

# Medical Pages

by Dr Nicole Phillips

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## PROCEEDINGS OF THE NINTH INTERNATIONAL IACFS/ME RESEARCH AND CLINICAL CONFERENCE RENO, NEVADA 12 - 15 MARCH 2009

### ABOUT IACFS/ME

Founded in 1990, the IACFS/ME (International Association of CFS/ME) is a multidisciplinary, non-profit organisation that sponsors biennial international conferences to stimulate research and collaboration in the study of CFS, ME and fibromyalgia. The biennial conference offers a unique experience for scientists, clinicians and educators from around the world to get the latest updates on cutting edge research, to present papers and participate in interactive seminars and to network with others. A separate patient meeting is also held. ([www.iacfsme.org](http://www.iacfsme.org)) 27N.Wacker Drive 416 Chicago IL 60606 Telephone 847-258-7248 Fax 847-579-0975 email [admin@IACFSME.org](mailto:admin@IACFSME.org).

I was incredibly excited to be attending my first IACFS/ ME meeting and, in particular, to meet with all my CFS heroes, those researchers and clinicians whose work I had read and admired over so many years.

Firstly, Reno –. OMG (as my daughters say) – what a ghastly place – nothing but a few seedy casinos, tattoo parlours, porn shops and car lots! However, the reason Reno was chosen was due to the opening of the Whittmore-Peterson institute for neuro-immune disease. This institute has been funded by the Whittmore family, whose daughter has CFS. Dan Peterson, CFS researcher, is at the helm.

The conference was predominantly research-based and disappointingly light on papers about treatment – it seems a lot of treatment trials have fallen by the wayside. Also, it confirmed that people seem to have their ‘pet’ interests, whether it be a particular virus or cytokine. I did meet or reconnect with most of the important “names” (see photos on page 20 of this section) including Leonard Jason, Fred Friedberg, Nancy Klimas, Anthony Komaroff, Chuck Lapp, Kenny De Meirleir to name a few. These dedicated people are inspiring and it was humbling when they also seemed inspired by my own work ‘downunder’.

So, I hope you all enjoy my summary, but as it is long and quite complex, please do so in small chunks!

**Nicole Phillips.**

# AGENDA

## THURSDAY 12 MARCH 2009.

This day had concurrent workshops for patients and clinicians/researchers.

### 1. TREATING SLEEP, PAIN AND FATIGUE:

Presented by *Charles W Lapp, Assistant Clinical Professor, Duke University Medical Centre, Medical Director, Hunter-Hopkins Centre and Lucinda Bateman, Board Member IACFS/ME Secretary Director, Fatigue Consultation Clinic, Salt Lake City UT, Adjunct Clinical Faculty, University of Utah School of Medicine, Department of Internal Medicine, Adjunct Instructor, University of Utah Family and Preventative Medicine.*

Dr Bateman spoke about the importance of taking a careful pain history and utilising pain diagrams and scales as required. She mentioned the importance of screening for other diseases that may mimic CFS or fibromyalgia (FM) such as rheumatologic diseases, malignancies, endocrine diseases, vitamin deficiencies and statin-induced myopathy. It is also important to screen for localised pain conditions that may respond to different medications such as osteoarthritis, cervical and lumbar spine disease, regional myofascial pain, temporomandibular joint dysfunction, headaches, irritable bowel syndrome, endometriosis, carpal tunnel syndrome and many more.

She divided pain into three categories: inflammatory pain (from tissue damage or inflammation), neuropathic pain (damage or injury to cells of the nervous system) and fibromyalgia pain (enhanced pain sensitivity, abnormal responsiveness or functioning of the nervous system, up-regulation of incoming sensory signals and down-regulation of inhibitory pain pathways). Nonpharmacologic treatment for fibromyalgia-type pain was discussed including pacing, stress reduction, restorative sleep, gentle disease appropriate physical conditioning and physical therapies such as massage. Pharmacologic treatments for central widespread pain syndromes (CWP) includes anticonvulsant drugs including a medication called pregabalin (also known as Lyrica) and others such as gabapentin, topiramate and zonisamide. The serotonin noradrenalin reuptake inhibitors (SNRI) group of antidepressants were also mentioned including venlafaxine, desvenlafaxine and duloxetine (all approved in Australia). Other medications under current study include dopamine agonists, hypnotics, tricyclic antidepressants and SSRI antidepressants. A study on Lyrica was mentioned which seemed to show both improvement in pain and sleep in a multicentre double-blind eight week randomised trial using 300 mg, 450 mg or 600 mg per day (all groups improved to a statistically significant level). The main side effects are dizziness, sleepiness and weight gain. Nonsteroidal anti-inflammatory drugs are not effective for fibromyalgia pain but do help inflammatory pain. SSRIs have been found to be partially effective for FM pain. Tricyclic antidepressants have shown mixed results. In summary, it is best to pick a medication that targets the type of pain and hopefully also improves sleep and mood and minimise fatigue/brain fog.

Dr Lapp dealt with sleep disorders and reaffirmed that non-restorative sleep is the most prevalent of the case-defining symptoms. All agreed that management of sleep is a key. There are nine characteristics seen clinically: nonrestorative sleep, difficulty initiating and maintaining sleep, restless legs syndrome/periodic leg movements, nocturnal myoclonus, vivid nightmarish dreams, 'tired but wired', phase-shifting and dysania. The reported prevalence of undiagnosed primary sleep disorders such as sleep apnoea, narcolepsy, restless leg syndrome and periodic leg movements in sleep varies from 0 - 62% in CFS. A high incidence of upper airway resistance syndrome (UARS), a lesser form of

obstructive sleep apnoea in which oxygenation drops and there are frequent arousals associated with daytime fatigue, has been found in a large percentage of FM patients. Dr Lapp reaffirmed the importance of sleep hygiene, that is: only going to bed when tired, using the bed for sleeping only, avoiding stimulant foods and beverages at night, get up and read or listen to music if unable to fall asleep within 30 minutes, keep a sleep schedule by getting up every morning at the same time, try to avoid daytime naps although short rest periods are fine, avoid watching TV or the computer at night and hiding the clock from view. He also discussed medications to improve sleep including simple over-the-counter medications such as antihistamines and melatonin, nonbenzodiazepine sleep medications, clonazepam which may help induce sleep, reduce restlessness and myoclonus, tricyclics and avoiding sleep disturbers such as benzodiazepines and alcohol. He asked the question "Do sleep disturbances contribute to or cause CFS/ME/FM?" and noted that treatment of UARS may produce significant improvement in symptoms although generally the response to CPAP has been disappointing.

He also spoke about general fatigue management which included the obvious things such as eliminating unnecessary or sedating medications, treating depression, sleep management, having a structured schedule with pacing and limit setting which he believes must include two to three rest periods a day in which one is lying down but not necessarily asleep, journals to identify behaviours such as push and crash or excessive resting, using a pedometer or an actimeter to measure activity levels, monitoring stimulants such as caffeine and using various cognitive-behavioural therapy techniques which included the Gupta course (mentioned in the poster writeup area).

## **2. BEHAVIOURAL ASSESSMENT AND TREATMENT OF ME/CFS:**

*Fred Friedberg PhD Board Member IACFS/ME Treasurer Assistant Professor Stony Brook University, Stony Brook NY and Leonard Jason PhD Board Member IACFS/ME, Vice President, Professor Clinical and Community Psychology, De Paul University, Chicago IL.*

Dr Freidberg talked about the differences between ME/CFS and depression including that ME/CFS has postexertional malaise, prolonged fatigue after exercise, flu-like symptoms, headaches, alcohol intolerance and has no loss of interest and cognitively ME/CFS patients tend to dwell on their fatigue and feel they have no control of their fatigue versus depressed patients who have more thoughts of worthlessness, self criticism and suicidal ideation. He brought up the question many people have discussed with respect to CBT "Does it improve coping with the illness or does it improve the illness itself?" He noted that the key factor in improvement was a balanced life regardless of illness severity. In a behavioural intervention program relaxation strategies are important and made the quote "rest does not mean doing absolutely nothing. Rest is repair". He also spoke about EMDR (eye movement desensitisation reprogramming) as a way of improving stress management and reducing anxiety and pain. He reiterated the importance of sleep hygiene, identifying and resolving anger and sources of anger include self anger such as "I should be able to control this illness" or "if I'm not giving and helping people will think I'm no good or worthless" to anger at dismissive physicians or unsupportive family and friends. He spoke about the importance of cognitive restructuring for some of these negative cognitions such as how to stop persistent self criticism "I am not equal to my limitations" or "I can regret what I cannot do but I need not berate myself" or coping statements to reduce anger and stress such as "I cannot convince anyone I am ill who does not want to believe it". He defined pacing as "the deliberate scheduling of activities so that it is energy conserving rather than depleting" and graded activity as "scheduling increased activity in small steps with minimal symptom increase". He spoke about patients who previously thrived on activity with overactivity now being their downfall. If activity is moderated patients should restore some energy and have less symptoms. With graded activity he spoke about starting small such as a five to 10 minute walk daily and increase after a few weeks by five to 10 minutes but reduce if symptoms worsen. He spoke of the importance of relieving oneself of worry and

guilt and grieving illness losses and the importance of easing into pleasurable feelings and pleasant events. Importantly he noted "healing attitudes will promote improvement".

Dr Leonard spoke more about case definition, diagnosis, psychiatric comorbidity and prevalence. He quoted a 1997 study by Salit that showed 15% of CFS patients had a gradual onset and 85% had an onset over a few hours or days (72% being viral or bacterial, 4.5% trauma, 4.5% surgery or childbirth, 2.2% allergic reactions and 1.7% stress/emotional trauma). He spoke about the various types of fatigue CFS patients suffer which were divided into five groups: molasses fatigue, wired fatigue, brain-fog fatigue, postexertional fatigue and flu fatigue. He noted that 45-82% of all patients with CFS have at least one comorbid psychiatric disorder, 21% report two, and 17% three or more. He also spoke about the potential difficulties in separating out CFS from depression and somatisation which, as many of you know, is a topic I have lectured on extensively. He commented that to differentiate CFS from somatisation disorder one notes that in CFS the fatigue is the primary feature, CFS having a sudden onset with symptoms of somatisation escalating over several years usually to a full-blown disorder by a person's twenties. He noted that women have a much higher rate of CFS than men (about twice as much), noted that the majority of CFS patients did not have an abuse history, spoke about the differences between various fatigue scales and discussed the differences between various diagnostic criteria.

## **FRIDAY 13 MARCH 2009.**

### **INVITED LECTURE.**

*Yasuyoshi Watanabe MD PhD Centre for Molecular Imaging Science, Riken Department of Physiology, Osaka City University Graduate School of Medicine, 21 st Century COE Program "To Overcome Fatigue" Mext Ristex, Japan Science and Technology Agency.*

## **FATIGUE SCIENCE FOR HUMAN HEALTH**

Professor Watanabe has an interest in fatigue states in general and has also done work in CFS. He has found that cluster analysis of gene expression in blood from CFS patients is different to controls in that there is an overexpressed gene related to cytokine signals. He has also looked at HHV-6 and HHV-7 reactivation and has found no increase in HHV-6 in saliva in CFS patients but did find an increase in HHV-7. He is involved in producing a kit which will hopefully be able to test for HHV-6 and HHV-7 reactivation.

He has also done work on the brain including various forms of scans such as PET, fMRI and MEG. It appears that the orbitofrontal cortex seems to sense fatigue. He has also found abnormalities in the serotonin system with decreased binding potential of the serotonin transporter in CFS. This is interesting as it also bears a relationship to pain centres. He has also found a higher turnover rate of L-DOPA in the amygdala in the brain. He has also shown with MRI a decreased volume of the prefrontal cortex in CFS but noted the brain has a great deal of plasticity (ability to change) and commented that the prefrontal cortical volume will increase after patients have had a course of CBT. Also using animal models he has found (replicated by others) a decreased uptake of glucose in the brain, degeneration of pituitary melanotropes and dysfunction of the dopaminergic pathway. He is interested in looking at "antifatigue food and substances" (see last lecture on Sunday).

# PHARMACOLOGIC AND NONPHARMACOLOGIC TREATMENT ADVANCES

## 1. **RESPONSE TO TREATMENT IN CHRONIC FATIGUE SYNDROME: EVALUATION OF COMBINING COGNITIVE BEHAVIOURAL THERAPY AND GRADED EXERCISE THERAPY:**

*Presented by Greta Mookens MD PhD, Department of Internal Medicine, Antwerp University Hospital, Belgium.*

In their study, 180 patients with CFS (24 male and 156 female) were referred to an expert centre for combined CBT and graded exercise therapy (GET). They were compared to 39 controls who were on a waiting list. They looked at triggers for the CFS group, finding infection in 23%, pregnancy in 9%, trauma in 6%, relationship problems in 15%, surgery in 5%, work-related problems in 10% and unknown in 32%. They also found certain vulnerability factors which included depression, a hyperactive lifestyle and violence (interestingly 28% of their sample had some violence past or present in their life). Fatigue severity was determined by the CIS (Checklist Individual Strength) and functional impairment by the SF36. People were evaluated before treatment, at six months and after completing the therapy program at 12 months. Their results showed that both the CFS treatment group and the control group had lower (better) scores on the CIS but were not statistically different and the CFS group did not get their scores down to the cutoff. With the SF36, the treated group did improve but not to the cutoff, with the controls not changing. Overall they found that in the treated group, a quarter of patients could go back to some form of part-time work. They conclude that although an improvement in physical functioning and a reduction of fatigue was mentioned by the majority of treated patients and definitely noticed by the clinical staff, statistical analysis could not show significant improvement in fatigue or physical functioning.

## 2. **THE INFLUENCE OF EMDR (Eye Movement Desensitisation Reprogramming) AND BIOFEEDBACK ON THE HYPERVIGILANCE IN CFS:**

*Professor Elke Van Hoof PhD, Faculty of Psychological and Educational Sciences, Vrije University, Brussels, Belgium.*

Professor Van Hoof talked about the sympathetic dominance or the loss of parasympathetic drive in CFS and spoke about the hypervigilance in which the body was trying to balance up these two parts of the autonomic nervous system. She spoke about stress-related symptoms which are influenced by dysfunctional cognitions and these are eventually developed into an enduring pattern with which patients constantly handicap themselves and put themselves under more stress. This results in biased information processing which EMDR tries to correct. She believes that EMDR can decrease the amygdala activation (this is the part of the brain involved in fear and other emotional responses). In their design they did two sessions for history and selection, four sessions of EMDR and four weeks of followup. They also used a control group. All subjects were female. They looked at a number of parameters and did find that EMDR had positive effects on daily function especially in peoples' ability to complete their physical roles. They found that the CIS20, the SF36 and the BDI (Beck Depression Inventory) all improved.

### **3. ALTERNATIVE MEDICAL INTERVENTIONS USED IN THE TREATMENT AND MANAGEMENT OF ME/CFS AND FIBROMYALGIA:**

*Natalie Porter PhD, Project Director, Centre for Community Research, De Paul University, Chicago, IL.*

Natalie's group looked at both randomised and nonrandomised controlled clinical trials of CAM (Complementary and Alternative Medicine) for these conditions. She divided them into two groups, firstly being physical therapies such as massage, balneotherapy, chiropractic and the second group into nonpharmacological supplements. In the physical group it appeared that 91% of the trials reported some benefit with 79% reporting improvement in symptoms. Out of these treatments, it appears that acupuncture and meditation have the strongest evidence. From the nonpharmacological supplement group, 78% of the trials showed some beneficial effect, 67% showed improvement in symptoms and the three supplements with the greatest evidence were magnesium, S-adenosylmethionine (SAME) and L-carnitine. She did note, however, that a lot of the studies were not well done, in particular did not have laboratory outcomes of such things as immune function.

### **4. COGNITIVE BEHAVIOUR THERAPY FOR CHRONIC FATIGUE SYNDROME: A DESCRIPTIVE STUDY OF THE PATIENT'S PERSPECTIVE:**

*Professor Elke Van Hoof.*

Professor Van Hoof talked about the fact that patients' perspective of CBT seems to be different to that of their treating doctors, often leading to conflict. Patients often do not get the same type of positive results that the research papers say they should be getting with CBT and GET. She also commented about the large drop-out rates in these studies which are usually not discussed in the papers. She surveyed 100 patients who had completed a CBT protocol in the previous six months. She noted that 30% dropped out, mainly due to inability to cope with the exercise part of the treatment. Only 2% reported that treatment had led to total recovery. 30% had some improvement without achieving recovery, another 30% reported no change, 38% reported deterioration. Thus, with 68% of participants indicating no change or deterioration, the results do not seem to confirm what the studies are showing. She concluded that her results do not support large-scale application of CBT for CFS.

### **5. CALLING IN COGNITIVE BEHAVIOURAL STRESS MANAGEMENT FOR CHRONIC FATIGUE SYNDROME:**

*Michael Antoni PhD, Professor of Psychology and Psychiatry and Behavioural Science, University of Miami, FL.*

Professor Antoni speculates that a reduction of chronic stress will lead to improved immunoregulation and decreased CFS symptoms. He has developed what he calls a cognitive behavioural stress management program (CBSM) which he believes can re-regulate the HPA-axis and immune dysfunction. It seems to be in two parts. Firstly, such things as progressive muscle relaxation, guided imagery, meditation, breathing exercises and autogenic training and the second part dealing with anger management, assertiveness training and negative cognitions. He concurs with other researchers regarding low cortisol, finding that when he does salivary cortisol output with a 48-hour sampling of saliva, on awakening CFS patients have a lower morning rise which is statistically significant compared to normals and also have diurnal dysregulation of their cortisol. He also noted that at the beginning of the study those with the greatest CFS symptoms had the greatest levels of proinflammatory cytokines and these were associated with lower cortisol output and poorer diurnal regulation. Due to the difficulty

of severely ill patients coming to the clinic, he has devised a course which can be done over the telephone which he said has been well accepted by participants.

## **6. TRAUMA TYPES, UNDERSTANDING TRAUMA INDUCED BY CFS/ME, FM AND OTHER CHRONIC CONDITIONS:**

*Patricia Fennell, Albany Health Management Associates.*

Patricia spoke about the different types of trauma for CFS patients.

1. Disease/syndrome trauma which is trauma from the diagnosis and the condition itself.
2. Iatrogenic trauma - this is where patients are traumatised by their treatment and due to the chronicity of their illness have multiple opportunities to have negative interactions with healthcare professionals.
3. Cultural trauma - because the disease is not a popular one.
4. Vicarious trauma - that is trauma that occurs to those people living with a CFS patient.
5. Premorbid/comorbid trauma - that is a history of trauma such as sexual abuse or domestic violence and other stress prior or during the illness.

Fennell has previously written up her "Fennell Four-Phase Model" which she believes is an effective method for assessing and treating illness-induced trauma. This is a four-phase model looking at crisis, stabilisation, resolution and integration with different goals of treatment for each phase of the trauma, for example, in phase one the importance of bonding, affirming and teaching versus phase three in which one needs to be helped to develop meaning in the illness and grieve losses.

## **7. IMMUNE AND VIRAL RESPONSE TO ISOPRINOSINE IN CFS:**

*Maria Vera MD, Centre for Multidisciplinary Research on CFS, Gulf War Illness, University of Miami and Miami Veteran Affairs Medical Centre, Miami FL.*

Isoprinosine, is a synthetic pyridine derivative. Maria presented results of 61 patients on a treatment protocol. Multiple immunological, viral and clinical assessments were done. At six months, 57 patients had shown significant clinical improvement. There was a 28% increase in the natural killer cell activity in 44 patients although no actual significant increase in number of natural killer cells. The clinical improvement was also noted at 12 months. There was improvement in the CD4 +, CD38 T cells at six and 12 months. EBV titres (VCA/G) had a highly significant decrease after six months of therapy. Gastrointestinal side effects were common (26%) and dose adjustment was required in 25%. No serious adverse reactions were reported.

# **NEW DEVELOPMENTS IN EPIDEMIOLOGY**

## **1. CAUSES OF DEATH IN PATIENTS WITH CHRONIC FATIGUE SYNDROME COMPARED TO DEATHS IN NON-CFS PATIENTS:**

*Rosamund Vallings, University of Auckland.*

Dr Vallings has 30 years experience treating approximately 6000 CFS patients in her practice in Auckland. She found that causes of death for those suffering from CFS were not generally significantly different from nonCFS patients with the main causes of death in both groups being cancers, cardiovascular disease, suicide and accidents. She did find though that there were more accidental

deaths in the CFS group. One could speculate many reasons for this but one possible reason may be due to increased suicide.

The average age of death in New Zealand generally is 68 but in Dr Vallings' CFS patients the average age of death was 58.

## **2. DEMONSTRATION OF A CORRELATION BETWEEN CFS AND THE INCIDENCE OF NONHODGKIN'S LYMPHOMA IN A NEVADA COHORT:**

*Julie Smith-Gagen, Nevada Centre for Health Statistics and Information School of Community Health Sciences, University of Nevada, Reno.*

Between 1984 and 1987 a cluster of CFS patients was found in Incline Village in Nevada, a town very close to Reno. This group has been studied over the years. While the incidence of nonHodgkin's lymphoma (NHL) is 0.02 % in the United States, nearly 5% of the Nevada CFS patients have developed NHL. Recently, a subset of the Nevada CFS cohort (59) have presented with clonal TCR rearrangements. This abnormality is predictive of the development of lymphoma. Also, 30% of the CFS cohort with lymphoma have developed a rare type called mantle cell lymphoma whereas generally only 5% of NHLs are MCL.

## **3. CLINICAL AND LABORATORY CHARACTERISTICS OF POSTINFECTIVE FATIGUE SYNDROME AFTER ACUTE Q FEVER: A PROSPECTIVE AUSTRALIAN COHORT:**

*Andrew Lloyd, University of New South Wales.*

Andrew discussed some interesting data that came out of the Dubbo Infections Outcome Study. In this talk he particularly looked at Q fever, one of the three infections studied (EBV and Ross River virus were the other two). Q fever is caused by a rickettsia-like bacterium called *Coxiella burnetii*. This has its reservoir in cattle, sheep, goats, cats and native animals and there are about 600 cases notified annually in Australia. Transmission is via inhalation which can occur from blood, milk, excreted birth products during slaughter and contaminated dust, wool and clothing. It has an incubation period of 19-21 days and then an abrupt febrile illness occurs with severe headaches, fevers, sweats, nausea and at times hepatitis. From 115 acute cases of Q fever, 9 went on to develop postinfective fatigue syndrome (PIFS). The group that recovered from their acute illness versus the PIFS were compared. Interestingly, prolonged symptoms after acute Q fever were associated with more severe acute illness but not with the persistence of genomes of the infecting organism in the peripheral blood cells, alterations in humoral responses, or changes in the proportion of immune cell subsets. In summary, Andrew's group found no persistence of the organism and no ongoing immune activation and they did find the same thing for the other infections looked at. This lack of evidence of ongoing immune activation seems to contradict many other studies.

## **3. GYNAECOLOGICAL HISTORY IN WOMEN WITH CFS - A POPULATION-BASED STUDY IN WICHITA, KS:**

*Roumiana Boneva, Centres for Disease Control and Prevention, Georgia.*

Thirty-six women with CFS and 48 well women were compared. The findings were as follows:

1. No difference in age of menarche. (age of onset of first period)
2. Menopause occurred at a younger age (approximately four years) in the CFS group.

3. A greater proportion of women with CFS had had a hysterectomy (53% versus 40% for controls).
4. A greater number of CFS patients reported oophorectomy (39% versus 25% of controls).
5. CFS patients were 13 times more likely to have chronic pelvic pain unrelated to their cycles but this was highly associated with having endometriosis (36% of CFS women had endometriosis versus 17% of controls) i.e. they were 2.8 times more likely.
6. There was a general trend for more gynaecological surgeries in the CFS patients, in particular D&Cs and the most common reason for this was miscarriage.

These findings are consistent with other studies, for example, Harlow et al in 1998 at the Harvard Medical School and implies that it is not just the HPA-axis that needs consideration in CFS but that we should also be looking at the HP gonadal-axis also.

#### **4. CLASSIFICATION OF PERSONS WITH ME/CFS BY TYPES OF FATIGUE:**

*Erin Boulton, Research Assistant, Centre for Community Research, De Paul University Chicago, IL.*

Recent evidence suggests that a multidimensional fatigue construct is needed and that fatigue in CFS patients is qualitatively different to that in healthy people. The need for subtypes has been discussed previously and five constructs of fatigue were discussed:

1. Brain-fog.
2. Postexertional.
3. Wired.
4. Energy.
5. Flu-like.

Within these groups three clusters of patients were found, those with mild, moderate and severe levels of fatigue. Interestingly, the postexertional fatigue and also the wired fatigue showed a lot of variability within patient groups.

## **NEUROENDOCRINE ADVANCES**

### **1. HORMONAL EVALUATION IN CFS:**

*A Suarez, University of Barcelona, Spain.*

CFS patients versus healthy controls were given a maximal exercise test on a bike and looked at before, 20 minutes and 40 minutes after maximal effort. They were also retested one week later. No significant differences in growth hormone secretion were found. No significant differences in prolactin levels were found although there was a trend to a slight increase in prolactin in controls. However, CFS patients were found to have low cortisol to a significant level of difference after each exercise test but there were no significant differences in ACTH.

### **2. ADRENERGIC AND SENSORY RECEPTOR EXPRESSION ON LEUKOCYTES INCREASES AFTER MODERATE EXERCISE IN CFS AND FIBROMYALGIA:**

*Alan Light, Department of Anaesthesiology, Salt Lake City, UT.*

Dr Light spoke about the normal definition of fatigue being "the inability to contract skeletal muscle" but said that this is not so for CFS patients. He said that the fatigue is more like pain, "you feel it", and

there is a distinct sensory system for pain and for fatigue. In CFS patients he believes the fatigue is a sensory phenomenon and these patients demonstrate sustained increases in gene expression for metabolite sensing molecular receptors and beta-adrenergic receptors on leukocytes from half to 48 hours after exercise, during which time fatigue and pain symptoms worsen. It is suggested that there is a predisposition for these receptors to increase dramatically after exercise, stress or infection in CFS patients and the resulting increases in these metabolite sensing and adrenergic receptors work together to enhance and prolong the sensation of muscle fatigue and pain, even when the muscles are not active. He believes that we have potential biomarkers here for CFS.

### **3. NEUROPEPTIDE Y (NPY): CORRELATES WITH SYMPTOM SEVERITY IN CFS:**

*Marianne Fletcher, Professor of Medicine Microbiology/Immunology and Psychology, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL.*

Dr Fletcher spoke about looking for biomarkers for CFS. She mentioned natural killer cell cytotoxicity but that this is expensive and you need fresh blood. One can also look at a molecule called perforin which is inside the natural killer cell and is responsible for the killing. She then mentioned neuropeptide Y (NPY) as another possible marker. This is stored in sympathetic nerve terminals. It is increased in CFS patients versus controls. It does require radioimmunoassay to assess and also has a high correlation with psychometric markers of stress, depression, anger and maladaptive coping skills. NPY is also associated with severity of clinical symptoms.

### **3. PRE-EXISTING PSYCHOLOGICAL STRESS PREDICTS ACUTE AND CHRONIC FATIGUE FOLLOWING SYMPTOMATIC PARVOVIRUS B19 INFECTION:**

*Jonathon Kerr, St George's University of London.*

Parvovirus B19 can be transmitted via multiple methods - respiratory, vertical, parenteral. It is more common in spring and one sees school epidemics. Common symptoms include "slapped cheek", arthritis, transient aplastic crisis, foetal death, pure red cell aplasia and less commonly can cause CFS. In his sample of 53 patients 2 (4%) went on to develop CFS in a 1996 study. In one of these patients, active virus was shown. In a follow-up study he looked at 39 people with acute parvovirus B19 and followed them up between one and three years. Five out of 39 (13%) developed CFS. Perceived stress and negative affect (mood) around the time of the infection was significantly associated with the development of CFS. He also did a treatment study with immunoglobulin which is the only current specific treatment for B19 and provides neutralising IgG. Of the five patients treated 4/5 were viraemic. Three patients completed the treatment and all were "cured" at one year and the virus was seen to be cleared from the blood.

### **5. SLEEP PATTERNS IN CFS PATIENTS:**

*Natalie Hone, Mexico City working with the Centre for Multidisciplinary Research on CFS and Gulf War Illness University of Miami FL.*

Natalie commented on the increased prevalence of primary sleep disorders in CFS patients and the well documented low sleep efficiency and interrupted sleep with alpha intrusions, these being more common in females than males. She also found 45.9% of the patients had sleep apnoea which is a higher prevalence than in the general population with men at higher risk.

# SATURDAY MARCH 14 2009

## INFECTIOUS DISEASE RESEARCH

### 1. **HERPES VIRUS AND PARVOVIRUS B19 DNA IN THE GASTRIC AND INTESTINAL MUCOSA OF PATIENTS WITH CFS**

*Kenny De Meirleir, Brussels, Belgium.*

Viruses including HHV-6, HHV-7, parvovirus B19 and EBV have been suspected to be triggering or perpetuating agents in CFS but are not consistently detected in the peripheral blood of patients. These viruses are well known to live in the gastrointestinal tract and CFS patients often present evidence of intestinal dysfunction. The study therefore looked at whether HHV-6, HHV-7, EBV and parvovirus B19 could be detected in the gastrointestinal mucosa of CSF patients. Gastric and intestinal biopsies were obtained from 40 CFS patients and 35 non-CFS controls. HHV-7 was the most frequently observed virus presenting in almost every sample (both CFS and controls). EBV could be detected in about 25% of biopsies. HHV-6 was less frequently observed. A significant difference was found between CFS patients and controls with respect to parvovirus B19. Significant loads of parvovirus B19 DNA were found in more than 40% of patients compared to 15% of controls. Parvovirus B19 DNA could not be detected in the peripheral blood of the biopsy positive patients.

### 2. **IDENTIFICATION OF DIFFERENTIALLY EXPRESSED VIRUSES IN AMERICAN CSF PATIENTS PROBED WITH A CUSTOM MAMMALIAN VIRUS MICROARRAY**

*Judy Mikovits, Whittemore Peterson Institute for Neuro-Immune Disease, Reno, Nevada.*

Dr Mikovits had previously mentioned that of the 300 cases of the CFS outbreak in Incline Village in Nevada, 77 of those had some suggestion of ongoing infection. Her group used a DNA microarray technology which is able to detect more than 100 viruses. They found herpes viruses predominating among the CFS patients significantly more than controls, in particular, cytomegalovirus (HHV-5) and HHV-7. Adenoviruses and rhinoviruses were the predominant viruses expressed in healthy controls.

### 3. **ACTIVE HHV-6 AND HHV-7 INFECTION AND CHRONIC FATIGUE SYNDROME**

*Modra Nurovska, Latvian Academy of Sciences, Latvia.*

Dr Nurovska postulated that in CFS, infectious agents such as viruses, in particular, HHV-6 and HHV-7 possess immunomodulating properties including the ability to alter the expression of immune activation molecules to modulate cytokines and chemokines and to induce apoptosis in lymphocytes, which may trigger and lead to chronic activation of the immune system. Blood was taken from 64 CFS patients and compared to healthy blood donors. Active HHV-6 infection (plasma viremia) was detected only in CFS patients (11 out of 64, 17.2%). The rate of active HHV-7 infection was significantly higher in CFS patients also (36/64, 56.3%) compared to 4% of controls. Importantly simultaneous activation of both viruses was detected only in CFS patients (10/31, 32.3%). TNF-alpha serum level in the CFS patients with simultaneous activation was significantly higher than in patients with single activation. Decreased numbers of CD3+, CD4+ T-cells and significantly increased number of CD95+ cells were found in CSF patients with active concurrent infection.

#### **4. SEROLOGICAL INVESTIGATION OF THE ROLE OF THE HERPES VIRUSES EBV, CMV AND HHV-6 IN POST-INFECTIVE FATIGUE SYNDROME**

*Barbara Cameron, University of New South Wales.*

Barbara took some statistics from the Dubbo Infection Outcome Study. The Australian group tended to differ from most other researchers in that they found that their data did not support the hypothesis of ongoing active EBV, HHV-6 or CMV infection in the pathogenesis of post-infectious fatigue syndrome of CFS.

### **THE LATEST RESEARCH IN IMMUNOLOGY**

#### **1. THE IMMUNOLOGICAL PROFILE OF AN AUSTRALIAN CHRONIC FATIGUE SYNDROME FEMALE POPULATION**

*Ekua Brenu, Bond University, Gold Coast.*

This was a small study looking at eight CFS patients. Comparable numbers of T-cells, monocytes and B-cells were observed amongst CFS and healthy participants but it appears that there was some decrease in some parameters of T-cell function. It was commented in this talk that in Australia in the year 2000, each CFS patient cost \$2746 per annum.

#### **2. IMMUNOLOGIC BIOMARKERS FAILED TO DISCRIMINATE BETWEEN CFS AND CONTROL SUBJECTS**

*Christopher Snell, University of the Pacific, Stockton, CA.*

This was a contentious talk as this group of researchers found that they could not validate the work of Kenny De Meirleir and the RNase L biomarker. In this study they found it impossible to conclude that either RNase L ratio or elastase levels have any efficacy as biomarkers for CFS. They commented that the high variability for both measures seen among CFS and controls suggest that levels may be influenced by factors other than illness state. They collected blood samples before and after a maximal exercise test in 22 CFS patients and 21 controls. The study was also repeated to validate their findings.

In a personal communication during the conference with Kenny De Meirleir, Kenny informed me that he believed the way they transported their samples was incorrect and that his work showing that RNase L and elastase are important biomarkers of CFS has been replicated in three European sites looking at the same samples. Kenny informed me that the Redlabs testing protocol which includes the RNase L, elastase tests (recently changed name to Viral Immune Pathology) is possibly due to be setup in Perth, later this year.

#### **3. ISOLATING CHARACTERISTIC IMMUNE SIGNALS UNDER CHALLENGE IN GULF WAR ILLNESS:**

*Gordon Broderick, University of Alberta, Can.*

They found that Gulf War illness subjects had significantly different neuroendocrine immune dynamics in response to exercise. Characteristic patterns in cytokines, neuropeptide Y and cortisol were evident both at rest and under challenge.

#### **4. SERUM CYTOKINE AND CHEMOKINE PROFILES OF INDIVIDUALS WITH ME/CFS DISTINGUISH UNIQUE SUBGROUPS AMONG PATIENT POPULATIONS:**

*Vincent Lombardi, Whittemore Peterson Institute, Reno Nevada*

The objective of this study was to show that serum cytokine and chemokine signatures can be used to distinguish subgroups of ME/CFS patients on a molecular level that correlate with distinct disease pictures. Using some fairly sophisticated technology their group have been able to delineate ME/CFS patients from healthy controls with 95% accuracy. They have also been able to show various subgroups that can be distinguished from each other. In particular, CFS patients with a clonal T cell receptor gene rearrangement can be distinguished from CFS patients without the clonality.

#### **5. PATTERNS OF PLASMA CYTOKINE EXPRESSION IN CFS:**

*Nancy Klimas, University of Miami Miller School of Medicine, Miami, FL*

Nancy's group have found the following cytokines to be elevated in CFS patients compared to controls: TNF beta, IL1 alpha, IL1 beta, IL4, IL5, IL6, IL12. Other cytokines were decreased - IL8, IL13 and IL15. The following cytokines were not different TNF alpha, IFN gamma, IL2, IL10, IL23 and IL17. The data from this study support a TH2 shift, proinflammatory cytokine cascade activation and down regulation of important components of cytotoxic cell function.

#### **6. THE IMPORTANCE OF VIRAL VERSUS NONVIRAL ONSET SUBGROUPING IN ME/CFS COMMUNITY SAMPLE: DIFFERENCES IN CYTOKINE PRODUCTION AND EXPRESSION**

*Natalie Porter, De Paul University, Chicago, IL.*

Natalie's group found that increased proinflammatory activity related to a viral cause. This suggests that amongst ME/CFS patients there is a viral subtype exhibiting evidence of a persistent hyperimmune response. In the nonviral subtype a bias was indicated towards production of anti-inflammatory interleukins on stimulation. In other words, in those with a viral onset there is a bias towards proinflammatory pathway activation with persistent hyperimmune response versus the nonviral group in which there is anti-inflammatory activity and chronic suppression of the immune system.

## **ASSESSMENT ISSUES FROM BIOLOGICAL TO BEHAVIOURAL**

#### **1. THE SEVERITY OF CFS CORRELATES WITH CHANGES IN BRAIN MAGNETIC RESONANCE (MR) IMAGES:**

*Leighton Barnden, The Queen Elizabeth, Royal Adelaide and Lyall McEwin Hospitals, South Australia.*

Leighton's group found that although there were no significant differences in global brain volumes between CFS patients and controls, in the CFS group:

As severity worsened, grey matter volume was found to shrink in the left insula and in the cerebellum while the white matter volume decreased in the dorsolateral prefrontal cortex and left frontal pole. Changes in the medulla and insula are consistent with the autonomic dysfunction reported in CFS. Changes in the cerebellum affect execution and programming of motor function. Medial post central changes are consistent with impaired motor imagery and action execution. Dorsolateral prefrontal changes can compromise a neural circuit that results in enhance fatigability. In other words, many of the brain locations identified have a function that when impaired is consistent with CFS symptoms. The

question that Leighton brought up was whether these findings are causative or a consequence of the illness.

## **2. A DIAGNOSTIC TEST FOR THE IDENTIFICATION OF METABOLIC DYSFUNCTION:**

*Mark Van Ness, Pacific Fatigue Lab, University of the Pacific, Stockton CA.*

This group postulated that metabolic dysfunction could be a mechanism that produces or contributes to postexertional malaise. They did two graded exercise tests with cardiopulmonary analysis within 24 hours of each other. They compared the following groups:

1. Twenty women with CFS.
2. Twelve age and gender-matched controls.
3. Eight physically active women.
4. Twenty-seven patients with high EBV/HHV-6 viral titres.

Firstly, the sedentary control subjects and the physically active women demonstrated a high reproducibility between the two exercise tests. The cardiopulmonary values between test 1 and test 2 among CFS and high viral load group displayed unusually high degrees of variability. Previous studies have indicated that test/retest declines in peak oxygen consumption and/or oxygen consumption at anaerobic threshold of at least 8% are indicative of metabolic dysfunction. Subjects that displayed metabolic dysfunction in the test/retest comparison were subgrouped and group means calculated separately. Of the 20 women with CFS, 10 displayed metabolic dysfunction and in the EBV/HHV-6 group 15/27 displayed at least an 8% reduction in oxygen consumption values. They therefore concluded that the reduction in peak oxygen consumption and/or oxygen consumption at anaerobic threshold in a subgroup of CFS patients and patients with high viral levels provide objective evidence and quantifiable measure of metabolic dysfunction. This "fatigue/effect" of prior physical activity on physiological function is an abnormal response that is not characteristic in other illnesses.

## **2. CFS AND MITOCHONDRIAL DYSFUNCTION:**

*Norman Booth, Mansfield College, University of Oxford.*

In Dr Booth's group a blood sample was taken for a commercially available ATP profile test designed for CFS and other conditions where energy availability is reduced. Five factors relating to the energy cycle were reduced into a mitochondrial energy score. A remarkable correlation was observed between the degree of mitochondrial dysfunction and the severity of illness. Only one of the 71 patients had an energy score that was in the normal range. Dr Booth concluded that the "ATP profile" test is a powerful diagnostic tool and can differentiate patients who have fatigue and other symptoms as a result of energy wastage by stress and psychological factors from those who have insufficient energy due to cellular respiration dysfunction. This test did not seem to be well known by most of the conference participants but it is done by a lab called Acumen and Dr Booth did say that blood samples could be sent from overseas.

## **NEW DEVELOPMENTS IN PAEDIATRIC ME/CFS**

### **1. INNATE IMMUNE RESPONSES DEFINE PAEDIATRIC CFS:**

*Ritchie Shoemaker, Medical Director, Centre for Biotoxin Associated Illnesses, Pocomoke.*

Shoemaker did a number of tests on a group of CFS patients between 10 and 17 years. These included TGF beta 1, HLA, MSH (melanocyte stimulating hormone), anticardiolipin (ACLA) and antigliadin (AGA) antibodies. He found that not one test separated all cases from controls. Two abnormal tests were found in 10% and any three lab parameters taken together identified all cases as no controls had three positive findings. He did find increased autoimmune abnormalities and in particular an elevated TGF beta 1, a cytokine associated with abnormalities in T regulatory lymphocyte function. MSH was found to be low as was vasoactive peptide (VIP).

### **2. EXAMINING CRITERIA TO DIAGNOSE ME/CFS IN PAEDIATRIC SAMPLES:**

*Leonard Jason, Professor and Director Centre for Community Research, De Paul University, Chicago.*

Dr Jason talked about the new paediatric case definition that was worked out at the last conference two years ago and stated that this needed further validation. In children you can diagnose CFS after three months rather than six months. They also have four groups, a severe group, a moderate group, an atypical group and a fourth group which they describe as ME/CFS- like, in which the symptoms are present for less than three months. They did validate that the Fukuda criteria are less effective than the new paediatric criteria in diagnosing paediatric cases, with the new paediatric criteria less likely to miss a case, and in a population with a low illness prevalence, the risk of under-diagnosis is always a key concern.

### **3. CLINICAL CHARACTERISTICS OF BELGIAN ADOLESCENTS WITH CHRONIC FATIGUE:**

*Greta Moorkens, Antwerp University Hospital, Belgium.*

Eighty-one adolescent patients with a complaint of chronic fatigue (not CFS) were investigated. One out of three complained of headache or a new kind of muscular ache. One out of five complained of concentration or memory problems. Polysomnography and/or psychiatric examination was only performed in 1/4 patients, apparently due to the opposition from the adolescents or their parents but interestingly was found to be abnormal in 60% of the adolescents looked at.

### **4. CHARACTERISTICS AND RECOVERY OF CHILDREN HOUSEBOUND WITH CFS/ME:**

*Esther Crawley, University of Bristol, UK.*

Esther is in charge of a large regional and national service for CFS in the UK. She found that up to 68% of kids had been housebound at some stage with only 10% accessing services. Interestingly, of all the children referred by paediatricians, 28% were found not to have a diagnosis of CFS (13/46), with those children having predominantly a psychiatric diagnosis. Of the 33 children with CFS, 15 were lost to followup, 4 (12%) had a full recovery over time, 6 (18%) showed improvement which meant somewhere between 20 and 80% school attendance, and 8 showed no improvement. Followup occurred between eight and 39 months.

#### **4. DO PATTERNS OF SYMPTOMS SUGGEST DISTINCT SUBTYPES OF PAEDIATRIC CFS?**

*Esther Crawley.*

Factor analysis was performed on symptoms in 333 young people under 19 with CFS/ME. Three factors were identified and symptoms were grouped together.

1. Somatic pain - predominantly muscle joint headaches and abdominal pain.
2. Hypersensitivity - such as to light and noise.
3. Sore throat with tender lymph nodes.

The somatic pain group was associated with worse function, poorer school attendance, the hypersensitivity group was in the middle and the sore throat group was associated with the best function. The combination of somatic pain and hypersensitivity was the worst with respect to function. She therefore proposed that maybe these groups have different prognoses, different treatments and perhaps different clues to pathology.

## **SUNDAY 15 MARCH**

### **RESEARCH DEVELOPMENTS IN GENETICS**

#### **1. GENE POLYMORPHISM STUDIES SUPPORT THE IMPLICATIONS OF INTESTINAL DYSFUNCTION AND ACTIVATION OF THE Th-17 AXIS IN CFS:**

*Marc Fremont, University of Brussels, Belgium.*

Dr Fremont's group previously reported the implication of T helper 17 (Th 17 cells) in the pathogenesis of CFS. Th-17 cells are crucial regulators of inflammation and autoimmunity. Activation of the Th-17 axis has been observed in intestinal diseases such as irritable bowel syndrome, ulcerative colitis and Crohn's disease. This group concludes that the induction of Th-17 cells in CFS is a consequence of intestinal dysregulations which are common in the disease - dysbiosis, viral infections of the gastrointestinal mucosa leading to mucosal dysfunction, increased intestinal permeability, and finally activation of the immune system by gram negative enterobacteria. They did find an association with CFS and polymorphisms located on the TLR-4 gene which is consistent with their theory of immune activation mediated by Th-17 cells.

#### **2. NATURAL KILLER CELL FUNCTION IS DEPRESSED IN GULF WAR ILLNESS:**

*Toni Whistler, CDC, Atlanta GA.*

This group compared Gulf War illness patients to controls and found that GWI patients demonstrated impaired immune function involving Th-2 and proinflammatory cytokines, cytotoxic NK cells and T cells and dysregulated mediators of the stress response such as salivary cortisol. An interesting and potentially important observation was that the exercise challenge augments these differences with the most significant effects observed immediately after the stressor. This has positive implications for the development of a laboratory diagnostic test and provides a paradigm for exploration of the immune - physiological mechanisms that are operating in GWI and similar syndromes such as CFS. The group found in gene expression analysis, 141 genes that were very highly correlated with natural killer cell numbers. The control group had 49 genes showing a more than two-fold up-regulation after exercise

versus only 1 in GWI. Intracellular perforin (the killer molecule inside natural killer cells) was found to be lower in GWI and this has also been found in previous studies in CFS.

### **3. A GENOME-WIDE ASSOCIATION STUDY OF CFS:**

*Mangalathu Rageevan, CDC, Atlanta GA.*

The CDC has used the Wichita, Kansas outbreak of CFS group, and these patients have been followed up from 1997. The study identified candidate genes not considered in prior CFS studies and supports endocrine psychoneuro and immune disruption in CFS. They have found 96 up-regulated genes and 70 down-regulated genes and have found genetic variants of GRIK-2 and NPAS-2, believing that these are two important genes involved in CFS symptoms.

### **4. CYTOKINE POLYMORPHISMS HAVE A SYNERGISTIC EFFECT ON SEVERITY AND DURATION OF ACUTE INFECTIVE ILLNESSES AND POSTINFECTIVE FATIGUE:**

*Andrew Lloyd, University of New South Wales.*

Andrew presented further thoughts on the Dubbo Infection Outcome Study. He had previously stated that he believes there is no evidence for persistent antigen and ongoing cytokine production in CFS. He found a 200-fold increased risk of prolonged illness with the severity of the acute illness and found genetically determined variations in the intensity of the inflammatory response underpin the severity of the acute illness and predict the duration of postinfectious fatigue.

## **ADVANCES IN BRAIN FUNCTION**

### **1. DO PHYSICAL COMPLAINTS NEGATIVELY INFLUENCE THE INFORMATION PROCESSING SPEED IN CFS?**

*Elke Van Hoof, Vrije University, Brussels.*

She stated that although studies show inconsistent results about the objective cognitive problems that CFS patients encounter, there is a consensus that they are slower on information processing. This study was to examine whether attention would be negatively influenced by external stimuli such as physical complaints. What was found was that in comparison with healthy controls, CFS patients were more distracted by their bodily focus which then negatively influenced their cognitive performance. The slowed cognitive processing speed found in previous studies was confirmed.

### **2. ELECTROENCEPHALOGRAPHIC (EEG) DATA DISTINGUISHED PATIENTS WITH CFS FROM HEALTHY AND DEPRESSED CONTROLS:**

*Frank Duffy, Department of Neurology, Children's Hospital, Boston, MA.*

This group sought to determine whether EEG-derived data could discriminate patients with CFS from healthy controls and patients with major depression. They looked at EEG data from 390 healthy controls, 70 subjects with CFS and 148 subjects with a provisional diagnosis of CFS and 24 patients with major depression. They found that spectral coherence EEG data could discriminate with nearly 90% accuracy patients with rigorously defined CFS from healthy controls and from subjects with major depression. It did not discriminate well with those patients referred with a possible diagnosis of CFS, suggesting that the diagnostic label of CFS may be often misapplied in community practice. However,

the group say that the study obviously requires replication before EEG can be considered a diagnostic technology for CFS.

### **3. COGNITIVE FUNCTION IN ADOLESCENTS AND YOUNG ADULTS WITH CFS:**

*Laura Younis, Deakin University, Melbourne.*

Laura commented that most CFS children adolescents miss about two days of school each week. She found that despite the fact that CFS adolescents reported high levels of distress and disability and given the impact that CFS had on their schooling, it was interesting that they performed as well as controls on a challenging and fatiguing neuropsychological test battery. However, she suggests that their strong motivation to perform to the best of their ability suggests that the findings may not reflect their typical performance in an educational setting.

### **4. ASSESSMENT OF AMINO ACID NEUROTRANSMITTER FUNCTION IN CFS, MAJOR DEPRESSION AND HEALTHY VOLUNTEERS IN VIVO USING HMR SPECTROSCOPY:**

*Dikoma Shungu, Professor of Physics in Radiology, Weill Cornell Medical College, New York.*

Shungu's group had previously reported increased lactate levels in the brain of CFS patients compared to those with generalised anxiety disorder. This study, due to the frequent misdiagnosis of CFS as major depressive disorder (MDD), tried to differentiate between the two looking at brain metabolism. Since significant alterations in brain GABA, glutamate and glutamine levels have been previously reported in MDD, this group compared cortical levels of GABA and glutamate in CFS patients to those with unmedicated MDD and healthy volunteers to look for a possible biomarker. This study did not provide evidence for significant abnormalities in regional amino acid neurotransmitter function in CFS but did confirm previously observed reductions in occipital GABA in major depressive disorder. Across all participants, fatigue severity was negatively correlated with GABA levels in the occipital region and within the major depression group was negatively correlated with GABA in the anterior cingulate cortex. The group also looked at other amino acids that they have looked at in their previous study with the generalised anxiety disorder and found no differences between the groups when they looked at such things as NAA and choline. Therefore, at this stage, the group's work, which previously showed differences in brain metabolites between CFS and Generalized Anxiety Disorder did not show the same differences with MDD.

### **THE JAPANESE EXPERIENCE:**

*Yasuyoshi Watanabe, Hirohiko Kuratsune.*

The Japanese group completed the conference with a discussion of "antifatigue foods". They have demonstrated antifatigue effects for the following substances.

1. Applephenon - a polyphenol extract that comes from unripe apples.
2. Coenzyme Q10.
3. Epigallocatechin gallate - an extract from tea.
4. Imidazole dipeptide - this is found in high amounts in mammalian skeletal muscles and is especially high in chicken breasts. It is also an antioxidant (they found in their studies that if this dipeptide was taken for two weeks before a fatiguing task subjects would be less fatigued).
5. Crocetin (carotenoid dicarboxylic acid) - this is an extract from the crocus plant.

They also found, comparing students and their levels of fatigue, that there is possibly a benefit in preventing the fatigue state from the traditional Japanese diet which is high in rice and fish.

## **POSTERS**

There were a number of interesting posters displayed during the course of the conference. Space does not allow me to discuss all of them but I shall pick out a few of interest.

### **CELL-ASSOCIATED THERAPY FOR CFS .. IS THIS THE NEXT FRONTIER?**

*Paul Cheney.*

Dr Cheney noted that in Europe, cell-associated therapies known as "live cell" products, also known as cell signalling factors (CSFs) have been used as injections for over 70 years in health spas as rejuvenation therapy and by physicians for the treatment of chronic disease. In this study, 18 patients had a one-year therapeutic protocol using porcine cell-signalling factors derived from heart and liver homogenates. Two patients failed to complete the study due to intolerances. There was no significant improvement noted in the first six months, however, during the next six months notable functional improvements were reported by most patients.

### **OXYMATRINE FOR THE TREATMENT OF ME/CFS ASSOCIATED WITH CHRONIC ENTEROVIRUS INFECTION:**

*John and Andrew Chia.*

Oxymatrine, a major ingredient of *sophora flavescens* extract, has immune-enhancing and possibly antiviral effects. In this study, the Chias imported a pure preparation of oxymatrine from China. Patients who had virological evidence of enterovirus infection were enrolled in the treatment study. Around 50% or so of patients tended to respond to the product but did relapse after discontinuation. They did find transient moderate increase in pre-existing symptoms to be reported in more than 50% with 10% stopping the herb in the first eight weeks due to intolerable side effects. They did find a shift in immune response towards the Th1 direction which seemed to correlate with symptomatic response and so they concluded that oxymatrine may be an effective immune modulator for ME/CFS patients before definitive antiviral therapy becomes available.

In a personal communication with Andrew Chia who had CFS and was diagnosed with enterovirus by his father, he told me that he has made a complete recovery on "Chinese herbs" and is now a great athlete and helping his father in the lab. He did not tell me which Chinese herbs he was on when we talked but it seems possible that it was the oxymatrine.

### **AMYGDALA RETRAINING TECHNIQUES MAY IMPROVE OUTCOMES FOR PATIENTS WITH CFS: A CLINICAL AUDIT OF SUBJECTIVE OUTCOMES IN A SMALL SAMPLE:**

*Gupta, A.*

Gupta's amygdala retraining therapy was developed subsequent to his hypothesis about the causes of CFS. In an earlier paper he hypothesised that during a traumatic neurological event often involving acute physiological stress combined with a viral infection or other chemical or physiological stressor, a conditioned network or "cell assembly" may be created in the amygdala (this is the part of the brain that deals with emotional responses). The unconscious amygdala may be conditioned to be chronically sensitised to negative symptoms arising from the body. Negative signals from body organs or other physiological stressors become conditioned stimuli and the conditioned response is a chronic

sympathetic outpouring from the amygdala via various brain pathways including the hypothalamus. This then produces a vicious circle where an unconscious negative reaction to symptoms causes immune reaction/dysfunction, chronic sympathetic stimulation leading to sympathetic dysfunction, mental and physical exhaustion and other symptoms and secondary complications. Amygdala retraining techniques attempt to control the amygdala's reaction to symptoms in the body. Gupta does say clearly that this treatment is still experimental. Amygdala retraining creates a hypothesised safety circuit from the cortex to the amygdala by inducing a relaxation response each time the conscious mind is alerted to a symptom. The patient is taught to recognise a fearful internal response to symptoms and then to act on these feelings in a way which dramatically interrupts the anxiety or the fear. In Gupta's study, 33 patients with a confirmed CFS diagnosis were recruited for one year. He found that 92% of the participants reported improvement. Sixty-seven percent made considerable recoveries, reaching 80 - 100% of preillness levels. Six participants dropped out. (This seems to be an individually-tailored therapy to each patient and does take much of its ideas from Eastern medicine including meditation and yogic practices.)

### **FREQUENCY AND CONTENT ANALYSIS OF CFS IN MEDICAL TEXTBOOKS:**

*Leonard Jason, De Paul University, Chicago.*

This was an interesting little study which revealed that after reviewing 129 medical textbooks from various medical categories, the authors found that only 53 (41%) of the medical textbooks included information on CFS and among the 140,542 total pages within those textbooks, the CFS content was presented on only 125 pages (0.089%).

### **A NEW DIAGNOSTIC METHOD FOR THE EVALUATION OF CFS?**

*Suarez A, University of Barcelona.*

The aim of this study was to analyse the differences between CFS patients and the control group in nitrate blood levels, presumably reflecting nitric oxide (NO) production and its correlation with the cardioventilatory response to physical exercise. Thirty-seven female CFS patients and 15 healthy women performed an exercise test. Nitrate concentration increased in relation to workload and reached higher values in the CFS group. The authors state that the combination of exercise plus NO response evaluation may be useful in CFS diagnosis.

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***Photos:***

***Left: Nancy Klimas (Left) and Dr Nichole Phillips***  
***Right: Dr Nicole Phillips (left) with Charles Lapp and Ros Vallings***