August 2003 Issue | Niloofar Afari, PhD Acting Assistant Professor

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Welcome to *Functional Medicine Update* for August 2003. Last month we discussed laboratory methods for assessing nutritional or functional status. I talked about the standard blood chemical test—the 24-panel analyte test—that is used for evaluating aspects of function and pathophysiology. I also talked about the hematology profile, but in a slightly different way. It is used to assay such things as mean corpuscular hemoglobin and volume, the indices of hemoglobin, and hematocrit, to identify areas associated with nutritional inadequacies. It might, for example, be used to identify malabsorption syndrome or antagonists such as lead or cadmium, which might adversely influence nutritional status.

That leads us into evaluating not only vitamin and essential fatty acid status, but also mineral status, particularly trace minerals. It is interesting how often we must come back and learn old things in new ways. Everyone who has had some experience in physiological assessment or nutritional physiology knows the trace elements play an important role in body chemistry. Trace elements present in the body in amounts less than 1 gram have remarkable effects as coenzymes in modifying specific biochemical functions.

Zinc, for example, performs more than 100 different functions in the body and has been identified as a cofactor for various enzymes. DNA-dependent RNA polymerase is the required enzyme for the synthesis of mRNA. mRNA, the message that comes off the genome and is translated into protein, is dependent upon zinc status. If you are zinc-deprived, the clinical manifestation could be protein insufficiency. Your body cannot manufacture enough *de novo* protein because the mechanism by which the message is transcribed off the DNA is impaired.

Zinc Requirements
The recommended daily intake for zinc is somewhere around 10 to 20 mg, a fairly small amount. It is just a few crystals on the end of a teaspoon. If a person does not get adequate levels of this mineral, however, he or she might exhibit a variety of symptoms associated with protein insufficiency. One such symptom is problems with taste perception. To assess zinc status, we frequently employ the zinc tally or zinc oral tolerance test. Failure to taste a 0.1 percent solution of zinc sulfate indicates an individual’s taste mechanism may be impaired by zinc insufficiency. You are probably familiar with this oral zinc tolerance test.

We know zinc status can affect night vision. Vitamin A non-responsive night blindness is associated with zinc insufficiency. Zinc can be involved in a condition in infants called acrodermatitis enteropathica. The condition begins with a rash in the anal region, and it can work its way over the whole body as a

consequence of zinc malabsorption syndrome. Zinc deficiency can relate to things like poor wound healing, immunosuppressive disorders in adults, or growth and developmental retardation in children and adolescents. All of these are protein-related conditions connected to insufficient manufacture of specific enzymes or structural proteins in the body.

Iodine and Copper
One should not assume, just because trace minerals are found in small amounts, that they are not important. Iodine is related to thyroid function. Low levels of iodine are associated with goiter; high levels are associated with thyroiditis. Copper is important in the formation of collagen, connective tissue, and hair. Menkes' syndrome, associated with copper insufficiency, leads to brittle hypochromotrichia in the hair.

Chromium
Chromium is related to glucose tolerance factor. In the liver, chromium plays an important role in insulin stabilization and insulin sensitivity in glucose removal. Chromium insufficiency was first identified in work with total parenteral nutrition.[1] Insufficient chromium in these formulas led to induced diabetes. Addition of chromium salts resulted in normalization of blood sugar.

Selenium
Selenium plays an important role as both a promoter of detoxification through its role in glutathione synthesis and activity, and as an antioxidant through its promotion of glutathione peroxidase enzyme activity. Peroxidase enzyme is involved in the glutathione recycling mechanism through glutathione disulfide and then back to glutathione through glutathione reductase.

All of these minerals play important roles in establishing appropriate function. Clinical symptoms associated with trace mineral deficiencies can include increased red cell fragility or increased bruising associated with low selenium levels. Low selenium levels can lead to increased serum lipid peroxides due to increased oxidative stress as a result of lowered activity of glutathione peroxidase

We need to develop a clinical method of evaluating nutritional status that relates to biomarkers that are more than just laboratory numbers of plasma levels for zinc, copper, manganese, magnesium, selenium, and chromium. Intracellular levels of these minerals are also associated with clinical patterns. In fact, some people believe serum levels represent the least important variable for determining chronic trace mineral insufficiency, because it is intracellular levels that are most important. In most cases, we do not have reliable methods for evaluating intracellular trace elements. [2]

There are some exceptions, however. We can, for example, assess an intracellular mineral from an easily harvested tissue biopsy. That would be red cells, the erythrocytes from a normal phlebotomy. Red cell intracellular magnesium levels are more diagnostically useful for evaluating chronic magnesium insufficiency than plasma magnesium. Often, when we look at a blood magnesium level in a traditional laboratory assessment, we are really looking at plasma serum magnesium. We are not looking at the red cell magnesium.

Evaluating Red Cell Minerals
From a methodological perspective, the difficulty in evaluating red cell minerals is to make sure the blood cells are harvested in such a way as to avoid lysis. If you lyse the cells, or increase their membrane

permeability to minerals by injury, you might get artifacts instead of the actual levels of minerals. The cells have to be fresh and minimally traumatized so you get good intracellular mineral data. When it is done correctly, intracellular red cell magnesium appears to be much more useful in clinically identifying magnesium insufficiency syndromes.

Dr. Sidney Baker has described the clinical signs of magnesium insufficiency as beginning with simple "zips" and "zaps," little darts, muscle twitches, and contractions, perhaps a little premature ventricular contraction (PVC) that comes and goes. You might miss these early signs of magnesium insufficiency from a clinical perspective if you simply assess serum magnesium. You might get a correlation if you looked at intracellular red cell magnesium levels, where selenium levels might be seen to be low.

Evaluating Functional Status
In evaluating nutritional or functional status, you need to create a mosaic of data from clinical experience, blood chemical information, and challenge testing. The oral glucose tolerance test, for example, provides information that differs from a fasting blood sugar test in describing the relationship of organ reserve to the glucose management ability of the body. Putting those assays together in a pattern-recognition profile, the functional medicine diagnostician can come up with operative hypotheses that lead to interventions with the patient with complex symptomatology.

This issue of FMU is the first of a two-month series on chronic energy-deficit disorders, those that represent conditions of the 21st century. These include chronic fatigue syndrome (CFS), its companion condition, fibromyalgia syndrome (FM), and other chronic energy-deficit disorders. This series represents a fairly well organized review of what we know about CFS and related conditions, both from the literature that has developed around this complex condition over the last decade, and from two experts in the field. Although there are many interesting avenues of research now underway, we have not seen a major, single treatment for CFS or FM emerge as the *sine qua non.* As a consequence, this particular field is more akin to what we might call a functional medicine illness—a term we apply to a series of symptoms that may derive from many etiological factors. Although we call these functional medicine-related chronic fatigue syndromes, they are plural in terms of their etiology. As a consequence, it is unlikely that a single treatment for CFS or FM will emerge. Therefore, these syndromes are amenable to functional medicine strategies. Because the issues surrounding CFS and FM are complex, we will try, over these two months, to review and analyze what is known about these puzzling conditions. We will also endeavor to apply these concepts in clinical presentations that might lead clinicians to designing personalized treatment strategies for the nearly 800,000 Americans with these fatigue and pain-related syndromes. I want to emphasize that it would be presumptuous to say that we know the cause of CFS or FM (as if there was a single cause), or that we can define a specific singular treatment regime covering all patients with 100 percent effectiveness of outcome. Neither do we have single laboratory diagnostic tests to discriminate CFS or FM from a myriad of other fatigue or chronic pain-related syndromes.

You might wonder why we are devoting two issues to this topic if we cannot answer those questions. It is because these conditions are real syndromes. They are not manifestations of psychosomatic illness. As we will learn from this month's Researcher of the Month, "psychosomatic" may be a pejorative term that defines the nature of many of these chronic illnesses. They are a very real interaction of the mind and the body.

In 1994, I published a paper in *Delicious Magazine* titled, "The Mystery of Chronic Fatigue

Syndrome."[3] In that article, I talked about the nature of the research we had been doing on this complex condition over the past five years at our clinical research center in Gig Harbor, Washington. Our work was done in collaboration with our colleague, Dr. Scott Rigden in Tempe, Arizona.[4] The average length of time patients had the condition before they came into Dr. Rigden's study exceeded three years. Many of them were occupationally disabled, and some were on assistance. This condition involves bone-weary fatigue, inability to function, low energy, and pain, all working together. As a consequence of the experiences we had with numerous CFS and FM patients, trying to put together a laboratory algorithm that would result in assessment of their physiology and how they differed from patients without these syndromes, we came to recognize the complexity of these conditions. From that complexity emerged a pattern, one that resulted in treatment regimes that are adjunctive, or perhaps even primary, in assisting patients to recovery. It is that kind of philosophy that will guide us during this two-month series to assist you in putting your own treatment programs together for these complex illnesses that may be represented as functional medicine-related conditions

Many practitioners tend to reject these conditions, which are real clinical entities, because they are too complicated and their symptoms too diffuse. We may label them pejoratively and dismiss them as "psychosomatic," as if that term means they do not really exist. It is just "all in the mind." I find the dismissive attitude toward "psychosomatic" disorders interesting, because all diseases are, in fact, "psychosomatic" (involving both the mind and the body).

I can't think of a disease of the body that does not affect the mind or one in which the mind does not influence the body. We have stigmatized the word "psychosomatic" when it is, in fact, probably the most definitive explanation. Obviously, there can be variations on a theme. Some diseases may be more "somatic" and less "psycho," and others may be the opposite. All disorders involve both variables because, in fact, they are not two distinct variables. They are parts of a common phenomenon called "physiology." Our bodies are holographs of mind/body or body/mind.

Assessing the Holographic Body

We take the concept of assessing status with biomarkers and combine it with clinical symptomatology and a good history. Then we add other specialized functional challenge tests that improve our understanding of the functional nature of physiological, structural, or psychological aspects of the individual. From that comes an operative personalized assessment of the patient's need. We don't simply plug the patient into an algorithm because we have a diagnosis suggesting that every diabetic or coronary heart disease patient is the same.

That is the difference between a functional medicine model and a model based on pathophysiology that leads to a discrete diagnosis and a standard treatment for all individuals who fall into that particular diagnosis. We are going to examine these functional somatic syndromes from the perspective of this integrated profile of assessment and diagnosis leading to a rational approach toward integrated therapy

We can begin by taking a look at the literature on a condition that was first discovered by Dr. Paul Cheney and his colleague in their practice of internal medicine in Incline Village, Nevada, back in the 1970s. After a bad winter in which there were many flu cases, Dr. Cheney and his colleagues had a cluster of patients who did not recover. They had resident, ongoing, long-term fatigue-related symptoms that later came to be known as CFS.

On Side II of this month's FMU we will hear from our Researcher of the Month, Dr. Niloofar Afari, about her work with CFS, FM, and other complex functional somatic syndromes. Dr. Afari and her colleagues are working to identify potential etiologies, with the ultimate objective of developing specific treatment protocols. This month, we will deal with exploration of this topic through her pioneering work at the University of Washington School of Medicine.

Assessing CFS

Let us talk about CFS as a condition. It is fascinating, if you look at the literature that has developed in this category over the last 30 years, to see how much controversy, confusion, and contradictory information has been generated by this condition. People say they have the solution, they have the answer, as if there is a single answer to the understanding and ultimate treatment of this complex functional somatic syndrome we have labeled CFS.

One of the individuals I mentioned who has been a primary investigator in this area is Dr. Afari's colleague, Dr. Dedra Buchwald. Recently, Dr. Buchwald was a principal author of a paper that appeared in Psychosomatic Medicine. The title of that paper is "Single-Photon Emission Computerized Tomography and Neurocognitive Function in Patients with Chronic Fatigue Syndrome."5 By looking at central nervous system CT-scans of CFS patients, the researchers found these patients have diffuse cerebral profusion. This may suggest some regions of the brain are getting more oxygenation and more glucose metabolic activity than others, which may be related to the inefficient neuropsychological performance often seen in CFS patients—or cognitive dysfunction. It may suggest there is some neurally-mediated effect that relates to cognition changes, sleep pattern changes, and energy level changes.

CFS and Quality of Life

Clearly, CFS patients experience significantly compromised quality of life. No matter what questionnaire one uses (the short-form questionnaire SF36 is an example), patients often report a lowered quality of life, which can show itself in lower vitality, sense of well-being, and libido.6 All kinds of things we ascribe to good health and high vitality seem to be suppressed. These symptoms persist for a long time—three to five years is common.

Varying Manifestations

The co-morbid illnesses seen in women and men with CFS are varied.7 It is therefore very difficult to get a singular diagnosis. There is a prevalence of many co-morbid illnesses in the presentation of CFS patients. But discrete similarities among CFS patients indicate there could be some type of singular etiology or common underlying thread in the conditions of these patients. That is, of course, the solution everyone has been searching for. How do these things fit together? What is the mechanism by which these diffuse symptoms occur?

Hans Selye, when he first described the General Adaptation Syndrome stress mechanism, was quite amazed to see that multiple triggers in the environment in animals could produce multiple symptoms of outcome, including such conditions as peptic ulcer disease, hypertension, coronary heart disease, diabetes, and obesity. A singular series of events in the environment could be translated through the individual animal's genotype into its phenotype into a variety of different illnesses.

A Different Model of Disease

That model of disease differs from one of infectious disease in which a single bacterium produces a single

disease, like a Pneumococcus bacterium producing pneumonia, for example. It is much simpler to understand the etiology of pneumonia and the single molecule, penicillin, that treats it. In the old days of diagnosis, single agents produced single diseases that were addressed by single molecules. Now we describe multiple agents producing complex symptoms that will probably require multiple agents for their management. There is not a single cause, but rather a state of function that leads to conditions like CFS.

If we look at CFS subtypes in community-based samples, we see a strong interrelationship among patients who say they have CFS, those with FM, and those with multiple chemical sensitivity. In their research, Dr. Buchwald and others have suggested that some common theme ties those conditions together. Some of the effects that lead to symptoms seem to be mediated through alterations in the hypothalamus/pituitary/adrenal axis (HPA).8 How and why that effect occurs is not yet fully understood, but we might call this a kind of Selye model of adrenal depletion, or adrenal exhaustion syndrome. There is a lowered level of HPA activity, as if the individual's neuroendocrine/immune state was metabolically exhausted.

Seeking a Cause of CFS

From various types of proton magnetic resonance spectroscopy and CT scanning, scientists have observed that metabolic changes in the brain occur consistently or commensurately with CFS symptoms.9 These changes suggest that something is the chicken and something else the egg, or maybe it's just an omelet. We can't really identify a causal factor as much as a functional change in the organism. Those changes include neurochemical changes, cellular metabolic changes, endocrine changes, and immunological changes. Together they comprise the complex constellation of symptoms unique to the individual that we label as a functional somatic syndrome—CFS.

A number of ongoing studies have sought to identify the metabolic influences these particular conditions involve. One observation that has emerged from this research is the relationship of the symptoms to alterations in the energy production centers of the cell, tissue, or organ, which are the mitochondria.

Changes in Mitochondrial Bioenergetics

The suggestion is increasingly made that CFS or the fatigue-related functional syndromes are related to altered mitochondrial bioenergetics. Something is causing changes in energy dynamics in the cell. Energy dynamics are what drive a number of very important functions of nutrient transport into the cell and the transport of waste products out of the cell. This might explain, for instance, why a report in the Lancet a number of years ago indicated some patients with CFS experienced symptom relief when they were injected intramuscularly with a high level of magnesium sulfate. Magnesium seemed to improve energy function, cognition, and sleep as it decreased fatigue.10

Unfortunately, the relief lasted only a short time. When the researchers evaluated red cell magnesium in CFS patients, they found it was very low. The suggestion was that magnesium depletion caused CFS. I would turn that around and ask why it is that CFS patients have a low level of intracellular magnesium. Could an ongoing process be contributing to lowered magnesium levels in cells? Magnesium should be inside cells, and calcium should be outside. A condition of imbalance, in which calcium comes into cells and magnesium leaves, is associated with calciphylaxis and many chronic disorders, the symptoms of which are related to CFS.

Magnesium Transport

That imbalance is not related to a lack of magnesium in the diet. Magnesium is an element that is concentrated some 10,000,000 times higher inside cells than outside cells. Concentrating any substance against an energy gradient requires expenditure of energy. It is not just passive diffusion; it is active transport. It is the enzyme magnesium/potassium ATPase that transports magnesium inside cells. ATPase (adenosine-triphosphate splitting enzyme) suggests that this is an energy-driven process that requires ATP.

ATP comes from oxidative phosphorylation, and the site at which this occurs in the cell is the mitochondrion. Perhaps low magnesium within cells is, in part, related to altered mitochondrial oxidative phosphorylated activity or changes in ATP and AMP ratios. That balance interrelates with bioenergetics. Perhaps many of the fatigue syndromes we see are a consequence of changing dynamics of the energy gradients, or the so-called redox potential (reduction/oxidation potential) within cells.

Influencing the Redox Potential of Cells
A number of variables could influence the redox potential of cells and result in altered mitochondrial function. Heavy toxic elements like mercury, cadmium, or lead can poison mitochondria. So can various medications (including drugs used to treat HIV), third-generation antibiotics, alcohol, and mold metabolites. The list of factors that might alter mitochondrial function is a long one. Oxidative injury can poison mitochondria and alter mitochondrial energy efficiency or effectiveness.

When you begin to examine a disorder associated with low energy, the cause of which appears to be associated with numerous triggers of environmental origin that work on genetic susceptibility, it is not too wild a hypothesis to suggest a mitochondrially-related dysfunction at some level. People carry their own unique mitochondrial DNA as a consequence of what they got from their mother. We inherit the majority of our mitochondrial information, our extra-chromosomal DNA, from our mothers. Our biochemical energy comes from our mothers through our mitochondrial DNA.

Interacting Variables in CFS
Genetic susceptibilities and environmental factors may combine to create the so-called “straw that breaks the camel’s back,” and eventually the stress syndrome pushes the mitochondrial energy dynamics over the top. Stress can increase oxidative injury; it can induce different kinds of neuroendocrine function that change mitochondrial activity and nitric oxide production. This is a complex web of interacting variables, but it is a model from which we can possibly better understand the etiology of a complex functional somatic syndrome like CFS.

That appears to be what is emerging from the literature published over the past several years on the clinical symptoms and profiling of CFS syndrome, and cellular mechanisms that might relate to it. Studies have been conducted on animal models of CFS, and researchers have sought the origin of a condition called “phantom lymphadenopathy” associated with CFS.K11Allergy, toxicity, and inflammatory mediators all are factors that may lead to a load or weight on energy biodynamics and translate into what we call CFS in certain individuals.

A Functional Program to Address CFS
That is a hypothesis, a model that seems to be emerging from the literature. One good thing about this model is that it leads to varying approaches toward remediation of the patient with CFS symptoms. It involves the concept of lowering a load of triggering agents on mitochondrial dysfunction. These may be

toxic metals, toxic chemicals, or antibiotics. A program to reduce toxicity includes the rebuilding of mitochondrial function by protecting electron transport and oxidative phosphorylation. This is accomplished through the use of appropriate antioxidants like carnitine, coenzyme Q10, vitamin C, and lipoic acid, which have been demonstrated in some studies to have positive benefit on the symptoms of CFS.12,13,14,15 It provides a model for how they might be proven useful.

The Role of Essential Fatty Acids and Antiinflammatories

This model also helps explain why some patients respond favorably to supplementation with essential fatty acids, particularly the long-chain omega 3 fatty acids like eicosapentaenoic and docosahexaenoic acids.16 These are the EPA/DHA fish oil derivatives. These fatty acids help rebuild mitochondrial membranes and mitochondrial activity. They help restore function in terms of the structure of the cell and lowered inflammatory potential.

The model may also explain why certain antiinflammatory substances have been useful in ameliorating some CFS symptoms. Even though we do not consider CFS to be an inflammatory condition per se, it may play a role in altering some of the mediators that are released, which in turn, alter mitochondrial function. These are nitric oxide-driven or cytokine-driven substances such as interleukin-1, interleukin-2, or perhaps even tumor necrosis factor alpha.17 These substances have all been associated with inflammatory potential at the cell level that could alter mitochondrial function.

Therapeutic Approaches

A number of potential therapeutic approaches emerge from this model. All are consistent with behavioral therapy, graded exercise therapy, rest, hydration, better nutrition, and lowering the toxic burden. All of those particular variables tie together in part to this model I am describing.

The literature on CFS that has evolved in the past 10 years suggests that things like multiple chemical sensitivity, the so-called Gulf War syndrome, and FM may all share some etiology with CFS.18 All of these conditions may involve energy-deficit disorders in specific tissues or organs related to electron transport and ATP formation and utilization.

Changes Occurring in CFS Patients

Changes in hemodynamics as well as neurotransmitter alterations occur in CFS patients.19 These hemodynamic changes are also potentially related to altered vasoreactive compounds like nitric oxide (NO), which was formerly called endothelial-relaxing factor.

We now recognize that NO from the immune system may play a role in hemodynamics through its vasoreactivity. You can get into a situation in which immune system activation can alter hemodynamics and vasoreaction. You can get into hypotonia and hypotensive disorders. The etiology of Gulf War syndrome, multiple chemical sensitivities, FM, and CFS appears to overlap. That shared etiology may, in part, be related to the energy deficit that occurs at the cellular or metabolic level and is connected to inappropriate redox control (reduction/oxidation control) in the cell.

Syndrome Similarities

A recent review paper describes the similarities among FM, CFS, and myofascial pain syndrome. This review appeared in the journal Current Opinion in Rheumatology.20 The author indicates that the prevalence of chronic widespread pain and fatigue in the United States, United Kingdom, and Canada demonstrates a co-morbidity with FM, CFS, irritable bowel, and somatic hyperalgesia. All sorts of

symptomatologies tend to go together.

This concept appears to be interrelated to alterations in the N-methyl-D-aspartate (NMDA) receptor site pathway. There are neurally active components related to altered triggers in the neuroendocrine immune system, with altered environmental factors that may play a role in triggering these outcomes. They are tissue-specific in individuals with differing cellular or genetic susceptibilities.

Depression and Mononucleosis

We see mood changes and sleep disorders in CFS, but these are different from standard depressive disorders, as Dr. Afari will explain. One can clearly differentiate a traditionally depressed patient from a CFS patient. A Lancet article looked at predictions and associations of fatigue syndromes and mood disorders, connecting them with what happens after infections such as infectious mononucleosis.21 Patients who have had mononucleosis may never feel quite right. They may have low energy for months after their blood cell counts return to normal range. They may still feel wiped out and tired.

Did it lead to any residual influence on a feed-forward cycle within cells that leads to the fatigue disorder? In other words, did the patient move to a different state of physiological function through the infection that left the memory of the infection, even after the infectious mononucleosis was gone? The patient remained feeling as though he or she had mononucleosis, even in the absence of an elevated monocyte count.

Feed-Forward Cycles and States of Homeostasis

An interesting thing often happens with other triggering events, such as acute stress exposure or acute toxic chemical exposure. The individual recovers from the immediate burden only to remain in a state of dysfunction, i.e., CFS, for some time thereafter because he or she got locked into a different state function of physiology. I call these feed-forward cycles, in which the neuroendocrine immune system has found a new homeostatic level.

We often associate the word “homeostasis” with health. But you can have homeostasis of diabetes or homeostasis of arthritis, in which the patient’s normal functioning state is one not of health, but of alarm, reaction, or altered blood sugar. In the case of CFS, certain events could trigger the physiological response into the feed-forward, self-replicating state of dysfunction we associate with CFS.

A Continued State of Alarm

We are beginning to understand, with this new model of CFS, that although the infectious organism may be gone, the condition lingers with the patient. In this sense it does not fulfill Koch’s postulate that if the infectious organism is gone, the infectious disorder disappears.

Within the HPA axis, there is a continued residual alteration in neurochemicals associated with alarm, such as interleukin-1 or interleukin-6. Authors of apaper in Arthritis & Rheumatism found that patients who had FM and CFS had an elevated level of interleukin-6, as contrasted to a cohort of age- and gender-matched patients who did not have the condition. They believe this suggests some functional state that follows the patient for years after and ties them into a different immunoneuroendocrine function. 22 This is an interesting part of the potential etiology of these complex symptoms associated with functional somatic syndromes—CFS, FM, and multiple chemical sensitivity.

Developing a Clinical Approach
We will take this more complex mosaic of our understanding of the etiology of these syndromes, tie it together with the Selye stress mechanism, try to incorporate the cellular physiological studies, and then come back to a reality base. In other words, clinically, what are we learning about the condition? What really works? This is not just an intellectual game of trying to speculate on hypotheses. The objective is to try to find better ways of managing these complex conditions using an armamentarium of the available tools to personalize the therapy for the patient.

That strategy will take us away from the one-disease/one-medication approach that has often been used in traditional medical management. It will take us to a tailored approach that will probably engage a variety of therapeutic tools personalized to the individual patient's need. Those tools will be based on genetic susceptibilities, environmental triggering factors, and the mediators that modify function and lead to the feed-forward states we call CFS, FM, or multiple chemical sensitivity.

This clearly ties together with some of the discussion we had last month related to autism, attention deficit disorders, and brain biochemistry. There may be molecules in the brain, levuglandins that are produced at higher levels in individuals who get locked into a different functional state of brain biochemistry. These chronic symptoms that stay with people, which we have often said are hard-wired into their genes, may not be hard-wired at all. They may be various functional states that are in their gene potential that, as a consequence of specific environmental factors, result in the expression of these outcomes as chronic conditions.

Diagnosing CFS Conditions
From a diagnostician's perspective, as we will learn in a continuation of this discussion on Side 2, the practitioner needs to throw a wide net in gathering data to understand the origin of these conditions. He or she needs to obtain a very good personal and family health history, and conduct a good physical examination of the patient. One needs to use a range of biochemical information to help understand where some of these metabolic influences might exist. The more information you can assemble in this pattern recognition profile, the more likely it is that you will be able to develop a personalized treatment plan to meet the patient's individual needs.

CFS does not arise from just one agent. It does not involve simply giving intramuscular magnesium injections, or an antiinflammatory, or an antidepressant medication. It is not just providing essential fatty acids; it is not just putting that patient through a detoxification program. A combination of many variables may be required to break the cycle of feed-forward physiology that results in what we call CFS.

This is a different model from the traditional one in treating patients. I want to emphasize the difference and also acknowledge and celebrate the complication and challenge it represents. It is not as simple as writing out a prescription and sending the patient to the pharmacy to get it filled. One needs to identify the complex psychosomatic variables that give rise to these complex functional somatic syndromes.

Let's move to our Researcher of the Month interview

INTERVIEW TRANSCRIPT

Niloofar Afari, PhD

Acting Assistant Professor
University of Washington
Department of Psychiatry & Behavioral Sciences
Box 359780
Seattle, WA 98195

JB: Once again, it's time for our Clinician/Researcher of the Month. As I mentioned, this is the first of a two-month series to gain a better understanding of the clinical presentation, definition, etiology, and management of complex syndromes like chronic fatigue syndrome (CFS), fibromyalgia (FM), and post-traumatic stress syndrome.

This month, we are pleased to launch this series speak with Dr. Niloofar Afari, PhD. She is a clinical psychologist who has been working at the University of Washington School of Medicine as an acting assistant Professor in the Department of Psychiatry and Behavioral Sciences. She has been a collaborator with a group involved in research and publication in the area of CFS. Dr. Dedra Buchwald is one of her colleagues. Dr. Afari has also been an associate director of the Chronic Fatigue Syndrome Cooperative Research Center in the Department of Internal Medicine at the University of Washington. She recently relocated to Washington State, having been a commuter between Temecula, California, and Seattle with her continued work at the University of Washington.

Defining Chronic Fatigue Syndrome
Dr. Afari, welcome to FMU. To begin our discussion, could you provide a clinical definition or clinical presentation that characterizes chronic fatigue syndrome?

NA: Dr. Bland, let me first thank you for inviting me to join you today. As to clinical presentation of CFS, in terms of its case definition or research criteria, CFS is a syndrome, not a disease. There are no tests that will definitively diagnose CFS. The basic presentation is persistent fatigue for six months or longer. Typically, people who come into a primary care physician's office are at the beginning/end of this syndrome and have experienced fatigue for six months or perhaps up to a year. Those who are moving on to a specialist's care have typically been dealing with their fatigue for much longer than that.

The fatigue has to be unexplained medically. CFS is a diagnosis of exclusion. Other illnesses that could account for the fatigue have to be ruled out so there is no known cause for the fatigue. The fatigue often occurs with pain, with a number of other symptoms. In fact, the Centers for Disease Control, in a Prevention Case Definition published in 1994, described eight symptoms related to CFS. The person has several of these other symptoms, such as sleep difficulties, pain, or cognitive problems.

Another unique thing that sets patients with CFS apart from those with other fatiguing illnesses is that rest does not alleviate the fatigue. On the contrary, activity, exercise, or exertion often worsens the fatigue. It's a paradoxical situation. For example, with depression, when people become more active, they feel better. With CFS, when they become more active, they feel worse physically and more fatigued. That's a brief case definition of CFS.

Diagnosing CFS
JB: Is there a diagnostic code that a physician can apply to CFS? How does a doctor actually diagnose it if it's a syndrome and not a disease?

NA: That's a very good question. Dr. Keiji Fukuda provided a formal case definition in a CDC publication published in 1994.23 It outlines what I just mentioned—six months of fatigue and the other fatigue criteria. It gives examples of conditions that include fatigue as a consequence or may complicate the picture, and describes what must be ruled out. In fact, there is a publication that also outlines a number of laboratory tests that can be done to rule out other conditions.24

There is very little that can be done to diagnose the fatigue. This is a diagnosis by exclusion. Once everything else that could cause the fatigue is ruled out and there are no other abnormalities, the fatigue can be diagnosed as CFS. The CDC guidelines can be used as a guide. They were devised mostly for research purposes, but more and more, physicians who are faced with patients they're not quite sure what to do with are turning to the CDC guidelines as the case definition to guide their decision-making.

Neuroimmune Disorders and CFS

JB: When I listen to the criteria you described, such as sleep disturbance and cognitive function problems, pain, lymphadenopathy, and intolerance to previously tolerated exercise, they sound like a neuroimmune-related dysfunction. Is CFS connected to disorders that are neuronally mediated, such as post-traumatic stress syndrome and fibromyalgia?

NA: That is a big area of research and an area of some controversy. A number of syndromes overlap in terms of both their symptoms and the characteristics of patients. In terms of what has seemed to work for the patient, because there is no known cure, there are symptomatic treatments. These overlapping conditions have been termed functional somatic syndromes—fibromyalgia, multiple chemical sensitivity. To some extent, PTSS (post-traumatic stress syndrome) also shares some symptoms that have been related to fibromyalgia. Some evidence indicates it might be related to the development of CFS as well, although my own personal research has not shown that.

A number of researchers believe that because of these overlapping symptoms, patient characteristics, and treatments, all of these conditions should be considered different manifestations of the same processes, whether they are biochemical processes or psychosocial processes. In other words, they are basically the same sheep in different clothing.

Functional Somatic Syndromes

JB: Your mention of functional somatic syndromes reminds me of a paper of that title that appeared in the Lancet a few years ago.25 As I recall, the authors concluded that medical specialties frequently tend to discard these disorders because they see things through the lens of their own specialty. How does that relate to a diagnostician's or practitioner's understanding of these syndromes? It sounds as though it may be difficult to separate the forest from the trees.

NA: I think that's very relevant. In terms of research, we're hoping to move in the direction of more collaborative and more multidisciplinary work so we can look at the commonalities and share the information. If there is indeed a common pathophysiology, then examining patients along this continuum of functional somatic syndromes would be a lot more useful than if we were all just looking at our own set of trees, so to speak.

There has been increasing collaboration, at least between our group and a number of other groups that primarily work with fibromyalgia or multiple chemical sensitivity. We are looking at the similarities and

sharing ideas of our series about pathophysiology and comparing these patients on a number of different indices.

Functional Syndromes and Psychosomatic Illness
JB: Your discussion of the origin of the term “syndrome” takes me back to a paper on diabetes published in the Lancet in 1949. The author said that well before one becomes diabetic, there are functional syndromes that precede the condition, involving altered glucose control and insulin sensitivity. It’s possible that the action for a lot of chronic illness might be in understanding more of these functional somatic syndromes.

On the other hand, a critic might point out that CFS has no diagnostic specificity and no known etiology. People are walking around tired and worn out, but so are all of us. Life is difficult; why call this anything but failure to cope? What is psychosomatic? It sounds as if it’s all in your mind. How does one respond to that kind of criticism that there is no such thing as CFS?

NA: I guess the clinician in me would say I have not seen these people. These are not people who are simply tired today. They have had months and months of continually decreasing physical, social, and health functioning. They are people who eventually may become bedridden, and they’re not unlike those with certain psychiatric conditions. The interest and willingness to do something different and to move on and have a fully functioning life is there, but the body does not seem to cooperate. The clinician in me recognizes that these people are ill. This is not all in their heads; they’re not faking it.

The researcher in me says that in any condition, there is an interaction between the psyche and the body. We may not have pinpointed the etiology of CFS and most probably, given the range of abnormalities that have been seen in immune functioning, virology, neuropsychology, and neuroanatomy, there probably isn’t one single cause. A number of different events, whether a virus or some other event, may set off the syndrome, but as with anything else, how the person copes, responds, and interacts with the illness certainly does affect it. If you want to call that psychosomatic, that’s fine, but then again, everything else is psychosomatic, too.

CFS and Post-Traumatic Stress Syndrome
JB: That’s beautifully said. Ever since September 11, 2001, we have seen an increasing prevalence of post-traumatic stress syndrome, as evidenced in articles in the New England Journal of Medicine. There seems to be a shift in the neurophysiology at the hypothalamus/pituitary/adrenal axis (HPA), in which one gets locked into a hypersensitized cortisol condition. Is that something like what we see in CFS?

NA: Interestingly, one finding that has been pretty consistent with CFS is hypocortisolism, which is different from what is seen in the person with hypercortisolism. I don’t know how that would work. Perhaps if you’re in a chronic stress situation, then you have a paradoxical effect. I’m not sure. I’m not a physician so I can’t really speak to that, but it does not seem to be an acute stress reaction, which would be hypercortisolism.
DHEA Effects
JB: This follows from what Hans Selye defined as the general adaptation syndrome. This model of fatigue, or a depletion effect, may explain why some reports have indicated that women with low energy and fatigue suggestive of CFS, when given low doses of DHEA, which supposedly enhances cortisol, experience symptomatic improvement. Does that follow from what you’re saying?

NA: It does. I'm not sure we're ready to prescribe DHEA to everyone, but it does follow and there have been several treatment studies, some double-blind, well-controlled studies and some not, that have looked at a number of products. I think the jury is still out. Some studies say that if you treat the HPA, you see improvement in symptoms. But in other studies, that has not been found. It's definitely an area that should be further studied.

Genes and Environment
JB: Let's move to a discussion of susceptibility. I just finished reading a book titled Nature or Nurture (HarperCollins; 2003), by Matt Ridley. Another of his books, Genome: The Autobiography of a Species in 23 Chapters (HarperCollins; 2000), won the Pulitzer Prize last year. In his current book, he tracks the long-standing nature/nurture debate that has persisted among philosophers, psychologists, and sociologists. Are we defined by our genes or by what happens to our genes in the environment? According to Ridley, the answer to both questions is "yes."

NA: Your genes may affect the environment.

Genetic Predisposition and CFS
JB: That's what he points out. Would you give us your thoughts about CFS and how the genetic predisposition may fit into the epidemiological patterns?

NA: In the last few years we've looked more and more at the genetics of CFS. It's pretty early on to consider finding a gene. We've done a number of twin studies, one in particular in which we looked at CFS-like illness. Obviously, one needs to do a comprehensive physical examination to rule out various conditions, but in terms of surveys, you can basically assess the symptoms for CFS. If they have not had any other conditions that would cause them to experience fatigue, you can call that "CFS-like Illness."

In examining twins, both identical and fraternal, who either would be concordant (both have CFS-like illness), or discordant (one has CFS and one does not), we discovered a higher prevalence of concordance among identical twins than fraternal twins. We've also found that both unique genetic and shared environmental components are involved. That is, both genetic and environmental factors account for a large portion of the liability for CFS. That suggests the incidence of CFS is probably familial. That is, there is a higher chance of occurrence within families, and both genetics and environment come into play. In other words, someone who is susceptible, given the right environment, will develop CFS.

A Syndrome without Diagnostic Criteria
JB: Given this complex nature, we have defined a syndrome that does not have specific diagnostic criteria.

NA: That's the key issue. We're not dealing with hypertension, in which you have a number and you know it's high blood pressure. We're not dealing with diabetes; we're not dealing with a disease at all. We're dealing with a syndrome that is not even well defined. Even for a syndrome that is not well defined, we are finding huge genetic and environmental contributions to it.

A Communicable Disorder?
JB: When Dr. Cheney and his colleagues first reported the outbreak of what he later called CFS, he thought it had a viral-related etiology. It seemed to be like a communicable disorder. Has that stood the

test of scrutiny, or do you think that's only one of a variety of contributing factors?

NA: I think it's probably one of a variety of factors. Actually, the field is slowly starting to move in the direction of sub-classifying groups of patients. There are patients whose problems started with a viral illness; others had some sort of psychosocial stressor. There are probably a number of different factors that may initiate the illness, and another set of factors that may perpetuate it or may complicate recovery from it.

Neuroendocrine Immune System Condition
JB: From what you've described, it sounds as if the condition is a manifestation of modified function of the neuroendocrine immune system. Many precipitating factors or triggers may create a tension on that system such that its functional state is changed, basically.

NA: And then behavioral factors complicate it.

Complex Disorder, Complex Therapy
JB: With all of that in mind, it's unlikely that anyone will find a single molecule to treat it. Does that leave open the door to integrative medicine or a more complex therapy to play a role in its management?

NA: Definitely. Unfortunately, the treatment research hasn't moved very well in that direction. Basically, it's been "let's treat the virus; let's treat the HPA; let's treat this and let's treat that." The whole person hasn't really been taken into consideration.

Right now, as the literature stands, the biggest "bang for the buck" is with more behavioral treatments that are designed not to cure CFS but to help the person adjust to and cope with the symptoms and live with what he or she has. It certainly would be good to move in the direction of adding other treatments to that base and see if functioning can be further improved.

Asthma and CFS
JB: You and Dr. Buchwald have collaborated on a number of studies related to asthma, which it would seem is considerably easier to diagnose. Asthma, too, however, seems to have a strong psychosomatic component. Do you see similarities between the two conditions?

NA: I do see similarities. Fortunately, with asthma, medical biochemical treatments can help improve the person's functioning. In addition, you can provide behavioral treatment to help the person adjust and cope. The thing that's missing for CFS is pharmaceutical or biochemical treatment.

Diffuse Symptoms, Difficult Mechanism
JB: If both asthma and CFS have a psychosocial component, why is it possible to ameliorate asthma symptoms with various airway-active compounds, but not possible to modify the symptoms of CFS? Is it because the symptoms are more diffuse, or have we not understood the mechanisms?

NA: Probably both. The primary symptoms are not the same. If you take a group of 100 people who have asthma, if their symptoms are not the same, they're very similar. On the other hand, if you take a group of 100 CFS patients, they will all complain of fatigue, but they will also all complain of a number of different symptoms. Some of them are part of the CDC Case Definition, and some have nothing to do

with that definition.

Then what do you do? Do you try to attack each symptom separately, or do you look to see what could be causing or perpetuating the symptoms so you have one central treatment? Part of the lack of treatment is related to a lack of understanding the etiology of the symptoms and part of it is that it's really not well defined. It looks similar, but it doesn't look similar enough in the patient population so we can come up with one, two, or three treatments.

Managing CFS

JB: Given this explanation of where we are, and recognizing that you are not a clinician (although you've obviously observed many CFS patients), can you provide any insight into remediation or management of the symptoms? Is the condition self-limiting? What do we do?

NA: What's interesting is that what we see as clinicians and researchers in clinical settings are the patients for whom nothing has worked. They've tried many different things and basically have not been able to find things that work. There are a number of people out there who have had CFS—they may have even been diagnosed as such—and they may not have fully recovered. They've not gone back to their previous level of functioning, but have, on their own or under some doctor's guidance, or in seeking alternative care, managed to put various things together in their lives that have helped them function adequately in their lives. They've adjusted to how they're going to live their lives with periods of fatigue.

We really don't see those folks. It would be interesting to try to get a better handle on what is working for these people, whether it's a combination of dietary and/or lifestyle changes, nutritional supplements, or whatever holistic treatment, acupuncture, acupressure, whatever are the various things that could potentially help. What is necessary after that is well designed controlled studies. We need the scientific support to have physicians or other providers advocate these treatments.

A Frustrating Syndrome

JB: That's an eloquent description of where we are. This family of syndromes or disorders, these functional somatic syndromes, pose a challenge to a type of medical practice that is accustomed to tidy diagnoses with tidy molecular treatments.

NA: I'm sure that physicians are very frustrated.

Understanding the Complexity

JB: I appreciate the way you've helped us understand the complexity of this whole situation. It's a great way to lead off our series of discussions on CFS that we will continue during the next few months. I hope we will be able to check in with you as you continue with this work. It sounds as though as you unfold more understanding, we will understand more on the complexity of many other disorders that may have this complex relationship between susceptibility and environment.

NA: I'd be more than happy to talk with you about a number of other studies that we have coming up in terms of family studies and looking more in depth at what's going on in the families that may be relevant to treatment.

Courageous Research

JB: That would be fantastic. I know this research requires courage, because it's not easy to understand all the variables. But it's through that kind of work that I think we will tease apart these complex issues.

Dr. Afari provided a fine introduction, from the perspective of a skilled researcher, for identifying the complexity of these conditions and explaining why, after more than 20 years, we still have no definitive means of diagnosing and treating these syndromes. It may be that we never will have the answer because it involves such a complex array of genotypes, environmental triggers, mediators, and symptoms. We may have to develop a general algorithm that is slightly empirical and more analog than digital.

This is probably one of the best examples of how functional medicine can be used effectively. Medicine based on pathophysiology may not lead to an effective outcome in these complex patients. As the 21st century unfolds, it may prove that the majority of chronic illnesses involve a strong combination of environmental triggers, psychosocial factors, and genetic susceptibilities, and that no single agent will lead to remediation of these chronic syndromes.

From the Lab to the Clinic

Therapeutic Potential for Functional Somatic Syndromes

I want to discuss therapeutic potential for CFS. Cognitive behavioral therapy and graded exercise are two therapies that were the topic of a paper published in the *Journal of the American Medical Association* two years ago.[26] They appeared, in published blinded trials, to have the greatest statistical significance for improving symptoms and function in individuals with CFS. That was compared to some 350 other published studies recommending various medications and other nutritional products. Based on the evidence, graded exercise therapy and cognitive behavioral therapy appeared most valuable.

Short-term Improvement

That does not mean that other interventions are not of some importance. Immune-modulating substances, which at one time were new drugs, were once hailed as the answer to the condition, but they have not proven to be formally effective. These medications, which modified immunological function in many patients, led to short-term improvement although the symptoms reappeared. It seems we need to address some underlying metabolic impact before we can get restitution and long-term management of the clinical symptoms.

Some treatments that have resulted in short-term benefit include low-dose DHEA.[27] More symptom management is needed while one is working on other factors associated with CFS. Long-term DHEA supplementation does not appear to be beneficial, although it may be a useful, adjunctive intervention in an attempt to replete the depleted cortisol levels and the adrenocortical pathway that may have been adversely affected through this process.

If the agent that is triggering the depletion of the cortisol and altering the cortical pathway is not removed, you will be caught in a dog-chasing-its-tail type of problem with diminishing returns. This is only part of the explanation.

L-Carnitine, Coenzyme Q10

The usefulness of therapeutic doses of L-carnitine has been documented. [12]

Carnitine helps improve mitochondrial energy dynamics through the transport of fatty acids across the mitochondrial membrane for use as metabolic fuel for energy dynamics. Again, that is only part of the story, but it certainly should be on the list for consideration.

Next is coenzyme Q10, which has been shown to improve energy, function, sleep, and immune function in CFS patients.[13] Once again, it is not the total answer, but it is part of the story.

Lipoic Acid
Similarly, some small clinical case trials that have been published have shown that doses between 600 and 1000 mg per day of lipoic acid have been useful for improving symptoms associated with CFS.[15] All of these nutrients affect the mitochondria, a fact I find interesting, based on the explanation I gave earlier in this discussion.

The Oxidative Stress Connection
All of these nutrients have a connection to oxidative stress, oxidative injury, protection against mitochondrial function interruption, and energy dynamics. Magnesium is another mineral that plays an important role in metabolic activity associated with energy dynamics through nutrient efflux and waste product elimination.

The B vitamins represent another family of nutrients to consider. Higher doses of riboflavin and thiamin are involved in the activation of flavin mononucleotide and transketolase. We have seen some reports about the effectiveness of the B vitamins in the management of CFS.[28] Again, these are nutrients related to energy.

Essential Fatty Acids
Next are the essential fatty acids. I mentioned the omega 3 fatty acids. A number of reports show that supplementation with omega 3 fatty acids, or an increase in omega 3 fatty acids in the diet, along with lowering the amount of saturated fats in the diet, can be helpful in managing CFS.[16] Doses would be on the order of 2000 mg per day. Most fish oil supplements contain about 35 to 50 percent total omega 3, so you have to increase the dose to approximately 2 to 6 capsules per day of the 1-gram capsules of EPA.

Part of the Picture
Any one of these nutrients by itself does not meet the level of statistical significance. Nor have there been controlled studies that unequivocally identify the value of these substances. I am just providing a sense of the landscape associated with nutritional agents that have been reported in the literature, either as clinical case studies or small clinical controlled trials that have shown some benefit in patients with CFS.

Some detoxification therapies have been used in an attempt to lower the body burden of xenobiotics and endogenous toxic substances. Dr. Scott Rigden was a co-author of an early published study showing some benefit in CFS patients who were put on an appropriate detoxification program.[4] That program helped balance phase 1 and phase 2 cytochrome P450 and conjugase enzyme systems in the liver, suggesting that part of the CFS could be an intoxication or toxicity-related problem.

Botanical Substances
Some preparations that have been claimed to have benefit in CFS patients include astralagus, borage seed

oil, bromelain, comfrey, Echinacea, garlic, *Ginkgo biloba*, ginseng, primrose oil, quercetin, St. John's wort, and Shiitake mushroom extract. Only primrose oil has been evaluated in a controlled study.[13] These botanicals deal with neurochemical immune function and protection of the liver against oxidative injury and improved detoxification.

In this first installment of two issues devoted to functional somatic syndromes, I hope I have provided an overview of this family of disorders that are increasing in prevalence in the Western world. We have discussed the reasons why a single diagnosis is complicated, why we do not understand the etiology (or, probably more appropriately, etiologies), and what questions we still need to ask about how to manage and personalize therapy for patients. This is a great way to apply functional assessment and functional medicine intervention.

We look forward to being with you in September. Thanks so much.

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