March 2015 Issue | Gregory Jicha, MD, PhD

http://jeffreybland.com/knowledgebase/march-2015-issue-gregory-jicha-md-phd/

DOWNLOAD AUDIO| DOWNLOAD SUMMARY NOTES |

Welcome to *Functional Medicine Update* for March 2015 and the third of our three-part series on functional neurology. By the way, we may have a bonus for you, don't tell anybody, but there may be a fourth component to this series. We've gotten such extraordinary response to this particular topic that we feel it might be very valuable to extend out our key opinion leaders into a fourth addendum, so I'm just giving you a little tip off as we move into the month of April.

This month, however, we have an extraordinary opportunity to visit with a clinician/researcher, who is both a PhD neurology researcher and an MD clinical neurologist who has really become an expert in Alzheimer's management care, both early diagnosis and treatment of various forms of dementia, including Alzheimer's. His name is Dr. Gregory Jicha, and you're going to learn much more about him, so let's turn to our third extraordinary clinical specialist in this area of functional neurology.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

Gregory Jicha, MD, PhD

Professor, Department of Neurology

Sanders-Brown Center on Aging

University of Kentucky

1030 S. Broadway

Lexington, KY 40536

We are so excited about having our third key opinion leader who is going to help us to understand much better the expanding domain that interfaces function of the nervous system with the environment and some of the remarkable things that are occurring right now in better understanding of early loss of function. That would be things like early diagnosis of conditions like Alzheimer's disease at a place where possibly we'd be more successful in intervention—the earlier that we can intervene and understand

the pathology before it becomes severe. And so our key opinion leader is a neurologist with an extraordinary background, Dr. Gregory Jicha, who is presently at the University of Kentucky.

I'm going to give you a little bit of his background and this is only a thumbnail of the extraordinary accomplishments that Dr. Jicha has been involved in: 172 citations in the peer-reviewed published literature. He is a professor in the department of neurology at the Sanders-Brown Center on Aging at the University of Kentucky School of Medicine. He serves on the executive committee and as the director of the clinical core for the University of Kentucky NIA-funded Alzheimer's Disease Center. He also directs the Telemedicine Cognitive Clinic at the University of Kentucky, which I think is a very interesting theme that's designed to reach out to rural populations across Kentucky for both clinical and research-related activities.

In the area of Alzheimer's disease and related disorders, Dr. Jicha holds the Robert T. and Niles Y. McCown Endowed Chair in Alzheimer's Research at the institution and his current interests lie in the areas of mild cognitive impairment, clinical pathological correlations in early pre-clinical disease states, and clinical trials of disease-modifying therapies for Alzheimer's disease. He is a principal investigator at the University of Kentucky for the National Alzheimer's Disease Cooperative Study Group, and serves on the clinical task force and steering committee for the National Institutes of Aging Alzheimer's Disease Center Program.

So, extraordinary background and skill level, and if I was just to cite some of the 2014 citations alone from Dr. Jicha's laboratories and efforts, they include things as far-ranging as assessing discriminate ability and reliability of very short forms of evaluating Alzheimer's disease early onset, looking at various genome-wide association studies that associate certain genomic profiles with relative incidence and risk to Alzheimer's disease, to looking at the prevalence and epidemiology of Alzheimer's disease, to examining the tau-ology (the tau pathology) that relates to beta amyloid accumulation and how that relates to the mechanism of pathophysiology of Alzheimer's disease, to looking at various new technologies that are involved with early assessment of onset of Alzheimer's disease before serious terminal pathology exists. So you can see, just from the 2014 publication list alone, which is more than 20 publications, Dr. Jicha is right at the cutting edge of this field.

Dr. Jicha, thank you so much for being a guest and a key opinion leader on Functional Medicine Update. As a neurologist, how did you fall into this area of research, which obviously goes back many years of your career, and what is it that draws your total commitment to the field?

GJ: Yes, you know that's always an interesting question because many of us just fumble around in life waiting until we discover our true calling, I guess, so to speak. In the 1980s I started out researching psychopharmacology of Parkinson's disease in an animal model of that, and I thought that that was fascinating, but at the time—as naïve as I was—I really believed that we had solved the major mysteries of Parkinson's disease and I still believe that to this day. I think translating them into more effective treatments and cures for Parkinson's is where we're still kind of suffering in the field.

Given my thought that the field of Parkinson's was rapidly coming to an end, I was searching for a bigger mystery. I started thinking about this and ran into and began working with patients who had experienced changes in their memory in thinking, changes in behavior that can accompany those changes in memory and thinking, changes in personality—in essence, the loss of the person through a disease process. And I

thought, “This is the cruelest of all diseases. This is a disease that robs us, literally, of who we are.” And if there is a great mystery that exists and if there is a great injustice that diseases do, truly working in the field of Alzheimer’s and related dementias fit the bill for both of those, and as I’ve become wrapped in this through my years of PhD training on the laboratory bench to my medical career, caring for thousands of patients, many of whom have been followed from when they were normal through the entire disease process, and—yes—I frequently attend the funerals of my patients as Alzheimer’s and other related dementias are universally fatal. Every year my passion for the work and impetus and drive to continue until we find cures for these diseases is strengthened really overall. So I hope that anybody out there that is looking for their future calling stumbles into it in as an effective a way as I have in my life.

JB: Wow, I couldn’t think of a more inspiring way to start this conversation. I felt the goose bumps just listening to you speak. It’s that level of advocacy that can change the world. Thank you for sharing that. I look at your background and you have multiple fellowships in your background, including Mayo Clinic at Rochester and your neurology residency, and I noticed that you’ve also done some training in behavioral neurology, which I find very interesting. Tell us a little bit about how that connects to your PhD lab-bench studies, this behavioral neurology connection?

Brain Connectivity to Function is the Focus of Many Translational Scientists and Clinicians

GJ: My basic lab bench neurology was in the area of tau biology and tau is one of the proteins that keeps neurons interconnected with one another—in essence, runs the telephone lines between nerve cells that are responsible for the communication in our memory and thinking in day-in-day-out lives and in many degenerative diseases this tau protein is altered, it begins to form insoluble, kind of concrete, inside the nerve cells, which is very deadly to the nerve cells and is part of the degenerative disease process in not just Alzheimer’s disease, but in many of the frontotemporal dementias, in many other age-related diseases—progressive supernuclear palsy, corticobasal degeneration, the lists goes on and on. So obviously a key element.

And so from a basic science perspective, looking at the molecular biology of how nerve cells interact with one another, how they communicate and send signals that lead to our higher order thought processes, really resulted in the natural evolution of clinical interest in how the brain puts this all together, and as nerve cells start to become damaged, how do we really change? And so the field of behavioral neurology encompasses higher order thought processes: how we receive sensory input and translate that into thought, convert that to actions that we may want to or not want to engage in, how we generate emotional context for the things we experience in our life, and truly—of all the mysteries of the brain that remain—these are the richest of the mysteries.

So brain connectivity to function and I think that’s what all of us, as translational doctors or translational scientists, are really trying to do: bring things together from the molecular and genetic side of things, all the way through to how this really impacts us all in our day-in-day-out lives. So that study of behavioral neurology, again, is the study not just of memory, but of all aspects of our cognitive functioning: how we use language, how we process or are able to multitask, perhaps, how we are able to manage our emotions, how we respond to emotionally or cognitively challenging situations. So, really, the two fit together incredibly perfectly. They are all part of the same continuum, and to really treat—and I think to understand—these diseases and to move the field forward, we really need to be able to grasp that breath from the bench to the molecular all the way to the bedside, to the real world, to the things that matter to

real people today.

JB: Well, I think you used a number of words there that are really powerful words, and one of them—which I think is a great segue—is the word "continuum." Because it's clearly obvious that a condition like Alzheimer's doesn't occur as a bump in the night--yesterday you weren't without Alzheimer's and today you have it—there's this continuum of progression of increasing severity and loss of function. I'd like to go to your work as it relates to these early cognitive changes and ask what's happening on the assessment front. We've heard things about measurements of things like balance, or smell acuity, or taste acuity, or recall. What's happening on the early assessment frontier to better understand what the trajectory might look like before we get to the end pathology?

The Challenges of Early Assessment in Degenerative Diseases

GJ: Yes, that's incredibly important, Jeff, because these diseases, unlike acute events that can occur medically—a heart attack that occurs almost instantaneously or a stroke that occurs instantaneously—we understand that these diseases are occurring over perhaps decades—perhaps over an entire lifetime. And in that respect, not so different from stroke or heart attack because the build-up of cholesterol and the like that eventually can lead to a heart attack and stroke through atherosclerosis, is again a lifelong process.

These degenerative diseases, however, have really been masked by the simple view that we've taken towards degenerative dementias and that is we've essentially been waiting over time for one to develop enough cognitive and functional disability—enough struggle with day-in-day-out activities—that essentially a patient's life falls apart, and that is traditionally where we've been diagnosing diseases like Alzheimer's: life has fallen apart, family is struggling with issues, now's the time to look at the disease. And we all know the major medical breakthroughs that have come about throughout the years have really been in the recognition of early disease and intervention: an ounce of prevention worth a pound of cure.

So going back to what we understand about Alzheimer's disease, a lot of this has come from autopsy studies and more recently from human biologic studies, but the biology of disease appears to involve both genetic and environmental factors, and they may begin to interplay really very, very early in life, and so some of the pathology may begin to appear as early as our teens or twenties. We clearly know that within ten to twenty years prior to one developing even the earliest of memory problems, that the brain is already filling with amyloid plaques, that the nerve cells are already beginning to die by dysfunction of tau and the build-up of neurofibrillary tangles. And yet we have been traditionally still waiting until—in essence—the brain and the person's life falls completely apart.

So these processes occurring over decades do have biological markers, and so there is a bit that folks have been doing. Number one: You know, in looking at our memory and thinking tests, we've been looking at more refined tests—computerized testing that can actually measure response times down to the milliseconds. We're looking at more challenging paradigms that can detect early change in folks, and that is an entire field of discovery, still, however, looking at a stage of disease when the brain is clearly not functioning well. Other folks have begun looking at other aspects of disease.

You know, I always find this and I have to make a small commentary on the smell test because we hear these constant, you know: "You can't smell peanut butter, you have Alzheimer's disease." The problem with smell tests is they're not specific. Aging, in and of itself, leads to a loss of smell, and

here—especially during allergy season—almost nobody in Kentucky can smell anything. And so that type of detection test is plagued by its lack of specificity. It's not that if you have trouble smelling something you are coming down with Alzheimer's disease. It's more likely you have allergies or an upper respiratory infection—a cold of some sort. I don't hold much stock in those as really being clear cut, definitive ways to diagnose the disease.

You know, the Holy Grail is the blood test, and all of us are used to that. We go to the doctor, the doctor takes our blood, and then we ask him, "Doc, do I have diabetes?" And we're looking for that kind of blood test. There's a problem in the field of Alzheimer's with that, and the problem results from something that we call the blood-brain barrier. The brain is privileged in the body. It has evolved to not want all of the toxins and other things that could be running around our bloodstream to be able to readily get into the brain and cause us injury because, of course, you know evolutionarily the brain is our greatest success story. It's really what makes us what we are. So this blood-brain barrier prevents things that are in the body—infections and toxins—from getting into the brain, but likewise it prevents things that are in the brain—markers of disease, tau and amyloid, other components of the disease process—from making it out into the bloodstream. So we have this limitation on reliable detection of disease.

A Spinal Fluid Test is Currently the Best Way to Track the Progression of Alzheimer's Disease

Nonetheless, people are still working on this and every few years we have a huge news release of the new blood marker for Alzheimer's disease. I'm waiting for it to happen, Jeff. And part of that is that all of these great discoveries that have come out, not a single one has ever been replicated by another researcher or another independent lab in an independent sample, and so they are certainly moving the field forward, but I think we have a ways to go because we don't understand how the blood-brain barrier is influencing what we're actually measuring within the body because we're not measuring the brain. That realization has brought us along to the point where, how can we measure what's happening biologically in the brain? And there are several ways that we can do this that track the disease process. One is spinal fluid. Many people cringe at that, but actually it's widespread in most of the major medical centers throughout Europe that, if you have a memory and thinking problem, one of the first things your doc does is draw your spinal fluid to test for these proteins because we've eliminated the blood-brain barrier. And that is a very safe procedure that perhaps been de-popularized in the United States through rock movies like Spinal Tap. It really is like a blood draw. I did two of them on two of my patients today in the office. It takes about 10 minutes. They get up and go afterwards; they're doing just fine. And that can give us some definitive measures of the rate of nerve cell death, the rate at which amyloid is building up in the brain, the rate at which tau is becoming abnormal, the rate at which the brain may be inflamed in any given disease state like Alzheimer's disease, or other features such as oxidative stress.

Functional MRI and New Imaging Techniques are Revolutionizing Diagnosis of Alzheimer's Disease

We can use imaging, and really imaging has advanced over the years—a picture of the brain, an MRI. CAT scans are less than useful. As I always tell people, I think they are like old black-and-white TVs with rabbit-ear antennas. You know, you see a fuzzy picture, and if that's all you've got you'll sit and watch it for an hour and a half, but when you have digital TV, you will turn right over to that. And that is the state-of-the-art for MRI technology nowadays—not just looking at a picture of the brain structure, where we can see shrinkage and we—and others—have published this over the past decade or more, that we can detect early patterns of shrinkage in the brain five years—maybe even ten years—before one comes down

with memory problems that illustrate or are representative of the pattern of nerve cell loss and brain shrinkage or atrophy that we see in Alzheimer's disease.[1],[2]

Newer techniques are able to look at the contributions of vascular disease, perhaps what a common person might refer to as mini strokes or pre-strokes or something of that nature—the wear and tear on the brain from vascular disease that could really be mimicking Alzheimer's disease. We can look at the white matter—the connections—between nerve cells to make sure that they're fully healthy and not suffering from a disease process. We can measure blood flow between brain areas. And with functional MRI we can actually look at brain areas that are communicating with one another at any individual instance.

So in the MRI machine we can actually give people tests to do—memory and thinking tests—and then look at which brain area is someone using to complete the task at any given moment. I find that data fascinating and we do a lot of functional MRI here. It turns out that as we're beginning early in life to learn tasks—tasks like reading or solving problems—the brain uses a tremendous amount of its area, and may be reliant on 20, 30, 40 percent of the brain to accomplish an individual task. As we mature and get better at that task, the brain doesn't learn to use more of itself, it actually learns to use less. So an accomplished violinist uses almost none of his brain to play the most beautiful music, whereas when they were initially training, they used a tremendous amount. We see the opposite occur in degenerative diseases. We see people go from using very little of their brain to complete a simple memory or language task to needing to use larger and larger portions of the brain, so functional MRI.

And then the final development, you know, which really we're right in the midst of right now, is the development of molecular imaging. So these are tracers that are typically injected into the vein and we use either PET or SPEC scan. These are scans that have been used routinely in medicine to detect tumors, to look at bone densities, things of that nature, over the years. We can actually inject medicines or tracers that will bind to amyloid plaque. Twenty years ago the only way to know definitively if someone had amyloid plaques in their brain from Alzheimer's disease was to either wait until they came to autopsy or to biopsy (take a piece of brain out and have the pathologist look under at it in the microscope), but now we can see this noninvasively in a living patient. New imaging agents have been developed that can look at the tau biology, and so more and more of these compounds are coming out that are enabling us for the first time to peer through that veil, through the blood-brain barrier and actually see what's occurring in the brain. That has revolutionized the field of diagnosis to the point where we can tell, 10 to 20 years before one is going to develop Alzheimer's disease, that they indeed are heading down that path.

JB: Well this has been the most comprehensive summary review I have ever heard of where we are in the whole assessment area. Thank you. That was brilliantly put together. So that leads obviously into a question that is on every clinician's (and probably every person's) mind, and that is, "Okay, what about this connection of genes? Is Alzheimer's really a genetic disease?" You know, everyone's heard about the double E4 allele, the so-called "death gene," and how that interrelates with Alzheimer's and cardiovascular disease risk. I think there's a perception that this disease is kind of hard-wired into our genes. Where are we on that whole part of the story?

Truly Genetic Alzheimer's Disease is Very Rare

GJ: Yes, you know, that is a great question and something that I'm commonly asked as well, because I think there are a lot of misconceptions out there. I think sometimes we as scientists and clinicians actually

create some of that confusion. If you ask a geneticist how much of Alzheimer's disease is determined by genetics, they may give you numbers as high as 90 percent. If you ask a non-geneticist who studies environmental real-world exposures for Alzheimer's disease, they may tell you that less than 10 percent of Alzheimer's is genetic. I think we need to be clear. I usually say—whenever there is a debate like that in the field, with two different parties saying 90/10 and 10/90—chances are it's more like 50/50, and I think that's probably about where we are.

We do know that there are some forms of Alzheimer's disease that are truly genetic. These are incredibly rare. There are three genes that we have identified—they've been identified, now, for almost 20 years, and those genes are all related to the build up of amyloid plaques in the brain. But there are certain mutations, and if you have that mutation, we know, 100 percent, definitely, you will get Alzheimer's disease. That is true genetic Alzheimer's disease.

And yet that is extremely rare, probably less than one to two percent of Alzheimer's patients; it's only 500 families, by estimate, in the world that carry that gene, and so what we really see in the real world is not genetic Alzheimer's in that context—not inescapable, autosomal dominant genetics. What we see instead are things like—as you mentioned—the apo E4 allele. And we now know that there are over ten of these risk genes, and they're risk genes, meaning you can get the gene, and yet you may never get Alzheimer's disease, but they're going to increase your risk. As I like to tell people, this is kind of like a gene that may cause family members to carry a little bit of excess weight. And so we may have an overweight family and it runs in the family, but that doesn't mean that an individual member of that family could not modify their environment, couldn't change their diet, exercise more, and not carry any extra weight around but be perfectly fit. So these genes are making it harder. Those of us that carry those risk factor genes for Alzheimer's disease, we have to work harder for our brain health, we have to work harder to avoid Alzheimer's disease, but if we have those genes, it's not an absolute sentence that we're going to come down with Alzheimer's, so I think that's important.

Medical Organizations Advise Against Genetic Testing for Alzheimer's Disease

That's one of the reasons why currently the American Academy of Neurology, backed by the American Medical Association, recommends against testing for those genes. If you come from a family where the onset of Alzheimer's is in the 40s or 50s and one out of every two in every generation of children comes down with Alzheimer's, then there's a possibility for true genetic Alzheimer's and genetic testing may be helpful. The problem with genetic testing with these risk genes is that if you are positive and that goes into your medical record, you could potentially be discriminated against despite the development of things like GINA, the Genetic Information Nondiscrimination Act, which our US government has as one of its key components in health privacy protections. It really doesn't matter. We really advise not to get these genes. They're still being used for research purposes and there's good reason for that. We make discoveries from these genes, and so these genes change how the brain functions, and understanding those changes is leading to new pathways—new ways that we can intervene and potentially prevent disease.

We've been working here at the Sanders-Brown Center on Aging and the University Alzheimer's Center on several studies that are looking at manipulating some of these genes in terms of how they express themselves. Whereas those genes want to turn on the Alzheimer's switch, so to speak, we're using medicines to turn off those same genetic switches. And so these will become very powerful in the future. We potentially foresee a day when that genetic testing may be needed to decide which medicines a person

may benefit most from, but at the present time, I think one should really take resolution in the fact that if you have a family member who suffered from Alzheimer's—a first degree family member (mom, dad, brother, sister, son, or daughter)—you need to work harder at your brain health and try to fight some of those environmental factors that are changing, because you can't change your genes.

JB: Well, this again is just an extraordinarily uplifting message that you're providing. It really speaks to these constructs of a constitutive effect, which is kind of hard-wired, versus an inducible or an expressible effect that can be modified through various choices that we can volitionally elect to either be exposed to or not exposed to, so that takes us into the whole discussion of lifestyle and environment as modulators of gene expression. Let's quickly review, from your observations, things like exercise, which I've heard in the news quite a bit related to Alzheimer's prevention, and also cognitive activities—social interactions and things that stimulate brain function. Where are we on those two as modulators of function?

Epigenetic Influences on Alzheimer's Disease: More Studies are Needed Before Official Consensus Will Be Achieved

GJ: Yes, yes, that's incredibly important. This is really the field that we call epigenetics—how genes interact with the environment to create disease burden. As I said, as of yet, you know, we haven't been able to change genes, but we can change the environmental factors that may influence whether or not those genes are expressed in a negative way and/or may have independent contributions to whether one comes down with a disease like Alzheimer's. You know, I'm a little disappointed in the field in some respects because it is in its infancy, but more disappointed, perhaps, by some of the consensus work in the field. So, for instance, the National Institutes of Health held a scientific roundtable several years ago—I believe 2011—when they pulled together experts to really discuss this issue. What can one do? Does exercise help? Does social interaction help? Does diet or other modifiable daily activities—do they influence your risk for Alzheimer's disease? And unfortunately the consensus from that roundtable was as of yet nothing is proven to be able to prevent your risk for Alzheimer's disease. I agree with that consensus statement, but it was misrepresented and, I think, mistaken and further propagated by some of the media and other lay folks in the community.

What they were really saying is that we need to do more studies, here. The animal data and the human data clearly demonstrate risk association with lower levels of exercise, and protective benefits with higher levels of exercise. This seems to be mediated through what's called brain-derived neurotrophic factor—MiracleGro for the brain, so to speak. And the more we exercise, and it doesn't take much—20 minutes a day of getting your heart rate and your breathing up a little bit—to increase circulating levels of BDNF, and, in animals, lead to the birth of new brain cells, especially in memory areas of the brain. The same thing appears to happen in humans. We do not take brain tissue after exercise to look at the birth of new nerve cells, so we have yet to prove that this definitively occurs, but we can clearly see, using functional imaging, glucose metabolism studies with PET in the brain, and even MRI scans, that we can reverse or stop some of the changes associated with Alzheimer's disease with this kind of an intervention.

The same holds true for dietary modulation. There's a wealth of data on social interactions and daily engagements and it's really lead us to what we really have known, and our ancestors have known more than likely, for hundreds if not thousands of years, the old adage, "Use it or lose it." And so the more we engage and strengthen our brain, the more it is going to be able to withstand the ravages of these types of degenerative diseases that are waiting to consume our brains as we age.

And so fighting back really requires this kind of a comprehensive program, which unfortunately I don't really understand why more people aren't thinking about this in a concrete fashion. We know that if we have a physical ailment—say we have a heart attack and we go to cardiac rehab, and the cardiac rehab doctors put together a comprehensive program for us, they say, "You need these kinds of exercises, this kind of aerobic exercise will build up your heart muscle, your diet needs to be modulated, so on and so forth,"—they work on lifestyle factors, and we know that cardiac outcomes are greatly influenced. And yet, people take for granted. If you ask folks who are having memory and thinking problems, "What do you do for your brain health?" They may say, "Well, you know, every Sunday I do the New York Times crossword," or "I read the newspaper every morning over coffee," those are great activities and I don't want people to give that up. But if you're going to go to the gym and work out, you get yourself a work out partner. You set a schedule: Monday, Wednesday, Friday, I'm going to the gym from 9 to 10. We don't do that for our brain, and I propose that folks should do this.

There actually is a study that was reported preliminarily from Finland; it's called the FINGER study (the Finnish Geriatric Intervention Study—I forget what the acronym fully is, Jeff). But basically it is the first study of its kind to come up with a comprehensive program where they're doing just that for brain health and aging. And the initial results, which were presented last July (2014) at the Alzheimer's Association International Conference, were incredibly intriguing, suggesting we get more bang for the buck if we don't focus in any one area, like exercise, social interaction, or diet, but rather develop this kind of comprehensive strategy to really strengthen the brain—make it resistant to disease, make it so the genetic risks are not stronger than the environmental risk pushing us towards brain health.[3]

JB: Oh boy, is this an illuminating discussion. This is stimulating my brain just to listen to you speak. I'm already engaged in this exercise. Let's segue over to one of the areas that I know you have put your thoughts to. It's not the only area, obviously, but one of the areas. The result of that is a recent review paper that you wrote, which I consider very well written called "Nutrition and Prevention of Alzheimer's Dementia."[4] Let's move over to the nutrition side. You know, I have yet to find someone that hasn't eaten at some time in their life, so this is shared common human experience, and as we eat, we eat information—we don't just eat calories—and that information is translated into gene expression patterns and modulates function. And, as you said, although the brain represents a fairly small percentage of overall body weight, it represents a very remarkable portion of calorie consumption, particularly glucose. With all of that in mind, nutrition, we feel, must play a role. Tell us a little bit about how you see the nutrition and Alzheimer prevention dyad fitting together as we evolve the science.

The Role of Nutrition in Alzheimer's Disease Prevention

GJ: Yes, this is incredibly important, you know, the aspects of nutrition. Because the brain is an organ in the body, certainly—as you have mentioned— one of the most metabolically active organs in the body, and it has a very unique make up. And so in order to keep the brain healthy, it needs different building blocks. It needs building blocks that may differ somewhat from the building blocks that you need to build up muscle if you're a body builder, or the building blocks that you may need to work on lung function. And nowadays we know that if you go into the supplement store, there you can pick up vitamins for your eyes, vitamins for your kidneys, vitamins for your heart, and now there is an emerging industry, which is vitamins and supplements for your brain.

Truly the vast majority of these are based on very sound, basic science, and based very well on animal

data where animals have been supplied these agents, and we can show they have a healthier brain or they are resistant to the modeling of Alzheimer's-type changes that we see in human beings. And yet we're lacking in many respects, taking this all the way—taking this into clinical studies where we can actually be clear on the benefit to individual human beings. So while there are a wealth of agents that are out there, the field has really been kind of road-blocked at the very end, and instead we have people making claims about nutritional supplements that may not have the real science to back them.

The reason for this, in part, is that it is very difficult to patent what may grow naturally or be part of a natural product, meaning things like fish oils, which may have very potent effects on the brain and brain health from the studies that have been done. If you spent the millions of dollars to do a human clinical trial with one of these, well your competitors would not pay anything and they would be able to jump on board with that. There are not many funding agencies that fund nutritional studies here in the United States at the National Institutes of Health. We have the National Institute of Alternative and Complementary Medicine, and so sometimes in collaboration or independently by the National Institutes on Aging we can get a study funded in this area, but not nearly to the extent that we need to do it. We've also been plagued by the fact that many people think that a single nutritional supplement or a single pill that is just going to be the panacea for brain health is the way to go, and it's unlikely to be the case.

The brain is so complex. It requires so many different components as building blocks for healthy nerve cells, that more than likely we're going to need some combination of nutrients, and they may be in different percentages to one another. So we may need some of the polyunsaturated fatty acids. We may need some of the antioxidant compounds. We may need some of the other energy substrates for the brain, and we may need them in a specific combination. The field is really just starting to explore these nutritional combinations. Again, I think we have a long way to go.

I do advise to everyone out there, if you're interested in nutrition and prevention of Alzheimer's or maintenance of brain health, to always please check up on whatever agent that you're thinking about taking. I think it's really important to discuss with your doctor. I had a patient come in and ask me about a particular product just a little over a week ago, and it was one that I was not familiar with and I'm familiar with most of them, and so I went and looked it up. And I always go directly to the FDA website first because I want to see if there is any danger or what's really been done clinically, and there actually were two warning letters in the FDA file. One that the company was making false claims about its use to prevent Alzheimer's disease, and then just a short while later that the company may have been hiding safety data that suggested that the nutritional supplement could increase risk of stroke and/or other neurologic diseases like multiple sclerosis. So, you know, it was clear in that case that this patient was going to go ahead and take that nutritional supplement, buying into the marketing and the advertising without actually investigating it. My strongest plea to everyone out there that is thinking about a nutritional supplement, please look into these. Make sure that they are safe. If they're safe, I think we're really at a point, Jeff, where as long as it's safe, if it might help and there's good science behind it, there is rationale to try to use it. If there are risks, however, one really needs to be concerned and I would be cautious until we have definitive studies.

JB: Thank you. I think that's really sage advice. And I also want to cite—because we're dealing, here in this series, with medical professionals principally—your review article in Frontiers of Aging and Neuroscience in 2014, volume 6, page 282, which is a public access article titled "Nutrition and Prevention of Alzheimer's Dementia." It does a beautiful job of reviewing the literature and you talk

about many, many different nutrients and different studies surrounding them, including, obviously, the antioxidant family—vitamin E, C, coenzyme Q10, selenium, lipoic acid. You talk about omega-3 fatty acids and B vitamins and folate. You talk about MCTs as brain fuel (medium chain triglycerides) and their effect on mitochondrial oxidative phosphorylation. And you talk about various types of phytochemical combinations that influence neuronal health, including things like huperzine A, and Gingko biloba, and resveratrol, and turmeric. I think that you've got a great review article that helps people to understand this field. Let me ask you a little bit about the concept of how much of these a person needs because there is always a question of do I need to supplement with mega doses, or is it in the diet, or what about this concept of hormesis that Dr. Mattson talks about at NIH, where a little goes a long way and you get unexpected synergy among the right combination of smaller doses and it's kind of a different dose response curve than we normally think of in pharmacology. What's your feeling about this whole neuronal hormetic concept and these nutrients that we find in food?

Nutritional Supplements: Clinical Trial Experience May Have Little Relationship to Real Life

GJ: I think that that is a great point. Dr. Mattson's research is well respected here. He was at the University of Kentucky many years before I came and before he went to the NIH. But that concept is very real. One of the things that we don't often appreciate when we read clinical studies, especially about nutritional supplements and the like, is that many of these are remarkable safe, and so we have a tendency to want to push the envelope with them and use higher and higher doses. And actually, in my opinion, the FDA actually propagates this. They always want to know what's the dose-limiting toxicity and at what dose do we achieve that? That pushes us always when we're looking at that upper level, maximizing the amount of nutritional supplement one takes in.

The other rationale frequently that is done in clinical trials, of course, is we want to saturate the brain as soon as possible because it leads to a shorter clinical trial. So the clinical trial experience may have little relationship to what is actually going on in real life. Meaning, just because the high doses of whatever nutritional supplement will saturate the brain within one month, once the brain is saturated we really don't know what the dose is that is required to maintain brain health. Equally important is the fact that we know that most medicines have an inverted, U-shaped, dose response curve, meaning we know that too little may not be beneficial, and we also know that too much, via toxic or other effects, is going to be less beneficial than the right amount. I believe, again, everything in moderation.

I think that that's really where we are in the field, and I think we really need to take that as sound advice that we can pass on to others and also apply to our own daily lives. I think that that's critical. On that concept I'll just say we have just recently done a study, which we have submitted for presentation at the American Academy of Neurology this spring looking at exercise (types of exercise) on the basis of the intensity of aerobic training, from very low intensity aerobic items all the way up to very high intensity aerobic items, and plotted that out against brain health in our longitudinal cohort we've been following for decades, and the answer is an inverted U-shaped dose response curve for exercise. Who'd have thought? If the aerobic exercise is either too low in intensity or too high in intensity, we're not getting the amount of brain benefit from an intermediate dose, and so I think that that really holds true in the area of nutritional supplements as well, and as we really do more studies in terms of these modifiable risk factors, modifiable environmental mediators of brain health and disease, I think we're going to find that to be true.

JB: Well I want to stop and just take a cerebral hypoxia break for a half-sec and just really honor the breadth and the depth of the information you've covered. This represents everything from early assessment to where we're heading and some of the landscape studies that are opening up new ways of examining function of the brain in intact human beings without intervention using imaging to look at this continuum from early stage into where we have significant neurofibrillary tangles and histopathology associated with Alzheimer's to the interaction of genes with our environment through inducible factors that give rise to epigenetic modulation of function and then deeper drilling down into the components of exercise and mental and social activities, and lastly diet and nutrition and nutrients and their role on neuronal function. What a landscape analysis you've given us in 50 minutes.

I was very pleased to see, and I think it is unique, actually, among researcher/clinicians as yourself, in the summary of your article the way that you phrased the future of the field as you see it. I quote, in the summary you say: "A nutritional approach to preventing Alzheimer's disease appears to be an innovative and safe approach that may be extremely cost effective, allow ease of administration, and importantly serve as socially acceptable intervention or adjunctive approach in the prevention and treatment of Alzheimer's disease. Despite years of scientific, medical, and clinical advances in this area, much remains to be discovered and proven in terms of specific nutritional interventions for the prevention of Alzheimer's, but promising agents such as vitamins, energy substrates, flavonoids, lipids, and modified diets functioning as antioxidants, metabolic enhancers, immune modulators, and direct disease modifying agents await further investigation." I think that is—just in three sentences—a tremendous review of literally hundreds of papers and where we are at this juncture where prevention may trump treatment in terms of Alzheimer's. What a remarkable contribution you've given us, Dr. Jicha. Thank you so much.

GJ: I appreciate that, Jeff. You know, I think that the model that is being built medically is early detection, pre-clinical detection, and intervention from either a primary prevention perspective or what we might consider secondary prevention (we can see the process already occurring, but the clinical symptomatology is not yet clearly evident). This is the model that we've taken with colon cancer, with screening for that, removal of a polyp before it turns into a cancer. It's the same model that we've used for breast cancers—let's remove some of the estrogenic agents that may predispose to the development of breast cancers, let's couple that with mammography or other screening measures (breast self-exams), and let's defeat diseases like breast cancer. And that is the model that we're really moving towards with Alzheimer's disease: biological detection and prevention in the primary and the secondary sense, because of course when the brain has been completely destroyed, we do know that we're light years away from being able to restore that brain or bring it back from the brink of a degenerative disease like Alzheimer's.

JB: On behalf of all of our listeners and the literally thousands of people that will benefit as clinicians listening to this, and the patients that will get the benefit translated through their practitioner of this information, thank you very much and we will be following your work very carefully and we hope to trace back with at a future time and check in, because this is certainly right at the forefront of the burden that we're all experiencing in our rising tide of chronic disease.

GJ: Fantastic. Thank you so much for having me today.

JB: It's been our great pleasure. Thank you and best to you

Bibliography

[1] Dubois B, Feldman HH, Jacova C, Hampel H, Molineuvo JL, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2criteria. *Lancet Neurol*. 2014 Jun;13(6):614-29.

[2] Bachman AH, Lee SH, Sidtis JJ, Ardekani BA. Corpus callosum shape and size changes in early Alzheimer's disease: a longitudinal MRI study using the OASIS brain database. *J Alzheimer's Dis*. 2014;39(1):71-8.

[3] Ngandu T, Lehtisalo J, Levälahti E, Laatikainen T, Lindström J, et al. Recruitment and baseline characteristics of participants in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)—a randomized controlled lifestyle study. *Int J Environ Res Public Health*. 2014 Sep 10;11(9):9345-60.

[4] Swaminathan A, Jicha GA. Nutrition and prevention of Alzheimer's dementia. *Front Aging Neurosci*. 2014 Oct 20;6:282.

[5] Farooqui, Akhlaq A. *Phytochemicals, Signal Transduction, and Neurological Disorders*. New York: Springer, 2012. Print.

p>