September 2005 Issue | Esther Sternberg, MD Director, Integrative Neural Immune Program

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Welcome to *Functional Medicine Update* for September 2005. This month, we are going to cover one of the most complex, but also clinically relevant topics we have had the fortune of exploring over the past few years—neuroendocrine immunology. Another way it might be expressed would be body/mind/nutrition and the modulation of inflammatory and immune disorders. We focused on this topic at the 12th International Symposium on Functional Medicine. The takeaway from that meeting was extraordinary. A great deal of thought-provoking material was presented at the plenary sessions and workshops. There was so much depth and density of infrmation that it was hard to take it all in over the course of the four days of the symposium. Since then, I have distilled some of the information and done some reflecting on it. With the help of one of our plenary lecturers, Dr. Esther Sternberg, from the National Institute of Mental Health at the National Institutes of Health, I would like to revisit some of he topics we discussed during the symposium that might be of clinical value

I want to begin by introducing the immune system, which is regulated by a variety of factors from within the body, such as regulatory T cell subsets that produce things like chemokines, complement, and antibodies, and by factors outside the body, including different hormones and neurotransmitters or neuropeptides in the microenvironment of individual cells. There is a whole milieu of different messenger molecules that serve as mediators for action at a distance, both autocrine and paracrine factors, and the immune-modulating molecules that have been found to have a great variety of effects on different cell and tissue types.

The central nervous system (CNS) afects the immune system through the neuroendocrine humoral outflow via the pituitary and through direct neuronal influences via the sympathetic, parasympathetic and sensory innervation of peripheral tissues. Thus, circulating hormones or locally released neurotransmitters and neuropeptides regulate major immune function, such as things related to allergy like antigen-presenting cells and, ultimately, the release of various types of cytokines, modulators that can affect work at a distance.[1] What happens locally might have a global effect on the body.

These compartmentalizations of immune, neurological, and endocrine system function, which we often study in chapters contained in anatomy and physiology textbooks, represent a web of interacting variables that alter function and allow for the proper physiological response to changing environmental stimuli. As with any web, when any component is distorted, the web itself changes. It is not just a single entity or a single function within the complex, interacting relationships in the neuroendocrine immune system, but rather, it is that any alteration in the web deforms or perturbs the whole shape or function of the web. We

can get systemic effects from these perturbations of the neuroendocrine immune system.

It has been proposed that the balance of immunological function is related to the equilibrium between the thymus-dependent 1 (Th1) and thymus-dependent 2 (Th2) lymphocyte responses. This leads to the balance of various types of immune-modulating substances that have impact upon the endocrine and nervous systems, resulting in a push/pull or feedback system related to environmental messages translated into immunological function, which influence endocrine and nervous system functions that, in turn, send out their own messengers, which ultimately have feedback effects upon the immune system. In self-regulation, all of the systems in this marvelous web somehow interact in such a way as to give normal immunological vigilance, normal immunological response, normal inflammatory balance, and proper nervous and endocrine system function.

In a system that is perturbed by exogenous or endogenous sources, the distortion of the web leads to alterations in the function of individual systems—nervous, endocrine, and immune. Furthermore, depending upon the nature of the perturbation, the strength of the stimulus, and the response in the individual to that stimulus, which is based upon individual genetic and environmental factors, different types of symptoms can arise. Hans Selye encountered a great deal of resistance from his colleagues when he proposed the stress mechanism of disease, because he was talking about so many different diseases that seemed to occur from a similar, non-specific condition that he termed "stress." At the time, if you believed that each disease was independent in and of itself, and that it had its own specific etiological agent separate from that of any other disease, it would seem strange and probably not realistic to propose that a general mechanism (in this case, what Selye termed "stress") produces the phenotype seen in so many different diseases. Peptic ulcer disease, heart disease, adrenal-related problems associated with hypertension, stroke, and ultimately, as we will learn in greater detail from Dr. Sternberg, even autoimmune diseases, in which imbalances of Th1 and Th2- mediated lymphocyte function are central, are part of this extensive list of stress-associated conditions.

An alteration in neuroendocrine immune system function results in an array of chronic symptoms that are very hard to put one's diagnostic finger on, and these symptoms often occur well before presentation of a defined disease. These would be things like recurrent fevers of unknown origin, sleepiness, fatigue, muscle pain, loss of appetite or increased appetite, decreased libido, and decreased response to various environmental agents and toxins as a consequence of altered detoxification pathways. All of these things are clinical manifestations of alteration of the neuroendocrine immune web.

Immune responses are regulated through antigen-presenting cells (APC)—monocytes/macrophages and natural killer cells that are components of what we call our *innate immunity.* They are also regulated by T lymphocytes that make up the Th1 and Th2 systems that are components of *adaptive* or *acquired immunity*. Innate immunity allows for instruction that enables the downstream adaptive immune function to select appropriate responses to the environment. There are alterations in the Th1 and Th2- modulated production of messenger molecules. There is a constant dynamic interaction between the environment and the sensory perceptions of the individual and their translation into the response of the Th1 and Th2 equilibrium, which alters the mediating molecules and the function of the neuroendocrine immune system. There could be focal infection, for instance, or exposure to a small toxic molecule, toxic stress, a mechanical injury, or poor alignment leading to poor distribution of mechanical forces in the body, such as through the spine. All of these things could serve as precipitating events that would be manifested through the neuroendocrine immune web to produce symptoms that could be quite diffuse and non-

specific, depending on the individual. These alterations can result in things like Th2-dominant conditions, which are called allergy and atopy, to Th1-dominant conditions that are normally associated with systemic inflammation, like arthritis. The clinical conditions that can arise out of alterations in neuroendocrine immune function cut across every subspecialty of medicine.

There is a strong interest in the Th2 responses that were initially directed at the protective effect seen in various helminthic infections that, I believe, is where they were first discovered and eventually seen to have a pathogenic role in allergy. The innate immune system, recently called the primitive immune system (Th1 responses and phagocytic responses of monocytes and macrophages) plays an interacting role with the Th2b cells that secrete antibodies. There is a web of interaction and communication between these cell lines that results in the function of the immunological system. We would not clinically separate a condition of chronic infection—for instance, a root canal gone bad leading to a low-grade dental infection—from an environmental exposure to a xenobiotic chemical, food allergen, or a highly distressful experience in life. All of those are perturbing factors to the equilibrium between Th1 and Th2, and the immunological status of the neuroendocrine immune system.

Diseases named through ICD9 codes that come out of these interactions would not have been seen historically as emerging from or related to alterations in the neuroendocrine immune system through the complex connection between environment, genes, and neuroendocrine immune signaling. As we will learn later in this issue, even conditions within the autoimmune family, such as systemic lupus erythematosis and rheumatoid arthritis, are related to alterations in neuroendocrine immune function, and the hypoactive hypothalamus-pituitary-adrenal axis (HPA) has to do with alterations in neurochemical and immune response, which can set the stage for the alteration of immunity associated with arthritis.

We are witnessing the emergence of a fundamental, scientific underpinning of what Dr. Selye started to bring to our attention some 60 years ago, from which the term "stress" was coined out of physics and appropriated into biomedicine. It is the most commonly used term in all of the language of biomedicine today. It is interesting that although the term "stress" is frequently used in all the research quarters of the world, it still hasn't "arrived" as the clinically important topic it probably deserves to be, in terms of therapies.

The body has evolved very adept mechanisms for managing the perturbing factors that lead to stress. Stress, in and of itself, is probably not damaging. The damage occurs when the control mechanisms for the management of an environmental change, which is translated through the HPA axis, are no longer able to be properly managed and lead to distortions of the web of the neuroendocrine immune system. The person begins to suffer from distressful conditions associated with alteration in these messenger molecules.

Often, we focus on one of those messenger molecules—the adrenal steroid, cortisol. Cortisol travels with altered mediators of the other families of the nervous and immune systems. If we looked at the web in total, we would not see cortisol changing by itself. We would see it as a marker for alterations in the whole of the neuroendocrine immune system.

How does the brain protect itself from certain kinds of adverse responses from long-term stress? This has been a topic of discussion within the basic sciences and the neurosciences for some time. Recently, we have begun to see some mechanistic understanding emerge as to how the brain has evolved the ability,

over millennia, to protect itself from conditions that ultimately might result in altered neurochemicals, neurotransmitters, and immune agents that could produce things ranging from depression to neuroinflammation. I am now talking about acute stress, or post-traumatic stress syndrome. An interesting review paper was published in *Nature Neuroscience* that followed from another paper I saw in the same journal. The latter paper was titled "Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus."[2] The review paper talks about how the impact of traumatic life events is often gauged by how well people appear to cope with their experience.[3]

The concept of coping is an important feature of living in the 21st century. We have to cope with a lot of things. We are on sensory overload most of the time dealing with time compression. The nervous system has to mobilize the neuroendocrine immune system's coping abilities. Obviously, there are psychological control processes that can buffer the adverse consequences of stress, but there are also neurophysiological, or neuroendocrine immune processes. It has been suggested that the interaction occurs between the prefrontal cortex, one of the "executive centers" of the brain, and the serotinergic system, which projects diffusely around the dorsal raphe nucleus. There are conditions under which psychological control over stress could be inferred in experimental animals. Rats exposed to inescapable shocks showed significantly more gastric ulceration and higher levels of stress hormone than rats receiving the same quantity, intensity, and scheduling of shock, but with the opportunity to voluntarily turn a wheel and stop the shock stimulus. That leads to the concept of both intentionality and locus of control. Built into our coping systems is the locus of control—the escape valve.

Locus of Control

There is a takeaway from this, not to focus so much now on neurochemistry, but on real-life clinical situations. How do we get a person to introduce a locus of control into his or her life when they have a runaway system of distress working within the neuroendocrine immune system and they have lost their ability to cope, both physiologically and psychologically?

The concept of establishing locus of control is a very important therapeutic guide, or potential tool. We cannot control everything in the universe as much as we might like to. The sun still rises in the east and sets in the west, and there are variables in our lives that we have to deal with as givens. What we can do in the face of those things that are dealt to us is to develop some guidelines as to a locus of control along the road of response; in other words, some sense that we are not out of control and just victims of circumstance. That has a dramatic impact upon altering the function of the neuroendocrine immune system. When we feel that our lives are out of control and there is no escape, there is a sense of hopelessness. We have a different neuroendocrine immune milieu of triggering or mediating molecules than if we introduce a locus of control.

There is a whole series of studies focused on this story from a neurochemical and neurobiological perspective. The article I referred to in *Nature Neuroscience* on controlling stress discusses this issue at some length—control mechanisms by which stress occurs through the serotinergic processes and raphe nuclei resulting in an altered sense of coping. Let's translate this into a therapeutic example—a visit to the dentist. We may not look forward to this because it is going to require some drilling for the dental procedure. For most of us, the dental drill does not represent an enjoyable experience. The dentist tells you that the procedure is going to require drilling and that he will do all he can to make you comfortable, but he doesn't tell you what to expect or how long the procedure might take. The moment the drill hits your tooth, there is a neuroendocrine immune response to your perceived lack of control because you are

not sure how long the procedure will take. The neuroendocrine immune response to uncertainty about the length of the procedure produces a different collection of messenger molecules than if the dentist had told you the procedure would take about 10 minutes and that you should indicate any discomfort by raising your hand. In that case, a different array of messenger molecules from the neuroendocrine immune system is produced because you sense a locus of control, which has a physiochemical, neurochemical effect and influences the web of the neuroendocrineimmune system.

If we use the simple model I just outlined as a metaphor to other conditions in life, what we should be doing to assist patients who are out of control and suffering from distress and a runaway alteration in neurochemical mediators, is to try and introduce the concept of a locus of control. What can be introduced that leads to a feeling of being in control? The concept of locus of control not only has a psychological impact, but it has a neurophysiological impact on neuroendocrine immune system function. If that person is going to be confronted with long-term alterations in his or her environment that could produce adverse effects of distress over some period of time, developing these markers for a locus of control is a very important clinical objective.

I am suggesting hypothetical situations and asking whether one could develop a locus of control. Let's say you have received a sudden diagnosis of cancer. That is a stress factor, in and of itself. Based on that response, how could you develop a locus of control? Obviously, there are many ways you could do that. One might be to decide to become informed about the particular type of cancer. Another might be to examine the treatment options and be involved in the selection of the treatment, interfacing with practitioners who will communicate with you, giving you a sense that you are part of the solution, not just the problem. Through that process, one develops a different connection to the neuroendocrineimmune system that results in a collection of molecules floating around in tissues that produces a different response of that complex system. These are some small examples of a general theme relating to the concept of locus of control, which has both psychological and neurophysiological endocrine and immune influences.

The Role of Nutrition

Taking that a step further, let me introduce the concept of nutrition. Often, we feel that the body/mind connection may be strong, but there is very little evidence that the mind is connected to the state of nutrition. Neurophysiologists, psychiatrists, neurologists, and psychologists often feel that there is very little their disciplines have to do with nutritional status and the outcome in patient response. I would like to change that perspective and spend a moment explaining why I think nutrition is part of this, and why I started this discussion by saying we were going to focus on the interface between environment and genes through the neuroendocrineimmune system, and how they relate to nutritional status.

This is an emerging story that is absolutely fascinating. Just as the Selye stress mechanism has evolved tremendously in our understanding over the past 10 to 15 years, so has the understanding of the role that nutrition plays in modifying brain chemistry and neuroendocrine immune function. I am going to focus on just one part of the story because to do an exhaustive job in understanding the role that nutrition plays in neurochemistry, immunity, and endocrinology would take many days of discussion. I will focus on one emerging point of the sphere—hypothalamic function related to fatty acid intake. You might ask if fats in our diets have some influence on hypothalamic function or if the hypothalamus is sensing fatty acids and can discriminate different types of them; for instance, saturated from unsaturated and omega 6 from omega 3. That is the theme that is emerging.

There is a review in the journal *Nature Neuroscience* that comes out of some very interesting work done at the Albert Einstein College of Medicine Diabetes Research & Training Center in New York.[4] These investigators looked at selective regions of the brain, including the hypothalamus, and found that they are capable of gathering information on the body's nutritional status. The hypothalamus is the seat of things like appetite and satiety, and it appropriates different neuroendocrine immune responses to the rest of the body and also has effects on programming metabolic responses to the availability of food and calories as fuel. This direct metabolic signaling in the hypothalamus is regulated, in part, by hypothalamic sensing of fatty acids. That is pretty remarkable—that there are receptor sites that will pick up information from dietary fats.

To understand this in great detail would not be possible from the standpoint of time, but let me hit some of the high spots. When we consume dietary fats, we normally eat them as triglycerides that are broken down into free fatty acids by lipase enzymes. Triglyceride lipase in the intestines is emulsified by bile salts. They are distributed through the lymphatic system ultimately back to the vasculature, and they make their way to the liver, where they are resynthesized and redistributed into the blood as apolipoproteins or as chylomicrons.

"Plasma long-chain fatty acids are bound to albumin and cross the blood-brain barrier mainly by simple diffusion in the unbound form. Unbound fatty acids can also be derived from hydrolysis of lipoproteins by lipoprotein lipases with the blood or the cerebral capillary bed. Overall, chylomicrons are likely to be a major circulating source of brain fatty acids after meals, whereas a combination of unbound fatty acids and locally hydrolyzed lipoproteins contribute to the brain fatty acid pool during fasting. A small proportion of fatty acid entry may also occur through direct uptake of lipoprotein particles mediated by lipoprotein receptors in the luminal surface of the cerebrovascular endothelium. Overall, the access of circulating free fatty acids to the CNS is generally proportional to the plasma concentration of fatty acids."[4]
In the case of a person with hypertriglyceridemia who has a lot of saturated fat occupying the triglycerides, the brain is going to be exposed to higher concentrations of saturated, long-chain fatty acids. Conversely, if there are higher levels of omega 3-rich triglycerides or free fatty acids, the brain will be exposed to higher levels of these fatty acids. There is a mechanism by which fatty acids can be taken up and influence brain function.

The ultimate effect of these fatty acids is not only to serve as energy fields, as fats always do, but also as a signal within the hypothalamus. Circulating nutrients can be derived from exogenous (such as food intake), or endogenous (liver glucose production) sources, and central neural circuits concomitantly modulate both exogenous and endogenous sources of energy, in keeping with a negative feedback system of appetite control and satiety. Circulating long-chain fatty acids signal the body's nutritional status to hypothalamic energy centers. The intracerebral ventricular administration of oleic acid, an omega 9 fatty acid, is sufficient to inhibit food intake and liver glucose production in the presence of similar circulating long-chain fatty acid concentrations.

We know from animal studies using instilled or directly administered fatty acids into various regions of the brain, that fatty acids have effects on appetite, energy production, and metabolic functions in the liver, such as glucose metabolism and glycogen synthesis. In light of these findings, the investigators asked whether a physiological elevation of circulating levels of long-chain fatty acids (LCFAs) could generate a measurable increase in the

LCFA-CoA pool within discrete regions of the hypothalamus and generate a metabolic signal of energy, which would ultimately alter things like appetite and energy economy at the liver and at the muscle cell. A sustained 2 to 3-fold elevation in circulating LCFAs was found to double LCFA-CoA concentrations within the mediobasal hypothalamus. This increase was found to influence a whole series of metabolic functions, including beta oxidation, glycogen synthesis, and fatty acid metabolism at the liver level in animal studies.

This is an interesting observation—that dietary fat plays a role in modifying brain hypothalamic function and that differing components of the fatty acid family have differing effects. If we look at long-chain saturated fatty acids, they have a different second-meal effect, or satiety-producing effect than omega 3 fatty acids. There is now evidence indicating that omega 3 fatty acids play a role in hypothalamic function in such a way as to lower appetite and improve thermogenesis, or the lipolytic breakdown of fatty acids. It would be possible to propose that consumption of fats, in this case the omega 3 family of fats specifically, could serve as appetite regulating and therefore, as weight loss agents. Does that sound paradoxical? I said that the consumption of fat could cause weight loss. That sounds very counter-intuitive. I am not talking about boatloads of fat; I am talking about the amount of omega 3 fatty acids necessary to promote proper hypothalamic and cellular signaling that results in appetite regulation and improved metabolic function. This is a fairly remarkable, perhaps even paradoxical, role that various fatty acids play in regulating neurochemical function pertaining to metabolism.

Part of the role these fatty acids have on function has been determined to be a consequence of the influence they have on gene expression. Fats have been thought to be calorie-rich storage nutrients that were basically providing energy economy to the body, but certainly not carrying gene expression messages, that is to say as information molecules. But, as has been pointed out in a variety of reviews over the past few years, including one that recently appeared in the journal, *Lipids*, we now know that there are a number of well-recognized mechanisms by which specific fatty acids regulate gene expression.[5] They regulate the expression of genes involved in lipid and energy metabolism. In particular, two transcription factors—sterol regulatory element binding protein-1c, or SREBP-1c, and the peroxisome-proliferated activator receptor α (PPAR α)—have emerged as key mediators of gene regulation induced by fatty acids. SREBP-1c induces a set of lipogenic enzymes in liver. Polyunsaturated fatty acids (PUFAs), particularly omega 3 oils, but not saturated or monounsaturated fatty acids, are known to suppress the induction of lipogenic genes by inhibiting the expression and processing of SREBP-1c. The unique effect of the PUFAs suggests that the SREBP-1 may regulate the synthesis of unsaturated fatty acids for incorporation into glycerolipids and cholesterol esters. PPARα plays an essential role in metabolic adaptation to fasting by inducing the genes for mitochondrial and peroxisomal fatty acid oxidation, as well as those for ketogenesis in mitochondria. Here we are talking about almost a thiazolidinedione-type effect that omega 3 fatty acids have by serving as PPARαagonists, or like fibrates, to use an example, that are known to be alpha agonists to increase lipolytic enzyme activity and break down fat. What I am trying to illustrate is that the fatty acids of specific families have effects both centrally, through hypothalamic functional

In the past, we have always focused our attention on the fatty acids themselves, not so much looking at their downstream metabolites. Now, there is more and more evidence indicating that fatty acids, particularly the omega 3 and 6 families, are converted into eicosanoid derivatives, which can have a variety of influences on the body. Beyond the eicosanoids, new families of fatty acid metabolites that have unique effects and serve as neuroprotectants are now being found and studied. These are the

resolvins that come from both docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), omega 3 fatty acids, and that serve as precursors to what have been termed neuroprotectins and resolvins.

It is interesting to note that there is a differential effect of EPA versus DHA in the modulation of neuroendocrine immune function. One might think of EPA-rich oils as being best for modifying inflammation, and DHA-rich oils as being better for modification of lipids (triglyceride-rich particles) and for modulation of neurochemistry. In part, these docosatrienes and their interrelationship with neuroprotectins and resolvins, form a matrix of protection in the nervous system that modulates neuroendocrine immune function. They are both neuroprotective and antiinflammatory. There is a good review of these resolvins, docosatrienes, and neuroprotectins in *Current Opinion in Clinical Nutrition and Metabolic Care*.[6] In view of the many beneficial actions attributed to these omega 3 fatty acids, these resolvins, docosatrienes, and neuroprotectins derived from them are being found to be some of the putative molecules that participate in the protection against neuroinflammation and alteration to the neuroendocrine immune system.

Another interesting paper that discusses resolvins, docosatrienes, and neuroprotectins appeared in the journal, *Lipids*.[7] The authors discuss that these mediators were only recently identified as metabolites from EPA and DHA, and they have potent bioactivity in resolving inflammatory exudates in which tissues are enriched with DHA. The trivial names resolvin (resolution-phase interaction products), and docosatrienes were introduced for the bioactive compounds from these novel series, since they possess potent anti-inflammatory and immunoregulatory actions. It is not just the fatty acids, in and of themselves, but also their metabolites that are of interest. Once the question of metabolites has been raised, there is differentiation from one individual to another.

That also begs the question about cholesterol. Cholesterol has had such a "bad rap," as if it is only a bad molecule and we should lower it with statins. Cholesterol is an important molecule for cell membranes as a precursor to hormones and to bile salts. We certainly want to keep cholesterol in mind as being a good molecule, despite the negative press it has received. In the mammalian brain, cholesterol plays an important role in determining and maintaining healthy function. Low levels of cholesterol in the brain are associated with neurodegenerative disease in animals, which raises the question, what is the best cholesterol status and how does it relate to brain function?

In one animal study, it was shown that CNS demyelination is associated with low cholesterol levels, and that cholesterol-deficient oligodendrocytes actively enriched cholesterol and assembled myelin with more than 70 percent of the cholesterol content of wild-type myelin.[8]This shows that cholesterol is an indispensable component of myelin membranes and that its availability in oligodendrocytes is a rate-limiting factor for brain maturation.

There is a lot that is special about cholesterol, as was described in a paper in the journal, *Lipids*.[9] Cholesterol plays an important role in neurochemical function. It raises the point of everything in balance, everything with omega 3, omega 6 fatty acid ratios, and even cholesterologenic enzyme processes may all play important roles in protecting neuroendocrine immune function. If cholesterol is too low, it may have an adverse effect on the cholesterol pool and unexpectedly have an adverse effect on neurochemistry. Omega 3 fatty acids are important and omega 6 fatty acids are important. Even arachidonic acid has an important role to play in maintenance of proper neuroendocrine

immune function, as does cholesterol in cell membranes and myelin.

Let us move to the Clinician of the Month, who will help us to better understand the interface between environment and neuroendocrine immune function and ultimate disease entities

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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JB: It's time for our Clinician/Researcher of the Month. This month, we are fortunate to have a person who fits into both of those categories—Dr. Esther Sternberg, Director of the Integrative Neural Immune Program and Chief of the Section on Neuroendocrine Immunology and Behavior at the National Institute of Mental Health at NIH. Those of you who were fortunate enough to attend our 12th International Symposium on Functional Medicine in Palm Springs had the pleasure of hearing Dr. Sternberg present there. All of us were rapt as she outlined the story of her own personal background in this area and, of course, the contributions she has made to the field, and how it is evolving. I was first brought to understand more of Dr. Sternberg's work in reading her book, The Balance Within—The Science Connecting Health and Emotions (W.H. Freeman; 2000). This book should be required reading for all of us in this field. It is the Magna Carta of laying the groundwork for understanding the connections between body/mind, the immune system, and diseases that result from immune dysregulation.

Dr. Sternberg's work is highly valued. In fact, she has established the field of neuroimmune interactions and collaborative networks and other interdisciplinary fields, including women's health. She's currently highlighted in the National Library of Medicine Exhibition on Women and Medicine under the title, "Changing the Face of Medicine." It's with great privilege and pleasure, Esther, that I would like to introduce you to our Functional Medicine Update audience.

You were a family doctor at one time after receiving your MD in Canada. You were trained in rheumatology at McGill University and now you're in neuroimmunology at the NIH. That's an interesting path. Would you tell us how you got there?

From Family Practice to Neuroimmunology

ES: First, it's a great pleasure for me to speak again to this audience and it was a great pleasure to speak at the meeting in Palm Springs. This audience is very receptive to the issues of the mind/body connection and the science that explains how these phenomena that we have recognized for thousands of years—that stress can make you sick; that believing can make you well; and that the social world has effects on health. We know now that is based in very strong science—the anatomical, hormonal, and neurochemical connections between the brain and the immune system—and that breaking those connections results in disease.

How did I get into this? Well, as you said, I did start off as a family doctor. At that time in Montreal, family practice was not yet a full-fledged specialty, so after my internship, I went into general practice. I loved it. I loved the interaction with patients. It was immensely rewarding to work with families of all ages and to actually see that interventions that I instituted did help. There's nothing more rewarding in medicine than that—the immediacy of helping people get through difficult spots in their lives. But after two years in practice, I looked down at my work sheet and noticed that about half my patients had some kind of aches and pains and the other half had some kind of mood problems—anxiety and depression—and I didn't feel well enough prepared to deal with either of those issues without going back and getting further training. I picked rheumatology and went back and got my specialty training in rheumatology at McGill University and the Royal Victoria Hospital. I was fully planning to go back into practice at the same clinic where I was a family practitioner. In the last months of my fellowship training, I was called to see a patient at the Montreal Neurological Hospital who had developed a scarring inflammatory autoimmune disease that resembled scleroderma. The only thing that he had been exposed to was an experimental drug for epilepsy that was designed to change brain serotonin.

That experience, seeing this man in excruciating pain with what was clearly an autoimmune inflammatory disease, appeared to me to be linked in some way to changing brain serotonin. That convinced me that the brain has got to have something to do with autoimmune inflammatory disease. That was in1978/1979. And I had no idea how that link could occur. There was some evidence in the literature to suggest that serotonin metabolism might be abnormal in scleroderma at that time, but the evidence was very thin. It was that patient that propelled me into a research career. I got together with a biochemist at McGill—Simon Young—and together we did research on this subject and on control subjects who had been treated with that drug and who did not develop any illness.10 We published that paper as a lead article in The New England Journal of Medicine. That's how research is. You see a patient; you do the study; you do a lead article in The New England Journal of Medicine. It turned out that was unusual, to say the least. But it did propel me into a research career, and I subsequently went to St. Louis where I trained in immunology, and then came to NIH to continue pursuing the concept, or the question, that the brain could have something to do with autoimmune inflammatory disease.

It was not an easy task because, at the beginning, those mentors that I worked with in the field of immunology and rheumatology didn't believe that the brain and the immune system could have anything to do with each other. It was the day when immunologists saw the immune system as completely independent, because immune cells could be cultured in tissue culture dishes and could function perfectly normally. The assumption was made that the immune system, since it works perfectly well outside the body, doesn't need the body to function, and this is true and false. Of course, the immune system works perfectly well outside the body, but when you put immune cells back into the body, they work very differently because they're exposed to many different nerve chemicals, hormones, and factors that do change the way they function.

At the beginning of my cellular immunology career, I wanted to test the effects of serotonin on macrophage activation—something that certainly doesn't sound flaky. It sounds very molecular, very cellular, but I was told by a supervisor that I was going to ruin my career. For some perverse reason, that only spurred me on to continue to do these studies and, indeed, I found that serotonin does change macrophage activation and drugs that block serotonin interfere with that. Finally, when I came to NIH, I decided that testing drugs in tissue culture really isn't going to lead to understanding how the system works in the whole organism, nor would it lead to finding therapeutic interventions or new drugs.

I did some studies on rats that were prone to developing arthritis and their very closely genetically matched cousins that are resistant to developing arthritis. I tested an anti-serotonin drug in these animals and, much to my surprise, rather than curing the animals with arthritis, the anti-serotonin drug killed the animals that were supposed to be resistant to arthritis. That was a great shock. It looked to me as if the animals were dying in septic shock. The way you induce arthritis in animal models, in rats, is that you expose the rats to any one of a number of proinflammatory triggers, or antigens. In this case, they were bits and pieces of streptococcal cell walls. What happens when you do that—give an animal strep cell walls—if there is no protective mechanism to prevent the immune system from overshooting, they could potentially die from septic shock. And that's in fact what happened. When we gave the anti-serotonin drug, and then when we gave a group of corticoid antagonists, we were removing one of the body's important mechanisms of preventing the overshooting of the immune system through the anti-inflammatory effects of the glucocorticoids.

The way I figured that out was at midnight when the student who was working in the lab called me and said that something had gone horribly wrong, and that all the rats were dying. Having been used to being in family practice and doing house calls, I did a house call on the rats in the middle of the night. I realized that it wasn't all the rats; it was just what were supposed to be the control rats that had received both the strep cell walls and the anti-serotonin drug. I knew that the drug had been developed for hypertension. By the way, it is not in use and was never developed further after this experience. A lot was known about what it did to the brain and one of things it did was to block the hypothalamic pituitary adrenal axis. I realized at that point that perhaps, by removing the HPA stimulus to cortisol, glucocorticoid production, that that was taking away the body's anti-inflammatory control through glucocorticoids in the immune system and allowing for the precipitation of shock.

That's what led me to hypothesize that the hypothalamus and a blunted HPA axis response and resultant blunted glucocorticoid response, could be associated with susceptibility to arthritis in the arthritis-susceptible rats and that conversely, a hyper-responsive HPA axis could be associated with resistance to arthritis in those animals. That hypothesis turned out to be correct. In fact, it has now been shown across species and across diseases from chickens with thyroiditis, some strains of mice with lupus, rats with a variety of autoimmune inflammatory diseases, and humans with Sjogren's syndrome, lupus, rheumatoid arthritis, CFS, irritable bowl syndrome, fibromyalgia, asthma, dermatitis—that all have a blunted hypothalamic- pituitary-adrenal axis response to a variety of stimuli. It's also been shown through intervention studies in animals that interrupting the axis at any point, whether it's at the hypothalamus, the pituitary, the adrenals, or the level of the glucocorticoid receptor, turns an otherwise inflammatory resistant animal into one that is so susceptible to inflammation that when exposed to bacterial products, they will die from septic shock, and that giving glucocorticoids reconstitutes this axis and prevents the overshooting of inflammatory responses. That was the trajectory of my career that led from an observation of a single patient that convinced me that this field was an important one to pursue.

JB: Not only is that a fascinating story, one of a great scientific series of discoveries, but it also obviously raises so many interesting questions about what Pasteur was quoted as saying: "Chance favors the prepared mind." How are people prepared to make these observations? I was struck when I heard the story. I know a little bit of this, having heard you speak and having read your book, so I'm asking a question for the rest of the audience that hasn't had the privilege of being familiar with that. It sounds like the HPA axis dysregulation associated with shock and autoimmune type situations through blunted glucocorticoid action, is somewhat reminiscent of hypoadrenalectomized animals. When we think of

McGill University, we think of Selye and I know a little bit about your history so perhaps you could tell our audience about the connection of your history to Selye. It seems that sometimes we weave an interesting web in our lives.

Hans Selye's Research on Stress

ES: You're right and until I wrote the book, it didn't occur to me that not everybody in the world grew up knowing Hans Selye. That may sound like an odd thing, but he was such a familiar figure to me. He and my father were professors in the same department of medicine at the University of Montreal. It's true that Selye and my father had started off at McGill and then moved to the French university. Montreal, at the time, was divided very much along language lines. McGill was the English university and the University of Montreal the French university.

As a child, I grew up visiting my father's lab and my sister and I would play on the stairwell at the University of Montreal and between floors, we would occasionally wander onto the floor where Hans Selye's labs were. I describe in my book, recollections of this very imposing figure and I also went back and talked to Selye's former colleagues, very close friends of my family, and former students to try to piece together a picture of this man who was the person who brought the word "stress" into the dictionary of virtually every language around the world. He borrowed it from the physicists and used it in the way that we understand it today, as the perturbation of the response of an organism to the various perturbations in the environment that we experience. It's an interesting story, the story of Hans Selye and his hypotheses and his attempts to prove them and to bring them to the rest of the world. It's an example of a man who was convinced of an idea, who was well ahead of his time and was rejected in many ways because at the time, there was not enough evidence to prove the connections in the way that we have today.

JB: I've always wondered why Hans Selye, at least more recently, wasn't awarded a Nobel Prize in Medicine and Physiology, given that stress is the most often cited word in the Index Medicus. Perhaps at the time there wasn't enough data, or whatever the reasons were for not selecting him, but it seems that now, it's a tremendous oversight.

Glucocorticoids and Stress

ES: Well, I can't speak for the Nobel Committee, but I can say that Nobel prizes are never awarded posthumously. It may be that he was way ahead of his time. Also, he made observations that were correct, but he made some predictions based on those observations, based on the knowledge that was available at the time that turned out to be wrong. His observations were right and the general concepts were right, but the direction of his predictions turned out to be wrong. He predicted that there would be a proinflammatory hormone discovered in the adrenal glands, and then glucocorticoids were discovered to be anti-inflammatory. The Nobel Prize was awarded to Hench, Kendall, and Reichstein who used glucocorticoids to treat rheumatoid arthritis. So, the prize was awarded for some part of that axis. It just was thought at the time that glucocorticoids were not physiologically important in regulating inflammation. It was thought that they were pharmacologic agents, which is an odd interpretation, since they were discovered in the adrenal glands. I suppose that scientists should have figured out that if they're in the adrenal glands, they must be doing something there physiologically. But they were used from the very beginning in pharmacological doses. The connection between how those glucocorticoids got released from the adrenal glands—that there was a connection from the brain, the hypothalamus, the pituitary, all the way to the adrenal glands, that was the physiological release mechanism that could occur during situations of stress.

It took a long time for that concept to be accepted. Possibly another reason for the resistance on the part of the academic community to accept the notion that stress was real is that it was a notion that was around for thousands and thousands of years. Going back to the ancient Greeks and Romans, as I do in my book. The Romans, when they discovered the Greek temples to Asclepius, the Greek God of Healing, wondered why it was that these temples were always built on the tops of hills away from the noise and bustle and dirt of the city, away from the stress of the city. Why is it that these temples were built in such a way and how is it that being in such a situation overlooking a beautiful ocean with fresh water source and good healthy food and social support and sleep and music and dreams. How is it that all that helped patients to heal? I think part of the issue is that these concepts were around for thousands and thousands of years and it's something your grandmother told you. How could that possibly be real? I think it was so embedded in the popular culture that it was hard for the academicians to believe these concepts until we could understand them in the language of science.

JB: It's very interesting. A few years ago, I had the pleasure of interviewing Dr. James Goodwin, a professor of medicine at the University of Texas School of Medicine in San Antonio. You may recall a paper he wrote that appeared in JAMA some years ago, titled "The Tomato Effect."11 His model, when he reviewed it, (he had a pretty interesting rationale for this, based upon looking at textbooks of medicine and the way they language things), is it's not that things like Selye's work were outside the range of good thinking. It was what they did in transgressing what he calls the covenant or the guild, by writing to the general public. He uses Galileo as an example. He said that Galileo was not the first person to talk about the heliocentric view of the universe. Kepler had done it years before, but Kepler wrote in the language of scholars, which was Latin, and Galileo wrote in the language of the people, which was Italian. Once you do that, you break the covenant. I guess he proposed that Selye did the same thing. It caused him to be an outlier within his own community because he took it to the public and didn't keep it within the guild.

Academicians and the Public

ES: There's no question that was part of it. I describe that in the book and the hushed conversations that my parents used to have over dinner, purposely not in English, so that my sister wouldn't understand them, but we did. And the faculty generally did resent Selye's grandiosity and attempts to communicate to the public. It has taken the scientific community until now, and even now, many of us who communicate with the public are still disparaged, much less so now than even five years ago, but there's no question that there is a feeling amongst academicians that if you do talk to the public, you're a lesser academician. I strongly disagree with that. Obviously, I wouldn't be going around lecturing and writing books for the lay public if I did agree with that. I think that it is our responsibility as scientists to return as much of the knowledge as we have to the public in an interesting and palatable way. It is our responsibility. Public information is public health. I think the public has got to know about the new advances that are happening, as they happen.

JB: I also had the pleasure of interviewing Dr. Robert Sapolsky on a couple of occasions, and obviously he's come at this from his experiences and his research over the last 20 years in a slightly different way as a primatologist, but he has drawn similar types of conclusions in the field in which you're working. And Dr. Ilia Elenkov, as well. In those conversations, there seems to be a common denominator, even today, among the three of you, and perhaps I'm being presumptuous in saying this, but still within our medical academic community, there is a resistance after 50 years to accepting the important role that these factors play in complex chronic age-related diseases, and the importance of building therapies that address the connections among these conditions.

Evolution of a Sea Change

ES: I think there is resistance, but much, much less so now than even ten years ago. I first started working hard at bringing the field to the awareness of the academic disciplines from which it sprang in the mid 1990s. I did several international conferences and workshops in a variety of locations, including NIH. It was very hard. There was a lot of resistance to doing the first few of these conferences, especially the first one. There was resistance from the academic disciplines, the parent disciplines of neuroendocrineimmunology. There's been a sea change. I would say that since 1996, when I did the first of these conferences, to 2001, when I did a follow-on conference, together with the MacArthur Foundation at NIH, there was a very palpable difference, a huge difference in the acceptance of the field by the community, a very rapid sea change that had to do with the exponential accumulation of very, very solid molecular neuroanatomical, physiological neuroimaging, genetic immunological studies in this field that proved beyond a shadow of a doubt the many, many connections between the immune system and the CNS and how when those connections are disrupted, disease results. I think that it was the weight of the science that eventually convinced the parent disciplines that this stuff is real.

JB: I'd like to gothrough a quick list with you of conditions that I know have, at least historically, been linked to some of the stress/immune responses, and see if you feel that in each of these areas, the science is advancing in making the connection more real. The ones I'm thinking about are heart disease, cancer, diabetes, and dementia. Do you feel that in those four areas, there is increasing strength of the connection, or are some of them still just speculations?

Stress and Heart Disease

ES: I think there is increasing evidence in all of those areas, at different levels. Of course, there's evidence in heart disease that there's an important element of inflammation. I was recently at a Directions in Research workshop, sponsored by the National Center for Complementary and Alternative Medicine, where there was a lot of discussion regarding trying to track the changes in brain function that occur during stress, all the way down to the effects on heart rate variability by the autonomic nervous system and potential effects on CVD. These are studies that are well beyond the realm of what was previously considered "flaky" mind/body medicine. These are solid neuroscience, physiological, and cardiovascular studies. I think the field has informed a lot of different aspects of CVD.

Stress and Diabetes

You asked about diabetes. Similarly, there's very clearly an immune component to diabetes. I wouldn't put that in the category of mind/body, however. I think one of the things that happens when a field becomes established and accepted, is that it can become part of many disciplines. It can become part of the explanation or understanding of pathogenesis of many different diseases.

Stress and Cancer

It's difficult to study stress effects on cancer, but there are outstanding studies by David Spiegel, who showed that certain kinds of psychological support groups definitely prolonged life span in breast cancer patients. There was some controversy about that with a recent study that failed to find this effect, but the important point that David Spiegel made was that when he carried out his first intervention study 15 years ago, these sorts of interventions were not standard practice, and they are now. Now, it's very hard to find a control group where there aren't standard practice interventions using psychological support, anger management, or these sorts of psychological interventions. These interventions have become standard management, standard therapy, because we understand their importance, and we understand that they

work.

JB: That leads to a question I'll bet you've been asked many times. We now have solid science. Your work and that of your colleagues has started to unravel this complex web of interaction of outside environment to inside neuroendocrineimmine function. What will be the way that this gets clinically integrated? Is it going to be pharmacology, or is it going to be self-regulation, or a combination thereof? Where are we on the therapeutics that one takes out of this?

Clinical Integration of Neuroendocrine Immune Concepts

ES: I think there's no question that it's all of the above. When you look at the advances and potential new therapeutics based on the understanding of these connections between the CNS and the immune system, they span the entire gamut. For example, one of the things we didn't talk about, but which you alluded to when you asked about dementia, is that when cytokines are overexpressed, or inappropriately expressed in the CNS, they can cause nerve cell death. On the other hand, cytokines and immune cells can be very important in nerve cell survival and regeneration, and they play an important physiological role in maintaining and pruning nerve cells during development. That is a huge area of advance that helps to understand the pathogenesis of diseases like multiple sclerosis or infectious diseases of the brain like neuro-AIDS or nerve trauma or dementia. Very interesting advances in therapeutics in these diseases have come from this.

For example, Michal Schwartz of the Weizmann Institute has shown that the use of specific activated T cells can prevent paralysis and actually reverse it, even up to 10 days after spinal cord injury.12 This is a huge advance. She has shown this very clearly in animal models so there are the beginnings of testing to prepare for potential human use. The hurdle in this mode of treatment is not going to be whether it works; it clearly works. The question is going to be how to treat humans with specifically activated T cells without risking the development of multiple sclerosis. There are tremendous potential advances in this area, but a lot still needs to be worked out.

Treatment Approaches

Similarly, the interleukin-1 receptor antagonist has been shown again in animal models to reduce the area of stroke by about 50 percent. There are many potential biologic and pharmacologic treatments, therefore, that come from understanding these connections that are molecular and at a cellular level. And similarly, understanding that stress can make you sick by an overreaction of these stress hormones, an over-suppression of immune responses, and interventions that reduce stress, therefore, can potentially ameliorate or prevent such effects1 It gives credence to the use of many psychological interventions, many salubrious activities like meditation or prayer, certainly exercise, as adjuncts to treating many diseases.

JB: I think you've set a vision as to where we're heading in medicine. Some people would call it integrated, but let's just call it good medicine, that leverages out of these discoveries. I want to thank you, Dr. Sternberg, both for the contributions and your vigilance. I know this hasn't been an easy path for you, but clearly, it's creating tremendous value for all of us in the clinical world. I want to thank you for sharing. For our listeners, Dr. Sternberg's book is required reading—The Balance Within: The Science Connecting Health and Emotions. It's the seminal kind of work to get us started in this field. Thank you again for all your contributions and we'll be following your work very closely as we move forward.

ES: Thank you so much. It's been a great pleasure talking to you, and it has been very rewarding for me to see this field embraced by practitioners who can really make a difference, who are at the forefront of instituting these approaches.

Nutrition and the Neuroendocrine Immune System

I would like to follow up from Dr. Sternberg's extraordinary insight with a few closing comments about the nutrition connection to neuroendocrine immune function. I was talking earlier about fatty acids and the role they play in hypothalamic and central and peripheral nervous system function. The nervous system is composed of a specific composition of lipids. They are an important part of the brain's structure and function. As we move to a better understanding of how fatty acids are metabolized, we need to recognize that in certain situations where there is auto-oxidation of fatty acids, that the oxidation products may be associated with oxidative stress. That is correlated with a variety of degenerative disorders, including things like heart disease, diabetes, kidney dysfunction, dementia, CNS function, neurodegeneration.

Does this mean administering supplementary omega 3 fatty acids will increase oxidative stress and lead them into a state that might be called biological rancidification, meaning we are increasing the potential damage by administering fatty acids? I have heard some individuals say that because we know omega 3 fatty acids are so easily oxidized, we had better give high doses of antioxidants to prevent them from being damaged when they are consumed as supplements.

Dr. Trevor Mori and his colleagues at the Western Australia School of Medicine, a very large group, focused on hypertension and conducted many studies in which they looked at the role fatty acids play in vascular diseases. They have come to recognize that the oxidation products of fatty acids, called the isoprostanes, play important roles in their human vascular disease.[13] The isoprostanes are a family of fatty acid oxidation products that have a chemical similarity to prostaglandins. They are like twisted prostaglandins that can have some adverse effects on the way prostanoids are normally received by cell receptor systems. Elevations of isoprostanes, particularly plasma F2-isoprostanes, have been associated with increased oxidation of fatty acids in the body and oxidative stress.

F2-isoprostane levels have been studied in individuals before and after high-dose EPA and DHA supplementation. Much to the contradiction of our prevalent thinking, subjects who are supplemented with fairly high doses (up to three times a day of an EPA/DHA mixture, have lower levels of F2-isoprostanes after the consumption of fatty acids, the omega 3 fatty acids, than before taking these fatty acids.[14] It's as if it serves as its own antioxidant, so to speak, if I can use that term euphemistically.

I believe there is now fairly strong evidence from this work that when an individual is properly metabolizing fatty acids in the absence of antioxidant consumption, the omega 3 DHA/EPA serves as its own antioxidant, meaning it helps to balance redox properties in the body. If you were to see elevated F2-isoprostanes, it would indicate that individual is undergoing increased oxidative stress and you would look for the source. It is probably not as a consequence of consumption of increased omega 3 fatty acids. It is probably due to ischemia, infection, or upregulation of the inflammatory system through immune dysregulation. These would undoubtedly be the more likely sources, or heavy metal toxicity, metallothionine alterations, glutathione peroxidase/glutathione reductase deficiencies. All those things that are related to altered cellular redox, not just because of supplementation with omega 3 fatty acids.

Studies in patients with coronary artery calcification have demonstrated a strong correlation between increased concentrations of F2 isoprostanes. Even young, healthy adults who have increased calcium artery scores appear to have increased evidence of oxidative injury through elevated F2 isoprostanes in their plasma.[15] In the journal, *Clinical Chemistry*, there is a review on oxidative stress and vascular disease, looking at the results of isoprostane measurement.[16] The authors state that over the last 20 years, there is overwhelming evidence indicating that oxidation of lipoprotein plays an important role in the development of atherosclerosis, and that the pathophysiology resulting in atherosclerosis is closely correlated with increased plasma levels of isoprostanes which, once again, implicates inflammation and oxidative stress with the etiology of coronary artery disease.

Association of F2-Isoprostane Levels and Angiotensin II Type 1 Receptor—153A/G Gene Polymorphism

Responses people have to increasing oxidative stress in their environment as a consequence of imbalance of the neuroendocrine immune system are polymorphic, meaning genetically unique. For instance, with isoprostane levels associated with angiotensin II type 1 receptor polymorphisms, some individuals have much higher levels as a consequence of the 153A/G polymorphism versus those that have the wild type. This was published in the journal, *Free Radical Biology & Medicine.*

Nutrigenomics and the Future of Dietetics Practice

In closing this issue of FMU, I want to talk about clinical dietetics as it relates to a nutrigenomic concept. I was pleased to see in a recent issue of the *Journal of the American Dietetic Association*, a mini review of articles talking about the role that nutrigenomics will play in the future of clinical dietetics and nutritional therapies.[18] One of the most compelling of these articles was written by our own Ruth Debusk, RD, PhD, titled "Nutritional genomics in practice: where do we begin?"[19] She states:

"Nutritional genomics which studies the genome-wide influences of nutrition, has far-reaching potential in the prevention of diet-related disease. It is highly likely that during the next decade the nutritional supplement and functional food industries will continue robust growth in response to advances in nutritional genomics research and its applications. Parallel to this growth will be impressive progress in understanding the specific influence of certain food components on metabolic pathways and on long-term risk for disease."

Parenthetically, I would say that much of this will come through our better understanding of how genomics interfaces with function of the neuroendocrine immune system and how nutrition plays a role in modulating these functions.[20]

In closing, I would like to say that this means that one size does not fit all and, as Selye pointed out, stress is variant in its response. As we saw from Dr. Elenkov at the 12thInternational Symposium on Functional Medicine, you can take different strains of rats and show one strain that is very responsive to a certain stress factor, such as an allergen or an immune stimulant, and another that is more responsive to psychosocial stress. Vastly different clinical outcomes result from genetic uniqueness.

The medicine for the future is personalized and it is built around the neuroendocrine immune system and

its interrelationship with the environment. The body/mind connection lives on to be a major tool in the future of a functional-based medicine.

We look forward to sharing with you in September.

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