

Chronic Fatigue Syndrome

By Ronald Steriti, NMD, PhD

Introduction

Chronic Fatigue Syndrome (CFS) is defined as debilitating fatigue and associated symptoms lasting at least 6 months. Even though the Centers for Disease Control (CDC) officially recognized chronic fatigue syndrome in 1988, it remains a controversial issue.

Chronic Fatigue Syndrome is closely related to another chronic condition, fibromyalgia (FMS). Muscle pain is the prominent symptom of fibromyalgia. However, preliminary studies by the Centers for Disease Control reveal that, for those individuals whose chronic fatigue does not significantly improve after a 5-year duration, the most prominent symptom changes from fatigue to muscle pain

Diagnostic Criteria

The criteria for diagnosing chronic fatigue syndrome was officially defined by the Centers for Disease Control (CDC) in 1988. They have recently revised their definition. The Oxford criteria differs slightly. The British criteria insists upon the presence of mental fatigue, while the American criteria includes a requirement for several physical symptoms, reflecting the belief that CFS has an underlying immune or infectious pathology. (Reid, Chalder et al. 2000) (Harrison 1999)

The CDC Criteria defines Chronic Fatigue Syndrome as: clinically evaluated, unexplained, persistent or relapsing fatigue that is: of new or definite onset; not a result of ongoing exertion; not alleviated by rest; and results in a substantial reduction in previous levels of occupational, social, or personal activity. Four or more of the following symptoms that persist or recur during 6 or more consecutive months of illness and that do not predate the fatigue:

- Self-reported impairment of short-term memory or concentration
- Sore throat
- Tender lymph nodes
- Muscle pain
- Multi-joint pain without swelling or redness
- Headaches of a new type, pattern, or severity
- Unrefreshing and/or interrupted sleep

Exclusion criteria includes:

- Active, unresolved, or suspected disease that is likely to cause fatigue
- Psychotic, melancholic or bipolar depression (but not uncomplicated major depression)
- Psychotic disorders, Dementia, Anorexia or bulimia nervosa
- Alcohol or other substance misuse
- Severe obesity

The Oxford (British) Criteria defines Chronic Fatigue Syndrome as: Severe disabling fatigue of at least six months duration that: affects both physical and mental functioning; and was present for more than 50% of the time. Other symptoms, particularly myalgia and sleep and mood disturbances, may be present. Exclusion criteria includes:

- Active, unresolved, or suspected disease that is likely to cause fatigue
- Psychotic, melancholic or bipolar depression (but not uncomplicated major depression)
- Psychotic disorders, Dementia, Anorexia or bulimia nervosa

Additional Symptoms

Although the symptoms listed above are the official diagnostic criteria, many patients with chronic fatigue syndrome present with a variety of other symptoms, including:

- Pain is almost universal in chronic fatigue
- Allergies
- Chemical sensitivities
- Secondary infections, including Candida and viral infections
- Cognitive impairment, including short-term memory loss, difficulty concentrating, word searching, and math problems
- Digestive disturbances, such as chronic constipation or diarrhea
- Night sweats or spontaneous daytime sweats, unaccompanied by fever
- Headaches, migraines
- Weakness (paresis), muscle fatigue and pain (fibromyalgia)
- Premenstrual syndrome (PMS)
- Sleep disorders, including excessive sleep (hypersomnia), light sleep or an inability to sleep for more than an hour (hyposomnia), disturbing nightmares
- A period of 1-3 hours after awakening during which they are too exhausted to get out of bed (dysania)
- Cystitis (inflammation of the urinary bladder), particularly interstitial cystitis in which urine cultures are negative
- Vision and eye problems, including sensitivity to light (photophobia), dry eyes, tunnel vision, night blindness and difficulty focusing

An initial office exam may also find the following signs:

- Low blood pressure, particularly on standing (orthostatic hypotension)
- Low oral temperatures (less than 97° F)
- Slightly elevated oral temperatures (less than 100° F), which are part of persistent flu-like symptoms.
- Increased heart rate (tachycardia)
- A positive Romberg test (unsteadiness when standing with eyes closed)

Conventional Lab Tests

Doctors usually perform the following labs when attempting to diagnose a patient with CFS:

- Complete blood count (CBC) with differential
- Chemistry panel
- Erythrocyte Sedimentation Rate (ESR), a marker of inflammation
- Urinalysis

Optional tests include:

- Anti-nuclear antibodies (ANA) and rheumatoid factor (RF). These are tests for rheumatoid arthritis and systemic lupus erythematosus (SLE)
- Thyroid tests (T3, T4, TSH)
- Adrenal tests (AM and PM cortisol levels)
- Lyme titers and HIV serology

Specific tests that support (but do not necessarily confirm) a diagnosis of chronic fatigue include: (Verillo and Gellman 1997)

- Tests for viral infections, such as cytomegalovirus, Epstein-Barr virus, Human herpes virus 6, and coxsackie virus
- Immune system tests, including low natural killer (NK) cell counts, elevated interferon alpha, tumor necrosis alpha, interleukins 1 and 2, T cell activation, altered T4/T8 cell ratios, low T cell suppressor cell (T8) count, fluctuating B and T cell counts, antinuclear antibodies, immunoglobulin deficiency, antithyroid antibodies
- Exercise testing may show decreased cortisol levels after exercise, decreased cerebral blood flow after exercise, inefficient glucose utilization, and erratic breathing patterns

Research into the cause(s) of chronic fatigue syndrome touches upon a vast array of systems and etiologies. Several lab tests, in addition to those mentioned above may be helpful in guiding appropriate treatment. These would include:

- Functional assessments of the adrenal gland, including measurements of cortisol, DHEA, and DHEA-S
- Assessments of oxidative stress
- Homocysteine levels
- C-reactive protein, a sensitive marker of inflammation
- Toxin analysis, including heavy metals, pesticides, and organic chemicals

Possible Causes of Chronic Fatigue

There is a considerable amount of research into the cause of chronic fatigue syndrome. Many researchers propose that there may be several different mechanisms that underly CFS. The possible causes of CFS fall into a few broad categories:

- Immune system activation, particularly by viruses
- Oxidative stress, glutathione deficiency
- Endocrine dysfunction, including adrenal fatigue, thyroid deficiency and hypothalamic-pituitary axis abnormalities
- Neurotransmitter deficiencies

- Drug-induced fatigue

As you will see from the following discussion, many of these causes are inter-related. For instance, oxidative stress can cause immune dysfunction through the nitric oxide and peroxynitrate systems. The immune system is also greatly influenced by the endocrine system (and the hormones involved, including DHEA, melatonin).

For many people (and physicians) chronic fatigue syndrome is very confusing. In this article we will present current research on each of the components followed by a section on natural therapies that have been shown to be effective.

The Immune System and Chronic Fatigue Syndrome

Viruses and CFS

Symptoms of CFS resemble a post-viral state and, for this reason, chronic viral conditions have been thought to contribute to CFS in some patients. Several viruses have been associated with CFS, including: (Manian 1994)

- Herpes virus, particularly human herpes virus 6 (HHV-6)
- Epstein-Barr virus (a herpes virus which causes infectious mononucleosis)
- Cytomegalovirus (a herpes virus)
- Coxsackievirus B1 and B4

Chronic viral infections have a detrimental impact on the body through several mechanisms:

- Chronic viral infections cause the immune system to be activated in an effort to fight the infection (Buchwald, Wener et al. 1997)
- Chronic infections are a cause of inflammation in the body

A primary strategy for chronic fatigue syndrome is to support the immune system in fighting viral infections.

The Immune System

The immune system is a complex system of cells and chemical messengers that work together to keep the body clear of pathogenic infections. The components specifically involved in viral immunity include:

- Antigens (viruses) attach to T-helper cells which secrete a variety of chemical messengers (including interferon and interleukin-2) that activate NK cells, macrophages, cytotoxic T cells, and memory B cells.
- Interferon is a group of glycoproteins that activate macrophages to form Natural Killer (NK) cells
- NK cells lyse (split apart) cells that contain viruses.
- Interleukin-2 stimulates proliferation of B and T cytotoxic cells.
- Cytotoxic T cells are formed to attack specific antigens (viruses).

NK Cells

An article published in the journal of *Clinical Infectious Disease* measured natural killer cell activity in 50 healthy individuals and 20 patients with clinically defined chronic fatigue immune dysfunction syndrome (CFIDS). The patients were divided into three groups based on severity of the clinical status. NK cell activity decreased with the increasing severity of the clinical condition. (Ojo-Amaize, Conley et al. 1994)

Researchers have found that human herpes virus 6 targets and kills NK cells. (Lusso, Malnati et al. 1993)

Supplements that have been shown to increase NK cell activity include beta-carotene, vitamin E, zinc, and DHEA. The herbs echinacea and ginseng have been shown to increase NK cell activity in CFS patients (see the Natural Therapies section).

Viruses that “Fool” the Immune System

There are two different types of T-helper cells which defend against different organisms:

- T-helper 1 (Th1) cells target intracellular pathogens (organisms that invade cells), such as viruses. Interleukin-12 (IL-12) stimulates Th1 activation.
- T-helper 2 (Th2) cells target organisms that are found outside of cells. T-helper 2 cells are involved in humoral or antibody-mediated immunity and are triggered by interleukin-10 (IL-10) which is stimulated by bacteria, parasites, toxins, and allergens.

Each of the T-helper cells are activated by different cytokines (see Table). In health, there is a balance between Th1 and Th2 activity. When presented with an acute infection, the Th1 system predominates (and Th2 is suppressed). In chronic infections, the Th2 system predominates leading to antibody production.

Table: Cytokine profiles and functions of T helper cells

Cell	Cytokines	Functions
T helper 1	Interferon-gamma Interleukin-2	Activates cytotoxic cells Inhibits Th2 cells
T helper 2	Interleukin-4, 5, 6, and 10	Activation and maturation of B cells Inhibits Th1 cells

Viruses, especially herpes viruses (like Epstein-Barr virus, cytomegalovirus, and human herpes virus 6) make proteins that mimic IL-10 which activates the Th2 system. Unfortunately, Th2 activation suppresses T-helper 1 (Th1) activity, particularly cytotoxic T cells and natural killer (NK) cells which are the main defense against viruses. In this way the viruses are able to “fool” the immune system and remain untouched by the bodies natural defenses.

Addressing the two different types of T-helper cells has been the focus of work by Paul Cheney, MD. His protocols are designed to stimulate Th1 and inhibit Th2.

Several nutritional supplements, including essential fatty acids, vitamin A, vitamin E, DHEA and melatonin, have been found to have beneficial effects of the Th1:Th2 ratio (see the Natural Therapies section below).

Infection and Inflammation

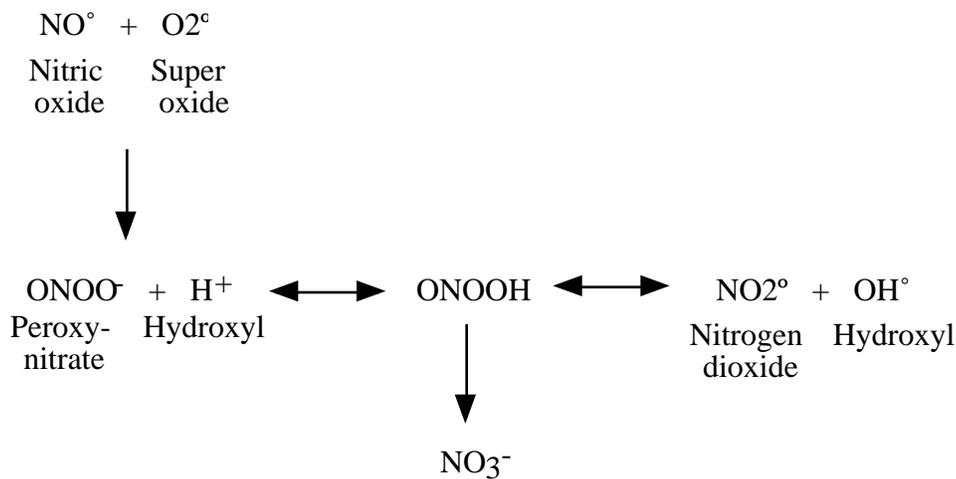
A new theory has been published by Dr. Martin L. Pall (Professor of Biochemistry and Basic Medical Sciences at Washington State University). The theory involves a chain of events:

- Chronic infections that often precede CFS act to induce excessive production of inflammatory cytokines.

- Inflammatory cytokines induce nitric oxide synthase (iNOS) which synthesizes excessive amounts of nitric oxide
- Nitric oxide reacts with superoxide to produce the potent oxidant peroxynitrite (nitrogen dioxide).
- Peroxynitrite acts to increase the levels of both nitric oxide and superoxide which react to produce more peroxynitrite

In this way, once peroxynitrite levels are elevated, they may act to continue the elevation, thus producing a self-sustaining vicious cycle. It is this cycle, according to the theory, that maintains the chronic symptoms of CFS and it is this cycle, therefore, that must be interrupted to effectively treat this condition. (Pall 2000)

Figure: Peroxynitrate metabolism



Breaking the infection-inflammation cycle

Breaking the chain of inflammation caused by chronic viral infections would require a three-part protocol:

- First, the underlying viral infection should be addressed with antiviral supplements (such as ginseng, echinacea and lactoferrin) and those that shift the Th1:Th2 ratio (such as essential fatty acids and vitamin E).
- Second, inflammation should be reduced with anti-inflammatory agents (such as essential fatty acids and curcumin).
- Third, the nitric oxide system should be supported with supplements such as arginine, vitamin B2 (riboflavin), vitamin B3 (niacin), and folate.

Supplements that Support the Immune System

Ginseng and Echinacea

Commission E, the group of scientists that advises the German government about herbs, endorses ginseng "as a tonic to combat feelings of lassitude and debility, lack of energy and ability to concentrate, and during convalescence." (Bahrke and Morgan 2000)

Ginseng is highly prized in China as an herb that increases energy. The higher grades are extremely expensive. Most of the studies on ginseng have focused on its use in enhancing sports performance.

Echinacea has become very popular in the United States as "the herb" to take for colds and flus. Echinacea has strong antiviral properties and has been shown to increase NK cell production. (Sun, Currier et al. 1999) (Currier and Miller 2000) (Currier and Miller 2001)

An article published in the journal *Immunopharmacology* found that both echinacea and ginseng (at concentrations greater or equal to 0.1 or 10 mcg/kg, respectively) significantly enhanced NK-function in patients with chronic fatigue syndrome or the acquired immunodeficiency syndrome. (See, Broumand et al. 1997)

Essential Fatty Acids

The use of essential fatty acids in chronic fatigue syndrome is controversial due to the results of one negative study. It has been proposed that essential fatty acids play a role in chronic fatigue syndrome. One possible mechanism is that viruses, as part of their attack strategy, may reduce the ability of cells to make 6-desaturated essential fatty acids. (Horrobin 1990) (Gray and Martinovic 1994)

The use of essential fatty acids for post-viral fatigue syndrome was examined in a double blind, placebo-controlled study of 63 adults. The patients had been ill for one to three years after an apparent viral infection, suffering from severe fatigue, myalgia and a variety of psychiatric symptoms. The patients received either placebo or a preparation containing linoleic, gamma-linolenic (GLA), eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) over a 3-month period (eight 500-mg capsules per day). Participants were asked to assess their improvement at months 1 and 3. The treatment group showed continual improvement, whereas many in the placebo group reverted towards baseline.

Table: Improvement with essential fatty acid treatment

Time	Improvement	
	Treatment group	Placebo
1 month	74%	23%
3 months	85%	17%

The essential fatty acid composition of their red cell membrane phospholipids was analyzed at the first and last visits. The essential fatty acid levels were abnormal at the baseline and corrected by active treatment. The authors concluded that essential fatty acids provide a rational,

safe and effective treatment for patients with post-viral fatigue syndrome. (Behan, Behan et al. 1990)

A follow-up study of 50 patients diagnosed with chronic fatigue syndrome found no significant difference between the placebo group and those treated with Efamol marine (a combination of Evening Primrose Oil and Marine Fish Oil that contains linoleic acid, GLA, EPA and DHA) In addition, no difference was seen in red cell membrane lipids between the patients and control group. These results sharply contrasted the previous study by Behan et al. (Warren, McKendrick et al. 1999)

Essential fatty acids have been shown to have an effect on the ratio of T-helper 1 and 2 cells. High dietary intake of linoleic acid results in high tissue production of prostaglandin E2, which in turn causes inhibition of the proliferation and cytokine production of Th1 cells, mediators of cellular immunity. (Sammon 1999)

A study examined the effects on the immune system of either a low-fat diet or a high-fat diet containing coconut oil (rich in saturated fatty acids), safflower oil (rich in omega-6 EFAs), or fish oil (rich in omega-3 EFAs) as the main fat sources on mice. The ratio of production of Th1- to Th2-type cytokines was lower for lymphocytes from mice fed the safflower oil or fish oil diets. Although all fatty acids decreased IL-2 production in a concentration-dependent manner, saturated fatty acids were the least potent and omega-3 EFAs the most potent inhibitors, with omega-6 EFAs falling in between in terms of potency. The authors concluded that EFAs act to inhibit production of Th1-type cytokines with little effect on Th2-type cytokines with omega-3 EFAs being particularly potent. (Wallace, Miles et al. 2001)

Essential fatty acids are named “essential” because they play a vital role in health. Essential fatty acids are found in healthy oils, such as fish, flax, borage, and perilla. Unfortunately fatty acids are damaged by heat and many people are deficient due to the high heats used to process packaged foods.

Fatty acid metabolism requires several nutritional cofactors. These include L-carnitine (to move fats in and out of cells), vitamin E (which protects fats against oxidation), and NADH (which breaks fats down to form energy). Each of these nutrients have been studied for use in chronic fatigue syndrome.

L-Carnitine

The amino acid L-carnitine is used in the body to transport fats across cell membranes. Carnitine is synthesized in the body from lysine (an essential amino acid that has antiviral properties) and methionine (an amino acid involved in homocysteine metabolism). L-carnitine is often included in weight-loss supplements to aid in moving fats. L-carnitine is also known to boost energy levels. (Kelly 1998) (Werbach 2000)

Several studies have found deficiencies of carnitine in patients with CFS, while more recent studies have contradicted these findings:

- A study of 35 CFS patients (27 females and 8 males) found significantly lower serum total carnitine, free carnitine and acylcarnitine levels, and that higher serum carnitine levels correlated with better functional capacity. (Plioplys and Plioplys 1995)
- Another study found low levels of acylcarnitine in both Japanese and Swedish patients with chronic fatigue syndrome. (Kuratsune, Yamaguti et al. 1994) (Kuratsune, Yamaguti et al. 1998a)

- A recent study of 25 women with CFS and 25 healthy controls in The Netherlands, however, found no difference in carnitine levels. (Soetekouw, Wevers et al. 2000)

A clinical trial of carnitine for the treatment of CFS found clinical improvement in 12 of 18 patients. The greatest improvement occurred between weeks four and eight of treatment. One patient was unable to complete the trial due to the development of diarrhea. (Plioplys and Plioplys 1997)

Vitamin E

Vitamin E is a powerful antioxidant that is found in vegetable oils. Vitamin E works to protect the fat-soluble parts of the body, such as LDL cholesterol.

Recent research in mice has found that vitamin E may enhance Th1 cytokines, possibly as a result of reduced prostaglandin E2 (PGE2, an inflammatory compound) production. (Han, Wu et al. 2000)

NADH

NADH (reduced B-nicotinamide dinucleotide) is a coenzyme molecule formed from vitamin B3 (niacin). NADH donates its hydrogen in many reactions throughout the body. It is involved in oxidative phosphorylation (the production of ATP, the energy molecule of the body), fatty acid oxidation (the breakdown of fats to make energy), and in carbohydrate metabolism.

A recent randomized, double-blind, placebo-controlled crossover study examined the use of NADH with chronic fatigue syndrome. Twenty-six eligible patients diagnosed with CFS received either 10 mg of NADH or placebo for a 4-week period. Eight of 26 (31%) responded favorably to NADH in contrast to 2 of 26 (8%) to placebo. Based upon these encouraging results the authors decided to conduct a larger study to establish its efficacy in CFS. (Forsyth, Preuss et al. 1999)

NADH (5 to 10 mg per day) is most effective when taken in the morning 30 minutes before breakfast.

Vitamin A

Vitamin A plays a role in the development of T-helper and B cells. Vitamin A deficiency impairs innate immunity by diminishing the function of neutrophils, macrophages, and natural killer cells.

Although vitamin A does play a role in balancing Th1 and Th2 function, it does so by down-regulating Th1 cell IFN-gamma secretion directly, decreasing activated antigen presenting cell (APC) function, and promoting Th2 cell growth and/or differentiation. Therefore, although vitamin A is an important nutrient for immune function, chronic fatigue syndrome patients should avoid excessively high doses. (Wiedermann, Hanson et al. 1993) (Cantorna, Nashold et al. 1994) (Cantorna, Nashold et al. 1995) (Watzl, Bub et al. 1999) (Stephensen 2001)

Whey Protein

Whey protein is perhaps the oldest and most well-known supplement used by athletes and body builders. In recent years, scientists have begun to investigate the health benefits of proteins to improve immunity and prevent diseases.

Whey has recently been shown to have significant antiviral properties (with much of the research on it's ability to increase glutathione levels and inhibit HIV). (Wang, Ye et al. 2000) (Neurath, Strick et al. 1998)

Lactoferrin

Whey protein is comprised of four major protein fractions and six minor protein fractions. The major protein fractions are beta-lactoglobulin, alpha-lactalbumin, bovine serum albumin, and immunoglobulins. Each of these components have important disease-fighting effects. Lactoferrin, in particular, has been shown to have significant antiviral activity. (van der Strate, Beljaars et al. 2001) (Swart, Kuipers et al. 1998) (Harmsen, Swart et al. 1995)

DHEA and Melatonin

DHEA (dehydroepiandrosterone) is the most prevalent hormone produced by the adrenal glands. It circulates in the bloodstream as DHEA sulfate (DHEAS) and is converted into other hormones, including estrogen and testosterone.

Melatonin is a natural hormone that regulates the human biological clock. Levels of melatonin are lower during the day and higher at night. Melatonin is commonly used before bed to aid in sleep.

An article published in the journal *Immunology* described a study of the immune effects of DHEA and melatonin in mice infected with a leukemia retrovirus that caused AIDS. Treatment with DHEA or melatonin alone, as well as together, prevented the reduction of B- and T-cell proliferation as well as of Th1 cytokine secretion caused by retrovirus infection. Supplementation also suppressed the elevated production of Th2 cytokines stimulated by retrovirus infection. (Zhang, Araghi-Niknam et al. 1999)

Arginine

Arginine is made in the body from glutamic acid, and is therefore considered semi-essential. Arginine stimulates the first step in the urea cycle, which rids the body of nitrogenous waste. Arginine is concentrated in muscles, where it is responsible for the high energy compounds guanidophosphate, phosphoarginine and creatine.

An article published in the *European Journal of Clinical Investigation* described a study of the effects of L-arginine on NK cell function in 20 subjects with chronic fatigue syndrome and 21 healthy individuals. Arginine was found to increase NK activity in the healthy subjects but not those with CFS. Further investigation, however, found that the effect of arginine on NK cell activity was mediated by nitric oxide. That is, the increase in NK activity induced by arginine was blocked by the addition of an inhibitor of inducible nitric oxide synthase. NK activity was increased by incubation with a nitric oxide donor. The authors concluded that a dysfunction in the nitric oxide mediated NK cell activation may exist in CFS patients. (Ogawa, Nishiura et al. 1998)

Caution – Arginine has been found to promote the growth of Herpes simplex, especially if lysine levels are low.

Both lysine and arginine contribute to immunity and have antiviral properties. Proteins (meats, fish and cheese) usually contain slightly more lysine than arginine, with eggs containing

equal amounts. Supplementation with equal amounts of lysine and arginine is recommended for those considering this therapy. One 500 mg capsule of each can be taken once or twice daily.

Antioxidants and CFS

Free radical damage (oxidative stress) is probably the most significant cause of biologic aging. Free radicals are unstable molecules that damage cells and are implicated in most diseases associated with aging. Antioxidants are the bodies natural defense against free radical-induced cell damage. Recent studies have shown that oxidative stress plays a role in the development of chronic fatigue syndrome. (Logan and Wong 2001) (Richards, Roberts et al. 2000) (Fulle, Mecocci et al. 2000)

Exercise

Exercise has been shown to increase the production of oxidants. Fortunately, regular endurance exercise results in adaptations in the skeletal muscle antioxidant capacity, which protects myocytes (muscle cells) against the deleterious effects of oxidants and prevents extensive cellular damage. (Powers, Ji et al. 1999) (McCully, Natelson et al. 1996)

A study of the oxygen delivery to muscles in patients with CFS found that oxygen delivery and oxidative metabolism was significantly reduced in CFS patients after exercise, when compared with sedentary controls. (McCully and Natelson 1999)

The issue of exercise in chronic fatigue syndrome is a topic of debate. Many women with CFS were active athletically. There is some overlap between CFS symptoms and overtraining syndrome. Physical exercise is sometimes recommended for those with CFS. Unfortunately, for some people with CFS even minimal exercise can cause extreme fatigue. The antioxidant theory offers a novel explanation for this situation and provides several powerful therapies for those who enjoyed an active lifestyle before the chronic fatigue symptoms developed.

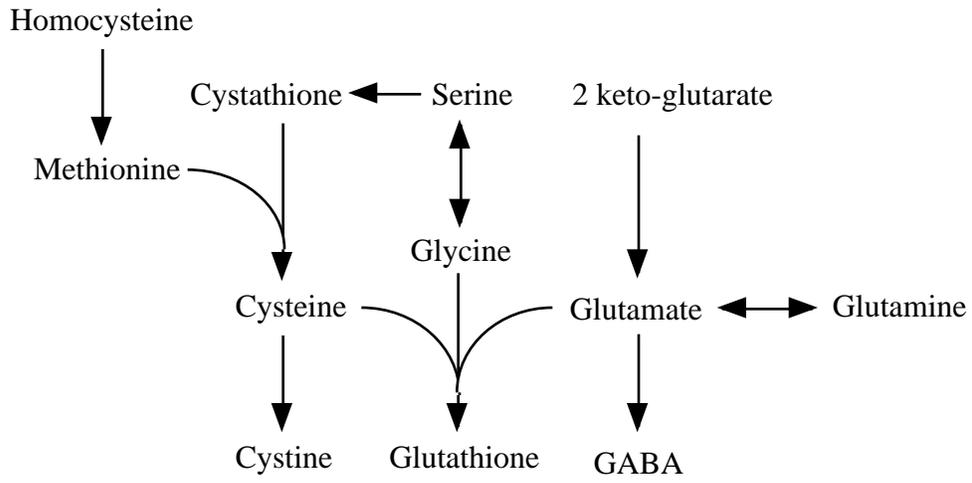
Elevated Homocysteine Levels and CFS

Homocysteine is a toxic intermediate molecule formed in the body during cellular damage. Homocysteine, although toxic itself, is normally metabolized into other nutrients that are beneficial to the body, including cysteine, taurine and glutathione. Homocysteine is so toxic to the body that many consider it to be much worse than cholesterol. (McCully 1996)

A study of 12 women who fulfilled the criteria for both fibromyalgia and chronic fatigue syndrome found that, in all the patients, the homocysteine levels were increased in the cerebrospinal fluid (CSF). There was a significant positive correlation between CSF homocysteine and B12 levels and fatigue-ability, as rated on the Comprehensive Psychopathological Rating Scale. The authors concluded: “increased homocysteine levels in the central nervous system characterize patients fulfilling the criteria for both fibromyalgia and chronic fatigue syndrome”. (Regland, Andersson et al. 1997)

Homocysteine and glutathione metabolism are related in biochemical pathways that involve cysteine, glutamine, glycine and GABA (see Figure).

Figure: Glutathione metabolism



Antioxidant Therapy for Chronic Fatigue Syndrome

Glutathione and N-Acetyl Cysteine

Glutathione is a peptide-like molecule naturally synthesized in the body from three amino acids: L-glutamic acid, L-cysteine, and glycine. Glutathione is one of the body's most important and powerful antioxidants. Glutathione also attaches to toxic molecules, which are then eliminated from the body (detoxification).

An article published in the journal *Medical Hypothesis* proposed that glutathione, an antioxidant essential for lymphocyte function, may be depleted in chronic fatigue syndrome patients. Glutathione is needed for both the immune system and for aerobic muscular contraction. The authors proposed that glutathione depletion by an activated immune system also causes the muscular fatigue and myalgia associated with chronic fatigue syndrome. (Bounous and Molson 1999)

Cysteine is a precursor to glutathione. It has been hypothesized that glutathione and cysteine metabolism may play a role in skeletal muscle wasting and muscle fatigue. The combination of abnormally low plasma cysteine and glutamine levels, low natural killer (NK) cell activity (with a resulting susceptibility to viral infection), skeletal muscle wasting or muscle fatigue, and increased rates of urea production defines a complex of abnormalities that is tentatively called "low CG syndrome." These symptoms are found in patients with HIV infection, cancer, major injuries, sepsis, Crohn's disease, ulcerative colitis, chronic fatigue syndrome, and to some extent in over-trained athletes. (Droge and Holm 1997)

N-acetyl-cysteine is a precursor of glutathione that has been shown to be helpful against viruses (most of the research has been with HIV and Hepatitis infections). (Sprietsma 1999) (Weiss, Hildt et al. 1996)

Coenzyme Q10

Coenzyme Q10 has long been prescribed for CFS patients. CoQ10 is a potent antioxidant that aids in metabolic reactions including the process of forming ATP, the molecule the body uses for energy. Virtually every cell in the body contains CoQ10. It is concentrated in the mitochondria, the area of the cells where energy is produced.

Judy presented a study of 20 female patients with CFS that required bed rest following mild exercise and 20 healthy controls. Eighty percent of the CFS patients were found to be deficient in CoQ10 which further decreased following mild exercise or over the course of normal daytime activity. After three months of CoQ10 supplementation (100 mg per day) exercise tolerance (400 kg-meters of work) more than doubled. All patients had improved. Ninety percent had reduction and/or disappearance of clinical symptoms, and 85 percent had decreased post-exercise fatigue. (Judy 1996) (Werbach 2000)

Coenzyme Q10, 100 mg taken 3 times a day, often helps victims of severe chronic fatigue syndrome.

Folate

Folate plays a role in many key biochemical reactions in the body. Folic acid is involved in homocysteine metabolism (with vitamins B6 and B12). It is needed to form glutamate (a

precursor of glutathione), and is involved in DNA replication. Folate is also needed to make SAMe (S-adenosyl methionine), a natural supplement which affects (and may improve) mood.

An article published in the journal *Neurology* described a study in which serum folate levels were measured in 60 patients with chronic fatigue syndrome. Researchers found that 50% had values below 3.0 micrograms/L (the normal values are 2-20). The authors concluded that some patients with CFS are deficient in folic acid. (Jacobson, Saich et al. 1993)

Most people do not consume the recommended amount of folic acid in their diet. Mild folic acid deficiencies are common in Western societies, and women taking birth control pills are at higher risk. It is recommended that women who are or could become pregnant should take 400-800 mcg per day to reduce the risk of birth defects. Most nutritionally-oriented doctors recommend that everyone take 400 mcg of folic acid per day.

Glutamine

Glutamine is a conditionally essential amino acid that is needed during periods of excessive stress. Glutamine is the preferred energy for enterocytes, the cells lining the gastrointestinal tract.

An article published in the *British Journal of Sports Medicine* described a study of athletes during an intense training period before the 1992 Olympics. The athletes were divided into three groups who differed in training fatigue and were considered separately. Group A (21 track and field athletes) had no lasting fatigue; group B (12 judo competitors) reported heavy fatigue at night but recovered overnight to continue training; group C (18 track and field athletes, one rower) had chronic fatigue and had been unable to train normally for at least several weeks. Plasma amino acid analysis showed that group A had a normal amino acid pattern, and both groups B and C had decreased plasma glutamine (average 33%) with, especially in group B, decreased histidine, glucogenic, ketogenic, and branched chain amino acids. Ten athletes in group C presented with infection.

After three weeks of additional protein intake, virtually all the low glutamine levels increased to above 500 micromol/L. Total amino acids increased, and the amino acid pattern normalized. Six of the ten athletes on this protein intake returned to increased training within the three weeks. (Kingsbury, Kay et al. 1998)

Glutamine is a non-essential amino acid that supplies energy to the brain. It has been found to be helpful in reducing fatigue, improving exercise endurance, alleviating hypoglycemia, and strengthening the immune system. One or two grams may be used as needed and is often recommended before exercise. Insomnia, however, may occur if glutamine is consumed too close to bedtime.

CFS and The Endocrine System

The Hypothalamus-Pituitary-Adrenal Axis

The HPA axis refers to the hypothalamus, pituitary, and adrenal glands which are part of the endocrine system. The hypothalamus secretes several hormones that control the pituitary gland. The pituitary gland is considered the “master gland” of the endocrine system because it secretes hormones that control other glands (including the ovaries, testes, adrenals, and thyroid glands).

A major role of the HPA axis is to restrain the immune system and prevent tissue damage. Reciprocal interactions between the HPA axis and immune system constitutes a new endocrine feedback loop that has given rise to the field of neuroendocrine immunology. (Torpy and Chrousos 1996)

"Many experts now think that chronic fatigue syndrome may be an example of the hypothalamus failing to properly regulate the brain's influence on the immune system," says Jay Lombard, M.D., assistant clinical professor of neurology at Weill Medical College of Cornell University in New York City and co-author of *The Brain Wellness Plan*. (Neeck and Crofford 2000)

Adrenal Fatigue

It has been proposed that CFS is a mild form of Addison's disease (which may be referred to as adrenal insufficiency, adrenal fatigue or hypoadrenalism). The following evidence is presented: (Baschetti 1999) (Baschetti 2000) (Jeffcoate 1999) (Jefferies 1994)

- Many of the symptoms of chronic fatigue syndrome overlap those of Addison's disease (adrenal failure).
- Improvement in CFS patients has occurred after supplementation with mineralocorticoids (fludrocortisone), low-dose hydrocortisone (cortisol), and licorice (an old herbal remedy for Addison's disease).

Cortisol is the main glucocorticoid secreted the adrenal glands. It has two main functions:

- Cortisol increases blood glucose levels during periods of stress (the “fight or flight response”) by mobilizing carbohydrates, lipids and protein. It also stimulates the breakdown of fats to release energy. Cortisol inhibits the effects of insulin and decreases the rate of glucose use by cells.
- Glucocorticoids, including cortisol, are anti-inflammatory. They inhibit histamine secretion, inhibit lymphocyte production, and stabilize macrophage lysosomes.

Cortisol production by the adrenal glands follows a diurnal rhythm: They are elevated in the morning and lower in the evening (during sleep). People under stress often have no diurnal variation in their cortisol levels.

An article published in the journal *Neuropsychobiology* described a study in which morning and evening serum cortisol and ACTH concentrations, and diurnal changes in hormone levels, were measured in 30 patients with chronic fatigue syndrome (CFS) but without concurrent depressive disorder and a control group of 15 matched healthy volunteers. The diurnal change in cortisol levels was significantly less in CFS than in controls. In CFS subjects, evening levels of cortisol correlated significantly with measures of general health and physical functioning, while

diurnal change in cortisol was positively correlated with measures of functional improvement over the past year and current social functioning. (MacHale, Cavanagh et al. 1998)

An article published in the *Journal Clinical Endocrinology Metabolism* described a study of cortisol levels in thirty CFS patients and 72 normal volunteers. Compared to normal subjects, CFS patients demonstrated significantly reduced basal evening glucocorticoid levels and low 24-hour urinary free cortisol excretion, but elevated basal evening ACTH concentrations. There was increased sensitivity to ACTH, but a reduced maximal response. The authors concluded that primary adrenal insufficiency or a pituitary source is unlikely, and that the data was compatible with a mild central adrenal insufficiency secondary to either a deficiency of CRH (a secretion of the hypothalamus) or some other central stimulus to the pituitary-adrenal axis. (Demitrack, Dale et al. 1991)

One study measured the morning and evening salivary cortisol levels obtained on consecutive days in the first 3 days of the menstrual cycle in 14 patients with chronic fatigue syndrome, 26 community cases of ICD-10 current depressive episodes and 131 healthy community controls. The mean evening cortisol was significantly lower in the chronic fatigue syndrome patients compared to controls with depression and healthy controls. Chronic fatigue syndrome patients without psychiatric disorder had significantly lower morning salivary cortisol levels compared to controls. (Strickland, Morriss et al. 1998)

An article published in the *Journal of Affective Disorders* described a study in which cortisol levels were measured in 10 patients with CFS, 15 patients with major depression, and 25 healthy controls. Baseline circulating cortisol levels were highest in the depressed, lowest in the CFS, and intermediate between the two in the control group. Prolactin responses to the selective serotonin-releasing agent d-fenfluramine were lowest in the depressed, highest in the CFS, and intermediate between both in the healthy group. The authors concluded that depression is associated with hypercortisolemia and reduced central serotonin neurotransmission and suggest that CFS may be associated with hypocortisolemia and increased 5-HT function. (Cleare, Bearn et al. 1995)

One interesting study measured the size of the adrenal glands in eight CFS patients that had evidence of adrenal hypofunction (determined by a subnormal response to an ACTH stimulation test). The right and left adrenal gland bodies were reduced by over 50% in the CFS subjects indicative of significant adrenal atrophy in a group of CFS patients with abnormal endocrine parameters. (Scott, Teh et al. 1999)

Natural Supplements to Support Adrenal Function

DHEA

DHEA (dehydroepiandrosterone) is a hormone secreted from the adrenal glands. It is a precursor of the sex hormones (estrogen and testosterone). DHEA-S has recently been shown to have beneficial effects on memory, stress, anxiety, sleep and depression. Therefore, the deficiency of DHEA-S might be related to the symptoms in patients with CFS. (van Rensburg, Potocnik et al. 2001) DHEA has been reported to improve energy levels in chronic fatigue patients. (Kuratsune, Yamaguti et al. 1998b)

One study showed the value of DHEA and vitamin C infusion treatment in the control of chronic fatigue syndrome. (Kodama, Kodama et al. 1996)

A study of 15 subjects with CFS, 15 subjects with major depression, and 11 healthy subjects found that DHEA and DHEA-S levels were significantly lower in the CFS compared to the healthy group. DHEA-S levels, but not DHEA, were lower in the depressives. The authors concluded that DHEA has a potential role both therapeutically and as a diagnostic tool, in CFS. (Scott, Salahuddin et al. 1999)

Another study of DHEA levels in 22 CFS patients and 14 healthy controls found normal basal DHEA levels, but a blunted serum DHEA response curve to ACTH (adreno-corticotrophic hormone) injection. ACTH normally stimulates the adrenal glands to secrete DHEA. The authors concluded that endocrine abnormalities play a role in CFS and that a relative glucocorticoid deficiency might contribute to the overall clinical picture in CFS. (De Becker, De Meirleir et al. 1999)

Licorice

Licorice is highly valued as a medicinal herb by the Chinese and is an ingredient in almost all of the Chinese patent herbal formulas. Licorice has a sweet taste and helps combat fatigue. The active constituent in licorice, glycyrrhizin, stimulates the production of hormones, including cortisone, and stimulates the production of interferon, which boosts immunity. Licorice is an old herbal remedy that was used medically for Addison's disease and adrenal insufficiency. (Baschetti 1995a) (Baschetti 1995b)

Licorice should be used with care since it is well-known to increase blood pressure. Two to four 500 mg capsules can be taken twice a day. Licorice may also be consumed as a tea (one cup in the morning).

Orthostatic Hypotension

Orthostatic hypotension is defined as an excessive fall in blood pressure on standing, usually greater than 20/10 mmHg. It is considered to be a manifestation of abnormal blood pressure regulation due to a variety of causes.

Hypotension, particularly orthostatic hypotension, is a common symptom in chronic fatigue patients. Many people with CFS have chronic low blood pressure (the normal is 120/80 mmHg), which is made even worse on standing. This may be a particular problem in the morning, when standing can cause dizziness. Exercise or a heavy meal may exacerbate the symptoms. Syncope is a loss of consciousness and postural tone caused by diminished cerebral blood flow. Syncope often occurs during the morning shower, perhaps due to the vasodilating effect of hot water.

There are several mechanisms that govern blood pressure. Upon standing, a large amount of blood pools in the veins of the legs and trunk. The transient decrease in venous return to the heart results in a low blood pressure. The body responds with a sympathetic-mediated release of catecholamines (norepinephrine and epinephrine) that increase heart rate contraction and vasoconstricts the arteries. With continued standing, antidiuretic hormone (ADH) is secreted which activates the renin-angiotensin-aldosterone system subsequently causing sodium and water retention and an expansion of the circulating blood volume.

There are many causes of orthostatic hypotension, including:

- Hypovolemia (low blood volume) induced by excessive use of diuretic agents (e.g., loop diuretics such as furosemide, bumetanide, and ethacrynic acid) and relative hypovolemia due to vasodilator therapy with nitrate preparations and calcium antagonists (verapamil, nifedipine, or diltiazem) or with angiotensin converting enzyme (ACE) inhibitors.
- Histamine, a key player in allergic reactions, induces vasodilation and hypotension.
- Potassium deficiency (hypokalemia) impairs the reactivity of vascular smooth muscle and may limit the increase in peripheral vascular resistance on standing.
- The adrenocortical hypofunction of Addison's disease may lead to orthostatic hypotension in the absence of adequate salt intake.
- Several classes of drugs reversibly impair autonomic reflexes and reduce blood pressure on standing as an important adverse effect. These include many drugs used to treat psychiatric disorders such as the monoamine oxidase inhibitors (MAOIs) (isocarboxazid, phenelzine, and tranylcypromine) used to treat depression; the tricyclic antidepressants (nortriptyline, amitriptyline, desipramine, imipramine, and protriptyline) or tetracyclic antidepressants; and the phenothiazine antipsychotic drugs (chlorpromazine, promazine, and thioridazine). Other drugs that may produce orthostatic hypotension are quinidine, l-dopa, barbiturates, and alcohol.

Vasopressin (ADH)

Vasopressin is a hormone secreted by the posterior pituitary gland that is also called antidiuretic hormone (ADH) because its principle effect is to cause retention of water by the kidneys. Vasopressin has several effects on the body in addition to the effect on water retention:

- Vasopressin causes vasoconstriction of blood vessels which can increase blood pressure

- Vasopressin induces secretion of ACTH in the anterior pituitary which stimulates cortisol production in the adrenal glands
- Vasopressin also has a role in memory.

Vasopressin is made from several amino acids, including cysteine, tyrosine, proline, glycine and arginine. Vasopressin secretion is affected by several stimuli, including:

- Increased secretion of ADH is diagnosed as syndrome of inappropriate antidiuretic hormone (SIADH) and can be caused by:
 - Increased osmotic water pressure
 - Decreased extracellular fluid volume
 - Nicotine; Morphine, barbiturates, chlorpropamide, clofibrate, carbamazepine, angiotensin II
 - Pain, emotion, stress, exercise, standing
 - Nausea and vomiting
- Decreased secretion of ADH can be caused by:
 - Decreased osmotic water pressure or Increased extracellular fluid volume
 - Alcohol
 - Butophanol, oxilorphan
 - Diabetes insipidus is decreased ADH or insensitivity to ADH which results in the passage of large amounts of dilute urine (polyuria) and thirst (polydipsia).

Several studies have linked problems with vasopressin to chronic fatigue: (Parker, Wessely et al. 2001) (Peroutka 1998)

- One study of 19 patients with chronic fatigue syndrome and 19 healthy controls found that patients with chronic fatigue syndrome had a reduced ACTH response to vasopressin infusion and a more rapid cortisol response to the infusion. (Altemus, Dale et al. 2001)
- Another study of nine patients with postviral fatigue syndrome found low baseline levels and an erratic secretion of arginine vasopressin in the patients with postviral fatigue syndrome. (Bakheit, Behan et al. 1993)
- An article published in the journal *Biological Psychiatry* described a study of chronic fatigue syndrome patients which found that the combination of CRH and desmopressin (a synthetic analog of vasopressin) normalized the pituitary-adrenal response to CRH. (Scott, Medbak et al. 1999)

The most common form of vasopressin available in the United States is lysine vasopressin made by Sandoz Pharmaceuticals in the form of a nasal spray called Diapid (Lypressin). Many people are experimenting with Diapid to help increase their memory. It may also be of use in chronic fatigue syndrome.

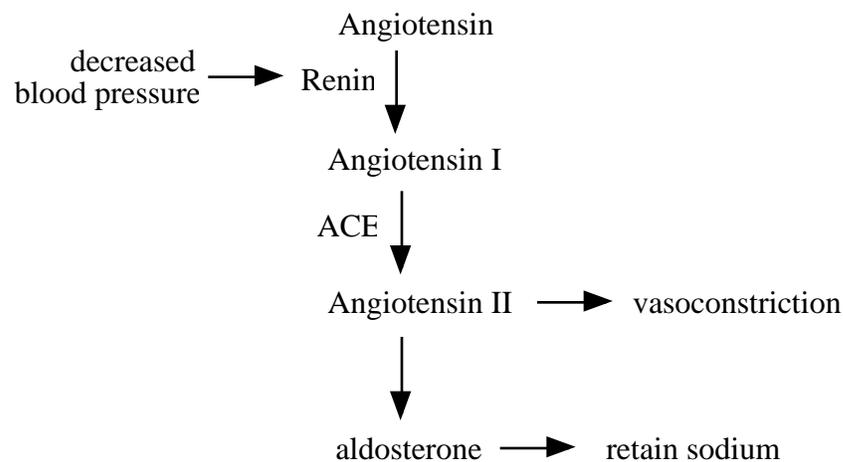
Sodium

Sodium is known to increase blood pressure and cardiac patients are usually placed on sodium-restricted diets. Chronic fatigue syndrome patients, however, often have hypotension.

One study examined the use of sodium chloride (1200 mg) in a sustained-release formulation for 3 weeks in 22 patients with CFS and orthostatic hypotension. Of these 22 patients, 10 redeveloped orthostatic hypotension, while 11 did not show an abnormal response to the test and reported an improvement of CFS symptoms. However, those CFS patients who again developed an abnormal response to tilt-test had a significantly reduced plasma renin activity compared both with healthy controls and with those 11 chronic fatigue patients who improved after sodium chloride therapy. (De Lorenzo, Hargreaves et al. 1997)

The testing of the renin levels of chronic fatigue syndrome patients that did not respond to sodium chloride is an important distinction in this study. As discussed earlier, orthostatic hypotension can be due to a several factors. The focus of this study was on adrenal hypofunction with inadequate salt intake. Those that did not respond to the salt intake had a reduction in renin, which increases blood pressure.

Figure: The Renin-Angiotensin-Aldosterone System



Sodium restriction has become a popular for those with high blood pressure (and associated increased cardiovascular risk factors). Chronic fatigue syndrome patients with low blood pressure and orthostatic hypotension do not need to restrict dietary sodium intake. Using sodium therapeutically should be done under the care of a well-trained and knowledgeable physician or cardiologist.

Neurotransmitters and CFS

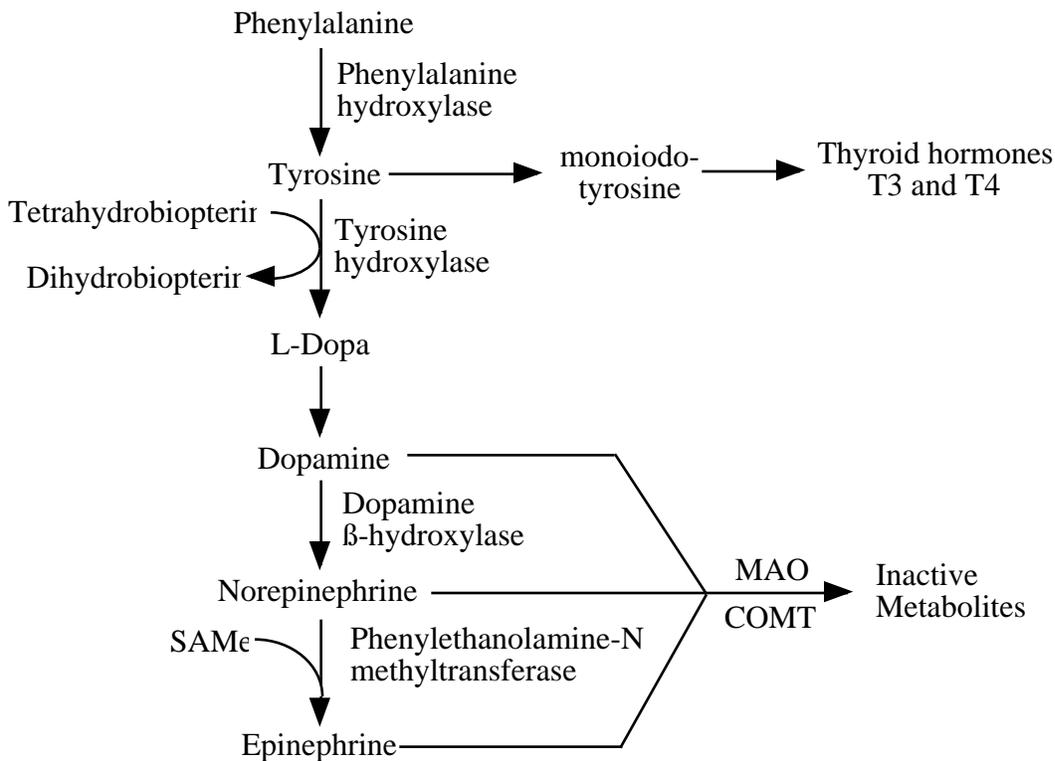
Deficiencies in brain hormones and neurotransmitters are also known to cause low levels of energy.

Table: Neurotransmitters

Excitatory Neurotransmitters	Inhibitory Neurotransmitters
<ul style="list-style-type: none"> • Acetylcholine • Norepinephrine • Glutamate 	<ul style="list-style-type: none"> • Dopamine • GABA • Glycine • Serotonin

Catecholamines are neurotransmitters that are primarily secreted during times of stress. The principal catecholamines found in the body include norepinephrine, epinephrine, and dopamine. They are formed from the amino acid tyrosine.

Figure: Tyrosine Metabolism



Supplements That Support Neurotransmitter Function

L-Tyrosine

A study of the catecholamine production was performed on rats after swimming for a period of 8 hours. There was a decreased production of catecholamines after swimming. In the presence of L-tyrosine, there is at first an activation of noradrenaline synthesis, followed by a gradual normalization (on the 7th day) of adrenaline formation. (Matlina, Vaisman et al. 1975)

One study examined the alterations in metabolism of catecholamines (adrenaline, noradrenaline, their precursors DOPA and dopamine, and their acid metabolites vanillyl mandelic acid) in sportsmen after development of acute fatigue as a result of the test physical loading. The authors found that excretion of catecholamines and their precursors was decreased for a long time after development of chronic fatigue in the resting state and the increase in excretion of the substances studied was not observed after physical loading. (Matlina, Vasil'ev et al. 1977)

An article published in the journal *Medical Science of Sports Exercise* described a study of the effects of tyrosine on exercise tolerance and brain neurochemistry of mice. Tyrosine injections improved maze performance and prevented increase of levels of serotonin (5-HT) in the hypothalamus that follows exercise. Tyrosine administration significantly improved food consumption, cognitive behavior, and activity performance. The authors concluded that tyrosine may improve exercise tolerance and delay fatigue. (Avraham, Hao et al. 2001)

An article published in the journal *Brain Research Bulletin* described a study of the effects of tyrosine on a group of 21 cadets during a demanding military combat training course. Ten subjects received five daily doses of a protein-rich drink containing 2 grams of tyrosine, and 11 subjects received a carbohydrate rich drink with the same amount of calories (255 kcal). The group supplied with the tyrosine-rich drink performed better on a memory and a tracking task than the group supplied with the carbohydrate-rich drink. In addition, the supplementation of tyrosine decreased systolic blood pressure. No effects on mood were found. The authors concluded that these findings suggest that supplementation with tyrosine may, under operational circumstances characterized by psychosocial and physical stress, reduce the effects of stress and fatigue on cognitive task performance. (Deijen, Wientjes et al. 1999) (Owasoyo, Neri et al. 1992)

The amino acids phenylalanine or tyrosine, taken in daily doses of 1500 mg, can boost epinephrine and norepinephrine levels. Caution – phenylalanine and tyrosine should not be taken by those using MAO inhibitors and should be used with caution in those on thyroid medication (Synthroid).

Magnesium

Magnesium is involved primarily with muscle relaxation. Acetylcholine is the neurotransmitter with calcium and magnesium regulating the amount of acetylcholine released. Calcium causes muscular contraction, while magnesium causes muscular relaxation.

Magnesium deficiency causes neuromuscular irritability with muscle tightness and spasm and nerve conduction problems. It also affects the heart and cause hypertension or hypotension. Magnesium deficiency is a common cause of premenstrual cramping, and also causes fatigue.

An article published in *Lancet* described a randomized, double-blind, placebo-controlled study of 20 patients with CFS. The CFS patients were found to have lower red cell magnesium concentrations. In a clinical trial, 32 CFS patients received either placebo or intramuscular magnesium sulfate every week for 6 weeks. Patients treated with magnesium claimed to have improved energy levels, better emotional state, and less pain, as judged by changes in the Nottingham health profile. Red cell magnesium returned to normal in all patients on supplemental magnesium but in only 1 patient on placebo. The authors concluded that these results show that magnesium may have a role in CFS. (Cox, Campbell et al. 1991)

One study, however, found no difference in red blood cell magnesium concentrations in samples from 89 patients with CFS when compared to age and sex matched group selected from the normal population. A magnesium-loading test on six patients found no evidence of deficiency. (Hinds, Bell et al. 1994)

A study of 97 chronic fatigue patients (chronic fatigue syndrome, fibromyalgia or/and spasmophilia) was conducted in Belgium. An IV loading test showed a magnesium deficit in 44 patients. After magnesium supplementation in 24 patients, the loading test showed a significant decrease in magnesium retention. Mean values of magnesium in the serum, red blood cell, and urine showed no significant difference between patients with or without magnesium deficiency. Serum magnesium levels were found to be significantly lower in the patients with spasmophilia (muscle cramps, twitching and spasms) than in the other patients. (Moorkens, Manuel y Keenoy et al. 1997)

A study of 93 patients with unexplained chronic fatigue (54% with CFS) examined the relationship between magnesium deficiency and oxidative stress. Magnesium deficient patients (47%) had lower total antioxidant capacity in plasma, which was related to serum albumin. Magnesium deficient patients whose magnesium body stores did not improve after oral supplementation with magnesium (10 mg/kg/day) had persistently lower blood glutathione levels. The authors concluded that magnesium supplementation was followed by an improvement in magnesium body stores, in serum vitamin E, and its interrelated stage of lipid peroxidation. (Manuel y Keenoy, Moorkens et al. 2000)

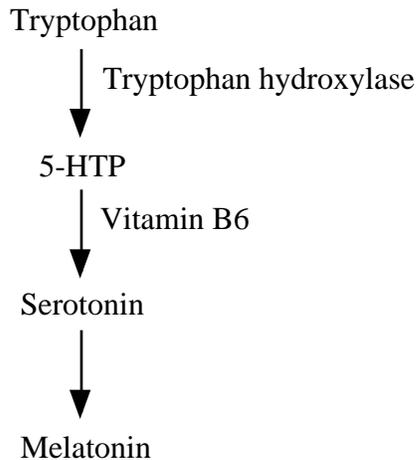
Magnesium plays a crucial role in metabolism. It is needed for activating B vitamins, relaxing muscles, and forming ATP, the energy molecule. Fatigue, muscle cramps and constipation are signs a magnesium deficiency. Normal concentrations of magnesium in blood do not rule out the diagnosis of the nervous form of primary chronic magnesium deficiency. The diagnosis of magnesium deficiency requires an oral magnesium load test. (Durlach, Bac et al. 1997)

Most people do not consume enough magnesium in their diet. Magnesium is often paired with calcium as they work together and compete for absorption. Determining the proper ratio of calcium to magnesium is important, but can be determined readily. Taking too much magnesium often leads to diarrhea. An easy method would be to begin with one capsule of magnesium once or twice a day. The dose is increased until the stools become watery, then backed off to maintain a normal consistency of stools.

Tryptophan and 5-HTP

Tryptophan is the precursor for the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT), which is involved in fatigue and sleep. It is present in bound and free form in the blood, where the concentration is controlled by albumin binding to tryptophan.

Figure: Tryptophan Metabolism



Several older studies found that tryptophan was helpful in chronic fatigue. (Lieberman, Corkin et al. 1982) (Lieberman, Corkin et al. 1985) A recent study found that plasma-free tryptophan was significantly decreased in CFS patients. (Vassallo, Feldman et al. 2001) Tryptophan was banned for use as a supplement by the FDA following several deaths due to contaminated batches.

Many companies are now making 5-HTP as a substitute for tryptophan. It has become a popular supplement used for depression. Unfortunately, 5-HTP is not as safe as tryptophan, particularly because it bypasses the enzyme tryptophan hydroxylase. As such, it can be converted into serotonin in peripheral tissue instead of in the brain. For this reason Life Extension Foundation recommends against the use of 5-HTP. Life Extension also encourages the FDA to reconsider its ban on tryptophan.

Of particular concern to those that are considering supplementing with 5-HTP is that abnormally high levels (which can be achieved by supplementation or by prolonged exercise) can cause central fatigue. (Castell, Yamamoto et al. 1999) (Blomstrand, Perrett et al. 1989)

Drug-Induced Fatigue

The following drugs are associated with side effects of chronic fatigue syndrome.

Table: Medications that may cause fatigue

Antidepressants	Clomipramine (Anafranil), Isocarboxazid (Marplan) Diazepam (Valium), Alprazolam (Xanax) Prazepam (Centrax), Trazodone (Desyrel) Sertraline (Zoloft), Buspirone (BuSpar)
Antihypertensives	Guanadrel (Hylorel), Doxazosin (Cardura) Metoprolol (Lopressor, Toprol), Hydrochlorothiazide (HCTZ), Acebutolol (Sectral), Atenolol (Tenormin), Tomolol (Blocadren) Atenolol and Chlorthalidone (Tenoretic), Carteolol (Cartrol), Clonidine (Catapres)
Muscle relaxants	Dantrolene (Dantrium)
Immune agents	Interferon Alfa (Intron, Roferon-A) Zalcitabine (Hivid) Interferon gamma-1b (Actimmune) Interleukin-2 (Proleukin)
Anemia	Erythropoetin (Epogen, Procrit), Filgrastim (Neupogen)
Miscellaneous	Antimalarial: Mefloquine (Lariam); Cystitis: Mesna (Mesnex) Antiprotozoan: Pentamidine (NebuPent) Biphosphates: Pamidronate (Aredia) Chelate: Succimer (Chemet) Hepatitis B vaccine (Engerix-B) Antiemetics: Metoclopramide (Reglan) Dermatology: Isotretinoin (Accutane), Etritinate (Tegison) Anticancer: Fludarabine (Fludara), Nipent (Pentostatin)

Source: Physicians Desk Reference. Compiled by www.HolisticOnline.com

Conventional Treatments

Prescription Medications

There are currently no prescription medications approved by the FDA for use in chronic fatigue syndrome. There are, however, quite a number of medications that are used to treat the various symptoms of Chronic Fatigue Syndrome. Many are recommended for effects that may be unrelated to their primary use. These may include anti-depressants, anti-fungals, anti-histamines, anti-virals, CNS depressants (or stimulants), immunoglobulins, cardiac medications, anti-inflammatories, anti-convulsants, corticoids, and expectorants.

Drug Research

Ampligen

Ampligen is an experimental anti-viral medication currently in phase III testing for the treatment of CFS. It is considered a “second generation interferon.” In clinical trials conducted outside the US, over 50% of test subjects taking Ampligen showed both physical and mental improvement of symptoms. Unfortunately, most of the study groups were too small for the results to be published in the scientific literature. Hemispherx, the drug manufacturer is hoping the current research trials will provide enough hard data to meet the criteria of FDA approval.

Hydrocortisone

Hydrocortisone is an anti-inflammatory that can be taken orally or administered topically. An article published in the journal *Lancet* described a study of 218 patients with chronic fatigue syndrome that received hydrocortisone (5 or 10 mg daily) for one month and placebo for one month. Self-reported fatigue scores for patients on hydrocortisone fell by 7.2 points, compared with 3.3 points for those on placebo. (Cleare, Heap et al. 1999)

One researcher, however, concluded that although hydrocortisone treatment was associated with some improvement in symptoms, the degree of adrenal suppression precludes its practical use for CFS. (McKenzie, O'Fallon et al. 1998)

Deprenyl, a MAO inhibitor

Deprenyl or Derprenil, is also known as Eldepryl (Selegiline). It is an MAO-B inhibitor that is commonly used in Parkinson's disease, in combination with levodopa or levodopa and carbodopa. Deprenyl inhibits the breakdown of dopamine by monoamine oxidase B (MAO-B).

An article published in the journal *Neuropsychobiology* described a 6-week clinical trial of selegiline in 25 patients with chronic fatigue syndrome (CFS). Participants received placebo for two weeks, then 5 mg selegiline per day for two weeks, followed by two 5 mg tablets for two weeks. A significant improvement in tension/anxiety, vigor and sexual relations was found as compared with placebo. The authors concluded that selegiline has a small but significant therapeutic effect in CFS. (Natelson, Cheu et al. 1998)

Summary

Chronic Fatigue Syndrome is debilitating fatigue and associated symptoms lasting at least 6 months. The cause of CFS is as yet undetermined, but it may be triggered by infectious agents (especially viruses), stress, vitamin deficiencies, immunologic dysfunction, neurotransmitter deficits, adrenal or thyroid deficiency.

1. Ginseng (500 mg twice a day) has been found to enhance NK function in CFS patients. Ginseng is commonly used to help increase energy levels.
2. Echinacea (500 mg twice a day) supports the immune system and has been found to enhance NK function in CFS patients.
3. Essential fatty acids may be of benefit in chronic fatigue.
4. Acetyl-L-carnitine (1000 to 2000 mg a day), Vitamin E (400 IU a day), and NADH (5 mg 2 times a day) support fat metabolism and may increase energy.
5. Whey protein should be considered as a source of amino acids and to enhance immunity and boost glutathione levels.
6. Lactoferrin (300 mg three times daily) has been shown to have significant antiviral properties and may be useful in chronic fatigue syndrome.
7. Glutathione (500 mg per day), and its precursors Glutamine (one gram per day) and N-Acetyl Cysteine (500 mg per day) are important antioxidants. Glutamine should not be taken at night as it may cause insomnia.
8. Vitamin B6, B12, folic acid (800 mcg per day) and trimethylglycine should be considered if homocysteine levels are elevated. S-AdoMet (200 to 800 mg a day), a methyl donor, may be beneficial for symptoms of depression.
9. Coenzyme Q10 (100 mg 3 times a day) may be helpful in CFS for increased energy.
10. DHEA and melatonin can be considered based on appropriate lab testing.
11. Licorice (250 mg three times a day) may help with fatigue, particularly when it's related to adrenal insufficiency. Care should be taken as high doses of licorice may increase blood pressure.
12. The amino acids phenylalanine or tyrosine, taken in daily doses of 1500 mg, will help to boost levels of brain hormones and neurotransmitters.
13. Magnesium may be deficient in 80% of all Americans and may be of particular importance in chronic fatigue. Everyone should consider supplementing with 500 mg of magnesium daily. Up to 3 grams of magnesium may be taken. Doseage should be reduced if an unwanted laxative effect occurs.
14. Few, if any, supplements contain sodium due to its adverse effect on blood pressure. Substituting sea salt for sodium chloride (common table salt) may be beneficial for those not on a sodium-restricted diet.

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