Dale E. Bredesen, MD: Reversing Cognitive Decline

Interview by Craig Gustafson

Facilitated by the American College of Nutrition 56th annual conference, "Translational Nutrition: Optimizing Brain Health," November 11–13, 2015, in Orlando, Florida.

***Dale E. Bredesen, MD,** is internationally recognized as an expert in the mechanisms of neurodegenerative diseases such as Alzheimer's disease. He graduated from Caltech then earned his MD from Duke University Medical Center in Durham, North Carolina. He served as chief resident in neurology at the University of California, San Francisco (UCSF) before joining Nobel Laureate Stanley Prusiner's laboratory at UCSF as a National Institutes of Health postdoctoral fellow. He has held faculty positions at UCSF; the University of California, Los Angeles; and the University of California, San Diego. Dr Bredesen directed the Program on Aging at the Burnham Institute before coming to the Buck Institute in 1998 as its founding president and CEO.*

***Integrative Medicine: A Clinician's Journal* (*IMCJ*):** Up to this point, cognitive decline, once identified, has been largely considered irreversible and unstoppable. Do you consider this the case now, and why?

Dr Bredesen: I do not consider this the case now. There has been tremendous progress in the last several years, and this is a very exciting time for studies of neurodegenerative illness. Although the dogma has been that there is nothing that prevents, slows, or reverses the course of cognitive decline in diseases such as Alzheimer's disease, there are clearly multiple studies now—in both anecdotal and controlled trials—that show examples in which there is indeed prevention and/or reversal of decline. We published the first paper to show that just last September with a small, anecdotal group.[1] We are looking at additional people now, but we are seeing the same sort of outcome again and again.

***IMCJ*:** In your paper, you talked about the monotherapeutic approach. Today, what are the drawbacks of a monotherapeutic approach?

Dr Bredesen: As you know, in many chronic illnesses, whether you are talking about osteoporosis, oncogenesis, or atherosclerosis, or you are talking about cognitive decline due to Alzheimer's or a pre-Alzheimer's condition, like severe cognitive impairment or mild cognitive impairment—in all of those cases, you are really looking at physiological imbalances. In other words, these are networks of molecular pathways that are out of balance, associated with a chronic disease process.

The idea of going after these with a single drug, although it has been successful in some cases under some circumstances, is not the optimal approach—either from the standpoint of theory or from the standpoint of practice. This is being shown more and more to be the case, whether you are talking about cardiovascular disease or you are talking about Alzheimer's disease or cancer. The idea of a cocktail approach to cancer has actually been in place since the 1960s and is the standard approach now.

The ideal of using triple therapy for HIV, of course, is the first approach that actually showed a real benefit and has been the standard of care since that time. I think that it is, perhaps, not surprising that we are seeing the same sort of thing with cognitive decline. I think that some of the drugs that have failed in clinical trials could actually succeed on the right foundation of additional therapeutics.

***IMCJ*:** How did you get interested in pursuing a different therapeutic approach toward cognitive decline?

Dr Bredesen: Our laboratory has been interested for many years in investigating the molecular underpinnings

of neurodegeneration. Why do you get Alzheimer's disease? Why is it so common? What are the drivers of this process? The idea is that if you could get at those specific molecular details, you could potentially work out therapeutics that would be effective.

Approximately 7 years ago, we started a large effort to do drug screening for therapeutics to address Alzheimer's disease. The first drug that we identified is currently in a clinical trial in Australia for early-stage mild, cognitive impairment. When we started looking at drugs that had an impact on a critical balance that is mediated by the beta-amyloid precursor protein, or APP, we found that we could identify drugs that would alter that balance in the direction of the anti-Alzheimer's protrophic cleavage of APP. However, when we then looked at what all of the inputs to that specific critical balance were—a plasticity balance if you want to think about it that way—we found that the drug alone addressed only some of these but did not address all of them. Therefore, it actually made much more sense to try to address additional input to that same balance.

In 2011, we proposed the first comprehensive, double-blind, placebo-controlled trial for early Alzheimer's disease therapeutics, which included 4 arms. The first was placebo and the second was the drug. A third arm, then, included an entire system of therapeutics. This is the same one that we ultimately published last year as MEND, or metabolic enhancement for neurodegeneration.[1] That third arm had placebo in addition to the system. The fourth arm was the system with the drug. The hope was that the drug would actually work much better on the backbone of the entire system. This was turned down by both the public and the private institutional review board, or IRB, as being too complicated. The IRB argued that we must not know how to do clinical trials because we were proposing something that had more than 1 variable. Our argument, of course, was that this is not a 1-variable disease.

I think that has been borne out. We now, actually, are recognizing multiple subtypes of Alzheimer's disease where we can clearly show with metabolic profiling that this is more than 1 illness. That perspective will be helpful going forward in terms of using different approaches, both polypharmacy and monotherapeutic.

***IMCJ*:** You seem to have a novel perspective on the progression of Alzheimer's that is, to a degree, contrary to prevailing wisdom. Would you please describe your ideas and how they are different from the mainstream view?

Dr Bredesen: Yes. If you look at the underlying molecular mechanistics of what we refer to as Alzheimer's disease, as I mentioned already, you see 3 subtypes. Two of these are actually not illnesses. They are much more of a strategic programmatic downsizing of synaptic density based on a mismatch between the multiple inputs that are literally summed by the molecules involved in Alzheimer's disease—by your APP.

Think about it a little bit like a company. Imagine that you have a bunch of accountants; each one specializes in a different area and they all report to a CFO. The CFO then takes a look at the ledger and asks, "Can we make it this year or can we not make it this year?" If the answer is, "We do not have enough to make it this year," then the CFO sends out a memo and the memo says, "We must downsize." The way we look at this is that APP is the CFO. APP is the molecule that is integrating many different inputs to determine whether a strategic downsizing must occur.

If it is required, then you are going to have to activate the compliance officer and you have to send out the appropriate memos. What you end up with is a very programmatic and well-orchestrated downsizing of the synaptic density. That is exactly what is seen in this illness. We tend to, as a dogma, call it Alzheimer's. We say we do not understand where it comes from and that there is nothing you can do about it.

If you look at the molecular mechanistics, what you will see is that this is actually a well-orchestrated, nondisease, strategic downsizing based on many different inputs and a mismatch of those with what is actually required to maintain those synapses and to continue with the remodeling that goes on throughout life. Essentially what you are doing is giving up the ability, early on anyway, to learn new information so that you can retain all the important things that you have learned during the rest of your life.

***IMCJ*:** From there, what led you in the direction of addressing this with a systemic protocol of lifestyle and nutritional interventions?

Dr Bredesen: This came directly from looking at the underlying molecules that mediate this change. For example, if you look at this model, then you will understand why simply reducing the amyloid-beta protein is helpful; it is something to think about, and it is certainly an important part of the overall plan. What you are really doing there is simply not sending out the memo. You are not telling people to downsize. You are ultimately going to fall short based on the mismatch between what is needed and what is coming in.

Here is a simple example: When you have estrogen, for example, one of the effects of its binding the estrogen receptors is to alter the cleavage of APP toward the trophic anti-Alzheimer's side—that is exactly what you want. If you want to push your APP in the direction of pro-Alzheimer's, or antitrophic, then you want to rapidly withdraw estradiol.

There is a direct molecular link between estrogen, its receptor, its gene activation, the molecule that cleave APP at the alpha site, and pushing the APP in the direction of supporting growth and maintenance. That is 1 of 36 different contributors we initially identified.

If there are all of these things that are playing on this same central mechanism and, ultimately, this central

mechanism is taking these into account and either deciding that there is support there or that there is not support there and that there must be downsizing, then the most appropriate physiological approach would be to address all 36 of the members of that network. That is how we started.

***IMCJ*:** Your protocol was published in the September 2014 edition of the journal *Aging*.[1] What are some of the key aspects of that protocol?

Dr Bredesen: To be fair, given the page limitations, we published what we could. There are many new instances and, of course, we have the follow-up to that. What we published was system 1.0. We now have system 2.0, but there are many pieces to that, and the most important aspect is to understand where the biochemistry is at the beginning. You want to know where you stand, as I mentioned in the paper, with respect to your reverse T_3/free T_3 ratio and your hs-CRP, or high-sensitivity C-reactive protein; your vitamin D level; your pregnenolone; your fasting insulin; and on and on and on.

As physicians, we have been hampered over the years by having to deal with very small data sets. We are dealing with extremely complicated organisms and yet we have very small data sets, such as what the sodium is or what the potassium is. In the field of oncology, the current excitement is in doing whole-genome analysis for the tumor and whole-genome analysis for the patient and comparing those to infer from that what the drivers are for the actual tumor. This is what has been referred to as 21st-century medicine.

What we are proposing is no different; it is just that we do not have a tumor to biopsy when you have Alzheimer's disease. We are looking at a large number of metabolic components and, of course, we also encourage people to get genome sequencing. Then we can infer from all those data what the most likely pathways are that contribute to this ongoing downsizing that is occurring in your brain.

***IMCJ*:** As you mentioned, this is fairly complex and there are many variables, as well as many therapeutic targets in the system. Is the result a protocol that is difficult for patients to adhere to? And as such, does it have to be followed to the letter?

Dr Bredesen: This is a really important point. First of all, this is a different way to do medicine. We are not saying, "Take a pill, then go home and forget it." It is complex, so what we are saying is, first of all, there is going to be a program. Instead of therapeutics, this is programmatics. I believe that is the future of the treatment of chronic illness: programmatics. Second, this is going to be personalized. This is going to be a program for you based on what is driving your particular problem.

Third, of course, now that we are seeing results, we are looking at how we can make this simpler. You have to remember, at the beginning, we did not know what was going to make people better and these were people dying of an untreatable terminal illness. We were pulling out all the stops; saying, "Do this, do that; do this, do that." One person complained that it was a "shotgun" approach. Well no, it is not a shotgun approach, but it is not a silver bullet approach. It is silver buckshot instead of silver bullets.

We want to hit everything that is contributing to your illness if we are going to have hopes of getting it to stop and then reverse itself. We are now working with health coaches who can help to make sure you do all the different parts of the program, because as you alluded to, it can be somewhat complicated. It needs to be complicated enough to address the underlying pathogenesis, but if it is so complicated that no one can do it, then of course it is not going to be very practically beneficial.

One positive note here: When you go back to the molecular details and you look at how this plasticity system actually works, what you find is that there are prionic loops. In other words, when you start going down one side or the other, it is like a snowball rolling downhill. You gather momentum on one side or the other. You have to get to the point of changing that. You have to get to a certain threshold, but once you do that, it will begin to gather momentum going down the good side instead of the bad side.

What that means, importantly, is that you don't have to do all 36 things, necessarily. At the beginning, we do not know how many, but when you start to get results, you can limit the program to those things that put you on the other side of the plasticity network, of the balance. For example, the first woman we reported on did 12 of the 36. Nobody has managed to do every single one so far, but when you get to enough, then you get over the threshold.

By the way, this is no different than what Dean Ornish, MD, has reported for years in atherosclerosis. You do enough of the right things, enough of his program, and he has documented the reversal of atherosclerosis. What we are doing here is a little bit like synaptoporosis. You get to the point where you are now able to support the production of new synapses and you start seeing improvement.

***IMCJ*:** Would you describe some of the results you have observed from use of the protocol?

Dr Bredesen: There have been about 70 people who have come through now. For example, I just got a call this morning from a man who started a year ago and had a hippocampal volume, before he started the program, quantified at less than the 20th percentile. It is now greater than the 75th percentile. He actually could not believe that his own hippocampus had gotten larger. He asked the MRI technicians, "Can you give me an explanation for that?" The guy said, "I don't understand it. I can't offer you an explanation."

This patient, by the way, was at a point where he was going to have to quit his job. He is doing very well at his job now, continuing to do his job very effectively. We have another person who is over 3 years out now, still back to work full-time and doing very, very well. We have had a couple of people now who have gone on and off the program a couple of times, either because of traveling, stressful things in their lives, running out of some of the components, or getting ill and not being able to take some of the components.

They have shown very clearly that when they get off the program, they get worse; then when they go back on the program, they get better again. That supports the idea that the program is actually helping them.

***IMCJ*:** Do you know how long it takes to observe the symptoms to start to resume going in the wrong direction when people go off the protocol?

Dr Bredesen: The return of symptoms when the program is discontinued has varied somewhat, but typically people have reported noticing some decline within 2 weeks. On the other side of the coin, symptom resolution on the program begins to be noticable in 3 to 6 months, but there are a couple of important modifiers there: Number 1, it depends on which subtype you have. Certain subtypes respond sooner and certain subtypes take longer. The second thing is that this is not something you start and then you do not change it. We continue to tweak it in time. For example, we had one woman who got a little bit better the first couple of months. Then she came back, we tweaked a few things, and she got further improvement, but she really did not get back to normal for about 10 months. The third tweak is the one that really seemed to help her.

***IMCJ*:** Let's get back to the concept of multipronged therapy and using the system you have developed to support enhanced drug therapy response. What is the potential for this type of combination?

Dr Bredesen: I believe that this overall approach will represent an excellent foundation on which to do all drug trials in the future, but that remains to be seen. We are just beginning to look into taking a standard Alzheimer's drug and adding it to the rest of the program. We will see whether, in fact, these two help each other.

***IMCJ*:** After reading the paper, the protocol seems to incorporate some aspects that are similar to recommendations that other doctors have given for general mitochondrial health. What role might that play in the success of the protocol?

Dr Bredesen: Certainly, mitochondrial health is extremely important. I think everybody agrees with that, but this certainly goes beyond mitochondrial health because you need to look at a number of critical features such as things like metal homeostasis and proteostasis and insulin resistance, which have been the subject of a tremendous amount of research and, of course, specific inflammatory pathways.

Interestingly, there is some work from Milan Fiala, MD, at UCLA suggesting that one can see certain cases in which there is inflammation, which, of course, everyone agrees with, but there are other cases in which the inflammatory markers are actually subnormal—actually below normal—so that there are many different components and, absolutely, mitochondria are important, as you well know. Even better data exist for their striking importance in Parkinson's disease, especially complex 1.

In Alzheimer's and, of course, in health in general, mitochondria are important, but they are by no means the only target of the therapy.

***IMCJ*:** As you will be presenting at the American College of Nutrition conference coming up in November, what more about reversing cognitive decline will people learn by attending your presentation?

Dr Bredesen: This is an exciting time for all of us with all the new things coming out of research. What I hope to show at that conference is that there are multiple subtypes of Alzheimer's disease and that they need to be approached differently, treated differently, and that they respond differently to therapeutics. In fact, some of these are actually, as I mentioned earlier, not diseases, but really programmatic downsizing, whereas others are actually true diseases. By understanding that and looking at the metabolic profiling, you can be ahead of the game in terms of understanding what is actually causing it.

I think that the time has come to quit asking what it is-"Is it Alzheimer's?"—and turn around and ask *why* it is very much of a functional medicine–type approach. Why did you get this problem and how, therefore, can we best go about reversing it?

Reference

1. Bredesen DE. Reversal of cognitive decline: A novel therapeutic program. *Aging*. 2014;6(9):707-717.