December 2012 Issue | Dale Bredesen, MD The Buck Institute for Research on Aging

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Welcome to our year-ending edition of *Functional Medicine Update*, the December 2012 issue. Always at the end of a year we try to highlight someone who really exemplifies where medicine is going, and the new technologies, and the new concepts that are going to advance healthcare delivery, and we're very, very fortunate to be able to finish up 2012 with just such an individual as our key opinion leader, clinician, researcher of the month. Dr. Dale Eric Bredesen is Professor and founding President/CEO of the Buck Institute for Research on Aging, which is in Novato, California. Probably you are mostly familiar with this as a world-renowned institute that is really focusing on biological mechanisms of aging and how that interrelates with age-related diseases.

INTERVIEW TRANSCRIPT

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Dr. Bredesen is a neurologist by background and training, and also an internist, but he has—I think—a much broader imprint in terms of what his accreditations imply. He got his Bachelor's degree—again kind of showing his Renaissance person background—in both biology and literature from the California Institute of Technology. He went on to get his MD at Duke University, and did his residency in neurology and became Chief Resident at the University of California, San Francisco. He went on from that to work in the laboratory of Dr. Stanley Prusiner, a Nobel Prize winner that you probably are all aware of because we've had the chance to speak about his work over the last 20 years, on the discovery of prions and how that relates to neurodegenerative diseases. He then became, obviously, an NIH postdoctoral fellow with Dr. Prusiner, and from there on, then, has a rich background at UCLA, at the Burnham Institute, at the UCSD neuroscience department, and now most recently at the Buck Institute, where he has led the charge in looking at neuroscience as it relates to neurodegenerative disease, specifically Alzheimer's disease is one of the major focuses.

When I first met Dale—to now go from the kind of academic to the real person—I was immediately struck by the breadth of his understanding, his interest, his compassion, and his willingness and receptivity of thinking out of the box. These are the kind of paradigm-shifting individuals that really create great advances in health care by their intelligence, wisdom, and background, but also their willingness to step out of the straight lines of their discipline and think cross-disciplinarily and maybe even be a little bit of kind of a fugitive in their own discipline. It's with unbelievable privilege that we have Dr. Bredesen as our Clinician of the Month, here for the month of December, and also, just as a person, Dale, I want to thank you for your advocacy, the work and your breadth of impact that you are having.

Let's start with the first question, and it's kind of a common question that I use to get into the topic: What led you into neurosciences? Obviously as a person with a background in biology and literature, you had a wide breadth of things you could have explored. Why neurosciences?

DB: Thanks, Jeff. First of all, let me thank you for your kind introduction, and also I comment on my own interest in what you're doing, which I think represents the future of medicine. So, thanks very much again for all the great work you do and for the invitation for today.

With respect to the question about neurosciences with a background in medicine, it was actually the other way around. I was a freshman at Cal Tech, and I read a book called The Machinery of the Brain, by Dean Wooldridge, of TRW fame, and I was so intrigued by his comparison of human brain function to the computer (this was in 1971).[1] I thought that the workings of the human mind were so incredibly interesting and had such far-reaching implications for whether we're ill or not, what we do, how we act, how we grow up—all of these important issues. I really fell in love with neuroscience. And then, at the time, Seymour Benzer (at Cal Tech) was doing some very exciting work. He was one of the fathers of molecular and behavioral genetics. Instead of just asking was the eye of a Drosophila white or red, asking whether the Drosophila could learn, whether the fruit fly could learn, and whether it had an appropriate 24-hour cycle, and these remarkable fundamental processes, which he was able to narrow down to single genes. In fact, his group was the first to find a gene called "Dunce" that was for memory.[2] I thought this was fascinating. So I took his course, and also, at the time, was fortunate enough to work in the lab of Nobel Laureate, Roger Sperry, who had done the split-brain work.[3] So it was a very exciting time, but as I got close to the end of my college career I thought, "Gee, I really want to understand how diseases happen to the nervous system. What actually happens to make things fall apart? What happens to make things go awry? Whether it is an affective disorder, or whether it is a neurodegenerative disorder." So that's how I got interested in medicine.

JB: Well, I think it's very interesting because undoubtedly you have run into in your career, as I have, with many people who have had a common maybe "a-ha," wanting to take on these very big questions, and then you ask: "What's the difference between those that have been aspirants and those that have been successful in really pioneering, and staying to the task, and over decades of contribution really carving out new disciplines?" Often that comes back to not only the intelligence, and inquiry, and hard work, and commitment of the individual, but also the mentors and the people that have affected their careers and kept them on their task. You mentioned Professor Sperry as a Nobel Prize winner that had an impact. Have there been others along your lines that you would say this becomes part of your guidepost as you have developed your career?

Work with Dr. Stanley Prusiner

DB: Yes. When I came here to UCSF to work as a resident first and then fellow, I ended up working in the laboratory of Stan Prusiner. Stan is a truly remarkable scientist. Stan made what I believe is one of the most important biological discoveries of the 20th century, which is to discover what he dubbed "prions."[4] Of course, up until that time the thought was that any sort of heritable trait had to be passed

on through nucleic acid, be it DNA or, of course in cases of some viruses and viroids, RNA. But he showed that in fact information could be transferred via protein, and initially with PrP it appears to be protein conformational changes to show that there is a protein only, and yet multiplying agent, which he named prion. That was a fascinating finding and it has turned out to be relevant for far more than just the scrapie and what were thought to be other prion diseases. It now looks as if it will have relevance for diseases like Alzheimer's disease, Parkinson's disease, and possibly even some things like diabetes.
JB: You know, I know that for many of us we've heard the story about Jakob-Creuzfeldt disease, and we've heard about the infection with prions by feeding one animal part to another animal (through sheep to cows), but I think we probably have a fairly unclear understanding as to the significance and the implications of this whole prion concept. Could you take us through a little bit more detail about this? Because I think this concept of shape versus function, which Linus Pauling talked about 60 or 70 years ago, really pertains so beautifully to this whole disease model.
Explaining the Concept of Prion Disease

DB: Yes, that's a good point. Of course, in the distant past the idea was one protein, one correct shape. You might have misfolding or unfolding, but in general the idea was you had one protein, you had one shape, you had one function. And of course it's become clear over the last couple of decades, now, that you can have one protein, multiple conformations, and interestingly, multiple normal functions, which makes things much, much more complicated. What Stan found was that in the case of what he named prion protein (PrP), there is a form—PrPC—which is the cellular isoform of prion protein that has a normal function. The function at this point is unknown, but it is clearly a normal part of all of our brains and actually cells outside the brain as well. On the other hand, there is a different folding—and I should add that the PrPC has a certain percentage (about a quarter of it or so) that is folded in a classical alpha helix (something that was originally described by Linus Pauling for proteins). And so about a quarter of it has this alpha helix, whereas when it converts what's called PrPSC, or the scrapie form (this is from the disease scrapie that affects sheep, and mule deer, and many other animals—similar to mad cow disease), when this protein folds in a different conformation, it loses, basically, its alpha helix and it features a much higher degree of beta pleated sheet, another classical protein conformation, and it changes its function, and importantly, it is able to seed a process that amplifies, that is to say it is able to beget more of itself through interactions with PrPC. It's not yet clear how this occurs, but in any case, it ends up with the protein refolding in a way that produces a protein that amplifies over time, and ultimately gives rise to a brain disease (a prion disease).
Now interestingly, this is a process that can be infectious because of the fact that PrPSC is so stable. However, what we now believe is that this is actually the tip of the iceberg for a much more general process: if you think about what we were all taught in medical school, we were taught about homeostatic feedback, and if you have a single-goal outcome and don't require amplification of a biological process, then homeostatic feedback is what occurs. As a simple example, we all want our serum pH to be 7.4, we never want it to be 10.4 or 2.4, so if you happen to drink a soda or something and it gets a little acidotic, of course you have respiratory and metabolic compensation, which drives it back to 7.4. However, if you think about it, there are other processes that require amplification and have multi-goal outcomes in which the system functions as a molecular switch. A simple example is blood clotting. If you've got a cave person who accidentally cuts off his finger, if he doesn't clot rapidly he's going to die, and so, of course, you have a system of serine proteases that in fact amplify their own activity, ultimately producing a thrombus that is then degraded proteolytically over time.
These systems feature anti-homeostatic feedback, and by definition then, they are essentially what we would call prionic loops. We find these to be very common, creating molecular switches, and believe that

these are actually at the heart of what, in the pathological case, becomes prion disease.
JB: Well that is unbelievably fascinating, both for the specific and the general concepts of pathology. I'd like to—before we move on a little bit more on that because I think that's a really fascinating concept—I'd like to just take a weigh station for a second and just do a historical review. I had the chance many years ago when I was at the Pauling Institute to meet Carleton Gajdusek, who had won a Nobel Prize for his discovery of "slow-reacting viruses" and their relationship to kuru.[5] I think there was a very significant interesting interplay between Gajdusek and Dr. Prusiner as it relates to this controversy. Could you kind of bring us up to speed, because I think that's kind of a specific example of a more general theme about controversy in medicine and paradigm-shifting thoughts?
DB: Yes, this is a very good point. Of course, Dr. Gajdusek brought these diseases to the attention of the world. Some of the original work on slow infections was written in 1954 by Sigurdsson, actually, who talked about his idea of chronic and very slow infections, assumed to be viral in origin (and in most cases, these did indeed turn out to be chronic viral illnesses).[6] And then later, Gajdusek identified these in kuru and studied them extensively, showing that what had been thought of as degenerative illnesses—kuru and Creutzfeldt-Jakob disease—could actually be transmitted as infectious processes, but at that time the nature of the agents themselves was not clear, and it was thought that most likely these were viral in origin. Stan then really brought beautiful basic chemistry and chemical approaches as well as genetics and biochemical approaches, to bear on this problem, and was able to show that these agents have no DNA or RNA, surprisingly. It was actually very reminiscent of the original work on DNA by Oswald Avery, showing that DNA was, in fact, the heritable agent. When Avery's work was initially published, the idea was "Well, you know, are you missing some small amount of protein in there?" because people weren't ready to believe that DNA was in fact the heritable agent. Stan essentially had the opposite problem of showing that you could have a heritable feature with protein only, but he did a beautiful job genetically and biochemically of showing exactly that.
JB: So, as this model now has gone from kind of "theory" to accepted, which is a major shifting paradigm within physiology and pathophysiology, then it starts raising questions about the structure of all sorts of macromolecules, and their different conformation, and their relationship to disease (this structure/function concept that we were describing earlier), and it takes us back to the whole family of amyloid-related disorders. How does this interrelate clinically with our looking at different conditions associated with amyloid accumulation?
The Theory of Prion-Nativity and Alzheimer's Disease as a Prionic Loop Process

DB: Yes, that's a great question. The original suggestion we now call "the special theory of prion-nativity," in which you have a conformational change in prion protein or other proteins, potentially things like alpha-synuclein that can also accumulate. However, what we now believe is that there is a much more general theory of prion-nativity, in which any x plus y, producing 2x, leads to amplification, and as I mentioned earlier, as long as this functions normally in things like blood clotting, then this is a physiological process. However, to do that you have to balance—of course, you have to degrade—the amplified product over time, which you do, of course, with things like a thrombus. When this gets out of hand you have things like disseminated intravascular coagulation (DIC), and our view of Alzheimer's disease as a prionic loop process is that it is essentially that same sort of process over a longer period of time in the nervous system. If you think about it, you will realize that prionic type amplification could, theoretically, occur not only with protein folding (which is the basis for the conversion of PrP-C to PrP-Sc), but also with imbalances in protease cleavage (which occurs in the conversion of APP to the A-beta peptides in Alzheimer's disease), kinase activity, transcriptional activity, and other processes, as well. And the bottom line is that these are not just single molecules altering conformation, but these are

biochemical loops. We now call these prionic loops. And things that dampen these down we call anti-prions, which can inhibit the loops. So you have exquisite modulation of these pathways that are physiologically relevant, but in the case in which there is amplification out of the physiological range—essentially like a snowball rolling downhill—you get to the point ultimately that these become pathological. And what we have found in the laboratory is that we can add small amounts of these seeding molecules, and through these prionic loops, amplify the original product and produce disease-related molecules. And in the case of Alzheimer's disease, we see this both at the level of the A-beta interaction with APP itself, and at the level of tau and phospho-tau, and there are likely to be others as well. But interestingly for these, the A-beta loop is a little bit like having a benign tumor—it's essentially the upstream part of the problem. And you can actually live for many years, as Pittsburgh compound B (PiB) scans are now showing us, with this A-beta prionic loop acting. On the other hand, the downstream loop, which would be analogous to the metastatic tumor, occurs when you have tau abnormalities and hyperphosphorylation of tau; this is more associated with symptomatic disease, so it's typically a later event in this chronic process.

JB: You just said something that to me is really a potential "a-ha." I go back and think about MS and neuritic plaques. The hallmark, traditionally, for the assessment of the severity of MS would be to look at the density of neuritic plaques. And then people started saying, "But hold it. If we really match up symptoms against neuritic plaques, they don't really correspond very closely. We can see plaques without severe symptoms in some patients, and in other patients we can see not-so-severe plaques and very severe symptoms." So we can't say necessarily the pathology that we call MS comes from the plaque. It is more kind of a second association. Is that at all related to what you were just describing? Is that a clinical example of this kind of sequence of events related to alteration of function and form?

DB: Yes. What's important here is that the pathological entity is essentially the end result of physiological processes that are normally in balance. Our view of Alzheimer's disease is quite different than the current dogma. It suggests that in fact you have a normal process of plasticity that is ongoing. What's really interesting is that the molecules already known to be involved in Alzheimer's disease, such as the amyloid precursor protein, and A-beta peptides, and tau, and presenilin 1—are all molecules that are involved in the normal process of plasticity, so literally they are involved in the physical events that lead to plasticity. They are involved in neurite extension, in synaptic maintenance, in synaptic efficacy and synaptic turnover, in caspase activation, neurite retraction, and ultimately programmed cell death. These are all processes that are involved in normal plasticity in the making and maintaining of the one quadrillion synapses that you have in your brain. And of course if you look at Alzheimer's disease, it actually works backward, starting from the most plastic synapses to the lesser plastic synapses, so that—no big surprise—you lose your memory early on, before you lose more basic and less plastic abilities. So the critical piece here is the synaptic efficacy and the loss ultimately of synapses. You begin with a chemical abnormality at the synapse, but you progress to a physical loss of the synapse, then you progress to neurite retraction, then of course you ultimately progress to neuronal loss. These are all essentially taking a physiologically balanced process and, unfortunately, imbalancing it toward one direction. So imagine that you have your car and normally you balance the forward and the reverse, to get where you want to go. Now imagine that every time you step on the pedal it will only go forward a few feet but it goes in reverse extremely well, so you are most of the time going in reverse. That's what's happening in the Alzheimer's brain. You have minimized the ability to go forward and you have maximized the ability to go in reverse. So it is a brain that is very good at forgetting, but very poor at learning new material. And the important part is that we can measure the molecules that are involved in the forward process—which supports memory formation and retention—and in the reverse process—which supports forgetting—and then identify both pharmacological and non-pharmacological processes that alter this critical ratio, favoring

memory formation and retention and improving Alzheimer's disease. This is analogous to identifying agents that improve the HDL:LDL ratio—we are altering a ratio, favoring a desired physiological process and inhibiting a pathological process.

Synaptic Processes Are Affected by Diet, Exercise, Stress, and Sleep

I should add, the big surprise to me and the big excitement to me occurred when I realized that the mechanisms that we're looking at—this critical balance—is affected by exactly what my wife has been telling me for over 20 years. My wife is a family practice physician, and she has always said, "Well, whatever it is you guys ultimately find, it's going to have some important relationship to DESS (Diet, Exercise, Stress, and Sleep)." And the surprise is that these very fundamental molecular mechanisms that balance the laying down and picking up of synapses, and the laying down and the reorganization of these synapses, are indeed affected heavily by exactly those processes of diet, exercise, stress, and sleep (as well as other things, of course). Things like where you stand with your homocysteine—this has a beautiful molecular mechanism, which is actually through its impact on protein phosphatase 2A and how PP2A is post-translationally modified. When your homocysteine rises, you in fact inhibit your protein phosphatase 2A, which leads to, interestingly, more phosphorylated tau, so you are unable to dephosphorylate your tau, and you are essentially throwing that neurite growth into reverse. With this higher phosphorylated tau, this pops the tau off the microtubules, and essentially now throws it into reverse, allows the microtubules to destabilize and drive back, and similar things occur with the mechanism of actin depolymerization.

So if you look at this from 30,000 feet, what you see is that this is fundamentally related to the process of plasticity, of making and reorganizing synapses, and it has an important relationship to your exercise state. Exercise drives up brain-derived neurotropic factor (BDNF) and actually puts you on the positive side with respect to laying down synapses. In contrast, as you know, if you eat simple carbohydrates, then in fact you drive up your insulin level. Insulin must be degraded, of course, by insulin-degrading enzyme, which interestingly also is one of the enzymes responsible for degrading A-beta. So if you drive up your insulin chronically, then in fact your A-beta accumulates because your IDE is breaking down your insulin. Multiple processes like this feed in beautifully to the molecular mechanisms involved with plasticity.

JB: The last five minutes was a gem of unmeasured consequences. I mean, just amazing density of insight that you just shared with us. One could tease apart almost every word in those sentences and have a deep learning opportunity, so I want to go back and just pick up a few thoughts because I think the way it just flows so beautifully off your logic trail may still leave a lot of us who are still in the learning curve a little bit trying to catch up. Let me, if I can, go back to this concept of the forward and reverse. We might call that a balance point. Every activator in physiology has a deactivator. Every accelerator has a break. This, in traditional Chinese medicine, might be called the yin and yang—the balance points that create regulatory networks that orchestrate functional changes against environmental perturbations. What I just heard you say is that it's not necessarily that these proteins that we've often associated with the pathology of Alzheimer's, like amyloid precursor protein, or presenilin, or phosphorylated tau, or A-beta are in and of themselves pathological molecules. They don't get labeled as bad. They have a function, but when that function is out of balance then you can get this accelerator/reverse gear type of imbalance, and now what you start doing is creating over time an alteration of function, in which the system loses its plasticity and we eventually start losing those functions that are associated with that plasticity. Am I all summarizing accurately, on a simplistic level, what you were sharing with us?

DB: Yes, absolutely. There are a couple of key points here. First of all, epidemiologically, there are many things that have been associated with Alzheimer's disease, and any theory that seeks to explain

Alzheimer's must take into account all of these remarkably disparate risk factors for Alzheimer's. So if you are a woman who had an early oophorectomy, at the age of 40 or earlier, you are at a two-fold risk for Alzheimer's disease, for example. If you had little education, if you hit your head, if your vitamin D levels are low, if your homocysteine is high, if you ate a lot of carbohydrate, if you have a large waistline—all of these things—as you well know, men with low testosterone levels, you can go on and on and on. There are remarkably disparate biochemical associations with this problem, so whatever we come away with here must explain the relationship.

The second thing is that there are a number of paradoxes that are unexplained by the current theories. As a simple example, there is some beautiful work out of Cattaneo's lab in Italy, in which he produced what's called the AD11 mouse. This is a mouse that simply has a germ line insertion of an antibody fragment against nerve growth factor (against NGF), and over time it develops both plaques and tangles, and classic theories of Alzheimer's do not explain that.[7] And there are many other currently unexplained apparent paradoxes. What we're arguing is that Alzheimer's disease is no different than other chronic illnesses, such as cancer, osteoporosis, and atherosclerosis. These all have to do with chronic imbalances that are because of the physiological set up—that these unfortunately feature amplification. As a simple example, if you look at cancer, cancer can result from a rare somatic mutational event because of the amplification. Once you have the imbalance between oncogene activity and tumor suppressor gene activity (both of which are normal, of course), you have an imbalance between your proliferation and survival of cells versus your programmed cell death (your turnover of cells), either because you've smoked cigarettes, or because you've been out in the sun too much, or you've been exposed to chemical carcinogens, whatever—anything that puts that out of balance leads to cells that select themselves in a Darwinian fashion because they now have an advantage in terms of proliferation rate and/or survival rate, so that you can end up with a clinical disease that we call cancer.

In the case of Alzheimer's disease, this is a molecular cancer, because the amplification process occurs not at the cellular level, as in a neoplasia, but at the molecular species level. This is a prionic loop disease. And instead of focusing on cellular proliferation, the focus is on plasticity, i.e., the making and breaking of synapses, the growth and retraction of neurites, and the modulation of synaptic transmission, etc. So Alzheimer's disease is in many ways analogous to cancer, but what's interesting is that instead of the amplifying process being at the cellular level, where you produce more cells, the amplifying process is now at the molecular species level, where you're producing more of a molecular species, be it prion protein, or be it A-beta, or be it phosphorylated tau, or be it alpha synuclein. In all of these cases, what we're suggesting is that there are biochemical feedback loops related to plasticity. As you will recall, we talked earlier about the idea of a thrombus: this is the structural result of the amplification process—in that case mediated by serine proteases—that results in a transient structural change that inhibits blood flow. So, in the case of AD, we're talking about the same thing, with the molecules involved in a transient change in structure, which is at the synapse level now, that has effects on information flow instead of blood flow, but it's the same idea with the same sort of amplification process. And it also tells you why it is that these different epidemiological processes all feed into this process that is involved with synapse maintenance.

The Role of Dependence Receptors in Alzheimer's Disease

About 20 years ago, actually, we discovered a new kind of receptor that we called dependence receptors, and these receptors essentially sample the milieu, which includes the hormonal state of the cell, the neurotransmitter interactions, trophic factor interactions, extracellular matrix, and so forth and so on.[8] And ultimately they integrate over that biochemical space to determine whether the cell is going to survive and is going to put out processes, maintain processes, or is going to pull back and ultimately commit suicide. This is what's occurring in Alzheimer's disease. The amyloid precursor protein, APP,

actually turns out to be one of these dependence receptors, so ultimately it senses the trophic/anti-trophic balance. One of the interesting corollaries, here, is that the A-beta peptides themselves actually have a physiological function as anti-trophins. They interfere with, for example, insulin signaling through the insulin receptor. They interfere with neural transmission through the cholinergic system, and affect glutamatergic transmission as well as other systems. They interfere with trophic signaling through NGF and BDNF, for example. So the literally have a physiological function as anti-trophins and anti-transmitters.

JB: So, as we hear you, it just strikes me so strongly, Dale, that this model that we birthed a little over 20 years ago—the functional medicine model—which has this functional medicine matrix in which you sieve antecedents, signs, and symptoms through this matrix to try to understand clinical imbalances, that that model really aligns itself so, closely, it would appear, with this emerging understanding of the etiology of Alzheimer's disease. This construct of balance, the construct of effectors and inhibitors, the construct of environmental interrelationships with gene expression factors that create new proteins that then have differing regulatory functions on cell outcome. It seems like these models are very consistent with one another. I'm just fascinated as to the precision by which you're developing this understanding at the Alzheimer's disease-level and how it—I think—relates with this kind of broad brush functional medicine matrix model that we've been working on for 20 years.

Approved Alzheimer's Drugs Have Minimal Therapeutic Effects

DB: Absolutely. I think that these chronic illnesses are network abnormalities and relate extremely well to the functional medicine model. This, to me, has very important implications. One of the implications is in the treatment of Alzheimer's disease—and as you know, this has been a real problem with literally billions of dollars spent so far developing therapeutics that have virtually all failed. The currently approved drugs for Alzheimer's disease, such as donepezil and memantine, have absolutely minimal effects on the disease. If you look at the last several years, it has been uniform failure, one drug after another, from Dimebon to Rember to Alzhemed to Semagacestat to Flurizan. You just go on and on and on, and there have been no successes. It may well be that the important point here is not what you choose to treat, but what you fail to include in your therapeutics. For example, just as it doesn't make sense to tell someone with atherosclerotic cardiovascular disease to stop their cheeseburgers, but leave the fries and the cupcakes—this makes no biological sense—it makes no biological sense to hand a single mechanistic drug to someone with Alzheimer's and then leave their homocysteine at 18, and their vitamin D at 17, and their cholesterol at 250, and so forth and so on. Here is another analogy: we know of over 30 molecular mechanisms underlying Alzheimer's disease pathogenesis, many of which are interconnected, so imagine a house's roof with over 30 holes, many of which are interconnected; now one drug company says, we've got a great drug that covers this hole over here very well; and another company says, we've got a drug that covers that hole over there very well; and everyone is arguing about which hole should be covered, but after every trial, the floor is still wet. Now, on the positive side, these "failed" drugs may ultimately turn out to be part of the optimal cocktail, but to know that, you need to get the rest of the holes covered. This requires understanding the critical thresholds for the various processes, because so many of these parameters play on to the ultimate thresholds. Just as people like Caldwell Esselstyn have shown, and Colin Campbell, and yourself and others, you have to get to a certain threshold before you are actually picking up plaques instead of laying down plaques in your vessels. The same, of course, occurs with cancer: as long as you're driving a cell toward proliferation and metastatic survival, you're not going to be successful in treating cancer. We believe now that the same occurs at the synaptic level with Alzheimer's disease. And the important point here is we don't know yet where that threshold is. Will we have to change seventeen parameters? Two parameters? If you go back to what happened with HIV,

which is likely to be a much simpler disease, in that case, you had three drugs that barely worked by themselves. Fortunately, they did work enough to have a statistically significant effect, and David Ho was able to put them together and create triple therapy, which works very well for HIV. Now, let's imagine for the moment that Alzheimer's is a more complicated illness, and let's imagine that it is going to take 15, or 20, or 25 different parameters that one has to normalize to hit that threshold where you are now forming and maintaining synapses instead of losing them. This is going to be difficult, and therefore what we want to do is create therapeutics that hit as many of those network abnormalities that feed into this ultimate decision as possible. In fact, we have our first clinical trial now coming up in just a couple of months, which will be the first trial to have a comprehensive approach, where it includes all of those different mediators that have an impact on this synaptic maintenance threshold, so things like exercise, and diet, and drugs, and a whole array of specific supplements and herbs that feed into this specific balance of synaptogenesis and synaptic maintenance.

JB: You know, you just continue to enrich the story as we listen. I'm just thinking, as you're speaking, about this book that I recently read that was recommended to me by Dr. David Jones, the president of the Institute for Functional Medicine, titled The Music of Life by Denis Noble, who is a cardiovascular researcher/physician at Oxford.[9] He's a professor emeritus, now, of medicine. He advances a very strong case, using his experience of over 40 years in the field of cardiac research, that the only solution to these chronic illnesses will be through the introduction and application of integrated systems physiology and integrated systems medicine—that you cannot treat these complex diseases one point at a time. I think this is obviously a very strong story that you are leading us to recognize as applicable to Alzheimer's as well—that there has to be a new system of medicine in order to get to these diseases whose etiology are associated with complex disturbances of network physiology. I think I'm reading your conclusion correctly. Is that okay? Am I on the right track?

DB: That's absolutely right, and what we've been talking about is that these chronic illnesses have revealed the fundamental flaw in our current medical practice. Our current practice tells people when you feel bad, when you feel sick, you come to your doctor; you are now at the symptomatic phase. Now that works well if you have pneumonia. If you've got bacterial pneumonia, we're probably going to cure you. However, as you well know, the problem with chronic illnesses, which are the ones that are killing most of us at this time in our civilization, is that by the time that you get the symptoms, the pathological process is typically approximately 80 percent over. Probably the best data for that come from Parkinson's disease, where by the time you get the first symptoms of Parkinson's disease, you've lost approximately 80 percent of the dopaminergic input to your striatum.[10] Perhaps not surprisingly, when the process is so far along, we haven't been able to do very well at the symptomatic stage with reversing it. That brings up two issues. One, as you said, is to attack this not with a monotherapy, and I think that chronic illnesses will ultimately be the death of monotherapies. We will ultimately realize that you need to attack these at multiple points in the pathological network. But secondly, of course, it brings back the fact that all of us should be practicing prevention from day one, and we should be looking for the earliest indicators. Don't wait until you have symptomatic Alzheimer's disease. We should all know what our CRP is. We should all know what our homocysteine level is. We should all know what our insulin level is. You can go on and on, and that includes genetic markers as well, so we know where we stand in this process. Of course, the Achilles' heel of these chronic illnesses is that you can see them coming in a way that you can't for the acute illnesses, so that you have a long-term warning system, if you choose to look at it, to warn you far ahead, and potentially avoid these illnesses. So I couldn't agree more that this will require a change in medicine, to focus on pathological networks and much more on prevention and on integrative ways to approach these diseases.

JB: Let me…first of all, I don't want to at all diminish, by a subsequent question, the significance of what

you just said. I mean, that in itself is iconic. It's almost like a haiku that ought to stand alone and be imprinted in every one of our nervous systems. With that said, I just would like to follow up on this question of genetic susceptibility. We've heard a lot about apoE4, double alleles, people call them the dementia genes or the death genes. What is the status of this as a guidepost for relative risk?

DB: This is a very good point. As you know, a number of people have looked at how much is nature, how much is nurture? Jack Rowe is among them, for example, with the MacArthur study, and interestingly, multiple groups have all come to a pretty similar conclusion: that in the big picture somewhere around 50 percent of what's going to happen is based on your choices, your lifestyle, etc., and somewhere around 50 percent is the result of your genetics.[11]

Now, obviously, in some cases, genetics trumps experience: for example, if you have an increased number of CAG repeats in your Huntingtin gene, then genetics is critical. But across the board, as an average for all of us, we're talking about something like half and half. So, in fact, you can have a huge impact on your risk of chronic illness, but yes, you're absolutely right, genetics plays an important role. As people used to say, if you want to live a long time, then choose your parents carefully, and of course there is some truth to that. With respect to apoE, it fits very well into the model we talked about earlier: when we first looked at this plasticity balance, we realized that you can measure this balance biochemically by looking at an interesting phenomenon: the way the amyloid precursor protein is cleaved.[12] It can be cleaved in two completely different ways, reflecting the fact that it functions as a molecular switch. If it is cleaved by proteases at three sites—at the beta site, the gamma site, and the caspase site—then it produces four peptides: sAPP-beta, A-beta (which of course is the one that has had so much work done on it), Jcasp, and then C31 (this this the carboxy terminal 31 amino acid peptide). Those four peptides all are physiological mediators of neurite retraction, synaptic reorganization, and ultimately programmed cell death. That is the one side of the switch, and on the other side, if you cleave it at the alpha site, you get two peptides: sAPP-alpha and alpha-CTF, that, interestingly, both inhibit programmed cell death and support synaptic maintenance and neurite extension. So literally these are diametrically opposed, and these have different impacts, and therefore of course the first question that came up was: What about the risk factors for Alzheimer's? So we were very interested to see what happens when you have apoE4 in that equation versus apoE3, and it is absolutely striking: ApoE4 pushes that balance toward the four neurite retractive peptides, whereas apoE3 does not do that. As you well know, that's not to say that if one has apoE4, he or she will necessarily get Alzheimer's disease, but it is a risk factor, of course, just like a high LDL and a poor HDL-to-LDL ratio would be a risk factor for atherosclerotic cardiovascular disease. So it is a risk factor, but it also suggests to you, "Okay. There are things that you can do ahead of time."

There was a very interesting presentation a few months ago showing that the impact of regular exercise on Alzheimer's risk is on the same order of magnitude as the effect of one apoE4 allele. So, in fact, there are things we can do to counter the impact of genetics, and I think it's actually important. It's certainly a good thing for people to know. I realize that a common question is, "Why would I want to know my apoE4 status since there's nothing I can do about it?" Well, in fact, there is a lot you can do about it, and it has to do with your lifestyle. It has to do with your exercise status, your dietary status, your homocysteine level, and on and on and on. There's a whole series of things that in fact you can do about your risk for dementia. Of course, the drug candidates that we've identified through our screens have impacts on that same balance, on that same 4-to-2 ratio of the peptides to essentially drive you toward the making and maintaining of synapses. So, you are absolutely right, genetics plays a key role. In fact, interestingly, the genetics of neurodegeneration appear to be fundamentally related to the genetics of aging and longevity. I think that this is also telling us something interesting about what was originally called antagonistic pleiotropy, this idea that you can evolve genetically characteristics that in the short

term increase fitness and thus give you a competitive advantage, but in the long run can be a disadvantage with respect to longevity.

JB: Well, you know, I gave an introduction to this discussion saying that this was the appropriate way to highlight and to celebrate the year end of 2012 in Functional Medicine Update, but I really under spoke. I think this was an epic chapter in the evolution of Functional Medicine Update, but more importantly in our understanding of how dysfunction arises from imbalance. That's a fundamental construct, I think, of the Institute for Functional Medicine and its paradigm. I just can't thank you enough, Dr. Bredesen. I think the work you're doing, the implications of it are significant for Alzheimer's and have broad spreading effects across the range of the other members of the family of chronic, age-related, degenerative diseases. This has been an epic discussion, and one that we feel like we've just taken a little vision into the future with you. We don't have all the answers, but we have a new model. This model that you're carving out is a model that gives us an opportunity--if we are willing to accept the challenge as a scientific medical community--to address these issues with a new lens, with a new frame of reference, from which we sieve observables through this new frame of reference to hopefully come out with more successful ways of both preventing and managing these complex diseases that are associated with 21st century living. I would say thank you—a deep thank you for what you're doing, you and your team, at the Buck Institute. I hope we'll be able to keep closely connected with progress that you're making because to me it is at the frontier of where medicine should be going.

Therapeutics for Neurodegenerative Diseases Possible this Decade

DB: Thanks very much. I think that this upcoming decade is going to be tremendously exciting because I think we will have the first real therapeutics for these neurodegenerative diseases, and really be able to prevent them and treat them in a very significant way. I'm honored that I got to talk with you about this because you've done so much—and so far ahead of most others—to put models into place that I think the rest of us have been able to utilize in developing new therapeutics for chronic illnesses, so thank you.

JB: Thank you, and we're going to keep very closely in touch as it relates to this extraordinary clinical trial that you've just queued up and will be starting. That, to me, sounds like it's something that every FMU listener, supporter, and every other member of our medical community will be interested in finding out about. The best of luck in the trial and we'll be checking in soon. Thank you so much.

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