January 2015 Issue | David Perlmutter, MD, FACN, ABIHM

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Welcome to *Functional Medicine Update* for January 2015, and oh my word, what a next three months we have in store for you with our mini-course in functional neurology. You are going to be informed, excited, emotionally moved, and, I think, get news to use that is going to make a real difference not only in your patients but in the world at large as you hear from our key opinion leaders.

We're starting this month as a wonderful lead in with Dr. David Perlmutter and you should probably know that Dr. Perlmutter comes with no small reputation and is a leader in the field of functional neurology. I want to just say a couple of things about the nature of this three-part series that I think you'll find will be the deliverables that we hope to be able to accomplish over the course of the months of January, February, and March.

Functional Neurology: New Technologies Have Lead to New Approaches

As you probably recognize, functional neurology is gaining a reputation in the traditional medical quarter, probably out of the constructs of functional MRI and functional radiology, using things like CT scans and PET scans and the ability to do brain mapping. So we're starting to actually look at function at a different level in terms of neurology than in the past, and I think this is opening up a whole approach towards systems biology that is very, very different than what we have had in looking at individual piece parts of the neurological system in isolation or in a reductionistic model. This really can apply to things as far ranging as seizure disorders and epilepsy and motor neuron diseases like Parkinson's and ALS, or cognitive dysfunctions and memory deficits in things like Alzheimer's disease, and even cognitive behavioral issues related to things like ADHD (attention deficit hyperactivity disorder) and autism.

I think that this model that you're going to be hearing developed of functional neurology over the next three months is a model that has applications across these many, many different DSMs, or diagnostic indicators. It also relates to what we see happening as it pertains to genetic evaluation, the so-called GWAS (genome-wide association studies) that have been done with diseases like Alzheimer's, trying to define specific families of genes that may be tied to risks to these neurological disorders. I think what we've seen is that the genetic risks are, at most, weak—that the more significant contributors to these disorders are things that relate to how our genes are exposed to various agents, either positive and/or negative agents that relate to the dysfunctions that we ultimately see downstream as the pathologies

associated with these neurological diseases. The good news part of the story is as we can identify the factors that are associated with individual gene expression patterns in the person, we can modify those factors because they're not hard wired; they are built into lifestyle and environmental considerations. And that's going to be a theme that you'll find weaves together our three key opinion leaders over the months of January, February, and March.

You're also going to hear some very interesting things that will trace back to discussions that we've had in the past with people like Abram Hoffer and his colleague, Humphry Osmond, who looked at dementia from the perspective of nutrient therapies and talked about things like orthomolecular medicine, which Dr. Linus Pauling and his colleague, Dr. Hawkins, wrote about in the 1970s and 80s. I think actually the first paper that appeared with that title in a large, well-recognized, peer-reviewed journal was the paper "Orthomolecular Psychiatry" in *Science* magazine in 1968 authored by Dr. Pauling.[1] And you recall that it was Dr. Hoffer, who was an MD/PhD, who had made observations as a farm boy from Saskatchewan that these nutrient deficiencies that were being discovered at that early part of the 20th century with names like pellagra had presentations of the three Ds: dermatitis, diarrhea, and dementia. And so he started wondering whether there was a relationship between some schizophreniform disorders in humans and various nutrients that could be tied together with things like pre-pellagrous dementia. And that led him into the whole discovery of the connections between things like tryptophan, and neurotransmitters of serotonin, and phenylalanine and tyrosine and the relationship to the dopaminergic neurons and ultimately to nutrients like B6, B12, vitamin C, niacin, vitamin B3, and how they related to neurological function. So it's a very interesting chapter in the development of this topic.

And then that takes us into things that we'll be talking about as it pertains to mitochondrial bioenergetics and neuronal function and how that interrelates with insulin and what's been called "type 3" diabetes, and how toxins like bisphenol A and other neuroendocrine disruptors play roles in these neurological disorders, and how chronic metabolic inflammation that might be tied together with what's called metabolic endotoxemia, the interrelationship between the gut microbiome and diets that are high in fat and sugar that can induce the release into the blood of these proinflammatory mediators like lipopolysaccharides and proinflammatory cytokines like TNF-alpha and IL-6. And how that then also relates to things like epigenetic modeling—things that we've discussed in the past like methylation of promoter regions of genes that you see with PTSD (post-traumatic stress syndrome). You'll recall the interview I had with Moshe Szyf at the McGill University stress research laboratories, in which he talked about PTSD and war and violence and how that triggers, in children, certain kinds of neurological, cognitive, and behavioral function throughout their lives. So all of these are really extraordinarily new concepts in the field of functional neurology that are opening up a very, very different epic period of discovery in intervention potential, and it's that that we'll be focusing on in this three-part series starting with an extraordinary introduction by Dr. Perlmutter.

INTERVIEW TRANSCRIPT

Clinician of the Month

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What better person to have as a lead off person for our mini-course in functional neurology than Dr. David Perlmutter? It was actually so recent ago, but also so long ago, that Dr. Perlmutter was a key contributor to Functional Medicine Update. When I went back I couldn't believe that it was August of 2005 that we had a chance to visit with David. So much has happened in those subsequent nine years, both in the field and his career, and there would be no better person to lead off the important topic of functional neurology than Dr. Perlmutter.

Grain Brain Has Become an International Bestseller

Let me just, for those of you not familiar with him, bring you up to speed. I'm sure if you're a reader at all you're familiar with the fact that his book, Grain Brain: The Surprising Truth About Wheat, Carbohydrates, and Sugar, has been on the best-seller NY Times list as number one for 55 consecutive weeks.[2] That's a pretty auspicious accomplishment. I think it is so because it's such an important book in terms of news to use.

Dr. Perlmutter is a board-certified neurologist and a fellow of the American College of Nutrition. He's a clinical associate professor of medicine at the University of Miami School of Medicine, where he was awarded the Leonard Rowntree Research Award as a medical student for the best medical project when he was at the University of Miami School of Medicine. He has contributed extensively to the world of clinical development of functional neurology and publications and research. His paper that I think was a landmark paper for those of us who have followed the field for so many years, which appeared in Movement Disorders in 2009, was titled "Randomized Double-Blind Pilot Evaluation of Intravenous Glutathione in Parkinson's Disease."[3] We'll have a chance to talk a little bit about that with Dr. Perlmutter. There are so many things that we could say about his background, his experience, and his contribution that it would take up the whole of the time, so rather than that let's jump right in.

David, thanks so much for leading this opening opportunity to discuss the history and development of functional neurology. The concept functional neurology…I was just on PubMed and I typed in "functional neurology" and asked how many citations have been published that have that descriptor somehow embedded within the manuscript, and according to this morning, it is 24,280 publications that have somehow talked functional neurology, and of those, 61 of them have talked about functional neurology and systems biology—areas that you are really a pioneer and a leader in.

Let's start down the Dr. Perlmutter path. How would you contrast your life as a leader in functional neurology to that of, say, a more garden variety, typical neurologist? What are the points of differentiation? How does your life vary? What is your perspective and how does it differ from that of

maybe the training that you had as kind of a down-the-middle-of-the-road neurologist?

Considering Lifestyle Influences is New to Neurology

DP: Well, thank you, Jeff, for that retrospective. When I hear you say those words, you take a moment and think back about not only where we have been but where I have been with reference to neurology and then embracing the notion that there is a moniker that can characterize the way that we practice, and that is functional medicine as it applies to neurology. And I would indicate that as a mainstream neurologist, my life was characterized, I think, by one word and that is “frustration,” because I realized we were really only treating symptoms and doing not a very good job at that. You know, as a neurologist, I think the main thing was determining where is the lesion, and then naming it, and if you did that that was a good day’s work and the patient was pretty much just the byproduct of how you arrived at that situation and we’re going to feel good about that.

You know, the medicines that were designed and are still used are basically an attempt to treat the smoke and not the fire—looking at the end results of a panorama of multiple events that ultimately conspire to give clinical outcome, each of which is fundamentally important if you’re going to really have leverage in terms of dealing with the disease itself and not simply remain focused on the symptoms, whether it is a tremor, Parkinson’s, headache, dementia, other cognitive issues. I really felt frustrated in accepting the notion that somewhere in the Physician’s Desk Reference would be a magic bullet—a reflexive, Newtonian response to an array of clinical manifestations—and realize that beyond my frustration those answers were not there.

Lo’ and behold, I began exploring the notion that, oddly enough, lifestyle factors may in fact be playing a role in the pathogenesis of neurological conditions at a time in medicine when we were just beginning to understand the notion that there were influences with respect to lifestyle choices as they related to heart disease, diabetes, and perhaps even cancer that were just beginning to enter the spotlight in terms of some powerful traction in terms of making lifestyle modification. And, you know, those were the years where—talk about being the odd man out—as a neurologist, this was anathema; no one would talk about these issues.

I recall that several years ago I became friends with a doctor, Amar Bose, and you may in fact be wearing his headphones right now, I don’t know, but an amazing physicist, a real pioneer. He proudly took me to his research facility in Massachusetts. What was most compelling for me and impressive was not his latest technology—and believe me, there were things that were 10, 20 years down the pipeline that were very exciting—but a quote that was on, actually, the glass door entering into his private office that said something like this: “On the pathway that leads to the future, each progressive soul is confronted by a thousand mediocre minds appointed to defend the past.” (A quote by Maeterlinck.) And when I saw that I realized first what he had gone through in his career and how he had to be iconoclastic, and how there is really nothing wrong with being that. I mean, we measure our progress in a salutatory way and I felt like it was time, at least in the area of neurology, to make quantum changes. And, as you well know, it’s bearing fruit. We’re seeing some very dramatic shifts now in our perception, with national and global recognition in work done by people who are embracing the notion that to consider neurologic disease from a Newtonian billiard ball—one illness, one name, one remedy—perspective is, to be nice we call that myopic, but the upside is to light the candle and not curse the darkness and embrace the notion that the pathogenesis of these diseases are multifactorial and therefore dealing with them requires an aggressive

approach that embraces a multitude of issues that will slowly but gently offload the camel's back, as opposed to trying to monetize a patentable one remedy approach. We know that isn't going to work—it hasn't worked—and yet, now for the first time in history, Dr. Bredesen has actually published results reversing symptoms of Alzheimer's disease, something that others of us who are using these types of approaches have now embraced and have also had the opportunity to experience. [4]

So Many Interview Topics: Oxidative Stress, Inflammation, the Microbiome, and More!

JB: That's a fantastic introduction not only to your work, but also to the whole nature of this mini-series on functional neurology. We are very fortunate that Dr. Bredesen will be your follow on in the second chapter of this three-part series. I'd like to have you take us through those areas that you have really been a pioneer in each of these areas in functional neurology over the last 20 years. I'll list them just for the sake of putting them out there for the listener, but then give you an opportunity if you would take us through how this evolved and how these are applied within your practice. These include oxidative stress and free radical pathology-related issues in neurological disorders, and of course you'll tell us about your glutathione work and your hyperbaric work, which is pioneering. Second—and these are all interrelated so I don't want to sound like they are siloed, but one might think of them as being differentiated although they are interconnected—the second is inflammation, chronic inflammatory disorders and how that relates to neurological function. The third is insulin resistance, which you've been a big pioneer in and obviously Grain Brain deals with that whole topic very eloquently and brings it to the reader in a sensible way that they don't have to be a neurologist to understand. The next is that of the microbiome—this gut/brain connection—and you recently became the author of a new journal, Gut Brain, which obviously is a very important medical topic that is emerging at the frontier that you have been a pioneer in. The next is what Abram Hoffer maybe would have talked about years ago as nutritional imbalances, and how do nutrition imbalances—it could be vitamins or minerals or other co-factors—interrelate with neurological disorders? Next is allergy and intolerance. We've had the privilege of interviewing Alessio Fasano in Functional Medicine Update, but I know you're taking that to the next level as it relates to some of these neurological sequelae. And then methylation as it relates to epigenetics; how does that whole methylome interrelate with neurological disorders?

I'm almost done…Toxicity and endocrine disruptors and how does neurotoxicity and environmental disruptors interrelate with neurological disease? And then lastly, these genetic risk factors that some people are so worried about—things like apo E double 4 polymorphisms and how does that play a role in what you might see as the future of functional neurology. So with that as an overview, let's start with the oxidative stress. Tell us how you got down the glutathione pathway and what you've helped pioneer and helped us to learn.

DP: First, let me just say that as you were listing all of those topics and to some degree they are a bit chronological, at least in my life, what's always been so incredible to me is that the margin between them is never distinct. It's always been blurred and they always circle back around and how fascinating it is to recognize the empowering role of the human microbiome in terms of regulating inflammation, inflammatory mediators. How those inflammatory mediators ultimately influence mitochondrial energetics and how the role of mitochondrial energetics is so profound as it relates to signaling for apoptotic pathways, for example, through the caspase system. And mentioning the work of Dr. Fasano in terms of gut permeability, I recently interviewed him actually for our new journal and his comment was that the most important factor related to the microbiome was the very food that we eat, so how validating

it is that the at the end of the day we keep coming back to the food that we eat. These days people say maybe it wasn't Hippocrates who said "Let food be thy medicine and medicine be thy food," but nonetheless the quote still stands. I don't care who said it, I think it's very important.

Mitochondrial Energetics and Brain Health

With that said, let's start off moving back to the work of Dr. M. Flint Beal, whose really pioneering work in dealing with the fundamental role of mitochondrial energetics in brain health I think really was an eye-opener for me because it became something applicable in the clinical arena that upregulating of mitochondrial energetics and protecting mitochondrial function through nutritional intervention and a reduction of entities that we know present as mitochondrial stressors really might have some important role in enhancing brain health and function and making the brain perhaps more resistant to disease, with the understanding that yes, the brain is a very energy-hungry organ, and you mentioned Mark Mattson earlier. Mark Mattson's work indicating that this thought that we need to power the brain with glucose—and he's really, with his work on caloric restriction and more of a ketogenic diet—I think has really opened the door for us to understand that a far more efficient and less radical producing approach to fueling mitochondria really has to do with allowing mitochondria the opportunity to metabolize ketones in terms of creating ATP with less cost in terms of radical production, and ultimately from that work has been the production of an FDA-approved medical food that we can write prescriptions for the actual treatment of Alzheimer's disease. So that said, what did Dr. Mark Mattson say? He said that calorie restriction—a mild state of stress for mitochondria—is actually a powerful hormetic approach to enhancing viability and enhancing function. And when you recognize that really as the cornerstone, the final common pathway, of neurodegeneration in general is mitochondrial dysfunction, then concepts like dietary intervention to reduce calories and allow the availability of ketone fuel sources, really get your attention.

What I've done is kind of embrace the publications that have been supportive, and then put them into implementation protocols in the clinical arena in a very nonacademic way, I'm happy to say, because I've not been constrained. That said, we've had great results in applying these ideas not only to neurodegenerative conditions but to issues as disparate as epilepsy and glioblastoma. We fully understand that a ketogenic approach, for example, to treating epilepsy, which has been popularized at least in children since 1928, a direct intervention focused on mitochondrial upregulation and salvaging mitochondrial function, it has now been validated as a profound intervention in adults, as was published just two weeks ago in the journal Neurology.[5] So anything, then, that leads to upregulation of the inflammatory cascade enhances risk for brain degeneration when we recognize that while we know multiple sclerosis, for example, is a prototypic neurodegenerative condition focused on inflammation, so is Parkinson's, so is Alzheimer's disease. As you well know, we can image activated microglia in the Alzheimer's brain, and we can see that they are upregulated. Measuring interleukin-6 tumor necrosis factor alpha—a variety of markers of inflammation—clearly points a finger at the role of inflammation in these degenerative conditions.

Understanding the Role of Gluten in Inflammation

So to flash forward a little bit, my interest has been: where does it begin? And that took me to understanding the role of gluten in terms of inflammation, and the work, as you mentioned, of Dr. Fasano indicating that gluten sensitivity is something that needs to be considered not in ten percent of humans or

even the 1.8 percent who may have an autoimmune condition called celiac disease, but he believes that through the mechanism of zonulin activation that there is some increased gut permeability induced in all humans when exposed to this protein—gluten—found in wheat and other grains (barley and rye). And that is a very profound notion that here is a gastroenterologist at Harvard talking about gut permeability, or leaky gut, that you and your team have been talking about for a long…I don't want to say how long, but for a long time.

And you know what, Jeff? You think back over the years when we've talked about leaky gut, that didn't come into the mainstream nomenclature until very, very recently, yet we've been talking about it for a long time. And now a leaky brain, that Dr. Fasano has demonstrated similar changes in the blood-brain barrier permeability brought on by similar changes in the blood-barrier permeability brought on by similar influences. So it takes us to a situation that all disease begins in the gut, and here you are having a conversation with a neurologist and what this neurologist is telling you is that that's where our focus needs to be; it needs to be on the gut. And I have a tough time convincing my neurology colleagues that there really are important issues below…south of the foramen magnum—that the gut has a very, very powerful role.

The Role of the Microbiome in Brain Health May Be Powerful

We're just beginning to scratch the surface in understanding this powerful role of the microbiome—the trillions of living organisms that reside mostly within the gut—in terms of their influence on seemingly distant parts of the body, my interest of course being the brain. We now know that there is this intimate and beautiful dance that occurs with respect to those organisms living within the gut and the health and vitality and resistance to disease in the human brain. Interesting work that was published in the Proceedings of the National Academy of Science in June of 2010, for example, looked at stool analysis of children in Burkina Fosa, a western African nation, and compared the stool specimens to similar age-matched children living in Europe, and did 16S rDNA analysis of the various organisms, and in addition looked at what are called short-chain fatty acid analyses of these individuals and found really remarkable differences based upon a rural environment and foods that were consumed versus children eating a more westernized diet.[6] And it was really quite interesting when you looked at the short-chain fatty acid array that overall the kids in Africa had much higher levels of short-chain fatty acids, but the array was different. The African children had much lower levels of propionic acids and higher levels of butyric and acidic acid. So the arrays are very important because we now recognize, for example, that this notion of elevated propionic acid that we see in the European groups and we're seeing in other Western groups may have a huge role to play in brain function.

We now recognize, for example, that propionic acid level is higher, and produced in higher quantity, in those individuals whose gut arrays are higher in the clostridial species, and where are we finding that? We're finding higher levels of clostridial species when we fingerprint the gut microbiome in autistic children. Dr. Derrik MacFabe at the University of Ontario has done some incredible work in looking at what happens when you inject, interventricularly, in the laboratory model, propionic acid? And creates a laboratory rodent that looks all the word like an autistic child: stays in the corner, will not socialize with others of his companions. So the idea that changing the milieu of the gut bacteria will have a powerful effect on the brain and that there may be clinical application of this science in moving forward, I think to me is super exciting because we now understand there have been some dramatic changes that have happened to the human microbiome in very, very recent years, and that—as Dr. Fasano would agree—much

of this has happened as a consequence of our dietary changes: favoring higher carbohydrate, less available good fat, and other changes to the human diet that change the ratio on a phylum level of the make up of the gut bacteria.

Now how do we know that? One report in PLoS Biology published in December 2012, a really interesting study, looked at the coprolites—fossilized stool and gut contents from individuals who had died years ago, some of whom were frozen, like Oxy the Iceman, and lived 5500 years ago (or before current times, years ago), and what they found was that their array of microbial organisms was pretty similar to non-urbanized humans living today.[7] The point is that this has been the type of bacterial array that we've had for a long, long time, and that the bacteria haven't changed over time, but little has our DNA or our genome changed significantly, so we co-evolved with this group of organisms for a couple of million years and suddenly we've turned the table on what represents 99 percent of the genetic material in your body. That's a pretty sobering number when you consider that we've been so excited with our 23,000 genes, thinking "Gee whiz, that's an awful lot that can make you who you are, Jeff Bland versus David Perlmutter." You know, when a rice plant has 50,000 genes, that's a sobering notion. I like to think that we have become efficient in off-loading or up-loading parts of our genome—most of our genome—to the cloud, so we don't have to walk around with it at all time. That cloud is the microbiome that we carry around as a reference source for powerful genetic information.

It takes us, then to the glutathione story. I'm going to try to get these in the order that you mentioned them. Really that was an attempt by me to directly intervene in terms of mitochondrial function, but beyond that, understanding that glutathione plays a pivotal role in detoxification at multiple levels, we began a protocol using intravenous glutathione with great success in treating Parkinson's and then published the article to which you referred, again demonstrating significant moment-to-moment improvement, as well as long-term reduction in the rate of decline in Parkinson's patients. Then as things moved on, we began recognizing that there were epigenetic pathways that are available to us to also enhance availability of reduced glutathione in human physiology and other forms of glutathione in terms of its detoxification of glutathione, peroxidase activity, glutathione-S-transferase activity, as well as—again, as you mentioned—inflammation, reducing the power of inflammation in human physiology by reducing what is called NFkappaB, and also enhancing other parts of antioxidant function and reducing even apoptosis by activating pathways like the NRF2 pathway, and began understanding why it is that things like turmeric, caloric restriction, aerobic exercise, DHA, resveratrol really have wonderful science behind them and allow us to pursue various dietary changes with the idea that we can enhance through epigenetics, taking advantage of our new knowledge that the notion of our genome being fixed is really something that is quite passé at this point, and really are beginning to see as our major research centers that the gatekeeper of longevity, NRF2 pathway, really may offer up some powerful leverage points in terms of dealing with neurodegenerative diseases that are predicated on upregulation of radical activity, oxidative stress, and inflammation. And basically, as I like to say, that's every neurodegenerative condition that has a vowel in its name, so the list is fairly long. That said, beyond the notion of specific food choices and supplement choices, it really also brings to mind the idea of simple calorie restriction again and aerobic exercise as epigenetic factors. We've now seen some exciting work that demonstrates that the simple notion of engaging in aerobic exercise is a powerful epigenetic modulator of brain drive neurotrophic factor, as is turmeric, for example. But that the simple act of getting aerobic exercise actually enhances neurogenesis, allows the hippocampal neurons to replicate and become function, and is associated with improvement in memory, and that is a claim that cannot be made by any pharmaceutical available as you and I have this conversation. Simple aerobic exercise that no one can own, it cannot be

proprietary, all you need to do is buy a pair of sneakers and have some motivation.

So how many points have we covered thus far?

Glutathione Treatment Produced Remarkable—But Not Sustainable—Results

JB: I think you've been doing a fantastic job. Let me trace back just briefly to the glutathione story because you talked about remarkable moments. I would say from my perspective and literally tens of thousands of my colleagues, your sharing your clinical videos of the response the Parkinson's patients to glutathione was more than an ah-ha experience; it was a remarkable, miraculous experience, and I'm sure it was even more so for you, living through that personally with your patients. But I'm sure there was also some disappointment that somehow you couldn't sustain those extraordinary benefits that you saw, post-infusion. Do you have any sense as to what's going on that leads to the decline of functions after the infusion of glutathione?

DP: Well, I think ultimately in Parkinson's we are dealing with a situation of increased oxidative stress, and I think basically the patient is shifting the ratio of glutathione from reduced to oxidized, and in terms of sustaining the benefit, that has required that these infusions be done about every three days or so, but I will say that in terms of the longevity of the benefit, my goodness, we have patients now 14 years using glutathione getting wonderful results from it, but it doesn't last more than a couple of days. My dream would be to somehow create technology that would allow a constant infusion, and even more than just a simple intravenous pump (the technology exists for that), even an intrathecal, or administering it into the spinal fluid, and that technology already exists for delivering antispasmodic medications, or analgesics. The problem, as we explored that, is glutathione is a very heat sensitive tripeptide, and as such exposing it to 98.6 in the reservoir became a conflict for us and we're still looking at how we can get around that, creating a product that could be more heat stable. But that's where we're going in the future.

I will say that I have been offered a research opportunity moving forward into 2015, and that's going to be one of the players on the top of the list. But it's been a big circle to come back through the years to the importance of diet—fundamental diet—and as of now we understand it relates to the microbiome, even as it relates to Alzheimer's disease. That may seem like a stretch, but we now understand there are clear indications that our obsession with hygiene and our lack of judicious use of antibiotics and the effects that that is having on the human microbiome may in fact extend in some correlative way to risk for Alzheimer's disease. In a study in Evolution Medicine and Public Health in August of 2013, British researchers showed that when you mapped out diversity of the microbiome in well over a hundred different countries globally, it lined up perfectly with the prevalence of Alzheimer's disease.[8] Those countries that had high levels of diversity and high levels of parasitic stress, for example, had the lowest prevalence of Alzheimer's disease.

Microbial Diversity is Key in Avoiding Gut Inflammation

Now again, some may say, "Well, correlation doesn't indicate causation," and the hair on the back of my neck when people make that argument because I think the argument is that we should ignore this data and absolutely not. The point is that with microbial diversity we maintain gut wall integrity, and gut wall integrity is seen to be breached in Alzheimer's. We are now able to measure lipopolysaccharide (LPS), the bacteria membrane coating found on Gram negatives, which, interestingly enough, getting back to the

Burkina Fosa stool analysis, we see much higher levels of Gram negatives in European western microbiome compared to rural Africans, but that said, lipopolysaccharide is a powerful marker of gut permeability. Lipopolysaccharide is used in the experimental laboratory to create inflammation in experimental protocols. So when you measure either LPS itself or antibodies against LPS, this is a powerful indicator of gut permeability. We see direct correlation between higher levels of LPS in Alzheimer's with amyotrophic lateral sclerosis, and it predicts the level of neurologic impairment. It's seen in major depressive disorder, and is dramatically associated with autism. So again, these are the powerful indications that something has gone awry with the gut that ultimately is paving the way for inflammation, a cornerstone of everything I've mentioned and then some.

So, it takes us back to then what do we do before we become interventional? What do we do from a preventive perspective in terms of preserving the bacterial array of the gut, and therefore preserving gut wall integrity? And, you know, from day one…let's go before day one. Let's go to when a baby is born. Clearly, we see very powerful data that is indicative of method of delivery playing a significant role in how that microbiome is created. When we see that the risk of autism is now 1 in 50 male births in America, and that risk is doubled if a child was born by Caesarian section, that's important information. Risk of ADHD is increased three-fold. Risk of type 1 diabetes, an autoimmune condition, is increased 75 to 80 percent. These are important statistics that need to be shared with mother, rather than just focusing on the length of the scar that she will have if she chooses to have a Caesarian section. I've got to qualify this statement by saying this is not mommy bashing. This is not telling mothers that they should feel guilty that they delivered by C-section. I want to be proactive. I want to just say that moving forward these are important life-changing decisions to make and weigh this information prior to Caesarian section. That's a procedure that saves lives, but the notion that that is what has to happen in one of three American births today I think is clearly stretching a point. Breastfeeding cultivates a wonderful microbiome, but by far and away I think we're focusing these days, as is so wonderfully described in the book, Missing Microbes, that antibiotic over usage is having a devastating effect on the human microbiome, both in terms of in the clinical arena and also in terms of the foods that we're eating—the antibiotics, 70% of which in America are used in cultivating our livestock.[9]

So I think we've really got to understand that threats to the human microbiome are real and present danger, and that there are things that we can do if we focus on therapeutic techniques at the level of the microbiome that can have powerful outcomes in terms of any degenerative condition that you can name, so clearly this is the future. I had the opportunity several months ago to lecture at Harvard on the microbiome as it relates to neurologic conditions. The following day, as fate would have it, in the exact same lecture hall at the exact same podium was another series of lectures for a different conference focused on probiotics. There was a lecturer named Dr. Nieuwdorp, from Amsterdam, who demonstrated that in his series of over 250 patients with type 2 diabetes, he was able to almost normalize their insulin sensitivity by reestablishing a healthy gut microbiome by doing—dare I say—fecal transplantation. Fecal transplantation for individuals with type 2 diabetes by reprogramming their gut bacteria. Wow. I mean, it literally took my breath away to see that, because we—"we" parenthetically—are focused on the development of drugs to influence the insulin receptor, to influence pancreatic output of insulin, PPAR-gamma activators that can affect insulin levels, metformin, and so narrowly focused on lifestyle factors that when we see that there is a role for the gut bacteria, which are influenced by diet, which may yet be another place that diet induces diabetes, it's really very interesting.

If I may say, of all the factors that increase permeability like antibiotics, xenobiotics, gluten, one factor

that we're now understanding also leads to breakdown of the tight junction is glycation of proteins—that these very advanced glycosylated end products that we use as markers (hemoglobin A1c) for glucose control in diabetes, aside from upregulating radical production and turning on inflammation dramatically in and of themselves because they are quaternary and tertiary characteristics have been changed, actually destabilize, deconstruct the tight junction and lead to gut permeability, so yet another way that diets higher in carbs and sugar can enhance the risk for diabetes by enhancing inflammation.

JB: I'd like to pick up on this—you've left us so many pearls, there, we could obviously…hey, I just thought about it: pearls from Dr. Perlmutter; it sounds like a pretty good aphorism…

DP: I'd better get the URL before you do…

JB: Let's talk about this fecal transplantation for a second. I know that you've had some observed clinical influence on some of your patients with that technology. Tell us a little bit about it because it sounds, in the minds of some, to maybe be way out, and in the minds of others who have been in this field, maybe a logical extension of what we've learned in terms of the clinical application.

Making a Case for Fecal Transplantation

DP: And it is the latter, clearly. It's clearly a logical extension, and let me just build the case for you if I may. So many have heard of fecal transplantation, or fecal microbial transplantation in America, because that has now assumed the number one position in terms of treating a specific bowel condition called Clostridium difficile infection. C. diff is potentially life-threatening; about twenty thousand Americans die annually from this gut overgrowth of bacteria, and I don't necessarily call it an infection because that connotes an invasion by a species that is foreign and overrides the system. In fact, nothing is further from the truth. Many of us are carrying C. diff. At nursing homes, 50 percent of the elderly individuals have levels of C. diff. And, in fact, newborns have high levels of C. diff as well. The problem arises when the balance of bacteria is disturbed and then C. diff is allowed proliferate, especially when individuals are exposed to a class of antibiotics called fluoroquinolones. With that said, the treatment for C. diff has been, historically, the use of a specific antibiotic called vancomycin, which is about 28 to 30 percent effective in eradicating C. diff on a permanent basis, and that's a pretty crummy metric.

We now understand that using fecal microbial transplant, and to be very specific that is to say, taking fecal material from a healthy individual who has been screened for communicable diseases like HIV, hepatitis, etc. That stool specimen has been screened for pathogenic parasites. And transplanting that material into the colon of the C. diff sufferer has been demonstrated to be between 92 to 96 percent effective in total eradication of the illness called C. diff. By far and away, the most effective treatment for C. diff in the world. Dr. Feingold published a report several years ago in which he used vancomycin to treat autistic children. Now, why would he do that? He did that because new research is demonstrating higher levels of clostridial species (Clostridium histoliticum, for example), to be found to be quite prevalent across the board in many autistic children. Dr. Feingold recognized this and began an open-label trial and demonstrated significant improvement in the autistic children, as well as fielded reports from his colleagues, who were doing the same thing—using the best treatment at the time, vancomycin, to reduce C. diff population, and therefore seeing clinical results.

So, the natural extension that you referred to stems, number one, from that work, and also from the work

of Dr. Derrek MacFabe at the University of Ontario that I alluded to earlier, demonstrating that perhaps the player is this abnormal ratio of short-chain fatty acid with higher levels of propionic acid. Dr. MacFabe has brought to our attention the notion that propionic acid is a mitochondrial toxin, which takes us back to our origins—a mitochondrial toxin that has a role to play in changing omega-6 to omega-3 ratios, increasing inflammation by increasing omega-6 availability by altering neurotransmitters, by enhancing glutamate influx into the mitochondria and thus serving as a mitochondrial toxin, and that, as mentioned, there are higher levels of propionic acid in those people whose gut microbial array has higher levels of clostridia.

So then, looking at Dr. Feingold's work, he's eradicating clostridia and finding results. I feel it is a natural extension, then, for me to have had discussions with parents of children devastated with autism, and parents devastated by the fact that their children have autism, to be a little bit outside the box and outside the envelope. I'm hopeful that your listeners will understand that this is natural extension and that there is perfect rationale. You know, Louis Pasteur said that chance favors the prepared mind, so we do the homework and then we move ahead for discovery. We've been, now, working with families to perform fecal microbial transplants on autistic children. To be clear, I'm not doing that procedure in my office, but parents are learning how to do the procedure, and we are seeing results that are profound. So, it's a new day.

I have to say I was lecturing recently in Frankfurt, Germany, and during the break I received a text message from a mother of a child who underwent this procedure. The mother actually found a donor—a 14-year-old healthy girl—who wanted to help this kid and donated her stool. The mother figured out how to do a fecal microbial transplant, and the child began speaking. This is a kid who couldn't be moved and the video she sent me was of this child jumping up and down on a trampoline, and she indicated to me in a phone conversation that after his sixth transplant she took him to the beauty parlor one day, he sat in his chair next to her having her hair done, and they had a 40-minute conversation. Now, this is in a day and age where there is no treatment for these kids whatsoever. That mainstream medicine is absolutely scratching their head because they are focused on the brain, and we've got to take a broader view. It is a holistic perspective that recognizes that we are a composite of multiple systems, and that when we embrace the notion the multiple systems come to bear, to manifest, as either health and disease, this is when we're going to have the best results and we're going to be able to push the reset button and give people another chance.

JB: What a message of optimism for many of our clinicians that are looking for solutions to these very complex problems. One of the other areas of the many that you have been a pioneer in maybe seems paradoxical to people, again, not familiar with this field, and that is hyperbaric oxygen. People might say, "Well, hold it. Aren't we exposing people now to an oxidant stimulus, and aren't we just promoting oxidative stress by giving them oxygen?" But we get into hypoxic-induced factors, and gene regulation, and so tell us a little bit about the hyperbaric oxygen approach towards normalizing mitochondrial bioenergetics.

Using Hyperbaric Oxygen to Normalize Mitochondrial Bioenergetics

DP: I will. Let me just take you back for just one moment. You know, you're bringing up mitochondria again. I think there's actually a very nice segue from our previous conversation about the microbiome when we recognize, in 1968, the work of Lynn Margulis, talking about this endosymbiotic relationship

that we have—that these were once free-living bacteria with their own circular DNA. They took up residence within us and have given us the gift of energetics, as well as regulating life or death wielding the sword of Damocles, as we talked about earlier. So there is this kind of intriguing segue to consider mitochondria as yet another part of the microbiome—that they are bacteria-like organisms and we need to embrace them as such and stop fighting these wars.

You know, many pesticides that are used are ultimately mitochondrial toxins, and I think when you recognize that mitochondrial toxicity is at the root of neurodegenerative conditions, it makes you want to, again, take pause to understand that we're exposing ourselves to mitochondrial toxins. In the Journal Archives of Neurology last year was a wonderful report that showed increased risk of Parkinson's in individuals exposed to various things like pesticides, etc., and there was one chemical called mancozeb that I was unfamiliar with.[10] I went on Wikipedia and learned about it, and it is a mitochondrial toxin that's used in the experimental rodent and primate model to create Parkinson's in the experimental laboratory. When you look further you see you can buy the stuff at the garden store to put on your vegetables. So something is very wrong. As Gregory Bateson said, "Man is the only animal who will befoul his own nest, a sure sign of madness."

So that said, we look at, what does a mitochondria need to be happy? It needs to have the right fuel. It needs to not have exposure to these toxins. And it needs a place to transfer that electron at the end of the day. And where that electron goes in the process of creating ATP is, of course, oxygen. So if we can enhance that activity of oxidative phosphorylation with hyperbarics, it seemed reasonable that this was the explanation as to why hyperbarics has proven so helpful in wound healing, in reversing the changes of osteoradionecrosis. Does the application of an increased oxidative state run the risk of those things that you mentioned, and I would say absolutely there is that consideration, but again we take a step back and look at risk/benefit ratios. Many of the mainstream therapeutics have, in fact, the notion of one-step-back/two-steps-forward, and what we understand happens when we increase oxidative stress is that we induce the upregulation of protective antioxidant systems, of detoxification systems, of inflammation-reducing activity as well.

As a matter of fact, oxidative stress is a very powerful upregulator of the NRF-2 pathway. Oxidative stress is a homeostatic mechanism that allows us, when we're suddenly involved in a situation of increased oxidative stress demand, to enhance our production of protective species, protective chemicals, antioxidants. So at the end of the day, we are putting our patients into a lower level of oxidative stress, while at the same time recruiting macrophages, enhancing phagocytosis, increasing detoxification, and reducing inflammation by this very, very powerful approach by putting people in a chamber pressurized with oxygen, to the extent that Israeli study that was published about 12 months ago—published in PLoS One—looked at actually functional MRI scans in individuals pre- and post-hyperbarics who had sustained a cerebrovascular event, showing that those areas of functional-but-not-functioning tissue came back online when they were treated in this way.[11] So I think we're going to see a lot more to come from the value of hyperbarics, especially in conjunction with the notion of reprogramming the gut bacteria.

Knowing Your apoE4 Status Does Not Mean Knowing Your Future

JB: Well, we just have a few minutes left. Obviously we could continue this discussion and we'd all be enlightened for going on for hours, but we're begging on your indulgence of time. Let's finish up talking about the concern a lot of people have with neurodegenerative disease—that it was passed on as a legacy

that they didn't fill out an application card for, which is called their genes. I find it very interesting, both sociologically as well as medically that many people are very resisting in knowing about their apoE genotype because they are fearful that this would be a death sentence if they understood something like the Huntington's disease gene, if they knew their apoE4 that would be kind of an end-of-life experience for them. Tell us a little bit, David, how you see genetic testing weaving itself into functional neurology, and maybe specifically related to the apoE4 double allele.

DP: Well, I think that first of all, this notion that carrying the apoE4 allele is a sentence for Alzheimer's is silly. I mean, the apoE4 allele is something that has evolved in recent times from our primate ancestors, and for a genotype like that to have persisted, I think it's not unreasonable to ask what there may be in terms of some advantage that has allowed it to persist. Why has it become prevalent? Why is it found in up to 20 percent of humans? There must perhaps be some advantage, and I think that you're about to learn about that with your next interview, and I'm not going to spill the beans on that (with Dr. Bredesen). New insights into possibly some other attributes that the apoE4 genotype and the phenotype that is a manifestation therefrom. But that said, I am not usually involved in that screen for my patients. The reason being is that it is not a sentence. It is a risk marker to some degree, but by no means is it a determinant. I feel that there is a fair chance I may carry the apoE4 allele in light of my father's Alzheimer's disease, and that said, I don't know whether I do or I don't, because I know that the notion of epigenetics, to me, carries a far more attraction in the idea that there are powerful things that I can do and that I am doing that will, I believe, clearly offset the notion that I carry or don't carry the apoE4 allele.

Now that is not to say that there are other aspects of looking at single nucleotide polymorphisms that aren't really important to know, as they may relate to an individual's choice of medication and his or her detoxification abilities. I think that's valuable information. Is the apoE genotype information that's important? To some degree. But with my patients, I pull out all the stops without regard to that metric, so therefore, they're getting soup-to-nuts the whole program because by and large these are people who I'm seeing because either they are beginning to have some issues with cognitive impairment, which we now understand are, in fact, reversible. That these mild issues, and even moderate issues, of cognitive impairment that go by the name Alzheimer's disease are, in fact, reversible, and the answer isn't on the prescription pad. There's no one approach that makes that happen. It is not definable, nor is it proprietary. The point is that, again, multiple lifestyle factors can undo this genetic predisposition, and we are just, just now beginning to embrace what Dr. Jeffrey Bland taught us many, many years ago, and that is we've got to pay attention to the web—the web of interacting, interrelating factors that can either conspire to manifest disease, or can be looked upon as powerful allies in creating health, wellness, and longevity.

JB: Well, Dr. Perlmutter, to say thanks to you would be a great understatement of our appreciation for your 20-plus years of work. You're pioneering, against a lot of conventional old thinking, a new model that is, I think, much more optimistic in terms of plasticity and opportunity for self-improvement and giving new tools to clinicians that have been probably frustrated they didn't have the tools they needed to their patients' problems. It's not an easy job. It's one that requires courage, and high intellect, and high communication skills. Fortunately you were gifted with all those from your parents and you've developed them very, very well. There would be no better person I could think of starting off this three-part mini-series on functional neurology than the person who has really birthed what I consider truly functional neurology. So thank you for your tireless work and contributions to the patients and the field at large.

DP: Well, I sure do appreciate those kind words, Jeff. And your work has had a very, very powerful influence on me in terms of allowing me to stay the course, and encouraging me, you know, at times when we've all had our moments of doubt—being the odd man out, that's for sure. But people have always said, "Gee, you know, all the stuff that you're doing is really…it's so outside the box and you're a really outside the box thinker, and I always like to come back and tell them that that's not the goal. The goal is to make the box bigger, so that we embrace these ideas because these are natural extensions from current science, and they work. Maybe ten years from now we're going to have another conversation. I can't imagine what we'll be talking about, but I'm looking forward to that day.

JB: Well, so am I, and I think of your book, Grain Brain and the millions of people that have been impacted by it. I think of other neurology journal articles that have been considered pioneer journal articles that have transformed neurology—how many of them have been read by millions of people? The impact of your book is a great social agent of change.

DP: Twenty-seven languages, and I have no way of reading those and knowing if they are giving the right message, but I've finished writing a new book called Brain Maker, and what's that about is dealing specifically with what we've talked about a lot: not just the role of the microbiome, but I think more importantly for clinicians and non-clinicians alike, what can we do about it, both in a preventive way and also in an interventional way?

JB: Well, you can be assured we'll be coming back to visit with you before ten years. Thanks a million, Dr. Perlmutter. We can't appreciate enough all of your contributions. And be well and best to you and your family. Thank you.

DP: Thank you, my friend. Bye-bye.

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