December 2013 Issue | Terry Wahls, MD, MBA, FACP Author, The Wahls Protocol

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BONUS INTERVIEW

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Welcome to *Functional Medicine Update* for December 2013. It's been quite a year, hasn't it? Quite a year in terms of the extraordinary advances that are being made in understanding about the origin of chronic disorders and actually what to do about them, based on their now putative mechanisms of action and understanding the cellular pathology—things that we didn't even begin to know anything about 30 years ago when we started this series, so it's quite remarkable just from an intellectual evolution perspective to see what's changed and how functional medicine is gaining an underpinning of really strong both basic science and clinical science support.

This month is certainly another good example of this. I'll call this the month of neuroinflammation. It's a very powerful topic and one that we have addressed multiple times. This will be another kind of facet on the diamond of this topic. We had an extraordinary interview in 2012 with Dr. Dale Bredesen, from the Buck Institute and from the UCSF Medical School, talking about Alzheimer's disease and its etiology and the complexity of the condition—how it's not just one condition, it's multiple conditions. It's going to require a complex intervention for a complex disorder to get improved clinical outcomes. Dr. Bredesen shared with us this whole evolving understanding of the origin of Alzheimer's disease as a neuroinflammatory condition. We have the past history of extraordinary discussions with Dr. David Perlmutter, a neurologist in Florida who has shared with us his brilliant insight as it relates to the neuroinflammatory processes, it pertains to Parkinson's and other neurodegenerative disorders, and the management of these conditions—at least the progression of their symptoms—using intervention that is focused on rising of antioxidant potential. He talked to us about his work on intravenous glutathione. Although it is a transient effect in these patients, it is aremarkable transient improvement they have in function as you raise their redox potential and improve their ability to manage both the toxic burden and the oxidative stress reactions associated with the disorder.

And then we've had previous discussions that have come through the brains and verbal elocution of clinicians talking about gluten-related enteropathy and gluten-related neurological dysfunctions and how that interconnects the gut-immune system to the nervous system, and how we have to look at a much broader perspective at the etiology of neurotoxicity and neuroinflammatory disorders to even talk about dietary components.

Just so we don't forget about the 2014 year coming up, that topic will be much more fully developed as we move into January of 2014, where you'll have the pleasure to hear the interview that I did with Dr. Alessio Fasano at Massachusetts General Hospital, and arguably one of the world's leading experts in the area of gluten and its association to inflammatory disorders. He'll be talking about neuroinflammation.

So this month, what is going to be our major focus? This month we will be through the lens of a clinician who is a brilliant seeker, searcher, discoverer, thought-provoker, a synthesizer of information who had no better reason for motivation than her own specific declining health as it relates to progressive multiple sclerosis (MS). Often we put names and labels on conditions for lack of a better understanding of the mechanism, and in this case the diagnostic criteria was MS, a member of the autoimmune disease family associated with neuroinflammation.

You're going to hear from Dr. Terry Wahls—as a medical professor at a very reputable medical school, and as a very highly motivated seeker of information, and as a convert to the functional medicine model—about how she has applied this model successfully, in her own case, with progressive MS, and now is spreading out with a clinical trial to work for—hopefully—the improvement of many thousands of people to come who share a common health challenge.

Neuroinflammation and Oxidative Stress

To set the context for this story, I want to go back for a moment and just talk a little bit about what is happening at the frontier of research pertaining to modulation of nervous system inflammation using what we might consider non-drug interventions. This would be things like nutrition, and lifestyle, and oxygen interventions. These have historically been parts of every indigenous culture in their arsenal of therapeutics. They may be called different things, like yoga, or tantric breathing, or dance, or physical therapy, but there are various types of techniques that have been found empirically to help people who we would now call having conditions associated with neuroinflammation, either the peripheral or the central nervous system.

We know that the biggest threat to the nervous system is oxygen deprivation, which seems paradoxical when we think of neuroinflammation as being associated with hyperoxygenation, or in other words, peroxidation (oxidative stress). Yet, paradoxically, the times of greatest oxidative stress in the nervous systems occur at times of oxygen deprivation, called hypoxia, so I want you to be reminded of a very simple thing: a person can live for literally weeks to months without eating; they can live for days to a week without taking in water; but they can live for only minutes without oxygen. It's the most critical nutrient of any of our nutrients in terms of its temporal effect on physiology, because we are oxidative organisms. We all know that. Aerobic metabolism is the way we primarily produce our energy by breaking down glucose into energy.

The effect of low oxygen (hypoxia), or in the worst case, complete absence of oxygen (anoxia) is that then the physiology of the nervous system shifts over from oxidative chemistry to what I would call anaerobic chemistry. Anaerobic chemistry produces a variety of secondary metabolites of cellular cytoplasmic metabolism that are acids—we know of lactic acid but there are many other intermediate substances that are acids that are not completely broken down. These change intercellular pH, and they change metabolic function—they poison cells, basically, and the organism, then, because it can't participate in the efficiency of oxidative metabolism, dies of internal toxicity that we call anoxia.

So high oxidative stress is associated with these conditions. You see the most significant levels of oxidants and peroxidized lipids, and proteins, and nucleic acids occurring during times of low oxygen tension in the nervous system. That's why, for instance, in the days of the heart-lung machine and its development, it was so important when you took the heart out of the system and you mechanically

transported blood through the machine and back to the body that you had proper oxygenation. That's also why we have things like reperfusion ischemia as a major problem in this procedure because you get a bolus of oxidants that are produced if you're not oxygenating the blood correctly and that can then put a huge challenge of oxidants on the body when you turn the heart back on (you restart the heart).

I think that all of these are parts of our increasing understanding of this balance between proper oxidation or oxygenation and absence of proper level of oxygen that we associate with oxidative stress. Oxygen and the processing of the oxygen by mitochondria in cells is so important, particularly neuronal cells that, as you know, are generating most all of their energy by the metabolism of glucose (blood sugar). Although the brain represents only three to four percent of the total weight of the organism it consumes 20 to 25 percent of blood sugar and a disproportionate amount of oxygen to power up that oxidative chemistry in the neuron. So as we start to see absence of appropriate oxygen and increasing oxidation—or let's call it inefficiency of mitochondrial oxidative phosphorylation occurring within neurons, we then start to get spin off of intermediary compounds and substances that we call the oxidative stress compounds. So now we get mitochondrial oxidative stress, neuronal oxidative injury, and ultimately this leads to triggering of gene expression of the death genes, so to speak, the caspase genes, and we get apoptosis or neuronal death, and that's what happens in Parkinson's or in Alzheimer's. In different regions of the brain we start getting cell suicide occurring as a consequence of these altered metabolic pathways.

That would then beg the question: In these times of great oxidative stress, what do you have resident (what reserve is resident)? When I say reserve I really am talking about organ reserve, going back to James Fries' concept of organ reserve that healthy individuals have reserves, multiple fold, greater for function of an organ, greater than what's required for homeostasis, and the problem with aging and biological function is we often lose organ reserve so that we don't have the ability to mobilize the reserve when we need it. How does the nervous system maintain this reserve? It does so by what's called redox buffering. I know that's a big chemical term, but what it really refers to is a reservoir of available redox-active substances and processes—enzymatically activated substances or things that can be upregulated as needed, like superoxide dismutase, catalase peroxidase, glutathione reductase, and so forth—that then are capable of accommodating this increased oxidative load, or oxidative stress, in the nervous system. So the body has those built-in mechanisms.

Genes, Environment, and Oxidative Stress

Now as you know, because we are unique each one of us, our genes code for different abilities to accommodate that level of oxidative stress, meaning we have different levels of neuronal reserve, or oxidative capacity to manage these challenges. This has been found in animal studies and in insect studies, even using *Drosophila melanogaster* (the fruit fly).

We recognize that these processes are partly genetically determined, but they are also sensitive to environmental factors. I've already talked about oxygen itself, and the absence of oxygen is like the greatest promoter of oxidative stress. So you might say, "Well, gee whiz, that would mean that anemia might have a detrimental effect on delivering oxygen, so maybe there's an association between anemias and neuronal injury." And, yes, there are some, certainly, examples of that.[3] Cutting off blood supply, like the carotid arteries, doesn't do your brain any good, does it? You start to get neuronal oxidative stress and dementia. We also recognize that heavy metals like mercury, or cadmium, or lead, or excess iron, like you see with various hemoglobinopathies. These also will increase oxidative stress in the

nervous system. We see that various types of petrochemicals, the so-called xenobiotics, will activate the monooxygenases associated with cytochrome P450 that can increase oxidative stress, because we know that cytochrome P450 splits the oxygen molecule, which is a diatomic, O2, into individual atoms of oxygen. That's why we call it a monooxygenase. It's used in oxidizing petrochemicals through the cytochrome P450 pathway, but what happens to the other half of the oxygen molecule? It can become a nascent contributor to oxidative stress. That's why we often think of toxicity associated with hepatic oxidative injury, because during the process of detoxification if there is not adequate protection of the liver, you get increased oxidative injury.

The nervous system—particularly the brain—is unfortunately exquisitely sensitive to these oxidants, because it has…I don't want to call it primitive, but let's call it lower-level antioxidant protection to that of other tissues, like the liver, the hepatocyte. And therefore the brain, when exposed to oxidants, has the potential for greater oxidative sensitivity, and injury, and apoptotic death. Where does that reserve come from? Well, here is the emerging, exciting story, and you're going to hear more about this as we get into the discussion with Dr. Wahls, and that is it has been found that the diet contains a rich array of phytochemicals that play roles in helping to maintain this neuronal reserve against oxidative stress. You might say, "Well, this sounds maybe like a bunch of hand-waving speculation." But actually there are an extraordinary number of good papers that being published recently. For instance, out of the laboratories of Dr. Mark Mattson at the National Institutes of Health, who has been publishing a number of papers looking at how phytochemicals are hormetic in protecting against neuronal oxidative injury, and that people who don't eat diets that are rich in these hormetic dietary phytochemicals, meaning they don't get plant food and they don't get a lot of color in their diet from natural plants, have a decreasing reserve of these important modulators of oxidative injury, neuronal oxidative stress, and at higher risk, then, to injury from neuronal oxidation. A wonderful review paper appeared in *Neuromolecular Medicine* in 2008, volume 10, page 236—this is Mattson and his group at NIH—titled "Hormetic Dietary Phytochemicals," in which they review this whole interesting signaling pathway that these phytochemicals play a role in, the so-called FOXO-NF?B pathway that relates to neuronal oxidative injury.[4]

Phytochemicals and Redox Potentiation

And then we start examining different families of phytochemicals, like the flavonoids, and the polyphenols, and the glucosinolates found in cruciferous vegetables, and we find that each one of those has a different role in influencing potential processes associated with what we used to call antioxidation, but now we call it redox potentiation. For instance, there is a very interesting paper that appeared in *Oxidative Medicine and Cellular Longevity* in 2013 talking about sulforaphane, which you know is in broccoli, Brussels sprouts, and cauliflower, as a potential protective phytochemical against neurogenerative tissues in which the mechanism has been fairly well, now, developed and explicated.[5] So this field of literature is really developing very, very strong support. I'm also interested in work that has been done by a variety of neurology investigators about dietary polyphenols; you know, these interesting compounds that we find in berries, and in various fruits, and to some extent certain vegetables that are extraordinary modulators of brain function. They have biological actions that underpin their action as a redox-active substance and buffer against oxidative stress in the brain.

And then we've got some of these intermediaries, as I've talked about: glutathione and its precursor N-acetyl cysteine, and N-acetyl carnitine, and essential fatty acids of the omega-3 family, docosahexaenoic and eicosapentaenoic (or DHA and EPA), and then alpha-tocopherol and tocotrienols from the vitamin E family, and the rich array of colored flavonoids and carotenoids like astaxanthin. All of these have been examined as potential contributors to providing neuronal reserve against oxidative stress. So I think we are witnessing a very, very dramatic increase in the overall important role that diet and lifestyle play in protecting against neuronal injury. Taking that from a theoretic umbrella of understanding down to the clinical, where-the-tire-meets-the-road, there is probably no better story that we could use to exemplify that than that of Dr. Terry Wahls, internal medicine, OB-GYN physician, whose own journey across this frontier I think symbolizes the extraordinary increasing understanding we have about mitochondrial function, neuronal activity, neuronal death, and the reversibility of many of these conditions by utilizing the appropriate lifestyle/diet to increase neuronal oxidative stress reserve, or what we call redox potential.

With that, let's move to this extraordinary story through the lens of Dr. Wahls personally.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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I have to say this month we're fortunate to not only have an extraordinary clinician, but also an extraordinary thought leader—a person who has really embodied the spirit of what I call research at the fundamental level. This is a very interesting theme that we've had in functional medicine throughout the last 30 years in that research really starts with good observation, and good observation starts with clinicians who understand how to put associations together to form hypotheses, and then from hypotheses how to develop them into models that can be tested and ultimately hopefully lead to outcomes that result in clinical improvement. I would say there is no better example of that model than Dr. Terry Wahls, who we'll be speaking to this month. We're very privileged. You probably already know of Dr. Wahls, her experience and her teachings and her extraordinary lesson for all of us. In fact, I think her YouTube video may be one of the most highly watched medical videos on YouTube. It's absolutely a fascinating journey with her through her own situation with—as she will describe—some her own health challenges.

Just to bring you up to speed, quickly, about Terry Lynn Wahls, who is a medical doctor and an MBA. She graduated from Drake University with her BA, went on to get her MD at the University of Iowa, and has been a very extraordinary contributing member to medicine through her training and certification in internal medicine. She has published highly, nearly 40 publications. She's a renowned lecturer. She is a renowned clinical professor of medicine. And she's a renowned patient as well, having fought her own illness successfully; she'll be telling you her story. I think that her work in OB/GYN and internal medicine probably put her into a very unique position to look at herself and at disease from a systems biology approach, and it's that perspective that she captures so beautifully in her work, and of course in her most recent book, which I think should be mandatory reading—The Wahls Protocol: How I Beat

Progressive Multiple Sclerosis Using Paleo Principles and Functional Medicine.[6] It's an extraordinary read. You're going to hear more about that from Dr. Wahls, now.

Terry, thanks so much for being part of our Functional Medicine Update series. I guess my first question should be, what brought you into medicine, some—nearly—35 years ago?

TW: Well, I started, actually, with a Bachelor of Fine Arts in studio art painting, and then decided no, I was not going to go into graduate school in painting, and went back to science—biology—and that took me around to medicine. I got into medical school not quite understanding just how long my training period was going to be, so I had a little bit of a shock there. It really has been very gratifying, and over time I came to appreciate that my fine arts background (the painting background) gave me a much greater ability to observe the patient and a more thoughtful application of listening than most of my colleagues who had gone through the usual science background to get into medical school.

JB: So as you applied that very, very—I would call it—remarkably broad-based perspective and you started to have experience in the practice of medicine and doing some extraordinary work, when were the first signs that you found in yourself that indicated things weren't going in the right direction?

Multiple Sclerosis Diagnosis Leads to Research on Mitochondria and Bioenergetics

TW: I was diagnosed with MS in 2000, and elected to do the usual conventional medicine route. So I found the best center in the country at the Cleveland Clinic and saw terrific people, took the latest newest drugs, including tizanidine, and I didn't have more acute lesions, but I had this very steady relentless decline. I was told that I had secondary progressive MS. I took Novantrone, I took tizanidine, and continued to decline. The reality that I saw ahead of me was that I was likely to become bedridden by my illness. I was having a lot of brain fog, and so I knew that cognitive decline was likely. That's when I decided I needed to take more personal responsibility, and so I started at first doing searches with the health science librarians, but as I got more comfortable and faster I started doing my own searches through PubMed.gov. I worked very hard to relearn some basic sciences. I started reading the animal models for MS, for Parkinson's, Lou Gehrig's disease (ALS), and Alzheimer's. From that, I started zeroing in on mitochondria and the bioenergetics and what I could do to resuscitate my mitochondria. That was sort of fun. I would see some interesting mouse studies and I would translate these mouse doses of various vitamins and supplements to human-size doses, and then check that against my med list for drug interactions, and start. I tinkered that way for about, I suppose, six months and then decided I was wasting my money and I just quit my vitamins and supplements. And the next day I was too exhausted to get out of bed. So I spent two or three days basically in bed, and then my spouse came to me with my supplements and said, "You know, honey, I think you ought to take these again." So I took them, and then the next morning I felt better. I was able to get up again and go to work. That was a very exciting, empowering moment; like, "Okay, my vitamins and supplements really are doing something here. Maybe they aren't making me recover, but they are clearly helping me in some fundamental way." And so I thought I could at least—with careful attention to the literature—maybe find a way to slow down the speed of my decline. And I did that for the next four years.

But by 2007 I was pretty much in a zero-gravity chair or in bed, so I was declining. I could walk short distances with two canes. That's when I discovered functional medicine. I took their neuroprotection course and had a much longer list of nutrients. I incorporated that into the Paleo diet that I had been

following already for a few years, and when I had reorganized my food to maximize the nutrients that I had learned from functional medicine, that's when the magic really began to happen. In the next year, I went from a tilt-recline wheelchair, to walking throughout the hospital without a cane, and even doing an 18-mile bicycle tour with my family. It completely changed how I thought about health and disease, and of course it changed how I practiced, it changed my approach to all clinical disease, and I became this big advocate for this more integrative approach (functional medicine, therapeutic lifestyle approach) to treating disease by creating health.

Origins of the Term "Mitochondrial Resuscitation"

JB: I just want to take a moment of pause to let everybody who is not familiar with your story to have this sink in because I think it has a deep and profound important message that hopefully gets beyond the first layer of the cerebral cortex of our listeners. It's a profound example of why I believe network physiology and systems biology is the way to be thinking about complex chronic illnesses, and your journey, and your pursuit of an understanding is a model for what I believe needs to happen throughout all sectors of our healthcare system so that we start really looking at some new truths that are emerging from discoveries that have been made over the last 15 to 20 years. I was very intrigued and pleased to hear you use the term "resuscitation of mitochondria." That was a term that was really born out of Functional Medicine Update in an interview we did with Paul Cheney back in the 1980s. It really started to resonate much more in the 90s when we founded the Institute for Functional Medicine, and one of our core principles was mitochondrial bioenergetics. We chose the Paul Cheney concept of mitochondrial resuscitation as kind of a thematic buzzword for what we were trying to achieve. I think that this construct that you've come up with of food, lifestyle, and supplements patterned to the individual need is a profound paradigm-shifting concept. It's born out of obviously many people's work previously, so it's certainly not a de novo new discovery, but I think the way you've applied it is a truly remarkable revolution in thinking in medicine, so I hope everyone just had a chance to allow your very easy way you present this to sink in deeply beyond the first layer of their cerebral cortex because it's a profound statement.

If I can ask a follow-on question, as you got into this—and I actually remember our first meeting, I think you were still in a wheelchair at that point, coming to some of the education events of functional medicine and were probably on your path to recovery or improvement—what were the steps along your road of recovery that gave you a sense that you were on the proper path, and how did you kind of make your own iterative adjustments as you moved down the path?

How Dietary Choices Influenced Multiple Sclerosis Symptoms

TW: Historically, in about 2002, I quit gluten and dairy and began a Paleo diet (so vegetables, meat, fish, eggs). That's what I consumed, but I continued to decline. In 2004 through 2007, I'm doing literature searches and adding vitamin supplements as I'm learning about them, so I'm adding more B vitamins, CoQ, lipoic acid, carnitine, creatine, omega-3s, and it certainly slows the speed of my decline, but I'm definitely still declining. Then when I had the neuroprotection course, it really deepened my understanding of molecular mimicry, gut resuscitation. I did some basic food sensitivity testing and found out I have a severe sensitivity, also, to eggs, so I took eggs out of my diet. I had a list of about 20 compounds from my research and the functional medicine neuroprotection course, so I added those. Really the magic happened when I did some more investigation on where these compounds were in the

food supply and reorganized my diet so it was focused entirely on creating the most nutrient density I could for the nutrients that were key for brain health. And it was really quite dramatic. I mean, my diet was really very good beforehand, but I took it to a new level, and within weeks my energy was steadily improving. My mental clarity was steadily improving. I also have to say that parallel at the same time, I was doing sort of a radical new treatment with neuromuscular electrical stimulation to my muscles while I was exercising. For the first time in many years I was able to sustain an exercise program, which also, of course, is very helpful for my brain as well. I got to experience intellectually what I thought was going on biochemically. Early on I would occasionally think, "Well, I could have a dietary indiscretion occasionally," and, at least for me, within 48 hours I would have a severe flare of my occipital neuralgia, which is horrifically painful. I learned early on that I was not going to stray from my dietary regimen because my energy dropped, and I had horrific pain that would take a course of Solu-Medrol to stop.

Pilot Study on 20 Patients with Progressive Multiple Sclerosis

The other thing that I, of course, wanted to do was test if this protocol could be adopted by others and what would it do for them. We wrote up the protocol. I went out and secured one hundred thousand dollars of funding for this pilot study, which we have now been doing for just a little over three years. I've got 20 other individuals with primary progressive/secondary progressive MS who have done my protocol. The last person is going to finish up in December. What I can tell you is people can adopt this very complicated regimen; they are willing to do it. The inconvenience is if you are overweight you'll lose weight, and there will be some dietary adjustments that will happen, so you have some GI distress initially. Some detox certainly happens to pretty much everyone, but there are no serious problems in terms of any kind of kidney damage, liver damage, heart damage. People's health indices all improve—their CRPs, their lipids, their cholesterol profile, their insulin sensitivity, homocysteines, all of that improved. Fatigue markedly improved. Gait is sort of variable. The reasons we can't walk with MS, of course, are quite varied, so not everyone improved their gait. But we do have some people who went from needing a cane to jogging within 12 months. There were some people who were able to experience really radical transformation of their health status, and others who experienced a more modest transformation of their health status.

JB: I think you're describing beautifully why I'm advocating so strongly that people read your book The Wahls Protocol. I think it really helps to provide the substance for people really starting to get started with this program. It's wonderfully done.

The Wahls Protocol: New Book Can Be Used as a Guide for Transforming Your Diet

TW: Yes, it's really quite remarkable. In The Wahls Protocol I lay out the science behind why we designed the protocol the way we did. We give people a very detailed step-by-step plan for how you would begin to implement and how you can transition from the standard American diet to a progressively more nutrient-dense, mitochondrial resuscitation-oriented diet and lifestyle plan. And we applied a lot of information for clinicians who are going to want to take this information and use it to transform how they think about creating health, and anyone with any type of chronic disease, whether it's an autoimmune or a disease that we don't yet think of so much as autoimmune, such as obesity, diabetes, or even heart disease.

JB: I want to make sure everyone understands its W-A-H-L-S—Wahls—protocol. I highly recommend it as

required reading. Let me ask you a follow on question. You're a professor—a clinical professor of medicine—at the University of Iowa College of Medicine, so you have peers that obviously knew about your illness, and were undoubtedly supportive in providing council and so forth. And then you made this decision as to how you were going to manage your trajectory and your journey with this illness. What kind of support/inquiry/interest/intellectual curiosity…whatever you might say the Zeitgeist of your environment…what was the kind of response that you were getting from your colleagues?

TW: As I declined, the university and the VA were extraordinarily generous in redesigning my job multiple times so I could continue to work. One of the things they did was they put me on the Institutional Review Board, so I was reading research and I asked, "Give me all the protocols having to do with the brain." That accelerated my understanding of brain physiology greatly. As I recovered, that was the summer that I was up for promotion, and yes, we have a promotion talk. You normally give a talk about your active research, but I decided instead to do a case report on myself detailing what happened to me, what my intervention was, and reviewing what I thought were the likely mechanisms behind my recovery. Then I added a proposed clinical trial to test whether or not these interventions would work in others. The promotions committee thought that was so interesting they suggested I give it in Grand Rounds to the entire department, which I did a couple of months later. That, of course, generated quite a buzz. I'd say about half the audience thought this was the most brilliant and most engaging Ground Rounds they'd ever seen, and the other half thought I was a nut and should be thrown out of the College of Medicine. That Ground Rounds let me attract a few more senior scientists to help me craft my study design and get it through our Institutional Review Board. They helped give me some suggestions on my grant writing and I got off a grant and came back with the funding so we could start the study. And then, twice a year we have Research Day, so we can have a poster up that presents the status of our research findings, and so people are seeing that, in fact, people can comply with this complicated regimen, that we are able to create this radical improvement in dietary intake in terms of the nutritional quality, and this very striking improvement in fatigue and cognitive performance in these individuals. And now that I can show these videos of how people's gaits were are the beginning and what their gait looks like at 12 months, I'm getting more and more recognition by the university. In fact, I've been nominated by the university as the University of Iowa's nominee for the 2013 Women of Innovation Awards in the state of Iowa. That organization asked me to be the plenary speaker. I think more and more people at the university and here at the state are recognizing the incredible brilliance of this very complicated, very messy, whole-systems biology approach that I'm doing, and that instead of this little tiny incremental improvement, I'm showing this radical improvement in health, which is probably the best way to treat, frankly, any of our chronic diseases that I treat in my primary care clinics, or in my traumatic brain injury clinic.

JB: What a remarkable story. Talk about motivating. Congratulations on every level, first to you personally and then second how you've been able to leverage this and make it available as a broad-based opportunity for many others who I think will follow in the wake and hopefully as more is done in this area we're going to get more "proof of concept" and more validation and those people that thought you were a nut either will retire out of medicine or be transformed and say they always believed that this was the best thing that could happen. That seems like the nature of the history of what we've observed over the years. Tell me a little bit about your support group, because obviously these are some fairly major changes in lifestyle and how you divvy up your time on a daily basis in terms of food preparation and thoughtful construction of your program. What would you say about people who are heading down this path as it relates to the development of their support group?

Wahls Protocol Study Design

TW: We have some tools that were very helpful in our study. We created a daily log so people would know precisely what food groups to eat and how to hit the nutritional goals every day. We also had them log every day their stress-reducing activities and their exercise and ESTIM. In the first two months, I had a coach for the exercise call them (the study participants) every week, and the nutrition support called them every week. We saw them at month one, month two, month three, then month six, nine, and twelve, and I would saw generally by three months people really understood the diet and the lifestyle. We had them complete the medical symptoms questionnaire monthly, so we could see that those numbers were continuing to improve, and whenever they had a bump, that was a sign for us to really explore with the study subject what was going on—where there was unresolved conflict. Was there a new infection issue? Or had they been feeling so well they thought they could begin to have a few splurge foods that created some nutritional compromise? I think the daily logs are very important. I think doing this as a whole family…and we explain that when people enroll—that it's a family commitment and if the whole family is not ready then they are not ready to be part of our trial. Actually it's really been pretty fun. So we watched the transformation of the subject, and then we also see this transformation of the other members of the family as they, too, adopt this very nutrient-dense diet, and their lives are transformed as well. Emotional support is very, very important to be successful here.

Paleo Principles and Nutrient Density

JB: Let me, if I can, follow on also on your really insightful comments as it pertained to the difference between taking, say, purified nutrients as pharmacological adjuncts or as tailored nutrients versus delivery of a high-nutrient density diet, where you saw your improvement markedly enhanced. Do you feel that this has to do with—and I'm probably asking it for some speculation, so I apologize—do you think it has to do with bioavailability, do you think it has to do with the complex nature of food versus individual supplements used as therapeutics, what's your view as to the benefit of the food versus the supplements alone?

TW: I think when we look at, for example, hunter-gatherer societies around the globe, they all have very different actual food stuffs, so what you do is a nutritional analysis. There are always one-half to ten times the RDA depending on which nutrient you're looking at. Ideally we want to have the most nutrient density we can per calorie, but since we are using agricultural foods instead of wild foods it becomes a lot more complex to figure out how to best organize the food to get the maximal nutrient density. And when I get the maximal nutrient density from food—we'll take some of the B vitamins, for example, or the antioxidants—in food there are thousands of other related compounds that will also interact with my cells, and I'm more likely to get nutrients in appropriate ratios, so I don't accidentally create an imbalance, say, of zinc because I get too much copper, or an imbalance of vitamin K because I get too much vitamin A. I think food provides additional compounds that are related, and it puts the nutrients in the balance that's more optimal, so you don't accidentally create compromise because you've got things out of range.

Multiple Sclerosis Research and Mitochondrial Function Linked in the Medical Literature

JB: I think that's a beautiful way of describing it. I'd like to do a little fun thing with you, here, if you wouldn't mind, and just take you through a couple of recent 2013 publications in this area of MS and

mechanism and its relationship to mitochondrial function, and get your comments. I know you've become an expert in this and I thought just giving a couple of parenthetical comments might be interesting. There was a model study just done in primates published in Frontiers in Physiology. This was work done at the Oregon Health Sciences group in Portland, Oregon. What they have demonstrated is this redox model for mitochondrial dysfunction appears to relate very closely in a primate model for MS, and they actually in this publication which appeared in the July 25th issue of 2013, have a very nice figure in which they talk about the MS disease process related to cellular endoplasmic stress, and the release of reactive oxygen species and how that activates certain kinds of intercellular signal transduction processes that ultimately influences mitochondrial complex I/complex II activities and becomes almost like a dog chasing its tail.[7] The person gets locked in to a self-perpetuating mitochondrial neuronal death spiral. Tell us a little bit about how your review of the literature tracks with that model and how it relates to your program.

TW: Well, I think mitochondria are absolutely key. When I was looking at this back in 2004, I saw that apoptosis/mitochondrial strain/excessive oxidative stress was being talked a lot about in diseases of neurodegeneration. People were not yet relating that—at least that I could find in the literature—in MS, but since you had steady indication of atrophy of the brain tissue and spinal cord in MS, it just seemed logical to me that apoptosis and oxidative stress were likely a big factor in MS. That's why I got into trying to understand what I could do to provide for the support of the mitochondria. I was doing it kind of piecemeal by piecemeal until I discovered functional medicine and really had, I'd say, a much more comprehensive toolkit for the mitochondrial resuscitation at that point.

JB: So that then leads us to the next question and that is, okay, if mitochondria are a potential target organelle that relate to the etiology of MS, then we might say why do some people get it? Is it a genetic sensitivity of mitochondria, or is it induced somehow by events that occur throughout the life of the individual? There are a couple of papers that have appeared recently that suggest that maybe both those models that I just suggested are present. One is a paper in Genetic Molecular Research in 2013, September issue, looking at mitochondrial nuclear genes as a cause of complex I deficiency in MS, and found there are some genetic sensitivities apparently to complex I activities, meaning there are different genotypes that reflect the phenotype of complex I activity.[8] And then another paper that I think follows along with that is in the International Journal of Molecular Science in October of 2013 looking at the pathogenesis of complex I/complex II problems in MS pertaining to petrochemical byproduct exposures, things like acrolein, and things that could initiate interruption of mitochondrial complex function and induce oxidative stress, so it would appear, from my reading, that there is evidence of both genetic susceptibilities coupled with environmental triggers. [9] Does that seem consistent with what you've read?

TW: Correct. And in my book what I talk about is there are about 100 genes that have been identified that slightly increase your risk of developing MS, and so it's your total burden of genetic SNPs that have increased your risk, plus your total burden of environmental exposures as your diet, toxins, stress level, exercise level, etc. So if you have a smaller number of genetic risk factors, it's going to take a higher dose of environmental problems to create a syndrome that will be diagnosed as MS. If you have more genes that increase your risk, it will take a smaller dose of environmental factors. And I also talk about there are probably an infinite number of ways to develop the damage that will be diagnosed as MS. This could come through a predominance of genetic risk factors, or it could come from infective factors, or mostly toxin factors, or a combination of all of that. There's never going to be just one path that explains

all of MS. That's never going to happen. This is a syndrome of many kinds of diseases that have many different ways of acquiring this symptomology and structural change that is diagnosed as MS. So a broad-based supporting of the environmental factors is a great way to start, and then if you don't get the full response that you're hoping for, then absolutely the person is going to need to have more detailed functional medicine testing to tease out what the burden of infection is, or the burden of toxins, or that there may be some truly exceptional nutritional needs to bypass some of the SNPs.

JB: I think that was a brilliant summary of so much information. I really appreciate the clarity. You know, it's interesting when we think back—again I'm thinking of the evolution of the functional medicine model to what I call the three Hs, or H-cubed, that was Heaney, Holick, and Hayes, who were our vitamin D triad that really set, I think, the tone of vitamin D as more than a nutrient for bone as a very important immune modulating nutrient. We're very fortunate. This was probably 15 years ago when we had the three of them present at our IFM symposium. Of course, Elizabeth Hayes was talking about her role in animal models—the EAE model of MS—with vitamin D deficiency, and providing a putative mechanism as to how vitamin D deficiency could result in MS-like symptoms and animal models and how that may connect together with the etiology seen in humans, and latitudes, and so forth. As you're pointing out, there are probably many paths that a person could be on that would lead to a diagnosis of what appears to be a singular disease coming from multiple etiological contributors, of which maybe vitamin D would be another thing in the laundry list of factors to evaluate.

TW: Yes, absolutely.

JB: There's another interesting paper, which I think is so wonderful because many times a hypothesis—and I'm using that term guardedly here as it relates to your observations and your program—would be valued when a person says, "Well, there's a respected animal model that's been able to demonstrate the proof of concept in reproducible controlled studies." Of course, this EAE model is the one that has often been used as the animal model in MS. That's the Experimental Autoimmune Encephalitis in mice. So there's a very nice paper that was just published in September of 2013 in what I consider one of the premier biochemistry journals, Biochemical Biophysical Acta, in which they actually report, using this EAE model of MS, on a mitochondrial resuscitation program using the nutrients that you've described against placebo controls and showing very dramatic improvement in function in these animals that go on and get these spontaneous MS-like symptoms.[10] It appears, now, we have a pretty good animal model that shows mitochondrially targeted therapy actually delays the progression and alleviates pathogenesis of MS. I think this type of work you must feel very good about.

TW: Yes, yes. I'll have to go find that paper. That sounds perfect.

JB: It's page 2322 of volume 1832, September of 2013. This work actually was also done at the division of neurosciences at the Neurogenetics Laboratory, Oregon Primate Center, in Portland. I think it is a very nice study design showing really remarkable (in that animal model) proof of concept.

TW: We have a lot of frozen blood. We're waiting until the last person gets through December, and then we'll begin to discuss a plan for what type of analyses we'll be doing in terms of monitoring how things have changed biochemically. I've got the head of the immunology department, and the head of our anti-aging department on the study team and we're having those conversations now about what further analyses we are planning, so we can go write the grants to get the money to do that as well. It's very

exciting stuff.

JB: It's more than very exciting; it's revolutionary. Again, I want to tell you how much we appreciate you sharing this journey with us. I think, you know, you're very courageous, not only in the way that you've approached your own health, but the way that you've been willing to share what I know has been at times probably extraordinarily frustrating and challenging for you, and opening yourself up to your journey so that other people can learn from it, and helping us to understand what it takes in terms of a support team and lifestyle changes and a dramatic re-patterning of our thinking in order to make this paradigm-shifting outcome. You're a model for us all, Dr. Wahls, and we can't thank you enough for sharing your experience with us.

TW: Thank you. Thank you very much.

JB: We wish you well. Is there anything you'd like to saw to our listeners, most of whom are obviously clinicians who are probably being very inspired by what they are hearing from you? Anything that you would give them as juice to move forward?

TW: I'd encourage them to get to my website—explore that—so they can share that information with their patients to help them get fired up and excited and see the initial steps and all of the stories from other people that have had their health transformations. We could, in theory, train an army of what I affectionately call the "Wahls Warriors" that are out there learning that food, and nutrition, and lifestyle is the real key to creating health and eliminating disease.

JB: You're the model—the quintessential model—as to why we started the Institute for Functional Medicine in 1991, and we hope that we can replicate your experience in millions of people over the years. Thank you very, very much and the best to you in all that you are doing.

TW: Great. Thank you so much.

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