

April 2012 Issue | Jay Lombard, DO Genomind, LLC

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Welcome to *Functional Medicine Update* for April 2012. The brain, neuronal function, diet, and genes. For some people those might sound as if they are really completely separate, independent, and unconnected topics. But from a functional medicine model, these are highly interconnected in a web-like series of cross communications, and it is that which we'll be talking about in this issue of *Functional Medicine Update*.

Hormetic Connections: Neuronal Function, Diet, & Genes

Dr. Mark Mattson, a senior research investigator at the National Institutes of Health (NIH), has been writing recently on the research they've been doing in his laboratory on what he calls neurohormetic phytochemicals.^{[1][2][3]} Now, what are neurohormetic phytochemicals? First we have to know what "hormetic" means. It is derived from the word "hormesis," and those of you that have been following *Functional Medicine Update* for some time know that "hormesis" is a term that refers to small things having much larger influence on function than we would have predicted. Hormesis works by different mechanisms than the traditional pharmacological mechanisms of dose response (increasing dose, increasing response). Rather, sometimes lower dose has bigger effects with hormetic substances. The reason for that is they have unique receptor interactions to—I'm going to call it "tickle"—specific receptors in such a way as to modulate their function, or send a signal through those receptors that are different than a hard-hitting, high-activity signal.

This would be like thinking of different effects of aspirin, for instance. You might think of aspirin taken at the baby aspirin level to prevent heart attack, or you might think of aspirin taken at a higher level to treat a headache, and then you might think of aspirin taken at a much higher level to treat the pain of rheumatoid arthritis; different activities at different concentrations of therapeutic dose. Now, I would say the baby aspirin analogy is not quite hormetic, because the level that I am speaking of related to hormesis may be even much lower than that of a baby aspirin (exposure to certain bioactive ingredients).

What Dr. Mattson has pointed out is that our nervous system and our neuronal function may be very sensitive to certain types of hormetic phytochemicals, meaning substances that are found within the diet, like epigallocatechin galate (EGCG) that is found in green tea (*Camellia sinensis*). Or he talks about the effects that resveratrol, which is found in peanut skins and in grape skins and may serve as a neurohormetic phytochemical. Or he talks about curcumin from the spice turmeric, which has been demonstrated to have the potential to serve as a neurohormetic phytochemical. So these are fairly interesting new developments in how the brain may be influenced by substances that come through our diet that plants make as anti-stress compounds that become influential on neuronal functioning even though they are at very low concentrations within the body, working by different kinds of structure/function relationships.

Homocysteine as a Biomarker for Alzheimer's Disease

I think this concept is interesting if we go back and examine a biomarker to Alzheimer's disease and its relationship to neural hormesis and nutrition, and that biomarker I'm talking to is homocysteine. Elevated homocysteine has been statistically associated with both increased incidence of Alzheimer's dementia and of coronary heart disease.^[4] It has been suggested the reason for this is that homocysteine is either a cause or an effect of inflammatory processes in specific tissues.

In actual fact, when we start looking at homocysteine, it often comes as a biomarker in conjunction with a couple of other biomarkers that are elevated, and those are high sensitivity C-reactive protein (CRP) and also uric acid, which we often associate with gout, but also is another marker that is associated with increased upregulation of oxidative inflammatory stress.^[5] So the combination of elevated homocysteine in conjunction with elevation of high sensitivity CRP and uric acid reflects a certain kind of metabolic disturbance that has a statistical association with Alzheimer's disease, with type 2 diabetes, and with coronary heart disease. It's interesting that it cuts across those very different disease entities and specialties of medicine.

One might ask: Are these, then, solely a consequence of the poor metabolism of homocysteine because it somehow is blocked in the tetrahydrofolate cycle in its ability to be appropriately metabolized and recycled? If so, does that mean it will be ameliorated solely by administering supplements of folic acid, and vitamin B12, and maybe betaine hydrochloride as the cofactors that are necessary—the nutritional cofactors—for stimulating the metabolism of homocysteine? There is the ability to lower homocysteine levels by supplementation by vitamin B12. This is seen even recently in population-based

studies.^[6] We've started to fortify grains with folate.^{[7],[8]} However, if you look at very detailed meta-analysis of tens of thousands of peoples' data, we don't find a very significant correlation with a reduction in incidence of either Alzheimer's disease or heart disease as the general trend of homocysteine has gone down.^{[9],[10]} Is the answer that homocysteine elevation is a biomarker for putative or occult B vitamin deficiency, or are there other things going on here in which homocysteine elevations, particularly in conjunction with elevations of uric acid and high sensitivity CRP, represents a disturbance in metabolism that reflects inflammatory oxidative stress in specific tissues that then demands other review, other than just supplementation with folic acid and/or vitamin B12?

A Recent Meta-Analysis of Modest Homocysteine Elevation

A recent paper published in 2012 in the February issue of *PLoS Medicine* looks at a meta-analysis across these thousands of case studies that have been published and tries to tease out whether homocysteine in modest elevation is, in and of itself, the cause or the effect of some of these problems.^[11] The authors of this paper concluded that in a large population, you do not find a statistically significant correlation between moderate homocysteine elevations in the blood and coronary heart disease incidence, and that although B vitamins will lower homocysteine, there is no statistically significant reduction in overall population-based coronary heart disease or Alzheimer's incidence. They then went on and asked the question: What about those individuals that carry a methylene tetrahydrofolate reductase polymorphism that makes their folate more challenging in terms of metabolism? They've got a block in conversion of folate to 5-methyl tetrahydrofolate (5-MTHF; the active form)? And even by segmenting it to that 5-methylenetetrahydrofolate reductase (5-MTHR) TT677 polymorphism, which is the genotype that has, in about 10 to 15 percent of the population, the greatest resistance to the proper metabolism of folic

acid—that even in that genotypic segmentation of the data, you don't find a strong correlation between elevated homocysteine and coronary heart disease.

Could it be, then, that homocysteine is more a marker for overall disturbance in metabolism that goes to only a part of its relationship directly to the cofactors that activate the enzymes in the folate cycle, and that is the folic acid, the vitamin B12, and betaine, and also deals with other factors that may serve as modulators of this inflammatory personality? We go back again to what we learned from Dr. Mattson, and that is that within foods there are neurohormetic substances that modulate the expression of genes in the nervous system and in the vascular system that can influence inflammatory response and oxidative response that then changes homocysteine, uric acid, and hs-CRP levels. It may be a much more complex topic than just supplementing alone with 5-methyl tetrahydrofolate, and methylcobalamin, and betaine. If a patient doesn't have a lowering of their homocysteine and a lowering of their hs-CRP as a consequence of B vitamin supplementation alone, then you need to look more broadly at the phytochemical families that might influence inflammatory potential. That's what we're going to be speaking to today as it relates to this genotropic relationship to neurological disorders and how that interrelates, then, with specific complexity within the diet and lifestyle.

In our own research laboratories, we have recently been screening families of various types of phytochemicals that are derived from foods for their abilities to modulate the intercellular regulating system called kinases. There are over 500 kinase enzymes found in different cells. These influence the signaling of environmental messages ultimately to the genome, which then causes transcription of various proteins and alters the function of the cell. And so as we start to use various cell models, like neuronal cell models, and we screen against various kinds of botanical extracts from foods and spices. What we find is that there are very differential effects in the ability of these phytochemicals found in various foods to serve as neurohormetic phytochemicals and modulate function of the cells. In fact, as we screen those various chemicals, we find they are involved with selectivity of modulating things like brain-derived neurotropic factor and how that interrelates with kinases like the MLK-3 family, which is associated with expression of neuronal function.

We see the same things with regard to kinases that modulate neurogenesis, and modulate anti-inflammatory processes within the neurons. I could go on at some length in this, but suffice it to say that what we are starting to recognize is that beyond that of just the B vitamins, this homocysteine/high sensitivity CRP/uric acid elevation profile is in fact related to something beyond B vitamin deficiency. It is related to the complexity of genotropic uniqueness interfacing with the environment and the signals that are being seen and picked up by different cell types, like neuronal cells, and transmitted, then, into gene expression functions and ultimately into either cells that are at peace or cells that are in a state of unrest that we call alarm or inflammation.

Inflammatory Mediators Seen in Many Disease Types

I think this is very interesting when you start examining, then, how that interconnects disease etiologies across multiple disease types. As I said, not just Alzheimer's disease and heart disease, but also type 2 diabetes and autoimmune disease. Recently there have been papers demonstrating that some of these inflammatory mediators I've been describing are seen not only in insulin resistance and type 2 diabetes patients, but also in patients with systemic lupus erythematosus (SLE), and seen in patients who have Alzheimer's disease.^{[12],^[13]}

Does that mean individual patients have all these diseases simultaneously, or does that mean there is a metabolic disturbance that occurs in that person that happens to cut across these different disease entities

as a consequence of disturbed gene expression patterns in different tissues and different cell types? In fact, if you look at an autoimmune disease like systemic lupus erythematosus, you'll find that it has very similar kind of alteration in kinase signaling to other diseases. Alterations in AKT, SX-kinase, mTOR, in the adenosine monophosphate kinase family are the same disturbances of these kinases that are seen in Alzheimer's disease, and seen in type 2 diabetes, and seen also in coronary heart disease. We also see mitochondrial oxidative stress and reduced function in SLE, just as we see in type 2 diabetes and Alzheimer's. We see elevated expression of gamma glutamyl transpeptidase (or GGT) and how that relates to altered glutathione physiology across those different conditions. We see increased autoantibodies obviously in SLE, but we also see increased autoantibodies in Alzheimer's disease and in type 2 diabetes. And we see increased inflammatory biomarkers, as I suggested, not just hs-CRP but also cytokines and prostanoids.

The point I'm trying to make here is that Mattson's concept of neurohormetic phytochemicals, the gene-environment interaction, how we look at neurological disorders and behavioral neurology may connect itself in a functional way beautifully to what might appear to be very divergent diseases that share common lineage in terms of metabolic disturbances, such as type 2 diabetes, heart disease, and autoimmune disease.

With that in mind, let's move to an expert who I believe is at the cutting edge of this gene-neuronal revolutionary breakthrough, and that's Dr. Jay Lombard.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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Can you hear the excitement in my voice? I hope you can because I'm really feeling a state of exalted energy in this opportunity to interview our clinician/researcher of the month. This is one of those privileged times that I have each month when I select a personality that I think is doing something quite remarkable in the field that we should all be aware of. Someone who is doing pace-setting work that helps us to understand what the landscape of medicine of the future might look like. We certainly are fortunate to have one of those individuals with us in the studio today, Dr. Jay Lombard.

Now, some of you probably know the name Jay Lombard. He is certainly a well-recognized personality in our field of functional medicine. You may not know some things about Jay Lombard, however, that I

know. There are no secrets here; it's all very above-board information. Dr. Lombard is one of those quite remarkable seekers. I value people who are seekers: What level of inquiry do they bring to their life? What level of commitment to excellence do they bring? How do they view their discipline in the broader context of the social milieu, and humanity, and time/history? Jay is one of those individuals. He is board-certified both in neurology and psychiatry. I first met him in 1984, when I was teaching at the Omega Institute in Rhinebeck, New York, and Jay was just finishing up his medical school training. Since that time I've gained a brother-at-arms, both intellectually and professionally, in the interaction that Dr. Lombard and I have had over the years.

Behavioral Neurology: Where Psychiatry and Neurology Meet

What I really want to do is talk with Jay in this interview about the nature of a field that I think he has really been the father of. I think he might not give himself credit for this, but I believe those of us who have observed his contributions over the years would certainly give him credit for the coining of the term "behavioral neurology." The concept ties together his psychiatric background and his neurologic background in a very unique way—really a translational way of taking science and understanding of neurologic function and translating it into understanding behavior and some of the issues that we are confronting, both individually and socially, as it relates to behavior patterns and what we might consider aberrant behavior, or antisocial behavior, or even DSM-related diagnostic behavior.

It's with that context that I'm so privileged to have Jay in the studio today, all the way from his home on the east coast here to the west coast. Jay, welcome to Functional Medicine Update. Let me start with a question which I think you addressed in our last interview, but might be useful for some of our listeners to hear to contextualize your path. How did you come to focus on behavioral neurology, which I think is so timely and important?

JL: Well, thank you, Jeff. You know, it's interesting. I think that many neurologists don't regard behavior as a brain-based function, and nothing could be further from the truth. Obviously both normal behavior and abnormal behavior have roots in how our brains are operating, and I think understanding the brain as best as we can—because it is still pretty much a black box but it is one the most important pursuits of our society as scientists—to realize what produces brain health and also what things are at risk to produce brain disorders.

JB: So taking that and looking at your career as I have seen it, which probably is at the 30,000-foot level (there's a lot more at the cornfield-level that has gone on that you know about in your life than I), it seems that your career has almost mapped against the evolution of this field. You've been very interested in molecular genetics. You've been very interested in metabolism. You were one of the first people to speak intelligently about the use of nutrients to modulate various neurologic functions, and later looking at various bioactive ingredients from plant products and how that interrelates itself mechanistically with the drugs that are commonly used for psychiatric and behavioral symptomatology. How did you actually start to put these things together? It seems like there must have been kind of a grand design for you, making what might have been appearing to be two separate worlds come together.

JL: I'm not sure. My wife thinks I'm an idiot savant. Maybe just the idiot part, I'm not sure. To answer your question, quite frankly, for anybody who practices in the field of neurology and psychiatry, if you have at all any sensitivity to humanity, it is quite a profound experience to be in front of people who are experiencing Alzheimer's disease, or a parent with an autistic child, or someone with intractable depression, or an adolescent who develops prodromal schizophrenia. These are disorders that affect us existentially. Other areas in medicine, with all due respect to my colleagues, you know, a dermatologist who is treating some skin disease, or a gastroenterologist who is treating gastrointestinal dysfunction—those are all important, obviously, to our overall health and well-being, but when someone is

affected by a behavioral neurological problem, the implications of this really affect us at our core. And I think that has been my motivation all along in my life: to really be able to add some value to understanding how these disorders come to be and how we can best understand ways of potentially diagnosing and treating them.

JB: So with that as a really great context, I think it's important for our listeners to recognize that this is much more than just theory for you. You're a great thinker, you're a great innovator, but you've also done the heavy lifting. You've worked at Bronx Hospital, and you've been at Cornell Medical Center. You've overseen patients who are in every degree of jeopardy. Maybe you could tell us a little bit about what you learned through the kind of hard knocks of dealing with fairly significant problems in patients.

JL: Well, I think that neurology, from my training back in the late 80s/early 90s, was a "diagnose-and-adios" field. I'll never forget a particular experience that really affected me profoundly, which was being with the chairman of neurology back during my residency program, and we saw a man who had developed weakness in his arms and had difficulty breathing. After an examination he was told he had amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). The family, when they understood what that meant, the doctor told them to just go ahead and get your life in order and get ready to die, which was true. I mean, there was really nothing to offer. But it was astonishing to me how we could be in a profession to heal and to improve lives, and be left with such a poor understanding about what things to offer a patient with that disease, or Alzheimer's, or other diseases. The good news is that we are much further along in terms of understanding the pathophysiology of these disorders and what risk factors there are, but we're also still in the dark regarding how to translate some of these discoveries into clinical practice and I think that's what we always need to keep our mind on whether we are clinicians or researchers: what the practical implications and ramifications of our discoveries are and how best suited to apply them to people who are suffering from these disorders.

Mental Health is Expected to Be Largest Category of Healthcare Expense Over Next 20 Years

JB: That's a fantastic next step. It's like we practiced this ahead of time. I'd like to segue from that to a little factoid that I learned recently. One of the most significant risks that we have in the United States as it relates to financial, economic, and maybe social peril, is the Medicare overhang for medical services to be offered to baby boomers over the next 20 years.[14] That overhang has been projected to be 37 trillion dollars, which is some seven times greater than the present national debt. Not only is this enough of a burden to bring the economy to its knees (which means society to its knees), we don't have a solution to the problem. If you were to categorize those expenses that lie under that 37 trillion dollar overhang, the largest single category is in the mental health area, with Alzheimer's rising up. So, you are, I think, one of the beacons of white light in helping us to understand some aspects of how we might at least address—conceptually, on the front edge—this overhang. Tell us a little bit about where you are heading in your discoveries/exploration in the understanding of the etiology and maybe prevention of Alzheimer's.

JL: First of all, I agree with you a hundred percent that this is a public health crisis, bar none, and we are in a collective state of denial about this disorder, and one of the reasons is that Alzheimer's doesn't clinically manifest until there is significant underlying pathology. The reality is that people are experiencing the degenerative properties of Alzheimer's many years before clinical symptoms actually set in, and our ability to treat Alzheimer's properly really requires us to identify the disease in prodromal, or preclinical, stages of the disorder. This is where a lot of my own personal efforts are right now. This is where a lot of the research in Alzheimer's is being applied, including both genetic detection of the disorder, which we can talk about a little bit in more detail if you like, and other things like looking for protein biomarkers that actually indicate the active expression of Alzheimer's disease, and also imaging, which is important, but still unresolved about what type of imaging (brain imaging, particularly) is most

sensitive and specific to pick up the degenerative changes associated with Alzheimer's disease.

These are all important efforts because if we are able to create a healthcare system that is able to pick up the problem earlier on, then our chances of success in reversing these trends is significantly higher than if we bury our heads in the sand and don't worry about the problem until it is fully expressed and we will have no chance of success. And the implications of this, as you mentioned, are truly catastrophic both at an economic level, but more importantly at a human level, because someone losing their cognition really strips from them the core of their identity. Our memory is in many ways our identity, and without our memory we have no identity. This is a very tragic consequence of Alzheimer's disease.

Alzheimer's Disease: The Search for Early Biomarkers

JB: Tell us a little bit about these biomarkers, because it seems the term "biomarkers" often has been applied to later stage diagnoses of disease versus what you are alluding to, which is maybe an earlier trajectory/understanding towards ultimate Alzheimer's disease.

JL: Absolutely. You know, the first biomarker really, in many ways, for clinicians to be aware about is to frankly acknowledge the elephant in the room and to ask patients a very simple question: Are you concerned about your memory? If the answer is yes, people should take that seriously. The reason people don't ask that question is because they don't know to do with the answer. If someone says, "Yes, I'm concerned about my memory," okay, well, now what? Don't worry about it? So we really need to create better algorithms to take next steps after asking this question.

Predicting Risk is Not Predicting Actual Disease

In my opinion, there are genetic tests that are useful that predict risk of dementia. One of the things that is important to understand is that predicting risk is not predicting actual disease, so if we say a patient who has a genetic test for any particular neuropsychiatric condition and they are at higher or lower risk, it does not mean that this is a fait accompli and they are actually going to develop a particular disease, which is one of the reasons that most clinicians have now adopted preclinical gene testing for Alzheimer's disease. We have not established what steps to take once a risk is identified. This is, I think, a big misguided assumption, because we do know that clearly there is strong evidence for prevention strategies. We should be taking those identifications and recommending preventative steps in patients who are identified with higher risk of Alzheimer's disease.

JB: So before we get to the gene test, which I really want to get into in a little bit more detail, I'd like to ask a clinical first-level question. I've been reading recently and hearing a number of people report that one of the early markers for Alzheimer's could be a rapid change in smell and taste. Is this at all a clinical part of the profile from your experience?

JL: Absolutely. This is not new news; this is old news that loss of olfaction may be a particularly sensitive biomarker—a clinical biomarker—which should be part of the routine cranial nerve examination. Never is. We always test cranial nerves 2 through 12. We skip cranial nerve number 1. But yes, loss of olfaction may be a very early warning sign of developing degenerative changes associated with Alzheimer's disease.[15]

JB: So now let's move from that to gene testing. This whole area of genotyping has become really a major area of both interest and controversy. In the cancer area now we get into tumor typing with specific genotype maps that leads to differential chemotherapy that are designed for the individual patient's tumor type. We're starting to see the same strategy spread out into other fields. How does this relate specifically to what we are learning in the area of Alzheimer's and other neurodegenerative diseases?

Many Disorders of the Brain are Protein Aggregation Disorders

JL: Great question. First of all, one of the opportunities to study genetics and psychologies and neurologies is really, in my opinion, for understanding the pathophysiology of a disorder as opposed to a diagnostic biomarker in its own right. So the opportunity here, if we listen carefully to what genes tell us, is a better appreciation of the fundamental mechanisms that produce degeneration of the brain. So for instance, some of the more commonly established genes which have been associated with Alzheimer's disease include the apo E gene, which has a lot of very important roles in brain physiology and particularly in lipid metabolism in the brain. We know that the E4 allele, although it is the minority allele in terms of its prevalence in the population, is substantially overrepresented in terms of risk for dementia. We need to understand how the E4 allele, particularly, leads to an increased risk compared to the E2 alleles. There are other genes also that are highly relevant and important to Alzheimer's disease. Another gene is called the apo J gene, which is associated with a protein called cholesterin, and cholesterin indicates protein aggregation. Many of the disorders of the brain, including Alzheimer's, are really protein aggregation disorders, and we think of proteins as being two dimensional. The reality is that proteins are three dimensional, and when we lose the conformational structure of that protein, like amyloid, this is what produces the pathophysiological changes. So these genes are telling us—they are really providing us—with clues into the underlying steps that are leading to brain loss in these disorders.

JB: So we've heard a lot about beta amyloid and its connection with Alzheimer's. We've also kind of got an association that it's connected to the apoE4 allele. We recognize that this amyloid form. We realize that this amyloid forms rope-like structure, as we can see it in hippocampal degeneration under cytology and fluorescence microscopy. Tell us a little bit about this amyloid story, because it sounds to me like this connects molecular genetics to cellular biology to ultimate pathophysiology.

JL: Amyloid—especially amyloid precursor protein—is a normal molecule in our brains. What happens is it is processed abnormally. Either we have increased deposition of amyloid, or we have decreased degradation of amyloid, or we have a combination of increased production and decreased degradation of amyloid. The other important pathophysiological protein involved here is something called tau, which is associated with microtubules. Microtubules are the pillars, if you will, of cellular function, regulating things like synaptic efficiency, neurotransmission, transport of intercellular machinery, mitosis, and clearly when microtubule dysfunction occurs as a result of either aging or head injury, which is one of the major causes of microtubule dysfunction, this also produces pathophysiological changes in the brain associated with dementia. So both of these aspects, the amyloid story and the production or abnormal phosphorylation of tau protein, are implicated in dementia.

JB: Tell us a little bit about this tau protein. When we talk about these kinase pathways that regulate phosphorylation of tau, that has a branching out into other physiological distortions, such as insulin resistance and insulin sensitivity, which then helps us to understand what we talked about some years ago as it relates to the influence that pre-diabetes and hyperinsulinemia might have to Alzheimer's. Tell us a little bit how that all connects together.

Studying Epothilones: Natural Compounds that Regulate Microtubules

JL: Well, I wish I knew. I can tell you, though, that tau dysfunction, or microtubule dysfunction in particular, is not only associated with Alzheimer's disease, but also has been implicated in other neuropsychiatric disorders, including schizophrenia and autism. And why wouldn't it? I mean, you'd think something with such a ubiquitous and required cellular functionality, when you disrupt those processes would lead to neurological dysfunction. Really the key things in my mind are: A) How do we identify microtubule dysfunction; and B) What do we do about it once we do identify it?

Interestingly—and this relates probably to insulin resistance as well—is that the phosphorylation/dephosphorylation of microtubule-associated proteins is what really essentially regulates

the microtubule and determines its activity. This is actually an opportunity for us to understand—because it is a variety or a family of compounds that regulate microtubules—very interestingly, one of the compounds that is found in the soil is called epothilones. Epothilones are a product of bacteria that exist in soil; they are like sort of a probiotic material, that are microtubule stabilizing agents. One of the theories of the increased risk of disorders that we are seeing in the brain is that we've moved away from eating farmed foods, which may have high amounts of these soil-based compounds in them that are actually preserving our brain function: these epothilones, which have been looked at in cancer as well.

JB: So when we start looking at this as a system of biology--you're raising all sorts of extraordinary little points on the landscape for us that are interconnected--we start talking about things like the ecology of the human being that sets up the state of function that we later diagnose as Alzheimer's disease. I know one of the things you've written about and talked about has to do with the ecology of our mouth and how that interrelates with the overall immunochemical competency or function of our body that has some aspect of relationship to the brain. Tell us a little bit about that.

One Theory of Alzheimer's Disease: Low Grade Infection and Antimicrobial Peptides

JL: This is work that really comes from Rudy Tanzi's lab at Mass General. We were discussing this a little bit earlier today. His lab identified that antimicrobial peptides, which are endogenous peptides involved in scavenging any kind of immune challenges, whether it is bacterial, viral, or even head injury, there's activation of these antimicrobial peptides. What is so interesting about antimicrobial peptide, which abbreviated as AMP, is that the conformational structure, the molecular makeup of antimicrobial peptide, very closely resembles amyloid. So the theory is—and, again, this is still a theory but there are lots of leading witnesses that point to this being a significant culprit in Alzheimer's disease—is that low grade infectious processes, in particular bacterium in the oral cavity, lead to increased expression of antimicrobial peptides. These antimicrobial peptides induce amyloid-like properties in the brain, and this is what's causing us to have an increased amyloid burden: an immune driven response to low grade infectious processes. This is also supported by the fact that there are higher rates of *Porphyromonas gingivalis* (*P. gingivalis*) in dementia patients, and other antibodies indicating an immune response. The implications of this, of course, are quite profound. Because if we truly can establish a link between high levels of persistent “benign” bacteria (chronic low grade inflammatory processes like gingivitis or periodontal disease), this may be a call to action to give people: A) much better vigorous oral hygiene; but B) consider a low dose of antimicrobial agents like doxycycline or something else to reduce the infectious process in people who are at risk of developing dementia as a result of that process.[16]

JB: So you spoke earlier about the higher prevalence of Alzheimer's dementia in people that carry the apo E4 allele. Is there a connection, then, between apo E4 and this antimicrobial peptide story?

The Role of the Blood-Brain Barrier in Neurological Diseases

JL: Well, one of the areas that Genomind, a company I work for, is interested in is looking at the blood-brain barrier. This is something that is very important not just to the nutraceutical industry, but also to the pharmaceutical industry, for a couple of reasons. One is that many neurological diseases, including stroke, primary hypertensive hemorrhage, multiple sclerosis, autism, schizophrenia, and Alzheimer's disease are associated in some way with perturbations of the blood-brain barrier. But in Alzheimer's disease, why is this important? Because these abnormalities in the blood-brain barrier may actually adversely affect the ability to degrade and remove amyloid. So in many ways, Alzheimer's disease may in fact, in some types of the disorder, be due to a reduced efficiency of efflux of these pathological proteins, as opposed to what we commonly think of as being an abnormality where there is too much influx of bad stuff going into the brain. Perhaps in Alzheimer's it is the opposite, where there is a reduced

sort of kicking out and departing of these abnormal proteins from the blood-brain barrier.

JB: So let's go back and pick up this extraordinary work that you're doing at Genomind because it seems to couple together so many of the things that we've talked about in this landscape: an assessment using biomarkers, genetic susceptibility, factors that then guide us towards individualized personalized preventive strategies, maybe the use of specific types of interventions. Tell us about Genomind.

Testing Profiles Being Developed by Genomind

JL: Thank you. We are in the process of looking at clinical application both in psychiatry and neurology. Our first test is a test that is primarily used by psychopharmacologists in treatment-resistant depression, in which we know that trial and error is the lay of the land in people who have been exposed to a series of antidepressants without clinical response. We believe that using genetic biomarkers will help to sub-endophenotype (that's a mouthful of a word, there) different subtypes of depression that will lead to more specific antidepressant interventions as opposed to continuing the trial and error approach. We are currently getting tremendous feedback from our psychopharmacological colleagues who have had the chance to use the test. We have a number of clinical trials right now looking at whether these patients, which are a difficult population of patients to treat to begin with, whether having the Genecept assay, which is part of the Genomind testing profile, is helping to reach a faster antidepressant response than they would have without the use of that tool.

The second effort of Genomind is, as we discussed, looking at how biomarkers play into Alzheimer's disease. Again, preclinical diagnosis is our mantra. We do believe that testing early and testing as many people as possible will ultimately be the way that we can reduce risk by preventing and applying preventative strategies. But we can't prevent unless we know there is a problem there. So therefore, preclinical testing of Alzheimer's disease becomes, in my mind, really a public health policy. It's not just a Genomind policy or philosophy; it's really a philosophy which I believe the neurological community needs to adopt, and the reason we've not adopted it is because we don't have clear establishment that preventive strategies do in fact reduce the onset of Alzheimer's disease or prevent progression.

Treatment of Nonresponsive Depression

JB: Wow. Really important stuff there. So there are three follow-ons that I would like to take from that that we can break out. Number one, let's talk about treatment of nonresponsive depression. There is some evidence suggesting that at least some forms of treatment resistant depression could respond to an adjunctive use of therapeutic 5-MTHF. Do you have any experience or thoughts about whether that looks, from your experience, to be realistic?

JL: Oh, absolutely. I think a lot of the credit for this really is due Mauricio Fava at Mass General, who is the vice chairman of psychiatry at Harvard Medical School. He has been sort of the granddaddy of methylation hypotheses and psychiatry, particularly in depression, for over 20 years. Finally I think that we are seeing the fruits of his insights, particularly in patients who have variance of the folic acid pathway in which they are unable to convert folic acid to the active form of methyl folic acid due to a genetic polymorphism called the MTHFR gene. This particular gene is responsible for activating methyl folate from folic acid. A common allele called the MTHFTT allele is essentially reducing the efficiency of this conversion process. We know patients with this particular allele have higher rates of depression and may be more likely to respond to methyl folic acid. There is lots of good evidence that this actually is indeed true.

JB: What doses are generally used, Jay, in those kinds of applications?

JL: Pretty high doses, Jeff. The doses in clinical trials are between 7.5 and 15 milligrams, which probably

is not the dose that people need who either don't have this genetic variant or don't have a syndrome associated with folic acid abnormalities. But it is not only potentially looking at depression, there is also a higher risk of other abnormalities associated with the folic acid pathway, including metabolic syndrome and also including vasculopathies, particularly venous vasculopathies, but also arterial vasculopathies as well.

JB: So when we look at 7.5 milligrams, just to make sure we're all on the same page here, that's 7500 micrograms to 15,000 micrograms we're calling it. The RDI is somewhere in the range of 400 micrograms. These are what we call nutritional pharmacological doses, and so the question might be asked: Could you do better by going upstream from 5-methyltetrahydrofolate and use S-adenosylmethionine (SAM-e), which is the principal methylating agent? I recall actually ten years ago or so you and I both spoke at a symposium in Aspen where I think you spoke about SAM. What's your thought on SAM versus 5-MTHF?

JL: Well, I love SAM. In fact, my best friend's name is Sam. That's not why I love SAM, though. S-adenosylmethionine is also a very interesting nutraceutical or pharmaceutical, if you will, also involved in methylation pathways. It has unique properties which are different than methyl folic acid. Particularly its activity on an enzyme called catechol-o-methyltransferase, which regulates dopamine metabolism in the brain. SAM-e (I guess we can call it SAM-e, or just SAM? I'm not sure what the proper way of calling it is), but there is very good evidence that as an antidepressant, which is either equally effective or even more effective than many standard antidepressants that are on the market today, and may even have a more rapid onset of antidepressant response.[17] My belief is that SAM-e (or SAM), like methylfolate, has a unique niche in terms of who is more likely to respond to it. Here again is where I think biomarkers become helpful, because perhaps polymorphisms in the catechol-o-methyltransferase pathway may indicate preferential response to this as an antidepressant as well.

DSM Disease Diagnosis

JB: Let's move from that to the second of my three takeaways from your previous discussions and talk about the Diagnostic and Statistical Manual of Mental Disorders (DSM) and disease diagnosis. One of the things that you've really helped me to understand is when you cohort stratify for various genotypic uniquenesses underneath a specific "DSM Disease Diagnosis," you may end up with several subvariants, some of which are sensitive and others of which are insensitive to specific interventions, which means our whole medical model of disease as independent, isolated independent kind of paradigm seems somewhat questionable in light of the age of genomics. Tell us a little bit about that.

JL: Jeff, what you just said is something that I wish I could duplicate and reproduce for all listeners on my side of the table because that is exactly correct. What Genomind's philosophy is, particularly as it applies to psychiatry, is that psychiatric disorders, and probably this is true not just for psychiatry but is true for all of medicine, that these are dimensional, not categorical disorders. We need to change the paradigm of how we understand psychiatric disorders in particular. There is not autism as a single disorder. Autism probably represents many different types of disorders. This is true for dementia. It's true for schizophrenia. It's true for depression. Until we are able to move away from a categorical diagnosis to a dimensional diagnosis, and what I mean by that is understanding the fundamental pathophysiological processes that are implicated in the manifestation of these disorders, we are going to be unsatisfactory in terms of how we treat them. We'll be basically putting Band-aids on these disorders, as opposed to addressing them from their principal pathophysiological processes. For example, schizophrenia. My belief is that schizophrenia may be related particularly to the adverse effects of reduced (or lack of) glutathione on D2 receptors. There is very, very compelling work that this is true, and that an inability to properly protect these D2 receptors from oxidation, particularly in vulnerable periods of

neurodevelopment, may lead to the structural changes that result in what we call schizophrenia[18],[19]. Schizophrenia is not a neuroleptic deficiency. Right now, in the last 40 years, all we have done is basically provide symptomatic treatment through drugs which block dopamine or modulate dopamine. We're never addressing the fundamental etiology of the disorder, which in my opinion may be due to a redox imbalance of D2 receptors in the brain.

B: Well, that's kind of fascinating just to speculate (if you take this as speculation). If you look at Abram Hoffer's work with niacin treatment, or nicotinic acid treatment, of schizophrenia, which we know is not applicable to every schizophrenic, but in certain individuals seems to have a remarkable effectiveness. High dose niacin (pharmacological dose of niacin) has an effect on glutathione biosynthesis by mass action, so one might speculate—at least it would be an operative hypothesis—that nutritional intervention at a pharmacological level in those subtypes could have a very interesting positive effect on regulating this redox potential as you are suggesting. This model opens up all sorts of differing ways of approaching hypotheses, that in the absence of what you are talking about (core stratification, gene interaction with the environment of the individual), you wouldn't even be able to generate these hypotheses.

JL: Or take any kind of actionable steps, so again the biomarker, in my mind, what it does is provide insight into the molecular abnormalities associated with a neuropsychiatric disorder, and therefore gives us a chance to intervene not just on a hypothesis but on sort of an evidence-based platform that we know there is this pathophysiological effect, which we can see either through a gene biomarker or a protein biomarker.

JB: You know, it's extraordinarily interesting, isn't it, as we see this evolving, how the term "functional medicine" really looks prescient? I think when we chose it over 20 years ago we kind of had a rudimentary feeling that it had a little trajectory into the future, but as we are talking, all of these are really functional disturbances in the individual between how their environment and genes interact to give rise to their expression of function. It seems like it cuts across all these disciplines. Once again, what Genomind is doing is forming a certain mosaic pattern of gene markers that help us to understand the unique way that that person's environment is influencing their—in this case—psychoneurological function.

JL: It seems so obvious now, doesn't it, Jeff?

JB: Yes. It's amazing.

JL: I always laugh at the expression of how the word du jour is "personalized" medicine, something Dr. Bland, the interviewer extraordinaire, has been the godfather for at least 30 years, so it is quite rewarding. What are the Preventive Strategies?

JB: Well, as long as we can make some good of it. We're at that very interesting place in our discussion where there's going to be a pay off, which I want to come back to and you've alluded to it, and that is once you've done the Genomind assessment and you've gotten some interesting insight into some genetic markers that may relate to the high degrees of susceptibility, now what are the preventive strategies that come out of that? Maybe you can tell us a little bit about what travels from the information?

JL: Yes, well I think that has to be on a particular case-by-case basis. That's a loaded question, by the way. But if you want to ask maybe for particular examples of that, because there's really a whole library of potentially effective agents which can be used dependent upon one's personal genotype or phenotype.

JB: Let's take maybe the more obvious example that we've alluded to, and that's apoE4 double hit allele Alzheimer's relative risk.

JL: Right. Well, the short answer is no one knows for sure. The particular hypothesis that we're looking at Genomind right now is that apoE4 represents, rather than a proinflammatory state, a defective immunological state in which the normal endogenous processes that are responsible for removal of

amyloid are impaired. And this normal physiological process relates to something called heat shock proteins. Heat shock proteins are chaperone proteins that the immune system actually induces to carry defective or senescent proteins sort of out of the war zone, taking them back to the recycling plant of the cell and using that material for resynthesis of other proteins. The senescent protein has to recognize it is currently senescent, which is a complicated molecular process, but these heat shock proteins sort of chaperone or identify the defective protein and chaperone it back to the endoplasmic reticulum. These heat shock proteins are up regulated by a variety of nutraceutical compounds; they are many of the things that plants use for resilience against extreme temperatures that are plant-based and possess high levels of these heat shock proteins. One certainly could speculate that this may be a novel intervention for patients with apoE4 subtypes who are at risk of developing dementia.

JB: So when we talk about plants that have developed this adaptive response to their environment, transference of that over into humans, where it has an impact in the human, that's kind of a xenohormesis concept. You start thinking of how plant interconnection/co-evolution with humans relates to these adaptive molecules and anti-stress molecules. Can you give us some of the things in the plant kingdom that are at least interesting from a speculative process as it relates to the regulation of these functions?

JL: Sure. I have to think particularly about which of the plant compounds are leading candidates in this regard. A lot of the ginseng-based molecules have effects in up regulating heat shock proteins particularly. Rhodiola, and some other plant-based extracts. But I think this needs to be looked at in a more systematic way in which you start with sort of cell-based cultures to see which of these natural compounds that exist in nature are able to increase heat shock proteins, and then apply those to animal models of Alzheimer's. The problem, quite frankly, is that these are expensive trials and if the drug companies don't recognize that these are potentially patentable processes that are worth their while, these will never get from pre-discovery to translational research. That's my concern: that we're never really going to be able address this question properly in the absence of adequate funding to demonstrate their potential efficacy in patients with risk of dementia.

JB: I know one of your colleagues at NIH, Dr. Mark Mattson, who I know you're familiar with, has written a series of wonderful articles. He is in the area of Alzheimer's research and neurology research and has been looking at hormetic phytochemicals and published a whole series of papers. He talks about the role on cellular regulatory functions in the neurological systems of green tea (epigallocatechin gallate), and resveratrol, curcumin, these are compounds that actually seem to be hormetic neuroregulators. Certainly what you are saying seems like it's getting—at least at the fundamental research levels—some traction now.

JL: Yes.

JB: Now how we can take that into clinical proof of concept and tie that together with the Genomind portfolio of evaluative biomarker gene tests that open up the dawn of a whole new era it seems in behavioral neurology?

JL: One hopes so. Absolutely.

JB: So as we bring this discussion to a close, knowing that it could go on for hours (and between the two of us, it has, with hopefully more hours to come), what's your outlook? How do you look at the landscape? Because there is certainly room for pessimism as it pertains to standard of care, kind of following lock-step into a guild-like mentality. And then there are opportunities for optimism, looking at the opening of new discoveries that really change the whole perspective as to the plasticity of the nervous system and how the environment influences its function. What's your take on this overall mosaic of the future?

JL: Well, first of all, it's my life mission. This is very important to me personally, again because of my direct experiences with literally thousands of people who have suffered from neurological psychiatric

disorders. I take these problems personally. I ruminate over them, much to my wife's dismay. I'm optimistic because I think that we do now have the tools, we've been given the insight through our explosion of genetic information about the biology of schizophrenia, bipolar disease, and Alzheimer's, and depression. Now the opportunity and the responsibility is ours to take this basic science and to move from basic science discovery to translational genomics and translational research, and certainly functional medicine and the recognition of how we are each individually different and it is now one-size-fits-all in terms of how we address these problems. It's just a matter of connecting the dots, and I think we are closer now than we have ever been before. There are still lots of battles to fight, but we at least have our gloves on and are in the ring.

JB: Well, Dr. Lombard, I want to say, as I have said in our previous interviews, you're a model on many, many levels. You're a seeker. You're courageous. You're an individual who has taken personal risk in your profession for stepping out and not being in a box of constraint. You're willing to paint on the whiteboard knowing that sometimes you're not sure if you put the exact right mark on the board, so you might have to come back and erase it and put a new mark. As I look at your track record over the last 30 years, I'd say you're a model to the functional aspect of neuronal plasticity, and to creative, innovative, absolute, dedicated patient management. Your dedication to patients both your individual patients and the collective patient (the collective brain and the collective nervous system of our society) is evident in the moment that someone meets you. I want to thank you very much for your courageous dedication and I continue to applaud you as you move forward. We're all chopping the wood and carrying the water to try to create a better healthcare system, and this, as I said in the opening, is really the gorilla in the corner, this burgeoning problem—this burden—of mental health and neurological difficulties in our society. Thank you very, very much for all of your hard work.

JL: It was my pleasure. Thank you for inviting me

Bibliography

- [1] Son TG, Camandola S, Mattson MP. Hormetic dietary phytochemicals. *Neuromolecular Med.* 2008;10(4):236-246.
- [2] Mattson MP, Son TG, Camandola S. Viewpoint: mechanisms of action and therapeutic potential of neurohormetic phytochemicals. *Dose Response.* 2007;5(3):174-186.
- [3] Mattson MP. Dietary factors, hormesis and health. *Ageing Res Rev.* 2008;7(1):43-48.
- [4] Hoffman M. Hypothesis: hyperhomocysteinemia is an indicator of oxidant stress. *Med Hypotheses.* 2011;77(6):1088-1093.
- [5] Pasalic D, Marinkovic N, Feher-Turkovic L. Uric acid as one of the important factors in multifactorial disorders—facts and controversies. *Biochem Med (Zagreb).* 2012;22(1):63-75.
- [6] Deshmukh US, Joglekar CV, Lubree HG, et al. Effect of physiological doses of oral vitamin B12 on plasma homocysteine: a randomized, placebo-controlled, double-blind trial in India. *Eur J Clin Nutr.* 2010;64(5):495-502.
- [7] Nagele P, Meissner K, Francis A, Fodinger M, Saccone NL. Genetic and environmental determinants of plasma total homocysteine levels: impact of population-wide folate fortification. *Pharmacogenet Genomics.* 2011;21(7):426-431.
- [8] Pfeiffer CM, Caudill SP, Gunter EW, Osterloh J, Sampson EJ. Biochemical indicators of B vitamin status in the US population after folic acid fortification: results from the National Health and Nutrition Examination Survey 1999-2000. *Am J Clin Nutr.* 2005;82(2):442-450.
- [9] Van Dam F, Van Gool WA. Hyperhomocysteinemia and Alzheimer's disease: a systematic review. *Arch Gerontol Geriatr.* 2009;48(3):425-430.

- [10] Marti-Carvajal AJ, Sola I, Lathyris D, Salanti G. Homocysteine lowering interventions for preventing cardiovascular events. *Cochrane Database Syst Rev.* 2009;4:CD006612.
- [11] Clarke R, Bennett DA, Parish S, et al. Homocysteine and coronary heart disease: meta-analysis of MTHFR case-control studies, avoiding publication bias. *PLoS Med.* 2012;9(2):e1001177.
- [12] Lozovoy MA, Simao AN, Hohmann MS, et al. Inflammatory biomarkers and oxidative stress measurements in patients with systemic lupus erythematosus with or without metabolic syndrome. *Lupus.* 2011;20(13):1356-1364.
- [13] Jefferson AL, Massaro JM, Beiser AS, et al. Inflammatory markers and neuropsychological functioning: the Framingham Heart Study. *Neuroepidemiology.* 2011;37(1):21-30.
- [14] The World Health Forum and the Harvard School of Public Health. "The Global Economic Burden of Non-communicable Diseases." September 2011. http://www3.weforum.org/docs/WEF_Harvard_HE_GlobalEconomicBurdenNonCommunicableDiseases_2011.pdf
- (November 15, 2011)
- [15] Li W, Howard JD, Gottfried JA. Disruption of odour quality coding in piriform cortex mediates olfactory deficits in Alzheimer's disease. *Brain.* 2012;133(9):2714-2726
- [16] Holmes C, Cunningham C, Zotova E, et al. Systemic inflammation and disease progression in Alzheimer disease. *Neurology.* 2009;73(10):768-774.
- [17] Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-adenosyl methionine (SAME) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. *Am J Psychiatry.* 2010;167(8):942-948.
- [18] Steullet P, Lavoie S, Kraftsik R, Guidi R, Gysin R, Cuenod M, Do KQ. A glutathione deficit alters dopamine modulation of L-type calcium channels via D2 and ryanodine receptors in neurons. *Free Radic Biol Med.* 2008;44(6):1042-1054.
- [19] Do KQ, Cabungcal JH, Frank A, Steullet P, Cuenod M. Redox dysregulation, neurodevelopment, and schizophrenia. *Curr Opin Neurobiol.* 2009;19(2):220-230.p>