PALMER: No. Technically, no. I had a gut, so that's a sign of insulin resistance, I know now. I didn't know it then. And he actually kind of leaned in at one point and said, do your parents have diabetes? Yeah. Do your parents have high blood pressure? Yeah. Are your parents overweight? Yeah. Oh, I'm really sorry, it's genetic. Basically, you're screwed. It's your genes. You're just going to have to bite the bullet and take meds. And as a physician, I knew what that meant. I knew that I'm in my 20s, if I'm already on three meds for metabolic syndrome, I'm going to be screwed by the time I'm 40 or 50. And I'm probably going to be having heart attacks. And I'd heard through the rumor mill that the Atkins diet could somehow help

people improve their cholesterol in pre-diabetes. I actually didn't really believe it. I was highly skeptical. And I believed everything I was taught in medical school. Why would my professors lie to me? They knew what they were talking about. Low-fat diet was the thing to do. And the Atkins diet was clearly dangerous and reckless. But I had been trying the medical dogma for years, and it wasn't working for me. And so for whatever reason, I decided this is going to be my last attempt at something different. And then I'll just bite the bullet and go on meds. So I tried the Atkins diet. I did my own special version of it. I still avoided red meat because I was terrified of red meat. I tried to do a healthy version, which it's probably more like the South Beach diet. This was before the South Beach Diet was invented. But within three months, my metabolic syndrome was completely gone. ANDREW HUBERMAN: So blood pressure normalized, lipids normalized. Did your weight change? You mentioned that you were of healthy weight but that you had a bit of abdominal-- CHRIS PALMER: Yes. ANDREW HUBERMAN: --fat. CHRIS PALMER: I lost the abdominal fat. I probably lost about 10 pounds through this process. But everything got normal. And when I went back to my doctor, he was shocked. He actually said, what the hell are you doing? ANDREW HUBERMAN: During the time before you switched to this new diet, how was your mental health, if you don't mind me asking? Because it sound like you're very clear that there was metabolic syndrome or you were headed towards more severe metabolic syndrome. You mentioned OCD. I actually am familiar with this. As a kid, I had a low level kind of Tourette's grunt. And probably me, obsessive still to some extent-- although not full-blown clinically diagnosed OCD, so I can relate somewhat. If you're willing, what was the context of all that before and after this nutritional switch? CHRIS PALMER: So before the nutritional switch, I was still struggling with low grade depression and OCD. Again, it wasn't necessarily interfering with my ability to function because I was functioning at a high level. Anybody looking from the outside, you're a top student. You just got into one of the most competitive-- actually, at that point, it was the most competitive residency program in the country for psychiatry. So they would have looked at me and said, you're fine. But I wasn't. I was actually on medications. I was trying different medications, trying to figure out how to feel better, how to stop obsessing so much, how to not be so depressed. And I found that those medications, they actually came with more side effects for me than benefits. I was on Prozac for a long time. It totally messed up my sleep. And then the psychiatrist was like, you need pills to help you sleep now. And I'm-- I just-- I'm like, that doesn't-- that's not really resonating very well with me. And I'm now a psychiatrist. I'm in

my psychiatry residency. And I'm thinking, you know what? That's just not sitting well with me that you're going to prescribe more and more meds for all the side effects that you're causing. And yet at the same time, I wanted to feel better. And I was learning chemical imbalances. This is what we do to get rid of depression and OCD. You're supposed to take your pills. And so I was taking my pills. I was in psychotherapy. I had been in psychotherapy on and off for years. I had received much more intensive treatment when I was younger. And that was essentially worthless for me. It actually probably just caused harm at the end of the day. ANDREW HUBERMAN:

Psychoanalysis? CHRIS PALMER: Various psychotherapies-- not psychoanalysis per se, but some of them were psychoanalytically-oriented psychotherapies. I was actually hospitalized at one point. I had been put on lithium and imipramine, which is a tricyclic antidepressant, and other things. And they were actually horrible. They were horrible. They did nothing beneficial for me. I gave them a decent amount of time to work. I really wanted to feel better. So at the time that I tried this diet, I certainly wasn't impaired in the same way. I wasn't struggling that much. But I was-- still have these low grade symptoms, was trying to feel better. And the thing that was the most striking to me, after doing the diet for three months, was not the fact that my metabolic syndrome was gone. That was my goal, and it was a seemingly miraculous achievement because I got rid of everything with one dietary change. But the thing that I noticed was dramatic improvement in my mood, energy, concentration, and sleep. I-- for the first time in my life, I started waking up before my alarm went off and feeling rested. That never happened to me before. I was meticulous about planning when my alarm went off and how many times I could push the snooze button in order to be on time for wherever I needed to be, whether it was school or the hospital or whatever. I had it. I had this good system. I was never late for anything. But that was shocking to me, that I felt so good. And one of the things that I've often said to people, prior to the diet, I always felt like there are two types of people in the world. There are "haves" and "have-nots." There are these happy, peppy people, who just are so positive, and they've got energy. And they have the saying, they like to work hard and play hard. And I always understood working hard. I totally got that because I was a hard worker and I understood the value of hard work. And you got to do something useful with yourself. But I never understood who the hell wants to play hard, like who's got energy for that? Aren't you tired from working so hard? How on Earth do these people have energy to go and play hard? And I assumed that they were just part of the "haves" in the world. And they were just lucky and

privileged. They either had good genetics or maybe they had good childhoods or good parents or something-- something that I didn't have. ANDREW HUBERMAN: The kids with genuine smiles in the yearbooks. CHRIS PALMER: Yes, exactly. ANDREW HUBERMAN: [LAUGHS] CHRIS PALMER: Yes. ANDREW HUBERMAN: Whereas, the rest-- and by the way, I really appreciate you sharing some of your personal story because I think it is very important for people to hear and understand that people like yourself, who are extremely high functioning and accomplished, that the road was-- from everything I'm hearing and understanding-- very choppy internally at times, and that you've overcome a lot in order to get there. And also, have been going through what sounds like a very long iterative process of trying to figure out what works and what doesn't work to finally arrive at a solution, and then make that the basis of much of the work that you're doing today for other people. I think it's very important because I think many people share with you this notion that there are indeed two groups-- a happy group and then fated-to-be unhappy group. And it speaks to the fact that-- your story, rather, speaks to the fact that what we see is not always what's going on internally with people and that this notion of there just being two groups-- the happy or the haves and the have-nots-- can't be the way that it works, and there are probably many more people suffering than we realize, and that there is an important need for tools to overcome that suffering. So I really just hear you. Even early in our discussion, I just want to extend a genuine thanks because so much of what I hear from people is questions about health, and mental health, and physical health. But that clearly point to the fact that many people are struggling to varying degrees. And even the people who are in this category of great childhood and happiness could do far better

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for themselves and then also for other people. So thank you for that. I want to know. At the point where you realized that nutrition can play a profound role in how you feel and operate in a large number of domains, you are still a student or a resident at that point? CHRIS PALMER: I was a resident. ANDREW HUBERMAN: At that point, did you decide that you were going to explore this in a professional context? CHRIS PALMER: Not yet. ANDREW HUBERMAN: OK. So what was the journey forward into the work that you're doing now? CHRIS PALMER: So the next step was that I just had friends and family who saw me, saw that I had improved my health, saw that I lost some weight pretty easily. In

particular, I remember my sister and sister-in-law, they got really pissed at me one Thanksgiving because I could resist all the pumpkin pie, and apple pie, and everything else. They were like, how the hell are you doing that? How are you resisting all of this food? And I said, I don't crave it anymore. I don't want it, I'm fine. I'm just-- I'm having turkey and green beans. And that's good enough for me. So I got them to do the diet. And they too noticed dramatic improvement in their moods, and energy, and sleep, and everything else. So within a few years, the primary thing I noticed is this powerful antidepressant effect. And now, I'm an attending physician. I've got all these patients in my clinical practice with treatment resistant mental illness. I'm in a tertiary care hospital. So I almost never get somebody off the street with their first episode of depression. Out of the gate, as part of my career, I get treatment resistant mental disorders. So I get people who've already been to 6-plus psychiatrists, therapists. They've usually tried dozens of different medications. They've been in decades of psychotherapy. They've often had ECT and other things. And nothing's working. And I'm thinking, well, we're kind of out of options for these other people. And this diet is having this really powerful antidepressant effect. I think I'm going to try it and just see if any of my patients are game to try it to see if it might help them. Sure enough, it did. Didn't help everyone and not everybody was interested and/or able to do it. But some of the ones who were able to do it ended up having a remarkable and powerful antidepressant effect. One woman actually became hypomanic within a month. And she had been depressed pretty much nonstop for over five years-- chronically depressed, suicidal, in and out of hospitals. And I saw her become hypomanic. And I'm thinking, wow, this really is a powerful antidepressant effect. This is amazing. This is like a medication but better because it actually is working for her. But I laid low at that point because, at that point, we didn't have many clinical trials of the safety or efficacy of the Atkins diet for even weight loss or diabetes, let alone any mental disorders. And so I really actually felt like I'm on the fringe here. And this is not going to be met with praise by anyone. So I'm just going to lay low. I'm going to offer it to patients. And I went along that way up until 2016. ANDREW HUBERMAN: And may I just ask about the diet? When you say "Atkins diet," so this is low to zero starch, so low carbohydrate diet, certainly low sugar. CHRIS PALMER: Yeah. ANDREW HUBERMAN: And was it traditional Atkins? Were you tailoring it to the individual patient depending on their psychiatric symptoms, whether or not they were overweight or not overweight? I'm assuming you're not a nutritionist, so how did you prescribe a nutrition plan for your patients? And what was involved in making sure that

they adhered to that, maybe even some of the things you observed in terms of who was more willing to try this or not try this? Any observations or maybe even data? CHRIS PALMER: So early on, I was winging it. And I was-- the first few patients, it was try this Atkins diet. I want to see ketosis, so I was going for ketones. ANDREW HUBERMAN: So they were pricking their finger, and they were doing a blood ketone test? CHRIS PALMER: I didn't know about blood ketone monitors if they existed back then. So I was-- we were using urine strips. ANDREW HUBERMAN: Which are not quite as accurate but still useful as a general guide, from what I understand. CHRIS PALMER: True. ANDREW HUBERMAN: Is that right? CHRIS PALMER: Absolutely. ANDREW HUBERMAN: OK. CHRIS PALMER: So I was strongly recommending that patients achieve urinary ketosis. And the interesting thing is I noticed a pattern, that when they were trying the diet and not getting ketones, they often did not get a clinical benefit. It was once they got into ketosis that I began to notice the clinical benefit and the powerful antidepressant effect. ANDREW HUBERMAN: So probably any nutrition plan, a.k.a diet, that elevated ketones in the urine to the point where you would say, this person is in ketosis-- or they would say I'm in ketosis-- that was a step in the right direction, independent of exactly what they were eating or not eating to get there, including fasting? At that time, probably, fasting wasn't as popular now. Thanks to the incredible work-- I think it's incredible, and he is a former colleague. And I know there's a lot of controversy about fasting. But I think, for many people, fasting is a powerful tool. For others, it's a less useful tool --of Satchin Panda and others. But fasting certainly will limit your carbohydrate intake and get you into ketosis. Correct? CHRIS PALMER: It will. ANDREW HUBERMAN: Did you have any patients fast or do intermittent fasting? CHRIS PALMER: I did. I had some patients who did what Atkins had called a fat fast, where they eat primarily fat. So they either fast and/or they eat primarily fats to try to get into a state of ketosis. So for some patients, it was actually quite easy to get into ketosis, especially overweight and obese patients. They have a lot of fat stores on their body and actually limiting carbohydrates usually results in high levels of ketosis for them. ANDREW HUBERMAN: And they probably feel better too, I imagine, because when we limit our starch intake, we start to excrete a lot of water. People can get some pretty quick weight loss that even though it may not be fat loss, makes them feel literally a little lighter and maybe a little more energetic. Is that right? CHRIS PALMER: Absolutely. And as the years went on, the field was advancing, more research was coming out. People were getting a little more sophisticated with blood ketone monitoring, with different

versions

00:27:52 Schizophrenia, Depression & Ketogenic Diet

of ketogenic diets. And I was evolving my practice. The thing that completely upended everything that I knew as a psychiatrist, though, was when I helped a patient in 2016 lose weight. So this was a patient, 33-year-old man with schizoaffective disorder. He had been my patient for eight years now. ANDREW HUBERMAN: Could you clarify for people what schizoaffective disorder is? I'm not a clinician. But as I recall, it's like a low level of schizophrenia. So there might be some auditory hallucinations. If I met this person, I might think they're kind of different, quote unquote, "weird." But they would not seem necessarily scary to me and to typically to other people. And I mean that with respect, of course. But oftentimes, people with schizophrenia can seem just like-- you don't even know how to interact with them because their world seems so altered because they have all these so-called positive symptoms-- hallucinations, and they're talking to people that no one else can see, et cetera. Is that schizoaffective? CHRIS PALMER: So no. So schizoaffective is the same as schizophrenia essentially. The only difference is it's schizophrenia with superimposed mood episodes. ANDREW HUBERMAN: Oh, so it's actually more severe than-- CHRIS PALMER: It can be. ANDREW HUBERMAN: OK. So I have it backwards. CHRIS PALMER: So schizoaffective disorder is essentially schizophrenia and plus some mood episodes. ANDREW HUBERMAN: Ah, maybe I'm thinking of schizotypal? CHRIS PALMER: Schizotypal is the low grade, kind of mild paranoia, or kind of eccentric beliefs, and other things. ANDREW HUBERMAN: OK. Folks out there, I have my nomenclature backwards. Schizotypal is the, quote unquote, lower-- "low level" schizophrenia or schizoid-like. Schizoaffective is as or more severe. CHRIS PALMER: Full-blown schizophrenia plus full-blown usually bipolarism. ANDREW HUBERMAN: And now, it's absolutely clear who the clinician in the room is. [LAUGHTER] Thank you for that reminder. CHRIS PALMER: No worries. So this man had schizoaffective disorder. He had daily auditory hallucinations. He had paranoid delusions. He could not go out in public without being terrified. He was convinced that there were these powerful families, that they had technologies that could control his thoughts. They could broadcast his thoughts to other people. They were trying to hurt him. They had targeted him for some reason. He wasn't quite sure why. He had some suspicions and beliefs about maybe

when he did this bad thing when he was 11 years old, that's why they decided to target him. This man was tormented by his illness, tormented. It ruined his life. He had already tried 17 different medications, and none of them stopped his symptoms. But they did cause him to gain a lot of weight. ANDREW HUBERMAN: These medications, as I recall, for schizophrenia-- the classical ones are dopamine receptor blockers-- caused people to-- huge increases in prolactin. That's why sometimes men-- CHRIS PALMER: Yes. ANDREW HUBERMAN: --will get breast development. And they'll put on a lot of weight. And they'll be catatonic-- or movement disorders. CHRIS PALMER: Yes. ANDREW HUBERMAN: They make you feel like-- I have to imagine, given how good most things that release dopamine make us feel, that blocking dopamine receptors with antipsychotics makes people feel lousy. CHRIS PALMER: Horrible. And it's a huge challenge in our field because a lot of patients don't want to take them. And then you get these rebound effects. If patients are on them for several months, and then they stop them cold turkey, they can get wildly psychotic and ill, end up aggressive or hospitalized or sometimes dead. So that's him. He weighs 340 pounds. And for whatever reason, he gets it in his head, I'm never going to get a girlfriend if I don't lose some weight. He also recognizes, I'm never going to get a girlfriend because I'm a loser. I'm schizophrenic. I live with my father. I have nothing going for me. But I could at least try to address one of these awful, horrible things about myself. And maybe I could lose some weight. So he asked for my help. For a variety of reasons, we ended up deciding to try the ketogenic diet. Now, at this point, I have no anticipation that the ketogenic diet is going to do anything for his psychiatric symptoms because this man has schizoaffective disorder. That's not depression. Depression is very different. They're totally different disorders. So he decides to give it a try. Within two weeks, not only does he start losing weight, but I begin to notice this dramatic antidepressant effect. He's making better eye contact. He's smiling more. He's talking a lot more. I'm thinking like, what's gotten into you? You're coming to life. Like you're-- I've never heard you talk this much. I've never seen you so excited or present or alive. I haven't changed his meds at all. The thing that upended everything that I knew as a psychiatrist was six to eight weeks in, he spontaneously starts reporting, you know, those voices that I hear all the time? They're going away. And he says, you know how I always thought that there were all these families who were controlling my thoughts and out to get me, and they had targeted me? And I'm thinking, oh, yeah. We've been talking about that for eight years. We can talk about that again. He says, you know what? Now that I think about it, I don't think that's true. And now that I

say it, it sounds kind of crazy. It probably never was. I've probably had schizophrenia all along like everybody's been trying to tell me. And I think it's going away. That man went on-- he's now lost 160 pounds and kept it off to this day. ANDREW HUBERMAN: Wow. CHRIS PALMER: He was able to do things he had not been able to do since the time of his diagnosis. He was able to complete a certificate program. He's able to go out in public and not be paranoid. He performed improv in front of a live audience. at? One point, he was able to move out of his father's home and live independently. And that completely blew my mind as a psychiatrist. And I went on a scientific journey to understand what in the hell just happened. ANDREW HUBERMAN: That is indeed mind-blowing. I'd like to take a quick break and acknowledge

00:34:32 AG1 (Athletic Greens)

one of our sponsors, Athletic Greens. Athletic Greens, now called AG1, is a vitamin mineral probiotic drink that covers all of your foundational nutritional needs. I've been taking Athletic Greens since 2012, so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and the reason I still take Athletic Greens once or usually twice a day is that it gets me the probiotics that I need for gut health. Our gut is very important. It's populated by gut microbiota that communicate with the brain, the immune system, and basically all the biological systems of our body to strongly impact our immediate and long-term health. And those probiotics in Athletic Greens are optimal and vital for microbiotic health. In addition, Athletic Greens contains a number of adaptogens, vitamins, and minerals that make sure that all of my foundational nutritional needs are met. And it tastes great. If you'd like to try Athletic Greens, you can go to athleticgreens.com/huberman, and they'll give you five free travel packs that make it really easy to mix up Athletic Greens while you're on the road, in the car, on the plane, et cetera. And they'll give you a year supply of vitamin D3/K2. Again, that's athleticgreens.com/huberman

00:35:38 Psychiatric Mediations, Diet Adherence

to get the five free travel packs and the year supply of vitamin D3/K2. I have a couple of questions. First of all, did he stay on any kind of antipsychotic or other medication? If so, were the dosages adjusted, excuse me, while undergoing this remarkable transition?

Because as we know, it's not an either or medication or nutrition changes, it can be both. And then the other question is one of adherence. I think about someone with schizoaffective disorder, who's suffering from all the sorts of things that you described. How does somebody like that organize themselves in order to stay on a ketogenic diet? And I say this with all the seriousness in the world. I think there are a lot of people who do not have schizotypal or schizoaffective disorder who have trouble, they claim, adhering to a ketogenic diet. It's not the easiest diet. Certainly in its extreme form at first, it's not the easiest diet to stick to. So how did he do it? That sounds like a remarkable individual. And I'd also like to just know your general thoughts about adherence to things when people are back on their heels mentally. How do they get motivated and stick to something? So the questions were, medication, yes or no? If yes, dosage adjusted, yes or no. And if people are suffering from depression or full-blown psychotic episodes, how does one ensure that they continue to adhere to a diet? CHRIS PALMER: So in terms of medications, he has remained on medication. So early on, I wasn't adjusting anything. I was just in disbelief and shock that this was happening. I didn't know what was going on. Over the years, we have slowly but surely tried to taper him off his meds. He has been on meds for decades. He started medications when he was a young child. His brain is as developed in response to all sorts of psychiatric medications. And it has not been easy to try to get him off. We continue to try to get him off medication. And it's challenging and difficult. And I just want to say for any listeners, it is-- getting off your meds is very difficult and dangerous. And you need to do it with supervision, with a mental health professional or a prescriber because it is dangerous. When people reduce their meds too much, they can get wildly symptomatic. ANDREW HUBERMAN: Is that true for depression as well? CHRIS PALMER: It's true for any psychiatric medication. The brain makes adaptations in response to psychiatric medications. And when you stop them cold turkey-- some people are fine. But I wouldn't recommend finding out because I've seen patients-- when they stop antidepressants, I've seen patients get flooredly depressed and suicidal within three months. I had one patient, almost quit her job because she became convinced that, well, my life sucks, and it's all because of my boss. And I know that she's just a horrible human being. And she's abusing me. And I was like, whoa, whoa, whoa. I think this is related to your medication change. We got her back on her meds, within three days, she said, oh my god, I can't believe that happened. I almost quit my job. And that would have been the most illogical and irrational decision I've ever made in my entire life. But somehow, it seemed so real just several days ago. And now

that I'm back on this medication-- and it doesn't mean that she needs the meds. But it doesn't mean that he needs the meds. It means that meds need to be adjusted very safely, and cautiously, and gradually. So that's the medication piece. The adherence piece was not easy for him and for other patients. It is very rare that I have a patient who I can say, do the ketogenic diet. Come see me in 3 months, and let me know how it was going. That almost never happens. It has happened, I think, on two occasions.

ANDREW HUBERMAN: But that is, if I understand correctly, what-- perhaps not you-- but many psychiatrists do with medication. It's, here's your prescription. Let's talk in--

CHRIS PALMER: Yes. ANDREW HUBERMAN: --a month or three months. CHRIS

PALMER: Yes. ANDREW HUBERMAN: So that's a variable that is probably worth us exploring a little bit here as the conversation continues. CHRIS PALMER: Absolutely.

ANDREW HUBERMAN: That frequent contact and making micro adjustments or macro adjustments to medication or nutrition, could be meaningful. CHRIS PALMER:

Absolutely. So with this particular patient, early on, he was actually pretty adherent. I was seeing him once a week. And so I could do a lot of education. I was weighing him. I was checking his ketones. I was checking his glucose levels. At that point, I had a blood ketone monitor in my office. So I knew whether he was compliant or not, which is so beneficial in doing clinical work and research on this diet. It's the only diet where within seconds, I can have an objective biomarker of compliance or noncompliance. ANDREW

HUBERMAN: Such a key point and again, brings to mind, for me, the parallel with medication. A patient can say they're taking their medication, and unless they're in a hospital setting, where somebody's checking under their tongue and all of this, they very well could not be taking it or taking more. And you and I both know that blood draws for neurotransmitter levels are complicated because you want to know what's in the brain and what's functional in the brain. And then we have to imagine that most people there prescribed drugs for any number of different psychiatric conditions are not giving blood every time they talk to their psychiatrist or psychologist. No? CHRIS PALMER: No. On that front, when we've looked at studies of compliance, the majority of patients are at least somewhat noncompliant with prescription medications. It's not on purpose. They forgot. They take it at night. They were out late. They were off their routine. They forgot to brush their teeth-- because that's when they take their meds. And so because it was so late, they just crashed when they got home. They forgot to take their meds. Happens all the time. If it's a medication that people take more than once a day, the noncompliance rates are much higher because it's just easy to forget. So it's not that

people are willfully disobeying their doctors or anything else.

00:42:35 Highly Processed Foods, Ketones & Mental Health Benefits

It's just hard to remember to take meds consistently every day. ANDREW HUBERMAN: When you say measuring ketones, I want to drill into this a little bit because it does seem that the presence of ketones and somebody being, quote unquote, "in ketosis," it turns out to be the key variable. Certainly, in your book, that's one of the major takeaways-- although there were many important takeaways-- that people get into ketosis. Do they have to stay in ketosis? So for instance, I've followed the-- I don't any longer. But I've tried, in the past, the so-called cyclic ketogenic diet, where every third or fourth day, get some pasta, or rice, et cetera. That was interesting as an experiment. But to stay in ketosis, what sort of blood levels of ketones do you like to see in your patients? What is the range that you think most people could aspire to? CHRIS PALMER: So it really depends on the patient and what I'm treating, quite honestly. And I don't think every patient needs the ketogenic diet. For some patients, simply getting rid of junk food can make a huge difference in a mood disorder, for instance. ANDREW HUBERMAN: So a junk food, meaning, highly processed food, food that could last on the shelf a very long time. CHRIS PALMER: Highly processed foods that are usually high in both sugar, carbohydrate, and carbs, and fats. Those seem to be the worst foods. That combination-- high sugar, high fat-- seems to be the worst combination for metabolic health. And lo and behold, we've got emerging data that suggests, that strongly suggests, it's also bad for mental health. Depression and anxiety are the most common mental disorders. And so we have the best data for those disorders. But we actually have a lot of data with even bipolar disorder and schizophrenia that insulin resistance, in particular, and insulin signaling in the brain is impaired in people with chronic mental disorders kind of across the board-- all the way from chronic anxiety, depression, to bipolar, to schizophrenia, and even Alzheimer's disease. We know that patients with all of those disorders have impaired glucose metabolism and that the insulin signaling system in the brain, which is different than insulin signaling in the periphery, seems to somehow possibly be playing a role. So to step back from that, so for some patients, I might just want to decrease glucose and insulin levels. And I can do that by getting rid of sweets. For other patients, like patients with schizoaffective disorder or schizophrenia or bipolar disorder, especially if it's chronic, if I'm using it as a brain treatment, then I do want a ketogenic diet. And I

usually want reasonably high levels of blood ketones. Usually, for depression, I want to see at least greater than probably 0.8 minimal. For psychotic disorders and bipolar disorder, I usually want to see levels greater than 1.5. That's what I'm shooting for, if at all possible. So yeah, I think that's what I'd go for. ANDREW HUBERMAN: Yeah, so-- and sorry, I didn't mean to imply that people need to be in ketosis in order to see some mental health benefits from changing their diet. You make very clear in your book-- and we'll go into this in more detail-- that avoiding insulin resistance, reversing insulin resistance, and essentially trying to reverse what earlier you described as this metabolic syndrome, which is a bunch of different things, is the target. And for some people, getting rid of highly processed foods and focusing mainly on nonprocessed or minimally processed foods will really help. For others, going straight to the full-blown ketogenic diet will be of most benefit. I'd like to back up a little bit in history

00:46:51 Ketogenic Diet & Epilepsy Treatment

and get to something which I find incredibly interesting, which is epilepsy and the longstanding use of ketogenic diet and fasting to treat epilepsy. And the reason I want to kind of rewind to that point in history is that, I think that for a lot of listeners and people out there who are familiar with how changing your diet or changing your exercise can positively impact sleep and weight and all these things, and it cascades into feeling better-- that makes perfect sense. But for a lot of the world still, the idea that changing or using nutrition as a dissection tool or as a treatment tool to understand and treat mental illness, is still a kind of heretical idea, that to them, it kind of falls in the, OK, well, that's like a woo science or something like that. Now, obviously you're a board-certified physician or psychiatrist at arguably one of the finest medical schools in the world, Harvard Medical School. Even though I'm on the Stanford side, we acknowledge-- we acknowledge our East Coast-- CHRIS PALMER: You're the Harvard-- ANDREW HUBERMAN: --friends. CHRIS PALMER: --of the West Coast. ANDREW HUBERMAN: We're not going to talk-- OK. CHRIS PALMER: [LAUGHS] ANDREW HUBERMAN: We're not going to talk-- CHRIS PALMER: Or we're the Stanford of the East Coast. ANDREW HUBERMAN: That argument could go back and forth a number of times. You're a serious clinician and a serious scientist. And you're a serious thinker. But for a lot of people out there, the notion of using diet, they immediately think, ah, well, that makes perfect sense. Or I think there's a category of people who think, well, yeah, didn't

Atkins die of a heart attack? I hear that a lot. That was crazy. People immediately discard the Atkins diet for that reason, which I do think is throwing the baby out with the bathwater. But it's an interesting thing nonetheless. And then I think that the majority of people sit in the middle and just want to see science and medicine come up with treatments that work. And I have to say, I'm very relieved to hear what you said earlier, which was-- you never said that people should come off their medication and just become-- go on a ketogenic diet and everything will be cured. You're certainly not saying that. CHRIS PALMER: No. ANDREW HUBERMAN: And rather you're saying, if I understand correctly, that nutrition needs to be considered one of the major tools in the landscape of effective tools and that it can be very effective, evidenced by the story that you shared. And there are many other stories in there as well of truly miraculous transformations. So let's talk about epilepsy and how the ketogenic diet is not just used for epilepsy but is one of the oldest, if not the oldest, examples of the use of nutrition to treat a condition of the nervous system that can be incredibly debilitating, even deadly. CHRIS PALMER: Yeah. And the reality is that this literature, and this clinical history, and all of the research we have was the godsend that I needed to do the work that I'm doing. Otherwise, I would have been discredited on day one. Chris Palmer is claiming that a dietary change can influence schizophrenia or schizoaffective disorder. That's impossible. And he's a quack. But the thing that immediately got me credibility was I didn't focus on it as a diet. I did a deep dive into the epilepsy literature. So the ketogenic diet, unbeknownst to most people, was actually developed a hundred years ago, 1921, by a physician for one and only one purpose-- to treat epilepsy. It wasn't developed as a weight loss diet. It wasn't developed as the diet that all human beings should follow. And the reason it was developed is because of this longstanding observation, since the time of Hippocrates, that fasting can stop seizures. Now, fasting is not a healthy diet. Fasting is the process of no diet. So we now understand a tremendous amount of science. Most people think going without food is bad. And they equate it with starvation. But in fact, when we go without food, it causes tremendous shifts in metabolism-- both brain and body metabolism. And it puts the body into a mode of autophagy, and conservation of resources, and all sorts of things that are beneficial to human health. And this is why fasting has been used as a therapeutic intervention in almost every culture, in almost every religion for a millennia. But for the most part, that was all thought to be religious folklore. That was just crazy talk. And those stupid people way back then thought God cured everything. And so they fasted. And they just assumed that they were getting

better. Well, in 1921, one physician used intermittent fasting on a child with seizures and found that, oh, Lo and behold, this religious folklore stuff has something to it. It actually worked. The problem with fasting is that you can only fast for so long before you starve to death. And that's not a very effective treatment. ANDREW HUBERMAN: And this child was ingesting water, correct? CHRIS PALMER: Yes. ANDREW HUBERMAN: It was just food elimination fasting. CHRIS PALMER: Food elimination. ANDREW HUBERMAN: OK. CHRIS PALMER: So no special diet. But the problem with fasting for epilepsy is that as soon as people start eating a normal diet again, their seizures usually come right back-- oftentimes, with a vengeance. And so it can be a good short-term intervention. The fasting can take a few days because it can take a few days to get ketosis. And then you can get some relief from chronic seizures. But it's not a good long-term treatment because, again, people will starve to death. As soon as they start eating, seizures come back. So it was actually Dr. Russell Wilder at the Mayo Clinic who developed the ketogenic diet with one and only one purpose. He wanted to see, can we mimic the fasting state, using this special diet, to see if it might stop seizures long-term? And lo and behold, it worked. Early results were extraordinarily positive. 50% of patients who use the ketogenic diet became seizure-free. And another 35% had a 50% or greater reduction in their seizure frequency, so about 85% efficacy rate. ANDREW HUBERMAN: Sorry to interrupt. I didn't mean to do that there. Was it just for pediatric epilepsy or for adult epilepsy as well? CHRIS PALMER: So back in the 1920s, we didn't have many anti-epilepsy treatments. And a lot of adults were struggling as well. So they were using it on anybody who would do the diet. By the 1950s, pharmaceuticals were coming out. And we had many more anticonvulsant treatments. And there's no question, they work for a lot of people. That's great. And taking a pill is so much easier than doing this diet. So the diet pretty much fell out of favor. And nobody was using it from the 1950s to about the '70s. But lo and behold, even to this day, people with epilepsy, about 30% don't respond to the current treatments that we have available. 30% will have treatment resistant epilepsy, which means they continue to have seizures no matter how many anticonvulsants they're taking, even if they've had brain surgery. It just doesn't stop their seizures. And so in the 1970s, the ketogenic diet was resurrected at Johns Hopkins for these treatment-resistant cases. And lo and behold, it works-- not for all of them, but it works in-- about 1/3 become seizure-free. And these are people who've tried everything and nothing's working. So 1/3 become seizure-free. Another third get a clinical benefit, meaning a 50% or greater reduction in their seizure frequency. And the other third, it

doesn't seem to work. It's not always clear if that's because of noncompliance or if that's because the diet's just not working. But about a third, a third, a third-- seizure freedom, reduction in seizures, or it just doesn't work. And so the reality, the godsend for me is that we have decades of neuroscience research on the ketogenic diet and what it is doing to the brain. We know that the ketogenic diet is influencing neurotransmitter levels-- in particular, glutamate, GABA, adenosine. It changes calcium channel regulation and calcium levels, which is really important in the function of cells. It changes gene expression. It reduces brain inflammation. It changes the gut microbiome. Gut microbiome is a huge topic right now. And there are some researchers who argue that is the primary benefit of the ketogenic diet-- it's changing the gut microbiome in beneficial ways. So it's doing a lot of things. It obviously improves insulin resistance.

00:56:10 Ketogenic Diet & Mitochondria Health

It lowers glucose levels, lowers insulin levels, which improves insulin signaling. The key for my research that I've outlined, the real magic, is that this diet stimulates two processes that relate to mitochondria. It stimulates a process called mitophagy, which is getting rid of old and defective mitochondria, and replacing them with new ones. And it also stimulates a process called mitochondrial biogenesis, which means that after people have done the ketogenic diet for a while-- months or years-- many of their cells in their bodies and brains will have more mitochondria. And those mitochondria will be healthier. And I believe that is the reason the ketogenic diet is such

00:57:05 Nutrition & Benefits for Neurologic/Psychiatric Disorders

a powerful treatment not only for epilepsy but also for people with chronic mental disorders. ANDREW HUBERMAN: Would you mind listing off a few of the mental disorders? And I know this is not meant to be inside ball, but we should distinguish between psychiatric disorders and neurological symptoms and diseases. The fields of psychiatry and neurology hopefully someday will just emerge. But for instance, typically if somebody is presenting with something that looks like Alzheimer's, dementia, they'll talk to a neurologist. Whereas, if somebody is presenting with symptoms, like schizophrenia, bipolar, they'll talk to a psychiatrist. But if you wouldn't mind wearing a dual hat, could you just quickly list off some of the neurologic and psychiatric disorders

for which ketogenic-- or let's just say-- nutrition changes have been shown to improve symptoms significantly. And then maybe we can dive into a couple of these as well as get more deeply into these two very interesting aspects of mitochondrial function and repair and turnover. CHRIS PALMER: Yeah. In terms of nutritional psychiatry, it's a broad field. And it's in its infancy, is the real answer. If you're looking for randomized controlled trials documenting efficacy in large numbers of patients with these disorders, we don't have them. They're underway now. But we don't have them yet. What we do have are case studies. We have a lot of mechanistic science papers by some of the leading neuroscientists and psychiatrists in the world-- and neurologists in the world kind of outlining, this is everything we know that the ketogenic diet is doing. These are the problems in the brains of people with these chronic mental or neurological disorders. So we know that they should work. But the disorders range from chronic depression to-- we've got a trial underway for PTSD. We've got one actually decent pilot trial from the National Institutes of Health for the ketogenic diet for alcohol use disorder, of all things. And we can go into that a little more. We've got a couple of pilot trials of the ketogenic diet for Alzheimer's disease. And those are randomized controlled trials. We've got case studies of the ketogenic diet for chronic depression, bipolar disorder, and schizophrenia. The largest study that we've got in that mental health sphere is a pilot study of 31 patients admitted to a French hospital. 28 of those patients were able to do the diet and stay on the diet. So 10%, off the bat, noncompliant, couldn't do the diet. So we need to include that. But of the 28 patients who were able to do-- and these are 28 patients with treatment-resistant mental disorders, chronic depression, bipolar, and schizophrenia. Of the patients who were able to do the ketogenic diet, 100% had at least some improvement in symptoms. 46% had remission of illness. Remission of illness, that does not happen with current treatments. And 64%, I think, were discharged on less medicine than they went into the hospital on. So it wasn't that the people were prescribing more medicine and that's why. They were being discharged on less medication. We've got at least-- again, a lot of the hard core scientists are going to say, show us the randomized controlled trial with hundreds of patients. And we've got five randomized controlled trials underway now, funded primarily through philanthropy. I can tell you that-- we've talked about that one index patient. But at this point, I have now treated dozens of patients. And I've heard from hundreds of patients who've been treated by other clinicians, researchers-- or I've just heard from patients from around the world-- who have shared stories of complete remission of long, chronic mental disorders-- like bipolar disorder and

schizophrenia-- off of psychiatric meds. Some of them-- not all of them, but some of them are able to get off all psychiatric meds and remain in remission. Again, I think I didn't say this before. But it's really important to mention. For people who might be unfamiliar with the mental health field and its connection with epilepsy, the reason that it's such an important connection is that we use epilepsy treatments in psychiatric patients every day in tens of millions of people. So a lot of people don't know this, but I'll list off some names that a lot of your listeners may have heard of. And they probably know them as psychiatric drugs. But in fact, these are epilepsy drugs. Depakote, Tegretol, Lamictal, Topamax, Neurontin or gabapentin, Valium, Klonopin, Xanax-- those are all medications that stop seizures. And many of them were developed initially for seizures. But we, in the mental health field, quickly steal them and start using them in tens of millions of people, even if they're off label. So that means, we don't have research studies documenting that they're effective. But we go ahead and use them anyway because the reality is far too many patients aren't getting better with the FDA-approved treatments that we do have to offer. So psychiatrists are just winging it in some cases. And we're just throwing whatever we can at them and we absolutely include epilepsy treatments. So in many ways, using the ketogenic diet as a treatment for serious mental disorders, is nothing new at all. It's an established evidence-based treatment for epilepsy. We use evidence-based treatments for epilepsy across the board for a wide range of mental disorders. And so in many ways, that's all I'm doing with the ketogenic diet. It just happens to be a diet. [CHUCKLES] ANDREW HUBERMAN: I love it. I love it. And I should say, I love it because we had a guest on here early days of the podcast. He's a colleague of mine at Stanford. He's a bioengineer, and a psychiatrist, phenomenal scientist and psychiatrist, called Deisseroth, who won the Lasker prize, and so on and so forth. And he made a really important point, which should have been obvious to me but wasn't until he said it, which was the psychiatrist has tools, just like the surgeon has tools. But the tools are language and observing behavior. Those are the dissection tools for what's going on in someone's brain. And then as a neuroscientist, I'm familiar with the neurotransmitters and neuromodulators. And you mentioned that-- and there are these tools of altering brain chemistry, which are of the sorts of drugs you just listed off, or antidepressants, or antipsychotics, that fall into these major bins of adjusting dopamine or adjusting serotonin or some combination of dopamine, serotonin epinephrine, adenosine, and on, and on, and on. And it seems to me, it's an incredible field. But that the field is still very much in its infancy that it wasn't about a hundred years

ago that people were measuring bumps on the head as a way to diagnose phrenology, and that there's still so much to learn. And so when I hear you say, adjusting nutrition or putting people into a ketogenic state or even just eliminating highly processed foods, sugars, et cetera, taking care of metabolic syndrome, and then observing tremendous relief in clinical syndromes of-- or symptoms, rather, of psychiatric disorders, it makes perfect sense to me. It's yet another dissection tool. And a tool for altering brain chemistry. If I think about the landscape, the sort of sociology out there of-- again, there seem to be these bins, like a third of people saying, of course, diet, and exercise, and social connection, and limiting stress, that's the good stuff. That's the stuff that we really works. And then about a third of people are sort of unclear. And then a third of people think, well, if it's not a prescription drug, then it just has no place in medicine. And hopefully, that's changing. And certainly, the work that you're doing

01:05:44 Mitochondrial Function & Mental Health

is going to be important in that transition that I think we will see. I'd like to talk about mitophagy and mitochondrial biogenesis. I think most people learn that the mitochondria are the energy factories of cells and that indeed, they are. As a neuroscientist, what I know about them is that they are present everywhere in neurons. Not just in the so-called cell body, but you can find mitochondria in the furthest little bits of neurons. And neurons can be quite big, very large. In fact, meters long or more in some cases and some species, including us. Depending on how tall somebody is, could be many meters-- or several meters rather. And that mitochondria do a lot of stuff besides just produce energy, because I think people hear "mitochondria," "energy," and they think, oh, so these patients felt better. They lost weight. They had more energy. And then they're doing better. But here we're talking about remission of auditory hallucinations, people feeling suicidal and then changing their diet and feeling like life is something they can deal with, and maybe even function extremely well, and et cetera. So maybe we could just talk about mitochondria for a moment. And then talk about these two major effects. What are some of the other things that mitochondria are important for in neurons and maybe other cells of the brain? Because as an access point for all this, I think it would be great if people could learn a little mitochondrial biology. CHRIS PALMER: So I guess the first thing that I'll say is that this field is one of the most cutting-edge fields in medicine right now. 20 years ago or so, I think the majority of research scientists thought of

mitochondria as nothing more than little batteries. They take food and oxygen and turn it into ATP. And that's really important. Yeah, we get that. But they're just little batteries. That's all they are. And so one of the reasons that this work is so important it's because it combines cutting-edge research in the metabolic field in the aging field. And we can start to pair it with a mental health and neurological health field. So mitochondria-- one scientist gave me this analogy. He said, if you think of the cell as a computer, a lot of people think of mitochondria as the power cord to that computer because they're providing the power. And they are, in fact, the power cord to that computer. But actually, their real function is the motherboard of that computer. So mitochondria are directing in allocating resources throughout a cell. That is their primary function. And then they happen to be powerhouses as well. And so to give some clear examples, mitochondria play a direct role in the production, and release, and regulation of some really key neurotransmitters, including serotonin, dopamine, glutamate, acetylcholine. Those are pretty powerful neurotransmitters. ANDREW HUBERMAN: Yeah, I would call those-- I would consider those the-- I know you listed more than three. But the sort of primary colors of neurotransmission. CHRIS PALMER: Yes. ANDREW HUBERMAN: Any one of those in excess or deficiency is going to have profound negative effects on a nervous system. Or it's going to alter the way that people and animals feel, think, move-- CHRIS PALMER: Yes. ANDREW HUBERMAN: --remember, et cetera. CHRIS PALMER: So mitochondria are providing both some of the building blocks, if you will, for some of those molecules that are part of the Krebs, citric acid cycle. Some of the intermediate products actually go into making those neurotransmitters. Much more importantly, mitochondria provide the energy for the production of those neurotransmitters. And fascinatingly, mitochondria are directly related to the release of neurotransmitters. ATP alone is not enough. There have been some research studies that have actually found that mitochondria move along the membrane of the synapse to release batches of vesicles of neurotransmitters, and that if the mitochondria are removed from the synapse and researchers flood that cell with ATP, neurotransmitters usually are not getting released. Mitochondria are doing other things. We don't entirely even understand what all they're doing or how they're doing it. But they're doing other things than just providing the power. Another really important example is that mitochondria are actually the primary regulators of epigenetics. If you look at any one factor-- so one study actually found that they're responsible for the expression of about 60% of the genes in a cell. And mitochondria do this through a lot of ways that have been known for years and

sometimes decades. So mitochondria are directly related to the levels of reactive oxygen species in a cell. They are managing calcium regulation in cells. And we know that those things play a role in epigenetic expression. We know the levels of ATP to ADP or AMP also play a role. And mitochondria are doing those things. But it turns out, mitochondria are actually doing much more sophisticated things than even those in terms of gene expression. Mitochondria at least play a role in all of the aspects of the human stress response. So when humans are stressed, either physically or psychologically, there are several things that happen-- increased cortisol increased adrenaline, noradrenaline, inflammation, and gene expression-- in particular, in the hippocampus-- occur with the stress response. And one group of researchers actually genetically modified mitochondria in four different ways, and found that all of the stress response, all those four buckets of stress response were impacted in one way or another, implying that mitochondria are somehow playing a role in those. In terms of their role in cortisol, we know that mitochondria actually have the enzyme required for the synthesis of steroid hormones. So that includes cortisol, estrogen, testosterone, and progesterone, some names that maybe everybody's heard of. so that means that if mitochondria are in short supply or dysfunctional, the production of those hormones may become dysregulated. Mitochondria play a direct role in inflammation. And they turn the inflammatory system both on-- or they at least play a role in turning the inflammatory system both on and off. I'm not going to be able to quote the exact study and author. But one paper in cell actually identified mitochondria as the key regulator in turning certain inflammatory cells off, and that when you inhibit mitochondrial function, those cells don't turn off, that mitochondrial levels of reactive oxygen species are a key signaling process to turn the inflammatory cell process off. Another study found that macrophages-- so macrophages are an important immune cell that play a role in healing. So if you cut yourself, your body will get-- send inflammation that way and send immune cells that way to try to heal your skin. And macrophages play an important role in that healing. One group of researchers tried to figure out how do macrophages know to switch between the different phases of wound healing because the macrophages do different things in the different phases of wound healing. And the conclusion of all of their research was that it's mitochondria. Mitochondria are sending the essential signals that change the state of the macrophages to induce these different phases of wound healing. So I've just talked about neurotransmitters, hormones, epigenetic expression, inflammation. For anybody familiar with the mental health field, they know these are some of the key variables that

researchers have been struggling with for decades, trying to figure out how do these fit together. We know that all of those buckets can be disrupted in people with mental disorders. And our field has struggled to understand, but how do they fit together? How can we make sense of this disruption? And I believe once you understand

01:15:12 InsideTracker

the science of mitochondria, you can actually connect all of the dots of the mental illness puzzle. ANDREW HUBERMAN: I'd like to take a brief break and thank our sponsor, InsideTracker. InsideTracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better understand your body and help you reach your health goals. I've long been a believer in getting regular blood work done for the simple reason that many of the factors that impact your immediate and long-term health can only be analyzed from a quality blood test. The problem with a lot of blood and DNA tests out there, however, is that you get data back about metabolic factors, lipids, and hormones, and so forth. But you don't know what to do with those data. InsideTracker solves that problem and makes it very easy for you to understand what sorts of nutritional, behavioral, maybe even supplementation-based interventions you might want to take on in order to adjust the numbers of those metabolic factors, hormones, lipids, and other things that impact your immediate and long-term health to bring those numbers into the ranges that are appropriate and indeed optimal for you. If you'd like to try InsideTracker, you can visit insidetracker.com/huberman to get \$200 off an ultimate plan or 34% off the entire site as a special Black Friday deal now through the end of November.

01:16:23 Mitophagy, Mitochondrial Dysfunction, Aging & Diet

Again, that's insidetracker.com/huberman and use the code Huberman at checkout. Super interesting little subcellular goodies, these mitochondria are. I come from a field where people are often divided into lumpers and splitters. And I'm somewhere in between. For those of you who don't know, lumpers are people that like to make things really simple-- lists of no more than three functions or dividing brain areas into no more than three. Splitters are people that like to subdivide into a ton of detail. There's a history of scientists being splitters in order to be able to name things after themselves because--

CHRIS PALMER: [LAUGHS] ANDREW HUBERMAN: There's more territory to go around if you're splitting than if you're lumping. But we are doing neither here. What I'm hearing is that mitochondria, in addition to being important sources of energy production and output in cells-- which, of course, they are-- probably have other roles. Maybe someday, what we call mitochondria will actually be two or three different little subcellular or organelles. There may be little bits in there that are controlling gene expression and little bits in there that are controlling neurotransmitter production. But at least for now, the name is mitochondria. And thank you, by the way, for illustrating some of the other things that they do because in the landscape of science education, oftentimes, people will think, OK, energy production. There'll be a picture or a cartoon of mitochondria flexing its muscles. People go, OK, energy, mitochondria, mighty mitochondria. And then they'll think, oh, they're just sort of like a dumb jock portion of the cell. They're not doing anything sophisticated. And everything you listed off is that they are doing many sophisticated intricate things within cells. So I think how things are cartooned and discussed actually has an impact-- and not just on the general public, but on the medical field and on the science fields. Anyway, that's more science sociology. But now that everyone is well aware that mitochondria are doing a large number of very important things in a very regulated way, let's talk about mitophagy. A few years ago, because a Nobel Prize was given for autophagy-- sometimes called autophagy. Look, people, you can say it either way. People will know hopefully what it means is more important, which is the gobbling up of one's own cells that are dead or injured. And this idea of autophagy, of cells being eaten up within a system-- nervous system or other system-- has come up again and again. I actually wasn't aware that mitophagy could be such an important lever. So tell us about mitophagy, which I have to presume is the, intentional or not, gobbling up of mitochondria, presumably to replace them with newer healthier mitochondria. Is that right? CHRIS PALMER: It is. So in many ways, mitophagy is a subset of autophagy. But it's got its own name because it is specific to mitochondria. There do appear to be some unique regulators of mitophagy compared to autophagy more broadly. Mitochondria actually are playing a role in autophagy itself. And this makes sense because one of-- so the global picture of autophagy is stimulated by fasting states or fasting-mimicking states. So when your body senses that you don't have enough food, it actually hunkers down and starts to recycle dead old parts in this kind of carefully orchestrated way. And it takes them to lysosomes. They get degraded. And then those degradation products get used for either energy or to build new things.

Autophagy is always occurring at a low level. But you can really hyperstimulate the process through fasting, calorie restriction, fasting-mimicking diets, other things. And this is why fasting and calorie restriction is so kind of such hot topics in the medical field now. It's because they've been shown to induce longevity. And we think it's probably through that process that you're stimulating the body to kind of become lean and conservative in terms of its allocation of resources. And the body doesn't just destroy the healthiest tissue along with the old dead stuff. It has these processes that identify the old and defective parts first. And they go first. And that's what's beautiful about the whole thing. And that's why fasting is so important. So mitophagy we know plays a really important role because-- so there's this term called mitochondrial dysfunction, which some researchers are actually wanting to get rid of and move away from because, as you just said, mitochondria do so many different things. And different mitochondria even within the same cell may very well be specializing in different tasks. And mitochondria from one cell to another are sometimes doing very different things, like not all mitochondria can produce cortisol. That's specific to specific cells where those genes are getting turned on. So it's not like all mitochondria are producing cortisol. Just the ones in your adrenal gland, for instance, are producing cortisol. But there is this term "mitochondrial dysfunction." And it has long been known, for decades, that mitochondrial dysfunction is associated with everything that ails us essentially. So in the 1950s, we had a theory of aging that was based on reactive oxygen species. And that's where all the inflammation is bad for you comes from. ANDREW HUBERMAN: And where all the noise about antioxidants-- CHRIS PALMER: Yes. ANDREW HUBERMAN: Like in the '90s, it was like, it contains antioxidants. Not to say antioxidants are bad, but they are certainly not the be-all-end-all of health. CHRIS PALMER: They are not. But that's exactly where that research came from, is that researchers were narrowing in on these reactive oxygen species are highly, highly correlated with all of the diseases of aging and poor health outcomes. It turns out, they're also highly, highly correlated with all chronic mental disorders interestingly. So researchers used the antioxidants to see if, well, maybe if we can stop, somehow tame these reactive oxygen species, we'll improve health outcomes. Doesn't seem to work. By the 1970s, our understanding of mitochondria and their role in the production of reactive oxygen species expanded. And that led to the mitochondrial theory of aging. So in the 1970s, we had this mitochondrial theory of aging, based primarily and exclusively on reactive oxygen species. Fast forward a couple of decades, that was disproven because we now reactive oxygen species aren't all bad. They

actually serve a signaling process. They're a normal part of human functioning and cellular function. So they're not all bad. But we still know high levels of reactive oxygen species are bad for you. Fast forward to just, I think, maybe last year, with this expanded role of all of the different things mitochondria are doing. So David Sinclair published a paper in one of the cell journals, I think, saying that, oh, mitochondria are actually the unifying link of everything that we know about aging. Mitochondria are the cause-- or defective mitochondria or defective mitochondrial function, mitochondrial dysfunction, is possibly the unifying cause of aging and all of the aging related disorders. So mitophagy is trying to address all that. It's trying to say, OK, this is bad. We don't want defective mitochondria and how can we get rid of old ones or defective ones and replace them with new ones. And I think the most powerful signal and tool that we have right now is, in fact, related to diet.

01:25:09 Neurons, Mitochondria & Blood Glucose

It's calorie restriction. That is the oldest, truest, kind of best-proven way to prevent aging in a wide variety of animal species-- fasting and intermittent fasting. And again, you can only do those things for so long. And then fasting-mimicking diets can also stimulate this process of mitophagy. ANDREW HUBERMAN: Before we talk about mitochondrial biogenesis, if-- and I certainly accept the idea that mitochondria are extremely important in physical health and mental health. That's, for me, is a straightforward conclusion at this point, based on what you've said, whatever and elsewhere, et cetera. And if various diets, including ketogenic diet, including fasting, reducing sugar intake, et cetera, can assist in mitochondrial function and mitophagy-- and that's at least one of the levers by which diet can positively impact mental health and physical health, can we conclude that there's something special about low blood glucose in the brain? The sort of common pathway of all of those things-- fasting, ketogenesis-- for some people, maybe they-- maybe some people have great insulin management, so just removing sweets, refined sugars, brings down their blood glucose level substantially. They don't need to go on a ketogenic diet in order to relieve a low level depression or something like that. Seems like the common theme here is that glucose levels in the brain need to be reduced, which for me, is surprising because neurons love glucose. There are some really nice studies. One that I can think of recently that was published in Neuron, if you just look at the tuning of a neuron, how well a neuron in the brain represents some visual image in

the environment in terms-- here, we can just generalize and say, more action potentials, more electrical signals from the neuron generally correlates with better high fidelity representation. It's sort of if everyone's time someone says, shout, and then someone shouts, the neuron is the one responding to the order. And these neurons just, when there's high glucose, they are faithful representatives of what's out there in the world. But then when you fast an animal, they become less faithful representatives of what's out there. And yet when I've done intermittent fasting, and I do a kind of modified version of it, my mental clarity is far better than when I've had a big bowl of pasta-- probably for other reasons related to serotonin and tryptophan. So I think for the typical listener out there, I have to imagine, it's got to be a little confusing. We hear neurons love glucose. They live on glucose. And here, we're saying, let's deprive them of some glucose. Or let's just bring glucose levels down. Or let's switch the fuel source of the brain from glucose to ketones. And now the brain really works the way it's supposed to. So this raises a little bit of just so story question, like why would it be the case that neurons love glucose, and yet if there's too much glucose around, they become sick? And of course, with any why-would-it-be story, as I would say, I wasn't consulted at the design phase. And I'm going to presume that you weren't consulted the design-- CHRIS PALMER: I was not. ANDREW HUBERMAN: --phase either. And that if any of us say that we are, then we are probably the patients that need evaluation. So I think there's a name for that. There's delusion-- CHRIS PALMER: Yes. ANDREW HUBERMAN: --right? OK. I threw out my first correct clinical assessment of myself. So how do I get my head around this? You've got me sold on mitochondria-- not that I needed to be sold. But that's an easy yes, yes, absolutely, yes. The idea that diet can impact mental health and physical health-- yes, absolutely-- by way of mitochondria-- at least in part, great. But then neurons love glucose. So what's going on? Or what do you think is going on? CHRIS PALMER: I am not convinced that glucose is the real story. Glucose may, in fact, be a symptom. We know that parts of the brain-- there have been a couple of studies that just came out in the last couple of weeks, I think, documenting that actually astrocytes in the hypothalamus play a key role in glucose regulation throughout the body. And it appears to be a metabolic role, which in my mind, implies that the mitochondria in those astrocytes are probably playing a key role because we know mitochondria play a key role in sensing glucose levels. They play a key role in the release of insulin from the pancreas. But mitochondria in the brain is also playing a role in kind of balancing how much glucose is around. And so it's a difficult question because I think in some cases,

high glucose levels are actually a symptom of metabolic dysfunction somewhere in the body or brain. And when I think about, well, what does that mean? In my mind, most of the evidence currently is pointing to mitochondrial dysfunction somewhere in the body or brain. That is the most likely cause of that dysregulation of glucose levels. But we know that if you consume massive amounts of junk food, sugar, and other things, that you can get dysregulation of glucose levels. The conundrum, though, is that that's not a universal response. ANDREW HUBERMAN: And what about the typical person? I've never really liked junk food that much. Maybe as a kid, I can recall liking candy. But I was a sandwich for lunch person for a long time. And as I've changed that out for salad and maybe a small piece of meat with my salad or something like that, I feel far better during the day, far more alert. But I do eat carbohydrates. I eat starches typically at night. But I tend to do some very hard training at some point during the day. So I imagine I have some glycogen to repack. OK. That's me. I only mentioned that because I'm not in ketosis

01:31:54 Obesity, Ketogenic Diet & Mitochondria

as far as I know. I haven't-- unless you brought the strips, I haven't done the blood glucose test today. So what about the typical person who's an omnivore eating some rice, some pasta, pasta salads, people that are eating not junk food massive amounts of sugar but have blood glucose that's in kind of moderate range? Do you think-- and here, feel free to speculate. Do you think that those people might feel far better-- or even a little bit better-- if they were in a lower glucose state? And I ask this because I think there are a lot of people out there who suffer from full-blown depression. But there are also a lot of people who suffer from moodiness and feeling not so great, subclinical depression. CHRIS PALMER: Yes, burnout is what I would call it. ANDREW HUBERMAN: Yeah, or just feeling some days are great, and then other days, they feel lousy for reasons they don't understand. CHRIS PALMER: Yeah. ANDREW HUBERMAN: And those make for less dramatic case studies. And yet I have to assume that that description will net a large fraction of the general public. CHRIS PALMER: So the way that I kind of break this field-- and I'm probably getting too nerdy right now. But I kind of break this field into cause-- what's the actual root cause-- and what are effective treatments. And I really see them as two separate things. Just because the ketogenic diet is an effective treatment, does not imply that the cause of the problem was eating carbohydrates. And I think that's a really important distinction. There are many people who disagree with me on that.

There's no doubt about it. And everybody's heard people say, sugar is the cause of everything that ails you. Or carbs are the cause of everything that ails you. If everybody does a low carb diet or a ketogenic diet-- and then they go to, so it must be sugar that was the cause. I don't see it as clearly black and white as that. Calorie restriction, ketogenic diet, carbohydrate restriction are inducing metabolic changes in the brain and body. And regardless of what the person was eating, they are inducing metabolic changes that can be really beneficial to brain health. So let me just give a clear black and white example of this. And then I can speak to the broader topic that you brought up about just the general population. The easy example of the ketogenic diet being an effective intervention for somebody who was not following a bad diet is an infant with epilepsy. There are lots of infants who have uncontrollable seizures. They are drinking breast milk. To the best of our knowledge, that is the primary, most beneficial food source an infant could be consuming. Now, some might say, well, maybe the mother is-- whatever, I don't buy that. The mother's breast milk is, in fact, the optimal food source for that infant. And yet that infant is still seizing. If we put that infant on a ketogenic diet, a lot of those infants seizures will stop. It doesn't mean that the cause of the infant seizures was a bad diet. But it means that dietary intervention can change brain metabolism and improve symptoms in that person. So going to your broader question about adults, modern-day, the real answer is-- there was just this conference in London, the Royal College of obesity medicine or something like that. That's not the name. But it's something along those lines. The conclusion of that conference that invited the greatest minds in obesity medicine, the overarching conclusion of that conference was we don't know what causes obesity. It's really important that we sit with that. We don't know what causes obesity. ANDREW HUBERMAN: They don't think excess caloric intake beyond one's daily metabolic needs is causing obesity? CHRIS PALMER: Some will argue that. And so some will say yes, it's all energy balance. But why do we have an epidemic of obesity? ANDREW HUBERMAN: Oh. Well, that's the N-gazillion dollar question. CHRIS PALMER: Yes. Some will say, it's all the junk food. But we had junk food in the 1970s. When I was growing up, I grew up on Kool-Aid, and Twinkies, and King Dons, and HoHos, and-- [LAUGHS] ANDREW HUBERMAN: I'm rewatching the Mad Men series now. I love that series, and I'm rewatching it. And I happen to know someone who worked on that series. They researched everything for the props, and the costumes, everything, right down to diet. And if you look at the diet, it was terrible. It was mostly-- yes, there was a lot of excessive amounts of drinking and cigarette smoking. But the

diets were terrible. It was pre-packaged foods. It was frozen dinners. That really came to prominence in the '70s and '80s. But even in the '50s and, from what I've been reading, even in the '30s and '40s, people were not eating grass-fed meat and Brazil nuts with a little bit of broccoli rabe on the side. That's not the typical intake. So something out there-- or maybe multiple things-- are at play to increase obesity. CHRIS PALMER: And at the end of the day, I believe-- some will call this speculative. But I actually think we've got a tremendous amount of evidence that continues to point in this direction. I believe that mitochondria are the key to the obesity epidemic, that there is something in our environment. So that is either our food, environmental toxins, stress levels, poor sleep, not getting adequate sunlight, whatever you want to speculate on, all of the above, all of those things are known to impair mitochondrial function. And if parts of your brain that regulate metabolism and that regulate eating behaviors are not metabolically healthy, it means that they will not stop you from eating. Or it means that your metabolism will not rise to the challenge of 10 donuts, because some people can eat 10 donuts and go on staying thin and healthy. ANDREW HUBERMAN: I totally agree. Although, I would just like to say that it seems to me that compared to when I was growing up-- and again, I haven't run the statistics-- there are fewer and fewer of those individuals around now. Just as when I was growing up, it was one or two kids in class that were quite overweight. And then there were some that were mildly overweight. But most were of healthy weight. Nowadays, that's dramatically altered. The landscape is dramatically altered in the other direction. It is rare when I encounter one of those can-eat-anything type people. I know one, he's actually an employee at Stanford. He's in our media team at Stanford. And this guy, when I take him to lunch, it's like-- he's in his early 70s, and he can eat. And he's incredibly lean. He exercises a little bit. But he's one of these mutants that just can eat, and eat, and eat, and he's lean and he's vital, and he's-- it's wild. And he's an expensive lunch. CHRIS PALMER: [LAUGHS] ANDREW HUBERMAN: But those people are seem rare. And even those kids are now seem rare. CHRIS PALMER: They're getting increasingly rare. And that leads me to think it may

01:40:00 Mitochondrial Function: Inheritance, Risk Factors, Marijuana

be epigenetic factors in the womb environment, so that kids are actually coming out predisposed to obesity. ANDREW HUBERMAN: Well, let me ask you about that because I had a note here to ask this later. But I'm going to interrupt you now in order to

capture this moment. My understanding is that-- well, as everyone knows, we inherit DNA. We get genes from both of our parents. And they mix. Although there are incredible data from Catherine Dulac's lab at Harvard and others showing that we actually have entire regions of our brain that carry neurons that are of purely of mom's or of dad's DNA, depending on the brain region. This is a wild finding. But it's accurate. And this has actually been known about in terms of heritability of disease, et cetera. Maternal DNA, DNA from mom, genes from our mother-- not to place blame on mothers at all. My understanding is that the mitochondrial DNA come exclusively through the maternal side. Is that true? CHRIS PALMER: So it's a great question. And I've been asked this before. And yeah, psychiatrists are known for blaming mothers. And some might say that I'm trying to redo that whole thing and blame mothers again. ANDREW HUBERMAN: The data are the data. I'm not trying to blame mothers here. Mothers play an essential role in everything. But if it is true that mitochondria are the linchpin of all this and maternal DNA is what determines the mitochondrial DNA, I think it's an important place to look. CHRIS PALMER: It's an important question. And the answer is unequivocally no. That's not the way it works. ANDREW HUBERMAN: Well, then vindication for anyone that was asserting that. CHRIS PALMER: And so let me explain it. So mitochondria have 36 genes unto themselves. 13 of those genes code for some of the mitochondrial machinery of making ATP. And the other 36 play roles in epigenetic regulation, play roles in whole body metabolism, and other things. So that is what you're inheriting from your mom. It's the mitochondria and those 36 genes for the most part. But the majority of proteins that make up mitochondria, over, I think, 1,300 genes that make up mitochondria are actually encoded in the nuclear DNA. And so you inherit a copy from both your mother and your father. So the majority of people who have mitochondrial defects or rare mitochondrial diseases actually could inherit them from either mom or dad because it can be a defect in the nuclear genes that code for proteins that make up mitochondria. The much bigger issue when-- so when I talk about mitochondrial dysfunction being a primary driver of mental illness, metabolic illness, it's not that people inherit a defective mitochondrion or mitochondria from mom, and then that just ruins their life forever. That's actually not the way it works. The beautiful thing about this theory is that it connects all of the risk factors that we already know play a role in mental health but also metabolic health. Sleep disruption impairs mitochondria and mitochondrial function. Stress, high levels of stress and trauma, impair mitochondrial function. Drug and alcohol use, alcohol, tobacco definitely-- in terms of the smoke-- and marijuana--

THC, in particular-- all impair mitochondrial function. ANDREW HUBERMAN: THC directly or the smoke? CHRIS PALMER: THC directly. Those studies have been done. So mitochondria actually have CB1 receptors right on them. And various researchers, a couple of studies from Nature actually documented this, that the mitochondrial CB1 receptors are primary-- kind of primary points of the influence of marijuana on human behaviors and effects. Because when they remove CB1 receptors in animal models, these changes don't happen. So the CB1 receptors-- we've got some large studies of adolescents who use a lot of marijuana. And the areas where the mitochondria have the greatest number of CB1 receptors are areas of their brains that actually are atrophied or shrunk compared to normal healthy controls. So that means their brain tissue is aging prematurely. It's shrinking prematurely. But the CB1 receptors on mitochondria also seem to play a role in the memory impairment that can be induced from THC. And they also play a role in the kind of lack of motivation, the behavioral amotivational state from THC. Now, again, for people who want to chillax, that's what they're looking for. They don't want to remember anything. They don't want to think. They want to be spaced out. They want to relax. That's great. But it's important that they know that they're actually harming the mitochondria in their brain cells. And that although there's always an opportunity to repair mitochondria and always an opportunity to stimulate mitochondrial biogenesis, so you can get it back, but if you keep doing it chronically, you're probably not helping your overall mental or metabolic health. ANDREW HUBERMAN: Yeah, I'm glad you brought up THC. We did an episode on cannabis. We also did one on alcohol-- probably lost some friends from that one. When you look at the data, it's very clear. I'm not arguing that people dislike the effects of these compounds when they take them. But it is clear that, at least to me, based on the data that regardless of what people have read about red wine, that not drinking any alcohol is going to be healthier than drinking alcohol, and that the thresholds for alcohol ingestion before people start to negatively impact their health is about one or two per week. And then THC, because of the very high concentrations of THC that are present in a lot of products now-- vaping and smoking THC and even edibles-- that it can be problematic.

01:46:34 Alcohol & Ketogenic Diet

You mentioned adolescents that predisposition, and brain atrophy, psychosis, et cetera. In any case, because you mentioned alcohol because it is a commonly used substance,

I heard you give a talk in which-- I think I have this right-- in which alcohol can disrupt the way that the brain uses fuels of all kinds, which may disrupt one's response to alcohol, make alcohol seem more rewarding to those that drink alcohol. So drinking alcohol makes alcohol more rewarding to the brains of alcohol drinkers, but that it also might alter glucose metabolism, that basically alcohol is not good for our brains. Do I have that correct? CHRIS PALMER: You do have that correct. ANDREW HUBERMAN: OK. What happens if you take an alcoholic or somebody that just drinks two to four nights a week a couple of drinks, which I think is pretty common out there, and you put them on a ketogenic diet? Has that experiment been done? CHRIS PALMER: That experiment has been done. ANDREW HUBERMAN: Ah. CHRIS PALMER: It led by none other than a woman named Nora Volkow, who is one of the leading neuroscientists and addiction researchers in the world. She is the director of the National Institute of Drug Abuse. She's been hot on the trail of metabolic abnormalities in the brains of people with alcohol use disorder, which I will just refer to as alcoholics because that's what everybody knows it as. So she's been hot on this trail for many, many years. And as you said, it turns out that the reward pathways, in particular, are metabolically compromised in alcoholics. And the metabolic compromise essentially, in a nutshell, means they aren't getting enough fuel from glucose. The interesting thing is that when people drink alcohol, your liver converts alcohol into a molecule called acetate. That acetate travels up to the brain and fuels brain cells, in particular, some of these reward pathway cells more than others. And so chronic alcoholics have this chronic deprivation of energy in these cells. And so Nora Volkow and other researchers at the National Institutes of Health did a study in which they set out to see if we can change this brain metabolic problem in alcoholics. Will that affect clinical symptoms of alcoholism? And will it do anything? It's clinically useful. And so they actually did a pilot randomized controlled trial, admitted alcoholics to a detox unit. Half of the patients got a ketogenic diet. The other half got the standard American diet. And then everybody else, all of them got the same detox protocol. The patients who got the ketogenic diet required fewer benzodiazepines for their detox. Despite that, they had fewer withdrawal symptoms from the alcohol. They reported fewer cravings for alcohol. And the researchers did brain scans, which showed improved brain metabolism in these key areas that they were looking at. And their brains showed reduced levels of neuroinflammation, which was also something they were really interested in. And so that one study says to us that even though most people would think alcoholism has nothing to do with diet, alcohol is just drinking too much. It's a matter of

willpower. Or it's somebody who's addictive. They've got an addictive personality, and it's that simple. You come out of the womb with an addictive personality. And those people are novelty seekers, and they're impulsive. And they have no patience. They have no discipline. They can't sustain any kind of rewarding experience. ANDREW HUBERMAN: Or childhood trauma. There's a-- CHRIS PALMER: Yes. ANDREW HUBERMAN: --story there, which there very well may be. But-- CHRIS PALMER: And there may be. ANDREW HUBERMAN: Yeah. CHRIS PALMER: But what that research study strongly suggests-- and again, yes, maybe we need larger controlled trials. But this is one of the leading neuroscientists in the world who's hot on this trail. This is what she believes. And this is what I believe. It's that if we can correct the brain metabolic defects from chronic alcohol use, we might be able to help people be sober and give them a fighting chance. Or give them an edge up or pull a lever that we can use in their favor, for their benefit. There's one caution to all of this research that I really do want to highlight. And so now, I'm going to get hate mail from all the keto community. ANDREW HUBERMAN: That's OK. I admire you for talking about nutrition at all because anytime one talks about nutrition, you're going to get hate mail from somebody. CHRIS PALMER: So the caveat to all of this is that as part of the research that those researchers were doing, they actually wanted to see what will happen to alcohol levels if an animal consumes alcohol while on a ketogenic diet. So they didn't do this in humans yet. This is a fairly easy study to do. So I'm hoping somebody will do this study soon. But they instead put rats half of them on a standard diet and half of them on a ketogenic diet. And then they exposed them to the exact same amount of alcohol. The rats who were on the ketogenic diet had a five-fold increase in blood alcohol levels. Five-fold increase. ANDREW HUBERMAN: Meaning, they drank more? Or-- CHRIS PALMER: No. ANDREW HUBERMAN: --it was metabolized differently. CHRIS PALMER: It was metabolized differently. The rats all got the same amount of alcohol. ANDREW HUBERMAN: So for people out there who are ketogenic, I'm chuckling, but who are not alcoholics-- please, alcoholics, please do something about it because it's so detrimental. But I guess does this mean that they can drink less in order to get the effect of alcohol that most people are seeking? CHRIS PALMER: Cheap dates. Cheap date is what you call that. You only need a half a drink instead of three drinks. ANDREW HUBERMAN: I would think the keto community would thank you for this unless they somehow have a stake in the alcohol industry. CHRIS PALMER: The reason that I put it as a caution is that if anybody is struggling with alcoholism and thinks hey, I need an edge up. I need a

lever to pull because I'm really struggling to give this stuff up. I just find myself going back. And if you're telling me my brain metabolism is messed up, and this might help it, I'm all in favor of that. And yes, that's what the researchers are pursuing. And that's what I'm saying with the following caveat-- that if you relapse while on a ketogenic diet, you better not drink the same amount of alcohol that you think you can drink. ANDREW HUBERMAN: It could be deadly. CHRIS PALMER: It could be deadly, and/or it could be really-- yeah, deadly to you or someone else because unfortunately, a lot of times when people drink, they get behind the wheel. And they think that they can handle two drinks safely. And they think, well, I can go out for dinner and have two glasses of wine and drive home safely. I know myself. If you go to a ketogenic diet, please don't drive with the same two drinks because it means your blood alcohol level-- if it models anything that we found in the rat study-- your blood alcohol levels may be five times higher than they would normally be. And that means you are really wasted. And you're probably not safe to be driving. ANDREW HUBERMAN: Probably the same is true for drinking on an empty stomach, right? CHRIS PALMER: Yup. ANDREW HUBERMAN: Yeah. Now, it's a very important point. And thank you for raising that. I hear this again about mitochondria, about blood glucose, you mentioned astrocytes. And for those of you-- that earlier astrocytes are a non-neuron cell type in the brain, a glial cell type that my postdoc advisor was known for popularizing the modern science of glia, which include astrocytes. And I'd be remiss if I didn't say that they are considered the cells that hold everything together in the brain and are kind of passive observers. But they do many things actively. I think now people appreciate the astrocytes at least as important as the neurons.

01:55:21 Brain Imaging, Alzheimer's Disease & Ketones

And certainly, for disease, they are often implicated in warding off of disease, et cetera. Everything that you're telling me about the fact that the brain can regulate things that are happening in the body, metabolism, et cetera, organ health, obesity, et cetera, to me, as a neuroscientist, that's not surprising. All of it just screams hypothalamus, hypothalamus, hypothalamus because here, you're telling me, it's regulating these basal functions like metabolism. It's regulating how much we crave things. And of course, hypothalamus is involved in motivation and craving. There are other areas, too-- other areas of the brain, too, of course. But I would imagine that someone ought to or has mapped out where the

receptors for all this business are in the brain. And I guess that raises the question of, when one goes on a ketogenic or low blood glucose diet or fast, has anyone observed changes in the brain? Has anyone had neuroimaging of humans and their brains under conditions of ingesting one diet or another, whether or not they're psychiatric-- suffering from a psychiatric disorder or not? I would think that's where the gold is. CHRIS

PALMER: We do have some of those studies. When you do a neuroimaging study, you can measure a lot of different things. So one thing with a PET scan, you can measure glucose metabolism. So a researcher, Stephen Cunnane is doing that research in particular in Alzheimer's disease patients and Alzheimer's disease models but in humans. And that's because we know that-- again, a common finding in patients with Alzheimer's disease is this glucose hypometabolism, some people are attributing it to insulin signaling impairment. And so some people are calling it type III diabetes. At the end of the day, I think the clearest signal that we have is that cells aren't getting enough energy from glucose as a fuel source. That is something that I think I can confidently say that's backed by numerous research studies. There's debate in the research field about whether that's a primary driver of the illness. I happen to believe it is. And if you ask the question, well, why would cells not be getting enough fuel from glucose? You have to focus on mitochondria because they're the ones producing the fuel from that glucose. So you somehow you have to implicate mitochondria in that process one way or another. Others will say, no, that's just a side effect of whatever's causing Alzheimer's disease. So Stephen Cunnane has done studies where he even gives ketone supplements.

ANDREW HUBERMAN: These are liquid ketone esters? CHRIS PALMER: Yeah, ketone esters or ketone salts. And it has actually found that these brain metabolism deficits can be corrected, at least short-term, by giving a ketone supplement. ANDREW

HUBERMAN: Is this in the context of people also ingesting some carbohydrate? Because I confess, I've tried the ketogenic diet. I probably did it wrong. This was years ago. And then the cyclic ketogenic diet. But in the last year or so, I've started using liquid ketone esters. And I do eat some carbohydrates each day, usually in proportion to how much high intensity exercise I'm doing. Those liquid ketone esters, for me-- at least subjectively-- I feel greatly increase my energy levels and my ability to focus mentally. And they improve my sleep. This is my observation tracking some data but just, again, subjectively. So in this example, are you talking about people taking ketone esters or ketone salts on a backdrop of a ketogenic diet or on the backdrop of a more typical diet?

CHRIS PALMER: So he's done both. So he's done studies where patients aren't doing

anything special with the diet. So they're eating whatever they normally eat, absolutely nonketogenic, giving them a ketone salt or ester, and then noticing immediate and direct changes in the metabolism of these metabolically compromised brain cells as measured by PET imaging. ANDREW HUBERMAN: These are not household pets, by the way.

Sorry, I have-- we have to just-- P-E-T, positron emission tomography, not pets.

Although, I'm sure that there are people out there who have their dogs, or cats, or whatever, or their pet kangaroos, whatever you might own, on ketogenic diet. OK.

CHRIS PALMER: Absolutely. So he's actually moved further. He's done a pilot trial in a nursing home actually, where he did not put the patients on a ketogenic diet. He simply reduced carbohydrate consumption at breakfast and lunch. They still got the same dinner as everyone else. And simply reducing carbohydrate consumption at breakfast and lunch resulted in cognitive improvement in a statistically significant way in some of those subjects. ANDREW HUBERMAN: Oh, I love that result. I'm sorry, I just have to

highlight this. I'm a huge believer in directing carbohydrates to specific portions of the day when one needs to be less focused and alert and yet can replenish glycogen.

Limiting carbohydrates most of the time during the day, for me, has been a game changer in terms of maintaining alertness, et cetera. I'm not aware that I have age-related cognitive decline. But then again, I would-- people around me may argue

otherwise. CHRIS PALMER: Let me say, you are Andrew Huberman. There is no way

you have [LAUGHS] cognitive impairment. ANDREW HUBERMAN: Although you didn't

know me as a six-year-old-- CHRIS PALMER: If you have cognitive impairment, we're all

screwed. ANDREW HUBERMAN: Well, I have plenty

02:01:05 Exogenous (Liquid) Ketones vs. Ketogenic Diet

of flaws and impairments-- well over 3,000 documented by people very close to me. But this is very interesting, I think, in the context of everything we've been talking about because could it be that supplementing with liquid ketones or prescribing liquid ketones to people who are challenged with mood disorders-- or things of that sort-- could be beneficial, even if they are not willing or able to adhere to a ketogenic diet? CHRIS PALMER: That is the million dollar question right now. And we don't have good trial data to say yes or no. My speculation, my hunch, having tried that clinically with patients, is it doesn't seem to work. It's not the same thing. The bigger reason for my feeling confident in saying that is that we've had ketone salts and esters available for over a decade now.

We have tens of thousands of children and adolescents who are following a strict, ridiculously strict, ketogenic diet to control their epilepsy. Those kids would love to be off the ketogenic diet. Their parents would love to have them off the ketogenic diet.

ANDREW HUBERMAN: They had no birthday cake, no ice cream. CHRIS PALMER:

There is not one case report of any child controlling his or her seizures using exogenous ketones without also doing the ketogenic diet. I just find it hard to believe that at least some of those people haven't tried it out to see. I do know some patients with bipolar disorder and even schizophrenia who are doing extraordinarily well on a ketogenic diet. They have tried to switch off the ketogenic diet using exogenous ketones. Their symptoms came back. And so they found that it just wasn't effective. Now, again, those are anecdotes. My scientific speculation about why is because the ketogenic diet is actually not necessarily about ketones themselves. Ketones are one of a multifaceted story there. And so when people do a ketogenic diet, they're also improving-- they're lowering glucose levels. They're improving insulin signaling. They're ramping up mitochondrial biogenesis, in particular, in the liver because mitochondria actually make ketones. That's where they're made. And they're primarily made in the liver mitochondria. So when somebody is on in a fasting state or on a ketogenic diet, their liver mitochondria go through the roof because they're being called to action. It's like, hey, body's in starvation mode. Get to work. And so the mitochondria-- the cell senses we need more mitochondria to process fat to turn it into ketones so that those ketones can get up to the brain and keep the brain fueled, because fatty acids can't fuel the brain. Only ketones can. Now, so my sense is that-- and the gut microbiome changes and everything, the changes in hormones-- so if you're eating a lot of donuts and drinking a bottle of ketones, the donuts are going to prevent your body from lowering glucose levels. You're still going to have the high glucose levels from the donuts. You're still going to probably have the impaired insulin signaling. You're probably still going to possibly have some inflammation from the inflammatory effects of that food. And so just drinking ketones alone won't be enough. I think for people who are metabolically healthy, I'll include you in that, I think ketones can play a really beneficial role, no doubt. I think exogenous ketones may, in fact, proven valuable in clinical use for patients who maybe can't follow a super strict ketogenic diet but maybe could do a low carb diet. And then given the research that's happening with alcohol use disorder, I could imagine a situation-- here's the million dollar tip to whoever wants to go out and get this, if it actually turns out to be true. I could imagine a scenario where we use exogenous

ketones with alcoholics. And that every time they have a severe craving for alcohol, they drink ketones instead. ANDREW HUBERMAN: Which sort of tastes like alcohol. The ketone esters, when I take them, I drink them straight. Sometimes I'll put them in seltzer. And I'm not a big drinker, as I mentioned. I might have an alcoholic drink every once in a while. I just don't ever crave it. I just do it every maybe-- I think 2020 was the last time I had a drink of alcohol. So obviously, I'm not a good representative example. But the ketones taste good to me.

02:06:27 Neuronal Damage, Ketones & Glucose

And they obviously don't get you drunk. They do seem to flick on my alertness pretty quickly. My understanding is that they are the brain's preferred fuel source. Meaning, they are going to be the first fuels used by the brain when there's a buffet of fuels available. If there's glucose in my bloodstream, there's circulating liquid ketones, the ketones would be used first or preferentially. Is that true? CHRIS PALMER: I think it's a complex question. Some research that we have suggest that there are brain areas or brain cells that require glucose and cannot use ketones. So 100% of the brain cannot be fueled with ketones as far as we can tell. So there are some areas that require glucose. And that's probably the reason we have gluconeogenesis to keep the body going and keep the brain going no matter what. But when ketones are available, especially if ketones are high, the way I think about it is not that ketones are the preferred fuel source and glucose goes to the wayside. But the way I think about it is that you have a range of cells with varying degrees of metabolic health. And some of those cells are going to be extraordinarily healthy with appropriate healthy abundant mitochondria. And those cells are probably going to continue to use glucose as a fuel source. But if ketones happen to be there, sure, they'll use that, too. Why not? But the real money is metabolically compromised tissues, whether it's brain cells or other tissues that-- we're talking about the brain. So if you've got metabolically compromised brain cells-- because it's not across the board. Like with Alzheimer's brain scans, there are specific regions that are more metabolically compromised than others. And that's why we see patterns of atrophy in specific brain regions. It's because those regions are dysfunctional metabolically for whatever reason. And we can get into why that might be. But my sense is that if you've got a metabolically compromised cell, that cell is sending out a distress signal. That cell is calling resources from the body, like feed me. Give me something. And if it can't use

glucose effectively, it is going to suck up those ketones and then start running on all cylinders or closer to it. And that process is so critical because what it means is that if that cell was barely getting by on 60% of its real ATP requirement, it means that it doesn't have enough energy for maintenance and repair functions. As soon as you give that cell a hundred percent energy or close to it, even if you get it up to 90% of its preferred energy amount, it can start to repair itself. That's the beauty of the human body in living organisms, is that they have a priority list of what they're going to do. If that cell senses that there are defective molecules, defective proteins in this cell that need to be replaced, once it gets enough fuel, it will start repairing itself and doing that work.

02:10:16 Alzheimer's Disease, Age-Related Cognitive Decline & Ketogenic Diet

ANDREW HUBERMAN: That makes sense. Thank you for that clarification. I'd like to talk about Alzheimer's and age-related cognitive decline generally. I know many people out there are just terrified of losing their memory for the obvious reasons. Memory sets context, et cetera. And many people have relatives that suffer from Alzheimer's or other forms of dementia. I've heard that the ketogenic diet and diets like it can be very effective for helping to offset some of the symptoms of Alzheimer's and age-related cognitive decline. In fact, I even have a friend I won't out by institution, who's the chair of Cardiology, who contacted me, of all people, asking whether or not I was aware of any studies or whether or not I knew of anybody who had benefited from ketogenic diet for Alzheimer's. And I thought, well, why don't you ask one of your colleagues in neurology? But his response was really interesting. He said there are many books out there for the general public. There are a lot of online discussions about this. There are a lot of assertions about this, and some animal studies. Again, these are his words. There are very few, if any, controlled clinical trials exploring the role of the ketogenic diet for the treatment or reversal of Alzheimer's and age-related cognitive decline. I'm hoping that statement was incorrect or soon will be incorrect-- because those trials are ongoing-- but he said, yeah, the people are most popular for telling us about the important role and positive role of being in ketosis for Alzheimer's, for some reason, they just won't do a clinical trial. And that's been frustrating to the community. So this is a very educated, very accomplished person who's a physician of heart medicine as opposed to something else related to the brain. But what is the story there. And for goodness' sake, why aren't there clinical trials on ketogenic diet and Alzheimer's? I don't expect you to be

responsible for that fact. But goodness, I would think this would be the obvious thing for NIH. I'm on study section but not for these sorts of experiments. Why isn't money just avalanching into this area based on all the anecdotal evidence that people are talking about? CHRIS PALMER: So we've got a couple of small pilot clinical trials. The best one was a randomized controlled trial. I think it only included 26 subjects, something like that, randomized to 12 weeks of a low fat diet, 10-week washout, 12 weeks of ketogenic diet. Some of the participants got keto first and then low fat. Other participants got low fat then keto. And that trial actually found that when patients were in ketosis, they had statistically significant improvement in activities of daily living and quality of life. And they did have improvement in cognitive function. But it didn't reach statistical significance, that improvement did not. We've got other trials. We've got several animal models showing that the ketogenic diet can improve biomarkers of Alzheimer's disease in Alzheimer's models. So it can reduce plaques and tangles, can even improve cognitive impairment in animal models. And we've got a couple of other small pilot trials of ketogenic diet in humans, showing that it improves biomarkers compared to, say, the low fat diet or the American Heart Association diet. So we've got those. I think one of the biggest challenges that I'll just share openly-- and this is-- I'm somebody who's pretty passionate about this research. And I believe it has a lot of potential. But Johns Hopkins' researchers attempted to do exactly this kind of a study, Alzheimer's patients' ketogenic diet versus the, I think, American Academy of Aging-- or something like that-- diet, is the controlled diet. ANDREW HUBERMAN: Which presumably has starches in there. CHRIS PALMER: Yes. ANDREW HUBERMAN: I think that's the key variable. CHRIS PALMER: Probably lots of-- yeah, lots of-- ANDREW HUBERMAN: And some potatoes-- CHRIS PALMER: Whole grains, lots of whole grains. ANDREW HUBERMAN: Yeah, some potatoes. CHRIS PALMER: And they spent, I believe, over three years. They screened over 1,300 people who expressed interest. At the end of the day, I think they only got 27 people to enroll. And only 14 of those people completed the study. ANDREW HUBERMAN: Wow. CHRIS PALMER: Despite that, what they found was that the subjects who achieved ketosis had cognitive improvement. But people on study section are going to look at a study like that and say, even if the science is there, if you can't get people to do this diet, why would we spend money on researchers trying to get people to do this diet? ANDREW HUBERMAN: I should mention, study section is this closed door panels of 40 or so people. There are many of these panels. Different divisions in the National Institutes of Health use different panels. And then grants are evaluated in a very

small, because of the size of the federal budget for research, a very small percentage. Usually, about 10% of these studies are funded. The rest generally don't end up happening. That is very informative. What you just described is very informative because now it makes sense to me. There's no conspiracy. It's not big pharma, I don't think, is trying to suppress trials of ketogenic diets on Alzheimer's because I would imagine the first thing that pharma would want to do is to see that study done. So they didn't have to. And then the moment it was done, if it showed a positive effect, they'd probably want to isolate the molecule and wrap it up in something that people would take, right? CHRIS PALMER: Yes. ANDREW HUBERMAN: So I don't think there's any active suppression by pharma. I think pharma would probably be cheering from the sidelines because they could capitalize on it, because ultimately, the studies are done by scientists. But the treatments are generally doled out by pharmaceutical companies and/or physicians. So I don't believe there's a conspiracy there. That is very interesting. And it's kind of amazing, given our discussion of earlier, which is that you had a patient that was having schizophrenic symptoms who managed to stay on this diet. So is there something special about Alzheimer's patients and people with age-related cognitive decline? Presumably, they're very dependent on others to cook for them and shop for them. I think that this is almost perfect controlled environment for getting this study done. CHRIS PALMER: I think that is the key issue. So again, I got patients-- I get patients with bipolar disorder, schizophrenia, extraordinarily impaired people to do this diet and stay with it. But it's because I'm providing a weekly session for them. And I imagine this study did not provide that kind of intensive support. In the pilot trial that I described to you, they actually got, I think, over 90% compliance with the different dietary interventions. So some of it is going to be dependent on the research group. And does the research group understand that this is not-- it's not like prescribing a pill. Here, take this pill. And take it every day and come back in three weeks. And even then, we don't know for sure that the patient took the pill every day. We just assume they took the pill every day. And studies say they probably didn't. So I think when we think about a dietary intervention, we need to think about more intensive support and education. And that support could be a health and wellness coach. It could be a dietician. It could be education of the family. It might even be providing them with dietary meals. That maybe for six months, we actually provide them with ketogenic meals-- once a week, put them in your freezer. Microwave them when needed-- to make this diet as easy and doable as possible. Because if we can get people to do the diet, if we can get them through the first couple of months, most

people can learn how to do this diet. More importantly-- I didn't mention this before. But the number one reason I am so successful at getting patients to stay on this diet for years, is because of the consequences to them when they go off of it. That is the reason I can get schizophrenic patients and bipolar patients to do this diet, whereas other people can't get an everyday human being to do it for weight loss because the weight loss patient doesn't experience devastating tormenting symptoms when they break the diet. Oftentimes, they are rewarded. They eat something they really enjoy. And they get a little bit of a dopamine rush from it. And they're off to the races. They're like, I'm going to-- oh, I've already cheated. I'll cheat again. I'll get back on it someday. And they never get around to it. My patients, when they go off the diet, they start hallucinating within 48-- or 24, 48 hours. And they quickly realize that was a really stupid thing to do. That piece of cake was not at all worth the torment that I'm experiencing now. So they get back on the diet. I suspect with Alzheimer's disease, we might notice something similar. Some of these people have very mild symptoms. So maybe they won't have that kind of a reinforcement, negative reinforcing kind of experience. But I think some of them will. Some of them recognize that they are impaired cognitively. And if this diet could help them remember better, if this diet could help them function better-- and again, that's what the pilot trial showed, is activities of daily living. That means these people are able to go to the bathroom on their own. They're able to get themselves dressed. Whereas, they needed help with those things before. Those are actually really important things to both the patient and the caregiver. And if they go off the diet and then quickly revert into a more symptomatic state, that might be reinforcing enough for them to figure out a way to do the diet on their own. And if we think about, if this really is an effective intervention-- and yes, we need longer trials, larger trials, all of that, because there are plenty of stories in the medical field where pilot trials looked really spectacular and promising. And then larger trials just failed to show the benefits. I believe, based on all the science of metabolism, mitochondria, glucose hypometabolism, all of that, I believe the science makes this an obvious treatment that has real potential. So people will call me biased. That's fine. I've got my bias. ANDREW HUBERMAN: No, based on clinical observation and extensive clinical observation at that-- I think biases that are simply because we want to feel a certain way or believe something are worth critiquing. But bias based on observation-- here, I should mention that most of what we know about human memory was sparked by one patient, a famous HM, who I think was living in Harvard Medical, in one of the hospitals around. There are many hospitals on Longwood Campus. But one

patient, the reason we associate the hippocampus with memory is because we knew that HM's the hippocampus was intentionally damaged for epilepsy treatment. So this idea that everything has to be a randomized clinical trial, to me, is crazy. Of course, that's a gold standard. And it's essential. But there's so much information in textbooks, medical textbooks in particular, that are gleaned from single-patient case studies or from three-patient neurostimulation in the brain or something of that sort. So to me, I'm still perplexed as to why there's this insistence on only one form of evidence. Clearly, what you're doing, the important work

02:23:45 Ketogenic Diet & Weight Loss

that you're doing clinically, and in the research side, and in public communication, is assisting this. I have a question about-- or more of a statement/question about the ketogenic diet. Based on everything that we've talked about, seems to me that the ketogenic diet for weight loss is a very interesting aspect of the diet as is intermittent fasting for weight loss even though it might just be by way of caloric restriction that occurs with fasting. But then in some ways, the effects of the ketogenic diet on weight loss are a bit of a decoy for most people. That's where their mind goes. This person lost X amount of weight. Maybe that made them feel better. Maybe that actually made them underweight. I think you've talked about it. For some people, it can actually bring them under weight. I'm glad that we got the chance to dive into the description of ketogenic diet for epilepsy because it really is a medical intervention that has a side effect of weight loss or could be used to treat obesity and induce weight loss. But it's really about far more than that. And that raises a question for me, which is-- we've been talking about the ketogenic diet as one thing. But I've heard you discuss this before, where just as a physician will prescribe different dosage ranges of a given drug, you can prescribe different dosage ranges of a nutritional plan, a diet. It's not one thing. It's not necessarily zero carbohydrates or 100 grams or 50 grams. It depends on the patient and a lot of other factors. I've heard you list off various things classic keto. Maybe you could just briefly tell us what that typically is, because I think most people think it means eating a lot of meat and not carbohydrates. But it might not be that. Fasting and then some of the other-- you mentioned Atkins earlier. We don't have to go into each of these in detail. And I know in your book, you talk about not just the science and clinical background but also some actionable steps that people could consider. So they can refer there for more

detail. But for somebody who, let's say, is depressed-- they've had some rounds of depression. Maybe they're on antidepressants, maybe not-- and they want to try something like this. Obviously, this has to be done in concert with a physician observing all this. But what is the typical thing that you probe with first? Just like with a drug, you might probe with 20 milligrams of a drug. What's your typical initial dietary intervention probe? Terrible languaging, I realize. And I'm criticizing myself for that. But I think people get the idea. CHRIS PALMER: The real answer is that I don't have a one-size-fits-all recommendation for any person. So the first thing that I'm going to assess with the patient is, what symptoms are they having? What is their current diet like? And what are they willing to do? I try to meet them where they're at. So if somebody-- and I want to point out. You mentioned the all-meat version of this diet, which is often referred to as the carnivore diet. ANDREW HUBERMAN: Very controversial diet. CHRIS PALMER: There is no doubt that exists. Some people swear by it. They swear they've tried other versions of ketogenic diets and only when they went to a carnivore diet did they get benefits. But there are vegetarian and vegan versions of the ketogenic diet. So in my mind, this is not at all about the diet wars of animal-sourced versus plant-sourced foods. It's about inducing a state of ketosis, which is mimicking the fasting state. That is what it's about. And you can do that by not eating anything, by fasting and/or intermittent fasting. And you get your results. So no diet is a ketogenic diet. So it's not about the foods or the types of foods that you're eating. It's about inducing a state of ketosis. The first variable I'm going to look at when I recommend this or prescribe this is the person's current weight. If somebody is obese versus somebody who's thin, I'm going to use different dietary strategies for those two situations. In the obese patient, they have tons of fat stores on their body already. Usually, it is a goal of theirs to tap into some of those. And they'd like to lose some weight if they're going to try a ketogenic diet for brain health anyway. And so I'm going to use that. So that person, really, the diet is carbohydrate restriction. And that usually is a sufficient intervention. ANDREW HUBERMAN: Both simple carbohydrates, meaning sugars and fructose also? CHRIS PALMER: Fructose, definitely. So no added sugars, essentially. You can have added natural sweeteners like stevia or monk fruit. You might use artificial sweeteners. Years of doing this, I'd probably recommend steer away from them if you can because I think they tend to stimulate cravings for high carb foods. So if you can kind of get through a couple of weeks without sweet things, your cravings for those will go down. And it'll make the diet easier and a little more sustainable. But let's say you can have your artificial sweeteners, if that's what

you really want. So I'm going to say less than 20 grams of carbs a day for those people. They can have all the protein they want. They can have vegetables. And they can have all the fat they want. But I'm not going to push fat on those people. I'm not going to tell them, eat a lot of fat, at the same time because I want to use the fat on their body as the fat source, at least early on. ANDREW HUBERMAN: Are you encouraging healthy fats like monounsaturated fats, like olive oil? Are you encouraging people to eat a little less butter, et cetera? CHRIS PALMER: I tend to encourage, again, a wide range of fats. And it's going to depend on the person. A lot of times, people come to me with very specific ideas. But I'm going to tend to encourage olive oil, avocados, nuts, which are usually considered, even by the American Heart Association, healthy sources of fat. The more controversial thing are things like coconut oil or coconut cream, which the American Heart Association might say is not a healthy fat, I kind of disagree with that and don't think it's unhealthy at all actually. And when you look at the epidemiological studies of saturated fat causing heart disease or causing adverse outcomes, at best, maybe increases your risk 10% to 15%-- at best. ANDREW HUBERMAN: How much coconut oil can people ingest, anyway, before they either develop diarrhea-- no joke-- or just sort of get tired of coconut oil? Anyway, your point is taken. But they can eat meat if they like meat? CHRIS PALMER: Absolutely. ANDREW HUBERMAN: Or they can eat eggs. Or if they don't like meat and eggs, they could eat sardines or things of that sort. I personally can't-- I can't even stomach the-- I don't even like the word "sardine." I have nothing against the actual fish. But that's just me. But obviously, people have-- I say this because people have different preferences, right? CHRIS PALMER: Yes. ANDREW HUBERMAN: I'll eat a steak. But I'm not going to eat a sardine. CHRIS PALMER: And I'm going to go with that. And again, there are vegan sources of protein that-- people can eat tempeh and other things. So that's the obese person. It's carb restriction as the primary initial phase. The thin person is going to need to eat a lot of fat because they don't have a lot of fat stores on their body. And if I want them in ketosis, clinical ketosis, I'm going to have to feed them fat. So that's the person that I'm going to say, make sure you get in avocados, olive oil, butter, maybe heavy cream. So heavy cream is delicious. It's a delicious way to get your fats in. I have one patient who just drinks it straight, to just try to get it in. ANDREW HUBERMAN: I get it. I've never had an appetite for sweets. I absolutely love savory fatty food. When I was in high school, I was thin. So I was able to do this. But I used to drink half-and-half. Sometimes I wake up in the middle of the night and drink it just because it tastes so, so good. CHRIS PALMER: It does taste good. So if

they're on a ketogenic diet, I'm going to push them away from half-and-half and toward heavy whipping cream. So you can whip that up. You can freeze it. It turns into ice cream. You can add vanilla. You can add cocoa powder. You can add all sorts of things. And you're off to the races with shakes, and ice cream, and mousse, and all sorts of things that you can have. With any of these patients, the beauty of this diet is I have objective biomarkers. I'm going to have them measuring ketones. And I'm going to adjust the diet based on their state of ketosis and/or the clinical benefits that I'm looking for. If it's an average person, who is not currently under psychiatric care, not taking prescription medicines but is saying, I'm burned out. I'm exhausted. I want some of that brain energy that Andrew Huberman is talking about. He talks about feeling good. I want some of that. I'm probably actually going to recommend the protocol you describe, which is, let's see if we can just carb restrict for a while and see if that produces clinical benefit. I have one-- he's not even a patient, just somebody who read my book. I didn't tell him anything. And he came away from it saying-- he was ready to start an antidepressant for his anxiety. He had chronic anxiety, was trying meditation, was trying all sorts of things. Nothing-- those things weren't enough. He was ready to go on prescription medicine. He read an early copy of the book. He took it upon himself without consulting with me to restrict carbohydrates alone. He did not go ketogenic. He is a vegetarian. He restricted carbs. Within three weeks, said, I don't need prescription medicine. I can't believe how much better I feel. And all I did was cut out some of the high carb foods in my diet. So I think for some people, it can be that simple. For people with serious mental disorders, if they are chronically depressed, if they're on lots of prescription meds, if they're disabled by their symptoms, and certainly, if you're bipolar or have schizophrenia or something, those are the people I really do want them to work with a medical professional because meds may need to be adjusted. They need a real shot at this diet. It's not like weight loss. Weight loss, everybody wings it. And either you're successful or you aren't. You look on the internet or you read a book or you do-- even the colleague that you mentioned, he's probably just reading-- who knows whether it's credible information or not-- and just winging it, and seeing whether it works or not. For people with serious mental disorders, I want you to treat it like you have epilepsy because you do have a serious brain disorder. It's impairing your ability to function in the world. It's impairing your health and happiness. You deserve a competent medical treatment. And we have that. We have a hundred-year evidence-based. We've got dieticians who know this like the back of their hand. They can monitor your level of ketosis. They can help look for

vitamin and nutrient deficiencies that can be a consequence of the diet, and make sure that you're not developing those. They can help tweak the diet if needed. They can give you ideas if you're getting bored with eggs every morning. They can give you ideas for what else you might have.

02:35:47 Ketogenic Diet & Fasting, Hypomania, Sleep

And if you're using it to treat a serious disorder, I think you need serious help. ANDREW HUBERMAN: A couple of questions, a little more detailed, but I think a lot of people will have this on their mind. Is it ever the case that you'll prescribe somebody the ketogenic diet in conjunction with intermittent fasting? So eat keto but eat between the hours of, whatever, 11:00 AM and 8:00 PM or something like that. That's the first question. CHRIS PALMER: Absolutely. And I have one patient with type 2 diabetes and chronic depression. And he will try to follow the ketogenic diet. And sometimes, his blood sugars are still very high. And sometimes I will ask him to do either intermittent fasting or even a three or four day water fast. And it is shocking. When he does a three or four day water fast, the first day or two, he feels like crap. I'll just say up front, don't do it if you've got an important meeting or business trip or anything. Don't be-- ANDREW HUBERMAN: So this is just consuming water. CHRIS PALMER: This is just consuming water. ANDREW HUBERMAN: No black coffee? CHRIS PALMER: I usually tell him he can have plain black coffee or tea. But-- ANDREW HUBERMAN: You have mercy after all. CHRIS PALMER: I have a tiny ounce of mercy. But when he does it, his blood sugars plummet in a good way, his blood sugars are normalizing. But the last time he did it, he actually got to seven days at one point. And he said, I feel great. I want to keep going. I can't believe that I'm not hungry. But I am not hungry at all. I don't miss food at all. And at seven days, I kind of cut the cord. I was like, no, no. We're done. ANDREW HUBERMAN: He needs to eat. CHRIS PALMER: [LAUGHS] We're done. ANDREW HUBERMAN: You got to eat. Well, I find it really interesting that the intermittent fasting, of course, controversial at some level, but as to whether or not it's just beneficial by way of caloric restriction-- because it is one way to achieve caloric restriction-- whether or not has additional benefits. But I'm very interested in the neural side of it. And it does seem that the fasted state can start to take on its own rewarding properties, where people get dopamine release not from eating, as most everyone does, but from abstaining from food. Now, this can be pathologic in the sort of example of anorexia nervosa, which is

we both know as the most deadly psychiatric illness. But for non-anorexics, I think it's interesting to note that eventually not eating can have its own rewarding properties to it that aren't just related to weight loss. But in the short-term, feeling-- in other words, feeling really good by way of abstaining from eating. CHRIS PALMER: Yes. And that's actually-- it raises an important risk that I haven't mentioned yet. But at least in psychiatric patients-- but even in some patients who just use the keto diet for weight loss, I have seen definite hypomania. ANDREW HUBERMAN: So these are people that aren't sleeping very much. Are they also getting kind of delusional, thinking they're going to run for president? CHRIS PALMER: No. So the distinction between hypomania and mania-- so mania, you might become psychotic and delusional. Mania, by definition, is problematic. It's causing a problem in some way or another. And if you have psychotic symptoms, it's definitely called mania, full-blown mania. Hypomania, for better or worse, is something every human being probably craves. So it is feeling extraordinarily good. It's getting by on less sleep. But you don't need to sleep. Who needs sleep? I've got things to do. My brain is running on all cylinders. I feel so creative. There have been lots of famous people through the ages who have been bipolar, probably bipolar. And some of their most productive periods of time, whether it's art or creating scientific models or what-have-you, were probably during hypomanic episodes. ANDREW HUBERMAN: So what do you do in that case? I'm obsessed with getting sufficient quality sleep. It's a kind of a repeating theme in our podcast and many of my social media posts. And I always recommend behavioral tools first, then exercise, viewing sunlight, et cetera, at appropriate times, avoiding late night artificial light exposure, et cetera, and occasionally, for people who are doing all that and still struggle with sleep, supplementation. One of the things that I've seen some data on is that for people who are following a low carbohydrate diet, that inositol, in particular, can be helpful for getting into sleep probably because it's a bit of an-- has a bit of an anti-anxiety effect. But presumably, there are other things out there, too. The magnesiums will generally do that. A hot bath will do that, too, for that matter. But what you're talking about is people who are going, what, a day and a half without sleep? Or they're just two hours of sleep a night? CHRIS PALMER: So the worst case I saw was actually a mental health professional who didn't recognize it initially. He went six months with two to four hours of sleep every night. ANDREW HUBERMAN: Because they were on a ketogenic diet? CHRIS PALMER: He was on a ketogenic diet, was getting by on two to four hours of sleep every night, did not initially recognize that this was a problem. He was feeling great. He was feeling that keto

high. And he was actually waking up at 4:00 AM, going for 10 to 20 mile runs most days. He finally stopped the ketogenic diet after about six months because he said, I can't maintain my weight. I'm losing too much weight. ANDREW HUBERMAN: Sorry, I didn't mean to interrupt. I was just thinking there are some social media personalities associated with nutrition that might be hypomanic. I'll let you do the clinical evaluation. So what does somebody do in that case? So I don't know that I've ever been hypomanic. But as I mentioned earlier, unless I've done a very high intensity workout early in the day and I need to replenish carbohydrates, I typically eat meat, fruit, and vegetables throughout the day-- minimum amounts of fruit but some. And then at night, I switch over to mainly carbohydrate. It really helps me sleep. It replenishes glycogen stores. I sleep really well, wake up the next morning, repeat. And of course, this goes against a lot of the dogma that, oh, you're not supposed to eat carbohydrates late in the day and [MUMBLES]. This is what works for me. And so I do it. For somebody like this mental health professional, who is hypomanic, would going off the ketogenic diet entirely be the best idea? Or could it be that adjusting when they eat their carbohydrates would be advantageous in order to make sure that they felt alert and great during the day? Maybe not hypomanic but then could have a four to eight-hour a night sleep as opposed to a two to four hours a night, which is really very little sleep. CHRIS PALMER: Yeah, it's not - ANDREW HUBERMAN: It can't be healthy. CHRIS PALMER: It's not healthy. ANDREW HUBERMAN: Even if you can do it and feel great, I imagine that the brain is suffering. CHRIS PALMER: It is. And the body is suffering. ANDREW HUBERMAN: And your friends and family are suffering. CHRIS PALMER: The body is repairing itself with sleep. And so yeah, it's-- if it's somebody who is not a patient, they're not a mental health patient. They're not using the ketogenic diet as a mental health treatment. They're simply doing it for whatever. I actually start with everything you've just outlined. Let's start with behavioral measures first. And the first intervention is education. You need at least six hours of sleep a night. Period, end of story. That's non-negotiable. If you're not getting at least six hours of sleep a night, we need to consider this a problem. So figure out a way to get 6 hours of sleep. For some people, that's enough, just the education. They don't get out of bed at 3:00 AM. It might take them an hour to fall back to sleep. They fall back to sleep. For most people, if you can get three nights of decent sleep in a row, the hypomania goes away. That is the way to extinguish it. And then they still go on feeling a high from it. They feel great. Their brain feels good in terms of memory, concentration, motivation, all of those things. But they're not hypomanic anymore. And then I might use

supplements, melatonin, others that you mentioned, magnesium is a big one. And for some, I will recommend exactly what you're doing-- eat some carbohydrates in the evening before you're going to bed. Either have them at dinner and then wait a few hours before you're going to go to bed or have them right before you're going to go to bed, just to try to calm your body down and get it going. When I'm using this as a clinical intervention, especially with patients with serious mental illness, I actually want them in a state of ketosis long-term. So I'm not going to do the carbohydrate intervention. I'm going to try all the other ones. But if they still can't sleep even with supplements, over the counter supplements, then I'm probably going to go with prescription, sleeping medicines, as a temporary stopgap to try to get them three to seven days of decent sleep. That usually breaks the hypomanic cycle. And then they stay on the ketogenic diet because it ends up resulting in all of these other improvements that I've described. Their illness can sometimes go in to full remission. ANDREW HUBERMAN: Is it low dose trazodone as a first line prescription? CHRIS PALMER: I would not use trazodone. I would actually specifically avoid trazodone because it's an antidepressant. And they're already hypomanic. And I certainly don't want to push that further. So as long as it's somebody without a history of addiction, I'm going to use a benzodiazepine or either commonly called the Z medicines for sleep-- zolpidem or Ambien or something like that. ANDREW HUBERMAN: Those tap into the opioid pathway? GABA opioid? CHRIS PALMER: GABA. I usually start with something like Ativan or Klonopin or something like that-- probably Ativan because it's shorter-acting. And again, I'm only looking to use it short-term. I let them know that up front. We're looking for three to seven days of decent sleep. And then we're going to try to get them off that medicine.

02:46:37 Low Carbohydrate Diets, Menstrual Cycles, Fertility

And usually, people are off to the races and can sustain it well. ANDREW HUBERMAN: A question about hormones. Many of the Huberman Lab podcast listeners will ask-- any time we're talking about something like exercise or a drug treatment or behavioral training, people will say, what about the menstrual cycle? How is that impacted by this? How does the menstrual cycle impact its efficacy, et cetera? Carbohydrates and caloric restriction have been implicated in different interactions-- are known to interact with the endocrine system. So what do you do if you have a patient who is depressed or could have psychotic symptoms-- but let's go with depression because that's probably a bit

more familiar to most people-- and then they're on a low carbohydrate or full ketogenic diet, but their menstrual cycles cease. How do you deal with those adjustments? And I guess we could expand this conversation and say, what about male fertility also? Because some caloric diets seem to-- my understanding is that submaintenance caloric diets, so weight loss diets, will improve testosterone-estrogen ratios in males that are obese. But for someone that's not obese, to go on a sub-caloric diet, that it can start to impair testosterone levels and-- probably not render them infertile but certainly adjust that whole axis. So what about interactions between ketosis, diets, et cetera, and the endocrine system? CHRIS PALMER: The real answer is, I don't think anybody knows. And there's not a one-size-fits-all answer because I've seen examples. And I'm aware of science to back up polar opposite conclusions. So the first general observation that I'll make-- I know so many couples, husbands and wives, boyfriends and girlfriends, heterosexual couples, who have tried the ketogenic diet to lose weight together-- ANDREW HUBERMAN: And end up with a baby? No, I'm just kidding. [LAUGHS] CHRIS PALMER: No. Almost universally, the men have a much easier time with it than the women. It's not across the board. But I know so many examples where the women say I couldn't tolerate that diet. It did not make me feel better. It actually made me feel worse. And I think in those cases, it probably does relate to hormones. I'm aware of animal models, of mice-- in particular, ketogenic diet in mouse models. One researcher shared with me, the thing that was striking is that the female mice never got pregnant on the ketogenic diet. Whereas, the mice on the standard diet were just having babies right and left. And it was just shocking, the difference. On the surface, it makes sense. The ketogenic diet is mimicking the fasting state. Women who are trying to reproduce should not be fasting. If your body is in a fasting state, it probably does not want to expend resources, metabolic resources, calories, nutrients, and other things, to creating a baby because your very life is being threatened by, quote unquote, "fasting" or starvation. That even though the ketogenic diet is a sustainable, nonstarvation diet, we're really using that diet to trick the body into thinking that it is in a fasting or starvation state. And so just from a kind of evolutionary stance, it makes sense that women's bodies may actually have significant changes in hormonal status to prevent pregnancy because a woman should not be having a baby when she's starving to death. I know of examples of women who are the opposite, though, who have benefited dramatically and tremendously from the ketogenic diet, have put schizophrenia, bipolar disorder into full remission. And I do actually know of one case, at least one case. A woman, infertile, she

and her husband had been trying for three years, no pregnancy. She went keto. Within four months, she was pregnant. How do I make sense of that? I don't know. And unfortunately, I don't think we really have good control data on what does the ketogenic diet do to male hormonal systems, what does the ketogenic diet do to female hormonal systems. But clearly, I think changes are happening. I don't have a way to predict it, at least. If somebody else has great insights, I welcome them. But I haven't seen them published. ANDREW HUBERMAN: It's a terrific answer because when things are all over the place and bidirectional, depending on one circumstance or the other, I think it screams for controlled studies, and more descriptions of case studies, and anecdotal data, too. So I think it's an excellent answer. It also calls to mind the important public service announcement that because of these bidirectional effects that you described, please don't use fasting or the ketogenic diet as a reliable form

02:52:23 Obesity Epidemic, Semaglutide & GLP-1 Medications

of contraception. CHRIS PALMER: [LAUGHS] ANDREW HUBERMAN: Yes, please don't. I have a final question, which relates to something that is very much starting to get buzz now-- and maybe more so for people that hang out in the Twitter space or the nutrition space. But there's a new class of drugs that I think initially were developed to treat diabetes but are now being evaluated for their efficacy to treat obesity. And these are the semaglutide drugs that are involved in-- they tap into these glucagon related GLP-1 pathways. And it is a story that we've talked about a little bit on the podcast before. But many people, I imagine, probably haven't heard that conversation. I would simply like to know what you think about these drugs. They obviously adjust the way that glucose and insulin are managing energy, both in the body and the brain, and can produce weight loss. So that to me, when I look at the data, it's impressive. But a good logical shift in diet and exercise could achieve similar weight loss. But a lot of people just won't do that. So the question I have is, what are your thoughts on semaglutide and other GLP-- I think I might have said GLT before, excuse me-- GLP-1 related compounds? And do you ever prescribe these in conjunction with these dietary shifts? Because it seems to me, they would fall right in with the catalog of other approaches that you have available. CHRIS PALMER: The real answer is, I am not at all an expert on these medications. ANDREW HUBERMAN: But what are your thoughts about them? They seem to be weight loss drugs, not unlike the fen-phen drugs of the '90s that then

were banned because a few people didn't handle them well. CHRIS PALMER: They are. We had fen-phen. And even before that, in the 1950s, and '60s, and '70s, Dexedrine-- ANDREW HUBERMAN: Amphetamine. CHRIS PALMER: Amphetamine-- ANDREW HUBERMAN: Mother's little helper. CHRIS PALMER: --was, yes, was the treatment of choice for women across the United States to keep their slim figures. And we created addicts and all sorts of problems. But they were widely used and probably millions of women because they work. ANDREW HUBERMAN: Because they kill appetite. CHRIS PALMER: They kill appetite. My overall thoughts are this. There is zero doubt in my mind that the obesity epidemic is a threat to human health and potentially the human species. If it keeps going at the rate it's going, it is a threat to our species. We have to figure out what on Earth is happening, and what can we do about it. These medications, in early studies, are highly effective over a year or two. That's promising. I am worried, though, that we're not attacking the root cause of obesity. If the root cause of obesity ends up being some kind of poisoning of the metabolic machinery in the brain or body-- and I would argue that probably relates to mitochondrial health and mitochondrial function-- I have every reason to believe that taking a medication that helps you lose weight may not be addressing that problem. And therefore, may not be addressing all of the negative health consequences of what we call obesity. So obesity, in it of itself, we know that excess fat can become inflammatory and can cause problems, in and of itself. But I actually see obesity as a symptom. I see obesity as a symptom of metabolic derangement in the body or brain. And that is why people become obese. And that if we're really going to get anywhere, we need to identify what is causing that metabolic derangement. Using a symptomatic treatment like a GLP-1 medication, to the best of my knowledge, is not addressing that core problem. And we're just ignoring it. Maybe I'll be wrong. And maybe these will be the wonder drug that saved the human species, and everybody will be thin and healthy forever and ever. I'm not hopeful, because we've never-- we've had so many promising drugs come along. Fen-Phen, Dexedrine, and other things, we've had so many promising drugs. And at the end of the day, when you try to muck with human metabolism using a single processed molecule, manmade, I can't think of even one example where it's been great for large numbers of people. Certainly, manufacturing insulin is life-saving for people with type 1 diabetes. So that would be an example. But giving massive doses of insulin to people with type 2 diabetes, actually is a downward spiral. I would much rather see people with type 2 diabetes control their diabetes through diet and lifestyle. And that might be a ketogenic

diet, or a low carb diet, or exercise or good sleep, or all of the other thing. All of it. I'd much rather see that because when people try to control their type 2 diabetes with a molecule, even though it's a natural molecule insulin, we know that that results in really poor health consequences, results in higher rates of cardiovascular disease, higher rates of mental disorders, higher rates of premature mortality. Do I think GLP-1 molecules are going to be different? No. I don't have any reason to think they are going to be. So that would be my two cents, but we'll see. Time will tell. ANDREW HUBERMAN: Time will tell. Meanwhile, I want to thank you for doing what is, without question, pioneering work. Again, I'm not a clinician. But I've been around this space long enough to know that indeed there there are no wonder drugs. There are drugs that certainly can help alleviate symptoms in some individuals. But that lifestyle and in the case of your work-- in particular, in the discussion today-- diet and, the ketogenic diet, in particular, it's clear, can have incredible effects, miraculous effects, in some individuals. And positive effects in others that might not be of the same magnitude but nonetheless are extremely important, so on behalf of myself, and the listeners, and and certainly, just on behalf of everybody out there-- because everyone does need to be concerned about mental health issues, whether or not they have them and in their family themselves. Or otherwise, because they impact everybody. Just really want to thank you for viewing the work that you're doing because it really is pioneering. And it's brave. And I can see now, based on our discussion, why it would work. You've given us a lot of hints into the underlying mechanisms that suggest as to why it would work. And you're going to given us examples as to how it has worked in patients that you've worked with. And this field is expanding fast. I think this is an area of psychiatry and medicine in general. Meaning, behavioral, nutritional interventions, that is expanding very fast. So thank you for being brave and for taking this on, and doing it in such a structured way, and for communicating it here today. And with the general public, through your book, and your online presence. We will certainly point people in the direction of those valuable resources. Thanks so much. CHRIS PALMER: Yeah, I know. ANDREW HUBERMAN: I appreciate it. CHRIS PALMER: Thank you, Andrew, for being brave and having me on your [LAUGHS] show--

03:01:01 Zero-Cost Support, YouTube Feedback, Spotify & Apple Reviews, Sponsors, Momentous Supplements, Neural Network Newsletter, Social Media

ANDREW HUBERMAN: And a pleasure. CHRIS PALMER: --and for a great conversation. ANDREW HUBERMAN: Thank you for joining me for my discussion with Dr. Chris Palmer. I hope you found it to be as informative, actionable, and exciting in terms of the various treatments that we can now think about when considering treatments for psychiatric disorders. Once again, if you're interested in his work or his new book, Brain Energy, I encourage you to go to his website. That's chrispalmermd.com. You can also find the book Brain Energy by Chris Palmer on Amazon and other sites where books are sold. And we provide links to the book and to Dr. Palmer's website in the show note captions. If you're learning from and/or enjoying this podcast, please subscribe to our YouTube channel. That's a terrific zero cost way to support us. In addition, please subscribe to the podcast on Spotify and on Apple. And on both Spotify and Apple, you can leave us up to a five star review. If you have questions or suggestions about topics and guests you'd like me to include on the Huberman Lab podcast, please put those in the comments section on YouTube. I do read all the comments. In addition, please check out the sponsors mentioned at the beginning of today's episode. That's the best way to support this podcast. During today's episode, we did not discuss supplements. But on many previous episodes of the Huberman Lab podcast, we do discuss supplements because while supplements aren't necessary for everybody, many people derive tremendous benefit from them for things like enhancing sleep, and focus, and hormone augmentation, and so forth. The Huberman Lab podcast has partnered with Momentous Supplements because they are of the very highest quality. And they ship internationally. And in addition to that, they have single-ingredient formulations that allow you to devise the supplement regimen that's most effective and most cost effective for you. If you'd like to see the supplements discussed on the Huberman Lab podcast, please go to LiveMomentous.com/Huberman. The Huberman Lab also has a zero cost newsletter that you can access. It includes summaries of podcast episodes as well as summaries of various protocols for mental health, physical health, and performance. You can sign up for the newsletter by going to hubermanlab.com. Go into the menu and look for the Neural Network Newsletter sign-up. You just provide your email. And I assure you we do not share your email with anybody. And again, it's completely zero cost. Again, go to hubermanlab.com and sign up for the Neural Network Newsletter. And if you're not already following us on social media, we are Huberman Lab on Instagram, Huberman Lab Lab on Twitter, and Huberman Lab on Facebook. And at all of those sites, I provide science and science-

related tools for mental health, physical health, and performance. Some of which overlap with information covered on the Huberman Lab podcast. But often which is distinct from information covered on the Huberman Lab podcast. So again, that's Huberman Lab on Instagram, Twitter, and Facebook. Once again, thank you for joining me for today's discussion with Dr. Chris Palmer. And last, but certainly not least, thank you for your interest in science. [MUSIC PLAYING]