Reversal of Cognitive Decline: 100 Patients: A Special Interview With Dr. Dale Bredesen

By Dr. Joseph Mercola

JM: Dr. Joseph Mercola
DB: Dr. Dale Bredesen

JM: Welcome, everyone. This is Dr. Mercola, helping you take control of your health. Today we're going to be discussing Alzheimer's with one of the leading experts in the field, bar none, Dr. Dale Bredesen. We've interviewed him before for his really epic book, "The End of Alzheimer's: The First Program to Prevent and Reverse Cognitive Decline." He's an amazingly innovative researcher and really leading the field in helping us understand the pathology of this disease. More importantly, strategies, practical, pragmatic interventions that we can take to not only improve it, but, I believe, more importantly, prevent the disease. Welcome and thank you for joining us, Dr. Bredesen.

DB: Thanks very much, Dr. Mercola.

JM: The reason we're having you on is because you published a compilation, a case report of 100 people who've used your therapies – not necessarily through yourself but through clinicians you're working with, I think, according to the paper – and reported the results on this.

Maybe you can start there and then we can go back to – Share some of your results and then we can go back – Or maybe let's start here. It might be better, just to frame this, because there are not many people better than you posed to help us understand the potential implications of this epidemic of Alzheimer's and what it has to impose on the population. Once we can understand and we can better appreciate the epic results you've had from these 100 case reports.

DB: Yeah. Thanks very much. You're right. This has been a major problem. It is a global problem that is set to bankrupt Medicare within the next about 15 years. This is an epidemic. Just as we had major efforts to prevent polio in the past, of course, and prevent smallpox in the past, I mean there needs to be a global effort to prevent Alzheimer's disease, because this is a growing problem. It has now become the third leading cause of death in the United States. That was reported recently by Professor Kristine Yaffe and her group. It's on the rise and has been poorly treatable.

As you know – we talked before – we had previously published case reports, initial 10, another 10 in 2014 and another 10 in 2016. And of course, one of the issues was, well 10, that's not a lot of people. "What does that really mean?" We published another 100 a couple of months ago. These were 100 people who have documented pre- and post-cognitive testing. Not only did those 100 all show improvement, which is not to say that every single person does, those 100 all did. These were from 15 different clinics of people who were using this protocol that we developed several years ago.

What's interesting is some of these people also had quantitative electroencephalographs (EEGs) showing improvement in their quantitative EEGs. Others also had magnetic resonance imaging

(MRI) with volumetrics, showing improvement in volumetrics. Other ones also had evoked responses from the brain, showing improvements in evoked responses. By all the criteria, these people showed improvement, subjective and objective.

JM: This is remarkable because to the best of my understanding – please correct me if I misunderstood this, there is no conventional treatment for Alzheimer's. There have been many trials, but I believe every single one of them has failed. I mean there are treatments, but none of them reverse it, I guess.

DB: Yeah. That's a really good point. First of all, as you know, there are a couple of medications, Aricept, Namenda, that sort of thing, but these have a very, very modest impact. The most important thing is their improvement is not sustained. They don't change the outcome of the disease. You get a little bump in improvement, then you go right back to declining. The most important part of the protocol that you and I have discussed before and the one that is published in the book, is that the improvement is sustained. You're actually going after the root cause, as you know, of what is causing the cognitive decline. That's a big difference.

JM: Yeah. The core, if you could summarize your approach in one sentence, it would be, "To improve the ratio between synaptoblastic and synaptoclastic activity, which is the brain's ability to create new neurons versus destroying them," very similar to osteoclastic and osteoblastic.

DB: Exactly. This is creating synapses again, so you're creating and maintaining the synapses.

JM: Okay. The synapses. Not the neurons, but the synapses. Yes.

DB: Exactly right. Yeah. The idea here is that we have tried to treat this illness without asking what causes it. Of course, in root cause medicine, of course we want to know what's actually driving the decline. When we look at that, it's typically – as you and I have talked about before – it's various ongoing inflammatory things, whether it's borrelia, whether it's babesia, whether it's herpes simplex, whether it's oral bacteria or it's glycotoxicity, people with prediabetes and people with insulin resistance and things like that, or it is an atrophic phenomenon, from low vitamin D, low testosterone, those sorts of things, or it is toxic exposure or vascular problems or trauma. Those are the big things.

When you look at this, you actually look at what's driving it. What you see is really interesting. The molecular biology of this disease shows that what we call Alzheimer's disease is actually a protective response. It's essentially a scorched-earth retreat. You're pulling back and saying, "We're not going to let this insult kill us, so we're going to scorch the earth so it can't take advantage, whether it's bacteria what have you, it can't take advantage of what's there." You're literally downsizing. As long as those insults are going on, you will be downsized.

JM: An essential part of this discussion, obviously focuses on beta-amyloid, which is a protein that is highly correlated with Alzheimer's. It's interesting because in your paper, you discuss the role of beta-amyloid, which many people aren't aware of as an AMP, an antimicrobial peptide. Basically, they're critically important for host immunity. They target lots of organisms, like bacteria, mycobacteria, viruses, fungi, protozoa. Can you discuss that? Because I think it's a really

intriguing concept and really relates to this scorched-earth policy or effect that you were referencing earlier.

DB: Right. This is a really good point. People have known for years that somehow, amyloid beta is involved in Alzheimer's. It is clearly a mediator. That's clear from the genetics. It's clear from the biochemistry. And yet, as you well know, all the attempts to remove it saying, "Ha. This is the bad actor. That's all it is. Let's remove it. Everything will be good," these have failed. Of course, most recently, aducanumab, which was so promising and was claimed in early studies to look very good, has turned out to fail.

Here is the trick. This is turning out that amyloid beta is really part of the innate immune system. Its antimicrobial effect that you mentioned was first discovered and published by Professor Robert Moir and Professor Rudy Tanzi at Harvard. This thing actually has, again, a protective response. Not only is it an AMP, but it also binds some toxins. For example, mercury, other diet-friendly metals, like iron and things like that. This thing has multiple effects. It is part of your response to insult. When you take that into account, you realize it's fine to remove amyloid, but please don't do it before you remove all the insults. We've seen numerous people now who have had the amyloid reduced and gotten worse because the ongoing insults are still there.

JM: Interesting. I think a week or two before we recorded this interview, there was a pharmaceutical giant, Biogen, that announced that they've halted Phase II clinical trials with one of the drugs that they were using to remove beta-amyloid. This is the typical story for drugs used in this area.

DB: Exactly. Yeah. You're absolutely right. Biogen removed or ended trials, basically, for aducanumab.

JM: What I'd like to talk about now is these misfolded proteins and how the body converts those back to normal. Part of the process, of course, involves heat-shock proteins. I'm sure you're really an expert on that, but I'm new to this. When I started digging into it, I found, to my amazing surprise, that literally one-third of the proteins that we make, the moment they're made, they're misfolded.

DB: Right.

JM: Thankfully, our body has a mechanism, heat-shock proteins primarily – I'm sure there are others – that help to refold them. If the misfolding is too severe, then they help actually remove them. Can you expand on that and how that relates to Alzheimer's?

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DB: Absolutely. What happens is you have a set of things that is actually required to make your cells function, including your neurons. As things start downsizing, you start losing critical pieces; ultimately, of course, leading to loss of synapses and ultimately to neuronal cell death. One of the critical ones as you indicated is protein folding, which is critical.

As you know, in all of these different neurodegenerative diseases, whether you're talking about Alzheimer's, Huntington's, Lou Gehrig's disease, Parkinson's disease (PD) or Lewy body, they all feature proteins that are aggregated and that are typically misfolded. They are not degraded appropriately. You lose not only the ability to fold but the ability to degrade these proteins. That is a critical piece.

In fact, you may be aware, just recently, an article came out on a common neurodegenerative condition, newly described, which is called LATE, L-A-T-E, which is essentially limbic-predominant, age-related TDP-43 encephalopathy. In other words, this is a little bit like Alzheimer's, not as common, but interestingly relatively common. Slightly more common than Lewy body and slightly less common than vascular-associated dementia and much less common than Alzheimer's – but still, one of the major players in elderly people. This features TDP-43, which is a protein that is involved in numerous things, including protein folding. It fits in exactly to what you're saying.

You're absolutely right. We lose that ability as we start to downsize, as you don't have an appropriate energy, you don't have the appropriate trophic support. You don't have the appropriate hormonal and nutritional support. That is one of the things that goes.

JM: Yeah. It tends to decrease as we age and acquire all these unhealthy lifestyles. The other function, which we alluded to is basically removing the damaged proteins. I didn't realize that heat-shock proteins actually are corollary of autophagy, which we'll talk about in a moment. But I want to finish up on heat-shock proteins. I'm wondering in your interventions if you have any specific strategies. I'm thinking specifically of things like near-infrared sauna that you've used. If you have, what types of results are you seeing with the integration of that?

DB: Right. When we target ketosis, when we target insulin sensitivity, when we target mitochondrial support, that typically allows you to generate the appropriate ability to refold misfolded proteins. I think you're going to see some exciting work coming out. I've just returned from an exciting meeting in Australia. One of the presentations was on the appropriate upregulation of heat-shock proteins in amyotrophic lateral sclerosis (ALS). I recommend – In fact, you may want to talk with a group that is focused on that. I think you're going to see some exciting results coming out in the next six to nine months on this whole approach. But with our approach, this is actually taken care of because you have all the pieces to do this.

Now, you're absolutely right. You can induce the heat-shock response. Part of what you're doing, as you said, by doing this combination of the sauna and then into the cold and then back to the sauna and then back to the cold, which, of course, as you know, has been used for many, many years as the nice approach. I think that that is one of its mechanisms. You are recurrently activating this critical response. There's no question it is going to be important, especially in ALS, but likely in all of the neurodegenerative conditions.

JM: I really wasn't aware, at least I don't recall reviewing this that ketosis and insulin sensitivity improvement had independently improved heat-shock proteins. But it makes sense. But it would seem there would be a powerful synergy. Because near-infrared saunas shouldn't be viewed as a magic bullet. None of these interventions should be. They need to be used collaboratively. The

synergy is far more powerful. Have you used the ketosis and insulin improving through the diet and cyclical ketosis that you're doing with the near-infrared sauna? Or is that something you haven't integrated into the strategy yet?

DB: Yeah. It's absolutely part of it. Yeah. This is if you look at the approach we've taken, that absolutely includes, especially, initially, as part of a detox of the infrared sauna. But you're absolutely right. It also has an effect on heat-shock proteins.

JM: Okay. Good. Perfect. I couldn't agree more. To me, it's almost essential. It's probably one of my most important biohacking tools to stay healthy. It's that when I'm home, it's daily near-infrared sauna. I like the near-infrared far better than the far-infrared because I think you'd also get the photobiomodulation benefits, in addition to all the other heat-shock protein elevation and the detox components.

But as I mentioned earlier, that heat-shock proteins, if they aren't able to properly refold that protein, they will tag it with a molecule called ubiquitin, then they send it to this UPS, ubiquitin/proteasome system, and target it for removal. It's a corollary to autophagy. Autophagy has gotten a lot of good press lately. Well, it should be because it's, in my view, probably 80% or more of the population is not regularly engaging in this vital, essential cleaning and repair process. I'm wondering if you could describe briefly how you're incorporating it into your program.

DB: Yeah. I should mention, not only – As you mentioned, it's related. There are three kinds of autophagy. There's the macro-autophagy, micro-autophagy and then chaperone-mediated autophagy. There are multiple ways to recycle these components. Specific proteins, for example, can be targeted, as you said, for chaperone-mediated autophagy. Or as you said, they can also be targeted through the ubiquitin system.

Actually, we published – We did research for years in the lab on the linkage between this activation of protein folding and apoptosis. In fact, if you fail to reform these, you literally activate an entire system that initially stops producing more protein. It's basically saying, "Okay. We're not keeping up with this. We're going to shut this down." It attempts to refold. Then it attempts to destroy the proteins if it can't refold them. Then ultimately, if it cannot, with all those changes, cannot keep up with things, it literally activates programmed cell death through specific caspases. There is a beautiful, orchestrated program that starts with "Are we keeping up with folding of proteins?" And ultimately does step-by-step that ends up – if you do not keep up with this – in cell death.

You're right. This is something where you want to intervene upstream, understand why this is happening. And then if you're unable to keep up with this, now, at least increase your heat-shock proteins so that you can refold. In this case, you prevent the induction of programmed cell death.

JM: Yeah. You and I both know what it is, but for the audience, just a slight clarification. Because there's a lot of confusion on this between apoptosis and autophagy. Many people think they're the same thing, but they're not. Autophagy refers to the repair or removal of the organelles within the cell. But apoptosis is the removal of the entire cell, sort of the suicide button. As I understand, it's mediated through the mitochondria. One of the reasons why you want healthy mitochondria is because if they aren't healthy, you can't initiate this event.

DB: Right. Two separate, in-general programs: so-called internal or intrinsic and extrinsic. So, yes, mitochondria, as you said, those are the intrinsic ways to induce the programmed cell death. There are also these receptor-mediated programmed cell deaths, which is an extrinsic approach. Two different ones. But, yes, ultimately they both include factors that can come from the mitochondria. You're absolutely right that the autophagy is something – It is a recycling.

In fact, what's interesting is if you simply shut down the recycling of the mitochondria, you will develop PD. This is absolutely critical that you keep your battery sharp. You recycle the ones that are not working very well. And then on the other hand, as you indicated, if that fails, if ultimately you don't recycle, if ultimately you don't keep up with these various critical parameters, such as protein folding, protein degradations, appropriate signaling, membrane potential, all of these things, then you will actually activate a suicide program. Of course, part of that is normal. We're activating a suicide program in our white blood cells, so that you lose one million white blood cells to suicide every two seconds. Of course, you replace those as well.

JM: Let's get back to autophagy, because as I mentioned, it's my belief that – these things are pretty well-supported in literature – that the vast majority of the public is not engaging in this process, primarily because they're insulin-resistant. If you're insulin-resistant, you cannot increase your adenosine 5' monophosphate-activated protein kinase (AMPK) levels, and then you're unable to inhibit mammalian target of rapamycin (mTOR), which is really one of the primary drivers of autophagy; mTOR inhibition.

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There's some confusion. I was confused up until recently. I still may be confused about this, which is why I'm excited to dialogue with you about this. That thinking that autophagy is so great, you should activate it all the time. But I think like most things in life, it needs to go in cycles. There are times when you don't want to activate autophagy for certain. You should not be in constant autophagy. I'm wondering what type of – You've been doing this for a long time. What have you evolved as your optimal cycling mechanism or frequency for going in and out of autophagy and how you do it?

DB: Yeah. It's a great point. This is why we are interested in fasting. Of course fasting is one of the best ways to do this. You can do this monthly. You can do this weekly. We are typically recommending the intermittent fasting approach. And then of course, sleep is a critical piece. You get those hours in. And then as you indicated, you don't want to flood the system with the sugar and things like that. That also inhibits it.

All of these things are inhibitory. You want to be able to use appropriate fasting and an appropriate diet to activate this autophagy. If you activate it each night, we recommend, on our approach, 12 to 16 hours if you are apolipoprotein E4-negative(ApoE4-negative). Twelve to 14 is better. If you are ApoE4-positive, you'd want to go longer – 14 to 16 hours. There's nothing wrong with doing a longer fast.

As you know, Dr. Valter Longo and his work suggest you do several days each month on the fasting-mimicking diet or another approach, essentially to inhibit mTOR. You don't want to keep stimulating that all the time with the amino acids that are stimulating it. That's the usual cycle.

Typically, we recommend it about once a week. But again, a longer fast once a month is a good idea. It depends a lot on your body mass index (BMI). What we found is people who have higher BMIs respond better to this fasting early on. They're able to generate the ketones. As you know, if you now lose both the carbohydrates and the ketones, you end up with someone who just feels completely out of energy. They actually take a step back on their cognition. We want to liberalize and cycle them. We are very careful when people are down below 20 on their BMI, especially the ones 18 or below. We want to be very careful to make sure to cycle them once or twice a week. I think you were the one who recommended before twice a week. I think that's a very reasonable frequency.

JM: Recommended what twice a week? The partial fasting?

DB: Essentially to keep metabolic flexibility to cycle out of ketosis.

JM: You've got to do that. Yeah. You've got to. Especially for – A BMI of 18 is extraordinarily low. I mean that person can't afford to lose any weight.

DB: You're exactly right. When we see people with cognitive decline, they are often either high on their BMI, in which case they tend to respond more quickly, they're able to generate these ketones. They're clearly going to be insulin-resistant most times. They can get into insulin sensitivity. They can generate ketones. They tend to do well with their cognitive improvement. On the other hand, the tougher ones to deal with are the ones who are below 20 on their BMI. Where now – I mean they're very fragile – if you're not careful, now they lose a little more weight as they're getting into ketosis. Now they go backwards. We, in fact, have to support them. These are the ones where, often, exogenous ketones can be very helpful early on.

JM: Let's go to the – I still want to finish up on autophagy. But as long as you mention exogenous ketone, that was one of my questions. I'm wondering – There are two types essentially, the ketone salts, which are less expensive but probably not as effective, and the ketone esters, which taste worse but they seem to be the real deal. I personally prefer the esters and use them myself when I need strategies to reduce oxidative stress, which we should talk about later. I'm wondering what your protocol is for integrating them into your approach.

DB: Right. We essentially have three different approaches. Number one, we would like, in the long run, to get you to make it so that you aren't generating endogenous ketones. That's the best way to go.

As a simple example, endogenous ketones will be inhibitory of NACHT, LRR and PYD domains-containing protein 3 (NALP3) inflammasome, so you're turning down that inflammation, which is involved not only with Alzheimer's, but also things like macular degeneration. Whereas if you take endogenous ketones and flood that system, you can actually create some degree of inflammation. You'd want to be minimizing these in the long run. But for getting started, because

the critical pieces, we're trying to supply that energy and trying to move you from a state of glycotoxic damage to a state of ketosis and a state in which you are insulin-sensitive. Initially, with the long run, we want to get you on, initially, we want to get this – We want to use either MCT oil, one way. Measure your ketones. It's simple to do. We want to get you into, ultimately, to the 1.5 to 4.0 millimolar betahydroxybutyrate. That is the goal: to get you there.

Again, essentially, take this in a couple of steps. Step one, you need to use exogenous ketones. You can start with medium-chain triglycerides (MCT) oil. If that doesn't give you the appropriate ketone level or if it's actually giving you problems with your low-density lipoprotein (LDL) particle number, we're now going to balance these. Then you can use the exogenous ketones as you indicated. We'd like to look at your LDL particle number and use that to titrate, to make sure that your LDL particle number is not too high.

JM: This is a point of reference. You may not be aware of this but I think you'll appreciate it. It's that there is a new ketone meter out. It's called KetoCoachX.com. The reason it's so great is that the strips, which are an enormous impairment to doing regular ketone assessments, because they're initially 4 dollars, and KetoMojo came out at a dollar. But KetoCoach has them down to 70 cents. But there are two other benefits. It's that they're individually foil-packed and the device is about half the size or thickness. It's real easy to travel with.

DB: Nice. Is this something that also looks carefully at the lower – Because one of the issues with a lot of these ketone meters, they're not very good in that 0.2 to 1.0 range. If this is good for that, that's huge.

JM: Yeah. It's a really clever device. It's become my device of choice at this point. But the reason why I wanted to ask you about the ketone esters is that a friend of mine, William Curtis, who is a research associate of Dr. Richard Veech at the National Institutes of Health (NIH), and has done a lot of landmark work in ketones. The reason he became so interested in this is he had PD.

Like many patients with PD or another neurodegenerative disease, of course, seems to have enormous improvement when he's taken these esters. He just falls apart when he's not on them. I'm just wondering if there's a similar observation with Alzheimer's patients. I know there's a Mary – I'm afraid I forgot her last name – but her husband had Alzheimer's and passed away from it.

DB: Yeah. Newport.

JM: Newport. Yeah. Mary Newport. But he was using coconut oil, then eventually medium-chain triglyceride (MCT) oil. But she didn't really have good access. I think she was trying to work with Veech, but they couldn't get the esters to him at that time.

DB: You bring up a really good point. Yes. We see the same sort of thing with Alzheimer's disease. What we've come to realize from the research over the years is that these diseases, these neurodegenerative diseases, whether you call it Alzheimer's or whether you look at macular degeneration, when you look at Lewy body, PD or ALS, they all have one thing in common. They are related to specific subdomains of the nervous system. Each of these has a unique requirement

for nutrients, hormones, trophic factors, et cetera. Each one, somewhat different. In each case, there is a mismatch between the supply and the demand. For most of your life, you're keeping up with that demand.

With all of these diseases, you have a repeated or a chronic mismatch between the support and the requirement. In PD, it's quite clear. As you know, you can create PD simply by inhibiting mitochondrial Complex I. That specific subdomain of motor modulation, which is what PD is all about, is the thing that is the most sensitive to reductions in mitochondrial Complex I support. Therefore, when people have this, you need to bring the supply back in line with the demand. A critical way to do that is to supply the appropriate ketosis, the appropriate energy.

Now, if the person is continuing to be exposed to whatever chemicals are inhibiting Complex I – and it's typically organics or it's typically, as you know, surge-related biotoxins – as long as these are ongoing, you're going to get a very temporary relief. The goal here is both to get rid of what is inhibiting Complex I and how to flood the system, to help the system by giving appropriate support for the energetics.

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As you indicated before, energetics are critical, especially in PD. Whereas with Alzheimer's, we're really talking about a mismatch in trophic support. You've got this ongoing need as you're making neuroplasticity. It's really interesting. In each of these ones, in each of these diseases, there's a different subdomain with its own unique set of requirements.

JM: Okay. Thank you. Let's get back to autophagy for a moment, because I've had a long personal journey in this process. I've come to some – I've made a lot of mistakes along the way, like most of us do. I've come to the conclusion though that for people with insulin resistance, the single most important step that they can take, independent of really looking at what they're eating, is to compress their eating window. You referenced that earlier. Those with the ApoE3s, which is what I am, I think you said it was a 14- to 16-hour intermittent fasting or time-restricted eating window. Those with ApoE4 would be 14 to 16.

DB: Fourteen to 16.

JM: Fourteen to 16. To me, that seems to be on the low side. I personally do an 18-hour. I try to get to 20-hour sometimes. That's what I encourage people, who are beginning this process to do first. Because just doing that, not even paying attention to the counting calories or looking at what you're eating, like restricting carbs, will have a massive improvement in metabolic flexibility. I'm wondering how you reach those numbers that you mentioned earlier and if you perceived any negatives for a longer, daily time-restricted eating.

DB: Yeah. This is a really good point, because the 12- to 14-hour originally was based on research of when you start to – When you go to sleep, for example, when you are now without eating. When you are fasting, how long does it take typically to kick into autophagy? The answer was it's kicking in. Again, there's wide variation here. It's around 12 hours. For the first several hours, you're not going to kick into this. Now, the reason we suggested longer for the ApoE4-positives, as you know, if you are ApoE4-positive, you are better at absorbing fat. It tends to take longer to enter autophagy.

But this comes back to a really important issue. You mentioned that you had looked at 18 and even 20. The important thing here – and we see this again and again and again for the people who do the best – is that they tweak the system constantly. They're looking at their own responses. Then they're looking at, "Okay. Should I go a little farther? Should I go a little shorter?" It depends a lot on whether you are very low on your BMI, whether you're able to generate ketosis or whether you are now converting. Where do you stand? Obviously, you've done extremely well with doing the window eating. Let me ask you a question. Do you see best beyond this? As Walter Longo has suggested that you go for a more extended period.

JM: Absolutely.

DB: Because you need to try to get rid of that glycogen. ---===

JM: That's the summary of my most recent book, which was actually just published last week. It's called "KetoFast: Rejuvenate Your Health With a Step-by-Step Guide to Timing Your Ketogenic Meals." I initially decided to write the book because I was enamored with multiday water fasting and the metabolic power that that had. Historically, it's been used for many, many centuries and virtually every major religion in the world uses it. But then I came to realize – somewhat similar to Dr. Valter Longo – that's probably not a good strategy, for different reasons though. Compliance was his primary concern.

But I think metabolically, when you're detoxifying and because most of us live in the 21st century now and we have exposure to all these fat-soluble toxins that get stored in our fat, that multiday water fasting doesn't really support your liver that well and exposes you to these toxins that are released. For that reason, I decreased it. I recommend – Well, personally I do a, 18-hour daily fast to 20 hours. And then once a week – I was doing it twice a week, but my weight was dropping too much. Once a week, I won't eat for a day. It'll essentially be a 42-hour fast once a week.

I think that really gives me a boost in activating autophagy. Because you're going to get some at 18 hours, but you're not going to get – I mean it's just minor compared to what you do at a longer one. I could tell that because my glycogen levels get depleted. Of course, I'm not eating so there's nothing in my bowels, so I'll lose weight from that perspective. But I'll lose glycogen. I know that because I'm losing water weight. I'll typically lose 4 pounds when I do that. I typically gain 4 pounds the day I eat.

DB: Interesting. Okay. Yeah. I think that those numbers basically came from "What does it take to enter this state of autophagy?" Of course, with it, to become more sensitive as you're essentially running out of the glycogen, as you indicated. It's now helping you to get into more of a ketone-based metabolism.

JM: One of the reasons that we do this and it's not typically referred to but the observation is it increases nicotinamide adenine dinucleotide (NAD+) levels, which are really very important for a variety of functions in our body. But it also increases – It increases NAD+ levels by 30% when you do this type of multiday fasting or two-day fasting. That is useful.

But another component of time-restricted eating or intermittent fasting is that even though you're eating in a restricted-eating window, it's best not to eat. I think this is universally acknowledged, at least from knowledgeable clinicians, that you don't want to eat at least a few hours before bedtime. But I was doing some research and literature review on nicotinamide adenine dinucleotide phosphate (NADPH).

I learned that the single biggest consumer of NADPH, which is essentially the true cellular battery of your cell because of your storage with reductive potential to recharge your antioxidants, that the largest consumer of that was the creation of fatty acids. If you're eating close to bedtime, then you're going to not be able to use that to burn that energy, those calories as energy. You're going to have to store them some way. To store them, you have to create fat, so you're basically radically lowering your NADPH levels. Which, to me, is one of the most profoundly useful metabolic justifications for not eating before you go to bed for at least three hours.

DB: Yeah. We have the same. We call the approach we take, KetoFlex12/3, because it is generating mild ketosis. It is flexitarian. You can do it if you're a vegetarian or not. It is a minimum of 12 hours fast and, as you indicated, three hours because bed time.

JM: I actually kind of do like six hours before bedtime, because I'm an obsessive-compulsive (OCD). I want to make sure that I'm optimized. It seems to work pretty well. But here's another strategy. You know there are a lot of great polyphenols: berberine, resveratrol, curcumin, fisetin and a variety of others that we know have profound influences and impacts on autophagy.

I'm wondering if you've integrated them into your program in some way to augment the benefits of autophagy aside from the nutritional timing of your food.

DB: Yeah. So it's a really good point. It brings up the fact that, as you know, sirtuin-1 (SIRT1) was identified as a critical molecule, both for longevity and has been studied extensively for its effects on longevity, but also for its effects on Alzheimer's disease. SIRT1 is actually associated with an increase in the production of A disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), which cleaves the amyloid precursor protein (APP), which is on the non-Alzheimer's side.

JM: Interesting.

DB: So it's a very unique molecule. In fact, what's interesting, ApoE4 actually enters the nucleus and downregulates the production of this critical molecule, so you can see one of its many effects on Alzheimer's disease. Well, when SIRT1 is made, it is actually made in an autoinhibitory fashion. It's just like having a gun in a holster. It's not active.

What then removes that auto-inhibition and lets it become active? Just what you would have said – NAD+. NAD activates these SIRT1. Of course, so does resveratrol. This is why people take resveratrol, also why people take nicotinamide riboside. These are both activating this program, which is moving you from, essentially, the use of one approach with your resources, which is more of a pro-inflammatory approach to now a longevity approach, a change in your metabolic pattern.

That includes activating things like autophagy and also having an anti-Alzheimer's and a pro-longevity effect.

JM: Are you actually using them specifically?

DB: We use both nicotinamide riboside and resveratrol.

[-----40:00-----]

JM: Interesting. Are you using them every day? That's an interesting question because I'm not sure that everyday use on the polyphenols – not nicotinamide riboside, obviously, and not polyphenols, which is a NAD+ precursor – but the polyphenols may be the wisest strategy. I thought it was initially, but then I've come to the conclusion that it may not be. Quercetin is another one too. I forgot.

DB: Yeah. Quercetin is turning out to be very interesting. As you know, quercetin also has an interesting impact on senescent cells.

JM: That was my next question. I was going to go to senolytic therapy because there was an interesting study published last month on the benefit of that in Alzheimer's.

DB: Right. I think senolytic therapy is going be interesting. As with so many of these things, I think that we're going to ultimately determine that senolytic therapy is a little bit like saying, "You're going to live longer if you take metformin." Well actually, if you do the right things, you don't necessarily need metformin.

JM: We're in agreement.

DB: As long as you're doing the wrong things, [then] metformin helps you. I think in senolytic therapy, we're going to have to find the same thing. If you're getting the appropriate lifestyle, getting the appropriate diet, then you're doing what the senolytic therapy is designed to do anyway.

But yes, quercetin, as you mentioned, is one of the things that's been demonstrated to have this interesting senolytic effect. I think that that's going to turn out to be an important way to impact a number of age-related conditions, including neurodegeneration.

JM: I would suspect you're not using it clinically now though. Because it's still really premature. The bioabsorption of these polyphenols, like quercetin, for example, is just horrendous. I mean if you look at the studies in animals, I mean they're injecting this. They're not giving it to them orally because they just can't absorb enough to get the benefits. Fisetin would be another one. Those are the two big polyphenols.

DB: You're right. What we are doing right now is we are coming straight from the 30 years of basic research. We are looking directly at what changes the balance of cleavage of adenosine triphosphate (ATP). There's a whole set of things that we've been talking about that all change that balance from pro-Alzheimer's to anti-Alzheimer's. You can literally trace the pathways from NF-KB. You can trace the pathways from estradiol, from vitamin D and on and on and on. We're

doing everything to change that balance toward a – as you mentioned earlier – toward a synaptoblastic balance.

JM: I'm sure you're familiar with urolithin A. It's a metabolic byproduct of pomegranate. It's probably the largest source of these ellagic acids and ellagitannins. But this urolithin A seems to have some profound benefit in neurodegeneration or neuroinflammation. I'm wondering if you've looked at that or have integrated that into your program.

DB: That's interesting. That's a good point. We have not integrated it. Of course, we're fine with people eating pomegranate, but we've not recommended that people take that specifically as an extract or anything like that. As we're going along, we're looking at how we can continue to tweak this program. I think for each person, the most important thing so far has been, "Continue to optimize." It's not the old-fashioned, in-and-out prescriptive medicine where you write a prescription and then you don't change anything. We're always looking at what can improve the person's status. That depends a lot on what their biochemical background is. But we have not specifically used that, so that's a good point.

JM: If you're interested, the highest concentration would be in the peel itself. You can get pomegranate peel. In fact, most of the studies are done with pomegranate peel extracts. Why not use the peel? The problem is it's a very, very bitter polyphenol. You have to make a capsule out of it because there's no way you're going to convince anyone to swallow that. But I think it could be very useful taken before they go to bed. I mean if I had Alzheimer's, I'd probably take that.

DB: Interesting.

JM: It's a useful strategy. You can get the pomegranate peel powder on Amazon and then just get some capsules and make it yourselves. It's easy to do. It's relatively inexpensive.

DB: Interesting.

JM: The other point I wanted to discuss – This goes back to the NAD. I was not aware that SIRT1 had an influence on ATP.

DB: Oh, yeah.

JM: I did not know that. Thank you for sharing that. But the oxidative stress – This is something I've become passionate about in the last few years. With respect to reducing it through pervasive exposures that virtually every single one of us viewing this has, that is the radio frequency exposures from our Wi-Fi and our cellphones. There seems to be some fairly powerful, convincing evidence of the mechanism, which ultimately results – if I can just summarize it here briefly – in these activations of voltage-gated calcium channels, which allow the release of extra nitric oxide, superoxide in the cell, which causes perioxynitrite.

Perioxynitrite causes very similar damages to ionizing radiation in the DNA, but also causes damages in the stem cells and the mitochondria and proteins and cell membranes. The issue

becomes that when you damage DNA, obviously our body has this profoundly magnificent repair systems that were developed years before electromagnetic field (EMF) ever existed.

DB: Right.

JM: Manmade EMF. That primary one is PARP, poly-ADP ribose polymerase. The way that it works – I'm sure you know this, I'm just saying it for the benefit of the people watching this – is that it sucks out NAD. Many don't know this, but NAD has within it, within the molecule of NAD, is an adenosine diphosphate (ADP) molecule. That's what it does. It sucks out that ADP molecule from NAD, and not just one NAD, but 100 to 150 to repair every single break of DNA. It increases matrix that allows DNA repair to go on and fix the damage.

That's all well and good, but if you continually damage it, you're just activating PARP continuously and you're decimating your NAD+ levels, allowing SIRT1 to work and do its magic and all the other benefits that NAD+ has. I'm wondering if you've ever looked at specifically reducing EMF exposures, like cellphones and Wi-Fi. It makes a lot of sense that it would benefit this because the highest density, one of the tissues with the highest density of voltage-gated calcium channels is the brain.

DB: Of course. Yeah.

JM: Yeah.

DB: You've mentioned this before. This is a critical area. The big problem we've had with this so far is that we can measure your NF-KB activation. We can measure your various nutrient, what your status of hormones, nutrients, magnesium, on and on and on. We can measure them. Typically, with our approach, we measure 150 different variables. There is no simple way to measure the effect of EMF on a given person's nervous system. I look forward to the day when we can do a test and say, "Aha. This person has 27.2 on their effects on their voltage-gated calcium channels because of EMFs." Because then we'll really be able to alter that.

For now, the best we can say is – just as we go after biotoxins and chemotoxins – This is a physical toxin. The best we can say is, "Minimize that to the extent you can." As you've mentioned before, you can certainly measure the exposure. We just don't have a good way yet to measure its effect on your brain.

JM: Well, I think you do. I mean you're doing the measurements. I mean you've got all the inflammatory markers. I mean the list of things that you test for is amazing. I mean I don't know what the – maybe you can tell us. It's like 10,000 dollars to do all those tests. I mean they're very comprehensive.

DB: We now have it down. You can do the initial test for about 1,000 dollars. It's much better. Of course, my hope in the long run is that we'll be able to do this and the insurance companies will recognize it's a good thing for all of us. Let's prevent this instead of dealing with it once it's there.

JM: I couldn't agree more. But couldn't you look at those inflammatory markers and then – Do you look at 2-deoxyguanine?

DB: Yeah. So the 8-hydroxy-2'-deoxyguanosine (8-OHdG).

JM: 8-OHdG. Yeah. I forget what they call it.

DB: That's a common one for DNA damage.

JM: Sure.

DB: But as you know, there are many causes of that: smoking to exposure to radiation to on and on – lots of things. In fact, just having a low ascorbate level will increase your 8-OHdG, for example. You're right. That's an indirect way. But it doesn't tell you what's actually coming from the EMFs. But you're right.

JM: But if you did an intervention, you measure it and you have a baseline, you've removed the EMF and you see it decreases, that's kind of a clue, wouldn't it be?

DB: That's a good point. You could do a before and after and hold everything else constant and see if you can actually pick that up on 8-OHdG. Interesting.

JM: I don't think that's a terribly expensive test. I think it's probably less than many of the tests that you're currently running.

DB: Yeah. It's actually not a terribly expensive test. That's a reasonable possibility. It would be interesting. I'm not aware that anyone has shown that just the presence of EMFs will bump your 8-OHdG, but it would be very interesting to know that.

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

JM: Yeah, yeah. Absolutely. Let me see. I think that's basically most of the questions I've compiled, because I had the opportunity – because I love to review the literature. My passion now is longevity and see if I can keep this body healthy enough to stick around for another 30 or 40 years and have all the function that I do now, especially cognitively, which is certainly your concern for Alzheimer's. I think most people watching this are aware of the dangers and the damage of Alzheimer's. No one wants to lose their brain.

For me, the benefit of engaging in these processes is to just assume that you're going to get Alzheimer's. Just assume it. Be proactive, because there is no question. There is not a microdoubt in the world that this disease is far easier – I want you to discuss or at least comment on this – is far easier to prevent than it is to treat.

DB: Absolutely. What we're seeing actually goes slightly beyond that. As you know, when you take a typical vaccine, you've got to have a vaccine before. It's only a prevention. What we're doing with Alzheimer's is really interesting because it is very good with prevention and early

reversal. We see people who are now symptomatic. Now as they become later and later in the disease, we see some improve, but it's harder and harder later in the disease.

You're absolutely right. This is all about prevention and early reversal. Those are the people where we see virtually 100% response. This is why I think there needs to be a global effort to decrease the global burden of dementia. I should say we're just now starting a clinical trial. We've been trying to get institutional review board (IRB) approval for years. We actually started back in 2011 and were turned down a couple of times, and then more recently in 2018.

This has finally been approved, so we're starting a trial with Dr. Ann Hathaway, Dr. Deborah Gordon and Dr. Kat Toups, who are all seeing patients as part of this trial. We're very excited to see what the trial will show with this approach. Because certainly, anecdotally, we're hearing it all the time. As you mentioned, we just published a paper a few months ago on 100 patients who showed documented improvement.

JM: Well, congratulations on the IRB approval. That's a long and hard victory to get, because I know you've been struggling with that for quite a while.

DB: As you know, it's hard to get people to approve multivariable approaches.

JM: Right that was the big issue.

DB: Because that's the way our body works. We need these multivariable approaches. There just has been no mechanism to get these approved in the past.

JM: Well, congratulations. That was the big issue. That's fascinating to hear that they approved that. They finally got some commonsense. That's great. I wonder if you can comment on this too: That if a person has integrated all the things that we're talking about that you recommend in your treatment strategy to treat Alzheimer's, if virtually you start it now before you have any signs, that essentially you could be immunized and the likelihood that you would ever have this type of dementia will be virtually nil. Would that be fair to say?

DB: Of course, nobody has those data yet. But our argument has been exactly that. This should be and can be, as of today, a rare disease, which is what it should be. In fact, we should be ending it with the current generation. This has been the scourge, as you know, of our generation. This should not even be an issue in our children's generation. They should be all preventing this, and this should be a very rare disease. That's exactly what we've been arguing. I couldn't agree with you more.

Now, are you still going to have – Less than 5% of all Alzheimer's is familial Alzheimer's disease. Can we impact those people as well? We don't know yet. We're just working with a few of those. We'll know in the future. But I think, I'm convinced, that in fact, we could, today, if everyone got an appropriate prevention, make this a very rare disease.

JM: That is great. I'm reminded, I interviewed an ophthalmologist recently. His name escapes me. He did some incredible research on age-related macular degeneration. Being an ophthalmologist,

he's basically the modern-day Weston Price, but instead of a dentist, he's an ophthalmologist. He scoured the ancient ophthalmology textbooks from the mid-1800s to the current day. It's widely assumed by virtually every ophthalmologist that we've always had age-related macular degeneration. It's not true. It never started. Really, it was never described before 1900. It just didn't exist.

DB: Interesting.

JM: I'm wondering what your understanding of the incidence of Alzheimer's was in about that timeframe. Is it a similar, rare occurrence?

DB: Well, that's a good point. Of course, it was described in 1906 by Dr. Alois Alzheimer. On the other hand, if you looked back at the ancient Ayurvedic text – We've published on this in the past. Dr. Rammohan Rao, who's an Ayurvedic physician, was a researcher in my laboratory. We worked together for many years. In the ancient Ayurvedic text, they do describe dementia. Now, of course, they didn't have the appropriate stains or have the appropriate autopsy to determine whether this was Alzheimer's.

Marcus Aurelius was another one who mentioned dementia a few thousand years ago. Certainly, the phenomenon of dementia has been around for thousands of years. What's not clear is whether it is the same as today. As you know, of all of us, hominids were ApoE4-4. That was the primordial gene. The ApoE3 that you and I carry only appeared 220,000 years ago. And then ApoE2 appeared 80,000 years ago. The question of "When did dementia appear?" It certainly has been around for at least a few thousand years.

JM: Okay. But we just don't know what. It's an artifact of not having the same diagnostic tools available to make that differentiation. But likely it was much lower.

DB: Likely it was much lower. Exactly.

JM: It's safe to assume on that. Well, I want to thank you for your time, for all the effort, the years of clinical work that you've put in to help us understand this disease at a better level. And even more importantly, not only understand but develop practical strategies that cannot only treat, but more importantly, prevent the disease. You're doing a great work out there and I really commend you for it.

DB: Thanks, Dr. Mercola. I think we're all in a very exciting period, because I think we're going to see a decrease in all of these. These chronic illnesses are going to be labelled, ultimately, 20th century illnesses that we mostly get rid of in this century.

JM: Yeah. Certainly, people can get your book. It's still every bit as useful today as it was when you first wrote it. It's "The End of Alzheimer's: The First Program to Prevent and Reverse Cognitive Decline." But are there any other resources that people can follow you at?

DB: They can follow me on Dr. Dale Bredesen on Facebook. There's also a website, which is DrBredesen.com. We have another book that will be coming out called, "The First Survivors of

Alzheimer's." We have some wonderful first-person stories from people who were diagnosed and then got better. They write about their stories. This will be coming out around the end of this year.

JM: Terrific. Alright. Thanks for all you're doing. It's been a great pleasure to connect with you again.

DB: Great to talk to you, Joe. Thanks again.

JM: Alright.

[END]