August 2007 Issue | Sonia Lupien, PhD Director, Laboratory of Human Stress Research

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Welcome to *Functional Medicine Update* for August 2007. The 14th Symposium on Functional Medicine in Tucson, Arizona focused on the effects from alteration of the function of the hypothalamus-pituitary-adrenal axis and the thyroid; and it was the most successful Symposium the Institute for Functional Medicine has organized to date. It was a very profound discussion of what I would call applied functional medicine across a wide rage of considerations. One of the Symposium themes that we are going to be focusing on in this month's *Functional Medicine Update* is related to what we have euphemistically called (since Dr. Hans Selye gave it this label) "stress."

What does stress mean? How does it influence the activity of the hypothalamus-pituitary-adrenal-thyroid axis? What are the clinical symptomatologies? What are some of the tools that one can use to evaluate it? And then, of course, how does one intervene? What are the ways that we can actually do something about this in a clinical program? That is going to be the focus this month. We have a clinician and researcher of the month who I think will add tremendous insight to this topic and give you 'news to use.' She will bring this topic down to a level of user-friendliness and describe how we can apply this information to the patient.

Before I get into this topic, let me first introduce the connection between stress and alteration of the hypothalamus-pituitary-adrenal-thyroid axis. This is the functional medicine perspective and what we will call "functional somatic syndromes."

It was very exciting for me to pick up my issue of *Lancet* magazine a few months ago and read a review paper titled "Management of Functional Somatic Syndromes."[1] This article was authored by Henningsen, Zipfel, and Herzog from the Department of Psychosomatic Medicine and Psychotherapy, University Hospital, University of Munich in Germany and the Department of Medicine at Tuegingen as well. These authors provided interesting insights that I thought gave some strong validation to the functional medicine model and its principles that we have been developing for nearly 20 years. These insights are useful tools for how we will sieve the information in this month's *Functional Medicine Update* .

Let me take you through a summary of this paper. The authors point out that although functional somatic syndromes show substantial overlap, research is mostly confined to looking at single syndromes. We know that in medicine there is a lack of valid and generally accepted diagnostic criteria that cross over from one medical specialty to another. The medical community likes to have conditions be seen as independent diseases that are siloed and uniquely defined within the concepts of medical specialties. Data for this article were drawn from systematic reviews and meta-analyses published since 2001, and it really demonstrates that functional somatic syndromes don't fall nicely into single diagnostic categories with

single diseases that can be identified. This article recognizes that there is a need for programs of intervention that take into account the fact that these syndromes show diverse symptomatologies and different mechanistic contributions to the signs and symptoms that a patient presents with. The authors indicate there is a need for personalized therapies and a differential approach overall (a stepped care approach is what they talk about).

Conditions that May Be Considered Functional Somatic Syndromes

The conditions these authors feel fulfill the concept or the definition of functional somatic syndromes include the following: irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity, nonspecific chest pain, premenstrual syndrome, non-ulcer dyspepsia, repetitive strain injury, tension headache, temporomandibular joint disorder, atypical facial pain, hyperventilation syndrome, chronic pelvic pain, sick building syndrome, Globus syndrome, chronic whiplash, chronic lyme disease syndrome, silicone breast implant effects, candidiosis hypersensitivity, food allergy, Gulf War syndrome, mitral valve prolapse, hypoglycemic syndrome, chronic low back pain, dizziness, interstitial cystitits, tinnitus, insomnia or sleep disorders, and pseudoseizures.

You'll notice that the conditions on this list don't fall within a specific diagnostic disease, but rather syndromes that defy simple explanation because there is no single etiology that has been identified as contributing to these. The authors state that pharmacological agents that have been used in the management of these conditions generally manage symptoms rather than a cause. In the case of functional somatic syndromes, a balance is required. Personalized therapy would take from biomedical, organ-oriented, and cognitive/interpersonal approaches.

You'll notice that all these functional somatic syndromes, as I have described them, might fall within the context of the kinds of presenting signs and symptoms that we often see in the patient with distress. In fact, all of the signs and symptoms that cluster around metabolic syndrome might be called functional somatic syndromes: increased weight gain of unknown origin, inflammatory conditions, altered triglyceride and HDL levels, craving for sweets, sleep disorders, sleep apnea.

A Model for Managing Functional Somatic Syndromes

The authors of the article say that if we are really looking at how to develop a model for the management of functional somatic syndromes, it should draw from the following: organic disease evaluation; dysfunctional peripheral stimuli, which has to do with distressful issues (or environmental agents that are received by the person and translated into altered mediators that then change their physiological function); dysfunctional early and current relationships, which has to do with what (in the functional medicine model) we call antecedents.

This is really another way of restating the functional medicine model of antecedents and triggers resulting in mediators that produce signs and symptoms, leading to bodily stress, anxiety and depression, and ultimately to the experience of chronic bodily symptoms. These symptoms accumulate, leading to the loss of functioning (or altered functioning). This is, in a sense, the functional medicine model that we have described in the *Textbook of Functional Medicine*. It was quite interesting to see these investigators come up with (through an independent perspective) a model that is so closely allied with that which we have been talking about for 20 years.

In assessing functional somatic syndromes, an organ-oriented approach is to look at those kinds of things

that relate to physiological dysfunction that can be measured and analyzed by traditional methods (through biochemistry in the clinical laboratory and other kind of objective determinations). A cognitive interpersonal approach looks at body and mental symptoms over time, with a focus on dysfunction of central processing and context factors, including things like memory. Interventions are then aimed at sensations and cognitions that affect behavior and restoration of overall functioning. That might be called a stress management approach or cognitive behavioral therapy.

Educating practitioners so they are better able to understand these problems and to recognize them early on is important. Practitioners can also learn how to communicate more effectively with a patient through this whole process about readiness to change, and they can also try to help patients avoid iatrogenic agents that might initiate problems (in other words, overuse of medications that might facilitate aggravation of the symptoms downstream). There must be a focus on the context, not just the treatment itself: What is the workplace of the patient? What is the patient's cultural belief system? Does he or she have access to proper health care and counseling and education? All of these things are a part, of what the investigators in the *Lancet* article think is the appropriate way to both assess and then manage functional somatic syndromes.

I think this is an extraordinarily useful article to highlight what we have been talking about for so many years, and it fits particularly well as we move into this discussion of psychosocial and distressful factors in our environment that translate themselves into alterations of the HPAT axis (hypothalamus-pituitary-adrenal-thyroid axis), which then gives rise over time to many signs and symptoms that can be classified as diseases in the late stage, but go through symptomatic syndrome-like changes that are very unique to each individual patient.

One person who has helped us to understand the physiological mechanism by which these things occur (the so-called organ-specific component of functional somatic syndrome) is Dr. Bruce McEwen. As you probably know, Dr. McEwen is regarded as one of the top stress researchers in the world today. He is with the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at Rockefeller University.

Dr. McEwen authored a very nice review paper that appeared in the *New England Journal of Medicine* in 1998 discussing the protective and damaging effects of stress mediators.[2] In this article, he really sets the stage of looking at the neurophysiology of stress and how it relates to these functional somatic syndromes. Dr. McEwen's work looks at environmental stressors, such as those found in work, home, or neighborhood, and how they get translated through the perception of threat, helplessness, and vigilance in ways that are individualized based upon each individual's own genes, development, and experience. Once again, this is the functional medicine model: the interconnectedness between genes and environment and the perceptual translation of observations in the environment into physiological alterations of mediators. These triggering effects in life (some of which are old memories that get reinitiated by recent experiences) can be translated in the body as potential alarm reactions that then develop physiological responses and contribute to the need for the body to adapt to these changes. This is what Dr. McEwen refers to as "allostasis," as contrasted to homeostasis.

The Allostasis Model

In the functional medicine model of the 1990s, we talked about "homeodynamic" change: the body does not remain constant (homeostasis); rather the body has to be dynamically changing in response to a

changing environment. So, the body is "homeodynamic." It is like a hummingbird that looks like it is stationary at a flower getting nectar, but in time-lapsed photographs, we see that its wings are moving at a very, very rapid speed in order to maintain its apparent stability at the flower. That's how our physiology works-it's like hummingbird wings beating at a very high speed to try to accommodate or adapt to those changing environmental conditions; that is called allostasis.

As the body goes into an adaptation phase over some period of time, Dr. McEwen calls this the "allostatic load." Over time, allostatic load charges a price to be paid from our physiological machinery, ultimately depleting functional status and reserve and what we have called "organ reserve" (taking from Dr. Fries work from many years ago about organ reserve, aging, longevity, natural death, and the compression of morbidity). Allostatic load depreciates organ reserve over time and ultimately leads to what later would be called a discrete diagnosed disease.

The failure to turn off the hypothalamus-pituitary-adrenal-thyroid axis and sympathetic activity efficiently after stress is a feature of age-related functional decline in both animals and in humans. Stress-induced secretion of cortisol and other catecholamines, such as epinephrine and norepinephrine, return to baseline more slowly in aging animals with other signs of accelerated aging. This is the negative feedback effect of cortisol that becomes reduced and is seen in elderly humans, making them more susceptible to triggering events.

Measuring Allostatic Load

Allostatic load, as measured by McEwen and others through the MacArthur Studies on Successful Aging, was approximated by determining the number of measures for which a person had values in the highest quartile from among the following physiological variables that are all associated with this distressed response: systolic blood pressure; overnight urinary cortisol and catecholamine excretion; the waist-to-hip measurement (which is, as you know, is also a surrogate marker for metabolic syndrome related to changes in insulin resistance); glycosylated hemoglobin value (a move up from 5.5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of total hemoglobin as glycosylated hemoglobin is an indication of altered allostatic load); the ratio of serum high-density lipoprotein cholesterol (HDL-C) to triglycerides (which also is a surrogate marker for metabolic syndrome). Based upon McEwen's definition of allostatic load, you'll notice that a lot these things track against physiological parameters that have been given the name "metabolic syndrome."

During three years of follow up to the MacArthur Studies on Successful Aging, from 1988 to 1991, people in the higher functioning group with higher allostatic load scores at baseline were more likely to have an incident of cardiovascular disease and also were significantly more likely to have declines in cognitive and physical functioning. This suggests that one of the prices that we pay over time for these impacts of maintenance of this allostatic load is adverse effects on the neuroendocrine immune system with loss of cognitive reserves (meaning changes in memory patterns and increased incidence of depression).

Repeated stress affects brain function, especially in the hippocampus, which has high concentration of cortisol receptors. The immune system, then, also responds by altering its function to pathogens and other antigens with its own form of allostasis that may include an acute-phase response as well as formation of immunological "memory" in which it becomes more intolerant to environmental substances. How many patients have we seen who become more environmentally sensitive and more allergic to things they could

previously tolerate as they grow older? This is another manifestation of immunological impact of an allostatic load.

You might say we are suppressing the immune system; however, not all effects are suppressive. Acute stress causes lymphocytes and macrophages to be redistributed throughout the body, such as to blood vessel walls and within certain compartments like the skin, lymph nodes, and bone marrow. This trafficking is mediated in part by glucocorticoids. When a challenge occurs, as is the case in delayed-type hypersensitivity, acute stress enhances the traffic of lymphocytes and macrophages to the site and therefore might be seen as a pro-inflammatory response. So we get these kind of unique and divergent effects of allostatic load, some of which look immunosuppressive, and others are immunoreactive (meaning increased inflammatory response).

Acute stress has the effect of calling immune cells to their battle stations, and this form of allostasis enhances responses for which there is an established immunologic "memory." So we recognize now that allostatic load has dramatic effects across a wide range of physiological parameters. It is associated with risk to heart disease, diabetes, memory loss, depression, and possibly even cellular-type effects that associate with cancer. Physicians and healthcare providers now are looking at how we can actually understand better the origin of allostatic load in the individual patient and what to do about it in individualized treatment prescription for that patient. That is the focus of what we are discussing in this issue of *Functional Medicine Update*: how the hypothalamus-pituitary-adrenal-thyroid axis affects the neuroendocrineimmune system, and how that ultimately translates itself into things that we try to diagnose and to put a diagnostic code on when they are really related to this altered physiological function associated with allostatic load.

We recognize that physiological-activating factors alter CRH and arginine vasopressin levels in the brain, which plays an important role in then altering gonadotrophic hormone secretion during stress, and affects, then, thyrotrophic releasing factor and thyroid-stimulating secretion, so we have effects on downstream corticosteroids, catecholamines, and on thyroid hormones. In fact, high stress deactivates the conversion of T4/T3 peripherally, so we end up with a secondary-induced hypothyroidism. This doesn't mean that the person needs thyroid hormone replacement. It means that what they need is to lower the load of catecholamines and glucocorticoids that then influence the conversion of T4 to T3 through the deaminase enzyme and thereby allow the more active T3 to be formed peripherally, which then controls cellular metabolism.[3]

The first step would be some kind of a program that is inducing lowered allostatic load. We recognize that the brain is, as I mentioned, significantly influenced by the allostatic load concept, with neuroplasticity of the hypothalamus-pituitary-adrenal axis altering, then, the stress-regulating brain regions and increasing neuronal apoptosis (or cell death) in certain regions of the brain.[4]

I have talked about the hippocampal impact of stress, so you might ask if chronic, long-term stress has any relationship to Alzheimer's disease etiology given that the hippocampal region of the brain is one of the regions associated with Alzheimer's disease and memory loss. We also recognize that these allostatic load concepts relate to increased inflammatory mediators that can be measured in the blood and circulating fluids, so there might be a link, then, between increased levels of tumor necrosis factor alpha or increased interleukin-6 and heart disease. This might be another example by which heart disease is connected to psychosocial stress and allostatic load. I'm now quoting from an article by John Yudkin and

his colleagues at the Department of Medicine, Centre for Diabetes and Cardiovascular Risk, University College London Medical School that was published in *Atherosclerosis*.[5]

So we know that perceived stress can promote inflammation, and it also increases the release of mediators that are associated with blood coagulability, which then increases the risk of thrombus formation and sudden coronary events. This is from a study published in *Psychophysiology* this year that looked at plasminogen activator inhibitor (PAI-1) and other inflammatory markers such as interleukin-6 (IL-6) and soluble adhesion molecule-1 (sICAM-1) in 180 healthy individuals.[6] The researchers rated stress-related effects on levels of these markers of inflammation and altered insulin sensitivity and found there was a very strong correlation between perceived stress (i.e. allostatic load) and increased stress markers and inflammation and, ultimately, coagulability or potential thrombus formation.

This is a very interesting story that shows that one of the least accepted etiological factors in traditional medical training may be one of the most important factors for contributing to the outcome that we call chronic disease. During the stages of the functional somatic syndromes that I described earlier, people have broad-range symptomatologies that are hard to diagnose, and some clinicians say, "Well, they are psychosomatic." And they use that term in a pejorative sense, indicating that there is no "organicity" with psychosomatic (it's all in the mind). But the mind is connected to the body. It is very important to emphasize that this connection is where all the action is: how we perceive outside events and how these perceptions get translated to interior function. This is the topic that our clinician/researcher of the month will be helping us to understand.

Organic Contributors to Allostatic Load

Let me, if I can, shift slightly from what we have been implying through this discussion (that stress factors are totally psychosocial factors) to talk about some of the organic factors that may be perceived through the stress mechanism as contributing to allostatic load. These have to do with things like infection, toxic exposures, and even dietary factors, which are normally not on everybody's list as potentially important stress factors, but are emerging to be so as seen from recent literature.

Let's talk first about diet because I think this is a modifiable factor that is often overlooked as an important regulator of the stress response. I'm now going to go back to a study that was published in the *Journal of the American Medical Association* a few years ago titled "Mediterranean Diet, Lifestyle Factors, and 10-Year Mortality in Elderly European Men and Women."[7] This is the so-called HALE project. This was published in the *Journal of theAmerican Medical Association* in 2004.

In this study (conducted from 1988 to 2000), the investigators looked at individuals who were in the latter phases of their lives (70 to 90 years of age) from 11 European countries. It was a longitudinal study, and the participants were enrolled in the Survey in Europe on Nutrition and the Elderly: a Concerned Action (SENECA) and the Finland, Italy, the Netherlands, Elderly (FINE) nutrition intervention program.

In this nutrition intervention program, they were looking at people between 70 and 90 years of age who decided to change their diets to a Mediterranean diet. The health outcomes of the participants were then evaluated in comparison to age and gender matched controls (people in the same-age cohort of 70 to 90 years who elected just to continue on as they had been eating and living prior to the study). So, basically it was not a controlled intervention trial; it was an evaluation of those individuals who elected to alter

their diet and lifestyle to be more consistent with a Mediterranean diet.

The investigators looked at health outcomes over this period of time. The outcome variable they chose was a pretty well-understood, non-equivocal outcome: death (all-cause mortality and cause-specific mortality). The results, when the data was worked up, were just quite remarkable. In fact, so remarkable that you wonder how this study didn't get more media play than it did. A more than 50 percent lower all-cause and cause-specific mortality was found among the individuals aged 70 to 90 years who decided to adhere to a Mediterranean diet and healthful lifestyle, compared to those of the same age who continued on ad lib as they had been doing all their years previously.

If I was to tell you that I saw a report in the *Journal of the AmericanMedical Association* about a pill that people could take that would lower (at the age of 70 to 90) the risk of all-cause mortality by 50 percent, how much media attention do you think that would get? I think we would be hearing about that. It would be a blockbuster drug. The drug company would suddenly be number one in its field. It would be sharing such huge profit with its shareholders.

But because it was a diet and lifestyle intervention trial, it was ho-hum. It didn't even get the Andy Warhol 15 minutes of fame. Why? That's a very interesting question, isn't it? Are we just so uninterested in this kind of information, which relates to having to make a change in our lifestyle as contrasted to taking a pill? Or is it that there is a suppression of the media? Or are we just kind of disillusioned about these diet studies? I don't know the exact reason. However, the editorial that followed this particular paper was quite interesting. It was titled "Diet, Lifestyle, and Longevity-the Next Steps?"[8]

The authors of the accompanying editorial say that if we start really looking at the studies that have been published on dietary intervention and effects on outcome of health, we have to be very impressed because it is not just one-off evaluation. The Lyon Diet Heart Study showed that people with established coronary disease who elected to have a dietary intervention had a reduction of 79{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} in heart disease after just a few years of following the Mediterranean-style diet: that is, 79{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}! And these are people with established coronary disease. Although these results may seem to be simply too good, given the 20-fold or more differences in coronary rates across countries, the results for this dietary change are entirely plausible because it actually shows us, from other studies, that they are reproducible. For instance, look at the Dietary Approaches to Stop Hypertension Study (the DASH study). That study showed an ability to reduce blood pressure after six months into ranges that could generally only be achieved by usually 2 to 3 antihypertensive drugs. And because it was a dietary intervention, there were no potential risks to adverse effects from medication.

We are starting to see more and more studies being published that are consistent with this HALE study of dramatic improvements in outcome and lowered mortality in people who elect to make these changes to a more Mediterranean-style diet. You'll notice that this probably-in some peoples' minds-is not very sexy. This is just another bit of diet information, so who cares? Well, we should care. Because what we are really saying is that these diets contain specific signatures from their ingredients (their nutrients) that modulate gene expression patterns in such a way as to serve as anti-stress factors.

This is the so-called xenohormesis hypothesis that we have talked about before. Xenohormesis can either

be inducing stress by factors that come from our diet and environment, or it can be altering the stress coping mechanism by improving stress response. There are food substances within Mediterranean diets that are minimally processed. There are complex foods that have color, and these color substances are, as you know, phytochemicals that modulate the stress response in such a way as to reduce its impact on inducing insulin resistance, dyslipidemia, inflammation, and chronic age-related diseases.

Another paper in the *Journal of the AmericanMedical Association* titled "Mediterranean Diet: Looking at the Effects on Endothelial Dysfunction and Markers of Vascular Inflammation in Patients with Metabolic Syndrome," confirmed the same thing.[9] In this randomized trial, the people who engaged in a Mediterranean diet had lowered inflammatory mediators, improved triglycerides, improved HDL-C levels, and improved insulin levels. This indicates that there was a very powerful signaling effect on overall functional somatic syndromes to normalize function and reduce relative risk.

Adaptogenic Substances

You can obviously see that there must be something in these plant materials and these dietary factors that induce altered physiological function (i.e., are anti-stress). That really takes us back to looking at indigenous medicines, well before the birth of the pharmaceutical industry, going back to the dawn of Ayurvedic Medicine or Traditional Chinese Medicine. We recognize that people didn't have access to patented drugs and that they used nature in such a way as to find the structure-function relationships between things that they could get in their natural environment and how they affected the body. They were very good observers.

In the case of natural pharmacology, which is the basis of botanical medicine, we have often said that the bioactive substances from some of these complex mixtures of molecules from plants affect the body in what we call an adaptogenic way ("adaptogenic" meaning if the body is upregulated in this activity it will lower its activity; if the body is low activity-hypofunctioning-it will raise the activity toward normalization), so an adaptogen is a normalizing substance. In the past that didn't (maybe), to a traditional pharmacologist, seem reasonable because it didn't fall within the guise of how we normally think of drugs working, but over the last couple of decades we have come to recognize there are very good ways in which these adaptogens work. They work as a result of being agonists/antagonists, just like selective estrogen response modulators work (or SERMS). They can upregulate estrogen activity or downregulate estrogen activity depending upon the state of the function, so these are adaptogenic. They are agonist/antagonist.

In the journal *Phytotherapy Research* in 2005, a marvelous review paper was published titled "The Effect of Adaptogens: An Overview with Particular Reference to their Efficacy Following Single Dose Administration," which looked at the influence that a whole range of different adaptogenic substances from traditional plants used as botanical medicine have on normalizing function.[10] This includes things that are derived from ginseng, *Rhodiola*, *Withania somnifera* (which is Indian ginseng), or *Schizandra*. These are all adaptogenic, anti-stress botanicals that have been historically used by different cultures to normalize the physiologic outcome that we associate with functional somatic syndromes that are titled "stress-related dysfunctions" and that have to do with what McEwen might call increased allostatic load. These plant adaptogens are historically a family of substances that were used prior to the onset of specific new-to-nature patented molecules that treat individual outcome parameters like elevated blood pressure, elevated insulin, elevated glucose, and elevated cholesterol. Before we had those molecules in our pharmacopoeia, we used these adaptogenic substances to normalize physiological function.

We know that things like tumeric, which contains curcumin, is found to reduce the effects of chronic stress of the HPA axis. It also influences brain-derived neurotrophic factor expression and lowers brain neuronal stress and inflammation. There was a paper published recently that really looks through the whole nature of how curcumin plays a role on chronic stress on the HPA axis. This is in an issue of *Brain Research* in 2006.[11]

We know that curcumin is but one of many phytochemicals that have been found in various plant foods that have been used historically for modulating inflammatory response and stress-mediated effects. We have started seeing that there is a…I guess you would call it learning old things in new ways, or back to the future. It is regaining an understanding and appreciation for the signatures that these complex mixtures have in various plants and plant foods that modulate stress response and modulate them through activities of cell signaling-things like gene expression patterns modulated through kinases, a family of enzymes that translate outside information to inside cellular function.

So I think that there is a regaining of interest in some of the traditional pharmacology that we associate with these complex mixtures found from certain plants that are of dietary origin. In pharmacology, where we look for the single molecule to treat the single outcome (i.e., the traditional kind of prescription medications of our age), these medicinal plants may have been lost along the way because they didn't work by that mechanism; they worked by a different mechanism, which was normalizing function across these ranges of cell signaling activities that we associate with allostatic load and altered adaptation.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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We are now at that most-looked-forward-to portion of Functional Medicine Update : our Clinician-of-the-Month section. This month we are very privileged to have both a clinician of the month and a researcher of the month in the same person. In fact, she was evaluated as the top presenter at the recent Institute for Functional Medicine Symposium. That's not too shabby for a person who actually spoke in her second language at the Institute, English; she is actually French-speaking and Canadian. She has a tremendous background in the area that she is going to be speaking to, which is stress.

Before I introduce Dr. Lupien to you I'd like to just say a couple of words about her. As you know, we have spent considerable time over the last 25 years (now moving into 26) to develop this whole concept of stress physiology. You have heard, over the years, from many of the premier investigators and clinicians in this area. Dr. Lupien has a background that I think is quite remarkable and certainly sets her up as being a world authority. Let me just summarize it for you.

She started off with a BS in psychology at the University of Montreal, but then went on to get her Masters in neuropsychology, and then later her PhD in neurosciences at the physiology department, faculty and medicine, at the University of Montreal. Then she did a postdoctoral fellowship in neuroendocrinology at the University of California at San Diego with Dick Hauger, who we heard speak many years ago. And then on to do another postdoctoral bit of work in the laboratories of one of the people who is (I think) considered by many to be at the top of the game of stress physiology, Bruce McEwen at Rockefeller University. We have talked about his book, The End of Stress as We Know It, and certainly he is a very well regarded person. She was really a very important person in his laboratory and doing extraordinary work.

Since then, Dr. Lupien returned to Montreal as a faculty member, first as an assistant professor in the department of psychiatry at McGill and now an associate professor there. She is director of the Laboratory of Human Stress Research at the McGill University/Douglas Hospital Research Center. I think that if you look at Dr. Lupien's research publication record it is absolutely sterling; it's at the head of the class.

In 1998 she found that high levels of stress hormones in older adults are linked with both memory impairments and atrophy of the hippocampus (as you know, the center of memory). She has done tremendous work in understanding stress in children, which we are going to be talking about. She was named one of the 50 top young people for the year in 2000, and received Canada's "Top 40 Under 40" award in 2002, and was named in the category "the top 20 Canadians who make a difference" by MacLean's Magazine in 2003. So she is a pretty busy individual, plus a mother, a wife, and a student of the universe. It is with great privilege that I introduce to all of you Dr. Sonia Lupien.

Sonia, good morning and thanks for being with us.

SL: Good morning, Jeff. It is my pleasure.

JB: Let's, if I can, just start this discussion by going to your institution. Most of us who have come up through the understanding of stress were kind of borne first through the Hans Selye model (and, of course, we know he was at McGill), so you're at the institution from which much of this was ultimately born. Can you tell us a little bit about how it is to be at McGill?

SL: Well it is a great institution, as you know, and each time I give a conference on stress I always say (I'm not sure if it is a good or a bad thing) the concept of stress and the etiology was born in Montreal, perhaps because we are more or less stressed than everyone else. It is a great institution. Dr. Selye left his prints, I would say, here at McGill, and you have a lot of scientists actually here at the Douglas Hospital and all throughout McGill University who are working on stress and are contributing extensively on stress research. I think Canada (Montreal) is one of the best places to work on stress.

JB: As you have worked your way into the position as the Director of the Laboratory of Human Stress Research, what kinds of things along your path have prepared you for this responsibility? I've looked at your publication record and read a number of your papers and it looks like you must have had a goal in mind throughout much of your academic history because it seems like it all lines up so beautifully.

SL: Yes. A very, very simple goal, actually. I wanted people to talk to. You know, you develop a high

level of expertise in a field such as stress and memory, etc., and you end up sometimes in your office because there are not a lot of people to talk about this. So I really worked hard to convince the university to recruit new scientists working on stress, and to train new scientists myself, so I could create a group of people to discuss and generate new ideas. I think that was the best thing I ever did because it is by collaborating and talking and fighting with all of these people that you come up with the best ideas. After that, what I have done is to found and create the Centre for Studies on Human Stress, which is now one step further, where all this knowledge that was generated by the lab is now translated for the public and for the health professionals in order to tell them what we learn in the lab and how they can apply it in their own lives.

JB: Before we get to talking specifically about what you have done and your beautiful website and your programs, I'd like to just get your insight as to why you feel, in medicine, there still seems to be some resistance in accepting stress into curriculum in medical school and actually doing something to help docs to better know how to manage this in their patients.

SL: That's a question I have been asking for awhile. You know, at the official opening of the center I had a colleague of mine give a conference. The title was, "Can Your Doctor Diagnose Your Stress and Does He or She Care?" I've been thinking about this for awhile and I think the main problem comes from the word because the word "stress" is now overused. You know, we always use stress by saying, "I'm stressed. I forgot something." etc. And anything that is overused and becomes nonspecific-so very difficult to measure or think about-is something that will die away, I would say. And it also always brings people back to this notion of mind/body, or mind over body. Kind of half of the population really gets the information from this and understands how the mind and the body can interact, and I think you have the other part of the population who see this as, you know, "soft science" or things like that, when actually when you read what has been done on stress and its impact on the mind, the brain, etc. there is a very, very good science behind this. I think that is our goal as scientists: to bring back this information and say, "Listen, there is science behind all of this and this is not just soft science."

JB: It strikes me very interesting and almost paradoxical as to why there is still some reticence to accept this at the level it should be accepted in medical school. I read a recent paper in The New York Times in which there were the results of a survey of educated individuals who were seeking out healthcare advice and they were asked to rate their most concerning health problems. Cancer and heart disease were on the list, but number one was loss of memory and loss of their minds. So this concept that somehow stress has an impact upon brain function seems like it is the number one thing people are concerned about, yet we're not paying as much attention to it in medicine as it probably deserves.

SL: Yes. And what I have realized is that we tend to be scared of what we don't know well. As much as we think we know stress, I don't necessarily consider that we have been informed-the public, the professionals, etc.-on what stress is. Most people-I did a survey one day with people from the public-told me they knew what stress was, and when I asked them what it was they told me it was time pressure. We know that stress is not time pressure. Now if you have the wrong definition of stress, you will use the wrong treatment. So I think that in medicine it is the same thing since you cannot diagnose this. Each time I talk to a doctor I say, "Listen, if someone breaks a leg and goes to you, it is easy. You know, there is blood, you know there is a broken bone, you can tell them you have a diagnosis, and then there is a treatment. If someone comes to you and says, 'Listen, I'm almost burned out, I'm probably stressed, etc.' you have nothing. There is nothing that you can do besides look at this patient crying and complaining

about all of these stress-related chronic disorders that we know about, and you have nothing." So I think that as long as we scientists aren't able to provide tools to doctors, we will be having the same problem and that is what we are working on, actually.

JB: Okay. So that's a good segue into the next area of discussion. Much of your work has really dealt with the effects of glucocorticoids on various physiological functions and that translates, for our listeners, into how does stress/glucocorticoid production relate to things like memory. Can you tell us about some of your work in that area?

Glucocorticoid Production, Stress Hormones, and Memory

SL: Well, the interesting thing is all glucocorticoids and the stress hormones have been related to a lot disorders (peripheral disorders like the metabolic syndrome or cardiovascular disease, etc.). But Bruce McEwen, in 1968, found that there is the presence of glucocorticoid receptors in the brain, meaning that the steroid can access easily (it is a steroid so it can easily cross the blood/brain barrier) the brain, and when it gets in the brain, for some weird reason it has an interesting preference for the hippocampus, which is the brain structure that is heavily involved in learning and memory. So this notion, this idea, that chronic stress could lead to memory impairment because of the action of these hormones was born, I would say, in the beginning of the 1970s.

Many studies have been done in animals confirming this. It has to be done in humans, so for this we have been doing a lot of studies in humans confirming, actually, the animal literature that stress does not only do something to your body, it will do something to your brain. This is very, very important. Not just because it will lead to memory impairment, decreasing your performance at work, or etc. It leads to another very important notion. It leads to the fact that it is able to explain why you lose control over your stress.

When you talk to a patient who is chronically stressed, the first thing they will tell you is, "I don't know anymore what is important." They have kind of a big cloud over their brain (their cognitive processes). And this is what renders them more vulnerable to develop stress-related disorders because they tend to see stressors everywhere. And what we are showing now in the brain is that this "fuzziness" of the mind, if I may say so, is induced by the stress hormones. So as weird as it may sound, the same stress hormones that you produce that help you mobilize the energy you need to fight back will go back to your brain if it is produced for too long and modify the way you will interpret the next situation. And then you end up with this loss of control over your stressors. So the first thing you need to do is to decrease these stress hormones-take out a bit of the clouds out there on the minds of the people so they will be able to listen to what you have to suggest in terms of treatment. So I think this notion of the effects of stress on memory is very interesting for everyone, but clinically there is something as well that is very important that we have to keep in mind.

JB: I know that Dr. McEwen introduced a concept (along with John Mason)-a kind of allostasis as contrasted to stress. Could you help us to differentiate the difference between those two terms?

SL: Yes. Sterling talked about the notion of allostasis at the beginning, and it was in contrast to homeostasis. This is an important notion. We learned about homeostasis-you know, you want to keep a set range of data (in a certain range of homestasis). And when you get out of this there can be some problems. Now, in the 1970s, I would say, Sterling and Eyer came back with a notion saying that

homeostasis is unable to explain most of what happens in life, meaning that the body is able to adapt. So the body, for some reason, when it is put in some types of environments, will change the range of set points and the normality range of any biological measure (will change it in order to adapt to the new situation). For us it can be called a dysregulation, but for the body it is just an adaptation. So they came up with this notion that we basically survive in life because our body is able to change the range of normality of values of any biological measure we have.

Bruce McEwen came up with the notion (then worked with Sterling more on this notion) of allostatic load, meaning, what happens when you ask a body to adapt too often? You cannot always adapt. There is going to be a problem in the long run. So they came up with the notion of allostatic load.

The notion is very simple. The first time you have a change in the environment, for example, you will change your range of normality of event. For example, the stress hormones are the first ones to respond to the environment. We know that there is a certain range of normality of stress hormones. However, if you measure stress hormones, for example, in poor environments, you will see that the stress hormones are always elevated compared to the norm. Now this is a change in the set point of this biological measure, and this is the body trying to adapt-mounting a stress response-because you are in an adverse environment. Makes sense: you will survive.

What happens if, for a long period of time, you do this all the time? What Bruce has suggested (and we know about) is the beauty of the endocrine system is that every hormone in your body talks to each other. So they will basically try to help each other. So if you have the first stress hormones at the beginning that have been dysregulated (in our language, adapted) for too long, all the other hormones in the brain will start to change their own set points. And this is when you are going to start to see allostatic load, meaning that you are going to start to show an increase in glucose, for example; an increase in cholesterol; an increase in insulin resistance. All of these hormones will start to be dysregulated, leading to a load on your system.

The allostatic load notion has been widely tested by the MacArthur Studies on Successful Aging in the US, and what they have shown is that the higher you are on an allostatic load score (so basically we are calculating the number of your biological measures that are getting very high and dysregulated), it is a good predictor that 3.5 years later it is starting to get very high allostatic load in the early 20s, and it is higher in poor people compared to rich people. Social support is a great way to decrease the allostatic load. So basically, this is where the science is.

Now, if we go back to the notion of a diagnosis for the doctor, I strongly believe that the allostatic load battery, as Bruce has started to develop with us here at the center, is one of the greatest tools that we can develop in order to detect stress in humans very early in the process, meaning way before your patient will start falling from chronic stress disorders.

JB: You've given us a lot to think about there. Let's follow up on the allostatic battery. Where can someone find that? Is that on your website?

A Useful Interactive Website for Practitioners

SL: It is not on the website right now because I am really working in trying to understand the time course of how things are starting to work, but what I am trying to do, actually, is to validate further the allostatic

load. I can provide a lot of information to doctors, but at the same time I think that we can create some nice collaboration all across the world. So what we are trying to do now is to work on the website, to put what I would call an allostatic load calculator, where doctors could enter a specific part of the website and enter the values that they have on a typical bloodwork for their patient (cholesterol level, etc.) and the machine (you know, the calculator) would calculate an allostatic load score. This is in association with the symptoms that the patient has, and then the next time you see the patient you re-enter the allostatic load score andthat would give you very important information.
First, it would tell you if your treatment is working on the physiology of your patient. So whatever treatment you will decide to do in order to work with your patient, you will see a change in the allostatic load score. That is the first thing. The second thing, for us scientists looking at different symptoms associated with different changes in these biological markers, it could give us a very good indication of different pathways of chronic stress disease-who is going to go down first, for example. So this is exactly what we are working on. It should be available in a few months on the website, but there are many things to do before that.

JB: So let's talk a little bit about your beautiful website for the Centre for Studies on Human Stress. First of all, where can they find it, and second of all, tell us a little bit about it.

SL: The website address is www.douglas.qc.ca/stress. This is my window to the public. I have a lab, that's fine, but I was walking the dog one day and telling myself that I have two choices in my life: I am having all of this great knowledge and just keeping it for my success or I am sharing it with people, and I decided to do that. So we have created the Centre for Studies on Human Stress. I call this a safe place on the web.

Because I wanted to do something with my students I said, go on the web, put stress management on Google, and give me the first 100 websites (the definition of stress they give you), and there was not one definition that was the same. So I can really understand why people have so much difficulty understanding what stress is and how to manage it because they don't have the same information. So this is a safe place to go where you have a bunch of scientists (we have about 90 scientists all across the world who are associated with the center) providing you with scientifically validated information on stress.

We have three sections. One is for the public, so if you have a patient who wants more information, it is free; it is there. Everything we know about stress is there. We have also a newsletter, which is called Mammoth Magazinev. It is written for the public. You can download it as a PDF and we have different issues (on aging, on children, etc.). This is the section for the public. It is very, very well appreciated by the public. We have these great emails that come back and this is good.

We have also a section for the health professionals and education professionals which we are still working on. In there, eventually, you will find the allostatic load calculators. For the education professional, what the center is doing as well is to translate the knowledge we have. So we have programs (education programs) for children, where we go into schools or we train people so they can go themselves into schools (parents or teachers, etc.).

The first one is for children between the ages of 7 and 10; it is called "My Amazing Brain." Basically, the children in the class become the scientists and do all these great experiments to learn more about the brain. They love it and it is very fun to give. Everything is on the website: the logbook, the activities for you and for the children, the slides-everything is there. And we are finalizing another one, which is very

important to me because this is based on one of my studies. I did this study awhile ago, showing that school transition (going from elementary school to high school) is where you have the largest stress response in children. This is when we start to see depression symptomatology in children, etc. Because of these results, we have created the "DeStress for Success" Program, which is a 12-session program given by school counselors (we will train them), where we will train and educate children on how to recognize stress and how to deal with it.

And then you have a section for scientists. You want to know everything about the stress meetings in the world? Everything about stress questionnaires or alpha measures, stress hormones, etc.? It will eventually, as well, be in this particular section.

JB: Well I can say, as a personal visitor (several times) to your site, it is brilliant. It is a tool that every clinician should have on their saved favorites so they can come back and visit on a routine basis. I really want to applaud what you have done. I know it is a work of love and a lot of tremendous effort, but it makes a huge difference in making this material accessible. We'll make sure that the URL for the site is on the summary card and on the end of the tape so people who may not have gotten it can come back and get it later.

SL: Thank you.

JB: By the way, I just wanted to ask you an aside. Would you tell us why you have used the mammoth as your icon on your website?

SL: If you read the second issue of the Mammoth (the first, I thought, was so wide and mammoth), and this is a very important notion and the reason is very simple: we have to make a distinction about an absolute and a relative stressor. Let me explain. What we know is that there are four characteristics of a situation (this is what science tells us) that will generate a stress response from your body. I say to people, burn-out or depression does not start in the liver; it starts in the brain. Why does it start in the brain? Because the stress hormones that you are secreting go to the brain when you are stressed (we talked about that).

So, what will make you generate a stress response? Research has shown there are four characteristics of a situation that will induce a stress response. There are additives to the situation-the more you have of these characteristics the worse is your response. So in order for a situation to induce a stress response it has to be novel. It has to be unpredictable or unpredicted. It must threaten some part of your personality. We now know that there are some personality traits that make you more reactive to stress. And the most important one: you must have the feeling you don't control the situation. So, these are the characteristics of the stress response.

Let's go back to the absolute stressor. An absolute stressor is a stressor for which it is a real threat for everyone that will not necessitate your brain to do this analysis of the four characteristics of the stress. For example, someone enters your office and says "Fire." You will not start by saying, "This is novel and this is unpredictable." You will start running. This is your brain telling you that you are in immediate danger, forget the analysis, run. And it will save your life.

The thing is that we are not surrounded these days, in our respective countries, to a lot of absolute

stressors. There are no more mammoths around. An absolute stressor was when we were chasing the mammoth in prehistoric times and you came face to face with this big thing, you would have an absolute stress response, which gave you the strength to kill the mammoth. These days we are surrounded by relative stressors, meaning situations that need to be interpreted by you as being novel, unpredictable, threatening to your ego, and without control in order for your brain to generate a stress response.

We have more relative stressors today than absolute stressors, yet the World Health Organization predicts that by the year 2020, stress-related depressive disorder will be the second cause of invalidity in the world after cardiovascular disease, which is, by itself, related to stress. Yet, we don't have anymore mammoth, and we are not in a war zone. Why are we going to die? And the reason is very simple: our body does not know we are in 2007. It doesn't make a difference between an absolute stressor and a relative stressor. So between you and me, what it means is that your brain does not make a difference between a mammoth in prehistoric times and Sarah at work stressing you, for example. The brain will do its job (generating a stress response) because you detect a threat. What we know now (and this is all my work on the brain and memory) is that we are very good at detecting threats, like something very, very important. If you change the mind-if you change the way people interpret the situation-you will change the stress response and you will diminish the stress response. We have a lot of data now showing exactly that. So it is just to remind us that there are no more mammoths around.

The NUTS Program

JB: Well, you know, you also brilliantly just gave us the acronym that you have come up with, N.U.T.S. (novelty, unpredicted, threatening, and sense of loss of control). That is your N.U.T.S. program, NUTS. Maybe you just want to take another summary of that because you said it so quickly, but I think it is a tremendously useful tool. In fact, I heard doctors just this last weekend, when I was in Australia, who had been at the Symposium where you had spoken about the N.U.T.S. program, who were already repeating your concept. So it is very useful for a person to gain this tool, so maybe you could reiterate it for us.

SL: I'm very happy to see that it gets there. This is a thing that I came up with. I was organizing the "DeStress for Success" program for the teenagers, and when you work with teenagers I think you have to come up with interesting stuff-that's the first thing. And there is something else I had realized in the past. I was giving a conference, for example, in the workplace, etc. and I decided to test whether people would remember the four characteristics of a stressor, which is the most important information to remember about stress. In the first conference I had given the information (the four characteristics) twenty-three times. I'm a scientist. I said, "I'm going to test this." I came back one month later and I said, "Can you remember the four characteristics?" I saw that the data showed that less than 10{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} remembered only one.

So I said the message doesn't get through, but I'm working on memory. I have to find an acronym that will stay there-stay in the brains of kids, adults, etc. I like the English acronym; I don't like the French so far. So in English it is "Stress: Don't go N.U.T.S." This is to remind you that there four characteristics of a situation that will induce a stress response, whoever you are, whatever you are, whatever your age, actually. "N" stands for "Novelty." "U" stands for "Unpredictability." "T" is for "Threat" to your ego or your personality. And "S" is for "Sense" of control, which is diminished. So, "Stress: Don't go N.U.T.S." is the acronym that is really working now these days.

JB: Thank you. That's a wonderful explanation. I'm sure it is going to stick. What I find is that the people

who listen to this often listen to this many times. It is amazing to me the work that they put into gaining competency in these concepts, so you are going to have people probably going nuts to learn N.U.T.S.

SL: And all the N.U.T.S. information is on the website, so if they forget about it they can always read it with examples and everything you need about that to understand. We call this now (the program we are putting together) is to "deconstruct your stress." It serves no purpose in life to say to someone, "You have to learn to manage your stress." Because you are going to have a patient go into their car in the parking lot and say, "How am I supposed to do this now?" Managing your stress. Everyone says this. What does it mean? It is meaningless. Now if I tell you, "Deconstruct the situation." Why is it stressful for you? Is it novel? No. Is it unpredictable? No. Is it threatening? Yes. Do you feel you have control? No." But by now you have two of the four characteristics that are out. A well-defined problem is a problem almost solved. Now, in order to "manage" your stress, it is meaningless. If I tell you, what can you do to increase your sense of control for this particular situation? What can you do decrease the feeling that it is threatening for you? And you will come up (this is reconstructing, which comes after) with your own answer, because stress is an individualized process, but it is much easier now by reconstructing it (because you deconstructed it in the first place) to understand what you have to do in order to deal with every stressor in your life. You will realize that the method you need for one particular stressor is not the same for the other stressors because they are not stressors for the same reason.

JB: So you now, I think (in the time we have remaining), led me to (I think, clinically) a very interesting question that comes up frequently. That is the question that you have already addressed, which is the correlation between a stress not regulated and (let's call it) your relative stressor that has a long time duration and its relationship to depression.

We recognize that depression is becoming almost a pandemic like essential hypertension in our society. You almost have to have it if you are a mid-life individual to be one of the norm. Depression medications are now one of the major categories of pharmaceuticals that are used, and we see its penetration of use down into younger age people.

And then we witness the correlation between depression and Alzheimer's disease and we see that the data that is now starting to emerge in the states indicate that as the baby boomers grow to be 80 and 90 the number of people with Alzheimer's disease in our country will basically bankrupt the disease-care system. So there is kind of a theme that seems to be going along. It takes stress to depression, depression to Alzheimer's disease and into the question of what the heck do we do because we really don't have effective drugs in treating Alzheimer's disease? If we were to look at this-and I guess we'd have to add to this the next confounder, which is the ever increasing use of statins to control hypercholesterolemia and the recognition now that statins have a correlation with lowering of neurosterols like allopregnenolone, which has something to do with mood and memory-people are now saying, "Well, gee whiz, is this very low cholesterol level why we see higher levels of suicide and violent death in people with very low cholesterol?" Because there is something adversely happening to their brains with too low cholesterol? There is this whole swirling story that seems to be going on right now that confuses docs about actually what to do with a patient.

Could you tell us a little bit about your thinking between the depression/stress model and the depression/Alzheimer's model and whether you see a sequence of events that we just need to start earlier in our understanding, before we get into medications?

SL: Wow. That's an interesting question. Let me just give you kind of a potpourri (as we say in French) of things that come to mind with regard to this one-million-dollar question.

First, it is always a question of diagnosis. I think that we are not that good at diagnosing depression and I'm not sure that what we are diagnosing all the time is depression. No wonder we have these increasing numbers of people being diagnosed. We have this kind of pandemic now, but is it depression? We have the same problem with Alzheimer's, by the way, and then we figure it out that they were different subtypes of Alzheimer's disease. That's the first thing.

The second thing is that we see treatment as something that we have to change (a dysregulation in the body), and then we give medication, and then (exactly as you said) it leads to a domino effect. The body is there to help you. It is your best friend. But there is one law of the body: don't change one thing without thinking about the rest. Because all the rest will follow and then you will end up with problems.

A journalist once asked me, "Does this mean, you know, that if you could find a pill to decrease stress hormones you could cure a lot of things?" I said, "Yes, I think you can cure a lot of things with a pill or with good social policies." Because we have shown that what increases the stress response in older people, for example, is social support. We are in an individualized society, and humans are interactive people; they love to be together. What we know from our work in stress is that the best buffer against stress is social support. We are starting to look at other variables that were not there at the time. So for sure it is going to become quite difficult.

A Theory of Stress and Evolutionary Biology: Randolph Nesse

The second thing I want bring up (and I have no answer, but I just want to share it with you): there is a scientist (he is a psychiatrist) named Randolph Nesse. When you talk about stress-anything related to stress-you have to think in terms of evolutionary biology. You will never understand stress or any stress-related disorder without thinking about that. Why would it be useful to still be here if stress is going to kill us? Survival of the fittest. We should all be dead in about 10 years from now. Why is it useful? Why is it that depression or depressed people survived across time? They should have been surely eliminated in terms of evolutionary biology. They have not been. So somehow this implies that depression has some importance in terms of evolution.

What some people are starting to say is that depression may not be a disorder like, for example, cancer, but it may be just a manifestation of a need to others. Because when you are depressed you don't feel good, you isolate yourself, which brings other people to come toward yourself, etc. That would send a signal to others (because animals can do this as well) to take care of you, etc. With this I just want to open up a mind and say what if this is something? Again, it is always like allostatic load: this is a system trying to adapt. By adapting, us humans, we call this a dysregulation. We try to fix it. But if we don't understand it first we will never be able to fix it.

That's my answer to your question. What is the purpose of depression, etc. and what can we do in order to understand this? And then we will understand why things work or things don't work. So I take a much more global approach to this. And, by the way, the evolutionary approach notion about depression would explain why you see it with so many "disorders"-with Alzheimer's, and with many other things as well. It could be one of the first manifestations, meaning it may not be a disorder.

JB: That is a beautiful thought, actually. That really sends so much of a different message rather than a defect or a disease -- to talk about a social condition, in which the person is trying to find a way to be healed and looking (through their affect) for support. I think that is a much more empowering concept than a defect.

SL: And I would strongly suggest if you are interested in that or the people listening to this show, to read some of the papers by Dr. Nesse. It is really worth thinking about. We'll never have the right answer, but opening your mind to mental health disorders this way is a very interesting process.

JB: Well this has been a most interesting discussion and I can't tell you how much we appreciate your time. What you are doing is just right at the forefront of really finding solutions to these complex chronic disease processes that we ultimately treat the endpoint of but we know the origins started much earlier with the things that you've been describing that are part of this allostatic load and the body trying to accommodate this chronic relative stressor environment that we live in. Dr. Lupien, I can't thank you enough. It has really been a great privilege and we'll be checking your website frequently.

SL: That's good and it was my pleasure.

I'm sure that you enjoyed Dr. Lupien's presentation as much as I did. What a tremendous resource of information and the density of information and how rapidly it comes across to us. I hope you are going to slow your recorder down and listen again because between the two of us, probably you're going to need to slow it down to pick up all the density of that information. That is really news to use.

Heart Rate Variability Measurement

One of the other things that I wanted to offer, as it relates to the wonderful comments that Dr. Lupien was providing to us in terms of stress management, has to do with another clinical tool for evaluating stress, and that is the heart rate variability measurement (HRV). I am becoming more and more convinced that heart rate variability is a very important early predictor of later-stage vascular and neuroendocrineimmune dysfunction associated with stress and other metabolic dysfunctions that we associate with chronic disease.

If you have been following the literature in this area you are probably aware of the fact that there is an emerging body of very good clinical and research literature that talks about the association between various stresses (including job stress) on heart rate variability and its interrelationship with the alteration of these physiological parameters that Dr. Lupien was talking about that track against things like cardiovascular disease risk and metabolic syndrome.

A paper that appeared in the *Yonsei Medical Journal* in 2004 was titled "Association between Job Stress on Heart Rate Variability and Metabolic Syndrome in Male Workers."[15] The finding of this study was that there is a very strong correlation between what we call loss of heart rate variability and increasing concerns of distress associated with metabolic syndrome. When I say distress I mean physiological distress, or changes in the web of the physiological interconnectedness between insulin, lipids, and inflammatory mediators. So this heart rate variability is an interesting question because as you probably recognize, when people get under stress physiologically, the line structure in their EKG or their electrocardiac rhythm starts to flatten out. As it flattens out, it loses its line structure-in fact, the simplest

EKG of all is, as you know, a flat EKG in a dead person. So somewhere between the extraordinarily complex EKG patterns found in a highly fit trained athlete and a flat-line EKG is the range of functional status of the neuroendocrineimmune system as reflected through heart rate variability.

We know that heart rate variability, and also alterations in heart rate variability, are associated with multiple contributors to metabolic syndrome. There are a number of interesting papers showing that heart rate variability becomes much less complex (meaning simpler) in people with metabolic syndrome, such as a study published in a recent issue of *Diabetes Care*.[16]

We know that even individuals who undergo a weight loss who have elevated body mass index and have increased ambulatory blood pressures and enhanced cardiac autonomic tone are seen to have improved heart rate variability as they control their weight and also control their metabolic syndrome. This was published recently in a very nice study that was showing the correlation between body mass index and ultimately metabolic syndrome and how the weight loss with the appropriate type of nutrition and lifestyle program, improved heart rate variability. This was in the *Journal of Hypertension*.[17]

And even toxic exposure to things like lead or cadmium or mercury has been associated with increasing incidence of lowered heart rate variability and metabolic syndrome. This was actually recently published in a Veteran's Administration study that I think is quite interesting in *Environmental Health Propectives* in 2006 titled "Low-level Lead Exposure, Metabolic Syndrome, and Heart Rate Variability: The VA Normative Aging Study."[18] The findings of this study showed that heart rate variability was decreased in individuals who had been lead exposed (low background lead; this is chronic lead exposure) as was measured by looking at lead concentration in the bone and that metabolic syndrome was enhanced in these individuals.

So you'll notice there is an interconnection of a number of factors. Psychosocial stress and chemical stress associate themselves with alteration in the metabolic web and are seen as lowered heart rate variability. So, another tool that you might consider of clinical importance.

Thanks for being with us in August and we look forward to continuing this theme as we move into September.

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