May 2007 Issue | JayLombard, DO Chief of Neurology

http://jeffreybland.com/knowledgebase/may-2007-issue-jaylombard-do-chief-of-neurology/

DOWNLOAD AUDIO | DOWNLOAD SUMMARY NOTES |

Welcome to *Functional Medicine Update* for May 2007. We had the decade of the brain in the 1990s, but certainly we are continuously learning more as to what brain dysfunction originates from and how it relates to functional medicine.

When we talk about hyperactivity attention disorders, autism, depression, dysphoria, and some cases of Alzheimer's dementia and cognitive dysfunction, we are talking about web of dysfunction that is not isolated in the brain itself. This web is signaled through much of the body: through the gut immune system, hepatic function, and vascular function. It is the interaction of those systems together in this functional web that gives rise to what we call neurological problems. There is even the environment and the perception of the environment-the epigenetic effects that occur through the process of modifying kinases and gene expression and signaling pathways. Traumatic life experiences, post-traumatic stress syndrome, violence, rejection, the feeling of no attribution or no love are translated through the same receptor sites and same signal transduction pathways and give rise to an amplified effect on the neuroimmune system that we see as these so-called neurological problems.

This is a very complex web giving rise to the challenge for professionals to figure out therapeutic approaches towards neurological difficulties. It is more than a single path to enlightenment; it is more than just one agent causing one disease. The application of functional medicine can help us to unravel and tease apart the multiple etiological factors that contribute to these dysfunctions..

Metabolic Syndrome and its Relationship to Cognitive Decline

There is no better example of this, I think, than the emerging story that surrounds metabolic syndrome and its relationship to the type of cognitive decline that we often call non-Alzheimer's, or even Alzheimer's-like, dementia. Many in the medical world first became aware of this relationship in 2004 when the article titled, "The Metabolic Syndrome, Inflammation, and Risk of Cognitive Decline," was published in the *Journal of the American Medical Association*.[1] The investigators were headed by Kristine Yaffe and included researchers at the Department of Psychiatry and Neurology and Epidemiology (as well as Geriatrics) at the University of California San Francisco School of Medicine, and also the National Institutes of Aging in Baltimore, MD.

This collaborative study looked at the effect of a five-year prospective observational evaluation conducted from 1997 to 2002 at two community clinic sites. Participants totaled 2632 black and white elders (mean age, 74 years), and investigators tried to tease apart whether there was an association between metabolic syndrome (or insulin resistance/hyperinsulinemia) and loss of cognitive function. The conclusion of this study was quite dramatic for individuals who were unaware of this connection between insulin resistance, inflammation, and brain function. The findings of the study supported the hypothesis that metabolic syndrome contributes significantly to cognitive impairment in elders, primarily in those with very high

levels of inflammation (as measured by increased levels of high sensitivity C-reactive protein above 1 gram per liter).

The Role of High Insulin on Neurological Function and Inflammation

The observation suggesting a relationship of elevation in inflammatory markers associated with metabolic syndrome and cognitive decline encouraged the research world to move at a faster pace to try and understand the mechanisms by which this could occur. A key relationship that was addressed was about what role high insulin would have on neurological function and inflammation. It is not an obvious connection in that we think of the brain as not being an insulin-requiring organ. It is now recognized that neurons have insulin receptor sites and that insulin activates at high levels of signal transduction NFκB transcription. NFκB plays an important role in stimulating gene expression of proinflammatory cytokines like tumor necrosis factor α and interleukin-6. This has been published in many different papers, including that of Benoliel, et al. in the *Journal of Cellular Science* in 1997.[2] ,[3]

This hyperinsulinemia connection to inflammation is becoming a very well understood gene expression outcome from high levels of insulin signaling. Studies implicate an inflammatory process in the pathogenesis of insulin resistance associated with many disorders, including central obesity with increased visceral adipose tissue accumulation, and in type 2 diabetes as well. As you have high levels of insulin, there is an activation of inhibitor kappa kinase beta (IKK beta) which then phosphorylates inhibitor kappa B, causing that to disassociate from the NF-kappa B complex, allowing NF-kappa B then to gain access to the genome, where it sits down on specific portions of your book of life (your genes) and causes them to be read. These stories that are read are the pro-inflammatory cytokines, including the cyclooxygenase enzymes and the production of proinflammatory prostaglandins. Insulin plays a very important role in modulating or mediating these immunological effects.[4]

Data have shown that mononuclear cells are able to be activated into a proinflammatory state with an increase with NF-kappa B binding, and that high plasma levels of free fatty acids can activate mononuclear cells to produce more proinflammatory mediators. High levels of free fatty acids are associated with metabolic syndrome and hyperinsulinemia, and insulin resistance is a function of inflammatory mediators. A number of papers have been published demonstrating this, including one that discussed circulating mononuclear cells and the proinflammatory condition associated with hyperinsulinemia. This article was in *Circulation* in 2004.[5] [6]

Free Fatty Acids Associated with Hyperinsulinemia

We know high levels of free fatty acids associated with hyperinsulinemia can result in lipid accumulation in tissues, such as the liver and in muscle. This can lead to localized tissue inflammatory signaling that causes apoptosis of cells in those tissues and loss of cell mass (in the liver, leading to hepatic inflammation through NF-kappa B activation). We don't think of the brain as becoming engorged with fat (it is not a tissue that we would normally associate with accumulation of triglycerides), but the same process of high levels of fatty acids that initiates the triggering of the proinflammatory mediators can have an effect across the blood-brain barrier and increase neuronal inflammatory response. It is both the direct and indirect effects of insulin through the inflammatory pathways that may be associated with the hyperinsulinemic state and metabolic syndrome and cognitive decline.

In the *Journal of theAmerican Medical Association* in 2006 there was a review titled, "Insulin Effects

Weigh Heavy on the Brain."[7] This article/review talked about insulin's best known role (as regulator of blood glucose and fatty acid storage), but also how it acts in the brain to aid memory and thinking. When insulin regulation is disrupted (as it is in many common medical conditions including diabetes) the risk for cognitive impairment rises.

Insulin dysregulation sets the stage for certain neurodegenerative disorders, particularly various forms of Alzheimer's disease, as was discovered by Dr. Suzanne Craft, professor of psychiatry at the University of Washington, Seattle. Craft and her colleagues have been studying the link between insulin and memory for the past decade. Their research is suggesting potential approaches to treat, delay, or even protect against Alzheimer's disease associated with hyperinsulinemia and altered insulin signaling. In normal physiology, and also when administered peripherally at optimal doses, insulin can enhance memory. Craft's team have found evidence that hyperinsulinemia is associated with inflammation in the brain and triggers the accumulation of the 42-peptide form of beta-amyloid, the precursor of amyloid plaques that are found in certain brain regions and are a hallmark of Alzheimer's disease. She has several publications in the journal *Neurology* about these findings.[8]

Insulin Resistance, Type 2 Diabetes, and Inflammation as Risk Factors for Alzheimer's Disease
So evidence now implicates insulin resistance, type 2 diabetes, and inflammation as risk factors for Alzheimer's disease. A high level of insulin seems to boost beta-amyloid levels and induce, then, this inflammatory state. This has become so well-recognized that recently, in the *Journal of Alzheimer's Disease*, an article was published titled, "Impaired Insulin and Insulin-like Growth Factor Expression and Signaling Mechanisms in Alzheimer's Disease-Is This Type 3 Diabetes?"[9] They are actually starting to name this condition of hyperinsulinemia associated with Alzheimer's disease and loss of cognitive function as a type 3 diabetes. In this article the authors say, "The strikingly reduced central nervous system expression of genes encoding insulin, insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 1 receptor (IGF-1R) as well as the insulin and IGF-1 receptors, suggests that Alzheimer's disease may represent a neuro-endocrine disorder that resembles, yet is distinct from diabetes and therefore might be termed, 'Type 3 diabetes'." Again, this was in the *Journal of Alzheimer's Disease* in 2005.

This brings us to the question, "How does one clinically evaluate the relative risk to cognitive decline and memory problems that are associated with insulin resistance/hyperinsulinemia?" In the past we thought we were just evaluating the potential risk to type 2 diabetes. Now we are looking at the risk to potential neurological dysfunction, and also to cardiac disease. Let's do a quick review of the kind of clinical markers we think are important for evaluating the relative risk of a patient having hyperinsulinemia/insulin resistance.

First of all, elevated serum triglycerides, generally graded at 130 milligram per deciliter. We might put under that another clinical parameter that is not normally measured, but maybe even has a higher clinical specificity to metabolic syndrome, and that is high serum free fatty acid levels. Free fatty acids, as you know, are the debris (or the breakdown products) of triglycerides. When triglyceride lipase, an enzyme that is present in plasma, operates on triglycerides, it liberates free fatty acids. This condition of high free fatty acids is tightly related to hyperinsulinemia in metabolic syndrome, even more so than that of serum triglycerides (although we would say fasting elevation of serum triglycerides is a good surrogate marker).

The second evaluative tool that is commonly used for evaluating the presence of metabolic syndrome is depressed high-density lipoprotein cholesterol, or lowered HDL levels. These would be males less than

40, females less than 50. Now that would beg the question, what, then, about the ratio of triglycerides to HDL? If we associate metabolic syndrome with elevated triglycerides and reduced HDL, then wouldn't the ratio of triglycerides to HDL even be a more sensitive marker? And that seems to be, "Yes," to that particular question. With serum triglyceride-to-HDL-level ratios greater than 4 to 1, you have increasing relative presence of insulin resistance. If you were to do euglycemic insulin clamp experiments on a person with an elevated triglyceride-to-HDL ratio, you would undoubtedly find that this person has insulin resistance. So, again, the ratio of serum triglyceride-to-HDL, when greater than 4, and with increasing levels of that ratio.

Let's take an example of a person with triglycerides at 160 and an HDL of 40. That would be a 4-to-1 ratio. If it goes up to a fasting triglyceride of 200 and an HDL of 40, that is a 5-to-1 ratio; that would be more evidence of metabolic syndrome and insulin resistance. If we went to serum fasting triglycerides of 240 and an HDL of 30, now you have an 8-to-1 ratio, and that would be even (obviously) more relative risk to metabolic syndrome and hyperinsulinemia. So the serum triglyceride-to-HDL ratio is a reasonably good surrogate marker for metabolic syndrome/insulin resistance. We have also put on the list (obviously) elevated high-sensitivity C-reactive protein (or HSCRP). Greater than 0.9 to 1 milligram per liter is suggested to be a relative risk factor to the inflammatory component, which is associated with metabolic syndrome.

The next is hemoglobin A1c (or glycosylated hemoglobin). We recognize that glycosylated hemoglobin has a very strong correlation to poor blood sugar control in the diabetic, but it also has been found (as a consequence of glycemic variability) to be associated with increasing risk to hyperinsulinemia/metabolic syndrome when it is marginally elevated (still within the normal range, but at the high end of normal range). In fact, it has been said that glycosylated hemoglobins greater than 5.5 percent of total hemoglobin may represent independent risk factors that are associated with the metabolic syndrome. I am now quoting from a recent paper that appeared in the *Journal of theAmerican Medical Association* in 2006.[10] So marginally elevated glycosylated hemoglobins (or hemoglobin A1c) increase levels of high-sensitivity C-reactive protein. There was a nice paper that discussed insulin resistance and its relationship to elevated CRP in *Metabolism and Clinical ExperimentalMedicine* in 2005.[11]

To continue our list of risk factors, we have elevated percent body fat, which is an anthropometric measurement and (as you probably know) can be done by bioimpedance analysis or hydrostatic weighing or even using the qualitative test of body mass index ratio (height-to-weight ratio). Next is elevated waist-to-hip ratio, generally greater than 1, using a tape measure, basically, to measure waist and hip measurements. To make it easier, we recognize that elevated waist circumference with men greater than 40 inches and women greater than 35 has a very strong correlation with metabolic syndrome.

Next is moderately elevated systolic and/or diastolic blood pressure, greater than 130/85; this is another risk factor to metabolic syndrome. Elevated uric acid in fasting plasma is another indication of metabolic syndrome (hyperuricemia). And then, of course, the last one (when we start viewing cardio-metabolic risk associated with metabolic syndrome) is elevated apolipoproteins.

These are factors that are emerging to have major clinical significance of relative risk assessment in the early stage. The two that have been in the news most recently are apolipoprotein B and apolipoprotein A-1 measurements. I want to speak a little bit, if I can, to atherogenic dyslipidemia associated with metabolic syndrome and insulin resistance. I think it is this new area that has really gained a lot of

prominence and we can connect, then, the heart to the brain to the liver to the pancreas through the assessment of these dyslipidemic transitions that occur with metabolic syndrome.

Scott Grundy, who is a very well-known champion for the metabolic syndrome concept (Professor of Internal Medicine and Director of the Center for Human Nutrition at the University of Texas Southwestern Medical Center in Dallas) has recently authored a very nice review in *Clinical Cornerstone* titled, "Atherogenic Dyslipidemia Associated with Metabolic Syndrome and Insulin Resistance."[12]
In this article Dr. Grundy writes, "Atherogenic dyslipidemia, a component of metabolic syndrome, is characterized by high levels of apolipoprotein B-containing lipoproteins... and a reduced level of HDL lipoprotein cholesterol."

A Review of Apolipoprotein
Let's mention (for review) what we mean by apolipoprotein. As I'm sure you recognize, lipids (which are fats-be it triglycerides or cholesterol) are not well solublized in water. The blood is made principally of water, so that would be like trying to dissolve oil in water. In order to transport these fats, which are critically important as both energy substrates and as messenger molecule precursors (as with the cholesterol that gets converted into things like not only bile acids, but hormones), there has to be a transport system, and the way that that transport system is manifest is through the body's ability to produce specific detergent-like molecules that are called apolipoproteins.

Proteins can be like detergents. They can have a nonpolar component and a polar component to make them both fat- and water-soluble. They can bind specific types of fats, just like detergent does in your washing machine, and allow them to be solublized into the blood. This process of forming these apolipoproteins is not a random process. The body doesn't make at random different detergent molecules; it makes specific molecules to transport specific types of fats and these apolipoproteins have names such as A, B, C, D, E, and they have different compositions.

These proteins trap and bind specific types of fats (cholesterol and triglycerides of different sizes and different shapes), and they then deliver them to specific receptors on the cell surface, triggered by the unique affinity between a specific apolipoprotein and a specific cell membrane receptor site. So it is not just random delivery of fats to cells. The fats are delivered in a very prepackaged and preprogrammed way through the communication between the apolipoprotein and the cell surface membrane receptor.

This is an important concept because I think in the past it has been felt that fats are the cause of heart disease-that when we have fats in the blood, somehow they glob on to the artery wall and they produce these plaques (like depositing grease debris on the side of a vessel), but that is actually not the process of atherogenesis. It is much more specific, related to intercellular communication between agents that are in the outside environments that get translated into the interior of the cells that make up the various layers within the artery wall that initiate the injury to the artery and are associated with what is called atherogenesis.

These apolipoproteins are able to deliver different messages to the artery wall cells (the vascular endothelium) and even into the internal portions of the vascular wall. Apolipoprotein physiology may be as important as the amount of fat that is floating around in your blood, And, the composition and communication of these apolipoproteins is very strictly regulated by environmental factors that signal the

synthesis of these apolipoproteins. It could be hormones that initiate this. One of the hormones, obviously, is insulin. It could be sex steroid hormones, like testosterone, androgens, and progesterone, and also estrogens. These hormones influence the synthesis of specific types of apolipoproteins.

We also know that environmental factors (such as stress) can modulate apolipoproteins, so here we get into behavioral neurology and behavioral cardiology, in which we start seeing how we think about our environment may influence, then, how our body synthesizes these specific transport proteins that ultimately deliver different messages and fats along the surfaces of different cell types. So the apolipoproteins are a very important player in cardiovascular function, and they are not just passive transport "detergent" molecules; they actually have their own personalities and their own distinctive influence on vascular dynamics. If we start talking about apolipoprotein A or B or E, we are talking about not just the fats that they transport, but also the message that they, in fact, bring by themselves as these bioactive transport proteins.

When Dr. Scott Grundy is talking about atherogenic dyslipidemia associated with metabolic syndrome and insulin resistance, he is saying that these apolipoprotein B particles are manifest at higher levels during states of hyperinsulinemia and they then transport various types of fats that include LDL remnants and small atherogenic LDL particles to the artery wall, where they can participate in what is called cardiometabolic syndrome. Cardiometabolic syndrome is a fairly new term that tries to define how people who do not have the traditional risk factors for cardiovascular disease, such as frank hypertension or elevated levels of cholesterol or smokers or diagnosed diabetics, may still be at significant risk to cardiovascular disease because they have this underlying (kind of smoldering) metabolic syndrome/hyperinsulinemia that alters their apolipoprotein distribution and alters the delivery of certain messages of their vascular wall cells and their vascular endothelium.

Specialists in metabolic syndrome and preventive cardiology are working closely together to try to understand this connection. There is a review paper, authored by Nathan Wong, on this topic that appeared in *Metabolic Syndrome andRelated Disorders* in 2006.[13] This article discusses the importance of doing an assessment in cardiology for the presence of insulin resistance/hyperinsulinemia so that you can pick up this cholesterol-independent component of risk to cardiovascular disease. In this article, it is suggested that a great percentage of people that died by sudden coronary events and did not have the traditional precedent risk factors to heart disease were those who really carried with them this metabolic syndrome/hyperinsulinemia that put them at risk (unknowingly).

Unless you analyze this risk, you are not likely to see it. This is a little bit like the example of blood pressure and stroke. No one really understood the correlation between elevated blood pressure and stroke risk until the development of the sphygomometer (the blood pressure measuring cuff), which then was able to actually measure relative risk and show an association between elevated blood pressure and stroke risk. By the same token, if you are not measuring these cardiometabolic risk factors that I've described, such as elevated fasting triglycerides, reduced HDL, the blood pressure changes, the body mass changes with central adiposity and a waist-to-hip increase, and even the apolipoprotein alteration that I'm now describing, you are not likely to understand that patient is at risk.

The apoB/apoA-I Ratio is a Strong Risk Factor for Cardiovascular Disease

What has emerged is the apoB/apoA-I ratio is a strong new risk factor for cardiovascular disease and a target for therapy that is associated with the risk to metabolic syndrome and hyperinsulinemia. I'm now

quoting from the *Journal of InternalMedicine*. This is a nice review paper by Walldius and Jungner, who have been principal researchers in this field for some time.[14]

What is apolipoproteinA-I? If apolipoproteinB transports the atherogenic-dense LDL particles and remnants of LDL, the apoA-I is the converse: it transports the backbone of what we call the HDL particle. HDL is involved with cholesterol efflux from the artery wall. It is like an unloaded flat-bed truck that arrives at the cell well. The apolipoprotein binds at the membrane of that receptor site, and then is involved with "loading up" the flatbed truck with cholesterol by effluxing it out of the cell and then taking it through the bloodstream to a place where it can be metabolized, converted into bile acids, and ultimately excreted in the bile (or made up as part of bile as the cholesterol esters). The apoA-I is an important apolipoprotein for cholesterol efflux, whereas apolipoproteinB is associated with delivery of cholesterol and lipids to the cell, so it is influx. So you want your apolipoproteinB level to be low because you don't want to deliver too much lipid to the cell itself, and you'd like your apolipoproteinA-I level to be high (that is, you have more available flatbed trucks to efflux the cholesterol out of the cell). When I say A-I, I want you to understand that is capital "A" dash "I." We are not thinking about apolipoprotein little "a." Little "a" is a subtype and that is an atherogenic apolipoprotein as contrasted with apo capital "A" "I," which is an antiatherogenic lipoprotein.

So the ratio of apoB/apoA-I you would like to go down, right? You would like it to be low. And when I say "low," I would suggest that number means less than or equal to 0.7 (the lower the better). So as your number goes from 0.7 to 0.8, that is increasing atherogenic risk associated with cardiometabolic syndrome. I would go on to suggest that based on Dr. Craft's and others' work, that that would also suggest increased risk to cognitive decline and Alzheimer's plaque and other kinds of dysinsulinism that is associated with altered neurological function (central neurological function). We shouldn't just focus solely on the effect of an altered apoB/apoA-I ratio as being cardiometabolic. We should also think of it in terms of neurometabolic as well.

If we were to compare apolipoproteinB/A-I ratios in subjects with (versus those without) metabolic syndrome, you might ask, is there a difference? Can you differentiate the two, based upon their ratios? As I've said, there is now very strong evidence that the apoB/apoA-I ratio predicts cardiovascular risk factor better than any of the cholesterol indices (that would be cholesterol HDL levels, for instance, or LDL levels).

In a more recent study that I'm quoting from (which is found in the *AmericanJournal of Cardiology* in 2006), investigators wanted to evaluate the apoB/apoA-I ratio related to metabolic syndrome.[15] They analyzed 2964 subjects, mean age 48 years, about 1516 men and 1448 women, from the National Health and Nutrition Examination Survey III, with apolipoprotein data that were evaluated for metabolic syndrome and its components. The metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III.

In this study, the mean values of the apo B to apo A-I ratio in subjects with and without the metabolic syndrome were compared. Overall, the median distribution of the apo B to apo A-I ratio was significantly greater in subjects with the ATCP III metabolic syndrome than those without. In fact, the difference was at the $P < 0001$ significance (a highly significant difference in differentiating between those with metabolic syndrome versus those without). In conclusion, this particular study finds that the apo B to apo A-I ratio is strongly associated with the presence of metabolic syndrome and can be used as a early- stage

interventional risk factor marker for what they call cardiometabolic syndrome, but we might also call it neurometabolic syndrome because of the emerging connection between hyperinsulinemia and neurological dysfunction.

When you look more in depth at what we know about apo B and apo A-I, it really is a very fascinating story. Just to review for you, over the last three decades it has been recognized that a high level of total blood cholesterol (particularly in the form of LDL cholesterol) is a major risk factor for developing coronary heart disease.As we look at more recent research, our understanding of lipoprotein functions and metabolism has been expanded. A considerable portion of patients with atherosclerotic disease have levels of LDL cholesterol and total cholesterol that are actually within the recommended range, and some patients who achieve significant LDL cholesterol reduction with lipid-lowering therapies still develop cardiovascular disease. Other lipid parameters associated with cardiovascular risk are these lipoprotein subfractions that are components of the lipoprotein particles that include protein and fat together.

We talk about apolipoprotein B existing in two forms: apo B-48 and apo B-100. Apo B-48 is synthesized in the intestine, where it is complexed with dietary triglyceride and free cholesterol absorbed from the gut lumen to form chylomicron particles that are generally cleared postprandially very quickly out of the blood within the first few hours after eating. Apo B-100, however, is synthesized in the liver and is present in LDL intermediate density lipoproteins and very low density lipoprotein particles. Only one apo B molecule is present in each of the lipoprotein particles, and therefore the total apo B value indicates the total number of potentially atherogenic lipoproteins.

Apo B is essential for the binding of LDL particles to the LDL receptor, allowing cells to internalize LDL. An excess of apo B-containing particles is the main trigger of the atherogenic process. Individuals with seemingly low or normal LDL cholesterol levels can still be at increased risk of cardiovascular events. In these patients, the risk of cardiovascular events appears to be more closely related to the increased number of small density LDL particles, in addition to hypertriglyceridemia, and low levels of the protective HDL cholesterol. This is a combination that we know as the atherogenic lipid triad, and it is associated with metabolic syndrome and hyperinsulinemia.

Target levels for apo B have now been included in a table on the treatment goals of the National Cholesterol Education Program ATP III Guidelines. Patients with diabetes or the metabolic syndrome can have normal LDL cholesterol levels, but possess aspects of atherogenic lipid profiles that are associated with a high ratio of the apo B/apo A-I. Apo A-I acts as a co-factor for lecithin acyl cholesterol transferase, which is important in removing excess cholesterol from tissues and incorporating it into HDL for first transport to the liver. Furthermore, apo A-I is the ligand for the ATP-binding cassette protein, which is called the ABC protein (ABC A-I), and hence is involved in the docking procedure by which excess cholesterol in peripheral cells is externalized to HDL for further reversed cholesterol transport, either directly or indirectly, via LDL back to the liver for metabolism.

HDL exists as particles of different sizes, with HDL-2 being the largest and containing the most lipid in its core, and having the highest efflux capacity for cholesterol. Apo A-I is a very strong predictor of HDL cholesterol 2 levels: high levels of apo A-I mean high levels of HDL 2. Apolipoprotein little "a," as contrasted to capital "A-I," is bound to LDL to form this apolipoprotein(a) LpA, which shares 80{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of its amino acid sequence with plasminogen, and competitively binds as surface binding and activation of plasminogen.

Elevated LpA has been associated with arterial wall thickening, and high blood concentrations of apo a have been suggested as a risk factor for atherosclerosis. But in evaluating all the risk factors, it appears as if elevated apo A-I is the most strongly associated with a decreased risk to cardiovascular disease.

Elevation of apo B is associated with an increased risk of cardiovascular disease. The apo B level was found to be the best predictor of the extent of cardiovascular disease after correction for age, as assessed by the number of stenotic arteries, and was the only statistically significant predictor of the presence of cardiovascular disease in patients without frank dyslipidemia. This is why we keep saying that the apo B/apo A-I ratio is a very interesting prognostic marker for not just cardiometabolic syndrome, but also neurometabolic syndrome associated with hyperinsulinemia.

There are a number of prospective studies that have evaluated this association, including the AMORIS Study. Compared with subjects in the lowest quartile, those in the highest quartile in this study, for apo B, had almost a three-fold increase in risk to cardiovascular disease. For the apo B to apo A-I ratio, the increase in risk was almost four-fold in men and three-fold in women, for those who had the highest quintile ratio of apo B to apo A-I. So we are talking about significant increases in relative risk as defined by the apo B to apo A-I relative ratio.

In multivariate analyses, high apo B levels and the high apo B to apo A-I ratio, and low levels of apo A-I, were stronger predictors of risk than LDL cholesterol, total cholesterol, and triglyceride levels alone. Based on all these findings, the ratio of apo B to apo A-I, meaning the balance between potentially atherogenic cholesterol-rich apo B-containing particles and the antiatherogenic apo A-I-rich particles, is proposed as the best integrated measure of cardiac risk associated with lipoproteins, and closely associates itself with metabolic syndrome and insulin resistance. Values of apo B should be less than 1.2 grams per liter, and for apo A-I, should be greater than 1.2 grams per liter. This is why I have said that the ratio for optimal function of the cardiovascular system should be a ratio of 0.7 or less between apo B and apo A-I. Thus, in those at the greatest risk, a target apo B level below 0.9 grams per liter is recommended, regardless of gender. Regarding cut-off values for apo B/apo A-I ratios, I said we would like it to be 0.7 or lower.

I think you can see that we are talking about a new emerging risk factor that not just ties itself solely to that of cardiometabolic risk, but also to the relative risk to neurologic problems. This will be described in much greater detail by our clinician of the month, Dr. Jay Lombard, a neurologist and a psychiatrist who really helps us to understand this broad connection in the web (the functional web) between hyperinsulinemia, inflammation, and other risk factors that are associated with neurodegenerative diseases.

As I close, I would like to think that we have all come to the same point here at the end of this discussion. There are a variety of surrogate markers that are used clinically for evaluating the presence of hyperinsulinemia, such as the elevated triglyceride HDL ratio, elevated waist-to-hip ratio, elevated waist, elevated percent body fat, increased uric acid, increased blood pressure, increased high sensitivity CRP, and increased marginal elevations of percent glycosylated hemoglobin or hemoglobin A-IC. But if we add to that the relative evaluation of apo B to apo A-I ratio, we might now form a panel of evaluative tools that really is helpful in looking much earlier at the potential risk to not just diabetes and cardiovascular disease, but also neurodegenerative problems that are associated with hyperinsulinemia, insulin resistance, and the deposition of beta amyloid plaque.

We are going to discuss this now with our clinician of the month, Dr. Jay Lombard.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
JayLombard, DO
Chief of Neurology
Bronx Lebanon Hospital
1276 Fulton Avenue
Bronx, NY 10456

This month I'm very privileged to have a long-standing friend, colleague, and a person I have tremendous respect for (and admiration for, professionally), as our clinician/researcher of the month, Dr. Jay Lombard. Dr. Lombard is the Chief of Neurology at Bronx Lebanon Hospital and is an Assistant Clinical Professor of Neurology at Cornell Medical School. He is dual boarded in both psychiatry and neurology, and has been a friend and colleague for more than 25 years (since we first met in Rhinebeck, New York at the Omega Institute).

Jay's career has really spanned a tremendous swath of clinical experience and he has managed some of the sickest of the sick. He has been able to bring tremendous vision and integration of various practice management and techniques into his skill set, and I think he has framed (for many of us) the model of what integrative, open-minded, lifelong learning in medicine really means.

Jay, it is wonderful to have you as a clinician of the month on FunctionalMedicine Update. You call yourself a behavioral neurologist and I think that is a very interesting term, so for the sake of our listeners, could you help us understand what that term means?

Defining Behavioral Neurology

JL: Behavioral neurology is, I think, the recognition that many disorders we encounter in our daily life in clinical practice have, in many ways, a direct relationship with our brains, our moods, and our emotional states. In terms of the specifics of what a behavioral neurologist is, my practice (and other neurologists who practice this way) is focused on disorders like autism and attention deficit disorder (t one extreme of the lifespan), and then Alzheimer's and dementias and cognitive problems (t the other extreme). It is also, I think, recognition of how critical emotional states are to our overall physiology.

JB: I think that is a very interesting and important part of the whole mind-body connection. There are still (believe it or not-in the 21st century) people who separate the mind from the body and try to dissect each component as if they were separate channels or silos of non-interacting function. Certainly from the functional medicine perspective and from your practice (in the way you have both treated patients and been a teacher) there is a very significant integration/marriage between the two. It seems, as I have listened to you, you can separate behavior from neurological function, and so it is a chicken-and-egg argument.

JL: That's right. It is probably a top-down and a bottom-up approach--the appreciation that mood states and emotional states can clearly affect our physiology. This is something that I have spoken to many physicians about just recently-this concept of neurocardiology and neuroimmunology. There is very

strong data, both epidemiological as well as physiological, on how alteration in brain states increase vulnerability to specific disorders. But I think the other piece of that, which is clearly as important as the bottom-up approach, is how systemic variables (whether it is dysbiosis or immune dysregulation) affect mood and cognition. There is a reciprocal, interdependent relationship between brain and body function that goes bidirectionally.

JB: Your books have been very instrumental in my learning in this field. Brain Wellness Plan, which was I think your first book (published by Kensington Press), and more recently, Balance Your Brain (a Wiley book). The books describe behavioral neurology from a perspective that the average reader can understand. I know in your research and in your practice you have been involved with brain imaging and neuropsychopharmacology, and many of your patients that you deal with at the neurology component of Bronx Lebanon Hospital are very seriously ill. It sounds like you have had the opportunity (professionally) to cover the whole waterfront. Is this an advantage to you, do you believe, in bringing perspective to manage problems?

JL: I certainly hope so. I mean, it is something one can never fully feel on top of because of the complexities of these relationships and the learning curve is continuous. There is never a day that goes by in which some unique aspect about this relationship reveals itself in some unexpected way. Choosing neurology as a profession in many ways is a blessing and a curse. The blessing is that you never fully can understand exactly what is happening and that is exciting, but it can also be terrifying when you appreciate the magnitude of those effects.

JB: For my definition, you are really kind of in the pinnacle of practicing functional neurology, and I think that is further supported by the reviews that you have had when you have been an instructor at the Neurology Module (from the Institute for Functional Medicine). In those presentations you have often talked about case histories and experience you've had. Can you share with us the kind of patients you see, or, through the eyes of some of your patients, some of the problems that you've encountered that describe how we would kind of contextualize behavioral neurology?

Research on Angiotensin Receptors in the Brain

JL: I think you can choose any number of examples of this relationship. Something I think you may find quite interesting, Jeff, is the area of research that I am pursuing currently, which is the recognition of angiotensin receptors in the brain.

For the listeners who are familiar with angiotensin, it is clearly something that cardiologists pay attention to because of its regulation of blood pressure, and it has a diverse effect on renal function, in terms of increasing sodium and water resorption. It increases vasoconstriction. It increases catecholine production, particularly norepinephrine. It has this very ubiquitous effect across many different organ systems and has not been thought about as being critical in brain function. This is a gross oversight, I think, on the part of both researchers and clinicians.

In fact, angiotensin has effects on the brain and is involved in the stress response, specifically what happens during periods of time when people are in a fight-or-flight situation or in depression. It also has applicability for what I believe are a number of neurodevelopmental disorders, like autism. Looking at this key effect or molecule (if you will) angiotensin, and ways that it is implicated in both systemic disorders and also neurological disorders, I think provides us with a quite unique opportunity and window

into understanding how to modulate this hormone, both for body problems (which is already being done through specific types of compounds like the ACE inhibitors and the angiotensin-receptor blockers), and also for mood and anxiety.

What is particularly interesting about angiotensin is that it is directly influenced by vitamin D levels. Something I think really caught my eye (in terms of looking at something nutritional and something that can be easily assessed which has been overlooked) is that vitamin D levels are inversely proportional to angiotensin. The lower a patient's vitamin D levels are, the higher angiotension (and particularly plasma renin levels are). Conversely, if we administer vitamin D (let's say to either a human or to an animal), we can lower angiotensin and plasma renin. This has implications for many, many disorders, not just the cardiac diseases in which vitamin D levels have been demonstrated to be lower in patients with congestive heart failure. For instance, vitamin D levels are also lower in stroke patients and in MS patients. Recently we have uncovered what we think are some very significant abnormalities in vitamin D in autism as well. It is a very exciting area, which integrates both functional medicine and mind-body medicine.

JB: That is a very interesting observation that I was unaware of. A number of years ago, I had the chance to present at Dr. Mark Houston's conference on hypertension at Vanderbilt University Medical School. One of the co-presenters there was a gentleman who had been researching angiotensin for 20 years and was talking about angiotensin receptor blockers and angiotensin converting enzyme inhibitor drugs as being anti-aging drugs because he felt that angiotensin was one of the critical factors associated with accelerated biological aging of the heart vasculature and brain. He was showing how low-dose use of these ARBs and ACE inhibitors actually could be seen (from animal studies) as preventing age-related deterioration. What is the story from your perspective on these pharmaceuticals that have been used to modulate angiotensin?

JL: I think there are clearly animal studies in which (particularly if you administer the angiotensin receptor blocking agents to animals prior to inducing a very traumatic type of stimulus)you can block a lot of the stress response. This is opening the door to looking at possibly using these agents for treating stress-related disorders like post-traumatic stress disorder or other disorders that you would normally not think of using an ARB for. Obviously the concern, I think (with ARB use particularly), is using them for purposes beyond what they are intended to be used for, and specifically what it is that has gone awry in our physiology that has created this disturbance in angiotensin to begin with.

I think that is where the vitamin D story is quite interesting. If we look downstream at how angiotensin modulates a variety of pathophysiological processes, particularly interesting is a matrix protein that is highly expressed in blood vessels called thrombospondin. Thrombospondin is an atherogenic protein that is highly upregulated during ischemic events, whether it is acute ischemic events or chronic ischemic events. What happens once thrombospondin is activated is it sets into motion a cascade that actually works particularly on transforming growth factor and other proinflammatory cytokines. What is interesting about this whole cascade is that the ARB drugs, like Losartan and other drugs, are actually thrombospondin-inhibitors; that is, they can block this immune response by virtue of downregulating the thrombospondin. So, they have an effect that is both anti-inflammatory and anti-ischemic. With regard to vitamin D, particularly to the ARBs, one wonders if vitamin D is an endogenous ARB-acting agent. That's something that I think we should be looking at.

Nutraceuticals as Natural ACE Inhibitors

JB: I have noticed there are a couple of nutraceuticals that have been developed and recently marketed to be natural ACE inhibitors. They are specific peptides of fish protein hydrolysate and casein hydrolysate. Do you have any clinical experience or thoughts about those?

JL: The bonito, right?

JB: Yes, bonito peptide.

JL: I haven't. I've not actually looked at those, but that would be an interesting compound to study to see if some of these anti-anxiety and anti-inflammatory effects that one sees with vitamin D would also be seen with the bonito peptide. I can tell you (just empirically) that I have seen many patients who are diagnosed with these very low vitamin D levels who do quite well (from a behavioral neurology perspective) with vitamin D supplementation. Again, I think the mechanism of action here is that it is acting as an endogenous angiotensin receptor blocker. I don't know whether the bonito peptides have that same effect or not.

JB: It has been very interesting to listen to you over the years because you can bring so many different disciplines into your presentations and into your perspectives. People listening might say, "I wonder what kind of training Dr. Lombard had?" If a person is on the path to gain mastery in this area, could you share with us the kind of training and postgraduate education prepared you with this perspective?

JL: I think first and foremost one should go to as many Jeff Bland seminars as possible, and I mean that sincerely. You are singularly the one person that allowed me to open my eyes to these very beautiful molecular events that are occurring beyond the surface of how we think of physiology and pathophysiology and pharmacology-to always ask, what's the next layer? It is like peeling the onion. I'll call you the first "onion peeler," Jeff.

I use that onion-peeling approach to my psychiatry training and my neurology training. With any disorder I would look at (whether it was schizophrenia or depression or bipolar disease, Alzheimer's or Parkinson's), I would keep asking the question, "Okay, this is what we know. What is it that is the next layer below that that is creating that disturbance and so on and so on?"

You end up at a very molecular level, looking predominantly intracellularly at mitochondrial energetics, specifically how all this relates to not just the mitochondria, but also peroxisomes, which I think is another area that we are bound to hear a lot more about in regards to its anti-inflammatory effects, cell survival, and the relationship of peroxisomes to mitochondrial function. This idea that the mitochondria are so instrumental in increasing vulnerability to disease by an energetic phenomena was something that I think you saw a long, long time ago and has come to fruition amongst many research scientists across a diverse span of disciplines, whether it is cardiology or neurology or psychiatry.

As you mentioned in the introduction, in traditional medicine we all look at our separate silos. The cardiologists don't really think about talking to neurologists or to the immunologists. To really get to the bottom of the fundamental elements of disease, as well as the introduction of positive health phenomena, we have to break down those walls and have each of the disciplines talk to each other and realize that we are talking the same language.

As an example, I'll be talking in '07. I had to kind of brush up on my immunology because it is not something that I am as familiar with as the literature in neurology and psychiatry. I was specifically looking at what kind of biochemical cascade occurs as a result of T cell activation (when it is actually responding to an antigen). That cascade is identical to the cascade that occurs when a neuronal cell is depolarized. It is identical. There is this depolarization of the neuron with influx of calcium, and activation of these proinflammatory cytokines like TGF, caspaces, and all of those immunogenic enzymes. Identical.

So here you have this biochemical pathway in immunology which is completely the same as the biochemical cascade that occurs when a neuronal cell is being excessively depolarized and perhaps going into an apoptotic mode. That really struck me as, "Wow, this is like a string theory, these identical modes of operation." If you think about it, it makes sense. Nature is redundant. Nature likes to use what works and it is parsimonious in its execution of biochemical pathways.

Neuronal Hyperexcitation

JB: You have raised a very interesting topic that I know is on the minds of a lot of people, even those who have only done a cursory review of the recent neurology literature. This is the association between certain neurodegenerative problems and what is called neuronal hyperexcitation (or NMDA excitation). Can you tell us a little bit about this? I know you have spoken very eloquently and (I think) very beautifully as to how that whole pathway can be triggered by environmental agents (the NMDA excitotoxic pathway)?

JL: Sure. That's something that has really expanded in the last ten years in terms of its appreciation for the involvement of excitotoxic pathways in a variety of neurological problems, not just Alzheimer's and Parkinson's disease, but also in MS, ALS (or Lou Gehrig's disease), diabetic neuropathies, epilepsy, bipolar disease, and autism. These-what I call the final common pathways of excitatory NMDA pathways in which glutamate is upregulated-occur (there are many roads that lead to Rome) particularly through the arachidonic acid pathway.

When we have a diet that is high in the omega-6 arachidonic acid content, this leads to an excess expression of NMDA receptors. Arachidonic acid blocks glutamate reuptake, so when glutamate is found in high concentrations in the synapses, it binds to the NMDA receptor and sets into motion these pro-apoptotic or neuro-inflammatory pathways that appear to be linked to a variety of neurological diseases.

One may say, "Well, how does that make sense because MS is very different than ALS?" This is true, but the explanation is that the phenotype is different because the disease process is occurring in different types of tissue, but the biochemical processes may be similar. For instance, bipolar disease and epilepsy are very different. Epilepsy is obviously a seizure disorder and bipolar disease is not a seizure disorder, but these glutamate pathways are disturbed in such a way that they are upregulated (in both diseases). Depending on which area of the brain in which that abnormal expression is reflected will give you the particular phenotype of the disorder. Is that clear? I'm not sure if I'm explaining that properly.

MSG and L-Glutamine

JB: Yes, it is, very much so. There are two molecules that have been in the news quite a bit and may connect to this NMDA glutamate excitation. One is MSG and the other is L-glutamine. Can you give us your top-line thoughts about each of those? There are people who are very concerned about MSG relative to this neurohyperexcitation, and there are those who will say if you supplement with L-glutamine you stimulate that same pathway.

JL: Right. This question comes up a lot in the seminars-concern about creating an excess glutamate state in patients inadvertently by glutamine administration. There is really no data to support that that is the case at all, for several reasons. First of all, glutamine is used both for the synthesis of GABA and glutamate. In fact, those two neurotransmitters, which are diametrically opposed in regards to their physiological function, are in many ways mirror images of each other.

Glutamate is used as the immediate precursor for GABA, which is kind of interesting (the poison [if you will] and the cure are within the same metabolic pathway). I think in regards to glutamine, specifically, there is no concern in my mind that giving glutamine to patients can theoretically increase glutamate in the brain.

The MSG story, I think, is something that is more complicated. I have read some data in which they have tried to confirm if giving MSG exogenously would increase glutamate receptors through these kind of in vitro analyses of brains of rats, for instance. They were not able to actually activate glutamate receptors through MSG administration. That conclusion (from that particular study) was that MSG did not have a bearing on brain glutamate receptors. I'm not sure if I believe that, but that's what the data currently demonstrate.

I think one of the points to keep in mind here (and this is one of the difficulties in doing any kind of neurological research) is the blood/brain barrier. We have this barrier to prevent these kinds of problems. If MSG were able (through oral ingestion) to penetrate the blood-brain barrier, then I think it is a different game than if it is not able to enter the blood-brain barrier. The same thing may be true to a lesser extent with L-glutamine. It is also true, by the way, with GABA administration. On the therapeutic end, the same limitations apply, and that is that GABA does not cross the blood-brain barrier very well. So I think that there is this concept of blood-brain barrier or neurologically privileged biochemical milieu that makes these questions a little bit less of a concern than one would have at first glance.

JB: You have raised a very interesting point that I actually had never thought about until you mentioned it. It has to do with the gut, which some call (as we interviewed Dr. Gershon several years ago) the second brain because it shares so many of the putative messaging compounds that the brain produces as neuroregulators. The gut doesn't really have the barrier, in terms of the blood-brain barrier, as that kind of compartmentalization that the brain itself has. Is it possible that some of the things that we think are neuroactive are really operating through gut-signaling phenomena?

JL: I think there is no question that there is signaling that takes place between peripheral biochemical factors and neurological factors, particularly as it relates to gut peptides like CCK, secretin, and other peptides. It has effects in changing brain signaling without directly crossing the blood-brain barrier, so I think that the subtext of your question is-if I'm reading this properly-is that, yes, it may be true that MSG does not cross the blood-brain barrier, and that glutamine or oral GABA don't, but is it possible that signals can be communicated through some biochemical cascade indirectly, without those molecules directly crossing the blood-brain barrier.

I think the answer is we don't know, but certainly (in my mind) it makes sense, and (to add another level of complexity to this) the blood-brain barrier itself is disturbed in many disease processes. For instance, in MS patients (particularly with disease exacerbations), one of the biggest problems is that the blood-brain barrier is more porous than in people who don't have MS.

I hate to contradict myself because that is probably what some of your listeners are thinking right now, but I think the blood-brain barrier, itself, is disturbed by many systemic disease processes that changes the equation in regards to, perhaps, our thinking that something is not getting across the blood-brain barrier. I hate to say it, but there is really no easy answer to some of the questions that you are bringing up. Many people like to have simple yes or no answers or responses to these kinds of questions, but there are more "we don't knows" in the fields of neurology and psychiatry than there are "yes, definitely" or "no, definitely." That is, again, the blessing and curse of being in this field of medicine.

JB: I know you have talked a little bit about the serotonergic pathways and how the gut secretes (I think) nearly two-thirds of the body's serotonin. People have asked the question, "What happens if you do gastric bypass for morbid obesity and you put to rest your gut? Are you altering serotonergic peripheral metabolism in such a way that it has a whole-body effect?" Do you have any thoughts about that?

Serotonergic Peripheral Metabolism Following Gastric Bypass Surgery

JL: I have some empirical observations. Many people (patients of mine) who have undergone gastric bypass have done really horribly after surgery. One can certainly posit that by taking away that reservoir of not just serotonergic neurotransmission, but also a huge amount of different gastrointestinal hormones and peptides, that you have disrupted their milieu, and that has consequences toone's health that we don't even know about yet. Just on empirical observation, many of my patients actually have gotten sicker post-gastric bypass, and one wonders if that is the mechanism of action of why that has happened.

JB: I want to go back and pick up something you said earlier about vitamin D. I have recently been following a blog that has been discussing the potential that vitamin D excess may have very serious adverse effects and that people should be managed to have low vitamin D levels because vitamin D has a serious of adverse triggering effects on the neuroimmune system. Have you followed this discussion at all? This contrarian view about vitamin D, (which I personally don't share) seems to be picking up steam. I am wondering if you have heard about it?

The Goldilocks Principle

JL: I haven't seen that literature. I think there is one thing to keep in mind with all of functional medicine in general, and this very much applies specifically to neurology and psychiatry. When we do any kind of intervention, whether it is pharmacological or nutraceutical, we have what I call it the "Goldilocks Principle"-it can't be a little too cold or a little too hot, it has to be just the right temperature. I think that concept applies to vitamin D administration. Low vitamin D has (in my mind) many pathophysiological consequences related to neurology and psychiatry. It relates to its effects on angiotensin and also on other pathways, including IL-10, and also its effects on brain serotonin receptors.

One can imagine that there are probably issues with high vitamin D (excess vitamin D). From a purely "Medical School 101" lecture, in some cases it can raise calcium and make patients hypercalcemic, and that is certainly a serious consequence without going into even more sophisticated explanations about vitamin D toxicosis. Beyond just that obvious concern about vitamin D intoxication are the anti-inflammatory effects of vitamin D-that high doses may predispose to one's vulnerability to diseases related to immune suppression. I think you have to look at this as a dose-range concept, not just for vitamin D, but for anything we do exogenously to patients at a biochemical level.

JB: I think that's a very good watchword. I think Mike Holick and Colleen Hayes who have talked more

about trying to get patients into the 40-50 nanograms per/mL 25-hydroxyvitamin D level and keep them in that range is a very good watchword rather than trying to say more is better.

JL: Absolutely.

JB: Could you tell us a little bit about your experience in behavioral neurology with natural products? You know we hear a lot of remarkable claims about certain botanical medicines and so forth. Obviously, ginko-biloba has gotten a huge amount of press, but there are many others (huperzine and others). Can you give us a sense, from your experience, where some of this really weighs out?

Huperzine and Studies on Alzheimer's Disease

JL: Well, you mentioned huperzine, and I think huperzine (in my mind) is going to be one of the most phenomenal stories in natural medicine in the next several years if it has not already caught steam. Huperzine, as many people know, is a natural compound from Chinese club moss that was used in China as a botanical. Years back, the Mayo Clinic discovered that huperzine possessed an effect which enhances brain acetylcholine levels by blocking an enzyme known as acetylcholine esterase and began studying it for Alzheimer's disease. Now the NIH is involved in some large-scale phase two studies with huperzine for Alzheimer's. The preliminary data looks very promising.

The other effect of huperzine, in addition to its effects as an acetylcholine agonist for the brain, is that it also acts as an NMDA antagonist, so it has an effect on upregulating acetylcholine and downregulating glutamate. It has an effect that is beyond its effect on just cognition. In this area, by the way-just as an aside which I also think is very interesting-there is a researcher not too far from where I practice at Northshore Medical Center by the name of Dr. Pavlov (and I think he may actually be related to the original Pavlov), who has done some very eloquent research on central cholinergic mechanisms having an anti-inflammatory effect. By stimulating central acetylcholine neurotransmission, one can decrease production of tumor necrosis factor and other proinflammatory cytokines. It is another area I think is emerging as one of these surprise findings of how the brain and the immune system are communicating indirectly through these very complex signaling mechanisms. I think huperzine is one example.

To answer your question in (hopefully) a not too circuitous way, Jeff, there are tons of compounds that surprise me in terms of their efficacy. I think what is interesting in neurology and psychiatry is that the effects are not subtle. When you have an effect on something, when you take an autistic child, for instance, or you take an Alzheimer's patient or a Parkinson's patient and you do an intervention, the effects are very obvious. There are no grey areas here-people either do a lot better, or they don't have an effect. When one challenges a patient with an intervention, whether it is pharmaceutical or nutraceutical, their report and their response is the harshest critic that one can have for a treatment. I tell patients this exactly. I say, "You are the harshest critic of a treatment-the response that you have. Nothing is more objective than how you feel after we do something or by taking something to help you with a problem."

JB: I'd like to do a little bit of a soundbyte with you here and get your quick vignette on each of these natural products, from your experience. Let's go to gingko-biloba with memory. What is your experience?

JL: Mixed. I think there are patients who have had benefit and there are patients who haven't had benefit. The patients who I have seen benefit with it have reported it as increasing attentional mechanisms, and I have seen it help in patients who have microvascular ischemic disease. I have not seen much benefit in

Alzheimer's disease.

JB: St. John's Wort and depression.

JL: I think it is an effective herb for depression. I have used it for mild to moderate depression. I have been reluctant to use it in more severe types of depression, but I think for dysthymic disorder, which is sort of a chronic low-grade depression, I find that it is at least as moderately effective as a typical SSRI or other traditional antidepressant drug.

JB: Valerian and sleep.

JL: I have found it not effective.

JB: B-12 and folate for dysphoria and mild depression.

JL: I have found methylfolate helpful for depression. I think the difference between methylfolate and folic acid is that the methylfolate is a preferred form to cross the blood-brain barrier. I have seen definite effects, not just in depression, but also in ADHD patients with methylfolate.

JB: Ginseng and stress-related phenomena.

JL: That's a tough one. I have not been overly satisfied with my patients with ginseng. I actually looked at ginseng particularly for ADHD because it has some effects on dopamine receptors as a dopamine agonist, but I know that I'm certainly not a ginseng expert and what I have learned is that there are many different types of ginseng-red ginseng and white ginseng, for cold versus hot conditions. I think that I would defer to my acupuncturist and Chinese herbal medicine doctor to give better opinions on ginseng in this area.

JB: Any botanical medicines you have found that are helpful in the area of stress-related dysfunction?

JL: I think passion flower is one of my favorite herbal treatments because I think we need to pay attention to sleep hygiene as a key element. I think sleep is the single best anti-inflammatory agent known to man-better than Motrin, better than Advil, better than any nonsteroidal. I think that we as clinicians do not understand or appreciate sleep and its critical effects in acting as an anti-inflammatory agent, and anything we can do to restore a patient to a proper sleep can have an effect not just on their mental status, but also on their physical well-being. Passion flower is certainly one of the things that I have found extremely effective to help patients with sleep.

JB: We have just a couple of minutes left and I'd like to at least touch upon something you said earlier. There is an emerging recognition of the importance of insulin resistance (hyperinsulinemia) and its relationship to dementia. I know you have had quite a bit of insight into that. Can you share some thoughts with us?

Insulin Resistance and Dementia

JL: How much time do we have left? I think this is one of the most phenomenally interesting areas of medicine that is emerging-that insulin resistance is a key factor, not just in one's risk of developing dementia, but a number of neurological, psychiatric, and systemic diseases, including cardiovascular disease. Beyond just the spectrum of diabetes, insulin resistance is a fundamental disturbance in a

pathway that leads to these very catastrophic disorders.

In regard to Alzheimer's disease, particularly, both Suzanne DeLaMonte at Brown University and Dennis Selko at Mass General (who are both very esteemed Alzheimer's researchers) have done a lot of the groundbreaking basic science work on detecting that insulin resistance is indeed a critical pathological disturbance in dementia and this is supported by epidemiological data. Patients who are diabetic or pre-diabetic have a greater risk of developing Alzheimer's disease, and anything we can do for our patients to improve insulin resistance, whether it be physical exercise or nutraceuticals or even the PPAR agents, such as the omega-3 fatty acids which have an effect on peroxisome proliferator-activated proteins, have effects as anti-inflammatory agents and neuroprotective effect by virtue of improving insulin signaling.

JB: Do you feel there is any difference between docosahexanoic acid and eicosopentaenoic acid in that regard, or is it that as long as get the long-chain omega-3s?

JL: I think the latter is probably true. I think there is more DHA expression in the brain than there is EPA. DHA is in high concentrations in both the retina and in synaptic vesicles, so as a neurologist, my interest is predominantly in DHA as a vital agent for neuroprotection. But I think that both EPA and DHA are certainly relevant because of their similarities and structure as their pleuripotent role in metabolic pathways, both in inflammation, platelet aggregation, neurotransmission, and peroxisomal activation. There are so many different ways that these compounds are found to be so vital to our healthy physiology that if I was on a deserted island and could take only one nutraceutical with me, it probably would be EPA/DHA for my patients.

JB: Jay, I can't tell you how much I've appreciated this. I know our listeners have as well. We have covered quite a wide domain here of discussion and you've done it eloquently, as always. I think it is a testament to your background and the birth of your understanding. Thank you very much. I know your patients have certainly valued from your years of training and perspective. I know you treat everybody from the sickest of the sick to the walking wounded and that requires many different skills and tools in your toolkit. You certainly fit and, I think, exemplify what we can a functional neurologist. Thank you so much for being with us. Continued good work and we'll look forward to talking with you soon.

JL: Thank you, Jeff. My pleasure.

Bibliography

1 Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004;292(18):2237-2242.

2 Benoliel AM, Kahn-Perles B, Imbert J, Verrando P. Insulin stimulates haptotactic migration of human epidermal keratinocytes through activation of NF-kappa B transcription factor. J Cell Sci. 1997;110:2089-2097.

3 Kurokouchi K, Kambe F, Yasukawa K, Izumi R, Ishiguro N, et al. J Bone Miner Res. 1998;13(8):1290-1299.

4 Shoelson SE, Lee J, Yuan M. Inflammation and the IKK beta/I kappa B/NF-kappa B axis in obesity-

and diet-induced insulin resistance. Int J Obes Relat Metab Disord. 2003;27 Suppl 3:S49-S52.

5 Ghanim H, et al. Circulating mononuclear cells in the obese are in a proinflammatory state. Circulation. 2004;110(12):1564-1571.

6 Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, et al. Local and systematic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappa B. Nat Med. 2005;11(2):183-190.

7 Friedrich MJ. Insulin effects weigh heavy on the brain. JAMA. 2006;296(14):1717-1718.

8 Fishel MA, Watson GS, Montine TJ, Wang Q, Green PS, et al. Hyperinsulinemia provokes synchronous increases in central inflammation and beta-amyloid in normal adults. Arch Neurol. 2005;62(10):1539-1544.

9 Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease-is this type 3 diabetes? J Alzheimers Dis. 2005;7(1):63-80.

10 Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. JAMA. 2006;295(14):1707-1708.

11 Behre CJ, Fagerberg B, Hulten LM, Hulthe J. The reciprocal association of adiopocytokines with insulin resistance and C-reactive protein in clinically healthy men. Metabolism. 2005;28(3):125-127.

12 Grundy SM. Atherogenic dyslipidemia associated with metabolic syndrome and insulin resistance. Clin Cornerstone. 2006;8 Suppl 1:S21-27.

13 Wong ND. The metabolic syndrome and preventive cardiology: working together to reduce cardiometabolic risks. Metabolic Syndrome and Related Disorders. 2006;4(4):233-236.

14 Walldius G, Jungner I. The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy-a review of the evidence. J Intern Med. 2006;259(5):493-519.

15 Sierra-Johnson J, Somers VK, Kuniyoshi FHS, Garza CA, Isley WL, et al. Comparison of apolipoprotein-B/apolipoprotein-AI in subjects with versus without the metabolic syndrome. Am J Cardiol. 2006;98(10):1369-1373.p>