Some findings presented at the American Association of Chronic Fatigue Syndrome Fifth international Research and Clinical Conference, Seattle, January 2001

It is perhaps worth reiterating that the American term "CFS" reflects patients who are likely to have ME / "core" CFS rather than psychiatric disorder as facilitated by the current CFS case definition: this situation is one which requires immediate international input to end what is obviously a most confusing and unsatisfactory situation for all involved.

In his keynote address, Professor Komaroff reminded physicians that with CFS, just because something is not yet written does not mean that it is not true.

Brain studies / Neurology

Different neurobiological profiles are found in CFS patients compared with healthy controls. Using assays which measured hormones and cytokines with a potential for affecting the central nervous system (cortisol, prolactin, oestrogen, progesteron, CRP, neopterin, TNFalpha, TGFbeta, DHEA-s), significant differences were found in CFS patients compared with controls. [1]

Both baseline heart rate and plasma epinephrine were increased in CFS patients, suggesting an activated sympathoadrenal state. [2]

Sympathetic nervous system dysfunction is integral to CFS pathology. [3]

A wealth of studies (about 85%) confirm autonomic nervous system (ANS) dysfunction in up to 90% of CFS patients, with resulting effects on many vital functions (blood pressure, pulse rate, breathing and body temperature). Professor Komaroff said that there is substantial evidence that both the sympathetic and parasympathetic nervous systems are abnormal in CFS.

CFS patients showed reduced activation of medial/basal frontal regions but a greater activation of dorsolateral frontal and temporal lobes than controls. This MRI study showed unique features of cognitive impairment, demonstrating that more areas of brain activity were used in task solving than in controls (ie. CFS patients are working harder than controls to solve the same problem and use more brain areas than controls). [4]

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[1] Neuroendocrinological Profiles in Patients with CFS. B Evengard et al. AACFS # 001
[2] Orthostatic intolerance and sympathoadrenergic reactivity in chronic fatigue syndrome. PMMB Soetekouw et al AACFS # 085
[3] Sympathetic Dysfunction Demonstrated by Isometric Hand-grip Response in Chronic Fatigue Syndrome. JN Baraniuk et al. AACFS # 126
[4] Brain correlates of cognitive effort in chronic fatigue syndrome and healthy control subjects. Mahurin RK, Buchwald DS et al AACFS # 088

A quantitative volumetric study suggests that some CFS patients show a lateral ventricular enlargement, which may be associated with white matter loss in the frontal as well as the parietal lobes. [5]

Psychopathology

CFS patients do not display the same improvement with treatment as seen in depressed patients. Little overall change is seen in CFS patients on either physical or mental scores after antidepressant treatment. [6]

Expectancy effects do not account for heightened pain sensitivity. [7]

Findings from one of the largest well-studied patient groups in the world which used a factor analysis (done by computer, which eliminates all bias by the researcher) suggests that psychiatric disorder is not a core aspect of CFS and that this is a strong argument against CFS being a psychosomatic or "functional somatic" disorder. [8]

Whilst significant neuropsychological impairment was found in CFS patients, no subject performed in the range suggesting lack of effort or feigned impairment. [9]

The often-proposed hypothesis that CFS is a form of somatisation disorder was tested. It is apparent that there is no relationship between the number of medically unexplained symptoms and psychiatric diagnosis. CFS has no relation to somatisation disorder [10]

Visual processing disabilities

Investigation of the biological basis of visual processing disability in CFS showed that alteration in visual processing response is associated with evidence of altered connective tissue turnover. [11]

Biochemistry

Symptom expression is associated with changes in serum lipid levels. Significant changes in glucose, amino acid and inflammatory mediating fatty acids may be involved in

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[5] Chronic Fatigue Syndrome: Quantitative Assessment of Cerebral Volumes. Gudrun Lange, Benjamin Natelson et al. AACFS # 045

[6] A comparison of treatment outcome in CFS and in major depression. SN Schwartz, R Jones. AACFS # 106

[7] Increased pain sensitivity in fibromyalgia/CFS. RH Gracely, DJ Clauw et al. AACFS # 141

[8] A factor analysis study of syptoms in 1573 patients with chronic fatigue syndrome. P De Becker, N McGregor, K De Meirleir. AACFS # 020

[9] Malingering in chronic fatigue sydrome: a neuropsychological investigation. Lana Tiersky Benjamin Natelson et al AACFS # 102

[10] The relationship between medically unexplained somatic symptoms and psychopathology in chronic fatigue syndrome. Daniel Cukor, Lana Tiersky, Benjamin Natelson. AACFS # 028

[11] Scotopic vision alterations in chronic fatigue syndrome. NR McGregor, RH Dunstan et al AACFS # 057

symptom expression. Increases in levels of polyunsaturated fatty acids had the highest correlation with both fatigue and muscle pain scores. [12]

Objective examination of skeletal muscle tissue in CFS patients (biopsy of the vastus lateralis muscle) showed that activity of all skeletal muscle anti-oxidative enzymes were significantly increased in CFS patients compared with controls. Lipid analysis showed fatty acid modifications in patients but not in controls. Fluorsecence polariztion showed a significant decrease of membrane rigidity with a consequent increase in membrane fluidity.
There is evidence of a dengenerative process of the muscle tissue in CFS patients, as typically occurs in mitochondrial myopathies. This may contribute to muscle fatiguability and it supports an organic origin for CFS. [13]

Virology

CFS patients with active HHV6 infection (viraemia) have activation of coagulation and are hypercoaguable. Since HHV6 is known to infect endothelial cells, there may be a resultant endothelial cell dysfunction triggering the coagulation system. [14]

Genetic abnormalities

Recent studies have demonstrated circulating plasma RNA in Gulf War Syndrome patients. A study was therefore conducted to determine the presence or absence of RNA in CFS patients and to determine if the amplified sequences of RNA were similar to or different from those found in GWS. All chronic illnesses studied (including GWS, CFS, AIDS and multiple myeloma) show prominent RNA not observed in normal controls. Prominent RNA bands so far sequenced show homology with human genes which are noted for their tendency for gene rearrangement under severe physiologic stress. The most amplified sequences appear to be disease specific. [15]

Dr N.Afari, Associate Director of the University of Washington CFS Research Centre said that genetic abnormalities may team up with environmental influences to produce CFS. Environmental influences which worldwide researchers are investigating include the frequent pairing of CFS with food and chemical sensitivities. [16]

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[12] Analysis of serum lipid changes associated with self-reported fatigue, muscle pain and the different chronic fatigue syndrome factor analysis symptoms clusters. McGregor NR, Dunstan RH, De Meirleir K et al. AACFS # 059

[13] Oxidative Damage in Chronic Fatigue Syndrome. D Racciatti et al. AACFS # 150

[14] Hypercoaguable state associated with active Human Herpes Virus 6 (HHV6) viraemia in patients with CFS. JH Brwer, D Berg. AACFS # 098

[15] RNAs in the plasma of patients with chronic fatigue syndrome: a novel mechanism for chronic illness expression with both treatment and diagnostic implications. PR Cheney, HB Urnovitz AACFS # 074

[16] Dr N Afari . Reporting on AACFS Conference. Judith Blake. Seattle Times 26 January 2001

Microbiology

The dysregulation of the important anti-viral 2-5 RNase L pathway in CFS is a potential biomarker for the disorder. The RNase L pathway is a series of enzymatic reactions which go on inside white blood cells when they perceive themselves to be challenged by viruses and possibly also by some toxic exposure. Elevated levels of RNase L are associated with reduced maximal oxygen consumption (VO_2max) and exercise duration in patients with CFS. Both abnormal RNase L activity and low oxygen consumption were observed in most patients with CFS. These findings demonstrate that patients' extremely low tolerance for physical activity is likely to be linked to abnormal oxidative metabolism, perhaps resulting from defective interferon responses. [17]

Much of the Belgian work focused on the abnormal enzyme pathways found in CFS. In healthy people, the enzyme breaks down viral RNA and destroys the infected cell. The 37 KDa (kiloDalton) low molecular weight (LMW) RNase L fragment found in CFS patients is produced by calpain (an apoptotic enzyme) cleavage, and the whole process affects the calcium and potassium channel mechanisms. The channelopathy will lead to low body potassium. Instead of the normal size 80KDa enzyme, those with CFS show only a
37 KDa size enzyme. Testing the ratio of the 37KDa and 80KDa enzymes has revealed that a high ratio is associated with more severe clinical symptoms. The 37KDa RNaseL is associated with incomplete cell death (which means that the cell constituents cannot be recycled for use by other cells). [18]

Patients suffering from CFS present many symptoms, including pain, which are likely to reflect dysregulation in cellular ion transport. Fragments released by a pathological protein cleavage result in dysregulation of sodium channels, which play a major role in the generation of pain and hyperalgesia in peripheral neurons, with a resultant shift in the pain sensitivity threshold as well as (if occuring in epithelial cells) to drenching sweats. An improper function of the sulfonylurea receptor (SUR1) could lead to an extreme loss of cellular potassium. Improper function of ATP binding cassette (ABC) transporters leads to serious neurological dysfunctions. Common symptoms of CFS could be due to a malfunction of various ABC transporters. [19]

Immunology

Increased apoptosis (programmed cell death) in peripheral blood mononuclear cells (PBMC) of patients with CFS has been suggested to contribute to the symptomatology.

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[17] Comparison of maximal oxygen consumption and RNase-L enzyme in patients with chronic fatigue syndrome. CR Snell et al. AACFS # 026

[18] The low molecular weight ribonuclease L present in peripheral blood mononuclear cells of CFS patients is formed by proteolytic cleavage of the native enzyme. P.Englebienne, RJ Suhadolnik et al. AACFS # 065

[19] The interaction of RNase L ankyrin domain with ABC transporters might explain pain and many of the physiological disorders of CFS. P Englebienne, K De Meirleir et al. AACFS # 069

RNase L activation has been directly linked to the induction of apoptosis. This study showed that the activation of RNase L in the PBMC of CFS patients upregulates apoptotic activity in these cells. This suggests that the peturbed apoptotic process may play a role in the altered immunologic functions in CFS. [20]

A large number of CFS patients have an abnormal immunological profile which can result in the production of immunologic mediators such as interferon, interleukin and other cytokines. The upregulation of the 2-5A Synthetase /Rnase L pathway shown in CFS patients indicates an activated immune state. According to their immunologic profile, CFS patients were divided into three groups. The results show that the presence of an increased amount of LMW RNase L correlates with higher levels of interferon gamma. [21]

Autoimmunity in CFS was reviewed. Low titres of antinuclear antibodies have been found in CFS patients. A major multi-centre study looked at the presence of autoantibodies to a cellular protein expressed primarily in neuronal cells (MAP2). Initial studies with immunohistochemistry showed a high percentage of CFS sera reactive to centrosomes. Preliminary evidence shows that other proteins beside MAP2 might also be target antigens in CFS autoimmunity. Of interest is the high frequency of reactors in lupus and rheumatoid arthritis compared with CFS patients. [22]

The intracellular content of the Natural Killer (NK) cell is perforin, a cell lytic protein common in many cells of the immune system which correlates with the cytolytic potential of the cell. In CFS, this chemical is reduced in NK cells. This finding substantiates claims of an NK associated defect in CFS and suggest a molecular basis for the reduced cytotoxicity (immune system killer cell function). This defect may not be NK specific but may encompass the cytotoxic T cell subset as well. Mice which were genetically engineered to have low or absent levels of perforin showed the same immune abnormalities as CFS. Other abnormalities found include activated lymphocytes in various subsets, elevated levels of immunoglobulins (IgG in particular) and increased levels of immune molecules called pro-inflammatory cytokines. Also found was a reduced activity of delayed hypersensitivity. [23]

Overlapping symptomatologies between CFS and Gulf War Syndrome have been observed by different investigators. It was therefore of great importance to verify whether various immunologic abnormalities found in CFS are also found in GWS. Overall differences between the two groups were not significant. The results indicate that, as in the case of CFS, Gulf War veterans are suffering from neuroimmunological disorder.

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[20] Apoptotic dysfunction consecutive to RNase L cleavage is likely to be central to the maintenance of chronic fatigue syndrome. P.Engelbienne, K De Meirleir et al. AACFS # 068

[21] Cytokine levels in patients with a different immunological profile. Kenny De Meirleir et al AACFS # 017

[22] A multi-centre study of autoimmunity in CFS. K Sugiura, D Buchwald, A Komaroff, E Tan et al AACFS # 037

[23] Flow cytometric measurements of perforin and natural killer cell activity. Kevin Maher, Nancy Klimas, Mary Ann Fletcher. AACFS # 047

Importantly, it was shown that basic laboratory testing is not sufficient for these groups of patient: advanced immunological tests including immune function and antibodies to the neurological system are needed. [24]

This needs to be compared with the recommendations in the Joint Royal Colleges' Report on CFS, which specifically state that no investigations should be performed to confirm the diagnosis *(page 45)* and that immunological abnormalities should not "*deflect the clinician from the biopsychosocial (psychiatric) approach….and should not focus attention towards a search for an 'organic' cause*" *(page 13).* It may also be salutary to reflect on the opinion expressed by Professor Pinching in his article on CFS in Prescribers' Journal ie. that *"over-investigation can (cause patients) to seek abnormal test results to validate their illness" .*

The practice of medicine ought not to be a pitched battle between patients and their clinicians. Such an unsatisfactory situation may have arisen because for the most part, patients with severe ME / "core" CFS are far better informed than their doctors.

[24] Immunological studies on the blood of patients with Gulf War Syndrome. A.Vojdani. AACFS # 076