Chronic fatigue syndrome (CFS), also known as chronic fatigue and immune dysfunction syndrome, is a mysterious medical condition that affects approximately 500,000 Americans (CDC 2005a). The disease has no known cause, and there is no test that can measure for it.

Rather, CFS is defined as a set of symptoms that include prolonged, overwhelming fatigue that begins on awakening and lasts throughout the day. The fatigue may worsen with exercise or physical activity. Other symptoms associated with CFS include mood swings, muscle spasms, pain, headache, sleep disturbances, and loss of appetite (Afari N et al 2003; Balch PA et al 2000). There is typically no evidence of muscle weakness or joint or nerve abnormalities, and CFS is not considered a primary psychological disorder, although it may have psychological elements, such as depression (CFIDS 2005).

CFS primarily affects women ages 25 to 45, but it can affect anyone. While the causes of the disease are uncertain, it appears it can be triggered by a number of factors, including infectious agents, mental or physical stress, nutrient deficiencies, immune system abnormalities or allergies, hormonal abnormalities, and low blood pressure. It tends to run in families, so some researchers have hypothesized there may be a genetic predisposition. Oxidative stress may also play a role in the disease (Afari N et al 2003; Borish L et al 1998).

Several famous clusters of cases have occurred, such as an outbreak in Los Angeles County Hospital in 1934, but no common environmental or infectious cause was ever discovered (Kasper DL et al 2005). In recent years, as researchers have learned more about the disease, some clinicians have begun calling for CFS to be classified into different subgroups, depending on what other factors are present (e.g., family history, viral status, sociodemographic factors, etc.) (Jason LA et al 2005). This thinking reflects the idea that CFS may have multiple, interlocking causes or triggers, including the following:

- **Infectious disease**. To date there is no specific correlation between any infectious agent and CFS (Kasper DL et al 2005). Anecdotally, many CFS sufferers believe that their condition began with a flu-like illness, although for others the disease arises spontaneously (CFIDS 2005).
- **Immune disorders**. Many patients with CFS have impaired immune function, as indicated by increased production of cytokines, decreased natural killer cells, alterations in T cell expression, or increased allergies or autoimmune diseases—although it is unclear whether these conditions were caused by CFS itself (Gerrity TR et al 2004; Patarca R 2001; Tirelli U et al 1994; Tomoda A et al 2005; Ur E et al 1992; Vernon SD et al 2005; Visser J et al 1998; Vollmer-Conna U et al 1998).
- **Dental amalgam toxicity**. Some research shows a possible correlation between dental amalgam, metal toxicity, and CFS symptoms. In one study, 83 patients (76 percent) reported long-term health improvement following the removal of dental metal. This effect is believed to be related to a hypersensitive allergic response (Stejskal VD et al 1999).
- **Oxidative stress**. Studies suggest that oxidative stress may play a role in the development of CFS (Fulle S et al 2000; Logan AC et al 2001; Richards RS et al 2000).
- **Endocrine system disorders**. Stress, both physical and emotional, can lead to increased levels of cortisol and other hormones. An article in the Journal of Affective Disorders concluded that CFS may be associated with low cortisol levels and increased serotonin function (Cleare AJ et al 1995). Aluminum is increased in CFS, while DHEA and iron are reduced in female patients (van Rensburg SJ et al 2001; Scott LV et al 1999a).
- **Low blood pressure**. Low blood pressure is a common finding in CFS. In one study, neurally-mediated low blood pressure was documented in 96 percent of CFS patients (Bou-Holaigah I et al 1995). Medications for the treatment of neurally-mediated low blood pressure resulted in improvement in two-thirds of patients (Calkins H et al 1998). Orthostatic hypotension (low blood pressure that occurs when going from a lying to a standing position) is also a common symptom in chronic fatigue patients (Streeten DH et al 1998).

## DIAGNOSING AND TREATING CFS

The diagnosis of CFS is difficult because its symptoms are vague and the disorder often mimics other syndromes or diseases, such as influenza or other viral infections (Aaron LA et al 2000; Borish L et al 1998; Bruno RL et al 1998; Demitrack MA 1994). Illnesses that may mimic CFS include hypoglycemia, hypothyroidism, depression, environmental illness, food allergies, eating disorders, sleep apnea, autoimmune disease, infections, mononucleosis, and cancer.

The diagnosis of CFS can be made only when the patient has suffered from persistent, unexplained fatigue for at least six months. In addition to the fatigue, four of the following symptoms must be present (CDC 2005b):

- Unrefreshing sleep
- Cognitive impairment, especially short-term memory or concentration

- Sore throat
- Tender lymph nodes
- Aching or stiff muscles
- Multi-joint pain without swelling or redness
- Headaches of a new type, pattern, or severity
- Post-exertion malaise lasting more than 24 hours
- Persistent feeling of illness for at least 24 hours after exercise

A number of other symptoms have been reported by CFS patients, including abdominal pain, alcohol intolerance, bloating, chest pain, chronic cough, diarrhea, dizziness, dry eyes or mouth, earaches, irregular heartbeat, jaw pain, morning stiffness, nausea, night sweats, shortness of breath, skin sensations, tingling sensations, and weight loss (CDC 2005c).

CFS tends to arise suddenly in otherwise active individuals. In a typical disease course, an otherwise ordinary flu-like illness or some other stressor will leave behind unbearable exhaustion and symptoms of CFS. This condition is frequently mistaken for a recurrence of the infection, sending the patient back to the doctor for more tests. Repeated tests will reveal no characteristic abnormalities, yet symptoms worsen, eventually resulting in sleep disturbances and depression. Many patients with CFS feel their concerns are initially dismissed by physicians, friends, and family, which may contribute to a sense of isolation.

Once diagnosed, the symptoms may fluctuate, but CFS is not a progressive disease. Instead, most patients tend to get better by degrees, and some will even fully recover (Kasper DL et al 2005).

There is no single laboratory test that confirms CFS. Instead, physicians should perform a wide variety of blood and cognitive testing in an effort to rule out other diseases. Recent research into CFS suggests that there may be several subclasses of the disease, based on differences in disabilities, sociodemographic factors, viral status, and other biomarkers, and thus different modes of diagnosis and treatment may be appropriate (Jason LA et al 2005).

### *Conventional Approaches to CFS*

There are no prescription medications approved by the U.S. Food and Drug Administration for use in treating CFS. There are, however, a number of medications used to treat the various symptoms of CFS, depending on the subclass of the disease and how it manifests itself. These medications include antidepressants, antihistamines, decongestants, central nervous system depressants (or stimulants), mineralocorticoids, and expectorants (Evengard B et al 2002; Kasper DL et al 2005).

One medication showing potential is Ampligen ® , an experimental antiviral medication that stimulates the production of interferon. In two studies, CFS patients treated with Ampligen ® demonstrated improvements in cognition and performance. The drug has not yet been approved by the Food and Drug Administration and is in various stages of approval around the world for a wide range of conditions (Anon 2005).

### *What You Have Learned So Far . . .*

- Chronic fatigue syndrome (CFS) is characterized by long-term fatigue, as well as sleep-related difficulties, cognitive difficulties, sore throat, tender lymph nodes, or other symptoms.
- The cause of CFS is unknown, although it can be triggered by a wide range of events. There may be multiple causes.
- It is estimated to affect about 500,000 people in the United States, although it mostly affects women aged 25 to 45.
- The diagnosis of CFS is made by excluding other conditions that can have similar symptoms, such as depression or viral illness. A variety of blood tests and other analyses are sometimes needed to rule out other conditions and correctly diagnose CFS. It is still frequently misdiagnosed.
- There is no standard, approved treatment for CFS.

## REGAINING ENERGY THROUGH NUTRITION

In most cases, CFS symptoms gradually improve over time. Life Extension believes that the best approach to CFS is to boost energy levels and support healthy immune function. A full evaluation of hormonal status can also be considered, with blood tests measuring the levels of hormones such as DHEA, pregnenolone, estrogen, testosterone, and others. If levels are low, bioidentical hormone replacement may be helpful. For more specific information on hormone restoration, see “Female Hormone Restoration” and “Male Hormone Restoration.”

Several nutrients have been suggested to be deficient in CFS patients, including B vitamins, antioxidants, vitamin C, magnesium, sodium, zinc, L-tryptophan, L-carnitine, CoQ10, and essential fatty acids. Nutritional deficiencies influence the symptoms of the

syndrome as well as the recovery process (Bounous G et al 1999; Grimble RF 1994; Vecchiet J et al 2003).

## FIGHTING FATIGUE: THE LEADING CANDIDATES

Free radicals and other potent oxidants may contribute to the development of CFS. One study showed that protein oxidation was significantly elevated in the blood of CFS patients (Smirnova IV et al 2003).

A number of studies have looked at nutrients or hormones with immune-boosting properties and found promising results with CFS. In one recent study, conducted at the University of Iowa, 155 patients with CFS were asked to report on their care regimens, including prescription medications, yoga, and nutrients. Three supplements in particular appeared to be beneficial (Bentler SE et al 2005).

**Coenzyme Q10.** Coenzyme Q10 ( CoQ10) is a potent antioxidant that aids in metabolic reactions, including the process of forming adenosine triphosphate, the molecule the body uses for energy.

In one study of 20 female patients with CFS (who required bed rest following mild exercise), 80 percent were deficient in CoQ10. After three months of CoQ10 supplementation (100 mg/day), the exercise tolerance of the CFS patients more than doubled: 90 percent had reduction or disappearance of clinical symptoms, and 85 percent had decreased post-exercise fatigue (Judy W 1996).

In the University of Iowa study, CoQ10 emerged as the leading therapy for CFS, with 69 percent of patients saying it was helpful.

**DHEA.** DHEA has also been singled out for its ability to help CFS patients. The DHEA levels of many CFS patients are low compared to optimal ranges (van Rensburg SJ et al 2001; Scott LV et al 1999b). One study speculated that the DHEA deficiency might be related to CFS symptoms (Kuratsune H et al 1998).

Produced primarily by the adrenal glands, DHEA is a valuable hormone whose levels decline with age. DHEA has been shown to improve energy levels in chronic fatigue patients (Kuratsune H et al 1998). Studies have demonstrated the following:

- In a study of 15 subjects with CFS, 15 subjects with major depression, and 11 healthy subjects, DHEA levels were significantly lower in the CFS subjects compared to the healthy group. The authors concluded that DHEA has a potential role both therapeutically and as a diagnostic tool in CFS (Scott LV et al 1999b; Scott LV et al 1999a).
- Another study of DHEA levels in 22 CFS patients found normal DHEA levels but a blunted serum DHEA response curve to adrenocorticotropic hormone (ACTH) injection. ACTH normally stimulates the adrenal glands to secrete DHEA. The authors concluded that endocrine abnormalities may play a role in CFS (De Becker P et al 1999).

## NUTRIENT DEFICIENCIES

CFS patients are also frequently deficient in a number of other vital nutrients. While the research is not exhaustive, CFS-related deficiencies may be helped through supplementation.

**Vitamin B6.** Some data provide evidence of reduced functional B vitamin status, particularly of pyridoxine (vitamin B6), in CFS patients (Heap LC et al 1999).

**Folate.** An article in the journal Neurology described a study in which folate levels were measured in 60 patients with CFS. Researchers found that 50 percent of patients had values below 3.0 mcg/L (Jacobson W et al 1993).

**Glutathione.** Glutathione has been shown to help prevent damage to DNA and RNA, detoxify heavy metals, boost immune function, and assist the liver in detoxification. Levels of intracellular glutathione decrease with age.

- An article in the journal Medical Hypotheses proposed that glutathione may be depleted in CFS patients. The authors proposed that glutathione depletion also causes the muscular fatigue and myalgia associated with CFS (Bounous G et al 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 glutathione levels, low natural killer cell activity, skeletal muscle wasting or muscle fatigue, and increased rates of urea production define 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, and CFS and to some extent in over-trained athletes (Droge W et al 1997).

Supplements used to raise cellular glutathione levels include N-acetylcysteine (with vitamin C), lipoic acid, whey protein, L-cysteine,

and glutathione.

**Lipoic acid.** Lipoic acid is known as the “recycler” antioxidant because it can restore the antioxidant properties of vitamins C and E after they have been neutralized by free radicals. It also stimulates the production of glutathione and helps in the absorption of CoQ10 (Balch PA et al 2000; Hendler SS et al 2001; Jamison JR 2003). The body produces this antioxidant (glutathione) in limited amounts.

**Essential fatty acids.** Essential fatty acids are the fatty acids that cannot be made by the body. These are crucial for rebuilding and producing new cells and are required for normal brain development (Balch PA et al 2000).

- The use of essential fatty acids for post-viral CFS 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 and had severe fatigue, myalgia, and a variety of psychiatric symptoms. Study subjects received either placebo or a preparation containing linolenic, gamma-linolenic, eicosapentaenoic, and docosahexaenoic acids (eight 500-mg capsules daily) over a three-month period. The treatment group showed continual improvement, compared with uneven results in the placebo group (Behan PO et al 1990). The essential fatty acid composition of the subjects’ 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 CFS.
- In a case series of CFS patients, researchers administered essential fatty acids with other treatment protocols and observed a 90 percent gain in improvement within three months among two-thirds of CFS patients (Gray JB et al 1994).

## ENERGY BOOSTERS

A number of nutrients have been studied for their ability to boost cellular energy—a possibly important concern among CFS patients. These include the following:

**NADH.** Reduced B-nicotanamide dinucleotide (NADH), along with CoQ10, is essential for the production of cellular energy.

- A randomized, double-blind, placebo-controlled crossover study examined the use of NADH in CFS: 26 eligible patients diagnosed with CFS received either 10 mg of NADH or placebo for a four-week period. Eight of 26 (31 percent) responded favorably to NADH, in contrast to two of 26 (8 percent) to placebo (Forsyth LM et al 1999).

**L-carnitine.** Although the research is somewhat inconsistent, s everal studies have found deficiencies of the amino acid L-carnitine among CFS patients. L-carnitine is known to boost energy levels. The lack of consistency in the research literature suggests a number of other nutritional deficiencies, including carnitine, B-complex vitamins, essential fatty acids, L-tryptophan, zinc, magnesium, and others, may be related (Werbach MR 2000).

- Studies show that carnitine given as a supplement to CFS patients result in better functional capacity and lessening of disease symptoms (Plioplys AV et al 1995; Plioplys AV et al 1997). Other studies have shown a dose of 1000–2000 mg daily has resulted in improvement (Kelly GS 1998; Werbach MR 2000).
- Acetyl-L-carnitine relieved mental fatigue, and propionyl-L-carnitine alleviated general fatigue in a study comparing the two types of carnitine in CFS patients (Vermeulen RC et al 2004).

**Magnesium.** Magnesium participates in energy metabolism and protein synthesis. The body vigilantly protects blood magnesium levels, in part because 350 enzymatic processes depend on magnesium for activation. Magnesium is stored in tissues and bone, sharing skeletal residency with calcium and phosphorus (Dimai HP et al 1998).

A randomized, double-blind, placebo-controlled study was conducted of patients with CFS who were found to have low magnesium levels. In the clinical trial, 32 CFS patients received either placebo or intramuscular magnesium sulfate every week for six weeks. Patients treated with magnesium reported improved energy levels, better emotional state, and less pain (Cox IM et al 1991).

However, another study found that magnesium supplementation resulted in a significant worsening of symptoms between 6 and 24 months (Bentler SE et al 2005). Thus some people may find magnesium supplementation helpful, but if symptoms worsen, it should be discontinued.

**Glutamine.** Glutamine is a conditionally essential amino acid needed during periods of excessive stress. Glutamine is the preferred energy for enterocytes, the cells lining the gastrointestinal tract. Glutamine is also one of the three amino acids necessary to make glutathione, a potent scavenger of free radicals.

- Supplementation with glutamine might benefit chronic fatigue patients by enhancing gut motility, improving plasma glutamine levels, and boosting glutathione (Kingsbury KJ et al 1998a; Kingsbury KJ 1998b)

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

For Immune Enhancement and General Nutrient Support

- **Life Extension Mix** (multinutrient formula)—as directed on label
- **Glutathione**—250 to 500 mg daily
- **N-acetylcysteine**—600 mg daily
- **R-lipoic acid**—420 mg daily
- **Folic acid**—800 mcg daily

For Energy Enhancement

- **CoQ10**—100 mg three times daily
- **Magnesium**—250 mg daily
- **DHEA**—A starting dose of 15 to 75 mg is reasonable. Blood testing to ensure optimal levels should be performed
- **NADH**—5 mg twice daily
- **GLA**—285 mg daily

Intestinal Tract Support

- **Glutamine**—1 g or more daily

## CHRONIC FATIGUE SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### Coenzyme Q10

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

### DHEA

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.

### Folic acid

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

### GLA

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

### L-Glutamine

- Consult your doctor before taking L-glutamine if you have kidney failure or liver failure.
- L-glutamine can cause gastrointestinal symptoms such as nausea and diarrhea.

**Lipoic Acid**

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

**Magnesium**

- Do not take magnesium if you have kidney failure or myasthenia gravis.

**NAC**

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

For more information see the Safety Appendix

***These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.**

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