February 2009 Issue | Brian Berman, MD Professor of Family Medicine

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Welcome to *Functional Medicine Update* for February 2009. As you probably recognize, the world is changing at a remarkably rapid rate. This is the case as we watch the evolution of the new medicine and healthcare system the Obama administration, and his new health policy directors and Secretary of Health and Human Services are defining. We are going back and reevaluating a lot of things that have been thought of as facts. We're looking at new things that might be part of a new information system that describes a new reality for health care. That's going to be the theme that you'll hear woven throughout *Functional Medicine Update* in 2009 and beyond.

A principal tenet in the field of functional medicine is based on the ability to modify various environmental agents that have effects on expression of genes and, ultimately via gene translation, on the phenotype (the health and disease patterns of the individual). This gene-environment interaction is a fundamental and conceptual component of the functional medicine model: the nature of a patient-centered personalized approach; looking at etiology from an antecedent-trigger-mediator-sign-and-symptom perspective; and examining fundamental underlying processes that lead to the disturbance of the network of physiology that we call dysfunction, which ultimately give rise downstream to pathology that we label as disease. All these components become the framework upon which the functional medicine process of thinking has evolved. This does not necessarily lead to specific therapies, but more a process of thought as to how we evaluate the patient, work up the patient, and understand the etiology of his or her specific condition (what types of factors lead to that condition and how they can be modified). We really focus on modifiable factors.

One modifiable factor, obviously, is diet and its constituent nutrients. In functional medicine, quite a large amount of focus and time is spent on examining the role that diet plays on gene expression. Over the course of 2008, a number of *Functional Medicine Update* clinicians or researchers of the month spoke about the role that various principles in diet play in modulating gene expression or influencing the epigenome (with methylation, acetylation, and phosphorylation of histone proteins). In addition to what we have historically known about diet and the regulation of metabolomic factors, we've started to evolve a molecular understanding of how diet (and the nutrients it provides) is the signature upon which the information from our genes will be expressed. These are things like the coenzymes that are derived from the B vitamins-for example, flavin adenine dinucleotide (or FAD) that comes from riboflavin, or nicotinamide adenine dinucleotide (NAD) coming from niacin vitamin B3, or thiamine pyrophosphate, or pyridoxal phosphate that come from vitamins--that then ultimately serve as cofactors in coenzymes and specific metabolic processes that activate apo enzymes into halo enzymes (the active form of these

enzymes that then do their work at specific places).

With all of that as a context, people have wondered for years about doing randomized placebo-controlled trials against specific disease endpoints using specific nutrients. What would happen? Would you be able to demonstrate, under these controlled conditions, that these vitamins, when given in supplementary doses, could either treat an existing condition or provide secondary prevention, or prevent a primary condition? This has been a longstanding debate, certainly in the 30+ years that I've been in the field. The National Institutes of Health National Center for Complementary and Alternative Medicine (or NCCAM) has been sponsoring a number of these intervention trials over the last several years.

The unfortunate thing about these trials (for those who are of the belief that they would demonstrate positive outcome), is that most of them are not positive in their outcome. The results are either ambiguous, neutral, or maybe even (to some extent) there are some negative implications of these vitamin intervention trials that have been published. This has caused a rude awakening for some of the strong proponents of giving single nutrients at high doses for the treatment or prevention of disease and has made it difficult to rationalize some of the observations made in these clinical trials. Basically, attacks have been made on the study designs: not stratifying to the appropriate patients; or the wrong doses; or the wrong formulations of these substances, be it either phytochemistry or botanicals (things like St. John's Wort for depression, or Gingko biloba for memory, or even looking at things like Echinacea on immune system function). The results of these clinical trials have not been uniformly positive; they have been either kind of neutral or maybe even showing no effect.

Study Results Have Led to Disillusionment

With all of that in mind, one might start to be somewhat disillusioned and maybe even come to the conclusion that nutrients don't play a role in prevention of chronic, age-related degenerative disease. Perhaps nutrients are just there to prevent nutrient deficiency disorders like scurvy, beriberi, pellagra, xerophthalmia, rickets, kwashiorkor, or marasmus, and beyond that--if you have proper hemoglobin levels and proper total protein in your blood--you really don't have risk or concern about malnutrition or undernutrition relative to these nutrients.

We can cite some recent studies that pertain to this disillusionment. There was a paper that was recently published looking at the long-term use of supplemental multivitamins (vitamin C, vitamin E, and folate) with regard to the risk to lung cancer. The results of this study were published in the *American Journal of Respiratory and Critical Care Medicine* in 2008.[1] This particular study, which was a cohort of 77,721 men and women, aged 50 to 76 years, all living in Washington State, was called the VITAL study (VITamins And Lifestyle study). Cases had been identified through surveillance epidemiological registry in the Seattle, WA area.

These individuals were looked at for their incident lung cancer and their voluntary use of supplementary multivitamins over an average of 10 years. A total of 521 cases of lung cancer were identified. The researchers adjusted for smoking, age, and sex and found there was no inverse correlation with the use of a supplement in these individuals. They concluded supplemental multivitamins (vitamin C, vitamin E, and folate) were not associated with a decreased risk of lung cancer and supplemental vitamin E was associated with a small increased risk. The conclusion of the study was that patients should be counseled against using these supplements to prevent lung cancer.

Another study result that shares some of this negative theme was published in the *Journal of the American Medical Association* in 2008 (the November 12th issue). This study was titled "Vitamins E and C in the Prevention of Cardiovascular Disease in Men."[2] This was the Physician's Health Study II randomized controlled trial. In contrast to lung cancer prevention in the previous study I mentioned, this was a randomized double-blind placebo-controlled factorial trial of vitamin E and vitamin C that began in 1997 and continued until August 31st, 2007. In the study there were 14,641 US male physicians enrolled who initially age 50 years or older, including 754 men with prevalent cardiovascular disease at the period of randomization. They received 400 IU of vitamin E every other day and 500 mg of vitamin C as a supplement daily. They looked at a composite endpoint of major cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular disease death. During this mean follow-up of 8 years, there were 1245 confirmed major cardiovascular events. Compared with placebo, however, vitamin E had no effect on the incidence of major cardiovascular events, and there was also no significant effect of vitamin C on major cardiovascular events. By looking at all the data and the relative risk factors from this large long-term trial of male physicians, the authors of this study conclude that neither vitamin E nor vitamin C supplementation at those doses reduced the risk of major cardiovascular events and there is no support for the use of these supplements for the prevention of cardiovascular disease.

Should We Be Disillusioned or Should We Ask More Questions about the Studies?

With these papers, I'm just giving two examples from what has been a fairly long list (over the last few years) of published randomized intervention trials that have failed to demonstrate significant positive health outcomes in the study populations that were used, under the conditions of supplementation, and the endpoints that were examined across a wide range of conditions. In the past we have discussed familial adenomatous polyposis with colorectal cancer risk and folate and B12, lung cancer, breast cancer, and now cardiovascular disease with these supplements. One starts to ask the question: are we at a point of disillusionment about this whole model? Is the use of high doses of specific nutrients really specious? Was it a great concept that really doesn't wash? We are going to be talking more about ways that information from the environment and from nutrients translate themselves through the genomic message into the phenotype later in this issue of *Functional Medicine Update*. I think we need to-again-ask the following question: are we sure there are not buried, within these specific data sets and these large randomized trials, cohorts of individuals, who as a consequence of their unique genetic characteristics, are high responders, but they get washed out or they get lost in the sea of non-responders that do not carry those characteristics?

The reason I bring this up is fairly simple. Let's assume that constituents within diet are reasonably low potency in terms of their impact on specific functional characteristics at the metabolic and physiologic level. This is in contrast to drugs that have been developed, designed, and screened for their very high affinity binding constants with specific substrates and have very low IC50s in the nanomolar or sometimes the picomolar levels, and they have been hand-picked/selected for their extraordinary affinity for the endpoint. If you do a test of these particular molecules on an outcome (let's say hypertension, in which you are looking at an antihypertensive molecule), it may wash out among different SNPs with differing levels of sensitivity within any one of the various genotypes. Some maybe get more effect than others, and those may be the people who have (at low potency) a high effect. On the other side of the bell-shaped curve, there may be those individuals who have very low affinity, who have to go to a higher dose to get response. Everybody gets some response. By the way, this probably also defines why there is (with these potent drugs), a very high risk to adverse drug reactions. Where one person is getting a favorable effect, those potent molecules at that same dose in another person with a high affinity may be getting an

adverse effect. The drugs are designed specifically for this very high activity (very high potency, low IC50 characteristic), and they do what they are supposed to do in the emergency room. There is no ambiguity. They come in and they don't allow a lot of room for conversation, in terms of the substrate and how they ultimately influence that function at the cellular level.

Nutrients, however, operate with a much more mild substrate-binding relationship for a much more benign effect (maybe wild-type SNPs). In a randomized trial of those nutrients, you may get (at best) ambiguous results because the cohorts that are most able to have a higher response to those nutrients at that dose that may be small. Remember a SNP is defined as a single letter alphabet change in the genetic code for one percent or more of the population. If you have low penetrant SNPs and you start looking at those individuals who have a higher response as contrasted to people without those SNPs, they may be lost in the noise of the study (washed out) by the average of the non-responders.

I think we have got ourselves into a little bit of a conundrum here as we start to try to study the responsiveness of specific nutrients in human populations with a double-blind placebo-controlled randomized trial for all genotypes. The people who go on to get heart attacks may be those individuals who have unique characteristics in their genetic lineage that make them more at risk to certain things. For those individuals, nutrients may be more responsive, but they get lost in an overall study. Saying it another way, if we look at things like methylmalonic aciduria or phenylketonuria, these represent genetic metabolism diseases of infancy that are very low in penetration in the genes of the human population. If we put those people on diets of average (diets of adequacy for the average individual) they might be inadequate or toxic for these genetic uniquenesses. In the case of phenylketonuria, we may want to, obviously, restrict phenylalanine in their diet. If we gave them the same amount of phenylalanine that would be considered adequate for the wild-type individual genes and good for their nutrition, it would produce a potential toxic effect, leading to neurological and hepatic injury in the children that consumed diets with that same level phenylalanine in their protein.

By the same token, methylmalonic aciduria is a little bit of the other side of the equation. If we feed diets to those children with the level of B12 that would be considered adequate (and maybe even good) for the average wild-type genotypes, those individuals would be vitamin B12 insufficient based on their need and would develop high levels of methylmalonic acid in their urine and have acidic pH changes intracellularly. Those things will sustain neurological damage and these individuals would have irreversible pathologies associated with this nutrient inborn error of metabolism. Given very high levels of folate and B12 (relative to the average person), these individuals can lower their homocysteine levels and their methylmalonic acid levels and achieve much better function. For them, the level they need is dictated not by their genes, but in the overall gene penetrance. If we just did a gross study of the role of vitamin B12 in neurologic function of the population at large, there are a small number of those individuals we might lose in the average

That's the rub, I think, when we have nutrients that we are studying with a pharmacological model because it is a model that is really designed for high potency molecules that can penetrate through the wide variety of different genotype responsiveness. A person who really understood this very, very well, way back when ("back when" means back in the 1940s), is a psychiatrist who grew up in Sascatchewan, Canada. He is a very remarkable guy who I have had the privilege of knowing for many years-actually several decades now-with whom just recently I had an extraordinarily warm and rich moment. I sat down with him and we talked about his 50 years plus of experience in this field, his views, and how this concept

emerged for him. You probably know who I'm speaking about. I'm speaking about the father of orthomolecular psychiatry, Dr. Abram Hoffer.

Dr. Hoffer grew up in the plains of Sascatchewan in a farming family. He is a guy who knew something about the soil and growing things. He went on to get his PhD in food chemistry. He recognized that things were being discovered (I want you to recall that Abram Hoffer is in his 90s and is still practicing orthomolecular psychiatry). In his earlier years, Dr. Hoffer was right at that interesting phase of understanding vitamins and their role in health and disease.

Early Years Influenced Future Study of Schizophrenia

He was a student of pellagrous dementia (the "3 Ds" of pellagra are diarrhea, dermatitis, and dementia. When people have vitamin B3 deficiency, clinically (or phenomenologically) they go through a schizophreniform stage of mental alteration in their function. and so he had always had in his mind, From the time of his PhD in nutritional sciences, Dr. Hoffer had always had it in his head that there was something about vitamin B3 and brain function and the manifestation of a condition that resembles schizophrenia.

Later, Dr. Hoffer went to medical school. He became a board certified psychiatrist, rose to great prominence in Canadian psychiatric circles, and is in decision-making and opinion-leading positions in high-order institutions. He was one of the first people to really learn about electroshock therapy and to be very skilled in it. Certainly he was very skilled in the dominant theme at his earlier age: Freudian psychotherapy; he was a very skilled psychotherapist. But he was very frustrated because many of the things he was trained to do and became an expert in really weren't producing very good outcomes. The results he was getting with schizophrenic patients were very marginal.

***Adventures in Psychiatry*: 2005 Autobiography**

Always thinking back to his PhD in nutritional sciences and food science
chemistry, Dr. Hoffer wondered if there could be some kind of a connection between what he learned about pellagrous dementia and what he was seeing in some people with schizophrenia. All of this is described in a wonderful autobiography Dr. Hoffer wrote and published (I treasure the copy he gave me). The book describes many years of his journey in understanding the role that vitamins play in mental health and neurochemistry.

I would almost call Dr. Hoffer one of the progenitor pioneers of the whole field of neurochemistry and how it interrelates with metabolism in the neuron and nutritional factors. *Adventures in Psychiatry,* his autobiography, was published in 2006.[3] The book describes the journey Dr. Hoffer has been on and that we (those of us who have been fortunate enough to come along in this field after him) have followed. In this discussion with Dr. Hoffer, I found that not only is he a gracious, warm, caring man and a person who is thoughtful about everything, but he is also a warrior. He is a willing participant in carrying his ideas against criticism-asking the right things, but willing to sustain the criticism of his peers who often don't understand.

Dr. Hoffer teamed up with Humphrey Osmond to form the Hoffer-Osmond duo back in the 50s and 60s. This was extraordinarily fortuitous because they brought the best of their energies and their intellect to this field and moved it ahead. He met Linus Pauling, the father of molecular medicine, and, with Dr. Pauling being very interested in the chemistry of the brain, this was an impactful meeting. Ultimately Dr.

Pauling published what had to be one of the landmark papers in the history of medicine, I think, in 1968 in *Science* magazine titled "Orthomolecular Psychiatry."[4] In 1968, this article really shocked the medical world. It talked about vitamin binding constants and sluggish enzymes, and also about the principle of pushing an enzyme to function by increasing the substrate (by mass action) with the substrate as a cofactor. It represented a very remarkable thought about how to promote function out of a genetic uniqueness; that is, you can't change the enzyme, but you can change the concentration of the coenzyme to force more of the coenzyme/enzyme-binding complex to get more activity out of that enzyme.

These constructs and how they relate to function marry themselves beautifully to Dr. Hoffer's practice of orthomolecular psychiatry, in which he was using niacin at high dose and pyridoxine and vitamin C in his schizophrenic patients for the modulation of schizophrenia. As Dr. Hoffer points out, not all schizophrenics respond to this therapy because schizophrenia, like so many diseases, is polygenomic and multiple etiologic; it doesn't have just one cause. Schizophrenia is a term that is a descriptor for a collection of signs and symptoms. It doesn't tell you, specifically, what is going on in the etiology of that condition. We often think a name tells us what something is, when a name actually just describes a set of symptoms. Dr. Sidney Baker calls this medical taxonomy, and it is the way that many of us learned: clustering conditions, signs, and symptoms that have similarity and calling it a disease, which assumes that when individuals have these common characteristics they are sustaining the same physiological disturbance at a molecular and cellular level. That turns out not to be true. At the mechanistic level, there may be more connection among different diseases than we previously ever recognized. These connections are called comorbidities. I find that interesting: looking at them as being manifestations of the same dysfunction at the cellular level that then express themselves in different ways in different tissues, and organs, and organ systems.

How does the orthomolecular psychiatry argument help us to understand better why some vitamin intervention trials have come out as not being positive? These are expensive, randomized, clinically controlled placebo trials. Orthomolecular psychiatry helps us to recognize that there may be, within any disease condition, various manifestations of that disease based upon different presentations at the cellular level, some of which may be more responsive to individual therapies than others. This is wonderfully described in a review article that appeared in the *Israeli Journal of Psychiatry and Related Science* in 2008.[5] This paper was actually authored by someone who shares a common last name to that of Abram Hoffer: Leonard John Hoffer, MD, PhD, professor of medicine at the McGill University Lady Davis Institute for Medical Research and the Jewish General Hospital in Montreal, Quebec, Canada. Leonard John Hoffer is Abram Hoffer's son (one of his two sons) and he has become an extraordinary researcher in his own right and carries a lot of these questions forward in his own work as a strong academic medical researcher. This article is a review of vitamin therapy in schizophrenia, going way back to the earlier discussions and observations of Abram Hoffer and Humphrey Osmond. The article states that we still, today, recognize schizophrenia as a devastating and poorly understood disease, for which the only accepted therapy is nonspecific anti-psychotic and anti-seizure medication. However, there is this other interesting history of vitamin therapy, and Dr. Hoffer summarizes evidence. There are some forms of schizophrenia that may really be latent nutrient insufficiency or deficiency based upon the genetic uniqueness of certain people, and in some cases, vitamin therapy can worsen the symptoms of schizophrenia. There is also evidence that large doses of certain vitamins can improve the core metabolic abnormalities that predispose some people to develop schizophrenia. This is a different model of schizophrenia that is still not generally accepted within the body of psychiatric medicine, even though there are now over 60 years of experiences in many clinical and scientific reports that tend to justify this

model.

Dr. Hoffer recounts the history of controversial, vitamin-based therapy for schizophrenia, which later got named-as you heard me mention before-orthomolecular psychiatry by Dr. Linus Pauling. This therapy advocates a process for discovering promising new schizophrenia therapies that involve small, carefully controlled clinical trials of nutrient combinations in appropriately cohort-selected patients with specific genotypes. Here, again, we are looking at stratification. How do we do the studies? Let's look at the right people so we can examine those who are more likely to show a response based upon their genetic uniqueness and responsiveness.

This same theme that I am describing with orthomolecular psychiatry and B vitamins could also hold true in the application of vitamin C and cancer. Years ago, Ewen Cameron, a Scottish surgeon, made an observation in the Vale of Leven Hospital that patients who had malignancies and got vitamin C therapy seemed to do much better, and even have prolongation of life; their energy levels and vitality seemed to improve. Dr. Cameron then co-authored a paper on this topic with Dr. Pauling.[6] In fact, when Dr. Cameron came from Scotland to become the medical director at the Pauling Institute in Palo Alto, CA, I had the privilege of having the office next door, in between he and Dr. Pauling. I was engaged in many discussions about the vitamin C-cancer relationship back in the early 1980s.

Some of you may recall, Dr. Moertel, a well-known oncologist at Mayo, who then took very strong umbrage about this vitamin C-cancer connection. He published a paper in which it was supposedly proven that intravenous vitamin C did not have a positive impact upon malignancy.[7] However, now some 25-26 years later, work is going on to reevaluate this whole connection.

New Studies on Nutrients Focus on Select Individuals

Dr. Mark Levine, an endocrinologist at the National Institutes of Health has done in situ kinetic studies looking at the adequacy of vitamin C to promote proper enzyme function. Dr. Levine has also been working in conjunction with investigators at the Linus Pauling Institute (now at Oregon State University), Dr. Balz Frei and Dr. Steve Lawson. Together they have been looking at this vitamin C-cancer connection in a revisited fashion and showing that high levels of ascorbate can induce and participate in certain kinds of free radical pathology that may be specific to the physiology of the cancer cell (the kind of hypoxic, acidic environment of a cancer cell). There may be, at a fundamental mechanistic level, some usefulness of intravenous vitamin C to induce hydrogen peroxide in these cells in situ, which cause selective tumoricidal effects. This was published in the *Proceedings of the National Academy of Sciences* in 2008.[8]

Two phase I clinical trials of cancer and vitamin C have recently been published demonstrating remarkable tolerance and safety for high-dose (up to 1.5 grams per kilogram of IV vitamin C) in patients screened to eliminate hyperoxaluria and glucose-6-phosphate dehydrogenase deficiency (that's G6PD deficiency), which is a genetic condition that is associated with increasing susceptibility to vitamin C toxicity. Case reports also have been published indicating that high-dose IV vitamin C was associated with long-term tumor regression in three patients with advanced renal cell carcinoma, bladder carcinoma, or B cell lymphoma. These findings were published in the *Canadian Medical Association Journal* in 2006.[9,10] More recently, clinical plausibility has been repeatedly suggested with studies by Chen, et al, that have appeared in the *Proceedings of the National Academy of Sciences*, one of which looked at

pharmacological doses of vitamin C as a pro-oxidant that decreased growth of aggressive tumor xenographs in animals.[11,12,13] These types of reports all tend to support what Ewen Cameron saw clinically in his Scottish patients and what Dr. Pauling was supporting back in the early 1980s.

There is a lot yet to learn about the pharmacology of specific nutrients at high dose, particularly in different disease states and in specific genotypes. I think that we should be very cautious not to throw the baby out with the bathwater. There is a very nice collaborative study co-authored by John Hoffer and Mark Levine that appeared in the *Annals of Oncology*in 2008 looking at high dose intravenous vitamin C and its safety (this is up to 1.5 grams of vitamin C per kilogram body weight, 3 times weekly, given intravenously).[14] What this study pointed out was that high-dose intravenous vitamin C, even at the high dose, was well-tolerated, but they could not demonstrate yet any anti-cancer activity. However, the promise to the approach, they say, may lie in the combination with cytotoxic or other redox-active molecules (so, a combination of chemotherapy with vitamin C may induce elective tumoricidal effects due to the participation of ascorbyl radical). I think you can see there is a lot yet to learn. We are still really developing the tools to examine some of the tenets that were observed clinically and phenomenologically, and we're trying to look at them in select populations of individuals that are more likely to respond.

Let me give you one other example of this. It is a paper that appeared recently titled "Intensive Nutritional Supplements: Improving Outcomes in Stroke Rehabilitation" in*Neurology*.[15] This particular study was a randomized prospective double-blind single-center study looking at intensive nutritional supplementation in 116 patients admitted to a stroke service. This group of researchers looked at individuals who received a high dose vitamin supplementation program after a stroke, and at those who were not supplemented. They evaluated if there was any improvement in motor function as measured by motor sub-scores or 2- or 6-minute time lock tests. All of these were found to be highly significantly improved at a $p<0.002$ level in those stroke patients that had the vitamin supplements post-stroke versus those that did not. Again, I think we need to be very open-minded about how we evaluate the role of supplements, whether it is one supplement at a time in the population at large or multiple supplements given together for specific cohorts of individuals. We have to name the specifics of what we are trying to do so we can understand better the outcome. In this particular paper in *Neurology*, the authors conclude: "Intensive nutritional supplementation, using readily available commercial preparations, improves motor recovery in previously undernourished patients receiving intensive in-patient rehabilitation after stroke.

That leads us to ask the question: how do you clinically apply this information? We apply it in the context of improving, overall, the diet and lifestyle of the individual. We know that the complex array of the signature of a good diet coupled with a good lifestyle and regular exercise gives an amplified outcome of benefit. Ralph LaForge-he was at Duke University, Division of Endocrinology and Metabolism and Nutrition-writes in a Duke University Newsletter about applying these things within the context of a therapeutic lifestyle change.[16]It is not just giving a pill for an ill, and not just using a green medicine (replacing a drug with a nutrient and saying we are getting the same results but less toxic).

Really, we ought be looking at the fact that this is a whole different strategy. It is a functional strategy that is based upon implementation with an array of agents that modulate the expression of genes in such a way as to create a different outcome, a different expression pattern, and a different functional phenotype (the healthy phenotype). This lifestyle change-type intervention produces pleiotropic (multiple) benefits

across a wide range of function. It's not like a drug against a single endpoint. It helps to reestablish the frame of reference of the physiology. It influences the network of physiology. As a consequence, therapeutic lifestyle change intervention--along with selective supplementation--can induce, in individuals, a much more positive outcome than just a single substance as an alternative to a single drug.

I think the combination of a physical activity, coupled with a dietary regimen (or you may call it a food plan), coupled with selective supplementation based upon the need of the individual, frames the context and strategy of an effective functional medicine intervention. It does so by looking at the whole system. This whole concept of homeodynamic balance, or homeostasis, is really achieved in an individual as a consequence of an equilibrium of various things that are going on in real-time, like a hummingbird's wings. A hummingbird may look like it is stationary at a flower getting nectar, but if you do a time-lapsed photograph of its wings, you will see they are beating very quickly; that's homeodynamics. The bird's homeodynamic activity maintains that static position, and that's the same thing that happens in physiology with a therapeutic lifestyle change intervention program and selected complex nutrient supplementation: you are balancing the web-like activities-what I call metabolic redundancy or the ability to maintain function against a changing environment.

You have to look at the whole system, things like the digestive system, where we know much of the immune system is clustered.. If you have a dysfunctional immune system, maybe you ought to be thinking about the gut. The gut is more than just plumbing; it is more than just a conduit that takes food from the north to the south and excretes it, digests it, and assimilates the nutrients from it. It is part of the gut enteric immune system and part of the second brain: by producing neurotransmitters and speaking to the body through these intercellular regulators, we ought to be looking at normalizing gut immune function, which leads to things like accessory types of nutritional support agents, like pro- and prebiotics.

There is more and more evidence now that probiotic supplementation can have a very favorable effect on systemic immune system function. A paper that appeared in the journal *Clinical Gastroenterology* in 2008 talks about the use of probiotics in allergic disorders by improving gut mucosal activity, or so-called GALT (gastrointestinal associated lymphoid tissue), activity.[17] Intestinal microbiological function can then communicate with the gut immune function in such a way as to lower inflammatory potential and to improve signaling through the immune systems of the rest of the body. Allergic problems and atopic disorder in children and neonatal problems of immunological dysfunction may all be very responsive to improving the gut floral environment by probiotic and prebiotic supplementation.

The next step is removing from the diet things that might be considered offenders-things that activate inflammatory reactions of the gut, like gluten, which is receiving much more attention recently. Literally hundreds of papers have been published over the last two years on the clinical concerns about gluten and its interaction with genetically susceptible individuals' immune systems. We'll talk about that more in a subsequent edition of *Functional Medicine Update*.

I hope I have set the tone for where we are going to go with our researcher of the month discussion. We will look at how signals from our environment are functionally modulated through the genome into the phenotype. There are myriad ways that epigenomic and genetic information gets translated into our health and we can change it with things like a therapeutic lifestyle change program and nutritional support. Let's move to our researcher of the month.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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Here we are again at that part of Functional Medicine Update that you and I both look forward to with great anticipation, our clinician/researcher of the month section of the edition. As our visitor this month we are very fortunate to have with us someone I would consider to be one of the top luminaries in integrative medicine as a clinician, Dr. Brian Berman. Let me just tell you a little bit about Dr. Berman. This is certainly a truncated biography of his very, very rich background.

Dr. Berman is a professor of family medicine and the founder and director of the University of Maryland Center for Integrative Medicine, which was the first center for research, education, and clinical care in complementary and integrative medicine in a US academic medical center. I think that just shows something about Dr. Berman's initiative and also about his political savvy, because as we all know it is not easy to start something new and try to carve out a domain and have affiliation and understanding.

Dr. Berman is very, very prolific in his writing, with over 200 peer-reviewed publications and 7 books to his credit. He is heavily funded through the NIH, and his focus is on traditional Chinese medicine (TCM) and its relationship to acupuncture. He is certainly a world authority in the whole area of acupuncture.

I think we have to contextualize this within the background of Dr. Berman's expertise as a family medicine specialist and also as an associate professor of medicine at the University of Maryland School of Medicine. Rich background. Tremendous successes. And, of course, in November 2005 Dr. Berman's was awarded the Bravewell Foundation Award for his contributions; the Bravewell Award is considered to be one of the most prestigious awards in the area of integrative medicine.

Dr. Berman, it is wonderful to have you as a contributor to Functional Medicine Update. Also, I need to say it's wonderful to have you as a colleague in the field. Your work has been a shining light, and the excellence that you have brought to your center at the University of Maryland has really been a beacon for many of us. Welcome to Functional Medicine Update.

BB:Thank you very much, Jeff, and it is really a pleasure to be here. I feel the same way about following your work over these many years and the impact that it has had on so many physicians out there.

JB:Thank you. Let me start with a question (always kind of the first question I have of a person who has been a leader and innovator such as yourself. You have a very solid background as a family physician and also as an academic physician. And with some-probably-risk, you moved into the area of TCM and acupuncture. (When I say risk I really mean professional risk because people start asking questions.)

What was it that drew you into these fields?

Lack of Answers Leads to Journey

BB:It was many years ago-it was really in the late 70s-when I finished my internship and my residency in family community medicine. I worked in the Shock Trauma Center here at the University of Maryland, which is one of the real leading lights in trauma care in the country, and my training was excellent for acute care. But when it came to a lot of chronic diseases (a lot of the things that people came into me on a daily basis for in my primary care practice), I found that I didn't have all the answers that I was looking for my patients. I was just getting frustrated with that. You know, I could either continue to tell them that the tests are normal and everything seems to be in order and they would say, "But why do I feel so terrible?" and I would basically say, "Well, maybe you need to see the psychiatrist." I just didn't have the tools and a way of relating to my patients in a way that was that effective or satisfying. So I really got into it more by looking for better ways to help my patients.

Back then, as you know, there wasn't a whole lot going on as far as training programs, so I kind of began a journey back in early 1980, 81, 82--during that time--and eventually started to look into things like how the mind affects the body (acupuncture, in particular). I spent a lot of time educating myself, first in this country (I was actually in the first class that Joe Helms--when he was doing his UCLA acupuncture continuing education classes-did; it has grown a lot since then). One thing began leading to another. It has certainly been a journey. It took me over to the UK (England) for most of the 80s, in fact. There wasn't much that I could find (in terms of people willing to take you on) in this country back then.

JB:It is very interesting when you talk about the timing. It seemed to me that the late 70s/early 80s was a really fertile time for birthing what has now matured over the last 25-30 years as this field. I was fortunate to be at some of the founding meetings of the American Holistic Medical Association with Norm Shealy back in La Crosse, Wisconsin back in the late 70s. Joe Helms, obviously, was one of the speakers on the podium in those early meetings, as were a lot of the people who have now kind of grown up to be the leaders in the field. What do you think it was back then that kind of started this movement going? Was it the disillusionment coming out of the 70s? What do you think actually was the germ seed of getting this thing started?

The Start of a Movement

BB:Probably if we looked at that timeframe, a lot of us were from the 60s (I was at Columbia University in the late 1960s). We were certainly taught to question and, you know, not to just accept the status quo; I think that was part of the education that we received. It was also part of the times back then to do that--I think that was true with everything we were doing, including those of us who went in to medicine. We started to really look at questions like, "What did this really mean for the way I related to my patients?" and not just saying "Well, this is how it has to be." So I think there was an element of that; if we kind of trace everybody's paths back then there was a lot of that kind of searching that was going on. It was certainly a fun time to be involved in it. Probably you had no idea what you were getting into. It was a real sort of pioneering feeling at the time. There wasn't sort of a path. There was not a way that you would go on to become a professor in your particular field. If anything, it was sort of the anti-tenure factor, following that path, but it was also an exciting time. There was certainly a group of people in a number of different disciplines that have emerged that were involved in that.

JB:Since you made that career decision to allow your seeking personality to prevail and have become

really a leader in this field, what kind of resistance have you confronted from your colleagues (if any)?

Establishing an Integrative Center at the University of Maryland
BB:I came back to the United States in 1991, and I really did that because I had trained extensively in things like mind-body acupuncture and homeopathy (I trained at the Royal London Homeopathic Hospital and worked with a colleague who had 25 years experience) and I had incorporated that into my family medicine practice. In a way I made a mental shift: it wasn't so much the tools as much as the relationship. It was really, in a way, getting back to good family practice. So that was the mindset that I had in coming back.

The University of Maryland, where I did my internship and residency, said, "Okay. We are willing to travel down this road together if you will do this in a scientifically rigorous way." In fact, the deciding moment was when the head of the cancer center (I was in a meeting with the dean, the head of the cancer center, and the fellow who came from the foundation that gave me my original funding in Great Britain) said, "Do you think you've got all the answers?" And I said, "No, not by any means. I have a lot more questions than answers. I just find it a more satisfying way to practice, and I think the results I am getting are better, but I have no idea what is working for what, or why it is working, or when it is working." And he said, "Well good, because we don't feel like we've got all the answers either, so if you are willing to collaborate together…" That was a very open-minded person, and at that time I thought, "This is great. We'll just get started," not really realizing all that goes into getting involved in an academic center. There were many different things. There was a lot of skepticism. This was 1991. The NIH had not opened up an Office of Alternative Medicine or-as it was actually called-the Office of Unconventional Therapies, when it first got started (OUT was the first acronym). That hadn't even occurred yet.

We started in the Pain Center at the University of Maryland, through anesthesiology, because that was where I had had a lot of patients coming to me for unresolved pain problems in my practice. We eventually developed it into a very interesting multidisciplinary center, which had the usual anesthesiology, psychology, nursing, and physical therapy, but in addition to that, had many other modalities, including acupuncture, different types of relaxation techniques, mind-body approaches, homeopathy-a wide range of things. It took us years, working together, to begin to really see where the strengths, limitations, and weaknesses were and how we could actually work together and communicate well. There was a lot of skepticism. There was not a lot of research going on back in 1991, and the skeptics would certainly hold up the first thing saying, "There is no evidence here." And they weren't far off; the evidence that did exist at the time was not very strong, methodologically.

We began to see who we could collaborate with, who was willing to work together, and eventually created a small team on the research end. Continuing with the clinical care, we began to get ideas about where we might put our best foot forward in doing research for different pain syndromes, acute and chronic. Ideas were emerging about what we might be able to tackle, and then we began to work with our colleagues in methodology and biostatistics, as well as experts in particular diseases and experts in the therapies that we were studying, starting with acupuncture and then eventually branching into mind-body therapies.

That has continued to this day. There is still skepticism out there, but I think it is a lot, lot less and there is a sea change in the people willing to collaborate with us. For example, this past year, a new colleague joined us from the NIH, Dr. Margaret Chesney, who was the deputy director of the National Center for

Complementary and Alternative Medicine. I wanted to introduce her around to potential collaborators, so we met with the head of the genomics institute here. They were very, very willing, and really thoughtful, about how we could use the full array of what they have to offer in a big genomics institute to explore some of these therapies. Same thing when we went in to meet with the head of molecular biology and biochemistry-the same willingness to apply some of their approaches (or techniques they have) to really looking at the cellular level at some of these therapies. This experience carried all the way through to the dean of the dental school, who is a real leading expert in imaging techniques in pain, as well as to the Shock Trauma Center and looking at some of these therapies in the acute care setting. These are world-class researchers and people who were really willing to look at what these therapies have to offer. So I think there is a shift that has been occurring over this past 17 years.

JB:That is really an exciting history. Congratulations. It seems to me from my kind of outside-looking-in experience that a lot of this interest is driven by patient response. I presume that on the other side of this question of how your professional colleagues responded, we then have the question: how did the patients respond? That sometimes seems to be the driver. What has been the patient response to your center?

Patients Vote with their Feet

BB:I think the patients are always voting with their feet. When I was in England I was outside of the National Health Service and had an extremely busy practice because people really wanted this type of care. They didn't want to forego their conventional care, but they really wanted to have a combination and a reasoned approach. Certainly in the United States I have found the same thing. In the beginning I think it was more people who were very desperate who would come to us. They had tried many different things and still had their particular pain problem. And then over time it was really shifting-there was a lot more referring. The patients were saying, "We want this type of care. We want to find ways where we can help ourselves and take on more responsibility, and offer good information, as well as to undergo certain types of treatments." That might be a particular block, or it might be acupuncture, or homeopathic treatment, but it would also be very much the self-help approaches related to lifestyle changes: diet, exercise, nutrition, things like that. The patients are very much there, and I think are looking more and more for this type of an approach.

JB:That leads me to a follow on to your previous point, which I thought was a really well-stated point, around the research methodology and the kind of evolution of research methods and strategies for trying to define some of these things in a reproducible epistemology. We've had the privilege, on Functional Medicine Update, actually just last month-our January issue of 2009-of interviewing Helene Langevin, from the neurology department at the University of Vermont on what I think is pioneering work on the evaluation on the mechanism of action at the cellular level (the physiological level) of acupuncture. Also there is Dr. John Longhurst, who I know you are familiar with, at the University of California, Irvine, Medical School, who has been a highly funded NIH grantee on his work as a cardiologist in acupuncture as it relates to vascular compliance in hypertension. These investigators kind of represent to me, from a pure science perspective, some of the crème de crème of what's happening in the field. But on the other side, then we see things like the book Snake Oil Science by Bausell, who I think at one time was a methodologist within the University of Maryland, and who-from his universal wisdom-has come to the conclusion there is nothing to any of these techniques that is beyond that of sham or placebo. As an expert in the field, can you help us to kind of balance between those two paradoxical and contradictory world views?

Addressing the Skeptics

BB:Well, there are always personalities, and in this country everybody can have their opinion, so we wind up with a lot of opinions. What we would say to the skeptics is that it is important to look at the science and to look at the evidence. I think the first two people you were talking about are really immersed, particularly in the basic science of acupuncture. They are really grappling with some of the issues, as is Dr. Lixing Lao from our own center, who is also really pioneering some of the very interesting breakthroughs with acupuncture research.

We are also doing the same approach that we have taken with herbal medicines (with Chinese herbal medicines)--so a formula of 11 herbs for arthritis--and really taking that same sort of stepwise approach. At our center, we go really from the bench all the way to the bedside, and then to the Cochrane systematic reviews. We have been coordinating that field since '96. We really believe in the idea of taking a phase I small study, seeing if there is some activity there and if it is safe, and then from there, building on that and going to a phase II study where you are adding in a control group, making sure it is still safe and looking at some efficacy, and then going to more of the phase III clinical efficacy study (so a large-scale, multi-center trial) like we did with our acupuncture/osteoarthritis-of-the-knee study. And then actually doing a systematic review of all the other studies. We feel that it is not one study that is going to be everything, but rather you are building up (like a mosaic) evidence, and that's really an important way to go.

I think some of the skeptics-certainly Arthur Bausell would be included in that-are not really looking at the evidence. I know in his book he said there is just nothing there, but I know (because he published some things with us) that he is aware of the Cochrane Collaboration. He is aware (or should be aware) that there are now over 20,000 randomized controlled trials, as well as over 500 systematic reviews. Everything in his book that he said about complementary therapies you could say about conventional medicine. There are gaps and there is small-effect science usually, and what we need to do is to keep building on the evidence and see where it is relevant (where it is clinically relevant), where it isn't, or where it is just not working. That's how science sort of builds upon itself. The sort of mindless approach to say, "Well, there is nothing there,"-it's hardly worth commenting on.

JB: I really appreciate you saying that. When I read the book (Snake Oil Science), I was offended because I thought it was a very selective, biased appraisal of the literature. I then went back and really looked at all of the articles that he had cited as negative articles, and then the ones that were either not cited (or not properly cited) as positive articles, and it lead me to write an article that appeared in Alternative Therapies that was kind of reviewing his review.18 I came to the same conclusion as you: that it seemed that there was an a priori set of assumptions that were trying to be proved rather than really having an open-minded methodological evaluation of the strengths and weaknesses of the field. I don't know where that was derived from, but it didn't seem like it served well to leading to clarity.

BB: No. Maybe it sold books-I don't know. If you look at some of his articles in the past…he actually published one article with an investigator at our own center and found opposite to what he was saying-that it's not all placebo. You know, it's hardly worth commenting. There are so many more important things.

We have been doing a lot of clinical trials, a lot of bench science and Cochrane reviews, and what we are sort of also grappling with now is…I don't quite know how to say it, but you're putting this ladder up with all of the studies, building up one at a time against this building, and then you get to the top and,

you know, you want to make sure that you are on the right building. Some of the approaches that I think people are starting to say we really need to look at (and this is not necessarily complementary and alternative medicine, this is just good, whole-person care, preventive medicine-what I really feel integrative medicine is about)-people are talking about, "How do we evaluate that?" Bringing in some of the things that we already know about behavioral medicine and its effect on some of these chronic diseases and then the effect of, say, adding health coaches, and then maybe judicious use of some particular therapies to that-those are the type of changes that we might need to be looking at and seeing the results of going forward.

JB: That really is a very nice segue into a question that I think is an affiliated question, which has to do with what has evolved in the field since its inception, and that's the development of various organizations to support both the research and also the dissemination of information clinically. I'd like to ask your opinion (being at a high level of oversight in your position): what is your impression of how the NIH Center for Complementary and Alternative Medicine has contributed to the development of this field over the last, say, 10 years? And then I think a companion to that is your involvement with the Consortium of Academic Health Centers for Integrative Medicine, and also the Bravewell Foundation-how do you see the three of those all making contributions?

Organizations Making an Impact
BB: Well, the NIH NCCAM I think has had a major impact by just existing and having a funding source and sort of a national agenda. Really the different leaders there have tried to set a very high bar, both for the basic science and the clinical trials. As they have gone on, they have been learning as well. They have had, certainly, a number of clinical studies recently that have not shown any effect, and I think they have said, "We are learning that the dose is a critical piece. Or the stabilization of a particular herb is very important." You know, there are different issues that they have found, which kind of gets back to that sort of very stepwise approach. But just the fact that they are there and holding some methodology meetings or meetings on placebo or bringing people together from different points of view I think is very, very important, so you get a lot of the universities involved.

They also had an emphasis on drawing together some of the different therapies, whether it is chiropractic, or naturopathic, or massage therapy and some of the academic health centers to collaborate together. I think all of those things encourage new ways of really doing research when you have the right people at the table. I think they have had a big impact. We had two NIH center grants-one working with people in Hong Kong-and the impact of NIH over in Hong Kong has really led-really encouraged-some of the health authorities to take things more seriously.

The Consortium of Academic Health Centers for Integrative Medicine I think is a wonderful thing. I was involved with it when it first started (I think our first meeting was in 1999 at the Fetzer Institute in Kalamazoo). It was really the idea of Jon Kabat-Zinn, who saw back then that a number of places were starting to emerge in the field and it would help if we just got together (especially with some of our deans or presidents so we could let them experience what some of these therapies were about), and really to talk about some of the challenges that we were facing, and some of the opportunities.

We started with, I think, six or seven places, and I was just recently at the last meeting in Texas and I think there are 43 universities now that are involved in the consortium, including some of the Canadian schools. What I was really struck by (this is the part that I really appreciated) was that there was so many

young people there. It wasn't just the old ones-like myself or you-that were standing around; there was like a whole generation of people who were really finding a path and a passion for doing good work in this field, whether it was in education and looking at new models of education and how you bring mind-body skills into the schools, or certainly a wide range of discussions about research, including complexity science and the meeting that is going to come up in Minneapolis in May of 2009. It is just sort of exciting. It is good because it gives people a place where they can really share experiences, maybe some places are, you know, maybe one or two or three years into the game at their own institutions, and other places have more years-you know, everybody is willing to learn from each other and share. I think it is still maintaining, although it is harder as it gets bigger to maintain that certain spirit, but I think there is a real willingness to share and collaborate.

And then the last group you mentioned was the Bravewell organization, which is a different type of organization. That is a group of philanthropists who are really doing good by coming together and raising the awareness of what integrative medicine is about, such as through their PBS series that they did a couple of years ago, and now they are hosting an Institute of Medicine summit meeting in February, I think it is.

JB: Sounds like exciting times. What an evolution, just in the last few minutes of your summary. If you think back 25 to 30 years, who would have guessed, right?

A Great Time (and Future) for Integrative Medicine
BB: Absolutely. Even in our own organization. I took that funding from the Bravewell Collaborative and seed funded an institute outside the university, one that could complement the hands-on work that different universities are doing, but to be able to take a step back, and to bring people together from very different disciplines to look at some of these healthcare questions and say, "Okay, maybe somebody from anthropology and social sciences, or somebody from the business world, or somebody from public health or medicine, and to really come together and grapple with some of these questions, and then to have some demonstration projects to really test out what people think is maybe a way forward with it. It's a great time, and it is certainly a needed time right now to make some changes.

And I guess the last thing I would say is that a lot of what we have been talking about (medicine and disease), certainly at the institute that we formed and I think a lot of people are saying, is that what the real focus (and maybe the real leap forward) is going to be more of the focus on health and well being. With the Greek gods (one was Asclepius of medicine and then Hygia of health), they knew the difference, and we kind of lumped it together. But we haven't put so much influence on the health side.

JB: That's a beautiful segue to really my last question (we could go on in this conversation for hours with the rich history that you have brought to this field). I'd like to close by just asking you, from your perspective, given that we are seeing a rising tide of certain chronic illnesses in our society, where do you think family medicine is going over the next, say 4 to 6 years? We have a new age coming up in 2009. What is your position as to where we might be going?

BB: My hope is that family medicine and primary care medicine will really focus on more of the prevention side. I think that we sort of give it lip service. What is it-2 or 3 percent of the total budget goes to that? So taking a whole-person approach-the biocycle, social side that people always talk about in family medicine, as well as not just taking people back to a neutral place, but really looking at a more

proactive way of looking at health, and health across the whole lifespan. That's where I think it has to go. I think people are talking about some of the medical models and home models and where that fits in to maybe extending that with electronic records and also the health goal-different ways of extending things. That is where I think things are going to go. That is my hope about where they will go because I think that will make a difference.

JB: Do you see any signs that third-party providers and institutional kind of assignments of fee-for-service are sympathetic in changing in that regard so that there will actually be an incentive to be able to keep the lights on by doing this kind of medicine?

BB: That's a key question. You know, I think there is certainly hope with the new administration. There are certainly newspaper articles (New York Times, Washington Post) saying that we really need to look at realigning our financial incentives towards keeping people well and out of hospitals. It's not going to change that easily from the insurance companies. I think it will need to come from people voting with their feet with their flex accounts and their health savings accounts, and then also maybe from the top saying, "We really do need some real change at this point in time."

JB: Dr. Berman, I want to thank you so much for what you have provided in the way of leadership and courageousness, really, to be the initiator, founder, and director of the first center of integrative medicine in an academic medical center in the United States. That sets a tone for the whole field. I bet you are very proud of seeing, now, those 43 medical schools that are part of the consortium. It certainly started first with your program. It is really a privilege to have you as part of the field.

BB: I really appreciate that. It is great to see a lot of people getting involved. I think it is what the people are demanding, and I think a lot of people who have gone into practicing this way are really enjoying more the practice. We just have to figure out some the ways to make sure-as you said-that it keeps the lights on and keeps people well.

JB: I'm with you. Thanks a million and best to you in 2009. We'll talk to you soon.

BB: You, too. Thanks very much.

I'm sure you were all as impressed as I was in listening to Dr. Berman recount this journey that he has been on in the development of what I might consider the new medicine-the medicine that takes the best from the past and couples it with the best of our future to create the new solutions to this rising tide of chronic disease. I think this thoughtful approach and the willingness to open minds, to be a recipient of information from different sources, to filter that and to see how it fits into the paradigm is all a very, very important part of developing clinical acumen and being a good evaluator (not being a sponge, but being a filter). I think if we try to be a sponge-with the weight of new information coming out-we are logged completely full so quickly. So we have to learn how to filter that information, information about the perspectives that we use to evaluate quality of information and how it has stickiness in our practice to create improved patient outcomes.

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