CHRONIC FATIGUE SYNDROME

(Myalgic Encephalitis/Chronic Fatigue Syndrome)

Whitepaper

PARK RIDGE MultiMed

Whitepaper

CHRONIC FATIGUE SYNDROME

Keith Berndtson, MD

Chronic Fatigue Syndrome (CFS) is a difficult-to-treat medical condition whose cause is not yet known. In its 23 October 2009 issue, *Science* published a study by researchers from the Whittemore-Peterson Institute (WPI), The Cleveland Clinic, and the National Cancer Institute implicating a potential causative role for a retrovirus known as XMRV.[1] This study reported that, compared to healthy people, persons with CFS are 18 times more likely to have XMRV DNA in their blood. Retroviruses, including the human immunodeficiency virus (HIV) are know to activate other latent viruses including several from the Herpesvirus family.

Unfortunately for sufferers, two years later the XMRV hypothesis went down in flames as several subsequent studies failed to confirm the genetic presence of XMRV in any CFS patients.[2] One study claimed to have proved that the original research had found contaminated DNA. Until the fall of 2011, XMRV presented a big challenge to retroviral researchers, as the studies were hard reconcile, meaning one or more of the research teams were getting it wrong.

CFS research is famous for producing false leads and misinterpretations of data.[3] Nothing gets attention like controversy. CFS is now drawing the attention of a new crop of disciplined, scientific minds. For patients with CFS, and the clinicians who treat them, this is a step in the right direction.

On August 23, 2010 a study appeared in the *Proceedings of the National Academy of Sciences* by Lo and colleagues reporting the presence of DNA fragments from a class of retrovirus known as MLV (mouse leukemia virus). MLVs were present in 85% of 37 CFS patients tested, and in 7% of 44 controls.[4]

These findings appeared to confirm some role for retrovirus in the pathobiology of CFS, but it was still unknown what role XMRV or MLV retroviruses play in CFS. Some observers felt that these retroviruses interact with other infectious or environmental agents to complicate and worsen CFS severity.[5] Some observers were convinced that these viruses play a major causative role in CFS. Still others argued that the data were unclear that these viruses were even present in patients with CFS.

In its 1 July 2011 issue, *Science* published an editorial expression of concern about the October 2009 study.[6] In that issue, a study by Tobias Paprotka and a national team of virology experts established that the XMRV DNA found by the WPI team was a

contaminant whose origin could be traced to ancestral mouse leukemia viruses whose DNA recombined during the course of studies using xenografts from a primary mouse prostate tumor that traces back to research done at Case Western Reserve University in the 1990s.[7]

The editorial expression of concern also referred to a study by Constance Knox and colleagues that found no evidence of XMRV in any of 61 blood samples from CFS patients who were in the same practice that whose CFS patients supplied the blood samples to the research team that was the first to report XMRV in patients with CFS.[8]

At this stage, it appears that the WPI team found evidence of recombinant DNA rather than XMRV, and that based on Paptroka's analysis, the odds of XMRV being a factor in CFS is less than 1 in a trillion. Combined with the findings of Knox, et al, which found no evidence for XMRV antigen or antibodies in CFS patients, the CFS community anxiously awaits more information about the possibility of retroviral involvement in CFS.

People with CFS can suffer from a variety of signs and symptoms that exist on a spectrum ranging from mild to severe. Within the broad range of CFS signs and symptoms, characteristic patterns of abnormality identify those with the more severe forms of the illness.

This condition caught the attention of the Centers for Disease Control (CDC) after an epidemic of a mysterious illness occurred near Lake Tahoe in 1984. The frustrating story of this epidemic and the CDC's early efforts to understand it are described in Hillary Johnson's book, *Osler's Web*.[9]

Background History

Following an acute onset of illness that seemed most like an infection, the Tahoe group of patients developed an otherwise unexplained form of fatigue accompanied by problems with brain function, including difficulties with memory and concentrating, an inability to produce restorative sleep, and malaise after mild to moderate exertion that would last for at least 24 hours and sometimes for days.

Blood samples at the time found evidence of viral activity involving the Herpesvirus family including Epstein-Barr Virus (EBV) and Human Herpesvirus-6 (HHV-6). Some sufferers in this outbreak noted acute worsening of key symptoms when in certain buildings or rooms, suggesting that building materials or a toxic form of indoor mold may have played a role. If so, some members of the Tahoe group may have suffered a double or triple whammy involving a viral infection and a reaction to biological toxins (from, say, toxic mold) or toxic chemicals (from, say, building materials).

Nearly 200 hundred people were affected but thousands were probably exposed to the same conditions at the time. The sufferers appeared more vulnerable to falling ill than the rest of the exposed population. Such predispositions are usually traceable to genetic variations and to the degree to which people are otherwise stressed or debilitated at the time they are exposed to infectious agents or toxins.

The members of the Tahoe group suffered an illness whose features bore a striking resemblance to previously reported outbreaks of a condition known as *myalgic*

encephalitis (ME).[10] In 1956 an outbreak of ME occurred in the Royal Hospital of London. The clinical presentations of these cases were described in meticulous fashion by the British physican, A. Melvin Ramsay, and have since been summarized by the Canadian physician Byron Hyde and the Nightingale Group.

In 1988 the CDC proposed its first set of diagnostic criteria as a way to define who has a case of CFS (known as the *Holmes* definition).[11] This definition included 2 major criteria and 14 minor criteria (11 for symptoms and 3 for physical signs). This rather cumbersome definition was revised in 1994 (known as the *Fukuda* definition).[12]

Both of these definitions included problems of brain function, lymph and immune system activation, or poor tolerance for exertion as minor diagnostic criteria, but they were criticized for ignoring the closeness of the resemblance to previously documented cases of ME, and for being too ambiguous when it came to distinguishing a case of CFS from a case of psychiatric illness.

Since the late 1990's a growing number of physicians, researchers, educators, and well-informed patients believe that the more accurate working name for CFS should be ME/CFS. A more practical case definition would emphasize the importance of measurable changes in brain function and in patterns of abnormality involving the neurohormonal and neuroimmune systems. It is also worth noting patterns of illness aggravation based on physical and cognitive exertion or overall stress, and the ability of certain rooms, buildings, or environmental exposures to trigger functional deterioration.

Detection of XMRV infection may become a way to split out patients with ME/CFS cases from the lumpier category of CFS. This would be a true advance, as the CDC's recent attempts to redo the CFS case definition is viewed by many clinicians and researchers as a step backward. Yet not all retroviral experts are convinced that CFS is a retroviral illness.

In 2003, Carruthers, et al, published their Canadian Consensus criteria for ME-CFS.[13] This paper was written by clinicians who treated patients rather than researchers who did not, and it placed more emphasis than previous case definitions on neuroimmune and neuroendocrine manifestations of the disease.[13]

In 2005 the CDC again revised the diagnostic criteria for CFS (known as the *Reeves* definition).[14] To identify a case of CFS, the *Reeves* team introduced a new assortment of fatigue and function scores. The result made the diagnosis less, not more specific, in that someone diagnosed with CFS using the *Reeves* criteria could have severe ME/CFS or simply a function-reducing mood disorder.

Early estimates by the CDC suggested a CFS prevalence rate of 2 per 1,000 people. In 1998, rigorous estimates by Leonard Jason and colleagues found that the frequency of CFS in a metropolitan area is four to five cases per 1,000 people.[15] Their survey took special care to distinguish CFS from mood disorders. When the *Reeves* criteria are used, however, the prevalence estimate for CFS climbs to 26 per 1,000 – over 6 times higher than Jason's estimate. This prevalence discrepancy complicates ongoing research attempts to refine the CFS case definition.[16]

It's now hard for researchers to decipher how multiple sets of diagnostic criteria are being applied in CFS research, and there is still too little interest on the part of the

research-funding establishment in distinguishing ME/CFS from CFS or from mood disorders.

By the same token, disability insurers and their independent medical and psychiatric examiners have a financial interest in supporting the position that in many, if not most, cases of CFS the primary problem is psychiatric. The XMRV discovery may play a corrective role here, as 67% of CFS patients tested showed evidence of XMRV infection,[1] but this finding has already been challenged by another retroviral research team.[2]

To illustrate the current difficulty in identifying a case of CFS, consider the common scenario where a research paper says it used CDC criteria to define its CFS cases without specifying whether the research used the Holmes, Fukuda, or Reeves definition. The *Fukuda* definition specifies that otherwise unexplained fatigue must persist for at least 6 months, and is accompanied by at least *4* out of the following 8 symptoms:

1. Substantial impairment of short-term memory or concentration
2. Sore throat
3. Tender lymph nodes
4. Muscle pain
5. Multi-joint pain without swelling or tenderness
6. Headaches of a new type, pattern, or severity
7. Unrefreshing sleep
8. Post-exertional malaise lasting more than 24 hours

In 2007, England's National Institute for Clinical Excellence (NICE) proposed a definition similar to the *Fukuda* definition except it required only *1* of the 8 minor symptom criteria to be present in order to make a diagnosis of CFS. [17]

The *NICE* definition is much looser than the *Fukuda* definition. At the same time, it is much tighter than what English psychiatrists had proposed in 1991 as a CFS case definition. Known as the *Oxford* criteria, this group required only the presence of severe fatigue, holding that "other symptoms may be present" but weren't necessary to justify the diagnosis.[18] With a case definition this loose, disability insurers can deny CFS cases as easily as shooting fish in a barrel.

Many physicians seem content to maintain a status quo where the evaluation and management of people with CFS is clouded with ambiguity and left up to each clinician. As one commentator put it, the status quo views "CFS as one of a number of different syndrome-lagoons which overlap to give a vaster sea of medically unexplained illnesses." The treatment of these vaguely defined illnesses will vary based on the bias a given physician has for one among several competing explanations for CFS.

In 2006, the CDC announced preliminary research in genomics that supports the biological basis of CFS. People with CFS appear to have a genetic make up that reduces the body's ability to adapt to change and molecular threats. Compared to the rest of the population, these genetic variations make them more vulnerable to CFS, to ME/CFS, and to the biotoxin and/or chemotoxin-mediated disruptions of metabolic balance that appear to be associated with some cases of CFS and ME/CFS.

For CFS sufferers the good news is that preliminary genomics research is focusing attention on mechanisms by which genetic variation predisposes people to falling ill in a

CFS way. The bad news is that the case definition criteria still fail to separate out ME/CFS subtype from the rest of what's being called CFS.
So in 2011, Carruthers, et al, a group of clinicians and clinician-researchers who treat people with ME-CFS, published their International Criteria for Myalgic Encephalomyelitis.[19] Patients with ME/CFS must meet their post-exertional neuroimmune exhaustion, as well as a certain number of neurological, immune, gastro-intestinal, genitourinary, and energy production or circulatory transport impairments. This is the most clinically grounded set of diagnostic criteria yet to appear in the medical literature on ME/CFS.

One can only hope that more research teams will gather to coordinate research into the causes and treatments of celiac disease, atypical multiple sclerosis, fibromyalgia, Gulf War Syndrome, chronic heavy metal exposures, multiple chemical sensitivities, and less well-defined syndromes related to biotoxicities, industrial chemical toxicities, immune-mediated sources of inflammatory and/or circulatory stresses on brain centers and circuitry, neuro-adrenal imbalance, chronic intestinal dysbiosis, and other conditions that are either associated with, or similar to, CFS.

Building on an established link between pro-inflammatory cytokines, viral persistence, and altered immune system function, WPI researchers are describing cytokine/chemokine signatures that can be used to target therapies toward individuals within the ME/CFS spectrum of illness.

On a separate track, Ritchie Shoemaker, MD and colleagues have been studying the effects of biotoxins on people with various illness presentations including ME/CFS.

In a study of people with *sick building syndrome* – a condition in which multiple organ system problems are triggered by exposure to the complex mix of fungi, mycotoxins, bacteria, endotoxins, lipopolysaccharides, antigens, and biologically active volatile chemicals that circulate in the air inside of water-damaged buildings, Shoemaker found a definite correlation between exposure to contaminated air, the occurrence of abnormal biomarkers, and severity of symptoms as a result of acute or chronic exposure. [20]

In this study Shoemaker reported an 80% reduction in symptoms with biomarker improvement when subjects avoided the contaminated air and used a binding resin to pull toxins out through bowel elimination.

Sufferers of sick building syndrome appear to be more vulnerable to both biotoxins and chemotoxins than most people suffering similar exposures. Their illness experience closely resembles ME/CFS and could qualify as a specific subset of ME/CFS.

Yoshitsugi Hokama and colleagues at the University of Hawaii recently found an association between chronic fatigue syndrome and anti-cardiolipin antibodies.[19] Cardiolipins are mainly found in the membranes of mitochondria. Hokama's team also found that among CFS patients forming anti-cardiolipin antibodies, 95% of them had antibodies that were reacting to ciguatera toxin.

Ciguatera is a food-borne illness that can cause severe gastrointestinal and neurological signs and symptoms. The name "ciguatera" is a transliteration from Spanish into English, meaning "seawater." Most early cases of ciguatera were associated with exposure to tropical seawater. The ciguatera toxin is produced by dinoflagellates, a type

of marine plankton increasingly found in fresh water. These organisms are the driving force behind many algal blooms in both types of water. Shoemaker and colleagues reported a pattern if innate immune system over-activation in patients exposed to ciguatera toxin compared to controls.[20] In this study, patients suffering symptoms related to ciguatera toxicity were more likely to have HLA-related genetic vulnerability, as well as elevations of C4a, MMP-9, and TGF-beta, as well as depleted levels of MSH and VIP.

These biomarkers are also more likely to be present in genetically vulnerable patients who suffer from toxicity symptoms when exposed to the air of water-damaged buildings, patients exposed to ciguatera, pfiesteria or other dinoflagellate-derived toxins, and in patients with active Lyme Disease whose symptoms persist despite antibiotic treatment that eradicates the organism that causes Lyme Disease. The latter patients have the condition known as *post-treatment Lyme syndrome*. They, too, seem to have difficulty clearing the Lyme-derived biotoxins that remain in cells and tissues after antibiotic treatment.

The toxin makes its way into algae, which is eaten by small herbivorous fish, in turn eaten by larger fish, which concentrate the toxin. The toxin is actually a family of toxins, all of which are harmless to fish but variably neurotoxic to humans.[21,22] Further research into this association may establish a causative or complicating role for these neurotoxins in ME/CFS.

Physician researcher Paul Cheney, MD, has done important work identifying higher rates of an unusual heart condition in ME/CFS patients that may account for the oxygen toxicity phenomenon seen in so many CFS patients.[23]

Cheney's theoretical work is consistent with the NO-ONOO concept of oxygen toxicity detailed by Martin Pall, PhD.[24] The theoretical framework outlined by Cheney, Pall, and others is a work in progress that is open to disciplined critique.[25] These highly promising ideas deserve research attention.

At *onebodymind.com* we believe that there are important differences between ME/CFS, fibromyalgia, mold toxicity, sick building syndrome, Gulf War syndrome, multiple chemical sensitivity syndrome, atypical multiple sclerosis, acquired patent foramen ovale syndrome, and other illnesses that hang with or mimic ME/CFS. That said, research may discover that these conditions share genetic predispositions as well as certain infectious and/or toxic environmental exposures. We may find that people with certain genotypes who were also exposed to certain environmental toxicants in the womb are the most at risk for developing adult ME/CFS after certain infectious and/or toxic exposures.

All of these clinical presentations have in common signs and symptoms of underlying neuroimmune disease. These signs and symptoms appear related to molecules and/or micro-organisms that have no business in human metabolism, which, when added up, translate into a new and especially complicated multidimensional disease of systems biology, best treated using an open-minded, clinical systems biology approach.

Time will tell whether viruses, bacteria, parasites, chemotoxins, biotoxins (from mold, cyanobacteria, dinoflagellate, pfisteria, ciguatera, contaminated wheat, or other sources) or other noxious agents are playing causative, co-causative, or complicating roles in these conditions.

At present it would seem that various permutations of these exposure types are capable of producing a clinical picture of ME/CFS, and that individual susceptibilities vary based on genetics, lifestyle, and general health status at the time of initial exposure to infectious or toxic triggers.

At this stage in our understanding of ME/CFS, mood disorders without signs or symptoms of neuro-immune disease should not be included in the ME/CFS spectrum.

The various triggers of ME/CFS seem to depend on genetics and circumstances at the time of exposure. The triggering exposure may be any combination of the following:

- **Infectious**
  Here are the intracellular pathogens categories that dominate the list of suspects:
    - Viruses (quite a few have been associated with neuro-immune disease)
    - Bacteria (Lyme Disease-like neuro-immune disrupters, atypical mycobacteria, mycoplasma, chlamydia)
    - Parasites (Malaria-like protozoans such as Babesia)

- **Toxicity**
  Here we find the accoutrements of wilderness, industry, construction, and water-damaged buildings:
    - Biotoxins (from mold, Lyme-type bacteria, dinoflagellates, or other living sources)
    - Chemotoxins (pollutants including volatile organic compounds, pesticides, and many families of synthetic, man-made chemicals)

In none of these CFS subtypes do we have an adequate explanation of what's really going on in an individual case of CFS. In all of these CFS subtypes we have the combination of infectious and/or toxic agents producing signs and symptoms that fall within the CFS spectrum in those who are genetically susceptible to neuro-immune disease. In each of these CFS subtypes we are gaining more precise ways of differentiating what's going on and finding out what treatments work best for one versus another.

Below find a summary of the clinical features of ME/CFS.

The Clinical Features of ME/CFS

The following description of the clinical features of ME/CFS blends the *Fukuda* definition and the Canadian *Nightingale Group* definition[25] with implications drawn from work by Shoemaker, the Whittemore Peterson Institute, and other contributors to the scientific knowledge base in ME/CFS research.

ME/CFS and its closely related conditions appear to have an acute onset that is commonly preceded by a series of minor infections or exposures in someone who was otherwise well, suggesting immune and neurohormonal systems that were growing vulnerable to losing some of their functional integrity for reasons of genetics, ongoing exposures, and/or stress overload.

Acute and Chronic Phases

The acute phase lasts 4 to 7 days and usually presents like an infectious process. Symptoms may include fatigue, aches, fever, sore throat, lymph node swelling and tenderness, and headache. The chronic phase follows within a week or so and is associated with *measurable diffuse changes in central nervous system function*.

Modifying the *Nightingale* definition of ME/CFS to incorporate current findings in research focused on ME/CFS cases, which includes the past and future work of many researchers not mentioned in the White paper, we can delineate several categories of dysfunction where measurable abnormalities are documented to occur at higher rates in ME/CFS than in the normal population, or in those who are chronically fatigued with no other symptoms, versus those who are psychologically depressed without evidence of subtle but significant systems biological imbalance.

Measurable Dysfunctions in ME/CFS Patients

- ***Neuropsychological/neurophysical dysfunction:***
    - Short-term memory loss, increased irritability, confusion, and/or perceptual difficulties
    - Visual contrast sensitivity (VCS) testing
- ***Hormonal dysfunctions:***
  Evidence for imbalance or abnormal regulation of the:
    - Thyroid system
    - Adrenal system
    - Hypothalamic-pituitary pathways involving leptin, anti-diuretic hormone (ADH), or melanocyte stimulating hormone (MSH)
    - Pathways involved in growth hormone release
- ***Sleep dysfunction:*** abnormal sleep architecture with less time spent in deep sleep
- ***Muscle dysfunction:*** abnormal reflexes, muscle fasciculations, twitches, jerks, weakness, or coordination problems
- ***Circulatory dysfunction:***
    - Low blood volume (compartment shifts, anti-diuretic hormone regulation problems) or apparent (due to venous pooling, baroreceptor problems, lymph congestion)
    - Raynaud's phenomenon (over-reactive constriction of the small arteries in the hands and feet)
    - Blood pressure regulation problems (postural orthostatic tachycardia syndrome, abnormal flow-mediated vasodilation, lack of oxygen desaturation with breath-holding)

- ***Cardiac dysfunction:*** impedance cardiography may show reduced cardiac output

- ***Bowel dysfunction:*** bloating, constipation, frequent loose or poorly formed stools, food sensitivities, and evidence of viral, bacterial, yeast, or parasitic infection

- ***Immune system dysfunction:***
  Evidence of recent or recurrent exposure to:

    - Viruses,including EBV, HHV-6 (especially type HHV-6a), cytomegalovirus, bornavirus, parvovirus, and enterovirus – as measured by antibody levels or more specific forms of identification
    - Biotoxins including those from Lyme Disease bacteria and indoor molds including stachybotris and aspergillus – as measured by levels of pro-inflammatory cytokines, including:

        - Tumor necrosis factor-alpha (TNF-a)
        - Interleukin-1-beta (IL-1b)
        - Interleukin-6 (IL-6)
        - Interleukin-8 (IL-8)
        - Interleukin-10 (IL-10)

      As well as other abnormal immune system activity, including:

        - High complement proteins C3a and C4a level (baseline and post-exposure)
        - High matrix metalloproteinase-9 (MMP-9)
        - Low alpha melanocyte stimulating hormone (MSH), vasoactive intestinal peptide (VIP), anti-diuretic hormone (ADH)
        - Inappropriate serum osmolality given the ADH level
        - Low or high vascular endothelial growth factor (VEGF) level
        - High transforming growth factor-beta 1 (TGF-beta1) level
        - Autoimmune activity including the production of various forms of anti-nuclear and/or anti-phospholipid antibodies
        - Low natural killer cell activity or levels

- ***Coagulation system dysfunction:*** high levels of plasminogen activator-inhibitor-1 (PAI-1), soluble fibrin monomers, fibrinogen, or anti-phospholipid antibodies, the presence of a Factor V Leiden mutation, or abnormal levels of protein C or protein S

- ***Mitochondrial dysfunction*:** evidence of reduced ATP regeneration and/or signs of ongoing oxidative damage to mitochondrial structures and/or DNA.

- ***Metabolic dysfunction:***

    - A high glutathione (oxidized) to glutathione (reduced) ratio
    - Elevated homocysteine level
    - A high level of lipid peroxidation
    - Increased level of 8(OH)-deoxyguanosine DNA fragments

- Abnormal levels of urinary organic acids

- ***Genetic vulnerabilities:***

  - Histo-compatibility antigen (HLA) markers associated with an over-reliance on the complement protein division of the immune system when exposed to biotoxins), including certain DRB1, DQ, DRB3, DRB4, and DRB5 alleles
  - Single nucleotide polymorphisms involving:

    - Folate methylation pathways
    - Glutathione synthesis or reduction pathways
    - Apolipoprotein E types
    - Cholesterol ester transferase types
    - Other genomic variants of interest as indicated

Evidence supports the idea that ME/CFS subtypes have in common a form of micro-vasculitis – endothelial cell irritation and activation that can be triggered by pro-inflammatory, barrier-breaching cytokine activity that, in turn, triggers additional cascade effects that disrupt metabolic regulation networks. ME/CFS is fertile territory for researchers interested in combining focused, mechanistic analyses of biochemistry with the computational and database scanning models of systems biology.

CFS and Depression

Research shows a relationship between ME/CFS, anxiety, and depression. Two thirds of people who suffer from chronic, excessive fatigue also report anxiety or depression. Low stress resilience often precedes the onset of chronic fatigue, and most cases of depression in chronic fatigue develop or worsen in reaction to having a mysterious, unexplained illness.

Doctors who treat ME/CFS should accept that they involve multiple underlying measurable abnormalities involving immune, hormonal, and nervous system function that will eventually explain the illness and its subtypes. In the meantime, doctors and researchers who cling to a psychiatric model for ME/CFS will betray their ignorance or their conflicts of interest as the science-based literature on biomarker abnormalities found in ME/CFS cases comes together in the next few years.

Disability Determination

ME/CFS has become controversial because it disables people without clear evidence as to how or why. Many people with milder forms of unexplained fatigue often use an ME/CFS diagnosis to apply for, and sometimes receive, long-term disability support when, in fact, they are either able to pursue substantially gainful employment, or unable to do so for psychiatric reasons.

That genuine ME/CFS has a vague cause and is difficult to treat doesn't make it a psychiatric illness. Long-term disability insurers and Social Security Administration need help sorting out whether ME/CFS cases in the severity gray zone genuinely warrant

long-term disability support. That said, it is shameful how some private disability insurers use harassment, video surveillance, and lapdog independent medical examiners to make chronically disabled people look like malingerers or hysterical psychosomatics.

Growing evidence suggests that many people with ME/CFS suffer from underlying neuroimmune disease that is accompanied by depression that may have existed before the disease but in many cases follows or gets significantly worse after the disease.

People with ME/CFS have cases of something that could be measured and described as diffuse, low-level encephalitis with neurohormonal regulatory imbalance related to immune system over-activity triggered by exposures to pathogens, biotoxins and/or chemotoxins, and that they were vulnerable to falling ill in this way due to their genetics, stress levels, and/or the presence of other complicating factors. Whether retroviral effects play a role in these interactions is at present unclear and apparently unlikely. The remaining third may have other causes, but their biomarker abnormalities will still be screaming "neuroimmune disease."

The conventional medical approach:

I would cross the hall to avoid ME/CFS patients before I had a clinical framework for making sense of their health problems. Then all I needed was time to think it through. For that, I had to ditch primary care because in today's medical system, primary care schedules kill high quality problem solving for ME/CFS patients. Here's how the conventional model for ME/CFS evaluation and management looks:

- The history is often compressed by time constraints and typically cannot get to all of the symptoms the patient has to report.

- Physical exam includes a blood pressure, a look at the throat, palpation of lymph nodes, liver, and spleen, lung and heart sounds, inspection of the skin, hair, and nails, and evaluation of muscle and joint function.

- Laboratory testing typically goes well beyond routine chemistries to look for signs of hormone imbalance, autoimmune activity, viral exposure, and Lyme Disease if exposure is suspected, and neurological testing with a brain MRI scan if multiple sclerosis or other central nervous pathology is suspected.

  The problem with viral and Lyme Disease "serologies" is that they usually provide indirect indicators of exposure. A positive Lyme serology that reflexes to a Western Blot test may show findings that do not meet the CDC's research definition for a case of Lyme Disease. The methods of detecting the presence of intracellular pathogens in the body are limited. Determining how the presence intracellular pathogens is related to the signs and symptoms of ME/CFS is a difficult process that warrants more time than most doctors have to give.

- Treatment emphasizes prescription drugs for pain, sleep, and/or mood. Most doctors are comfortable giving these medications a try. Sometimes they work so well that what seemed like a genuine case of ME/CFS was actually a case of neurochemical imbalance. But in many cases the ME/CFS patient's response to

prescription medication is poor toleration or no obvious benefit. Commonly prescribed drugs include:

- Antidepressants: amitryptiline, nortriptyline, fluoxetine, paroxetine, sertraline, citalopram, escitalopram, venlafaxine, duloxetine, Cymbalta,
- Non-steroidal anti inflammatory agents (NSAIDs): ibuprofen (e.g., Advil), naproxen (e.g., Aleve), celecoxib (e.g., Celebrex).
- Sleep and anti-anxiety medications: zolpidem, Ambien CR, Lunesta, alprazolam, clonazepam, temazepam, trazodone.
- Narcotic analgesics (such as tramadol or hydrocodone), are commonly prescribed to reduce symptoms of pain, with little thought as to underlying issues that cause, aggravate, or amplify pain (such as low serotonin or magnesium levels).
- Muscle relaxants: cyclobenzaprine, carisoprolol, metaxolone.
- Antivirals: acyclovir, valacyclovir, famciclovir
- Blood pressure stabilization: fludrocortisone, midodrine

Note that the conventional treatment of ME/CFS places little emphasis on lifestyle or natural therapies. Most severe ME/CFS patients have such a poor tolerance for exertion that for them, aggressive rest therapy seems to work better than graded exercise therapy.

It appears that their cells cannot convert oxygen into energy in the usual way, and that when exertion is forced the oxygen is converted into its free radical forms that cause biological rust. This would accounts for their post-exertional malaise and prolonged recuperation times, their blood and lymph microcirculatory problems, their immune and neurohormaonal problems, and their signs of mitochondrial dysfunction.

Many people with ME/CFS have alterations in their systems for digestion and assimilation. They may follow advice, begin a healthy Mediterranean diet, and feel worse because they can't digest the protein or complex carbs well, leading to food sensitivities. The more severe the ME/CFS case, the more likely the person will have signs and symptoms of a brain simmering in a cortisol cause peppered with pro-inflammatory cytokines.

Diffuse, low-level, cytokine-driven encephalitis and blood-brain barrier compromise can lead to blood pressure regulation problems and metabolic systems that slowly drift away from being able to figure out solutions to problems on their own. Patients with an ME/CFS subtype illness need doctors whose clinical problem-solving mindset is both science based and patient-centered with an emphasis on restoring functional integrity at root metabolic levels.

When primary care advice isn't helping, deciding where to refer the ME/CFS patient often comes down to a spin of the wheel. ME/CFS patients commonly feel tossed around like hot potatoes.

Many doctors don't want to inflict a ME/CFS patient on a colleague because the problems are too draining to understand let alone treat. Often they'll say, "I don't know what else to do for you" and refer you to a psychiatrist. A psychiatrist will find new medications worth trying. A good psychiatrist will advise counseling on how to cope with your dilemma. A "name the disease, name the drug for the disease" routine may

help a few, but it misses the boat for most. What's needed is an open-minded integrative approach.

The integrative approach:

I crossed over from a faculty position in an academic medical center to a neighborhood holistic practice in 1996. My goal was to close my knowledge gaps about alternative medicine, sort fact from fiction, and then go back to start an academic integrative medicine program.

I entered the world of alternative medicine with chips on both shoulders that had me programmed to approach every new frontier with the question, "Where's the data?" I learned that the knowledge gaps grow wider, and that treatment results can be excellent even when there is no data to support it.

Today I use an integrative medicine consultation model to help people prevent chronic illness or to help them care for complex forms of chronic illness. I bring a clinical mindset that seeks to find *whatever works*. It's labor intensive, it requires patience and persistence, and it looks something like this:

- The history of how the illness unfolded over time is methodically assembled, including multiple sittings if needed. This history generates clues as to how and why health declined gradually over time, or rather suddenly after an infection, toxic exposure, accident, pregnancy, or a period of unrelenting stress.

  The diagnoses of ME/CFS and fibromylagia are often used interchangeably even though the standard methods for making each diagnosis use very different criteria. Although roughly 50% of those who qualify for a diagnosis of ME/CFS also qualify for a diagnosis of fibromyalgia, there is no evidence to show that these two conditions are variants of one and the same cause. Because the signs, symptoms, and functional problems related to these conditions overlap, we are reminded to place less emphasis on diagnostic labels than on explanations of what's going on in each individual case.

- Physical exam is focused on tender points, blood pressure (with particular attention to abnormal changes in blood pressure or pulse when moving from lying down or sitting to the standing position), nutritional status (skin, hair, nails, abdominal obesity), sinuses, throat, lymph nodes, muscle tone and reflexes, balance and coordination, mental status, the presence of any tissue inflammation zones, and other areas as warranted based on the history.

- Laboratory testing may include:

  - ciguatera toxin assay (through the University of Hawaii)
  - blood chemistries with particular attention to markers of acid-base balance (e.g., low carbon dioxide, low phosphate, low sodium-chloride ratio, low albumin, and high free calcium) and protein status (where levels of total protein, globulin, and total immunoglobulin levels can indicate poor protein recycling when high within the reference range, or poor protein assimilation when low within the reference range)

- allergy testing (usually IgE antibody reactions to inhaled or ingested antigens as measured in the skin or blood)
- food sensitivity testing (other methods used to assess delayed reactions to foods mediated by IgG4 blocking antibody reactions or by cytokine-mediated changes in lymphocyte behavior)
- Urinary neurotransmitter testing (not diagnostic for any particular condition, but sometimes helpful when interpreted in the context of an individual's condition)
- Hormonal evaluation (blood, urine, or saliva measures are valid and reliable measures for some, but not all hormones, and data capture can vary from a blood snapshot to a 24-hour urine collection to a hormone stimulation test)
- Western blot for Lyme disease (Borrelia) and Lyme-related co-infections (Ehrlichiosis, Babesia, Bartonella).
- Serologies for viral, mycoplasma, and Chlamydia infections.
- Chronic Inflammatory Response Syndrome (CIRS) testing including HLA DRB1, DQ, DR3,4,5 haplotyping, visual contrast sensitivity, C3a, C4a, MMP-9, VEGF, alpha-MSH, ADH/osmolality, VIP, and TGF beta-1.
- Celiac haplotyping and serologies
- Urine for toxic metals pre- and post-provocation (through Doctor's Data)
- Blood screening for autoimmune and hypercoagulation activity, including:

    - Anti-nuclear antibody screen with reflex analysis of antibody types if the screen is positive
    - Anti-phospholipid antibodies (anti-cardiolipins, anti-beta-2-glycoproteins, anti-phopshatidylserine, dilute Russell's viper venom
    - Plasminogen activator-inhibitor-1 (PAI-1), fibrinogen, soluble fibrin monomers
    - Factor V Leiden mutation, abnormal protein C or protein S levels

- Treatment emphasizes lifestyle changes and natural therapies and is focused on restoring balance to the metabolic systems that, based on history or exam, appear to have lost their functional integrity. The systems under review typically include those most responsible for maintaining metabolic balance within the system as a whole. They include your systems for:

    - Digestion and assimilation of nutrients (ability to break down and absorb good things while keeping bad things out of the system), treatments for which include:

        - Digestive support
        - Avoidance of reactive foods (e.g., gluten, dairy, sugar, food additives, etc.)
        - Restoration of ecological balance involving bowel flora, emphasizing various combinations of natural antimicrobial agents and probiotics, and using prescription-strength antimicrobials when warranted

- Treatment of persistent tissue infections (mycoplasma, tick-borne infections, etc.)

- Microcirculation of blood and lymph (ability to move oxygen and nutrition in, and trash water out, of tissue zones), treatments for which include:

    - Proteolytic enzyme combinations (e.g., Vascuzyme, Biozyme)
    - Fibrinolytic enzyme (e.g., Nattokinase)
    - Red blood cell flexibility enhancers (e.g., omega-3 fatty acids derived from uncontaminated, carefully processed fish raised in pristine conditions)

- Detoxification (toxin detection, handling, and elimination), treatments for which include:

    - Avoidance of exposure to known toxins and their sources
    - Support for systems involved in the transport of fat soluble toxins being released from fat stores (e.g., in people with a high burden of fat soluble toxicity, healthy fats and ample levels of HDL, triglycerides, and non-oxidized LDL may add protection from lipid peroxidation of vessels and tissues during weight loss efforts that are releasing fats from their storage sites)
    - Strategically targeted dietary, nutritional, and herbal support for liver detoxification pathways, biliary excretion, and regular bowel movements
    - Use of adsorption agents to bind toxins excreted in the bile to help assure elimination via stool (cholestyramine, bentonite clay, brown algae fucoidan extracts, vegetable and fruit fibers, pectins, and lectins, etc.)

- Restoration (hormone and neurotransmitter balance), teraments for which include:

    - Strategically targeted amino acid supplementation to help correct suspected imbalances between excitatory (accelerator) and inhibitory (brake) neurotransmitters
    - The closely monitored use of low-dose bio-identical hormones to correct suspected imbalances between the catabolic (cortisol-led) damage control team and the anabolic (DHEA-led) restoration team
    - Strategically targeted use of sleep hygiene rules, amino acids, herbal formulas, and/or medications to promote restorative sleep

- Inspiration (conscious and unconscious brain effects on behavior), treatments for which include:

    - Psychological counseling with emphases on self-understanding, healthy behavior change, and strong coping skills
    - Body work (e.g., massage therapy, craniosacral therapy) or energy work (e.g., Reiki therapy, orthobionomy) with emphases on

learning more about how you stress in your body, and how releasing this stress can make it easier to release emotional stress as well.
- Relaxation methods such as simples breathing exercises and stretching routines, including those taught in the various systems of yoga, tai chi, and chi gong
- Meditation or contemplative prayer
- Acupuncture or Ayurvedic therapies
- Systematic efforts to identify your main sources of positive meaning (e.g., faith, family, nature, hobbies, creative activities, music, art, literature, pets, service to others, etc.) and how to pull these sources closer into your daily life.

Therapeutic Lifestyle Change

Eating the healthy foods that are especially good for you, combined with regular exercise, regular periods of relaxation, positive social connections, an optimistic attitude, and a sense of being connected to something greater than yourself together predict not just a longer lifespan, but a longer productive, self-dependent life of quality, dignity, and meaning. Good quality of life and cognitive behavioral therapy are part of a panel of treatment options that include other mind-body techniques for managing stress:

- Addressing potentially maladaptive psychological defenses
- Learning techniques for quieting the mind and body at will
- Meditative practices including contemplative prayer, yoga, and Tai various stretching and breathing routines.

Conclusion

The psychiatric model for the evaluation and treatment of ME/CFS has been an unqualified failure. The infectious disease model has generated plenty of data that demonstrate the involvement of stealth infections, viral activation, and a host of immune and neurohormonal system abnormalities. This work is finally opening the door to a clinical systems biology model for the evaluation and management of this complex chronic illness.

The puzzle form of CFS is slowly becoming more clear and coherent, though we have much more to learn. The interaction effects of what might be called the "dirty dozen" - susceptibility genetics, activation of latent viruses, biotoxicity, chemical toxicity, electromagnetic toxicity, gluten-mediated toxicity, intestinal hyperpermeability, methylation block, redox imbalance, matrix dysfunction, autonomic dysfunction, and excitotoxicity - will result in a need for more than reductionistic, randomized, controlled clinical trial methods of analysis.

At *onebodymind.com*, we view ME/CFS the same way we view everything else: as a multidimensional metabolic rehabilitation project that applies specifically to you, and that is amenable to some degree to proper self-care.

Our system of self-assessment and care is consistent with an emerging understanding of the origins of chronic illness that is based on systems biology research. We believe that

wise self-care methods should be part of any plan to get key your bodily systems working better together as a team.

Should retroviral research determine a role for high intensity anti-retroviral therapy or intravenous antiviral therapy in ME/CFS, *onebodymind.com* will help guide its subscribers through the process of finding proper sources of care.

Compared to the psychiatric model, the antiviral/metabolic rehabilitation model has more power to explain and treat ME/CFS. The challenge for ME/CFS patients is to find a center with both the *time* and the *experience* needed to apply principles of metabolic balance to complex health problems, and the *time* to apply these principles in a thoughtful and systematic way.

That is how an integrative approach to ME/CFS looks at the unique big picture for each patient, and continually adjusts itself to achieve better results by restoring functional integrity to metabolic systems that have fallen out of balance.

References:

1. Lombardi VC, et al. Detection of infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. Online October 8, 2009. *Science*. http://www.cancer.gov/newscenter/pressreleases/CFSxmrv

2. Erlwein O, Kaye S, McClure MO, Weber J, Wills G, et al. 2010 Failure to Detect the Novel Retrovirus XMRV in Chronic Fatigue Syndrome. PLoS ONE 5(1): e8519. doi:10.1371/journal.pone.0008519 www.plosoneo.rg/article/infor%3Adoi%2F10.1371%2Fjournal.pone.0008519

3. Kean, Sam. An indefatigable debate over chronic fatigue syndrome. *Science*. 15 Jan 2010;137:254-55.

4. Lo SC, et al. Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors. *PNAS Online*. 2010 Aug 23 http://www.pnas.org/cgi/doi/10.1073/pnas.1006901107

5. Courgnaud V, et al. Mouse retroviruses and chronic fatigue syndrome: does X (or P) mark the spot? *PNAS Online*. 2010 Aug 23. http://www.pnas.org/cgi/doi/10.1073/pnas.1007944107

6. Alberts, Bruce. Editorial expression of concern. *Science*. 2011 Jul 1:35

7. Paprotka t, Delviks-Frankenberry KA, Cingöz O, et al. Recombinant origin of the retrovirus XMRV. *Science*. 2011 Jul 1:97-101,

8. Knox, C, Carrigan D, Simmons G, et al. No evidence of murine-like gammaretrovirus in CFS patients previously identified as XMRV-infected . *Science*. 2011 31 May. DOI: 10.1126/science.1204963.

9. Johnson, Hillary. (2006) Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic, Author's Guild, iUniverse: Lincoln, NE.

www.iuniverse.com/Bookstore/BookDetail.aspx?BookId=SKU-000027141

10. Basset, Jodi. (2004-2009) What is Myalgic Encephalitis? www.ahummingsbirdsguide.com

11. The 1988 Holmes Definition of Chronic Fatigue Syndrome. www.cfids-me.org/holmes1988.html

12. The 1994 Fukuda Definition of Chronic Fatigue Syndrome www.cfids.org/about-cfids/case-definition.asp

13. Carruthers BM, et al. Myalgia Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. *Journal of Chronic Fatigue Syndrome*. 2003;11(1).

14. The 2005 Reeves Definition of Chronic Fatigue Syndrome www.cdc.gov/CFS/publications/casedef_10.htm

15. Jason, Leonard, et al, (1999) A Community-Based Study of Chronic Fatigue Syndrome. http://archinte.ama-assn.org/cgi/content/full/159/18/2129

16. Jason, Leonard. (2009) Problems with the New CDC CFS Prevalence Estimates. www.iacfsme.org/IssueswithCDCEmpiricalCaseDefinitionandPrev/tabid/105/Default.aspx

17. The 2007 NICE CFS/ME Guidelines. www.nice.org.uk/guidance/index.jsp?action=folder&r=true&o=34186

18. The 1991 Oxford CFS Criteria. http://uk.geocities.com/me_not_cfs/oxford_criteria.html

19. Carruthers, et al. Myalgic encephalomyelitis: International consensus criteria. *Journal of Internal Medicine*. 2011; doi: 10.1111/j.1365-2796.2011.02428.x

20. Shoemaker, RC, House, D. Sick building syndrome and exposure to water-damaged buildings: Time series study, clinical trial, and mechanisms. *Neurotoxicology and Teratology*, 2006;28(5):573-588. www.biotoxin.info/current_research

21. Hokama Y, Campora CE, Hara C, Kuribayashi T, Le Huynh D, Yabusaki K. Anticardiolipin antibodies in the sera of patient with diagnosed chronic fatigue syndrome. J Clin Lab Anal. 2009;23(4):210-2.

22. Shoemaker RC, House D, Ryan JC. Defining neurotoxin derived illness chronic ciguatera using markers of chronic systemic inflammatory disturbances: a case/control study. *Neurotoxicology and Teratology*. 2010. DOI: j.ntt-06154.

23. Wang DZ. Neurotoxins from marine dinoflagellates: a brief review. *Marine Drugs*. 2008. Jun 11;(6)2:349-71.

24. Kalaitzis JA, Chau R, Kohli GS, Murray SA, Neilan BA. Biosynthesis of toxic naturally-occuring seafood contaminants. *Toxicon*. 2009 Sep 15 [Epub ahead of print].

25. http://cfsfm.org/index.php?option=com_content&view=article&id=2095:oxygen-toxicity-as-a-locus-of-control-for-chronic-fatigue-syndrome&catid=56:dr-paul-r-cheney&Itemid=3637

26. http://www.thecanaryreport.org/2009/08/12/interview-with-martin-pall/

27. Hyde, Byron. (2209) Nightingale Research Foundation Definition of Myalgic Encephalitis. www.nightingale.ca/index.php?target=def_ME_splash