CUTTING EDGE Health

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

This is part 2 of a 2-part interview with Dr. Dale Bredesen.

Jane Rogers: People seem to think that cognitive decline is a natural part of aging, and it is not. Doctors still tell patients with Alzheimer's that there's nothing they can do for them. My mother was told that as I sat beside her. Dr. Dale Bredesen changed all that. I already had subjective cognitive impairment, SCI as it's called or memory loss, at 54 years old, the same age as my father's symptoms and he later passed with Alzheimer's. I was scared and Dr. Bredesen provided a lifeline.

I did everything as the New *York Times* best-selling book, *The End of Alzheimer's,* said to do and it worked. In addition to this book, he's authored two more, *The End of Alzheimer's Program* and *The Survivors of Alzheimer's*. This is part two of a two-part interview with Dr. Bredesen, currently the chief science officer of Apollo Health and a professor at UCLA. I'd like to throw a couple of things out and get your idea on what's needed. Research funding, you're in the middle of research. What's wrong with our research funding today for Alzheimer's? Do I probably have hours to talk about.

Dr. Bredesen: Well, unfortunately, the system is broken in this area because what happens, everyone started out years ago with a very positive attitude, "We're going to figure out this disease and we're going to develop something for it." Now, what's happened is that it's become political. It's become financial. People are basing their whole careers and all of their finances. As you know, if you get a drug that actually works for Alzheimer's, this is going to be a multiple hundred billion-dollar drug.

For aducanumab, $28 billion was spent to develop this. No surprise, doctors are being paid as consultants to say that it's a good drug when everybody knows it's not. In fact, the expert panel that wasn't being paid to say that it was a good drug said that it was not a good drug. This is the problem. Unfortunately, when you have peer review of research, you're being reviewed by your competitors.

Competitors who are interested in going the way that we're going, which hasn't resulted in anything positive, are going to continue to support going in the same direction. For anyone to say, "No, that's the wrong way to go. We're going to have to go in a new direction," and that's not going to get funding. As you know, people tend to bet on the horses after they finish across the finish line. We do need to have some way to support novel research, in different directions.

When you've got essentially what's been called the Alzheimer's mafia, when you've got a group of people that are basing their careers and their finances on one way of thinking, of course, they're not going to support a different way of thinking, especially when that way of thinking says, "Look, what you guys are doing is wrong. You've been going in the wrong direction." Actually, I wrote about this in the recent book, *The First Survivors of Alzheimer's.*

You go there, there's an old African proverb that said, "If you want to go fast, go alone. If you want to go far, go together." What happens when you're going together and you are going far but you're going in the wrong direction, that is a huge problem. Then you start to try to convince each other that you're going in the right direction. Yes, you're right. This is where private philanthropy is going to change the world. Unfortunately, the pharmaceutical approaches and the NIH-supported approaches have not yielded anything of significance in terms of therapeutic benefit for Alzheimer's disease.

Jane: That's where you secured private funding for your first clinical trial last year, and now your new one with 100 people. It's private funding.

Dr. Bredesen: Yes, exactly. We're grateful to Diana Merriam and to the Evanthea Foundation and the Four Winds Foundation for their tremendous and visionary support of doing something different. Now, for years and years and years, we did have NIH funding. We did basic research with that. I was on the NIA council for years. We're grateful to the NIH for the basic research it funded.

What happened was as we now said, "Okay, the research is actually pointing us in a new direction," then you've got the group there that's sitting, the peers who are sitting there saying, "Well, we don't want that new direction. We want to stick with where we're going here." It's unfortunate. I think this is the history of medicine. You look at what happened with scurvy. Very interesting.

16th century, 17th century, 18th century, 19th century, every century, you would see someone would come up with, "Oh, wait a minute. We need to understand this disease. We can do better. That was the whole limey, citrus fruit. This can help." Then the doctors would say, "No, that's not the way it works." It would be lost for a while again, then it would be brought up again. It took a long time for doctors to change their approach.

You go back to Dr. Semmelweis, who was the one who said, "Look, when women are dying when they give childbirth, they give birth to children, to babies because we're not keeping our hands clean." People said, "No, you're crazy." One expert at the time, it's the early 1800s, said, "There's no way you can get enough stuff under your fingernails to kill a whole human being. That's silly," because they didn't understand what germs

were there. This guy was ultimately forced into an insane asylum where he died within a couple of weeks, ironically, from an infection.

This is the history of medicine. It hasn't been about disruption, the way Silicon Valley has been. It's been about tradition and permission. Of course, it's worse than ever now because people have to ask permission from their insurance agencies. "Am I allowed to give this treatment? Am I allowed to give that treatment?" It's hilarious. Yes, medicine is leading us back into the 19th century. It's really, really out of date. 21st-century medicine needs to fundamentally change the way we think about health care and the way we deliver health care.

Jane: I bet sometimes you feel like one of those guys from the past. You've been up on the mountaintop kind of by yourself and received a lot of criticism because you were the first rabbit out of the hole with something that worked and it was different. I bet it's been hard sometimes.

Dr. Bredesen: I have to say, yes, the science part was the fun part, the interesting part, the intriguing part. The activism. I never signed up to be an activist but to be able to get out there and say, "Look, this is what the data actually looks. These people are actually getting better and the people in these drug trials are not." As you said, we've had a tremendous amount of criticism, marginalization, getting invited to be on various shows, and then canceled.

I had an invitation to be on *The Today Show*, which was then summarily canceled when the Alzheimer's Association went on before. We've had a lot of pushback. I think the only thing you can do, get the trials done, get the data, publish the data, show that, in fact, the science works. One of the things that's been intriguing to me is we're simply doing what the test tube research that we did for 30 years showed is the right way to attack this.

It shows that this is the nature of this illness. What's interesting to me is that other physicians coming from completely different angles, Dr. Jeffrey Bland, Dr. Mark Hyman, Dr. David Perlmutter, who are coming from different approaches ended up at the same place. That really shows me that we took different paths to get there, but we all ended up at very much the same place.

Jane: What would you like to say? If you're at maybe the end of your research career toward the end, what do you want to say to those young bucks coming up and the young women who are going to be carrying the torch? What do you want to tell them?

Dr. Bredesen: The first thing to do is not start your research where you think the current field is. Question what's already out there. In other words, people who start their

research, young people, start with, "Okay, we're told that this is a disease of amyloid and tau. What's the next step?" There's a huge mountain of assumptions there, which have turned out to be incorrect. Start with first principles, please.

Look at, does this really make sense? You have to pass the straight-face test. You have to be able to say, "Why is it if this is a disease of amyloid and we remove the amyloid and people get worse instead of better, maybe we should question this theory instead of let's just get a different--" that people say, "Well, let's do it earlier. Let's do it with a different drug. Let's do a different antibody," and so forth and so on. Please question the basics and look at what actually is going on here.

The second thing is it has to be internally consistent. If you know that whatever answer you come up with, whatever model you come up with must be compatible with the fact that type 2 diabetes increases your risk, various toxins increase your risk, various pathogens increase your risk, sleep apnea increases your risk. Again, there are over 150,000 papers published on Alzheimer's.

Whatever you come up with, you can probably reject very quickly based on what's already been published. It's got to be compatible with that. Then once you get a model that is compatible with all those things, then use it. Try it in human beings. Ultimately, the ultimate test is to make human beings better. Not just a transgenic mouse, but to make human beings better.

I should say the mice have been one of the big problems because they are a poor model for what happens in human beings. When you induce in mice, you induce Alzheimer's. It's genetics and only 5% of Alzheimer's, those types of genetics. In fact, the type that's typically used for the mice, even less than 5%. You're really creating a poor model, and then looking at things that help that disease but not things that help the vast majority of people who have this problem.

Jane: We talked about what your thoughts are on changes needed in funding, changes in the research community. What changes do you think we're facing in this pandemic? 45 million Americans who are living today will die of Alzheimer's. What needs to change within our communities? I know you talked about assisted living and how we need to embrace your research and findings in the assisted living environment instead of just feeding them jello and stuff that won't help them at all. What needs to change in our communities other than assisted living?

Dr. Bredesen: Public health is what has to change. 100 years ago, people realize, "There are a lot of problems with infections. We need to have safer water, better public health." Between antibiotics and public health improvements, that was really what led to better health spans in the 20th century. That was the big medical success of the 20th

century. The medical success of the 21st century, which hasn't happened yet, but we now know what we need to do to make it happen, is to address complex chronic illnesses.

I'm talking about Alzheimer's, cardiovascular disease, cancers, lupus, autoimmune diseases, all of these sorts of things, metabolic diseases. Again, Dr. Robert Lustig does a great job in his book going through all the things that are critical. This is the problem, the healthcare problem currently. It is why we're spending close to 20% of our GDP on health, and yet we have horrible health.

We're something like 41st in terms of our health span in the world. It's just horrible, and even in terms of lifespan. We live a lot of our lives in sick-span in a relatively small amount of our lives with healthspan, so this is what's going to change. To do that, we need to get people checked earlier. We need, as I said, to get people on prevention and be able to have simple ways to measure the things that are actually driving this. There are some basic things you can do for everybody, but then don't stop there.

For the ones that then fall through the cracks and are continuing to develop problems, take that next step. We can have a tiered system that is highly efficient. That will literally make Alzheimer's a rare disease. During this century, the 21st century, we should see a virtual end to these rare diseases. Alzheimer's, schizophrenia, cancer, lupus, all of these things that are these complex chronic illnesses, they are the illnesses of the 21st century.

Now, once we deal with these, the next thing is likely to be aging itself. Then we'll start looking at, "Okay, what are the things that are still driving us?" Of course, we may still have pandemics to deal with because people interact with each other. They get this as hard as we try to treat these and prevent them. There still may be other viruses coming. Now, there's some very exciting work from Dr. Vishu Lingappa from UC San Francisco and, now, his company Prosetta that is developing antivirals that are resistant to all mutations.

Jane: Really?

Dr. Bredesen: I think that's one of the most exciting things on the horizon. You can have Omicron, you can have Omega. You pick it. Have whatever you want. You'll still have an excellent and non-toxic antiviral. I'm very excited as it begins to get out there. To me, that's where things are going. Yes, this will include targeted drugs, but we won't be asking for the drugs to do too much. Right now, we're trying to take one little drug for this incredibly complex network dysfunction and say, "Okay, you should do 100 different things." Frankly, it doesn't pass the straight-face test. It's laughable.

Jane: Okay, I'd like to geek out on some things, kind of more down in the weeds and see, "What do you think?" Hormetic stress. Hormetic stress is good for you, except when it's pushed too far and then it becomes a bad thing.

Dr. Bredesen: That is the trick. Again, epigenetics will help us to say, "Okay, did you push too hard?" "Yes, you're absolutely right." I like the laugh that we talk about, the Wim Hof Method of getting cold, getting your mitochondria charged. On the other hand, there's the Wim Hof Method, where you don't even want to get cold. You want to stay warm. You don't want to do these things. Yes, there's some hormesis there. That's why you get out there. Get in the surf. Get in the ocean. Get cool.

You're right. Hormesis is good for you, but, yes, to a point. You've got to learn where that point is. You don't want to push it. People who've tried to do, for example, many, many marathons, they're breaking down. It's hurting them. Don't push your heart too hard. Don't go too quickly. Biological systems were not made to function in square wave jerks. That is to say, we weren't meant to do no exercise and then to do a ton of exercise. You have to ramp up and then you have to ramp down.

If you're now going to stop a drug, for example, got a ramp-- Don't cold-turkey it. Ramp down. Biological systems were meant to go up slowly and down slowly. Yes, hormetic stress, great. Please be careful. Don't kill yourself. Same thing with things like HIIT, high-intensity interval training. People are starting to now realize, "What can be developed around these things?" I'm sure you've heard about these resistance bands. You can put on resistance bands, so you basically get more bang for your buck when you're doing exercise. Again, tremendous numbers of things that are coming up around physiological optimization.

Jane: Speaking of cold, I like to ramp it up. First, I start a hot shower, and then I slowly go down to the cold. You don't realize you're getting so cold, but I'm working on that.

Dr. Bredesen: That's helping your mitochondria.

Jane: It is and you feel better after you've cold-showered for 30-40 seconds.

Dr. Bredesen: No question.

Jane: Cerebral blood flow, why is it important? How can you measure it? What do you think of the EWOT?

Dr. Bredesen: Right, I like EWOT, Exercise With Oxygen Therapy. Absolutely helpful. There's some nice work actually out of Israel recently, showing HBOT, hyperbaric oxygen, helpful for cognition as well. Here's the thing. Out of the four as I mentioned

earlier, the big four groups that are actually driving our cognitive decline ending ultimately in what we call Alzheimer's disease. Energetics, the number one of the four, it's the big one.

Then there's, of course, inflammation and there's trophic activity and there's toxicity. With energetics, there are mainly four big things. Blood flow, you have to deliver the energy to your mitochondria, right? Oxygenation, so people who have sleep apnea or people who are dropping their oxygen saturation at night. There's a beautiful paper showing if you simply look at the average oxygen saturation at night for each person, it correlates beautifully with the size of specific nuclei within their brain, including the hippocampus.

If you're dropping your oxygen at night, it's likely that your brain is a little bit smaller. Let's make sure that the oxygen is good. Mitochondrial function is the third piece of this and then ketosis. To get the ketones, you need to burn either glucose or ketones. When you're in good shape, you're metabolically flexible. You're able to burn glucose. You're able to burn ketones. You don't want to have so much glucose that you're now getting insulin resistance.

What happens to us as we start to develop cognitive decline? We lose both of those. What's happening is we're losing the ability to get glucose. That's what the PET scans show in Alzheimer's, a reduction in glucose utilization in the temporal and parietal regions. We're not getting the glucose ability. We have insulin resistance, but we also are not able to develop and use ketones. We're not keto-adapted.

One of the things that inhibits the production of ketones is, guess what? Insulin. Until you get your insulin sensitivity back, you won't have either of those things. That's a critical piece. Absolutely, blood flow, people who have vascular disease are unquestionably at increased risk for Alzheimer's. In addition to that, of course, you have leaky vessels. You have not only poor flow, but you also have leaky vessels and, unfortunately, blood-brain barrier breakdown as you're developing cognitive decline.

Jane: You just helped me there because I've had some blood sugar issues. I always had trouble getting into ketosis. Flipping from burning sugar to burning fats has always been a struggle.

Dr. Bredesen: Do it slowly. That's why just use exogenous ketones at the beginning to get those ketones up. Then slowly, you can get yourself into an endogenous ketosis.

Jane: How can you tell if you are synaptic blastic or synaptoclastic?

Dr. Bredesen: Great point. The idea here is no different than with osteoporosis. You have osteoblast that make the bone. You have osteoclast that pick up the bone. When you're getting osteoporosis, your osteoblastic activity is being exceeded by your osteoclastic activity. When you're developing cognitive decline, your synaptoblastic activity, the ability to make and store synapses, learn new things is being exceeded by your synaptoclastic activity. What happens is you have this molecule in the middle here, this amyloid precursor protein.

This is the parent of the amyloid that we study in Alzheimer's disease and so many people have studied. It's not just about the amyloid. This is a signaling molecule that, interestingly, is a switch. When things are good, it goes into the synaptoblastic mode. It makes two fragments that tell you, "Yes, make new synapses store," just like your country would do and say, "Okay, we're going to make new bridges. We're going to make new highways," these sorts of things.

When you are insulted, you've got poor dentition, you've got poor oxygenation, all the things we talked about, this same molecule switches into a different mode saying, "We have to pull back and protect." By the way, the same thing that happened to our country with COVID. There was an insult. In this case, SARS-CoV-2. Everyone was told, "Socially distance, et cetera, shelter in place." What happened? We went into a recession.

Same thing happens in your brain. You are going into a protective mode. That amyloid is, actually, a protective antimicrobial peptide. It's killing the things that are coming into your brain and attacking it. What you need to be doing then is getting yourself back into a synaptoblastic mode. Now, you mentioned, how do you know you're in a synaptoblastic mode? This is where epigenetics will be really helpful. They can actually tell you what your rate of brain aging is.

It's where the phospho-tau in the bloodstream is helpful to tell you, "Are you damaging your neurons or not?" You can get a first-order approximation by looking at your basics, at your HOMA-IR. Are you insulin-sensitive? At your hsCRP, it's the very things that we put together in the protocol we developed, which we call RECODE. The idea is we're looking at this whole set of biochemical parameters that tells you, "Are you doing the optimal things to get you to heal, to get you back into the synaptoblastic, into the building mode, and out of this protective downsizing mode?"

Jane: One more geeky thing and then I know you've given us so much of your time. Thank you.

Dr. Bredesen: Thank you.

Jane: What do you think about KAATSU? K-A-A-T-S-U. What do you think?

Dr. Bredesen: I think it's fantastic. Obviously, I was skeptical about this. KAATSU are these resistance bands that I mentioned earlier. You can put them around your arms and legs and things like that. You want to be careful. Don't make them too tight. You don't want to stop the blood flow. What they do is they basically restrict to the point that you're getting a little bit of additional lactic acid.

There's a slightly reduced flow, and so you're saying to your body, "Okay, we need to now support this." It is, essentially, a hormesis type of effect that allows you then to push back. It allows people to build muscle better, to become more insulin-sensitive. Having muscle is actually helpful for being insulin-sensitive. It's supportive in that way, so I think it's great stuff.

Jane: Where do people turn? Let's say I have a family member that has subjective cognitive impairment. I'm feeling it myself. Maybe I'm losing things, forgetting things. Where should they turn?

Dr. Bredesen: There are a number of ways that you can look this up there. There's some books that you mentioned you can look at, *The End of Alzheimer's*, which goes into some basics here. You can also check the website. You can go to mycognoscopy. Please, people, get evaluated. Get things checked out and make sure that you don't-- Nobody has to get this disease virtually. We can essentially make this-- I know this sounds crazy. We can make this disease optional. We should be making it a rare disease.

Let's not have cognitive decline. Let's try to keep people sharp. I love for people to get to their 90th birthday and be sharp, not have to worry about this problem. Please get checked for your APOE status and for your basic biochemical status, as I said, that you'll get with cognoscopy. You can also go to apollohealthco.com. I'm working with a group of software engineers from Silicon Valley. A number actually who have come from Apple who are looking at, "How can we get larger data sets, better algorithms for better outcomes?" Again, that's part of the future of health care.

Jane: Then my final question, and I know you are a very humble, modest person, but you've done incredible work. What are you most proud of in your life?

Dr. Bredesen: As I said, the thing that gets me most excited is to hear from people who have gotten better, who went from hopeless to hopeful and from Julie who is in the book, and Sally who is in the book, and Edward who is in the book, and Frank who is in the book, and all of this people. We'd like to see that. We now have hundreds and thousands of people. We'd like to see that for millions of people. We want to see a world

in which cognitive decline is rare. We want to see a reduction of the global burden of dementia. That's what translates our research into practical things. I recognize it's not as practical as it should be yet. We're getting there. That's what I'm most happy about. Thank you.

Jane: Thank you so much for what you've done for our world. Thank you for what you've done for our family and your time.

Dr. Bredesen: Thank you, Jane. I look forward to talking anytime. Please keep optimizing and keep me up to date.

Jane: I will. Thanks. Have a great day.

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