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| Ivor Cummins | 00:39 | I'm here today in Marin County and I'm meeting with Dr. Dale Bredesen who is a world authority on Alzheimer's disease specifically, but any neurological conditions really. You've been researching for over 30 years? |
| Dr. Dale Bredesen | 00:54 | We have, yeah, and the lab's up and running for 30 years. |
| Ivor Cummins | 00:57 | Yeah, and I might start with a bit of your backstory. I read your book, "The End of Alzheimer's" a couple of days ago, and it was actually given by my sponsor, David Bobbett, who founded Irish Heart Disease Awareness. And he's particularly interested in ApoE4 and heart disease and Alzheimer's. So he sent me the book quite a while back. But I read it, and it's amazing because a) it's all focused on root cause and multiple root causes, which we'll talk about today, but b) all of the root causes that are addressable, they overlap so much with what you need for cardiovascular disease prevention also. |
| Dr. Dale Bredesen | 01:32 | Absolutely. |
| Ivor Cummins | 01:33 | And you originally did the chemistry, biochemistry basically, and then moved on to do an MD following that. |
| Dr. Dale Bredesen | 01:40 | Right. I was originally actually interested in computers. I read a book called "The Machinery of the Brain" by Dean Wooldridge. And he talked about the similarities between computers on the one hand and neural networks. And I got interested in the brain and how it works, which I just found absolutely fascinating. I was hooked. I was 18 at the time. So it's been many, many years. And as we started to get into the brain and I started to read and learn about how the brain functions and how learning and memory are created and things like that, I became fascinated by the diseases of the brain. And of course, I decided to go to medical school, and then as I started to learn about these, I realized that this is the area of greatest biomedical therapeutic failure. As they say, everybody knows a cancer survivor; no one knows an Alzheimer survivor. So I really wanted to understand what's the problem here? Why are we not doing well against Alzheimer's, Parkinson's, Lou Gehrig's, Frontotemporal dementia, on and on. The whole era of molecular neurobiology was getting started. And I thought that was really a fascinating way, very reductionistic but very powerful. So that you can look at very specific, not just genes, but you can look at the single amino acid on any given protein and ask what's actually driving the process. |

03:01 So initially, we got interested in setting up the first models where you could study neurodegeneration in a dish, because there hadn't been such models as you know, great models for studying cancer and dish. But there hadn't been anything for neurodegeneration. But as we started looking through those models, we started seeing, “Okay, here's the beginning of the basis of neurodegeneration.” And we really wanted to know, “What is the essence?” “What is this phenomena?” and “Why is neurodegeneration so common?” So about 15% of the population will get Alzheimers, it's incredibly common. It has become the third leading cause of death, if you look at the autopsy reports. And so very common. And of course, on the rise, this is a trillion dollar global problem. And of course, as you indicated, other neurodegenerative diseases as well, ALS particularly difficult one to improve.

03:55 And so, as we began to look at what is the actual essence of this, we could see that there are molecular signals that are related to neuroplasticity. And you could actually see that there's essentially a central switch that the amyloid precursor protein (APP) itself is like a molecular switch when things are good, it actually is sampling many different factors. And when things are good, it is cut at a single site to give you two peptides, essentially one extracellular, one intracellular. And these two are essentially saying, just like your CEO would say, things are good, and we can now go ahead and make new connections. And we call this synaptoblastic signaling. You're making more synapses, you're supporting your neural network.

04:47 And on the other hand, if you now have pathogens or inflammation, again as you said, similar to what happens in cardiovascular disease, you can literally trace the molecular pathways of these, of the NF-κB that's involved with the inflammation, for example. Or the lowered estradiol that occurs with menopause, for example, and on and on. Vitamin D, nerve growth factor, brain derived neurotrophic factor. These all feed into that same central switch. And now it's saying wait a minute, things are not so good. This is now synaptoclastic signaling; they're pulling back by analogy with osteoblastic and osteoclastic. This is synaptoblastic and synaptoclastic. So to some extent, what we call Alzheimer’s is really about synaptoporosis. You're signaling that, you know, things aren't good and you're going to pull back. It is a bit of a scorched earth retreat. You're often saying, “Okay, we've been invaded by various pathogens,” and we know of many now you look in the brain of an Alzheimer's patient, what do you see? You see P gingivalis from the oral cavity. You see T denticola from the oral

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| | | cavity. You see herpes simplex from the lip. You see HHV-6A, which appears to come in through the sinuses. You see various mold species from the sinuses. What we call Alzheimer's turns out to be a protective response to numerous different insults. But as you're protecting yourself, you're saying, "Okay, I'm going to put out this as part of my innate immune system, but I'm going to downsize." Again, no different than your CEO would do with your company. If you were under assault, "Okay, we're going to fight that off, but we're going to downsize." |
| Ivor Cummins | 06:36 | And that actually came up Dale, very early on the book. I was particularly fixated by that, that Alzheimer's is a normal brain response. It's an appropriate brain response. And the amyloid which they chased with drugs for decades quite sadly, the amyloid is part of that normal response to injury, and the amyloid can be anti inflammatory and protective and even work against those mold agents. So it's not the amyloid that's the enemy, it's your system has been triggered to produce that amyloid in response to a real root cause or many real root causes. |
| Dr. Dale Bredesen | 07:09 | Yeah. So you again, you can literally trace these root causes. You know, "What's driving these molecular species that are now tilting you one way or the other?" And you can see, okay, you've got to get rid of those insults. So the idea is not to get rid of the mediator. This is like saying, you know, "We're overspending in our company, let's kill the CFO." Well, okay, you kill the CFO, you can spend a little more but not for very long. So what we argue is actually these anti amyloid drugs are going to be wonderful drugs, but first you have to get rid of what's causing the downsizing. Then you want to get rid of the amyloid, which is there because as I say, it is a scorched earth retreat. So this idea, it's not all good or all bad. It is a mediator, it's part, again, part of the chain. Again, if you're not happy with your company, you don't kill the HR director, you know? You say, "Hmm, what's going on with the company here. Let's see if we can fix this." |
| Ivor Cummins | 08:06 | In many times in my corporate career, I didn't feel like that way. But no, point well taken. That's a great analogy. The reality is and it's very similar to calcification and heart disease. So my world is more heart disease related, but the calcification is more the response to injury, it has some inflammatory properties in and of itself, calcium crystals too, but the primary thing is it's been brought in as a response. So the same thing for heart disease, you fix the root causes. |

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| | 08:32 | Now you had three layers of root causes, actually four, I'll see if I can remember them. The first is the inflammatory drivers. The second then is the trophic factors, a lack of healthy things supporting the brain. And the third then are more of the toxin type category. So I'd love you, for the viewer to go through those. They're probably in order of importance or in terms of percentages of people affected by Alzheimer's. Maybe the first one is pretty huge, do you think or…? |
| Dr. Dale Bredesen | 09:03 | You know, in no surprise, many people have more than one. You know, that's life. You know, life is messy. As you get fairly poor with getting rid of your toxins, guess what? You're more susceptible to other toxins. But yes, you're right. As we started to look at this and you know, the surprise to me is, when you go in with cognitive decline, your doctor will tell you, "Oh, yeah, this is Alzheimer's disease. And you say, "Well, why did I get this?" "Well, we don't know." "Well, aren't you going to do any tests?" "Well, they're not reimbursed." So you know, you get a very small data set. |
| | 09:35 | You know, you're trained as an engineer. So imagine I brought a problem to you as an engineer. And the problem is I had this incredibly complex machine that we call a human organism, and it's now malfunctioning in a major part of it. And I'm going to tell you for data, your serum sodium and your serum potassium. Now I want an answer from you, what's going wrong and how do we fix it? You would laugh me out of the room. That you can't do that. So there is a huge what I call a complexity gap. In medicine, if you tried to do this with a driverless car, you'd be killing people left and right. So the same thing is happening with Alzheimer's, you go with cognitive decline, you don't get a data set that is appropriate for the problem. |
| | 10:21 | Now, as you start, we've only expanded this, you know, it's small amount, we're looking at a few hundred variables instead of five, essentially. But you know, in this day and age with Silicon Valley and all the engineering, look, there's much more complex data sets, just telling Google where you're shopping today, right? So why aren't we using these more complex algorithms for helping people so that they won't die from Alzheimer's? When we simply dial this up by one or two orders of magnitude, still not looking it enough. You know, you can look at a genome that's still unidimensional value. You can look at various things related to various pathogens, various toxins, various metabolic changes, exposom the mitochondrial status, microbiome, these sorts of things. Then as you indicated, you |

come away with many of the same things that you found in heart disease.

11:20 So the first thing we noticed is there is a group of people where the main abnormality seems to be inflammation and it can be inflammation due to leaky gut, it can be due to poor oral dentition, it can be due to metabolic syndrome, common one, just you know, lousy eating, a standard Western diet. These happen all the time and you get, you know, an increase in your girth, hypertension, dyslipidemia, insulin resistance, all these sorts of things. And there can be pathogens also. So for whatever reason, if you now are inducing an inflammatory state systemically, you are now going to be at increased risk. And of course, that part has been known and the epidemiologists have told us that for years. But this now tells us why. If you literally can trace the pathway from for example, NF-κB activation to the specific molecular scissors that are cutting your APP, to put it on the synaptoclastic side, which is from four peptides. And as soon as you say that, then we call that Type 1, or Inflammatory or Hot Alzheimers.

12:29 And then as you said, there's also Type 2. Anytime you're running any sort of system, you can have a problem because you're overloading the system, okay, but you can also have a problem because you're under serving the system. So it's a supply and demand issue. If there's no supply there, you can't handle much of a demand. No surprise. So you drop your trophic factors, you drop your hormones, you drop your nutrients, you can't keep that system going. And again, no surprise, people with very little Vitamin D have an increased risk for Alzheimer's disease. People who have specially sudden drops in their estradiol, increased risk. People who are in the lowest quintiles, for example, of their testosterone, increased risk for Alzheimer's. And you can just go right down the list. BDNF is important, nerve growth factor, all of these things. Thyroid is another good example, yeah. All these things are critical to support that very complicated network. You've got over 500 trillion synapses in your brain that you've got to support. And that requires a lot including good blood flow. One of the common things we see is people who have sleep apnea that's been undiagnosed, and they are dropping their oxygen concentration at night. And when you restore that, they do better as part of an overall program.

13:49 That's Type 2 or Atrophic, or Cold, and then Type 1.5. And we named it that because it's got features of both and it's kind of the worst of both worlds. And that is literally sugar induced. So

if you now eat a lot of sugar, which we weren't evolutionarily designed to do, then not only do you get heart disease and hypertension and things like that, but you get both of these, you get some inflammation because you now glycated your proteins and we measure it, of course, it's hemoglobin A1c, but there are hundreds of proteins, of course, that are glycated, they don't function as well as they should, and they can be antigenic. So you get some inflammation there, but you also get the worst of the atrophic side. Because now what happens you literally change your signaling of insulin, you phosphorylate your IRS-1 on specific serines and threonines instead of on the tyrosines. So now you have an insulin resistance state. You have an atrophic state, you're not responding to insulin as you should. And that's a very important trophic factor for neurons. And so you get the worst of both worlds there. And so we call that Glycotoxic or Sweet Alzheimer's disease. Very common.

15:00 And then type three, as you mentioned, is due to toxins. And they kind of come in three flavors. It can be inorganic metallotoxins, and the big one is mercury, but there are others. And then the second one is organics. So people who are exposed to benzene toluene, we've seen people, for example, who were first responders in the World Trade Center disaster. There was an interesting paper actually written by a group of doctors out of New York showing that 12.8% of these people already had cognitive decline by 2015. So, you know, this is a huge issue going forward. Now we've got of course, all the California fires, no question that's going with all that air pollution. Of course, there's a lot of work now showing air pollution is a risk factor for Alzheimer's disease. So this is all part of type three.

15:48 And then the third one, of course, is biotoxins and these are toxins made by various species like molds. And so you see things like Stachybotrys that produces these trichothecenes. They are fighting for their own survival. These toxins were probably made originally so that these molds could survive with bacteria around them because the molds grow more slowly than the bacteria. How do you fight something that's growing faster than you and it's going to crowd you out? You spray it with some toxin, and hey, you can survive. And that's what they've done. And as Dr. Ritchie Shoemaker has pointed out, these things are probably more common since the widespread use of fungicides.

16:27 So this is turning out and I have to say, when we started the research, we had no idea that mold toxins were going to be part of Alzheimer's disease. But we started seeing people where it

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| | | wasn't clear what was going on. They didn't have Type 1 and they didn't have Type 2, so what the heck was this? And I started actually calling the spouses and looking into the backgrounds, “What happened to these people?” And it turned out that they didn't start getting better until we started addressing these toxins. |
| Ivor Cummins | 16:56 | That's a needle in a haystack type scenario there because Type 1 and Type 2, you were using the science and all your laboratory work to drive towards through the pathways of NF-κB and all the others finding the drivers. But this last one is a real tricky one, because you've got an open book, if it's not the main ones we understand, it could be anything. That must have been a real tough one to nail down. |
| Dr. Dale Bredesen | 17:20 | And, you know, I had a little bit of a hint. I had seen a TV show about 10, 12 years ago. And they were talking about a guy who had moved into a home and become demented. They had no idea what was going on at the time. And they ultimately found out that in that home, there was just massive, massive black mold infestation. And as a neurologist, I looked at that show and thought, “Wait a minute, nobody ever taught me in residency that molds… I better start reading, I better start understanding this.” And so I thought, “Hmm, is it possible that these various people who turned out to have Type 3, is it possible they could be related to this, you know, random guy I saw on TV years ago?” And so that was kind of a hint. And not all of them turned out to have that, but a lot of them do turn out to have mycotoxins and it's a lot. And by the way, mycotoxins not only damage your nervous system, they are important immunotoxins. So they give us yet another hand, these things are impacting your ability to deal with the pathogens. So now the pathogens come in more easily. You are literally in an immunosuppressed state. And you can measure that. You can measure you know,, and show that yes, a lot of these people actually do have immunocompromised. |
| Ivor Cummins | 18:42 | Right. Directly as a result are connected very much to it. And people who are skeptical about mycotoxins or potential effects, well, the statin drugs are essentially a mycotoxin, right? And that's a trillion dollar business. So these things matter. |
| | 18:57 | So, the three, well it's really four because of the 1.5. The 1, the 1.5, the 2, would cover probably the lion's share. And then you've got these more special cases, the 3 that could be any of a range of different toxins. So quite hard to root out. |

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| Dr. Dale Bredesen | 19:12 | So good point. And we've also now noted that there's Type 4 and 5. So Type 4 is predominantly vascular. So there is this important relationship between vascular support and then type 5 is traumatic. So people who had head trauma are at increased risk, but now of course they also get CTE. So this is chronic traumatic encephalopathy. And that's the big problem, of course, with footballers and with pugilists, but it also increases your risk for Alzheimer's disease. It really boils down to, “Are you clearing your amyloid?” They both get this tau pathology. |
| Ivor Cummins | 19:48 | And it’s kind of, it was originally called vascular dementia, essentially? |
| Dr. Dale Bredesen | 19:54 | You know, interestingly years ago, the thought was that these are completely separate and there was in fact something you called Hachinski score that we would all do on the wards to say, “Oh, is this person more likely to have vascular dementia?” or “Is this person more likely to have Alzheimers?” Well guess what, it turned out that pathologically there is a close relationship. Yes, there are people where it's 99% vascular, yes, there are people where it's only 1% vascular, but there are a lot of people that have both mixed pathologies. |
| Ivor Cummins | 20:21 | And actually that resonates somehow because again, we see all the root causes and a lot of the NF-κB pathways and all are common to the heart disease and vascular disease. So they're going to be intertwined at multiple points. My own father, actually, his last years of life were destroyed by vascular dementia, it was called. Now he may have also had a certain amount of Alzheimer's, but he died at 72, you know, at his first heart attack in the 60s,. But the tragedy I think, in his case, he was taking hypertension meds in his 40s and he had the protruding stomach. So I'd say essential diabetes was probably there for 20 plus years. |
| Dr. Dale Bredesen | 20:57 | Yeah. |
| Ivor Cummins | 20:58 | It’s tragic. Diabetes at this stage is stunning in terms of some of the figures. So recently I analyzed a spreadsheet of figures from the US database, the Institute of Health, and it looks like 64% of over 45 year old adults are now prediabetic or diabetic. So if you measured insulin, it'll probably be a 75 plus. That's kind of a stunning thing, the three quarters of your adults over 45 are essentially diabetic, they share one disease state. |
| Dr. Dale Bredesen | 21:28 | What it really says, it's scary as you say, is that prediabetes is within normal limits. When you go to get, “Oh, yeah, you're |

normal." "Yeah, you've got prediabetes, you're fine." And that's really scary, because it really brings back another thing, which I mentioned in the book as well, which is that we no longer should be talking about WNL (Within Normal Limits.) Whereas some people joke we never looked, but we need to talk about optimization. Published great examples of these, if you look at homocysteine, it used to be said homocysteine is fine up to 13. At the same time beautiful work out of the UK actually showing that you really do much better seven or below. And when you're there, you're not getting the cerebral atrophy. As you go up, you literally can follow the cerebral atrophy that is associated, even 10, 11, 12. And then as you get above 13, it just keeps going up.

22:28 It's the same story for B12. A B12 of 320 is "within normal limits." Not good for you. And in fact, people can have anemia, they can have dementia associated with that, even though we call it within normal limits. So we really need to be thinking much more because again, what's within normal limits is purely a statistical argument. It has nothing to do with what optimizes your biochemistry. So wouldn't we all be doing better if we didn't have prediabetes? Absolutely. And we're seeing that again and again and again. And it's very important. It's one of the most important features in risk for Alzheimer's disease. If you have prediabetes, you have a clear increased risk. If you have Type 2 diabetes, even more so. And of course, this is part of the Type 1.5. So this is a huge issue, yeah.

Ivor Cummins 23:22 Yeah. I love that Dale, abnormal lemons. Something just occurred to me at that moment, the one place where they do put the optimum, and then they kind of sanctioned you, if you're outside the optimum is LDL cholesterol.

Dr. Dale Bredesen 23:35 Yup.

Ivor Cummins 23:36 So that gets the proper treatment. They don't just look and say, "Hey, this is normal." But there's reasons for that, because there's a big business behind it, I guess.

23:44 One other thing that popped into my mind when I thought of cholesterol there is the big question, and I've been asked this a lot online about ApoE4. Now, I will tell you, I have a disclosure to make. I'm E3/E4, my wife, E3/E4, my fifth child we checked, because he had very strong sensitivities to food, and he was EE4. And we haven't checked the others. Also, my sponsor, David Bobbett who got the huge heart disease, why he set up the charity, he's E3/E4, and he has very strong feelings about

dietary regimes for people who have metabolic disease who are E4, who need to be very careful. So we might talk a little around first, the ApoE4, where it comes from for people, and then around the best regimes for them.

Dr. Dale Bredesen 25:06 That's a great point. And I think you know, there are books that could be written about this. It's such an interesting... I mean, some people argue it should be called the God gene, because it does so many things. As you indicated it's critical for vascular compromise, it's critical for Alzheimer's disease, it's critical for inflammation, it's critical even for longevity. It has effects on longevity, as you know. And so if you go back five to seven million years, when the hominids appeared from the simians, what happened to us? ApoE4 appeared as far as we know, with early hominids. Chimps don't have it. And you look at the specific residue, which was a threonine 61 in a chimp, and is now an arginine 61 in ApoE4. So ApoE4 was the primordial ApoE. And for 96% of hominid evolution, we've all been ApoE4 homozygotes. Only in the last 4% of our evolution, so 220,000 years ago, ApoE3 appeared and that's kind of the vanilla one now as you know. So I checked, I'm a 3/3 as an example. ApoE2 just appeared about 80,000 years ago.

26:20 It's interesting people say, "Well, is it better or worse?" It's not better or worse, it's advantages and disadvantages. And in fact, you have some real advantages as an ApoE4 positive. You do better with inflammation, responding for example, to pathogens. So for example, if you are a Tsimané Indian living in Bolivia, most of them have parasites, they live longer, better, smarter, with ApoE4. If you are a Ghanaian Indian, as Professor Finch has pointed out you live longer, better smarter, if you are ApoE4 positive. If you're in a situation where you don't have those parasites and you're now eating a high fat diet, a typical standard Western diet with a lot of sugar in it, that actually gives you a disadvantage. Fine, you can fix that. And there's a wonderful website, I'm sure you're aware of, apoe4.info, which was started by Julie G number of years ago, and there are over 3500 people and many of them are on the protocol that we developed or some variation of that protocol.

27:24 So, as you indicated, this is a common thing and 75 million Americans are single copy, about 7 million double copy ApoE4 homozygotes. And if you have no copies, your chance during your lifetime of developing Alzheimer's is about 9%. If you have a single copy, it's about 30%. If you have two copies, it's well over 50%. Nobody should develop this disease. This should be a rare disease, it really should. So if you have one or two copies,

fine. You get evaluated, get a, what we call a cognoscopy. When you turn 40 or 45, get on the appropriate prevention. You can change your cardiovascular risk, as you well know, you can change your Alzheimer's risk. And that's becoming more and more clear and multiple things published, finger study and, you know, on and on and on. We've published a number of things showing reversal of cognitive decline. And by the way, our protocol actually works a little better in people who are ApoE4 positive. It's a little easier to reverse their cognitive decline than in the ones who are ApoE4 negative. Probably in part because they tend to have more of the toxic exposure, whereas the ones who are ApoE4 positive tend to have more inflammatory because they're very good.

28:40 And so as Professor Finch pointed out, and I think he's right, what did it take for us to come down out of the trees as simians and become hominids? Well, we're now in a dirtier environment. We are walking along the savanna and we are stepping on things and puncturing our feet. We are fighting with our brethren and we are fighting with our food. And we are going for longer periods without food. So ApoE4 essentially helps you with all of those. It gives you a more proinflammatory state. You as an ApoE4 positive individual can do better with eating uncooked meat than I can. So I may die from an infection, whereas you'll live. If they cut off food to both of us, you will live longer because you're a better absorber of fat than I will because I'm a poor absorber of fat.

29:31 His argument was that this really helped us to graduate from being simians to being hominids. And so in that sense, if you look at the changes, there are so few changes, as you know, we're about 99% identical with the chimp genome. And so the first time I told my wife and I said, “Do you realize my genome overall is more similar to that of a male chimp than it is to yours?” And she said, “Well, duh!” So you know, I like The Three Stooges, the chimp likes The Three Stooges, she doesn't like The Three Stooges, that sort of thing. But the bottom line is there aren't that many differences. And among the differences, interestingly, there is an inordinate percent that turns out to be related to inflammation. And of course, ApoE4 is part of that. It is a proinflammatory gene in some ways. And we noticed this a number of years ago and published that this actually has an effect on the way you express specific genes that are related to inflammation. So it is one of the controllers of inflammation. And what is Alzheimer's? It is with the amyloid that's part of the innate immune system. And as Professor Robert Moir and Rudy

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| | | Tanzi showed a number of years ago, in fact, the amyloid is actually an antimicrobial. So this all fits together beautifully. |
| Ivor Cummins | 30:55 | Very much so. And if you then take 6, 7 million years ago, the ApoE4 genotype emerged with the hominids and then we became bipedal striving hunters. The hunting was a huge part of it, the damage to the feet, the eating of rotten meat, I guess we were scavengers early on. So the ApoE4 enabled us for all of this rapid inflammatory response to threats. Then it was around, I think it was only 220,000 years ago was it, the ApoE3 came in? |
| Dr. Dale Bredesen | 31:24 | That's right. |
| Ivor Cummins | 31:25 | And then only 80,000, the ApoE2. The funny thing is that the ApoE4 is like knowledge now to be a particular genotype where you can get inflamed very easily. Modern foods, modern contaminants are a big problem. So the diet is suggested to be not just low carb, which is a no brainer for all Apo types, lower carb, lower sugars, no industrial vegetable oils, but the ApoE4, the tendency is to say, "Well be careful with the saturation fat." And a lot of people wonder about that, and they probably wonder, because evolutionarily, if we became the hunters, you know, and that was ApoE4 that defined us, then why should saturated fat be a problem, or meat, because the guidelines clearly indicate: "Be careful with meat and cheese and saturated fat." So maybe that's a question we could tease out a little just for people to explain. |
| Dr. Dale Bredesen | 32:23 | You know, that is a really good point. Because, you know, hey, if we're meat eaters, why don't we eat a lot of saturated fat? And the bottom line is, you can, if you are getting plenty of fiber, if you are getting… we think of this as what we call the Bermuda Triangle. It's a silly way to think about it, but it's a combination of three things. And Mark Hyman pointed this out years ago, that it's three things that when you put them together are absolutely explosive. You don't want to have a lack of fiber with saturated fats with sugar. You know, you go get a cheeseburger, fries and a soft drink, that's exactly what you're doing. You are killing yourself when you do that. So as long as you are getting plenty of fiber, as long as you are not having the sugar, you can have some saturated fat. |
| | 33:10 | So what we usually recommend to people because of course saturated fat can be helpful, especially at the beginning of cognitive decline, you want to get those ketones up. Now in the long run, we'd like to get your endogenous ketones up and you don't want to have or need to have saturated fats. But at the |

beginning, you may want to do this. And this is actually suggested originally by Julie G from apoe4.info, that essentially you undergo this conversion event. When you have the early cognitive decline, you want to get yourself to be keto adapted, you want to get yourself to be insulin sensitive. Fine, use the MCT oil or the coconut oil during that time or even exogenous ketones. And if you're concerned about your lipids, use exogenous ketones, ketone salts or ketone esters, fine. As you now become sensitive, as you now get yourself into ketosis, check your LDL particle number. Some people do just fine with a fair amount of these fats, especially when they've got plenty of fiber around and they're not eating any sort of simple carbs. Other people are more sensitive and they will need to be lower on their saturate. So again, I don't think it's necessarily good or bad. I think each person is a little different. And you want to monitor yourself, you may be able to do just fine.

34:26 So what we suggest then is what we call Ketoflex 12/3. So this means mild ketosis, flexitarian and metabolically flexible. So yeah, you want to be a vegan? Fine. You want to be a vegetarian? Fine. Check your numbers. Make sure your B12 is okay, your vitamin D is okay, your choline is okay. Lots of people who are deficient in choline, and that's another big one for cognitive decline. And so on the other hand, if you are finding that your LDL particle number is now rising above 1200, then you want to be cutting back on that.

34:59 This is the idea. So Ketoflex flexitarian 12/3. means 12 hour minimum fast and if your ApoE4 recommendation is 14 to 16 hours between finishing your dinner, starting your breakfast or brunch or lunch, whatever you like. And then three hours minimum between finishing your evening meal and going to bed. So with that, you get the advantages of autophagy, you get the advantages of insulin sensitivity, you get all the things that you really need for optimal cognition as well as optimal support for your vascular tree.

Ivor Cummins 35:34 Yeah, and that fasting is a crucial one. I think I tend to do 20/4.

Dr. Dale Bredesen 35:39 Wow!

Ivor Cummins 35:40 Generally speaking, but I eat a lot and really enjoy it when I do eat but I leave long gaps. On the ApoE4 and the saturated fat, I guess it's not so much meat per se because there's a tendency to say less meat, less cheese, but it's more the saturated fat, specifically then than meat as a natural real food. It's the saturated fat element maybe is the concern.

Dr. Dale Bredesen 36:04

Yes. There's additional thing here. With the meat, there are other issues. Number one, there are toxins in the fats of the meat often. So these animals have sequestered their toxins. When you are exposed to various toxins, the hydrophobic ones, where do you put them? You put them in your fat. And unfortunately, as you're now losing that fat, you're emptying them back out. So you've got to be careful about that. You've also got to be careful about infection. So there are a lot of issues with meat. But you know, again, we think of it as a good condiment. The diet is a plant rich, high fats, good fats, especially polyunsaturated, monounsaturated, etc. Intermediate protein, typically .8 to one grams per kilogram of lean body weight. And then, very low on simple carbs. But complex carbs, great, you want to… I think one of the things that we don't talk about enough with our patients is the importance of fiber. This stuff, you know, again, something that we used to have, hundred grams a day, and we now have about 10 grams a day. So, you know, we just again, we were not made to have the small amount of fiber that we do. And this stuff, lowers your cholesterol. This stuff improves your toxicity. This stuff improves your insulin sensitivity. I mean, this stuff is just amazing stuff. And so we recommend that people get at least 30 grams per day. This helps again in so many ways. So all of these things are critical.

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Yeah, for me, you know, whether you like grass fed beef, fine,. Again, be careful. If you're eating something that's largely grain fed, that's got its own issues with inflammation. If you're going to have chicken, pastured chicken, good stuff to have, and again, be careful about the inflammagens. And if you're going to have fish, great, you don't want to have something incredibly toxic. A fish farm, you want to have something that's wild caught, and it has a good omega-3 to to omega-6 ratio. And of course, the same thing is true for eggs. Make sure you've got the appropriate pastured eggs that have a good omega-3 to omega-6 ratio. We're fooling ourselves. So many people are out there eating horribly toxic salmon, raised in a terribly toxic farm and saying, “Wow, this is great. I'm really doing good for myself.” And they're really not. The omega-3 to omega-6 ratio is not so good. The toxins, not so good. And so you want to be careful about that.

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So you're right. Saturated fat is important, but part of an overall picture of trying to optimize your energetics, your inflammation status, and your insulin sensitivity.

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| Ivor Cummins | 38:51 | Yeah. So I suppose the old meat and two veg or meat and lots of fibrous vegetables without all the rice or sugars or potatoes was probably a pretty good diet overall. |
| Dr. Dale Bredesen | 39:00 | Absolutely. |
| Ivor Cummins | 39:01 | If we had only kept at it. |
| Dr. Dale Bredesen | 39:02 | Yeah. It's a good point. And you know, again, these diseases have increased dramatically. I mean, you can follow with various things. As you know, with the low fat fad, you can follow the increase in obesity, you can follow the increase in diabetes. And so as we've changed, I think part of the problem is that we've made all these assumptions over the last hundred years, we've assumed that it's fine to raise animals on a CAFO. We've assumed that it's fine to feed them something that's not typical for them to eat. We've assumed that it's fine to crowd them into small spaces. We've assumed that we could farm the fish in these crowded spaces. These assumptions have all proven to be incorrect and we're paying for it now. |
| Ivor Cummins | 39:45 | Yeah, well, industrialization has had a huge effect. Just swinging to the keto. I see all the time, the attacks on keto, and they're quite amusing on Twitter but mainly in the media, the mass media constantly, but the place of keto diets within this, obviously it's part of your protocol. It's not hugely accentuated. But interestingly, as case history came out recently, I don't think it was connected with you, but they had a guy who was ApoE4 for with brain fog, I think it was in his 40s or 50s. And his MoCA score was really bad. And they gave him a hard keto diet, and it was only two or three months, the score came up 40% and the insulin went down, I think the HOMA went down 80%. So keto is a big thing. But is it not ironic that Alzheimer's is a massive disease, as you said, it's going to be a catastrophe in coming decades, cardiovascular disease similar, and yet keto type diets are a linchpin of a multifactor intervention to fix them, and yet, the whole world wants to fight against keto. How do you see that? |
| Dr. Dale Bredesen | 40:52 | You know, I do think that people have misunderstood what keto is all about and everyone says, "Oh, keto. I'm going to have a bunch of bacon." What we're talking about is really different. This is what we call a keto flex. It's really about a plant rich, good fats rich, ketogenic diet. So you are getting the fiber, you are getting the phytonutrients, you are getting the vitamins that you're not going to get with just a bunch of meat. |

41:16 Now I understand if you are an athlete and you're trying to build muscle, it may be different, but we're now dealing with people who have cognitive decline or risk for cognitive decline. And there are repeated studies showing that ketogenic diets, just as you mentioned, I'm familiar with the paper you're talking about, improve the scores. And we see it every day. It's what's been called by some of the doctors "low hanging fruit." People come in with cognitive decline, and they've got type 1, type 1.5, type 2, those are easy. It's the ones who are very far along who have major toxicity issues. Unfortunately it reminds me of when someone has cancer and you go in to find the cancer and, "Oh my gosh, it's spreaded here, it's spreaded there! It's spreaded here! Oh my gosh! We didn't know how bad it was." That's what we're finding with people with toxicity. "Oh my gosh! They've got mercury everywhere." "Oh my gosh, they've also got organic toxins." "Oh my gosh, they've also got mycotoxins." It's common. You just have lost the ability to deal with these things.

42:20 You know, we're living in this dynamic situation. You're fighting entropy every second of every day. When your systems stop doing that, and I thought [Joe Prasorno recently made a great example. "Humans were made to excrete stuff all the time with all this fiber they were taking. Now we live in a situation where there's virtually no fiber. So what happens, you're secreting this stuff and it's just going around your enterohepatic circulation, you are reabsorbing your very toxins for years." So I mean, it's just not the way humans were designed to be. And the biggest problem for all these things heart disease, as you know, that's number one killer, certainly Alzheimer's and probably cancer as well, is that the human species has tried to live in a way that we are not evolutionarily designed to live. And so it's silly. It's as if we all spent each day jumping out a second-floor windows. We would get broken legs, we would get arthritis much earlier, we're doing the same thing. We're simply doing this with sugar, and with CAFO meat, and with toxic food, all this sort of stuff, processed food, on and on. So we're really trying to exceed our evolutionary design capacity and we're failing.

Ivor Cummins 43:39 Yeah, and the pushback against this kind of almost obvious in retrospect view of the world which you've just described, the pushback is huge, I guess, because the industry has a lot at stake with processed food, sugars, breads, pastas, all the junk cereals. So, we will continue to see huge pushback against this approach, I guess. Though you are getting more and more

accepted, shall we say. I think in your book, you said you had 450 doctors that you've already gone through the method.

Dr. Dale Bredesen 44:08 1500 now.

Ivor Cummins 44:10 And now it's 1500 and the book was only about a couple of years ago, really. So is that everything, including the keto, low carb aspect is all being more accepted now increasingly? Are you getting momentum? Do you think in the next 10 years, they're going to be a golden 10 years for this information to come out?

Dr. Dale Bredesen 44:28 Yeah, no, I think you know, we're going to look back on the last 50 years, and realize that these were kind of the Dark Ages, when you talk about Alzheimer's disease. People didn't understand what was causing it. I think of the 16th century and like, "Yeah, they were thinking of, you know, is this coming from some sort of, you know, God arguments or something?" It was something that's crazy because we didn't really understand the disease and we didn't really understand where it was coming from. We had no ability to do much about it at all. I think that things are starting to change. People are reporting the first improvements. You're seeing now for the first time success with prevention, success with reversal in at least some cases, there are now multiple clinical trials. By the way, we started this clinical trial 2011, we propose the first comprehensive clinical trial for cognitive decline. And it was not allowed, it was turned down by the review boards, because they said, "You're trying to do a multivariable trial." We said, "Yeah, but this is a multivariable disease, so you're going to have to do." So I think you are seeing the beginning of a change. But you know, never, underestimate the persuasive ability of billions of dollars. So when you've got this going on, and you've got the establishment with billions and billions of dollars at stake, it's going to be hard to change those minds.

Ivor Cummins 45:54 It is indeed. And that trial, actually, I remember you mentioned in 2011, they didn't want the multi intervention which is of course is absurd. The trials were designed mainly for drugs, which is the single factor and they want clarity on the single drug. But this requires multiple synergistic factors. You haven't really probably tried to get another trial on since or you have?

Dr. Dale Bredesen 46:15 Yeah, I have, and in fact, we got turned out again in 2008. But we actually were approved in 2019. So we are now actually in the midst, And it's been truly fantastic. Three outstanding doctors, Dr. Ann Hathaway, Dr. Kathleen Toups, and Dr.

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| | | Deborah Gordon, who are all working with me on this trial. We're about halfway through at this point. We're very excited, we should have some data in 2020. |
| Ivor Cummins | 46:44 | Excellent. I really look forward to that. And the good thing is, you know when you have utter confidence in your whole protocol, in reCODE protocol, and you're being allowed to use all the elements of that that you wish. |
| Dr. Dale Bredesen | 46:58 | Yes. So, it's Interesting. Again, all previous trials have pre determined a treatment. So imagine that. Imagine that every time they tried to do something new to fix your car, they determine ahead of time what they're going to do to fix your car before it could drives in. It makes no sense. So this is actually the first trial in history in which we look at all the different contributors. You know, do you have specific mycotoxins? Do you have specific metallotoxins? Do you have insulin resistance, on and on and on? And then actually target those things. Instead of saying, "We're going to treat everybody with blank," whether it's a drug, or whether it's a lifestyle change, that's fine, but you're still doing it then without looking at what's actually causing the decline, which really makes no sense. |
| Ivor Cummins | 47:49 | Yeah, if you're going to look at a really effective treatment, and if you're going to trial that treatment, it has to be the way you just described. |
| Dr. Dale Bredesen | 47:54 | Exactly. |
| Ivor Cummins | 47:55 | I mean, that's the only thing that makes sense. And is a placebo or element of people with nothing don't help them at all, or…? |
| Dr. Dale Bredesen | 48:02 | So here's the other interesting thing. When you're trying to change the way people think about things, it takes some time. The board said, "We will not allow you to do in this first study, a control group," which again makes absolutely no sense. Now I understand the point that you wouldn't and you shouldn't be doing a placebo control, because there are already drugs that have a very modest effect, but you would want to use the standard of care. On the positive side, what you can do now is you can use historical controls. |
| | 48:38 | There's just a nice paper actually published on that. So you can use it because there's so much known now about what happens to people with now, again, it's a population group, so you don't know for each person, but you can get a general idea of a population, what is the rate of decline? We know that these |

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| | | people aren't going to improve on their own. This doesn't spontaneously get better. And so that makes it a little easier. It's not like you know, a lot of people are just spontaneously getting better. So you know, we'll see what happens with the group, but everybody will get the treatment. |
| Ivor Cummins | 49:12 | Very good, which is great for everybody in the trial I'd say, for sure. But also that historically, it's pretty solid. And I think Virta Health came out with their reversing diabetes trial. And yes, they didn't have a control, and it was accused of being not placebo controlled, but the reality was, it's so clear, like Alzheimer's, what happens with our standard of care with type 2 diabetes, that you just have to show, "Hey, this is way better than what could ever be expected." And then you can go on maybe do another trial to cover all aspects… |
| Dr. Dale Bredesen | 49:46 | Absolutely. This has really shown us, the people think and that the irrationality of some of these things, When you have a situation where nobody's getting better, and now you're saying, "Well look here some people who are getting better." That gives us a toehold. It's a toehold. We just reported 100 more cases where we have documented improvement, improvement in their cognition, quantitative cognitive assessments, improvement in MRIs, and some of them that have had volumetric MRIs, improvement in quantitative EEGs in evoked responses. I mean, these are clearly documented improvements. And the response was, "Oh, well, you know, this has to be done in a trial." Well, look, what you want to do is do better than what currently exists. That's the goal. Do you really want to let people die while you're saying, "I'm going to put together a big control group and do a big trial." Let's do the best we can for the patients. And as they're improving, of course, we'll do a trial which we're now doing. |
| | 50:48 | As I said earlier, we started this with a trial that was turned down. So you can just say, "Well, okay, we're going to go home," or you can say, "Well, okay, let's see if we can now at least get enough anecdotal data to allow us to have a trial improved." And that's where we stand now. |
| Ivor Cummins | 51:04 | Yes, we are. And when you mentioned billions of dollars as well, to be honest, any non drug regime that's showing data that shows that it's vastly more effective possibly than all the drugs, it won't be inherently very popular. You could understand a reticence to approve the trial if the results may be very embarrassing for the establishment. But that might be conspiracy theory somewhat. |

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| Dr. Dale Bredesen | 51:29 | Here's what's interesting. I believe that this approach, these sorts of approaches will make the drugs work better. We always tell the patients, "Imagine you have a roof with 36 holes in it," we use that number because that's the number of mechanisms affecting your beta cleavage site, affecting your gamma cleavage site, affecting your alpha cleavage, on and on and on, and you add them all up in there about 36 of those mechanisms. So imagine that you have a roof that's got 36 holes in it, and you've got an incredibly good patch for one hole. And that patch is called drug A. Okay, it's doing a lot, but you can't see it until you now start patching some of those other holes. And now you start saying, "Wait a minute, this is a really great drug." So I actually think that it's kind of ironic that there's a lot of pushback from the standard approaches with drugs because the drugs should work better. And I mentioned earlier, the anti amyloid drugs, I think are going to be incredibly helpful. As you now get rid of the insults, now you want to get rid of that amyloid that's there. But we've seen a number of people where you get rid of the amyloid without doing anything else. What do you think? They get worse. They were using this stuff to protect themselves. So no surprise, they get worse when you take it away. |
| Ivor Cummins | 52:47 | So there could be a really good synergy between some of the better drugs, and the whole protocol together could be a real win win. |
| Dr. Dale Bredesen | 52:54 | I think that's the way of the future is to combine the drugs and that'll also give us some new targets as well as we understand all these different contributors with a personalized, what is literally a precision protocol. |
| Ivor Cummins | 53:08 | Exactly. I'm conscious, you have somewhere to get to now so I'm going to wrap it up now. But that's a great way to kind of pull it together, the protocol plus the best of medical technology and pharmaceutical technology working together. That would be a great kind of marriage, if you say, if you will, to put together. |
| Dr. Dale Bredesen | 53:31 | You know, it's interesting, I think that Alzheimer's is going to be a disease best treated by a combination of pharmaceuticals, functional medicine and computation. We need computationally based algorithms, which we're using for subtyping people and we're using for generating these initial protocols. I think that that's the sort of combination that's going to give us the best results in the long run. By the way I should |

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| | | add, the best thing of all is when these people get better, they stay better, because you're actually getting at the root cause. With everything else, as you know, they get a bump up and they go right back down to declining. These people, and we now have the longest people started early 2012. So we're now up to over seven and a half years, people. That's unheard of for people to be getting better and staying better for all that time. And a couple of them have gone off and back on. When they go off, they get worse within a couple of weeks. They go back on, they get better within a few weeks. |
| Ivor Cummins | 54:28 | And you have people going from like scores down to 30th percentile up to the 90th. |
| Dr. Dale Bredesen | 54:33 | Oh, yeah. Absolutely. And higher, 98th. That's one of the people from apoe4.info. And we see these sorts of improvements all the time. And again, the earlier the better. No surprise! As with virtually all chronic illnesses, the earlier you jump on it, the better. And therefore, my argument is we need to have a global just as we had global vaccines for polio and things like that. We need to have a global program to reduce the global burden of dementia. And that's possible now. |
| Ivor Cummins | 55:07 | Excellent. Well, here's to in the next 10 years everyone using the reCODE protocol, and whatever selection of the best drugs they can come up with. |
| Dr. Dale Bredesen | 55:17 | Absolutely, yeah. Thanks very much. |
| Ivor Cummins | 55:19 | Thanks very much, Dale. Pleasure to be here. |