Health Condition: Pain-, Fatigue-, & Stress-Related Syndromes

"Neighbors liked to speculate about her financial lineage. A few confused souls were amused by the notion that the heir to the West's largest raisin dynasty lived among them. To those people she was 'Mrs. California Raisin.' To most of the citizens of Incline Village, however, she was just one more rich person who spent her summers in a town on the rim of Lake Tahoe. In truth, she was not the raisin heiress; she was married to a prosperous oilman, and each winter the couple returned to their home in Houston. Her life was one of ease and affluence. When her health began to fail in late August, she went directly to the Cheney-Peterson Medical Office on Alder Street in Incline Village. A number of such folk residing in the mountain hamlet routinely packed their overnight bags when they wanted to see a doctor and headed for the Reno airport an hour away. However much Incline was loaded with wonders of the natural world, it had—for years—been short on doctors, until it had the benefit of getting Dr. Daniel Peterson and Dr. Paul Cheney as the principal physicians serving the community. It was not entirely surprising, then, when her fatigue struck—This intense and sudden fatigue—that the oilman's wife went directly to the medical offices on Alder Street of Dr. Cheney and Dr. Peterson."

—Hillary Johnson
Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic, 1996

Who has Pain-, Fatigue-, & Stress-Related Syndromes?

In 1955 at the Royal Free Hospital in London, there was an outbreak of a fatigue-associated disorder with three clinical features: muscle fatigue, circulation impairment, and cerebral dysfunction. Following this incident, research determined a disorder with similar symptoms was found among the general population and the condition was given the name myalgic encephalomyelitis (ME) by Dr. Melvin Ramsay. In the 1980s, 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.

Chronic fatigue syndrome (CFS) is not a disease, *per se*, but rather it is a complex condition—a state of energy deficit—that ranges with differing degrees of severity, duration, and frequency from patient to patient. It should not be thought of as a single entity, but rather as a kind of resting place for a series of multiple etiologies that contribute what appear to be immunological deficiencies or dysfunctions, alterations in the hypothalamus-pituitary-adrenal/thyroid axis, changes in musculoskeletal function, changes in cardiac function, and a general alteration in the systemic ways that the web of physiological function is balanced. CFS occurs four times more often in women than in men, which has raised the possibility of an endocrine component to the condition. The complex symptomatology associated with CFS has come to be associated with a range of other functional somatic syndromes, such as fibromyalgia

(FM), multiple chemical sensitivity (MCS), myofascial pain syndrome, and Gulf War syndrome. There is evidence that various types of immune hypersensitizing agents may contribute to these syndromes. Although not classified as true autoimmune disorders, they are commonly called arthralgias, and 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. The cause of these immune dysregulations has yet to be discovered. Nor do we yet understand how to restore patients to normal function.

From the research and literature that has emerged over the past several decades, defining conditions such as CFS and FM as neuro-endocrine-immune-related disorders is a reasonable way to approach understanding them. The concept is that 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.

Diagnosis

There are no tests that will definitively diagnose pain-, fatigue-, & stress-related illnesses. Typically, people who come into a primary care physician's office for assessment have experienced fatigue for six months or perhaps much longer. In the case of CFS, 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. The fatigue often occurs with pain, with a number of other symptoms. In 1994, the Centers for Disease Control (CDC) described 8 symptoms related to CFS and at least 4 of the 8 must occur concurrently:

- post-exertion malaise lasting more than 24 hours
- unrefreshing sleep
- significant impairment of short-term memory or concentration
- muscle pain
- pain in the joints without swelling or redness
- headaches of a new type, pattern, or severity
- tender lymph nodes in the neck or armpit
- a sore throat that is frequent or recurring

From a diagnostician's perspective, 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 the 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.

The Search for Causes

"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."

—Jeffrey Bland, PhD , August 2003

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, any number of factors could be relevant: chemical agents, low- grade infections, inflammatory conditions, xenobiotic exposure, drug and alcohol excess, emotional stress, and trauma. 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. Stress, allergy, toxicity, and inflammatory mediators all are factors that may lead to a load or weight on energy biodynamics.

In 2003, Dr. Dedra 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."[1] By looking at central nervous system CT-scans of CFS patients, the researchers found these patients have diffuse cerebral profusion. This result 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 (cognitive dysfunction) often seen in CFS patients. 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).[2] How and why that effect occurs is not yet fully understood, but we might call this a 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.

Within the HPA axis, there is a continued residual alteration in neurochemicals associated with alarm, such as interleukin-1 or interleukin-6. Authors of a paper published in *Arthritis & Rheumatism* in 2000 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.[3] This is an interesting part of the potential etiology of these complex symptoms associated with functional somatic syndromes.

The Role of the Mitochondria

One observation that has emerged from ongoing research is the relationship of fatigue-related symptoms to alterations in the energy production centers of the cell, tissue, or organ, which are the mitochondria. We inherit the majority of our mitochondrial information—our extra-chromosomal DNA, our biochemical energy—from our mothers. 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.

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.

Researchers have 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. 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. A number of clinicians and researchers began to evaluate energy-deficit disorders at the metabolic or cellular level.

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.[4] This topic was also the subject of a review article in The New England Journal of Medicine, titled "Mitochondrial Respiratory-Chain Diseases."[5] Age-associated alterations of the mitochondrial genome occur, and deletion mutations do accumulate. It is not just what you were born with. Certain people are born with unfortunate constitutive mitochondrial mutational illness like Kearn-Sayre syndrome and Leber's optic neuropathy, but in the case of functional somatic syndromes, we are concerned with those individuals who collect increasing injury to their mitochondria over life and time.

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 effect can be accomplished by removing the precipitating triggers and improving their function by "feeding" them correctly with appropriate nutrients for proper mitochondrial function.

Therapeutic Approaches

A number of potential therapeutic approaches have been suggested and studied for pain-, fatigue-, & stress-related conditions. 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 being described. Each patient will undoubtedly require some form of personalized therapy based upon his or her own unique manifestation of the condition. Patients with chronic illness have distributive problems that require distributive systems. No one practitioner is a master of all therapies that are necessary for that patient, so coordinating the best treatment program for each patient may require multiple practitioners with different expertise.

In 2006, a systematic review summarizing all interventions for the treatment, management, and rehabilitation of patients with chronic fatigue syndrome was published in the *Journal of the Royal Society of Medicine*.[6] The authors reviewed and graded the quality of the research on chronic fatigue randomized controlled trials (RCTs) that have been published to date. According to this analysis, most of the pharmacological interventions that have been used have not been successful. The pharmacological intervention trials mostly have very low-graded scores (meaning they didn't really work much better than placebo). Many different drugs have been attempted, including SSRIs, corticosteroids, anti-virals, and immunologically active agents.

There are some modalities, however, that seem to suggest improvement after therapy (against placebo). The first is cognitive behavioral therapy (CBT). There are multiple studies that seem to all demonstrate improvement. The other is what we would call graded exercise therapy. There are five RCTs that concluded that graded exercise therapy is a promising intervention. Those, along with the three relevant randomized control trials on cognitive behavioral therapy, appear to be the best clinical outcome studies that have been published to date with regard to chronic fatigue syndrome.

The next therapy that rose up in the meta-analysis—which reviewed about 10,768 publications published on interventions surrounding chronic fatigue syndrome and selected 70 that met the selection criteria—was the use of inosine pranobex. A couple of clinical trials seem to demonstrate improvement in patients with the use of inosine pranobex, although there were side effects with this treatment. Inosine is an orthomolecular material that tends to improve cardiac function. Other papers (2) describe some positive benefit using hydrocortisone given at fairly low dose (these are physiological doses of hydrocortisone).

There is no one magic bullet that is going to lead to complete remediation of pain-, fatigue-, & stress-related syndromes. Determining treatment requires a much more complex review of systems and a whole-person approach to understand how an alteration in a patient's web of physiological function might result in these energy-deficit-disorder symptoms.

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