Chronic fatigue syndrome (CFS), also known as chronic fatigue and immune dysfunction syndrome (CFIDS), is a debilitating illness with no known cause, diagnostic test, or universally effective treatment, in spite of 25 years of research and more than 5,000 studies in the peer-reviewed literature. This article is an overview of the signs and symptoms of CFS, solid research findings, and new directions being pursued by scientists in the United States and abroad.

**Characteristic Symptoms of CFS**

As the name chronic fatigue syndrome suggests, this illness is marked by fatigue—a severe, incapacitating fatigue that isn’t improved by bed rest and that may be worsened by physical or mental activity. Although its name trivializes the illness as little more than tiredness, CFS brings with it a constellation of debilitating symptoms. The bone-deep fatigue of CFS is accompanied by characteristic symptoms lasting at least 6 months, which include: sleep difficulties (e.g., falling asleep, staying asleep, and waking unrefreshed), problems with concentration and short-term memory, joint pain (without swelling), muscle pain, tender lymph nodes, sore throat, and headache. A distinctive hallmark of the illness is postexertional malaise, a worsening of symptoms following even very modest physical or mental exertion that can persist for days or weeks.

The severity of CFS varies greatly from patient to patient, with some people able to maintain fairly active lives within strictly observed limits. For others, CFS has a profound impact, and they may be housebound or bedbound most of the time. About 25% of people with CFS are fully disabled by the illness (1). There is
often a pattern of relapse and remission. Most symptoms are invisible to others, which makes it difficult for caregivers, friends, family members, healthcare professionals, and the public to understand the challenges of CFS.

In addition to the 8 case-defining symptoms above, it is not uncommon for people with CFS to have additional symptoms (Table 1). Because these symptoms are shared with many other illnesses—and because many of these conditions lack a diagnostic test or biomarker—unraveling which illnesses are present can be difficult. Some patients receive diagnoses for multiple conditions. Because CFS can resemble other comorbid conditions (Table 2), as well as medical disorders like mononucleosis, multiple sclerosis, chronic Lyme disease, and lupus, it is frequently misdiagnosed.

**Risk and Diagnosis**
Research indicates that at least one million people in the US have CFS and millions internationally (2,3). Other research has shown that CFS is about 4 times as common in women as men, but it strikes people from every age, racial, ethnic, and socioeconomic group (4).

Studies also indicate that fewer than 20% of CFS patients in the United States have been properly diagnosed (2, 4). Diagnosing CFS is a challenging process because there is no diagnostic test or biomarker to clearly identify the disorder, and other medical conditions must be ruled out before a diagnosis of CFS can be established. Diagnosis can also be complicated by the fact that the symptoms and severity of CFS vary considerably from person to person. A CFS case definition from the International Chronic Fatigue Syndrome Study Group (5) was intended to help researchers select appropriate cases for study; however, it is also used by many clinicians to make the diagnosis of CFS. In 2003, a Canadian consensus definition (6) was developed for use in clinical settings, and a pediatric case definition was published in 2008 (7). Diagnosis requires a thorough physical examination and health history to ascertain the presence of case defining symptoms and exclude other possible treatable causes, such as multiple sclerosis, lupus, or malignancies.

**Symptom-Based Treatment Still the State of Care**
Since no cause or cure for CFS has been identified, treatment programs are directed at relieving symptoms, which can allow people with CFS to engage in some of the activities of daily living. Sleep problems, pain, heart rate irregularities, gastrointestinal difficulties, allergies, and depression are some of the symptoms that can

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**Table 1: Additional Symptoms Associated with CFS**
- Visual disturbances (blurring, light sensitivity, eye pain)
- Chills and night sweats
- Gastrointestinal disturbances
- Allergies and sensitivities to foods, odors, chemicals, medications
- Brain fog and cognitive impairment
- Psychological problems (irritability, mood swings, anxiety, panic attacks)
- Difficulty maintaining upright posture, dizziness, balance problems, and fainting
- Gynecological problems, including premenstrual syndrome and endometriosis

**Table 2: Common Comorbidities of CFS**
- Fibromyalgia
- Irritable bowel syndrome (IBS)
- Postural orthostatic tachycardia syndrome (POTS) or neurally mediated hypotension (NMH)
- Interstitial cystitis
- Temporomandibular joint disorder (TMJ)
- Chronic pelvic pain
- Multiple chemical sensitivity (MCS)
**Major Research Findings**

We have learned an enormous amount about the biology of CFS in the past 25 years. Here is a brief summary of 10 major research findings:

1. CFS is not a form of depression, and many patients with CFS have no diagnosable psychiatric disorder. As with most chronic illnesses, such as MS and lupus, many CFS patients become depressed because of the impact of the illness on their lives, but most studies find that the great majority have not experienced depression before the onset of illness.

2. There is a state of chronic, low-grade immune upregulation in CFS. There is evidence of activated T cells, stimulation of genes reflecting immune activation, and increased levels of immune system chemicals called cytokines, which act as chemical messengers between cells.

3. There is substantial evidence of poorly functioning natural killer (NK) cells, white blood cells that are important in fighting viral infections. Studies differ as to whether there are increased numbers of NK cells in CFS patients.

4. Abnormalities in the white matter of the brain have been found in CFS patients using magnetic resonance imaging (MRI) scans. Typically, these are small (fraction of an inch) areas of what just below the cerebral cortex, the outermost area of the brain hemispheres.

5. Abnormalities in brain metabolism describe further as above, as indicated by single photon emission computed tomoscopy (SPECT) and positron emission tomoscopy (PET), have been discovered. Not many patients have had repeated studies over time, but in the few who have, it appears that the abnormalities come and go and predominantly affect the temporal lobes of the brain.

6. CFS patients have abnormalities in multiple neuroendocrine systems in the brain, particularly depression of the hypothalamic-pituitary-adrenal (HPA) axis, but also the hypothalamic-prolactin axis and hypothalamic-growth hormone axis.

7. Cognitive impairment is common in CFS patients. The most frequently documented cognitive abnormalities are difficulty with information processing efficiency, memory, and/or attention.

8. Abnormalities of the autonomic nervous system have been found by numerous independent researchers. These include a failure of the body to maintain blood pressure several minutes after a person stands up, abnormal responses of the heart rate to standing, and unusual pooling of blood in the veins of the legs. Some have also found low levels of blood volume.

9. CFS patients have disordered expression of genes that are important in energy metabolism. Each cell requires energy to survive and perform its function. Energy comes from certain natural chemicals that are processed by enzymes inside each cell, and that rely on nutrients in the diet. The enzymes are controlled by specific genes.

10. There is a growing body of evidence of more frequent latent active infection with various herpesviruses and enteroviruses in CFS patients. The herpesviruses include Epstein Barr virus, HHV-6 and cytomegalovirus, but not the herpesviruses that cause cold sores and genital sores. Other infectious agents also can trigger CFS, including the bacterium that causes Lyme disease, giardia duodenalis, Ross River virus, Q fever, West Nile virus and human parvovirus B19.

Vigorous aerobic exercise may be beneficial for many chronic illnesses, but patients with CFS are unlikely to be able to tolerate even light exercise. Gentle movement and stretching with help from an occupational or physical therapist can be the start of an individualized exercise program that focuses on short intervals of activity followed by 2 or 3 times as much rest. Recumbent or water exercises can be beneficial for those who have orthostatic difficulties.

New Directions in CFS Research
CFS research is conducted with support from the National Institutes of Health, Centers for Disease Control & Prevention, and nonprofit organizations like the CFIDS Association of America. The CFIDS Association is the largest source of research funding outside the federal government, working to build, support, and link a critical mass of innovative and credible researchers focused on early detection, objective diagnosis, and effective treatment and to create, identify, and leverage new private and federal funding sources and opportunities for CFS investigators. Its mission is to make CFS widely understood, diagnosable, curable, and preventable. The following research is being supported by a combination of public and private funds.

Research on a novel infectious agent and its role(s) in triggering and/or perpetuating CFS has accelerated in recent months. In the October 8, 2009 issue of *Science*, researchers at the Whittemore Peterson Institute, the Cleveland Clinic, and the National Cancer Institute reported that 67% of 101 CFS patients tested positive for infection with xenotropic murine retrovirus (XMRV), a gammaretrovirus associated with a subset of prostate cancer (9). Only 3.7% of 218 healthy subjects tested were positive for the virus. At the end of the article, the authors raise questions about this discovery, including “Is XMRV infection a causal factor in the pathogenesis of CFS or a passenger virus in the immunosuppressed CFS patient population?”

Additional questions were raised after a January 6, 2010 report, by researchers at the Imperial College in London, found no evidence of XMRV by polymerase chain reaction testing in 186 CFS patients’ banked samples (10). A third study reported finding no evidence of XMRV infection in 186 CFS patients in the United Kingdom (11). Laboratory methods and patient selection criteria differed between the 3 studies in substantial ways. Further research is under way at several other institutions in the US and other countries, and more reports are forthcoming. There is currently no FDA-approved test available for XMRV and clinical studies of antiviral and antiretroviral treatments must be conducted to test their efficacy against XMRV infection and their safety in XMRV-positive patients. The US government is also coordinating a study to ascertain whether XMRV poses a risk to the safety of the blood supply (12).

Another exciting recent development is a potential blood biomarker for pain and fatigue identified by a team of investigators at the University of Utah. Kathleen Light, PhD, and colleagues are detecting receptors specific to metabolites created by the muscles during a moderate exercise challenge. The markers are not present when CFS subjects are at rest; however, after moderate exercise on a stationary bicycle, the expression of these markers on blood cells increases dramatically in CFS subjects, but not in healthy controls or patients with multiple sclerosis (another condition with substantial pain and fatigue) who exercise the very same way. This means that, so far, these markers appear to detect the postexertion relapse that is the hallmark of CFS. Preliminary data were described in the October 2009 *Journal of Pain* (13).
Another team employing an exercise challenge to further our knowledge about CFS is being led by Sanjay Shukla, PhD, at the Marshfield Clinic Foundation in Wisconsin. Dr. Shukla hypothesizes that people with CFS do not have the right kind and balance of intestinal microbes and that exertion causes the microbes to leak across the intestine causing inflammation and metabolic disturbance. He has assembled a team of experts in internal medicine, exercise physiology, and bacterial phylogeny to assist him in this innovative study. They will collect blood and stool samples before and after an exercise challenge to study how exertion affects gut function and ecology.

Finally, a pair of investigative teams at Weil Cornell University School of Medicine (NY) and New York Medical College (NYMC) has developed a model of CFS that is based on infection causing inflammation and oxidative stress that alters blood flow and increases brain lactate. Dikoma Shungu, PhD, at Weil Cornell has detected elevated lactate in the brains of CFS patients by magnetic resonance scanning, a noninvasive imaging test. He will test patients also studied by Marvin Medow, PhD, at NYMC for blood flow abnormalities and the presence of molecules that cause oxidative stress and that can affect the function of blood vessels.

These studies and others, linked through formal and informal research networks, will improve our understanding of CFS, lead to better diagnostics and treatments, and ultimately cure and prevent the suffering caused by CFS.

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The CFIDS Association of America is the nation’s largest philanthropic supporter of CFS research.

REFERENCES


