February 2015 Issue | Dale Bredesen, MD

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Welcome to February 2015 *Functional Medicine Update*. This is the second of our series—our mini-course—on functional neurology. And those of you that had the chance to review chapter one of our series, you had to be as enthralled as I was in hearing Dr. Perlmutter lay the landscape out. I would call it fertilize the field of discovery and opportunity for progress to be made in these intractable neurological diseases using a new model. And you're not going to be disappointed this month. This is an extraordinary next step in our evolving model. We're going to be moving from what I think is a landscape discussion and particularly focusing on things that may appear so remotely removed from the traditional field of neurology, like the gut-brain connection. Over many years we've seen the evolution of this model, and now Dr. Perlmutter talking about fecal transplants and how that can influence neurological function. So we're seeing the interweaving—the interpolation of these various perspectives in developing the new model, the new medicine, the functional systems biology-based medicine that is going to define 21st century medicine.

Are We Entering an Era of Treatable Alzheimer's Disease?

And we are very privileged in the February issue of 2015 to have the second step in our journey in functional neurology with Dr. Dale Bredesen. Dale will open up for us clinical news to use as it relates to what, for many people, is considered an irreversible, downslide-sloping concern called Alzheimer's disease. His work as an extraordinary research neurologist now moving into clinical applications at the UCLA Alzheimer's Research Center has really opened up many of the areas that we feel are going to pioneer new discoveries, new opportunities, and better outcomes for the Alzheimer's patient. I think it will cut across many other areas, as you'll see, in how you approach complexity in science. It will open up our minds to new experimental models to discover how we explore networks and systems rather than just look at particular binary relationships between A goes to B, a ligand binding to a receptor producing an outcome. And it's that kind of new model—that systems thinking model—that is going to really help us to transform the way that we will personalize treatments for individuals with complex chronic illness and improve clinical outcome. The old models of medicine of the average are dying. The new models of medicine for the individual are emerging. And you're going to hear that beautifully stated, using the example of Alzheimer's disease, from Dr. Bredesen in his presentation.

And Dr. Bredesen comes with no small reputation or background. A person who has authored over two hundred scientific papers in the peer-reviewed literature, who has worked for a Nobel Prize-winning laureate in the area of neurological disease discovery. A person who has pioneered pathways of

understanding about neurogenesis and plastogenic effects that relate to nervous system function, to cell signaling, to the relationship of neurological development, and ultimately the interrelationship of these two general pathways and processes that, under the concepts of functional medicine, we call seven core physiological processes is really what I would call the premier functional medicine neuroscientist. So you're going to have the opportunity to not only be titillated by the process of discovery and how one lays the bricks down in the road to move from hypothesis to proof, but also how one then moves to employ and deploy these concepts into clinical management programs, not waiting for 50 years for all the answers to be in before we actually start doing something to reduce the burden of this reducible disease that we call Alzheimer's disease.

So with that in mind, let's move into our discussion with our second key opinion leader on our journey in functional neurology, Dr. Dale Bredesen.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

Dale Bredesen, MD

Augustus Rose Professor of Neurology

Director, Mary S. Easton Center for Alzheimer's Disease Research at UCLA

Director, Alzheimer's Disease Program Director, Neurodegenerative Disease Research

David Geffen School of Medicine at UCLA

We are so fortunate to have, following Dr. David Perlmutter, our lead interviewee, Dr. Dale Bredesen, who is an extraordinary contributor to the development of this field. Our longstanding FMU subscribers are aware of Dr. Bredesen's work because we've had the pleasure of interviewing him in the past. Those of you who have not heard him or about his work are in for an extraordinary treat because the progress he is making in the area of neurodegenerative diseases and its relationship to functional neurology is nothing short of miraculous.

Let me give a quick biography for Dr. Bredesen. He's the Augustus Rose Professor of Neurology, Director of the Mary S. Easton Center for Alzheimer's Disease Research at UCLA. You probably are aware of his work if you're involved at all in this field in that not only does he have a very prestigious background—an undergraduate degree from Cal Tech, his MD at Duke, and he completed his neurology residency at UCSF—but he was also an NIH Fellow in the laboratory of Nobel Laureate Stanley Prusiner, who was awarded the Nobel Prize for his discovery of prions. In 1989 he joined the faculty at UCLA, where he was awarded the Elizabeth R. and Thomas E. Plott Chair. He then was recruited to Burnham Institute to direct the program on aging, and in 1998 became the founding president and CEO of the Buck

Institute for Research on Aging, which is the nation's only independent institute devoted to research on aging and age-associated diseases. So he has held faculty positions at UCSF, at UCLA, and at the University of California at San Diego. His work spans an extraordinary array of contributions in the field.

I went back and looked at his more than 160 publications, and if you go back to the early days of Dale Bredesen you find that some of his early papers back in the 1980s were involved with the development of understanding of cell signaling, and neuronal pathways, and apoptosis, and neuronal cell death, looking at whole mechanisms of disease, platform technologies, understanding the complexity of synaptic plasticity and synaptic signaling, really being, I think, one of the fundamental pioneers in the understanding of the complexity of brain and brain function and how, in fact, the brain is connected to the overall scheme of the network of physiology of the body and things like brain-derived neurotrophic factors, and various kinase-signaling pathways that relate to gene expressions that are triggered by inflammatory mediators and neuronal oxidative stress. He was an early pioneer really looking at mitochondrial neuronal function and how that relates to the presence and absence of various redox-active substances and the establishment of proper neuronal bioenergetics.

So his footprint in the field has been nothing short of remarkable, and there could be no one I could think of that would be more suitable to help us to understand what is really happening on the cutting edge of 21st century functional neurology than Dr. Bredesen. And on this day that we're having this interview, we're very privileged to see a CNN health article that has been published titled "We May be Able to Reverse Signs of Early Alzheimer's Disease."[1] That's by Stephanie Smith and it's talking about none other than Dr. Bredesen and the work that he is doing at UCLA and the results that were encoded within a paper that was recently authored by Dr. Bredesen that is titled "Reversal of Cognitive Decline: A Novel Therapeutic Program."[2] This appeared in the journal Aging in the fall of 2014. So with that and much more that I could say, Dale, thanks so much for being available to talk with us about what's happening in your laboratory and in the field in general in this extraordinary age of functional neurology.

DB: Thanks very much, Jeffrey. I have never been, in my entire career, more excited and more enthusiastic than I am right now because I think we are now at what I would say is the dawn of the era of treatable Alzheimer's disease.

JB: Well, there's a great way to start the discussion! I could tell you, there's probably no better way to get us off the launching pad than that statement. Before we jump out and talk about the most recent extraordinary experiences that you're having clinically, let's go back and talk about this thing that Dr. Perlmutter actually brought up, which was a quote from Louis Pasteur, which is chance favors a prepared mind. You've been preparing your mind professionally for many decades to be able to make these observations and these understandings and the association. Maybe you could take us back a little bit in your career—I don't want a complete biography—but if you could take us through kind of how you see the topography of your professional career as an experimental neurologist and primary research investigator leading you up to this opportunity to have this ah-ha experience, it might be very helpful for all of us to see the evolution of ideas through the life of Dale Bredesen.

Investigating the Science of Cell Death

DB: Thank you, Jeffrey. So we started with the very simple question and have asked a couple of very simple questions through the research over the last 25 years, and the initial one was: What is it that drives

neurons to die? Why do you have neurodegeneration occurring so frequently? As you probably know, just recently it was shown that Alzheimer's has now become the third leading cause of death, after heart disease and cancer, in the United States. There are about 30 million people globally. So a huge problem and so we wanted to know, what are the molecular mechanistics that go into loss of neurons, loss of synapses, loss of neurites, etc., as we age, and we started this actually back in 1989, and we identified specific gene products, and we published—in Science, back in 1993—that there are specific receptors that we dubbed dependence receptors, and that these receptors induced a program of cell death when they do not interact with their appropriate trophic ligands.[3]

So what was happening there is that these were essentially backwards from what had been described in the immunological literature, where you bind a ligand—for example, fast ligand—and you induce the death of the cells. These were receptors, and we now know of over two dozen of these, where they are literally waiting for a trophic ligand, such as nerve growth factor or brain-derived neurotrophic factor—things like that. And when they bind, then it turns off the cell death and when they then lose those, it turns on the cell death.

It was interesting because I had been interested in work from back in the 1930s, as you probably recall, with Dirac, when he pointed out when the electron was first identified he said, "Well maybe there is something where there is something that is like a hole." He described it as a hole, and of course this turned out to be the positron. And so we thought, "Okay, if you take away neurotrophic factors from these important receptors, is it possible that there is also an anti-trophin out there? And at the time there was no such thing as an anti-trophin, but what we found later is, in fact, that Abeta, the very peptides that are increasing in the brains of Alzheimer's (and you have about a thousand-fold too much of this Abeta in the brain of an Alzheimer's patient), they fulfill all the criteria as an anti-trophin. So they block the trophic activity of insulin and insulin signaling, for example. They block the activity of NGF. They block the activity even of acetyl choline at the alpha-7 receptor. So it turns out that in fact there are anti-trophins, and these can also trigger this process.

So we began to look at APP (the amyloid precursor protein that interacts with—as we found—netrin), whether or not that actually functioned as one of these dependence receptors. That is to say, does it mediate things like programmed cell death, neurite retractions, synaptic reorganization when you pull back a trophic factor, when you take away the trophic factor? And we found out, in fact, that APP is indeed a dependence receptor. Its trophic ligand is netrin-1, and there are other things that are trophic; for example, it also binds with laminins. And its anti-trophic factor is Abeta; it interferes with that activity and induces neurite retraction, induces programmed cell death.

Alzheimer's Disease is an Imbalance in Brain Plasticity

So we thought, okay, this is very interesting because it gives us a handle for the first time on what Alzheimer's disease may actually be. It actually may be an imbalance in the fundamental nature of plasticity in the brain. So over the last ten years, we've made transgenic mice to show that in fact this is exactly the case. So we can engineer these transgenic mice so that their APP—this balance of signaling—is imbalanced toward better, more trophic, signaling. And as you might imagine you get mice that are smarter, that remember more, and that forget over a longer period of time. And on the other hand you can go the other way and engineer ones that are actually worse and in fact will get Alzheimer's disease. So this told us that in fact APP is an important contributor. People have focused on just one of its derivative

peptides, i.e. Abeta, rather than on the entire picture. But if you take a step back what you can see is that APP mediates this synaptic plasticity balance, and that that's what we've after in our treatment for Alzheimer's disease.

JB: Well this is an incredible model. I think for most people, unless they are specialists, they probably can't understand all the piece parts like you, obviously, as an expert in the field, but I believe that the model that you're providing is understandable by everyone—this concept of a balance point and equilibrium, because it seems to fit in to the whole model of cellular regulation at many levels that we've learned, this almost yin and yang between activators and inhibitors. So this whole concept of synaptogenesis versus synaptolysis, or how we would find these balance points, appears to be a very central theme in establishing proper function of the organism. Can you give us a little bit of a description of the teeter-totter, as you have described it, in terms of neurological function? I believe that's a wonderful metaphor and learning tool for all of us.

DB: Absolutely. And so what we found is that all this complexity really boils down to something that is relatively straightforward, and that is to say if you think about osteoporosis, as you know you—throughout life—have a beautiful balance in osteoblastic signaling, when the osteoblasts are putting down more bone than the osteoclastic activity. And of course your osteoclasts are phagocytosing and pulling up the structure, and so I often tell people, "Imagine that you've got two sets of contractors coming to your home for many years. You've got the ones that are doing the demolition and you've got the ones that are doing the construction. You might want to add a room here or take something off. Well, imagine that for 20 years the ones that are doing the demolition always did more than you asked them to do, and the ones that were doing the construction never showed up." Your house would dwindle, and that's exactly what's happening in the brain in someone with Alzheimer's disease.

So what we've found is that synaptoblastic activity has a number of signals that contribute to it. Things like: are you learning new items? Are you exercising regularly? Are you in good health? Is your inflammation at a minimum? All the things, of course, that functional medicine directs and functional medicine studies turn out to impact this critical balance, and so, you know, you're actively forgetting the seventh song that played on the radio on the way to work yesterday, and that's very normal. That's part of the synaptoclastic effects. And there are many things that contribute to this. So, for example, reducing vitamin D, reducing hormones, and things like that all contribute to the synaptoclastic activity. Throughout much of your life you have this beautiful balance—you're learning new things but you are also forgetting things appropriately and physiologically. Unfortunately, as you age, and depending on your genetics and depending on many lifestyle things, etc., you can have this chronic imbalance in the synaptoblastic versus synaptoclastic.

And I should add a new concept. We all think about carcinogens, but we never talk about dementogens. And in fact we are realizing more and more that there are many things out there that are dementogens, and this has to do, in fact, with everything from your diet, to whether you're drinking from things with plastic, whether you're eating processed foods—all these things. So we're very used to hearing about the carcinogen concept but not about dementogens, and yet we're exposed to them.

So when we did the transgenic mouse studies, we were able to make very precise changes genetically. As we then went from the mouse to the human, we realized that with a human you're not going to be able to do genetic engineering prior to the human being born. You're presented with someone who's already

early in the course—hopefully very early in the course—of Alzheimer's disease. So we looked at all of the things that can affect the synaptoblastic-to-synaptoclastic ratio, and fortunately, for many of these things, we can actually measure them. A simple example: homocysteine. Turns out that as you increase your homocysteine, in this beautiful work showing biochemically that it leads to a post-translational modification on one of the subunits of the PP2A phosphatase, and what that does is reduce its effect, and therefore the net effect is to increase phospho-tau. Now, phospho-tau, again, is a physiological signal for pulling back the neurites. Again, if you want to pull back your house, you've got to pull out the rivets that are holding the structure together, and that's exactly what happens; the tau stabilizes the microtubules, stabilizing those interactions. So if you want to pull back on them critically, you phosphorylate the tau, which pops it off of the microtubules and allows you to pull back on the structure. So no big surprise: when you look in an Alzheimer's patient's brain, you find a massive increase in phospho-tau. Literally it is telling you there is an ongoing signal for neurite retraction.

The Synaptic Symphony Has 36 Players

So when we then asked, "Okay, what can we do for humans?" we used the analogy that it's a little bit like the 36 holes in the roof. If you try to fix just one hole with a drug, you're not going to get very far because you've got 35 other ones. I say 36 because we identified 36 different players in this beautiful network—this synaptic symphony, as it were—and we can now change all of them. So the good news is we can affect all of those parameters. The bad news is that there may be some other ones out there that we don't know about yet. But what we're hoping is that now that that you affect these other parameters, if you want to use a drug and certainly that's going to be appropriate at certain times, now use the drug appropriately. The drug is a little bit like the dessert; instead of starting with the drug, do all the right things first, and then if you need that drug, now you're doing it in the right background. So we think that this will be a wonderful platform going forward, for testing drugs that have a single mechanism of action or a limited number of mechanisms of action.

So we use the analogy with other chronic illnesses—such as osteoporosis—to direct us, to guide us for what we can do with Alzheimer's disease. And the excitement is that—as you mentioned—we just published the first paper showing that we can reverse cognitive decline. There are lots of open questions. We don't know yet how late in the process we can reverse this. We don't yet know whether this is helpful in other disease processes. There are a lot of things we don't know yet. We don't know whether you need all 36. But the exciting part is you can see, typically within 3 to 6 months, rather dramatic improvements in these patients, so we're very enthusiastic about that.

JB: So before we go on into the details of your clinical observations and the description in the journal Aging, I'd like to do a weigh station check in with you here for a moment because I think there are so many things that you said that have profound, deep implications. One of those was this concept of post-translational effects. I want to just take a moment to hang out with you on that topic.

For many people who think about the way genes regulate function, they may have learned and understand that genes control the production of proteins, and ultimately proteins which can be enzymes (or structural proteins) then control function of cells, which then aggregate to make tissues and organs and so forth. And so we have this kind of fairly linear thought that genes ultimately must control the outcome of function directly.

But the word that you use—"post-translational"—is a very interesting term because it implies that there are things that happen after the genes have been transcribed or translated into proteins that can modulate their function, and obviously one of those is work that you did with Dr. Prusiner, which is conformational changes in protein that we call prions. So if you would help people to understand that even structural changes in proteins at the three dimensional level can have profound effects upon outcome and these may not be genetically linked directly, that's a pretty interesting concept, I think, in terms of a different approach towards the hard-wired, bad gene concept.

DB: Yes, this is a really important point. As you know, going forward it's just been increasing, increasing levels of sophistication that people have understood, now, about your genetics and the gene products. So it's like multiple checks and balances. As you know, you're given a specific gene, but then there are somatic mutations that occur. Then of course, as you mentioned, transcriptional—the whole field of epigenomics is just blowing up right now—so many new observations there. So that's an issue. Then, of course, RNA processing is a huge issue, so there you've got all sorts of different possibilities. And then, of course, there are all sorts of microRNA control on whether you're going to make protein, whether you're going to have a short-lived mRNA or long. So there are all sorts of microRNA controls. And then as you mentioned, once you finally get to the point of actually exporting, processing, all that sort of stuff, and you now get the ribosome and you now actually make the protein, you've also got things like where are you directing the protein? How are you making the protein in terms of its confirmation?

There is, of course, beautiful work—as you mentioned—from Stan Prusiner, also from people like Vishu Lingappa, showing that you can actually direct different topologies of the same protein with the same coding sequence by changing the region just upstream from the start site, which is, again, amazing. Then once you make it, as you said, you've now got the ability also to change its function through things like protein phosphorylation, methylation, sumoylation, you know, on and on and on—acetylation. And you've got things like the sirtuins that are protein deacetylases. So you've got beautiful cycles here, where you can change protein function and structure at multiple levels, at multiple times, and at multiple different locations.

What I mentioned with respect to homocysteine is there is now identified a specific post-translational modification that changes the function of this protein phosphatase-2A, reducing its overall effectiveness and leading, therefore, to a net increase in the phosphorylation of tau, so that you're changing the balance toward pulling back of neurites, toward a positive programmed cell death, and toward synaptic reorganization. Similar things, for example, also occur with what's called WAV1, which is involved with actin depolymerization (so, to pull back neurites). And you've got similar kinases involved, similar phosphatases involved. So what it really shows is that in this beautiful dance, you have higher order organization through specific nodes and that there are controlling features. And one of the ones that we identified, for example, is this balance between SirT-1 and NFkappaB.

The apoE4 Gene Increases a Proinflammatory State

A few years ago we started a new project to ask: why is it that apo E4 is such an important risk factor for Alzheimer's disease? As you know, apo E4 is present, typically, in 60 percent of all people with Alzheimer's disease. It is also a big risk factor for cardiovascular disease, and also for chronic traumatic encephalopathy, and actually other neurodegenerative conditions such as Lewy Body disease. It's been unclear why and the suggestion has been very simple—that it somehow changes the clearance of Abeta,

but it turns out to be much, much more interesting than that. Apo E4, by the way, is one of the genes that changed between the Simians and the Hominids, so it has been argued that apo E4 is a critical gene for allowing us to be human. It turned out to increase the proinflammatory state. You'd think that would be a bad thing, and in fact it is as you get older, but when you are young, in fact, the idea of the Simians coming out of the trees and walking in the savanna and doing all the things that the early Hominids did that we were doing 5 to 7 million years ago, it turns out that apo E4 was quite helpful because it allowed us to eat raw meat, with the many microbes that are associated with it. It allowed us to do things like walk with dung in the savanna. It allowed us to fight with each other and get cuts and scrapes and things like that, and to kill animals (again, with the associated cuts and scrapes) that turned out to be much better addressed by a proinflammatory state, but it's never been clear why this proinflammatory state exists.

What we published just recently is, in fact, that apo E4 reduces the levels of SirT1 markedly, and it turns out that it changes the balance.[4] There is this beautiful balance, with mutual antagonism, between SirT1 and NFkappaB, and specifically it turns out that the apo E will interact and operate at the level of the NFkappaB. And so what it really does is to change your cell programming from the SirT1 side, which is the longevity side, the reduced inflammatory side, the oxidative phosphorylation side. It's a little bit like having a country that's interested in recycling and research, and it switches it over to the NFkappaB side, which is a little bit like a country that puts a lot of its resources into weapons: very good for the short term, very good for fighting things off, not so good for the long run. Just like Louis the XIV—very powerful guy, put a lot of money into weapons and fighting wars. As you know, that didn't turn out so great for the Louis the XVI and Marie Antoinette. So it's the same sort of story: when you have apo E4, you're putting more of your resources into the proinflammatory NFkappaB side—great for walking in the savanna, great for 5 to 7 million years ago, but not good for being over 50 here. But the good news is we can now look early and we can now make a big impact on the future of these patients, and, in fact, a number of these initial patients were apo E4 positive patients with either mild cognitive impairment (a pre-Alzheimer's condition) or early Alzheimer's disease, and they've done very, very well on the approach we've taken.

JB: Again, I want to loop back with you just for a second, because I think you said something very, very important there as it relates to your approach, which we're going to describe. You know better than I—and you've helped educate us—that the approach that the pharmaceutical industry has taken towards remediation and treatment of these neurodegenerative diseases is to find a target and then a high-ligand-binding target to that drug to that target and then trying to block or inhibit it very effectively, assuming that that's going to be an effective treatment. At present it appears as if that model has not been very successful in bringing safe and effective drugs to treat Alzheimer's or Parkinson's. So we get to the question that you just raised: if you have all this complexity out there, is Alzheimer's one disease, or is it a just a phenotype that happens to have certain presenting characteristics that come from multiple arrays of differing genetic and environmental post-translational influences, for which, then, the solution is—as you said—in treating the nodes of the network rather than treating the individual targets downstream?

DB: Well, you bring up a good point, and let me quote from Jeffrey Bland: The Disease Delusion. As with these other chronic illness—obviously you've written a whole book about this—and what we're seeing is that these chronic illnesses tend to be physiological pathway imbalances that are present chronically, and so one needs to identify all of the disparate factors that contribute to this specific network. So we're actually working with a connectomics expert and looking at all the things that contribute to this network imbalance. This is where, I think, the drug companies are going to play a huge

role, as long as you address all of the other features, because, yes, these are powerful drugs, but trying to use them without the arrest of the change in the network is not the best way to go.

So as a simple example, in the decade from 2002 to 2012, 244 clinical trials were conducted for Alzheimer's disease at an aggregate cost of over a billion dollars, and 243 failed outright. The only one that was considered a success was for Namenda, which is memantine, which was such a minimal success that the families could not tell who was on it and who was not on it, so it's a very modest impact. So the idea here is that if we now use all the appropriate changes in this network, then we should be able to see which drugs are actually having the appropriate impact, are actually targeting the right thing, and are actually making a big impact. Right now I believe we are asking these drugs to do much more than they can do. We're asking something that's an excellent patch for one hole to patch 36 holes. It's just not capable of doing that.

Now on the positive side, what we found is that there is a very interesting phenomenon of feedback. You know, in medical school we're all taught about homeostasis and homeostatic feedback, and this is feedback that is negative feedback that drives you back toward a mean. A simple example is your serum pH is 7.4; you never want it to be 2.4 or 12.4. So if you drink an acidic cola, then in fact you'll have respiratory and metabolic compensation that will drive you back towards 7.4. On the other hand, what we're not typically taught in medical school is that there is a very different form of feedback. When you have a multi-goal outcome and you require amplification, you literally have a molecular switch, and a simple example is you want to have blood clotting either activated or not activated. If a cave person cuts their finger off, they're going to bleed to death if you don't very quickly amplify that signal and create the clot. And then, of course, over time you can destroy the clot with specific proteases, etc. That system actually is a positive feedback system. And what we've come to realize is that that is the origin of what we call prionic loops.

Balancing Peptides: Memory versus Forgetting

So in this situation, your input is amplified instead of inhibited, and that's exactly what we see when we look at the amyloid precursor protein—the parent of the Abeta and these other peptides that we've studied. When you cleave this APP at three sites (the beta site, the gamma site, and the caspase site), you produce four peptides (SAPP beta; Abeta, that everyone is focused on; J-Casp; and C31) that are all physiological mediators of neurite retraction and synaptic reorganization, caspase activation, just as you might imagine. These are forgetting peptides, literally. On the other hand, if you cleave it at a single different site—the alpha site—this produces two peptides, SAPP-alpha and alpha-CTF (C Terminal Fragment). Both mediate—guess what?—neurite extension, caspase inhibition, synaptic maintenance. So these are literally memory peptides. And no big surprise: when you have Alzheimer's, you're on the wrong side of that balance. But it turns out that many things will contribute to that balance, just as we discussed. What's interesting is these peptides turn out to feedback positively, not negatively. For example, the Abeta peptide inhibits the alpha cleavage, so you don't go down that side. And on the other hand, the SAPP-alpha will inhibit the beta secretase cleavage and the alpha-CTF inhibits the gamma CFT secretase cleavage. That's all been published. It's a beautiful, beautiful system that literally functions as a molecular switch, so it's a little bit like a snowball rolling downhill. Once it picks up some snow it's going to tend to go down that same side instead of rolling itself back up and going down the other side of the mountain.

So our job in the therapy side, then, is to get that thing to the other side—to reduce the side of the synaptoclastic peptides and to increase the side of the synaptoblastic peptides. So you're absolutely right. You can look at it as multiple diseases, but they all have in common that they feed into this network. And by the way, getting back to your point of multiple diseases, one of the things that's become very clear from these patients we're looking at is that Alzheimer's can come in different flavors. We call this—as a simple example—hot Alzheimer's and cold Alzheimer's. So when you look at the patients with hot Alzheimer's, they have all their inflammatory markers, for example, the hs-CRP, and IL-6, and IL-8, and things like this. These are all increased. The albumin-to-globulin ratio is decreased. These are inflammatory patients, where that's an important contributor. And interestingly part of that, of course, is NFkappaB, which—by the way—the many genes that it activates includes—guess what?—beta secretase, gamma secretase. So it's clearly putting you on the side of these "forgetting" peptides. On the other hand, if you look at the two peptides, then in fact you are supporting the memory. The other patients—the ones who don't have hot Alzheimer's, so they don't have this inflammatory state but nonetheless they are clearly presenting with the same loss of memory, the same imbalance in synaptic plasticity—when you look at them, their hs-CRPs are normal. Their IL-6s are normal. But what they have is a decrease in, for example, hormonal support, so they often will have a very low vitamin D level. Or they will have, for example, a very high homocysteine level. Or they will have a very low testosterone or estradiol level. And so forth and so on. So they are, as we say, cold Alzheimer's patients. They don't have this massive inflammatory system activated.

Reversal of Cognitive Decline Study at UCLA

JB: So with that extraordinary background…I want to again compliment you for the ability that you have, which is very unique among scientists, to take very, very sophisticated information and weave it together into metaphors that—for those of us who are not specialists in the field—are understandable and give us our balance points (our reference points) from which we can draw. I want to go into a discussion now of your article "The Reversal of Cognitive Decline: A Novel Therapeutic Program" in which you describe the clinical outcome of these patients, but before I do that I wanted to return back to this little CNN article that just appeared authored by Stephanie Smith, and I'm going to quote because this will bear on a question I want to ask you about the process of innovation.

So she says in this article, and I'm selectively quoting now: "Yet a very small study out of UCLA is offering a glimmer of hope of those with what is often a hopeless diagnosis of Alzheimer's. Nine out of the 10 patients involved in the study…"—that's your study—"who were in various stages of dementia, say their symptoms were reversed after they participated in a rigorous program. The program included things like optimizing vitamin D in the blood, using DHA supplements to bridge broken connections in the brain, optimizing gut health, and strategic fasting to normalize insulin levels." Then—I'm going to segue forward in the article—she says the following: "Hendrix with the Alzheimer's Association said one sound element of Bredesen's study, given the complexity of Alzheimer's disease, is its focus on addressing multiple risk factors. He cites as an example a two-year, 1200-person clinical trial out of Finland, the results of which were presented earlier this year at the Alzheimer's Association International Conference. Among study participants engaging in nutritional changes, physical activity, brain training, social activities and management of risk factors for heart problems, cognitive performance improved. Bredesen stresses that identifying the culprit for early Alzheimer's symptoms must be based on a patient's specific deficits and imbalances." I'm going to stop there.

So clearly, Dale, with any kind of work of your magnitude of paradigm-shifting conceptual framework you're going to have people who get it and people who don't get it, people who are supporters and people that are detractors, people who use old metaphors to describe new knowledge which doesn't really fit and those that have new language to describe new observations that does fit. Can you tell us a little bit about how you're seeing the landscape of understanding respond to your work?

DB: Yes, that's just a great question, Jeffrey. So the people who are invested in keeping the status quo, whether it's related to drug development, philanthropy, grant support, long-term laboratories, any of these things, are not surprisingly skeptical and often quite negative. You know, she mentioned something in the article about, you know, not recommending that people go out and do these things. Yes, certainly don't go out and eat well and improve your health. That's absolutely right. But it is, in that sense, a little bit silly. As I mention in the paper, one of the side effects of the program is that you improve your BMI, and you improve your health. So there has been skepticism, and the response—and I know this happens often when you are doing something that is a bit disruptive to the system that is in place, and so we need more patients. We need more documentation and we're in the middle of doing that right now.

You mentioned the Finnish study, and the Finnish study actually had little to do with what we're doing in that we're taking people who were symptomatic with early Alzheimer's or it's precursors, and looking at all their various parameters and then optimizing them. I think it's important to say not just normalizing them, but optimizing. So as you well know, a homocysteine of 12 is considered normal. It's certainly sub-optimal and that's been well studied, published, etc. You know, we look at that with all these parameters because we're trying to change that threshold. So we want more documentation. We want continued number of patients, etc. And we want to optimize these parameters. Now, what the Finnish study did, was simply to take people who had some cardiovascular risk factors. That was it. So none of them was symptomatic from the standpoint of cognitive decline—nobody had Alzheimer's—and they simply said, "Okay, you know, you should eat better and exercise." They used four different parameters. They had four different things on the protocol. They didn't evaluate all these other things. So a very, very different sort of study. [5]

What we're looking at here is to understand why it is that you are on the wrong side of this synaptoblastic/synaptoclastic balance, and then to change that so that you can literally reverse the cognitive decline. Now obviously when I first talked to some of my colleagues about this a couple of years ago, they said, "Well, that's impossible because you can't reverse neurodegeneration. Once the degeneration is there it's there." Well, it turns out it's not quite that simple, as you know. It's turned out that in fact there's a lot of chemical abnormality, and there's also a fair amount of reversible synaptic loss, it appears, so that in fact there is a lot that can be done, at least up to a point. And one of the things we're most interested in is when you reach that point where you can't reverse this—wherever that may be and we don't yet know where it is—then, okay, what do you do next? Is it possible that with the addition of stem cells to critical areas, for example in the hippocampus or potentially in the cortex, is that good enough? Or do you now need to add trophic factors intracerebroventricularly? There are a number of possibilities to take this to the next step. Right now, there's a lot we can do for people not only at the prevention level but at the reversal level for SCI, as I mention in the paper (subjective cognitive impairment—the earliest stage), then even through mild cognitive impairment (the next stage), and even through early Alzheimer's, and we've seen improvements in all of those. I doubt if we're going to be able to do anything in the later stages. We only had one patient who was literally end-stage when we started. She was only on this for four or five months. She did not show improvement and we mentioned

that in the paper, but that's an n-of-1. We'll see going forward. What about when we have the next hundred?

I think there are many questions, and as you mentioned, this is something that not just our study, but many, many studies in functional medicine have gone up against. When you're trying to change the paradigm, there's going to be a lot of pushback.

JB: So let's now talk a little bit specifically about this extraordinary paper that you've recently had published. I want to go to page four of the paper, which is your Table 1 Therapeutic System 1.0, in which you outline some of the multiple indices or contributors (your 36-hole model). So you have—and I'm just going to list the kind of categories so that the listener will understand a little bit as to where these fit into—first we have optimizing diet, minimize simple carbohydrate, and minimize inflammation. Enhance autophagy through ketogenic effects, and that is, I think, a very interesting part of what Dr. Perlmutter was talking about as well. Autophagy is another part of how we modulate mitochondrial bioenergetics. Reducing stress, optimizing sleep, exercise, which you've already spoken to and Dr. Perlmutter spoke to as it relates to the impact of aerobic exercise and neurogenesis. Homocysteine (lower than 7), serum B12 (greater than 500 micrograms per mL), CRP (C-reactive protein) that you mentioned, hs-CRP less than 1 milligram per dL. Fasting insulin less than 7. Hemoglobin A1c less than 5.5 percent. These are indications, obviously, of insulin sensitivity. Hormonal balance—you've talked about thyroid, and testosterone, progesterone, pregnenolone, cortisol (the stress hormone). GI health—again coming back to some things that Dr. Perlmutter mentioned as it relates to what we call leaky gut. Reduction of Abeta, which you've talked about considerably. There are some botanicals seem to have positive impact on reducing Abeta. Cognitive enhancement through training and exercise. There are a variety of tools on the computer now that are available to do that. Vitamin D levels greater than 50 nanograms per mL. Synaptic structural components, optimize antioxidants to reduce oxidative stress, optimize the zinc-to-copper ratio. Ensure nocturnal oxygenation so you don't have people that have obstructive airway conditions or that are having problems that need to be on the CPAP machine. Optimizing mitochondrial function, improving SirT1 function, as you mentioned, like resveratrol. Exclude heavy metal toxicity (mercury, cadmium, lead), and effects of medium chain triglycerides. So that is your list in Table 1.

So when you have a person come in, how do you go about clinically evaluating what holes to start repairing first?

Dietary Links to Alzheimer's Disease

DB: Let me just say at the outset that you could spend hours on each one of these things, as you well know. I mean just the diet part alone, we've just scratched the surface—you know, the obvious, very critical things, like sugar. Simple carbohydrates—and I realize I'm sure that David Perlmutter has talked a lot about this—this is a huge issue. What's really intriguing to me is that when you look at the actual function in the brain, and there is some beautiful work that has just come from Ed Goetzl, who studies neural exosomes, so these are these very small, hundred-nanometer fragments that break off from cells and you have 1.2 billion of these per cc of blood. It turns out about 10 to 15 percent of these are derived from the nervous system, so you can look at neural markers and identify these as having come from neurons, which is amazing. So for the first time, then, we really have a window on the mind. You can isolate blood, isolate the exosome, and then isolate from those the neural exosome, and then you can study these, and you find the obvious things, like it increases Abeta peptides, and like an increase in

phospho-tau just as you'd expect, but then it allows you to start studying the biochemistry that's actually going on in the neurons. And one of the things that he found was that all of the patients with Alzheimer's disease—and this is beginning about 10 years before they had the diagnosis of Alzheimer's disease—they had insulin resistance. So the classical thing that we think about for type 2 diabetes was part of the picture, and it really supports this notion that signaling is imbalanced in this condition even long before you have the condition itself. So this is a critical piece and we can see that—how people are contributing to their own development of Alzheimer's disease. And so he actually used a specific approach where he looked at IRS-1, a signaling molecule, and he looked at the ratio of serine-threonine phosphorylation, which is essentially what's downregulating its activity to the tyrosine phosphorylation, which is the active part, and showed that these people had an increase in the serine-threonine phosphorylation. Literally, so he is looking at insulin resistance.[6]

So what we do, then, to get back to your question, is to do a typical evaluation. We want to know what the MRI looks like. We want to know, what about the PET scan? So that you can look at whether there is a change in metabolism that has the typical distribution of Alzheimer's disease, which is a temporal-parietal decrease in glucose utilization by the brain. And then what we want to do, which isn't typically done, is we want to look at all these other serum parameters that you just mentioned a minute ago. So we want to know what your copper-to-zinc ratio is, what your free copper-to-zinc ratio is, what your hs-CRP is, and all the things that you just mentioned, because these are all things that we've identified as being critical mediators of that balance. Then what we want to do is to optimize all of those parameters and then follow you. And then of course part of this is to iterate. So in other words, you want to continue, instead of giving someone one pill on one day and saying, "Go home and come back in three months," we want to work with these people to change things a group at a time. You can't change all 36 things on one day—no one's been able to do that. The good news is that because of this prionic loop feedback that I mentioned, what happens is that you reach a threshold. For example, one of the patients we worked with started eight things at the beginning. She noticed a little improvement, but it wasn't spectacular. A few months later we added another several things. Again, she noted additional improvement. And it wasn't until that third set that now at the third set she said, "Oh my gosh, things are now really back to normal." And so we got over that threshold, and it really fits exactly, again, with the biochemistry. One of my favorite quotes is from Richard Feynman who said, "Nature uses only the longest threads to weave her patterns, so each small piece of her fabric reveals the organization of the entire tapestry." This is what we see with the APP cleavage. We see the prionic loops in it. We see that things actually mediate synaptic loss with synaptic reorganization, and other things mediate caspase inhibition. We see the basic biochemistry that forms—it allows you to form the memories—and we see how it is altered in Alzheimer's disease, and of course we see what we can do about it.

JB: Just listening to you is such a treat because you really are speaking—in specific examples—around this general theme (this philosophical theme) of network biology, systems biology in medicine. As I'm hearing you speak about the insulin receptor substrate 1 (IRS-1) and its phosphorylation, I'm reminded that we just completed a mini-course in type 2 diabetes in which one of our three experts was Dr. Ron Kahn who is the head of the Joslin Institute at Harvard Med—a diabetes expert—and he was credited as the discoverer of the phosphorylation of IRS-1 and the kind of initiation of our understanding of insulin signaling some 25 years ago. What we are talking about are interwoven patterns. As you've said, it's almost like holographic. You can pick out any part of the puzzle and you can understand the whole puzzle because they are all interwoven, one with the other. That is a very, very different model, as you spoke to, than the way most of us were trained: differential diagnosis, reducing large to small until we get to

knowing everything about nothing. I think that this construct of assembly out of a structural, complex level so that we can then actually see the forest for the trees is a very, very powerful new concept in medicine. This early paper that you've now published with these clinical outcome studies of real people I think are the proof of the pudding. This is very difficult work to do. It's much easier to have one drug for one disease with one outcome. It's much more complex to deal with the complexity of chronic illness as it really exists in biology and then to design different approaches to prove a hypothesis in knowing that each patient is kind of an n-of-1 in their own discovery of life. I believe all of us who are listening want to compliment you for the courage, and the resourcefulness, and the scholarship, and the extraordinary precision that you're bringing into really defining a whole new field in medicine.

DB: Thanks, Jeffrey. Of course we're using the functional medicine approach that you've pioneered over the last 30 years. You know, we have to quit asking what it is and start asking why it is. I think that's where the excitement is. When we can understand why it is, we can really do something about it.

JB: Dr. Bredesen, I want to—on behalf of all of our listeners—send a large amount of support and encouragement to you. I know it's not easy getting grants to do this kind of work. I know it's not easy, sometimes, for your faculty colleagues and peers to understand exactly what's going on when you've taken this different approach. I think that this is the kind of groundbreaking systems approach that will change medicine and allow the move-forward in the management of these—as you said, the third major cause of death now is Alzheimer's-related illness, which we need a new model to approach. On behalf of all of us we send our strongest support and encouragement for your continued work in this area.

DB: Thanks, Jeffrey, and thanks for all the great things you're doing.

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