CUTTING EDGE Health

Welcome to the Cutting Edge Health Podcast with Jane Rogers, where we discuss science to help prevent cognitive decline.

Jane: I listened in 2016 to a podcast where Dr. Dale Bredesen was interviewed. I'd never heard before the ability to prevent and even reverse Alzheimer's. It was an aha moment that changed my life. I already had subjective cognitive impairment, SCI as it is called, at 54 years old, the same age as my father's symptoms. He later passed with Alzheimer's. I was scared, and Dr. Bredesen provided me with a lifeline. I did everything that his book, *The End of Alzheimer's,* said that I should do and it worked.

I'm incredibly grateful that now six years later, I'm able to launch my own podcast to help others do the same thing that I just did. I'm honored to have as my guest today, Dr. Dale Bredesen, an internationally respected researcher into the causes of neurodegenerative diseases. He's a *New York Times* bestselling author with three books. *The End of Alzheimer's, The End of Alzheimer's Program* and *The First Survivors of Alzheimer's*.

He's currently the Chief Science Officer at Apollo Health, and he's a professor at UCLA. I broke the interview into two parts. He's got that much to say. Here's part 1. I beat Alzheimer's in large part because of you, because of your research, because of your willingness to share with everyone. What you've done changed my life. There just aren't words to express how much I appreciate what you've done. Thank you.

Dr. Bredesen: Thank you so much, Jane, and thank you for mentioning that. There is nothing that makes my life better than to hear about people who had, what was otherwise, a terminal illness and who got back to their families, and back to their lives, and back to their happiness, and back to their future. That's why I wrote the book *The First Survivors of Alzheimer's,* and it had seven people who gave their wonderful stories in there. It's really heartwarming to see that. That's really what 30 years of research in our lab was all about, let's find a way to attack this.

Jane: Well, I read the book and I could relate to all the examples, all the people who shared their stories. I thought, "Oh, that's me. That's me." As I'm sure many in our audience right now are feeling the same way.

Dr. Bredesen: Thank you.

Jane: 800,000 Americans have died, approximately that many, have died so far from COVID-19. I have heard you say that of the currently living Americans, we're going to lose 45 million to Alzheimer's.

Dr. Bredesen: Yes. About 50 times.

Jane: It's scary. Just, just scary. We had a vaccine for COVID-19. We finally were able to have a vaccine for smallpox and one for polio, but a vaccine and a pill are not on the horizon for this disease. Are they?

Dr. Bredesen: No. The fundamental problem here is that we understand what a virus is. We have sequence, we have the variance, we know about Omicron, and we know about Delta and all these different things. It's a simple illness. You get it, it starts to replicate, and you have to do something about it. You can target that problem. Now, of course, we know that the immune system is important.

People realize, "Oh my gosh, I got to get my zinc right. I got to get my vitamin D right. I got to get my glucose right and all those things, because my immune system has to work right as well." In general, it's about the virus. Alzheimer's is completely different. There has never been, as you know, agreement about what Alzheimer's represents. There are dozens of theories. You've heard people say, "It's type 3 diabetes. No, it's all about herpes in the brain. No, it's all about P gingivitis from the dentition, which is getting into the brain.

No, it's all about reactive oxygen species. No, it's about preon. It's about TAO. It's about amyloid." There has never been agreement and most importantly, all of the treatments that have targeted these various things have failed. It's critical, as you understand, it's critical to have an understanding of this that is predictive of treatment. Whatever your theory is, it has to make sense. It has to make sense with all the epidemiology.

There are over 150,000 papers published on this illness. It's got to make sense with the epidemiology, the microbiology, the pathology, the genetics, all of this, and nothing has done that. Therefore, as you know, one drug, one drug, one drug, it just hasn't helped this disease. Now, Jane, imagine for a minute that you just bought a driverless car. That's the future we're going to be. You're going to be using driverless cars.

Imagine that you just bought one and now it's just not working right. It's not braking correctly. It's hitting people when it shouldn't. It's just not working right. It's stopping when it shouldn't stop, et cetera. You take it in, and you say to the mechanic, "You got to help me. There's something wrong with this very complex driverless car." He says, "Well, we'll fill it up with some gas, and then if that doesn't work, we'll fill it up with a different kind of gas."

It's like, "No, it's a more complicated system." That's what's going on with our brains. We have a very, very complicated brain that has nearly one quadrillion connections

inside your beautiful brain, and yet we keep going after these with one small molecule, "Okay, let's try this drug. Let's try that drug. Let's try this drug."

The brain is not that simple. The bottom line here is you need to understand this is network medicine, and you need to understand the players in the network, and then you need to go after them. It's a little different for each person. That's the future.

Jane: Now I know this works, because it's worked for me, but the exciting thing is I've read about the research trial, the clinical trial, you were just able to do. Results were highly successful last year. One of its kind, because you had, instead of, "I will test this drug," you said, "No, I'm going to test a whole number of multi variables. What's your inflammatory load, what's your blood sugar level, what do your hormones look like?"

All those things. When you are able to include in a clinical trial all those different parameters to help the person individually, precision medicine, you found this really works, didn't you?

Dr. Bredesen: Yes. 84% of the people actually improve their scores. It's important to point out in the drug trials, they're not seeing improvement. They're trying to look just at slowing the decline, and even that is barely working. In the best-case scenario, there was a 22% slowing in this drug that there was such controversy over recently, and understandably so. In our trial, you're actually seeing improvement in cognition in 84% of the people. That's unheard of.

It's because each of these people is looking at, as you said, is there insulin resistance? What's the status with the glucose? What's the status with inflammatory burden? Are there specific pathogens? Have you changed your gut microbiome, which is critical? On and on and on. All these things are critical. What's your vascular status? Part of the equation here is that you have to have appropriate energetics.

In our research lab, when we looked at what Alzheimer's is, what is the fundamental nature of this disease? It's not a viral infection. The fundamental nature of this disease is that it is a network insufficiency. In other words, you're not supplying enough energetics, whether it's because you have sleep apnea, or whether it's because you have poor mitochondrial function, or whether it's because the blood flow's not there. Whatever it is, it's energetics, it's trophic activity, it's toxins, and it is your various pathogens and inflammation. Those are the big four things.

If you can optimize each of those, as you're doing, you get tremendous results, and in fact, Dr. Heather Sandison, who's one of the practitioners who's doing a great job down in San Diego and has opened a wonderful assisted living facility called Morama, and now a new one called Solcere, as she points out when people do the right things, you

target the right things, you do have them do the right things, virtually everybody gets better.

Jane: You are going to expand that clinical trial now. You did 25 people in this first one. Now you're stepping up and saying, "We want to do a bigger one with 100 folks."

Dr. Bredesen: Jane, when you're trying to do something different, and when you're actually going after the way this works scientifically, what you find is that there's such backward thinking about it. Everyone is stuck with what drug you are going to use, et cetera. We went a few years ago to the IRBs. First of all, we were turned down in 2011 by the IRB. They wouldn't even let us do this trial, because-

Jane: I remember

Dr. Bredesen: -they're saying you're doing something that is more about a network instead of about one drug, and that's the way trials should be one drug, which is really crazy for this disease. We finally got them to approve it. It took all the way till 2019, but they said, "Well, you first have to do a proof of concept. You can't do a control group. You're just going to look at historical controls."

That's what we did, we got very good results that supported this next upcoming trial, which now is looking at a randomized control trial where we'll have people who do the standard of care for nine months, delay and then will be able to start the program at the end of the nine months, versus people who started on day one. We're very excited about that.

Furthermore, as you know, this field is continuing to progress. [coughs] Excuse me. There's a tremendous amount that can be done and people will be able to do testing and treatments that were not available even a year or two ago. Things like looking at epigenetics for their biological age, for their biological brain aging, which will be really exciting.

Looking at phosphor-tau within the blood that was not available before. I think we'll have better and better looks at what's actually driving the illness in these people.

Jane: I want to talk to you further about the things that you're seeing, the future of what's exciting, but one other question before we leave this. We now know through your trials that this is successful, and I'm sure this is the question that keeps you up at night, how can we roll this out to more people? How can we make it maybe just a little bit easier, because you really have to be motivated to do it?

I don't often find people as motivated as we need to be to get this done. It's a lifestyle change, it's important, but it really takes some effort. Critics say it's expensive and difficult, how can we roll this out so that all of my neighbors can participate?

Dr. Bredesen: This is such a great question and you're right. My wife, who's a functional medicine physician, and I discuss this all the time. She always says, "You have to Apple it, you have to make it straightforward." Here's the thing, that you can't make it so simple that it doesn't work. This is a complex problem. Your brain has complex issues, and you have to identify those, step one, and then you have to address those, step two.

On the other hand, if you make it so complicated, you're going to hit all the things but as you said, you're only going to have a few people who will actually do these. The way to go is a tiered system. Let me just take one moment and address your point about expense. Here's the point, the drug that just came out originally was $56,000 per year plus additional scans et cetera. It was going to end up being about $100,000 per year. Now they have-- [crosstalk]

Jane: It doesn’t work. [chuckles]

Dr. Bredesen: That doesn't work. It's going to still cost about $50,000. $50,000 a year for something that causes brain swelling and brain hemorrhage and doesn't work and just, unfortunately, killed someone a few weeks ago. Probably I should say it was associated with death in someone who used it. This is a huge problem. If on the other hand, you don't do anything, and you go into a nursing home, then you're going to spend about $100,000 a year on a nursing home.

Now the average person who develops Alzheimer's spends $350,000 by the time they pass away. It's a horrible expense. It's the most expensive problem in terms of health in the country. What we're doing, yes, it's expensive. It is less than 10% more like 2% to 5% of that. Actually, it's a good financial investment if you look at it that way.

Jane: Oh, that’s a good way to put it.

Dr. Bredesen: Yes, it's going to cost you hundreds of dollars. The typical initial evaluation is close to $1,000 to look at that. Again, compared to $100,000 this is really helping you, and it's going to give you a much better outcome so you do need to look at this. This has been one of the problems because we're so used to being told there's nothing you can do, people just say, "Well, I'm not going to try."

Well, if you take this seriously and actually make this a high-priority item, then just as you've indicated, people do well, and we hear about it all the time. That's the goal. Now

in the long run it’s going to be a combination of some targeted drugs, a few, plus an overall precision medicine type or functional medicine or networks systems medicine. Network medicine protocol that is personalized. That's going to be the goal.

We have to get everybody thinking in the same way to make that understandable and that's the way things are going. As people say, to some extent, "We're building the plane as we're flying it." That's always the tough thing, because you're trying to enhance this just as you say. Now I do think the future is going to be a tiered system. Here's what will happen for public health, anyone who hits 45 you get evaluated, you get a cognoscopy as we say.

You're going to look at just as we all know when we turn 50 we should get a colonoscopy. 45 or 50, we should get a colonoscopy. If you hit 45 or if you're already past 45, please get a cognoscopy. That's easy to do, it's a set of blood tests, it's an online cognitive assessment which takes about 30 minutes, very easy. Then if you already have symptoms where you're scoring poorly on the test, please also get an MRI with volumetrics.

If you're not, don't worry about it, you don't have to do that. You’re going to get this initial thing and get on active prevention. 90% of the people will never have a problem if they're on active prevention. By the way, we've never had a single person who actually did the prevention, who started out when they were asymptomatic, and yet still developed dementia. The problems are when people don't do this then you keep going, and you keep doing the wrong things.

Ultimately, and then people will say, "Well, I'm going to put it off because it's probably not Alzheimer's." Then the doctor says, "Well, oh sorry, it's Alzheimer's, there's nothing I can do." That'll take care of most people. Now, a small percentage of people will then say, "Oh, wait a minute, I am beginning to have some problems," or, "I haven't done enough." Okay, now we take the next tier. Those people will have a little more extensive testing. They will work with a health coach and a physician who's trained, and then do the right things.

These are the people who are just beginning in this second phase which is called SCI, Subjective Cognitive Impairment. A very small number of those will then continue to progress. Okay, they need to have additional and then the ones that continue to progress need to go actually into the hospital for a couple of days and look at, "Okay, what is being missed here?" What we find is that when people are continuing to progress, either something is being missed, or they are not doing the right things.

They are not getting themselves into the right biochemistry for making and maintaining new synapses. As a simple example, I'm sure you know Julie Jean. We've worked with

Julie for years who is APOE4/4. She's in a very, very high-risk group. The vast majority of people who are 4/4 are destined to get Alzheimer's if they don't get on active prevention. She already had symptoms, she did very, very well.

After several years she was now getting a little worse, it turned out we said, "Well, something's being missed," started doing additional testing and it turned out she had an undiagnosed babesia infection. When that was treated, she did very, very well, and she went from 35th percentile to 98th percentile. She wrote a significant part of the second book with me. She's just an amazing and brilliant human, a real citizen scientist. She's a great example.

This is the sort of thing we see again and again and again. I think that's the way to make this available to everybody. There's some simple things, do at the beginning. Now, if you're going past that because of something we don't know, some toxins you're being exposed to, we can deal with that.

Jane: Part of that beginning tier would be to have your genetics done, so you know if you're APOE4.

Dr. Bredesen: Absolutely, and it's easy to do. That's the only thing. When you have a model of a disease that's incorrect, it's this idea that it's just about reactive oxygen species or it's just about amyloid or something like that. It tells you to do things that are all wrong. One of the things that's been said over the years is, "Don't bother to get your APOE checked, because there's nothing you can do about it." Nothing could be further from the truth. Everybody should check their status. If you'll allow me a moment to preach here.

Jane: Please.

Dr. Bredesen: I apologize for that. Yes, please, everybody, everybody should know their APOE status. 3/4 of the population is APOE4 negative, so you want to know if you have a single copy, two copies, or zero copies of APOE4. The 3/4 your chance during your lifetime is about 9% of getting Alzheimer's. Not terribly high, but it's not zero either, so please still get on active prevention. If you're APOE4 positive you really want to focus even more.

Single copy, that's 75 million Americans. Your chance is about 30% during your lifetime. Then if you have 2 copies and that's about 7 million Americans, but unfortunately the vast majority don't know it, your chance is over 50% and in some studies, close to 90% that you will develop Alzheimer's. Please get on active prevention. Virtually none of these people need to ever develop Alzheimer's disease.

Let's make it a rare disease, we should be able to make it a rare disease. One other key point here is that we have something that people call MCI, and I'm sure you're aware of this. Mild Cognitive Impairment. That is a horrible term that's hurt a lot of people. Here's why. When you develop cognitive decline and you're on your way to Alzheimer's, you go through four stages.

The first stage you have the beginning of the biochemical changes, you can pick it up on a PET scan or in spinal fluid, but you have no symptoms. Second phase, you have subjective cognitive impairment as we talked about just a moment ago, and that lasts on the order of 10 years. It will last about 10 years, people know there's something wrong but they often put things off, "Well, you know my spouse isn't that great either. Everything's probably going to be okay. It's probably not Alzheimer's."

You really want to get in one of those first two phases. The third phase which should be called relatively advanced Alzheimer's disease is called mild cognitive impairment. This is like telling someone, "You have mildly metastatic cancer, don't worry." People say, "Oh, it's just mild cognitive impairment, come back next year. There's really not that much you can do about it anyway. Come back next year." Again, this is a late stage of the disease.

We want to get in earlier but the good news is, in our trial, people had either mild cognitive impairment or actual full-on Alzheimer's which is the fourth and final stage, and they did very, very well. Please don't wait. As you get farther and farther along, you have to do more and more, just like any other complex chronic illness. Please, please, if you don't get on prevention which I recommend everyone do, then at least get on as early a reversal as possible.

Jane: I was amazed in looking at the results from that first clinical trial that you did, that you had a number of individuals who were classed as mild cognitive impairment, so their scores when they were asked what year it is and what month is it, and when is your birthday, some pretty simple things, they couldn't answer them. Their score was 22 or 24.

I remember I sat in with my mother when she had that done at her family doctor, and she didn't remember what year it was, and so they labeled her a 22. In your clinical trial those 22s, they jumped up to the very top tier to 30 which is completely normal under this protocol.

Dr. Bredesen: Yes. We had two people who were actually at 19. This is out of a total of 30 on this, on the MoCA test. This is the Montreal Cognitive Assessment. These are

people who they've actually crossed into that fourth phase of Alzheimer's disease, and they both ended up with 30s, perfect scores.

Jane: You can gain--

Dr. Bredesen: Yes. Do the right things and as you indicated, it's not always that easy, just take it one step at a time. I think the health coaches are so helpful, because they can help people stick with it, keep optimizing, and do the right things. This is complex, don't try to do everything at once. Start doing the right things, add, keep optimizing and then keep tweaking to see, "Okay, can I maybe get things a little bit better, a little bit better, a little bit better?

We have people now who are now 10 years on this trial, not this particular trial, but the protocol that was that we used in the trial, who have improved and stayed improved for 10 years. Again, that's unheard of. On the drugs, if you get a little bit, better you go right back to declining again. We're very excited that when you actually do the right thing on the protocol, you sustain your improvement, because you're now attacking the causes of the decline.

Jane: Let's look to the future. It's going to be exciting. I'm sure you see interventions on the horizon that we don't have quite yet, but you see them coming. Can you think of some?

Dr. Bredesen: Oh my gosh, yes, there's so much, and we look all the time at where this is headed, how can we continue to enhance it, make it better? There's so much. One of the things that we're already beginning to do is now to apply the same approach because what it really says is when you have a neurodegenerative disease, and this has been the area of greatest biomedical therapeutic failure, it really is representing a mismatch between the supply of the system, of the neural subsystem and the demand.

You've got more demand than you do supply, so you're now involuting, you're losing. Whether it's ALS, frontotemporal dementia, whether it's Lewy body disease, vascular dementia, Alzheimer's, what have you. We're actually starting with macular degeneration, that's another great example where the demand outstrips the supply. Part of this is going to be adapting it for each subsystem has its own specifics, so you need to do things a little differently for each of them.

The second thing is as you said, there are new things that haven't been available before. One of the things is you can now get very rapid feedback looking at epigenetics and say, "Okay, have we addressed the appropriate methylation pathways, the appropriate detox pathways? Have we addressed these things? Now, we've been

looking at these biochemically. What happens to your homocysteine? What happens to your C4A and TGF beta-1 which are markers of inflammation?

What happens to these things? What happens to the pathogens? Things like that. We'll now be able to see the response more quickly, so you'll be able to say, "I'm on the right track or I'm on the wrong track." If you look at something like an MRI, that takes months to change, and by the way in the trial, we did see improvements in the MRIs, not just in the cognitive testing, so we're very enthusiastic about that, because it provides confirmation that we're on the right track.

Part of this is going to be getting quicker feedback. Also, we're going to be able to look and see, okay did you improve? The blood markers like phosphotal telling us that the brain is beginning to heal itself. There's going to be more use of stem cells in the future. Right now what's happening is, as you know, stem cells are being tried and being trialed as monotherapies. A wonderful idea except that it's a little bit like trying to build back a house as it's burning down. You've got all these things damaging the brain, and you're just going to try to throw stem cells and nothing else in there. Might work for a short period of time, but it's not the optimal way to go after this.

Jane: Have you done stem cells yet, yourself?

Dr. Bredesen: I have not done them myself.

Jane: I have neither.

Dr. Bredesen: Actually, I've been in discussion with a guy who's an expert at this, and now I'm about to turn 70. I'm getting up there. At some point, I will probably do that as part of an overall program to improve my health-span.

Jane: Speaking of getting older, I just turned 60, you turned 70. There are recent studies that show that if we can slow aging, then we can slow the age-related diseases that come with it. Problems cardiovascularly, problems with your brain. What do you think about that line of thought saying, "Should we work on some of the anti-aging things to help slow Alzheimer's?"

Dr. Bredesen: Great point. It's half the equation. Here's the thing. As you indicated, a piece of this is your aging rate, and some beautiful studies that just have appeared from a number of people including Dr. Kara Fitzgerald who also published and wrote a beautiful book called *Younger You*. This is a wonderful thing and also Dr. Levine who wrote *True Age.* These are people who are showing for the first time that you can actually gauge a person's biological age.

Tom Brady is 44 but his biological age is probably about 33 or so. He does not act or look like a 44-year-old average human. This is telling us, where do you stand? Of course, people have talked about things like telomeres and other things as well, but these are looking at methylene, so it's one way to look at your biological age. Numerous laboratory studies over the years do suggest exactly what you've said, that when you slow the aging process, you also delay the changes in health-span, the loss of health-span, that we associate with aging.

People begin to develop arthritis and cardiovascular disease and dementia and things like that. As I said, that's half the equation. The other half is that we are as I said to Dave Asprey, half of aging is you suck at living, so that the issue here is-- [crosstalk]

Jane: Your lifestyle is a mess.

Dr. Bredesen: Exactly. Those are things where the changing and aging is not going to help you that much. If you have metabolic syndrome, you've got a leaky gut, you're eating the wrong things, you have a sedentary lifestyle, these things are horrible for you. The good news is we now know it, and we could actually measure the impacts that each of these things is having. There's been a lot of interest in senolytics lately as well, so there are all these things that are going on.

Yes, when you do the right things, now you're starting to look at the true aging process, the underlying, endogenous aging process. Until then, there's so much that we're doing that's actually hurting ourselves. For example, many people end up with cognitive decline not realizing a key contributor is that they're living in a moldy home with mycotoxins. These molds actually produce mycotoxins.

Doctors are not looking for that, they're not measuring it, and yet we know that these are contributors. We usually find around 10 different contributors. When we see someone who truly has cognitive decline, it's rarely one contributor. They often have some insulin resistance. They often have some changes in their oral microbiome. They often have leaky gut. They often have some sleep apnea or some desaturation, at least at night while they're sleeping so it is important to evaluate these.

We need to have the physicians understand, and we've now trained over 2,000 from different countries and all over the US. We need to have people look at these various things to understand why each person is undergoing cognitive decline, and then target those things to get best outcomes.

Jane: I had my biological aging done. That's a scary thing, and I'm 60, but my biological age is 59. I still have something to work on to get it.

Dr. Bredesen: You can get it lower, that's one.

Jane: That's one you can.

Dr. Bredesen: Well, and that's the other thing is people have pointed out you now, this is what Dr. Fitzgerald and Dr. Levine show that you can actually do things to lower that. Reducing your biological age is a whole new field. Lots of people are very interested in this, and more and more we understand what you can do to achieve that.

Jane: You don't have any-- We talked about stem cells. Do you have any thoughts on, we know blood sugar is one of the drivers when it's not working right in your body. It's one of the drivers for cognitive decline. I've seen research that if you go on Metformin, even if you're not diabetic, it still helps your own blood sugar and it prolongs a life. What are your thoughts on that?

Dr. Bredesen: Yes. This comes up all the time. It's a great point. Dr. Robert Lustig has a wonderful book called *Metabolical* about all the issues and metabolic issues. As you say part of the problem is that we are attempting to live as a species in a way that we were not evolutionarily designed to live. We were evolutionarily designed to live with very small amounts of sugar, we've now because people like it because it tastes good.

People just eat massive, massive-- Literally like, jumping off a building, it's simply, we were not set up to do that. Our bodies don't take that. They literally are falling apart because they're doing it. It's one of the more common things. There's also processed food, all the issues with dyslipidemia and on and on and on. Yes, we are damaging our bodies each day. That's one of the most important things.

Now here's where I have a little bit of a problem with Metformin. For all of these pharmacological interventions, they're attempting to trick your body into doing the right thing when it's doing the wrong thing. It's much better to do the right thing. It's much better. If you actually do appropriate fasting, and have a low carb diet, we recommend a plant rich, ketogenic, mildly ketogenic diet with appropriate fasting periods of 12 to 16 hours.

Of course, there's also the fasting mimicking diet that Dr. Lustig has described in his research. There are lots of ways to get at this in a much more appropriate way. Now, when you take Metformin, what you're actually doing is preventing your body-- You're inhibiting your body from making the ATP that it's trying to make. Therefore, you get stuck with more AMP, which is the lower energy.

You don't have that ATP energy. Your body recognizes that, it thinks it's fasting. Now you activate AMP kinase, you get this longevity effect, but again, if you do it the right

way, you're actually going to get even more benefit. If you take Metformin, there was a study a few years ago that showed that people who had taken Metformin did increase their risk for Parkinson's and increase their risk for Alzheimer's. The region that's inhibited in your mitochondria by Metformin it's the same molecular complex that's inhibited by Rotenone, which gives you Parkinson's.

Now you do it right with Metformin. Yes, you're just tweaking it mildly. That's the idea, but you're really giving yourself a mild poison, so that you can trick your body into doing the right thing, so much better to do the right thing for your body, and get the right outcome. Yes, for some people, they may think that's the right thing. Fine. Great, but beware, be careful, you may have some side effects from that drug.

Jane: Good explanation.