August 2005 Issue | David Perlmutter, MD Commons Medical and Surgical Center

http://jeffreybland.com/knowledgebase/august-2005-issue-david-perlmutter-md-commons-medical-and-surgical-center/

DOWNLOAD AUDIO |

Welcome to *Functional Medicine Update* for August 2005. I think it would be noteworthy for us to spend this issue of FMU revisiting some of the topics that were so eloquently discussed at the 12th International Symposium on Functional Medicine—The Immune System Under Siege: New Clinical Approaches to Immunological Imbalances in the 21st Century. I'd like to reiterate a couple of thoughts for those of you who weren't fortunate enough to be there. For those of you who were there, perhaps this will remind you of some of the high points and clinical takeaways.

We started off the plenary sessions with an eloquent presentation by Dr. Esther Sternberg, Director of the Integrative Neuroimmune Program at the National Institutes of Mental Health. The theme of her presentation was, does stress make you sick? Dr. Sternberg did a very nice job of reviewing a tremendous body of recent information related to the neuroendocrineimmune system. It followed very nicely from the precourse discussion by Dr. Ilia Elenkov, who had also been at the National Institutes of Mental Health. He described some of the remarkable relationships between the outside and inside worlds, and the signaling processes through which the neuroendocrineimmune system modulates function across many organ systems and gives rise to conditions as disparate as depression, inflammatory bowel disease (IBD), multiple sclerosis (MS), coronary artery disease (CAD), and cancer. The concept of the stress connection to illness—pioneered by Hans Selye some 40 years ago—helped to focus the broad-based mechanisms of dealing with complex, chronic diseases of the immune system

We would be remiss if we didn't acknowledge that in the spring of 2005, a major new document was published by the Institute of Medicine (IOM) of the National Academies. The book is titled *Complementary and Alternative Medicine in the United States*,by the Committee on the Use of Complementary and Alternative Medicine by the American Public, Board on Health Promotion and Disease Prevention.[1] It is now available for purchase from the Library of Congress and the IOM, and is a manifesto for what is happening in the changing environment of health care today. I urge you to read this book. I believe it contains tremendous insight pertaining to the resistance of accepting some of the concepts that were described at the 12th symposium. It seems so self-evident to those who have been in this field for some time, but for others who may be outside the field, complementary or alternative still means "scientifically unproven." Dr. Sternberg helped us to understand why the acceptance of some of these ideas is so complex, and that they cut across disciplinary boundaries and are easily compartmentalized into silos. The book, *Complementary and Alternative Medicine in the United States*,demonstrates the complexity required in understanding how one cuts across disciplines of organ-system thinking.

The book goes through a number of very interesting concepts that pertain to the acceptance and rising popularity of CAM in the United States. About 27 billion dollars a year are spent on CAM therapies. Forty-two percent of Americans report that they have used at least one CAM therapy. Less than 40 percent of these individuals tell their doctors about their CAM visits, because they feel they wouldn't understand. In 1997, 629 million visits were made to CAM providers and 386 million visits made to primary care doctors, suggesting that there are almost twice the number of visits to CAM providers as there are to primary care providers in the U.S. each year.

Dr. Stephen Straus, Director of the NIH's National Center for Complementary and Alternative Medicine recently praised the report and said it is:

"an achievement that elevates the discussion of CAM beyond the advocacy and skepticism that has long hampered the evaluation of CAM science. It will further the scientific investigation of this new field, increase its legitimacy as a research area, and ultimately improve public health."[2]

We are witnessing a change in the paradigm, a changing of the guard, a transition to a healthcare system that better integrates techniques and strategies that will be directed toward the chronically ill patient, rather than focusing primarily on the application of research for the management of acute disease, with an absence of understanding how to set up a chronic disease management system that will draw from the replicable components of the CAM tradition.

This theme was certainly borne out through the discussions at our 12th symposium. Each investigator outlined the basic science, the underlying physiology, and the connection of their discipline to the broad arena of chronic disease prevention and health management.

We moved from Dr. Sternberg's presentation into that of Dr. Michael Holick, who talked about how vitamin D modulates immune and inflammatory processes. This resulted in a standing ovation from the attendees for the brilliant and eloquent tour de force that Dr. Holick presented about how vitamin D is more than just a vitamin to prevent rickets. Its interrelationship with immunological function, neurological function, cardiovascular function, and endocrine function, illustrates its principal role as an important prohormone in the regulation of gene expression, and ultimately, the defense against many chronic diseases of aging.

We proceeded into a discussion of gene/environment interactions underlying immunological function. Dr. Peter LeSouef from the School of Pediatrics and Child Health at the University of Western Australia, did a magnificent job of outlining aspects of the gene/environment interaction with immunological problems, focusing on Th2-dominant conditions, such as B cell-mediated asthma and eczema, showing that the concept of the environmental hygiene theory of asthma is too simplistic, and that there are remarkable relationships between the environment and asthma that go beyond those of specific genotypes. He showed that there are greater diversities of response to the environment in one individual ethnic group than there are across all ethnic groups, suggesting that race is not the determinant for asthma, but that the environment is a primary factor. He went on to point out that 65 percent of asthma cases appear to be environmentally related, whereas only 35 percent are related to genotype. There is a genetic linkage, but it's not the overwhelming cause of the increasing prevalence of asthma and atopy—the Th2-mediated immunological disorders.

That was a theme that ran through the entire week of the symposium—conditions that modulate the subtle immunological balance between Th1 and Th2 immunological functions, one being more related to innate immunity, the other more to acquired or adaptive immunity. It was pointed out that imbalances, infections, trauma, ischemia, poor-quality diets, and psychological stress can relate to dysfunction in that balance, tipping it toward a Th1-dominant or a Th2-dominant condition. Systemic inflammatory conditions like rheumatoid arthritis (commonly considered Th1-dominant), have their own constellations of inflammatory mediators, such as interleukin-1 (IL-1), interleukin-2, (IL-2), or tumor necrosis factor alpha (TNFα). Th2 conditions are associated with adaptive or acquired immunity, which have to do with a different family of cytokines, such as interleukin-4 (IL-4), interleukin-10 (IL-10), and interleukin-12 (IL-12), and the different constellations of conditions associated with these cytokines which are more tissue-specific, such as asthma and eczema.

As we went through the week, we recognized that the best medicine for the management of many of these conditions is the one that leads to normalization, or balance, of the imbalanced immunological, neuroendocrine functions. That is an overview of what was achieved throughout the week, beginning with the precourse and working through the plenary sessions into the workshops. In a symposium of this breadth, it is difficult to leave with *the* takeaway. Rather, there are many factors contributing to the dysregulation of the immune system that cut across many different clinical conditions, ICD9 diagnostic codes, and subspecialties of medicine. No one "owns" this particular area of concern; it is part of all of medicine.

We learned that beautifully from the eloquent presentation by Dr. Colleen Hayes from the Department of Biochemistry at the University of Wisconsin, who talked about the vitamin D endocrine system and its relationship to autoimmune diseases, specifically focusing on multiple sclerosis (MS). In her discussion, it was obvious that there are many variables that influence the balance of the immunological system and, as a consequence, regulate signaling at the gene expression level, creating the outcome in the cells, tissues, organs, organ systems, and the whole body that we call function or dysfunction. Her topic was well organized, magnificently presented, and resulted in another standing ovation.

That was followed up with a magnificent presentation by Dr. Burton Berkson. Many of you will recall that he has been a guest on FMU on two occasions. He talked about the work he shared with us on FMU related to hepatic inflammatory disorders and what he calls his "triple therapy"—use of lipoic acid, selenium, and silymarin for the management of various types of hepatic, inflammatory, oxidative stress-related illnesses. He went through a number of case histories and experiences with patients, and the basic science behind them. He was very convincing about the important therapeutic role triple therapy plays in these conditions.

Last in the plenary sessions, we finished up with a call to arms by Dr. Wafaie Fawzi from the Harvard School of Public Health. Dr. Fawzi is the principal author of work published in *The New England Journal of Medicine* pertaining to nutritional supplementation in individuals who are HIV positive, in which he demonstrated clear evidence that nutritional intervention with greater-than-RDA levels of specific nutrients can enhance survival, lower infection, and attenuate some of the adverse consequences of AIDS in people living in sub-equatorial Africa. That reminded us that sometimes inexpensive therapies can be very important for supporting proper immunological function.

That was mirrored in the precourse presentation by Dr. Meydani from Tufts University School of

Medicine and the Human Nutrition Center on Aging in Boston, describing her work on the impact of nutrients on immunological function. She showed that vitamin E plays an important role in improving immunological function in older-age individuals. She conducted a dose-response clinical intervention trial which I thought was quite fascinating, showing that somewhere around 200 IUs per day seems to be the maximum effective daily dose of vitamin E for the promotion of good immunological function. At too low a level, there is lowered activity; and at too high a level, there is also a lowered activity. Instead, there was a bell-shaped, parabolic dose-response curve, which I think we can say holds true for many, if not virtually all things. There is a parabolic dose-response curve for water and for oxygen. Too little, and we die of dehydration or hypoxia; too much, and we die of hyperhydration or hyperoxygenation.

The parabolic dose-response curve is similar in many substances. We want to be "in the zone" for optimal regulation. This zone is individualized to some extent in each person. That's why personalized medicine becomes very important, and why the medicine for the averages is probably going to produce the outcome of the averages relative to health care. As we move in the direction of personalizing medicine in the post-genomic era, it takes us beyond asking the question of what the diagnosis is, to understanding what the functional medicine assessment is. What are the antecedents that trigger the mediators that ultimately result in the signs and symptoms that are expressed in the patient? How does that relate to interactions with and alterations of the neuroendocrineimmune system? It is that complex system that seems to be the switching device between external agents in the environment and internal functional changes in the neuroendocrineimmune system.

The symposium helped to bring greater clarity in these areas and gave us some new tools and insights. We had a number of remarkable workshops that dealt with specific implementation of these concepts. Dr. Robert Rountree's workshops on nutrient interventions to regulate Th1 and Th2 function were stellar, including a tremendous review of the literature and a lot of clinical wisdom. These perturbing environmental factors play a major role in modulating immunological, endocrine, and neurological functions that ultimately give rise to a trajectory of either high function or disease.

We should remind those of you who may not have had the privilege of attending the symposium, or those of you who might have felt overwhelmed by what you experienced there, that you might want to acquire the symposium tapes. They will turn out to be classics relative to the evolution of this field. I wish every one of the contributors to the IOM's book on CAM might have attended the symposium. Had they been there, I think we would have been able to raise the bar even higher, with the understanding that many of these concepts have very strong, scientific underpinnings and that they fulfill the criteria of the rule of reasonableness, in terms of their effectiveness and safety.

With that in mind, let's focus this issue of FMU on some of the impact of what we learned about the neurological system at the symposium. There were a tremendous number of outcome variables related to the presentations on immune function that had a relationship to the neurological system.

There are immunological cells embedded within the nervous system—the microglial cells. They get their messages, in part, from the neurological system, but also from the environment and cues from the immune system. We learned at the symposium that there are routes of entry across the blood brain barrier (BBB) for immune system messages from the Th1 and Th2 cytokines that can modify the functional outcome of the microglia, and which then communicate with the neurons through the release of second-signal messengers, such as nitric oxide (NO). That means that the brain can be influenced by the

immunological status of the host. When you have the flu, your brain does not feel capable of carrying on high-level function. In the case of a very bad flu, where there is a serious immunological upregulation, you not only have a fever, but you also have all sorts of "funny thoughts." Your brain chemistry is disturbed as a consequence of the high load of various inflammatory mediators that are trying to defend against the infection.

The antigen-presenting cells, the dendritic cells, and the interrelationship they ultimately have with response to immunological activators, can influence brain chemistry. This may explain, in part, why it is that some individuals who are gluten sensitive present with neurological-related symptoms—perhaps the interrelationship between immune upregulation and brain chemistry connects to neuronal apoptosis, or cell death and dementia. I am speculating here, but it has been recommended that patients presenting with non-specific neurological problems, such as gait disturbances, should have gluten-sensitivity testing for presence of anti-gliadin or antiendomysial antibodies,

The dendritic cells link the innate (preformed) and the adaptive or cognate (specificity and memory) immune systems through the B cells, the Th2 system. As these specialized antigen-presenting cells have profound influence over immune response, they induce specific leukocyte populations that release their own types of immune modulators, the Th1 and Th2 cytokines.

There is a tremendous amount yet to learn about the basic biology of these dendritic cells; however, we now recognize that the toll-like receptors that sit on the surface of the innate immune system sense pathogen-associated molecular patterns, and go on to release substances that influence the Th2 system, or the acquired immune system. These are in communication, one with the other, through the toll-like receptors that appear on the surface of the innate immune system. This finding has ramifications for clinical immunotherapy protocols, and provides a satisfying link between the morphology of the dendritic cells and their migration into other tissues. The active movement of membrane extensions of the dendritic cell, like phagocytosis, and the simultaneous disappearance of various podosomes, suggests a coordinated redeployment to fuel the pathogen-driven increase in endocytosis.[3] We see this vigilant system in real time, morphing its way through the body's tissue, doing a "seek-and-destroy" type of recognizance mechanism, or mission. That explains how, even in the brain, immune cells can be found doing seek-and-destroy. If they are activated, they can produce their own oxidants as these phagocytic cells do, through the generation of chloride ions that go on to produce superoxide and hydrogen peroxide, and even possibly hydroxyl radical through the Fenton reaction, so it increases oxidative stress. One of the things we can say about activating the immunological system is that it is associated with increased oxidative stress. Or, oxidative stress is often associated with immunological alteration. They go hand in hand.

This raises questions about things in our diets that are commonly associated with being immunological activators, such as gluten. Gluten is food for some, but may be poison for others. The question is how early to expose the immunological system to a potential antigenic stimulant for something that can activate toll receptors and initiate a memory effect of alarm in immune cells. That leads to the concept of infant exposure to glutinous grains or cereals.[4]

In the *Journal of the American Medical Association*, there is an article, titled "Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease."[5] The authors state that there should not be early introduction of gluten-containing grains to a nave immune system in infants at risk of celiac disease, which was defined as the presence of HLA-DR3 or DR4 alleles,

or having a first-degree relative with type I diabetes. They are waiting six to eight months before introduction of cereal grains containing gluten. It is dependent on the immunological uniqueness of the infant as to how susceptible they might be. Once the system is primed, as these authors discuss, there is a tolerance problem that may persist throughout the rest of that individual's life because of a heightened response to that potential antigenic protein. The authors discuss the relative frequency of CD4-positive individuals and those who carry specific genetic risk factors such as HLA, DR3 or DR4 alleles who have increasing sensitivity to gluten in their diets.

The next area I want to discuss is emotional stress, as a toxic event that can prime or modify the immunological system and the balance between Th1 and Th2. There is an interesting article that appeared in *The New England Journal of Medicine*, titled "Neurohumoral features of myocardial stunning due to sudden emotional stress."[6] The authors looked at how neuroendocrineimmune functions are modified by sudden, acute emotional stress. In this paper, it was shown that emotional stress could precipitate severe, but reversible, left ventricular dysfunction in patients without coronary disease. In the absence of elevated cholesterol, hsCRP, and triglycerides, these individuals had left ventricular dysfunction following a serious stress response. The exaggerated sympathetic stimulation is probably central to the cause of this syndrome, and demonstrates the close connection between the hypothalamus/pituitary/adrenal (HPA) axis and myocardial function. This was one of the features of the Selye stress model that Dr. Sternberg addressed in her presentations at the 12th symposium.

As a consequence of these catechol-driven functions in the vascular system, we also recognize that heart rate profiles during exercise are very important predictors of sudden death and may be one of the better diagnostic tools for defining whether a person is at risk to sudden cardiac death. I am now quoting from a paper that appeared in *The New England Journal of Medicine*.[7] The authors of this paper found that the heart-rate profile during exercise and recovery was a predictor of sudden death, and was probably more predictive than things like serum lipids and other traditional cardiovascular risk factors. This was a study done in 5713 asymptomatic working men between the ages of 42 and 53 years, none of whom had clinically-detectable cardiovascular disease. They underwent standardized graded exercise testing between 1967 and 1972. Data were examined on the subjects' resting heart rates—the increase in rate from the resting level to the peak exercise level—and the time it took for recovery back to their basic resting pulse and the pulse level after one minute, post-exercise. It was found that the more resilient the heart function (the faster the heart rate went up on exercise), the more it was able to recover after exercise and come back down to the resting pulse. All were indicators of good cardiovascular function. I would call it cardiovascular organ reserve, to continue to use the term we have employed over the years. As the resting pulse goes up, as the differential between resting and exercise pulse goes down, and as the rate of recovery of pulse is slowed, it demonstrates lowered plasticity in the cardiovascular system and indicates increased relative risk to sudden cardiac death upon a precipitating event.

The concept of homeodynamic function—plasticity and organ reserve as measures of functionality—as contrasted to looking for alterations in an EKG that are suggestive of cardiopathology, may be a better marker for picking up earlier states of dysfunction that are modifiable by intervention.

That raises the question of cardiac rhythm variability, or the so-called heart math approach. I find autonomic tone and its relationship to cardiovascular risk profiles to be a very important part of our learning system. These are the dangers of chronic fight or flight, the chronic stress effect on vascular function. I owe Dr. Jayne Alexander, one of our functional medicine colleagues, a thank-you for tipping

me off on an extraordinary paper published in the *Mayo Clinic Proceedings*.[8] I believe it is a valuable tool to add to our assessment armamentarium. The title of this paper is "Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight." This is work done by Brain Curtis and James O'Keefe in the Mid-America Heart Institute of Saint Luke's Hospital and University of Missouri, Kansas City. They looked at things that were traditional biochemical markers of hypertension and cardiovascular function, such as angiotensin-converting enzyme, calcium effects, relationship with serum lipids, congestive heart failure, and left ventricular function. They found that autonomic dysfunction is a very powerful risk factor for sudden coronary events. Confirming what was discussed in the recent *New England Journal of Medicine* paper, looking at heart rate recovery after exercise, a five-year mortality was extraordinarily lower in patients who had very rapid recovery, compared to those with low recovery rates after exercise.

To extrapolate, we could say that fine structure EKG or electrocardiogram diversity may be seen as increasing physiological degrees of freedom that indicate plasticity that indicates organ reserve. Highly trained athletes who are very fit have a tremendous amount of fine structure variability in their heart rhythms, whereas in people who become less healthy and lose cardiovascular reserve eventually becoming ill and having cardiopathies, the fine structure simplifies and their EKG gets simpler rather than more complex. The more complex EKGs are associated with biological variability, which is associated with fitness. When I say fitness, I mean physiological biological fitness, as contrasted to those individuals with simpler EKG patterns. Of course, the simplest is a flat-line EKG, which we associate with death. The point the authors are making in this article on autonomic tone, however, is that it is driven by adrenalin, by the flight or fight response, and causes lowered heart rate variability, poor recovery after exercise, and is as important a risk factor as any specific risk factor that has ever been evaluated for determining the relative risk to sudden coronary events.

Therefore, things we ought to be looking at clinically are a resting heart rate greater than 90 beats a minute, inability to achieve 85 percent of predicted maximum heart rate on a treadmill test, and abnormal heart rate recovery, which is failure to decrease heart rate 12 beats per minute during the first minute after peak exercise. When you take your peak exercise pulse rate, you sit down and rest for a minute after exercise and, if it doesn't come down 12 beats, it's an indication of poor recovery and abnormal heart rate variability, meaning failure to change heart rate, or the resting rate interval, by 10 beats per minute during one minute of slow, deep breaths after exercise. These are indications of significant reduction in what might be called vascular fitness, or vascular plasticity. This study on autonomic tone related to cardiovascular risk ties beautifully together with the paper in *The New England Journal of Medicine* on heart rate profile during exercise.

As you do cardiovascular testing, the concept of heart rate variability during and after exercise, resting pulse rate, and recovery rate are extraordinarily important in defining some of the things related to the psychology, neuropsychology, and neuropsychoimmunology of stress driven by the autonomic nervous system.

Hemodynamic Responses to Stress

Let's talk about hemodynamic responses to stress and their relationship to plasma homocysteine. If we are talking about immunological, neurological, and endocrine imbalances based on clinical chemistry, one that has emerged is the Kilmer McCully concept of hyperhomocysteinemia, or elevated homocysteine levels in the blood. Researchers have been looking at ways of modulating homocysteine levels in the

blood and also looking at the effect that high homocysteine has on endothelial function. It might be endothelial function of the vasculature, which could include not only the cardiovascular system, but the brain system itself, and how these interrelate to a variety of clinical outcome variables.

I was pleased to see a paper in the *Journal of Nutrition*, titled "Oral L-arginine improves hemodynamic responses to stress and reduces plasma homocysteine in hypercholesterolemic men."[9] It follows nicely from the presentations Dr. John Cooke from Stanford University made at our symposium a few years ago in Tucson, AZ, during which he described the work he had been doing in the area of cardiovascular biology, looking at the role of arginine supplementation in improving vascular endothelial function. first in baboons and then in humans.

It has been shown in other studies that L-arginine, administered intravenously, substantially reduces blood pressure and peripheral vascular resistance in patients with vascular disease. In this *Journal of Nutrition* study—a randomized, placebo-controlled crossover study with oral arginine at 12 grams per day for three weeks—hemodynamic factors were studied in 16 middle-aged men with hypercholesterolemia, at rest and after two standardized stressor tasks: a simulated public speaking task and a cold pressor. As expected, the stressor task increased blood pressure and heart rate but, relative to placebo, L-arginine lowered cardiac output by 4 liters per minute, decreased diastolic blood pressure by approximately 2 mm Hg, had a positive impact on the pre-ejection period, and lowered plasma homocysteine by about 2 umol/L. The change in plasma L-arginine was inversely correlated with a change in plasma homocysteine. Contrary to results of previous studies with L-arginine administered intravenously, oral L-arginine did not affect total peripheral resistance or plasma insulin. Oral L-arginine also did not affect plasma glucose, CRP, or lipids. The pattern seems to be consistent with the hypothesis that oral L-arginine reduces blood pressure when administered in fairly high doses—in this case, about 12 grams per day, given in 3 to 4 gram divided doses.

Diets high in L-arginine derive protein primarily from nuts and fish, as they are higher in L-arginine composition and lower in L-lysine composition than meat protein. These diets are also associated with lowered levels of CRP, inflammatory mediators, and reduced blood pressure. This may be one of the many variables that influenced the outcome of the DASH trials, in which vegetable-based diets were employed to stop hypertension and lower blood pressure. Not only is blood pressure related to calcium, magnesium, and potassium, but it may also be related to things like amino acid composition, with increased arginine dietary intake in the vegetable proteins. I am now quoting from a paper, titled "Association between dietaryarginine and C-reactive protein," that appeared in the journal, *Nutrition.*[10] The results of this study showed a strong inverse relationship between dietary arginine intake and a CRP level that persisted after controlling for other factors that can influence CRP. The authors conclude that individuals may be able to lower their risk for cardiovascular disease by consuming more arginine-rich foods, such as nuts and fish.

It is interesting to note that arginine's effect on endothelial NO causes vasorelaxation and has a positive effect on endothelial redox levels. Could similar effects be achieved by giving a drug like sildenafil? Sildenafil, or Viagra, influences NO through its effect on the signaling molecule cyclic guanosine monophosphate cGMP, sosssss might that have a positive effect on cardiovascular function in some individuals? Ironically, there is now emerging evidence that sildenafil is being used in individuals with specific types of cardiopathies. I am now quoting from a paper that appeared in *Nature Medicine*.[11] The author states that Viagra, or sildenafil, operates by increasing the levels of cyclic GMP in target cells.

This mechanism underlies the discovered action of how it may improve heart function in individuals with hypertrophic heart activity. By modulating these endothelial NO functions via cyclic GMP in endothelial cells, there can be some very profound, positive, normalizing effects. I am not advocating sildenafil; I'm advocating a diet that is immune-modulating that contains nutrients that help to regulate endothelial NO function.

What about simple things, like play and exercise? Can they help prevent immunological imbalance that can lead to an inflammatory response that can result in things like amyloid buildup in the brain? That's a fairly interesting concept—that by proper play and proper exercise, one can protect the brain from amyloid buildup. That's not just speculation. Recently in *Science* magazine, there was a wonderful article that described work that is being published on how play and exercise in animals is able to protect against neuritic plaque, or amyloid buildup, and may thereby be seen as a preventive agent for things like Alzheimer's disease.[12]

What about neurotoxicity that relates to heavy metal association, things like mercury and lead? We come back to revisit old things in new ways, and certainly those also influence neuroendocrinemmune function and can lead to neurobehavioral dysfunction. In a recent paper in *JAMA*, the authors state that the data do not provide strong support that blood mercury levels are associated with worse neurobehavioral performance, but if we look closer, we find that increasing blood mercury levels were associated with worse performance on Rey complex figure delayed recall, but with better performance on a test for manual dexterity.[13]Certainly, the response to heavy metals is very individualized and may influence specific functions differently. We learned that from Vera Stejskol many years ago, the scientist from Ostra who showed us that there can be an extremely large variation of response to heavy metal toxicity from person to person.

What about neurotoxicity that relates to heavy metal association, things like mercury and lead? We come back to revisit old things in new ways, and certainly those also influence neuroendocrinemmune function and can lead to neurobehavioral dysfunction. In a recent paper in *JAMA*, the authors state that the data do not provide strong support that blood mercury levels are associated with worse neurobehavioral performance, but if we look closer, we find that increasing blood mercury levels were associated with worse performance on Rey complex figure delayed recall, but with better performance on a test for manual dexterity.[13]Certainly, the response to heavy metals is very individualized and may influence specific functions differently. We learned that from Vera Stejskol many years ago, the scientist from Ostra who showed us that there can be an extremely large variation of response to heavy metal toxicity from person to person.

Follow-up Testing Among Children with Elevated Screening Blood Lead Levels

Don't forget lead. We know that lead has a detrimental effect upon brain biochemical and neurocognitive function. There is a good article in *JAMA* on the follow-up testing of children with elevated blood lead levels, showing increased neurobehavioral difficulties.[14] This confirms what we learned nearly 30 years ago from work accomplished at Mass General Hospital, showing that children with marginal elevations of blood lead levels had reduced neurocognitive performance and behavior.

There is much about the immune system that interfaces with the neurological system that interfaces with

the endocrine system that gives rise to dysfunction. We are talking about good science based upon good medicine. Perhaps functional medicine from this perspective would be considered the best medicine for these kinds of chronic problems.

That leads us into our Clinician of the Month. We are excited to share advancing concepts related to the neurological implications of these concerns.

INTERVIEW TRANSCRIPT

Clinician of the Month
David Perlmutter, MD
Commons Medical and Surgical Center
800 Goodlette Road, Suite 270
Naples, FL 34102

JB: It's time for our Clinician of the Month. One of the dominant themes at the 12th International Symposium on Functional Medicine was the topic of neuroendocrine immunology relating to complex disorders that cut across subspecialties of medicine. It's difficult to isolate individual organ systems. We need to look at things from a systems biology level to understand conditions like multiple sclerosis (MS), systemic lupus erythematosus, or inflammatory bowel disease (IBD). That message came through loud and clear at the 12th symposium. Following up on that theme, I thought it would be timely to revisit a clinician visionary whom we have had the privilege of talking with before—Dr. David Perlmutter, a neurologist in Naples, Florida. Dr. Perlmutter has helped all of us with his perspective on functional neurology and how it relates to immunology and endocrinology.

For those of you who may not be familiar with Dr. Perlmutter's background, he graduated from Florida State University and the University of Miami School of Medicine, and did research in neurosurgery and microneurosurgery at the University of Florida. He has been in private practice in Naples, Florida for a number of years, where he established the Perlmutter Health Center, which focuses on complex relationships related to neurological function. He has been a pioneer in the area of hyperbarics and nutritional intervention, and is the author of the best-selling book, The Better Brain, published in 2004. He has received a tremendous amount of media attention for his work and his book.

Welcome back to FMU, Dr. Perlmutter, and thanks for spending some time with us.

DP: It's my pleasure.

JB: Let me go back and pick up from where we left off in May of 1999 when you were last on FMU. At that time, you painted a mosaic of what functional neurology looked like. There was an article on Parkinson's disease in the Journal of the American Medical Association a couple of years ago that reminded me of the picture you painted in 1999, suggesting that even JAMA was picking up on recent trends. What has changed in the field you have so significantly contributed to?

Recent Trends in Functional Neurology
DP: I'd like to paint a better picture and come to you from a position of more optimism, but I'm afraid I'm not seeing a lot of progress, at least from the general purveyance of neurology to the American populace.

We don't focus on prevention of disease at all, and yet we know that diseases like Alzheimer's and Parkinson's have obvious causes and should be considered preventable. Over the past couple of years, I've been doing a lot more mainstream media education, along with educational pursuits with our peers. I've been trying to get the word out in the mainstream that these are diseases for which we have no cure and yet, they are preventable, and that this is where the emphasis needs to be.

You mentioned JAMA. I would call attention to other publications by the American Medical Association, such as the Archives of Neurology. In fact, in January of 2004, they published an article that demonstrated that individuals with the highest levels of vitamins C and E had a much higher risk reduction for Alzheimer's disease.15 There was another report that those with the highest levels of DHA had a 70 percent risk reduction for Alzheimer's disease. These articles were followed in October 2004 by a very interesting report in The Lancet that demonstrated that the main drug used for the treatment of Alzheimer's—donepezil—doesn't work.16 Here we have a situation where the public is being led to believe they should live their life, come what may, and then, suddenly, when you don't have both oars in the water at the same time and you're starting to forget where you put your keys, there's a pharmaceutical rescue called donepezil, and that's going to be the way out. We see this drug advertised on the evening news every night, and in every trade magazine.

We now know that the drug doesn't work. There is no drug to cure Alzheimer's and yet, there's powerful information indicating that there are very important risk factors to which we should pay attention, things we have talked about for a long time—antioxidants, risk markers such as homocysteine or C-reactive protein (CRP), and even genomic testing looking at the apo E alleles. It's difficult to conceive of a way to light a single candle in the darkness, when the darkness is almost overpowering the American population with media, convincing them that lifestyle doesn't have any role to play and that when these problems arise, whether it's heart disease, hypertension, malignancy, depression, or dementia, that there's going to be a quick drug fix. Unfortunately, this is the American way and it's taken hold.

We're going to stay out there and try to be the candle in the darkness, but it's very difficult to see what's happening to the American population, both young and old. For example, the rates of autism from the 1980s to the present have increased tenfold, to the extent that one in every 166 children is going to be autistic. We know there are powerful risk factors that are modifiable. Based on genomic testing, we know there are individuals who can be identified to be at risk for that problem. We can make changes in their environment. We can identify these kids up front and make changes to reduce risk and therefore the incidence of these devastating issues.

JB: That's a good way to start this discussion. When I look back to when I started in this field in the late 1960s, there was an analogous ongoing discussion related to the prevention of heart disease. The principal thought at that time about diet and heart disease was the polyunsaturate-to-saturate ratio. That's what most people were focusing on. The problem was really everybody else's problem, because there wasn't a marker for individual risk to heart disease. With the development of the fingerstick cholesterol test and the Framingham Study, people could determine their own cholesterol number. The risk went from somebody else's to his or her own specific risk. Coupled very closely with that was the development of the statin drugs for management of that indicator.

There might be some kind of analogy here, because you've articulated very clearly that we have a near epidemic of dementia-related disorders that is going to increase in frequency with an aging population,

yet we're not responding in the way that we should to prevent unnecessary health expenditures and human suffering. Is this analogous to the heart disease issue?

Dementia-Related Disorders

DP: I think it is. I think it's very clear that the most important factor in raising public awareness is the development of a drug to treat a specific illness. We've seen that with attention-deficit hyperactivity disorder (ADHD) and we've seen it with cholesterol, as you pointed out. What has caused the rise in public awareness of cholesterol is creation of the cholesterol-lowering drugs. Why have 90 percent of the patients I see every day never heard of homocysteine? Because there's not a drug fix for homocysteine and therefore, they've not been made aware of it. The control of the media and the role it plays in terms of public awareness is absolutely vast.

You brought up the issue of cholesterol. Certainly, we're all aware of the new information indicating that individuals involved in determining what the safe levels of cholesterol are, have been involved in some way with the pharmaceutical industry which is, in many ways, an issue that needs more attention. Therefore, the edicts they issue, in terms of what a safe cholesterol level should be, are influenced by the manufacturers of the various drugs to lower cholesterol. There are significant issues regarding the safety of cholesterol-lowering drugs. There's a large segment of the population who develop transient myalgias, muscle pain, and disability from those drugs, and a certain percentage of them are left with permanent issues with reference to muscle dysfunction which ultimately, is probably going to turn out to be a mitochondrial dysfunction at the level of muscle. There's a 16-fold risk of neuropathy in individuals taking statin drugs.

There is a report in the journal, Neurology that was published just three or four days0ago from researchers at Johns Hopkins, titled "High total cholesterol levels in late life associated with a reduced risk of dementia."17 Now, what did I just say? I said that dementia risk was reduced in individuals with the highest cholesterol levels. Maybe cholesterol does play some important, positive roles in our physiology. Cholesterol is a precursor to hormones, but it also functions in the brain as an antioxidant. These researchers demonstrated in individuals of age 70 that the risk of dementia was decreased by almost 70 percent in those in the highest quartile of total cholesterol. That tells us it's time to take a step back and reevaluate, at least from a general population perspective, exactly what we are doing when we pump the population full of these statin drugs that have such devastating effects on enzyme pathways, which can modulate and reduce the availability of important antioxidants like coenzyme Q10. Shouldn't we take a step back when the FDA is considering making statin drugs over-the-counter, like they've done in England? We now see that, in fact, cholesterol is not such a terrible thing; that perhaps it's there for some important reasons.

JB: You hit on some very important issues. Cholesterol became a buzz word because it was easily analyzed and was associated with a relative risk that came out of epidemiological studies. One might ask the same question relative to dementia-related illnesses. Are there any functional markers that you could see using in patients for evaluation of functional neurological problems before the onset of dementia, the same as we do with cholesterol for heart disease?

Functional Markers for Evaluating Neurological Problems

DP: Oh, absolutely. We've been talking for a long time about the role of free radicals and the role of antioxidants in reducing risk. One of the studies we like to use is looking at urine lipid peroxides. We use

that as one of the four key markers of risk prediction in terms of neurodegenerative conditions like dementia and Alzheimer's, along with CRP, homocysteine, and looking at the apo E alleles. An article about the idea that oxidative damage may relate to cognitive decline was recently published in the journal, Neurology.18 Researchers at the University of Kentucky in Lexington demonstrated a direct correlation in risk for minimal positive impairment all the way to early Alzheimer's disease, and correlated that risk with measuring the TBAR study, which is something that you and I have been lecturing about for years. Now, it turns out that there is a direct relationship, which we all suspected. But even more importantly, the pathological changes taking place in the brain, i.e., the development of the so-called neuritic plaques in the superior and middle temporal gyrus regions of the brain, has a linear correlation with measurement of the thiobarbituric acid reactive substances, which is a simple, at-home study that has profound implications.

Taking it a step back, what can a person do lifestyle-wise that might modify these fats by action of free radicals? There's perfect support for the role of antioxidants. That supports the study I talked about earlier about reduced risk of Alzheimer's in people with the highest levels of vitamins C and E. So, absolutely, there are things that can be done that are not overly invasive, such as looking at studies of serum or urine for thiobarbituric acid-reactive substances, which is a simple test. We can look at high sensitive CRP (hsCRP) as a marker of inflammation, knowing that the balance of various fatty acids in the body plays a very important role in the inflammatory cascade, and therefore has a bearing on the outcome of that test. We can look at homocysteine, recognizing that risk for Alzheimer's will double at the level of 14 and above. We owe Dr. Kilmer McCully a great debt for bringing homocysteine to the public's attention, because it's desperately important.

Finally, we can look at the apo E profile to determine who is at increased risk for carrying the apo E4 allele. When we identify people who carry that allele, we know it has a direct relationship on the outcome in terms of the thiobarbituric studies. Carrying the apo E4 allele downregulates the brain's antioxidant protective abilities and, therefore, places a person at increased risk for diseases like Alzheimer's, and also increased risk for having a worse outcome following head injury, having a more rapid decline following the diagnosis of amyotrophic lateral sclerosis (ALS), and an increased risk of having prolonged seizures following a seizure in childhood—a variety of issues that we all now know are antioxidant-dependent.

JB: That leads to a thought that you pioneered in the functional medical community, and that's the connection of these antioxidants to the glutathione/glutathione disulfide couple, one of the principal antioxidant systems in the body. In fact, in terms of numbers of molecules, it is probably the most prevalent antioxidant system in the body. What's the status of your extraordinary work with intravenous glutathione and some of the work that you are going to be engaged in?

Treatment of Neurological Disorders with Intravenous Glutathione

DP: We stumbled into the glutathione thing about 12 years ago with one of our patients on whom we were using glutathione. I had attended a lecture on chronic fatigue and one of the lecturers mentioned that low levels of glutathione had been noted in chronic fatigue patients. We started giving glutathione to our patients with chronic fatigue. I had one patient carrying that diagnosis and a diagnosis of Parkinson's. And it was one of those "aha" moments, as Jeff Bland would say. When we gave him the glutathione, he got out of his wheelchair. You hear stories like that, and I'm such a non-believer, but when I watched that happen in my office, I had to take notice and pursue it. As Pasteur said, "chance favors the prepared mind."

We began digging deep and found that a study had been done in Italy that demonstrated significant improvement in people with CFS receiving intravenous (IV) glutathione. We researched it and began using it with our Parkinson's patients. Over the years, as I'm sure you're well aware, glutathione has become a real focal point as a key brain antioxidant, as a chelating agent in the body, a key player in hepatic detoxification and, therefore, a very important focal point in neurodegenerative conditions. We've been able to obtain an IRB for a research study giving IV glutathione to Parkinson's patients, and we are one patient away from completing the study. We're very excited about being able to publish the results which, hopefully, will demonstrate that this IV glutathione is effective, not only in symptom management, but also in terms of reducing the progression of the disease. The code hasn't been broken, but I'm hopeful that it's going to prove positive. Along the way, so many other literature citations have come out that support the contention that glutathione may play an important role.

There is a study due to appear in the Proceedings of the National Academy of Science where researchers looked at glutathione-S-transferase activity. They found in Drosophila, the fruit fly that carried a mutation of the parkin gene which led to the degeneration of the dopaminergic neurons, that the loss of function of these dopaminergic neurons because of the parkin gene mutation was enhanced when there were mutations of the glutathione-S-transferase S1 gene, and that with overexpression of the glutathione-S-transferase S1 gene, there was profound suppression of the neurodegeneration.19 The abstract went on to indicate that this finding could lead to potential therapeutic interventions in the treatment of Parkinson's disease. That certainly sounds like great support.

The whole idea that these genetic risk factors can be played upon by environmental exposures is central to where functional medicine is these days. That is, we recognize individuals with certain genetic mutations and, therefore, risks, may or may not express disease unless acted upon by an environmental factor. That certainly would support, for example, the recent finding of these temporal and geographic variations in ALS. This would not be expected if it were a purely genetic issue, nor would it be expected if it were purely an environmental issue. There's interplay between individuals at risk and subsequent environmental exposure. Indeed, the work done recently by Dr. Jill James in Arkansas identifying these genomic issues with reference to glutathione in at-risk children for autism, makes a very strong case for a reassessment on the art of science.20

According to science, there is no link between thimerosal exposure (either ethyl mercury found in thimerosal or methyl mercury found in foods and fish), in women who are pregnant and the subsequent development of autism. Now that we recognize that there are profound genetic risk markers for glutathione-S-transferase activity, we should redo those studies and determine whether or not children who carry those genetic markers are at increased risk. Then, science might indicate that this is a very fundamental strong indicator, and it would offer a strong explanation as to why kids are now developing autism at the rates I quoted earlier.

JB: I want to go back to the glutathione question. I had a couple of interesting conversations with your colleagues at the 12th International Symposium on Functional Medicine, two of whom gave me anecdotes from their experience using intravenous glutathione in patients with various types of viral liver-related conditions, like hepatitis C or chemical hepatitis. They both reported that using your procedure in those conditions led to significant improvement—reduction of liver enzyme profiles and reduction of inflammation in patients with those liver inflammatory disorders. If you think of the liver as part of the immune system, which is part of the nervous system, which is part of the endocrine system, then perhaps

these observations you've made specific to the brain are generalized to many conditions associated with enhanced upregulation of immune inflammatory conditions.

DP: What is the bottom line in terms of how any of these inflammatory issues ultimately cause illness? I think we all recognize that it disrupts mitochondrial activity. That's been one of the motivating forces for us to expand our usage of IV glutathione to a variety of illnesses. To take it past the viral hepatitis, we have included IV glutathione as a very integral part of our protocol in treating chronic Lyme disease. We have found that coupling IV glutathione, along with hyperbarics and an appropriate antibiotic regimen, has been a very powerful approach to getting these people back on their feet, quite literally, for a disease that many of my mainstream colleagues still choose to believe doesn't exist. They tend to look at Lyme disease as a fairly monophasic event—you're diagnosed, you're treated with an antibiotic, and then you are better. We now know that patients with Lyme disease are debilitated long term and that this issue does not just necessarily go away with a quick blast of doxycycline. It's also been shown quite recently that Lyme disease Ultimately does its damage by causing mitochondrial dysfunction in a variety of tissues in the body.

Getting back to liver disease, there's no doubt that hepatitis and other inflammatory issues of the liver are vastly improved when using IV glutathione, and also to provide other oral nutritional precursors to upregulate glutathione production. We've seen hepatitis C viral counts go down dramatically following the inception of IV glutathione therapy.

The real issue of late for me has been the questions raised by my neurology colleagues about blood brain barrier penetration of the glutathione. I don't have any doubt that this penetration is vast and significant, because of the systematic improvement that we all observe. I've been working at the M.D. Anderson Center in Texas, and we are about to start a study giving glutathione intrafecally to sheep, with the understanding from the University of Miami that once we've completed the study and demonstrated safety, we're going to move ahead with treating ALS patients with intrafecal pumps delivering glutathione 24/7. It's certainly taking it a lot further out of the box than the IV glutathione, but I think it's time to make the box a little big bigger.

JB: That's certainly very consistent with one of the things we learned at the 12th International Symposium. We saw some brilliant data, showing that even large 56 kilodalton molecules—members of the cytokine family—can travel across the blood brain barrier (BBB). I recall one of the remarkable slides of the BBB and there was a big X across it, with a note—"it's not as impermeable as we thought." There may be transport mechanisms or actual portals of entry for larger molecules that were previously unrecognized, that allow the brain to have a relationship with the rest of the body in ways that we now are only starting to recognize.

Pathophysiology of Multiple Sclerosis

DP: To get back to clinical applications, I hardly ever treat an MS patient during an acute flare-up with a protocol of IV solumedrol or steroids. My feeling about MS is that we may have been led down a path that needs reevaluation, much as we have been with cholesterol. If I may be so bold, I'll say that MS may not fundamentally be an autoimmune disease. I know that statement is going to raise a lot of eyebrows, because that's been the thesis for a number of decades. It's been the justification for all of the developed pharmaceutical interventions. But I would propose that we should consider that there are a variety of bits of data that need to be reevaluated in light of the possibility that the fundamental issue in MS may

actually be a metabolic, or even an energetic failure, an energetic issue, which thereafter paves the way for this hyperimmune response. The models that have been used for MS over the years have been the cases of acute disseminated encephalomyelitis in humans and the experimental allergic encephalomyelitis, EAE, in laboratory animals which, in many ways, are somewhat similar to MS, but in many other important ways, have very little to do with MS when you look at the pathophysiology of that disease. Those are both acute and monophasic issues where there is specific damage to myelin which follows damage to the endothelium. In reality, MS is nothing like that at all. The hallmark of those two diseases is a huge lymphocytic infiltrate. In fact, many times in MS, there's very little lymphocytic infiltrate around the plaque.

Scientists claim that because of autoreactive T cell clones to brain antigens, that's an indication that of an autoimmune acute disease. As a matter of fact, we see those antigens in other neurologic problems. We see antigens directed against myelin in a variety of other neurologic issues, including stroke, where that rise may be as high as 7-fold. We see complement activation, which is talked about as being a hallmark of MS, in head injury and other neurodegenerative conditions. I think it's time to reevalaute this, especially in light of new data using functional MRI proton MR spectroscopy, showing that there is widespread neuronal loss, even at the very earliest stages of this disease. When you scan specifically for N-acetyl-aspartate (an indication of functionality of brain tissue), this is a very early predictor of risk of relapse in MS, indicating that the very first event may be an energetic event, a loss of neuronal function preceding the inflammatory reaction.

Shouldn't we be paying more attention to neuronal energetics and preserving neuronal function, using the techniques that we've talked about to upregulate mitochondrial activity and to salvage mitochondrial activity into optimal function? Things like coenzyme Q10 and, when need be, techniques to upregulate glutathione availability and production, and even more aggressively, IV glutathione. I've seen the proof in the pudding in my own practice when patients have come in with the acute throes of a MS flare-up. We choose not to load them with steroids. Instead, we give them IV glutathione and see resolution of symptoms, often within hours, when it might take several days with steroids and choosing a therapy that doesn't have the down side or the risks of steroids. In fact, it has virtually nothing but an up side.

JB: That was a remarkable, optimistic, and encouraging note. It is an interesting perspective that fulfills the rule of reasonableness. Thanks for sharing that. We have just a few minutes left. I would be remiss if I didn't ask you a question that is probably on the minds of many of our listeners. Between May 1999 and the present, are you aware of any new clinical tools that you're really excited about, perhaps not comparable to IV glutathione, but those that have been added to the tool bag over a six-year period that look interesting?

Future Clinical Tools in Neurology

DP: We're looking at a couple of things. I'm sure you're aware of Dr. Patricia Kane's work. She has added phosphatidylcholine to our glutathione protocol because of its role in membrane activity. I think that's going to turn out to be very exciting. Regarding trends, cranial magnetic approaches may also prove to be pretty exciting. We're seeing a lot of interesting work coming out of several laboratories, and I know you're aware of that information. I think that's going to come into its own very soon.

There are a lot of new techniques using some time-honored nutritional supplements. We're quite excited about the role of resveratrol acting as a COX-2 inhibitor, not only in neurologic issues, but even in terms

of malignancy. The biggest and most exciting thing is new recognition of the expanding role of the fatty acid DHA as a COX-2 inhibitor and even more important, in terms of its role in genetic expression. I know that's an area of much importance for you. The role of DHA in general health is going to become much more widespread and much more understood by the general public. Foods will soon be enriched with DHA because of the important role it plays in gaining public awareness. Getting back to something I think I spoke to at the 9th IFM symposium in Ft. Lauderdale, Florida about fatty acids and immune modulation and the role they play in brain health, it's exciting that it looks like science is revisiting that. We've come full circle in recognizing that there is some very important new information about the modulation of genetic expression with the fatty acids, which we'll be getting into in the years to come.

JB: In closing, I want to say that as the seventhwinner of the Linus Pauling Functional Medicine Award, you continue to uphold the tradition and honor of that award with very high integrity. We're all pleased with the kind of reception you've received from your book, The Better Brain, and the positive ways in which you've affected people by believing that many neurological disorders are not irreversible and that, in fact, the brain can heal. That's a major change in what I learned about neurology. You've served as a beacon, and we really appreciate your continued leadership. Thanks for being with us today.

DP: Jeff, it has been an honor.

Gulf War Illness

I would like to add a few follow-up concepts to Dr. Perlmutter's wonderful explanation of the progress occurring in the area of functional neurology. After 14 years, I would like to revisit the problems of veterans connected to what is now accepted as Gulf War Illness. Approximately 11 percent of the deployed veterans from the Gulf War have reported significant health problems similar to things we attribute to toxicity. They have a whole range of differing clinical symptoms. Questions have been asked as to whether these are real or psychogenic, or whether it is a post-tramautic stress syndrome. People have said that these veterans were exposed to all sorts of potential causal factors that may have had adverse impact upon their neuroendocrineimmune systems, things like multiple vaccinations, exposure to organophosphate pesticides, prophylactic use of nerve-agent pretreatment compound pyridostigmine bromide (found in the cerebral spinal fluid of some of the veterans when they returned to the U.S.), inhalation of depleted uranium dust, exposure to low doses of the nerve agent sarin after the destruction of chemical munitions, and exposure to the fumes of burning oil wells. All of these things together produce a total load. Perhaps the conditions we were seeing in these veterans were not just post-traumatic stress syndrome; they were a combination of post-traumatic stress that was overlaid with modulators of neurological function.

In England, there is a dramatic reevaluation now ongoing to look at the potential association between exposures during the war and the disabilities of these veterans. For those of you who want to learn more about this, there is a good discussion that recently appeared in *The Lancet*.[21] I take a personal perspective on this, because a number of years ago, I was asked to present at the Bureau of Veterans Affairs and the Department of Environment Medicine on some of the studies we had done on detoxification enzyme profiles and whole-body toxicity in veterans who had symptoms of Gulf War Illness. We found significant alterations in their urinary organic acid profiles and significant alterations in their acetaminophen challenge detoxification results.

After I presented that information, I recall the cab ride back to the airport after the meeting. I happened to be with one of the high-ranking officials in the cab, and we were alone. We got into a discussion about this, and he said that, off the record, he would like me to know t1at this is a real problem, but the difficulty is, we do not really know what to do about it. What I think will happen is that it will smolder until it goes away because if we took it seriously, we're not sure exactly what to do about it. That discussion has remained resonant in my mind for the past 10 years, because for many things we see that are chronic in nature, we have some fairly good evidence as to what the etiological factors are, but because we do not know how to put that through the traditional medical system to get an outcome, it is easier to either avoid the problem or say we do not have enough data, than it is to try to do something.

The situation is similar with lead intoxication in children. If it was acknowledged by our government to what degree this problem occurred in the United States, it would force action, and we are not sure we have enough money to chelate every child with elevated blood lead levels that might have adverse neuropsychological or biobehavioral effects. These are political and economic issues that often overlay and complicate some of the fundamental issues related to the connection between an exposure and a dysfunction.

Homocysteine and Fracture Prevention

That also relates to the homocysteine story, which has been continually considered controversial, even in the face of all the evidence amassed over the last few years. Now, we see elevated homocysteine is associated with fractures and spontaneous imperfections in bone density and bone formation. I am quoting from recent papers in the *Journal of the American Medical Association*, showing that folate and vitamin B12, when given at high doses, can help prevent hip fractures in patients who have had a stroke.

Factors Affecting Deoxynucleotide Synthesis and DNA Methylation in 1-Carbon Metabolism

Homocysteine problems are genetically linked through various polymorphisms, such as the methylenetetrahydrofolate reductase (MTHFR) polymorphism that is present in 20 percent of the population, or 1 in 5 people. This and other related polymorphisms indicate an increased risk of homocysteine-related dysfunction. People with these polymorphisms may also have increased risk of changes in DNA methylation. This was discussed in a marvelous paper recently published in the *Journal of Nutrition*, showing that people with the MTHFR 677C→T polymorphisms have increasing relative risk of altered DNA methylation, which may relate to potential carcinogenesis.[24]

What we are starting to witness is the transition of medicine from silos of individual specialties to general themes surrounding mechanisms; by understanding that, we can better discuss the relationships of genotype to environment to produce specific outcomes. This leads to the concept of personalized medicine that Dr. Perlmutter was talking about, and it was the focus of the 12th International Symposium on Functional Medicine with regard to immune imbalance. This theme will be continued throughout the year, and we look forward to sharing how we are going to travel into the 2006 symposium year, which will be focused on detoxification and the environment/gene interaction.Thanks for being with us. We will talk to you next month.

Bibliography

1 Committee on the Use of Complementary and Alternative Medicine by the American Public. Complementary and Alternative Medicine in the United States. Washington, DC: The2National Academies Press; 2005.

2 Marwick C. Complementary, alternative therapies should face rigorous testing, IOM concludes. J Natl Cancer Inst. 2005;97(4):255-256.

3< Hart DN. Dendritic cell biology evolves into clinical application.>Lancet. 2005;365:102-104.

4 Farrell RJ. Infant gluten and celiac disease. Too early, too late, too much, too many questions. JAMA. 2005;293(19):2410-2412.

5 Norris JM, Barriga K, Hoffenberg EJ, et al. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. JAMA. 2005;293(19):2343-2351.

6 Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352(6):539-548.

7 Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med. 2005;352(19):1951-1958.

8 Curtis BM, O'Keefe JH. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. Mayo Clinic Proceedings. 2002;77(1):45-54.

9 West SG, Likos-Krick A, Brown P, Mariotti F. Oral L-arginine improves hemodynamic responses to stress and reduces plasma homocysteine in hypercholesterolemic men. J Nutr 2005;135:212-217.

10 Wells BJ, Mainous AG, Everett CJ. Association between dietary arginine and C-reactive protein. Nutr. 2005;21:125-130.

11 Mendelsohn ME. Viagra: now mending hearts. Nature Med. 2005;11(2):115-116.

12 Marx J. Play and exercise protect mouse brain from amyloid buildup. Science. 2005;307:1547.

13 Weil M, Bressler J, Parsons P, Bolla K, Glass T, Schwartz B. Blood mercury levels and neurobehavioral function. JAMA. 2005;293(15):1875-1882.

14 Kemper AR, Cohn LM, Fant KE, Dombkowski KJ, Hudson SR. Follow-up testing among children with elevated screening blood lead levels. JAMA. 2005;293(18):2232-2237.

15 Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements. Archives Neurol. 2004;61(1):82-88.

16 Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's

disease (AD2000): randomized double-blind trial. Lancet. 2004;363(9427):2105-2115.

17 Mielke MM, Zandi PP, Sjogren M, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurol. 2005;64(10):1689-1695.

18 Keller JN, Schmitt FA, Scheff SW, et al. Evidence of increased oxidative damage in subjects with mild cognitive impairment. Neurol. 2005;64:1152-1156.

19 Whitworth AJ, Theodore DA, Greene JC, Benes H, Wes PD, Pallanck LJ. Increased glutathione S-transferase activity rescues dopaminergic neuron loss in a Drosophila model of Parkinson's disease. PNAS. 2005;102(22):8024-8029.

20 http://www.rxpgnews.com/psychiatry/learning-disabilities/autism/article_931.shtml
21 Deahl M. Smoke, mirrors, and Gulf War illness. Lancet. 2005;365:635-638.

22 Van Meurs JB, Uitterlinden AG. Homocysteine and fracture prevention. JAMA. 2005;293(9):1121-1122.

23 Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of folate and mecobalamin on hip fractures in patients with stroke. JAMA. 2005;293(9):1082-1088.

24 Quinlivan EP, Davis SR, Shelnutt KP, et al. Methylenetetrahydrofolate reductase 677C®T polymorphism and folate status affect one-carbon incorporation into human DNA deoxynucleosides. J Nutr. 2005;135:389-396.p>