June 2013 Issue | Bruce McEwen, PhD Rockefeller University

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Welcome to *Functional Medicine Update*, June 2013. You know this old statement you've heard many times from the movies, "Houston, we have a problem."? Well, so it is in health care. As you know, we see this rising tide of chronic illness, and this model that we've been using, which is to treat each condition with a single drug to get a single outcome, doesn't seem to be beating back the rising tide of chronic illness; it continues to grow in prevalence and severity. It's been suggested that maybe we need a new model, and that's where the functional medicine model can play a role.

This month we're going to be talking through the lens of this mind-body connection: the psychoneuroimmunology, the psychoneuroendocinology connection, through arguably one of the world's great contributors to our understanding of this field, Dr. Bruce McEwen. Many of you know his extraordinary work as it relates to allostasis and his remarkable book, *The End of Stress As We Know It*.[1]

Multiple Conditions in Single Patients: A Trend Identified in Medicare Patients

Before we get to Dr. McEwen and the discussion with him, I'd like to just set the context as to why this area is so important for us to understand and to start implementing within clinical practice. As you recognize, we are seeing a very rapid increase in multiple chronic conditions people have, particularly older age individuals in our society. Medicare review of degree of concerns now indicates that most Medicare recipients have two or more different diseases that are being treated. Often these diseases are considered to be independent and isolated, so they end up with two sets of doctors with two sets of drugs, for two different sets of conditions, even though they may all be related to disturbances that are associated with altered gene-environment interactions, from a functional perspective. So rather than treating the cause we often end up treating the effect.

There's a wonderful paper that appeared recently in the journal *Health and Quality of Life Outcomes* that discusses this whole area of the increasing prevalence of multiple conditions in single patients in the Medicare population, tracking patients from 2006 on and looking at the increasing number of multiple conditions.[2] We recognize that this co-occurrence of diseases is really very strongly lifestyle-related. A data was assembled from 2002 to 2009 and was published in another very interesting paper that appeared in *Prevention of Chronic Diseases* in 2013 in the April issue.[3]

In another paper where we looked at multiple institution quality improvement initiatives to transform chronic illness care, this is a pretty discouraging review of what's really going on. According to this article that appeared in 2011 in the *General Internal Medicine Journal*, we still have very significant

challenges as it relates to institutional delivery of programs that will transform chronic illness care, and we really need to start looking at other ways of evaluating or implementing strategies.[4] In fact, it's interesting to note that this paper that appeared in 2011 was a consortium of different institutional groups, including the Oregon Health Sciences University, faculty of medicine of the University of New South Wales in Australia, the Feinberg School of Medicine at Northwestern University in Chicago, Stanford University School of Medicine, University of Texas, the Southwestern School of Medicine, and the MacColl Institute for Healthcare Innovation at Group Health in Seattle, Washington. All of these collaborated together to come to this data set that says there's a long way to go in managing chronic illness and the model that we're using doesn't seem to be delivering the goods.

What can we then take away from all of this that will lead into hopefully improved healthcare effectiveness, improved outcome, and reduced expenditures? That really has led us into the development of a new institute, the Personalized Lifestyle Medicine Institute, that really is a hopeful partner with the Institute for Functional Medicine in developing health conscious consumer education as it relates to alternatives and where we are going that will couple together with the healthcare provider education that is necessary to provide quality intervention and quality care. And there are some precepts of the Personalized Lifestyle Medicine Institute that I think are important as we move into the discussion with Dr. McEwen, for us to understand. Let me just talk a little bit about the precepts.

The Personalized Lifestyle Medicine Institute: Coupling Together Consumer Information with Healthcare Provider Training

First of all, it is believed that health care is in turmoil; I don't think there is much debate about that. With all the money spent on disease care, we're still globally witnessing an increase in lifestyle-related diseases. Number two, that new models for improving healthcare efficacy will arise out of new institutions that don't have the vested interest in the old models, and so we kind of have to look for where innovation might arise, which may be in different places than where the status quo is now being practiced. Number three, the successful new models for healthcare delivery will be disruptive and incorporate characteristics of a disruptive, distributive healthcare system, where it is not top-down with a few people controlling the whole system; it will rather be cooperativism across many different areas of distributive function, with different skills working together collaboratively to improve, hopefully, integrated systems, biology-based health care. Number four, decision-making for the incorporation of new models for health care will not rely solely on the double-blind, placebo-controlled trial, but will incorporate clinical case histories and other evidence in decision-making, and this has to happen if we are dealing with a personalized medicine model because each person is their own control and you can't do a study with randomized controls when each person is little bit different than everybody else, so you need new models for evaluating how to assess outcome in that kind of a personalized regime. Number five, the evaluation of new therapeutics will be contextualized through a personalized medical perspective, and the concept of disease emerging from the interaction of genes with environment will be a dominant paradigm in the new medical era. That is, obviously, an emerging thought which we are getting more and more reinforcement from with the literature that is being published as we speak.

Prevention will be a public health issue and prospective medicine will become the new medical strategy, and reimbursement for medical services will become more outcome- rather than procedure-focused, and I think that's a really interesting trend that we're seeing right now. The internet, smart technologies, and social media will frame much of how the new medicine will be executed, so the person will be measuring

their own body function using smart technologies and interfacing with healthcare providers in ways that were never imagined even five years ago. We'll be witnessing a bifurcation in medicine, with training and credentialing in crisis care that will continue, but also a training and credentialing in chronic care, using this distributive healthcare system. Enlightened healthcare consumers will demand and support a two-tiered system of medicine that will deliver high-quality crisis care, hospital-based medicine, and chronic-illness-focused community clinic-based health care, so there will be excellence at both levels, but you can't be a master of all disciplines; you'll have to find out where you want your specialty to be, be it either the chronic care management at the community-based level, or more of a crisis-focused, hospital-based medicine in institutional settings.

Medicine will become more participatory and require higher health consumer advocacy and knowledge—much more is being pushed back to the consumer and they'll have to be responsible for a lot more of their health, and therefore advocacy around health knowledge will become very important. Fortunately we have the internet to deliver information but we have to separate the wheat from the chaff in terms of internet; we can't be delivering information that is not well-grounded and reproducible, evidence-based application. And then lastly, the largest financial growth engine in health care, I think, in the future will come from the wellness healthcare innovations and not from the traditional economic drivers of drugs and surgery. So that's a new business model that will really fuel a lot of this innovation.

So those are pretty important standards of change. Those are write-them-on-the-wall-and come-back-and-review-a-few-years-in-the-future and see if we really were pretty good predictors of what the future may look like. But they circumscribe a very dramatic change in the way people think about health, the way professionals are trained, how reimbursement is delivered, and how a person will ultimately be managed as part of their own healthcare continuum.

BRCA1 and BRCA2: Questions about Genes and Environment Through the Lens of Breast Cancer

Now, you might say, "But, Jeff, our genes are not going to change. Maybe the way we see this whole thing will change, but if we've got these genes that encode for disease, how is this going to really make any difference?" Let me look at that genes and disease question for a second. And I look at it through the lens of a very remarkable investigator, a woman who I have a tremendous amount of respect for, Dr. Mary Claire King. Some of you know her as the discoverer of the BRCA1 and BRCA2 genes that code for significant increased incidence of breast cancer in women that carry the homozygous recessive double allele for these characteristics.

This has been such a remarkable discovery that now, as you probably know, there's a whole medical ethical procedure that a woman would through to evaluate whether she'd be a candidate for prophylactic double mastectomy as preventive medicine. This is probably the most aggressive form of preventive medicine that you can imagine, taking off breasts. And there are people making this decision, like the celebrity, Angelina Jolie, who recently had this procedure done and sent a message to many women across the world, probably. So when Angelina Jolie does this and we found out later her aunt has just recently died of breast cancer, which probably was part of her decision-making, it brings this concept of genes up very strongly (genes and disease).

But I want to go back and review Mary Claire King's work with you for a second, because I think it's very insightful relative this question that we're talking about in terms of decision-making, consumer

participation in health care, and taking charge of one's health. I'm going to go back with you to 2003 in *Science* magazine in a paper that was authored by Dr. King and her colleagues, the New York Breast Cancer Study Group, that was entitled, "Breast and Ovarian Cancer Risk Due to Inherited Mutations in the BRCA1 and BRCA2."[5] These are the genes that we are talking about that give rise, when they are mutated, into this very high incidence of breast cancer. I think you'll find this interesting if you haven't been familiar with this work in the past because she goes on to say the following. I think this says it all so I'm going to quote directly: "Risks of breast and ovarian cancer were determined for Ashkenazi Jewish women with inherited mutations in the tumor suppressor genes BRCA1 and BRCA2. We selected 1008 index cases, regardless of family history of cancer and carried out molecular analysis across entire families. The lifetime risk of breast cancer among female mutation carriers was 82{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}, similar to risk in families with many cases." Now here's where it gets interesting: Risk appeared to be increasing with time. Breast cancer risk, with women who had this BRCA1/BRCA2 mutational characteristic at age 50, among these carriers born before 1940, was 24{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}. But among those born after 1940, these same genetic characteristics, it was 67{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}. And women born after 1960, it's 82{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}.

You get where I'm going with this, I'm sure. The genes have not changed. These are the same cancer genes. But we have seen the cancer penetrance in the phenotype go from 24{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of women born before 1940 to 82{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} in women born after 1960. So, what's going on here? What it says—I think—is it's more than genes. There's another variable called environment. That even in these very severe cases where women would say, "This is so concerning to me that I will have my breasts removed for prevention," that in these very severe linkages between a genetic determinant and a disease, in this case breast cancer, there is wobble related to modifiers of the environment. And we don't know exactly what those modifying factors are in the environment. I wish I could tell you exactly what a woman would have to do, but in this article they go to say, "Physical exercise and obesity seem to be related to delayed breast cancer onset." So, there are variables that are modifiable if you ask the right questions or you have broader perspective on how the genes influence the outcome called breast cancer.

I don't want to leave you with the impression that what I'm saying is no woman should ever have a radical preventive double mastectomy, because this is a very personal question and it depends on all sorts of variables and relative penetrance, and if your mother and your sister and your aunt had breast cancer then probably you're going to be very concerned as well, so I don't want to say this is never a good decision. But what I want to say is that there are modifying factors in these outcome that we call disease from genes that we might say, "Oh, I inherited a gene for cancer, or for heart disease, or for diabetes." Most of these are not single gene conditions; there are modifiers of multiple genes that modify the penetrance into the phenotype and those factors are influenced by environment.

That leads, then, to what do we really mean by modifying the penetrance into the phenotype? Well, that in part relates to something above the genome, right? Above the genome, which is epigenetics: things that occur that regulate how the genes are expressed. If you think of the genes as the hardware of your system, then what's the software that runs it and tells how it's going to produce the printout or the calculations of

your body? And the software is your epigenetics, which are these marks that are put on your genes that either say “Read this gene” or “Don’t read this gene” or “Read this family of genes,” altering promoter region stories, the so-called methylation of the promoter regions of genes, then, can cause the stop reading of a certain, like stop reading an oncogene for instance; that might be a desirable thing.

Breakthrough: Epigenetics is Relevant Far Beyond Fetal Development

These effects that we call epigenetic, we used think were only important in the early stage of development, like embryogenesis, after the sperm and the egg met as the cells would divide. Clearly, from the single cell you’re going to have to have it differentiate into the skin, and the brain, and the heart, and the bones, and so that same cell type is going to have to differentiate its message or you would end up with just one cell type. We know that epigenetics occurs embryologically to shut down certain messages, so because all cells have the message to make any other cell, but you don’t want your liver cell making a brain cell, so how do you stop that message? You do so by translating only certain messages in your book of life: the liver messages in the liver cell, and only the brain messages in the brain cell, hopefully. So that’s epigenetics. But what is more recently, I think, a breakthrough, is the recognition that this epigenetics is not just solely seen in the differentiation process of embryogenesis (fetal development). That it goes on, certainly much more slowly, as you are born than it did when you were the first few cell divisions are forming a new embryo, but it is still there, present, to reconstruct yourself based on your environment throughout the course of your whole life.

You might say, “Well, how about stem cells, because aren’t stem cells constantly getting epigenetic messages to create different types of cell types to rejuvenate your body?” Yes, they certainly are, and so some cells are much more influenced by the environment than others, and some genes within those cells are more influenced by the environment, that then can be epigenetically marked to translate one message versus another message into your phenotype, like the BRCA1 BRCA2 genes that get expressed into breast cancer. So it’s not just the gene in and of itself that causes breast cancer; it’s the expression pattern in the presence of other genes that are functioning simultaneously, which are influenced in their expression by the environment of the host, right? What they are doing in their life, what they are eating, thinking, living, exposed to—all of things play roles in modulating the orchestration of those genes.

So epigenetics is a new, I guess you would call it, back-to-the-future concept. It’s been around for a lot of years in explaining developmental biology, but only more recently has it been talked about more in the adult or the post-embryo state as influencing things that might relate to increasing risk. Think of the increasing prevalence of autistic spectrum disorder or autism. Now many people are thinking there’s an epigenetic link there that’s being discussed that might be related to methylation patterns or phosphorylation patterns of the genes from some kind of environmental factors that women and their embryos have been exposed to that would then translate into these neurological/neurodevelopmental alterations.

The question is, are there implications for personalized health and personalized nutrition based on this epigenetic new discovery? The answer appears to be yes. There are a number of really nice review papers on this, advances indicating that epigenetic variation is an important influence in the interaction between nutrients in the genome, which can modify disease risk, and that there are certain genes that are called metastable epialleles. Now there’s a new term that you can throw into your lexicon: metastable epialleles.[6]

Metastable Epialleles: Genes that Can Modify Disease Risk

Now, what does that mean? It means that in people that are not embryos or infants, that there are still genetic characteristics, so let's call it genes or regulators of genes, that are sensitive to epigenetic modulation by environmental factors, and therefor they are metastable, meaning they don't just stay fixed throughout your whole life; they can be modified by what your environment might be. So a certain message can be wiped off, and another message can be added over the course of living so that you can get a different expression of their function. So that metastable epiallele concept is a fairly interesting concept because it doesn't say all twenty five thousand genes are going to be constantly exposed to epigenetic change or we'd probably be a mess with all the changing stuff in our environment, but certain genes may be very susceptible or sensitive to this regulatory effect of epigenetics, and those are the ones that then ultimately give rise to different disease patterns in a population based upon a changing environment.

So, that's one big interesting new concept. Another big interesting concept is how these epigenetic effects influence metabolism. We think of the chronic, age-related diseases as being disorders that are associated with disturbed metabolism. They're not single allele diseases. Like you can't say that type 2 diabetes came from a single, or you can't say heart disease came from a single gene, or arthritis came from a single gene, or really we could go down virtually the list of the whole family of chronic illnesses and not a single of them are monoallelic or monogenetic. They are poly genetic. They have multiple families of genes that work together to give rise the expression of these factors. So you might say the name of that disease could be the same from Mary Smith and Paul Jones, but the genetic modulation that gives rise to that disease could be very different between the two of them, because multiple genes are involved.

The question is, does epigenetic alteration then influence the expression of genes to disturb the metabolic outcome that can be expressed in these diseases of chronic illness, and the answer is yes. There is ever-increasing support for this model that we might call a disease a single thing, but it actually comes from multiple different potential sources through complex interaction of genes with the environment to alter genetic expression through these epigenetic factors that ultimately gives rise to what call that disease. Although we might give it one disease code for reimbursement, it probably had multiple sources upon which it was experienced at the physiological level. We call this disturbed metabolism that occurs from modulation of this gene-environment interaction.

There's a very beautiful review paper that discusses this in *Cellular Molecular Life Sciences*that appeared in March of 2013 that really goes through the detail of how these transcriptional factors that modulate gene expression can be regulated and modified in their activity on the basis of epigenetic environmental changes.[7] So it could be toxins, it could be stress, it could be poor quality diet, it could be chronic infection. All of these factors play roles, then, in modulating how a genetic predisposition, or a genetic uniqueness, would be expressed into the phenotype that's called the health and disease pattern of the individual. What this says to me is that there is really no disease of the chronic disease family that comes from a single gene that is caused by, "Oh my word, the bad luck of the draw. I just got that gene." What you get are genes that are uniquely responsive to your environment, which can undergo metastable alterations through epigenetics to express their function in a different way that ultimately becomes what we call a disease. I hope you understand the difference between those two models because I think it's very important in that this model is much more susceptible, or let's call it sensitive, to plasticity, rather than the determinism that these chronic diseases come from genes alone.

So this really leads us into this concept of systems biology and aging in linking, then, systems network effects that tie to diseases of aging. There's a wonderful paper in *Current Genomics*in 2012 that really describes how these factors regulate the system of function, not just a single step in this network of biology.[8] That they disturb metabolism so you get a network effect, and that's why you see multiple biomarkers often changing. It's not just like one variable like cholesterol changes all by itself. You get a disturbance that might show changes in inflammatory mediators. It might show changes in cell regulator neurotransmitters. It might show changes in sex steroid hormones. There is this web of changing architecture from the disturbance of multiple genes that give rise to that disease.

How Can Intervention be Measured in Systems Biology? Pattern Recognition: The Patient Becomes Their Own Control

Now what does that mean about, then, testing intervention? If we're looking at a traditional model of a double-blind, placebo-controlled trial, which is you have one agent against one outcome, that's great for a drug, in which you're looking at the effect of, say, a molecule on blood pressure. You take the drug against a placebo. Maybe you look at it against one end point, which is blood pressure. And you see, does it work or doesn't it work? Well, that's great if you want to validate a drug on the model of one agent against one outcome, but I've just told you there are many agents against complex genes that gives multiple effects on expression, so it could be multiple outcome determinants. How do you do that in an individualized population? How do you study it?

Well, these particular models require an alternative strategy and there are a number of methodologists who have really been working on that, and it would be a little bit presumptuous of me, in five words of less, that I could say that there is one path to understanding, but they basically come down to a different methodology that is related to pattern recognition, and to nearest neighbor analysis, and what's called dendritic analysis clustering, and starting to look at how certain genetic characteristics cluster with certain outcomes, and how these relate to certain environmental perturbance. There's a wonderful paper on methodological developments that appeared years ago that looks at this alternative strategy for clinical trials that's based upon randomization of intervention, but looking at the pattern recognition within patient indicators.[9] So the patient becomes their own control. Rather than everything being Gaussian and statistically analyzed around some kind of a parametric analysis with standard deviations from the mean, you're looking at individual variations of patient against him- or herself, and then you're grouping them as it relates to different status evaluations of their lifestyle and their genes against their outcome. So, patient individualized intervention, standardizing the patient against themselves as a control. It's a different way of doing these types of studies.

The Unique Issue of Evaluating Stress Response

Now, how then do you evaluate, going back to Hans Selye's stress model of disease, the complexity of something you can't smell, taste, or touch, like stress, and its effect on chronic illness, based on this model. Here's where we start to get in the correlation of stress signals in the environment producing altered cellular genetic response that then changes the phenotype and changes the pattern by metabolic disturbance that measure, then, of the patient against him- or herself. It's a way of utilizing this particular model versus the double-blind placebo-controlled trial of an agent against the endpoint, which is the drug model. And there are a variety of wonderful papers that have been discussing this, like stress response and how it relates to alteration in metabolic patterns, particularly related to changing in energy patterns or cell

regulatory patterns, things like the mitochondria, the energy powerhouse of the cells, how it can alter mitochondrial bioenergetics and change intracellular function.

So we now recognize that this concept of moving towards a personalized medicine requires different methodologies, and the stress response and how it signals into the genome through these epigenetic effects can cause disturbed metabolism that then shows patterns of change: different regulatory mediators, different inflammatory cytokines, different growth hormone-related substances, different cytotoxic agents, alterations in detoxification mechanisms, changing in neurochemicals/neurotransmitters. This pattern becomes a very, very important way of evaluating the influence in that individual of how their lifestyle and lifestyle behaviors influence their genomic signaling and ultimately give rise to their phenotype. It's that model that we're going to be discussing with our extraordinary clinician of the month, Dr. Bruce McEwen, and I think you'll see how this weaves itself into a very, very important model for the future of what I would call functional medicine and managing through both experimentation and research these very hard to quantify connections of environment and lifestyle to outcome called health.

INTERVIEW TRANSCRIPT

Researcher of the Month

Bruce McEwen, PhD

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So here we are again at that point in Functional Medicine Update that I know you, as I, always look forward to with great anticipation. I'd have to say that for me personally, and I think as you will find out for yourself as well, this will turn out—the next half an hour or so—to be one of the most important, clinically relevant discussions that we've had the privilege of having on Functional Medicine Update over the last 30 years.

The person you're going to be hearing from who is an expert in the field is Dr. Bruce McEwen. The name, alone, probably you already know where we're going with the concept of allostasis. You know, we've been very privileged over the years. I had the chance to meet Hans Selye prior to his death, up at McGill. We interviewed Robert Sapolsky at Stanford a number of years ago. But Dr. McEwen, who is the Alfred E. Mirsky Professor of the Harold and Margaret Millken Hatch Laboratory of Neuroendocrinology at Rockefeller University, I think, is at the peak of this understanding, and discovery, and innovation in the area of neuroendocrinology, and really what I might even call neuroimmunoendocrinology, because there is a portion of the immune system obviously involved here as well.

Dr. McEwen was the past president of the Society for Neuroscience, a member of the National Academy of Sciences and the Institute of Medicine, and has received numerous awards. Just a few to kind of highlight his accomplishments: In 2011, he was the recipient of the Edward M. Scolnick Prize in

Neuroscience; in 2009, the Gold Medal Award from the Society of Biological Psychiatry; and in 2005, the Pasarow Award in Neuropsychiatry.

I first really got clued in to Dr. McEwen's work when I had the chance to read his book The End of Stress As We Know It, which was in 2002, I recall. From that moment on, I kind of stepped over into the McEwen camp and have followed his work very carefully since. He has collaborated with a number of very well-renowned investigators, one of whom I had the privilege of meeting at a recent meeting that Dr. McEwen and I both attended, Dr. Teresa Seeman, who is at the David Geffen School of Medicine at UCLA, at a conference that we were involved in related to the concept of resilience in returning service veterans from war (men and women). Dr. McEwen and Dr. Seeman had considerable to contribute to that group that hopefully will weave its way into new programs that the military will be introducing (the Veteran's Administration) for returning service people.

Those of you not familiar with The End of Stress As We Know It (the book), when you read the editorials that follow the book, one of the things that will be said is, "There's a whole new way to think about stress that comes from this book. Sure, some stress is inevitable, but some stressed out and being stressed out isn't. In fact, we can learn to re-channel the powerful stress activators in our lives to make us even more effective. The good news is that there are definite things that can be done to prevent the process of being stressed out from ultimately taking the wrong turn. New research in brain functioning from the Dr. McEwen laboratory allows us to understand and harness the energy stored within us and to channel it in positive ways. The End of Stress As We Know It leads us to a new appreciation of the mind-body connection so that we can learn how to reduce stress and increase our overall sense of health and well-being, and even turn aside the slings and arrows of life." That's a pretty strong endorsement for the book, and I have say that's how I felt in having read it myself. I think it was a very powerful manifesto of taking stress as kind of a negative connotation in physiology (in common parlance), and turning it into an operative term that allows something to be done to harness it.

Dr. McEwen, it's a great privilege to have you as a clinician/researcher of the month for Functional Medicine Update and thank you for spending the time with us.

BE: Thank you very much. It's great to be here, and I might mention, by the way, that The End of Stress As We Know It was out of print as a print book but is now available as an e-book, costing very little money. It is accessible on Kindle, and Barnes and Noble, and so on.

JB: Well, I recommend it as kind of mandatory reading for all of our long-standing Functional Medicine Update subscribers. It's really a seminal work. Let's start down the road, here. We could obviously go back and start from square one with your chemistry undergraduate degree and work up, but let's start a little bit more contemporary and talk about how you came on to the concept of allostasis and allostatic load. What is it, and how does it play a role in our better understanding of the stress that we're experiencing today in our society?

Early Research on the Concept of Allostatic Load

BE: Okay. Well, go back to when I, as a young faculty member, came back to Rockefeller University, where I got my PhD, to join the laboratory of the late Neal Miller, who was a very famous psychologist, the father of behavioral medicine. I also, at the same time, was influenced by my mentor, Alfred Mirsky,

to think about how genes are regulated in the brain and the body, and hormones (steroid hormones) were the new candidates, and still are important regulators of gene expression. So I began to study how hormones (sex hormones and stress hormones)—how and where they affected brain function, and made the discovery that an area of the brain called the hippocampus, which is very important in memory and also, now we know, mood regulation, is a major target for these stress hormones (for cortisol and the like). This sort of clued me in to the importance of not just the hypothalamus but higher cognitive centers, so for a number a years we worked on (and continue to work on) these very specific questions of how stress hormones and also sex hormones affect brain function, especially higher cognitive functions, mood regulation, and so on.

But in the late 1980s I was asked to join the MacArthur Network on Health and Behavior headed by a woman named Judy Rodin and another man I consider my other mentor besides Neal Miller and Alfred Mirsky, the late Eliot Stellar from the University of Pennsylvania, a famous physiological psychologist. And it was there I was introduced to two people, Peter Sterling and Joe Eyer, who had introduced a concept they called allostasis, which literally means achieving stability or homeostasis by an active process of responding to a challenge. This fit perfectly because the term homeostasis really implies stability. People have used reactive homeostasis and other things, but allostasis, like producing adrenaline, raising your blood pressure, producing cortisol, which is important for adapting to stressful experiences—that process of allostasis leads to adaptation, but then we thought a little bit, and as I became more and more familiar with issues pertaining to human beings in relation to stress and health, and I certainly had help ultimately from people like Teresa Seeman and Eliot Stellar, we thought that there was a price that the body and brain pays for being under a lot of stress or not being able to handle it very well, and so we coined the term allostatic load to refer to this wear and tear. Over time, that term has begun to take hold, and I think more and more people appreciate what it is telling us.

JB: You know, we had the privilege a number of years ago, at the Institute for Functional Medicine, in having one of your ex-post-doctoral students, Dr. Sonia Lupien, from Canada.

BM: Oh, yes.

JB: She is such a great advocate and ambassador for your work because she has done some really great in-the-trenches evaluation in clinic of applying your principles. Her results look absolutely superb, and I know you've done not only the exquisite laboratory work (animal models and others), but you've also translated this over into clinical application. Has this been well received by your colleagues, or how do they see a translational individual in this field, bringing these concepts into practice?

Allostatic Load Concept Helps to Simplify How the Body Reacts and Adapts

BM: Well, I think that initially the people who really caught on to allostasis and allostatic load were people in epidemiology and public health, people in psychology (some in health psychology, some in sociology), because I think the concepts of allostasis an allostatic load help to simplify or organize the great complexity that is how the body responds in many ways and adapts; I mean, through the immune system, the cardiovascular system, the metabolic system. It helps people understand it. I think just the notion of the metabolic syndrome is itself a recognition that it is more than just a single system of the body or a hormonal system that's responding, but a series of interacting mediators that operate in a nonlinear manner. And so I think as we appreciate the complexity of the body's adaptive responses and

also of what leads to and exacerbates and causes disease. I think these concepts that are intrinsic to the terms allostasis and allostatic load, of nonlinearity, are beginning to be appreciated more and more, and whether you call it allostatic load or not, the fact that when something happens you've got your autonomic nervous system, your HPA axis, your metabolic hormones, your inflammatory pro- and anti-inflammatory cytokines, and on and on, all changing and changing each other. And so what it comes down to is, of course, the question of: Given this complexity, what should we do about it? And this brings up, of course, the more what I call top-down interventions like physical activity, things that we do that actually help the body help itself to do the right thing.

JB: I'd like to come back in just a moment to this metabolic syndrome question because I think that's a very interesting part of the spectrum of the clinical manifestations of the disorder, or of the influence of allostatic load. And I'd like to stop for a second in a weigh station and talk a little bit, if you would, about the difference between where Hand Selye took us, recruiting the term "stress" out of physics into physiology, which has now, I think, become the number one English word in medicine that is used. Interestingly I did a search on that and found that it trumps every other word in physiology and medicine right now. You and your colleagues have advanced this concept. Where did the Selye model leave off and where did your work take on?

Explaining Exhaustion: The Hormonal Response and How the Body Adapts

BM: Good question. I think it's amazing that Selye had such insightful ideas when there was so little specific information about—and ability to measure—these different adaptive systems in the body. One of his concepts was the concept of exhaustion when the body has undergone a lot of stress. Exhaustion sort of implies the failure of hormonal and other systems to respond, and while that may be the case in maybe something like burnout, when there is, for example, low level of cortisol and a lack of responsiveness, the general idea of the imbalance of these adaptive systems that are counterbalancing each other, what Selye referred to as exhaustion I think is really what we would call the development of allostatic load, and the manifestation in different ways. If you have too much cortisol and become glucocorticoid resistant and have inflammatory processes and metabolic syndrome and so on, that's one thing. If you don't have enough cortisol and you have more, say, autoimmunity and various things of that sort, that's another. And these things manifest themselves in different ways in different disorders. That's sort of what I think he meant, but as I said, he did not have the knowledge that we have.

JB: Yes, I think that it's really, to me, so fascinating to read your work, and that's again another of my ah-has in reading The End of Stress As We Know It, is that when you start using this network biology or systems biology approach, that you're advocating to look at the interface between immune-related mediators, endocrine-related mediators, and nervous-system-related mediators. So you start, as you said, with neurotransmitters, neuroexcitatories like glutamate NMDA, and neurotrophic factors like BANF and you put it into a systems biology way of thinking, it really helps you to understand why so many symptoms can be manifest. It's not like a pneumococcus bacteria produces one disease called pneumonia. You get all these vastly diverse symptoms that derive out of the tissue-specific activities of this web. It's a very powerful concept for a different model of disease, really.

BM: Yes, we talk about comorbidities and realize that often with, say, depression there are comorbidities in terms of cardiovascular disease, metabolic syndrome, and so forth. And it's rare in the modern world to have one disorder without some others to some degree lurking as well.

Allostatic Load and Research on Metabolic Syndrome and Cardiovascular Disease

JB: Let's, if we can, move that over into the topic that you introduced briefly here a minute ago, which was metabolic syndrome. Fortunately we've had Gerald Reaven as one of our clinician/researchers of the month on a previous issue of Functional Medicine Update as well, talking about his Syndrome X and insulin resistance phenomenon. The confluence, or let's call it the connection, between what you've been doing with allostatic load and what he's been doing coming from the endocrinology side with diabetes seems quite amazing when you start looking at these putative biomarkers. Could you tell us a little bit about that, because it's fascinating?

BM: Yes. Actually, maybe you can remind me of some of the biomarkers for metabolic syndrome, but basically I can start out by saying that what the allostatic load battery that Teresa Seeman now uses as an adjunct to the cardio study, is a battery that taps into autonomic (both sympathetic and parasympathetic); it taps into metabolic, looking, for example, at glycosylated hemoglobin; it taps into immune/inflammatory, looking at CRP and I think, possibly, IL-6. Now it's possible to look at a whole panel of pro- and anti-inflammatory cytokines, and so it's really tapping into the major systems that are struggling with each other, shall we say, and I think that's the idea behind the metabolic syndrome measure, and the more and more people that are looking at metabolic syndrome and then at all of the diseases of modern life, the more we realize that a common denominator is a pro-inflammatory tone. That, of course, doesn't exclude all of these other mediators, because when you have inflammation the body is also to trying to produce cortisol to calm it down, and this also then interacts with the metabolic system, in which the regulators that have to do with insulin resistance and control of appetite, like leptin, are distantly related to the cytokine family.

JB: Yes, I think that you have hit exactly, from a different perspective, what Dr. Reaven was talking about. He started with things like elevated triglycerides, low HDL, decreased apoA1, increased apoB, increased hs-CRP, increased blood pressure, with an increased PIE1 plasminogen activator inhibitor one level, and increased waist-to-hip ratio with central adiposity. These track right across, it seems, with what you and Dr. Seeman have been looking at in allostatic load.

BM: Yes, it's very close to what I have just now in front of me, her list of markers for the allostatic load battery that she's using in this cardio study. So we're really talking about the same kind of thing: this multi-systems, nonlinear type of thing. Of course, then you think what the interventions are, and we have to also think about the role of the brain in all of this, but with what the interventions are, any kind of drug is going to perhaps help calm down or elevate one system, but it's going to cause compensatory reactions in others, and that's not necessarily going to help the body put itself right. Drugs can help with too much or too little as long as they don't push it too far, but ultimately we have to have these top-down, more holistic interventions that will actually help the body help itself.

Allostatic Load and the Obesity Epidemic

JB: So that relates a little bit—and I don't want to put you on the spot, here, but just get your opinion—about this obesity epidemic, because we seem to focus all of our attention on what I would call the thermogenic of the calorie; it's that we have a calorie consumption problem is the singular in an exercise in efficiency, or an activity in efficiency or inactivity component, and in between we have this thing called metabolism, which is regulated by all these factors that you've been describing. Do you feel

that what from what you've observed that some of this obesity epidemic is related to the biobehavioral response to our psychosocial environment? It's not just calories in and of themselves?

BM: For sure. I mean, I think we know that, for example, people on the average are sleeping less, often because they're getting up early or getting or getting home late and commuting long distances. We live in this go-go atmosphere in which people are rarely sitting down as a family unit, or at least with other people and having a slow and deliberate meal. It's the fast food, cram it down. And then, of course, it's the kind of food—the energy-dense foods—which immediately may be satisfied. And then it's the overconsumption of calories, and, of course, based upon, for example, Robert Lustig's new book Fat Chance, the recognition of how much sugar we have in our diets, and how some sugars, like fructose, are more likely to lead to the generation of obesity because of the way they are metabolized.[10] All of these things are almost like a perfect storm. And then if you add to that the fact that there is increasing evidence of epigenetic factors, even transmission in modified DNA in the sperm of the father and possibly changes in the mother which will pass on a propensity towards obesity. The notion of starvation, as in the Dutch hunger winter, where the pregnant woman (and the fetus) is somewhat starved, or overnourished, and the consequences there may be very similar in that the offspring will then have this propensity towards metabolic syndrome, obesity, and diabetes.[11],[12]

JB: Those are really powerful game-changing concepts that you're bringing up because they really relate to how we design large societal intervention programs to reduce this rising burden of obesity-related diseases. We had the privilege also of interviewing Dr. Moshe Szyf, from McGill, on his behavioral epigenetics and the work that he is doing there, and that seems also to fit very nicely into your model as well because it's one way that these epigenetic marks are put under conditions of adaptation. We have different kinds of regulators on gene expression. Some are long term.

BM: Absolutely.

JB: Have you done any collaborative work or had any discussions with the group that is involved with this behavioral epigenetics?

BM: Well, Michael Meaney, for one thing, is a former postdoctoral fellow, and also the research mentor for Sonia Lupien, so we are interrelated—an expanded family of science. And I know Moshe; I like him very much. Actually my PhD thesis was with Alfred E. Mirsky. They were the ones who really pioneered what we now call epigenetics, the modification of histones, which affect the folding and unfolding of DNA and its ability to be expressed, and so I've lived with the notion of epigenetics (whatever it was called then). It's a way of talking about how the environment regulates the genome, and we are actually presently doing studies on how stress changes the epigenome of brain regions like the hippocampus, and how that is related to the action of certain antidepressant drugs, the action of stress hormones, and also just related to what happens when an animal experiences something different that is perhaps somewhat stressful or enriching, and so on. It's a fascinating topic and it's now gotten to the point where we recognize that there are parts of the DNA that are not coding for proteins but are coding for RNAs that have a regulatory function, so that's another aspect of epigenetics, and then there are DNAs that rearrange themselves. There is Barbara McClintock who studied corn maize and how it got the variegated color; it's because DNA is being rearranged so that different things can be expressed or not expressed, and this is happening also in our genomes and may contribute to something called genomic instability that may actually make the brain or cells of the body more vulnerable to cancer, to degeneration, and so on.

JB: Wow, what you just said was gold. There was a lot of density in the information you just shared with us. Barbara McClintock, to me, is such a remarkable figure in genetics and I was pleased that she finally was recognized for her extraordinary work on transposons, and how this jumping genes concept is not really not just found in Indian corn; that it's a really very powerful concept that helps us to understand a little bit about genetic variability and also, as you said, genetic instability.[13] So it seems like there's a lot of confluence among multi-disciplinary fields to start to understand the fabric of human function and how it interfaces with the environment. I guess that then begs a question. You, being at the leadership in the wheelhouse of this field, so to speak, do you feel that there is getting more traction about this way of thinking? That people are starting to understand it and incorporate it? That it's part of training and taken seriously? What's your assessment?

BM: I think it is. I'm aware of the fact that a number of medical schools there is an interest and also even a demand on the part of students, but an interest on the part of the faculty in traducing more these problems that we face that have to do with our social environment and the concepts of integrative medicine and the importance of looking beyond drugs and the development of pharmaceutical agents to think about these kind of top-down interventions. And this is particularly so since, as the progress with the healthcare reform goes forward, there will be—as I understand it—more of an emphasis on producing results rather than just doing procedures, and this puts medical groups into the pressure of actually showing that their patients—their subjects, the people they cover—are actually improving in their health. That then makes us think about all things are fair game in terms of treatment. It's not just giving a drug perhaps; it's getting people involved in watching their diet, exercise, sleep, their commuting patterns, the kind of stresses in their lives, need to be brought under control.

JB: So when you are out there teaching, lecturing, communicating do you find that people are asking questions of how to do this, or are they still at the level of what is it all about? Where are they, generally, in their readiness to change model?

Physical Exercise and Stress Reduction Can Affect Brain Structure, Studies Show

BM: I think the thing that I find and I often will bring it up, is that they find most amazing the notion that, for example, as was shown by a group at the University of Illinois led by Arthur Kramer, if you get sedentary elderly adults to walk 60 minutes a day, five out of seven days a week, and they can sustain this on a regular basis over six months to a year, their hippocampus gets larger because of (probably) the generation of new nerve cells, and also some of these plastic changes that we've seen in the brain, and their memory gets better, and also their prefrontal cortex shows improved function, blood flow, and peoples' ability to make decisions—their executive function—is improved by something as simple as this very modest level of physical activity.[14] And if this works, there are studies that are being done on mindfulness-based stress reduction, for example, that show that if you can successfully treat an anxiety disorder there are actual physical changes in size of the amygdala, which is involved in fear and anxiety.[15] So behavior can change the brain, and I think the more people see that this is possible—that you don't simply just need drugs although of course they could be helpful—and begins to empower people to think that relatively simple things can help yes, but we have to get the word out.

JB: That's a marvelous proactive statement for every one of us to listen to. One of the questions that I ask all of our luminaries is, in the bibliography of articles and papers that you've been a principal author of (of which there are many), are there some that stand out in your mind as seminal? I asked Linus Pauling

this question, actually, about 30 years ago. Out of his some thousand papers I thought there probably would be one or two, but he was able to pick out a paper that he felt was the most important of his work. I remember reading your New England Journal of Medicine paper, I think it was, on protective and damaging effects of stress mediators.[16] Are there articles within your publications?

BM: Well, I think that that paper was the…you know, has certainly been very highly cited and was the thing which really turned things around. There was a previous paper that I did with Eliot Stellar in 1993 in Archives of General Medicine that sort of started it off, but it was the New England Journal paper that was very important.[17] I think more recently I wrote with Richie Davidson, a professor at Wisconsin, a paper in Nature Journal on the impact of the social environment.[18] There are others in between, but it's the New England Journal article that I think really got people thinking about this, and there have been a lot of filling in of the details since, and certainly Teresa Seeman's operative rationalization of allostatic load has been extraordinarily important.[19]

JB: My last question—and by the way, you've been very gracious to give us this amount of time—I'd like just to get a sense from your vision on high about what you see on the horizon as it relates to this field and its incorporation, both in terms of the research and clinical applications in the body politic of medicine. Do you have some thoughts as to where you see the trajectory taking us?

Research is Now Focusing on Mental Health of Children

BM: Well, one thing that I'll be doing next week with some of my colleagues from the National Scientific Council on the Developing Child—this is headed by Jack Shonkoff, a pediatrician at Harvard—is to focus on those early life adverse experiences and the importance of trying to improve parent/child relationships because adverse childhood experiences, as was documented by Felitti and Anda in the California Kaiser Permanente middle class population, has a huge impact on lifelong physical and mental health, and contributes disproportionately to the woes that we see around us, and so that aspect is important.[20] There is a new realization that the brain is more plastic than we have given credit for, and there are attempts to change the brain. There was a Sackler Symposium published a year ago as a special issue of the Proceedings of the National Academy of Sciences on biological embedding—I think it is from fruit flies to kindergarteners; it has some marvelous articles there on this plasticity issue and some of the future-looking steps.[21] The social environment the MacArthur Network on Socioeconomic Status and Health, and people simply look on macses.ucsf.edu—I think it is UCSF—website. They will get two publications that they can download, one on reaching for a better life, which is a lay sort of view of the social environment and health, and the other is a New York Academy symposium on the social environment and its impact.[22] I think that's where we are going. We have to deal with what the social environment is doing to our brain functions and our physical and mental health, and maybe the hope is that the brain and body are more plastic than we've given it credit for if we can get people to do these things that we know are good for us but don't often find time to do.

JB: Thank you, Dr. McEwen. That was a very uplifting and I thought very expansive review of many, many years of extraordinary work. By the way, one of the articles that I know you've published that I really appreciate—a recent article—appeared in Annual Review of Medicine in 2011 titled "Stress and Allostasis-induced Brain Plasticity."[23] I think this brain plasticity concept that you are alluding to is very encouraging because it doesn't suggest determinism, it suggests opportunity.

BM: That's right, and I'm glad you mentioned that because this was one of the first, more or less, official recognitions by the medical community that this is something worth paying attention to.

JB: Well, you've made many contributions that have gotten our attention, so thank you very much and we appreciate everything you've done and spending the time with us. We look forward to following your work very closely.

BM: Thank you very, very much. I've enjoyed talking with you.

JB: Thank you. Best to you.

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