Cell Extracts:  
A Natural Approach to Chronic Fatigue Syndrome  
by Ramon Scruggs, MD  
New Hope Health Center, California

Introduction to CFS  
Despite an always increasing medical and technical knowledge, chronic fatigue syndrome (CFS) remains an elusive pathology. Unfortunately, there is no simple test for CFS and diagnosis still relies on clinical evaluation and exclusion of other possible diseases with overlapping symptoms. In 1994, in an effort to harmonize clinical evaluation and research, the Center for Disease Control has defined Chronic Fatigue Syndrome (CFS) by “the presence of unexplained persistent fatigue that is not relieved by rest and that results in a substantial reduction in occupational, social and personal activities.” Moreover, as criteria for CFS diagnosis, at least four of the following symptoms must have been present for a minimum of six consecutive months with a history of previous wellbeing:  
• Unrefreshing sleep  
• Impairment of short-term memory or difficulties concentrating  
• Sore throat  
• Tender neck or armpit lymph nodes  
• Muscle pain or weakness  
• Migratory painful joints with no swelling or redness  
• Headache  
• Lost or depressed vision  
• Visual intolerance to light  
• Unusual irritability  
• Post-exertional malaise lasting more than 24 hours

In the USA, it is estimated that 200-700 per 100,000 people (0.2% to 0.7%) suffer from CFS. The syndrome potentially affects people of all ages (including children) but the onset is most common in the early thirties (Dowsett, 1990; Shepherd, 1999). CFS afflicts women twice as much as men (Ho-Yen, 1991). Social background seems to be irrelevant although upper-class, well educated Caucasians are more likely to consult for CFS.

Proposed etiology  
No single cause can explain CFS. It is generally accepted that CFS develops through exposure to convergent factors such as:

Neurohormonal factors  
There is a high incidence of abnormalities in the HPA axis of people suffering from CFS. The HPA axis is a major component of the body’s response to stress and refers to the hypothalamus, pituitary, and adrenal glands. The hypothalamus is located in the brain where it physically interacts and stimulates the pituitary gland through the release of the corticotrophin-releasing hormone (CRH). The pituitary gland itself is considered as the key master of the endocrine system. Hormones that are produced by the pituitary control other glands activities at distant sites throughout the body. As an example, liberation of the adrenocorticotrophic hormone (ACTH) in the blood stream by the pituitary commands the adrenal to secrete cortisol. Cortisol is a glucocortical hormone also referred as the “stress hormone.” Its role is to mobilize the glucose reserves so that the body can respond quickly to a challenging situation. Both CRH and cortisol influence the immune system and cortisol additionally can suppress inflammation.

CFS has been associated with smaller adrenal glands (Scott, 1999) and mild signs of adrenal failure as well as reduced levels of related hormones are seen in almost half of the people suffering from CFS (Demitrack, 1998). The CRH and cortisol levels are generally low, although still in the normal range, in these patients. The negative feedback loop of the HPA axis is prolonged, contributing to maintaining the cortisol level in its lower range (Gaab, 2002). Moreover, the CRH response to exercise is reduced (Ottenweller, 2001) and the response to cortisol inducers is impaired (Scott, 1998). Lower levels of CRH and cortisol, per se, are known to result in extreme fatigue, decreased plasma volume, myalgias, arthralgias, fever, allergic responses, as well as mood and sleep disturbances, all common complaints in CFS.

Immune Imbalance  
Several immunological anomalies have been inconsistently reported in CFS. For instance, decreased number and activity of natural killer cells are sometimes seen in CFS (Levine, 1998). In other cases, the RNAse antiviral pathway is impaired – opening the door to infections (DeMeirleir, 2000). Other patients have higher titers of infection-fighting CD8+ T cells combined with a low count of suppressor T cells, leading to an exhausting immune overactivity (Landay, 1991). But the most striking immunological trait in CFS remains a shift from cell-mediated (Th1) to humoral immunity (Th2). The shift to humoral immunity is marked by an increased production of Th2 type cytokines. More IL-5 is produced that stimulates antibodies formation. The levels of IL-6 and IL-8 are raised as well, and these cytokines are presumed to be involved in myopathic pain and hyperalgesia respectively, as seen in CFS (Wolfe, 1997).
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Infectious Agents
A viral origin has long been suspected for CFS. Indeed some features of CSF are reminiscent of those of viral infection. For instance, a sudden onset of illness and a high level of antibodies to many viruses are commonly seen in patients with CSF (Manian, 1994). Arguing against an infectious origin are the facts that most cases of CSF appear sporadically (US Dept. of Health, 1995), CSF does not spread through contacts of any kind and no single pathological agent could be pointed out (Farrar, 1995).

Oxidative Stress
Recent studies are suggestive of oxidative stress involvement in CFS (Logan, 2001; Richards, 2000; Fulle, 2000). Oxidative stress results from the accumulation of free radical species inside the cell. Free radicals are molecules with an impaired electron. This makes them very unstable molecules that react quickly with neighboring molecules from which they try to steal the missing electron. Once started, the process may generate a cascade of oxidation reactions ending in serious damage to the cell. Free radicals arise spontaneously during normal metabolic activities so the cell has evolved antioxidant defenses to handle them. But the cell defense system may become overwhelmed by excessive oxidative assaults generated by environmental factors or in the course of illness. Mitochondrial dysfunction can further exacerbate this oxidative stress phenomenon by releasing additional oxidants.

Signs of oxidative stress involvement in CFS include a high level of oxidative damage to DNA and lipids, as seen in biopsy samples of patients with CFS (Fulle, 2000). Reduced oxidative metabolism (McCully, 1996) and mitochondrial abnormalities in CFS (Behan, 1991) also support a mitochondrial defect as a contributor. Moreover, since mitochondria supply energy to the cell through oxidative phosphorylation, the lower level of ATP that results from a low mitochondrial activity may explain the low exercise capacity reported in patients with CFS (Lane, 1998).

Psychological Factors
Fatigue is a frequent complaint in psychological disorders. Conversely, a long lasting fatigue can generate emotional problems and be a source of anxiety. In CFS, psychological distress and depression are commonly seen (Katon, 1993). Whether this is a cause or a consequence of chronic fatigue can be debated. In any case, psychological wellbeing should be addressed in the management of CFS since it may exacerbate and/or perpetuate the illness.

Genetic Factors
Some of the biological and physiological parameters known to be involved in CFS etiology, such as hormonal and immunological functions as well as aerobic capacity, are heritable and a growing number of studies point toward a genetic influence on chronic fatigue. For example, in one study, specific HLA antigens (HLA-DQ3 and HLA-DR5) were found in association with CFS (Keller, 1994). Moreover natural killer cell dysfunction was reported in siblings with CFS (Levine, 1998). A high incidence of auto-antibodies against specific phospholipids and gangliosides is also found in families where CFS runs (Klein, 1995). Globally these findings are interpreted as signs of an inherited predisposition to CFS. A recent twin study estimated the liability of CFS to be around 19% (Buchwald, 2001). Nevertheless, the often CFS-associated psychological distress showed no evidence of genetic covariation (Walsh, 2001).

CFS Treatment
In treating CFS patients, an empathic approach is crucial. CFS is a long and frustrating illness with no specific cure. The treatment is symptomatic and should be tailored to each individual with increased patient quality of life as a target. A combination of drugs is generally prescribed along with promotion of mild but regular physical activity as well as healthy dietary and sleeping habits. Behavioral cognitive therapy may help patients to cope with CFS limitations. Other potentially useful non-pharmacological therapies include massage, acupuncture, chiropractic, homeopathy, hypnosis, yoga and relaxation techniques. Current options for prescription medication are as follows:

For muscle pain:
• Non steroidal anti-inflammatory drugs (NSAIDs) such as naproxen (Aleve, Anaprox, Naprosen), ibuprofen (Advil, Bayer Select, Motrin, Nuprin), and piroxicam (Feldene)
• Cox-2 inhibitors such as celecoxib (Celebrex), and refecoxib (Vioxx)
• A centrally acting synthetic analgesic named tramadol hydrochloride (Ultram)

For sleeping problems:
• Low-dose antidepressants such as doxepin (Adapin, Sinequan), amitriptyline (Elavil, Etrafon, Limbitrol, Triavil), desipramine (Norpramin), and nortriptyline (Pamelor)
• Antihistaminics like diphenhydramine (Benadryl)
• The hypnotic drug zolpidem (Ambien)

For depression:
• Serotonin reuptake inhibitors, such as fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil)
• Antidepressants such as venlafaxine (Effexor), trazodone (Desyrel), bupropion (Wellbutrin) and nefazodone (Serzone)
For anxiety:
- Anxiolytic agents such as alprazolam (Xanax), lorazepam (Ativan), and clonazepam (Klonopin)

For fatigue:
- Corticosteroids such as DHEA and low-dose hydrocortisone

For central activation:
- The wake-promoting agent modafanil (Provigil)
- Amphetamine-based stimulants (Dexedrine)

For dysautonomias including neurogenic hypotension, postural orthostatic tachycardic syndrome, and vasovagal syncope:
- Beta-blockers such as atenolol (Tenormin) and propranolol (Inderal)
- The peripheral alpha agonist midodrine (ProAmantine)
- The corticoid fludrocortisone (Florinef)

Other experimental drug avenues are being explored. For example, a synthetic nucleic acid (Ampligen) with anti-viral and immune modifying activities has shown some positive results. The drug is currently undergoing phase III clinical trial for CFS and results are expected by September 2003.

Nutritional supplementation with Vitamins (B12, C and A), coenzymes (Q-10, NADH, adenosine monophosphate and glutathione), minerals (iron, zinc, germanium and selenium), essential fatty acids and some amino acids (L-tryptophan, L-carnitine) may be of value as adjunctive therapies. On the herbal side, numerous preparations are claiming to have positive effects on CFS symptoms. These include astragalus, borage seed oil, bromelain, comfrey, echinacea, garlic, Ginkgo biloba, ginseng, primrose oil, quercetin, St. John’s wort, and Shiitake mushroom extract. With the exception of primrose oil, for which there is a documented clinical trial with positive results (Behan et al 1990), the rationale for the use of these herbs with CFS is based on *in vitro* studies. Another herb, *Ruscus aculeatus*, has some potential in treating orthostatic hypotension that would deserve further evaluation with CFS patients (Redman, 2000).

**CF Support, a New Natural Therapeutic Approach to CFS**

There is an additional option for dietary supplementation in CFS patients. The product is called CF support and it is a blend of adrenal and mesenchymal cell extracts derived from mammalian tissues. Both extracts are obtained by breaking down cells of the corresponding tissues to liberate active molecules. These active biofactors are then selectively picked up to obtain a liquid extract that provides a natural rich source of cellular growth factors and other signaling molecules.

**Adrenal Extract to Support the Hypothalamus-Pituitary-Adrenal Axis**

Adrenal extract from the gland of mammals has a long history of use as a booster for adrenal functions. Originally administered in an injectable form along with vitamins, it is currently more conveniently available for oral administration. Animal studies have shown that both forms had comparable activities (Craveri, 1971).

Adrenal extract acts by supplying small amounts of adrenal hormones and factors that promote an improved adrenal function. The adrenals are little triangular-shaped glands located on top of each kidney. The inner part of the adrenal, called the medulla, produces epinephrine (adrenaline) that is directly involved in the “fight or flight” response to a perceived danger. Epinephrine raises pulse rate, blood flow and blood sugar. The outer part of the adrenal, called the cortex, secretes three major corticosteroids: 17-ketosteroids (DHEA), mineralocorticoids (aldosterone) and glucocorticoids (cortisol and corticosterone). These hormones have diverse functions in the body. Androgen precursors such as DHEA have anti-inflammatory and growth-promoting functions and are believed to have anti-aging properties in both men and women. Aldosterone controls sodium excretion by the kidney to maintain blood volume and blood pressure. Cortisol is the most potent glucocorticoid produced by the adrenal. It is structurally derived from cholesterol and acts on specific receptors throughout the body to influence glucose homeostasis, fat and protein metabolism, immune function, vascular tone and bone metabolism. It also has potent anti-inflammatory effects. As mentioned before, cortisol secretion is controlled through the HPA axis via ACTH secretion by the pituitary gland. Cortisol secretion is subjected to circadian variations with peaks in the early morning and at night. Cortisol can also be triggered in situations of physical and psychological stresses.

In CFS, the adrenal can still produce minimal level of these hormones but the normal circadian rhythm of cortisol secretion is disrupted and the adrenal reserve is low (MacHale, 1998). As a consequence, the depleted adrenal cannot respond adequately to any stressful situation whether physical or psychological. Adrenal depletion results in reduced physical and emotional resistance as well as general exhaustion and weakness. Supplementing with adrenal extract may stimulate such a sluggish gland by providing the little hormonal kick needed to get back in the right gear.

**Mesenchymal Extract to Regenerate Functional Tissues, Relieve Muscle Pain, and Boost Energy Level**

Mesenchymal extract is prepared from mammal extra-embryonic connective tissue and, like other gland extracts, also has a long history of use. Dr. Niehans (a reputed Swiss endocrinologist) used it in the 30s to
Cell Extracts

> rejuvenate aging cells (Niehans, 1960). Mesenchymal stem cells are undifferentiated cells that, when triggered under appropriate conditions, can become almost any type of cells to help restore damaged or aging tissues (Caplan, 1994). Mesenchymal extract is obtained by breaking down mesenchymal stem cells to liberate active molecules.

Myalgia is a significant feature of CFS. The diffuse muscle pain seen in CFS is, in fact, quite reminiscent of that observed in fibromyalgia, a rheumatoid disease. Recent studies have linked insufficient plasma levels of growth hormone to both conditions (Berwaerts, 1998; Bennet, 2002) and administration of growth hormone to patients with fibromyalgia was able to reduce pain symptoms (Leal-Cerro, 1999). Mesenchymal extract being a rich source of growth factors, is expected to be helpful in reducing the chronic pain experienced by many CFS sufferers.

Additionally, as demonstrated in vitro, mesenchymal extract has the capacity to increase mitochondrial metabolism, the primary aerobic source of energy for cells (Fig. 1).

Two sets of experiments revealed that mesenchymal extract contains a biological activity capable of inducing aerobic respiration (as measured through WST-1 mitochondrial activity) in fibroblast, while negligibly affecting their proliferation (as measured through Hoescht DNA count). Such a biological activity supports the use of mesenchymal extract as a nutritional supplement in physiological conditions for which an increase in cellular metabolic activity may bring benefits. This is certainly the case with CFS.

Muscle weakness is a common symptom among CFS patients and is believed to be linked to reduced oxidative metabolism (McCully, 1996) caused by some mitochondrial defect (Behan, 1991). As reduced mitochondrial oxidative phosphorylation directly affects ATP synthesis, there is less energy available for physical activity. As a metabolic booster, mesenchymal cell extract may help restore the body energy level to relieve the fatigue and the muscle pain of CFS patients. As a result, mesenchymal cell extract should increase their capacity to exercise, an important step in the recovery process.

Conclusion

Chronic fatigue syndrome with its wide range of symptoms and multiorgan involvement, is a challenge for any health care practitioner faced with its treatment and a source of frustration and anguish for the patient who suffers from it. The etiology of CFS remains largely undefined but appears to develop through exposure to convergent factors. There is no single treatment for CFS. A supportive program of patient management should include empathic listening, education about the disease, symptom-based treatment, a mild exercise program and incentives for better diet and sleeping habits when necessary. Symptomatic treatment options can be found in the conventional Western pharmacopoeia but also in various alternative approaches including diet supplementation. CF Support is a new diet supplement that was specially formulated to alleviate the symptoms of chronic fatigue syndrome. CF Support is a unique blend of adrenal cell extract to support the hypothalamus-pituitary-adrenal axis, and mesenchymal cell extract to regenerate functional tissues, relieve muscle pain, and boost energy level. Its efficacy in alleviating CFS symptoms is supported by in vitro studies and a growing number of anecdotal case reports. CF Support is the newest addition to the NatCell line products of Atrium Biotechnologies.

Correspondence:
Atrium Biotechnologies Inc.
1405 Boul. Parc Technologique
Quebec, Canada G1P 4P5
418-652-8525
Fax 418-652-0861
mjpquin@atrium-bio.com

Bibliography


Figure 1

Effect of mesenchymal cell extract on fibroblast mitochondrial activity and proliferation.

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TOWNSEND LETTER for DOCTORS & PATIENTS - APRIL 2003


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