September 2003 Issue | Anthony Komaroff, MD Professor of Medicine

http://jeffreybland.com/knowledgebase/september-2003-issue-anthony-komaroff-md-professor-of-medicine/

DOWNLOAD AUDIO |

Welcome to *Functional Medicine Update* for September 2003. This month we continue the two-part series we began last month on chronic fatigue syndrome (CFS), fibromyalgia (FM), and other chronic pain- and fatigue-related dysfunctions. Last month we introduced the basic concepts of CFS and FM, discussed what is known about them, and reviewed the ways we assess and diagnose them. Our August Researcher of the Month, Dr. Niloofar Afari, discussed diagnosis of these conditions by exclusion.

This month we continue our discussion with an internationally recognized leader in the field of infectious disease—Dr. Anthony Komaroff from Harvard Medical School. He will review the history of chronic fatigue syndrome, describe its differential assessment, and discuss some things we can look forward to in the future as we explore this condition more fully.

First, I would like to review some things we learned last month. In a 1994 issue of Delicious! magazine, I wrote an article titled “The Mystery of Chronic Fatigue Syndrome.” 1 In that article I reviewed the work that began in the 1980s when Paul Cheney and Daniel Peterson—physicians at Incline Village, Nevada—treated a number of patients who shared similar symptoms following a serious outbreak of flu that winter. These patients all suffered from an infection similar to a herpes-type virus that produces mononucleosis.

What set the Incline Village patients apart from others, however, was the fact that they did not appear to get better after they recovered from the initial infection. In fact, they continued to have bone-weary fatigue, sleep disturbances, mood swings, lymphadenopathy, and intolerance to exercise. This series of symptoms was not characteristic of normal recovery from flu. As a consequence, Dr. Cheney coined the term “chronic fatigue syndrome” to describe this condition. An ensuing report described similarities between this condition and myalgia encephalitis, or ME, as it was called in England.

CFS History
Looking back over the history of these conditions in the medical literature, people found a number of reports going back to the previous decade. Several individuals asked whether this condition resulted from psychological changes the patients were experiencing, or if psychological changes were occurring as a consequence of somatic changes, in some kind of pathophysiological process. Could it be related to an infectious agent? Research ensued, along with heightened interest that was further fueled by a number of veterans returning from the Gulf War Campaign with a similar constellation of fatigue, and CFS- and FM-related symptoms called “Desert Storm Syndrome.”

After 10 years of looking at the parameters for these conditions, as we learned last month from Dr. Afari, diagnosis for these conditions is best accomplished by exclusion. The clinician first makes sure the patient's fatigue and muscle pain are not related to other diagnosed conditions, such as autoimmune disorders or multiple sclerosis. This diagnosis of exclusion can ultimately lead to an assessment of CFS, FM, or a combination of the two.

Neuro-Endocrine-Immune Involvement

Many people experience a combination of both sets of symptoms. The fact that this condition occurs four times more often in women than in men raised the possibility of an endocrine component to the condition. People began to see the condition as a neuro-endocrine-immune type of disorder, taking it beyond single organ specificity into complex multiple organ symptomatology. It cuts across medical disciplines and introduces the possibility of interrelationships of mechanisms that could account for this broad range of symptoms.

Today, from the literature that has emerged over the past decade, the definition of CFS and FM as a neuro-endocrine-immune-related series of disorders is a reasonable way to approach understanding them. The cause of these immune dysregulations has yet to be discovered. Nor do we yet understand how to restore patients to normal function. As you will discover in this month's FMU discussion, we are beginning to understand these hypotheses a bit better, and models we can test are emerging.

Functional Improvement

At the end of the 1994 Delicious! article, I described a series of patient histories collected by Dr. Scott Rigden, a co-investigator on CFS and a collaborator in the ongoing work at the Metagenics Research Center in Gig Harbor. Dr. Rigden reported on a number of positive results he had observed in seriously disabled CFS patients whose average duration of impairment was over three-and-a-half years.2 Many of these individuals had been unable to participate in their normal occupations. They experienced remarkable recoveries when they became involved in a nutritional support program that focused on improving their neuro-endocrine-immune function.

I was reminded just last week of the reasons why we continue to explore this field. In a single day I had meetings with a number of different people—a breakfast meeting, one at an airport later in the day, and a meeting in the evening far across the country. During each of those meetings, individuals talked to me about their personal experiences with CFS. Each one indicated, much to my surprise, that he or she had engaged in primary therapy leading to improvement in function, and that matched the approach I will describe in this month's FMU.

It is important to emphasize, as a caveat, that this approach is not a panacea. It is not the final answer to CFS and FM. It is a model that appears to provide fairly significant opportunity for improvement in patients who have had long-term disability with CFS. It deserves some consideration as one starts to assemble a treatment program for the management of patients with this symptomatology.

A Fortuitous Meeting

The first of these encounters I had last week was quite unusual. That morning, when she heard my name, the woman preparing breakfast at the B&B where I was staying came up and hugged me. I was quite surprised, since I had never met her before. She said she wanted to thank me personally, that meeting me was such a fortuitous thing because she felt her life had been saved as a consequence of seeing a

physician who was applying what she called “the Jeff Bland approach toward CFS.”

Giving the treatment that name was a gracious act, since I am just the communicator of the work of many others in this field. Her physician was using the integrated approach I will discuss later in this month’s FMU. The woman said she had been unable to work for a number of years, had been seriously disabled, and had been managed by a very well regarded department of rheumatology at the local medical school in North Carolina. She had experienced serious disability for more than five years before starting the functional program. Over the course of a year, the program she was following helped her regain her energy and strength, return to work, and lead a normal life again. That was a remarkable start to my day. Experiences such as those make the work we are doing worthwhile for all of us.

Emerging Understanding of CFS

How did this particular program come about, and how does it relate to the program Dr. Afari talked about last month and that which Dr. Komaroff will speak to this month? We can attribute it, in part, to emerging understanding. A number of studies in 2002 indicated that growth hormone seemed to ease the pain of FM, suggesting low IGF-1 levels occur in this condition, as if the endocrine system is under some kind of an insult.3 This is the hypothalamus-pituitary-adrenal (HPA) axis. There is also evidence that exposures to chemical toxins ranging from pesticides and biocides to heavy metal toxicants like lead, cadmium, or mercury, may be associated with fatigue and pain syndromes.

There is evidence that various types of immune hypersensitizing agents may also contribute to these syndromes. They may not been seen as true autoimmune disorders, but they may be what are called arthralgias. They may be related to immune responsiveness to the environment that somehow activates the reticular system to alter function, producing fatigue and chronic pain at the trigger points—we call this FM. These are all bits of information and observations in search of an explanation. What is the origin of these particular conditions?

Dr. Guy Abraham’s Work on CFS and FM

More than 20 years ago I had the good fortune to meet Dr. Guy Abraham, who was working on the nutritional link to FM. In 1992 he published a paper in the Journal of Nutritional Medicine, titled “Management of Fibromyalgia: Rationale for the Use of Magnesium and Malic Acid.”4 He was looking at the potential that the trigger-point pain components of FM are a consequence of altered biochemical energetics, and that cell physiology is changed because of what we might euphemistically call chronic metabolic poisoning. Poisoning may be a strong word, but it refers to altered metabolic function that leads to less efficient mitochondrial oxidative phosphorylation. Altered organic acid accumulation at the trigger points may lead to proprioreceptor activation that results in the pain of FM.

That would be an occurrence similar to that of a runner who “hits the wall” during a marathon. The difference here, however, is that the “marathon” may be just normal living. The person is unable to effectively metabolize the energy precursors such as glucose, fatty acids, or amino acids into energy and end-product metabolites such as carbon dioxide, water, urea, phosphate, and sulfate. Non-end-product materials such as organic acids can build up lactic acid, which alters intracellular pH, changing the tonicity of muscles and ultimately triggering pain syndromes. That was part of Dr. Abraham’s hypothesis in the early 1990s.

Magnesium and Malic Acid

Dr. Abraham's paper describes intervention with FM patients using high doses of magnesium and a Krebs cycle intermediate, malic acid, in an attempt to feed into the Krebs cycle to promote proper bioenergetics. Dr. Abraham had a good rationale to explain why malic acid might be an important central intermediate. This is consistent with Dr. Linus Pauling's theme in orthomolecular medicine, which is to improve metabolism by providing intermediary metabolites or substrates that are native to human physiology.

Dr. Abraham reported that the use of 300 to 600 mg of magnesium and 1200 to 2400 mg of malate in these FM patients resulted in significant improvement versus placebo. That was an interesting early observation. There was no connection to etiology or speculation at that point. Patients simply seemed to respond favorably.

A Follow-up Study

In 1995, Dr. Abraham wrote a second paper, which was an amplification of his first observations. This paper, which appeared in the Journal of Rheumatology,5 discussed a randomized, placebo-controlled, crossover pilot study. It was a small study, but the results were both interesting and encouraging. Twenty-four sequential patients with primary FM were given 1600 mg of malate and 400 mg of magnesium per day, a much lower dose than reported in the 1992 study, against placebo in a four-week course. And the outcome was positive.

There was significant improvement over placebo, and it appeared to support that something about these Krebs cycle intermediates, magnesium and malic acid, was related to the improvement of FM and fatigue-related symptoms in the patients studied. Once again, no mechanism was identified, but there was some speculation about the potential role of these nutrients in fatigue- and pain-related symptoms of this type.

Studying Cell Bioenergetics

The field evolved significantly during the next eight years. Researchers looked increasingly at specific "energy nutrients" like malic acid or magnesium as important minerals in a number of enzymatic reactions. They sought to determine how these minerals could influence conditions that may be associated with low bioenergetics, i.e., fatigue- and pain-related symptoms. A body of literature emerged as a number of clinicians and researchers began to evaluate FM associated with energy-deficit disorder at the metabolic or cellular level.6 That raises questions about the location of bioenergetics in cells.

We know the mitochondrion is the energy powerhouse of the cell, the organelle responsible for processing most of the oxygen in the cell and oxidizing substrate. The ultimate result is the production of a high-energy cofactor, ATP, which then becomes the energy fuel of the cell, tissue, organ, or organ system of the body. The natural consequence of this evolving story was to ask if there could be a mitochondrial connection to CFS and FM. If we could understand that, perhaps we could intervene selectively.

Dr. Martin Pall's Work on CFS

The investigator who took up this challenge is Dr. Martin Pall, our FMU Researcher of the Month in March, 1999. At the time, hewas advancing his hypothesis about the bioenergetics and mitochondrial dysfunction associated with CFS and FM. He has continued with this research at the School of Molecular Biosciences at Washington State University, where he is a faculty member in biochemistry. He has focused on this question in his research. Those of you who want to follow up on Dr. Pall can listen to our

interview with him on the molecular relationship of mitochondrial function to fatigue-related syndromes.

Dr. Pall recently published some data that defines the relationship he was talking about.7 I will quickly give you the concept, and we will discuss at greater length the way it translates into clinical protocol.

The Feed-Forward Cycle of Immune Activation

The concept is that CFS, FM, and possibly other fatigue-related conditions may be related to activation of the immune system that leads to what we call a feed-forward cycle of self-replicating immune activation, inducing a functional change in the nervous and endocrine systems. This change results in an altered neuro-endocrine-immune state of physiological function that later translates into depletion of ATP and an energy-deficit disorder. This immune activation can come from many sources, including viruses, parasites, and chemical exposures. Even traumatic stress could be considered toxic to the immune system.

By altering the HPA axis, one can change immune function, with a subsequent effect on the endocrine system. The body moves from a homeostasis of health to one of dysfunction. The viral/bacterial infections may even relate to chronic infections in the gut. The concept of low-level gut dysfunction is another part of the total load Dr. Pall talks about that can contribute to immunological activation. Physical and emotional trauma, along with chemical and other toxic exposures, can exert influence through a variety of well-defined mechanisms. Many of these references are listed in Dr. Pall's papers.8 ,9

Peroxynitrite Production

These mechanisms ultimately trigger the production of immune-inducible nitric oxide (NO) synthase activity and release of NO and superoxide, which combine to produce a highly reactive nitrosating agent called peroxynitrite. Peroxynitrite may be the central feature in the replication and perpetuation of the symptoms through feed-forward cycles in the immune and endocrine systems that continue to trigger the loss of mitochondrial bioenergetics and reduce energy effectiveness in cells.

The cells and tissues most influenced by this process are the oxygen-rich, post-mitotic tissues, including those in the nervous system, brain, cardiovascular system, and muscles. Symptoms of CFS and FM may be concentrated in these tissues when uncoupling of these energy centers occurs, inducing altered mitochondrial function or injury. This feed-forward cycle depends on the complex interrelationship between the environment, genetic susceptibilities, and various exposures that perpetuate superoxide and NO overproduction, leading to peroxynitrite, and engaging in what Dr. Pall calls a "self-sustaining vicious cycle" that leads to a sustained series of symptoms.

Seeking a Clinical Definition

This is a good hypothesis. Everything I have said, although supported at least theoretically by observations in the literature, does not lead to an unequivocal clinical definition for which the mechanism is known. This information is still speculative and hypothetical. Interestingly, it can lead into ways of evaluating the patient and providing adjunctive support that can be of potential advantage in treating some of the contributors to CFS and FM.

Dr. Pall discusses 12 different observations that support this theory of a perpetuating, sustaining vicious cycle. I will quickly review those 12 areas.

Dr. Pall's 12 Observations

1. The levels of neopterin, a marker for the induction of the inducible nitric oxide synthase, are reported to be elevated in CFS. As noted by Dr. Pall, some studies suggest that serum neopterin levels are often elevated in CFS. Neopterin is produced at a higher level when NO synthase is activated, resulting in immune-inducible production of NO. It is an indirect marker of immunological activation and increased NO output in the immune system. It does appear to be elevated in CFS.

2. Mitochondria are reported to be dysfunctional in CFS, and mitochondria are known to be attacked by peroxynitrite and by nitric oxide. We know that peroxynitrite is a powerful mitochondrial uncoupler. Elevated production of peroxynitrite can induce mitochondrial injury and reduce mitochondrial effectiveness. Mitochondrial function has been found to be lowered in many CFS patients.

3. Both cis-aconitate and succinate levels are reported to be elevated in CFS, and the enzymes that metabolize these two compounds are known to be inactivated by peroxynitrite. That seems to relate to the observation that Krebs cycle intermediates from specific enzymes are elevated in CFS, which may be a consequence of inhibition of enzymes required for their metabolism. Those enzymes are known, at least in vitro, to be sensitive to peroxynitrite levels.

4. The four inflammatory cytokines implicated have been reported to be elevated in 10 different studies of CFS. This suggests that Th1, or thymus-dependent 1, cytokines, such as interleukin-1, interleukin-2, tumor necrosis factor-a , and interferon y-c , when elevated, may lead to immunological activation. These are also associated with increased production of immune-inducible NO and peroxynitrite. Again, the model seems to grow with some validity from these observations.

5. These same inflammatory cytokines have been reported to induce fatigue when injected into humans.

6. In an animal (mouse) model of CFS, "fatigue" is induced by a bacterial extract that can induce both the inflammatory cytokines and also the inducible nitric oxide synthase. That is, if you administer something like lipopolysaccharides (SLPs) from gram-negative bacterial wall debris to a specific strain of mice, you can induce mitochondrial dysfunction, resulting in myopathic conditions and a fatigue syndrome. This is not a human model, but it is related to our discussion.

7. Polyunsaturated fatty acid pools are reported to be depleted in CFS, and such polyunsaturated fatty acids are known to be oxidized by oxidants such as peroxynitrite. Polyunsaturated fatty acids (particularly omega 3 fatty acids—specifically docosahexaenoic acid (DHA), the 22-carbon atom 6 unsaturate—are observably low in many CFS patients as indicated by plasma fatty acid or red-cell fatty acid analysis. DHA, the principal fatty acid in mitochondrial membranes, is easily oxidized, demonstrating a key route by which peroxynitrite (and other oxidants) injure mitochondria.

8. Anecdotal evidence has suggested that antioxidants such as coenzyme Q-10, flavonoids and glutathione precursors (such as N-acetyl-cysteine)may be useful in CFS treatment, consistent with a role for an oxidant such as peroxynitrite. Although this is anecdotal and observational, it also connects to what is known about mitochondrial inborn errors of metabolism. Some of these nutrients given at high doses can facilitate improvement in Krebs cycle or mitochondrial function.

9. Women are reported to produce more nitric oxide than men. This effect is possibly a consequence of endocrine uniqueness and may explain why women develop more autoimmune disorders, such as lupus

and rheumatoid arthritis. We also see a lot more CFS and FM in women. As Dr. Pall mentions, this may explainthe gender bias seen in CFS. A similar gender bias is seen in autoimmune diseases characterized by excessive peroxynitrite (i.e., lupus, rheumatoid arthritis).

10. Cases of CFS are associated with high levels of deleted mitochondrial DNA, suggesting, but not proving, that that mitochondrial dysfunction can produce the symptoms of CFS. This may be related to the susceptibility of mitochondrial DNA to such injuries. Collection of those injuries in mitochondrial DNA may also contribute to other low-energy deficit-related disorders.

11. Biochemical similarities such as âC“ depletion of glutamine and cystine pools have been reported in CFS and several diseases characterized by elevated peroxynitrite levels, suggesting a similar biochemical basis for all of these conditions via the depletion of specific oxidatively sensitive amino acids.

12. Because peroxynitrite is a potent oxidant, this theory predicts that oxidative stress will be elevated in CFS. There was no direct evidence for this when the theory was published, but three subsequent papers have reported substantial evidence for such oxidative stress in CFS. These results may, therefore, be considered to confirm important predictions of the theory, although the authors were unaware of this theory when they initiated these studies. If true, antioxidants may play a role and the oxidative/reductive machinery of the cell may be important in signaling certain phenotypic outcomes to the cell. This can be described as “phenomic medicine.” If we think about genomic medicine, proteomic medicine, and metabolomic medicine, those all ultimately translate into phenomic medicine. “Phenomic” refers to the outcome in the patient (i.e., phenotype). What clinical signs and symptoms does the patient exhibit in relation to his or her combination of genetic susceptibilities, their translation to active protein, the way that the process influences metabolism, and how the symptoms, signs, and the function of a person develop?
I think Dr. Pall is onto something very interesting. We have raised more questions than we have answered, but this provides an operational hypothesis that connects a number of observations catalogued in this complex family of disorders. They are genotypically related to specific environmental exposures that give rise to the outcome of chronic functional changes.

Let me fill in the gaps with a few observations about the mitochondrial connection. This information does not constitute proof, but it provides supporting information for consideration in this model.

Aging and Collective Injury
Some good evidence indicates that as one ages, post-mitotic cells, such as muscle cells, collect injury, which can be seen particularly in altered mitochondrial DNA deletion mutations. A hypothesis paper, titled “Accumulation of Mitochondrial DNA Mutations in Ageing, Cancer, and Mitochondrial Disease: Is there a Common Mechanism?” appeared in the Lancet. 10

The authors of this paper, which provides a good overview of this concept, suggest the accumulation of cells that contain high levels of mutated mitochondrial DNA may be an inevitable result of mechanisms associated with oxidative injury and may be part of the natural aging process. But in accelerated function, they may contribute to age-related dysfunctions often first seen as energy-deficit disorders that can have pain and fatigue as symptoms.

Effects of Proinflammatory Mediators

This article follows from other papers describing cell and animal model systems. An example is an article titled “Mitochondrial DNA Mutation Associated with Aging and Degenerative Disease,” which appeared in the Annals of the New York Academy of Sciences.11 This paper goes into much greater detail about mitochondrial cytopathies and how they can be induced by exposure to various oxidants or substances that upregulate the immune system to increase the production of proinflammatory mediators.

These proinflammatory mediators include cytokines, which engage in signal transduction that alters cellular cycling and may result in an increased level of nuclear factor Kappa B, which is associated with altered mitochondrial function, leading to cellular suicide, or apoptosis. This is a loss of post-mitotic tissue (such as neurons) over time that could lead to dementia, cognitive impairment, or loss of cardiac or muscle reserve. These are examples of conditions that could contribute to cellular “pruning” at an advanced or accelerated rate, which could lead to injuries associated with aging and degenerative disease.

This model that seems to be emerging in the literature has functional considerations that lead to energy depletion. In fact, that is an interesting subtitle of the paper I am describing—the functional considerations for energy-depleted cells.

Inducing Increased Mitochondrial ATP Production

The authors of another paper from the New York Academy of Sciences, published in 1998 and titled “Mitochondrial Decay in Aging,” ask why, if that is so, we continue to support proper energy economy in conditions in which mitochondrial function is being lost.12 In this case, acetyl L-carnitine was given to improve fatty acid transport across the mitochondrial membrane and to improve bioenergetics. The investigators were able to demonstrate increased mitochondrial ATP production in a cell model system. When we interviewed Dr. Bruce Ames in FMU in November 2000, he discussed acetyl L-carnitine, N-acetyl-cysteine, vitamin E, and coenzyme Q10. He has been studying these nutrients, which appear to improve mitochondrial function, reduce mitochondrial injury, and improve oxidative phosphorylation.

Mitochondrial Deletion Mutations

In another study, rat muscle fibers appeared to exhibit mitochondrial DNA deletion mutations. These were co-localized with electron transport system abnormalities, muscle fiber atrophy, muscle fiber splitting, and oxidative damage that is ultimately seen as sarcopenia. This paper appeared in the journal FASEB.13 Loss of muscle mass, or sarcopenia, may be related, in part, to mitochondrial energy deficits and cellular apoptosis of the sarcomere (muscle cell). It may be induced by immunological upregulation associated with viral infections, toxic exposures, toxic thoughts, and other nervous and immune system activities related to HPA axis activation.

We are starting to see supporting information for this model. Age-associated alterations of the mitochondrial genome occur, and deletion mutations do accumulate. It is not just what you were born with. Certain unfortunate people are born with constitutive mitochondrial mutational illness like Kearn-Sayre syndrome and Leber’s optic neuropathy, but we are concerned with those individuals who collect increasing injury to their mitochondria over life and time.

Compensating for Lost Mitochondria

Is it possible to get these mitochondria back? The answer is no. Once these deletion mutations occur, effective function of those specific mitochondria is lost. But remember that the mitochondria that are still healthy, the undamaged mitochondria, can still replicate in the absence of cellular replication. They have

their own genomic material. There can be a compensatory effect of the functionally intact mitochondria if they receive the right substances. This can be accomplished by removing the precipitating triggers and improving their function by "feeding" them correctly with appropriate nutrients for proper mitochondrial function. This also leads to lowering oxidant exposures by shifting the immunological threshold and restoring redox balance with glutathione in its reduced form versus its oxidized form.

There should be about 100 times more reduced glutathione than oxidized glutathione in the cell for the mitochondria. Redox control has a lot to do with how the cell performs. It is not just giving more supplements such as vitamin E, coenzyme Q10, lipoic acid, and N-acetyl-carnitine to the patient. We also need to reduce the precipitating factors that increase oxidative injury. What is needed is a balance of these factors with rebuilding of mitochondrial membrane function by supplementation with the appropriate essential fatty acids, such as those of the omega 3 family—EPA and DHA.

Mitochondrial oxidative stress does play a role in aging. CFS and FM, with their cognitive, immune, and muscular dysfunctions, may be associated with conditions of accelerated biological aging. A paper in Free Radical Biology and Medicine discusses the role of mitochondrial oxidative stress in age-related phenomena and how mitochondria respiratory chain disorders can translate into fatigue and pain syndromes.[xiv] This was also the subject of a review article in The New England Journal of Medicine, titled “Mitochondrial Respiratory-Chain Diseases.”15

INTERVIEW TRANSCRIPT

Anthony Komaroff, MD
Professor of Medicine
Harvard Medical School
Editor-in-Chief and Publisher
Harvard Medical Publications Division
10 Shattuck Street, Suite 602
Boston, MA 02115

JB: It is time for our Researcher of the Month interview. We have been focusing on chronic fatigue syndrome (CFS), its etiology, and its relationship to clinical medicine. In that regard, there is no better person we could have as our guest today than Dr. Anthony Komaroff. Those of you who have followed the literature on CFS will know he is one of the most prominent investigators in this area.

Dr. Komaroff received his medical degree at the University of Washington School of Medicine in Seattle. He has been at Harvard Medical School for many years as a professor of medicine. He is also editor-in-chief and publisher at the Harvard Health Publications Division of Harvard Medical School. He has been a primary contributor in the CFS area for the last 30 years.

CFS Background
Welcome to FMU, Dr. Komaroff. Let’s start off by having you give us a brief history of the emergence of CFS onto the radar screen over the last 25 years.

AK: I think it may have re-emerged, because illnesses very much like CFS have been described in the medical literature going back hundreds of years. There has been a waxing and waning of interest. The

latest wave of interest began in the mid-1980s when, for the first time, people tried to link specific infectious agents to the illness and thought they might have found evidence that the Epstein-Barr virus was involved in creating the illness. The evidence since that time implicating the Epstein-Barr virus has weakened considerably, although there are a handful of cases in which that virus may, in fact, have triggered the illness.

It was with the resurgence of interest in the 1980s that the latest wave began, and this one has led to many more studies by many more research groups around the world, and many more publications than was true of the previous episodes of interest in this illness.

Differentiating CFS

JB: In looking at earlier publications on post-viral fatigue syndrome, reported out of Incline Village back in the early 1980s, there has been a lot of speculation that we are just looking at variant forms of depression or autoimmune disorders like multiple sclerosis (MS). How does one differentiate this condition from pathology-based fatigue disorders?

AK: First of all, depression is a common cause of the complaint of fatigue. In fact, depression is almost surely a much more common cause of fatigue than CFS is. Various autoimmune disorders also frequently manifest with fatigue as a cardinal symptom. In fact, many people with relapsing, remitting MS really don't have paralysis, blindness, or focal neurologic deficiencies as their main kind of suffering. The main suffering in their illness is a debilitating chronic fatigue. The same is true of lupus, rheumatoid arthritis, and of many, if not all, patients with thyroiditis and a variety of other autoimmune disorders.

On the other hand, CFS, by definition, can't be diagnosed when any of these other disorders is diagnosed. In CFS, for instance, there are not the multiple episodes in both central nervous system (CNS) space and time that characterize MS, let alone the several laboratory manifestations of MS that are not seen in CFS. They all share the symptom of fatigue, but they have different manifestations.

Case Definition of CFS

JB: In 1996, you were the principal author of a paper published in the American Journal of Medicine that described a working case definition of CFS.16 It might be useful if you were to share that definition with us.

AK: It's a complex case definition. The primary features include a truly debilitating fatigue that is interfering with a person's life or work, and has been going on for at least six months, is not relieved by rest, and is not an experience they have had at some point earlier in their lives. After all of that, they also must have four of eight different chronic symptom complexes. That includes sore throat, swollen glands, sleep disorders in which they awaken unrested, something called post-exertional malaise where, following physical exertion, there is a flair-up of many of the symptoms of the illness, apparently triggered by physical exertion, not while people are exerting themselves, but the next day typically. A flare-up of low-grade fevers, swollen glands, sore throat, difficulty with cognition, muscle pain, joint pain—these are all ancillary chronic symptoms that must be present along with this at least six-months-long, chronic debilitating state of fatigue.

Epidemiological CFS Information

JB: When we look at those case definitions, it would seem, on a daily basis, that physicians see new cases of CFS that fulfill those criteria. Yet some doctors report apparently episodic outbreaks of CFS. The

illness seems to flare up in a patient population and then decline, resembling an infectious disorder. What is your opinion about the occurrence of CFS?

AK: There are no good epidemiological studies that address the question of whether this illness is more or less common today than it was five or ten years ago. Most people who, like me, have taken a special interest in the illness, are in the worst position to make a judgment about whether the instance of the disease is declining or rising, because we're seeing a very skewed and selected group of people referred to us.

There is no doubt that a large number of apparent epidemics of this illness have been described in the medical literature going back to the early 20th century. There is no doubt that this illness can occur in outbursts within geographic areas. But there are also many cases that occur endemically, not epidemically, that are sporadic and not apparently tied to an epidemic, that also occur in the background population. I think we finally have some pretty good epidemiological data on how prevalent this illness is among adults in the United States. That is, about 4 out of 1000 women and 1 to 2 out of 1000 men have this illness. Whether it is increasing or decreasing in frequency or incidence is much less clear.

Neuro-Endocrine-Immune Involvement in CFS

JB: In 1996 and 1997, you were a co-author of three published papers. One was related to cognitive deficits in patients with CFS; 17 another related to immunoglobulin subclass levels in CFS;18 and a third looked at insulin-like growth factor 1 levels in patients with CFS.19 I thought they suggested a neuro-endocrine-immune complex associated with this condition. Is that fair to say, in terms of organicity?

AK: Yes, I think it's fair to say. A wealth of peer-reviewed, well-controlled studies now show that a lot is going on in the CNS and the autonomic nervous system (ANS). Some of what is going on in the brain does involve neuroendocrine abnormalities. Various tests of the hypothalamic/pituitary/adrenal (HPA) axis, HPA prolactin production, and HPA growth hormone production, are aberrant. Objectively, they are not normal, and they objectively are different from the same kinds of tests done in patients with major depression.

Many imaging studies using MRI, SPECT, and PET show objective abnormalities in the brains of patients with CFS, and a wealth of literature shows disturbed autonomic function—impaired control of blood pressure and pulse rate with changes in posture. An abundance of objective, biological evidence indicates something is wrong beyond the imagining of the patient—something that can be measured and cannot be fabricated—and it involves the brain. But no unifying synthesis explains why all of these CNS and autonomic abnormalities are occurring. Nothing ties them together into a very satisfying explanation of the pathogenesis of the illness.

Which Changes Came First in CFS?

JB: You have also looked at various inflammatory cytokines and mediators of the thymus-dependent 1 (Th1) and thymus-dependent 2 (Th2) lymphocyte system. The evidence seems to suggest immunological upregulation in certain areas of the immune system, together with endocrine and neurological changes. It makes one wonder, which came first, the immunological insult or the biochemical disturbance? Did an immunological insult create a CNS biochemical disturbance, or is it an interrelationship of all of them together?

AK: That's a very good question. Even those of us familiar with this literature cannot give you a confident answer. You're right, though. I would agree, and many others would agree, that in addition to the wealth of evidence that there are CNS and ANS changes, there is also a lot of published evidence that the immune system is in a chronic state of activation. As you say, a variety of cytokines are produced in higher amounts than would be normally true at basal state. And circulating cells that bear on their surface markers of activation are more frequent in patients with CFS than in a variety of healthy or depressed, controls, those with several other autoimmune diseases.

Whether and how this state of chronic immune activation is linked to what's going on in the brain is speculative. To me, there are two attractive hypotheses, both of which are difficult to prove. The first is that a state of peripheral activation of the immune system, caused, for example, by a chronic infectious process, could lead to the production of immunologic mediators like cytokines that travel in the bloodstream. Some of these are able to breach the blood/brain barrier, get into the CNS, and affect neurotransmitters and the things that go on in the brain that cause it to perceive the state of fatigue, the state of pain, and other symptoms of this illness. That's one model.

The other model is that a chronic infectious process directly affects the brain. This process is chronically eliciting a response from immune cells in the brain, not traversing the blood/brain barrier, but immune system cells that reside in the brain and generate the immune response of the brain. That's another attractive hypothesis, but you'd need consistent, reproducible evidence from multiple laboratories of one or more infectious agents that are in the CNS chronically and shouldn't be.

That's a hard kind of evidence to get in a living human being because you're not going to biopsy the brain. The spinal fluid is not a terribly sensitive marker of CNS infection, although it's not bad. There's no animal model in which the animal can tell you it is fatigued. You might hear that from a parrot, but you wouldn't necessarily believe it. It's a tough disease to study, especially the part of it that involves the brain, because there is no animal model whose brain you can examine directly, and because it's very hard to get useful information indirectly from the human brain.

Two Hypotheses

JB: I'm intrigued with those two hypotheses. When you look at some of the supposed multifactorial triggers associated with CFS, maybe we can't say they are specific etiological agents. You have written an article relating to raised IgE levels, however, perhaps suggesting an allergy component.20 There is the infectious component. There is an endocrine disrupter component. You and others have written about a stress component. There may be a toxin component, whatever that means. It appears in looking at all these exogenous agents that, somehow, it must involve either one or both of those systems you just described in your two hypotheses.

AK: I think that's right; at least, I think that's a very attractive hypothesis. As I said, there's lots of evidence that both the CNS and the immune system are involved. But how they talk to each other and which comes first—which is the chicken and which is the egg—is a tougher thing to have a confident judgment about.

The Mitochondrial Pathophysiology Connection

JB: The meeting of the Federation of Experimental Biology last year featured a presentation connecting mitochondrial deletion mutations with something we call chronic fatigue, which is progressive. They

talked about feed-forward cycles of nitric oxide (NO), peroxynitrite with immune upregulation, subsequent centrally mediated effects, and an accumulation of mitochondrial pathophysiology over time. From your experience, could you speculate on the plausibility of this model?

AK: I agree with you, Dr. Bland. In the last couple of years, a group of articles all seem to be saying there is a state of increased oxidative stress in CFS that also begged the question of what's causing that state of increased oxidative stress. I think it's a very plausible hypothesis.

It may seem a glib simplification to say that a lack of energy on the part of the organism might be simply explained by impairment of energy metabolism within each cell of the organism, but it doesn't seem like a glib simplification to me. It sounds like a very plausible possibility. That idea has been bruited about for a decade or more, but there is finally starting to be a decent literature that seems to support it. I'm not biochemist enough to be able confidently to evaluate that literature. I am impressed that a large number of laboratories from different parts of the world are converging on this as a possible explanation, at least a partial explanation, of what may be causing the symptoms of this illness.

Clinical Options

JB: Given the complexity you've shared with us, and knowing it appears to be diagnosis by exclusion, how do responsible physicians move forward in assisting their patients? What range of options is available?

AK: The complaint of fatigue, and even the complaint of chronic fatigue, which means patients have not had the normal amount of energy for at least the last six months on a regular, chronic basis, is pretty common in any medical practice. CFS accounts for only a very small fraction of people with that complaint. I think the clinician's first responsibility is to look for the more common causes of that complaint, and depression is certainly one of them.

Another one you don't find in the textbooks, but which I think is a very real issue, is overwork. We in our society, as we enter the 21st century, are working longer hours and harder, more intensely, than was true 40 years ago. Interestingly, that is not true of the other developed nations of the world—Europe, Scandinavia, and in Asia—with which we are locked in a global economic competition. We in the United States are pushing ourselves harder. I see an awful lot of people who come to me with the complaint of chronic fatigue where I don't think they have CFS; they don't have depression; they don't have any autoimmune disease; in fact, they don't have any diagnosable disease. They are simply pushing themselves beyond the limits that their body can tolerate. When and if they slow down (I cannot always convince them), many of them have a great improvement in their state of fatigue. That's not to be minimized. It's plain old overwork as a cause of the complaint of chronic fatigue.

Diagnosing CFS

Literally hundreds of diseases can cause the symptom of fatigue. You do what a good clinician does—take a general review of systems, ask about other symptoms besides fatigue. You try to get a sense of whether you might be dealing with congestive heart failure (CHF), with sleep apnea, with chronic renal failure, with chronic hepatic disease, with any of a huge number of diseases that can cause the condition of chronic fatigue. But at the end of the day, if you can't find evidence for any of those things, and the patient meets the case definition of the Centers for Disease Control for CFS, then I think you can tell them they have CFS.

You explain that doctors don't know what causes it, but that there's growing evidence that it's a real illness. If any friends, family, or other doctors have implied to the patient that he or she is just imagining or even faking this condition, that's not likely to be true. Unfortunately, there are very few treatments that have been studied scientifically and proven to be beneficial, but there are some things we can try. I think explaining that doctors recognize the condition, that they are not alone, that doctors are studying it, that there's good evidence that patients are not "faking it," and that we're going to try to find something to help them, is therapeutic for most people.

Complex Disorders/Complex Treatments

JB: We seem to be developing more and more disorders in this overworked population that 40 years ago Hans Selye would have called "stress-related symptoms." You recently discussed the placebo effect in some of your work and writing. 21 Where are we going in medicine with a diagnosis and treatment under the DRGs with these complex, multi-organ, psychosocial conditions? It seems paradoxical that there will not be a single pill for a single diagnosis in these conditions.

AK: I think that's right. Like possibly every illness except a rock dropping off a building onto your head, illness is function both of nature and nurture, of our genes and our environment, and the environment we've created for ourselves in the late 20th and early 21st century is one that challenges our genes. Some people are going to be more vulnerable to that environment than others.

A paper published in Science two weeks ago discussed a gene for depression that could be shown to make people who had certain life experiences fall into an episode of major depression.22 Other people with the same constellation of major life experiences, on the other hand, did not fall into depression. It was a combination of a gene that made you vulnerable and an environment that pushed you over, if you were vulnerable. My guess is that there are many of what Selye might have called stress-related illnesses or symptom complexes at play in our society today.

Scientific, Reductionist Progress

Having said that, I think science, in a reductionist way, is progressively going to figure them out and determine how better to diagnose and treat whatever the objective change in our body is that leads to that complex of symptoms. It's fine to say if you are in an environment that stresses you in certain ways, you're going to experience these symptoms. For me it is hard to imagine there's not a physical, chemical link between that environment and the symptom you feel.

I think we're going to find such links. We're going to find subtle perturbations of neurochemistry that explain many of these symptoms and symptom complexes. Once we figure that out, we will be able to offer more precise and effective interventions, chemical interventions, while simultaneously working on the human-to-human kinds of treatments that are a part of medical practice and the treatment of every illness that we are challenged by.

Exploring the Links

JB: When we started the Institute for Functional Medicine 11 years ago, we wanted to provide a forum and an incubator to explore those very questions across disciplines. I don't think you could have said that any more succinctly. I thank you for your work, for your insights, and for spending time with us today.

AK: It was my pleasure, Dr. Bland. Thank you for inviting me

From the Lab to the Clinic

I thank Dr. Komaroff for his insightful comments and for improving our understanding of chronic fatigue syndrome. I emphasize that neither Dr. Komaroff nor anyone else necessarily shares the speculations I made on Side 1 of this month's *FMU*. Those comments represent a collection of information from the literature, from my personal experience, and from collaborative work with other clinicians in applying some of these concepts in clinical practice.

Poor Tolerance to Exercise in CFS

Going from theory to clinical practice, we all want to know what we can do with this information. Poor tolerance to exercise that was previously well tolerated is one of the hallmarks of CFS. A few years ago *The New England Journal of Medicine* published a paper titled "Exercise Intolerance Due to Mutations in the Cytochrome *b* Gene of Mitochondrial DNA."[23] This article featured a case history of five patients, none of whom had family histories of neuromuscular disorders.

Upon examination of mitochondrial DNA by muscle biopsy, pathogenic mutations were revealed in at least 50 percent of the mitochondrial DNA. That suggested an induced factor had occurred in each patient's adult life, possibly by exposure to a biocide that created injury to mitochondria, resulting in an onset of fatigue.

In a follow-up letter to the editor on this article, a number of individuals shared their experiences with adults experiencing rapid-onset fatigue that may also have been associated with altered mitochondrial function.[24]

Factors Affecting Changes in Mitochondrial DNA

Changes in mitochondrial DNA occur as a consequence of exposure to various nucleosides in drugs used in the treatment of HIV infection. These changes may be associated with fatigue-related symptoms experienced by patients who use these medications. These drugs alter mitochondrial function.[25]

The interrelationship of altered hypothalamus and pituitary function and the general endocrine/nervous/immune relationship to CFS and FM suggest that many of these conditions may have a connection to thyroid dysfunction, as well. These patients appear to be hypothyroid. On examination, however, their thyroid dysfunction appears to be related more to the effect of T3, not necessarily low T4 levels. T3 plays an important role in activating mitochondrial function. This again suggests a mitochondrial/endocrine connection. I am now referring to one of many papers on this topic.[26]

Nutritional Modulation of Mitochondrial Function

What about nutrients that modulate mitochondrial function? I have mentioned the N-acetyl-carnitine, N-acetyl-cysteine, glutathione, coenzyme Q10, vitamin E, and lipoic acid family of nutrients, the selenium-activating glutathione peroxidase, and riboflavin vitamin B2 necessary for activating the production of FAD, which is important for glutathione reductase activity. All of these nutrients may play important roles, as well as the magnesium/malate connection we talked about in Dr. Abraham's work from a number of years ago.

A 1989 review in the *Annual Review of Nutrition,* titled "Nutrient Supply and Mitochondrial

Function," [27] discussed nutrient effects on mitochondria, and today we still find their observations useful as we consider the management of children with inborn errors of mitochondrial DNA and serious encephalopathies and myopathies.This is the outlying extreme of these conditions, and treatments are generally empirical and not quantified.

We also discussed rebuilding mitochondrial membranes through supplementation with DHA, which is rapidly incorporated into brain and mitochondrial membranes.[28] Repletion of omega 3 fatty acids, therefore, is undoubtedly important as part of a nutritional support program.

Developing a Program to Support Patients

If we take all of this information and distill it down into a patient support program, how would it look? We must first identify in the patient precipitating factors that may be constantly activating the immunological system. We can examine a variety of factors, including food allergies, toxic exposures, and psychogenic or psychological stress. We can look at areas of activity that may cause overactivity of the immune-activating Th1-dominant components of the immune system. A comprehensive immune evaluation would be an important first step.

Once we have identified these factors, we can work to lower the precipitating triggers as much as possible. It is sometimes impossible to change the entire life of a patient, but we can clean up the environment and lower the patient's psychological stress, which means rest and relaxation, meditation, and graded exercise therapy. Getting the patient into a program to lower food antigens and allergens would be important if there is an underlying food antigen component.

Restoring Healthy Intestinal Function

That also relates to the microbial health of gut flora, making sure there are friendly bacteria in the gut. A number of reports suggest that reinoculation and rebalancing of gut microflora may be an important contributor to improving immunological function. That would be the use of things like *Lactobacillus acidophilis* or *Bifidobacteria* supplementation and prebiotics—fructooligosaccharides or fructan-rich dietary components that would help feed the proliferation of friendly bacteria that have trophic and immune-stabilizing effects.

In looking at all these immune-related factors, we should remember that about 60 percent of the immune system is clustered around the gut-associated lymphoid tissue (GALT). Looking at gut immunological function should be part of the overall review.

Lowering Peroxynitrite, Supporting Mitochondria

Next, we should work to lower the NO immune-induced activation by reducing immunological triggers and getting antioxidants to lower the production of peroxynitrite. This would include traditional antioxidants—vitamin E, vitamin C, and various flavonoids. There is the mitochondrial resuscitation issue, making sure the mitochondria are being properly supported with the substances necessary for protection of the electron transport chain, the factor 1 through factor 5 complex and through mitochondrial inter-membrane protection. This would include lipoic acid, coenzyme Q10, and tocopherol (perhaps even *gamma* tocopherol, part of the natural mixture of vitamin E that may be more active in quenching NO and peroxynitrite). Vitamin C, N-acetyl-cysteine, and N-acetyl-carnitine all seem to be implicated as important nutrients to improve mitochondrial function when under oxidative stress.

Next, we should consider EPA/DHA omega 3 fatty acid supplementation. We must remember that we do not want to be adding a lot of EPA and DHA, which are readily oxidized, until we cool off some of the oxidative storm. We can accomplish this by balancing the redox potential of the cell and following lipid peroxides in the urine or serum and 8-hydroxydeoxyguanosine (8OHdG) levels to make sure we are not feeding a combustible fuel in the form of highly unsaturated fatty acids. These would probably be added later in the therapy after nutritional support has reduced the triggering factors for immunological activation.

Restoring Proper Bioenergetics

The next part of the program would be to consider agents engaged in restoring proper bioenergetics. That is where graded exercise therapy becomes important. We must remember that oxygen can be a limiting nutrient. Proper delivery of oxygen to tissues can actually help improve redox capacity of cells.

Behavior and cognitive therapy is another factor useful in managing symptoms in CFS patients. Behavior and cognitive therapy, graded exercise therapy, nutritional support, lowering environmental triggers, gut restoration—this would be a good beginning to an adjunctive program to support other agents being used.

Some people call this environmental detoxification. I prefer to call this a program based on mitochondrial energy function and nutrient and environmental support for proper function.

I hope this discussion has been helpful in looking at CFS and FM in 2003, knowing that these are disorders of the 21st century. I look forward to talking to you in October.

Bibliography

1 Bland JS. The mystery of chronic fatigue syndrome. Delicious!. 1994.

2 Rigden S, Barrager E, Bland JS. Evaluation of the effect of a modified entero-hepatic resuscitation program in chronic fatigue syndrome patients. J Advancement Med. 1998;11(4):247-262.

3 Moyer P. Growth hormone eases fibromyalgia pain. WebMDHealth. June 27, 2002.

4 Abraham GE, Flechas JD. Management of fibromyalgia: rationale for the use of magnesium and malic acid. J Nutr Med. 1992;3:49-59.

5 Russell IJ, Michalek JE, Flechas JD, Abraham GE. Treatment of fibromyalgia syndrome with Super Malic®: a randomized, double blind, placebo controlled, crossover pilot study. J Rheumatol. 1995;22:953-958

6 Hyams I. Fibromyalgia associated with energy metabolic deficiency syndrome. www.ukfibromyalgia.com/nutrition/emds.html

7 http://molecular.biosciences.wsu.edu.Faculty/pall/pall_cfs.htm

8 Pall ML. Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite. Med Hypotheses.

2001;57(2):139-145.

9 Pall ML. MNDA sensitization and stimulation by peroxynitrite, nitric oxide, and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity. FASEB J. 2002;16:1407-1417.

10 Chinnery PF, Samuels DC, Elson J, Turnbull DM. Accumulation of mitochondrial DNA mutations in ageing, cancer, and mitochondrial disease: is there a common mechanism?" Lancet. 2002;360:1323-1325.

11 Nagley P, Mackay IR, Baumer A, et al. Mitochondrial DNA mutation associated with aging and degenerative disease. Ann NY Acad Sci. 1992;26:673-692.

12 Hagen TM, Wehr CM, Ames BN. Mitochondrial decay in aging. Ann NY Acad Sci. 1998;854:214-223.

13 Wanagat J, Cao Z, Pathare P, Aiken JM. Mitochondrial DNA deletion mutations colocalize with segmental electron transport system abnormalities, muscle fiber atrophy, fiber splitting, and oxidative damage in sarcopenia. FASEB J. 2001;15:322-332.

14 Sastre J, Pallardo FV, Vina J. The role of mitochondrial oxidative stress in aging. Free Rad Biol Med. 2003;35(1):1-8.

15 DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. N Engl J Med. 2003;348:2656-2668.

16 Komaroff AL. The biology of chronic fatigue syndrome. Am J Med. 2000;108(2):169-171.

17 Marcel B, Komaroff AL, Fagioli LR, Lornish RJ 2nd, Albert MS. Cognitive deficits in patients with chronic fatigue syndrome. Biol Psychiatry. 1996;40(6):535-541.

18 Bennett AL, Fagioli LR, Schur PH, Schacterle RS, Komaroff AL. Immunoglobulin subclass levels in chronic fatigue syndrome. J Clin Immunol. 1996;16(6):315-320.

19 Bennett AL, Mayes DM, Fagioli LR, Guerriero R, Komaroff AL. Somatomedin C (insulin-like growth factor I) levels in patients with chronic fatigue syndrome. J Psychiatr Res. 1007;31(1):91-96.

20 Kowal K. Schacterele RS, Schur PH, Komaroff AL, DuBuske LM. Prevalence of allergen-specific IgE among patients with chronic fatigue syndrome. Allergy Asthma Proc. 2002;23(1):35-39.

21 Kaptchuk T, Eisenberg D, Komaroff A. Pondering the placebo effect. Newsweek. 2002;140(23):71,73.

22 Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003;301(5631):386-389.

23 Andreu AL, Hanna MG, Reichmann H, et al. Exercise intolerance due to mutations in the cytochrome b gene of mitochondrial DNA. N Engl J Med. 1999;341:1037-1044.

24 Vladetiu GD, Tabone E. Mitochondrial disease in patients with exercise intolerance. N Engl J Med.

2000;342(6):438-439.

25 Cote HC, Brumme ZL, Craib JP, et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. N Engl J Med. 2002;346:811-820.

26 Horrum MA, Tobin RB, Ecklund RE. Effects of 3,3',5-triiodo-L-thyronine (L-T3) and T3 analogues on mitochondrial function. Biochem Mol Biol Int. 1995;35(4):913-921.

27 Aw TY, Jones DP. Nutrient supply and mitochondrial function. Ann Rev Nutr. 1989;9:229-251.

28 Suzuki H, Manabe S, Wada O, Crawford MA. Rapid incorporation of docosahexaenoic acid from dietary sources into brain microsomal, synaptosomal and mitochondrial membranes in adult mice. Internat J Vit Nutr Res.p>