

# **CHRONIC FATIGUE SYNDROME A BIOLOGICAL APPROACH**

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## ***A summary by Paula M. Carnes***

De Meirleir and Englebienne have done a masterful job giving an overview of the biological studies of the origin and damage of what is currently known as “chronic fatigue syndrome. They have referenced literally hundreds of scientific research articles. I will not presume to restate in any detail these studies. Those who read my summary and have some knowledge of molecular biology will want to own and read this book. Those patients who want to understand the state of current biological study into CFS may find my summary sufficient to give them further leads into potential treatments.

Interferons (IFNs) have been studied because of their ability to protect cells from viruses. One of the pathways cells use to communicate is 2-5A/RNase L. This pathway is activated by interferons when the cell is threatened with a viral infection. In chronic fatigue syndrome immune activation and infection by viruses is common. Several laboratories are reporting dysfunctioning of the 2-5A/RNase L pathway in CFS patients. The dysfunction is not that the pathway is upregulated as it would be in any viral infection. The ongoing problem in CFS is that the binding polypeptide which must bind to the RNase L pathway in order for it to function is a low molecular weight. It binds but it does not function. The native 83 kDa RNase L instead of being “83” has been “chopped” into a 37 kDa 2-5A weight, and it simply does not work. This low molecular weight polypeptide may be a marker or diagnostic tool for CFS. Certainly the malfunction of the RNase L pathway is going to have major repercussions for the health of the individual.

When the polypeptide 83 kDa RNase L is chopped up it produces m-calpain, elastase, and cathepsin\_G. These cause cell death (apoptosis) and inflammation, processes observed in CFS. New treatment approaches may involve immunomodulators such as bile salt or retinoic acid derivatives.

In a study conducted by De Meirleir the low molecular weight 37-kDa RNase L was found more frequently in CFS patients than normal controls, 72% in CFS while only 1% in healthy controls. Interestingly in a control group of depressed patients and fibromyalgia patients there were NO low molecular weight polypeptides. Two studies has shown that the presence of the low molecular weight form of RNase L correlate with the severity of CFS symptoms. The most severely disabled patients demonstrated ONLY the 37-kDa RNase L.

One study indicated that protease inhibitors prevented the breakdown of the native 83 kDa RNase L in vitro. This may indicate that protease inhibitors will be useful in treating CFS.

Ribonuclease L or RNase L is regulated by its natural inhibitor protein or polypeptide, RNase L inhibitor (RLI). Vojdani et al found that RLI is down regulated in CFS patients. This would lead to overactive or dysfunctional RNase L activity. Englebienne writes, “all the ABC transporters identified as analogous to RLI play physiological roles of which a dysfunction can be related to various CFS symptoms. The occurrence of channelopathies in CFS had already been suspected on grounds of clinical observation with cardiac muscle thallium uptake.” P. 90 Some of the symptoms which are linked to this RLI dysfunction are chemical sensitivities, pain, night sweats, muscular and cardiac symptoms, irritable bowel, abnormal glucose metabolism, and cholesterol and phospholipids transport.

Viruses such as HTLV II, mycoplasmas, and HIV type 1 have been demonstrated to alter ion channel functions such as RLI and others. There is need for further study in this area.

Another result of the dysfunctional cellular communication in CFS is the resistance of cells to the hormones which regulate them. “one can reasonably consider that the dysregulation of the IFN (interferon) regulating pathway in these patients can be responsible for a peripheral resistance to thyroid hormones, explaining the extreme fatigue with a normal or subnormal thyroid hormone profile.” P. 116 Growth hormone replacement seems to aid a subset of patients as well.

Apoptosis, or cell death, is related to the extent of RNase L cleavage. The higher the RNase L damage the higher the rate of apoptosis. It is not clear whether this apoptosis is cause or effect. It is certainly possible that this cell death is being caused by opportunistic infections which are intracellular or live inside the cells. These infections would include viruses, chlamydia, and mycoplasmas.

In those patients who have this dysregulated RNase L pathway what would their disease look like? It would be a complex disease with secondary diseases superimposed upon it. The researchers grouped symptoms in four categories, general, neurocognitive, musculoskeletal, and psychiatric. Mood change, the psychiatric factor did not vary between CFS patients and controls. Those patients with the higher level of the 37kDa RNase-L were sicker. There was also indication of viral reactivation in these patients.

“this would suggest that the general CFS symptoms are the normal reactions associated with a reactivated virus or infection and most likely represent an increase in total RNase-L activity and the fragmentation of the RNase-L enzyme system proteins.” P. 181

Amino acid abnormalities seem to cause muscle pain and fatigue. Some of these were similar to patients with rheumatoid arthritis. There was an upregulation of nitric oxide. “Analysis of the data from over 1500 patients shows that the more severe the pain and fatigue symptoms in a patient, the higher the level of serum lipids and lower the excretion of amino acids.” P 186-7

Much like HIV patients, CFS patients develop secondary conditions. These fall into two categories: 1. infections that activate cytokines and 2. factors that reduce energy supply.

The infections may be reactivated viruses such as herpes, adenoviruses, and CMV. The infections may be L form bacteria such as the mycoplasmas, with *m. fermentans* being the one most commonly found in up to 60% of patients. De Meirleir found that antibodies

to mycoplasma was unrelated to RNase L defects but a positive PCR for mycoplasma was related to RNase L defect level.

Azithromycin has been found to reduce symptoms and RNase L levels it is not clear exactly what the antibiotic is doing. It may be mycoplasma is damaging the RNase L, or mycoplasma is opportunistic, ie there because the RNase L pathway is already malfunctioning, the PCR may actually not be recognizing mycoplasmas but some DNA fragments from the RNase L pathway, or the antibiotics may be inhibiting the mechanisms of cell death.

Bacteria toxins also activate cytokines. Myofascial pain syndrome frequently found in fibromyalgia patients and the general public may be caused by staphylococci infections. Gastrointestinal symptoms may be related to enterococcus and this bacteria may also be related to the musculoskeletal symptoms of CFS. Candida species did not seem to be related to these symptoms.

Factors affecting energy would be depletion of amino acids and glucose intolerance. Reduced arginine has profound effects on nitric oxide production.

Also, inflammatory bowel disease and malabsorption disorders lead to problems with metabolism and energy. Patients with orthostatic hypotension benefit from increased salt in their diet.

What are the most likely causes of CFS? The simple answer is CFS is an acquired immune dysregulation with persistent ongoing infections. But what causes this? Approximately 72% of CFS patients came down with an infection initially. No one has found a single precipitating virus but that does not mean there is not one. It does seem that EBV and HHV-6 are reactivated with CFS rather than the cause, as most people on earth have had these viruses in childhood.

Upper respiratory infection, blood transfusion and hepatitis B vaccination were important factors in two clusters of CFS. Another possibility is stealth infection with pathogens that live inside the cells such as Burcella, Mycoplasma, and Chlamydia pneumoniae.

Many patients experienced stress prior to illness onset. Immune dysfunction induced by viruses, a virus, or stealth pathogens occurring at the same time as some form of stress may lead to CFS.

Was the immune system malfunctioning in the first place? Several studies suggest there was a long-term shift toward T2 cytokine balance in CFS patients. But we do not yet know which came first, infection or immune system disruption.

NK cell function has been measured as low, normal and high, but several studies seem to suggest NK cell function is low. Variables such as medication, alcohol ingestion, smoking, and anxiety have not been controlled for. [It is of interest that such factors could reduce NK cell function.] It is possible that increased nitric oxide levels are toxic to NK cells.

Vitamin B 12 is an NO scavenger and may be useful in treatment.

A high percentage of CFS patients have allergies. This may indicate immune system irregularities. "Recently a remarkably high percentage of bronchial hyperreactivity has

been demonstrated in CFS patients.” p. 206 “The presence of rheumatoid factor, anti-nuclear antibodies, antithyroid antibodies.

Antismooth-muscle antibodies, antigliadin, cold agglutinins, cryoglobulins, and false serological positivity for syphilis have also been reported.” p.

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What is the role of infection in CFS? Herpes viruses, enteroviruses, and retroviruses have been discussed. The list is long, EBV, HHV-6, group B Coxsackie viruses, HTLV II, spuma virus, Hepatitis C, HHV-7, a novel CMV related stealth virus, Borna disease virus, Chronic parvovirus, and Ross River virus.

Two viruses may interact to produce CFS. The spuma viruses and HTLV-II may interact in this way. Patients infected with HTLV-II may be contagious to their non sexual contacts as higher portion of these people were positive although to a lesser degree.

Hepatitis B vaccinations have triggered CFS in some cases. “Given the fact that hepatitis B can trigger the onset of multiple sclerosis (MS) in some cases, the authors suggest that CFS can be an autoimmune reaction without the consequences of demyelination seen in MS.” p. 209

Mycoplasma, Chlamydia, Brucella, Rickettsia, Coxiella and others including “Human Blood Bacterium” discovered by Lindner and MacPhee may cause or exacerbate CFS.

Mycoplasma is found by PCR in 50 to 70% of CFS patients. Mycoplasmas have been found to modulate autoimmune reactions and promote the rheumatic diseases, multiple sclerosis, amyotrophic lateral sclerosis, lupus, autoimmune thyroid disease and others. Asthma is also known to be associated with mycoplasma infection. Mycoplasmas are able to cleave the RNase L.

Chlamydia is widely recognized as involved in atherosclerosis, sinusitis, bronchitis, pneumonia, and asthma as well as heart infections. Patients respond to one to two months of azithromycin. *C. pneumoniae* seems to be capable of becoming a chronic infection inside of cells which makes it difficult for the immune system to attack it. “Monocytes and macrophages have recently been shown to be responsible for dissemination of the infection from the respiratory tract to other organs, providing a theoretical basis for multiorgan involvement as seen in CFS.” p. 213

A treatable subset of CFS patients are infected with borrelia, brucella and rickettsia. Treatment is long-term antibiotics. Dr. C. Jadin had diagnosed rickettsial infections using an immunofluorescence test. She has seen recovery of 84 to 96% using tetracyclines and other antibiotics.

Seven onset mechanisms are listed:

Cellular stress due to blood transfusions, fetal cells, or radiation exposure.

Toxins such as heavy metals, organophosphates, and pentachlorophenol (PCP) In particular zinc, cadmium, lead, chromium, nickel, mercury, and arsenic in particular are presented.

Accute viral infections such as EBV, CMV, which suppress the immune system for long periods of time, and hepatitis B vaccines.

Longstanding physical and mental stress which depress the immune system.

Pregnancy and situations that produce high estrogen levels shift the immune system from T1 to T2 allowing pathogens to grow inside of cells.

Infections that are eliminated slowly from the body can produce a shift from T1 to T2 balance. Infections which enter the body during transfusions or immediately after pregnancy are more likely to succeed. Intracellular organisms like chlamydiae and mycoplasmas are more likely to survive and thrive under these conditions.

Some people may just have a T2 dominant immune system which will predispose them to intracellular infections.

To reiterate, there are many symptoms of intracellular infection in CFS.

Some of these symptoms are increases in T1 cytokines causing flue-like symptoms and tender lymph nodes. Other symptoms of increase RNase L and dysfunctional RNase L activity are: hypoglycemia, night sweats, low pain threshold, chemical sensitivity, drug sensitivity, depression due to poor tryptophan uptake, loss of potassium, visual problems, loss of urine concentration during the night, sodium retention, fatigue and sleep disturbance, low magnesium levels leading to muscle weakness, weakness of respiratory muscles leading to respiratory problems, hyperventilation, abnormal response to exercise, low blood volume, ectopic heart beats, prominent U-wave on ECG, bladder problems, premenstrual syndrome, slow wound healing, resistance to hormone uptake in cells, elasticity of tissues damaged leading to hernia and myral valve prolapse, and increased incidence of cancer. (found in one report)

“Clinical trials in CFS are difficult to perform and evaluate because of the heterogeneity of patient populations and the complexity of illness origin.” p. 230 Patients with this disease are severely disabled with only about 10% returning to normal functional levels. Since so few completely recover this has major socio-economic consequences.

Depression and anxiety are secondary conditions in CFS. The following are drugs used to treat these conditions in CFS, generally at doses lower than for healthy patients:

### ***Benzodiazepines***

Modafinil (used for epilepsy and may be useful in CFS) Tricyclic antidepressants may help sleep disturbances Fluoxetine “a recent study has shown that , at a 20 mg daily dose, it does not have a beneficial effect on any characteristic of CFS, including fatigue severity, depression, functional limitations, sleep disturbances, and cognitive functioning.” p. 232 Doxipin “Had a 70% success rate in an uncontrolled trial.” p. 232 Terfenadine “.unlikely to be of clinical benefit in CFS.” p 232 Moclobemide was useful especially in depressed patients. Antidepressants which affect catecholamine seem to work best.

5-hydroxytryptamine - affects catecholamine Galantamine - mixed results so far Drugs affecting endocrine functions are as follows:

## **Growth hormone**

### **Fludrocortisone**

DHEA promotes Th1 immune response. Preliminary studies indicate this hormone helps some patients. Further studies are needed.

Immune modulating and antiviral drugs have been used. Immunosuppressive therapy has not been found effective. The following are a list of immune modulating, antiviral and antibacterial drugs:

Ampligen is both immune modulating, antiviral, and anti-tumor. [It is probably effective in reducing the intracellular L form bacteria as well since they deregulate the RNase L pathway.] “In CFS, the 2-5A pathway has been shown to be dysregulated in up to 70 to 75% of subjects. Therapy with ampligen resulted in a downregulation of the 2-5A oligoadenylate synthetase/RNase L pathway toward normal and was associated with clinical improvement related to exercise tolerance and neurocognitive impairments.

These initial findings were confirmed in a second study including 92 CFS individuals entered into a controlled trial of ampligen (AMP502).” p. 237 Ampligen is administered by IV infusion. This drug is currently in Phase 3 studies.

Immunoglobulins are not currently recommended to treat CFS. However there is a subset of adolescents with CFS who seem to have a post infective cases with immunologic abnormalities who do respond to IV immunoglobulin therapy.

Transfer Factor has not demonstrated any effect in CFS in one double blind study.

Isoprinosine, an immune system stimulator, has given considerable improvement in one study. The author found that about one third of his patients showed improvement when given 1.5 g Isoprinosine per day over a few months time.

Amantadine is an antiviral which inhibits entrance of a virus into a cell.

“Interestingly, amantadine was found to be a very effective treatment of fatigue and pain in multiple sclerosis Although the precise mechanism of the action of amantadine on the CNS [central nervous system] is unknown, it could be a nonspecific general CNS stimulator.” When amantadine was tried for CFS only fifteen of 28 patients were able to tolerate the drug due to side effects.

Lentinan is a mentinus edodes mushroom abstract. It is being studied in Japan as a cancer treatment because it can correct the balance between T1 and T2 in the immune system. The author suggests that it should be studied for use in CFS.

Kutapressin, a pig liver extract, blocks HHV-6 and EBV infection.

Acyclovir, an antiviral, showed no beneficial effect over placebo in one double blind study.

Interferons are proteins that are produced by the body as the first defense against viral infection. “A proportion of CFS patients may benefit from interferon-a therapy. The rationale resides in the association between CFS and persistent viral infection. A subset of CFS patients who had diminished NK function and normal lymphocyte proliferation

benefited from this therapy.” Patients with hepatitis C who were treated with interferon developed symptoms of CFS such as fatigue, pain, and mood change.

Antibiotics used to treat bacteria can have a significant effect on the level of illness in CFS. “In 71% of CFS and fibromyalgia patients mycoplasma spp. were detected, multiple infections being found in approximately one-half of the patient population. In healthy individuals the incidence of mycoplasmal infections was only 6%. These results are similar to those reported by Choppa et al. and Vodjani et al. who showed increased PCR-detectable mycoplasmas in patients.” p. 241 “Mycoplasmas penetrate into nerve cells, synovial cells, and other cell types and are also very effective at evading the immune system.” p. 241 “In our studies using PCR with gene tracking, which involved 272 Belgian CFS patients, one or more mycoplasma infection were identified in 68% of the patients. The following species were identified: Mycoplasma fermentans (25%), Mycoplasma pneumoniae (26%), and Mycoplasma hominis (36%.) Interestingly, Mycoplasma spp. were found to be associated with increased low molecular RNase L levels, suggesting that they more readily invade cells that have defects in this enzyme system or that they are able to induce changes in the RNase L pathway.” p. 242 Nicolson et al. have recommended the use of four antibiotics, doxycycline (200-300 mg a day), azithromycin (500 mg a day), minocyclin (200-300 mg a day), and ciprofloxacin (1000-1500 mg a day). Many weeks of therapy are required. Oxidative therapy and nutritional supplements in addition result in gradual recover of patients with these bacterial infections. Chia et al. have done a study showing that chronic Chlamydia infection can be treated with azithromycin.

Some studies suggest that up to 60% of CFS patients suffer from myofacial pain syndrome. This syndrome is caused by toxin-producing staphylococci. They can be treated with “rotating nasal antibiotics (nasal Bacroban, Neomycin, and Kenacomb), using each for one week and rotating back to the initial antibiotic.”

p. 242 Since staphylococci are normal skin inhabitants they cannot be eliminated entirely and relapse is common. A staphylococcal toxoid vaccination study for CFS found that there was significant improvement in symptoms.

Other agents mentioned were antihistamines, analgesics and anti-inflammatories, antifungals, and calcium antagonists.

Nutritional factors were listed as follows:

### ***Vitamins***

Folic acid may be useful in those who test deficient at 10,000 u daily for 2 to 30 months

Vitamin B 12 (cobalamin) from 1000 to 5000 u showed symptom improvement in 2 to 3 weeks. This is administered by injection every 2 to 3 days. A rationale for the effectiveness of vitamin B 12 is that it is a scavenger for nitric oxide and its oxidant product peroxynitrite which may be responsible for CFS symptoms.

Other B vitamins may be helpful.

Vitamin C enhances NK activity and has been found useful in CFS. “Greater

improvement was observed when DHEA was added.” p. 246

### ***Minerals***

Magnesium deficiency has been reported in several studies. One study of magnesium given intramuscularly showed improvement. If muscle pain is a key symptom magnesium combined with malic acid may be useful. The dose used in one study was 200 to 600 mg of magnesium and 1200 to 2400 mg malate per day.

Sodium increase in patients with neurally mediated hypotension is useful.

Zinc deficiency can cause immune depression, myalgia, and fatigue. Patients with multiple infections as found in CFS sometimes need increased iron. It is important, however, to be sure the patient does not have hemochromatosis before supplementing iron.

### ***Amino acids***

L-Tryptophan, 5HTP, L-Carnitine, and glutamine were discussed. However, the conclusion for all amino acids was “.supplementation with a single amino acid cannot be recommended.” p. 248

### ***Other nutritional factors***

Essential Fatty Acids may reduce muscle pain, however, again, the author recommended supplementation only where there is a demonstrably low level of any fatty acid.

### ***Food intolerance***

Dealing with food intolerance often relieves gastrointestinal distress. It has not been found to aid any other CFS symptoms, but is recommended to aid in digestion.

Miscellaneous treatments mentioned were as follows:

Coenzyme Q10 - There are no double blind studies.

LEFAC - no effect observed

Lymph node extraction designed to change the cytokine pattern may be useful.

Plasma Exchange showed mild improvement but the effect wore off in 2 weeks.

Staphylococcus Toxoid Vaccine in a double-blind study showed some improvement in symptoms.

Cognitive behavior therapy reduced fatigue but patients were still significantly sicker than healthy individuals. “.cognitive behavior therapy is of benefit in facilitating patients’ acceptance of the disease, particularly in those with mood disorders, but of little balue in altering the organic basis of the disease.” p. 251 Psychotherapy was no more effective than a support group.

Exercise has been followed by a period of worsening of symptoms by about 6 to 48 hours. A study of graded exercise showed minor improvement of symptoms but also had a high dropout rate as the more severely ill patients simply could not follow the program.

Massage therapy showed improvement in generalized distress, sleep, anxiety, pain, depression, and fatigue.

Basic conclusions of the state of the science at this point would be that several subset populations will emerge in CFS patients. Further analysis of the TRase L pathway defects in CFS will be a marker and also a way of distinguishing subsets of the disease. Major causes coming together to cause the dysfunction in the pathway are viral and bacterial infections, cellular stress from radiation and toxic chemicals, and stress. “In a large study group including 1546 patients, we observed that, in their majority, and infectious event concomitant to a noninfectious event occurred simultaneously at the onset of the disorder.” p. 273 CFS and MS may be two extremes of a similar immune dysfunction. CFS has elevated nitric oxide levels and MS has decreased nitric oxide levels. “Between the two extreme situations presented for the worst CFS and chronic MS cases, several graded autoimmune pathological conditions may fit, including acute MS, lupus erythematosus that shares with CFS the presence in serum of antinuclear antibodies, and type 1 diabetes, in which the abnormalities in the PKR/2-5A pathway receive sustained attention.” p. 271 It was found that there is a higher percentage of CFS among teachers and healthcare professionals.

A partial overview of diagnostic procedures is as follows: [I am only listing tests which many doctors currently do not include]

### ***Intracellular red blood cell magnesium***

Infectious serology: toxoplasmosis, cytomegalovirus mycoplasma Chlamydia, Epstein-Barr virus, herpes simplex virus, human herpes virus 6, human immunodeficiency virus

Serology for rickettsia, dengue, hepatitis B/C, syphilis, yersinia, babesia

based on patient history and symptoms

Rule out: Addison’s disease, Cushing’s syndrome, thyroid disorders, abnormal iron levels, anemia, diabetes, rheumatic disorders, cancer, Lyme disease, multiple sclerosis, Parkinson’s disease, masthenia gravis, sleep apnea.

### ***Low molecular weight RNase L***

“It is clear from our work and from that of others that we report here that the use of immunotherapy, immunomodulators, and antiviral- and antibio-therapy will gain a prominent place in the therapeutic arsenal and strategies aimed at fighting the syndrome.”

p. 278