Emily: I'm Emily Kumler and this is Empowered Health. I remember so clearly having a debate with friends about whether or not it would be a good idea to get genetic testing done for Alzheimer's. Alzheimer's is a neurogenerative disease that affects your memory and then eventually sort of takes over your whole body. For me personally, it's probably the most torturous way to imagine dying. To start to lose your memories and not even recognize people in your own life feels incredibly personal in a way that I guess some of the other diseases don't have that same feeling for me, but what's interesting is that people used to say, don't get tested genetic testing to show whether you have the genes that put you at a much higher rate of the likelihood of developing this because there's nothing you can do about it and you'll just live the rest of your life feeling super depressed that that's how you're going to die. Well, it turns out that's not really true. There's a researcher, Dr. Bredesen[1], who we're going to talk to today and he is reversing this disease in patients. He's also helping people who have the genetic predisposition for Alzheimer's to kind of starve it off longer. So we're going to get into all the research with him. One of the reasons that we wanted to do this episode is cause another thing that people don't know about Alzheimer's is that two thirds of all Alzheimer's patients are women.[2] And it turns out that women are more likely to be the caretaker[2] of somebody with Alzheimer's in that exact same proportion. So there are 15 million caretakers, two thirds of whom are women, and there's about 5.5 million Americans living with Alzheimer's right now. Two thirds of whom are women.

Dr. Bredesen: So I am Dale Bredesen. I'm a physician-scientist. I trained in neuroscience and neurology and currently in the Department of Pharmacology at UCLA[3]. And I've spent my career with laboratory work studying the neurodegenerative process. Before we get started though could I ask you one question?

Emily: Of course.

Dr. Bredesen: So I understand from your background that you are interested in, and I read a little bit about you, you are interested in bringing things to women and to women's health that aren't typically out there. Which I think is fantastic. So my question for you is how provocative do you want to be here? What we're working on is controversial right now. We have multiple publications and hundreds of people who have improved, and yet the Alzheimer's Association[4] denies the very existence of the publications, basically saying we don't believe this yet. On and on and on. So although I spent my whole career in academia and we've published over 220 papers[5], we've become, by claiming that we're making people better, which we're approving and have published, we've certainly run a foul of groups like the Alzheimer's Association. I've talked to them directly on the phone. I used to serve on their scientific advisory board, but disagreements about what's actually happening. So how much do you want me to go into things

[1] https://www.ahnphealth.com/dr-bredesen.html
[2] https://www.alz.org/alzheimers-dementia/facts-figures
[3] https://www.pharmacology.ucla.edu/about-us/our-department
[4] https://www.alz.org/
[5] https://www.ncbi.nlm.nih.gov/pubmed/?term=Bredesen+D

that are relatively controversial and how much do you want me to stick with kind of the more standard line?

Emily: So my instinct on that is I don't actually want a filter. I kind of feel like if you're doing work and you're getting results, then it's important for people to realize that. I think one of the biases that I have is that so much of the information that's being filtered prevents patients from making appropriate decisions for themselves. And so I think we should get into all of that if you're comfortable talking about it.

Dr. Bredesen: Okay, sounds good.

Emily: So you have something where you talk a little bit about the 36 holes in a roof.[6] Would you mind explaining that for us?

Dr. Bredesen: Right. So the analogy there was I spent my whole career with 30 years in the lab of looking at one question: what underlies the phenomenon of neurodegeneration? What are the molecular species that drive this phenomenon of neurodegeneration? Could we understand it enough that we could begin to fashion the first effective treatments? So as we looked at Alzheimer's disease in particular, we could see that in fact, what's at the heart of Alzheimer's disease is a molecular switch. And if you ask what's controlling it, we identified 36 different mechanisms, 36 different things. So for example, if you're going to get Alzheimer's, it matters whether you have insulin resistance. It matters whether you are APOE4[7] positive and on and on. And on, and we initially identified 36 different mechanistic inputs you want to get after the root causes of these illnesses and for Alzheimer's we noticed initially there are 36 different potential contributors. All of these things can potentially contribute. It's different for each person and therefore if you want to be successful in preventing and treating Alzheimer's disease, it is like having 36 holes in your roof. You need to patch as many as possible to have an effect. And in fact, we've published, we were the first to publish improvement in patients with Alzheimer's[8] disease and pre Alzheimer's. That was in 2014 and we've published numerous things since then. We've recently published a hundred cases that showed documented improvement[9] from 15 different clinics using the protocol that we developed. So this is why we make the analogy. Now, of course, everyone's roof has different sizes of the different holes. Your hole that's related, for example, to insulin resistance, maybe better or worse than someone else's. Therefore you may have to patch it differently and it may not be so important to you as it is to someone else. But all of these things, your estradiol level, your progesterone level, pregnenolone, free T3, TSH, on and on and on. Vitamin D, testosterone, these things are all

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6 https://www.clinicaleducation.org/resources/reviews/36-holes-in-the-roof-the-dawn-of-the-era-of-treatable-and-preventable-alzheimers-disease/#_ftn1

7 https://ghr.nlm.nih.gov/gene/APOE

8 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4221920/

9 https://www.omicsonline.org/open-access/reversal-of-cognitive-decline-100-patients-2161-0460-1000450.pdf

critical. They all feed in and actually you see at the molecular level where these feed into the equation. And as a simple example, estradiol interacts with the estrogen receptor of course, which enters the nucleus and alters the transcription of hundreds of genes. And among these is a gene that actually interacts directly with this switch that's at the heart of Alzheimer's. So you can trace a direct path from estradiol to Alzheimer's risk.

Emily: And so that brings me to the, I feel like there's a lot of controversy, at least in my sort of cursory knowledge of this idea of like women are developing Alzheimer's at a greater rate because they live longer versus some drop in estrogen around the time of menopause.

Dr. Bredesen: So first of all, one of those is a mechanism drop in estrogen. The other one is an observation, they live longer. So they're probably both correct. So yes, women live longer[10], but even if you take age into account, they still get Alzheimer's at a higher rate. So there is something you're right about being female that increases your risk for Alzheimer's. And yes, one of the possibilities is that men, when they decrease their testosterone, as you know, it goes array rather slowly over many years. Whereas women with menopause do tend overall to have a more rapid drop.[11] Is that the reason that there's more? It's not known. It is certainly one of the possibilities.

Emily: Can you talk a little bit about why that might be? Like what is the interplay between say brain health and estrogen or estradiol, which is the primary hormone in estrogen, right?

Dr. Bredesen: Absolutely. So yeah, so there's E1, E2, E3, and estradiol.[12] E2 is the most important one. And so yes, as I mentioned, there is a direct link.[13] Estrogen binds to the estrogen receptor. It enters the nucleus of your cells. It changes the production of hundreds of proteins because of its effect on DNA. And among these happen to be proteins that are literally at the heart of Alzheimer's disease. So when you think about Alzheimer's disease, there is the production of what's called Beta amyloid. This is a little fragment, it's a little bit like looking at molasses. It is stuff that collects in your brain and it is associated with Alzheimer's disease. People have argued about it's relevance as a direct mediator. Certainly the evidence would suggest it does play a mediating role, but it is not the cause. The cause is all these other things that cause you to respond. So what our research suggested was that in fact the amyloid production is actually a protective response to these various different insults.[14] And Alzheimer's is therefore a response to a number of insults that occur. And in fact it is a downsizing response. So the amyloid comes from a protein, it's called amyloid precursor protein. And this sits in your neurons, especially at synapses and to a lesser extent in other cells. And this interesting molecule APP can be cut in two different ways. So it's literally like your CEO of your company that's saying, okay, are we going to downsize or are we going to grow? And so when things are

[10] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4932837/
[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6198681/
[12] https://medlineplus.gov/lab-tests/estrogen-levels-test/
[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4318702/
[14] https://www.ncbi.nlm.nih.gov/pubmed/25805829

good, your APP actually senses this and it is cut into two fragments that literally support the growth and maintenance of connections. So again, it would be just like your company's doing well. You say, we want to make more contacts, we want to hire more people, we want to do more things. Your brain supports the production and the maintenance of synapses. You have an active and healthy brain. On the other hand, that same molecule, when it senses that things are bad, and that can be again, 36 different things as we talked about before. It can be because your estradiol has dropped precipitously. It can be because your vitamin D is too low, because you have a poor nutrient status, because you have ongoing inflammation, because you have poor dentition on and on and on. Insulin resistance again among another one, toxins. These things are all critical. Your APP actually senses this. It literally sends out a downsizing signal. In this case, that same molecule is cut at three sites producing four fragments, and guess what? The amyloid that we associate with Alzheimer's is one of those four fragments. So people have tried to say, well, you know, Alzheimer's is all about amyloid. Well, yeah, that's a part of the overall story, but it's a much bigger story than that. And as you indicated, this is about brain health. It is about your brain's response to decline in hormones, decline in nutrients, decline in trophic factors, ongoing inflammation, poor metabolism, leaky gut, all of these things contribute to poor brain health. And so you can again trace a direct molecular pathway to where this stuff is produced and to why this stuff is produced.

Emily: But it almost sounds like that's a protective response. Like the body is actually trying to help solve a problem.

Dr. Bredesen: Exactly. So when your CEO comes to you and says, okay, Emily, things aren't going well and we're going to have to downsize the company, then that is a protective response. You're not going to go bankrupt because you're going to downsize. But what happens when you downsize? The first thing is that they say, we're not going to hire anybody else. And that's exactly what happens in Alzheimer's. You have many people with early Alzheimer's who can do everything. They can drive, they can do their jobs, they can play tennis, but they can't learn new things. It's the same thing as your company not hiring new people

Emily: Or a computer with a full hard drive or something almost.

Dr. Bredesen: Exactly right. So the bottom line here, people have said before, well gee memory is so important. Why would that go first? Well, because there's a tremendous amount that you can do with what you've learned as an adult. And so if I gave you the choice, I said, okay, Emily, you're gonna wake up tomorrow. Either you can forget how to speak or how to do your job or how to calculate or how to drive. Or you can forget the friends rerun from tonight. That's an easy choice. And that's essentially what your brain is doing when it protects you. Now the problem is if you don't address the root causes, you continue in this downsizing response until you have nothing left. So you just continue. Your company gets smaller, smaller, smaller, smaller, until it's only got one employee. And so when you don't address what's actually causing this downsizing, and this is exactly what's going on at all the centers, they're not addressing the very things that are causing the downsizing. So no surprise, you continue to get worse and worse Alzheimer's

and you'll ultimately, of course you can't dress yourself and you can't do anything for yourself. So the key is to get in as early as possible and to address those things so that you now get the signaling that says, yeah, we are going to be able to support and maintain synaptic connections.

Emily: And so in your case studies that you've published and that you've been working on, you have had some reversals of Alzheimer's, is that correct?

Dr. Bredesen: Yeah. So we just published a hundred patients[15], all of whom showed documented improvement. This is from 15 different clinics for people that have trained. We've trained now 1500 physicians from 10 different countries and all over the U.S. And we see repeatedly people improving. Now that doesn't mean at all that every person gets better. That's not the case. The people who are earlier on do better. No surprise. So as you know, there are four stages.[16] You go from presymptomatic to SCI which is subjective cognitive impairment. You know that things have changed. Your spouse often knows it, but you are still testing quote in the normal range. Now often that just means you are very smart and you're still testing quote within the normal range, but you're not testing the way you would have. We call that SCI subjective cognitive impairment. Virtually all of those people show improvement

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Dr. Bredesen: Even though you can demonstrate that they have, they're early on the pathway to Alzheimer's. That can last 10 years. Then you progress to what's called MCI, mild cognitive impairment. Now not only do you know that there's a problem, but in fact the tests are showing it as well. You do a cognitive test, you're scoring very poorly on that and that is a precursor to Alzheimer's and about five to ten percent of those people convert to full-blown Alzheimer's per year. Most of those people show improvement on the approach that we designed. Then when you finally convert to full-blown Alzheimer's, some of those people show improvement. And we do have examples of people who had MOCA scores[17]. That's Montreal Cognitive Assessment scores of zero that improved. In fact, I just got an email this morning. There's someone who went from a three to 20 on there MOCA, which is dramatic improvement. But typically when we see people improving, they're improving typically five on their moca score. So they might go from 15 to 20 or from 20 to 25.

Emily: In what period of time is that happening?

Dr. Bredesen: So typically it takes three to six months to show improvement. Not always. Sometimes it's quicker, but in general, this is something that's been going on for years and so it takes some time to turn the ship around, no surprise and other people will continue to improve after a year or two. And so we suggest that people continue and we've had many people who will stop and then get worse. And typically it only takes one to two weeks to begin to note

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[15] https://www.omicsonline.org/open-access/reversal-of-cognitive-decline-100-patients-2161-0460-1000450.pdf

[16] https://www.nia.nih.gov/health/what-are-signs-alzheimers-disease

[17] https://www.massgeneral.org/neurology/assets/epilepsy/MoCA-Test-English_7_1.pdf

decline again when you stopped doing the right things that actually lead to improvement. Now again, if you've got full-blown Alzheimer's, if it's been around for a while, and especially if you are the type three which is the toxic type, these are the tough ones and fewer of those people get better. Some of them do, some of them don't.

Emily: And so you have three classifications.[18] I attribute this to you, so correct me if it's from somewhere else, but type one is inflammatory and you call it hot. Yes. Type two is atrophic, which is a lack of growth and cold type three is this toxic vile, and you tend to get that earlier, right?

Dr. Bredesen: It tends to be younger people. And then there's a type 1.5 which has both the inflammatory part and the atrophic part and that's because you have insulin resistance and glycotoxicity. So yeah, you can look to see whether people have mostly inputs and contribution from one or another thing.

Emily: But those aren't, it's not like cancer where those are, that's a progression. Or is it? Where you start type one and then you go to type two, type three, so forth.

Dr. Bredesen: That's correct. Yeah. So it's more about what's actually driving the process. Should we be focusing more on inflammation that's ongoing or is this problem that you don't have enough appropriate hormones and trophic factors and nutrients and therefore we need to address those things.

Emily: And so in terms of the treatment the notes I have sort of talk about a few different things, which I feel like would be really interesting to break down. So you have this idea of preventing and reducing inflammation, which it sounds like the primary way of doing that is to change your diet to be more of an anti-inflammatory kind of diet and probably reduce stress because we know that that has an inflammatory reaction too, and then optimizing hormones and growth factors and eliminating toxins. And if you wouldn't mind, I feel like we've talked a little bit about the reducing inflammation, but in terms of optimizing hormones and growth factors, like in a very sort of simple way where somebody's listening could actually go to the doctor and say like, I would like to have these tests done to know if my hormones are optimized or how my growth factors are performing. What are some ways that people can learn that about their own bodies?

Dr. Bredesen: Yeah, it's straight forward. You can literally do it online, direct to consumer, so you can actually get these tests or you can go to your doctor and get these things and get on the appropriate things. And just to finish the type one part, there are other things such as what are called specialized pro-resolving mediators[19] that help you to resolve inflammation. So again, for each of these things, if we don't make things better than the person is going to die. So this is a very significant issue. You want to pull out all the stops to make these things improve. You

[18] https://www.ncbi.nlm.nih.gov/pubmed/26343025
[19] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5242505/

mentioned the nutrients and trophic factors and hormones. So yes, you want to know, again, your doctor can check these things or you can get it done online. You want to know your various hormone status. You want to know your free T3 that's your thyroid status, your reverse T3, your TSH, you'd like to know your pregnenolone. That is the master hormone that's going to go both down the stress pathways with cortisol and down the sex steroid pathways. With things like progesterone and estradiol, you'd like to know your estradiol and your progesterone. All of these things are important contributors to your brain health and to your risk for cognitive decline and for progression of cognitive decline. You'd also like to know your vitamin D. Now we don't have a simple direct way to measure your nerve growth factor unfortunately, but we do have ways to increase your nerve growth factor[20] and to increase your brain-derived neurotrophic factor and as an example, you can increase your brain-derived, that's called BDNF[21]. You can increase this with exercise. You can increase it with something called whole coffee fruit extract[22], now available. You can increase it with something called 7,8-dihydroxyflavones[23]. So there are a number of ways to improve the situation there. You can increase your NGF with Hericium erinaceus[24], which is a lion's mane mushroom and there's actually an ongoing trial. I don't particularly like the idea of trials of monotherapies because you're not addressing all the different things that are contributing to the problem, but there are certainly these trials on these various monotherapies including Hericium, and they're ongoing. And then the Alcar which is Acetyl-L-Carnitine, another way to increase your nerve growth factor[25]. So there are ways that you can deal with these various deficiencies. These start with things like eating the right food, having the right prebiotics, probiotics, having a healed gut, all these sorts of things, minimizing your stress. All of these things are contributory. And then of course there's the whole issue of toxins. And unfortunately we swim in a sea of toxins every day and they come essentially in three varieties, metals and other inorganic toxins.So if we're exposed to mercury because we're eating high mercury fish, that is increasing our risk for Alzheimer's disease.[26] If we have high exposure to other metals such as iron or copper, that can potentially be a problem for our cognition. Secondly organics. So if we're exposed to benzene, toluene, formaldehyde. As an example, if you are exposed long term to paraffin candle burning, that is actually increasing your risk.[27] And then third are biotoxins. These are toxins that are actually produced by things like molds. So if you're working in a moldy environment or living in a moldy environment, now if you're lucky, you'll be living with molds that aren't producing neurotoxins cause many of them don't. But if you're unlucky, you're going to be living in a place that has stachybotrys or penicillium or aspergillus or chaetomium or wallemia. These are things that actually produce neurotoxins. And so again, you are increasing your risk for cognitive decline. So you could actually check these things. Certainly, Dr. Ritchie Shoemaker[28] has spent his career looking at

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[20] https://ghr.nlm.nih.gov/gene/NGF
[21] https://www.ncbi.nlm.nih.gov/pubmed/15518235
[22] https://www.ncbi.nlm.nih.gov/pubmed/23312069
[23] https://www.ncbi.nlm.nih.gov/pubmed/24022672
[24] https://www.ncbi.nlm.nih.gov/pubmed/18758067
[25] https://www.ncbi.nlm.nih.gov/pubmed/8187841
[26] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4789584/
[27] https://www.ncbi.nlm.nih.gov/pubmed/24318837
[28] https://www.survivingmold.com/about/ritchie-shoemaker-m-d

the effects of molds and mycotoxins and looking at ways to treat this successfully[29], whether it's causing cognitive decline or whether it's causing things like asthma or rashes or chronic fatigue or other things like this.

Emily: But the thought is that those environmental toxins are turning on underlying gene. Is that correct?

Dr. Bredesen: So they are changing that balance. We talked about earlier where you have literally a balance in your brain. Are you going to be able to upscale and make more contacts and keep the contacts you have. You've got over a hundred trillion contacts in your brain. Are you going to be able to keep these or do you not have what it takes to keep them unfortunately, and you're going to have to downsize. So yeah, this is what is determining that and all of these different factors are contributing to your ability to keep and maintain and produce new contact.

Emily: And then in terms of sort of getting a baseline, is there any recommendation for women to get a baseline before they're presenting any symptoms or is that not something that's relevant?

Dr. Bredesen: No, I think it's a very important. Nobody's surprised when someone says, you know, you should have a baseline mammogram or something like that. In fact, we recommend just as you should have a colonoscopy when you turn 50, we recommend that everybody get a cognoscopy if 45 years of age or older. So the simple way you can look at specific blood tests, the ones that we've just been talking about, and then some simple online cognitive assessment to see where you stand. Unfortunately, of course this is something that sneaks up on you. So there are many people who feel, well, I'm really here for prevention, but it turns out that when they're tested, they're already in the earliest stages and because it's happens very slowly, they haven't really noticed it. Now down the line they would have problems. So we recommend that everybody who's 45 or over get these basic tests, get a baseline, see what your hsCRP is, see what your pregnenolone is, see what your status with respect to fasting insulin. Do you have insulin resistance already? See if you've got various toxins that could potentially contribute to your future cognitive decline. These things are relatively easy to do and the reality is Alzheimer's disease should be a rare disease, and if everybody would do the right thing and get on appropriate prevention or early reversal, in fact, we could make it a rare disease.

Emily: You're sort of the rebel within the research field, it sounds like. Can you talk a little bit about what happened or why that has, why there has been this break?

Dr. Bredesen: Yeah, so I spent 30 years in the lab, so I'm a neuroscientist and neurologist by training and we published over 220 papers looking at what actually causes the neurodegenerative phenomenon. So when you actually look at the mechanisms, it leads you to

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29 https://books.google.com/books?hl=en&lr=&id=uLqBDwAAQBAJ&oi=fnd&pg=PT8&ots=EgN_L2Ew5T&sig=9ObEJJSSclXKXEREfSexWENYJkc

understand that these mechanisms. Just going from test tube to practice, translating what's the result from the test to it actually fits much better with what we call functional medicine[30] or integrative medicine or what professor Lee Hood has called P4 medicine.[31] This is 21st-century medicine. It's root cause medicine. It fits much better than it does with the kind of medicine I learned in medical school, which was 20th-century medicine. It's prescriptive medicine. You wait for problems to come up, you write a prescription, you send people home. That actually doesn't fit and that's why we're not seeing improvement. That's why it has been such a problem to find effective treatment for Alzheimer's disease. There's no prescription you can write that makes people better. I believe in the long run, the drugs are going to be very important. But on the backbone of personalized algorithmic programs where you're looking at, okay, here are the things that are the root cause. And so, okay, we began to publish starting in 2014. Here's something you can actually do about this. And we're publishing people who are getting better repeatedly. And we actually started this by trying to do the first comprehensive trial. And this was turned down multiple times by the institutional review boards that would not allow us to do a trial of more than one variable. But the problem is the disease is a disease of more than one variable. So yes, this is controversial and we've got a lot of people screaming and yelling at us because we're saying don't do things the classical route because that doesn't work. Writing up simple prescription for Alzheimer's does not work. But what we're doing is coming straight out of the research. This is what the research dictates when it comes to treatment of these complex chronic illnesses. And so the goal as you indicated earlier is to reduce the global burden of dementia and other complex chronic illnesses. So we're getting to work with people who have other neurodegenerative diseases as well. Again, looking at what's actually driving them. It's a little bit different for each of these than it is for Alzheimer's, but there are some similarities as well.

Emily: Well, and it also feels like, I mean, Alzheimer's is such a, I mean I'm sure any chronic illness is intensely personal, but there's something so important or beautiful about our memories that from a preventative stance, in some ways somebody might say like, oh, if you keep doing this thing, you're going to get cancer or you're going to get diabetes. Like that's awful. Right? But the idea that you wouldn't remember the people that you love the most in your life or you wouldn't be able to care for yourself from the perspective of your, of your mind, I think holds a particular sort of torturous quality, at least for me. And I wonder whether this idea that there is a prevention program right that maybe you're a 44 maybe you're a 33, you've had this genetic testing, which I feel like for a long time people said like, you know, don't get tested because for your genes, because there's nothing you can do and then you'll just be horribly depressed about the fact that you're going to develop this thing. And one of the things that I admire about your work is that I feel like you're saying, no, wait a minute. There are things you can do. So you have to get the knowledge first about where you fall in this sort of risk stratification so that you can take the appropriate measures to try to protect yourself.

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[30] https://www.ifm.org/functional-medicine/what-is-functional-medicine/
[31] https://p4mi.org/leroy-hood-md-phd

Dr. Bredesen: Exactly right. So as you said, Alzheimer's strikes at the very heart of what makes us human, which is why I went into neurology to begin with because this is what makes us human and what is taken away with Alzheimer's disease. So although you may be still Alice, in fact, you're not the same Alice, and ultimately you're not Alice at all.

Emily: What was the moment at which you realized that you were on to something with this?

Dr. Bredesen: So what happened was, I mentioned this in the first book, "The End of Alzheimer's."[32] So what happened was we had been doing this in the lab and in research, and I got a call from a woman in San Francisco who had a best friend who lived and worked for the government and lived in Washington and who had been diagnosed with Alzheimer's and was actually going to commit suicide. And so the woman in San Francisco, who was her friend, called me up and said, would I see this woman? I said, well, I'm a researcher. I haven't seen patients in 20 years. We had just been turned down for the trial. And so I said, you know I can tell her what we were going to do on the trial, but that's all I can really do. So she said, well, yeah, if you could please just do that. So this woman came out, we spent two and a half hours.

Dr. Bredesen: As she said in her story, she, you know, she wrote this stuff down because she couldn't remember anything at the time. She couldn't remember, even four digit numbers, couldn't do her job, et cetera. So I said to her, look, you know, we're not going to be able to do the trial and we were going to do, but I can tell you the background, I can show you how the research, what it showed us, how this, what I see as a beautiful balance occurs and why all these different factors contribute to it. So she wrote all this stuff down, took it back. I thought I would never hear from her again. Three months later, Saturday morning at my home, this is now July of 2012. I got a call from this woman. She said, I can't believe it. She said, my memory's better than it's been in 30 years. I'm back at work. I'm doing great. And I just kinda, my jaw dropped and I looked over at my wife and I said we were on the right track cause we didn't know. We could make mice better with mouseheimers[33]. But that was the first human, so we call her patient zero. And she hadn't stuck to the program, if she hadn't been diligent, which she really is. If she hadn't been a detail-oriented person, which she really is, we wouldn't have known and we wouldn't have been able to help all the other people.

Emily: Well, and what an incredible sort of coincidence in terms of time or serendipity, I don't even know the right word for it. But that you're going through this sort of moment of failure or feeling frustrated and a stalling out of the trial being rejected and then somebody comes to and basically allow, you know, gives you the opportunity to test your hypothesis out. That feels like divine intervention or some sort of bigger thing, doesn't it?

Dr. Bredesen: I couldn't agree more.

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[32] https://www.amazon.com/End-Alzheimers-Program-Prevent-Cognitive/dp/0735216207?tag=theultheapo05-20

[33] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3972274/

Emily: And so I want to talk a little bit about genes and I think that APOE[34] is probably something that some of our listeners will be familiar with, but the vast majority probably won't be. So just as like a sort of overview, everybody gets a copy of this gene from their mom and one from their dad and you can have two, three or four, right? There's no one.

Emily: And if you have two copies of four, you are, it's like 15 times more likely.[35] Is that right–

Dr. Bredesen: That's right.

Emily: –to develop Alzheimer's and 33 is the most common, but that doesn't mean that you're safe basically. Right? 44 doesn't even seem conclusively to be a predetermined that you will get it, but it just increases your likelihood. And there was something somebody had said to me, which they attributed to the right person and now I'm not gonna remember, but that when you think about genes, if you think of it as like your genetics or your sort of what you were born with is loading the gun, but it's your environment that pulls the trigger. I think that sort of perfect in terms of we can talk about like BRCA1 or other genes where there is a high likelihood[36] that you may develop it, but it's really that there's something in the environment that's turning it on. Can you talk a little bit about this in terms of Alzheimer's? Like what are some of the environmental things that people could be aware of just in terms of overall health that you sort of think like if you are a 44 what are some really important sort of tangible things you can do in your life?

Dr. Bredesen: So the analogy you made is a very good one. And in fact, as you know, BRCA1 has turned out to be an important risk factor recently, but it's turned out, if you look at the old cases decades ago, BRCA1 was much less of a risk factor, again telling you that it's a lot about the environment. And so the same thing is true as you indicated, you have zero copies of APOE4 and that's the three-quarters of the population. Zero copies of APOE4 your chance is about 9% through your life. It's not zero, but it's not high. If you have a single copy, it's about 30%. If you have two copies, it's well over 50% but none of those is 100% and none of those is 0%[37]. so it's a fascinating story in that APOE4 essentially appeared with hominids five to seven million years ago, a single change at a specific amino acid, amino acid 61, which is not present for example in chimps is present in humans.

Dr. Bredesen: And we were all APOE44 for 96% of hominid evolution. It's only been in the last 220,000 years that APOE3 appeared[38], which is now the dominant one. And then just in the last 80,000 years that APOE2 appeared. So unfortunately a quarter of the population, so about 75

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[34] https://ghr.nlm.nih.gov/gene/APOE
[35] https://www.ncbi.nlm.nih.gov/pubmed/9343467
[36] https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet
[37] https://www.endalznow.org/news/the-role-genetics-will-i-get-alzheimers-disease
[38] https://www.amazon.com/End-Alzheimers-Program-Prevent-Cognitive/dp/0735216207/ref=sr_1_1?ie=UTF8&qid=1501612928&sr=8-1&keywords=recode+bredesen

million Americans have a single copy of APOE4, they're at about 30% risk. And then about 7 million Americans have two copies and they're at well over 50% risk. So it's important to know what you have and to get on appropriate prevention. Now what do I mean by that? We several years ago published that there are different subtypes of Alzheimer's. So you can look at the different subtypes and type one is inflammatory. So APOE4 is actually a proinflammatory gene. And Professor Tuck Finch[39] from USC has argued that in fact, having APOE4 helped[40] by early hominids to come down out of the trees. You walk on the savannah, you puncture your feet, you get wounds, they're full of bacteria. You eat raw meat, you're exposed to all these microbes. So having a proinflammatory gene like APOE4 was actually quite a good thing. But of course, long term inflammation is associated with heart disease, is associated with Alzheimer's disease and shorter longevity. And all these things have been associated with APOE4. So we want to be, we want to have a less inflammatory lifestyle. And there's a wonderful website, APOE4.info[41] in which people share their protocols. And many of them are on the protocol or the variation of the protocol that we developed a few years ago.

Emily: So I happen to have somebody in my life who is following these protocols very carefully. Her mother was diagnosed with Alzheimer's about two years ago and shortly after that she did the genetic testing and found out that she has two copies of the APOE4 so she's at an incredibly high risk to develop this and is taking a really proactive stance on it. Sandy is one of the managers who works for me at a company called Prime Fitness and Nutrition, which are wellness centers specifically dedicated to the health and wellness of middle-aged women. I own three of them. It's not something we're going to talk a lot about in the podcast because it's not always relevant, but in this case it definitely is. Sandy, will you just explain to us a little bit about what in terms of Bredesen's protocols you've been following and why?

Sandy: I did the research on Bredesen made a list of the things I felt were very, I could shift and have followed that pretty strictly. So as far as food goes, I eat a very anti-inflammatory, low glycemic diet. I tried to keep my blood sugar as even as possible by not eating things, not eating anything processed, anything in a powder form, any, if I can't read it, I don't eat it. So it's essentially whole foods I've taken out sugar, dairy, wheat, alcohol, grains, legumes and processed soy. Which is essentially the whole, I stay on a Whole 30[42] type protocol. And when I go off, I go off with stuff, exactly what I want. So I don't feel deprived. But if I have ice cream once every two years, I'm having the hot fudge brownie, I stay hydrated. I sleep as much as I possibly can. I'm working on moving into seven hours. Six is, six and a half is about where I sit.

Emily: Is that just natural your whole life you've been like that?

Sandy: No. I can survive on very little sleep.

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[39] https://gero.usc.edu/faculty/finch/
[40] https://www.pnas.org/content/107/suppl_1/1718
[41] https://www.apoe4.info/wp/
[42] https://whole30.com/

Emily: Okay.

Sandy: Very little sleep. And that's not necessarily a good thing.

Emily: Yeah.

Sandy: But it wasn't until recently that people stopped, you know, or even stop to think about when they said stuff like, I'll sleep when I'm dead. So as far as lifting weights, I'm very conscious about, you know, about weight training three times a week, not only to keep my muscles strong and my bones strong. But also there's been lots of research that associate quads and brain and memory. So, I even if it's– I make myself lift weights three, four times a week. I do intervals probably four or five times a week. Again, brain research has said that that's to clear out the tau tangles and the amyloid plaque and

Emily: And so that's like on a treadmill running?

Sandy: On a treadmill outside on a bike. You know, so I'm huffing and puffing, you know, so I can't speak. And that's different than going out for a jog. That definitely changed once I read Bredesen stuff. And I keep my weight where the BMI is in a safer zone. I have to say I've never been a 33 BMI, but I'm much more conscious of that being a factor, you know, as far as inflammation, having problems.

Emily: And then in terms of the women that you care for at Prime, do you feel like there is like a general awareness that women do have the potential to kind of curve this or starve it off or prevent it by doing the right things? Like, I'm sure that's a big piece of what you talk about with them, but when people come in, do they have any sense of that?

Sandy: No, I think that the idea of fueling versus eating food is a learning curve. And I feel like fueling goes along with good health because it's never any one Thanksgiving or one ice cream sundae with a brownie. It's what do you do day in and day out? What do you layer in your body every single day and what are your longterm goals? Sure. People come in here, women come in here to lose weight, but you constantly hear I know what to eat but I'm just not doing it. And to untangle some of that shame and habit and give them a whole nother hill to look at versus the same old scale hill. Information is the key to that. And getting women to think about how does their body respond to sugar? How does it respond to dairy? You know? Sure, losing weight is a byproduct of good health, but most of the time as I stated before, women come in here and we talk a lot about staying as active as long as they possibly can. A lot of women don't want to be left in the ski lodge babysitting their grandkids. They want to be out there skiing.

Emily: Right. Right.

Sandy: So as long as they can do that. A lot of women come in carrying extra weight and that has an impact on their joints. And it does sometimes take a long time to talk about, forget about

food, but you know, talk about the impact of weight and motion and hydration on what they're doing and then getting to inflammation. It's a hard conversation.

Emily: We're going to go back to Dr. Bredesen and ask him why these protocols are so important.

Dr. Bredesen: So number one, anything that produces longterm systemic inflammation. That can be leaky gut and it's an important thing to know whether you have leaky gut, it can be because of poor dentition. It can be because of poor food choices. Can be because of undiagnosed chronic infections like Lyme disease or tickborne coinfections, bartonella, babesia, anaplasma, ehrlichia, on and on. It can be because of exposure to various mycotoxins that are inflammatory. Anything that is chronically inflammatory.

Emily: So for people that would be like a CRP test or C-reactive protein[43]?

Dr. Bredesen: Get hs-CRP, you can get on appropriate diets to decrease your inflammation, treat what is inflammatory, et cetera. And then second thing is insulin resistance. So you want to know your hemoglobin A1c.[44] You want to know your fasting insulin[45] and [?] it would also be nice to know your fasting glucose[46]. Those three things. Simple to do. Very important to know. Most people are insulin resistant. It's very common. About 80 million Americans are insulin resistant,[47] incredibly common. You're probably aware of this new thing called the FreeStyle Libre. [48]I have nothing to do with that company, but it's helpful to chart your glucose for two weeks and it's noninvasive. You basically stick it on your arm so it doesn't require repeated blood draws and you can actually track your glucose and people are shocked to see how it goes up when they eat certain things, how it actually can go too low at night sometimes. So very helpful–

Emily: So is that like a continuous glucose monitor?

Dr. Bredesen: Yes, it is. And so you can get an idea of where things stand. You can find out about insulin resistance and you can treat insulin resistance with, again, appropriate diet, appropriate exercise, et cetera.

Emily: I mean, I think the other thing that's a big factor in that that people don't realize, I mean I think we all know about the diet or most of us know about the diet factor, right? And that eating carbs and sugar are going to make you more prone to insulin resistance than eating fat and protein. Is that your feeling on that?

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[43] https://medlineplus.gov/lab-tests/c-reactive-protein-crp-test/
[44] https://www.mayoclinic.org/tests-procedures/a1c-test/about/pac-20384643
[45] https://labtestsonline.org/tests/insulin
[46] https://labtestsonline.org/tests/glucose-tests
[47] https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.html
[48] https://www.freestylelibre.co.uk/libre/

Dr. Bredesen: Yes. Again, there are, there's a little more to it than that in that if you eat too much protein, you will also drive up your glucose too high[49], unfortunately. And if you eat the wrong kinds of fats, so the idea of let's go out and eat bacon we'll be healthier. That's actually not true. Too many nitrates, it's actually not– so what you really want is a plant-based or plant-rich, ketogenic, mildly ketogenic diet with a [?} fasting times. So yeah, so we have something we call Ketoflex 12/3 which turns out to be appropriate for brain health. So yeah, there's some things you can do absolutely around diet. Fasting itself is very important. Exercise turns out to be incredibly important. Again, each one of these things by itself is no cure for Alzheimer's disease. Of course not. But getting the appropriate coordinated program turns out to be very powerful.

Emily: And so with the fasting, we can talk a little bit about the idea of autophagy.[50]

Dr. Bredesen: Autophagy is a way to clean things out. You are recycling the batteries, for example. You are recycling your Mitochondria, you're breaking things down. You have lysosomes inside your cells that are breaking down damaged proteins, damaged lipids and things like that. So yes, you're right. That is a healthy thing and thing that gets turned on during the process of fasting. So you want to fast 12 to 16 hours between finishing dinner and starting breakfast, brunch or lunch and you want to fast for at least three hours between finishing your dinner and going to bed.

Emily: And how many days a week do you recommend that?

Dr. Bredesen: So for that kind where you're simply doing it intermittently, you can do that everyday of the week. Now some people, you're right like to do more fasting where you do it for an entire day or you do every other day eating and that you can do, you know, a few days a month. And in fact there's a fasting mimicking diet from professor Valter Longo[51] where they typically recommend five days per month. So you can get some benefits from just doing this a few days per month. What we're talking about is simply having time between finishing dinner and starting breakfast, which gives you time for autophagy.

Emily: And is that the same for women as it is for men? Because I know anecdotally the longest fast I've ever done is six days, but I have definitely found that I start storing fat. Like my body fat percentage will go up after I have fasted and my husband does not have that response.

Dr. Bredesen: Yeah that's really interesting. So first of all there is a difference in your genetics. So in fact for APOE4 negative people, 12 to 14 hours is good. For APOE4 positive, because they are better fat absorbers, then they should go a little longer and it's typically 14 to 16 hours. Yes, you are correct. You know your body recognizes this and ultimately does store some fat.

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[49] https://www.ncbi.nlm.nih.gov/pubmed/22139560
[50] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3106288/
[51] https://stm.sciencemag.org/content/9/377/eaai8700

So what we recommend is that people about once a week or so cycle, so liberalize a bit, especially if you're on the thin side. You want to liberalize once or twice a week, have some things like sweet potatoes and things like that. And it's interesting you mentioned that women tend to store a little more fat. Yeah, although certainly many of us guys do store fat as well. It does tend to be determined by the protein you're eating by what your testosterone levels are and things like that.

Emily: So I wondered, what did Dr. Bredesen think about this ethical debate about whether people should get tested or not?

Dr. Bredesen: Everyone's been sticking their heads in the sand saying, don't tell me about my APOE because I don't want to know because there's nothing I can do about it. No, there's a tremendous amount. The armamentarium for Alzheimer's disease prevention and especially early reversal, which we've been told is nothing, is massive. It has to do with all the things we've talked about today. These things all impact your synaptic formation. This is essentially "synaptoporosis.[52]" Just like you would get osteoporosis and fight it, this is synaptoporosis. An imbalance in synaptic production versus retraction. So yes, we'd like everyone to get involved with prevention or early reversal and let's all reduce the global burden of dementia.

Emily: And so then are there things that you've come across sort of like that that were, I guess, stigmas in the culture that you feel like have an impact on the treatment of this disease?

Dr. Bredesen: When you mean stigmas that have an impact on that treatment, what do you mean?

Emily: Well, I mean I guess are there generally we could say like are there things in the course of your work that have really surprised you about the way that we've approached this problem or that have surprised you in the treatment of the program?

Dr. Bredesen: Oh my gosh. Repeatedly. So one of the things that surprised me the most is I went into academics because I saw academics as the place for ultimate truth. The truth wins out as Feynman[53], the brilliant physicist, said "nature cannot be fooled." So ultimately it can't be about politics. It's going to be about nature. And the shock to me has been to see my colleagues ignore and deny what is right before them. That in fact people are getting better. The response is typically been well we want to see a big trial. Fine. Well, there's a catch 22. This started by asking to do a trial and having the trial to turn down repeatedly because it wasn't a single drug trial. So in fact, just ignoring the data. If you look at the data, what you see is that this is a complex illness, that there are many things that contribute to it and that in fact, you can address it with many pieces that include all the things we've talked about. One of the surprises to me was to see how important ketosis was. I did not believe in that at first. I did not believe in a

[52] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4712873/
[53] https://www.nobelprize.org/prizes/physics/1965/feynman/biographical/

number of things that have turned out to be surprising to me, like telling people that meditation was helpful as a scientist, I thought meditation was a joke. In fact, it turns out it affects neuroplasticity, it affects blood pressure, it affects stress. It's remarkable how important meditation is.[54] It's remarkable how important joy is, how important sexual interaction is. All the things that we kind of knew as kids or as younger people, but as scientists, you tend to forget these sorts of things and your focused on one molecule. I had told my wife, my wife is an integrative physician. She had told me when we started this research years ago, whatever you guys find, it's gonna turn out to have something to do with basics like what you eat and how much stress you're under and things like that. And of course, I laughed at her at the time. I said, no, we're going to find one molecule in one domain, one region within that molecule, and we're going to get a drug against that and everything's going to be great. Well guess what? I should have listened to my wife all those years ago, three decades ago now. She was absolutely right. I could've saved myself a lot of time in the lab. So it turns out that when you actually trace the molecular pathways, what do they come back to? They come back to your stress levels and your gut. But the interesting thing is there's this whole new area of medicine, functional medicine [55], where people are looking at root cause. They're finding things like, hey, guess what? It's important that you have a gut leak. Guess what? It's important whether you had kimchi and whether in fact you have an appropriate microbiome[56]. So the cool thing is the science is coming together with this new medicine and it's showing us that the old fashion medicine simply, it's telling us why it doesn't work. The patients see it, they go into the standard doctor. The doctor doesn't do much for them. I always say telling someone that they've got Alzheimer's is like telling someone that their car isn't working because they have car not working syndrome. It doesn't tell you why the car is not working. You need to measure these various variables to be able to know why you got it. So it's been shocking to me to see that what we used to call quote alternative medicine is in fact a thing that lines up much better with the basic science than standard of care medicine. So when it comes to Alzheimer's, it's of course been no alternative medicine because there's no alternative. And so following the chemical pathways, the metabolic pathways, the biochemical pathways, these are the things that are actually showing us what to do and we see striking examples time and time again, that's been the most exciting to hear from people. And actually we have a book that's going to come out later this year that has five different people who all write in first person what it felt like to be told that they had Alzheimer's to have no hope and then what it felt like to get better. So it's wonderful to hear these stories. I can tell you about Debra. She's one of the people who actually wrote a wonderful first person story. And so she's someone brilliant who was an attorney and her father and grandmother both died. Her grandmother died of Alzheimer's. Her father died of Alzheimer's and she watched both of them decline. And her father actually told her early on in his own situation, I know what I have and there's nothing anyone can do about it. And so when she began to have similar symptoms and she documented them beautifully, problems with recognizing faces, problems with mixing things up, problems with having trouble coming up with the right word. She could actually speak a couple of foreign languages. She lost those. She had been able to play the piano. She lost the

[54] https://www.ncbi.nlm.nih.gov/pubmed/26445019
[55] https://www.ifm.org/functional-medicine/what-is-functional-medicine/
[56] https://www.ncbi.nlm.nih.gov/pubmed/27634977

ability to sit down and read music, all of those things and went actually to a major medical center on the east coast where they tested her and her tests were already abnormal, so by definition she would be in the early stages of NCI. She actually heard about our program through her sister in law, started it and then wrote to me and told me how much better she had gotten after several months. Then went back to the university center where they tested her again. They asked her, what the heck have you been doing and her tests are all now normal. She's now several years into this doing extremely well and continuing, as people do, continuing to tweak to optimize things. Again, that's another thing that's different from standard medicine and you don't just give up after the beginning. You continue to tweak things. So interestingly, what happened with her, she visited a place that happened to have a piano and sat down and was able to play once again. So she got back the ability to read music, which she had lost and she was really surprised and really excited and she plays all the time now. She also began to get back some of the languages that she had lost. She said she was driving and suddenly all of these words started flooding back. So you can kind of actually imagine the synapses beginning to work again within her brain. So things that you know, we tend to think that you get back the ability to learn new things. But in fact some people also get back the ability to do things that they thought they had lost, things that they had learned when they were younger, like playing the piano or speaking foreign languages. So it's a beautiful story. And the thing that was exciting to me is that she's now stopped this, this was in her family line. It is no longer in her family line. She won't get it. Her children won't get it because they will do the right things ahead of time to make sure that they don't get it.

Emily: So just as Dr. Bredesen just explained to that one patient, the fact that this is something that you could end for yourself and for the rest of your family feels so significant to me. It's about 15 million Americans who are caring for somebody with Alzheimer's right now. Two thirds of those are women, female caretakers mostly taking care of family members. The out of pocket cost of that is estimated to be around $259 billion with projections, putting in at $1.1 trillion[57] out of pocket for these families within the next 10 years or so. And so it begs the question, if there's something that you can do about it, both for yourself and for the people that you're caring for or for the people who will have to care for you, why would you not do that? So as always on Empowered Health we're trying to get good information out to women so you all can make the best decisions for your lives possible. And I think the Bredesen Protocol is something that's not so crazy. It's not like you have to, you know, overhaul your entire life. Like yes, there are definitely modifications that you'll have to make. But when you think about how hard it is to care for somebody with this disease and how devastating it can be, we're going to have sandy talk a little bit about how since she's become the primary caretaker for her mom, she has help from her siblings, but she's over there a lot. And she's sort of seeing this, you know, the degeneration happen right in front of her. She's doubled down on her commitment to following these protocols and really leading a sort of anti-inflammatory life because she doesn't want her kids to be in the position that she's in right now.

[57] https://www.alzheimers.net/resources/alzheimers-statistics/

Sandy: But there's different stages of Alzheimer's, you know, without going to the textbook that, you know, that we've experienced. She's still living on her own. We have people go in and work with her, but she's very physically fit. So she can go out and walk about and do everything in her house. She no longer drives or writes checks or manages her household, but she does have people come visit her and there's days that she's really happy and then there's days that she's sad. She spends a good amount of time really angry at the people that take care of her. So, without remembering what's happened, like for example, her and I went to the lockbox at the bank and put all of her significant jewelry in there, but she won't remember that. And so she'll call me saying that she's going to call the police because I've stolen her things. And that she's really disappointed in how devious I am at stealing all of her things. And then I have to call the police to make sure that Scott knows that my mom– see, I'm even on first name basis with the police in Concord– so that my mom may call. So she's not a threat to herself and she's not in a dangerous situation right now. She barely cooks and we bring her food. So, but it's occasionally she'll snap out of the anger piece and she'll get to sadness of, sorry that we have to spend so much time. But most of the time it's just she's unaware of how she has really three out of the four siblings circling her at all times to arrange things to make her safe, to tell caregivers what's going on, alerting the police to paying her taxes, etc. Just to visit the joys for a second. There are a lot of joys, but it involves getting out of the present minute. Like I've learned more about my mother and her experience during World War II then I ever, ever heard about my entire lifetime. You know, the happy things she forgets too. So if you bring her flowers for example, which I do every time I visit her. Well I bring her flowers once a week cause they last. And if she starts to get frustrated or specifically angry at me for taking away her license, which I didn't do, but she gets angry anyway, I'll simply turn the conversation to the flowers because they make her really happy, you know so, and she'll go "oh, thanks for bringing the flowers." And she could sing that like 20 times in an hour and a half. So the joy is not remembered as well. So that's, that comes up again and again, not just the anger.

Emily: I'm Emily Kumler, and that was Empowered Health. Thanks for joining us. Don't forget to check out our website at empoweredhealthshow.com for all the show notes, links to everything that was mentioned in the episode as well as a chance to sign up for our newsletter and get some extra fun tidbits. See you next week.