December 2015 Issue | Michael Stone, MD and Leslie Stone, MD

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Hey, here we are at the year-end December 2015 *Functional Medicine Update* and, oh my word, do we have something in store for you and me as well, and that is a discussion with two of my favorite clinician/functional medicine resource/thought leaders/extraordinary parents and citizens, and that is Drs. Michael and Leslie Stone. If you are in the functional medicine community both their names are very well known.

Just to give you a quick background of the Stones, they both were University of Washington Medical School graduates. Michael came up through Washington State University. He was at Washington State and got his Bachelor's and Master's in nutrition there. Leslie did work in psychobiology at Washington State, so presumably many years ago—we won't say how many, but a couple—they met and later then became husband and wife and have practiced medicine for many years. They took over Dr. David Jones's practice in Ashland, Oregon to free him up to become the president of the Institute for Functional Medicine, and they have done an extraordinary job in Ashland after being in practice in Idaho for a number of years prior to that. They are both extraordinary thought leaders, as you know, in bringing their background and vision as it relates to how to do good medicine into the training of practitioners coming up the ranks in functional medicine.

FMU Closes One Chapter and Begins Another

I've asked them if they would be our celebratory last clinician-of-the-month interview in *Functional Medicine Update* under the terms and conditions that we have done it for 34 years, which has been a subscription-based service that Jay Johnson and I have been producing. Hard to believe 34 years, so since 1982, without the loss of a month. That's a testament, probably, to Jay's and my endurance, because there have been times where we probably would have liked certain issue to have passed, but we've been very fortunate over those years to have an extraordinary number of thought leaders that passed over our frontal lobes, and really I consider myself a mosaic of those many, many people we've been privileged to interview.

I thought the Stones would be a perfect vision of what we've been trying to accomplish in *Functional Medicine Update* all these years, not just because they're experts in the field, but also because they represent everything from pre-conception care up through conception, infancy, childhood, adolescence,

young adult, adult, mid-life, older age, geriatric, and end of life. They are really the quintessential examples of where functional medicine really applies, which is throughout the whole life process, starting even pre-conceptionally. That's a topic that we don't spend a whole lot of time over the years actually exploring, and there's no better place to explore it than with Michael and Leslie. And in fact they were authors of what I think is an extraordinary study that was published recently that we'll talk about. This is titled "Customized Nutritional Enhancement for Pregnant Women Appears to Lower Incidence of Certain Common Maternal Neonatal Complications."[1] I think that that title alone gives you the landscape of what we want to talk about over the course of the next, say, 50 or so minutes.

Both Leslie and Michael, welcome to *Functional Medicine Update* and thank you so much for being the last of our 34-year process as we move into this open-access in 2016.

INTERVIEW TRANSCRIPT

Clinicians of the Month

Michael Stone, MD and Leslie Stone, MD

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MS: Well, what an honor to be on this program with you and we've talked to so many people who have been influenced and their lives have been changed and there are thousands of patients that you've touched through this work, so everyone on your production team and you bringing this stuff forward so people can listen to it and apply it every day, Monday morning, as we say, has truly changed hundreds of thousands of lives and we just honor that, for all that you've done. It's a wonderful vision and just a great, great, great service you've provided.

LS: Absolutely, thank you.

Diversity in Undergraduate Training Lays Foundation for Functional Medicine Path

JB: This is kind of the proverbial starting place because some of our listeners may not be so familiar with how your journey in life got you to this point where you've really refined your model and you're applying it and you're recognized opinion leaders. I mean, we start off on a journey and we're not sure exactly where it's going to take us, so maybe, Leslie, we can begin with you and this background you had in psychobiology. I can identify with that, actually, because one of the most interesting courses I took as

an undergraduate at the University of California at Irvine was in psychobiology with Dr. Weiner. We did animal taxonomic surgeries and things, and I'm thinking back to how extraordinary that was in enlightening me to how things like taste, and thirst, and all sorts of biological functions are tied to perception and neuroanatomy. Tell us a little bit about your background. How did you get from where you were to where you are today?

LS: Well certainly my initial interests were in large animal veterinary care. It turns out my undergraduate research took me to the vet school, which was looking at behavior of dry- versus wetland rodents, and I think this is at a time period when neurochemistry was just a new thought, and the idea that we could measure different neurochemicals in specific areas of the brain, isolate their pre- and post-synaptic locations, and be able to predict or describe their behavior was novel and new and quite exciting.

JB: So from there, what got you then to say, "Okay, medical school is where I'm going to take this background and training," and then from that into where you have found your niche and ultimately to Ashland, Oregon? How did that travel for you?

LS: So, my interests have always been based in that concept of what is it about us—biochemically, neurochemically—that is both impinged upon our behavior but also predicts our behavior, drives our behavior? That seemed to translate very much to me in that early developmental time period. The question was always, in my mind, as we were going through the education process learning how to take care of patients, why is it we do what we do, and how is it that I can influence that? It became more obvious to us that as technology allowed us to understand the influences on behavior, such as that early undergraduate research, morbidities that we had accepted as static and unchangeable such as hypertension in pregnancy, such as diabetes in pregnancy, such as these chronic diseases of aging, instead of accepting those as static and unchangeable, that by influencing our health in a pre-conceptual manner in those early time periods—that plastic time period—that we can truly impact our global health. This came to us over 30 years of observing maybe not the fastest change in health that we really wanted to achieve, and yet not being willing to accept that as something that was unchangeable. The good news is we do have some tools in our toolbox that let us investigate and drive change that is going to improve our health in first and second generations.

JB: That's a powerful summary. Maybe I could just ask you a quick sidebar: What made you then decide not to, say, go into OB or pediatrics, and to stay in family practice?

Family Practice: The Magic of Caring for Patients at Every Stage of Life

LS: Well, I'll just take it from a personal note, and that was I did take it into OB/GYN initially as an intern, and I came to the end of my internship year, and having been totally enamored with the concepts of reproductive endocrinology and all of the shifting remarkable mutable changes of physiology throughout the woman's body and the changes that happen with development, and found that, boy, at the end of that one year I have to say goodbye to the concepts of what happens next to that neonate as an adolescent and as an adult and as one of our treasured elders—what happened to them and how did what I did during this one year with their lives impact their future health? As an obstetrician I was not able to ask those questions or observe those questions and be able to see what it was that was going to make a difference—a true difference—in their lives. And so I stopped and decided to go into family practice because I knew that that was something that came across the life cycle. And of course that combination,

along with an additional education experience in high-risk obstetrics, gave us that unique perspective that says all that we do pre-conceptually, which for me starts as soon as that baby is out of the womb all the way through to the point where they are now of reproductive capacity—all of that plasticity impinges on that health. I think of that neonate as an 85-year-old healthy elder.

JB: Yes, I have to honest up to you and do a mea culpa here. The reason I asked that question, which you and I have never spoken about personally nor did we do any preparation on this, was because my intuition told me that you were going to answer that question exactly as you've answered it—that your thought process was the timeline approach. I guess I give myself a gold star; I must have hit the right intuition.

LS: You're right, the concept of timeline, of context, of each event impinging on the next, that's exactly how to think about this, and our position here gives us a unique perspective to be able to observe and query it and ask it and demand more of it. I mostly deal in a low-risk obstetric process population, but for the most part even those morbidities that we were experiencing seemed like they just didn't change and so we really needed another way of making a difference in those lives. We needed another way of asking the questions, another way of intervening on those answers, and remarkably I believe that we have some really different outcomes.

JB: Thank you. Michael, let's move over to you. A Master's in nutrition…clearly you had some thoughts as to where your professional life was going to take you at your completion of your work at Washington State. So how did that then travel into your medical school training and how do you think that that forged your template—your epigenome, so to speak—as you moved forward?

MS: It was very impactful because I always say that my undergraduate/graduate degrees and training in nutrition in which we spent laborious hours in pathophysiology of nutritional and medical issues with some brilliant professors in nutrition was so influential because once I made a shift to human nutrition from zoology at Washington State University I was suddenly in a very applicable, bite-by-bite world of understanding. Through my Master's work in which I dove deeper into the mesenteric work—I looked at rats and seeing how they adapted to different monosaccharides and disaccharides—and I got into the University of Washington School of Medicine, it was really washing my medical education over my nutrition foundation, and so I saw things differently.

JB: Yes, I bet you did and I bet your fellow classmates probably wondered why the heck you were asking or thinking about certain things that were not even on their radar screen, I have a suspicion.

MS: Well, that's true. In fact, one of my summer projects as a TA was to help assess the nutrition knowledge of the third- and fourth-year medical students and residents at the University of Washington. I documented that and in the whole curriculum, if you cobbled things together, there were only 15 ½ hours of any nutrition exposure during the whole medical school experience at the University of Washington, which wasn't necessarily taken kindly to as I brought that forward as maybe something we should change. But then what really totally changed my life and perspective was when Leslie was starting her fourth year of medical school and I was finishing my first year of medical school we were at the headwaters of the River Kwai on the Thai-Burma border. She had a lot more experience and had a lot more rotations under her belt, so in a one-doctor hospital with two hours of electricity a day through a generator and a hand-crank centrifuge she could participate primarily in surgery and all that, and for me, I was an observer. But my task was to do a nutrition assessment on all the children in an orphanage in the

Karen tribe—over 250 kids—and trying to do a nutrition assessment on those kids with the same gifts and tools that the physicians of the millennia had: they had their eyes, they had their ears, they had their sense of smell, they had the ability to look, listen, feel, and in this case, set out difference bowls of food to try to do, through a translator, some idea of a 24-hour recall. And the results of that experience, with a hanging scale and a hand-crank centrifuge if the child had to have a formal hematocrit checked, really catapulted me into this love and appreciation of the physical exam. So we could take those tools, and eventually, through a functional medicine model, begin to develop points of connection. So between the patient's context that you see this physical exam finding, the context of their story with the company that it keeps, you immediately begin to tie it to the quality and quantity of their lifestyle and diet. We can take the same launch point and we can begin to see more through our understanding of epigenetics and the genome now. I would say that the nutrition foundation, washed over with the medical education, and then catapulted forward through the functional medicine model has totally changed how we communicate and how we see the patients.

Development of a Nutritional Enhancement Program for Pregnant Women

JB: Well now I want to thank you both. That was a really great landscape understanding of this extraordinary training and background that you bring into your work and how it has evolved over the decades now. I'd like to take you both back to a little story that you may not be familiar with, and that's a David Jones story—Dr. David Jones, your colleague there in Ashland. David and I were speaking—and I'm going back now to the early 80s, actually—and we were talking about an impact that Dr. Brewer made on him as it related to toxemia pregnancy. As I recall the story—and this is coming from memory—when he was a medical student at the University of California at Davis he was very impressed with the work that Brewer had done on trying to reduce the adverse effects of toxemia pregnancy through nutrition and he was considered to be a heretic in his own profession as I recall (Dr. Brewer), and was excoriated for whatever reason that this was not how you reduced hypertension and preeclampsia and so forth, and eclampsia was not a nutrition-related problem.[2] Now we move up to 2015 with what you all are doing in this nutritional enhancement program for pregnant women to lower both maternal risk and neonatal risk, and it seems like we go back to the future; we learn old things in new ways and support them. Am I making a story, here, that has any sense from your perspective?

LS: Absolutely. I know that even currently the concept that we can manipulate the expression of our genes, that we can manipulate the enzymatic activities in such a way as to promote or reduce the morbidities in pregnancy and developmental programming is a concept that is hard for people to wrap their brains around. You know, it still remains so, and yet we now have available to us great epidemiology that what we do in this peri-conceptual time absolutely without a doubt influences our chronic diseases as we age. That leaves the question hanging out there: Okay, then, if our nutritional and our stressor inputs during this very plastic time period…if it can give us a deleterious outcome, that means that it can be manipulated and if it can be manipulated for the worse, it also means it can be manipulated for the better. And that is what actually provoked us to take a look and say, okay, where are the vulnerabilities in that peri-natal time period? Where are they? Because you're obviously not looking at them now. Let's find them. And, as a course, as a happenstance of where we are in our technological timeline, it turns out that we do have a human genome from which we can draw enormous amounts of data that apply to how we are intervening, that if we can do it prospectively and say, "Oh, we now know that if you have certain constellations of single nucleotide polymorphisms, we already know their metabolomes." We know where we ought to be able to intervene, and then all we have to do is take that

and apply it and say, okay, here's the study population that has nutrient sufficiencies that let them be vulnerable, and then here we have the ability to take a look at their genome in a small way—we're not where we need to be, we're not going to be as good as we are in the future, right, but we can still take a look right now—and apply that information, and lo and behold, get better outcomes in our immediate measurement tool, which is in the health of the mother and health of the neonate.

JB: So let's take that from the broad brush into the more specific, because when you talk about customiz[ing] that sounds like some degree of personalization, so the questions we ask determine the answers we get, so if you want to be personalized you're going to have to ask probably a different set of question than you'd ask just for one-size-fits-all. How do you actually approach this? What's the schema that led to development of your program and ultimately to your study?

MTHFR: A Metabolic Kingpin

LS: Well, as we've learned more about the genome itself and specific single nucleotides, I think the kingpin for us was a single nucleotide polymorphism: MTHFR. And we realized because it is such a centerpiece in setting the pace on many, many metabolisms in the body—you know, inflammation, detoxification—we realized that would be a great place to start, and we knew enough about what its predispositions would be. If somebody had an MTHFR single nucleotide polymorphism we knew that they were going to be at increased risk for such things as Alzheimer's and such things as depression, and autism, and several other issues. The most important sentinel study that I think I'll let Michael talk about was certainly about the risk of autism in the face of an undernourished population: a mother who is not receiving B vitamins in the proper amounts, and if she has a certain set of polymorphisms and her offspring has yet one other, then the chances of that baby developing autism is dramatically, dramatically increased.

MS: Yes, that was a study out of UC Davis, and I would say that was one of our go to papers. It came out in 2011 in Epidemiology, and it was looking at one carb metabolism in prenatal adequacy of methylation factors. It looked at whether the mom had MTHFR homozygous recessive along with cystathionine beta synthase and if the fetus had certain CMT SNP.[3] If the mother didn't have adequate methylation factors three months prior to conception and one month after then there was this increased relative risk of autism in the offspring. Now, that combined with our population here in Ashland really having significant insufficiency of vitamin D, along with our growing understanding of the role of carnitine and the carnitine shuttle and free fatty acid elevations in early pregnancy turning on IGF-1 issues and the whole interplay between IGF-1 and IGF-2 is setting people up for gestational diabetes and the frequency of MTHFR heterozygosity/homozygosity in our population. With the understanding and our assurance based everything from socioeconomic disease the diet was worsening, we posited that our population would be nutritionally insufficient, and so we started looking at just the basic SNPs (MTHFR, COMT), we started looking at zinc levels, vitamin D levels, we were doing diet records and seeing that their essential fatty acid levels, magnesium levels, were low in their diet and we started looking at carnitine levels.

What we did is with clinical nutritionists in our clinic, Emily Rydbom and Lindsay Jones initially, we really started trying to put together how could we educate the moms? How could we bring this forward in such a way that was empowering and we could start seeing shifts in not only the degree of morbidities during pregnancy, but how could we improve outcome? And so to answer your question, we had a very finite number of things: we looked at COMT, MTHFR, we looked at SNPs 1298 and 677, and then we

started doing a few more additional labs. We call it the standard of care plus, so our plus was checking zinc, and carnitine, and 25-hydroxyvitamin D levels, and being more aggressive about augmenting nutrition in the different trimesters, focusing on whether it's organogenesis or proliferation, and then really in your zinc, and vitamin A, and magnesium, and essential fatty acid low patients, putting together supplement bridges and food bridges through education that would allow this to happen.

JB: Wow, every neuron in my frontal lobe is lit up if we were doing some kind of a scan here—a spectral scan—because I'm being taken back by this discussion, believe it or not, to 1985 FMU: Dr. Derrick Lonsdale, who was our clinician of the month. I don't even know how I remember this was 1985, but it's just beaming through. Dr. Lonsdale at the time was a professor of medicine at the Cleveland Clinic. Later he went into private practice, and his colleague was Raymond Shamberger, who was his laboratorian, and they developed a considerable body of data about preclinical beriberi and preclinical pellagra and its effects in children. And they published, actually, a paper in the American Journal of Clinical Nutrition—I think it was 1981 or 82—and they talked about this condition.[4] They proposed that psychological disturbances occur in these children well before you would ever see frank signs of beriberi or pellagra. In fact Victor Herbert even wrote a rebuttal to their paper—I recall it in the same journal—saying that this was an interesting observation and was probably not true because you only have vitamin deficiency or sufficiency, you don't have any intermediary states, but I think we've proven over the years that's not true. So you get into the question of what is a deficiency and what is an insufficiency, and that's what you guys are really pioneering. And then even to go back to Leslie and your point about MTHFR, we now recognize that there are a number of polymorphisms within any specific gene, and some have different penetrance to the phenotype than others, so with MTHFR you have three or four major types of SNPs—maybe CT677 is the major, but there are several others that can also participate. So if you've got several SNPs in your MTHFR, which is certainly possible and people do have that, it becomes a loaded dice with increasing frequency into the phenotype, and now you have this graded response, right? You're still not deficient, but your levels of insufficiency become more tissue specific, and I think that's what you are speaking to and it's a brilliant evolution of the model that, when we didn't have these tools of nutrigenomics back in the 80s, that people were observing just phenomenologically.

Nutrient Deficiencies are Alarmingly Common in Healthy, Well-informed Communities

LS: Yes. You know, I think the other piece of this that alarms me is that as we began looking at different nutrient insufficiencies/deficiencies and struggling with that definition, we found that even if we used a standard definition of deficiency—a laboratory definition of deficiency, not a functional one—we've found that, remarkably, in our healthy, middle class population here we had a large story here—the underlying, seeded story—is that we also have those kinds of deficiencies that in my mind should never occur in a healthy, smart, educated, activated community. We found that 60 percent of our population were laboratory zinc deficient. Well, if zinc is one of those enzymes that is required in over 300 different metalloenzymatic reactions, and we know—to emphasize that further—that it's the neural development, and we actually demonstrated that we have these deficiencies, what about that functional deficit that we are leaving out? If we don't treat that, what does that mean for the intellectual capabilities of that offspring? What does that mean if we're not investigating and intervening in these underserved populations? Are we holding them under the thumb of their underprivileged, nutrient-deficient beginnings? We have something that is malleable that we can deal with, and we've got to get in there and get it done.

JB: Well, Leslie, if I can just once again throw a parenthetical in here…this is really so much fun for me because in 1987 we interviewed K. Michael Hambidge at the University of Colorado School of Medicine pediatrics department, who at the time was the reigning expert in zinc and development in children. He had published a number of papers on Hispanic children in the Denver area and had shown that short stature for age was tied to their zinc status—that these kids just weren't born with genes to make them short.[5]

LS: That's right!

JB: So here we are…this is 30 years, right? It's even scary for me to say this—30 years ago ago—that this thing has evolved to where now you have really codified this. This is the back-to-the-future ah-ha.

LS: This is the moment. It seems like all of these giants, all of these thought leaders, all of this good information, all the technology now says, "Okay, apply it, make it happen." And that's what we're trying to do.

MS: And isn't it that the pressure of the application is our worsening morbidity in our population. The pressure of the application is recognizing that autistic children and their mitochondropathies, and Frye's work looking at NADH and NADPH levels, and is autism an aspect of that as a mitochondrial pellagra? You know, we can begin to look at mitochondrial exhaust, and we can begin to see how we might influence, in the setting of the timeline of the family and the setting of the pregnancy timeline, if we know X and Y, then we can get just a glance at the genome just by using food and nutritional bridges, and doc[umenting] observable insufficiencies, and we can have altered outcomes and we can have an altered imprintome. We can have a different outcome and trajectory for that child and for that mother and for that father taking care of that child, when we begin to use and capture and enlighten and show and inspire change in the time of life that there is no greater desire to change and that's during pregnancy.

JB: Oh boy, was that well said. And again—this is so fun—Leslie, do you remember the first time we met, which was at an IFM meeting I think that you were coerced into coming to, in which the theme of my presentation was on mitochondria and biochemical energetics?

LS: I do.

JB: And I recall you said something to me about intellectually interesting, but where does it actually apply? And I think we've all been on this path of recognizing how many of these discoveries do apply clinically as we get down the wormhole, right, and we start to really understand how they interconnect into the web of function. It's just another little interesting memory factoid about this whole process of this community that we're developing this model and putting the right kind of robustness on the model as we subject it to scrutiny.

LS: Exactly.

JB: So Michael, your story of the young man that you have as a patient and the unbelievable response that he had to this whole concept of methylation has become the buzz of our field and it's dramatic. Tell us a little bit about how you think that that observation—because we often learn from our most remarkable case histories—how that can be generalized into other conditions that maybe aren't quite as dramatic.

Functional Medicine is Personal and Local

MS: Well, thanks for asking. There are a couple of sentinel cases. One was our daughter, who started having 20 to 30 syncopal episodes a day after being a two-time All American while in college. We took her through all the regular, allopathic physicians—neurologists, cardiologists—and in the end, her youngest brother ended up being her catcher because he could tell when she was about to have a syncopal episode at just over the age of 21. And for about five months there was quite a bit of care and then Leslie staying with her, and shortly after the international symposium where I was asked a talk on vitamin D, essential fatty acids, and folate, and role in mood disorders, where I really began to understand a lot more of the work in neurotransmitter balance and sympathetic tone, that it came bubbling forward. And she has the SNPs and it was a miraculous response to fairly high dose methylfolate, and then we started looking at not just methylfolate and improving neurotransmitter balance, but we started looking at all the different B vitamins and their roles and that chicken wire of one carbon metabolism and the different minerals, and we started bringing balance and seeing that it was really multiple different cofactors that would help to bring balance in the sympathetic/parasympathetic nervous system and neurotransmitter balance. And she went back, after taking a medical red shirt year, to be a third time All American, and that was a stunning, very personal story.

JB: Oh my word.

MS: And it stops us in our tracks, because all functional medicine is personal and local.

JB: That's beautifully said. Wow.

MS: And then we start looking. Lindsey, our canary MTHFR person in our family, helped us look at 300 different people. We checked MTHFR SNPs and, in some, COMT, and she looked at medical symptom questionnaires that came, as you know, out of the whole functional medicine movement. And I said, after looking at all of these, "Lindsey, what you just saw. What are some of the first symptoms?" She said, "In women, it is hormonal disruption. It's disruption in their menstrual cycles, and once they start seeing that, that's followed with neurologic issues: depression and anxiety." She said, "I saw that pattern all the time."

A Remarkable Case History of Autism

So then, feet forward with the autism issue and that one case. I was asked to give a talk about methylation and rheumatologic disease, and it took me into methylation and medications (methotrexate and varying metabolism of seizure meds), which ended up taking me into the whole concept of cerebral folate deficiency. How did it do that? It's because in autoimmunity, if you have a trigger and you have a permeability issue and you trigger immunologic response and you develop an antibody to a homolog that is very similar to a protein in your body, as in bovine milk folate receptor protein in bovine milk or in mammal milk, then it can actually bind to your blood-brain barrier folate receptor (one of the two main receptors), and you can have normal serum folate levels or methylfolate levels and you can be deficient in the CSF. In autistic kids, in variable size studies, up to 70 percent of kids who are autistic have some component of cerebral folate deficiency, a compartmental deficiency.[6] And if the only thing you do is through folinic acid or through methylfolate, you encourage different transport of that folate precursor or methylfolate into the CSF, then you get marked improvement—marked improvement—in these cerebral-

folate-deficient autistic children.

JB: When you say high dose, probably our listeners are thinking, "I wonder what high dose means," given that we talk about 800 micrograms. What are we talking about when we say high dose?

MS: Well, in the studies that were done with cerebral folate deficiency and autism, they moved toward giving 1 to 2 milligrams per kilogram of folate.[7]

LS: Milligrams per kilogram. Not micrograms.

MS: Milligrams per kilogram. So in that one case with the video, through tertiary care center, we had a cerebral folate level that was the lowest point of normal, and Frye's work showed that if you were in the lower half, and especially the lowest quartile, of normal folate levels in the CSF and autistic kids and the only thing you did is you gave folinic acid or methylfolate that you got a response. And so in this child, where there had been a tertiary care workup and I saw the cerebral folate level being lowest point of normal and this desperate mother and this 4-year-old who could say one word—"eat"—after she stopped the cow's milk, it was those points of connection, and I just asked her if she was willing to give a therapeutic probe to see if we could follow this hunch that he had cerebral folate deficiency as one of the layers of the onion that we are trying to understand as autism. And within three weeks, he had a profound turnaround, and we continue to uncover different layers of the onion in him, but it was such a remarkable single nutrient, compartmental deficiency case of cerebral folate deficiency that it has forever changed our perspective of the power of targeted nutrition at the right point at the right time in the right life.

JB: Did he, then, receive more than 10 milligrams of 5-methyltetrahydrofolate?

MS: Yes, actually he did. This was just in the early phases of where we are beginning to understand the terrain of the different B vitamins, so he received phosphorylated or activated Bs, including pyridoxine-5-phosphate and methylcobalamine, and then his peak dose then we were able to back off. He received about 40 milligrams of methylfolate.

JB: Yes, I think that's really, really an important little point for all of our listeners to take into consideration because that's 40,000 micrograms, right, when we say that above a thousand micrograms you get into all these issues that people are talking about, which are really non-issues, but they become issues for some. I think that this is, again, another back to the future. I'm now talking about 1968—I'm even going farther back than FMU—to Linus Pauling and what I consider to be a landmark paper in Science magazine, "Orthomolecular Psychiatry," in which he lays out this whole concept of mass action, that you can't change an enzyme so you have to change the substrate or you have to change the apo enzyme and you did try to drive things to completion.[8] When people say that you're just making expensive urine and this has no effect, the question we would always ask them is then why does megaloblastic anemia need several thousand micrograms a day of vitamin B12 in those genetically inherited individuals to get their B12 to be "normal" for them? And I think this is what you're talking about, and of course Bruce Ames talked about this in his article in the American Journal of Clinical Nutrition as well.[9] I think this is just a fantastic clinical example of how that mass action principle works, because normal for these individuals is super-normal or super amounts for another individual.

MS: It absolutely is true and isn't that the shoulders of giants? You know, you mentioned very quickly

the people that we pull on and have built our understanding, who helped form our neural network that allows us to see therapeutic possibilities in the people on the other side of the stethoscope, and you joined those ranks in this translation from Linus Pauling to Bruce Ames, Jeff Bland, David Jones. These true thought leaders who help us make these points of connection—this constellation—that allows us to have, in many ways, the courage to step forward in communication with our patients to together try therapeutic interventions that may be the first time in the literature, if we were to write them up, they occurred. That is really what this is, isn't it? It's really looking across the stethoscope, or listening to the mother or the parent who says, "Is there anything else that can be done? Is there anything else we can do? Do you see? Can you help us figure out how we can help our child, or our mother, or our aunt, or our spouse?" I mean, that's what this is all about, isn't it?

JB: Yes, absolutely. With that said, you know, both of you are extraordinarily thoughtful about how you proceed with your patients. Someone listening to this who may be unfamiliar with this whole concept might be saying, "Well, everything is toxic at some level, even air and water, so how do you know that you're still within the boundary of not doing harm?" Tell us a little bit about how you deliberate on that issue of threshold relationships to safety.

MS: That's a good question. We do a couple of things. First of all, we try to see if we're in the ballpark when it comes to the literature, okay. For example, methylfolate—some of the early work with schizophrenia and severe depression, when you go back, they were dosing folate using 50 and 100 milligrams of folate in these studies with variable response and not marked untoward effect for a short period of time. So you look at it the body of the history. Then we look at it in the body of symptoms. So if there is a toxicity issue, or if there is an untoward symptom, we follow those folks pretty closely. If we're going to mess with neurotransmitters, we're going to talk about if you have increased depression, increased anxiety, increased dizziness, please we need to know. Then thirdly, we look at metabolomics. If you have some idea from their family history or from their genomics what they're doing, then we look at the cell exhaust. We will look at organic acid levels in these folks frequently, and we will use that as a buffer to help us fine tune. Those are different lenses that help us begin to approach therapeutic trials. And when it relates to methylfolate, we appreciate the combination of SNPs, whether it's MTHFR with COMT. If you crank up serotonin, dopamine, norepinephrine, and they can't break it down via the COMT enzyme (the catechol-O-methyltransferase), then yes, people have increased anxiety, increased bad dreams. So we don't start at massive doses. We will gradually go up. We appreciate the dynamism of the metabolism. In short, we try to put it in the context of the timeline and their genome, if we have it. We try to put it in the context of metabolomics, if we have it. And then we put it in the context of the symptomatology and the relationship you really have with them, especially in a primary care family practice setting.

JB: Leslie, did you want to add anything to that?

LS: I think I would like to approach it from the other end of that spectrum. If we are using what seems like incredibly super-physiologic levels to deal with a complex state within an individual that might require the super-physiologic levels, we also understand theoretically, using Ames' triage theory, that it may not be that we're aiming for these super-physiology levels. It may be that we are looking for complexity of different nutrients and looking for their activities in concert. You know, when we talk about nutrient deficiencies, the question is: is this a deficiency as measured in the serum, where it may or may not actually be active? Or is it a deficiency at the receptor site, where it may or may not be a

deficiency? Or is it intracellularly within an organelle, within an enzyme, is that where the true deficiency lives, and is it that we really don't have the sorts of tools at our fingertips at this point that can let us investigate, give us a functional answer, at least a biochemical functional answer, at that very molecular and sub-molecular level? So what we have to rely on, then, is the macroscopic function. So then we blow it right back out to, so, if I know the richness that is necessary to make MTHFR function at its best, if I know that it's multiple micronutrients, and that I can't really say how much of each one of these pieces it is (not in a mechanistic sort of way), but that I can answer that question by being excellent in my critical thinking, making sure that my perspectives are broad, and take into consideration all the information, all the context that I can gather, and then I apply those more like a complex soup, a complex dish, and I give that to this patient, this n-of-1, and then I look at their response. I look at do they have less pregnancy-induced hypertension? Do they have fewer small-for-gestational-age babies? And that functional definition tells me if we've gotten it right or not.

MS: And I would also say that what we, in our transition…you know, if you only have a hammer in your toolbox then everything looks like a nail, so I would say in the triad of important components in this program, one of the most important is really the education and the power of food, and the phenomenal orchestra of phytonutrients and minerals and vitamins that you can bring forward in the food form and let the prenatal supplement pack, or the essential fats, or the different minerals, or the different vitamins, be really a bridge while you develop a food model that really has the wisdom of the ages that allows and empowers the patient to really change their choices and change their physiology and then change the outcome of the child.

LS: And then also knowing that that very state of empowerment influences electrochemically the effect on their biome, right? So we have to take that into consideration as well. It's not just what I give them, it's how I give it to them and how they receive it.

MS: So some people ask us in this program, is it the prenatal vitamins that are nutrients that are far more extensive than what you normally get in a prenatal vitamin, or is it the nutrition classes (the empowerment), is it Emily Rydbom, the nutritionist who coaches these people so exquisitely, is it the app that she developed so they can track and follow, is it the sense of caring and nurturing that occurs through nine months of belief and experience all the way through delivery? What is it? And I would say the answer is yes.

JB: Yes, that is exactly right. This is a new way of looking at the systems biology of health, right? That's what we're talking about. And it's very interesting. You both said something—I just want to make a little parenthetical for people that may be new to this model—if we start using the serum to measure what's going on in cells, then we have to ask, when we're measuring blood sugar in the diabetic and it's very high, does that mean the cell is deficient of glucose? And the answer is no, it's the opposite, right? Or if we start asking what does high cholesterol mean? Does high cholesterol mean you're making too much or does it mean you're not converting enough into bile salts and getting rid of it? The concept of systems thinking is a whole different way of looking at the network of biology versus just the simple-minded "this high, then I give this; this low, I give this." It requires you to look at these interconnections, as you are so beautifully describing.

And so some people might say, "Well this is way too complicated and too time consuming, and, you know, I just have an algorithm and I plug things in and it's a six-minute office visit, so how the heck am I

going to do all this?" And so, what do you say?

Incorporating Functional Medicine into an Insurance-based Family Practice

MS: Well, we say it's a lens that you look through, and then you meet the patient where they are at. And so you learn more as you look through this lens. So we have an insurance-based family practice model. The longest appointment is one H & P a day, and the rest are 15- or 30-minute appointments. You meet the patient where they are at, so if they are at the place in their allopathic travels that they just need a prescription, then you keep bringing up, "Well, I'll write this prescription. However, why aren't we getting any movement in your hypertension?" And then you start working with them. That's the power of the relationship in the primary care setting. So when you have nurse practitioners, and physicians assistants, and nutritionists, and physicians, providers, all in the same family practice clinic looking through a lens—a systems lens—at ICD-9, ICD-10, in coded conditions, you don't see that condition only in itself; you see the person, and then why isn't there movement, and are they ready to move? And then once they are, you can tie it together in the systems point of view. It is really a different set of glasses that you're putting on that you can apply in the ER, in the ICU, and on the OB suite, in primary care, you can apply this across all healing paradigms, and that's just our belief, and our knowledge, and our experience.

JB: You know I started this discussion off with you, here, nearly an hour ago in which I said that you're my model of how this form of healthcare should be and will continue to be evolving to be practiced. The model that you have been describing, which we focused a lot of our discussion on pre-conceptual/conceptual and neonatal care, but the model is—as you just described, Michael—applicable across the whole life process. I mean, the same interrogation process goes into childhood, adolescence, young adult, adult, midlife, older age, geriatrics, and even at end of life because you're asking similar questions but in a different context at each of those stages. So this is an applicable system—it's like what we call an operating system—for the way you take information in.

MS & LS: Yes.

JB: And I think for a lot of people, when they hear the term "functional medicine," and this is a great place for us to complete this part of our journey in our December 2015 issue after 34 years, they think of it as, okay, what's the lab test and then what's the supplement? That's not really what we're talking about. We're talking about a way of processing information: taking it in, asking the right questions, and interconnecting that information in ways that tells the patient's story in a meaningful way that helps you to develop a program that they'll participate in to improve their outcome.

MS: Absolutely.

JB: In the final closes, here, are there any words to the wise or words to the aspiring wise that you'd like to share from this vast experience that you've amassed over the many years of your collaboration?

LS: Yes, I'll go first with that. If it sounds intimidating to folks at the beginning, to think in this systems manner, what reassures me about the human body is that there is not just one way. If methylation is important in the human body, then the human body is going to be able to do it in multiple, multiple, multiple ways. There is an economy of redundancy. Rather than having efficiency, the human body—our life around us—is that of redundancy. And so in our journeys as we are finding the answers in our patients,

when you ask a question, there's going to be more than one answer. There's going to be more than one solution. Even if you don't get it 100 percent on every single answer, because of the multiplicity of answers, because of the redundancy of the human body in all of its crucial functions, you can get most of it right and get great outcomes. So the more elaborate, the more elegant you are about your hour interrogations, I believe the better outcomes we will get, but that means start down the path, ask the questions, do the interrogation, be critical, and then apply the push and pull to those systems that we do understand, and then carefully observe the outcomes.

JB: Michael, your comments?

MS: I would say no matter where you are in your interaction with somebody that you're trying to help, the important question is to ask how they got there. What were the balances and imbalances? What were the issues that allowed them to turn toward more health or turn toward more disease? And then once you ask that question, then it is the inspiration of seeking answers, and it is the power of instilling hope in movement, in change. And that's the hope in human. We're at a wonderful spot here, Jeff, after your 34 years of doing FMU. When you look across the landscape and you see residency programs incorporating functional medicine as the standards in their training, and you start hearing about Fellows in functional medicine, and you start talking about systems medicine, and centers for functional medicine at Cleveland Clinic, and you start getting the conversations across all healing paradigms that tie the millennial brilliance of the traditions of the past with the genomic/epigenomic/omic revolution where we are now…tie that in with the informatics and we are about to blast off into one of the most exciting times in medical education and changing the paradigm and in changing our understanding of healing and health. We're at the beginning of this new frontier. So I just want to say that this is a spectacular time. I hope people just join in and enjoy the ride and enjoy the wonder and enjoy the miraculous, as we do every time we see a child being born.

JB: Wow, I don't think there would be a better and more fitting transition from our 2015, 34-year experience than Leslie, you and Michael's advocacy. I am, as I close here, reminded of the interview that I did in 1982 with Linus Pauling in his office, which was the start of this whole journey for us on this celluloid version back in the cassette tape days. So much of what he talked about—the reduction of human suffering and the preservation of the uniqueness of the individual and this whole concept of individuality—was expressed by him that initial first issue of the recording I did at his office desk, actually. It's a tremendous back-to-the-future enrichment that we all share in this legacy. I just personally want to thank you for the contributions you're making, obviously, to all of your many patients that are benefitting from this process, but also from the extraordinary number of people that will be affected through the training of functional medicine practitioners in their service to their patients, which will be—we hope—millions of people that will catalyze this transformation. So thank you very, very much. What a great way to move to our 2016 version, which will be an open version of Functional Medicine Update going into next year. Thank you very, very much for closing this chapter of our book.

MS: Thank you so much.

LS: Thank you.

JB: Much love to you both. We'll talk soon

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