Nutrition News and Views

November/December 2015 Vol.19, No.6 For health professionals

CHRONIC FATIGUE SYNDROME

By Judith A. DeCava, LNC, CNC

'Fatigue' does not even begin to describe Chronic Fatigue Syndrome (**CFS**). It is a constellation of symptoms, some disabling. Women are affected more than men. Children can be afflicted. The causes and exact nature of the syndrome remain controversial. Medical researchers continue to seek a single cause. So far, only two interventions are medically deemed useful—exercise and cognitive behavioral therapy. "Neither is remotely curative." Drugs have failed to produce worthwhile results. Focus is on managing symptoms with sleep-inducing drugs, antidepressants, and non-steroidal anti-inflammatory drugs plus recommending avoidance of overexertion and stress. CFS is known as myalgic encephalomyelitis (ME) abroad and by the World Health Organization. The **definition** of CFS according to 1994 Centers of Disease Control and Prevention (CDC) stipulations is: Persistent, debilitating or relapsing fatigue that has lasted at least six months and is not caused by any other known condition. The fatigue is not relieved by rest and it significantly reduces the ability to pursue normal activities. It's accompanied by at least four of the following symptoms: substantial impairment in memory or concentration; sore throat; muscle pain; pain in multiple joints; tender lymph nodes; sleep disturbance; headache of a new type, pattern or severity; extreme fatigue lasting 24 hours or longer following physical or mental exercise. There may also be low grade fever, lowered immune response, digestive ailments, nausea, visual disturbances, spatial disorientation, photophobia, disequilibrium, dizziness, tachycardia, mood swings, numbness and tingling, labored or difficult breathing, intolerance to alcohol, or seizure activity. There are commonly symptoms of fibromyalgia with widespread pain. Children may exhibit sadness, hyperactivity (initially), episodic tension headaches, abdominal pain, tachycardia, and orthostatic hypotension. Some people gradually develop CFS. Others experience it full-blown after an illness or trauma. Epigenetic ('turning on' of genes) causes have been explored. But nothing consistent has been found. The problem affects multiple areas in the body including the nervous, immune, endocrine, digestive and cardiovascular systems. Most people eventually recover. Some suffer for many years. [1] There is more than one cause, there are various individual manifestations, and therapies need to be geared to underlying causes, not just to symptom relief. [2]

IMMUNE DYSFUNCTION. For years, various viruses have been accused of causing CFS: Epstein-Barr (EBV), some enteroviruses, herpes virus-6, Coxsackie, CMC, influenza, Powassan, and others. Beyond viruses, other factors such as 'sick' bacteria, Candida albicans, borrelia, fungal overgrowth, and the like have been thought to cause the disorder. But not all CFS patients have antibodies to these and no viruses or other pathogens are consistently found. In 2009, a retrovirus (xenotropic murine leukemia virus) was linked to CFS. But the virus was not found in people with CFS and the study was flawed and had to be pulled. Viruses or other pathogens are opportunistic stressors that may trigger the developing disorder but are **not** the cause. Instead, it is agreed that there is an immune dysfunction. [3] Parts of the immune system that play roles in dealing with such things as viruses, toxins, insults or injuries are activated in people with CFS. Specific biological abnormalities are found. But immune system test results are not consistent; they are often contradictory. However, **trends** are found such as disturbances in the function of natural killer cells (high or low activity), ups and downs of IgG cells, impaired T- and B-cell memory, increased T cell activation, increases and decreases of other immune cells. [4] Levels of immune components such as cytokines are raised or abnormal in some people, but not all. Allergic reactions to various toxic substances such as nickel or mercury are prevalent. Overall, immune abnormalities are inconsistent, but what is consistent is **immune dysfunction**. [5]

Once a person's immune system is weakened or compromised, 'sick' microorganisms or toxic particles may get into cells where they don't belong and dysfunctional immune cells can't appropriately get rid of them. Even common "noninfectious" microorganisms or low levels of toxins can cause problems for an already troubled immune system. People with CFS have more inflammatory activities going on in their bodies than is normal. Inflammation is the biochemical process the body uses to attempt repair of cells and tissues that have been impaired or harmed or to remove waste or toxic substances. If there is frequent or consistent cellular damage, or if there are malfunctioning immune cells, or if there is a lack of needed nutrients, inflammation can become chronic. This drains the body and makes it more susceptible to illness. Immune responsiveness is an energy-

dependent, so inflammation-driven fatigue may be an aspect of CFS. Chronic inflammation can cause fatigue **and** fatigue can cause reduced immune system responsiveness. About 65% to 70% of the immune system is in the digestive tract. Altered composition of gut microorganisms (dysbiosis) may lower tolerance and increase inflammation. Increased intestinal permeability (leaky gut due to toxins, medications, poor diet, excess stress, etc.) means intestinal injury. With a damaged digestive tract, more 'sick' bacteria and viruses can develop, nutrients can't be properly absorbed and can't get to the immune system, endocrine system, brain or other areas; energy is drained. Gut inflammation is often found. Chronic inflammation has detrimental effects on the brain and over-stimulating effects on the hypothalamus-pituitary-adrenal (HPA) axis. [5]

BRAIN, STRESS, HPA AXIS. The central nervous system (includes the brain) is a prime player in CFS. Common are difficulty with memory, concentration, and/or attention; phobias; paresthesias (numbness, stinging or burning feelings); depression; anxiety; and disrupted sleep. Physical disruptions of the nervous system can produce depression or other psychological afflictions; conversely, depression can produce physical disruptions. There is "a complex interaction between" physical dysfunction and psychological processes. Tests show abnormalities of both sympathetic and parasympathetic nervous systems. [6]

The connection formed by the hypothalamus, pituitary and adrenal glands, the **HPA axis**, is crucial in stress reactions. It is through the HPA axis that stressors exert huge effects on the immune system, nervous system, and other organs and tissues—how the body gets ready for fight, flight or freeze. When stress occurs (physical, chemical, toxic, mental, emotional), the hypothalamus in the brain stem releases corticotropin-releasing hormone (**CRH**), which travels a short distance to the pituitary at the base of the skull. The pituitary, stimulated by CRH, releases adrenocorticotrophic hormone (**ACTH**) which is carried by blood to the adrenal glands which sit on top of the kidneys. ACTH acts on the adrenal cortex so that it secretes corticoid hormones, mainly **cortisol**. Cortisol acts on almost every tissue in the body in one way or another including the brain, immune system, digestive tract, and so on. The aim is to dampen the stress reaction for safety. Activation of the sympathetic nervous system causes the adrenals to release epinephrine and norepinephrine that affect many physiological responses and lead to a number of metabolic changes. Blood vessels to the digestive tract, hands and feet are constricted; vessels to the heart, large muscle groups and brain dilate. Metabolism speeds up, liberating glucose into the bloodstream. Respiratory rate increases and brochi dilate to allow more oxygen in. Muscles become tense. The immune system is subdued. Sexual feelings are reduced. Over time, when this stress response is repetitively triggered, problems occur. The above processes don't work properly; organs and glands become overtaxed and under-functional. Eventually cells can't respond to hormone signals. Less blood gets to the brain. Self-repair functions are quelled. The adrenals become fatigued. Instead of cortisol production peaking in the morning and falling as the day goes on, cortisol levels are lower upon awakening, have more disorganized variability during the day, and do not fall sufficiently in the evening. Growth hormone (**GH**) levels are lowered, causing major fatigue, compromised tissue repair, lowered protein production and **DHEA** (dehydroepiandrosterone) production by the adrenals. GH is produced during deep sleep stages which are often limited or missing in CFS. **Prolactin** increases, causing sex hormone levels go down and possibly affecting mental processes. Lowered vasopressin (**ADH**, antidiuretic hormone) can cause low blood pressure and fatigue. About 40% of people with CFS have low **thyroid** hormone production, also causing fatigue. [7]

Neurally mediated hypotension (**NMH**) occurs in about 70% of people with CFS. When someone stands for an extended time, blood pressure falls as blood pools in the legs. Normally the body adjusts this by increasing heart rate and constricting blood vessels to normalize blood pressure, ensuring enough blood returns to the brain. But with NMH, nerves in the heart's left ventricle signal the brain that the blood pressure is too high rather than too low. The brain lessens the heart rate which decreases blood pressure even further, causing continued blood pooling in the legs and less blood reaching the brain. Lightheadedness, dizziness, exhaustion and sometimes fainting can result. **Orthostatic hypotension**—a sudden drop in blood pressure when standing up after sitting or lying down—may also occur due to adrenal under-functioning. It leads to lightheadedness, dizziness, blurred vision and possibly fainting. Adrenal fatigue can lead to sodium and potassium imbalances so more fluids enter cells, causing fluid retention inside cells (not pitting edema). Nerve transmission becomes abnormal and sporadic. Low adrenal function impairs adrenal hormones such as aldosterone that regulate fluid and electrolyte retention by the kidneys. [8] But the adrenal glands are not **the** problem; it is the **combination** of hypothalamus, pituitary and adrenals (possibly thyroid too).

During the late 1980s and early 90s, there was much controversy over whether CFS was a physical reality or all in the mind. It was called a "fad" disease or "Yuppie Flu." So, though most people with CFS have **psychological** difficulties such as depression, they often avoid psychological references. Physical processes in the brain, elsewhere in the nervous system, or other areas of the body can underlie mental and emotional processes. In CFS, brain responses to stress are not ordinary. Whether they are a result of symptoms or biochemical interactions is not clear. **Stress** challenges the body's coping mechanisms. Either the body can adapt to the stress and overcome the effects, or it eventually succumbs to stress and becomes overtaxed, weaker and susceptible to cellular and biochemical interference or breakdown. To build tolerance to stress involves a number of factors. Nutrition is certainly one of them. [9] A 2008 Cochrane Collaboration analyzed randomized controlled trials and concluded that cognitive-behavioral (psycho)therapy (**CBT**) was more helpful for CFS than usual care such as general support, rest, less activity and antidepressants in relieving symptoms. But they felt further studies would be useful. A 2011 study published in *The Lancet* concluded that graded exercise and CBT were helpful, but "this does not mean that CFS is necessarily psychological in origin." Psychotherapy can, for instance, improve symptoms of diseases such as rheumatoid arthritis and cancer. Plus CBT is not effective for all people with CFS. Reduced blood flow to the brain or brain-function abnormalities can cause psychological disturbances. [10] Decreased parasympathetic and increased sympathetic nervous system function is common. Inflammation occurs in several key brain regions, the degree correlating with symptom severity. Reduced white matter and abnormalities in gray matter may relate to cognitive difficulties and brain fog. Reduced brain-derived neurotrophic factor suggests an obstacle in nerve cell plasticity. [11]

Abnormally-shaped red blood cells or slightly abnormal ECG (electrocardiogram) readings due to **heart** and **vascular** irregularities may occur. Either way, there is inadequate oxygen delivery. Blood flow to the brain and muscles is significantly reduced. Mitochondria, including those in the heart's cells, may not produce enough energy. There may be a higher heart rate and reduced heart-rate variability due to an overactive sympathetic nervous system (fight, flight or freeze reactions) and a weakened parasympathetic nervous system (relax, rest and digest reactions). The result is difficulty handling stress and lowered emotional control. Dysregulations of the HPA axis are imminently involved in anything requiring outlays of physical or mental energy. Excess stress—'**excess**' depending on the capacity of the individual—affects the body and bodily disturbances affect the mind. Studies find that, in childhood, up to two-thirds of people with CFS experienced physical, emotional, or sexual abuse or emotional or physical neglect. CFS rates are highest for those who cite more than one type of childhood trauma and/or endured especially severe ordeals. Depression, anxiety, and post-traumatic stress disorder are common. Profound stress can impair the brain's responses to new challenges, setting the stage for physical ailments including CFS. Nearly a fourth of people with CFS described their present lives as "very stress filled" compared to 13% of controls. [11] CFS is associated with altered amounts of slow wave **sleep** that can impair sleep regulation. Basic sleep drive and homeostasis response are affected. The hypothalamus exerts a lot of control over sleep. Does sleep dysfunction contribute to CFS or vice versa? Not known. [11,12]

TOXINS. DIGESTIVE TRACT. Levels of a number of **toxic** chemical compounds are often higher in people with CFS than in others. These can include chlorinated hydrocarbons, organochlorines, ciguatoxin (from fish), organophosphates, aluminum hydroxide, pesticide residues (head lice treatments, insect repellents, pesticide residues in non-organic foods), solvents, formaldehyde, heavy metals (such as arsenic, cadmium and lead which can also appear in non-organic foods from contaminated soils and fertilizers, fungicides containing mercury, runoff from industry-polluted waters), food additives (MSG, salicylates, nitrates, amines, tartrazine, synthetic preservatives, etc.). Aluminum hydroxide, a vaccine adjuvant, can cause chronic fatigue, joint and muscle pains, muscle weakness, and cognitive dysfunction. Many people with CFS exhibit multiple chemical sensitivity—hypersensitivity to a host of chemicals that worsen immune responses. Toxins affect inflammatory levels in the brain and other areas in the body. Poor digestion and/or nutrient deficiencies can increase absorption of toxins. Inadequate function of detoxifying systems (liver, kidneys, lymphatic system, etc.) can lessen the body's capacity to rid itself of toxins. Toxic exposures should be avoided. Good nutrition helps to reduce absorption and enhance excretion of many toxicants. A program to support the detoxification pathways may be invaluable. **Food intolerances** usually cause chronic fatigue, sometimes along with disruption of the nervous and immune systems. Toxins and nonfoods may damage the lining of the digestive tract, making it reactive to various foods. Leaky gut and intestinal mucosal dysfunction can occur. These result in partially digested food particles, wastes, endotoxins and other substances being inappropriately leaked into the blood-

stream and lymphatic system. Then any area of the body may be adversely affected—the brain, rest of the nervous system, endocrine system, immune system, musculoskeletal system, and elsewhere. [13] Problems with the digestive tract's immune system can contribute to dysfunctions in immune response, endocrine system, nervous system, and more. Chronic stress and HPA activation affect digestion by lowering blood circulation to the intestines, compromising digestion and leading to excessive inflammation, poor mood, fatigue, and pain susceptibility. Called the "second brain," the digestive tract and its nervous system play a major role in producing neurotransmitters, including serotonin (often low in CFS). Malabsorption and GI inflammation can affect production, levels, or receptor function of serotonin, dopamine, GABA, epinephrine, and glutamate. [14]

SYNDROME. Causes of CFS involve **stress**—amount, severity, duration, and individual tolerance. A number of body burdens—injuries, illnesses, early childhood trauma, emotional or mental strains at any time, poor diet, nutritional deficits, chemical and toxic exposures, lifestyle lacks—can lead to onset. After a buildup of other stressors, for example, an illness can tip the scales and initiate the CFS crash. Depending on individual biochemistry, severity, impact and stress load, various bodily systems can be affected.

NUTRITION. Imbalances and insufficiencies of numerous nutrients are involved in CFS. Dietary indiscretions, toxic load, and needed adjustments in lifestyle all need to be taken into account. The levels of a number of nutrients are commonly below normal values, so malnutrition is probably involved in the syndrome's creation and effects. Among the nutrients often found to be deficient are magnesium, zinc, copper, selenium, chromium, vitamins A, B vitamins including B_{12} and folate, choline, essential fatty acids (including EPA, GLA, DHA and CLA), vitamin C (including flavonoids), vitamin D, vitamin E (including all tocopherols, tocotrienols, selenium), carotenes, alpha-lipoic acid, coenzyme Q-10, and amino acids such as tryptophan, glutamine and others. [15]

Impairment of fatty-acid metabolism may partly explain some functional changes in the central nervous system. Low levels of essential fatty acids (EFAs) are common, possibly due to abnormalities in EFA metabolism or consumption of refined, altered fats and oils. Excessive stress reactions can change the rationing of EFA metabolites and contribute to immune, endocrine, and nerve dysfunctions. Consuming only quality, unrefined, unaltered, unpolluted sources of EFAs improves symptoms including fatigue, aches, pains, and depression. [15] Deficiencies in thiamine (B_1), riboflavin (B_2), niacin (B_3), pyridoxine (B_6), folate, B_{12}, biotin, and pantothenic acid occur frequently. Homocysteine levels are often elevated, indicating vitamin B_{12} and folate deficits. Deficiencies of vitamin B complex and its co-workers can cause fatigue, weakness, anxiety, insomnia, depression, digestive disturbances, neuralgia, forgetfulness, headaches, confusion, dizziness, and more. A low or subclinical level of magnesium is classic. With under-functioning adrenals, levels of sodium and potassium can be imbalanced. Low zinc is associated with immune dysfunction, muscle pain and fatigue. Copper is involved in superoxide dismutase (SOD) function. Copper must be balanced with zinc. Chromium aids proper blood sugar metabolism and insulin sensitivity. Selenium and iodine are critical for thyroid function. Vitamin C complex is vital to immune and adrenal function; the whole complex (including flavonoids, rutin, and other cofactors) must be provided. Vitamin A is involved in proper immune function including that of mucous membranes (respiratory, gastrointestinal). Carotenes are converted to vitamin A in the body. CoQ10 deficiency is related to fatigue, cardiac irregularities, and nervous system symptoms (such as memory impairment). A number of nutrients are needed for adequate mitochondrial function: B complex stimulates coenzymes; magnesium is a cofactor in ATP metabolism; CoQ10 is needed for mitochondrial energy metabolism and membrane potential; carnitine is responsible for transport of acetyl-CoA into the mitochondria during fatty acid oxidation; and so on. [15]

Amino acids are building blocks for every bodily protein including many immune factors, neurotransmitters, GI and musculoskeletal cells, and more. Amino acids are essential for the production of adenosine triphosphate (ATP) in the cells' mitochondria for cellular energy. Carnitine, for example, is needed to transport long-chain fatty acids into the mitochondrion for beta oxidation and helps regulate the ratio of acetyl coenzyme A to free coenzyme A. Commonly deficient in CFS, carnitine is made from the amino acids lysine and methionine. Other amino acids are often inadequate in supply or availability. This may be due to poor digestion or assimilation because of inadequate hydrochloric acid production, food intolerances, depletion of pancreatic enzymes, leaky gut, dysbiosis or other factors. There may be increased need for amino acids due to excessive stress, toxins, consumption of over-processed nonfoods, chronic inflammation, certain medications or other factors. Plasma tryptophan may be excessive or depressed; levels fail to rise and fall normally. Tryptophan is one ingredient

needed to produce the neurotransmitter serotonin; too much and persistent fatigue can develop; too little and mood is influenced. Most serotonin is produced in the digestive tract, so the gut's health must be considered. Nicotinamide adenine dinucleotide (NADH), the coenzyme form of niacin, may help balance serotonin levels. Tyrosine is needed to produce dopamine and norepinephrine; low levels of either can contribute to fatigue and cognitive dysfunction. Use of isolated amino acids can cause problems including serious imbalances and does not usually help symptoms. Real whole-food sources of amino acids allow the body to choose what is needed, do not cause imbalances, and contain many other nutrients that work with the amino acids. [16]

D-ribose supplements are used to improve energy, sleep and mental clarity and to reduce pain. Ribose is produced in the body. It is a component of ATP, RNA, NADH, and coenzyme-A for maintenance of cellular energy balance. Free ribose is not found in foods, so taking it as a supplement is not really nutrition; it is used for quick symptom relief as a drug. The nutritional approach is to obtain raw materials from foods needed to produce ribose, including B vitamins such as riboflavin and niacin for NADH. Ribose pills or powders can cause gastrointestinal discomfort, nausea, diarrhea, headache, low blood sugar, excess stimulation, and other side effects. The question is whether a patient produces insufficient ribose or if sufficient ribose is inefficiently used. Whole food nutritional complexes supply the materials for production and efficient use of ribose. [17]

Gastrointestinal (**GI**) dysfunction is common in CFS and may contribute to its development. GI changes include dysbiosis, leaky gut, and altered mucosal immunity with low-grade inflammation. Low levels of healthy bacteria and high levels of 'sick' bacteria are found. Dietary changes and appropriate food supplements can support healing of the GI lining. A quality pre- and probiotic supplement not only aids dysbiosis, but can attenuate inflammation and improve HPA-axis function, cognitive function, anxiety, mood and general health. [17] Many people with CFS (more than 80% according to some studies) have **food intolerances** that affect nutrient absorption and can affect mood, energy pain, and immune responses. Foods causing the most reactions are dairy products and meats (both can contain high amounts of toxic residues), wheat, eggs, nuts and soy. Low stomach acid impairs absorption of amino acids and some vitamins and minerals. Leaky gut results in food intolerances, poor nutrient absorption and decreased protection from toxins. A quality diet, eliminating food intolerances, using fresh juices and supplements that may include digestive enzymes and/or hydrochloric acid and pepsin can make a big difference. One study found that elimination of wheat, milk, benzoates, nitrates, nitrites, food colorings and other additives from participants' diets resulted in 90% improvement. There were significant reductions in fatigue, recurrent fever, sore throat, muscle pain, headache, joint pain and cognitive dysfunction, plus improvement in irritable-bowel-syndrome-like symptoms suffered by some. Another study concluded that choosing organically raised foods was important as people with CFS tend to have elevated blood levels of pesticides. To avoid triggering immune responses, foods should be whole, natural, organic, unrefined and unprocessed. Avoid refined, altered, over-processed concocted nonfoods. Supplements need to be whole food complexes. [15,17,18] Consuming items largely stripped of micronutrients, excessively processed or cooked, containing artificial chemicals or toxic residues, or subject to other industrial manipulations cause far more than a deficit of one or two nutrients. Coffee may temporarily boost energy, but excess caffeine can take away more energy than it gives. Alcohol should be limited to one or two drinks a day. [19]

HERBS. An adaptogen such as ginseng, schizandra, eleuthero or ashwaganda may increase resistance to stress. Kerry Bone, FNIMH, FNHAA, suggests that rhodiola can help depression and is unlikely to interact with anti-depressant drugs. It also improves burnout fatigue, attention and cortisol response. Rehmannia, licorice, Panax ginseng and reishi mushroom are supportive to the adrenal glands. Siberian ginseng increases levels of certain white blood cells and supports proper inflammation and repair processes among other immune system benefits; it may also support the HPA-axis. To bolster the nervous system and help muscles to relax, skullcap, valerian, hops, chamomile, kava or crampbark may be used. Essential-oil aromatherapy with lavender, chamomile, sandalwood, orange or yiang-yiang has relaxant, stress-reducing effects. Herbs for immune support include Rehmannia, bupleurum, St. John's wort, eleuthero, and Astragalus. For cardiac and circulatory abnormalities, hawthorn may assist. Withania somnifera is a tonic, but does not over-stimulate. [20]

EXERCISE. OTHER THERAPIES. People with CFS face a catch-22: Common forms of exercise can worsen their fatigue, but without exercising their condition deteriorates. Graded exercise—a very gradual building up from a gentle beginning—can improve symptoms. Both graded aerobic exercise and progressive resistance

training significantly improves physical capacity and quality of life. Exercise can boost immune function as well as improve depression, anxiety, fatigue severity, and other symptoms as it enhances general health. It is important to regulate intensity and duration of a workout. A work and rest strategy should be determined. For example, starting with 10 minutes of exercise with short periods of rest can be performed three times a week. After several weeks, the workout length can be gradually increased to 15 minutes, eventually to 20, 25 and then 30 minutes. This progression occurs over three to six months. Each person has a different threshold. A trained therapist can offer guidance. Yoga gets positive results; 24% of CFS participants in one study had substantial improvement in fatigue. Practicing the Feldenkrais method and a form of qi gong called bone-breathing helped manage symptoms and reconditioned the body gradually. Massage, acupuncture, sauna therapy, relaxation techniques, and mindfulness meditation have all shown benefits. Acupuncture has a clear history of benefit, especially for physical and mental fatigue and quality of life improvement. Natural sunlight for vitamin D production and feelings of relaxation by being in nature has been shown to help. [21]

ASSISTANCE. Numerous natural therapies geared to the individual can help CFS, including real nutrition.

1 J Prins, J van der Meer, et al, *Lancet*, 28 Jan 2006, 367(9507):346-55; S Straus, *JAMA*, 8 Sep 2004, 292(10):1234-5; T Hampton, *JAMA*, 7 Jun 2006, 295(21):2466-7; S Horowitz, *Altern & Complem Ther*, Jun 2008, 14(3):121-31. **2**. B Harder, *Sci News*, 1 Jul 2006, 170(1):10-11; N Seppa, *Sci News*, 26 Mar 2011, 179(7):12. **3**. J Dawson, *Br Med J*, 1990, 300:832; D Dooley, *JAMA*, 19 Aug 1992, 268(7):873-4; V Lombardi, F Fuscetti, et al, *Science*, 23 Oct 2009, 326(5952):585-90; K Knox, D Carrigan, et al, *Science*, 1 Jul 2011, 333(6038):94-101; *Science*, 7 Oct 2011, 334(6052):25. **4**. P White, J Thomas, et al, *Lancet*, 8 Dec 2001, 358(9297):1946-54; M Rosenbaum, Physician Conference on CFS and Fibromyalgia, Los Angeles, CA, Sep 2002. **5**. M Maes, I Mihaylova, et al, *Neuro Endocrinol Lett*, 2007, 28(4):Epub; M Maes, F Twisk, et al, *J Affect Disord*, Feb 2012, 136(3):933-9; R Dantzer, JC O'Connor, et al, *Nat Rev Neurosci*, 2008, 9:46-56; S Lakhan, A Kirchgessner, *Nutr Metab (Lond)*, 12 Oct 2010, 7:79; C Raison, J Lin, et al, *Brain Behav Immun*, 2009, 23:327-37; J Teitelbaum, *Integrat Med*, Dec 2011/Jan 2012, 10(6): 44-8. **6**. P Bongiorno, *Townsend Lttr*, Oct 2012, 351:62-8; D Mant, *Lancet*, 24 Sep 1994, 344(8926):834-5; R McKenzie, A O'Fallon, et al, *JAMA*, 23/30 Sep 1998, 280(12):1061-6; A Komaroff, *JAMA*, 8 Oct 1997, 278 (14):1179-85. **7**. A Komaroff , *JAMA*, 11 Feb 1998, 279(6):431-3; T Friedman, R Poland, *JAMA*, 26 May 1999, 281(20): 1888-9; A Cleare, D Blair, et al, *Am J Psychiatry*, Apr 2001, 158(4):641-3; L Scott, et al, *J Affect Disord*, 1999, 54:129-37; J Teitelbaum, *Townsend Lttr*, Aug/Sep 2004, 253/254:136-7; J Gaab, D Huster, et al, *Psychosom Med*, Nov/Dec 2002, 64(6):951-62; A Cleare, et al, *J Affect Disord*, 1995, 35:283-9; B Wikland, et al, *Lancet*, 2001, 357:956-7; B Wikland, et al, *Lancet*, 2003, 361:1305. **8**. I Bou-Holaigah, PC Rowe, et al, *JAMA*, 27 Sep 1995, 274(12): 961-7; J Tietelbaum, *Integrat Med*, Dec 2011/Jan 2012, 10(6):44-8. **9**. L Marshall, *Nat Solutions*, Jun 2008, 108:16; M Wallace, *JAMA*, 3 Jun 1998, 279(21):1697. **10**. S Wolfe, *Hlth Research Group Lttr*, Apr 2012, 28(4):6-7; B Natelson, *JAMA*, 23/30 May 2001, 285(20):2557-9; D Costa, C Tannock, et al, *Q J Med*, 1995, 88:767-73; P Jaret, *Hlth*, May 1999, 13(4):115-22; P Bongiorno, *Townsend Lttr*, Oct 2012, 351:62-8. **11**. B Natelson, et al, *J Neurol Sci*, 1993, 120:213; R Schwartz, et al, *Am J Roentgenol*, 1994, 162:935; D Cook, et al, *Int J Neurosci*, 2001, 107:1; L Kruff, et al, *Arch Neurol*, 1994, 51:705; J DeLuca, et al, *J Neurol Neurosurg Psychiatry*, 1995, 58:38; J Gaab, D Huster, et al, *Psychosom Med*, Nov/Dec 2002, 64(6):951-62; T Hampton, *JAMA*, 27 Dec 2006, 296(24): 2915; K Kato, P Sullivan, et al, *Arch Gen Psychiatry*, 2006, 63:1267-72; C Heim, U Nater, *Arch Gen Psychiatry*, Jan 2009, 66(1):72-80; R Boneva, M Decker, et al, *Auton Neurosci*, Dec 2007, 137(1-2):94-101; D Denoon, WebMd, 14 Apr 2003, www.webmd.com/news20030414; A Peckerman, J Lamanca, et al, *Am J Med Sciences*, Aug 2003, 326(2):55-60; C Johnson, *CFIDS Chron*, Winter 2008:13-15; C Heim, D Wagner, et al, *Arch Gen Psychiatry*, Nov 2006, 63(11):1258-66; M Giuliucci, www.cfids.org/archives/2003rr/2003-rr2-article01.asp; www.cfids.cab.org/MESA/Lerner.html; M Sorenson, L Jason, et al, *J Neurol Neurophysiol*, 2014, S12:S2-13. **12**. R Armitage, C Landis, et al, *Sleep*, 1 May 2007, 30(5):657-62; J Teitelbaum, *Townsend Lttr*, Nov 2009, 316:102-7. **13**. S Horowitz, *Altern & Complem Ther*, Jun 2008, 14(3):121-31; D Hugh, et al, *Med J Australia*, 18 Sep 1995, 163:294-7; Natl Coalition Against Misuse of Pesticides, *Tech Report*, Feb 2002, 17(2):1-2; R Miller, *Med Hypotheses*, 2005, 64(5):1063-4; J Pearn, *J Neurosurg Psychiatry*, 2001, 70:4-8; C Exley, L Swarbrick, et al, *Med Hypotheses*, Feb 2009, 72(2):135-9; R Gherardi, F Authier, *Lupus*, Feb 2012, 21 (2):184-9; D Racciatti, J Vecchiet, et al, *Sci Total Environ*, 2001, 270(1-3):27-31; M Sears, S Genuis, *J Environ Public Hlth*, 2012. 356798.doi:10.1155/2012/356798; M Marchese, *Townsend Lttr*, Nov 2014, 376: 38-9. **14**. S Lakhan, A Kirchgessner, *Nutr Metab (Lond)*, Oct 2010, 7:79; B Evengard, H Grans, et al, *Scand J Gastroenterol*, 2007, 42(12):1514-5; M Maes, F Twisk, et al, *J Affect Disord*, 2012, 136(3): 909-17; A Logan, R Venket, D Irani, *Med Hypotheses*, 2003, 60(6):915-23; J Sheedy, R Wettenhall, et al, *In Vivo*, 2009, 23(4):621-8; M Maes, I Mihaylova, I Leunis, *J Affect Disord*, 2007, 99(1-3):237-40; M Maes, J Leunis, *Neuro Endocrinol Lett* 2008, 29(6):902-10. **15**. B Brown, *Altern Therapies*, Jan/Feb 2014, 20(1):29-40; J Teitelbaum, *Integrat Med*, Dec 2011/Jan 2012, 10(6):44-8; M Werbach, *J Amer Coll Nutr*, Oct 1996, 15(5):539; M Kaminski, delivery, Amer Coll for Advancement of Med, 26 Apr 1997, Chicago, IL; M Werbach, address UCLA School of Med, 25 Apr 1997, Westwood, CA; W Jacobson, T Saich, et al, *Neurology*, 1993, 43(12):265-264; A Plioplys, S Phioplys, *Neurology*, 1995, 32(3):132-8; L Heap, T Peters, S Wessely, *JR Soc Med*, Apr 1999, 92:183-5; I Bou-Holaigah, et al, *JAMA*, 1995, 274(12):961-7; A Cordova, M Alvarez-Mon, *Neurosci Biobehav Rev*, 1995, 19(3):439-45; J Cartmell, *Frontier Perspectives*, Spring 2000, 9(1); Temple Univ; J William, delivery 37th Ann Mtg Amer Coll Nutr, 13 Oct 1996, Bradenton, FL; J Gray, A Martinovic, *Med Hypotheses*, 1994, 43(1):31-42; Maes Clinics, *Neuro Endocrinol Lett*, 2009, 30 (4):Epub; S Berkovitz, S Thurood, et al, *Int J Vitam Nutr Res*, 2009, 79(4):250-4. **16**. E Newsholme, E Blomstranc, *Experientia*, 1996, 52:413-5; C Vassallo, et al, *Psychol Med*, 2001, 31(4):585-91; M Spath, et al, *Scand J Rheumatol Suppl*, 2000, 113:72-7; L Forsyth, et al, *Ann Allergy Asthma Immunol*, 1999, 82: 185-91; J LaPuma, *Altern Med Alert*, Decd 1999, 2(12):143; H Kuratsune, et al, *Clinical Infect Dis*, 1994, 18(Suppl.1):S62-7; P Levine, Symposium Amer Coll Nutr, 37th Ann Meeting, 11-13 Oct 1996; A Plioplys, S Plioplys, *Neurophyshobiology*, 1997, 35:16-23; S Reuter, A Evans, *J Intern Med*, Jul 2011, 270(1):76-84; E Brass, *Am J Clin Nutr*, 2000, 72(Suppl):618-23; E Brass, *Am J Clin Nutr*, 2000 72(Suppl):618-23. **17**. B Gebhard, J Jorgenson, *Pharma-cotherapy*, 2004, 24(11):1646-8; J Teitelbaum, *J Altern Complement Med*, 12 Nov 2006, 12(9):857-62; Y Hellsten, L Skadhauge, et al, *Am J Physiol Regul Integr Comp Physiol*, 2004, 286(1):R182-8; S Myhill, N Booth, et al, *Int J Clin Exp Med*, 2013, 6(1):1-15. **18**. J La Boesch, et al, *Proc Nutr Soc*, Aust, 1998, 22:82; R Jaffe, *Townsend Lttr*, Jan 2008, 294:87-94; M Messaoudi, R Lalonde, et al, *Br J Nutr*, 2011, 105(5):755-64; A Rao, A Bested, et al, *Gut Pathol*, 2009, 1(1):6; A Sullivan, C Nord, et al, *Nutr J*, 2009, 8(1):4; M Fremont, D Coomans, et al, *Anaerobe*, Aug 2013, 22:50-6; J Trabal, et al, *Nutr Hosp*, 2012, 27(2):659-62. **19**. J Teitelbaum, *Townsend Lttr*, Feb/Mar 2003, 235/236:54-5. **20**. K Keville, *Herbs for Chronic Fatigue*, 2000, New Canaan, CT: Keats Pub, Inc; W Tang, Y Gao, et al, *J Medic Food*, 2005, 8(1):53-8; AJ Hartz, S Bentler, et al, *Psycholog Med*, 2004, 34(1):51-61; A Lerner, et al, *Chest*, 2005, 8(1):53-8; K Bone, *Townsend Lttr*, Feb/Mar 2008, 295/296:62-4; E Olsson, B von Scheele, et al, *Planta Med*, 2009, 75:105-12; J Barker, C Meletis, *Townsend Lttr*, Feb/Mar 2004, 247/248:66-8. **21**. Z Yan Jiu, *J Tradit Chin Med*, 2009, 34:421-8; *Fam Practice News*, 1 Jan 2003:13; K Singh Khalsa, *Herbs Hlth*, Sep/Oct 2003, 8(4):47-50; T Shepherd, et al, *J Sports Med Phys Fitness*, 2005, 45(3):381-2; S Miller, *CFIDS Chron*, Winter 2008:16-8; R Inbar, et al, *Med Sci Sports Exerc*, 2001, 33:1463-70; *Hlth News*, Oct 2000, 6 (10):7; F Wildman, feldendrais.com/method/article/learning_alleviating_chronic_pain, 11 Aug 2009; A Edwards, M Bentley, et al, *Psychophysiology*, Jan 2011, 48(1):136-41; B Fulcher, et al, *J Neurol Neurosurg Psychiatry*, 2000, 69:302-27; P White, K Goldsmith, et al, *Lancet*, 2011, 377:611-90; B Brown, *Altern Ther Hlth & Med*, Jan 2014, 20(1):29-40.